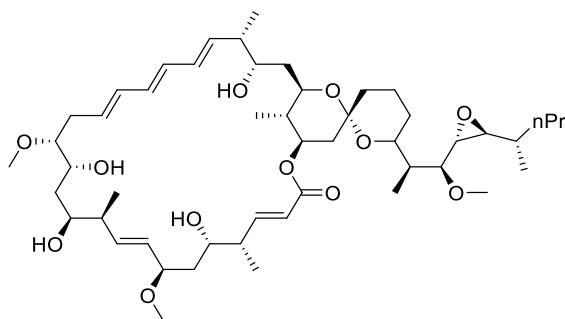




Studies towards the total synthesis and structure revision of neaumycin B



Dissertation

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Publikationen

- [1] M. F. Bieber, X. Gao, R. Wagner, B. Holzapfel, P. Tomczyk, D. Menche, *Eur. J. Org. Chem.* **2024**, 27.
DOI: 10.1002/ejoc.202400491
- [2] M. Schrempp, R. Wagner, H. Gleich, A. Gansäuer, D. Menche, *Org. Lett.* **2023**, 25, 8089.
DOI: 10.1021/acs.orglett.3c03181
- [3] P. Wollnitzke, R. Wagner, S. Y. Afsar, M. Werner, R. Geschold, C. E. Müller, O. Werz, G. Van Echten-Deckert, D. Menche, *Bioorg. Med. Chem. Lett.* **2023**, 94, 129464.
DOI: 10.1016/j.bmcl.2023.129464
- [4] R. Wagner, P. Wollnitzke, S. Essig, J. P. Gölz, D. Menche, *Synthesis* **2023**, 55, 3927.
DOI: 10.1055/a-2126-0720

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List of abbreviations

AcOH	Acetic acid	EDC	1-Ethyl-3-(3-dimethylaminopropyl) Carbodiimide
atm	Atmosphere		
aq.	Aqueous		
9-BBN	9-Borabicyclo[3.3.1]nonane	ee	Enantiomeric excess
BAIB	(Diacetoxyiodo)benzene	Et	Ethyl
Boc ₂ O	Di- <i>tert</i> -butyl dicarbonate	EA	Ethyl acetate
brsm	Based on recovered starting materiel	<i>et al.</i>	<i>Et alii</i> (lat.: “and others”)
<i>cf.</i>	<i>Confer</i> (lat.: “compare”)	equiv.	Equivalents
CH	Cyclohexane	HMBC	Heteronuclear multiple bond correlation
conc.	Concentrated	HMPA	Hexamethylphosphoramide
CSA	Camphorsulfonic acid	HSQC	Heteronuclear single quantum coherence spectroscopy
dba	Dibenzylideneacetone		
DCM	Dichloromethane	IBX	2-Iodoxybenzoic acid
DCC	<i>N,N</i> -Dicyclohexylcarbodiimide	<i>i</i> Pr	Isopropyl
DDQ	2,3-Dichloro-5,6-dicyano- <i>p</i> -benzoquinone	LAH	Lithium aluminium hydride
DIAD	Diisopropyl azodicarboxylate	LDA	Lithium diisopropylamide
DIBAL-H	Diisobutylaluminium hydride	m	Multiplet
DIPEA	<i>N,N</i> -Diisopropylethylamine	Me	Methyl
DMAP	4-Dimethylaminopyridine	min	Minutes
DMB	3,4-Dimethoxybenzyl	MOM	Methoxymethyl
DME	Dimethoxyethane	MTPA	α -Methoxy- α -trifluoromethylphenylacetic acid
DMF	Dimethylformamide	NIS	<i>N</i> -Iodosuccinimide
DMP	Dess-Martin periodinane	NMI	1-Methylimidazole
DMS	Dimethyl sulfide	NOESY	Nuclear Overhauser enhancement spectroscopy
DMSO	Dimethyl sulfoxide		
<i>dr</i>	Diastereomeric ratio	Ph	Phenyl
dtbbpy	4,4'-Di- <i>tert</i> -butyl-2,2'-dipyridyl		

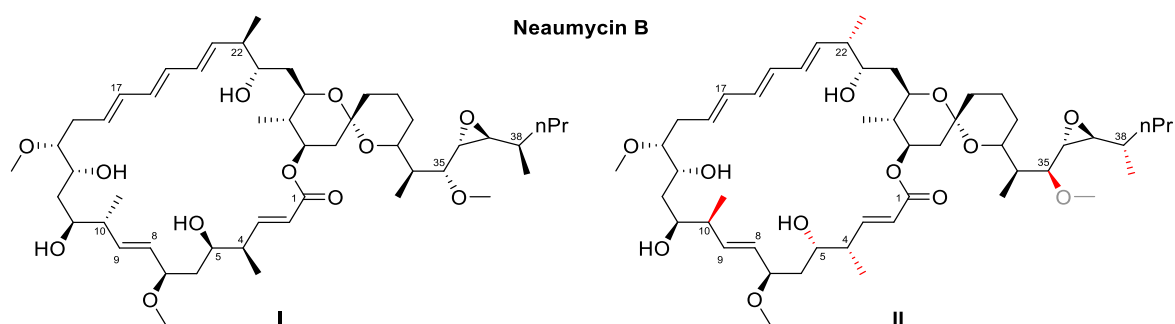
Pin	Pinacol	TES	Trimethylsilyl
PPh ₃	Triphenylphosphine	THF	Tetrahydrofuran
PPTS	Pyridinium	THP	Tetrahydropyran
	<i>p</i> -toluenesulfonate	TLC	Thin layer
q	Quartet		Chromatography
quant.	Quantitative	TMSE	2-(Trimethylsilyl)ethyl
R	Organic residue	TS	Transition state
r.t.	Room temperature	xs.	Excess
s	Singlet		
SAD	Sharpless asymmetric dihydroxylation		
sat.	Saturated		
t	Triplet		
TBAF	Tetra- <i>n</i> -butylammonium fluoride		
TBHP	<i>tert</i> -Butyl hydroperoxide		
TBS	<i>tert</i> -Butyldimethylsilyl		
TBSCl	<i>tert</i> -Butyldimethylsilyl chloride		
TBSOTf	<i>tert</i> -Butyldimethylsilyl Trifluoromethanesulfonate		
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl		

Abstract

Neaumycin B is a highly complex natural product that exhibits a strong synergistic effect with Ramoplanin against methicillin-resistant *Staphylococcus aureus* (MRSA) and shows potent cytotoxic activity against U87 human glioblastoma cells, highlighting its potential for further pharmacological development.^[1,2] Its structural complexity also presents a significant challenge in total synthesis.

The structure elucidation by the Fenical Group initially proposed the structure of neaumycin B (I) based on bioinformatic predictions and NMR analysis.^[1] However, in 2023, total syntheses of neaumycin B (I) by the Smith^[3] and Chen^[4] groups resulted in NMR spectra identical to each other but inconsistent with the NMR data of the isolated compound from Fenical's group. Consequently, the initial structural prediction was deemed incorrect. A subsequent structure revision to neaumycin B (II) by the Ziemert group,^[5] utilizing bioinformatic prediction identified six stereocenter changes at C4, C5, C10, C22, C35, and C38 (marked in red).

Due to the temporal overlap between the start of this study and the structure revision, efforts were made to synthesize the C1-C17 fragment with both the original stereochemistry of neaumycin B (I) and the revised stereochemistry of neaumycin B (II). Additionally, authentic fragments of neaumycin B (II), specifically C1-C9 and C8-C17, were synthesized and their NMR spectra compared with those from the Fenical, Smith, and Chen groups. The promising results suggest that the revised structure of Neaumycin B (II) is likely correct.



Reference:

- [1] M. C. Kim, H. Machado, K. H. Jang, L. Trzoss, P. R. Jensen, W. Fenical, *J. Am. Chem. Soc.* **2018**, *140*, 10775
- [2] M. Simone, S. I. Maffioli, A. Tocchetti, S. Tretter, M. Cattaneo, I. Biunno, E. Gaspari, S. Donadio, *J. Antibiot.* **2015**, *68*, 406.
- [3] J. Ding, A. B. Smith, *J. Am. Chem. Soc.* **2023**, *145*, 18240.
- [4] S. Zhang, S. Zhang, Y. Fan, X. Zhang, J. Chen, C. Jin, S. Chen, L. Wang, Q. Zhang, Y. Chen, *Angew. Chem.* **2023**, *135*.
- [5] Unpublished results.

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1 Introduction

1.1 Natural Products

The investigation of natural products has been a cornerstone of medicinal chemistry for centuries. Early civilizations employed plant-derived bioactive molecules for therapeutic purposes, as evidenced by Mesopotamian clay tablets (2600 BC) and the Egyptian Ebers Papyrus (1500 BC), which documented intricate pharmaceutical formulations.^[1] However, the chemical composition and mechanistic basis of these remedies remained obscure until the 19th century. A landmark achievement in 1804 occurred when Friedrich Sertürner isolated morphine from opium, demonstrating that discrete chemical entities within medicinal plants were responsible for their pharmacological properties.^[2] This breakthrough signaled the advent of natural product chemistry and spurred further advancements in the field.

Natural products, defined as organic compounds biosynthesized by living organisms,^[3] were categorized by Albrecht Kossel at the end of the 19th century into two primary classes: primary and secondary metabolites.^[4,5] Primary metabolites, such as amino acids, carbohydrates, and lipids, are essential for cellular function and viability. In contrast, secondary metabolites including alkaloids, terpenoids, polyketides, and phenylpropanoids are not requisite for basic metabolic processes but confer adaptive benefits such as antimicrobial activity, chemical defense, and intercellular signaling. These metabolites frequently modulate enzymatic pathways, receptor binding, and nutrient transport, although many of their biochemical roles remain only partially understood.^[6] Owing to their structural intricacy and pronounced bioactivity, these compounds have been rigorously investigated as lead structures for pharmaceutical innovation.

Despite their significant therapeutic potential, the practical application of natural products is often hindered by factors including limited natural abundance, complex molecular architectures, and challenging isolation processes. To circumvent these issues, total synthesis, the laboratory construction of complex molecules, has become a crucial strategy in natural product research.^[7] A seminal moment in synthetic organic chemistry was Friedrich Wöhler's synthesis of urea in 1828, which refuted the vitalist notion that organic compounds could only be produced by living systems.^[8]

Currently, natural products and their derivatives constitute approximately 39% of marketed pharmaceuticals.^[9] Many modern drugs have been developed through the chemical modification of natural scaffolds to enhance efficacy, stability, and bioavailability. Given their historical and ongoing contributions to drug discovery, both the isolation and total synthesis of natural products continue to be essential research avenues, driving innovation in therapeutic development.

1.2 Neaumycin

Neaumycin B (**1**) represents a structurally complex and highly challenging natural product that has intrigued the synthetic community for years (**Figure 1.2-1**). Its intricate macrocyclic framework, bearing multiple stereogenic centers, poses a significant challenge for total synthesis, establishing it as a compelling target for synthetic strategy development. Beyond its architectural complexity, neaumycin B (**1**) displays distinctive biological activity, further intensifying interest in its synthesis and functional characterization.^[10,11]

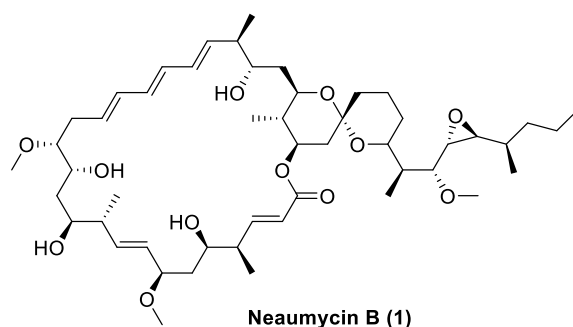


Figure 1.2-1. Proposed structure of neaumycin B (**1**) by Fenical *et al.*^[11]

Moreover, the isolation of several natural derivatives suggests the existence of a broader family of structurally related analogs with yet unexplored properties.^[10] Despite substantial progress in structural elucidation, neaumycin B (**1**) has undergone multiple revisions, and notably, synthetic efforts have yet to yield a compound that fully corresponds to the originally isolated natural product.^[12,13] This unresolved inconsistency highlights the intricate nature of its structure and reinforces the need for further studies, solidifying neaumycin B (**1**) as a captivating target in natural product chemistry.

1.2.1 Structural Elucidation of Neaumycin by Shen *et al.* (2012)

The structure of neaumycin (**2**) was first determined by Shen and his team in 2012 after isolating the compound from *Streptomyces* sp. NEAU-x211 (**Figure 1.2-2**).^[14] Their structural analysis was conducted using comprehensive mass spectrometry (MS) and nuclear magnetic resonance (NMR) spectroscopy. The molecular formula of neaumycin (**2**) was determined as C₅₅H₈₆O₁₅, indicating 13 degrees of unsaturation. The ¹³C NMR spectrum revealed resonances corresponding to three carbonyl groups and six double bonds, accounting for 9 of the 13 unsaturations and suggesting the presence of a tetracyclic core.

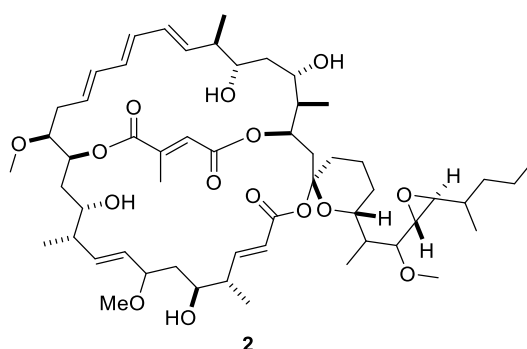


Figure 1.2-2. First structural elucidation of neaumycin (**2**).^[14]

Further structural details were obtained through 2D NMR techniques, including COSY, HMBC, and ROESY experiments. These analyses allowed the determination of connectivity between proton and carbon atoms, as well as spatial relationships between different structural units. The unique feature of neaumycin (**2**) was identified as a 30-membered macrolide ring system containing an internal diester bridge, a unique architectural motif among known macrolides.^[15]

1.2.2 Structural Revision of Neaumycin by Simone *et al.* (2015)

A structural revision of neaumycin was prompted by its re-isolation from *Actinoplanes* sp. ATCC 330766, a known producer of Ramoplanin in 2015 by Simone *et al.*^[10] Optimization of fermentation conditions for Ramoplanin revealed several lipophilic HPLC peaks that were distinct from the Ramoplanin complex. Characterization of these peaks confirmed that one was identical to neaumycin (**2**) based on UV, MS, and ¹H and ¹³C NMR data. In addition, four

novel congeners, neaumycin B–E, were isolated, all displaying the same UV absorption pattern as the parent compound.

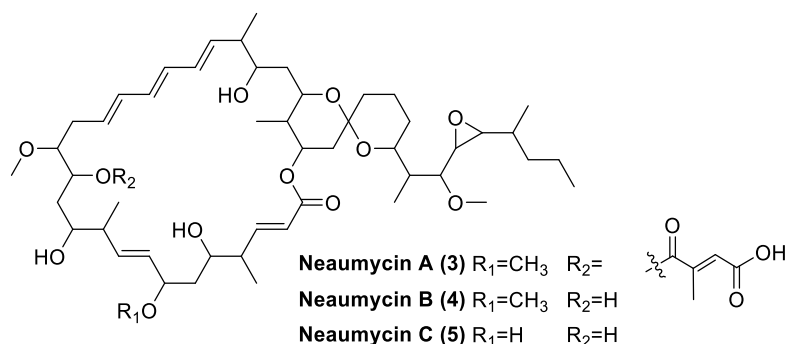


Figure 1.2-3. Structural revision of neaumycin A-C (3-5).^[10]

NMR analysis of neaumycin A–C (3-5) revealed new structural features, including the presence of a spiroketal and the absence of a diester bridge, prompting a revision of the initially proposed structure (**Figure 1.2-3**). However, stereochemical information remained unresolved.

1.2.3 Full Stereostructure of Neaumycin B (1) by Fenical *et al.* (2018)

In 2018, Fenical determined the full structure of neaumycin B (1) by employing an integrated approach combining bioinformatics and spectroscopic techniques (**Figure 1.2-4**).^[11]

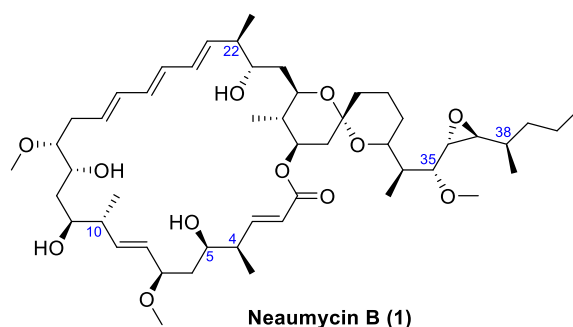


Figure 1.2-4. Full structural determination of neaumycin B (1).^[11]

They identified neaumycin B (1) from the marine bacterium *Micromonospora*^[16] sp. (strain CNY-010) and, through complete genome sequencing, provided insights into its polyketide synthase (PKS) biosynthesis.

A key breakthrough was the determination of the absolute configurations of all 19 stereogenic centers in neaumycin B (**1**). This was achieved by integrating bioinformatic predictions with 2D NMR spectroscopy (**Figure 1.2-5**).

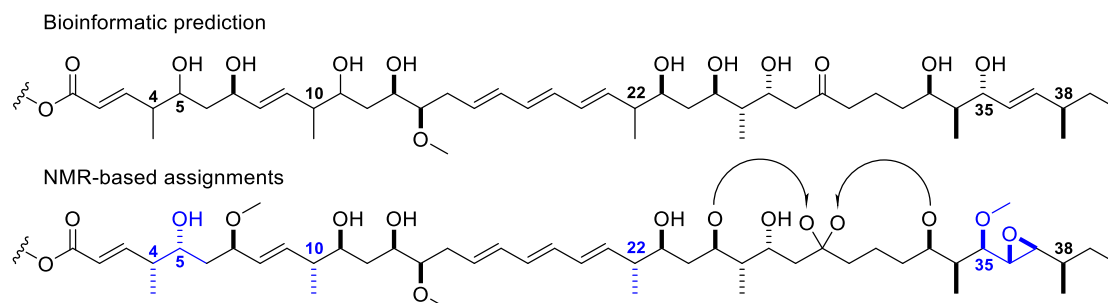


Figure 1.2-5. Bioinformatic prediction and NMR-based assignments of neaumycin B (**1**).^[11]

Through analysis of the PKS gene cluster, 11 of the 19 stereocenters were assigned and validated by NMR, while the remaining stereocenters were resolved through detailed NMR correlation studies, resulting in a comprehensive structural revision of neaumycin B (**1**).

1.2.4 Biological activity of Neaumycin

Neaumycin has demonstrated selective antibacterial activity, particularly against Gram-positive bacteria. Neaumycin A (**3**) exhibited moderate inhibitory effects, with minimum inhibitory concentrations (MICs) of 64 $\mu\text{g/mL}$ against *Staphylococcus aureus* and *Streptococcus pneumoniae*, and 16 $\mu\text{g/mL}$ against *Streptococcus pyogenes*. In contrast, neaumycin B (**1**) showed no significant antibacterial activity. Both compounds were inactive against Gram-negative bacteria (*E. coli*, *P. aeruginosa*) and *Candida albicans*.^[10]

A notable synergistic effect was observed when neaumycin A (**3**) or B (**1**) was combined with Ramoplanin, a glycolipodepsipeptide antibiotic known for its potent activity against multidrug-resistant Gram-positive bacteria,^[17,18] in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA). In a checkerboard dilution assay, the MIC of Ramoplanin was significantly reduced from 4 $\mu\text{g/mL}$ to 0.015 $\mu\text{g/mL}$ in the presence of either 4 $\mu\text{g/mL}$ neaumycin A (**3**) or 16 $\mu\text{g/mL}$ neaumycin B (**1**), suggesting a promising combinatory therapeutic strategy. However, no similar enhancement was observed when combined with Vancomycin, a glycopeptide antibiotic commonly used in clinical settings.^[10]

Preliminary *in vitro* studies also revealed cytotoxic activity of neaumycin B (**1**) against selected cancer cell lines. It displayed significant potency, with an LD₅₀ value of 5.6×10^{-5} $\mu\text{g/mL}$, showing particular selectivity toward U87 human glioblastoma cells.^[11] These findings highlight neaumycin's potential as a lead structure for further pharmacological investigations, particularly in antibacterial and anticancer research.

1.2.5 Previous work on Neaumycin B (**1**)

Since 2018, the presumed correct structure of neaumycin B (**1**), including the absolute configuration of all stereogenic centers, has been established. Since then, multiple research groups worldwide have undertaken efforts to achieve the total synthesis of neaumycin B (**1**), driven by its unique biological activity and therapeutic potential (**Figure 1.2-6**).

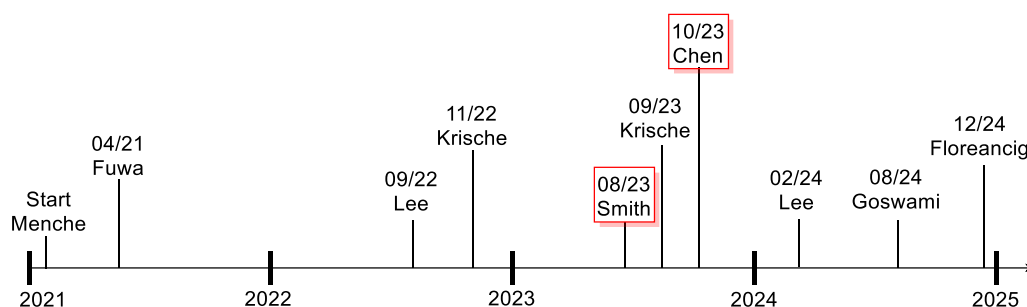


Figure 1.2-6. Chronology of all published studies on the synthesis of Neaumycin B (**1**).

Soon after we began our efforts towards the total synthesis of neaumycin B (**1**), Fuwa *et al.* reported the first synthesis of the southern hemisphere of neaumycin B (**1**) in April 2021.^[19] Over a year later, in September 2022, Lee *et al.* published an independent synthesis of the southern hemisphere, further refining synthetic strategies.^[20] In November 2022, Krische *et al.* introduced a novel ruthenium-catalyzed butadiene-mediated crotylation reaction, applying this methodology to the synthesis of the southern fragment.^[21] This development provided a new tool for the stereoselective construction of key substructures within the molecule.

The first reported total synthesis of neaumycin B (**1**) was achieved by the group of Smith in August 2023.^[12] However, discrepancies in the NMR spectral data were noted when compared with those published by Fenical in 2018, raising concerns about the originally proposed structure. This discrepancy suggested that the assigned structure of neaumycin B (**1**) might require reassessment.

In September 2023, Krische *et al.* continued their synthetic pursuits, publishing a synthesis of the northern hemisphere.^[22] Shortly thereafter, in October 2023, Chen *et al.* disclosed an alternative total synthesis of neaumycin B (**1**).^[13] Notably, the NMR data obtained from Chen closely matched that of Smith *et al.* but also deviated from the spectral data reported by Fenical, further reinforcing the hypothesis that the originally proposed structure may not be entirely accurate.

In February 2024, Lee *et al.* reported their second fragment synthesis, this time focusing on the northern portion.^[23] This was followed by Goswami *et al.* in August 2024, who contributed another synthetic approach targeting the northern hemisphere.^[24] Finally, in December 2024, Floreancig *et al.* reported an in-depth investigation into the stereochemical aspects of singly anomeric spiroketals present in neaumycin B (**1**).^[25] Their work proposed a stereocenter reassignment, further refining the structural understanding of the molecule.

Notably, all of these studies have been conducted only after the commencement of this dissertation, highlighting the increasing interest in the synthesis of this complex natural product.

1.2.6 Retrosynthetic Analysis of Fragment Synthesis

In the following, all fragment syntheses of neaumycin B (**1**) reported by various research groups will be briefly discussed with respect to their retrosynthetic approaches, while the total syntheses by Smith^[12] and Chen^[13] will be elaborated in detail in the next chapter. Across all studies, neaumycin B (**1**) has been divided into two nearly identical major fragments, commonly referred to as the northern and southern hemispheres (**Figure 1.2-7**).

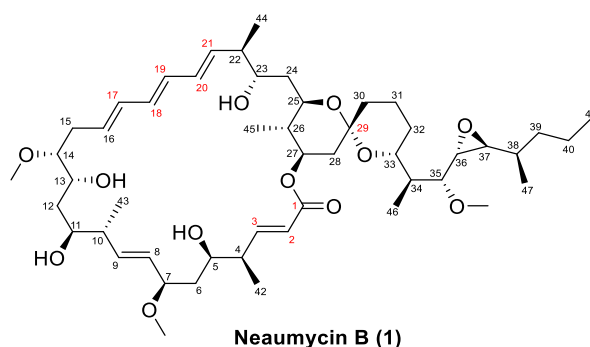
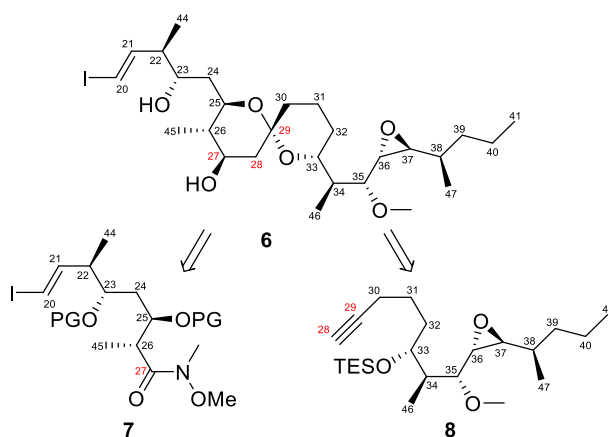


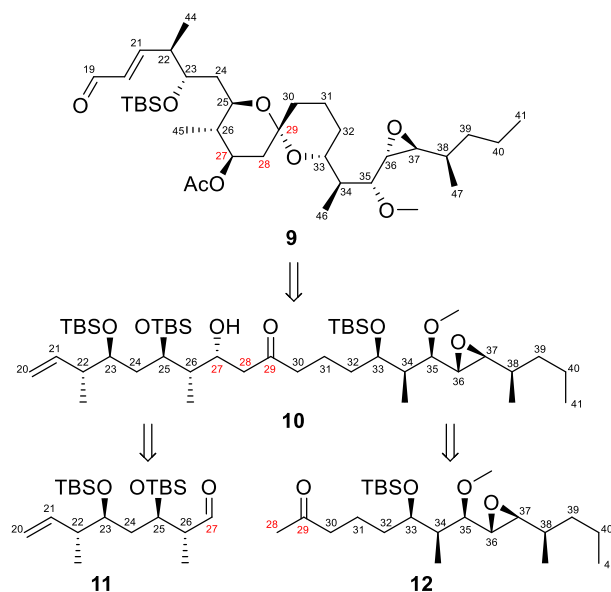
Figure 1.2-7. Neaumycin B (**1**) and its commonly used numbering.

The disconnection is consistently made at the triene, with flexibility between C17 and C21 depending on the research group, and at position C1, the ester moiety, with the intent of utilizing a Yamaguchi esterification for final coupling. A few notable exceptions exist in these fragmentations. Fuwa's approach in his partial synthesis of the southern hemisphere initially introduced a PMB-protected alcohol at C3.^[19] Additionally, Floreancig focused on NMR studies and synthesized only a neaumycin-like spiroketal rather than attempting fragment assembly.^[25]



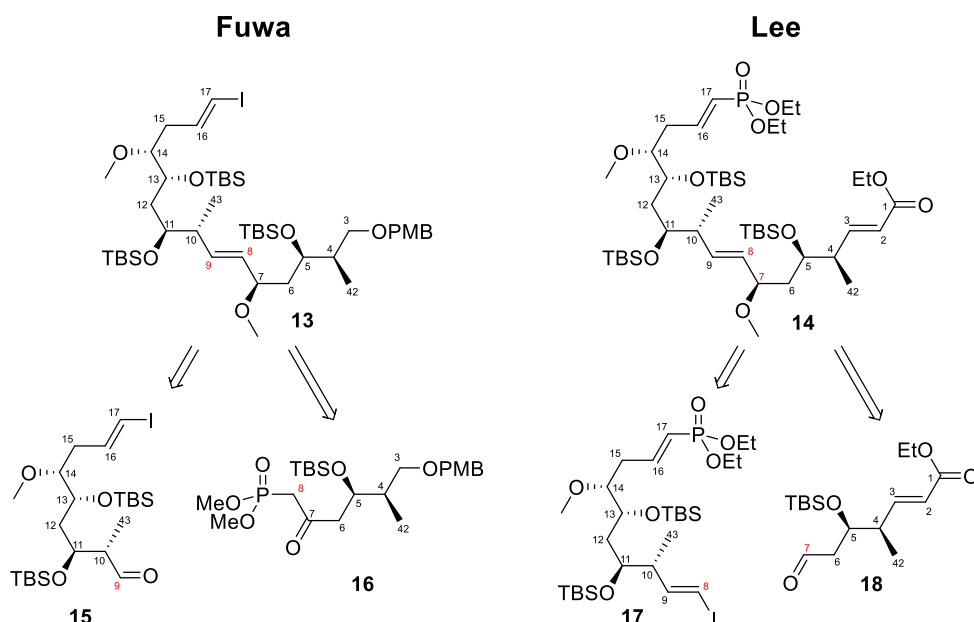
Scheme 1.2-1. Krische's retrosynthetic approach to the southern hemisphere **6** of neaumycin B (**1**).^[22]

Additional subdivisions of the northern and southern hemispheres have been explored. Krische *et al.* separated the northern fragment **6** into two linear subunits (**Scheme 1.2-1**): one extending from C20 to C27 (**7**), terminating in a Weinreb amide, and the other spanning C28 to C41 (**8**).^[22] The coupling of these fragments forms an acetylenic ketone at C27. Subsequent acidic deprotection followed by NaBH₄ reduction ultimately induces intramolecular spiroketalization,^[26–29] yielding a single epimer through ketone reduction at C27.



Scheme 1.2-2. Lee's retrosynthetic approach to the northern hemisphere **9** of neaumycin B (**1**).^[23]

Conversely, Lee adopted an approach wherein the spiroketal **9** was formed intramolecular from the ketone **10** at C29 (**Scheme 1.2-2**).^[23] His linear C20-C41 fragment **10** was synthesized through an aldol reaction between aldehyde **11** and methyl ketone **12**. The same intramolecular spiroketalization strategy via a ketone at C29 was employed by both the Goswami^[24] and Floreancig^[25] research groups.



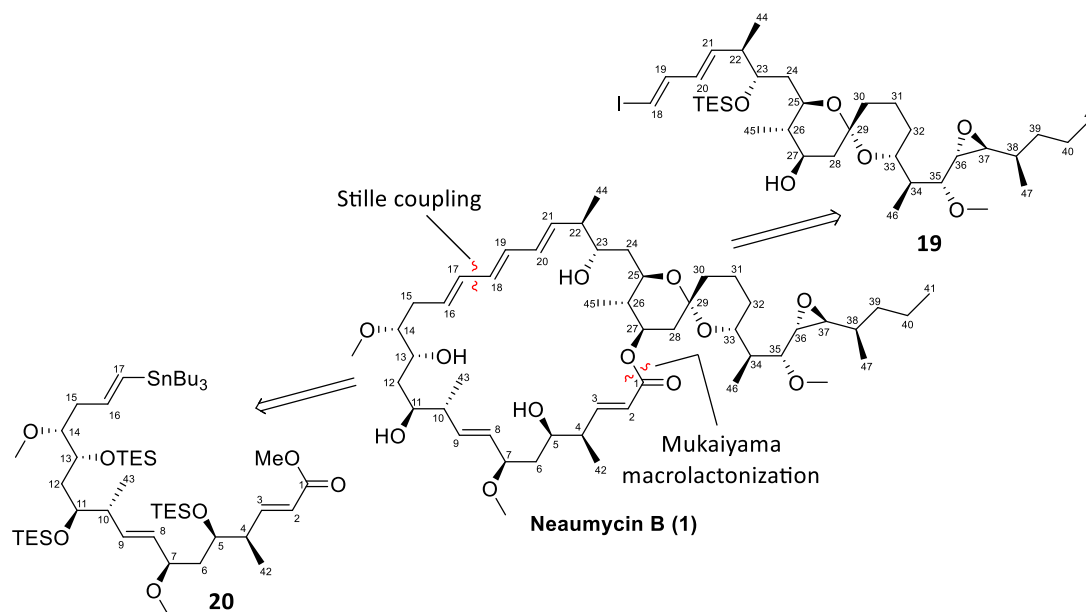
Scheme 1.2-3. Fuwa's and Lee's retrosynthetic approach to the southern hemispheres **13** and **14** of neaumycin B (**1**).^[19,20]

Regarding the southern hemisphere, Fuwa *et al.* and Lee *et al.* divided this region into two additional fragments, joining them at the olefin between C8 and C9 (**Scheme 1.2-3**).^[19,20] Specifically, Fuwa's southern hemisphere **13** spans from C17 to C3, as previously mentioned. To achieve this, he couples aldehyde **15** and phosphonate **16** using a Horner–Wadsworth–Emmons (HWE) reaction.^[30] In contrast, Lee *et al.* synthesized fragment **14** via a Nozaki–Hiyama–Kishi reaction between vinyl iodide **17** and aldehyde **18**.^[31] However, the resulting selectivity of the secondary alcohol at C7 was only 1.8:1. To overcome this issue, the alcohol was first oxidized to a ketone and subsequently reduced via CBS reduction, thereby improving the selectivity.

Krische, however, pursued a distinct route, incorporating his newly developed ruthenium-catalyzed butadiene-mediated crotylation and oxazaborolidine-catalyzed vinylogous Mukaiyama aldol reaction as key transformations in his synthetic strategy.^[21]

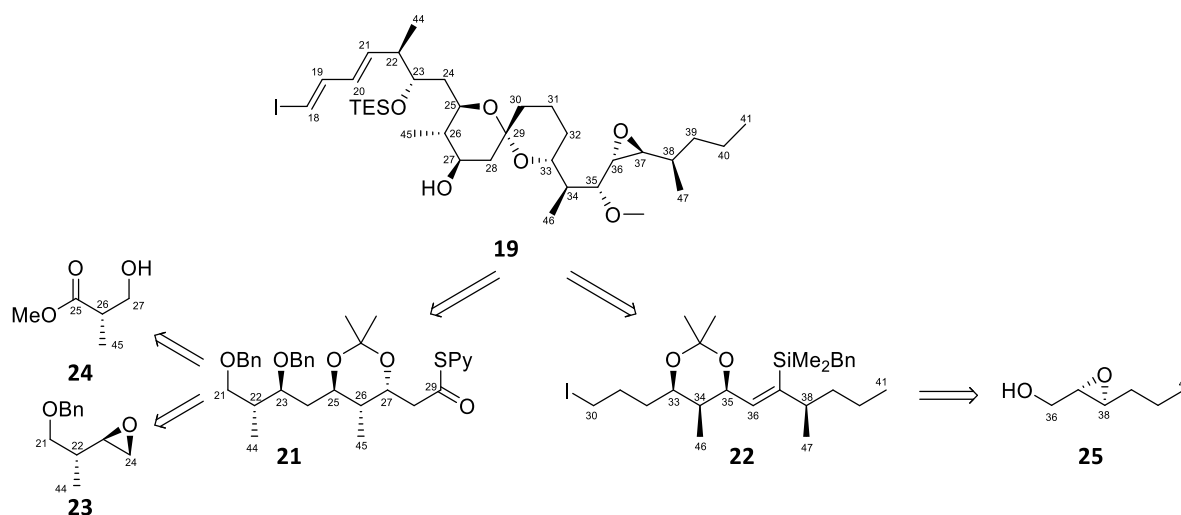
1.2.7 Total Synthesis of Neaumycin B (**1**) by Smith *et al.*

In August 2023, Smith *et al.* published the first total synthesis of the assumed correct structure of neaumycin B (**1**, see **Chapter 1.2.5**).^[12] Like all other research groups that had previously contributed to this topic, Smith *et al.* divided **1** into a spirocyclic northern hemisphere **19** and a southern hemisphere **20** (**Scheme 1.2-4**). The final assembly of these two hemispheres was designed to proceed via a Stille coupling at the triene unit between C17 and C18, followed by a Mukaiyama macrolactonization between C1 and alcohol at C27.



Scheme 1.2-4. Retrosynthetic analysis of neaumycin B (**1**), revealing the northern hemisphere **19** and southern hemisphere **20** by Smith *et al.*

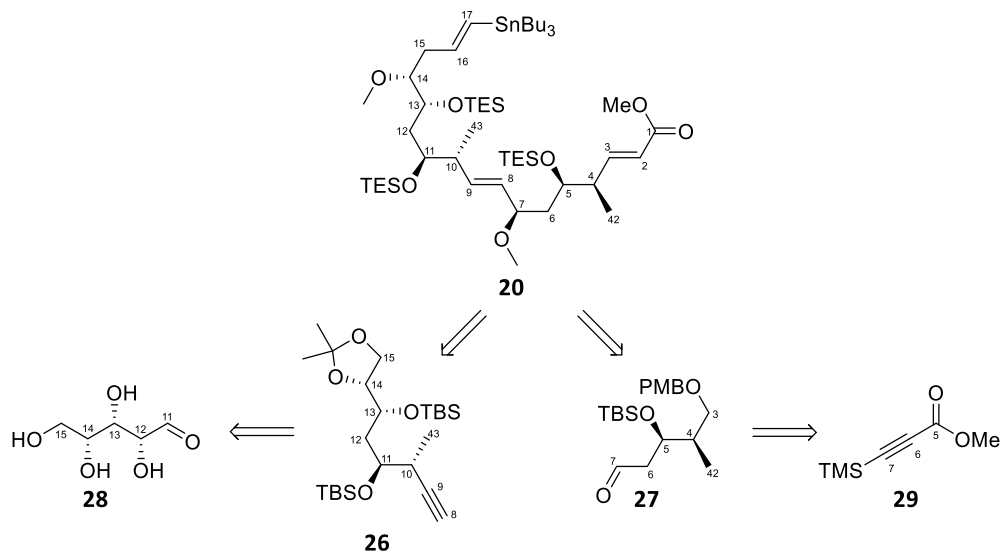
The northern hemisphere **19** was further subdivided into fragments **21** and **22**, which were planned to undergo a Ni-catalysed coupling to generate a ketone at C29 (**Scheme 1.2-5**). This ketone would subsequently undergo an intramolecular spiroketalization. The synthesis of **21** was envisioned from epoxide **23** and (*S*)-Roche ester (**24**), while fragment **22** was to be derived from epoxide **25**.



Scheme 1.2-5. Retrosynthetic analysis of the northern hemisphere **19**.

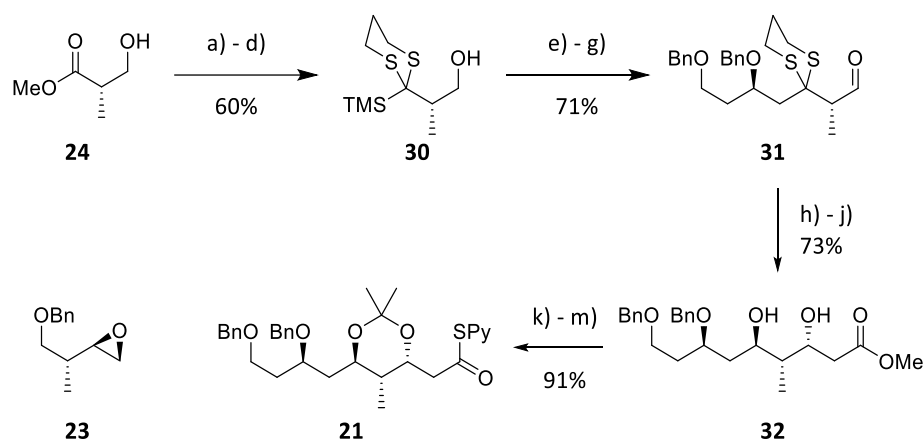
For the southern hemisphere **20**, Smith *et al.* further divided this region into alkyne **26** and aldehyde **27**, which were intended to be coupled via a Carreira asymmetric alkynylation^[32]

followed by a *trans*-reduction of the alkyne (**Scheme 1.2-6**). The precursor alkyne **26** was synthesized from D-xylose (**28**), whereas aldehyde **27** was derived from alkyne **29**.



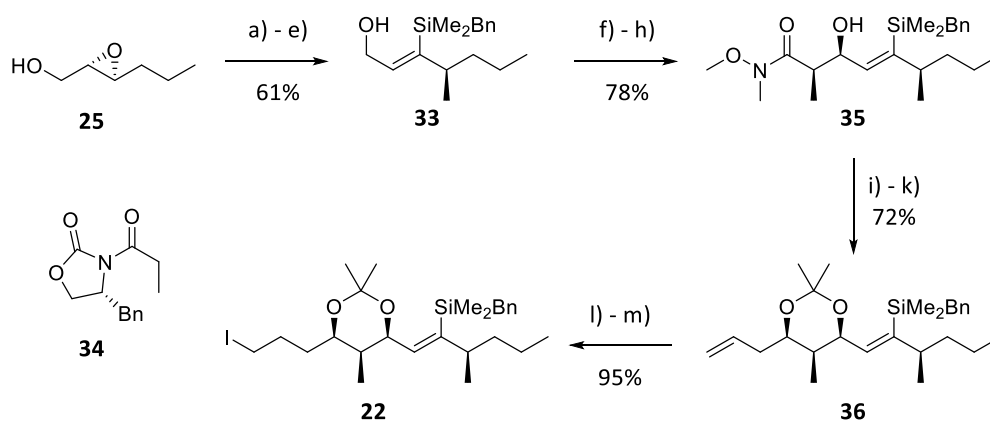
Scheme 1.2-6. Retrosynthetic analysis of southern hemisphere **20**, revealing commercial available substrates **28** and **29**.

Starting from (*S*)-Roche ester (**24**), fragment **21** was synthesized in 13 steps (**Scheme 1.2-7**). The key intermediate, dithioacetal **30**, was obtained through acid-mediated PMB protection of the hydroxyl group of **24**, followed by DIBAL-H reduction to the corresponding aldehyde. Subsequent thioacetalization and silylation under basic conditions yielded **30** with a 60% yield. The synthetic route proceeded through a Brook rearrangement, followed by epoxide opening of **23**. Further benzyl protection, primary TMS deprotection, and Cu/TEMPO-catalysed aerobic oxidation of the free alcohol afforded aldehyde **31** in 71% yield. Aldehyde **31** was then coupled via a Felkin-Anh selective aldol reaction using the enolate of methyl acetate, achieving excellent diastereoselectivity (*dr* = 15:1). The dithioacetal was subsequently cleaved, and an Evans-Saksena reduction^[33,34] furnished diol **32** in 73% yield. The 1,3-diol was protected as an acetonide, confirming the *anti*-configuration. Saponification of the methyl ester, followed by thioesterification, yielded fragment **21** on a decagram scale with a 91% yield.



Scheme 1.2-7. Synthesis of fragment **21** over 13 steps, starting from (*S*)-Roche ester (**24**). Conditions: a) PMBTCAI (1.27 equiv.), CSA (10 mol%). DCM, r.t., 24 h, 97%; b) DIBAL-H (1.0 M in toluene, 1.09 equiv.), DCM, -78°C , not purified; c) 1,3-Propanethiol (2.50 equiv.), $\text{BF}_3\cdot\text{Et}_2\text{O}$ (2.5 equiv.), DCM, -78°C , 2 h, then r.t., 2 h, not purified; d) *n*-BuLi (2.5 M in hexanes, 2.25 equiv.), THF, 0°C , 1 h, then TMSCl (2.5 equiv.), 0°C to r.t., 2 h, 62% over three steps; e) **30** (1.30 equiv.), *n*-BuLi (2.5 M in hexanes, 1.30 equiv.), Et_2O , -78°C , 10 min, then **23** (1.00 equiv.), HMPA, -78°C to 0°C , 3 h, 82%; f) KHMDs (0.5 M in toluene, 2.50 equiv.), BnBr (6.00 equiv.), THF, -30°C to 0°C , 10 min, then $\text{HCl}_{(\text{aq})}$ (1 M, xs.), 0°C to r.t., 1 h, not isolated; g) $\text{Cu}(\text{MeCN})_4\text{OTf}$ (5 mol%), TEMPO (5 mol%), 2,2'-bipyridinyl (5 mol%), NMI (10 mol%), MeCN, air (1 atm), r.t., 16 h, 87% over two steps; h) *i*Pr₂NH (2.00 equiv.), *n*-BuLi (2.5 M in hexanes, 2.00 equiv.), THF, -78°C , 30 min, then methyl acetate (2.00 equiv.), -78°C , 50 min, then aldehyde **31** (1.00 equiv.), -78°C , 20 min, quant., *dr* = 15:1; i) CaCO_3 (10.0 equiv.), $\text{Hg}(\text{ClO}_4)_2\cdot 3\text{H}_2\text{O}$ (2.00 equiv.), THF/ H_2O , 0°C to r.t., 40 min, not purified; $\text{NMe}_4\text{BH}(\text{OAc})_3$ (7.00 equiv.), MeCN/ HOAc , -20°C , 40 h, 73% over two steps; k) 2-Methoxypropene (2.01 equiv.), PPTS (5 mol%), DCM, r.t., 16 h, 96%; l) LiOH (1 M in H_2O , 2.00 equiv.), THF, r.t., 16 h, not purified; m) PPh_3 (4.00 equiv.), $(\text{SPy})_2$ (2.00 equiv.), DCM, r.t., 16 h, 95%.^[12,35]

In parallel, alkyl iodide **22** was also synthesized over 13 steps, beginning with epoxide **25** (**Scheme 1.2-8**). This epoxide was regioselectively opened using trimethylaluminum^[36] (*dr* > 20:1), followed by periodate cleavage and dibromo olefination. Treatment of the resulting dibromo alkene with *n*-BuLi and formaldehyde yielded a propargylic alcohol, which underwent ruthenium-catalysed trans-hydrosilylation to afford alcohol **33** in 61% yield over five steps, with excellent selectivity (α/β > 20:1, *E/Z* > 20:1). MnO_2 oxidation of the primary alcohol generated an aldehyde, which was subjected to an Evans aldol reaction^[37] with **34**. Subsequent transamidation yielded Weinreb amide **35**. Nucleophilic attack on **35** with vinyl magnesium bromide, followed by Narasaka-Prasad reduction^[38,39] of the resulting ketone, enabled the selective protection of the 1,3-diol as acetonide **36**. Hydroboration of the terminal alkene, followed by an Appel reaction,^[40] completed the synthesis of fragment **22**.



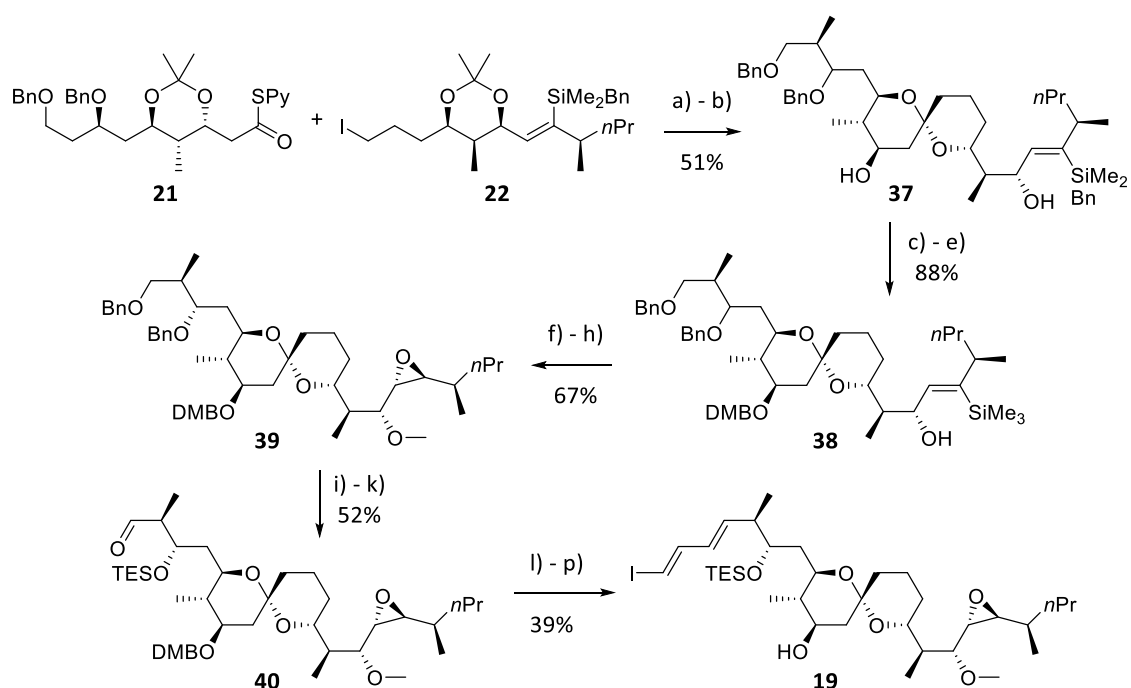
Scheme 1.2-8. Synthesis of fragment **22** over 13 steps, starting from epoxide **25**. Conditions: a) AlMe_3 (2.0 M in hexanes, 3.00 equiv.), C_6H_{14} , -40°C to 0°C , 1 h, 95%, $dr > 20:1$; b) Bu_4NIO_4 (5 mol%), NaIO_4 (2.00 equiv.), $\text{DCH}/\text{H}_2\text{O}$, 1:2, 0°C , 40 min, not isolated; c) PPh_3 (4.00 equiv.), CBr_4 (2.00 equiv.), DCM , 0°C , 1 h, then r.t., 16 h, 95% over two steps; d) $n\text{-BuLi}$ (2.5 M in hexanes, 2.20 equiv.), THF , -78°C , 1.5 h, then 0°C , 30 min, then $(\text{CH}_2\text{O})_n$ (2.00 equiv.), r.t., 14 h, 84%; e) BnMe_2SiH (1.30 equiv.), $\text{Cp-Ru}(\text{MeCN})_3\text{PF}_6$ (3 mol%), acetone, r.t., 16 h, 91%, $\alpha/\beta > 20:1$, $E/Z > 20:1$; f) MnO_2 (10.0 equiv.), DCM , r.t., 18 h, 95%; g) **34** (1.18 equiv.), Bu_2BOTf (1 M in DCM , 1.24 equiv.), NEt_3 (1.28 equiv.), DCM , 0°C , 1 h, then -78°C , 16 h, not purified; h) N,O -Dimethylhydroxylamine hydrochloride (2.28 equiv.), AlMe_3 (2.0 M in hexanes, 2.28 equiv.), DCM , 0°C to r.t., 2 h, then -20°C to r.t., 16 h, 82% over two steps; i) AllylMgBr (1.0 M in Et_2O , 3.00 equiv.), -78°C to -10°C , 1 h, not purified; j) Et_2BOMe (1.0 M in THF , 1.10 equiv.), -78°C , 2 h, then NaBH_4 (2.00 equiv.), 17 h, not purified; k) 2-Methoxypropene (1.08 equiv.), PPTS (10 mol%), DCM , r.t., 17 h, 72% over three steps; l) 9-BBN (0.5 M in THF , 1.08 equiv.), THF , 0°C to r.t., 16 h, then NaHCO_3 (aq. sat.), H_2O_2 (xs.), 96%; m) PPh_3 (1.20 equiv.), Imidazole (2.00 equiv.), I_2 (1.20 equiv.), THF , 0°C to r.t., 1 h, 99%.^[12,35]

With both fragments **21** and **22** in hand, they were coupled via a Ni-catalysed reductive cross-coupling,^[41] generating a ketone that was deprotected under acidic conditions to facilitate spiroketalization (**Scheme 1.2-9**). This transformation afforded spiroketal **37** in 51% yield over two steps. Selective DMB protection of the spiroketal hydroxyl group was achieved in two steps. Due to the presence of two free hydroxyl groups, selective protection was necessary. The addition of TBAF facilitated the formation of a five-membered siloxane ring from the secondary hydroxyl, allowing selective protection of the spiroketal hydroxyl using DMB-Br. Treatment with MeLi induced the formation of the corresponding TMS group, yielding spiroketal **38**.

Next, a stereoselective vanadyl-catalyzed epoxidation^[42] was performed adjacent to the silyl ether. The TMS group was then removed with TBAF, and the remaining secondary alcohol was methylated, affording fragment **39**. Benzyl deprotection, followed by oxidation of the primary

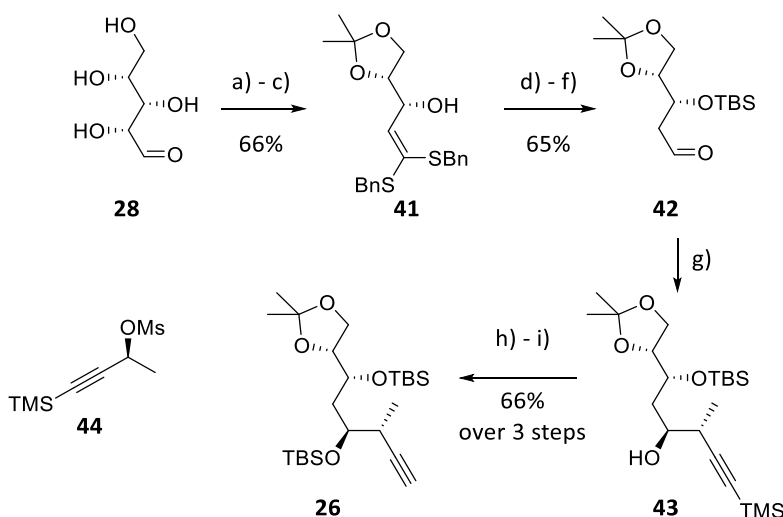
alcohol to a β -hydroxy aldehyde, allowed selective TES protection of the secondary hydroxyl group, furnishing fragment **40** in 52% yield over three steps. Takai olefination of aldehyde **40** resulted in excellent *E*-selectivity (*E/Z* >20:1), and subsequent iodination afforded the corresponding vinyl iodide. The DMB group was then removed using DDQ.

To extend the vinyl iodide, germylstannane-mediated^[43–45] elongation was employed to generate the corresponding dienyl germane, which, upon iodination, furnished the fully extended vinyl iodide and completed the synthesis of the northern hemisphere **19**.



Scheme 1.2-9. Synthesis of northern hemisphere **19** in 16 steps, starting from previously synthesized fragments **21** and **22**. Conditions: a) (1.20 equiv.), Zn powder (4.00 equiv.), Cp_2ZrCl_2 (1.00 equiv.), $\text{NiBr}_2(\text{dtbbpy})$ (10 mol%), DMI, r.t., 2 h, 76%; b) $\text{TsOH}\cdot\text{H}_2\text{O}$ (18 mol%), DCM/MeOH , r.t., 1.5 h, 67%; c) TBAF (1.0 M in THF, 20 mol%), THF, r.t., 15 min, 96%; d) KHMDS (0.5 M in toluene, 1.88 equiv.), DMBBr (1.01 equiv.), THF, $-20\text{ }^\circ\text{C}$ to $0\text{ }^\circ\text{C}$, 20 min, 92%; e) MeLi (3.1 M in DME, 1.96 equiv.), THF, $78\text{ }^\circ\text{C}$, 45 min, quant.; f) TBHP (5.5 M in decane, 2.00 equiv.), $\text{VO}(\text{acac})_2$ (5 mol%), DCM , $0\text{ }^\circ\text{C}$, 20 h, 83%; g) TBAF (1.0 M in THF, 4.00 equiv.), DMF, r.t., 70 h, 96%; h) Ag_2O (11.9 equiv.), MeI (15.0 equiv.), DMF, r.t., 72 h, 84%; i) $\text{Pd}(\text{OH})_2/\text{C}$ (22 wt%), H_2 (1 atm), EtOAc, r.t., 45 min, 62%; j) TEMPO (19 mol%), BAIB (1.19 equiv.), DCM , $0\text{ }^\circ\text{C}$ to r.t., 7 h, not isolated; k) TESCl (8.93 equiv.), DMAP (2.93 equiv.), NEt_3 (12.0 equiv.), $0\text{ }^\circ\text{C}$ to r.t., 30 min, 84%; l) $n\text{Bu}_3\text{SnCH}_2\text{I}$ (4.00 equiv.), CrCl_2 (19.9 equiv.), DMF, $0\text{ }^\circ\text{C}$ to r.t., 16 h, 78%; m) NIS (1.20 equiv.), THF, $0\text{ }^\circ\text{C}$, quant.; n) DDQ (2.00 equiv.), pH 7 buffer, DCM , $0\text{ }^\circ\text{C}$, 30 min, 90%; o) $n\text{Bu}_3\text{SnC}\equiv\text{CGeEt}_3$ (2.22 equiv.), CuTC (2.22 equiv.), $\text{Pd}(\text{PPh}_3)_4$ (5 mol%), DMF, $0\text{ }^\circ\text{C}$, 5 h, then r.t., 3 h, 63%; p) NIS (1.10 equiv.), MeCN/DCM , $0\text{ }^\circ\text{C}$, 1 h, 89%.^[12,35]

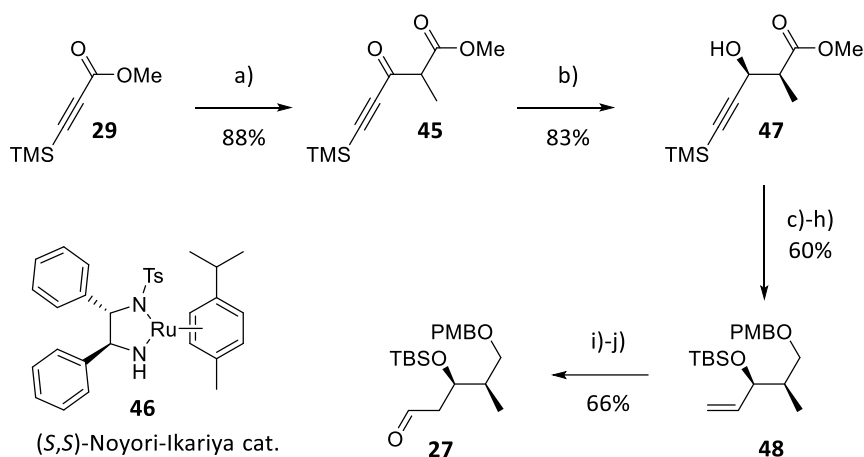
Fragment **26**, required for the southern hemisphere **20**, was synthesized in nine steps with an overall yield of 28% (**Scheme 1.2-10**). Starting from D-xylose (**28**), the aldehyde was initially converted into a dithioacetal, followed by acetonide protection of the four free hydroxyl groups. Under basic conditions, the alcohol adjacent to the dithioacetal was removed, leading to the concomitant deprotection of the acetonide and yielding alkene **41**. Subsequent treatment with LAH resulted in the reduction of the newly formed double bond. Protection of the free hydroxyl group and subsequent oxidation gave aldehyde **42**.^[46,47] This aldehyde was then subjected to a Marshall asymmetric propargylation,^[48] delivering alkyne **43** with moderate selectivity ($dr = 4:1$). However, the diastereomers could be separated in the following step via chromatography after TBAF-mediated deprotection of the silyl group. Finally, re-protection of the free alcohol with TBS furnished alkyne **26**.



Scheme 1.2-10. Synthesis of fragment **26** over 9 steps, starting from D-Xylose. Conditions: a) ZnCl (25.0 equiv.), PhSH (2.00 equiv.), HCl_{aq}(conc.) r.t., 1.5 h; b) 2,2 Dimethoxypropane (8.00 equiv.), *p*-TsOH·H₂O (10.0 equiv.), Acetone, r.t., 72 h, 75% over two steps; c) *t*BuOK (2.40 equiv.), THF/DMSO, r.t., 1.5 h, 89%; d) LiAlH₄ (4.00 equiv.), THF, 0 °C, 3 h, 72%; e) no procedure given; f) I₂ (3.00 equiv.), NaHCO₃(aq.)/Acetone, 0 °C, 2 h, 90%; g) **44** (1.50 equiv.), Pd(OAc)₂ (5 mol%), PPh₃ (5 mol%), Et₂Zn (1.0 M in hexanes, 3.00 equiv.), THF, −78 °C, 30 min, then −20 °C, 16 h, $dr = 4:1$; h) TBAF (1.0 M in THF, 2.50 equiv.), THF, 16 h, 71% over two steps; i) TBSOTf (2.40 equiv.), 2,6-Lutidine (4.00 equiv.), DCM, −78 °C, 1 h, 93%.^[12,35]

The second fragment **27** required for the southern hemisphere **20** was synthesized over ten steps, starting from alkyne **29**, with an overall yield of 29% (**Scheme 1.2-11**). A Claisen condensation between alkyne **29** and methyl propionate yielded β -keto ester **45**. Utilizing (*S,S*)-Noyori-Ikariya catalyst (**46**) in an asymmetric dynamic kinetic resolution^[49] provided

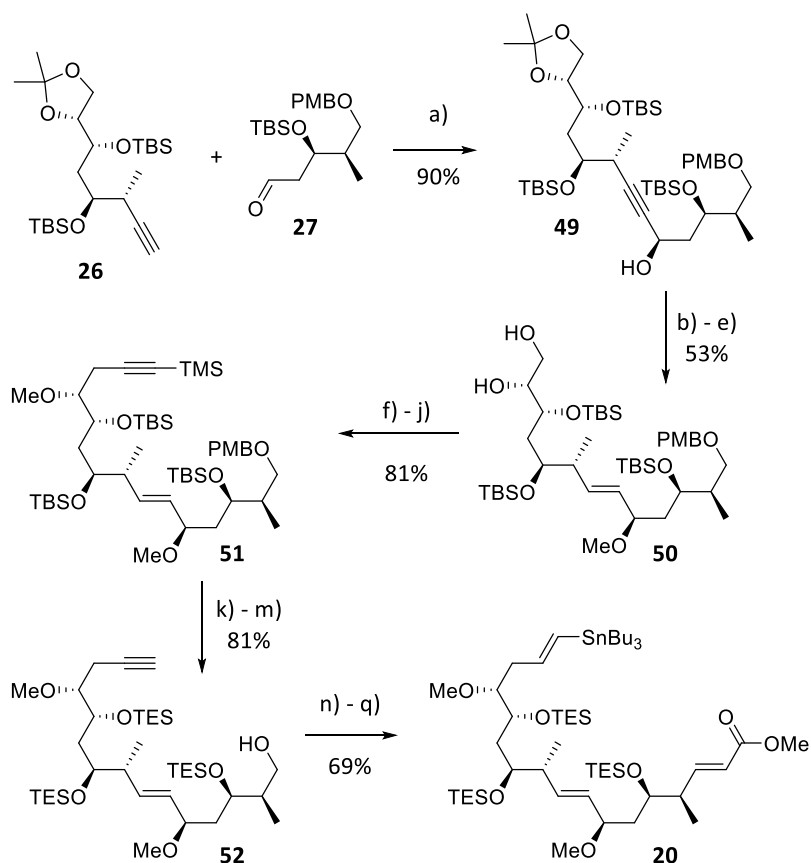
alcohol **47** with high selectivity ($dr = 18:1$, $>99\%$ *ee*). The free hydroxyl group was then protected with TBS, followed by ester reduction using DIBAL-H to yield the corresponding alcohol, which was subsequently PMB-protected. Mild basic conditions enabled selective removal of the TMS group, allowing Lindlar-catalysed reduction of the alkyne to the corresponding alkene, producing **48**. Hydroboration and subsequent oxidation of the resulting alcohol to an aldehyde furnished fragment **27**.



Scheme 1.2-11. Synthesis of fragment **27** over 10 steps, starting from commercial available substrate **29**. Conditions: a) Methyl propionate (3.00 equiv.), LDA (3.00 equiv.), THF, 30 min, $-78\text{ }^{\circ}\text{C}$, then **29**, 2 h, $-78\text{ }^{\circ}\text{C}$, 88%; b) (S,S)-Noyori-Ikariya cat. (**46**) (3 mol %), HCOOH/ NEt_3 (xs.), 5:2, DCM, r.t., 13 h, $dr = 18:1$, $> 99\%$ *ee*, 83%; c) TBSCl (1.20 equiv.), Imidazole (1.50 equiv.), DCM, r.t., 16 h, 90%; d) DIBAL-H (1.0 M in toluene, 2.50 equiv.), DCM, $78\text{ }^{\circ}\text{C}$, 2 h, not purified; e) NaBH_4 (1.32 equiv.), MeOH, $0\text{ }^{\circ}\text{C}$, 89% over two steps; f) PMBTCAI (1.30 equiv.), CSA (5 mol%), DCM, r.t., 19 h, not purified; g) K_2CO_3 (1.00 equiv.), MeOH, r.t., 2 h, 80% over two steps; h) Lindlar's cat (5% Pd on CaCO_3 , 1 wt%), H_2 (1 atm), MeOH, r.t., 1 h, 95%; i) 9-BBN (0.5 M in THF, 1.10 equiv.), THF, $0\text{ }^{\circ}\text{C}$ to r.t., 16 h, then $\text{NaHCO}_3(\text{aq.})$, H_2O_2 (30%), $0\text{ }^{\circ}\text{C}$, 30 min, 76%; j) $\text{Cu}(\text{MeCN})_4\text{BF}_4$ (5 mol%), 2,2'-bipyridinyl (5 mol%), NMI (10 mol%), TEMPO (5 mol%), O_2 (1 atm), MeCN, r.t., 3 h, 87%.^[12,35]

With both fragments (**26**, **27**) in hand, they were coupled using a Carreira asymmetric alkynylation^[32] to yield fragment **49** with excellent diastereoselectivity ($dr >20:1$, **Scheme 1.2-12**). The alkyne was then reduced to the corresponding *trans*-alkene via a Ru-catalysed hydrostannation/destannation strategy.^[50,51] The resulting free allylic alcohol was methylated, and the acetonide group was selectively deprotected using TFA, which also removed one of the TBS groups to yield triol **50**. Selective tosylation and subsequent epoxide ring closure followed, along with reprotection of the remaining free hydroxyl group as a TBS ether. The epoxide was then opened under basic conditions, allowing methylation of the

resulting free hydroxyl group, affording species **51**. A protecting group exchange from TBS to TES, followed by benzyl deprotection under oxidative conditions, yielded primary alcohol **52**. Oxidation of this alcohol to the corresponding aldehyde and subsequent Horner-Wadsworth-Emmons olefination produced the required methyl ester. The final steps involved bromination of the terminal alkyne and subsequent conversion into the vinylstannane, ultimately affording the southern hemisphere **20**.

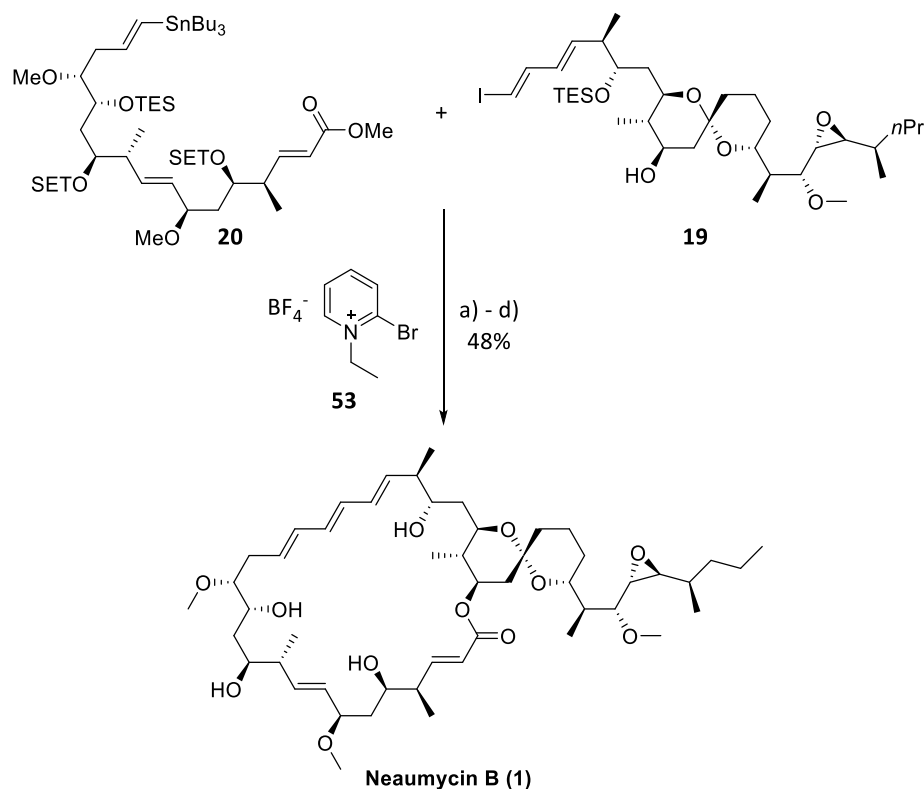


Scheme 1.2-12. Synthesis of the southern hemisphere **20** over 17 steps. Conditions: a) $\text{Zn}(\text{OTf})_2$ (1.30 equiv.), (+)-*N*-methylephedrine (1.30 equiv.), NEt_3 (3.70 equiv.), PhMe, r.t., 2 h, then **26** (1.30 equiv.), r.t., 2 h, then **27** (1.00 equiv.), 20 h, 90%, *dr* >20:1; b) $[\text{Cp}^*\text{-RuCl}]_4$ (5 mol%), Bu_3SnH (1.22 equiv.), DCM, -20°C , 1.5 h, then 0°C , 10 min, 72%; c) CuTC (2.20 equiv.), $\text{Bu}_4\text{NPh}_2\text{PO}_2$ (2.50 equiv.), DMF, r.t., 16 h, quant.; d) Me_3OBf_4 (4.20 equiv.), Proton-sponge[®] (8.50 equiv.), DCM, r.t., 5 h, 84%; e) TFA(aq.) (50%, 7.00 equiv.), DCM, 0°C , 2 h, 88%; f) Bu_2SnO (20 mol%), NEt_3 (3.00 equiv.), TsCl (1.10 equiv.), DCM, 0°C , 19 h, 95%; g) NaH (1.50 equiv.), THF, r.t., 20 h, 98%; h) TBSCl (2.00 equiv.), imidazole (3.00 equiv.), DCM, r.t., 1 h, 99%; i) TMS-acetylene (6.00 equiv.), *n*-BuLi (2.5 m in hexane, 5.50 equiv.), $\text{BF}_3\cdot\text{Et}_2\text{O}$ (5.50 equiv.), THF, -78°C , 16 h, 95%; j) Me_3OBf_4 (5.00 equiv.), Proton-sponge[®] (8.00 equiv.), DCM, r.t., 5 h, 90%; k) TBAF (1.0 M in THF, 6.00 equiv.), THF, r.t., 16 h; l) TESCl (6.00 equiv.), imidazole (10.0 equiv.), DCM, r.t., 2 h, 90% over two steps; m) DDQ (3.00 equiv.), phosphate buffer (1 M, pH 7, xs.), DCM, 0°C , 1.5 h, 90%; n) DMP (1.50 equiv.), NaHCO_3 (3.00 equiv.), DCM, 0°C to r.t., 2 h; o) $(\text{MeOOC})\text{CH}_2\text{PO}(\text{OMe})_2$ (2.00

equiv.), DIPEA (2.00 equiv.), LiCl (2.00 equiv.), r.t., 24 h, 79% over two steps; p) NBS (1.20 equiv.), AgOAc (10 mol%), acetone, r.t., 2 h, 96%; q) Bu_3SnH (2.10 equiv.), $\text{Pd}(\text{PPh}_3)_4$ (10 mol%), THF, -78°C to r.t., 0.5 h, 91%.^[12,35]

With both hemispheres **20** and **19** synthesized, they were coupled via a Stille cross-coupling reaction^[52] to construct the triene framework (**Scheme 1.2-13**). Esterification of the methyl ester to the corresponding carboxylic acid enabled an intramolecular Mukaiyama macrolactonization^[53] using pyridine **53**.

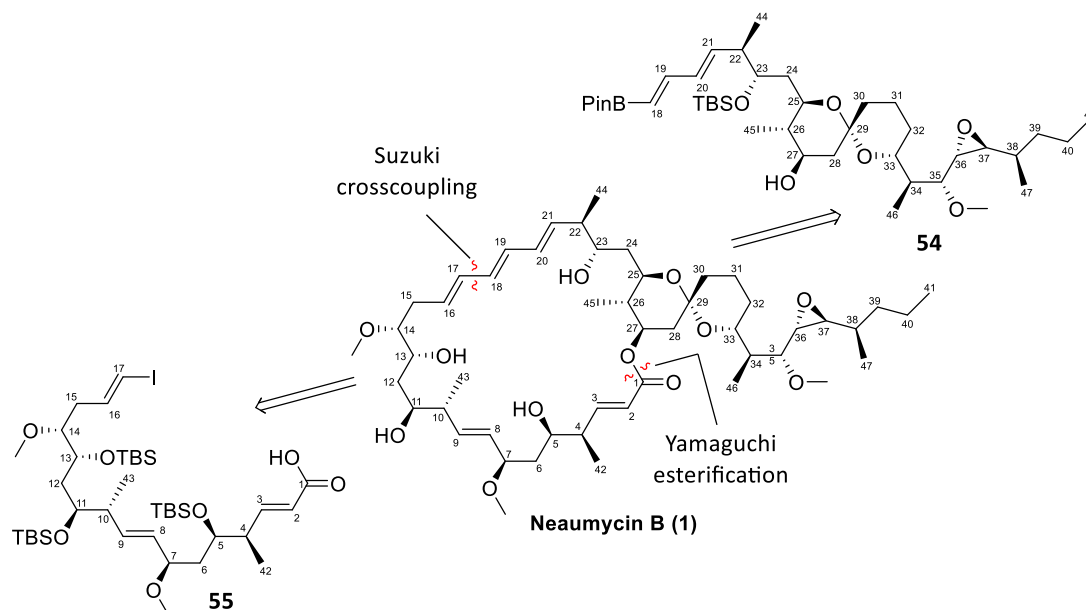
Finally, global deprotection provided neaumycin B (**1**) with an overall yield of 0.76% over 33 linear steps (LLS), starting from (*S*)-Roche ester (**24**).



Scheme 1.2-13. Final coupling of northern hemisphere **19** and southern hemisphere **20**. Conditions: a) **19** (1.00 equiv.), **20** (1.50 equiv.), $\text{Bu}_4\text{NPh}_2\text{O}_2$ (5.00 equiv.), Pd_2dba_3 (5 mol%), AsPh_3 (40 mol%), DMF, r.t., 3 h, 89%; b) Me_3SnOH (1.00 equiv.), PhMe, 90°C , 24 h, 86%; c) **53** (20.0 equiv.), NaHCO_3 (200 equiv.), DCM, r.t., 48 h, 80%; d) TBAF (1.0 M in THF, 107 equiv.), HOAc, THF, 0°C , 48 h, 80%.^[12,35]

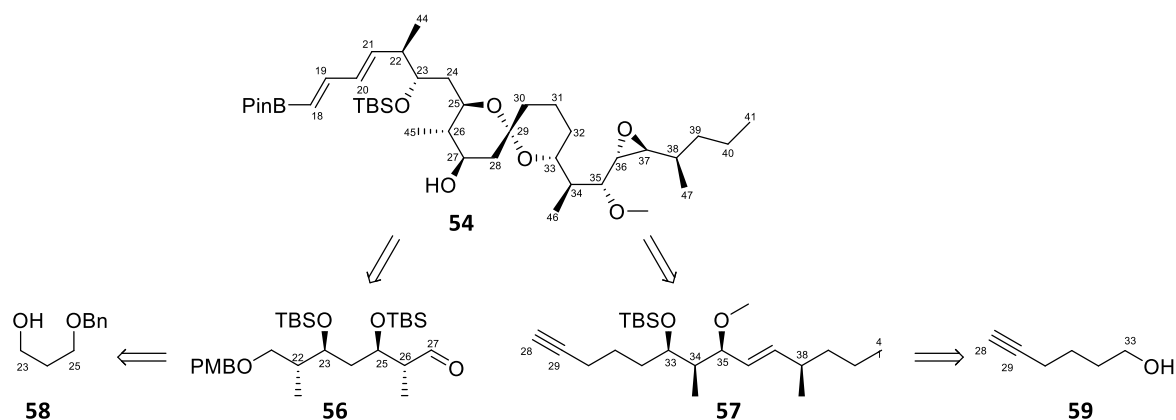
1.2.8 Total Synthesis of Neaumycin B (1) by Chen *et al.*

Similar to the total synthesis previously reported by Smith *et al.*, Chen *et al.* dissected neaumycin B (1) at the same positions, specifically at the triene between C17 and C18, as well as at the ester at C1 (**Scheme 1.2-14**).^[13] This approach resulted in the northern hemisphere **54** and southern hemisphere **55**, which were to be assembled via a Suzuki cross-coupling reaction and a Yamaguchi esterification.



Scheme 1.2-14. Retrosynthetic analysis of neaumycin B (1), revealing the northern hemisphere **54** and southern hemisphere **55** by Chen *et al.*

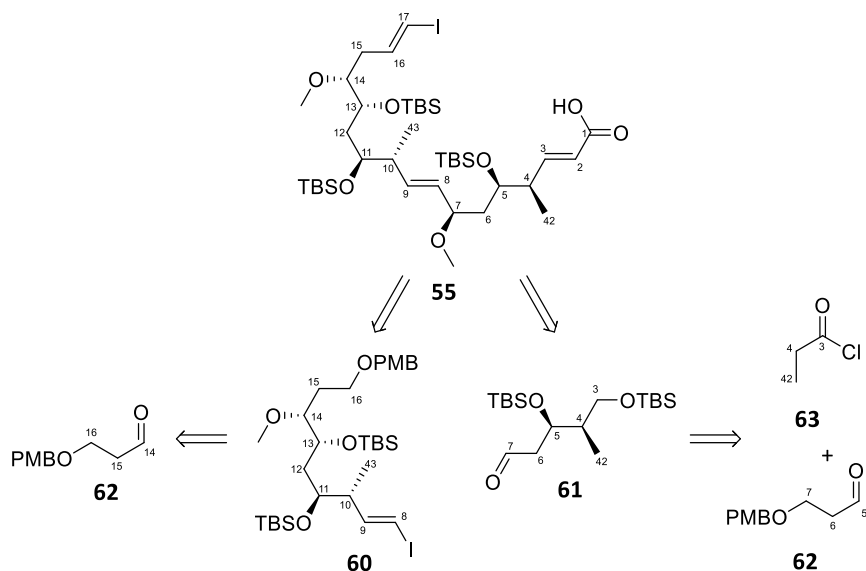
The northern hemisphere **54** was further divided into aldehyde **56** and alkyne **57**, which were to be coupled via a classical nucleophilic addition reaction (**Scheme 1.2-15**).



Scheme 1.2-15. Retrosynthetic analysis of northern hemisphere **54**.

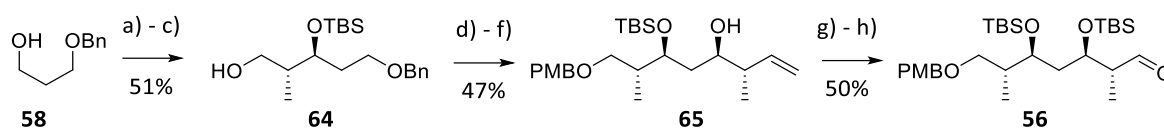
Aldehyde **56** was synthesized from alcohol **58** through two Krische crotylations,^[54–58] while alkyne **57** was constructed between C33 and C34 via a Brown crotylation,^[59] and the double bond between C37 and C38 was installed using a Julia-Kocienski olefination,^[60–65] starting from alkyne **59**.

The southern hemisphere **55** was also divided into two fragments: vinyl iodide **60** and aldehyde **61**, which were coupled using a Nozaki-Hiyama-Kishi reaction (**Scheme 1.2-16**).^[66–69] Vinyl iodide **60** was constructed from aldehyde **62** through a Fürstner Ni-catalyzed vicinal diol formation^[70,71] followed by a Marshall propargylation.^[72–74] Aldehyde **61** was synthesized via a halide-aldehyde cycloaddition,^[75,76] starting from aldehyde **62** and acetyl chloride (**63**).



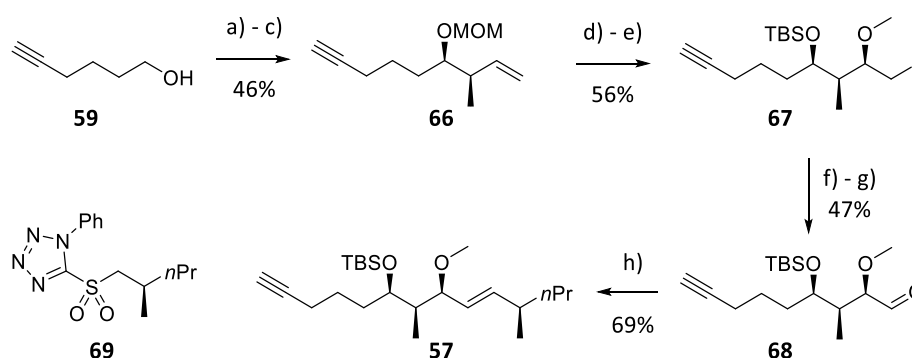
Scheme 1.2-16. Retrosynthetic analysis of southern hemisphere **55**.

For the synthesis of the northern hemisphere **54**, aldehyde **56** was obtained from alcohol **58** over eight steps with an overall yield of 12% (**Scheme 1.2-17**). The process commenced with a Krische crotylation,^[54–58] which afforded an excellent *ee* of 98% and a *dr* of 10:1. The resulting alcohol was protected with TBS, and subsequent ozonolysis led to cleavage of the double bond, yielding the primary alcohol **64**. Protection of this primary alcohol with PMB, followed by deprotection of another benzyl-protected primary alcohol, enabled a second Krische crotylation at the opposite side of the molecule, affording alcohol **65**. A second TBS protection of the secondary alcohol and another ozonolysis then delivered aldehyde **56**.



Scheme 1.2-17. Synthesis of fragment **56**, starting from 3-(benzyloxy)propan-1-ol (**58**). Conditions: a) (*R*)-SEGPHOS-Ir (5 mol%), K_3PO_4 (1.10 equiv.), α -methyl allyl acetate (6.66 equiv.), THF/ H_2O , r.t., 30 min, then 70 °C, 72 h, *dr* >10:1, 98% *ee*; 82%; TBSCl (1.50 equiv.), imidazole (2.00 equiv.), DCM, r.t., 16 h, 90%; O_3 (1 atm), DCM/MeOH, -78 °C, 20 min, then $NaBH_4$ (2.50 equiv.), r.t., 2 h, 70%; d) PMBTCAI (1.50 equiv.), CSA (3 mol%), DCM, r.t., 7 h, 75%; e) 2,6-Lutidine (3.00 equiv.), Pd/C (10 mol%), 1-Me-CHD (10.0 equiv.), MeOH, 50 °C, 80%; f) (*S*)-SEGPHOS-Ir (5 mol%), K_3PO_4 (1.10 equiv.), α -methyl allyl acetate (5.00 equiv.), THF/ H_2O , r.t., 30 min, then 70 °C, 48 h, *dr* = 5.3:1, 78%; g) TBSCl (2.00 equiv.), imidazole (3.03 equiv.), DCM, r.t., 16 h, 90%; h) O_3 (1 atm), DCM, -78 °C, 10 min, then PPh_3 (3.00 equiv.), -78 °C to r.t., 12 h, 56%.

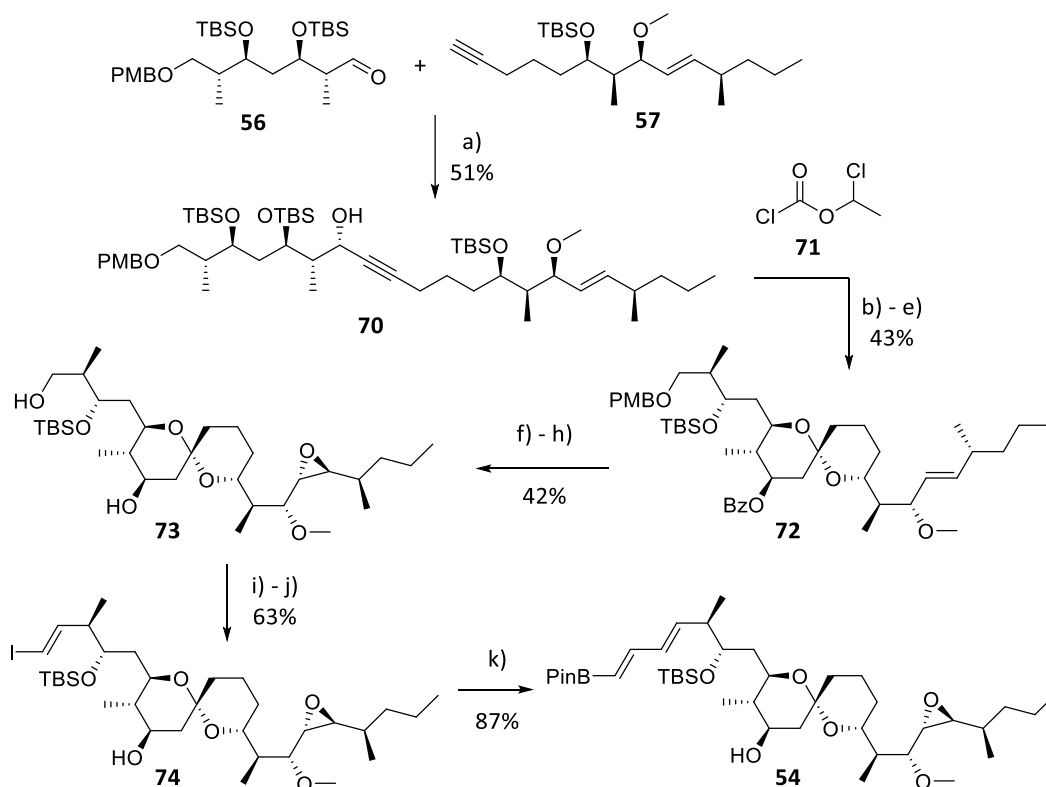
Alkyne **57** was synthesized from alkyne **59** over eight steps with an overall yield of 8% (**Scheme 1.2-18**). The sequence started with a Dess-Martin oxidation. Unlike previous cases, elongation was not performed via Krische crotylation but instead through a classical Brown crotylation,^[59] yielding a remarkable *dr* of >20:1 and an *ee* of 87%. The resulting secondary alcohol was MOM-protected to obtain alkyne **66**. The olefin was then subjected to electrophilic activation with IBr, introducing Taylor's ether transfer,^[77–80] yielding iodomethyl ether **67** with a *dr* >10:1. The alkyl iodide in **67** was converted into a C-OH bond via a radical process^[81] and subsequently oxidized to aldehyde **68**. Finally, a Julia-Kocienski olefination^[60–65] with sulfone **69** provided alkyne **57**.



Scheme 1.2-18. Synthesis of fragment **57**, starting from commercial available hex-5-yn-1-ol (**59**). Conditions: a) DMP (1.51 equiv.), $NaHCO_3$ (2.00 equiv.), DCM, r.t., 5 h, not purified, 84% crude; b) *t*BuOK (2.00 equiv.), *cis*-2-butene (1.1 equiv.), THF, -78 °C, then -45 °C, 50 min, then (-)-Ipc₂BOMe (2.07 equiv.), $BF_3 \cdot Et_2O$ (2.11 equiv.), 5-hexynal (1.00 equiv.), -78 °C, 11 h, then $NaOH_{(aq)}$ (3 M, 1.67 equiv.), H_2O_2 (35%, 3.48 equiv.), r.t., 1 h, then reflux, 1 h, *dr* > 20:1, 87% *ee*, 76%; c) MOMCl (1.50 equiv.), DIPEA, DCM, 0 °C, 5 h, 72%; d) ICl (1.0 M in DCM, 1.22 equiv.), toluene, -80 °C, 2 h, then *i*Pr₂NH (1.50 equiv.), H_2O (1.25 equiv.), -80 °C to r.t., 40 min, not purified;

e) 2,6-lutidine (3.00 equiv.), TBSOTf (2.00 equiv.), r.t., 2 h, 56%; f) AIBN (1 mol%), $n\text{Bu}_3\text{SnH}$ (1.99 equiv.), O_2 (1 atm), $h\nu$, r.t., 24 h, then NaBH_4 (2.00 equiv.), 65%; g) DMP (2.00 equiv.), NaHCO_3 (2.0 equiv.), DCM, r.t., 2 h, 73%; h) **69** (3.36 equiv.), KHMDS (1.0 M in THF, 3.36 equiv.), DME, HMPA, -78°C , 1 h, then **68** (1.00 equiv.), -78°C to r.t., 3 h, 69%.

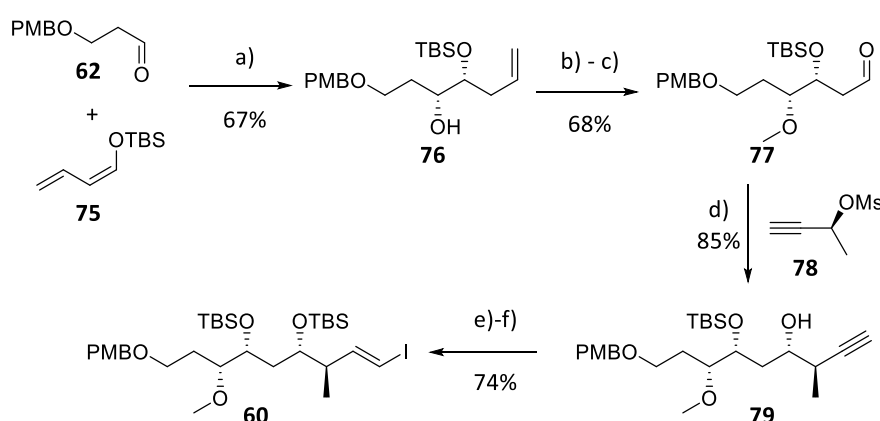
With both fragments, aldehyde **56** and alkyne **57**, in hand, their coupling was achieved via a nucleophilic attack of the deprotected alkyne **57** on aldehyde **56**, affording alkyne **70** with a *dr* of 7.8:1 (**Scheme 1.2-19**). Subsequent borylcupration^[82,83] of **70**, followed by oxidation of the resulting vinyl boronate, led to the formation of a β -hydroxy ketone. The free alcohol was then benzyl-protected. To initiate spiroketalization, a desilylation was performed, inducing a concomitant spiroketalization to afford fragment **72** with a *dr* of 4.7:1. Next, the epoxide was formed in two steps, yielding a *dr* of 2:1, and the primary PMB group was removed, generating primary alcohol **73**. Oxidation, followed by Takai-Utimoto olefination,^[84–86] afforded vinyl iodide **74**. A final Stille coupling^[87–89] generated vinyl boronate **54**, completing the synthesis of the northern hemisphere **54**.



Scheme 1.2-19. Synthesis of northern hemisphere **54**. a) **57** (2.50 equiv.), $n\text{BuLi}$ (1.6 M in hexanes, 2.48 equiv.), THF, -78°C to -30°C , 1 h, then **56** (1.00 equiv.), -78°C , 10 h, *dr* = 7.8:1, 51%; b) MesCuCl (10 mol%), $t\text{BuONa}$ (15 mol%), PCy_3 (12 mol%), B_2Pin_2 (1.19 equiv.), THF, 0°C to r.t., then **70** (1.00 equiv.), MeOH (2.93 equiv.), 0°C , 89%; c) $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$ (5.00 equiv.), THF/ H_2O , 0°C to r.t., 91%; d) BzOTf (5.00 equiv.), pyridine (10.0 equiv.), DCM,

–78 °C, 30 min, then –78 °C to r.t., 1 h, 77%; e) **71** (3.00 equiv.), MeOH/DCM, 0 °C to r.t., then 2,6-lutidine (3.00 equiv.), TBSOTf (2.00 equiv.), DCM, –78 °C to r.t., 30 min, *dr* = 4.7:1, 70%; f) K₂CO₃ (23.1 equiv.), MeOH, r.t., 24 h, 91%; g) Na₂HPO₄ (50.0 equiv.), CF₃CO₃H (1.0 M in DCE, 5.00 equiv.), DCE/THF, –78 °C to 0 °C, 16 h, *dr* = 2.0:1, 53%; h) DMDO (0.35 M in acetone, 4.82 equiv.), acetone, 88%; i) NaHCO_{3(aq.)} (4.71 equiv.), TEMPO (5 mol%), KBr (10 mol%), NaClO (1.7 M in H₂O, 2.35 equiv.), DCM, 89%; j) CrCl₂ (9.84 equiv.), CHI₃ (2.93 equiv.), THF, –10 °C to r.t., 10 h, 71%; k) *n*Bu₃Sn(CH=CH)BPIn (3.03 equiv.), Pd(MeCN)₂Cl₂ (10 mol%), DMF, 35 °C, 87%.

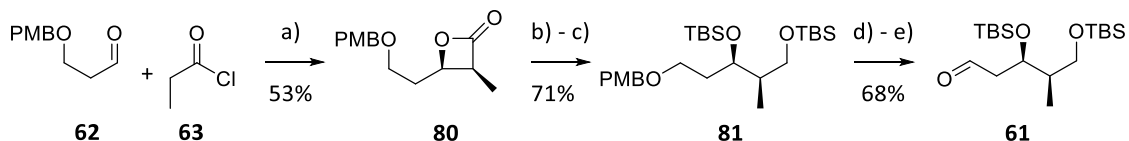
For the synthesis of the southern hemisphere, vinyl iodide **60** was obtained from aldehyde **62** over six steps with an overall yield of 29% (**Scheme 1.2-20**). The sequence began with a Fürstner Ni-catalyzed vicinal monoprotected diol formation^[70,71] of aldehyde **62** and silyl ether **75**, yielding alcohol **76** with a *dr* >20:1 and an *ee* of 69%. A Meerwein methylation^[90] followed by ozonolysis afforded aldehyde **77**. Marshall Pd-catalyzed propargylation^[72–74] with alkyne **78** then yielded alcohol **79** (*dr* >10:1). Finally, TBS protection of the secondary alcohol and conversion of the alkyne moiety into vinyl iodide under Schwartz reagent treatment,^[91] followed by iodination, yielded vinyl iodide **60**.



Scheme 1.2-20. Synthesis of fragment **60**. Conditions: a) **75** (2.50 equiv.), Ni(cod)₂ (10 mol%), (*S*)-VAPhos-NEt₂ (10mol%), BEt₃ (1.0 M in hexane, 1.50 equiv.), PhMe, r.t., 48 h, then phosphate buffer (0.1 M, pH 7.2, xs.), H₂O₂ (30%, xs.), *dr* >20:1, 79% *ee*, 69%; b) Me₃OBf₄ (2.00 equiv.), Proton-sponge[®] (3.00 equiv.), DCM, 0 °C, 2 h, 89%; c) O₃ (1 atm), DCM, –78 °C, 10 min, then PPh₃ (3.00 equiv.), –78 °C to r.t., 16 h, 76%; d) **78** (1.50 equiv.), InI (2.20 equiv.), PPh₃ (10 mol%), Pd(dppf)Cl₂·DCM (10 mol%), THF, HMPA, 0 °C, 2 h, *dr* >10:1, 85%; e) TBSOTf (2.00 equiv.), 2,6-lutidine (3.00 equiv.), DCM, 0 °C, to r.t., 3 h, 88%; f) Cp₂ZrHCl (1.50 equiv.), THF, 0 °C, 2 h, then I₂ (0.85 equiv.), r.t., 2 h, 84%.

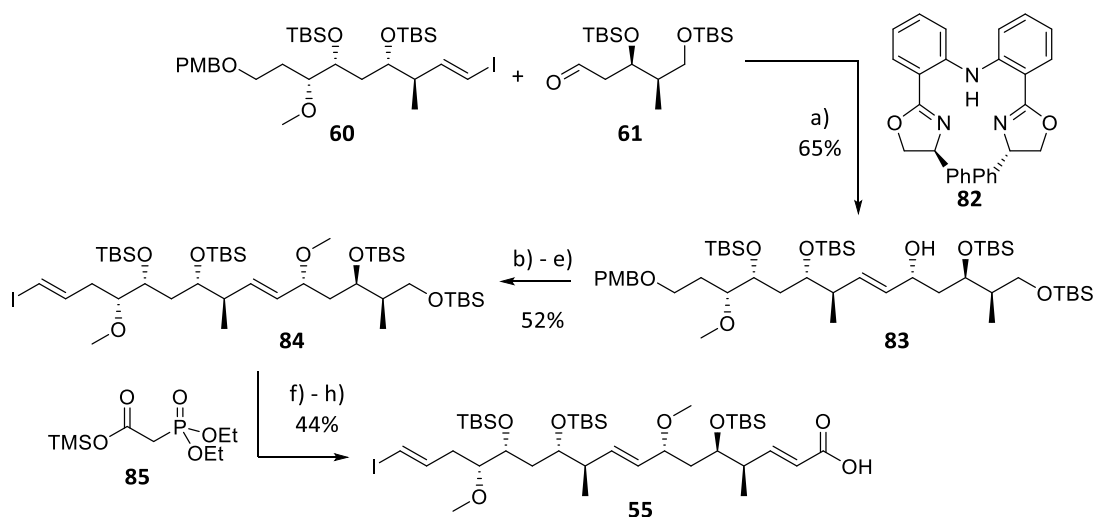
The second fragment **61**, required for the synthesis of the southern hemisphere **55**, was synthesized over five steps with an overall yield of 26% (**Scheme 1.2-21**). A base-catalyzed asymmetric ketene [2+2] cycloaddition^[75,76] of acetyl chloride (**63**) and aldehyde **62** produced

β -lactone **80**, which was subsequently reduced. The resulting alcohol was TBS-protected, yielding silyl ether **81**. PMB deprotection and primary oxidation then afforded aldehyde **61**.



Scheme 1.2-21. Synthesis of aldehyde **61**. Conditions: a) **62**, *O*-TMS-quinidine (25 mol%), LiClO₄ (50 mol%), DIPEA (3.00 equiv.), **63** (2.30 equiv.), Et₂O/DCM, −78 °C, 18 h, 98% *ee*, 53%; b) LiAlH₄ (1.10 equiv.), THF, 0 °C, 2 h, 81%; c) TBSOTf (2.00 equiv.), 2,6-lutidine (3.00 equiv.), DCM, 0 °C to r.t., 1 h, 88%; d) DDQ (1.50 equiv.), phosphate buffer (0.1 M, pH 7.2, 10 mol%), DCM, r.t., 1 h, 85%; e) DMP (2.00 equiv.), NaHCO₃ (2.00 equiv.), DCM, r.t., 2 h, 78%.

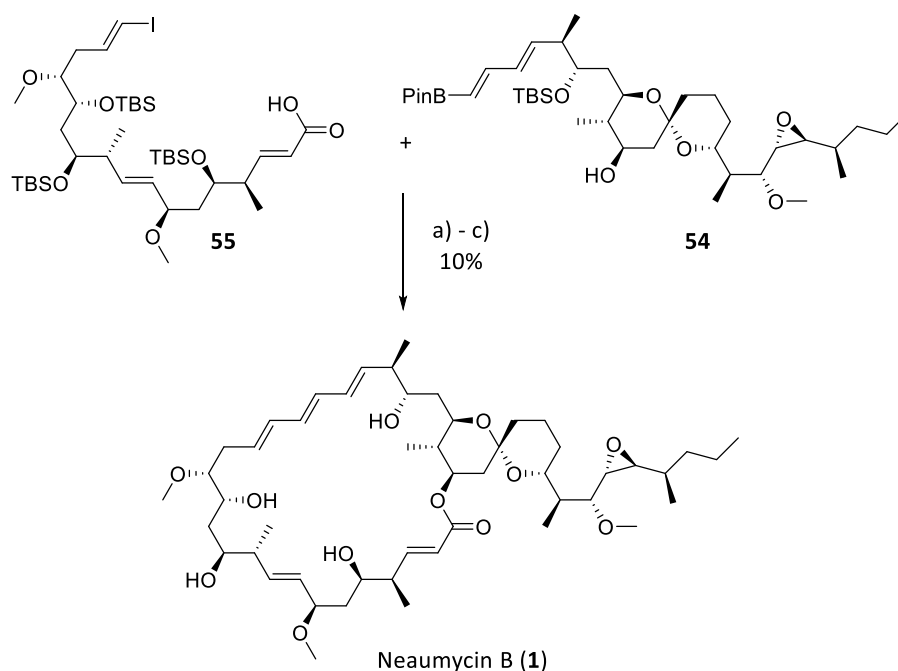
The southern hemisphere **55** was synthesized over eight steps with a yield of 15% from the two fragments, vinyl iodide **60** and aldehyde **61** (**Scheme 1.2-22**). These fragments were coupled via a Nozaki-Hiyama-Kishi reaction^[66–69] to produce olefin **83** (*dr* = 4.3:1). The secondary alcohol was then methylated via Meerwein methylation,^[90] the primary PMB group was deprotected using DDQ, the primary alcohol was oxidized to an aldehyde, and a Takai-Utimoto olefination afforded vinyl iodide **84**. Finally, selective deprotection of the primary TBS group using CSA, oxidation to an aldehyde, and a subsequent Horner-Wadsworth-Emmons reaction^[30] with phosphonate **85** yielded the southern hemisphere **55**.



Scheme 1.2-22. Synthesis of the southern hemisphere **55**. Conditions: a) **61** (1.00 equiv.), **60** (1.05 equiv.), **82** (10 mol%), Proton-sponge[®] (10 mol%), CrCl₂ (4.9 equiv.), NiCl₂ (5 mol%), DMSO, 0 °C, 16 h, *dr* = 4.3:1, 80%; b) Me₃OBf₄ (2.00 equiv.), Proton-sponge[®] (3.20 equiv.), DCM, 0 °C, 2 h, 94%; c) DDQ (1.80 equiv.), phosphate buffer (0.1 M, pH 7.2, 30 mol%), DCM, 0 °C, 1.5 h, 78%; d) DMP (2.00 equiv.), NaHCO₃ (2.00 equiv.), DCM, r.t., 2

h, 90%; e) CrCl_2 (10.0 equiv.), CHI_3 (3.00 equiv.), THF/dioxane, 0 °C, 6 h, 80%; f) CSA (1.00 equiv.), DCM/MeOH, –30 °C to –20 °C, 2 h; g) DMP (2.00 equiv.), NaHCO_3 (2.00 equiv.), DCM, r.t., 2 h; h) **85** (3.00 equiv.), $n\text{BuLi}$ (1.6 M in THF, 3.00 equiv.), THF, –78 °C, 1 h, then 40 °C, 2 h, 44% over three steps.

The final assembly of the northern hemisphere **54** and southern hemisphere **55** commenced with a Yamaguchi esterification,^[92–94] followed by a Suzuki coupling^[95,96] to close the macrocycle (**Scheme 1.2-23**). A final global deprotection step then yielded neaumycin B (**1**), completing the total synthesis by Chen *et al.* in 22 linear steps (LLS) with an overall yield of 0.04%.



Scheme 1.2-23. Final coupling of the northern hemisphere **54** and southern hemisphere **55** to Neaumycin B (**1**). Conditions: a) **55** (1.00 equiv.), 2,4,6- $\text{Cl}_3\text{-BzCl}$ (1.50 equiv.), NEt_3 (1.50 equiv.), toluene, 0 °C to r.t., 2 h, then **54** (1.00 equiv.), DMAP (1.00 equiv.), –20 °C, 5 h, 68%; b) $\text{Pd(PPh}_3)_4$ (10 mol%), Ti_2CO_3 (30 mol%), $\text{H}_2\text{O/THF}$, r.t., 5 h, 44%; c) $3\text{HF}\cdot\text{NEt}_3$ (30 mol%), NEt_3/MeCN , r.t., 5 d, 35%.

2 Motivation and Objective

2.1 Aim of the Project

Neaumycin B (**1**) is a highly complex natural product that presents a significant challenge for total synthesis (**Figure 2.1-1**). Its structure comprises a large macrocyclic core, a spiroketal subunit, and 19 stereogenic centers, making it an intriguing target for synthetic research. In addition to its structural complexity, neaumycin B (**1**) exhibits notable antibacterial activity and potent cytotoxicity against U87 human glioblastoma cells, one of the most aggressive adult cancers, with an LD₅₀ value of 5.6×10^{-5} $\mu\text{g/mL}$.^[10,11] These biological properties underscore its relevance in medicinal chemistry and make it an attractive subject for further investigation.

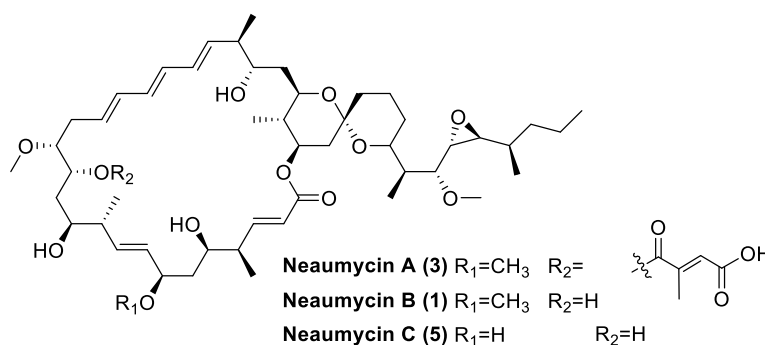


Figure 2.1-1. Proposed structure of neaumycin B (**1**) by Fenical *et al.*^[11] includes stereochemical information, whereas the structure of neaumycin A (**3**) and neaumycin C (**5**) by Simone *et al.*^[10] lacks stereochemical details.

A reliable total synthesis is necessary to provide access to neaumycin B (**1**) and its derivatives in sufficient quantities for further biological studies. The aim of this dissertation is to develop an efficient synthetic route to neaumycin B (**1**), while also designing the retrosynthetic approach to allow for the synthesis of structurally related analogs, such as neaumycin A (**3**) and neaumycin C (**5**).

A convergent synthetic strategy was chosen to enhance the flexibility and efficiency of the synthesis. By constructing key fragments separately and coupling them at a later stage, this approach offers advantages over a purely linear strategy, particularly in terms of overall yield and modularity. This methodology is expected to facilitate the future synthesis of additional derivatives with minimal adjustments.

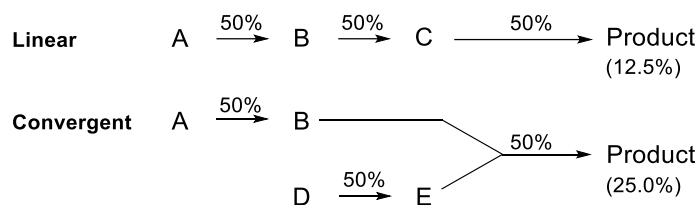
Due to the structural complexity of neaumycin B (**1**), this project is being carried out in collaboration with Christina Braun. While the completion of the total synthesis remains an ambitious goal, all intermediate results contribute valuable insights into synthetic methodology and the feasibility of accessing this class of natural products.

3 Results and Discussion

3.1 Convergent Total Synthesis

Synthesizing a complex and structurally intricate molecule like neaumycin B (**1**) represents a significant challenge due to the numerous synthetic steps required. As the molecular complexity increases, so does the difficulty of controlling selectivity, regioselectivity, and functional group compatibility. To address these challenges, a convergent total synthesis approach is employed, offering several advantages over a traditional linear approach.

In a linear total synthesis, the construction starts from a simple precursor and proceeds step by step until the target molecule is reached. However, as the synthesis progresses, the molecule becomes increasingly complex, incorporating multiple functional groups that must be selectively manipulated. While protecting group strategies can help manage this complexity to some extent, they have inherent limitations—only a finite number of distinct protecting groups exist, making it increasingly difficult to selectively modify only specific functional sites.^[97]



Scheme 3.1-1. Comparison of the linear and convergent total synthesis approaches, highlighting the advantages of the convergent strategy.

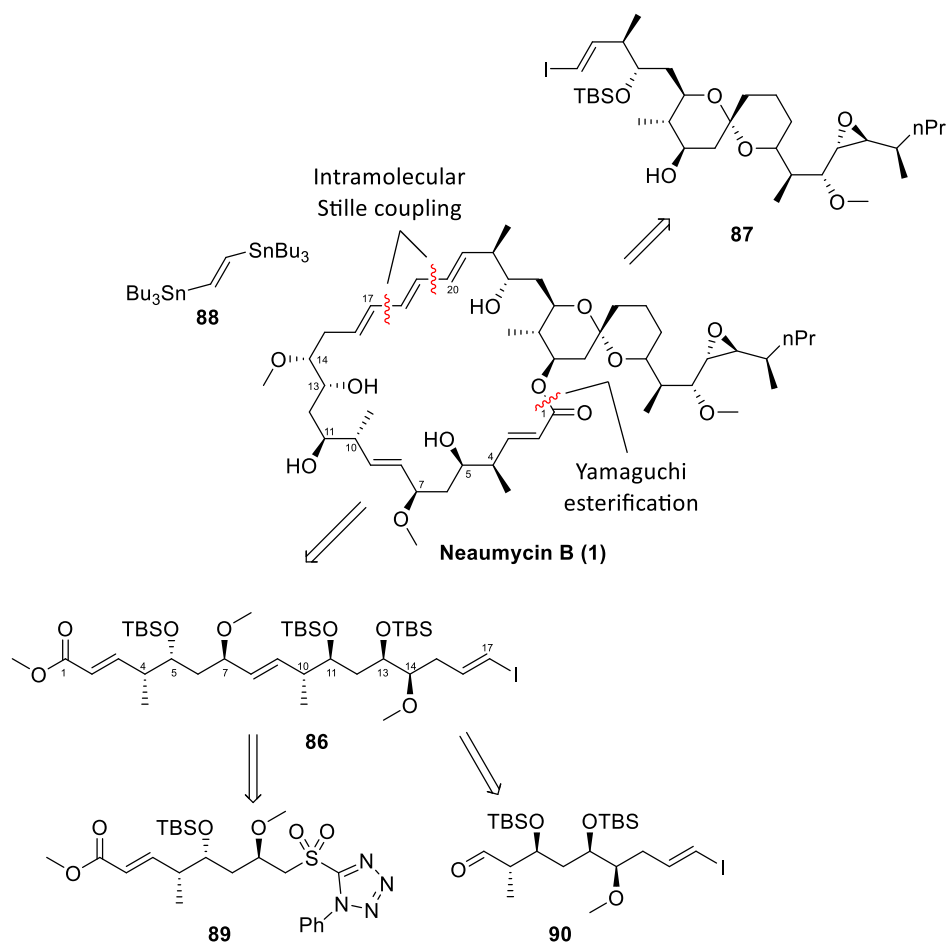
Another major drawback of a linear approach is the impact on overall yield (**Scheme 3.1-1**). If each step in a three-step sequence has a yield of 50%, the final product is obtained with an overall yield of only 12.5%. In contrast, a convergent strategy divides the target molecule into key fragments that are synthesized separately before being coupled in the final stages. Using the same three-step example, if two intermediates (B and E) are synthesized separately and later combined, the final yield improves to 25%, effectively doubling the efficiency compared to the linear approach. This difference becomes even more pronounced in complex total syntheses like that of neaumycin B (**1**), where multiple steps are required.

Beyond improving yield and efficiency, a convergent approach also facilitates late-stage derivatization.^[98] By assembling the molecule from well-defined building blocks, structural modifications can be introduced more easily, enabling access to analogs and derivatives. This is particularly relevant for neaumycin B (**1**), as several related natural products have been isolated, making the ability to generate derivatives an important aspect of the synthetic strategy. Given these advantages, a convergent approach is indispensable for the total synthesis of neaumycin B (**1**), offering both practical benefits and broader applicability in synthetic and medicinal chemistry.

3.2 Retrosynthetic Analysis

When embarking on a total synthesis, the first step is retrosynthetic analysis. The goal of this process is structural simplification by strategically disconnecting the target molecule at key functional groups to generate smaller, more manageable precursors, known as synthons. This iterative process continues until the retrosynthesis leads to simple or commercially available building blocks. Additionally, smaller known fragments can be identified in the literature, allowing existing synthetic methods to be adapted accordingly.^[99–102]

Since retrosynthesis does not follow a strict right or wrong approach, multiple synthetic routes are often possible. In the case of neaumycin B (**1**), key disconnections were made at the triene unit, specifically between C17 and C20, as well as at the ester moiety at C1 (**Scheme 3.2-1**). This strategy resulted in two major fragments: the southern fragment **86** and the northern fragment **87**. This dissertation focuses on the synthesis of the southern fragment **86**, while details on the retrosynthesis and synthesis of the northern fragment **87** can be found in the dissertation of Christina Braun.^[103]

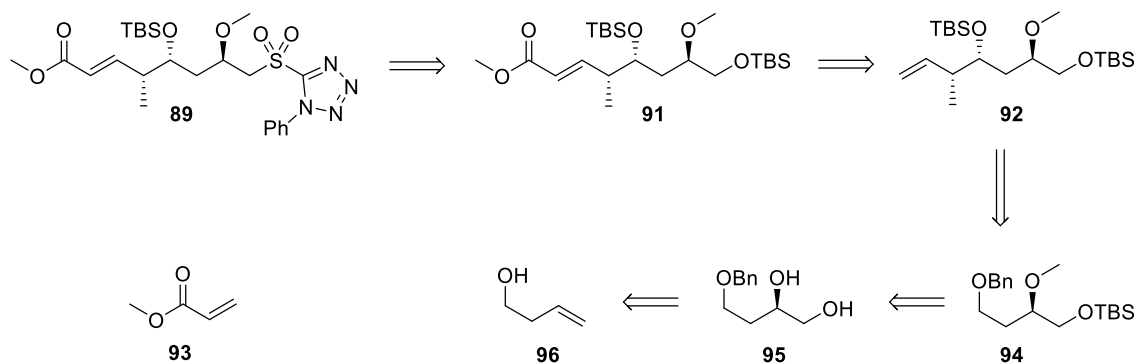


Scheme 3.2-1. Retrosynthetic analysis of neaumycin B (**1**), dividing it into northern fragment **87** and southern fragment **86**.

The final synthetic plan involves coupling both fragments using a Yamaguchi esterification,^[104] followed by an intramolecular Stille coupling^[105,106] between the corresponding vinyl iodides, utilizing (*E*)-1,2-bis(tributylstannyl)ethane (**88**) as the linker unit. A final global deprotection would then yield the desired neaumycin B (**1**).

Given the structural complexity of the southern fragment **86**, it was further divided into two smaller fragments to exploit the advantages of a convergent total synthesis approach. Specifically, the southern fragment **86** was fragmented into sulfone **89** and aldehyde **90**, which should be coupled via a Julia-Kocienski olefination to obtain the *E*-olefin.^[107]

The synthesis of sulfone **89** was planned to originate from commercially available 3-butenol (**96**, **Scheme 3.2-2**). The key steps include deprotection of silyl ether **91**, followed by the introduction of a phenyltetrazolylthiol group under Mitsunobu conditions, and an oxidative transformation using H₂O₂ to yield the corresponding sulfone **89**.^[108,109]



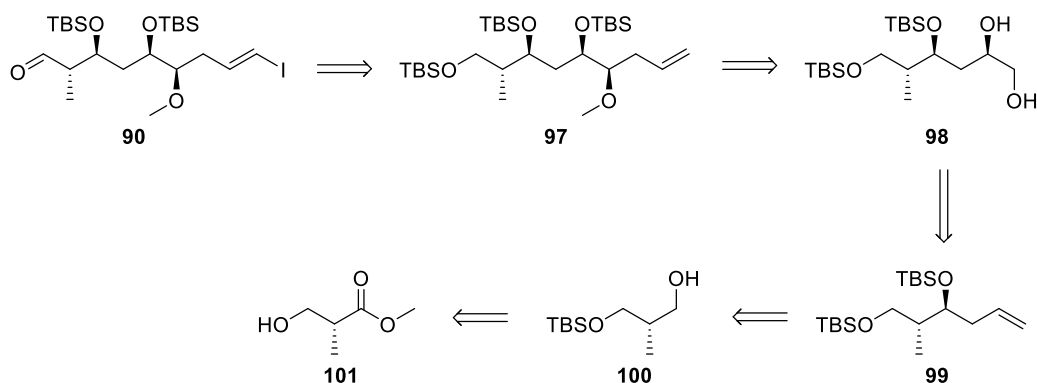
Scheme 3.2-2. Retrosynthetic analysis of sulfon **89**, outlining its synthetic strategy beginning with 3-butenol (**96**).

Furthermore, ester **91** is envisioned to be synthesized via a Grubbs metathesis reaction of alkene **92** with methyl acrylate (**93**).^[110] Alkene **92**, in turn, is derived from benzyl ether **94** through a sequence involving deprotection, oxidation to the corresponding aldehyde, followed by a Brown crotylation^[59] and subsequent TBS protection of the resulting secondary alcohol.

The synthesis of benzyl ether **94** is planned to be achieved from diol **95**. The key step involves the primary TBS protection of the hydroxyl group, which enables a Meerwein methylation^[90] at the secondary alcohol, affording benzyl ether **94**.

Diol **95**, in turn, is envisioned to be synthesized from 3-butenol (**96**). The synthetic route starts with benzyl protection of the hydroxyl group, followed by a non-stereospecific epoxidation.^[111] The stereogenic center of diol **95** is then introduced via a hydrolytic kinetic resolution (HKR), ensuring high enantiomeric purity.^[112–115]

Additionally, aldehyde **90** is planned to be synthesized from the commercially available (*R*)-Roche ester (**101**, **Scheme 3.2-3**). The synthesis begins with a hydroboration^[116] of alkene **97**, followed by oxidation of the resulting alcohol to the corresponding aldehyde. A subsequent Takai-Utimoto reaction^[85] converts the aldehyde into a vinyl iodide. The sequence continues with the deprotection of the primary TBS group and oxidation of the resulting primary alcohol, ultimately yielding aldehyde **90**.



Scheme 3.2-3. Retrosynthetic analysis of aldehyde **90**, outlining its synthetic strategy beginning with (*R*)-Roche ester (**101**).

Furthermore, a temporary TES protection of the primary alcohol in diol **98** enables selective TBS protection of the secondary alcohol. The TES group is then selectively removed, followed by oxidation to the corresponding aldehyde. A Brown allylation,^[117] followed by Meerwein methylation^[90] of the resulting secondary alcohol, leads to allyl **97**.

The synthesis of diol **98** is envisioned to proceed from allyl **99** through an asymmetric dihydroxylation using AD-Mix.^[118] Allyl **99** itself is to be obtained from alcohol **100** via oxidation to the corresponding aldehyde, followed by a Brown allylation^[117] and protection of the resulting secondary alcohol.

Finally, **100** would be derived from commercially available (*R*)-Roche ester (**101**). The synthetic known sequence begins with TBS protection of the hydroxyl group, followed by reduction of the ester to the corresponding alcohol.^[119]

This synthetic approach, based on a convergent strategy, not only enhances efficiency in fragment assembly but also enables easier access to structural modifications.

3.3 Implementation of the Retrosynthetic Analysis

3.3.1 Synthesis of Sulfone **89**

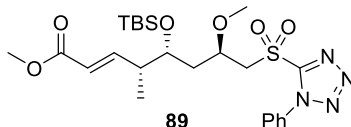
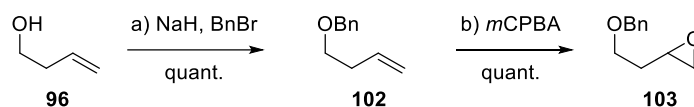


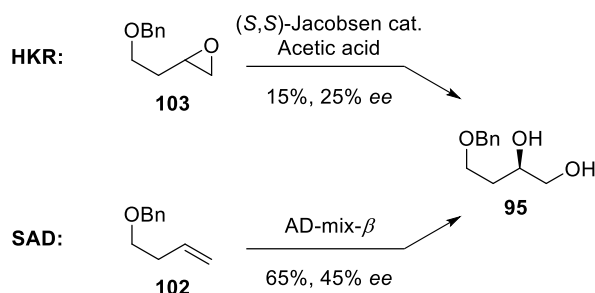
Figure 3.3-1. Target molecule **89**.

In this chapter the synthesis of the target molecule **89** is described (**Figure 3.3-1**). The initial investigations of this dissertation focused on the deprotonation of 3-butenol (**96**) using NaH, enabling its protection with BnBr (**Scheme 3.3-1**). This transformation was achieved in quantitative yield on a deca-gram scale. The successfully synthesized benzyl ether **102** was subjected to a classical epoxidation using *m*CPBA,^[111] affording epoxide **103**, again on a deca-gram scale.



Scheme 3.3-1. Synthesis of epoxide **103**, starting from 3-butenol (**96**). Conditions: a) **96** (1.00 equiv.), NaH (1.50 equiv.), BnBr (1.50 equiv.), THF, r.t., 18 h, quant.; b) **102** (1.00 equiv.), *m*CPBA (1.50 equiv.), DCM, 0 °C → r.t., 3 h, quant.

With epoxide **103** in hand, the first key reaction of this dissertation was investigated. The goal was to apply the Hydrolytic Kinetic Resolution (HKR) established by Jacobsen to achieve enantioselective ring-opening. Using a chiral Co(III)-salen complex, water is activated as a nucleophile to promote a selective ring-opening reaction. The asymmetric hydrolysis results in two distinct products: one enantiomer remains as an unreacted, enantiopure epoxide, while the other is converted into an enantiopure diol via nucleophilic attack. As a consequence, the maximum theoretical yield for each compound is 50% based on the starting material. Due to their significantly different polarities, the resulting epoxide and diol can be efficiently separated, either by distillation or column chromatography, ensuring the successful isolation of both enantiomerically enriched compounds.^[112–115]



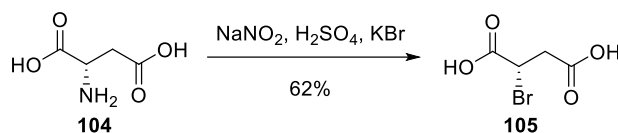
Scheme 3.3-2. Enantioselective synthesis of diol **95**, achieved either through HKR from epoxide **103** or via SAD from alkene **102**. Conditions: HKR: (*S,S*)-Jacobsen cat. (0.01 equiv.), acetic acid (0.50 equiv.), toluene, r.t., 30 min then **103** (1.00 equiv.), H₂O, r.t., 40 h, 15%; SAD: **102** (1.00 equiv.), methansulfonamide (1.00 equiv.), AD-Mix-β, H₂O, *t*-BuOH, r.t., 96 h, 65%.

Applying HKR to epoxide **103** by using (*S,S*)-Jacobsen cat. yielded diol **95** (Scheme 3.3-2). However, the results were not satisfactory, with an enantiomeric excess of only 25% (detected by HPLC). Such a low *ee* is unacceptable for the initiation of a total synthesis. As an alternative, a different approach to setting the stereocenter was explored.

A logical next step was to explore the Sharpless Asymmetric Dihydroxylation (SAD), a *syn*-dihydroxylation of an olefin using osmium tetroxide (OsO₄) as the key oxidant. Due to the high toxicity and cost of osmium, it is only employed in catalytic amounts. However, after OsO₄ adds to the olefin and forms the diol, the osmium species needs to be reoxidized to maintain catalytic turnover. Therefore, an additional oxidant is used to continuously regenerate OsO₄. To achieve enantioselectivity, a chiral ligand, typically derived from cinchona alkaloids, is introduced, directing the formation of the enantiopure product.^[120–122]

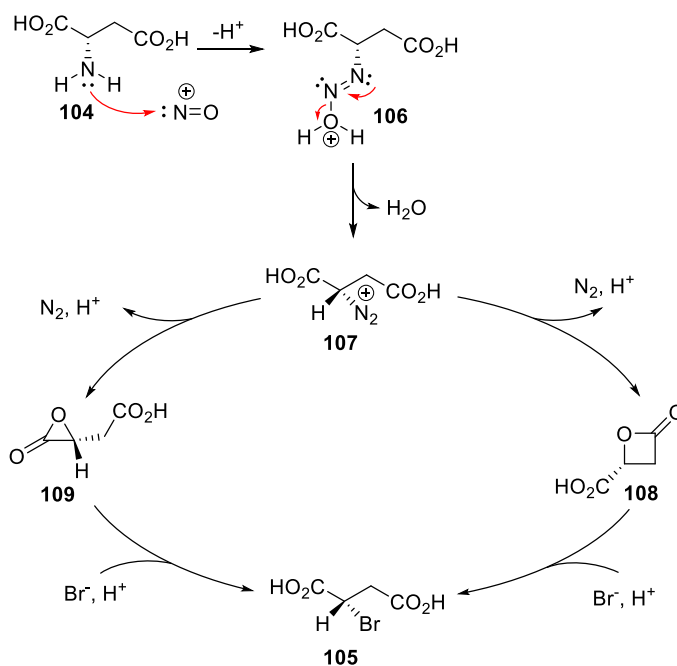
To implement this approach, benzyl-protected alcohol **102** was subjected to AD-mix-β, leading to the formation of diol **95**. This strategy resulted in more than quadruple the yield and significantly improving the *ee* to 45% (detected by HPLC). However, even this improvement remained insufficient for the precise control required at the beginning of a total synthesis.

Consequently, a different approach was pursued, involving the construction of the stereocenter from a commercially available chiral building block. Amino acids are particularly suitable for this purpose, as they occur naturally in enantiopure form, are readily accessible and cost-effective.^[123] L-aspartic acid (**104**) was chosen as the starting material, following a well-established sequence that allows its use as a general building block in total synthesis.^[124]



Scheme 3.3-3. Synthesis of bromide **105**. Conditions: **104** (1.00 equiv.), 6 M H₂SO₄ (5.00 equiv.), KBr (2.20 equiv.), NaNO₂ (1.20 equiv.), H₂O, r.t., 2 h, 62%.

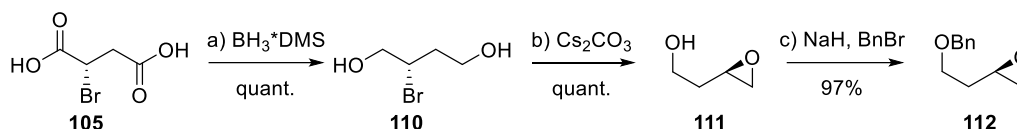
The first step in this sequence involves the replacement of the amino group with a bromine atom to bromide **105** (Scheme 3.3-3). Notably, this transformation occurs with retention of configuration due to a neighboring group effect.^[125] The reaction proceeds via an initial diazotization, where the amino group is converted into intermediate **106** and immediate to a diazonium intermediate **107** (Scheme 3.3-4). This intermediate **107** undergoes nitrogen elimination, leading to an intramolecular attack by one of the carboxylate groups, to form a β -lactone **108** with inversion of configuration.



Scheme 3.3-4. Bromination of L-aspartic acid (**104**).

The preference for β -lactone **108** formation is explained by lower ring strain compared to a three-membered α -lactone **109** and is supported by computational data, which indicate a lower activation barrier for β -lactone **108** formation.^[126–128] The resulting intermediate is then attacked by a bromide ion with again inversion of configuration, leading to ring opening of the lactone and formation of the desired brominated product **105**. This constitutes a double inversion of configuration, thereby preserving the original stereochemical information.

Next, the two carboxyl groups of **105** were reduced to the corresponding alcohols using borane-dimethyl sulfide complex, yielding diol **110** (Scheme 3.3-5). Subsequently, an intramolecular attack of the primary alcohol facilitated the formation of epoxide **111**, following a previously developed protocol employing cesium carbonate.^[129] Finally, benzyl protection of the resulting alcohol afforded benzyl ether **112**, all with remarkable efficiency—achieving an overall yield of 97% over three steps.



Scheme 3.3-5. Synthesis of epoxide **111**, beginning with carboxylic acid **105** and proceeding through bromide **110**. Conditions: a) **105** (1.00 equiv.), $\text{BH}_3\cdot\text{DMS}$ (4.00 equiv.), THF, $-78\text{ }^\circ\text{C} \rightarrow \text{r.t.}$, 48 h, quant.; b) **110** (1.00 equiv.), Cs_2CO_3 (1.80 equiv.), DCM, r.t., 45 h, quant.; c) **111** (1.00 equiv.), NaH (2.00 equiv.), BnBr (1.50 equiv.), THF, r.t., 4 h, 97%.

To obtain enantiomerically pure epoxide **112**, four synthetic steps were required instead of the initially planned two-step route starting from 3-butenol (**96**, see Scheme 3.2-2). The original plan involved benzyl protection, epoxidation, and enantioselective opening via HKR. However, the revised strategy delivered an enantiomerically pure epoxide in only two additional steps while maintaining excellent yields. Furthermore, the entire process was successfully conducted on a decagram scale.

Epoxide **112** was now subjected to ring opening to get diol **95** (Table 3.3-1). To retain the stereocenter, a basic epoxide opening was required, following an $\text{S}_{\text{N}}2$ mechanism. In contrast, an acidic epoxide opening would proceed via an $\text{S}_{\text{N}}1$ mechanism, leading to racemization.^[130]

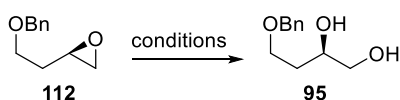
Detailed studies were conducted to optimize the basic epoxide opening. Initially, mild conditions were tested using 1-2 equivalents of KOH with only water as solvent (entries 1-2). However, no product formation was observed at temperatures ranging from room temperature to $60\text{ }^\circ\text{C}$. Instead, only starting material was recovered.

The first successful conversion was achieved under harsher conditions. A strongly basic environment was applied, along with a biphasic solvent system to improve substrate solubility. *tert*-Butanol was chosen as the co-solvent due to its poor nucleophilicity, thereby

preventing unwanted side reactions. Under these conditions, yields increased with temperature up to 80 °C, but further heating (110 °C) led to decreased yields (entries 3–5).

Despite a yield of 68% under optimized conditions (entry 4), additional modifications were explored to improve efficiency. Due to the high reaction temperatures, the use of additives for epoxide activation was explored. Magnesium bromide ethyl etherate as a Lewis acid was added to facilitate the ring opening. However, no conversion was observed at room temperature (entry 6), and only trace amounts of product were detected at 70 °C (entry 7).

Table 3.3-1. Studies on the epoxide ring-opening of **112** to diol **95**.



Entry	Solvent	KOH [equiv.]	Additive	Temperature [°C]	Time [h]	Yield [%]
1	H ₂ O	1.00		60	20	-
2	H ₂ O	2.00		r.t.	48	-
3	H ₂ O/ <i>t</i> -BuOH	50.0		60	18	45
4	H ₂ O/ <i>t</i> -BuOH	50.0		80	96	68
5	H ₂ O/ <i>t</i> -BuOH	50.0		110	48	37
6	H ₂ O/ <i>t</i> -BuOH	50.0	MgBr ₂ ·OEt ₂	r.t.	1	-
7	H ₂ O/ <i>t</i> -BuOH	50.0	MgBr ₂ ·OEt ₂	70	20	traces
8	H ₂ O/ <i>t</i> -BuOH	50.0	MgBr ₂ ·OEt ₂	135	20	42
Methansulfonamide						
9	H ₂ O/THF	50.0		80	96	23
10	H ₂ O/THF	50.0		115	65	84

Compared to entry 3 and entry 4, which yielded 45% and 68% at 60 °C and 80 °C, respectively, the use of this additive significantly worsened the outcome. Even at 135 °C with a phase-transfer reagent, the yield remained at 42%, failing to offer any improvement (entry 8).

Best results were achieved with changes in the solvent system from H₂O/*t*-BuOH to H₂O/THF (entries 9-10). Yields at 80 °C were slightly lower than in entry 4, further temperature increases led to an improvement, unlike entry 5, where excessive heating had reduced yields. Ultimately, an optimized yield of 84% was achieved, marking a significant enhancement of the reaction conditions.

To ensure that these harsh conditions exclusively yielded the enantiomerically pure product, the enantiomeric excess was determined via HPLC. The measured *ee* was 92%. Given that the manufacturer specifies an *ee* higher than 96% for L-aspartic Acid, the slight decrease could be attributed either to the harsh reaction conditions or to an inaccurate manufacturer specification. However, since the result with an *ee* of 92% was considered more than satisfactory, no further investigations were conducted.

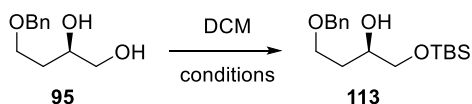
Finally having diol **95** in hand, the primary alcohol could be selectively protected. Initial investigations attempted selective protection of the primary alcohol using THP. The rationale behind this approach was that the primary THP group could later be easily and selectively removed in the presence of a secondary TBS group. However, only the doubly protected product was isolated, even when the reaction was carried out at temperatures as low as – 50 °C.

As a result, an alternative approach was pursued, aiming to protect the primary alcohol with TBS to get silyl ether **113** (Table 3.3-2). More extensive studies were conducted to optimize the conditions. In the first two attempts (entries 1-2), TBS protection was performed using TBSOTf with a slight excess (1.05 equiv.). This method was successful, and no significant difference in yield was observed between reactions carried out at –78 °C to r.t. or at 0 °C. However, the yields were still deficient.

A significant improvement was achieved with freshly opened TBSOTf. This suggests that the previously used TBSOTf had been exposed to moisture from the air, leading to partial hydrolysis. As a result, the actual amount of active reagent was lower than the intended 1.05 equivalents. With freshly opened TBSOTf, the yields improved to 49% at –78 °C and 55% at 0 °C (entries 3-4). However, these results were still inadequate. Increasing the amount of TBSOTf slightly to 1.10 or 1.15 equivalents did not further enhance the yield but led to an increase in the undesired doubly protected product (entries 5-6).

Since TBSOTf appeared to be too reactive, producing the doubly protected product even at low temperatures, TBSCl was considered as a less reactive alternative. The first attempt with TBSCl gave similar results to previous trials. However, a trend was observed: increasing the equivalents of TBSCl led to improved yields (entries 8-9).

Table 3.3-2. Studies on the primary TBS protection of diol **95** to corresponding mono protected silyl ether **113**.



Entry	TBSOTf [equiv.]	TBSCl [equiv]	Lutidine [equiv.]	Temperature [°C]	Time [h]	Yield [%]
1	1.05		5.00	-78 -> r.t.	2.5	35 ^[b]
2	1.05		5.00	0	3.0	32 ^[b]
3	1.05 ^[a]		5.00	-78	1.0	49
4	1.05 ^[a]		5.00	0 -> r.t.	72	55 ^[b]
5	1.10 ^[a]		10.0	-78 -> r.t.	20	44 ^[b]
6	1.15 ^[a]		10.0	-78 -> r.t.	16	46 ^[b]
8		1.00	5.00	0 -> r.t.	1.0	41%
9		1.05	3.00	0 -> r.t.	22	55%
10		2.00	5.00	0 -> r.t.	1.0	90 ^[b]
11		1.50	5.00	0 -> r.t.	1.0	96%

^[a] Fresh opened TBSOTf.

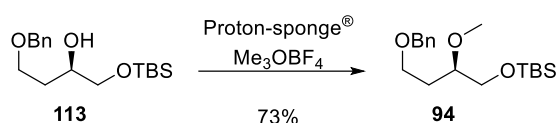
^[b] Partially double protected.

A significant increase to 2.00 equivalents of TBSCl resulted in a 90% yield of the mono-protected alcohol with a short reaction time. However, traces of the doubly protected product were also detected, indicating that either the TBSCl equivalents were too high or the reaction time was too long.

For optimization, the amount of TBSCl was reduced to 1.50 equivalents and yielded in results of 96% within a reaction time of 1 hour. No traces of the doubly protected alcohol were observed and no further modifications were pursued.

The silyl ether **113** was transformed into methyl ether **94** by Meerwein methylation (**Scheme 3.3-6**). Me₃OBf₄ as an alternative to carcinogenic methyl iodide^[131] has several advantages, since it offers high reactivity, is non-volatile, and is not carcinogenic.^[90,132]

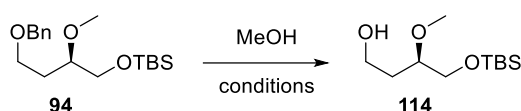
The reaction worked excellently on a small scale (quantitative yield) and remained highly decent on a larger gram scale, achieving a yield of 73%.



Scheme 3.3-6. Methylation of alcohol **113** to corresponding methylated product **94**. Conditions: **113** (1.00 equiv.), Proton-sponge[⊕] (5.50 equiv.), Me₃OBf₄ (5.00 equiv.), DCM, r.t., 6 h, 73%.

The benzyl-protected alcohol **94** needed to be deprotected to get alcohol **114** to allow further fragment extension (**Table 3.3-3**). For this, a classical hydrogenation was employed, specifically, a Pd/C reduction.

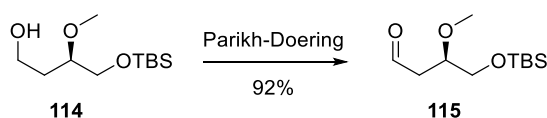
Table 3.3-3. Studies on the benzyl deprotection of benzyl ether **94**.



Entry	94	Pd/C	Concentration	p (H ₂)	Time	Yield
	[g]	[equiv.]	[M]	[bar]	[h]	[%]
1	0.1	0.1	0.1	1	24	quant.
2	2	0.1	0.1	1	120	57
3	13	0.1	0.1	1	64	traces
4	13	0.1	0.5	20	2	traces
5	13	0.1	0.5	40	19	6 (47 brsm)

Good results were obtained on a small scale (entry 1). However, when scaled up to 2 g, the yield dropped significantly to 57% (entry 2). On a decagram scale (entry 3), no satisfactory results could be achieved. Increasing the hydrogen pressure to 20 bar by using an autoclave, did not improve the outcome (entry 4). Further increasing the pressure to 40 bar and extending the reaction time to 19 hours allowed product isolation, but also led to side products, making complete recovery of the starting material impossible. Fortunately, thanks to the large reaction scale (13 g), a sufficient amount of the primary alcohol could still be isolated to proceed with fragment extension. Optimization of this process or an alternative approach, such as modifying the protecting group, was planned for later, after successfully establishing the intended synthetic route.

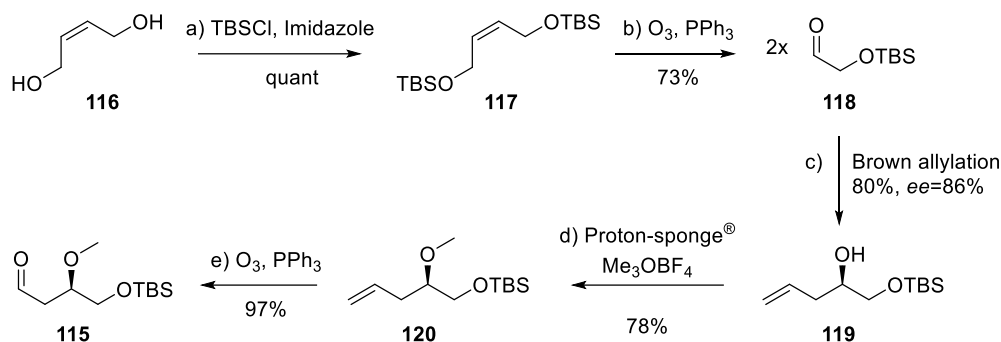
The primary alcohol **114** was then oxidized to the corresponding aldehyde **115** using a Parikh-Döring reaction (**Scheme 3.3-7**).



Scheme 3.3-7. Parikh-Doering oxidation of alcohol **114** to the corresponding aldehyde **115**. Conditions: **114** (1.00 equiv.), DIPEA (4.00 equiv.), DMSO (10.0 equiv.) sulphur trioxide pyridine complex (3.00 equiv.), DCM, 0 °C → r.t., 1 h, 92%.

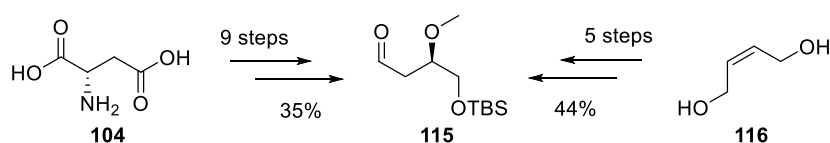
To access aldehyde **115**, the initial synthetic route required nine steps, yielding the target compound with an overall efficiency of 35%. While this represents a reasonable yield, the number of steps is quite high considering the relatively small size of the molecule. Therefore, an alternative synthetic approach was explored to minimize the number of steps while maintaining efficiency.

This revised strategy began with (*Z*)-but-2-ene-1,4-diol (**116**, **Scheme 3.3-8**). A double TBS protection afforded silyl ether **117** in quantitative yield on a decagram scale. The symmetrical nature of silyl ether **117** allowed for its cleavage via ozonolysis, yielding two equivalents of aldehyde **118**. The key stereocenter was introduced through a Brown allylation,^[117] achieving an enantiomeric excess of 86% with a satisfactory yield of 80%. Following the previously established route, alcohol **119** was subjected to a Meerwein methylation, converting it into methyl ether **120** in a respectable 78% yield. Finally, ozonolysis furnished aldehyde **115** in 97% yield.



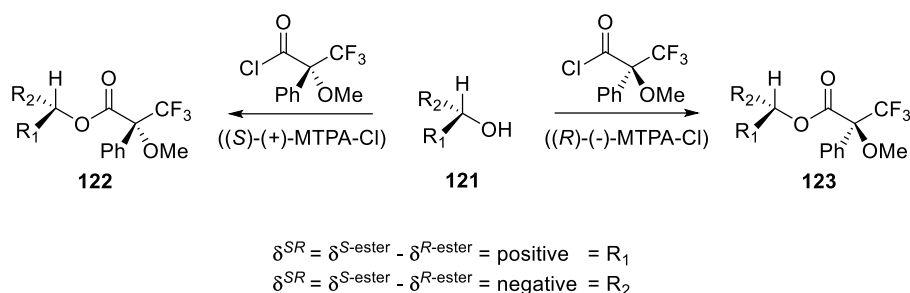
Scheme 3.3-8. Alternative route for the synthesis of aldehyde **115**, beginning with diol **116**. Conditions: a) **116** (1.00 equiv.), Imidazole (4.00 equiv.), TBSCl (3.00 equiv.), DCM, 0 °C, 90 min, quant.; b) **117** (1.00 equiv.), O₃ (xs.), DCM/MeOH, -78 °C, 45 min, then PPh₃ (2.00 equiv.), -78 °C → r.t., 2 h, 73%; c) (+)-*B*-Methoxydiisopinocampheylboron (1.25 equiv.), allylmagnesium bromide (1.20 equiv.), Et₂O, 0 °C → r.t., 1 h, then **118** (1.00 equiv.), -78 °C, 2.5 h, then NaOH (xs.), H₂O₂ (xs.), reflux, 2 h, 80%, ee=86%; d) **119** (1.00 equiv.), Me₃OBF₄ (2.00 equiv.), Proton-sponge[®] (2.00 equiv.), DCM, 0 °C → r.t., 72 h, 78%; e) **120** (1.00 equiv.), O₃ (xs.), DCM/MeOH, -78 °C, 15 min, then PPh₃ (1.50 equiv.), -78 °C → r.t., 2 h, 97%.

Compared to the initial nine-step sequence, this optimized route from diol **116** to aldehyde **115** required only five steps and achieved a higher overall yield of 44%, compared to 35% in the original approach from L-aspartic (**104**) to aldehyde **115** (Scheme 3.3-9). Only a slightly lower enantiomeric excess of 86% was observed (92% in the previous route).



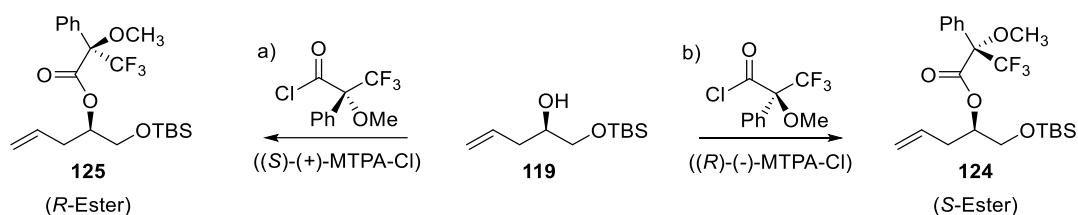
Scheme 3.3-9. Comparison of the two synthetic routes: starting from L-aspartic acid (**104**) to synthesize aldehyde **115** in 9 steps with a 35% yield, or beginning with diol **116** to obtain aldehyde **115** in 5 steps with a 44% yield.

To verify the stereocenter of **119** the absolute configuration was elucidated by Mosher ester analysis, a widely used method for determining the absolute configuration of a secondary alcohol **121** (Scheme 3.3-10). Mosher ester analysis involves the derivatization of a secondary alcohol **121** into two diastereomeric esters by transformation with both enantiomers of MTPA-Cl (α -methoxy- α -trifluoromethylphenylacetyl chloride), resulting in the formation of two distinct diastereomeric esters, *R*-ester **122** and the *S*-ester **123**. Both diastereomers exhibit characteristic differences in their ¹H NMR spectra.



Scheme 3.3-10. Mosher ester analysis of secondary alcohol **121**.

To confirm the absolute configuration of alcohol **119**, the *S*-ester **124** and *R*-ester **125** were synthesized (**Scheme 3.3-11**). Analyzing the chemical shift differences between the *S*-ester **123** and the *R*-ester **122** ($\Delta\delta^{SR} = \delta^{S\text{-ester}} - \delta^{R\text{-ester}}$), reveals insight into the stereochemistry of the chiral center of the secondary alcohol. A positive shift indicates correspondence to the R_1 residue, whereas a negative shift corresponds to the R_2 residue.^[133] The assignment of *S* or *R* configuration to the stereocenter is based on the correlation



Scheme 3.3-11. Synthesis of (*S*)-ester **124** and (*R*)-ester **125** for Mosher analysis.^[133] Conditions: a) **119** (1.0 equiv.), (*S*)-(+)-MTPA-Cl (3.0 equiv.), pyridine (0.2 mL), r.t., 2 h, 38%; b) **119** (1.0 equiv.), (*R*)-(-)-MTPA-Cl (3.0 equiv.), pyridine (0.2 mL), r.t., 2 h, 28%;

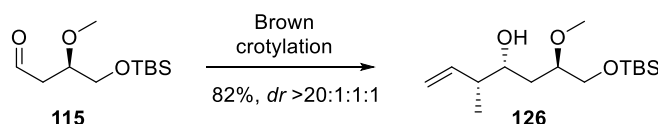
Comparison of their respective NMR data are shown in **Table 3.3-4**.

Table 3.3-4. Significant ¹H NMR signals of **124** (*S*-Ester) and **125** (*R*-Ester) and their use in Mosher ester analysis.

Atom	δ_H of 124 (<i>S</i> -Ester) [ppm]	δ_H of 125 (<i>R</i> -Ester) [ppm]	$\Delta\delta^{SR} = \delta^{S\text{-ester}} - \delta^{R\text{-ester}}$
1	5.17-5.10	5.06-4.99	(+0.11)-(+0.11)
2	5.80	5.67	+0.13
3	2.52/2.43	2.42-2.29	(+0.10)-(+0.14)

4	-	-	-
5	3.72-3.64	3.80-3.70	(-0.08)-(-0.06)

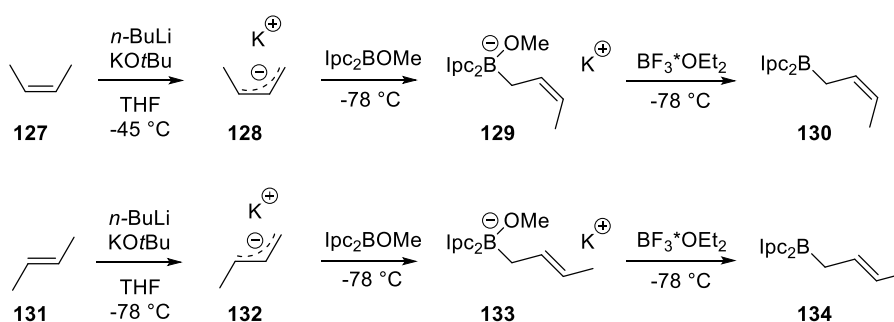
Mosher analysis confirms (*R*)-configuration of the stereogenic center. The aldehyde **115** was then elongated in a Brown crotylation, resulting in *anti*-diol **126** in remarkable 82% yield (**Scheme 3.3-12**) with an excellent diastereomeric ratio of >20:1:1:1.



Scheme 3.3-12. Brown crotylation of aldehyde **115** to corresponding crotyl **126**. Conditions: (*Z*)-Buten (**127**, 5.00 equiv.), KOtBu (1.30 equiv.), *n*-BuLi (1.30 equiv.) THF, -40 °C, 15 min then (-)-*B*-Methoxydiisopinocampheylboran (1.30 equiv.), -78 °C, 30 min then BF₃*Et₂O (1.35 equiv.), **115** (1.00 equiv.), -78 °C, 2.5 h then NaOH (xs.), H₂O₂ (xs.), reflux, 1 h, 82%, *dr* >20:1:1:1.

The remarkable diastereoselectivity observed in the Brown crotylation reaction warrants a more detailed discussion of its mechanism.

The first step of the Brown crotylation involves the *in situ* generation of the active boron species **130** and **134** (**Scheme 3.3-13**). This step is generally performed *in situ*, as preformed crotylboranes can undergo a borotropic rearrangement, leading to interconversion between (*Z*)- and (*E*)-crotyl species, thereby compromising the selectivity of the reaction.^[134]

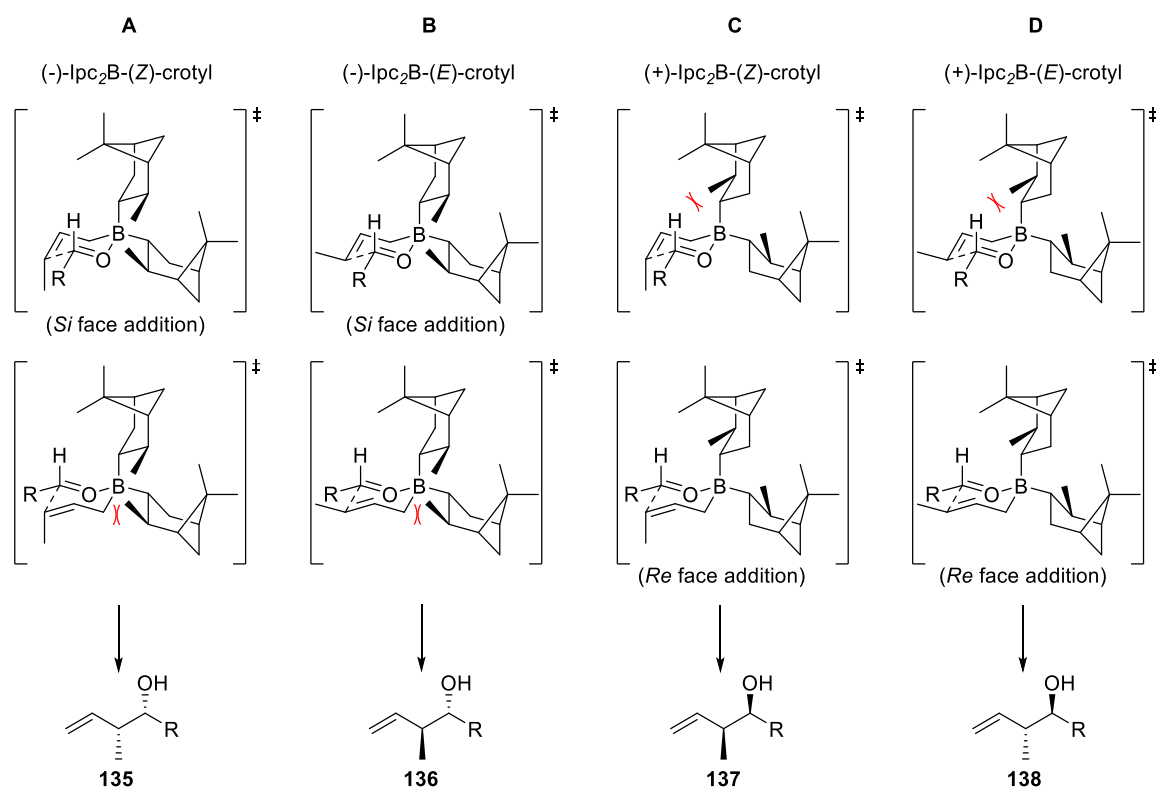


Scheme 3.3-13. A general approach for synthesising the active species **130** and **134**, essential for the Brown crotylation.^[59]

Deprotonation of *cis*-butene (**127**) or *trans*-butene (**131**) with *n*-BuLi and KOtBu (Schlosser-Base)^[135] in THF, forming organometallic species **128** and **132**, which forms a Lewis-acid-base-adduct with methoxydiisopinocampheylborane resulting in intermediates **129** or **133**.

Treatment with boron trifluoride etherate generates the active trialkylborane species **130** or **134**.^[136]

When the active species is introduced to an aldehyde, the stereoselectivity can be explained by a Zimmerman-Traxler transition state (**Scheme 3.3-14**). The presence of a chiral ligand, in this case, either (+)- or (-)-lpc, dictates the preferred transition state. Aldehyde residue R is located in equatorial position to avoid the 1,3-diaxial interaction. In the lower transition states (pathway A-B), steric interactions between the equatorial methyl group of the lower lpc ligand and the CH₂-group of the crotyl unit render these configurations unfavorable. Consequently, the upper transition states are preferred, leading to *Si*-face addition and the stereochemical control of the resulting alcohols of products **135** and **136**.

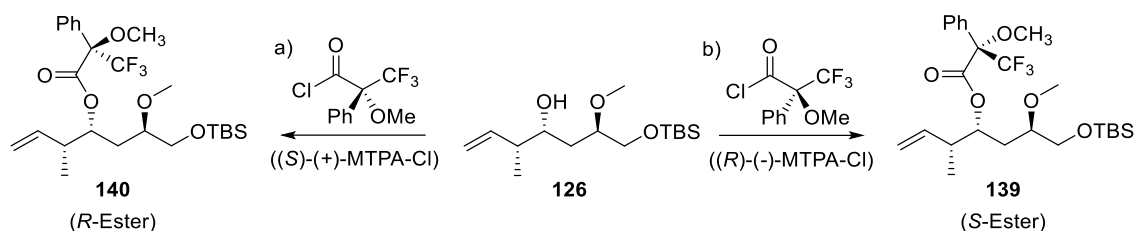


Scheme 3.3-14. Explaining the four stereoisomers of the Brown crotylation through the transition states of the aldehyde and the active boronic species **130** or **134** within the Zimmerman-Traxler transition state model.

In the case of (*Z*)-crotyl species **130** (Pathway A), the terminal CH₃-group of the crotyl unit adopts an axial position, favoring the formation of the *syn*-product **135**. Conversely, when employing (*E*)-crotyl species **134**, the CH₃-group is equatorial, resulting in the *anti*-product **136**.

Similarly, when the (+)-Ipc ligand is used, steric repulsion between the CH₂-group of the crotyl moiety and the equatorial methyl group of the upper Ipc ligand renders the upper transition states unfavorable (pathway C-D). As a result, *Re*-face addition occurs, establishing the stereocenter of the alcohol in products **137** and **138**. The formation of the *syn*-product **137** is observed when (*Z*)-crotylborane **130** is used, whereas employing (*E*)-crotyl leads to the *anti*-product **138**.

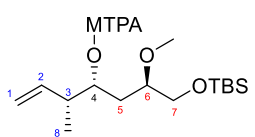
This methodology allows for the installation of two stereocenters in a single reaction. By selecting the appropriate combination of reagents, all four possible stereoisomers can be synthesized with high selectivity.^[59,137,138]



Scheme 3.3-15. Synthesis of (*S*)-ester **139** and (*R*)-ester **140** for Mosher analysis.^[133] Conditions: a) **126** (1.0 equiv.), (*S*)-(+)-MTPA-Cl (5.0 equiv.), pyridine (0.2 mL), r.t., 2 h, quant.; b) **126** (1.0 equiv.), (*R*)-(-)-MTPA-Cl (5.0 equiv.), pyridine (0.2 mL), r.t., 2 h, quant.

Analogously to the former approach, absolute configuration of β -methylhomoallylic alcohol **126** was verified by Mosher ester analysis (**Scheme 3.3-15**).

Table 3.3-5. Significant ¹H NMR signals of **139** (*S*-Ester) and **140** (*R*-Ester) and their use in Mosher ester analysis.

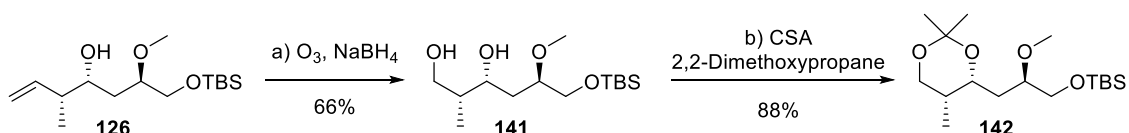


Atom	δ_H of 139 (<i>S</i> -Ester) [ppm]	δ_H of 140 (<i>R</i> -Ester) [ppm]	$\Delta\delta^{SR} = \delta^{S\text{-ester}} - \delta^{R\text{-ester}}$
1	5.03-4.89	5.10-5.04	(-0.15)-(-0.07)
2	5.68	5.82	-0.14
3	2.50	2.59	-0.09
4	-	-	-
8	0.97	1.04	-0.07

5	1.78/1.66	1.70/1.62	+0.08/+0.04
6	3.63	3.52	+0.11
7	3.53-3.49/ 3.17-3.07	3.48/2.98	+0.02/+0.02

The differences observed in the ^1H NMR spectra of the (*S*)- and (*R*)-MTPA esters **139** and **140** enabled the assignment of the absolute configuration, confirmed *anti*-configuration of diol **126** (Table 3.3-5). For further details, refer to Scheme 3.3-10 or the relevant literature.^[133]

To confirm the absolute configuration of the methylhomoallylic alcohol **126**, the double bond was first cleaved via ozonolysis, followed by NaBH_4 reduction, yielding the corresponding 1,3-diol **141** (Scheme 3.3-16). Subsequent acetonide protection of both hydroxyl groups afforded acetonide **142**.



Scheme 3.3-16. Synthesis of acetonide **142** to verify the stereo configuration of the methyl group. Conditions: a) **126** (1.00 equiv.), O_3 (xs.), DCM/MeOH, $-78\text{ }^\circ\text{C}$, 1 min, then NaBH_4 (5.00 equiv.), $-78\text{ }^\circ\text{C} \rightarrow \text{r.t.}$, 2 h, 66%; b) **141** (1.00 equiv.), CSA (0.01 equiv.), 2,2-dimethoxypropane (xs.), r.t., 1 h, 88%.

With both hydroxyl groups now protected as an acetonide, the chemical shift of the ketal carbon provided insight into the conformation of the 1,3-diol (Figure 3.3-2). A ketal carbon shift above 100 ppm indicates a twist-boat conformation (1,3 *anti* diol), while a shift below 100 ppm is characteristic of a chair conformation (1,3 *syn* diol). In this case, the ketal carbon shift was below 100 ppm, confirming that the molecule adopts a chair conformation.^[139]

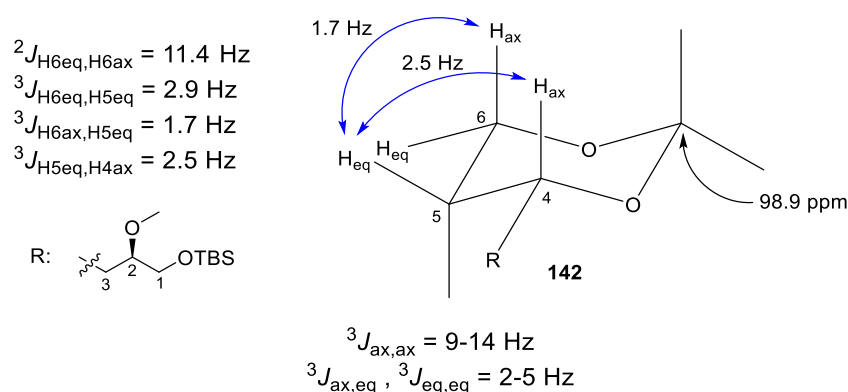
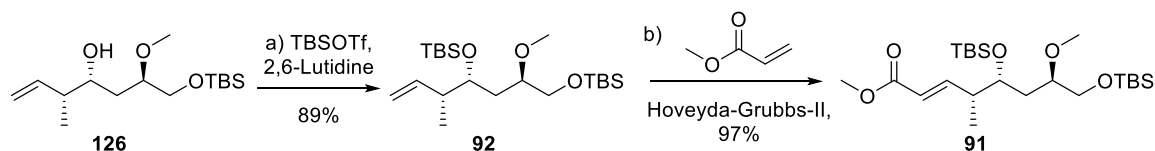


Figure 3.3-2. Depicted is the chair conformation of **142** for verifying the 1,2-*syn* configuration.

Once the chair conformation was established, the coupling constants of the protons were analyzed to determine whether the methyl group is positioned axially or equatorially. This distinction ultimately allowed differentiation between the 1,2-*syn* configuration and 1,2-*anti* configuration, depending on whether the methyl group occupies the axial or equatorial position. The observed coupling constants confirmed an axial orientation of the methyl group, as evidenced by a 3J coupling between H6_{ax} and H5_{eq} of 1.7 Hz and a 3J coupling between H4_{ax} and H5_{eq} of 2.5 Hz. If the methyl group had been equatorial, a significantly larger coupling of approximately 9–14 Hz would have been expected between H6_{ax} and H5_{ax}, as well as between H4_{ax} and H5_{ax}. Since no such large couplings were observed, the data conclusively confirmed that the methyl group is in the axial position, establishing a 1,2-*syn* configuration.^[140]

With **126** in hand, the hydroxyl group was TBS-protected, yielding the corresponding silyl enol ether **92** (Scheme 3.3-17). The terminal alkene in **92** provided an excellent opportunity for elongation via Grubbs metathesis.^[110] This transformation was carried out using methyl acrylate, successfully affording olefin **91** with an outstanding 97% yield.



Scheme 3.3-17. Synthesis of olefin **91** via alcohol **126** protection to corresponding silyl ether **92** followed by a Grubbs metathesis. Conditions: a) **126** (1.00 equiv.), TBSOTf (3.00 equiv.), 2,6-lutidine (10.0 equiv.), DCM, 0 °C→r.t., 2 h, 89%; b) **92** (1.00 equiv.), Hoveyda-Grubbs-II (0.07 equiv.), methyl acrylate (5.00 equiv.), toluene, 120 °C, 20 h, 97%, *E/Z* >20:1.

The next step involved the selective removal of the primary TBS group while ensuring that the secondary TBS group remained intact to yield **143**. For this purpose, a classical CSA deprotection in DCM/MeOH was employed.

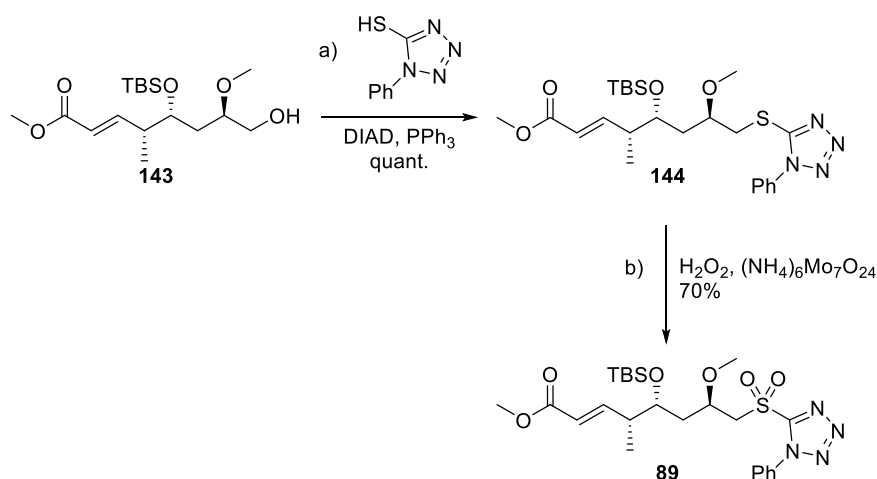
To prevent undesired cleavage of the secondary TBS group, a cautious approach at low temperatures of $-50\text{ }^{\circ}\text{C}$ and $-40\text{ }^{\circ}\text{C}$ and catalytic amounts of CSA was employed (entries 1-2, **Table 3.3-6**). First traces of the desired primary alcohol **143** appeared after 24 h at $-30\text{ }^{\circ}\text{C}$ (entry 3). At $-20\text{ }^{\circ}\text{C}$ the reaction proceeded significantly faster with achieving 42% yield after 6 h (entry 4). Notably, the brsm yield was quantitative, suggesting that further optimization was possible.

Table 3.3-6. Primary deprotection of silyl enol ether **91** to primary alcohol **143**.



Entry	CSA [equiv.]	Temperature [$^{\circ}\text{C}$]	Time [h]	Yield
1	0.1	-50	72	-
2	0.1	-40	24	-
3	0.1	-30	24	traces
4	0.1	-20	6	42% (quant. brsm)
5	0.5	0 $^{\circ}\text{C}$ $\rightarrow$ r.t.	1.5	81 %

An increase to 0.50 equivalents of CSA, a slow temperature increase from $0\text{ }^{\circ}\text{C}$ $\rightarrow$ r.t. and a shorter reaction time (1.5 h) successfully afforded the desired mono-deprotected alcohol **143** in 81% yield (entry 5). TLC analysis revealed an additional, more polar spot, indicating the onset of double deprotection, which likely contributed to the yield not exceeding 81%. The yield was considered decent and the minor byproduct observed on TLC was not further investigated.



Scheme 3.3-18. Mitsunobu reaction of primary alcohol **143** to thioether **144** and additional oxidation to sulfone **89**.

Deprotected primary alcohol **143** was further modified by a Mitsunobu reaction.^[108,109] Finally, primary alcohol **143** was converted into thioether **144** and subsequently oxidized to the corresponding sulfone **89** (**Scheme 3.3-18**). The fragment was now fully prepared for a Julia-Kocienski reaction with an aldehyde counterpart to form the *E*-olefin.^[107]

3.3.2 Synthesis of primary alcohol **145**

This chapter describes the synthesis of primary alcohol **145**, which differs from sulfone **89**, discussed in the previous **Chapter 3.3.1**, by featuring a TBS-protected hydroxyl group at the 1,2-diol instead of a methoxy group (**Figure 3.3-3**).

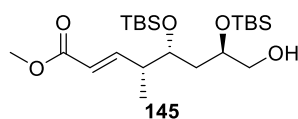
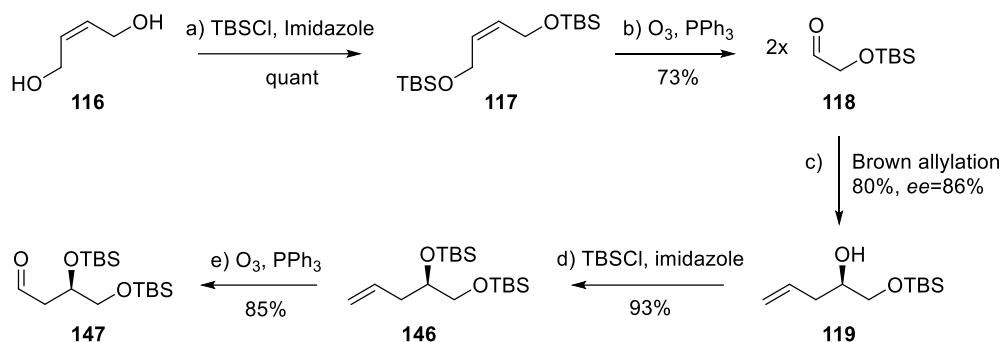


Figure 3.3-3. Target fragment **145** for neaumycin C (**5**).

Fragment **145** is essential for the synthesis of neaumycin C (**5**, see **Chapter 1.2.2**).^[10] Following the previously established synthetic route (see **Chapter 3.3.1**), the synthesis starts from diol **116** (**Scheme 3.3-19**). A double TBS protection afforded silyl ether **117**, which was then subjected to ozonolysis and a Brown allylation, yielding the known allyl **119**.

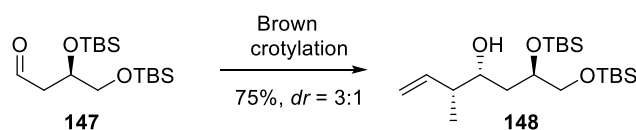


Scheme 3.3-19. Synthesis of aldehyde **147**, beginning with diol **116**. Conditions: a) **116** (1.00 equiv.), Imidazole (4.00 equiv.), TBSCl (3.00 equiv.), DCM, 0 °C, 90 min, quant.; b) **117** (1.00 equiv.), O₃ (xs.), DCM/MeOH, –78 °C, 45 min, then PPh₃ (2.00 equiv.), –78 °C → r.t., 2 h, 73%; c) (+)-*B*-Methoxydiisopinocampheylboran (1.25 equiv.), allylmagnesium bromide (1.20 equiv.), Et₂O, 0 °C → r.t., 1 h, then **118** (1.00 equiv.), –78 °C, 2.5 h, then NaOH (xs.), H₂O₂ (xs.), reflux, 2 h, 80%, ee=86%; d) **119** (1.00 equiv.), TBSCl (2.00 equiv.), imidazole (2.00 equiv.), DCM, 0 °C → r.t., 2 h, 93%; e) **146** (1.00 equiv.), O₃ (xs.), DCM/MeOH, –78 °C, 15 min, then PPh₃ (1.50 equiv.), –78 °C → r.t., 2 h, 85%.

At this stage, instead of methylation as in the previous synthesis, the free hydroxyl group was TBS-protected to silyl ether **146**. Finally, following the same approach as before, the double bond was cleaved to furnish the corresponding aldehyde **147**.

Aldehyde **147** was elongated by Brown crotylation to obtain homoallylic alcohol **148** (**Scheme 3.3-20**). In higher gram scales the reaction showed poor diastereoselectivity (*dr* = 3:1). Smaller scales improved the selectivity to approximately 5:1.

In comparison to sulfone **89** (see **Chapter 3.3.1**), the diminished selectivity might be caused by the bulky TBS-ether at the β-position.

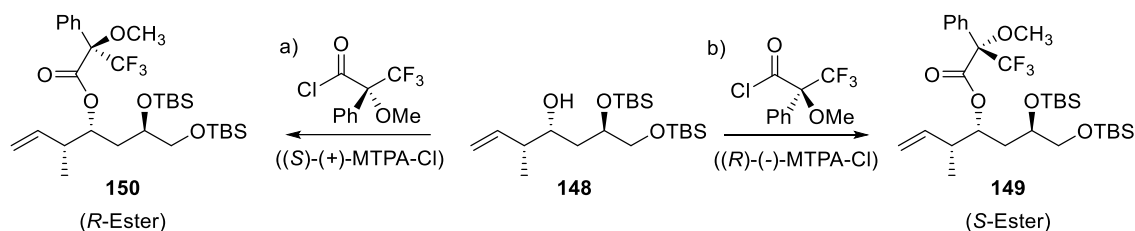


Scheme 3.3-20. Brown crotylation of aldehyde **147** to corresponding alcohol **148**. Conditions: (*Z*)-Buten (**127**, 5.00 equiv.), KOtBu (1.30 equiv.), *n*-BuLi (1.30 equiv.) THF, –40 °C, 15 min then (–)-*B*-Methoxydiisopinocampheylboran (1.30 equiv.), –78 °C, 30 min then BF₃·Et₂O (1.35 equiv.), **147** (1.00 equiv.), –78 °C, 2.5 h then NaOH (xs.), H₂O₂ (xs.), reflux, 1 h, 75%, *dr* = 3:1.

Nevertheless, the diastereomers could be efficiently separated via HPLC in later stages. Since this fragment primarily served to demonstrate the flexibility of the synthetic route, confirming

that all neaumycin derivatives could be accessed, no further efforts were made to optimize the reaction's selectivity at this stage.

To confirm absolute configuration, a Mosher analysis was performed. *S*-MTPA ester **149** and *R*-MTPA ester **150** were synthesized analogously to previous approaches (see **Chapter 3.3.1**) from alcohol **148** (**Scheme 3.3-21**).



Scheme 3.3-21. Synthesis of (*S*)-ester **149** and (*R*)-ester **150** for Mosher analysis.^[133] Conditions: a) **148** (1.0 equiv.), (*S*)-(+)-MTPA-Cl (5.0 equiv.), pyridine (0.2 mL), r.t., 2 h, quant.; b) **148** (1.0 equiv.), (*R*)-(-)-MTPA-Cl (5.0 equiv.), pyridine (0.2 mL), r.t., 2 h, 73%.

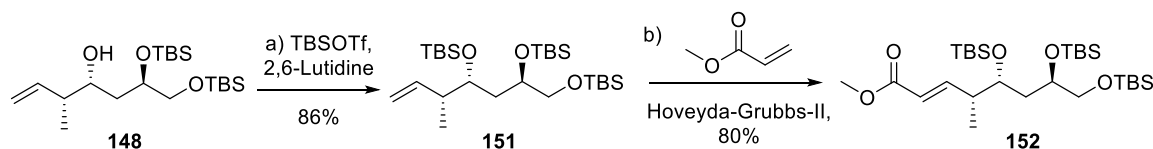
The differences observed in the ¹H NMR spectra of the (*S*)- and (*R*)-MTPA esters **149** and **150** enabled the assignment of the absolute configuration (**Table 3.3-7**). For further details, refer to **Scheme 3.3-10**.^[133] The Mosher ester analysis confirmed (*R*)-configuration.

Table 3.3-7. Significant ¹H NMR signals of **149** (*S*-Ester) and **150** (*R*-Ester) and their use in Mosher ester analysis.

Atom	δ_{H} of 149 (<i>S</i> -Ester) [ppm]	δ_{H} of 150 (<i>R</i> -Ester) [ppm]	$\Delta\delta^{SR} = \delta^{S\text{-ester}} - \delta^{R\text{-ester}}$
1	4.99-4.87	5.08-5.00	(-0.09)-(-0.13)
2	5.66	5.77	-0.11
3	2.54	2.66-2.58	(-0.12)-(-0.04)
4	-	-	-
8	0.99	1.03	-0.04
5	1.90/1.56	1.83/1.54	+0.07/+0.02
6	3.65	3.59-3.54	(+0.06)-(+0.11)

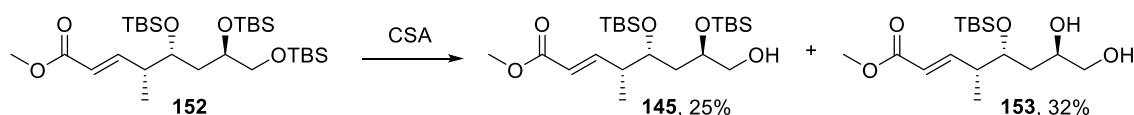
7	3.55-3.53/ 3.32	3.51-3.47/ 3.30	(+0.04)-(+0.06)/ +0.02
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Homoallylic alcohol **148** was TBS-protected and silyl ether **151** was subsequently elongated with methyl acrylate via a Hoveyda-Grubbs-II catalyzed metathesis to yield olefin **152** (**Scheme 3.3-22**) in high yields (86% and 80%).



Scheme 3.3-22. Synthesis of olefin **152** via alcohol **148** protection to corresponding silyl ether **151** followed by a Grubbs metathesis. Conditions: a) **148** (1.00 equiv.), TBSOTf (3.00 equiv.), 2,6-lutidine (10.0 equiv.), DCM, 0 °C→r.t., 2 h, 86%; b) **151** (1.00 equiv.), Hoveyda-Grubbs-II (0.03 equiv.), methyl acrylate (5.00 equiv.), toluene, 120 °C, 20 h, 80%, *E/Z* >20:1.

The final step involved primary TBS ether cleavage of silyl ether **152** (**Scheme 3.3-23**). Analogously to the synthesis of **143**, CSA was employed under the previously optimized reaction conditions (**Table 3.3-6**).



Scheme 3.3-23. Deprotection of silyl ether **152**, yielding primary alcohol **145** and 1,2-deprotected compound **153**. Conditions: **152** (1.00 equiv.), CSA (0.50 equiv.), DCM/MeOH, 0 °C, 30 min, then → r.t., 3 h, **145** (25%), **153** (32%).

Compared to the previous fragment **91**, the deprotection proved to be more challenging (see **Chapter 3.3.1**).

The desired product **145** was successfully isolated with 25% yield and the undesired 1,2-deprotected byproduct **153** was obtained in a higher yield of 32%. This suggests that the previously optimized conditions were not directly applicable to this particular substrate.

Nevertheless, this demonstrated the accessibility to fragment **145** by using the previously described steps. The primary alcohol can be functionalized as needed, depending on the chosen coupling strategy for the next fragment.

3.3.3 Synthesis of Aldehyde 154

This chapter outlines the synthesis of aldehyde **90**, a key precursor for coupling with the previously synthesized sulfone **89** (see **Chapter 3.3.1**) via a Julia-Kocienski reaction to generate the corresponding *E*-olefin.

However, due to a copying error, the synthesis was initially conducted based on the incorrect scaffold **154**, resulting in the formation of the wrong diastereomer.

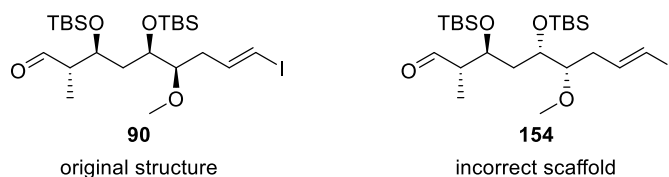


Figure 3.3-4. Depicted is the target fragment **90** and the incorrect scaffold **154** whose synthesis is discussed in this chapter.

The fragment synthesis of **154** starts from commercially available (*R*)-Roche ester (**101**), already including the asymmetric methyl group, and was elongated by an allylation reaction.

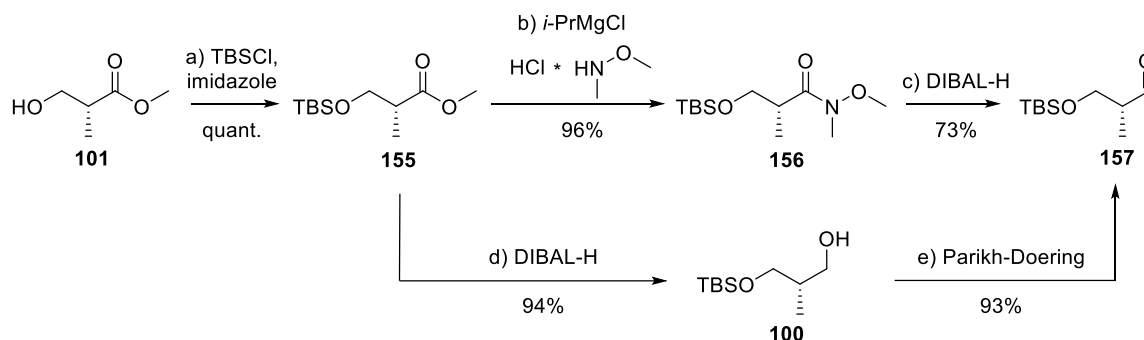
Initial attempts to perform a direct Krische allylation^[141] resulted in complete lack of selectivity (*dr* = 1:1). The methyl group in α -position may interfere sterically and causes no stereoselectivity.

As an alternative, the free hydroxyl group of (*R*)-Roche ester (**101**) was TBS-protected to silyl ether **155** (**Scheme 3.3-24**). Intermediate **155** was converted into Weinreb amide **156** in excellent yield (96%).^[142] DIBAL-H reduction of Weinreb amide **156** finally furnished aldehyde **157** without further reduction to the corresponding alcohol **100**. With an overall yield of 70% for three steps, this sequence was decent, but considering these as initial steps of the fragment synthesis, improvement was necessary.

For optimization, ester **155** was fully reduced to alcohol **100** using DIBAL-H, followed by a Parikh-Doering oxidation to afford aldehyde **157**.^[143] Both reactions proceeded with yields exceeding 90% on a multi-decagram scale.

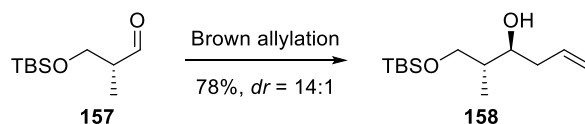
An alternative approach was also tested, attempting a direct DIBAL-H reduction of ester **155** to aldehyde **157**. Cooling issues at bigger scale (multi-decagrams) led to a mixture of alcohol

100 and aldehyde **157**. Since the reaction vessel was only cooled externally, the actual temperature inside the flask may have been higher, leading to over-reduction to alcohol **100**.



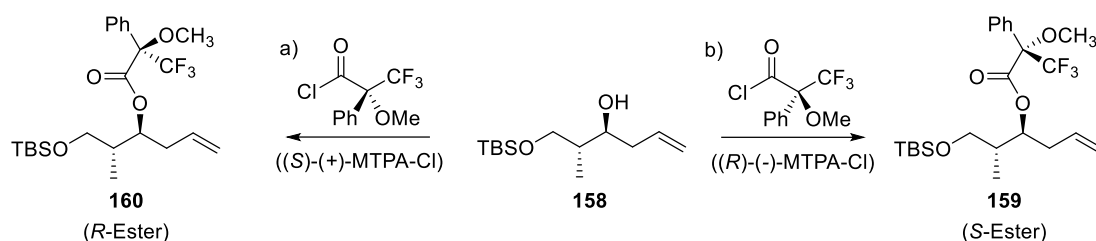
Scheme 3.3-24. Synthesis of aldehyde **157**. Conditions: a) **101** (1.00 equiv.), TBSCl (1.50 equiv.), imidazole (1.50 equiv.), DCM, 0 °C→r.t., quant; b) **155** (1.00 equiv.), *i*-PrMgCl (4.00 equiv.), *N,O*-dimethylhydroxylamine (2.00 equiv.), THF, 0 °C, 2 h, 96%; c) **156** (1.00 equiv.), DIBAL-H (1.50 equiv.), DCM, –78 °C, 2.5 h, 73%; d) **155** (1.00 equiv.), DIBAL-H, (3.00 equiv.), DCM, –78 °C, 2.5 h, 94%; e) **100** (1.00 equiv.), DIPEA (4.00 equiv.), DMSO (10.0 equiv.), sulfur trioxide pyridine complex (3.00 equiv.), DCM, 0 °C→r.t., 1 h, 93%.

As previously mentioned, aldehyde **157** was elongated via a Brown allylation,^[117] yielding corresponding homoallylic alcohol **158** in high yield (78%, **Scheme 3.3-25**). The diastereoselectivity (*dr* = 14:1) was consistent with previous Brown allylations (see **Chapter 3.3.1**), achieving a diastereoselectivity of 14:1.



Scheme 3.3-25. Brown allylation of aldehyde **157** to the corresponding allyl **158**. Conditions: allylmagnesium chloride (1.20 equiv.), (–)-*B*-Methoxydiisopinocampheylboran (1.25 equiv.), Et₂O, 0 °C, 45 min, then **157** (1.00 equiv.), –78 °C, 1.5 h, then NaOH (xs.), H₂O₂ (xs.), reflux, 1.5 h, 78%, *dr* = 14:1.

Stereoconfiguration of alcohol **158** was confirmed by transformation with MTPA-Cl, analogously to previous approaches (**Scheme 3.3-26**).



Scheme 3.3-26. Synthesis of (*S*)-ester **159** and (*R*)-ester **160** for Mosher analysis.^[133] Conditions: a) **158** (1.0 equiv.), (*S*)-(+)-MTPA-Cl (3.0 equiv.), pyridine (0.2 mL), r.t., 2 h, 37%; b) **158** (1.0 equiv.), (*R*)-(-)-MTPA-Cl (3.0 equiv.), pyridine (0.2 mL), r.t., 2 h, 27%.

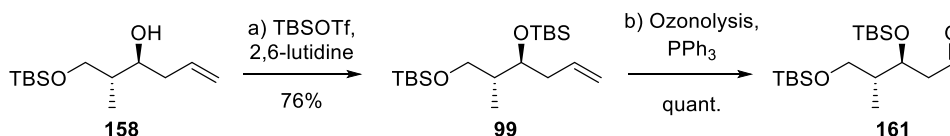
The differences in the ¹H NMR spectra of the (*S*)- and (*R*)-MTPA esters **159** and **160** enabled the assignment of the absolute configuration (**Table 3.3-8**).^[133] Evaluation confirmed (*S*)-configuration of the hydroxy function.

Table 3.3-8. Significant ¹H NMR signals of **159** (*S*-Ester) and **160** (*R*-Ester) and their use in Mosher ester analysis.

Atom	δ_{H} of 159 (<i>S</i> -Ester) [ppm]	δ_{H} of 160 (<i>R</i> -Ester) [ppm]	$\Delta\delta^{SR} = \delta^{S\text{-ester}} - \delta^{R\text{-ester}}$
1	3.60-3.53	3.51-3.46/3.41	(+0.09)-(+0.07)/ (+0.19)-(+0.12)
2	2.04	2.05-1.96	(-0.01)-(+0.08)
3	0.94	0.89	+0.05
4	-	-	-
5	2.52-2.41/ 2.33	2.55-2.48/ 2.40	(-0.03)-(-0.07)/ -0.07
6	5.71-5.58	5.80	(-0.09)-(-0.22)
7	5.04-4.96	5.16-5.08	(-0.12)-(-0.12)

Alcohol **158** was TBS-protected by using TBS triflate, yielding the corresponding silyl ether **99** in 76% yield (**Scheme 3.3-27**). An attempt to perform a Sharpless asymmetric dihydroxylation (SAD) on olefin **99** to obtain directly the desired 1,2-diol moiety proved unsuccessful. This was tested in a preliminary experiment and is therefore not discussed in further detail. However,

the reaction exhibited almost no selectivity, producing a near 1:1 mixture of diastereomers when using the AD-mix.

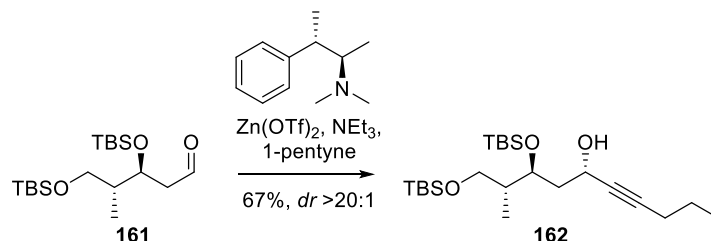


Scheme 3.3-27. TBS protection of alcohol **158** to silyl ether **99** and subsequent ozonolysis to aldehyde **161**. Conditions: a) **158** (1.00 equiv.), TBSOTf (2.00 equiv.), 2,6-lutidine (4.00 equiv.), DCM, 0 °C→r.t., 45 min, 76%; b) **99** (1.00 equiv.), O₃ (xs.), DCM/MeOH, -78 °C, 90 min, then PPh₃ (1.50 equiv.), -78 °C→r.t., 2 h, quant.

Ozonolysis afforded aldehyde **161**, which was now ready for further elongation reaction.

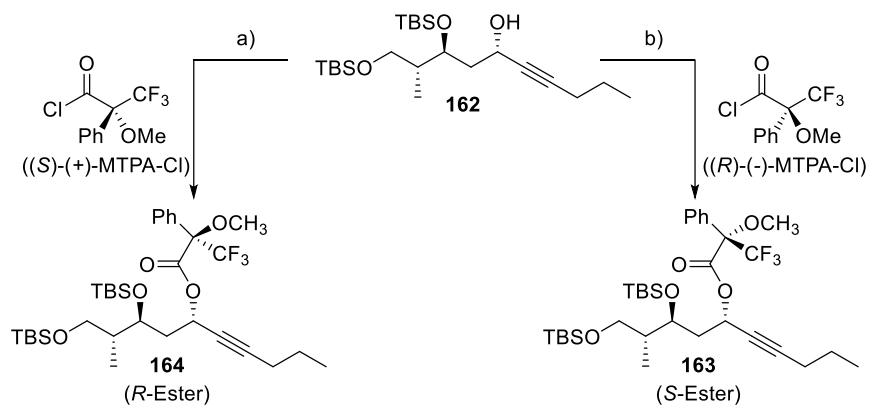
Since the planned asymmetric dihydroxylation (SAD) was unsuccessful, an alternative approach was required. A Carreira reaction was selected, enabling the asymmetric addition of alkynes to aldehydes using *N*-methylephedrine as the chiral auxiliary.

In this case, aldehyde **161** was elongated using (1*R*,2*S*)-(-)-*N*-methylephedrine and 1-pentyne, yielding alkyne **162** with a decent yield of 67% and an outstanding diastereoselectivity (*dr* >20:1, **Scheme 3.3-28**).



Scheme 3.3-28. Carreira's asymmetric addition of 1-pentyne to aldehyde **161**. Conditions: NEt₃ (2.40 equiv.), Zn(OTf)₂ (2.20 equiv.), (1*R*,2*S*)-(-)-*N*-methylephedrine (2.40 equiv.), toluene, r.t., 2 h, then 1-pentyne (2.40 equiv.), r.t., 15 min, then **161** (1.00 equiv.), 2 h, 67%, *dr* >20:1.

Confirmation of the newly generated stereogenic center was performed by Mosher analysis (**Scheme 3.3-29**).



Scheme 3.3-29. Synthesis of (*S*)-ester **163** and (*R*)-ester **164** for Mosher analysis.^[133] Conditions: a) **162** (1.0 equiv.), (*S*)-(+)-MTPA-Cl (5.0 equiv.), pyridine (0.2 mL), r.t., 2 h, quant; b) **162** (1.0 equiv.), (*R*)-(-)-MTPA-Cl (5.0 equiv.), pyridine (0.2 mL), r.t., 2 h, quant.

The differences observed in the ¹H NMR spectra of the (*S*)- and (*R*)-MTPA esters **163** and **164** confirmed (*S*)-configuration (**Table 3.3-9**).^[133]

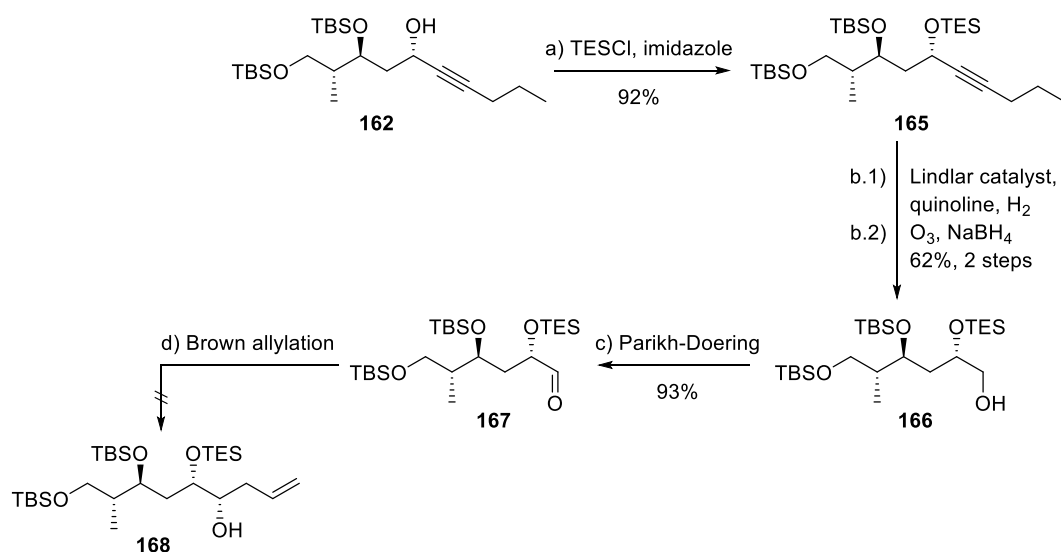
Table 3.3-9. Significant ¹H NMR signals of **163** (*S*-Ester) and **164** (*R*-Ester) and their use in Mosher ester analysis.

Atom	δ_{H} of 163 (<i>S</i> -Ester) [ppm]	δ_{H} of 164 (<i>R</i> -Ester) [ppm]	$\Delta\delta^{SR} = \delta^{S\text{-ester}} - \delta^{R\text{-ester}}$
1	3.48/3.35	3.53/3.43	-0.05/-0.08
2	1.85	1.94-1.90	(-0.09)-(-0.05)
3	0.86	0.90	-0.04
4	3.80-3.70	3.90	(-0.10)-(-0.20)
5	2.04/ 1.85	2.06/ 1.90-1.88	-0.02/ (-0.05)-(-0.03)
6	-	-	-
7	-	-	-
8	-	-	-
9	2.21	2.17	+0.04

10	1.55-1.48	1.49	(+0.06)-(-0.01)
11	1.00-0.93	0.95	(+0.05)-(-0.02)

For flexible functionalization in later stages, alcohol **162** was protected as TES ether (**Scheme 3.3-30**).

In the case of neaumycin B (**1**), this hydroxyl group remains free, whereas in neaumycin A (**3**), it is ultimately converted into a mesaconic acid ester moiety (see **Chapter 2.1**). To ensure compatibility with both pathways, TES was selected as the protecting group, as it can be selectively removed later in the synthesis without affecting the other primary and secondary TBS groups, thus allowing for the introduction of the ester functionality when required. An attempt was also made to use a PMB group instead of the TES group, as it can also be selectively cleaved. However, this approach did not yield promising results.



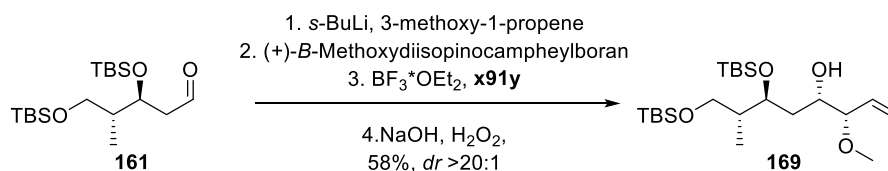
Scheme 3.3-30. Synthesis of aldehyde **167**. Conditions: a) **162** (1.00 equiv.), TESCl, (2.00 equiv.), imidazole (4.00 equiv.), DCM, 0 °C→r.t., 2 h, 92%; b.1) **165** (1.00 equiv.), Lindlar catalyst (Pd-600%), quinoline (0.20 equiv.), H₂ (xs.), hexane, r.t., 16 h, filtered over celite[®], then O₃ (xs.), DCM/MeOH, -78 °C, 30 min, then NaBH₄ (5.00 equiv.), -78 °C→r.t., 2 h, 62%; c) **166** (1.00 equiv.) DIPEA (4.00 equiv.), DMSO (10.0 equiv.), sulfur trioxide pyridine complexe (3.00 equiv.), DCM, 0 °C→r.t., 30 min, 93%.

The TES protection of **162** proceeded with high yield (92%), affording silyl ether **165**. A subsequent Lindlar reduction converted the alkyne to its corresponding alkene, which was subsequently cleaved in an ozonolysis, furnishing primary alcohol **166** in 62% yield over two

steps. Parikh-Doering oxidation of primary alcohol **166** successfully generated aldehyde **167**. Attempts to achieve a direct ozonolysis of alkyne **165** to aldehyde **167** were only in a small scale possible. Unfortunately, the subsequent Brown allylation at aldehyde **167** to allyl **168** also proved unfeasible.

Given the low atom economic efficiency of the Carreira reaction, which involves attaching a pentynyl group only to later remove it through ozonolysis, and the unsuccessful Brown allylation from aldehyde **167** to homoallylic alcohol **168**, the synthetic route required reconsideration. The strategy was therefore revised, returning to aldehyde **161**, the step preceding Carreira's asymmetric addition of alkynes to aldehydes (**Scheme 3.3-28**).

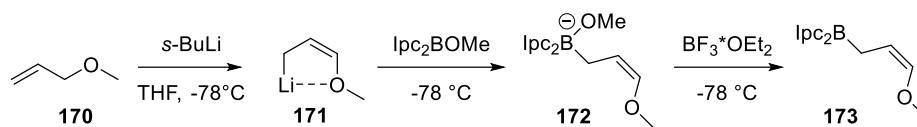
An alternative strategy involved a Brown alkoxyallylation, enabling the direct conversion of aldehyde **161** to alkoxyallyl **169** (**Scheme 3.3-31**).^[144] With a moderate yield of 58%, the reaction exhibited excellent diastereoselectivity (*dr* >20:1). This step introduced two stereocenters and incorporated a methoxy group in a single transformation. Compared to the previous strategy, which required six steps (**Scheme 3.3-30**), this method provided a more concise and efficient route, which significantly streamlined the synthesis.



Scheme 3.3-31. Brown alkoxyallylation of aldehyde **161** to corresponding alkoxyallyl **169**. Conditions: *s*-BuLi (1.30 equiv.), 3-methoxy-1-propene (1.50 equiv.), THF, −78 °C, 10 min, then (+)-*B*-Methoxydiisopinocampheylboran (1.30 equiv.), 30 min, then BF₃·OEt₂ (1.35 equiv.), **161** (1.00 equiv.), 2 h, 58%, *dr* >20:1.

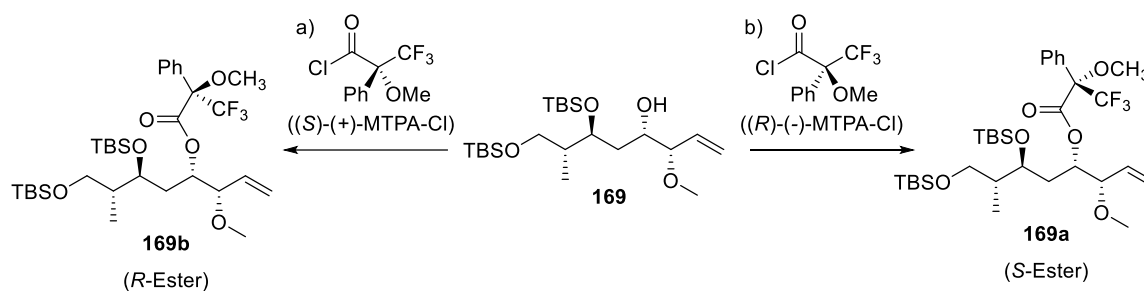
The stereoselectivity of the alcohol, previously described in the Brown crotylation, applies similarly to this reaction (see **Scheme 3.3-14**). In the Brown crotylation, the observed *syn*- or *anti*-selectivity was attributed to the choice of either *cis*- or *trans*-butene as the starting material (see **Scheme 3.3-13**). However, in the alkoxyallylation exclusively the *syn* product is obtained. This can be explained by the deprotonation of 3-methoxy-1-propene (**170**), where coordination of the lithium atom to the oxygen results in the formation of organolithium compound **171** (**Scheme 3.3-32**). This coordination enforces *cis* selectivity in the double bond, stabilizing its conformation and leading to the formation of *cis* compound **172** upon the

addition of Ipc_2BOMe , which is then activated by $\text{BF}_3 \cdot \text{OEt}_2$, yielding **173**. The *syn*-selectivity observed in the alkoxyallylation is now identical to that of the Brown crotylation, as a result of the formation of the *cis*-species **173**.



Scheme 3.3-32. Deprotonation of 3-methoxy-1-propene (**170**) yielded organolithium compound **171**. Subsequent addition of Ipc_2BOMe led to species **172**, which can be activated using $\text{BF}_3 \cdot \text{OEt}_2$ to form active species **173**.

Mosher analysis was performed for absolute stereochemistry elucidation. To achieve this, *S*-MTPA ester **169a** and *R*-MTPA ester **169b** were synthesized from alcohol **169** (Scheme 3.3-33).



Scheme 3.3-33. Synthesis of (*S*)-ester **169a** and (*R*)-ester **169b** for Mosher analysis.^[133] Conditions: a) **169** (1.0 equiv.), (*S*)-(+)-MTPA-Cl (2.0 equiv.), pyridine (0.2 mL), r.t., 2 h, 62%; b) **169** (1.0 equiv.), (*R*)-(-)-MTPA-Cl (2.0 equiv.), pyridine (0.2 mL), r.t., 2 h, 27%.

The differences observed in the ^1H NMR spectra of the (*S*)- and (*R*)-MTPA esters **169a** and **169b** confirmed (*S*)-configuration (Table 3.3-10).^[133]

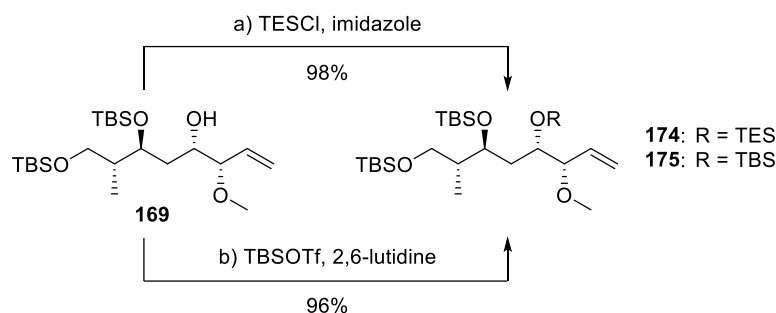
Table 3.3-10. Significant ¹H NMR signals of **169a** (*S*-Ester) and **169b** (*R*-Ester) and their use in Mosher ester analysis.

Atom	δ_H of 169a (<i>S</i> -Ester) [ppm]	δ_H of 169b (<i>R</i> -Ester) [ppm]	$\Delta\delta^{SR} = \delta^{S\text{-ester}} - \delta^{R\text{-ester}}$
1	3.39/ 3.22-3.18	3.48/ 3.37-3.33	-0.09/ (-0.15)-(-0.15)
2	1.75	1.86-1.80	(-0.11)-(-0.05)
3	0.81	0.85-0.83	(-0.04)-(-0.02)
4	3.62-3.59	3.78	(-0.16)-(-0.19)
5	1.70-1.64/ 1.60-1.56	1.73-1.63	(-0.03)-(-0.07)
6	-	-	-
7	3.64-3.62	3.60-3.57	(+0.04)-(+0.05)
8	5.62	5.55-5.48	(+0.07)-(+0.14)
9	5.36-5.33/ 5.28	5.26-5.23/ 5.16	(+0.10)-(+0.10)/ +0.12

The relative *syn*-orientation of the OH and OMe groups was assigned based on the expected simple diastereoselectivity of the *Z*-configured boron reagent **173** (Scheme 3.3-32) and was further supported through coupling constants (Table 3.3-11). By applying the Karplus equation, the coupling constant between H6 and H7 provided insight into the stereochemistry at C7. In the Newman projection along the C6-C7 axis, a *syn*-configuration requires H6 and H7 to be on the same side, which is supported by an observed coupling constant of 7.0 Hz, corresponding to a dihedral angle of approximately 45°.

Conversely, in an *anti*-configuration, where H7 and the methoxy group are swapped, placing H7 in the bottom left position, the H6-H7 dihedral angle is expected to be in the vicinity of 180°, resulting in a coupling constant of approximately 10 Hz, which was not observed.^[140]

Table 3.3-11. Chemical shifts (δ) of alkoxyallyl **169**, 700/176 MHz, CD₂Cl₂, r.t.



Scheme 3.3-34. TES or TBS protection of alcohol **169** to corresponding silyl ether **174** or **175**. Conditions: a) **169** (1.00 equiv.), TESCO (2.00 equiv.), imidazole (2.00 equiv.), DCM, r.t., 30 min, 98%; b) **169** (1.00 equiv.), TBSOTf (2.00 equiv.), 2,6-lutidine (4.00 equiv.), DCM, r.t., 96%.

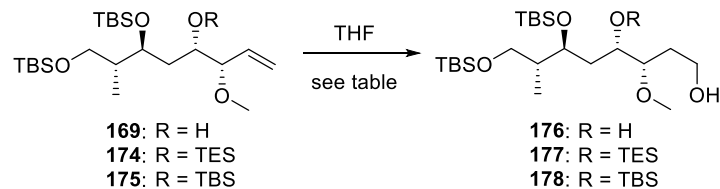
The next step involved C₁-elongation of the methoxyallyl ether to a homoallylic ether. Initial attempts using enol ether Wittig reactions, which required prior ozonolysis to generate the corresponding aldehyde, were unsuccessful. Similarly, efforts to couple MIDA boronates via Grubbs metathesis also failed. As a result, the synthetic strategy was modified. A classical hydroboration followed by oxidation, a subsequent Takai olefination, and the conversion of the primary TBS group into an aldehyde were planned to obtain the target aldehyde **154**.

In consequence, a classical hydroboration approach was explored, aiming to introduce a primary alcohol (**Table 3.3-12**). First approaches used 9-BBN to transform TES-protected silyl ether **174** to alcohol **176** (entry 1). However, no reaction occurred and only the starting material was recovered. Increasing the reagent to 2 equivalents (entry 2) yielded product **177** in low yield (25%), but higher equivalents resulted in even lower yields (entry 3). Alternative hydroboration reagents such as BH₃·THF (entry 4) and BH₃·DMS (entry 5) also failed to produce the desired product **177** in acceptable yields. The poor yields raised the suspicion that the TES protecting group might be cleaved during oxidative workup. For confirmation the reaction was attempted using free alcohol **169**, but only traces of the product **176** were obtained (entry 6). Yields increased to around 30% at 60 °C reaction temperature (entry 7), indicating that the substrate was not the limiting factor, but rather the choice of hydroboration reagent.

Consequently, dicyclohexylborane was generated *in situ* and added to olefin **169**. Usage of a slight excess of dicyclohexylborane (entry 8) showed no conversion and the starting material was fully recovered. Using a larger excess led to a decent yield (60%, entry 9), revealing

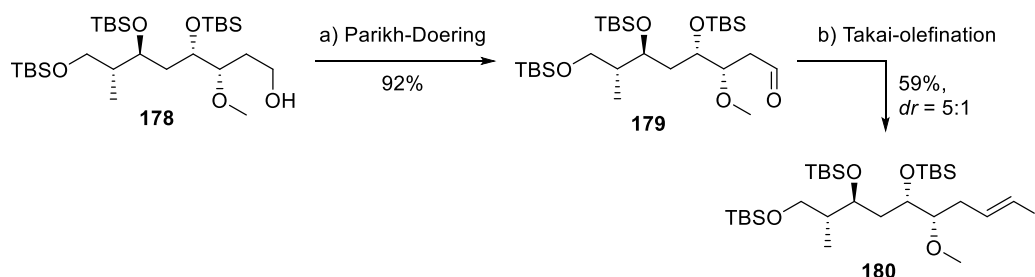
dicyclohexylborane as the preferred reagent. Product **178** was formed in excellent yields (94%), when TBS-protected alcohol **175** was used (entry 10).

Table 3.3-12. Hydroboration of olefins **169**, **174** and **175** to the corresponding primary alcohols **176-178**.



Entry	Substrate	Reagent [equiv.]	Time	Temperature	Ox. Work up	Yield
1	174	9-BBN (1.05)	1 h	r.t.	1 h, r.t.	Substrate recovered
2	174	9-BBN (2.00)	2.5 h	0 °C -> r.t.	1 h, r.t.	177 , 25%
3	174	9-BBN (10.0)	1 h	r.t.	1 h, r.t.	177 , 16%
4	174	BH ₃ *THF (20.0)	1 h	-78 °C -> r.t.	0.5 h, 70 °C	Substrate recovered
5	174	BH ₃ *DMS	1 h	r.t.	1.5 h, 68 °C	177 , 30%
6	169	9-BBN (1.50)	2 h	0 °C -> r.t.	1 h, 70 °C	176 , Traces
7	169	9-BBN (1.20)	20 h	60 °C	1 h, 70 °C	176 , 30%
8	169	HB(Cy) ₂ (1.15)	1 h	0 °C -> r.t.	1 h, r.t.	Substrate recovered
9	169	HB(Cy) ₂ (5.30)	1 h	0 °C -> r.t.	1 h, r.t.	176 , 60%
10	175	HB(Cy) ₂ (5.30)	1 h	0 °C -> r.t.	1 h, 50 °C	178 , 94%

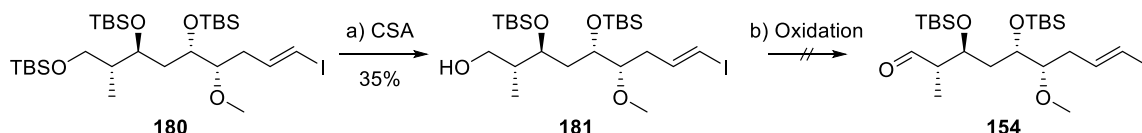
A Parikh-Doering oxidation of primary alcohol **178** furnished aldehyde **179**, which was immediately transformed in a Takai olefination to vinyl iodide **180** in a moderate yield of 59% and a diastereomeric ratio of 5:1 (**Scheme 3.3-35**).



Scheme 3.3-35. Parikh-Doering oxidation of alcohol **178** to aldehyde **179** and an additional Takai-olefination to vinyl iodide **180**. Conditions: a) **178** (1.00 equiv.), DIPEA (2.00 equiv.), DMSO (10.0 equiv.), sulfur trioxide pyridine complex (3.00 equiv.), DCM, 0 °C→r.t., 1 h, 92%, b) **179** (1.00 equiv.), CrCl₂ (6.00 equiv.), iodoform (2.00 equiv.), THF, 0 °C, 16 h, 59%, *dr* = 5:1.

To obtain alcohol **181**, the selective removal of the primary TBS group from vinyl iodide **180** was necessary (**Scheme 3.3-36**). Previous approaches for TBS protection (see **Table 3.3-6**) were implemented. Further oxidation to aldehyde **154** using Parikh-Doering-, IBX-, or DMP-oxidation were unsuccessful.

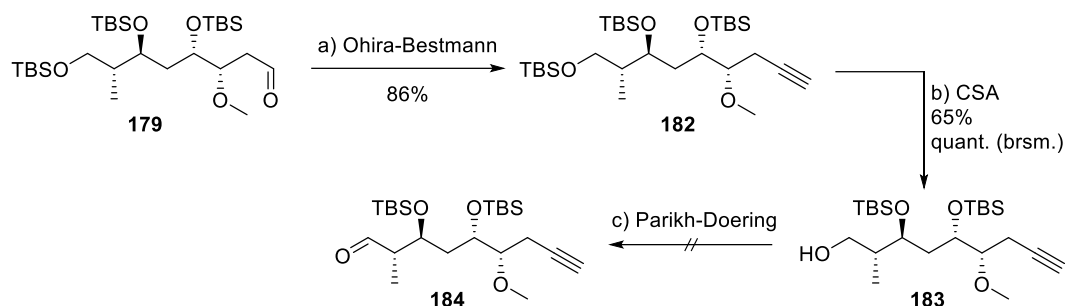
Traces of product **154** were detected in the crude mixture by mass spectrometry, but could not be fully characterized by NMR due to impurity issues. Probably the vinyl iodide moiety might not withstand the subsequent reaction conditions, potentially explaining the failure of oxidation.



Scheme 3.3-36. Primary deprotection of silyl ether **180** to corresponding primary alcohol **181**. Subsequent oxidation to aldehyde **154** was unfortunately not possible. Conditions: a) **180** (1.00 equiv.), CSA (0.50 equiv.), DCM/MeOH, r.t., 1 h, 35%.

Considering the low yield for primary TBS protection and the unsuccessful transformation of alcohol **181** to **154** (**Scheme 3.3-36**), the synthetic approach was modified. Alkynylation of aldehyde **179** to alkyne **182** could later be converted into the corresponding vinyl iodide, preferably after fragment coupling. Hence aldehyde **179** was transformed in an Ohira-Bestmann reaction, yielding alkyne **182** (**Scheme 3.3-37**). Selective deprotection of the primary silyl group afforded alcohol **183** in decent 65% yield (quant. brsm.). Strict reaction

times were crucial, because longer reaction times resulted in multiple deprotection products. Oxidation of the resulting alcohol **183** to aldehyde **184** remained unsuccessful.



Scheme 3.3-37. Ohira-Bestmann alkylation of aldehyde **179** to form alkyne **182**, followed by primary TBS deprotection to yield alcohol **183**. Subsequent oxidation was again unsuccessful. Conditions: a) **179** (1.00 equiv.), dimethyl (1-diazo-2-oxopropyl)phosphonate (2.00 equiv.), K_2CO_3 (2.00 equiv.), MeOH, r.t., 72 h, 86%; b) **182** (1.00 equiv.), CSA (0.10 equiv.), DCM/MeOH, r.t., 2 h, 65%, brsm.: quant.

3.3.4 Synthesis of the Mesaconic Acid Moiety **185**

This chapter presents the investigations into the synthesis of the mesaconic acid moiety **185** (Figure 3.3-5).

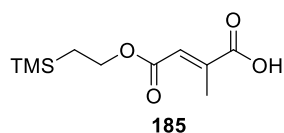
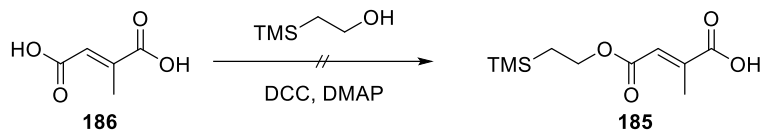


Figure 3.3-5. Target molecule **185**.

Mesaconic acid (**186**) contains two free carboxyl groups, but only the one with the methyl group in the alpha position should be esterified, the other carboxyl group needed to be protected. The global deprotection strategy for the synthesis of neaumycin A (**3**) is based on TBS ether moieties, therefore a silyl-based protecting group would also be feasible for carboxyl group protection. TMSE was selected as it is a commonly used protecting group for carboxylic acids in total synthesis.

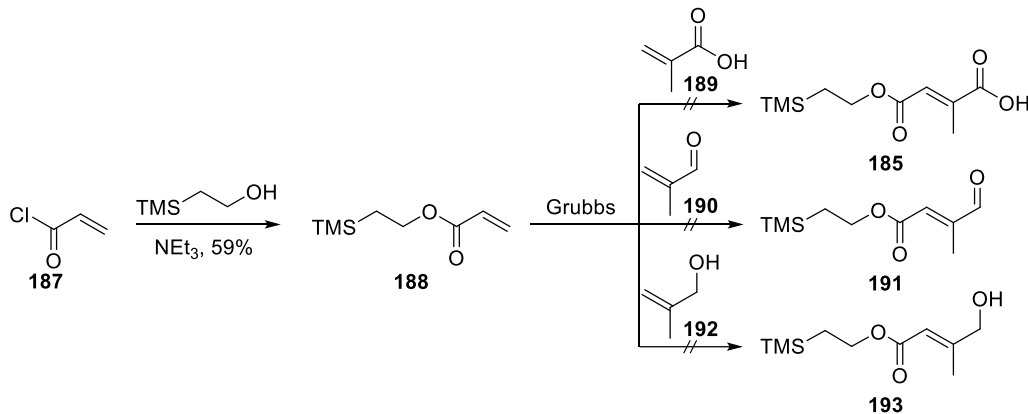
The left-side carboxyl group of mesaconic acid (**186**), lacking a neighboring methyl group with a positive inductive effect, is more acidic than the right-side carboxyl group (Scheme 3.3-38). Therefore, an attempt was made to selectively protect the left carboxyl group with TMSE to get direct the target molecule **185**. However, this approach was unsuccessful, leading to either

a fully protected product or a mixture of mono-protected mesaconic acids. These two species could not be separated.



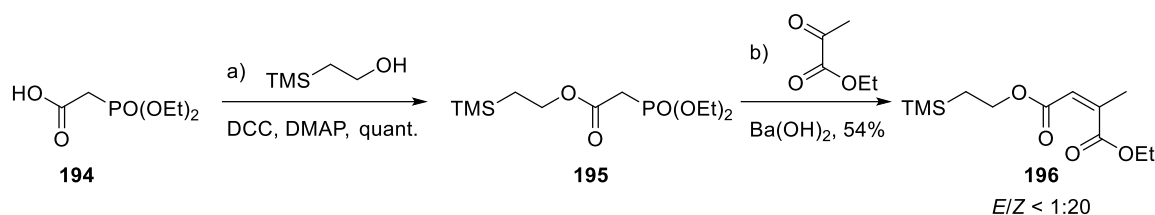
Scheme 3.3-38. Unsuccessful mono TMSE protection of mesaconic acid (**186**).

Since the two mono-protected regioisomers could not be separated, this strategy was abandoned in favor of a synthetic route that would allow selective protection of the left carboxyl group while introducing the right-side carboxyl group at a later stage. The approach involved TMSE-protection of acryloyl chloride (**187**) to TMSE ester **188** (**Scheme 3.3-39**). Grubbs metathesis allows the metathesis to three different products, depending on the substrate: product **185** by usage of methacrylic acid (**189**), aldehyde **191** by usage of methacrylaldehyde (**190**), or alcohol **193** by usage of 2-methylprop-2-en-1-ol (**192**). The two latter products could be oxidized to the corresponding acid (**185**). However, all attempts at the Grubbs metathesis failed.



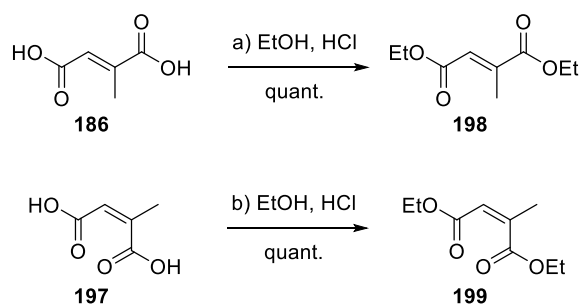
Scheme 3.3-39. TMSE protection of acryloyl chloride (**187**) to olefin **188**. Subsequent Grubbs olefinations were unsuccessful. Conditions: **187** (1.40 equiv.), 2-(trimethylsilyl)ethan-1-ol (1.00 equiv.), NEt₃ (1.50 equiv.), Et₂O, 0 °C→r.t., 15 h, 59%.

In consequence the metathesis approach was abandoned, and a Horner-Wadsworth-Emmons (HWE) reaction was pursued. Phosphonate **194** was first protected with TMSE to yield ester **195**, which was transformed with ethylpyruvate to olefin **196** (**Scheme 3.3-40**). The reaction proceeded with a moderate yield of 54%, but with the wrong diastereoselectivity (revealed later). The non-preferred *Z*-isomer had an *E/Z* ratio of <1:20.



Scheme 3.3-40. TMSE protection of acid **194** to phosphonate **195** with subsequent HWE reaction to olefin **196**. Conditions: a) **194** (1.00 equiv.), 2-(trimethylsilyl)ethan-1-ol (1.40 equiv.), DCC (1.60 equiv.), DMAP (0.15 equiv.), THF, r.t., 14 h, quant.; b) **195** (2.50 equiv.), $\text{Ba}(\text{OH})_2$ (3.00 equiv.), ethyl 2-oxopropanoate (1.00 equiv.), THF/ H_2O , r.t., 3 h, 54%, E/Z : <1:20.

Determining the olefin geometry via ^1H NMR coupling constants was not possible, as the olefinic proton was adjacent to a methyl group rather than another proton. Therefore, mesaconic acid (**186**) and citraconic acid (**197**) were esterified to their respective ethyl esters **198** and **199**, and the chemical shifts of their olefinic protons were analysed (**Scheme 3.3-41**).



Scheme 3.3-41. Esterification of mesaconic acid (**186**) and citraconic acid (**197**) to ethyl ester **198** and **199**. Conditions: a) **186** (1.00 equiv.), HCl (5 drops), EtOH, 100 °C, 1 h, quant.; b) **197** (1.00 equiv.), HCl (5 drops), EtOH, 100 °C, 1 h, quant.

The proton in the *E*-ester **198** appeared at 6.77 ppm, while the *Z*-ester **199** showed a signal at 5.84 ppm (**Figure 3.3-6**). Comparison with the previously synthesized **196**, which exhibited a signal at 5.82 ppm, confirmed that the product formation was indeed *Z*-selective.

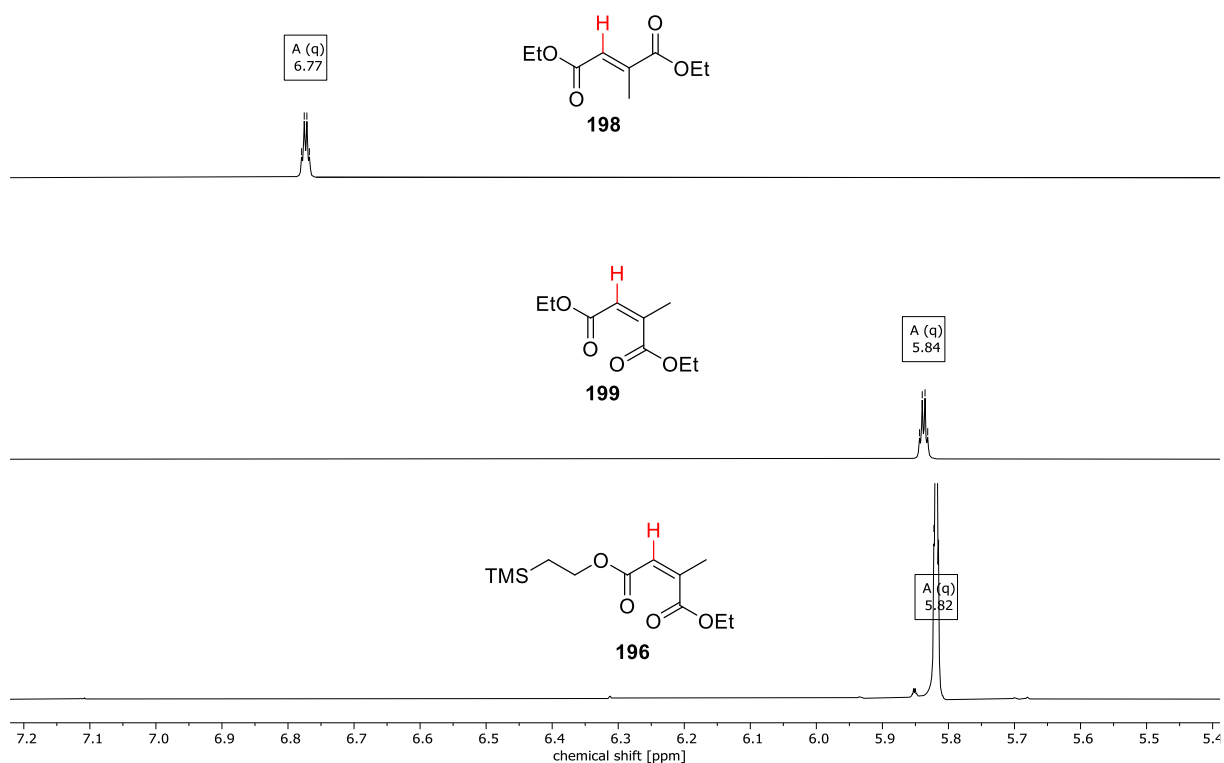
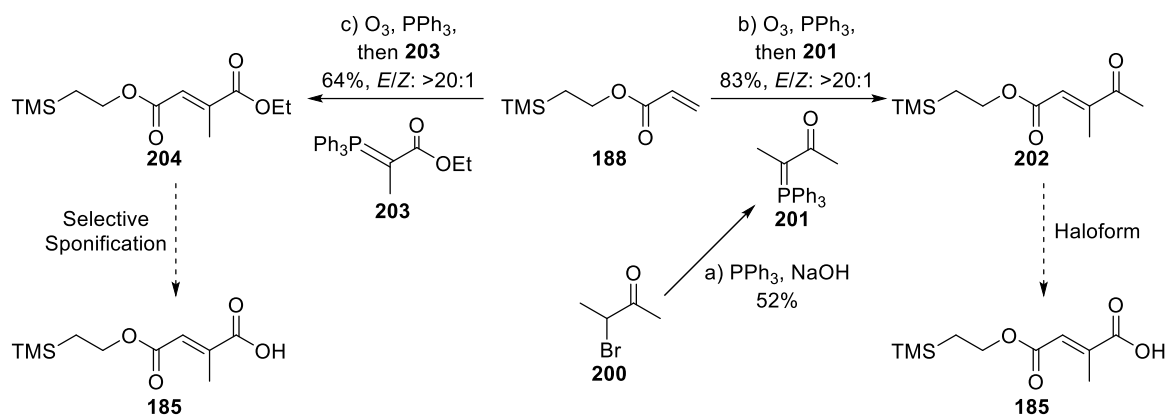


Figure 3.3-6. Comparison of the ¹H-NMR (in CDCl₃) of *E* ethyl ester **198**, *Z* ethyl ester **199** and HWE product **196**.

Since the HWE reaction produced the undesired *Z*-olefin, an alternative olefination method was necessary and a classical Wittig reaction was investigated. Olefin **188** was first oxidized to the corresponding aldehyde via ozonolysis and either the methyl ketone **201** or ester **203** was added subsequently to get methyl keton **202** or ethyl ester **204** (Scheme 3.3-42). The *E*-selectivity was again determined via ¹H NMR chemical shifts, confirming that the Wittig reaction successfully yielded the desired *E*-isomer. Both products can be converted to mesaconic acid **185**. The ethyl ester **204** can be selective saponificated, which required detailed investigations. The methyl ketone **202** can be converted using a classical Haloform reaction. This establishes a synthetic route for the mesaconic acid moiety **185**, a crucial fragment for the total synthesis of neaumycin A (**3**).



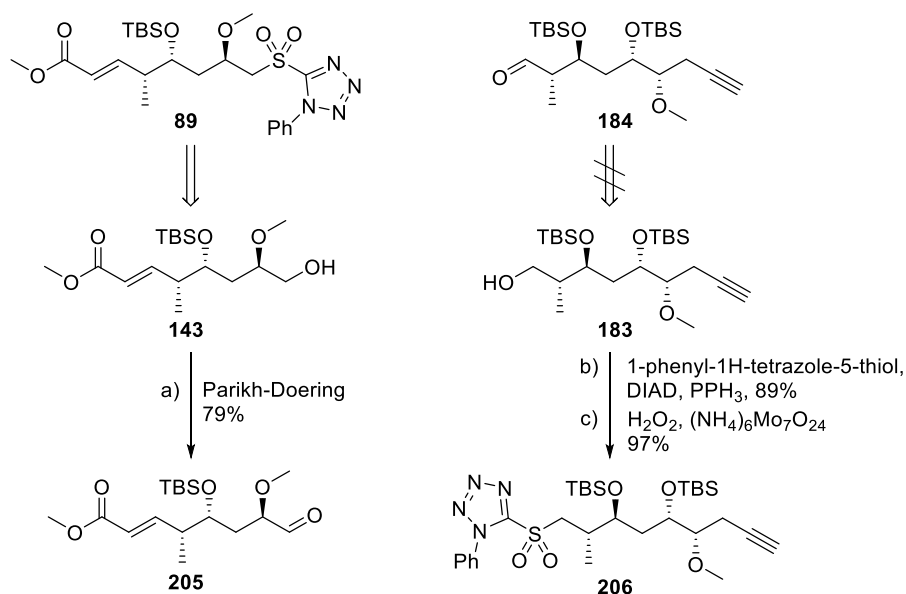
Scheme 3.3-42. Wittig reaction of olefin **188** to corresponding methyl ketone **202** and ethyl ester **204**. Both can further be transformed into acid **185**. Conditions: a) **200** (1.00 equiv.), PPh_3 (1.10 equiv.), toluene, r.t., 72 h, then NaOH (xs.), 1 h, 52%; b) **188** (1.00 equiv.), O_3 (xs.), DCM/MeOH , -78°C , 10 min, then PPh_3 (1.50 equiv.), $-78^\circ\text{C} \rightarrow \text{r.t.}$, 2 h, work up, then **201** (1.50 equiv.), DCM , r.t., 12 h, 83%, *E/Z*: >20:1; c) **188** (1.00 equiv.), O_3 (xs.), DCM/MeOH , -78°C , 15 min, then PPh_3 (1.50 equiv.), $-78^\circ\text{C} \rightarrow \text{r.t.}$, 2 h, work up, then **203** (2.00 equiv.), toluene, 60°C , 14 h, 64%, *E/Z*: >20:1.

3.3.5 Modification of Coupling Fragments and Coupling Process

The desired sulfone **89** was successfully synthesized from alcohol **143**, whereas the conversion of alcohol **183** to aldehyde **184** remained unsuccessful (see **Chapter 3.3.1** and **Chapter 3.3.3**, **Scheme 3.3-43**).

As a result, the synthon polarity of fragments **89** and **184** were interchanged: an aldehyde group was introduced at the western fragment **89**, while the eastern fragment **184** was modified to contain the corresponding sulfone for the Julia-Kocienski reaction.

Therefore, alcohol **143** was subjected to a Parikh-Doering oxidation, furnishing aldehyde **205** in 79% yield. Alcohol **183** was converted analogously using the same conditions as previously applied for sulfone **89**. Sulfone **206** was synthesized in high yields of 86% over two steps.

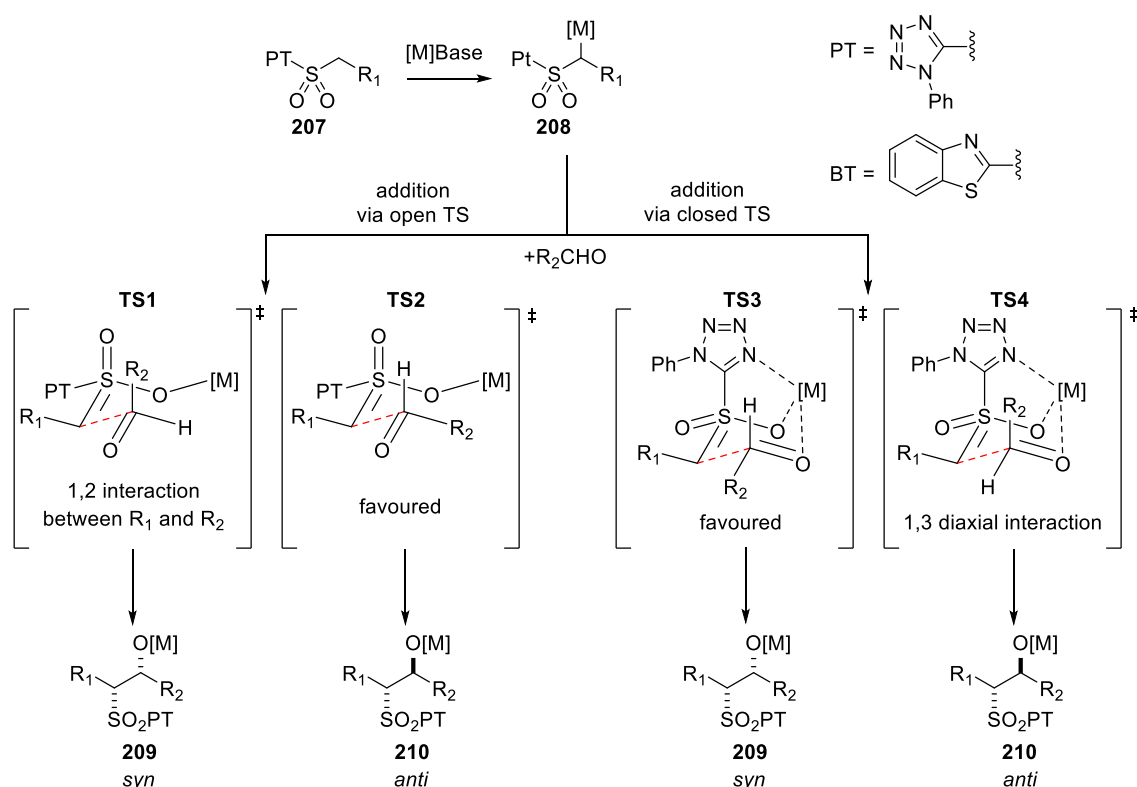


Scheme 3.3-43. Shown are fragments **89** and **184**, initially planned to be synthesized from alcohols **143** and **183**. Instead, aldehyde **205** was obtained from alcohol **143**, while sulfone **206** was derived from alcohol **183**. Conditions: a) **143** (1.00 equiv.), DIPEA (4.00 equiv.), DMSO (10.0 equiv.), sulfur trioxide pyridine complex (3.00 equiv.), DCM, 50 °C, 3 h, 79%; b) **183** (1.00 equiv.), DIAD (2.50 equiv.), PPh₃ (2.50 equiv.), 1-phenyl-1H-tetrazole-5-thiol (1.30 equiv.), THF, 0 °C→r.t., 14 h, 89%; c) product from b (1.00 equiv.), H₂O₂ (xs.), ammonium heptamolybdate (2.00 equiv.), EtOH, 40 °C, 14 h, 97%.

Both fragments **205** and **206**, were utilized in a Julia-Kocienski olefination. To better understand the reaction, a general mechanistic explanation follows. In the first step, sulfone **207** is deprotonated by an organometallic base, generating the organometallic species **208** (**Scheme 3.3-44**). The reaction outcome can be explained by two competing transition states: the open transition state (left) or the closed transition state (right). Furthermore, the addition step is irreversible when using an unstabilized sulfone, as in this case.^[145]

In the open transition state model, the reaction proceeds through either **TS1** or **TS2**. This pathway is favored when a polar solvent and deprotonating reagents with non-coordinating metal ions are utilized.^[146] In this scenario, the sulfone nucleophile attacks the aldehyde from two possible orientations, leading to the formation of either the *syn*-addition product **209** or the *anti*-addition product **210**. The *anti*-product **210** is preferred, as **TS2** avoids 1,2-interaction between R1 of the sulfone and R2 of the aldehyde. In contrast, **TS1** introduces a destabilizing 1,2-interaction of both residues.

The closed transition state is preferred in apolar solvents and with strongly coordinating metal ions such as lithium. Here, the metal cation is chelated by the sulfonic oxygen, and a tetrazolic nitrogen, forming a stabilized intermediate by additional aldehyde coordination. In this case, the competing transition states **TS3** and **TS4** arise. In **TS3**, the aldehyde substituent R_2 is positioned equatorially, whereas in **TS4**, it is axial. **TS3** is preferred because **TS4** experiences both a 1,2-interaction between R_1 and R_2 and a strong 1,3-diaxial interaction between R_2 and the bulky 1-phenyl-1*H*-tetrazol-5-yl (PT) group.^[147] Consequently, the *syn*-addition product **209** is favored when the reaction follows the closed transition state.



Scheme 3.3-44. General addition of an aldehyde to organometallic species **208** through the four possible transition states (**TS1–TS4**), leading to either *syn*- or *anti*-addition products.

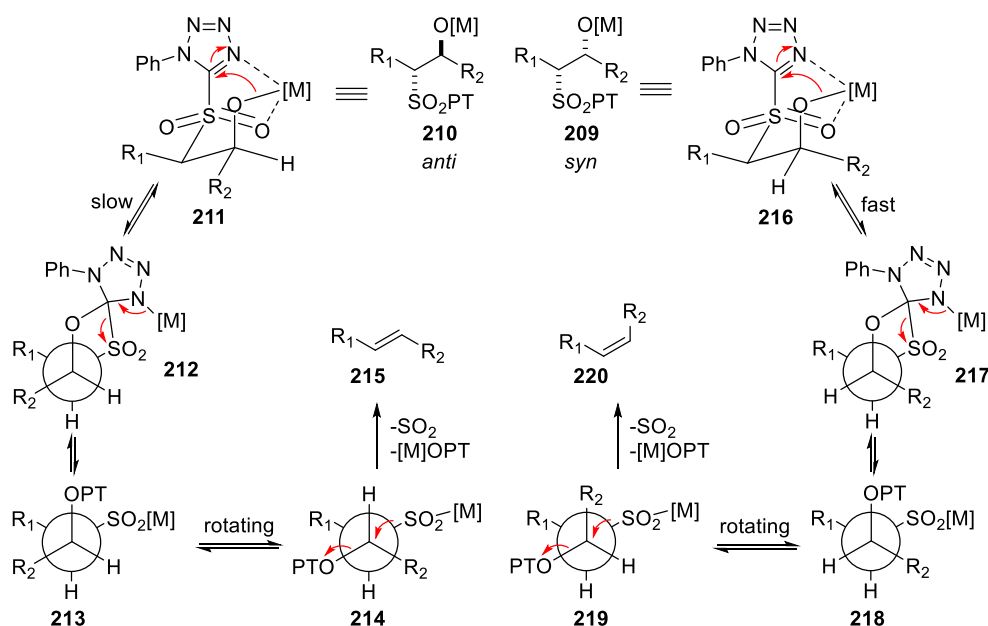
These initial steps are critical, as they control the selectivity of the Julia-Kocienski olefination. The subsequent Smiles rearrangement^[148] and β -elimination steps,^[149] responsible for the formation of the double bond, are both stereospecific.

If the *anti*-addition product **210/211** is formed (left pathway, **Scheme 3.3-45**), it undergoes a Smiles rearrangement, where the oxygen attacks the tetrazole carbon, shifting a π -electron pair onto nitrogen and forming a new five-membered heterocyclic intermediate **212**.^[150] This

step proceeds slowly due to gauche interactions between R1 and R2 in **212**. The lone pair on nitrogen shifts back, breaking the carbon-sulfur bond and forming species **213**, in which the PT group and the metal cation have interchanged positions. This transformation where a sulfone group exchanges its position with an oxygen-bound residue is the defining feature of the Smiles rearrangement.

A subsequent rotation leads to intermediate **214**, where the bulky PT and sulfone groups are positioned opposite each other. The final β -elimination then expels sulfur dioxide and the metallated OPT group, affording the desired *E*-olefin **215**.

The same Smiles rearrangement pathway applies to the *syn*-addition product **209/216**, where R1 and R2 are initially positioned away from each other. Cyclization leads to the heterocyclic species **217**, a step that occurs faster than the *anti*-pathway due to the lack of steric interactions between R1 and R2. A subsequent shift in substituents within **218** follows, where a rotation to **219** aligns R1 and R2 *syn* to each other, ultimately leading to the formation of the *Z*-olefin **220** via β -elimination.

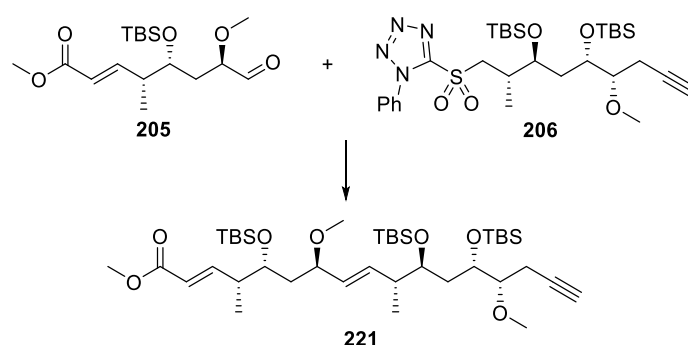


Scheme 3.3-45. Proposed mechanism of the Julia-Kocienski olefination using 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfone.

Experimental evidence has demonstrated that the use of PT sulfones predominantly results in the formation of the *E*-olefin. Assuming that the addition of the aldehyde to the sulfone is irreversible, this outcome likely arises because the reaction proceeds exclusively via the open

transition state (**Scheme 3.3-44**). This preference can be attributed to steric interactions between the phenyl group of the tetrazole and the R1 substituent, which prevent the reaction from proceeding through the closed transition state.^[147] Consequently, the *anti*-addition product **210** is favored. Since both the subsequent Smiles rearrangement and β -elimination are stereospecific, the *anti*-addition product **210** inevitably leads to the formation of the *E*-olefin **215** as the final product.

Table 3.3-13. Julia-Kocienski coupling of aldehyde **205** and **206**.



Entry	205 [equiv.]	206 [equiv.]	1 M NaHMDS in THF	Conditions	Yield	Notes
1	1.50	1.00	1.10	DME -55 °C → r.t. 16 h	0	
2	2.50	1.00	2.00	THF -55 °C → r.t. 72 h	traces	• Reaction with ground molecular sieve
3	1.00	1.20	1.30	DME -78 °C → r.t. 72 h	2% <i>E/Z</i> = 1:10	• Freshly distilled DME • Reaction with ground molecular sieve

With both fragments in hand, sulfone **206** and aldehyde **205** were subjected to the Julia-Kocienski reaction (**Table 3.3-13**). To achieve high *E*-selectivity, a protic solvent and non-coordinating metal cations were preferred, leading to the choice of DME and THF as solvents. NaHMDS was selected as the base, as it offers a suitable balance between selectivity and yield. Although KHMDS is reported to provide higher *E*-selectivity, experimental studies suggest that

it also leads to lower overall yields. Therefore, NaHMDS was chosen as the initial base to optimize the reaction conditions.^[151–153]

In the first attempt, using DME as the solvent and an excess of aldehyde, no product was isolated (entry 1). In the second attempt, the aldehyde excess was further increased, and 2 equivalents of base were used in THF under ground molecular sieve conditions (entry 2). This led to the detection of trace amounts of the desired product **221**, though only observed via MS.

Alternatively, a slight excess of sulfone **206** was used (entry 3). Freshly distilled DME and ground molecular sieves were again employed, yielding a low 2% product yield. Interestingly, analysis of the coupling constant of the olefinic protons ($^3J = 11.3$ Hz) revealed a preference for the *Z*-isomer over the expected *E*-isomer, with an observed *E/Z* ratio of 1:10.

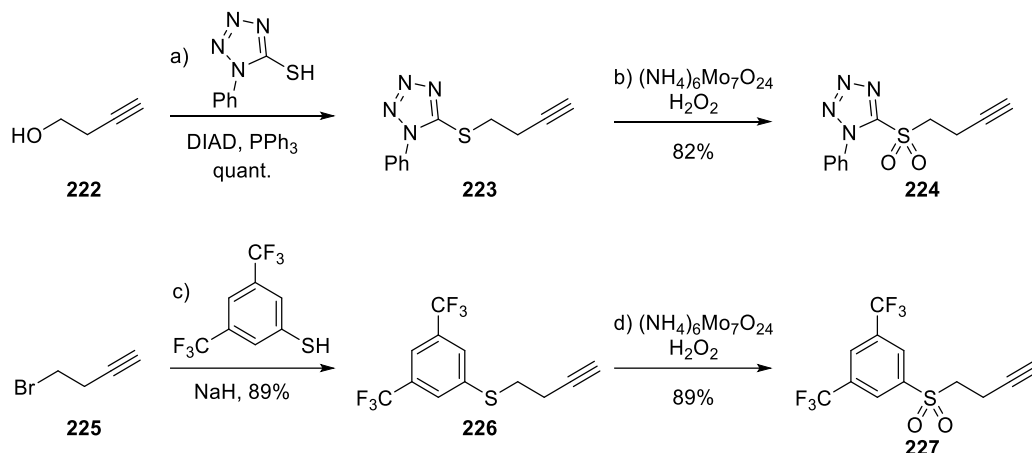
To ensure that the effort of resynthesizing aldehyde **205** and sulfone **206** for further Julia-Kocienski coupling investigation was worthwhile, test systems were first developed to optimize the Julia-Kocienski olefination. If these model reactions proved successful, the full synthesis of both fragments could proceed with confidence.

The test systems were designed to be quickly accessible, minimizing the time investment in their synthesis while still accurately representing the key functional groups of the original fragments. In particular, the sulfone **206** included an alkyne moiety, as alkynes could potentially be deprotonated under the strongly basic conditions of the Julia-Kocienski reaction, leading to unexpected side reactions.

As part of this study, two sulfone test systems, **224** and **227**, were synthesized (**Scheme 3.3-46**). The variation in the sulfone substituents allowed investigation into whether the sulfone moiety itself played a critical role in the Julia-Kocienski olefination.

For sulfone **224**, synthesis started from but-3-yn-1-ol (**222**), which underwent a Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol to afford thioether **223** in quantitative yield. Subsequent oxidation using ammonium heptamolybdate and hydrogen peroxide yielded sulfone **224** with a decent yield of 82%.

Sulfone **227** was synthesized from bromide **225** via a classical S_N2 reaction, affording **226** in 89% yield. Analogous oxidation as previously mentioned gave sulfone **227** in an equally high yield of 89%.



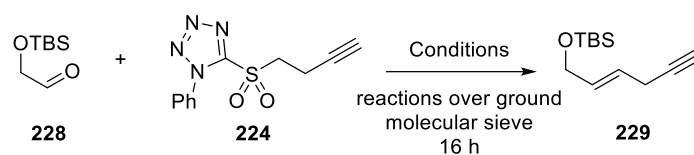
Scheme 3.3-46. Synthesis of test fragment **224** and **227**. Conditions: a) **222** (1.00 equiv.), DIAD (1.25 equiv.), PPh₃ (1.25 equiv.), 1-phenyl-1*H*-tetrazole-5-thiol (1.10 equiv.), THF, 0 °C→r.t., 14 h, quant.; b) **223** (1.00 equiv.), H₂O₂ (xs.), ammonium heptamolybdate (2.00 equiv.), EtOH, 50 °C, 16 h, 82%; c) **225** (1.20 equiv.), 3,5-bis(trifluoromethyl)benzenethiol (1.00 equiv.), NaH (2.00 equiv.), H₃CCN, r.t., 72 h, 89%; d) **226** (1.00 equiv.), H₂O₂ (xs.), ammonium heptamolybdate (2.00 equiv.), EtOH, 60 °C, 72 h, 89%.

For aldehyde **205**, it was suspected that the methoxy group in α -position might sterically hinder the reaction. To investigate this, commercially available 2-((*tert*-butyldimethylsilyl)oxy)acetaldehyde (**228**) was selected as an test system, as it also features a sterically demanding group at the α -position.

Initial trials using THF as the solvent and NaHMDS mediated deprotonation showed first promising results, yielding 22% of the product **229** with an *E/Z* ratio of 5:1, albeit only when using one equivalent of the base (entries 1-2, **Table 3.3-14**). When LHMDS was employed, an even higher *E*-selectivity of 6:1 was observed when DMPU was used as additive (entries 3-4). Interestingly, this improved *E*-selectivity contrasts with the general trend observed in the Julia-Kocienski olefination, where smaller coordinating cations typically favor higher *Z*-selectivity.^[153]

3 Results and Discussion

Table 3.3-14. Julia-Kocienski olefination with test fragments **228** and **224**.



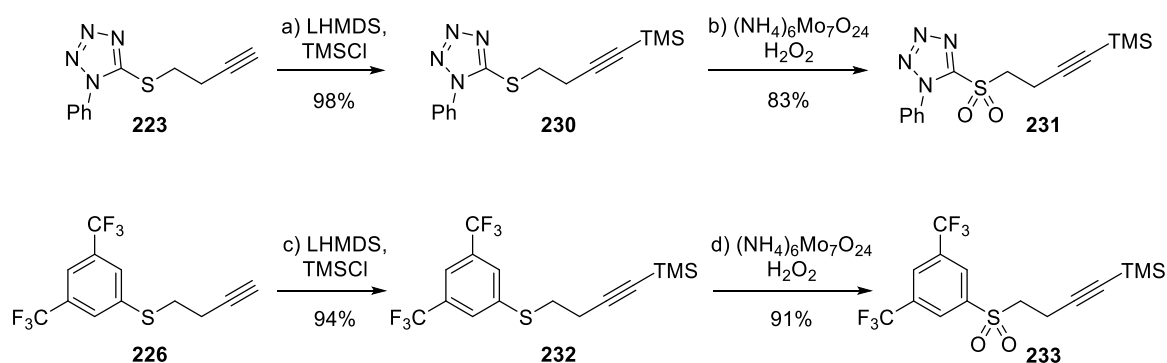
Entry	Solvent	Base	Base [equiv.]	Additive [equiv.]	Temperature [°C]	Yield	E/Z
1	THF	NaHMDS 1 M in THF	1.00		-78 -> r.t.	22%	5:1
2	THF	NaHMDS 1 M in THF	2.00		-78 -> r.t.	0%	-
3	THF	LHMDS 1 M in THF	1.00		-78 -> r.t.	0%	-
4	THF	LHMDS 1 M in THF	1.00	DMPU (xs.)	-78 -> r.t.	13%	6:1
5	THF	KOtBU	1.00		-78 -> r.t.	32%	5:1
6	THF	KOtBU	2.00		r.t.	traces	-
7	THF	NaH	1.00		-78 -> r.t.	40%	3:1
8	THF	KHMDS solid	1.00	LiCl (2.00)	-78 -> r.t.	40%	5:1
9	THF	Cs ₂ CO ₃	1.00		80	44%	3:1
10	DCM	Cs ₂ CO ₃	1.00		r.t.	18%	3:1
11	DME	NaHMDS 1 M in THF	1.00		-60 -> r.t.	27%	3:1
12	DME	NaHMDS 1 M in THF	1.00	TBSOTf (1.00)	-60 -> r.t.	25%	3:1
13	DME	NaHMDS 1 M in THF	2.00	TBSOTf (2.00)	-60 -> r.t.	25%	3:1
14	DMF	NaHMDS 1 M in THF	1.00		-50 -> r.t.	0%	-
15	DMF	NaHMDS 1 M in THF	1.00	DMPU (xs.)	-50 -> r.t.	0%	-
16	DMF	NaHMDS 1 M in THF	1.00	DMPU (xs.)	-50 -> r.t.	0%	-
17	DMF	KOtBU	1.00		-50 -> r.t.	traces	-

KOtBu as base improved the yield to 32%, but only at low temperatures (entries 5-6). Higher yields up to 40% were obtained with either NaH or KHMDS, with the latter requiring LiCl as additive (entries 7-8). A slight further increase to 44% was achieved using Cs₂CO₃ at elevated reaction temperatures (80 °C) in THF (entry 9). When the reaction was performed in DCM at room temperature, the yield dropped significantly to 18% (entry 10). Attempts using DME as

the solvent and NaHMDS as the base showed little variation, with yields ranging between 25% and 27% regardless of whether one or two equivalents of base were used (entries 11-13). When DMF was used as the solvent, no product formation was observed, regardless of whether NaHMDS or KO^tBu was employed as the base, and irrespective of the presence of DMPU as an additive (entries 14-17).

With the testing system sulfone **227**, no product were obtained in the Julia-Kocienski reaction, when using NaHMDS, the phosphazene base P₂-Et, or additional DMPU, as suggested in the literature.^[154]

The test systems indicated a general trend, assuming that milder bases provided the best yields (entry 9, **Table 3.3-14**). However, none of the tested conditions led to acceptable yields. It was suspected that the alkyne moiety might undergo deprotonation, leading to undesired side reactions. To prevent this assumption, both test fragments were TMS-protected at the alkyne functionality.



Scheme 3.3-47. TMS protection of alkynes **223** and **226** with subsequently oxidation to sulfone **231** and **233**. Conditions: a) **223** (1.00 equiv.), LHMDS (1.20 equiv.), TMSCl (1.40 equiv.), Et₂O, -78 °C→r.t., 1 h, 98%, b) **230** (1.00 equiv.), H₂O₂ (xs.), ammonium heptamolybdate (0.20 equiv.), EtOH, 50 °C, 16 h, 83%; c) **226** (1.00 equiv.), LHMDS (1.20 equiv.), TMSCl (1.40 equiv.), Et₂O, -78 °C→r.t., 14 h, 94%, d) **232** (1.00 equiv.), H₂O₂ (xs.), ammonium heptamolybdate (0.20 equiv.), EtOH, 60 °C, 72 h, 91%.

Accordingly, thioether **223** was TMS-protected to afford **230**, followed by oxidation to sulfone **231** (**Scheme 3.3-47**). Similarly, thioether **226** was converted to **232** via TMS protection and subsequently oxidized to the corresponding sulfone **233**.

TMS-protected alkyne **231** was reevaluated with aldehyde **228** in the Julia-Kocienski olefination (**Table 3.3-15**). Initial investigations immediately demonstrated formation of

product **234** in a significantly higher yield of 54%. (entry 1). Compared to the unprotected alkyne, which had previously provided only 22% yield under identical conditions (entry 1, **Table 3.3-14**), this represents an increase of 32%. Attempts to further improve the results using Cs_2CO_3 , which had previously shown the most promising outcomes, did not lead to any enhancements (entries 2-3). A notably higher yield was achieved with KHMDS, which also improved the *E/Z* selectivity from 3:1 to 5:1, although the addition of LiCl did not have any noticeable effect (entries 4-5). These promising results suggested that the optimized conditions could now be applied to the actual synthetic fragments.

Table 3.3-15. Julia-Kocienski olefination with test fragments **228** and **231**.

Entry	Base	Base [equiv.]	Additive [equiv.]	Conditions [°C]	Yield [%]	<i>E/Z</i>
1	NaHMDS 1 M in THF	1.00		-78 -> r.t.	54	3:1
2	Cs_2CO_3	1.00		80	43	3:1
3	Cs_2CO_3	2.00		80	39	3:1
4	KHMDS solid	1.00		-78 -> r.t.	71	5:1
5	KHMDS solid	1.00	LiCl (4.00)	-78 -> r.t.	69	5:1

As previously observed, the Julia-Kocienski olefination with sulfone **227** failed when employing the phosphazene base $\text{P}_2\text{-Et}$.^[154]

3.4 Structure Revision

During this work, two total syntheses of neaumycin B (**1**) were published: one by Smith *et al.* and another by Chen *et al.*^[12,13] The NMR spectra of the synthetic neaumycin B (**1**) obtained by both research groups were nearly identical, with deviations only in the 0.01 ppm range. However, the NMR spectrum of synthetic neaumycin B (**1**) did not match that of the isolated natural product (**Figure 3.4-1**).

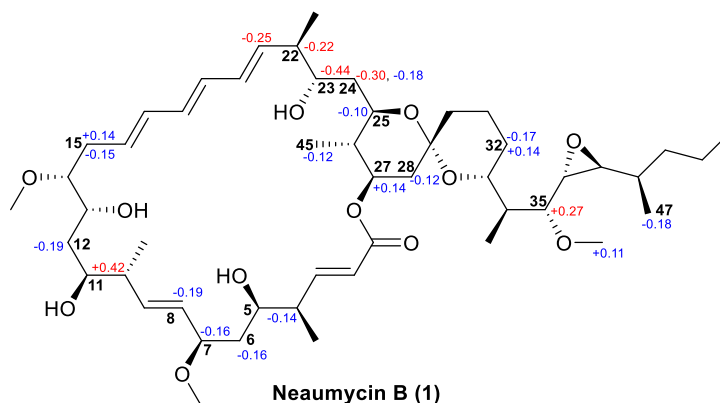


Figure 3.4-1. ^1H NMR comparison of synthetic neaumycin B (**1**) by Chen *et al.* with natural neaumycin B (**1**).

As illustrated in **Figure 3.4-1**, significant discrepancies (marked in red) were observed at positions 11, 21-24, and 35 in the ^1H NMR spectrum when compared to the isolated neaumycin B (**1**). Additionally, several other notable differences, marked in blue, further indicated that the previously proposed structure by Fenical *et al.*^[11] was likely incorrect.

To resolve this discrepancy, a structural revision was carried out in collaboration with Prof. N. Ziemert from the University of Tübingen. This revision was guided by bioinformatic predictions, incorporating an antiSMASH^[155] analysis alongside Kalesses profile hidden Markov model prediction.^[156] The results were remarkable: as shown in **Figure 3.4-2**, the stereocenters predicted by Fenical *et al.* using bioinformatic tools were in agreement with the predictions made by Ziemert *et al.* (marked in green). However, all stereocenters previously assigned by NMR analysis were found to be inverted (marked in red).

Furthermore, Ziemert *et al.* predicted the presence of a methyl group at C12, which was not observed in the NMR data reported by Fenical *et al.*, suggesting that this methyl group is likely absent in the actual structure of neaumycin B.

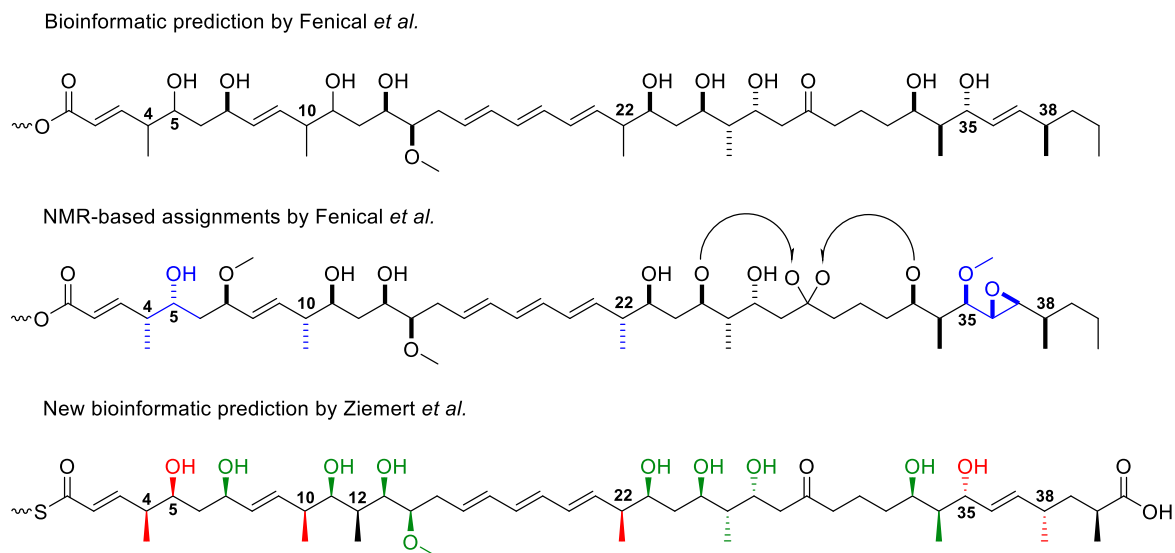


Figure 3.4-2. Bioinformatic prediction and NMR-bases assignments by Fenical *et al.* and new bioinformatics prediction by Ziemert *et al.*

It is likely that the stereocenters at positions with significant NMR deviations are incorrectly assigned. Nevertheless, this assumption should be approached with caution. Neaumycin B is a highly complex and conformationally flexible molecule that does not adopt a planar structure. Instead, its folded conformation means that not only directly adjacent groups influence NMR shifts but also more distant interactions can contribute to spectral deviations.

Still, largest NMR discrepancies are found precisely at positions 4, 5, 10, 22, 35, and 38, where the bioinformatic analysis also predicts the opposite stereochemistry. This observation strongly supports the reliability of this computational approach. Ultimate confirmation requires the total synthesis of the revised structure, followed by a direct comparison of its NMR data with natural neaumycin B.

3.5 Revision of the Retrosynthetic Analysis

The revised structure of neaumycin B (**235**) is shown in **Figure 3.5-1**. Modified stereocenters are highlighted in red. Initially the newly assigned stereocenters were transferred into the previously established synthetic route, as described in **Chapter 3.3.1**. This approach quickly encountered obstacles for the setting of the stereocenters at the positions 4 and 5. The reaction yielded an insufficient diastereoselectivity of 3:1. Alternative approaches, such as a Leighton crotylation, also failed to deliver improved selectivity.^[157]

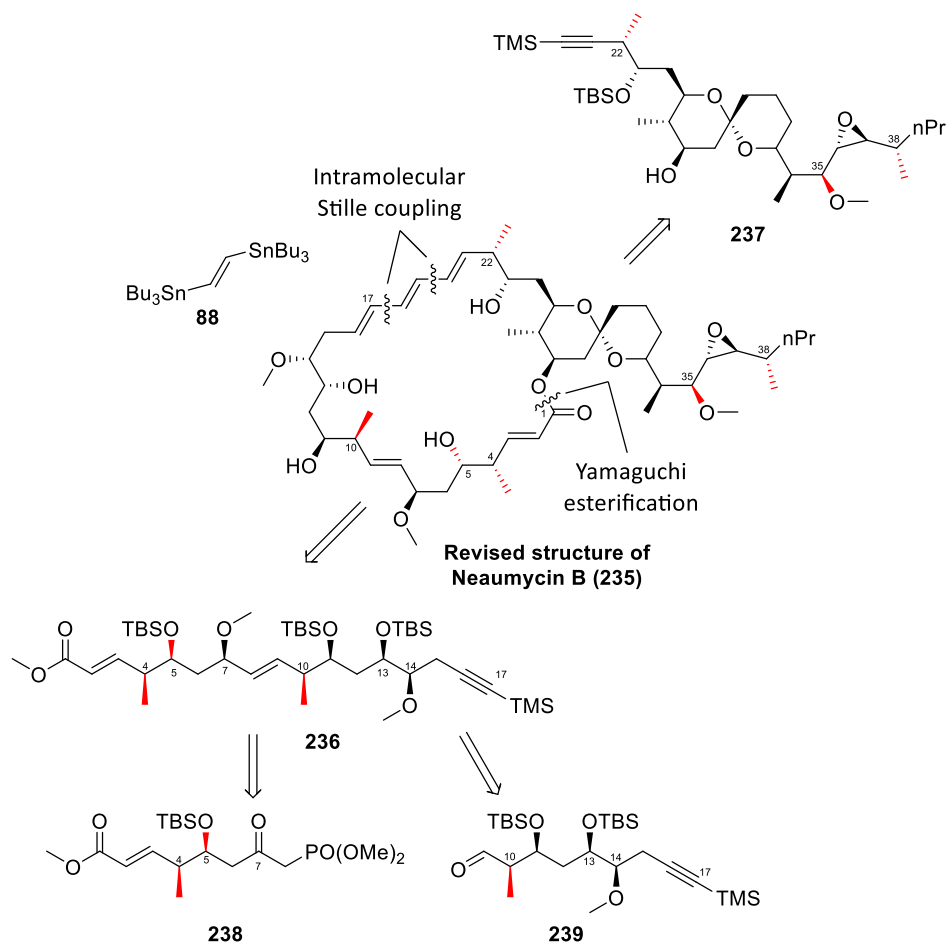


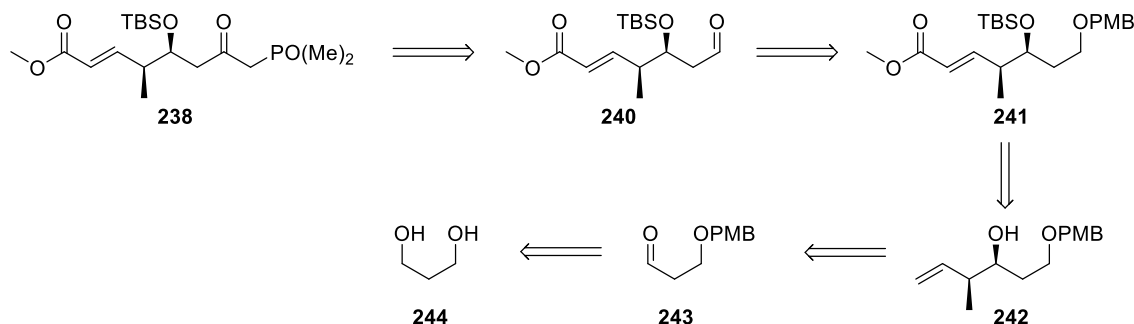
Figure 3.5-1. Revised structure of neaumycin B (**235**) with an adjusted retrosynthetic approach.

Due to these inadequate results and the hampering Julia-Kocienski olefination (see **Chapter 3.3.5**), the retrosynthetic strategy was revised. The southern fragment **236** were now designed to be coupled via a classical Horner-Wadsworth-Emmons (HWE) reaction of phosphonate **238** and aldehyde **239**, followed by a CBS reduction and methylation of the C7 alcohol.

To enable this approach phosphonate **238** was designed with a ketone function at C7-position ensures the formation of a phosphonate-stabilized carbanion.

The modified eastern fragment **239** was designed to contain the aldehyde moiety. Aligning the revised structure, the synthesis had to start from the corresponding alternative Roche ester to achieve the inversion of the methyl group at C10. Additionally, the alkyne was now planned to be TMS-protected, as previous experiments showed improved yields under the basic conditions of the Julia-Kocienski reaction (see **Table 3.3-15**). While the current approach

no longer involves a Julia-Kocienski olefination, the same bases are used in the HWE reaction, making it a reasonable choice to protect the alkyne.



Scheme 3.5-1. Retrosynthetic analysis of phosphonate **238** revealed the starting material propane-1,3-diol (**244**).

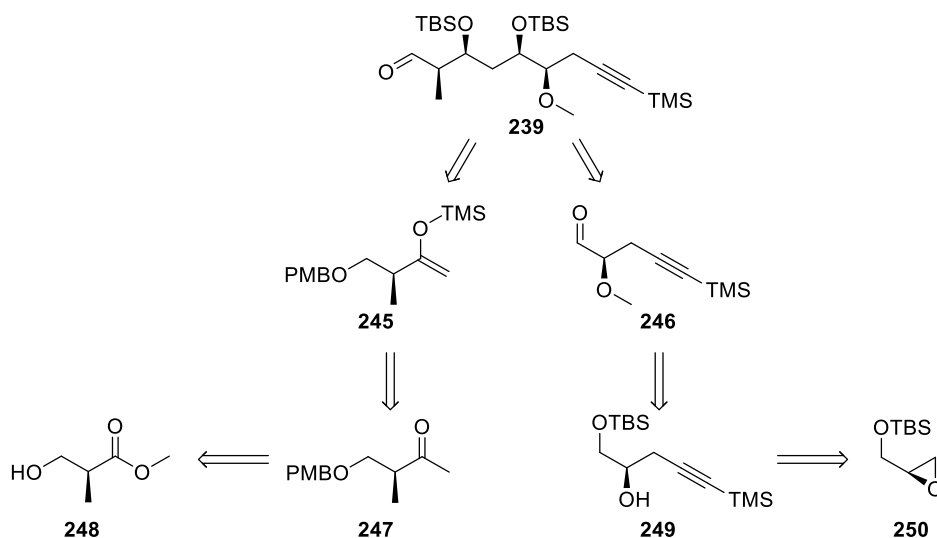
The retrosynthesis of phosphonate **238** starts from commercially available diol **244** (**Scheme 3.5-1**). The key steps involve a nucleophilic attack of deprotonated dimethyl methylphosphonate on aldehyde **240**, followed by oxidation of the resulting secondary alcohol back to the ketone to yield phosphonate **238**. Aldehyde **240** is derived from the primary PMB-protected alcohol **241**, which undergoes deprotection and subsequent oxidation to form the aldehyde **240**.

PMB ether **241** is synthesized from alcohol **242**, which is first TBS-protected and then subjected to a Grubbs metathesis with methyl acrylate to furnish **241**. Homoallylic alcohol **242** itself is obtained from aldehyde **243** through a Brown crotylation, establishing the two stereocenters. Finally, aldehyde **243** is prepared from commercially available propane-1,3-diol (**244**) by selective PMB protection of one hydroxyl group, followed by Parikh-Doering oxidation of the other hydroxyl to generate the aldehyde **243**.

The previous synthesis of the eastern fragment **154** followed a highly linear approach, which, despite overcoming multiple challenges, resulted in a reduced overall yield (see **Chapter 3.3.3**). To address this, an alternative route was developed as part of a master's thesis by Niclas Gaida. This new strategy aimed to construct aldehyde **239** via a Mukaiyama aldol reaction between enol ether **245** and aldehyde **246** (**Scheme 3.5-2**).^[158]

Following the aldol reaction, the resulting aldol product would require primary PMB deprotection, followed by oxidation of the emerging alcohol to furnish aldehyde **239**. Enol ether **245** is to be synthesized from (*S*)-Roche ester (**248**) by first protecting the primary

alcohol of **248** with PMB, converting the ester into a Weinreb amide, and subsequently reducing it to methyl ketone **247** which then can be transformed into silyl enol ether **245**.



Scheme 3.5-2. Retrosynthetic analysis of aldehyde **239** revealed epoxide **250** and (*S*)-Roche ester (**248**) as starting materials.

Aldehyde **246** is derived from commercially available epoxide **250**, where nucleophilic opening with deprotonated ethynyltrimethylsilane provides alkyne **249**. Methylation, followed by selective deprotection of the primary TBS-protected alcohol and subsequent oxidation, yields aldehyde **246**.

This revised route introduces greater flexibility in the synthesis of neaumycin B (**235**) while reducing linear synthetic steps through the fragmentation of aldehyde **239** into enol ether **245** and aldehyde **246**. Such an approach is crucial for improving efficiency in the total synthesis of a complex molecule like neaumycin B (**235**).

3.6 Implementation of the Revised Retrosynthetic Analysis

3.6.1 Synthesis of Phosphonate **238**

This chapter describes the synthesis of phosphonate **238** (Figure 3.6-1), which will later be utilized in a Horner-Wadsworth-Emmons (HWE) reaction with the corresponding aldehyde to form the desired *E*-olefin.

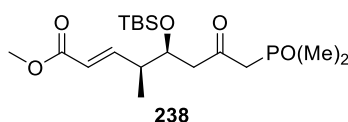
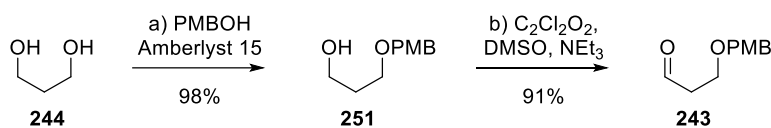


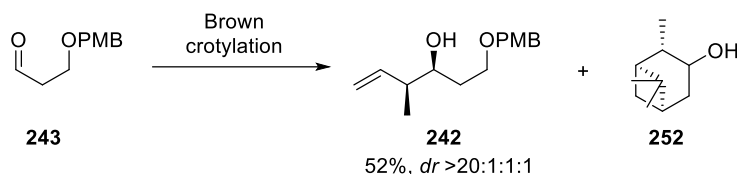
Figure 3.6-1. Target molecule **238** which is going to be synthesised in this chapter.

The synthesis begins with commercially available and low-priced propane-1,3-diol (**244**), which is selectively mono-protected as PMB ether **251** using 4-methoxybenzyl alcohol and Amberlyst[®] 15 hydrogen form as acidic catalyst, yielding 98% (Scheme 3.6-1). The remaining hydroxyl group is then oxidized to aldehyde **243** via a classical Swern oxidation.



Scheme 3.6-1. PMB protection of diol **244** to PMB ether **251** with subsequent oxidation to aldehyde **243**. Conditions: a) **244** (1.50 equiv.), 4-methoxybenzyl alcohol (1.00 equiv.), Amberlyst[®] 15 hydrogen form (10% w/w), 45 °C, 96 h, 98%, b) oxalyl chloride (1.20 equiv.), DMSO (2.60 equiv.), DCM, -78 °C, 30 min, then **251** (1.00 equiv.), 45 min, then NEt₃ (5.00 equiv.), -78 °C→r.t., 30 min, 91%.

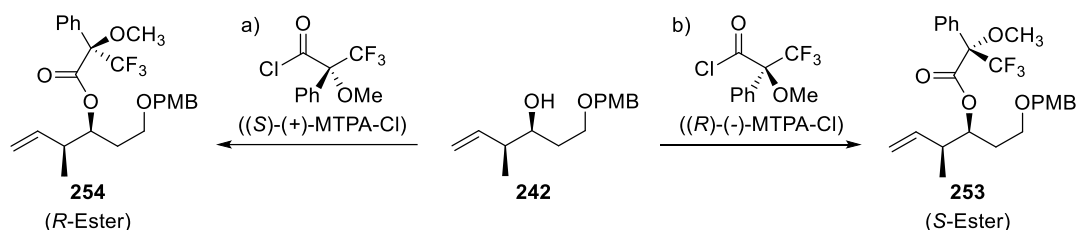
Aldehyde **243** is transformed in a Brown crotylation, analogously as described in Chapter 3.3.1, introducing two stereogenic centers simultaneously (Scheme 3.6-2). The resulting homoallylic alcohol **242** is obtained with moderate yields up to 52%, on a decagram scale with remarkable diastereoselectivity (*dr* >20:1). This high selectivity makes the transformation particularly valuable.



Scheme 3.6-2: Brown crotylation of aldehyde **243** to corresponding alcohol **242**. Conditions: (Z)-Buten (**127**, 5.00 equiv.), KOtBu (1.30 equiv.), *n*-BuLi (1.30 equiv.) THF, $-40\text{ }^{\circ}\text{C}$, 15 min then (+)-*B*-Methoxydiisopinocampheylboran (1.30 equiv.), $-78\text{ }^{\circ}\text{C}$, 60 min then $\text{BF}_3\cdot\text{Et}_2\text{O}$ (1.35 equiv.), **243** (1.00 equiv.), $-78\text{ }^{\circ}\text{C}$, 2.5 h then NaOH (xs.), H_2O_2 (xs.), $70\text{ }^{\circ}\text{C}$, 14 h, 52%, $dr > 20:1:1:1$.

Due to the large reaction scale, some contamination with pinene alcohol **252** was observed. However, this impurity was removed in the following step, making its presence inconsequential at this stage.

Stereochemistry was confirmed by Mosher analysis. Alcohol **242** was converted into the corresponding *R*-MTPA ester **254** and *S*-MTPA ester **253** (Scheme 3.6-3).



Scheme 3.6-3. Synthesis of (*S*)-ester **253** and (*R*)-ester **254** for Mosher analysis.^[133] Conditions: a) **242** (1.0 equiv.), (*S*)-(+)-MTPA-Cl (2.0 equiv.), pyridine (0.2 mL), r.t., 2 h, 17%; b) **242** (1.0 equiv.), (*R*)-(-)-MTPA-Cl (2.0 equiv.), pyridine (0.2 mL), r.t., 2 h, 41%.

The differences observed in the ^1H NMR spectra of the (*S*)- and (*R*)-MTPA esters **253** and **254** confirmed (*S*)-configuration (Table 3.6-1).^[133]

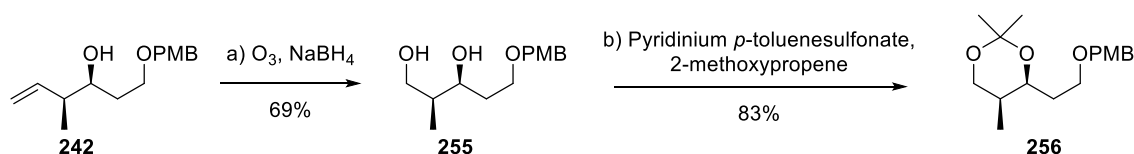
Table 3.6-1. Significant ^1H NMR signals of **253** (*S*-Ester) and **254** (*R*-Ester) and their use in Mosher ester analysis.

Atom	δ_{H} of 253 (<i>S</i> -Ester) [ppm]	δ_{H} of 254 (<i>R</i> -Ester) [ppm]	$\Delta\delta^{SR} = \delta^{S\text{-ester}} - \delta^{R\text{-ester}}$
1	5.11-5.05	5.01-4.90	(+0.10)-(+0.15)
2	5.82	5.66	+0.16
3	2.57	2.50	+0.07

4	1.05	0.97	+0.07
5			
6	1.90	1.95	-0.05
	1.81	1.87	-0.06
7	3.35, 3.27	3.47-3.37	(-0.12)-(-0.10)

After determining the stereochemical configuration of the alcohol of **242**, the configuration of the methyl group also needed confirmation, following the same approach as described in **Chapter 3.3.1** (see **Figure 3.3-2**).

For this, the vinylic moiety of alcohol **242** was first cleaved via ozonolysis, yielding alcohol **255** (**Scheme 3.6-4**). The resulting 1,3-diol **255** was then converted into the corresponding acetonide **256**, allowing the *syn*-selectivity to be verified through coupling constant analysis.



Scheme 3.6-4. Synthesis of acetonide **256** to verify the stereo configuration of the methyl group. Conditions: a) **242** (1.00 equiv.), O_3 (xs.), DCM/MeOH, $-78\text{ }^\circ\text{C}$, 1 min, then NaBH_4 (5.00 equiv.), $-78\text{ }^\circ\text{C} \rightarrow \text{r.t.}$, 2 h, 69%; b) **255** (1.00 equiv.), pyridinium *p*-toluenesulfonate (0.10 equiv.), 2-methoxypropene (2.00 equiv.), DCM, r.t., 16 h, 83%.

The chair conformation of compound **242** was confirmed by the chemical shift of the ketal carbon in the ^{13}C NMR spectrum, which appeared below 100 ppm (**Figure 3.6-2**). The *syn*-selectivity of the alcohol and methyl group was verified by analyzing the coupling constant between $\text{H}_{3\text{ax}}$ and $\text{H}_{4\text{eq}}$, which was measured at 2.7 Hz. This value is indicative of a $^3J_{\text{ax,eq}}$ or $^3J_{\text{eq,eq}}$ interaction between the hydrogen atoms. A higher coupling constant, in the range of 9–14 Hz, would suggest that both hydrogen atoms at C3 and C4 were in axial positions, implying that the methyl group at C4 would be in the equatorial position rather than the observed axial orientation.

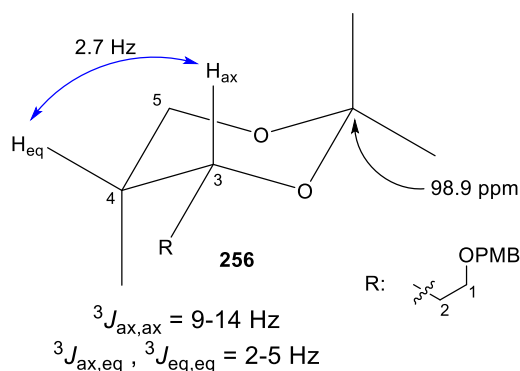
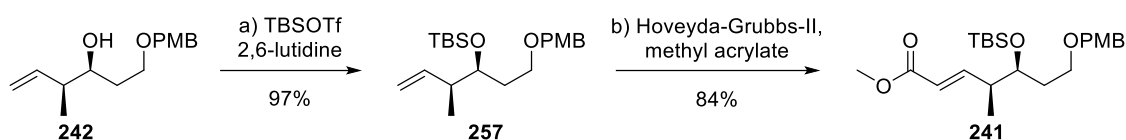


Figure 3.6-2. Depicted is the chair conformation of **256** for verifying the 1,2 *syn* configuration.

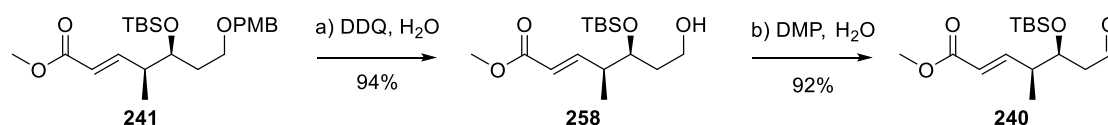
With the stereocenters successfully confirmed, alcohol **242** was protected as TBS ether **257** (**Scheme 3.6-5**). Subsequently, the terminal alkene underwent elongation via a Grubbs metathesis with methyl acrylate, affording olefin **241**.



Scheme 3.6-5. TBS protection of alcohol **242** to silyl ether **257** and subsequent Grubbs metathesis to olefin **241**. Conditions: a) **242** (1.00 equiv.), TBSOTf (2.00 equiv.), 2,6-lutidine (5.00 equiv.), DCM, 0 °C→r.t., 2 h, 97%; b) **257** (1.00 equiv.), Hoveyda-Grubbs-II (0.02 equiv.), methyl acrylate (5.00 equiv.), toluene, 120 °C, 22 h, 84% *E/Z* >20:1.

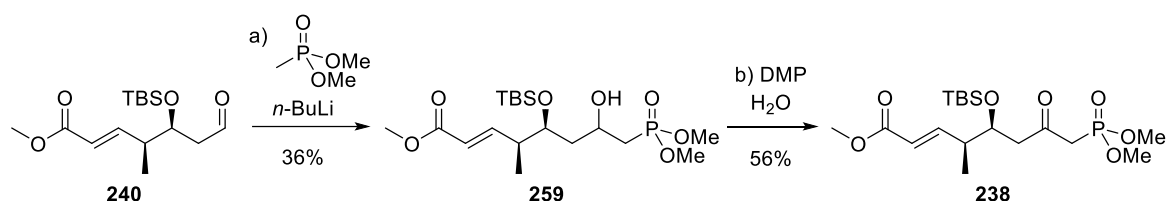
Next, the initially installed PMB protecting group of **241** needed to be removed to allow oxidation to the aldehyde **240** (**Scheme 3.6-6**). This was achieved by DDQ-mediated deprotection of **241** to yield primary alcohol **258**, followed by oxidation with DMP to furnish aldehyde **240** in 92% yield.

Up to this stage, all reactions proceeded with remarkable yields and excellent selectivity, even on a multigram scale, making the synthetic sequence highly efficient and practical.



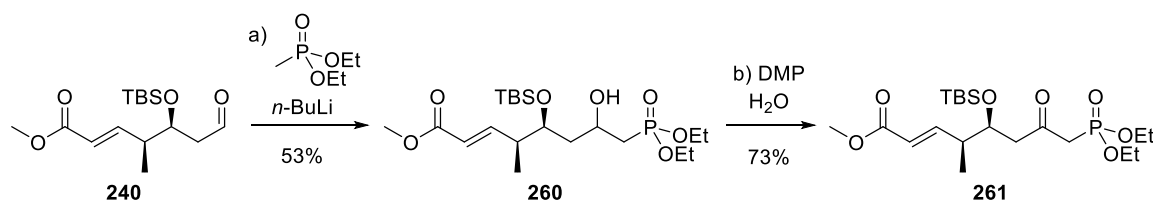
Scheme 3.6-6. Deprotection of PMB ether **241** with DDQ to primary alcohol **258** and additional oxidation to aldehyde **240**. Conditions: a) **241** (1.00 equiv.), DDQ (1.40 equiv.), H₂O (5.50 equiv.), DCM, r.t., 2 h, 94%; b) **258** (1.00 equiv.), DMP (2.00 equiv.), H₂O (1.20 equiv.), DCM, 0 °C→r.t., 4 h, 92%.

Aldehyde **240** was converted into alcohol **259** through a nucleophilic attack by deprotonated dimethyl methylphosphonate, yielding 36% of product as a mixture of diastereomers (**Scheme 3.6-7**). Stereocontrol was not necessary, as the alcohol was subsequently oxidized to ketone **238** with 56% yield. The overall yields were rather moderate and not entirely satisfactory, likely due to the presence of an ester group on the opposite side. Although aldehydes are generally more reactive, and the reaction was conducted at low temperatures to minimize side reactions, ester reactivity could not be entirely excluded.



Scheme 3.6-7. Synthesis of phosphonate **238**, starting from aldehyde **240**. Conditions: a) dimethyl methylphosphonate (1.30 equiv.) $n\text{-BuLi}$ (1.15 equiv.), THF, -78°C , 30 min, then **240** (1.00 equiv.), 30 min, 36%; b) **259** (1.00 equiv.), DMP (1.50 equiv.), H_2O (1.20), DCM, 2 h, 56%

For yield improvement, dimethyl methylphosphonate was substituted by diethyl methylphosphonate (**Scheme 3.6-8**). This modification led to significantly improved yields, and the target phosphonate **261** was successfully synthesised and ready for use in the HWE reaction.



Scheme 3.6-8. Synthesis of phosphonate **261**, starting from aldehyde **240**. Conditions: a) diethyl methylphosphonate (1.50 equiv.) $n\text{-BuLi}$ (1.20 equiv.), THF, -78°C , 30 min, then **240** (1.00 equiv.), -90°C , 15 min, then -40°C , 40 min, 53%; b) **260** (1.00 equiv.) DMP (2.00 equiv.), H_2O (1.20), DCM, 2 h, 73%.

3.6.2 Synthesis of Aldehyde **239**

This chapter describes the synthesis of aldehyde **239**, following a newly designed route aimed at increasing flexibility by introducing a Mukaiyama aldol coupling at the 1,3-diol (**Figure 3.6-3**). This approach facilitates potential late-stage derivatization while also reducing the number of linear synthetic steps.

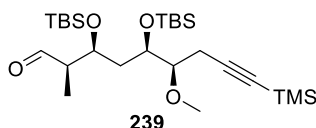
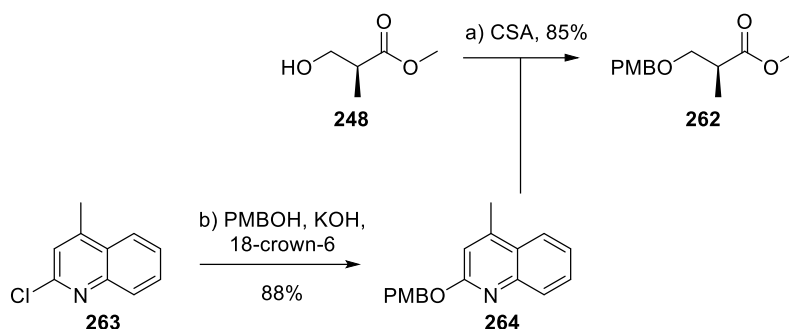


Figure 3.6-3. Target molecule **239**.

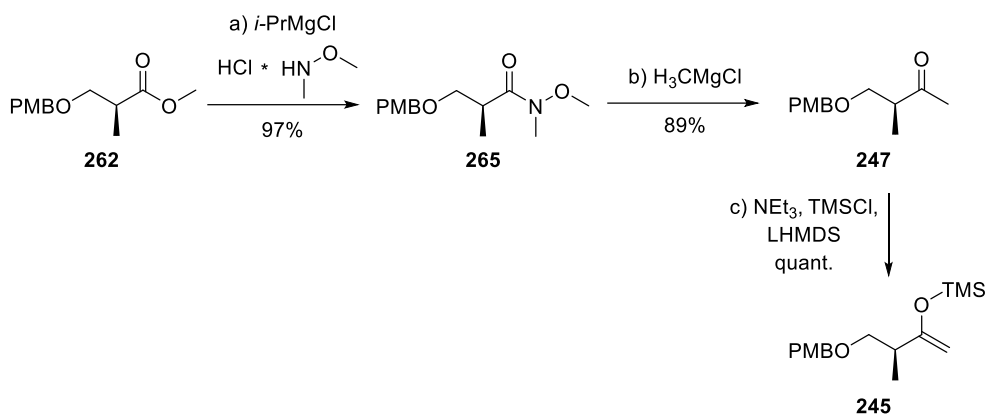
The synthesis started with the (*S*)-Roche ester (**248**), which was protected to PMB ether **262** (**Scheme 3.6-9**), since previous attempts to remove a primary TBS group selectively alongside secondary TBS ethers had shown limitations. PMB deprotection should offer better yields in later steps (see **Scheme 3.3-36** and **Scheme 3.3-37**).



Scheme 3.6-9. Synthesis of the PMB-protecting reagent (Dudley reagent, **264**) and PMB protection of (*S*)-Roche ester (**248**) to corresponding PMB ether **262**. Conditions: a) **248** (1.00 equiv.), **264** (2.00 equiv.), CSA (0.10 equiv.), DCM, r.t., 72 h, 85%; b) **263** (1.00 equiv.), *p*-anisyl alcohol (1.20 equiv.), 18-crown-6 (0.05 equiv.), KOH (4.00 equiv.), Dean-Stark trap, toluene, 140 °C, 1.5 h, 88%.

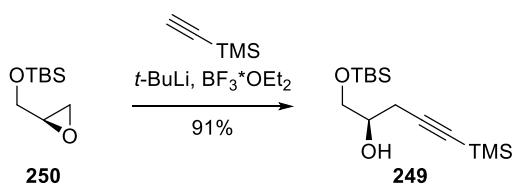
To install the PMB protection, the Dudley reagent (**264**) was first synthesized from quinoline **263**. Using this reagent, Roche ester **248** was successfully converted to PMB ether **262** with 85% yield without workup difficulties, even on a large scale.

PMB ether **262** was subsequently transformed into Weinreb amide **265** and reduced to methyl ketone **247** (**Scheme 3.6-10**). Methyl ketone **247** was further transformed into silyl enol ether **245**, completing the first key building block for the Mukaiyama aldol reaction.



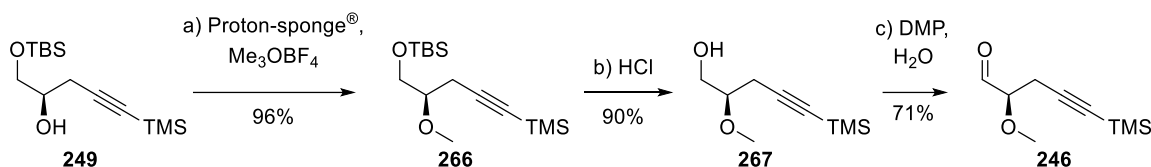
Scheme 3.6-10. Conversion of ester **262** into Weinreb amide **265**, followed by methylation to the methyl ketone **247**, enabling the formation of silyl enol ether **245**. Conditions: a) **262** (1.00 equiv.), isopropylmagnesium chloride (3.00 equiv.), *N*-methoxymethylamine hydrochloride (1.55 equiv.), THF, $-20\text{ }^\circ\text{C}$, 40 min, then $\rightarrow\text{r.t.}$, 2 h, 97%; b) **265** (1.00 equiv.), methylmagnesium chloride (3.00 equiv.), THF, $0\text{ }^\circ\text{C}$, 30 min then $\rightarrow\text{r.t.}$, 2 h, 89%; c) **247** (1.00 equiv.), NEt_3 (3.00 equiv.), TMSCl (3.00 equiv.), LHMDS (1.70 equiv.), $-78\text{ }^\circ\text{C}$, 3 h, quant.

The second key fragment was derived from commercially available epoxide **250** (**Scheme 3.6-11**). Epoxide opening was implemented by using *t*-BuLi and ethynyltrimethylsilane, yielding secondary alcohol **249** in 91% yield.



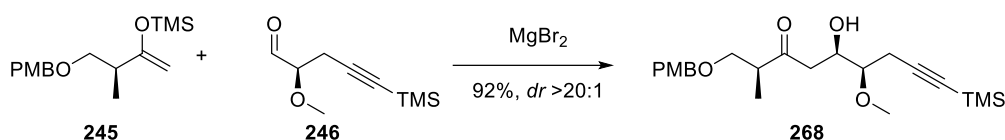
Scheme 3.6-11. Opening of epoxide **250** to alcohol **249**. Conditions: ethynyltrimethylsilane (1.30 equiv.), *t*-BuLi (1.40 equiv.), THF, $-78\text{ }^\circ\text{C}$, 30 min, then **250** (1.00 equiv.), $\text{BF}_3\cdot\text{Et}_2\text{O}$ (1.30 equiv.), $-78\text{ }^\circ\text{C}\rightarrow\text{r.t.}$, 3 h, 91%.

Alcohol **249** was methylated using a Meerwein methylation to get methyl ether **266** in an excellent 96% yield (**Scheme 3.6-12**). Subsequent deprotection of the primary TBS group proceeded smoothly, affording primary alcohol **267** with 90% yield. Since no other silyl ethers were present in the molecule, unwanted side reactions were avoided. Finally, alcohol **267** was oxidized to the corresponding aldehyde **246**, completing the second key fragment required for aldol coupling.



Scheme 3.6-12. Methylation of alcohol **249** to methyl ether **266**, followed by TBS deprotection to primary alcohol **267** and subsequent oxidation to aldehyde **246**. Conditions: a) **249** (1.00 equiv.), Proton-sponge[®] (4.00 equiv.), Me₃OBF₄ (3.00 equiv.), DCM, 0 °C→r.t., 16 h, 96%; b) **266** (1.00 equiv.), aq. 3 M HCl (0.30 equiv.), MeOH, r.t., 45 min, 90%; c) **267** (1.00 equiv.), DMP (2.00 equiv.), H₂O (1.20 equiv.), pyridine (3.00 equiv.), DCM, 0 °C, 3 h, then r.t., 3 h, 71%.

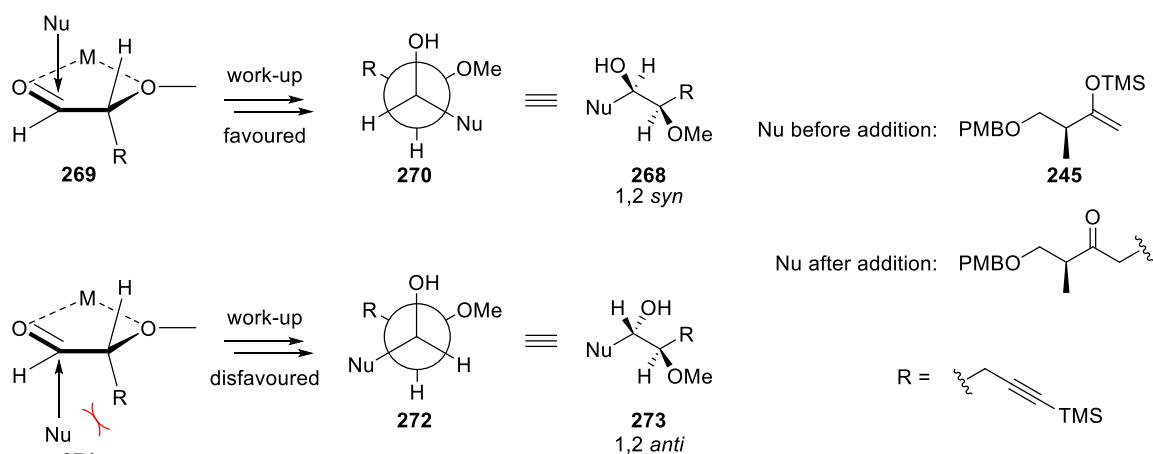
Silyl enol ether **245** and aldehyde **246** were coupled via a Mukaiyama aldol reaction (**Scheme 3.6-13**).^[158] This transformation proceeded on a gram scale with an excellent yield of 92% and remarkable diastereoselectivity (*dr* >20:1). In this process, Mg²⁺ acted as a Lewis acid to activate aldehyde **246**, facilitating the nucleophilic attack of enol ether **245**.



Scheme 3.6-13. Mukaiyama aldol reaction of enol ether **245** and aldehyde **246** to corresponding aldol coupling product **268**. Conditions: **245** (3.00 equiv.), **246** (1.00 equiv.), MgBr₂·OEt₂ (3.00 equiv.), DCM, −78 °C, 3 h, 92%.

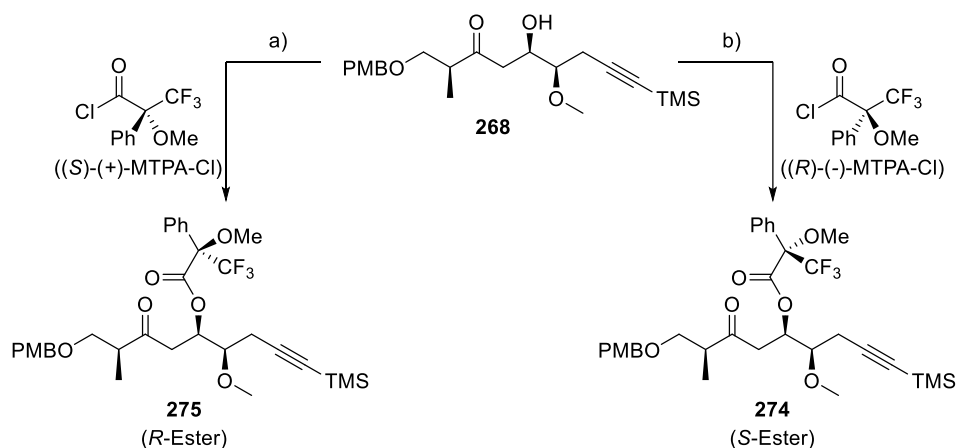
The excellent stereoselectivity of this reaction can be explained by the Cram-chelate transition states.^[159,160] In this mechanism, the oxophilic Mg²⁺ cation coordinates both to the aldehyde and the methoxy group, which is in α -position to the carbonyl group (**269** and **271**, **Scheme 3.6-14**). As shown in **269** and **271** the carbonyl oxygen and the oxygen of the methoxy group are locked in *syn*-position, due to chelation of Mg²⁺.

Consequently, two distinct transition states are possible, in which the nucleophile **245** attacks the aldehyde from either the *Re*-face (**269**) or the *Si*-face (**271**). Steric hindrance between the nucleophile and the bulky aldehyde substituent in transition state **271** makes this pathway less favorable. Thus, transition state **269** is preferred. Following nucleophilic attack and subsequent workup results in the formation of product **270**, which corresponds to the 1,2-*syn* product **268**. In contrast, the disfavored transition state **271** would lead to Newman-projection **272**, which corresponds to the 1,2-*anti* product **273**.



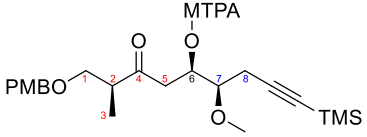
Scheme 3.6-14. Illustration of the 1,2-syn selectivity in the Mukaiyama aldol reaction via the Cram-chelate transition state.^[161]

The *S*-ester **274** and *R*-ester **275** were synthesized from alcohol **268** to confirm the stereochemistry by Mosher analysis (**Scheme 3.6-15**).



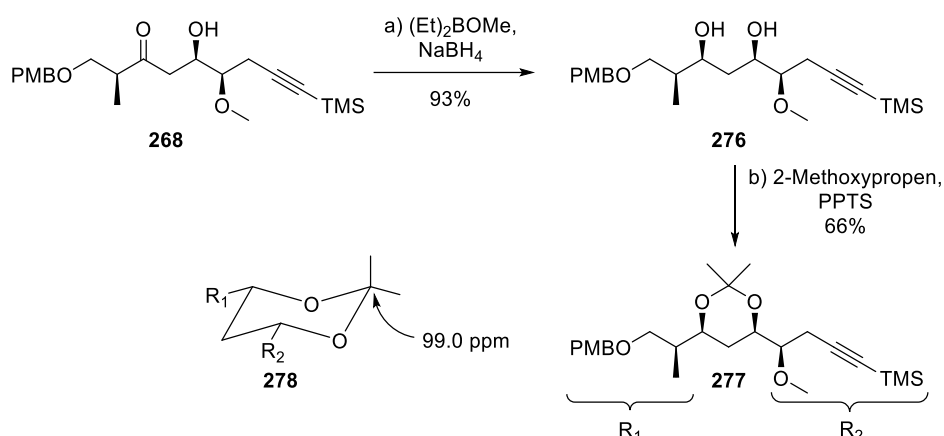
Scheme 3.6-15. Synthesis of (*S*)-ester **274** and (*R*)-ester **275** for Mosher analysis.^[133] Conditions: a) **268** (1.0 equiv.), (*S*)-(+)-MTPA-Cl (4.0 equiv.), pyridine (0.2 mL), r.t., 2 h, 65%; b) **268** (1.0 equiv.), (*R*)-(-)-MTPA-Cl (4.0 equiv.), pyridine (0.2 mL), r.t., 2 h, 65%.

The differences observed in the ¹H NMR spectra of the (*S*)- and (*R*)-MTPA esters **274** and **275** confirmed (*R*)-configuration (**Table 3.6-2**).^[133]

Table 3.6-2. Significant ¹H NMR signals of **274** (*S*-Ester) and **275** (*R*-Ester) and their use in Mosher ester analysis.


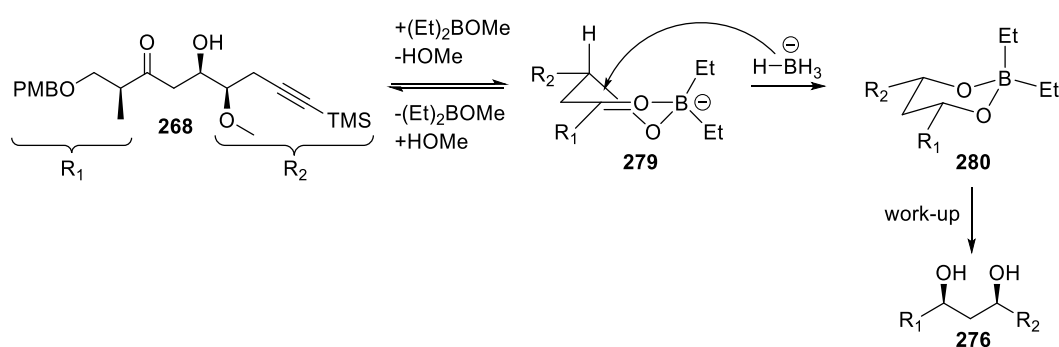
Atom	δ_H of 274 (<i>S</i> -Ester) [ppm]	δ_H of 275 (<i>R</i> -Ester) [ppm]	$\Delta\delta^{SR} = \delta^{S\text{-ester}} - \delta^{R\text{-ester}}$
1	3.57-3.52	3.53-3.51	(+0.04)-(+0.01)
	3.46	3.41	+0.05
2	2.86-2.79	2.78-2.69	(+0.08)-(+0.10)
3	1.03	0.96	+0.07
4	-	-	-
5	3.03	2.93	+0.10
	2.86-2.79	2.81	(+0.05)-(-0.02)
6	-	-	-
7	3.57-3.52	3.59	(-0.02)-(-0.07)
8	2.26, 2.03	2.47, 2.37	-0.21, -0.34

After successful confirmation of alcohol **268**, the corresponding *syn*-diol **276** was synthesized via a Narasaka-Prasad reduction with 93% yield (**Scheme 3.6-16**).^[162] The *syn* selectivity of this transformation was verified through conversion into acetonide **277**. The chemical shift of the ketal carbon with 99 ppm provided further confirmation. A value below 100 ppm (**278**) indicated a 1,2-*syn* product, whereas a shift above 100 ppm would have suggested a 1,3-*anti* selectivity and the presence of a twist-boat conformation (refer to **Figure 3.3-2**).^[139]



Scheme 3.6-16. Narasaka-Prasad reduction of ketone **268** to *syn*-diol **276** and subsequent transformation into the acetonide **277**. Conditions: a) **268** (1.00 equiv.), (Et)₂BOMe (2.00 equiv.), NaBH₄ (1.10 equiv.), THF/MeOH, –78 °C, 3 h, 93%; b) **276** (1.00 equiv.), 2-methoxypropen (2.00 equiv.), PPTS (0.10 equiv.), DCM, r.t., 14 h, 66%.

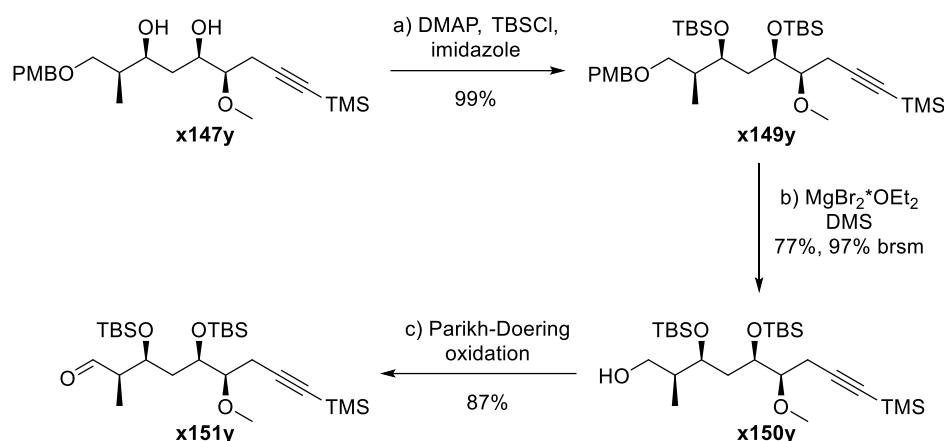
The observed *syn*-reduction in the Narasaka-Prasad reaction can be explained by the six-membered transition state **279** (Scheme 3.6-17). In an equilibrium process between (Et)₂BOMe and ketone **268**, the loss of methanol generates transition state **279**, where the boron atom coordinates to the hydroxyl and the carbonyl oxygen. The subsequent hydride transfer occurs in an axial position, in *syn*-configuration to the β -oriented hydrogen atom and leads to the formation of the more stable chair conformer **280**, yielding the 1,3-*syn* product **276**. In contrast, if the hydride transfer were to take place from the bottom, the unfavorable twist-boat conformer would be generated, resulting in a 1,3-*anti* diol product, which is energetically disfavored.^[163]



Scheme 3.6-17. Illustration of the Narasaka-Prasad reduction, highlighting the stereocontrol of the reaction.^[162]

With the successful confirmation and explanation of the *syn* selectivity in the Narasaka-Prasad reduction, diol **276** was subsequently protected as a TBS ether, yielding silyl ether **281** (Scheme 3.6-18). The initial PMB-protected alcohol was then selectively deprotected to afford

primary alcohol **282**. A final Parikh-Doering oxidation converted this intermediate into aldehyde **239**, completing the synthesis of the target fragment with considerable yields. Aldehyde **239** was utilized in an HWE coupling with the previously synthesized phosphonate (see **Chapter 3.6.1**).



Scheme 3.6-18. TBS protection of diol **276** to silyl ether **281**, followed by selective PMB deprotection to primary alcohol **282**, and subsequent oxidation to aldehyde **239**. Conditions: a) **276** (1.00 equiv.), DMAP (0.05 equiv.), TBSCl (3.00 equiv.), imidazole (4.00 equiv.), DMF/DCM, r.t., 14 h, 99%, b) **281** (1.00 equiv.), $\text{MgBr}_2 \cdot \text{OEt}_2$ (15.0 equiv.), DMS (50.0 equiv.), DCM, sealed, 96 h, 77%, 97% brsm.; c) **282** (1.00 equiv.), DIPEA (4.00 equiv.), DMSO (10.0 equiv.), sulfur trioxide pyridine complex (6.00 equiv.), DCM, 0 °C→r.t., 1 h, 87%.

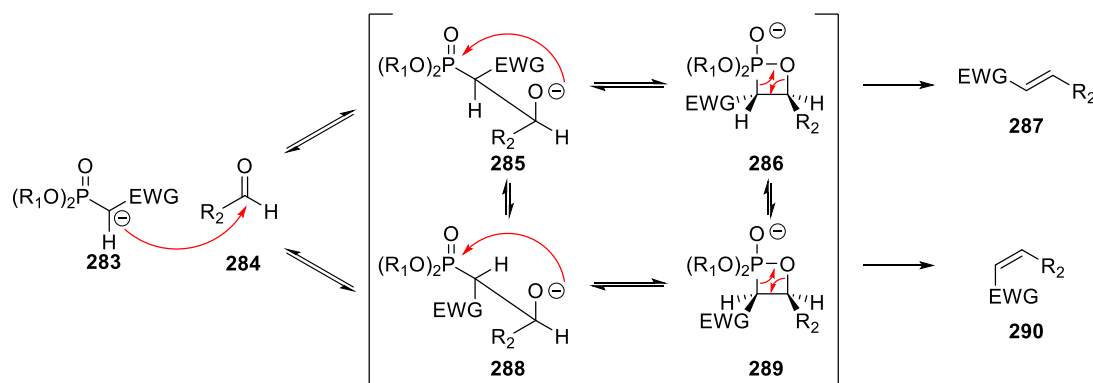
3.6.3 Coupling of Phosphonates **238** and **261** with Aldehyde **239**

Phosphonates **238**, **261** (see **Chapter 3.6.1**) and aldehyde **239** (see **Chapter 3.6.2**) were coupled via a Horner-Wadsworth-Emmons (HWE) reaction to generate *E*-olefin bond formations selectively. A general reaction mechanism is outlined in **Scheme 3.6-19**.^[164]

Carbanion **283** is generated by deprotonation and remarkably stabilized by phosphonate and the electron-withdrawing group (EWG). This carbanion **283** undergoes nucleophilic attack on aldehyde **284**, leading to the formation of either addition product **285** or **288**. Subsequently, the oxygen performs an intramolecular attack on the phosphorus atom, forming a four-membered heterocyclic oxaphosphetane **286** or **289**. Significantly the transition states **285** and **286** can interconvert between **288** and **289**.^[165]

In the final step, elimination of phosphate results in the breakdown of oxaphosphetane **286** or **289**, yielding either the *E*-olefin **287** or the *Z*-olefin **290**. Although the HWE reaction typically

favors the formation of the *E*-olefin, the selectivity between *E*- and *Z*-isomers can be influenced by various factors, including the alkyl groups on the phosphonate, the choice of coordinating or non-coordinating metal ions, reaction temperature or the steric demand of the aldehyde substituent.^[166]

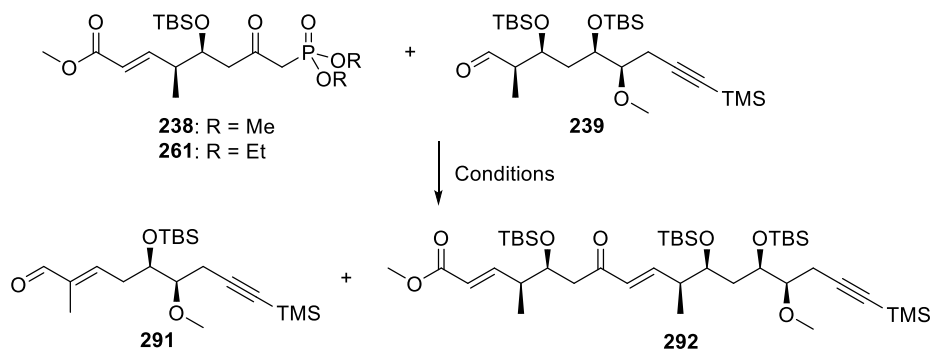


Scheme 3.6-19. General mechanism of the HWE reaction.^[164]

Considering the reaction mechanism, the HWE reaction was first attempted using ethyl phosphonate **261**, as it had previously provided better yields (*cf.* **Scheme 3.6-7** and **Scheme 3.6-8**).

NaHMDS, a commonly used base for HWE reactions, was employed in the initial attempt (entry 1, **Table 3.6-3**). Even under low temperatures with slow warming and prolonged reaction times of 16 hours, only trace amounts of the desired HWE product **292** were detected. Instead an elimination product **291** was obtained in over 90% yield. Base-induced elimination removed the TBS-ether group in the β -position relative to the aldehyde. Temperature increase and shortened reaction time did not improve the outcome (entry 2).

Table 3.6-3. HWE coupling of phosphonate **238/261** with aldehyde **239** to corresponding HWE coupling product **292** and side product **291**.



3 Results and Discussion

Entry	Phos- phonate	Solvent	Base [1.10 equiv.]	Additives	T [°C]	Time [h]	Yield 291 [%]	Yield 292 [%]
1	261	THF	NaHMDS (1M in THF)		-78 → 0	16	>90	Traces ^[a]
2	261	THF	NaHMDS (1M in THF)		-78 → 50	3	>90	0 ^[a]
3	261	THF	BaOH	H ₂ O (2.00 equiv.)	r.t.	16	>90	Traces
4	261	THF	BaOH	H ₂ O (10.0 equiv.)	r.t.	16	>90	Traces
5	261	THF/H ₂ O 40:1	BaOH		70	3	>90	Traces
6	261	THF	NaHMDS (solid)		-78	16	0	0 ^[a,b,c]
7	261	THF	NaHMDS (solid)		-78 → r.t.	16	27	3 ^[a,b]
8	261	THF	NaHMDS (1M in THF)	ScOTf (2.00 equiv.)	-78 → r.t.	16	0	0 ^[a,b]
9	261	THF	NaHMDS (1M in THF)	BF ₃ ·OEt ₂ (1.00 equiv.)	60	16	0	0 ^[a,b]
10	261	MeCN	DBU	LiCl (5.00 equiv.)	r.t.	1	48	Traces
11	261	DMF	K ₂ CO ₃		r.t.	2	48	Traces
12	261	Toluene	NaH		100	4	>90	Traces ^[a,b]
13	238	THF/H ₂ O 40:1	BaOH		40	16	51	12
14	238	THF	NaHMDS (1M in THF)		-78 → 0	16	3	18 ^[a]

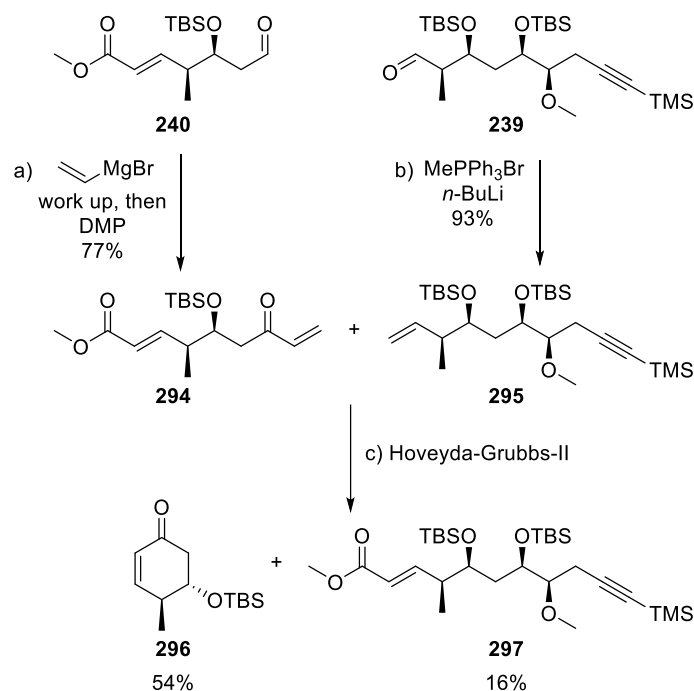
^[a] Substrates dried with Freeze-Pump-Thaw.

^[b] Reaction was conducted over ground molecular sieve.

^[c] No conversion.

Similarly, attempts using Ba(OH)₂ as a base with varying amounts of water did not yield improvements (entries 3-5). It was suspected that the elimination reaction was facilitated by traces of moisture, possibly introduced via the NaHMDS solution. To prevent moisture contaminations, the reaction was repeated using solid NaHMDS. Additionally, all reagents

To achieve this, aldehyde **240** was first treated with vinylmagnesium bromide as a nucleophile, to form the corresponding alcohol, followed by oxidation using DMP to afford olefin **294** with 77% yield. Aldehyde **239** was converted into olefin **295** via a Wittig reaction, achieving a yield of 93%.

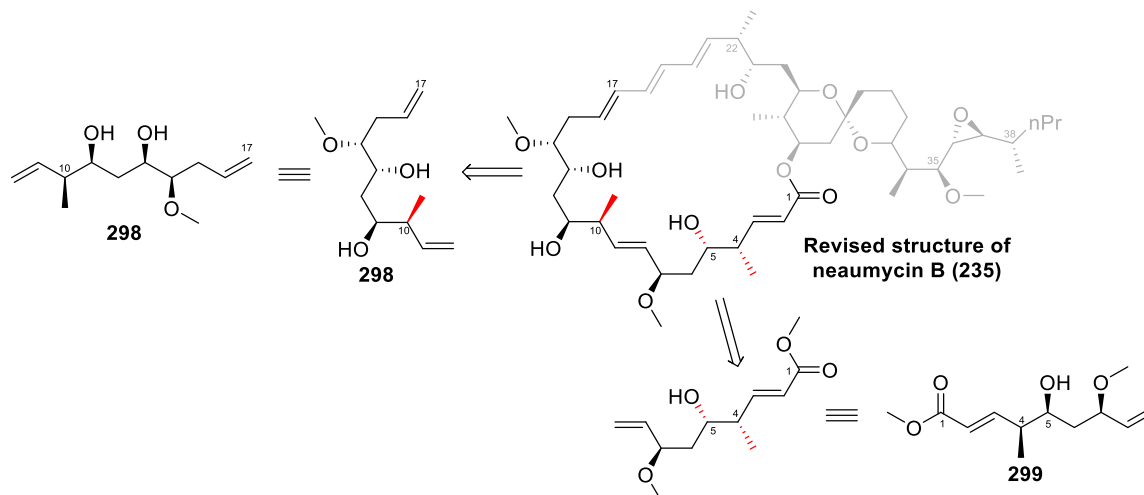


Scheme 3.6-21. Conversion of aldehyde **240** to olefin **294** and aldehyde **239** to olefin **295**, followed by a Grubbs metathesis reaction with both olefins to yield **296** and **297**. Conditions: a) **240** (1.00 equiv.), vinylmagnesium bromide (1.50 equiv.), THF, $-78\text{ }^{\circ}\text{C}$, 1 h, then $-78\text{ }^{\circ}\text{C} \rightarrow -30\text{ }^{\circ}\text{C}$, 45 min, aq. work up, then DMP (3.00 equiv.), DCM, r.t., 1 h, 77%; b) Methyltriphenylphosphonium bromide (1.50 equiv.), *n*-BuLi (2 M in cyclohexane, 1.20 equiv.), THF, $-78\text{ }^{\circ}\text{C}$, 30 min, then $-78\text{ }^{\circ}\text{C} \rightarrow \text{r.t.}$, 10 min then $-78\text{ }^{\circ}\text{C}$, **239** (1.00 equiv.), $-78\text{ }^{\circ}\text{C} \rightarrow \text{r.t.}$, 14 h, 93%; c) **294** (1.00 equiv.), **295** (1.00 equiv.), Hoveyda-Grubbs-II (0.10 equiv.), toluene, $120\text{ }^{\circ}\text{C}$, 20 h, 54% of **296** and 16% of **297**.

These two olefins were then subjected to a Grubbs metathesis. Instead of the desired coupling product **292** formation, the reaction predominantly led to the formation of cyclohexene **296**. This cyclic product is formed by an intramolecular Grubbs metathesis of olefin **294**, leading to the elimination of methyl acrylate. The released methyl acrylate then participated in another Grubbs metathesis with olefin **295**, generating methyl ester **297**. While these findings are intriguing, they unfortunately did not provide the desired product, indicating that Grubbs metathesis is not a viable strategy for this system.

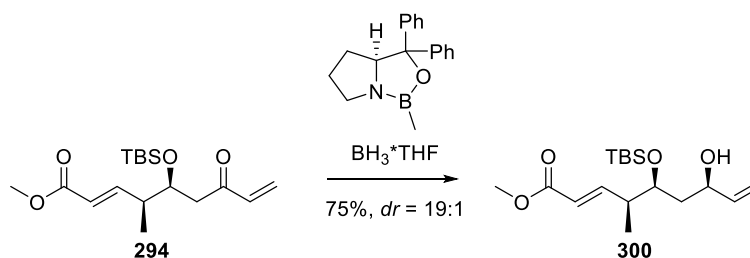
3.6.4 Synthesis of Authentic Fragments 298 and 299

Since the fragment coupling proved to be extraordinarily difficult (see **Chapter 3.3.5** and **Chapter 3.6.3**), authentic fragments **298** and **299** were synthesized (**Scheme 3.6-22**). These fragments correspond exactly to specific regions of the revised structure of neaumycin B (**235**) and appear as if they were directly excised from the neaumycin molecule, meaning they contain no protective groups or modifications.



Scheme 3.6-22. The authentic fragments **298** and **299** from the revised structure of neaumycin B (**235**).

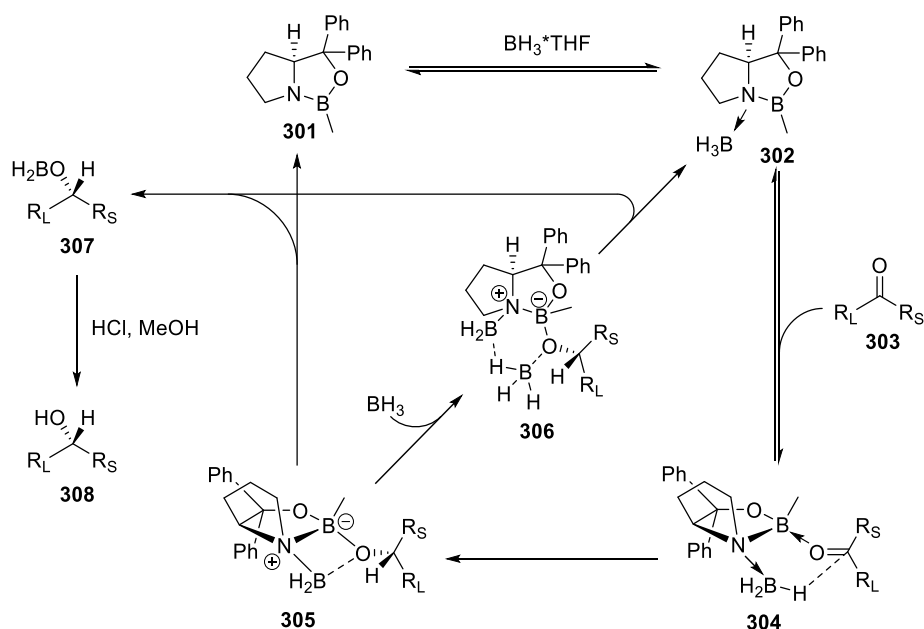
The goal of this fragment synthesis was to compare their NMR data with those of the neaumycin B (**1**) isolated by Fenical *et al.* and the synthetically produced neaumycin B (**1**) by Smith *et al.* and Chen *et al.* Hopefully, due to the altered stereocenters at the relevant positions, a better match of the NMR data would be achieved, which would indicate that the revised structure of neaumycin B (**235**) is correct.



Scheme 3.6-23. CBS-reduction of keton **294** to alcohol **300**. Conditions: **294** (1.00 equiv.), $\text{BH}_3 \cdot \text{THF}$ (1 M in THF, 1.50 equiv.), (*S*)-2-methyl-CBS-oxazaborolidine (1 M in toluene, 1.10 equiv.), THF, -20°C , 2.5 h, 75%, $dr = 19:1$.

For this purpose, the previously synthesized vinyl ketone **294** (see **Chapter 3.6.3**) was selectively reduced to alcohol **300** using a Corey-Bakshi-Shibata (CBS) reduction (**Scheme 3.6-23**). This reaction proceeded with a yield of 75% and a remarkable diastereoselectivity of 19:1.

The mechanism of the CBS reduction is explained below in **Scheme 3.6-24**. CBS reductions utilize a chiral auxiliary, specifically the oxazaborolidine catalyst **301**. Upon addition of BH_3 as the reducing agent, it coordinates to the catalyst **301** via the nitrogen atom, forming species **302**. This coordination activates the BH_3 as a hydride donor and simultaneously increases the Lewis acidity of the endocyclic boron atom.



Scheme 3.6-24. Mechanism of the CBS-reduction.^[169]

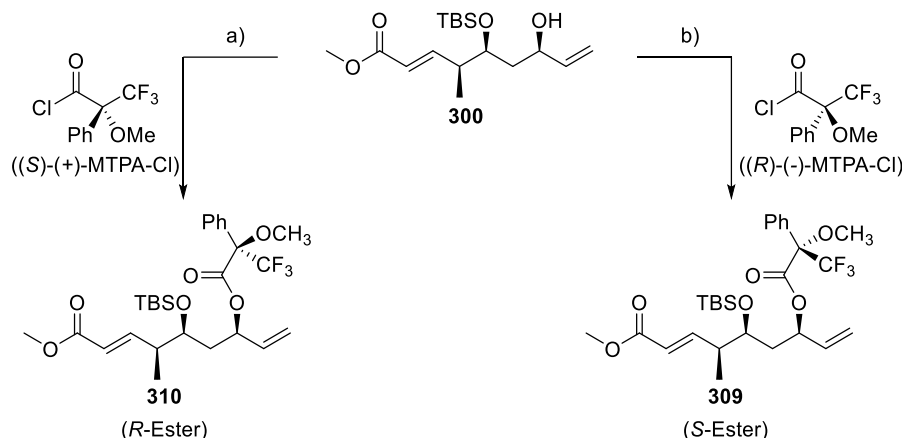
Due to this increased Lewis acidity, the ketone **303** can coordinate to the Lewis-acidic endocyclic boron atom through its sterically more accessible lone pair (R_S pointing upwards, R_L pointing downwards), with the adjacent BH_3 group positioned in *cis*-configuration, enabling a hydride transfer in the six-membered transition state **304** to form reduction product **305**.

The detachment of the oxazaborolidine catalyst can then proceed via two pathways. In one pathway, a cycloelimination takes place, where the bond between the endocyclic boron atom and the oxygen shifts to the BH_2 group and the bond between the nitrogen atom and the BH_2

group shifts back to the nitrogen atom. This regenerates the oxazaborolidine catalyst **301** and forms the borinate **307**, which is then converted into alcohol **308** upon work-up.

Alternatively, another BH_3 molecule can coordinate to complex **305**, forming the six-membered species **306**, which subsequently converts into species **302** and the borinate **307**.

Mosher analysis was performed for absolute stereochemistry elucidation. To achieve this, *S*-MTPA ester **309** and *R*-MTPA ester **310** were synthesized from alcohol **300** (Scheme 3.6-25).



Scheme 3.6-25. Synthesis of (*S*)-ester **309** and (*R*)-ester **310** for Mosher analysis.^[133] Conditions: a) **300** (1.0 equiv.), (*S*)-(+)-MTPA-Cl (2.0 equiv.), pyridine (0.2 mL), r.t., 2 h, 60%; b) **300** (1.0 equiv.), (*R*)-(-)-MTPA-Cl (2.0 equiv.), pyridine (0.2 mL), r.t., 2 h, 69%.

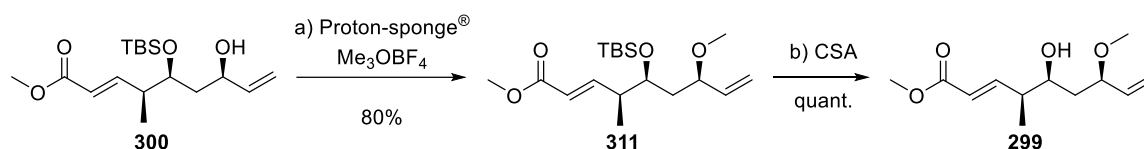
The differences observed in the ^1H NMR spectra of the (*S*)- and (*R*)-MTPA esters **309** and **310** confirmed (*R*)-configuration (Table 3.6-4).^[133]

Table 3.6-4. Significant ^1H NMR signals of **309** (*S*-Ester) and **310** (*R*-Ester) and their use in Mosher ester analysis.

Atom	δ_{H} of 309 (<i>S</i> -Ester) [ppm]	δ_{H} of 310 (<i>R</i> -Ester) [ppm]	$\Delta\delta^{SR} = \delta^{S\text{-ester}} - \delta^{R\text{-ester}}$
1	-	-	-
2	5.79	5.77	+0.02
3	6.96	6.86	+0.10
4	2.53	2.37	+0.16

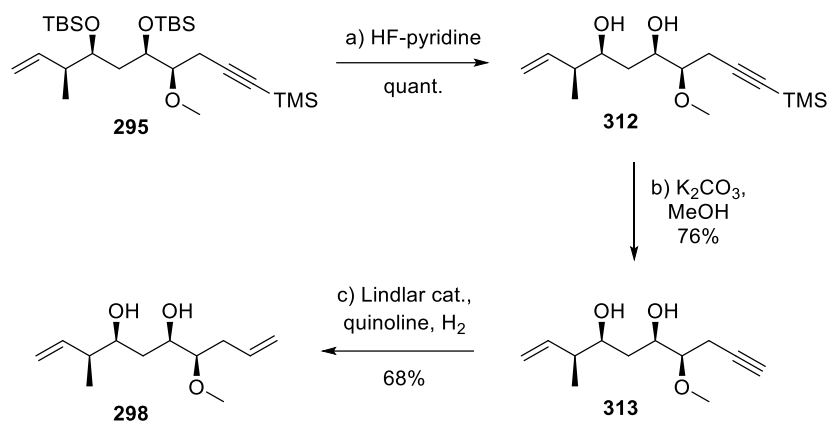
5	1.00	0.92	+0.08
6	3.72	3.59-3.55	(+0.13)-(+0.17)
7	1.82	1.77	+0.05
8	-	-	-
9	5.73	5.83	-0.10
10	5.37-5.25	5.44-5.33	(-0.07)-(-0.08)

After stereocenter verification of alcohol **300**, the alcohol was converted into the corresponding methyl ether **311** via Meerwein methylation (Scheme 3.6-26). Subsequently the secondary TBS protecting group was quantitatively removed using CSA as catalyst, completing the first authentic fragment **299**.



Scheme 3.6-26. Meerwein methylation of alcohol **300** to methyl ether **311** and final deprotection to alcohol **299**. Conditions: a) **300** (1.00 equiv.), Proton-sponge[®] (6.00 equiv.), Me₃OBf₄ (4.00 equiv.), DCM, r.t., 20 h, 80%; b) **311** (1.00 equiv.), CSA (1.50 equiv.), DCM/MeOH, r.t., 18 h, quant.

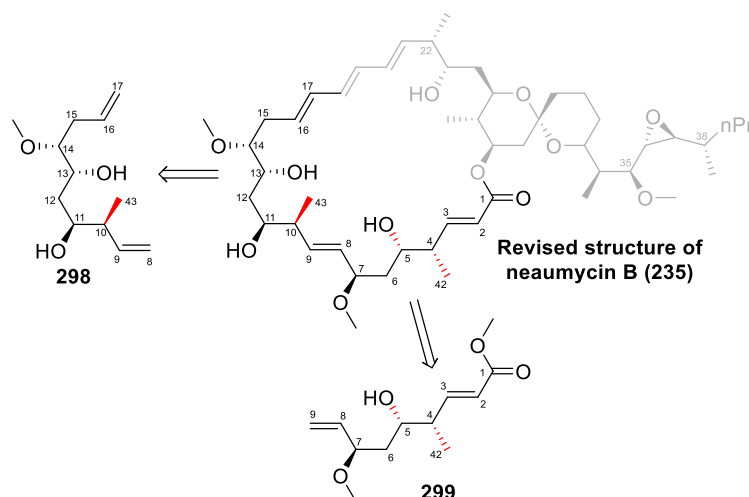
The second authentic fragment, **298**, was derived from the previously synthesized silyl ether **295** (Scheme 3.6-27, see Chapter 3.6.3). Deprotection by using HF-pyridine formed the 1,3-diol **312** in quantitative yield, followed by the removal of the TMS group with K₂CO₃. A Lindlar reduction^[170] of alkyne **313** to olefin **298** completed the synthesis of the authentic fragment.



Scheme 3.6-27. TBS deprotection of silyl ether **295** to diol **312** with subsequent TMS deprotection to alkyne **313** with final poisoned reduction to authentic fragment **298**. Conditions: a) **295** (1.00 equiv.), HF-pyridine (50.0 equiv.), THF, r.t., quant.; b) **312** (1.00 equiv.), K₂CO₃ (10.0 equiv.), MeOH, r.t., 2 h, 76%; c) **313** (1.00 equiv.), Lindlar cat. (Pd-50%), quinoline (2.00 equiv.), H₂ (xs.), hexane, r.t., 30 min, 68%.

3.6.5 Comparison of NMR Data from Authentic Fragments **298** and **299**

With the successful synthesis of the two authentic fragments, **298** and **299**, their NMR data could now be compared to the originally isolated neaumycin B (**1**) reported by Fenical *et al.* (Scheme 3.6-28).^[11]



Scheme 3.6-28. Revised structure of neaumycin B (**235**) with the authentic fragments **298** and **299**.

Table 3.6-5, presents the ^1H and ^{13}C values from Fenical's isolated neaumycin B (**1**, left) and the corresponding data for the synthetic authentic fragments **299** (atoms 1-9, right) and **298** (atoms 8-17, right). Since both fragments share atoms 8 and 9 due to the overlap of the double bond, the table includes two entries for these atoms. The data in the table is limited to C1-C17, as this corresponds to the range covered by the authentic fragments.

The authentic fragments show fewer multiplets and possess a noticeable improvement in signal resolution. This can be attributed to the lower proton density in the fragments compared to the full neaumycin B (**1**), where extensive signal overlap occurs, making differentiation more challenging. Additionally, the fewer signals not only allow better resolutions, but also a more precise determination of coupling constants. Ideally, it would have been beneficial if the NMR signals in Fenical's neaumycin B (**1**) had been fully resolved with coupling constants, allowing for a direct comparison, particularly at positions where stereocenters were revised (see **Chapter 3.5**). However, in the absence of such resolved data, a comparison based on chemical shifts must suffice.

3 Results and Discussion

Table 3.6-5. NMR data of isolated neaumycin B (**1**) by Fenical *et al.* and NMR data of fragment **299** and **298**.^[11]

Isolated neaumycin B (1) by Fenical <i>et al.</i> (500/125 MHz, CDCl ₃ , r.t.)					Fragments of neaumycin B (235 , revised structure) this work (700/176 MHz, CDCl ₃ , r.t.)			
Atom	δ_{H} [ppm]	m	<i>J</i> [Hz]	δ_{C} [ppm]	δ_{H} [ppm]	m	<i>J</i> [Hz]	δ_{C} [ppm]
1				165.9				167.2
2	5.76	D	15.6	122.0	5.85	dd	15.8, 1.3	121.2
3	6.75	dd	15.6, 9.2	151.2	6.97	dd	15.8, 7.8	151.3
4	2.31	m ^[a]		44.1	2.41	dddd	8.0, 6.9, 5.8, 1.3	42.9
5	3.56	m ^[a]		75.0	3.76	m ^[a]		74.6
6a	1.50	m ^[a]		40.6	1.61	dt	14.6, 9.9	39.5
6b	1.50	m ^[a]			1.56	ddd	14.6, 3.7, 2.0	
7	3.68	dd	8.6, 5.0	84.3	3.77	m ^[a]		84.3
8	5.22	dd	15.5, 8.5	129.8	5.63	m		137.57
9	5.68	dd	15.6, 7.2	137.9	5.21/5.23	ddd	6.6, 1.5, 0.8	118.04
8	5.22		15.5, 8.5	129.8	5.06	m		115.3
9	5.68		15.6, 7.2	137.9	5.79	d	0.8	141.0
10	2.22	m ^[a]		41.7	2.27	m		44.1
11	3.89	dd	12.0, 10.3	70.1	3.72	ddd	10.1, 5.8, 1.9	75.5
12a	1.65	m ^[a]		36.2	1.68	dt	14.3, 2.2	35.9
12b	1.40	m ^[a]			1.46	dt	14.4, 10.3	
13	3.72	ddd	9.7, 6.0, 2.1	70.3	3.77	ddd	10.5, 5.8, 2.4	73.9
14	3.05	ddd	9.5, 5.5, 2.7	83.9	3.10	q	5.6	83.7
15a	2.57	br d	15.0	33.5	2.42	dddt	14.9, 6.8, 5.4, 1.4	34.0
15b	2.28	m ^[a]			2.23	m		
16	5.49	m ^[a]		129.3	5.82	m ^[a]		134.1
17	6.13	m ^[a]		133.6	5.08	m ^[a]		117.7
42	1.10	m ^[a]		16.1	1.09	d	6.9	14.7
43	0.83	d	6.9	12.2	1.05	d	6.9	15.0
7-OCH₃	3.23	s		56.0	3.29	s		56.1
14-OCH₃	3.41	s		57.3	3.42	s		58.2

br = broad signal.

^[a] Overlapping signal.

Although some chemical shifts exhibit similarities and fall within the expected range, none are entirely identical. This discrepancy arises because the authentic fragments represent only small sections of the molecule, whereas neaumycin B (**1**) is a large and complex macrocycle

with numerous structural factors influencing chemical shifts. A more meaningful comparison can be made by examining the ^1H and ^{13}C NMR data from the synthetic neaumycin B (**1**) reported by Smith and Chen, alongside Fenical's data and this work.

A close examination of the Smith and Chen datasets reveals nearly identical NMR spectra (**Table 3.6-6**).^[12,13] The largest deviation in the ^1H spectrum is only 0.01 ppm, while in the ^{13}C spectrum, deviations are generally within 0.1 ppm, with the notable exception of C13, which shows a 1.8 ppm difference. Similarly, coupling constants are highly consistent, with the most significant discrepancy being the coupling constant of H16, which Smith reported as 13.9 Hz and Chen as 14.6 Hz. Apart from these exceptions, the data strongly suggest that both Smith and Chen synthesized the same molecule with identical stereocenters.

Table 3.6-6. NMR data of synthetic neaumycin B (**1**) from Smith *et al.* and Chen *et al.*^[12,13]

Synthetic neaumycin B (1) by Smith <i>et al.</i> (600/150 MHz, CDCl ₃ , r.t.)					Synthetic neaumycin B (1) by Chen <i>et al.</i> (800/201 MHz, CDCl ₃ , r.t.)				
Atom	δ_H [ppm]	m	<i>J</i> [Hz]	δ_C [ppm]	δ_H [ppm]	m	<i>J</i> [Hz]	δ_C [ppm]	
1	0.00			165.6	0.00			165.6	
2	5.75	d	15.9	122.1	5.76	d	15.9	122.1	
3	6.77	dd	15.8, 8.0	150.3	6.78	dd	15.8, 7.9	150.3	
4	2.38	m ^[a]		43.4	2.38	m ^[a]		43.3	
5	3.70	m ^[a]		72.0	3.70	m ^[a]		72.0	
6a	1.66	m ^[a]		39.7	1.66	m ^[a]		39.6	
6b	1.57	m ^[a]			1.57	m ^[a]			
7	3.83	dd	7.4, 4.0	80.7	3.84	dd	7.4, 4.0	80.7	
8	5.40	dd	15.5, 8.4	129.2	5.41	dd	15.6, 8.4	129.2	
9	5.72	dd	15.0, 7.4	138.2	5.73	dd	15.3, 7.7	138.2	
10	2.17	h	6.9	43.0	2.18	q	7.5	42.9	
11	3.47	d	9.2	76.4	3.47	d	9.2	76.4	
12a	1.83	br d	14.3	36.7	1.84	d	14.1	36.6	
12b	1.34	m ^[a]			1.34	m ^[a]			
13	3.72	m ^[a]		76.4	3.72	m ^[a]		74.6	
14	3.06	td	6.5, 4.1	84.0	3.07	td	6.5, 4.1	84.0	
15a	2.43	m ^[a]		32.6	2.43	m ^[a]		32.6	
15b	2.43	m ^[a]			2.43	m ^[a]			
16	5.60	dt	13.9, 7.2	128.4	5.60	dt	14.6, 7.3	128.4	
17	6.07	m ^[a]		133.4	6.07	m ^[a]		133.4	
42	1.12	m ^[a]		15.7	1.12	m ^[a]		15.7	
43	0.85	d	6.5	16.6	0.86	d	6.5	16.5	
7-OCH₃	3.25	s		56.2	3.25	s		56.2	
14-OCH₃	3.42	s		57.4	3.43	S		57.4	

br = broad signal.

^[a] Overlapping signal.

When comparing these results with Fenical's data, substantial discrepancies become apparent. Significant deviations in chemical shifts are observed across almost all atoms, with the most pronounced differences at H11 (0.42 ppm), H5 (0.14 ppm), and H6a (0.16 ppm, **Table 3.6-7**). Additional discrepancies are found at H4 to H8, H12, and H15 to H17. The same

trend is evident at the ^{13}C chemical shifts, where atoms C3 to C8 show variations of up to 3.6 ppm, along with large differences at C10-C16 and the methyl group C43. These inconsistencies strongly indicate that Fenical's proposed structure does not represent the correct structure of neaumycin B (**1**).

Table 3.6-7. Comparison of the NMR data from Fenical *et al.*, Smith *et al.*, Chen *et al.* and this work.^[11–13]

Atom	$\Delta \delta_{\text{H}}$ [ppm]			$\Delta \delta_{\text{C}}$ [ppm]		
	Fenical -Smith	Fenical -Chen	Fenical -this work	Fenical -Smith	Fenical -Chen	Fenical -this work
1				0.3	0.3	-1.3
2	0.01	0.00	-0.09	-0.1	-0.1	0.8
3	-0.02	-0.03	-0.22	0.9	0.9	-0.1
4	-0.07	-0.07	-0.10	0.7	0.8	1.2
5	-0.14	-0.14	-0.20	3.0	3.0	0.4
6a	-0.16	-0.16	-0.11	0.9	1.0	1.1
6b	-0.07	-0.07	-0.06			
7	-0.15	-0.16	-0.09	3.6	3.6	0.0
8	-0.18	-0.19	-0.41	0.6	0.6	14.7
9	-0.04	-0.05	0.45	-0.3	-0.3	-3.0
10	0.05	0.04	-0.05	-1.3	-1.2	-2.4
11	0.42	0.42	0.17	-6.3	-6.3	-5.4
12a	-0.18	-0.19	-0.03	-0.5	-0.4	0.3
12b	0.06	0.06	-0.06			
13	0.00	0.00	-0.05	-6.1	-4.3	-3.6
14	-0.01	-0.02	-0.05	-0.1	-0.1	0.2
15a	0.14	0.14	0.15	0.9	0.9	-0.5
15b	-0.15	-0.15	0.05			
16	-0.11	-0.11	-0.33	0.9	0.9	-4.8
17	0.06	0.06	1.05	0.2	0.2	15.9
42	-0.02	-0.02	+0.01	0.4	0.4	1.4
43	-0.02	-0.03	-0.22	-4.4	-4.3	-2.8
7-OCH₃	-0.02	-0.02	-0.06	-0.2	-0.2	-0.1
14-OCH₃	-0.01	-0.02	-0.01	-0.1	-0.1	-0.9

Further insights can be gained by comparing the authentic fragment data with the NMR values from Fenical's structure. Since the fragments are relatively small, and chemical shifts depend

on neighboring groups, the terminal atoms (1-2, 8-9, and 16-17) are marked in gray to indicate that their values are not fully reliable due to the significant structural differences in their surroundings. This is confirmed by the large chemical shift deviations observed at H17 (up to 1.05 ppm) and C17 (15.9 ppm). However, within the central regions of the fragments, several improvements in chemical shift alignment can be noted compared to Smith and Chen's data.

In the ^1H spectrum, notable improvements in alignment with Fenical's data are observed at H6a, H7, H11, H12a, and H15b. No direct improvements were achieved at H4, H5, or H10 where the stereocenters were modified (marked in red). Adjacent atoms such as H6a showed a reduced discrepancy from 0.16 ppm (Smith/Chen vs. Fenical) to 0.11 ppm in the authentic fragment, indicating a better match. Similarly, H7 improved from a deviation of 0.16 ppm to 0.09 ppm. A particularly striking example is H11 and H12a, where the chemical shift discrepancy was reduced from 0.42 ppm to 0.17 ppm for H11 and from 0.19 ppm to 0.03 ppm for H12a. These atoms are located near the methyl group at C10, which possesses the revised stereochemistry in the authentic fragments. Furthermore, H15b exhibited an improvement in deviation from 0.15 ppm to 0.05 ppm.

Examining the ^{13}C shifts, improvements were achieved in fragment **299** at C3, C5, and C7. The deviation at C3 decreased from 0.9 ppm to 0.1 ppm, while C5, one of the modified stereocenters, showed a significant reduction from 3.0 ppm to 0.4 ppm. Additionally, C7 displayed a perfect match with Fenical's data, whereas it showed previously a deviation of 3.6 ppm in Smith and Chen's reports. Thus, both H7 and C7 demonstrated improved agreement. Furthermore, at C11 and C12, the deviations were reduced from 6.3 ppm to 5.4 ppm and from 0.5 ppm to 0.3 ppm, respectively. However, at C13, while Smith and Chen had achieved an exact match in the ^1H spectrum, their deviations in ^{13}C shifts were substantial (6.1 ppm for Smith and 4.3 ppm for Chen). The authentic fragments showed an improved agreement in ^{13}C shift (reduced to 3.6 ppm), although at the cost of a slight deterioration in the H7 shift (now deviating by 0.05 ppm). Similarly, improvements were observed at C15, where the deviation was reduced from 0.9 ppm to 0.5 ppm, and at the methyl group C43, where the difference decreased from 4.4 ppm to 2.8 ppm.

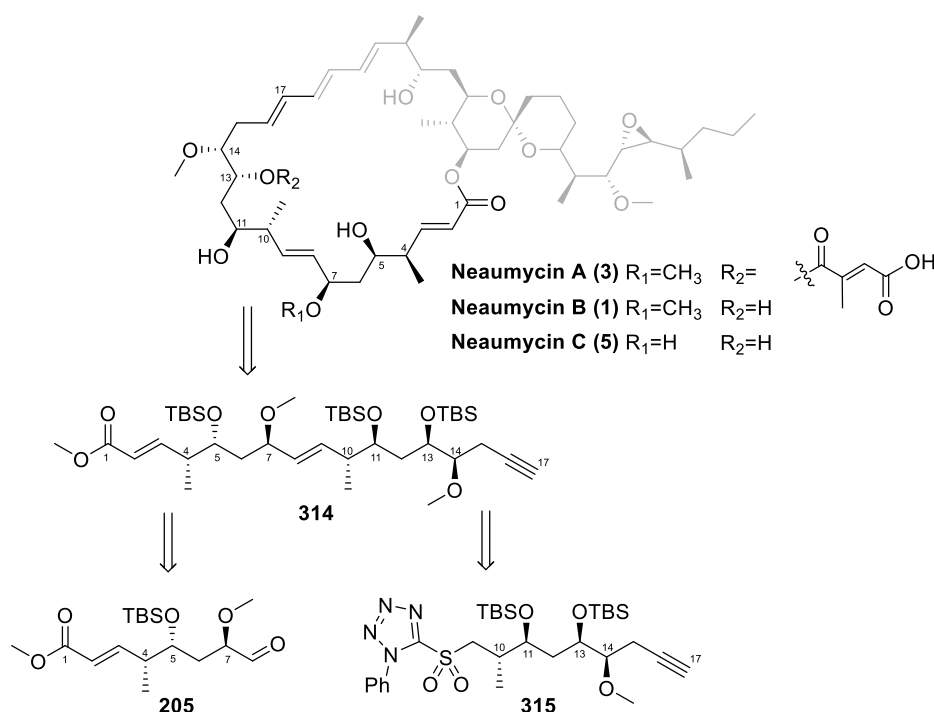
In summary, comparing small fragments to a large and complex macrocycle like neaumycin B (**1**) is inherently challenging, especially because the folded nature of the macrocycle

significantly influences chemical shifts. In summary, this study demonstrated improvements in key regions of the molecule. Although a perfect match has not yet been achieved, which was expected, the results indicate that the revised stereochemistry may indeed be more accurate. The next logical step is to synthesize the full neaumycin B (**235**) with the revised stereocenters and directly compare its NMR data to confirm this hypothesis.

4 Conclusion

4.1 Summary

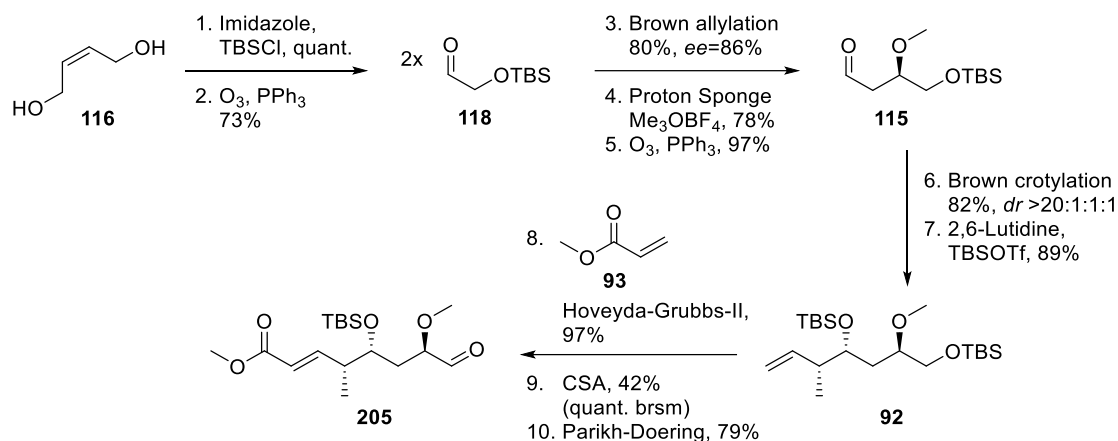
Neaumycin B (**1**) is a highly complex natural product that exhibits a strong synergistic effect with Ramoplanin against methicillin-resistant *Staphylococcus aureus* (MRSA) and shows potent cytotoxic activity against U87 human glioblastoma cells, highlighting its potential for further pharmacological development.^[10,11] Its structural complexity also presents a significant challenge in total synthesis, which is why this work focused on synthesizing the southern fragment **314** of this intricate molecule (**Scheme 4.1-1**).



Scheme 4.1-1. Retrosynthetic strategy for the southern fragment **314** of neaumycin B (**1**).

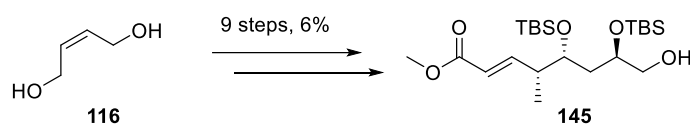
In this work, the synthesis of the southern fragment **314** was explored, aiming to connect aldehyde **205** and sulfone **315** through a Julia-Kocienski olefination. The synthesis starts from commercially available diol **116**, which was doubly protected as TBS ethers and subjected to ozonolysis to yield aldehyde **118** (**Scheme 4.1-2**). Due to the molecular symmetry, two equivalents of aldehyde **118** were obtained. A Brown allylation introduced the first stereocenter with an enantiomeric excess of 86%. The resulting alcohol was methylated using a Meerwein methylation, and a second ozonolysis converted the terminal double bond into

aldehyde **115**. A subsequent Brown crotylation delivered an excellent diastereoselectivity ($dr > 20:1:1:1$) with 82% yield. The alcohol was protected to obtain silyl ether **92**. A Grubbs metathesis with methyl acrylate (**93**), followed by primary TBS deprotection and a final Parikh-Doering oxidation, yielded aldehyde **205** in 10 steps with an overall yield of 25%.



Scheme 4.1-2. Synthesis of aldehyde **205** over 10 steps with an overall yield of 25%, starting from diol **116**.

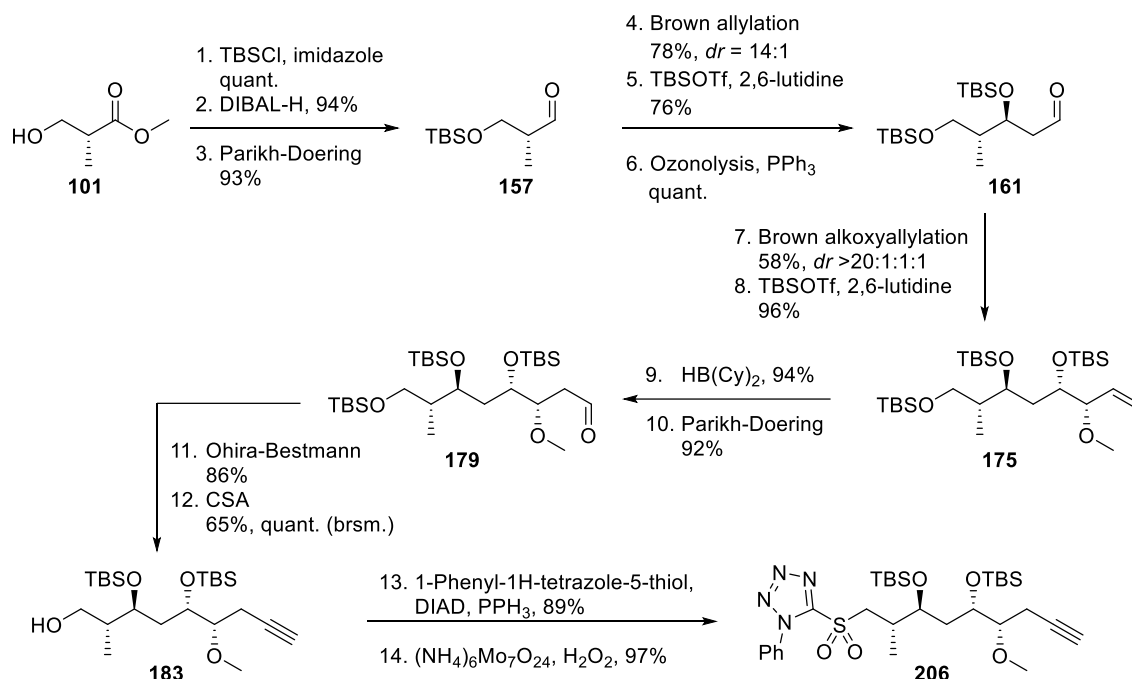
Similarly, alcohol **145**, required for the synthesis of neaumycin C (**5**), was synthesized in nine steps but with a significantly lower yield of 6%, primarily due to a challenging primary deprotection step, which resulted in only 25% yield (refer to **Chapter 3.3.2, Scheme 4.1-3**).



Scheme 4.1-3. Analogous synthesis of the silyl ether derivative **145**.

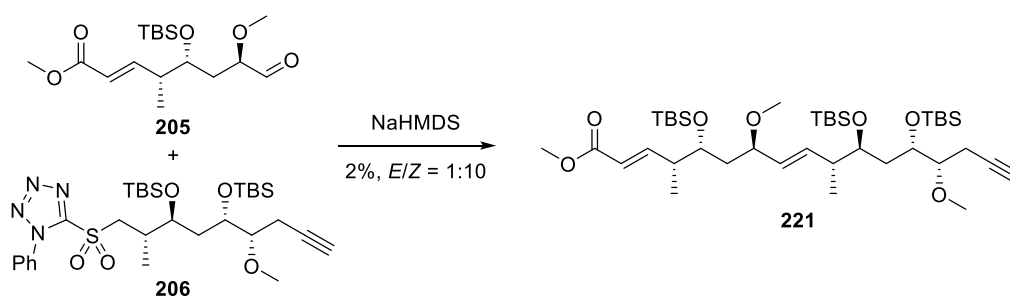
For the synthesis of sulfone **206** (unintentionally, the incorrect diastereomer **206** was synthesised instead of **315**, differing in the stereochemistry at the 1,2-diol moiety), the starting material, (*R*)-Roche ester (**101**), was initially protected as a TBS ether (**Scheme 4.1-4**). The ester was reduced by DIBAL-H to an alcohol, and oxidized via a Parikh-Doering reaction to yield aldehyde **157**. Following Brown allylation, provided a dr of 14:1 and subsequent TBS protection and ozonolysis of the double bond afforded aldehyde **161**. A challenging alkoxyallylation with 3-methoxy-1-propene introduced two stereocenters simultaneously, forming both an alcohol and a methoxy group with excellent diastereoselectivity ($dr > 20:1:1:1$). The alcohol was then TBS-protected to obtain silyl ether **175**. Hydroboration using *in situ* prepared dicyclohexylborane, followed by a Parikh-Doering oxidation, furnished

aldehyde **179**, which was converted into an alkyne via an Ohira-Bestmann reaction. The primary TBS group was then deprotected using CSA to obtain primary alcohol **183**, which was further transformed into sulfone **206** in two steps via a Mitsunobu reaction to form the corresponding thioether, followed by oxidation to the sulfone **206**.



Scheme 4.1-4. Synthesis of sulfone **206** over 14 steps, starting from *(R)*-Roche ester (**101**) with an overall yield of 20%.

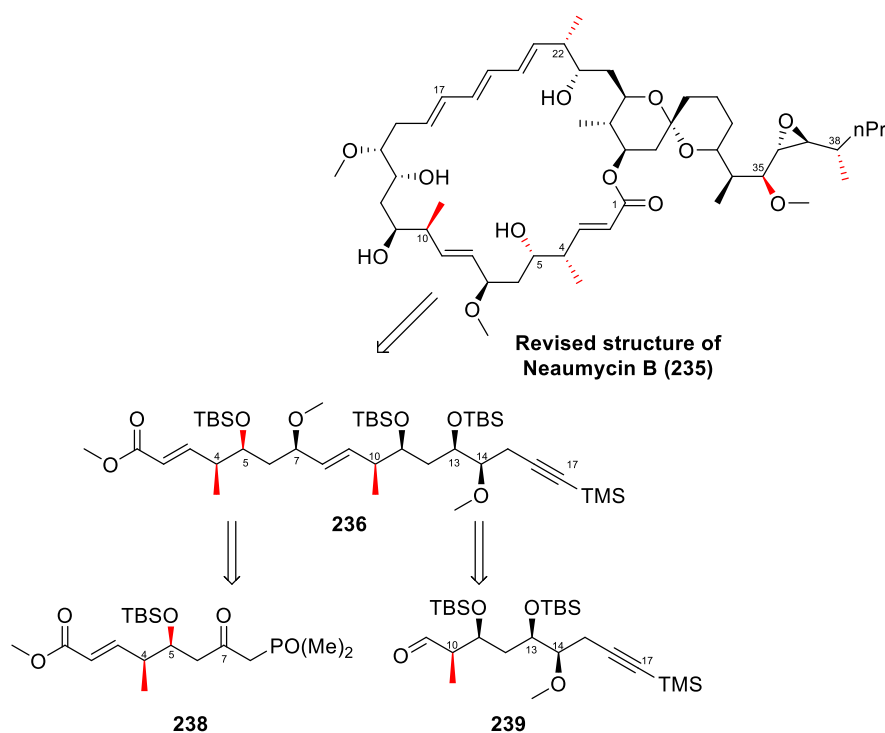
Aldehyde **205** and sulfone **206** were converted in a Julia-Kocienski olefination to yield olefin **221** (Scheme 4.1-5). Unfortunately, the best yield was only 2%, with an *E/Z* selectivity of 1:10, favoring the wrong diastereomer.



Scheme 4.1-5. Julia-Kocienski olefination of aldehyde **205** and sulfone **206** to olefin **221**.

At this stage, two total syntheses of neaumycin B (**1**) had already been reported. However, the NMR data did not match the originally isolated neaumycin B (**1**) reported by Fenical

et al.,^[11] who first proposed its stereochemical structure. This discrepancy suggested that the predicted structure was incorrect. Consequently, a structure revision was conducted in collaboration with Prof. N. Ziemert, revealing that the revised structure of neaumycin B (**235**) featured six different stereocenters (marked in red) at C4, C5, C10, C22, C35, and C38 (Scheme 4.1-6).

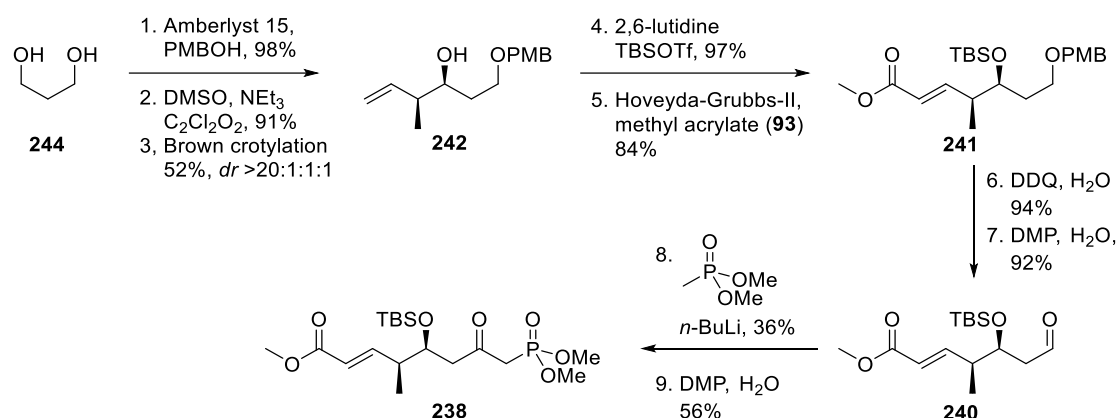


Scheme 4.1-6. Structural revision of neaumycin B (**235**) and the retrosynthetic strategy for synthesizing the southern fragment **236** from phosphonate **238** and aldehyde **239**.

In consequence the synthetic strategy was adjusted. The new approach focused on synthesizing the southern fragment **236**, incorporating the revised stereocenters. Additionally, a TMS-protected alkyne was introduced to avoid complications in base-mediated couplings. Since the previous synthetic approach was not directly applicable to the new stereochemical configuration (see **Chapter 3.5**), the southern fragment **236** was synthesized via a Horner-Wadsworth-Emmons (HWE) coupling between phosphonate **238** and aldehyde **239**.

The synthesis of phosphonate **238** started from diol **244**, where one hydroxyl group was selectively protected as a PMB ether, and the remaining hydroxyl was oxidized to aldehyde via a Swern oxidation (**Scheme 4.1-7**). A Brown crotylation introduced the first two

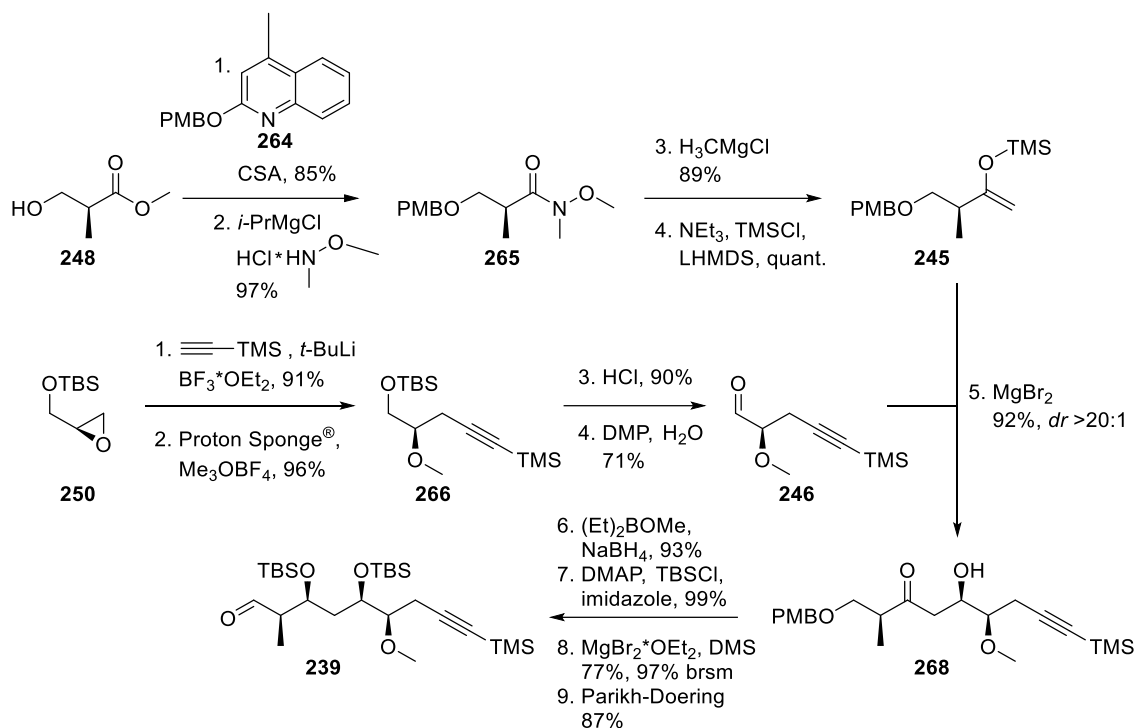
stereocenters with remarkable diastereoselectivity ($dr >20:1:1:1$) to yield alcohol **242**. Notably, this selectivity was maintained even at a decagram scale. Alcohol **242** was then TBS-protected and converted into olefin **241** via Grubbs metathesis with methyl acrylate (**93**). The primary PMB ether was removed with DDQ, and the resulting alcohol was oxidized with DMP to aldehyde **240**. A nucleophilic attack of deprotonated dimethyl methylphosphonate on aldehyde **240**, followed by oxidation of the resulting secondary alcohol, yielded target phosphonate **238** over nine steps with an overall yield of 7%.



Scheme 4.1-7. Synthesis of phosphonate **238** over 9 steps, starting from diol **244** with an overall yield of 7%.

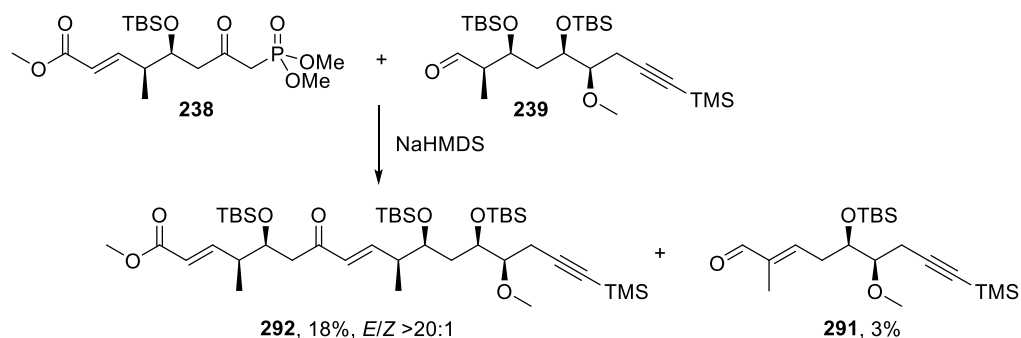
The synthesis of aldehyde **239** started from (*S*)-Roche ester (**248**), by PMB-protection using the previously synthesized Dudley reagent (**264**, **Scheme 4.1-8**). The ester was converted into amide **265** and a Grignard reaction yielded the corresponding methyl ketone, which was subsequently transformed into silyl enol ether **245**.

Epoxide **250** was subjected to basic ring-opening, and the resulting alcohol was methylated via a Meerwein methylation to yield methyl ether **266**. The TBS group was removed, and the alcohol was oxidized with DMP to the volatile aldehyde **246**. Aldehyde **246** was coupled with silyl enol ether **245** in a Mukaiyama aldol reaction, providing ketone **268** with an excellent yield of 92% and a dr of $>20:1$, even on a multigram scale. A Narasaka-Prasad reduction, followed by selective TBS protection of the resulting 1,3-diol, PMB deprotection, and a final Parikh-Doering oxidation furnished aldehyde **239** in an impressive 52% yield over nine steps.



Scheme 4.1-8. Synthesis of aldehyde **239** over 9 steps (longest linear sequence) with a yield of 52%, starting from (*S*)-Roche ester (**248**).

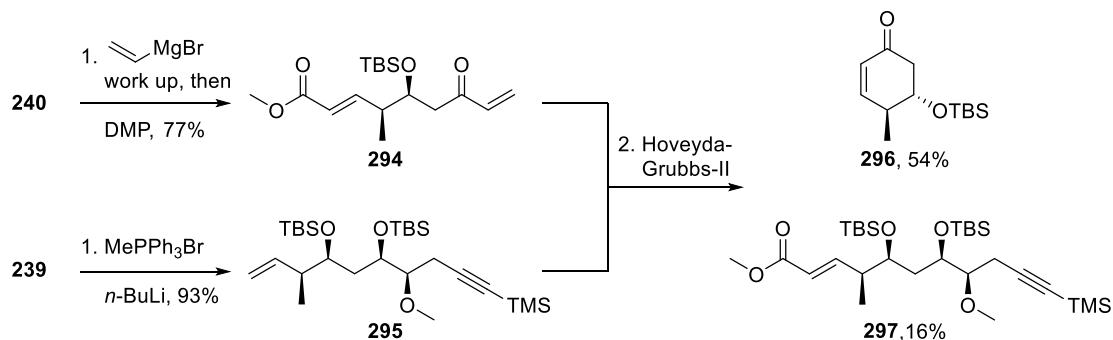
The HWE coupling yielded the desired olefination product **292**, albeit with a modest yield of 18% (**Scheme 4.1-9**). This time a favored *E/Z* selectivity of >20:1 was achieved. Nevertheless the elimination byproduct **291**, was also isolated, causing complications in the reaction (refer to **Chapter 3.6.3**).



Scheme 4.1-9. HWE reaction of phosphonate **238** and aldehyde **239** to yield olefin product **292** and the eliminated aldehyde **291**.

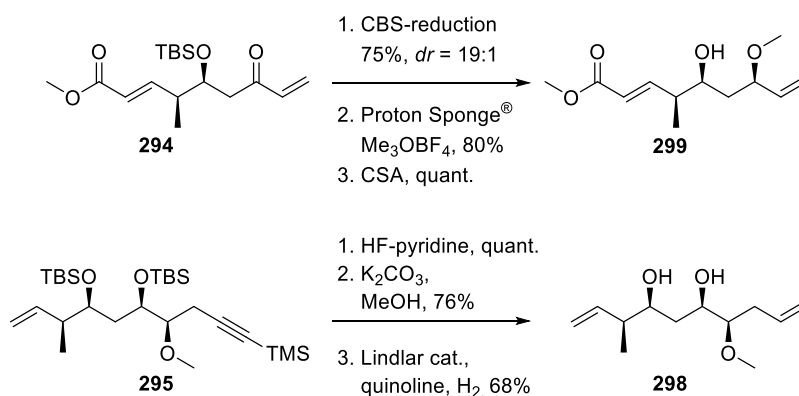
To circumvent base-induced elimination, alternative strategies were pursued by synthesizing olefins **294** and **295** (**Scheme 4.1-10**). Olefin **294** was obtained via a Grignard reaction with aldehyde **240**, while olefin **295** was synthesized through a Wittig reaction from aldehyde **239**.

Attempts to couple these intermediates via Grubbs metathesis were unsuccessful, as the reaction led to undesired cyclization of **294**, forming compound **296**, instead of the expected olefination product **292**. Methyl acrylate, released during intramolecular metathesis of substrate **294**, underwent an additional Grubbs metathesis with olefin **295**, yielding olefin **297**.



Scheme 4.1-10. Grubbs metathesis of olefin **294** and **295** to cyclohexenon **296** and olefin **297**.

Finally, authentic fragments **299** and **298** (Scheme 4.1-11), containing the revised stereocenters, were synthesized for NMR comparison with Fenical's isolated neaumycin B (**1**) and the previously synthesized structures by Smith *et al.*^[12] and Chen *et al.*^[13] Fragment **299** was obtained by reducing vinyl ketone **294** via CBS reduction, followed by a Meerwein methylation and TBS deprotection using CSA. Fragment **298** was synthesized by sequentially removing the TBS groups from **295** using HF-pyridine, deprotecting the TMS group with K_2CO_3 in MeOH, and reducing the alkyne to a double bond via Lindlar catalysis.



Scheme 4.1-11. Synthesis of the authentic fragments **299** and **298**.

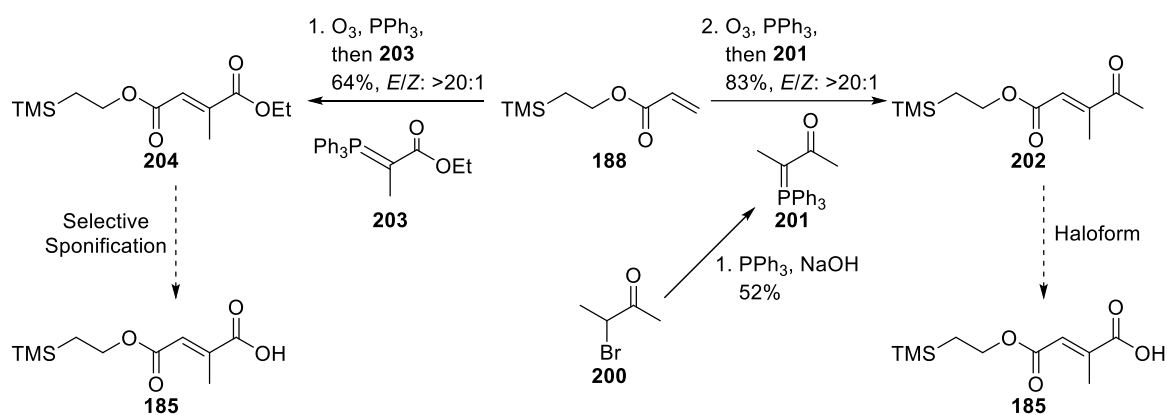
Comparing the authentic fragment data with Fenical's structure reveals notable improvements in chemical shift alignment, particularly in the central regions (Table 4.1-1). While terminal atoms show large deviations due to structural differences, significant

reductions in discrepancies were observed for key protons (H6a, H7, H11, H12a, and H15b) and carbons (C3, C5, C7, C11, and C15). The revised stereochemistry appears more accurate, but full confirmation requires synthesizing complete neaumycin B (**235**) and comparing its NMR data. For further details see **Chapter 3.6.5**.

Table 4.1-1. Comparison of the NMR data from Fenical *et al.*, Smith *et al.*, Chen *et al.* and this work.^[11–13]

Atom	$\Delta \delta_{\text{H}}$ [ppm]			$\Delta \delta_{\text{C}}$ [ppm]		
	Fenical -Smith	Fenical -Chen	Fenical -this work	Fenical -Smith	Fenical -Chen	Fenical -this work
1				0.3	0.3	-1.3
2	0.01	0.00	-0.09	-0.1	-0.1	0.8
3	-0.02	-0.03	-0.22	0.9	0.9	-0.1
4	-0.07	-0.07	-0.10	0.7	0.8	1.2
5	-0.14	-0.14	-0.20	3.0	3.0	0.4
6a	-0.16	-0.16	-0.11	0.9	1.0	1.1
6b	-0.07	-0.07	-0.06			
7	-0.15	-0.16	-0.09	3.6	3.6	0.0
8	-0.18	-0.19	-0.41	0.6	0.6	14.7
9	-0.04	-0.05	0.45	-0.3	-0.3	-3.0
10	0.05	0.04	-0.05	-1.3	-1.2	-2.4
11	0.42	0.42	0.17	-6.3	-6.3	-5.4
12a	-0.18	-0.19	-0.03	-0.5	-0.4	0.3
12b	0.06	0.06	-0.06			
13	0.00	0.00	-0.05	-6.1	-4.3	-3.6
14	-0.01	-0.02	-0.05	-0.1	-0.1	0.2
15a	0.14	0.14	0.15	0.9	0.9	-0.5
15b	-0.15	-0.15	0.05			
16	-0.11	-0.11	-0.33	0.9	0.9	-4.8
17	0.06	0.06	1.05	0.2	0.2	15.9
42	-0.02	-0.02	+0.01	0.4	0.4	1.4
43	-0.02	-0.03	-0.22	-4.4	-4.3	-2.8
7-OCH ₃	-0.02	-0.02	-0.06	-0.2	-0.2	-0.1
14-OCH ₃	-0.01	-0.02	-0.01	-0.1	-0.1	-0.9

Additionally, a synthetic strategy was developed for mesaconic acid **185**, required for the synthesis of neaumycin A (**3**, **Scheme 4.1-12**). The synthesis begins from TMSE ether **188**, which can be obtained through the reaction of acryloyl chloride with 2(trimethylsilyl)ethanol (TMSE). Ozonolysis of **188** furnishes the corresponding aldehyde, which is transformed into ketone **202** via a Wittig reaction using triphenylphosphonium salt **201**, prepared from bromide **200**. Alternatively, the aldehyde can be converted into ethyl ester **204** employing triphenylphosphonium salt **203**. Both **202** and **204** can subsequently be converted to mesaconic acid **185** through selective saponification or a classical Haloform reaction, respectively.

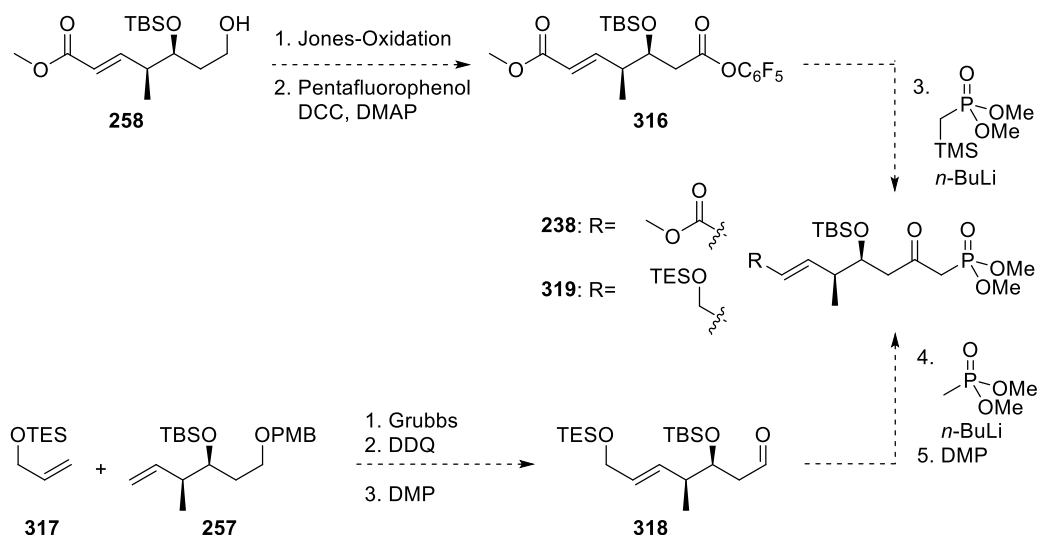


Scheme 4.1-12. Synthesis strategy for mesaconic acid **185**, which is essential for the preparation of neaumycin A (**3**).

4.2 Outlook

Since the HWE coupling ultimately yielded promising results with methylphosphonate **238**, and the undesired elimination reactions could be effectively suppressed, this approach should be further pursued (see **Chapter 3.6.3**). The synthesis of methylphosphonate requires optimization, as previous attempts did not yield satisfactory results, possibly due to the ester functionality present in the molecule. To address this issue, Cossy *et al.* developed a system that successfully introduces methylphosphonates in the presence of an ester group.^[171]

In this approach, alcohol **258** is oxidized to the corresponding acid utilizing the Jones oxidation conditions, followed by Steglich esterification with pentafluorophenol (**Scheme 4.2-1**). The resulting pentafluorophenyl ester **316** acts as electrophile and is attacked by the lithiated dimethyl ((trimethylsilyl)methyl)phosphonate to afford the desired methylphosphonate **238**. Alternatively, the synthesis could start from homoallylic alcohol **257**. In this case, rather than reacting with methyl acrylate in a Grubbs reaction as previously attempted, the alkene **257** would be coupled with silyl ether **317**. Subsequent PMB deprotection and oxidation would yield aldehyde **318**, which could then be attacked by the lithiated species of dimethyl methylphosphonate and further oxidized to ketone **319**.

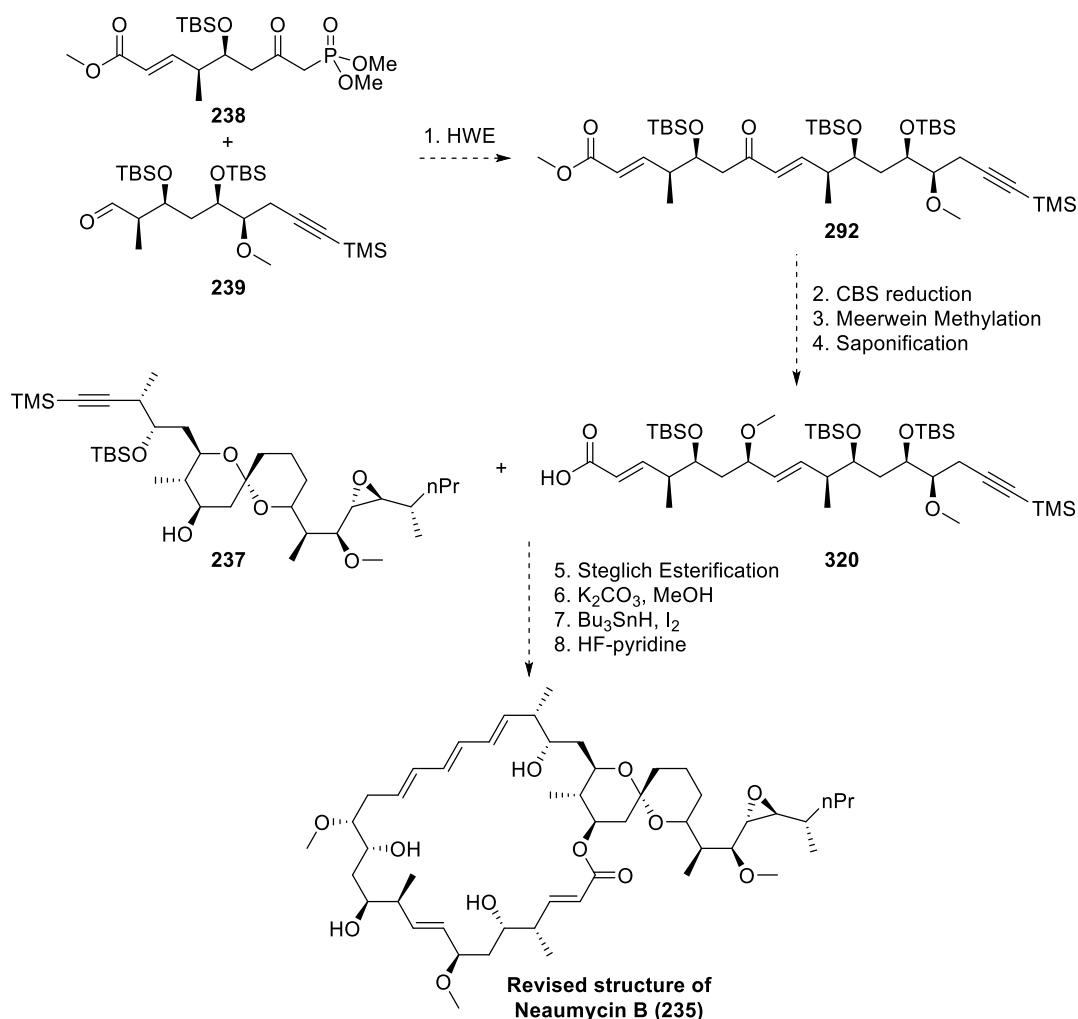


Scheme 4.2-1. Synthesis strategy for methyl phosphonate **238** or **319**.

With the successful synthesis of methylphosphonate **238** (for simplicity, only **238** is depicted here, omitting **319**), further investigations into the HWE reaction with aldehyde **239** could be conducted to obtain olefin **292** in improved yields (**Scheme 4.2-2**). Subsequent CBS reduction,

methylation of the resulting alcohol and saponification of the methyl ester to the corresponding acid would afford the final southern fragment **320**. This fragment could then be coupled with the northern fragment **237** via a Steglich esterification, utilizing the carboxylic acid functionality of **320** and the alcohol at the spiroketal moiety of **237**.

Finally, TMS deprotection and functionalization of both alkynes to the corresponding vinyl iodide following the mild and functional group tolerant methodology reported by Chong *et al.* would enable an intramolecular Stille reaction.^[172] The final step would involve global deprotection of all protecting groups using HF-pyridine, ultimately yielding neaumycin B (**235**).



Scheme 4.2-2. Final steps towards the total synthesis of neaumycin B (**235**).

5 Experimental Procedures

5.1 General Information

Reaction handling: Unless stated otherwise, all non-aqueous reactions were performed in flame-dried glassware under an argon atmosphere. All flasks were equipped with rubber septa or were sealed with a glass stopper and a PTFE-collar. Temperatures above r.t. (23– 27 °C) refer to oil bath temperatures, which were controlled by a temperature modulator. The following baths were used for cooling: water/ice (0 °C), acetone/dry ice (–78 °C) and acetone/liquid nitrogen (–90 °C). Reactions were magnetically stirred and monitored by TLC, unless otherwise noted.

Solvents and reagents: Unless stated otherwise, solvents were purchased from the central chemical store (ZVE) of the University of Bonn. Cyclohexane (CH) and ethyl acetate (EA) were distilled over a Vigreux column. Dry solvents like dichloromethane, toluene, diethyl ether and acetonitrile were taken out of a solvent purification system MB-SPS 800 from MBraun, Garching. THF was freshly distilled over sodium/benzophenone before use. Reagents were purchased from the following companies: Acros Organics, Geel (Belgium); Alfa-Aesar, Ward Hill, MA (USA); Sigma-Aldrich, St. Louis, MO (USA) and TCI Chemicals, Antwerp (Belgium). Unless stated otherwise all of these chemicals were used without further purification.

Flash column chromatography was accomplished according to the method introduced by G. Nill using silica gel (pore size 60 Å, 0.040 – 0.063 mm) purchased from Merck Millipore, Massachusetts (USA). The given yields refer to the purified products.^[173,174]

Optical rotations were measured with a MCP 150 polarimeter (Anton Paar) in a 1 dm cuvette using a sodium lamp.

¹H-NMR spectra were recorded at room temperature (298 K) on Bruker Avance I spectrometers with a ¹H operating frequency of 300, 400 and 500 MHz and Bruker Avance III spectrometers with a ¹H operating frequency of 500 MHz and 700 MHz. Unless stated otherwise, all spectra were recorded at room temperature. All chemical shifts are given in δ units relative to the residual protiated solvent residual peak (CDCl₃: δH = 7.26 ppm, CD₂Cl₂: δH = 5.32, d₆-acetone: δH = 2.05 ppm, d₆-DMSO: δH = 2.50 ppm).^[175] Analyses followed

first-order principles and the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants through n bonds (nJ) are given in Hertz [Hz].

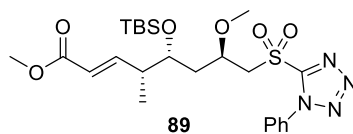
^{13}C -NMR spectra were recorded at room temperature on Bruker Avance I spectrometers with a ^{13}C operating frequency of 75 and 100 MHz and Bruker Avance III spectrometers with a ^{13}C operating frequency of 125 and 175 MHz. Unless stated otherwise, all spectra were recorded at room temperature. All chemical shifts are given in δ units relative to the residual protiated solvent residual peak (CDCl_3 : $\delta\text{C} = 77.16$ ppm, CD_2Cl_2 : $\delta\text{C} = 13.84$ ppm, d_6 -acetone: $\delta\text{H} = 29.84$ ppm, d_6 -DMSO: $\delta\text{C} = 39.52$ ppm).^[175]

* chem. shifts associated with the major diastereomer are marked with an asterisk.

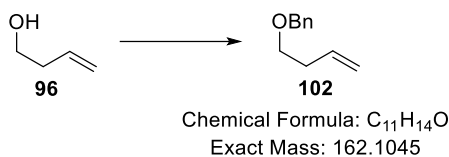
chem. shifts associated with the minor diastereomer are marked with a hash.

Mass spectra (MS) and high-resolution- mass spectra (HR-MS) were recorded on a MAT 95 XL sector field device from Thermo Finnigan (Bremen), mircoTOF-Q from Bruker Daltonik (Bremen) and LTQ Orbitrap XL mass spectrometer from Thermo Fisher Scientific (Bremen). Ionization processes and mol peaks were given in combination with characteristic fragmentations.

5.2 Experimental Details for Chapter 3.3.1: Synthesis of Sulfone **89**



5.2.1 ((But-3-en-1-yloxy)methyl)benzene (**102**)



Sodium hydride (28.2 g, 706 mmol, 1.50 equiv., 60% dispersion in mineral oil) was added carefully to a solution of 3-butenol (**96**, 40.0 mL, 470 mmol, 1.00 equiv.) in THF (200 mL) and stirred for 2 h. Benzyl bromide (83.8 mL, 706 mmol, 1.50 equiv.) was added and the reaction was stirred for 18 h. H₂O (100 mL) was added, the aqueous phase was extracted with Et₂O (3 x 100 mL) and the combined organic layers were washed with brine (20 mL). Drying over MgSO₄, removal of the solvent *in vacuo* and purification of the residue by distillation under reduced pressure (bp ~130 °C @ ~80 mbar) yielded ether **102** (76.2 g, 470 mmol, quant) as a colourless oil.

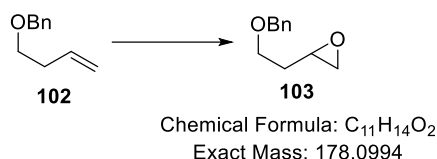
R_f = 0.28 (CH/EA 40:1)

¹H NMR (CD₂Cl₂, 400 MHz): δ = 7.37 – 7.29 (m, 5H), 5.87 (ddt, 1H, J =17.0, 10.2, 6.7 Hz), 5.17 – 4.95 (m, 2H), 4.50 (s, 2H), 3.53 (t, 2H, J =6.7 Hz), 2.37 (qt, 2H, J =6.7, 1.4 Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 139.2, 136.0, 129.4, 129.2, 128.7, 128.0, 127.8, 116.3, 73.2, 70.1, 34.7 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 163.1117; found: 163.1117.

The experimental data are in agreement with those previously published.^[176]

5.2.2 2-(2-(Benzyloxy)ethyl)oxirane (**103**)

A solution of **102** (25.0 g, 154 mmol, 1.00 equiv.) in DCM (77 mL) was cooled to 0 °C. *m*CPBA (39.9 g, 231 mmol, 1.50 equiv.) was carefully added and the reaction mixture was stirred at 0 °C for 1 h, then allowed to warm to r.t. and stirred for additional 2 h. Aq. sat. Na₂S₂O₃ (300 mL) was carefully added, the reaction mixture stirred for 30 min. and then aq. sat. NaHCO₃ (300 mL) was added and the reaction mixture was stirred for additional 30 min. The aqueous phase was extracted with DCM (3x 100 mL). The combined organic layers were again washed with aq. sat. Na₂S₂O₃ (100 mL) and aq. sat. NaHCO₃ (100 mL), the aqueous phase was extracted with DCM (3x 100 mL) and the combined organic layers were dried over MgSO₄. Removal of the solvent *in vacuo* yielded epoxide **103** (24.7 g, 154 mmol, quant.) as a colourless oil, which was used in the next step without further purification.

R_f = 0.29 (CH/Ea 6:1)

¹H NMR (CD₂Cl₂, 500 MHz): δ = 7.38 – 7.32 (m, 4H), 7.31 – 7.25 (m, 1H), 4.51 (s, 2H), 3.68 – 3.53 (m, 2H), 3.02 (dddd, 1H, *J*=6.5, 4.8, 4.0, 2.7 Hz), 2.73 (ddd, 1H, *J*=5.1, 4.0, 0.5 Hz), 2.48 (dd, 1H, *J*=5.1, 2.7 Hz), 1.87 (dddd, 1H, *J*=14.3, 7.3, 6.1, 4.8 Hz), 1.75 (dq, 1H, *J*=14.3, 6.0 Hz) ppm.

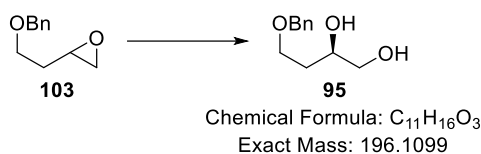
¹³C NMR (CD₂Cl₂, 126 MHz): δ = 139.1, 128.7, 128.0, 127.9, 73.3, 67.6, 50.2, 47.2, 33.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+Na]⁺: 201.0886; found: 201.0886.

The experimental data are in agreement with those previously published.^[177]

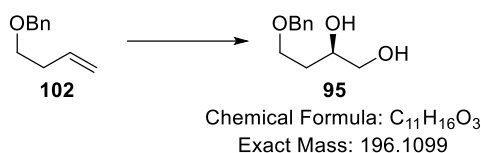
5.2.3 (R)-4-(Benzyloxy)butane-1,2-diol (**95**)

Procedure a:



((1*S*,2*S*)-(+)-1,2-Cyclohexanediamino-*N,N'*-bis(3,5-di-*tert*butylsalicylidene)cobalt(II)) (559 mg, 926 μ mol, 0.01 equiv.), acetic acid (5.29 mL, 92.6 mmol, 0.50 equiv.) and toluene (4.90 mL, 46.3 mmol, 0.25 equiv.) were placed in a round flask and stirred for 30 min at r.t. under air. The solvents were removed under reduced pressure, the resulting residue were cooled to 0 °C and epoxide **103** (33.0 g, 185 mmol, 1.00 equiv.) and H₂O (1.83 mL, 102 mmol, 0.55 equiv.) were added. The reaction mixture was allowed to stir for 40 h. H₂O (100 mL) and Et₂O (300 mL) were added, the aqueous phase was extracted with Et₂O (3x 100 mL) and DCM (3x 100 mL) and the combined organic layers were dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography over silica gel (CH/EA 1:2) to yield diol **95** (5.58 g, 28.4 mmol, 15%, *ee* = 25%, detected by HPLC, *n*-Hexan/2-propanol 98:02, DAICEL Chiralpak IH-U, flow: 0.85 mL/min, pressure 191 bar, retention time 20 min) as a yellow oil.

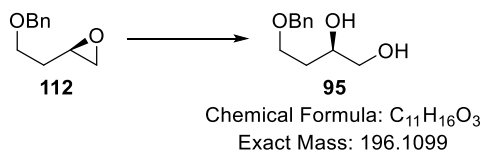
Procedure b:



To a solution of methansulfonamide (58.6 mg, 616 μ mol, 1.00 equiv.) in H₂O (1 mL) and *t*-BuOH (0.3 mL) was added AD-mix- β (864 mg) and the mixture was cooled to 0 °C. Alken **102** (100 mg, 616 μ mol, 1.00 equiv.) was transferred to the mixture by using *t*-BuOH (0.7 mL). The reaction mixture was allowed to warm to r.t. and stirred for 96 h. Aq. sat. Na₂SO₃ (1 mL) was added and the mixture stirred for 30 min. The aqueous Phase was extracted with Et₂O (3x 2 mL) and DCM (3x 2 mL), the combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel (CH/EA 1:2) to yield diol **95** (79.0 mg, 403 μ mol, 65%) as a yellow oil with an *ee* of 45%

which was detected by HPLC (*n*-Hexan/EtOH 98:02, DAICEL Chiralpak IH-U, flow: 0.85 mL/min, pressure 192 bar, retention time 20 min).

Procedure c:



112 (6.09 g, 34.2 mmol, 1.00 equiv.), THF (57 mL) and sodium hydroxide (3 M in water, 57.0 mL, 170 mmol, 5.00 equiv.) were placed in a sealed pressure tube and stirred for 65 h at 100 °C. The reaction mixture was allowed to cool to r.t., aq. sat. NH₄Cl (400 mL) was added and the aqueous layer were extracted with EA (3x 200 mL). The combined organic layers were washed with brine (300 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 1:2) yielded diol **95** (22.6 g, 115 mmol, 84%) as a yellow oil.

$R_f = 0.18$ (CH/EA 1:2).

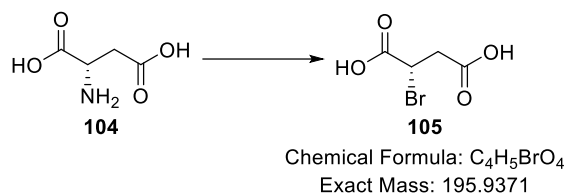
$[\alpha]_D^{20} = -6$ (DCM, $c = 0.5$).

¹H NMR (CD₂Cl₂, 499 MHz): $\delta = 7.51 - 7.05$ (m, 5H), 4.51 (s, 2H), 3.89 – 3.81 (m, 1H), 3.67 (qdd, 2H, $J=9.4, 6.8, 4.7$ Hz), 3.57 (ddd, 1H, $J=11.1, 6.7, 3.7$ Hz), 3.44 (ddd, 1H, $J=11.2, 6.5, 5.4$ Hz), 2.96 (d, 1H, $J=3.5$ Hz), 2.21 (dd, 1H, $J=6.8, 5.5$ Hz), 1.83 – 1.67 (m, 2H) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): $\delta = 138.6, 128.8, 128.1$ (d, $J=1.5$ Hz), 73.6, 71.6, 68.7, 67.0, 33.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 197.1172; found: 197.1171.

The experimental data are in agreement with those previously published.^[178]

5.2.4 (S)-2-Bromosuccinic acid (**105**)

3N aq. sulfuric acid (195 mL, 1.13 mol, 5.00 equiv.) and L-aspartic acid (**104**, 30.0 g, 225 mmol, 1.00 equiv.) were added to a stirring solution of potassium bromide (60.0 g, 270 mmol, 2.20 eq.) in H₂O (200 mL) at 0 °C. NaNO₂ (6.24 g, 90.1 mmol, 1.20 equiv.) was added and the solution stirred vigorously for 2 hours. Urea (6.78 g, 113 mmol, 0.50 equiv.) and EA (100 mL) were added, the layers were separated and the aqueous layer was extracted with ethyl acetate (4x 40 mL). All organic phases were combined, washed with brine (50 mL) and dried over MgSO₄. Removal of the solvent *in vacuo* yielded carboxylic acid **105** as a colourless solid, which was used in the next step without further purification (27.6 g, 140 mmol, 62%).

R_f = 0.50 (CH/EA 1:1 containing 5% AcOH).

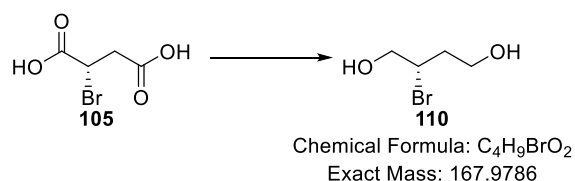
$[\alpha]_D^{20}$ = -36.0 (H₂O, c = 1.0).

¹H NMR (MeOD, 500 MHz): δ = 4.56 (dd, 1H, J =8.7, 6.2 Hz), 3.18 (dd, 1H, J =17.2, 8.7 Hz), 2.95 (dd, 1H, J =17.2, 6.2 Hz) ppm.

¹³C NMR (MeOD, 126 MHz): δ = 173.2, 172.4, 40.8, 40.2 ppm.

HRMS (ESI (-), 6.0 eV): calculated for [M-H]⁻: 194.9298; found: 194.9282.

The experimental data are in agreement with those previously published.^[124]

5.2.5 (S)-2-Bromobutane-1,4-diol (**110**)

Borane dimethylsulfide complex (42.6 mL, 560 mmol, 4.00 equiv.) was added to a solution of carboxylic acid **105** (27.6 g, 140 mmol, 1.00 equiv.) in THF (200 mL) at $-78\text{ }^{\circ}\text{C}$ and stirred for 90 min. The reaction was allowed to warm to r.t. and stirred for addition 48 h. Methanol (100 mL) was added slowly at $0\text{ }^{\circ}\text{C}$, and stirred for additional 20 min at r.t. The solvent was removed *in vacuo* the residue was dissolved in methanol (100 mL) and evaporated *in vacuo* (2x) to yield diol **110** as a yellow oil, which was used in the next step without further purification (4.32 g, 25.5 mmol, quant.).

$R_f = 0.3$ (CH/Ea/MeOH 6:6:1).

$[\alpha]_D^{20} = -31.0$ (CHCl_3 , $c = 1.0$).

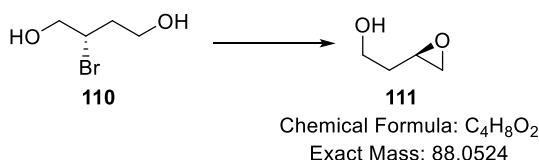
$^1\text{H NMR}$ (CD_2Cl_2 , 500 MHz): $\delta = 4.33$ (dddd, 1H, $J=10.3, 5.9, 5.3, 2.7$ Hz), 3.88 – 3.74 (m, 4H), 2.52 (s, 1H), 2.17 – 2.02 (m, 2H), 1.87 (s, 1H) ppm.

$^{13}\text{C NMR}$ (CD_2Cl_2 , 126 MHz): $\delta = 67.5, 60.4, 56.1, 38.2$ ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 168.9864; found: 168.9862.

The experimental data are in agreement with those previously published.^[124]

5.2.6 (R)-2-(Oxiran-2-yl)ethan-1-ol (**111**)



Caesium carbonate (14.9 g, 45.7 mmol, 1.80 equiv.) was added to a solution of diol **110** (4.29 g, 25.4 mmol, 1.00 equiv.) in CH_2Cl_2 (90 mL) and stirred at r.t. for 45 h. The reaction mixture was filtrated over a plug of celite[®] and rinsed with CH_2Cl_2 (40 mL). Removal of the solvent *in vacuo* yielded epoxide **111** as a yellow oil, which was used in the next step without further purification (2.24 g, 25.4 mmol, quant.).

$R_f = 0.35$ (CH/Ea 1:1 containing 5% AcOH).

$[\alpha]_D^{20} = +25.0$ (DCM, $c = 1.0$).

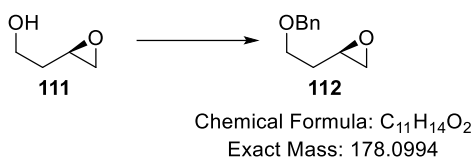
^1H NMR (CD_2Cl_2 , 500 MHz): δ = 3.75 (dt, 2H, J =6.2, 5.4 Hz), 3.06 – 3.00 (m, 1H), 2.77 – 2.72 (m, 1H), 2.53 (dd, 1H, J =5.0, 2.7 Hz), 1.95 – 1.86 (m, 1H), 1.77 (td, 1H, J =5.3, 3.5 Hz), 1.70 – 1.62 (m, 1H) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): δ = 60.2, 50.6, 46.7, 35.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 89.0603; found: 89.0609.

The experimental data are in agreement with those previously published.^[129]

5.2.7 (*R*)-2-(2-(Benzyloxy)ethyl)oxirane (**112**)



Sodium hydride (11.3 g, 282 mmol, 2.00 equiv. 60% dispersion in mineral oil) was added to a precooled solution (0 °C) of alcohol **111** (12.4 g, 141 mmol, 1.00 equiv.) in THF (250 mL). After 30 min of stirring, benzyl bromide (25.2 mL, 212 mmol, 1.50 equiv.) was added slowly and the reaction was allowed to warm to r.t. and stirred for additional 3.5 h. H_2O (50 mL) was added, the aqueous layer was extracted with EA (3x 200 mL), the combined organic layers washed with brine (300 mL) and dried over MgSO_4 . Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 6:1) yielded ether **112** (24.4 g, 137 mmol, 97%) as a colourless oil.

R_f = 0.22 (CH/EA 6:1).

$[\alpha]_D^{20}$ = +13.0 (DCM, c = 1.0).

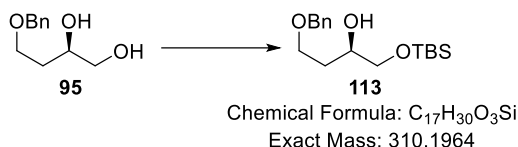
^1H NMR (CD_2Cl_2 , 500 MHz): δ = 7.38 – 7.32 (m, 4H), 7.31 – 7.25 (m, 1H), 4.51 (s, 2H), 3.68 – 3.53 (m, 2H), 3.02 (dddd, 1H, J =6.5, 4.8, 4.0, 2.7 Hz), 2.73 (ddd, 1H, J =5.1, 4.0, 0.5 Hz), 2.48 (dd, 1H, J =5.1, 2.7 Hz), 1.87 (dddd, 1H, J =14.3, 7.3, 6.1, 4.8 Hz), 1.75 (dq, 1H, J =14.3, 6.0 Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): δ = 139.1, 128.7, 128.0, 127.9, 73.3, 67.6, 50.2, 47.2, 33.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{Na}]^+$: 201.0886; found: 201.0866.

The experimental data are in agreement with those previously published.^[178]

5.2.8 (R)-4-(Benzyloxy)-1-((*tert*-butyldimethylsilyl)oxy)butan-2-ol (113)



Imidazole (173 mg, 2.55 mmol, 5.00 equiv.) was added to a solution of diol **95** (100 mg, 250 μ mol, 1.00 equiv.) in DCM (3 mL) at 0 °C and the reaction was stirred for 30 min. Then a solution of TBSCl (115 mg, 764 μ mol, 1.50 equiv.) in DCM (2 mL) was added dropwise over a period of 10 min and the reaction was allowed to stir for additional 60 min at 0 °C. The reaction was quenched with H₂O (20 mL) and the aqueous phase was extracted with DCM (3x 20 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO₄ and concentrated under reduced pressure. Purification by flash column chromatography over silica gel (CH/EA 6:1) yielded silyl ether **113** (151 mg, 486 μ mol, 96%) as a colourless oil.

R_f = 0.25 (CH/EA 6:1).

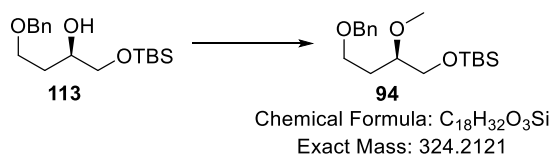
$[\alpha]_D^{20}$ = +20.0 (DCM, c = 1.0).

¹H NMR (CD₂Cl₂, 499 MHz): δ = 7.36 – 7.31 (m, 4H), 7.30 – 7.26 (m, 1H), 4.50 (s, 2H), 3.78 (ddq, 1H, J =8.2, 7.0, 3.9 Hz), 3.70 – 3.63 (m, 1H), 3.63 – 3.57 (m, 2H), 3.47 (dd, 1H, J =10.0, 6.7 Hz), 2.66 (d, 1H, J =3.5 Hz), 1.76 (dddd, 1H, J =12.7, 5.6, 4.4, 2.8 Hz), 1.73 – 1.65 (m, 1H), 0.90 (s, 9H), 0.07 (s, 6H) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 73.4, 70.7, 68.3, 67.7, 33.5, 26.1, 18.6, -5.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+Na]⁺ : 333.1856; found: 333.1859.

5.2.9 (R)-(4-(Benzyloxy)-2-methoxybutoxy)(tert-butyl)dimethylsilane (**94**)



Proton-sponge[®] (9.45 g, 44.1 mmol, 5.50 equiv.) was added to a solution of alcohol **113** (2.49 g, 8.02 mmol, 1.00 equiv.) in DCM (150 mL) at 0 °C. After 30 min of stirring, trimethyloxonium tetrafluoroborate (5.93 g, 40.1 mmol, 5.00 equiv.) was added. The reaction was allowed to warm to r.t. and stirred for additional 6 h. Aq. sat. NaHCO₃ (200 mL) was added and the aqueous phase was extracted with DCM (3x 100 mL). The combined organic layers were washed with brine (50 mL), dried over MgSO₄ and celite[®] (10 g) was added before the mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 15:1) yielded methyl ether **94** (1.91 g, 5.87 mmol, 73%) as a yellow oil.

$R_f = 0.23$ (CH/EA 15:1).

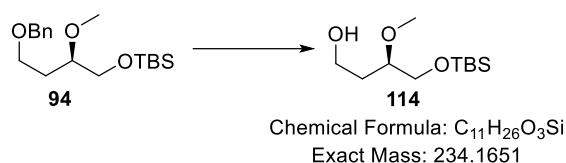
$[\alpha]_D^{20} = +12.0$ (DCM, $c = 1.0$).

¹H NMR (CD₂Cl₂, 499 MHz): $\delta = 7.36 - 7.25$ (m, 4H), 4.56 – 4.43 (m, 2H), 3.61 (d, 2H, $J=5.0$ Hz), 3.60 – 3.50 (m, 2H), 3.37 (s, 3H), 3.35 (s, 1H), 1.81 (dddd, 1H, $J=14.3, 7.8, 6.6, 4.4$ Hz), 1.68 (dddd, 1H, $J=14.1, 8.0, 6.0, 5.3$ Hz), 0.90 (s, 9H), 0.06 (s, 6H) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): $\delta = 139.4, 128.6, 128.0, 127.8, 79.4, 73.2, 67.4, 65.5, 58.1, 32.2, 26.1, 18.6, -5.3$ ppm.

HRMS (APCI (+), 5.0 eV): calculated for [M+H]⁺ : 325.2193; found: 325.2190.

5.2.10 (R)-4-((*tert*-Butyldimethylsilyl)oxy)-3-methoxybutan-1-ol (114)



10 wt.% Pd/C (11.1 mg, Pd-10%) was added to a solution of benzyl ether **94** (34 mg, 105 μ mol, 1.00 equiv.) in MeOH (1 mL) and the reaction vessel was filled with hydrogen. After stirring for 16 h, the suspension was filtered over a plug of celite[®] and washed with MeOH (3 mL). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography over silica gel (CH/EA 3:1) to yield alcohol **114** (24.5 mg, 105 μ mol, quant.) as a colourless oil.

R_f = 0.26 (CH/EA 3:1).

$[\alpha]_D^{20}$ = +10.0 (DCM, c = 0.2).

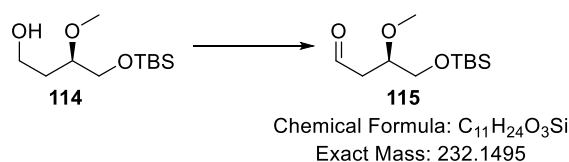
¹H NMR (CD₂Cl₂, 500 MHz): δ = 3.72 – 3.66 (m, 3H), 3.61 (dd, 1H, J =10.6, 5.3 Hz), 3.41 (s, 3H), 3.40 – 3.35 (m, 1H), 2.42 (td, 1H, J =5.3, 2.8 Hz), 1.81 – 1.66 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 81.7, 65.1, 60.8, 58.0, 34.6, 26.0, 18.6, -5.3 (d, J =1.4 Hz) ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺ : 235.1724; found: 235.1724.

5.2.11 (R)-4-((*tert*-Butyldimethylsilyl)oxy)-3-methoxybutanal (115)

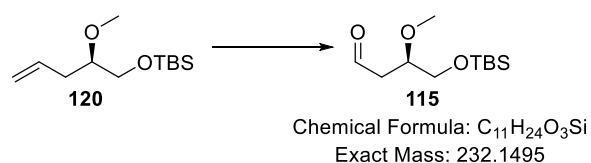
Procedure a:



DIPEA (639 μ L, 3.67 mmol, 4.00 equiv.) was added to a solution of alcohol **114** (215 mg, 918 μ mol, 1.00 equiv.) in DCM (3 mL) and DMSO (651 μ L, 9.17 mmol, 10.0 equiv.) at 0 °C. After stirring for 5 min, sulfur trioxide pyridine complex (438 mg, 2.75 mmol, 3.00 equiv.) was added

and the reaction was allowed to warm to r.t. and stirred for 60 min. DCM (10 mL) and aq. sat. NaHCO_3 (5 mL) were added and the aqueous phase was extracted with DCM (2x 5 mL). The combined organic layers were washed with CuSO_4 , NH_4Cl and brine (each aq. sat. 2x 5 mL) while the aqueous phase was extracted each time with DCM (2x 5 mL). The organic phase was dried over MgSO_4 and concentrated *in vacuo* to yield aldehyde **115** (197 mg, 848 μmol , 92%) as a yellowish oil.

Procedure b:



Alkene **120** (1.32 g, 5.63 mmol, 1.00 equiv.) was solved in MeOH (57 mL) and DCM (57 mL) together with a tip of a spatula NaHCO_3 (~10 mg) and cooled to -78°C . The reaction vessel was filled with ozone and stirred for 15 min. PPh_3 (2.27 g, 8.67 mmol, 1.50 equiv.) was added and the reaction mixture was stirred for 10 min at -78°C . The reaction was allowed to warm to r.t. and stirred for additional 2 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography over silica gel (CH/EA 9:1) to get aldehyde **115** (1.30 g, 5.57 mmol, 97%) as a colourless liquid.

$R_f = 0.58$ (CH/EA 9:1).

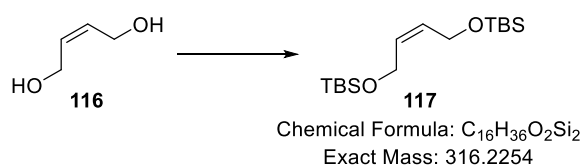
$[\alpha]_D^{20} = +17.0$ (DCM, $c = 1.0$).

^1H NMR (CD_2Cl_2 , 500 MHz): $\delta = 9.77$ (dd, 1H, $J=2.4, 1.9$ Hz), 3.77 – 3.69 (m, 2H), 3.63 – 3.59 (m, 1H), 3.38 (s, 3H), 2.63 – 2.52 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): $\delta = 201.4, 77.5, 64.5, 57.9, 46.4, 26.0, 18.5, -5.4$ ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 233.1567; found: 233.1563.

5.2.12 (Z)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodec-6-ene (**117**)



TBSCl (20.5 g, 136 mmol, 3.00 equiv.) was added to a solution of diol **116** (4.00 g, 45.4 mmol, 1.00 equiv.) and imidazole (12.4 g, 182 mmol, 4.00 equiv.) in DCM (90 mL) at 0 °C and stirred for 5 min before the reaction was allowed to warm to r.t. and stirred for additional 90 min. Aq. sat. NH_4Cl (100 mL) was added, the aqueous phase extracted with DCM (3x 100 mL) and the combined organic layers were dried over $MgSO_4$. Concentration *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 50:1) yielded silyl ether **117** (14.4 g, 45.4 mmol, quant.) as a colourless liquid.

R_f = 0.27 (CH/EA 50:1).

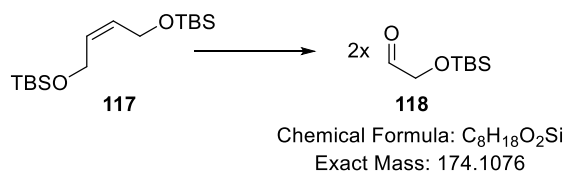
1H NMR ($CDCl_3$, 400 MHz): δ = 5.55 (ddd, 2H, J =4.1, 3.2, 0.8 Hz), 4.25 – 4.21 (m, 4H), 0.90 (s, 19H), 0.07 (s, 12H) ppm.

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 130.3, 59.8, 26.1, 18.5, -5.0 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 317.2327; found: 317.2326.

The experimental data are in agreement with those previously published.^[179]

5.2.13 2-((*tert*-Butyldimethylsilyl)oxy)acetaldehyde (**118**)



Alkene **117** (12.0 g, 37.9 mmol, 1.00 equiv.) was solved in MeOH (50 mL) and DCM (50 mL) together with a tip of a spatula $NaHCO_3$ (~10 mg) and cooled to -78 °C. The reaction vessel was filled with ozone and stirred for 45 min. PPh_3 (19.9 g, 75.8 mmol, 2.00 equiv.) was added and the reaction mixture was stirred for 10 min at -78 °C before the reaction was allowed to

warm to r.t. and stirred for additional 2 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography over silica gel (CH $\rightarrow$ CH/EA 15:1) to get aldehyde **118** (9.64 g, 55.3 mmol, 73%) as a colourless liquid.

R_f = 0.21 (CH/EA 15:1).

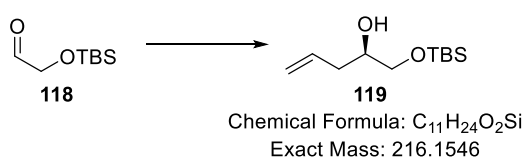
^1H NMR (CD_2Cl_2 , 400 MHz): δ = 9.66 (t, 1H, J =0.7 Hz), 4.22 (d, 2H, J =0.8 Hz), 0.93 (s, 9H), 0.10 (s, 6H) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): δ = 202.3, 70.1, 25.9, 18.6, -5.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 175.1149; found: 175.1150.

The experimental data are in agreement with those previously published.^[180]

5.2.14 (*R*)-1-((*tert*-Butyldimethylsilyl)oxy)pent-4-en-2-ol (**119**)



Allylmagnesium bromide (1 M in Et_2O , 41.3 mL, 41.3 mmol, 1.20 equiv.) was added over a period of 30 min to a solution of (+)-*B*-Methoxydiisopinocampheylboran (13.6 g, 43.0 mmol, 1.25 equiv.) in Et_2O (110 mL) at 0 °C. The reaction was allowed to warm to r.t. and stirred for additional 60 min before the reaction was cooled to -78 °C. Then aldehyde **118** (6.00 g, 34.4 mmol, 1.00 equiv.) was added over a period of 25 min and the reaction was stirred for 2.5 h. The mixture was diluted with THF (300 mL), NaOH (3 M, 100 mL) and H_2O_2 (35%, 50 mL) were added and the reaction mixture was refluxed (55 °C) for 2 h. The aqueous phase was extracted with Et_2O (3x 100 mL), washed with brine (50 mL) and concentrated *in vacuo*. The residue was again solved in Et_2O (100 mL) and H_2O (100 mL). FeSO_4 (~25.0 g) was added and the mixture was stirred overnight (14 h) at r.t. On the next day, the aqueous phase was extracted with Et_2O (3x 100 mL), the combined organic layers were washed with brine (50 mL) and dried over MgSO_4 . Removal of the solvent and purification of the residue by flash column chromatography over silica gel (CH/EA 9:1) yielded alcohol **119** (5.94 g, 27.5 mmol, 80%, *ee* = 14:1) as a colourless oil.

$R_f = 0.31$ (CH/EA 9:1).

$[\alpha]_D^{20} = -2.0$ (CHCl₃, $c = 1.0$).

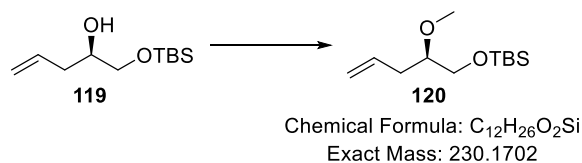
¹H NMR (CD₂Cl₂, 700 MHz): $\delta = 5.85$ (ddt, 1H, $J=17.2, 10.2, 7.1$ Hz), 5.16 – 4.98 (m, 2H), 3.66 (tdt, 1H, $J=6.9, 5.6, 3.9$ Hz), 3.62 (dd, 1H, $J=10.0, 3.8$ Hz), 3.45 (dd, 1H, $J=10.0, 6.9$ Hz), 2.31 (d, 1H, $J=4.0$ Hz), 2.25 – 2.15 (m, 2H), 0.91 (s, 10H), 0.08 (s, 6H) ppm.

¹³C NMR (CD₂Cl₂, 176 MHz): $\delta = 135.3, 117.2, 71.6, 67.1, 38.1, 26.0, 18.6, -5.3$ (d, $J=5.4$ Hz) ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 217.1618; found: 217.1624.

The experimental data are in agreement with those previously published.^[181]

5.2.15 (*R*)-*tert*-Butyl((2-methoxypent-4-en-1-yl)oxy)dimethylsilane (120)



Trimethyloxonium tetrafluoroborate (4.48 g, 30.3 mmol, 2.00 equiv.) was added to a solution of Proton-sponge[®] (6.50 g, 30.3 mmol, 2.00 equiv.) and alcohol **119** (3.28 g, 15.2 mmol, 1.00 equiv.) in DCM (30 mL) at 0 °C. After 5 min of stirring, the reaction was allowed to warm to r.t. and stirred for additional 72 h. The mixture was diluted with DCM (100 mL) and aq. sat. NaHCO₃ (200 mL) was added and the reaction stirred for 1 h. The aqueous phase was extracted with DCM (3x 100 mL), the combined organic layers washed with aq. sat. NaHCO₃ (20 mL), brine (20 mL) and dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the product by flash column chromatography over silica gel (CH/EA 30:1→20:1) gave desired ether **120** (2.74 g, 11.9 mmol, 78%) as a colourless oil.

$R_f = 0.19$ (CH/EA 9:1).

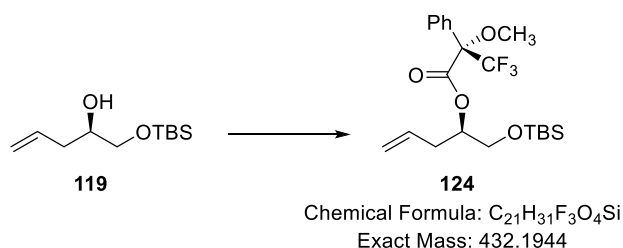
$[\alpha]_D^{20} = +5.0$ (DCM, $c = 1.0$).

^1H NMR (CDCl_3 , 500 MHz): δ = 5.84 (ddt, 1H, J =17.2, 10.2, 7.0 Hz), 5.09 (ddt, 1H, J =17.2, 2.1, 1.5 Hz), 5.05 (ddt, 1H, J =10.2, 2.2, 1.1 Hz), 3.65 – 3.53 (m, 2H), 3.42 (s, 3H), 3.28 (dq, 1H, J =6.4, 5.4 Hz), 2.32 (dddt, 1H, J =13.9, 6.9, 5.5, 1.4 Hz), 2.27 – 2.20 (m, 1H), 0.90 (s, 9H), 0.06 (s, 6H) ppm.

^{13}C NMR (CDCl_3 , 126 MHz): δ = 135.0, 117.0, 81.6, 64.6, 57.9, 35.7, 26.1, 18.4, -5.2 (d, J =5.5 Hz) ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 231.1775; found: 231.1778.

5.2.16 (*R*)-1-((*tert*-Butyldimethylsilyl)oxy)pent-4-en-2-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**124**)



(*R*)-(-)-MTPA-Cl (16 μL , 83 μmol , 3.0 equiv.) was added to a solution of alcohol **119** (6.0 mg, 28 μmol , 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO_3 (1 mL) was added, the aqueous phase was extracted with Et_2O (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO_4 . The residue was purified by flash column chromatography over silica gel (CH/EA 50:1) to yield ester **124** (3.3 mg, 7.6 μmol , 28%, dr = 14:1) as a colourless oil.

R_f = 0.39 (CH/EA 50:1).

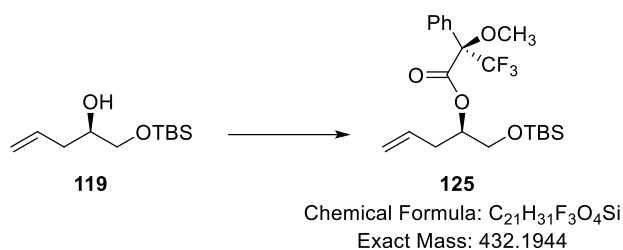
$[\alpha]_D^{20}$ = -30.0 (DCM, c = 1.0).

^1H NMR (CD_2Cl_2 , 500 MHz): δ = 7.56 – 7.52 (m, 2H), 7.44 – 7.39 (m, 3H), 5.80 (dddd, 1H, J =16.9, 10.2, 7.5, 6.6 Hz), 5.21 – 5.18 (m, 1H), 5.17 – 5.10 (m, 2H), 3.72 – 3.64 (m, 2H), 3.53 (q, 3H, J =1.2 Hz), 2.52 (dddt, 1H, J =15.0, 6.9, 5.6, 1.4 Hz), 2.43 (dtt, 1H, J =14.6, 7.3, 1.2 Hz), 0.86 (s, 9H), 0.01 (d, 6H, J =2.6 Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): δ = 166.5, 133.5, 132.7, 130.0, 128.7, 128.0, 118.7, 77.1, 63.7, 55.8 (d, $J=1.5$ Hz), 35.3, 25.9, 18.5, -5.5 (d, $J=6.2$ Hz) ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{Na}]^+$: 455.1836; found: 455.1834.

5.2.17 (R)-1-((*tert*-Butyldimethylsilyl)oxy)pent-4-en-2-yl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**125**)



(S)-(+)-MTPA-Cl (16 μL , 83 μmol , 3.0 equiv.) was added to a solution of alcohol **119** (6.0 mg, 28 μmol , 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO_3 (1 mL) was added, the aqueous phase was extracted with Et_2O (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO_4 . The residue was purified by flash column chromatography over silica gel (CH/EA 50:1) to yield ester **125** (4.5 mg, 10 μmol , 38%, dr = 14:1) as a colourless oil.

R_f = 0.39 (CH/EA 50:1).

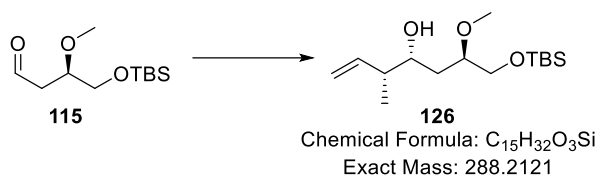
$[\alpha]_D^{20}$ = +21.0 (DCM, c = 1.0).

^1H NMR (CD_2Cl_2 , 500 MHz): δ = 7.58 – 7.55 (m, 2H), 7.43 – 7.38 (m, 3H), 5.67 (ddt, 1H, $J=17.2$, 10.2, 7.1 Hz), 5.23 – 5.16 (m, 1H), 5.06 – 4.99 (m, 2H), 3.80 – 3.70 (m, 2H), 3.57 (q, 3H, $J=1.2$ Hz), 2.42 – 2.29 (m, 2H), 0.89 (s, 11H), 0.07 (d, 8H, $J=2.6$ Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): δ = 166.4, 77.1, 64.1, 55.9 (q, $J=1.6$ Hz), 35.2, 25.9, 18.5, -5.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{Na}]^+$: 455.1836; found: 455.1834.

5.2.18 (3*R*,4*R*,6*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-6-methoxy-3-methylhept-1-en-4-ol (**126**)



Cis-2-buten (~1 mL, ~5 equiv.) was condensed at $-78\text{ }^{\circ}\text{C}$ in the reaction vessel. Potassium *tert*-butoxide (225 mg, 2.01 mmol, 1.30 equiv.) was added together with THF (3 mL). *n*-BuLi (2.5 M in hexanes, 803 μL , 2.01 mmol, 1.30 equiv.) was added over a period of 10 min at $-78\text{ }^{\circ}\text{C}$ and the reaction was allowed to warm to $-40\text{ }^{\circ}\text{C}$ and stirred for additional 15 min before it was recooled to $-78\text{ }^{\circ}\text{C}$. (–)-*B*-Methoxydiisopinocampheylboran (635 mg, 2.01 mmol, 1.30 equiv., solved in 2 mL Et₂O) was added over a period of 10 min and the reaction was allowed to stir for additional 30 min before boron trifluoride etherate (262 μL , 2.09 mmol, 1.35 equiv.) was added over a period of 2 min. Aldehyde **115** (359 mg, 1.54 mmol, 1.00 equiv., dried 14 h over 3 Å molecular sieve in 1 mL THF) was added and the reaction mixture was stirred for 2.5 h before MeOH (2 mL), NaOH (3 M, 5 mL) and H₂O₂ (35%, 5 mL) were added and the reaction mixture was refluxed (70 $^{\circ}\text{C}$) for 1 h. Aq. sat. Na₂S₂O₃ (10 mL) was added to quench the reaction, the aqueous phase was extracted with Et₂O (3x 5 mL), the combined organic layers washed with aq. sat. NH₄Cl (2 mL) and brine (2 mL). Drying the organic layer over MgSO₄, removal of the solvents *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 6:1) yielded title compound **126** (367 mg, 1.27 mmol, 82%, *dr* = 20:1) as a colourless oil.

R_f = 0.23 (CH/EA 6:1).

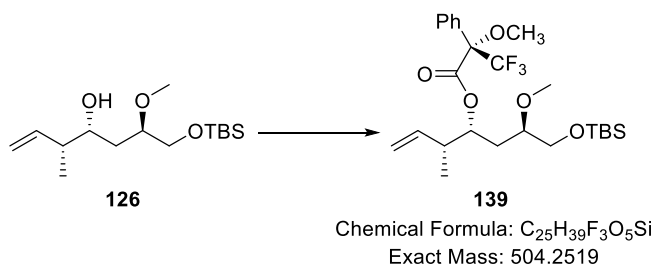
$[\alpha]_D^{20}$ = +23.0 (DCM, *c* = 1.0).

¹H NMR (CD₂Cl₂, 500 MHz): δ = 5.82 – 5.73 (m, 1H), 5.08 – 5.00 (m, 2H), 3.70 (dd, 1H, *J*=10.5, 5.3 Hz), 3.64 (dddd, 1H, *J*=9.9, 6.2, 3.8, 1.9 Hz), 3.59 (dd, 1H, *J*=10.5, 5.6 Hz), 3.48 (dtd, 1H, *J*=7.3, 5.4, 3.9 Hz), 3.41 (s, 3H), 2.63 (d, 1H, *J*=4.4 Hz), 2.25 – 2.17 (m, 1H), 1.67 (ddd, 1H, *J*=14.6, 7.3, 2.3 Hz), 1.58 – 1.52 (m, 1H), 1.03 (d, 3H, *J*=6.8 Hz), 0.90 (s, 9H), 0.07 (s, 6H) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): δ = 141.8, 114.9, 80.3, 72.1, 65.0, 58.2, 44.7, 35.8, 26.0, 18.5, 15.4, -5.3 (d, $J=1.5$ Hz) ppm.

HRMS (APCI (+), 5.0 eV): calculated for $[\text{M}+\text{H}]^+$: 289.2193; found: 289.2190.

5.2.19 (3*R*,4*R*,6*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-6-methoxy-3-methylhept-1-en-4-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (139)



(*R*)-(-)-MTPA-Cl (16 μL , 87 μmol , 5.0 equiv.) was added to a solution of alcohol **126** (5.0 mg, 17 μmol , 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO_3 (1 mL) was added, the aqueous phase was extracted with EA (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO_4 . The residue was purified by flash column chromatography over silica gel (CH/EA 9:1) to yield ester **139** (8.8 mg, 17 μmol , quant.) as a colourless oil.

R_f = 0.51 (CH/EA 9:1).

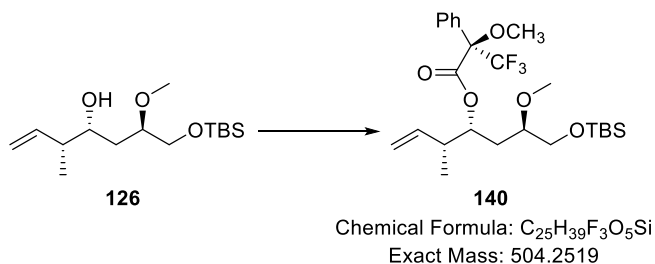
$[\alpha]_D^{20}$ = +5.0 (DCM, c = 1.0).

^1H NMR (CD_2Cl_2 , 400 MHz): δ = 7.57 (ddq, 2H, $J=5.6, 3.1, 0.9$ Hz), 7.45 – 7.37 (m, 3H), 5.68 (ddd, 1H, $J=17.4, 10.5, 7.1$ Hz), 5.03 – 4.89 (m, 2H), 3.63 (dd, 1H, $J=10.5, 4.7$ Hz), 3.54 (q, 3H, $J=1.2$ Hz), 3.53 – 3.49 (m, 1H), 3.35 (s, 3H), 3.17 – 3.07 (m, 1H), 2.50 (tdt, 1H, $J=7.2, 4.9, 1.3$ Hz), 1.78 (ddd, 1H, $J=15.0, 9.8, 2.5$ Hz), 1.66 (ddd, 1H, $J=14.9, 10.2, 2.5$ Hz), 0.97 (d, 3H, $J=6.9$ Hz), 0.89 (s, 9H), 0.05 (s, 6H) ppm.

^{13}C NMR (CD_2Cl_2 , 176 MHz): δ = 166.1, 139.0, 129.6, 128.3, 127.5, 115.5, 77.8, 77.0, 64.4, 60.2, 57.8, 55.5, 41.3, 33.8, 25.6, 20.8, 18.1, 14.3, 14.0, -5.8 ppm.

HRMS (APCI (+), 5.0 eV): calculated for $[\text{M}+\text{NH}_4]^+$: 522.2857; found: 522.2857.

5.2.20 (3*R*,4*R*,6*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-6-methoxy-3-methylhept-1-en-4-yl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (140**)**



(*S*)-(+)-MTPA-Cl (13 μ L, 69 μ mol, 5.0 equiv.) was added to a solution of alcohol **126** (4.0 mg, 14 μ mol, 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO₃ (1 mL) was added, the aqueous phase was extracted with EA (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO₄. The residue was purified by flash column chromatography over silica gel (CH/EA 50:1) to yield ester **140** (7.0 mg, 14 μ mol, quant.) as a colourless oil.

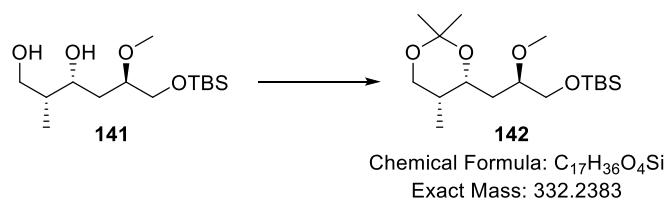
R_f = 0.44 (CH/EA 9:1).

$[\alpha]_D^{20}$ = +54.0 (DCM, c = 0.5).

¹H NMR (CD₂Cl₂, 700 MHz): δ = 7.59 – 7.54 (m, 2H), 7.43 – 7.38 (m, 3H), 5.82 (ddd, 1H, J =17.3, 10.5, 6.9 Hz), 5.34 – 5.30 (m, 1H), 5.10 – 5.04 (m, 2H), 3.53 (q, 3H, J =1.3 Hz), 3.52 (d, 1H, J =4.8 Hz), 3.48 (dd, 1H, J =10.6, 5.2 Hz), 3.32 (s, 3H), 2.98 (dtd, 1H, J =10.1, 5.0, 2.4 Hz), 2.59 (dddd, 1H, J =10.0, 6.2, 2.9, 1.6 Hz), 1.70 (ddd, 1H, J =14.9, 10.1, 2.4 Hz), 1.62 (ddd, 1H, J =14.9, 10.2, 2.4 Hz), 1.04 (d, 3H, J =7.0 Hz), 0.87 (s, 8H), 0.02 (d, 6H, J =3.7 Hz) ppm.

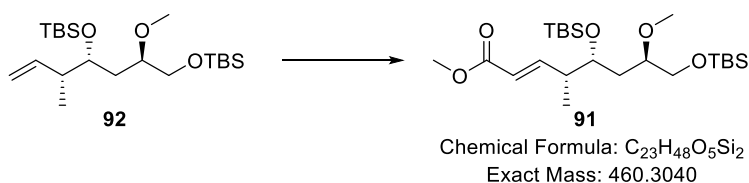
¹³C NMR (CD₂Cl₂, 176 MHz): δ = 166.5, 139.5, 132.6, 130.0, 128.8, 128.0, 124.8, 123.1, 116.0, 78.0, 77.6, 64.8, 58.1, 55.8, 41.6, 33.8, 26.0, 18.5, 14.8, -5.4 ppm.

HRMS (APCI (+), 5.0 eV): calculated for [M+NH₄]⁺ : 522.2857; found: 522.2856.



HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 333.2456; found: 333.2457.

5.2.24 Methyl (4*R*,5*R*,7*R*,*E*)-5,8-bis((*tert*-butyldimethylsilyl)oxy)-7-methoxy-4-methyloct-2-enoate (**91**)



Hoveyda-Grubbs-II (100 mg, 159 μ mol, 0.07 equiv.) was added to a solution of alkene **92** (926 mg, 2.30 mmol, 1.00 equiv., dried with 3x Freeze-Pump-Thaw cycles) and methyl acrylate (989 mg, 11.5 mmol, 5.00 equiv.) in toluene (12 mL) and the reaction was refluxed (120 °C) for 20 h. Celite[®] (~20 g) was added to the mixture and the solvent was reduced under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 15:1) yielded methyl ester **91** (1.03 g, 2.23 mmol, 97%, *E/Z* >20:1) as a yellowish oil.

R_f = 0.24 (CH/EA 15:1).

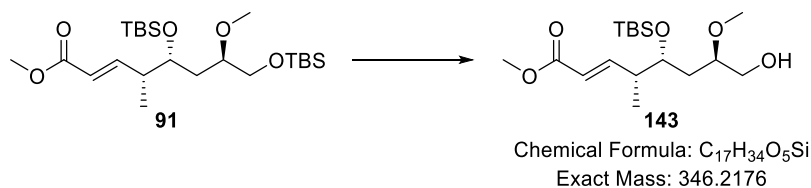
$[\alpha]_D^{20}$ = +150.0 (DCM, c = 0.2).

¹H NMR (CD₂Cl₂, 500 MHz): δ = 7.06 (dd, 1H, J =15.9, 6.5 Hz), 5.80 (dd, 1H, J =15.9, 1.6 Hz), 3.91 (dt, 1H, J =9.1, 3.4 Hz), 3.69 (s, 3H), 3.63 – 3.52 (m, 2H), 3.38 (s, 3H), 3.36 – 3.28 (m, 1H), 2.58 – 2.49 (m, 1H), 1.49 (ddd, 1H, J =14.3, 9.7, 3.1 Hz), 1.39 (ddd, 1H, J =14.3, 9.1, 2.8 Hz), 1.01 (d, 3H, J =6.9 Hz), 0.90 (s, 9H), 0.89 (s, 9H), 0.08 (d, 6H, J =6.9 Hz), 0.05 (s, 6H) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 167.2, 151.9, 121.1, 78.4, 72.7, 65.3, 57.4, 51.6, 42.8, 36.3, 26.1, 26.0, 18.6, 18.4, 14.1, -4.0, -4.4, -5.3 (d, J =1.3 Hz) ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺ : 461.3113; found: 461.3115.

5.2.25 Methyl (4*R*,5*R*,7*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-7-methoxy-4-methyloct-2-enoate (**143**)



CSA (50.4 mg, 217 μmol , 0.50 equiv.) was added to a solution of silyl ether **91** (200 mg, 434 μmol , 1.00 equiv.) in DCM (50 mL) and MeOH (50 mL) at 0 °C. After 30 min of stirring, the reaction was allowed to warm to r.t. and stirred for additional 4.5 h. The reaction was quenched with aq. sat. NaHCO_3 (10 mL) and the aqueous phase was extracted with DCM (3x 20 mL) and EA (3x 20 mL). The combined organic layers were dried over MgSO_4 and the solvent was removed *in vacuo*. Purification of the residue by flash column chromatography over silica gel (CH/EA 2:1) yielded primary alcohol **143** (126 mg, 364 μmol , 84%) as a colourless oil.

R_f = 0.19 (CH/EA 2:1).

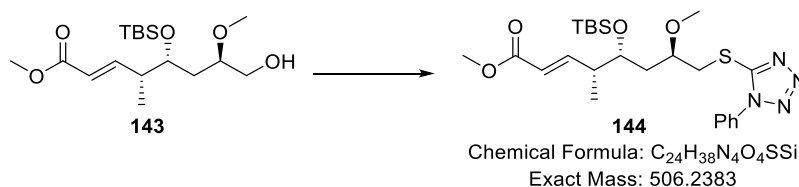
$[\alpha]_D^{20}$ = +75.0 (DCM, c = 0.2).

^1H NMR (CD_2Cl_2 , 700 MHz): δ = 7.06 (dd, 1H, J =15.9, 6.5 Hz), 5.81 (dd, 1H, J =15.9, 1.6 Hz), 3.89 (dt, 1H, J =9.2, 3.4 Hz), 3.77 (dd, 1H, J =11.4, 3.3 Hz), 3.69 (s, 3H), 3.41 – 3.36 (m, 2H), 3.36 (s, 3H), 2.58 – 2.52 (m, 1H), 1.74 – 1.71 (m, 1H), 1.70 – 1.66 (m, 1H), 1.32 (ddd, 1H, J =14.3, 9.2, 3.4 Hz), 1.03 (d, 3H, J =6.9 Hz), 0.91 (s, 9H), 0.09 (d, 6H, J =4.7 Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 176 MHz): δ = 167.2, 151.4, 121.3, 78.1, 72.8, 63.5, 56.6, 51.6, 42.6, 35.5, 26.1, 18.4, 14.2, -4.2 (d, J =75.9 Hz) ppm.

HRMS (ESI +), 6.0 eV: calculated for $[\text{M}+\text{H}]^+$: 347.2248; found: 347.2251.

5.2.26 Methyl (4*R*,5*R*,7*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-4-methyl-8-((1-phenyl-1*H*-tetrazol-5-yl)thio)oct-2-enoate (**144**)



DIAD (41.8 μL , 79.4 μmol , 2.50 equiv.) was added dropwise to a solution of alcohol **143** (11.0 mg, 31.7 μmol , 1.00 equiv.), PPh_3 (20.8 mg, 79.4 μmol , 2.50 equiv.) and 1-Phenyl-1*H*-tetrazole-5-thiol (6.22 mg, 34.9 μmol , 1.10 equiv.) in THF (1 mL) at 0 °C. The reaction was

allowed to warm to r.t. and stirred for additional 60 min. Celite[®] (1 g) was added and the solvent was removed under reduced pressure. Purification by flash column chromatography over silica gel (CH/EA 2:1) yielded sulfide **144** (16.1 mg, 31.7 μ mol, quant.) as a colourless oil.

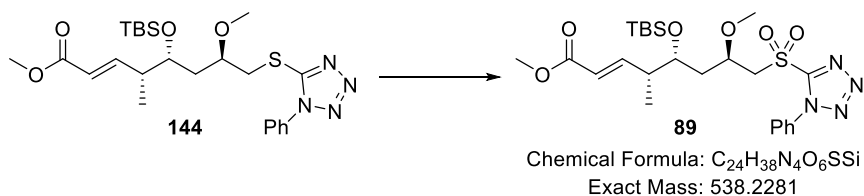
R_f = 0.44 (CH/EA 2:1).

$[\alpha]_D^{20}$ = +22.5 (DCM, c = 0.4).

¹H NMR (CD₂Cl₂, 400 MHz): δ = 7.62 – 7.55 (m, 5H), 7.03 (dd, 1H, J =15.9, 6.5 Hz), 5.81 (dd, 1H, J =15.9, 1.6 Hz), 3.90 (ddd, 1H, J =9.2, 3.9, 2.8 Hz), 3.77 – 3.70 (m, 1H), 3.69 (s, 3H), 3.49 (dd, 1H, J =13.3, 6.3 Hz), 3.41 (s, 3H), 2.60 – 2.50 (m, 1H), 1.70 – 1.56 (m, 1H), 1.54 – 1.44 (m, 1H), 1.00 (d, 3H, J =6.9 Hz), 0.84 (s, 9H), 0.05 (d, 6H, J =9.1 Hz) ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 507.2456; found: 507.2452.

5.2.27 Methyl (4*R*,5*R*,7*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-4-methyl-8-((1-phenyl-1*H*-tetrazol-5-yl)sulfonyl)oct-2-enoate (**89**)



H₂O₂ (35%, 1 mL) was added to a solution of sulfide **144** (16.1 mg, 31.7 μ mol, 1.00 equiv.) and ammonium heptamolybdate (3.70 mg, 3.18 μ mol, 0.10 equiv.) in EtOH (1 mL) and the reaction stirred for 13 days. Aq. sat. Na₂S₂O₃ (2 mL) was added and the aqueous phase was extracted with EA (3x 2 mL). The combined organic layers were washed with brine (1 mL) and dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 3:1) yielded sulfone **89** (12.0 mg, 22.3 μ mol, 70%) as a colourless oil.

R_f = 0.22 (CH/EA 3:1).

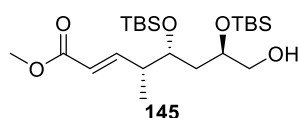
$[\alpha]_D^{20}$ = +38.0 (DCM, c = 1.0).

¹H NMR (CD₂Cl₂, 700 MHz): δ = 7.69 – 7.65 (m, 1H), 7.64 – 7.60 (m, 4H), 7.00 (dd, 1H, J =15.9, 6.4 Hz), 5.81 (dd, 1H, J =15.9, 1.6 Hz), 3.99 (ddt, 1H, J =8.1, 6.8, 4.5 Hz), 3.89 – 3.82 (m, 2H), 3.73 (dd, 1H, J =15.1, 4.6 Hz), 3.70 (s, 3H), 3.20 (s, 3H), 2.58 – 2.52 (m, 1H), 1.77 (ddd, 1H, J =14.5, 8.2, 2.8 Hz), 1.48 (ddd, 1H, J =14.5, 9.3, 4.3 Hz), 1.01 (d, 3H, J =6.9 Hz), 0.87 (s, 9H), 0.07 (d, 6H, J =9.5 Hz) ppm.

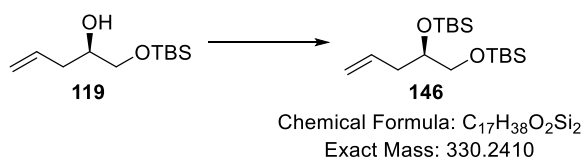
¹³C NMR (CD₂Cl₂, 176 MHz): δ = 167.0, 154.7, 150.2, 133.5, 132.0, 130.0, 126.1, 121.8, 73.0, 72.7, 60.1, 56.5, 51.7, 42.4, 37.7, 26.0, 18.3, 14.5, -3.9, -4.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺ : 539.2354; found: 539.2354.

5.3 Experimental Details for Chapter 3.3.2: Synthesis of Alcohol 145



5.3.1 (*R*)-5-Allyl-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecane (146)



TBSCl (219 mg, 1.45 mmol, 2.00 equiv.) was added to a solution of alcohol **119** (157 mg, 726 μ mol, 1.00 equiv.) and imidazole (98.8 mg, 1.45 mmol, 2.00 equiv.) in DCM (1 mL) at 0 °C. After 5 min of stirring, the reaction was allowed to warm to r.t. and stirred for additional 2 h. The reaction was quenched with aq. sat. NH₄Cl (5 mL), the aqueous phase extracted with DCM (3x 3 mL) and the combined organic layers were washed with brine (1 mL) and dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 50:1) yielded silyl ether **146** (223 mg, 674 μ mol, 93%) as a colourless oil.

R_f = 0.48 (CH/EA 9:1).

$[\alpha]_D^{20} = +3.0$ (DCM, $c = 1.0$).

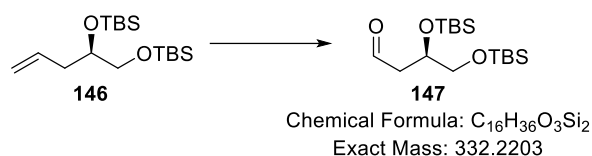
$^1\text{H NMR}$ (CD_2Cl_2 , 500 MHz): $\delta = 5.90 - 5.80$ (m, 1H), $5.08 - 5.00$ (m, 2H), 3.71 (tt, 1H, $J=6.2, 5.2$ Hz), 3.51 (dd, 1H, $J=10.0, 5.5$ Hz), 3.44 (dd, 1H, $J=10.0, 6.2$ Hz), 2.34 (dddt, 1H, $J=14.7, 6.6, 5.1, 1.4$ Hz), 2.16 (dddt, 1H, $J=13.9, 7.5, 6.2, 1.2$ Hz), 0.89 (s, 9H), 0.88 (s, 9H), 0.06 (s, 6H), 0.05 (d, 6H, $J=1.8$ Hz) ppm.

$^{13}\text{C NMR}$ (CD_2Cl_2 , 126 MHz): $\delta = 135.8, 116.9, 73.3, 67.3, 39.3, 26.1$ (d, $J=9.9$ Hz), 18.5 (d, $J=25.1$ Hz), -4.4 (d, $J=36.9$ Hz), -5.3 (d, $J=7.0$ Hz) ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 331.2483; found: 331.2488.

The experimental data are in agreement with those previously published.^[182]

5.3.2 (*R*)-3,4-Bis((*tert*-butyldimethylsilyl)oxy)butanal (**147**)



Alkene **146** (220 mg, 665 μmol , 1.00 equiv.) was solved in MeOH (6 mL) and DCM (6 mL) together with a tip of a spatula NaHCO_3 (~ 10 mg) and cooled to -78°C . The reaction vessel was filled with ozone and stirred for 15 min. PPh_3 (262 mg, 998 μmol , 1.50 equiv.) was added and the reaction mixture was stirred for 10 min at -78°C . The reaction was allowed to warm to r.t. and stirred for additional 2 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography over silica gel (CH/EA 30:1) to get aldehyde **147** (188 mg, 568 μmol , 85%) as a colourless liquid.

$R_f = 0.38$ (CH/EA 30:1).

$[\alpha]_D^{20} = +9.0$ (DCM, $c = 1.0$).

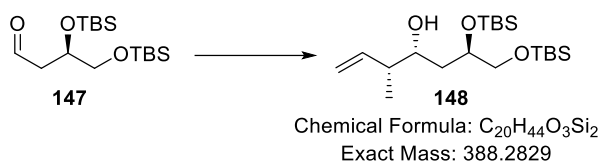
$^1\text{H NMR}$ (CD_2Cl_2 , 700 MHz): $\delta = 9.78$ (dd, 1H, $J=2.9, 2.1$ Hz), 4.20 (tt, 1H, $J=6.7, 5.0$ Hz), 3.64 (dd, 1H, $J=10.0, 4.9$ Hz), 3.47 (dd, 1H, $J=10.0, 6.8$ Hz), 2.62 (ddd, 1H, $J=15.8, 5.1, 2.1$ Hz), 2.49 (ddd, 1H, $J=15.8, 6.5, 2.9$ Hz), 0.89 (s, 9H), 0.87 (s, 9H), 0.08 (d, 6H, $J=9.4$ Hz), 0.06 (d, 6H, $J=1.9$ Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 176 MHz): δ = 201.9, 69.5, 67.5, 49.2, 26.0 (d, $J=24.5$ Hz), 18.4 (d, $J=52.3$ Hz), -4.6 (d, $J=90.4$ Hz), -5.4 (d, $J=4.5$ Hz) ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 333.2276; found: 333.2262.

The experimental data are in agreement with those previously published.^[183]

5.3.3 (3*R*,4*R*,6*R*)-6,7-Bis((*tert*-butyldimethylsilyl)oxy)-3-methylhept-1-en-4-ol (**148**)



Cis-2-buten (~4 mL, ~5 equiv.) was condensed at -78°C in the reaction vessel. Potassium *tert*-butoxide (1.03 g, 8.91 mmol, 1.30 equiv.) was added together with THF (7 mL). *n*-BuLi (2.5 M in hexanes, 3.56 mL, 8.91 mmol, 1.30 equiv.) was added over a period of 10 min at -78°C and the reaction was allowed to warm to -40°C and stirred for additional 15 min before it was recooled to -78°C . (–)-*B*-Methoxydiisopinocampheylboran (2.82 g, 8.91 mmol, 1.30 equiv., solved in 9 mL Et_2O) was added over a period of 10 min and the reaction was allowed to stir for additional 60 min before boron trifluoride etherate (1.16 mL, 9.25 mmol, 1.35 equiv.) was added over a period of 2 min. Aldehyde **147** (2.21 g, 6.64 mmol, 1.00 equiv., dried 14 h over 3 Å molecular sieve in 20 mL THF) was added and the reaction mixture was stirred for 2.5 h before MeOH (20 mL), NaOH (3 M, 40 mL) and H_2O_2 (35%, 20 mL) were added and the reaction mixture was refluxed (70°C) for 1 h. The aqueous phase was extracted with Et_2O (3x 50 mL) and concentrated *in vacuo*. The residue was again solved in Et_2O (50 mL) and H_2O (25 mL). FeSO_4 (~10.0 g) was added and the mixture was stirred overnight (14 h) at r.t. On the next day, the aqueous phase was extracted with Et_2O (3x 50 mL), the combined organic layers were washed with brine (30 mL) and dried over MgSO_4 . Removal of the solvent and purification of the residue by flash column chromatography over silica gel (CH/EA 15:1) yielded alcohol **148** (1.93 g, 4.97 mmol, 75%, *dr* = 3:1) as a yellow oil.

R_f = 0.09 (CH/EA 15:1).

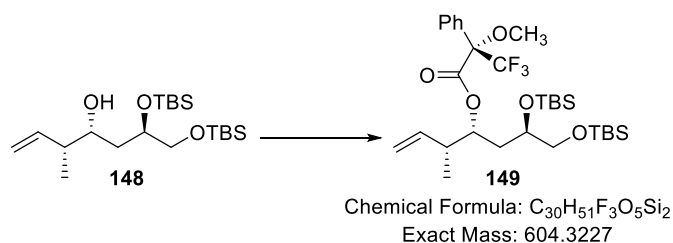
$[\alpha]_D^{20} = +19.0$ (DCM, $c = 1.0$).

$^1\text{H NMR}$ (CD_2Cl_2 , 700 MHz): $\delta = 5.81 - 5.74$ (m, 1H), $5.06 - 4.98$ (m, 2H), $3.98 - 3.92$ (m, 1H)^{*}, $3.92 - 3.86$ (m, 1H)[#], 3.70 (ddt, 1H, $J=10.5, 5.6, 2.2$ Hz)^{*}, 3.65 (ddd, 1H, $J=9.9, 5.1, 2.3$ Hz)[#], $3.64 - 3.60$ (m, 1H)^{*}, 3.60 (dd, 1H, $J=4.8, 2.1$ Hz)[#], 3.52 (dd, 1H, $J=10.0, 7.3$ Hz)^{*}, 3.47 (dd, 1H, $J=10.1, 6.6$ Hz)[#], 3.01 (d, 1H, $J=2.9$ Hz)^{*}, 2.95 (d, 1H, $J=2.6$ Hz)[#], 2.20 (dtt, 1H, $J=13.8, 6.9, 1.1$ Hz)^{*}, 1.85 (ddd, 1H, $J=14.5, 4.8, 2.1$ Hz)[#], 1.72 (ddd, 1H, $J=14.4, 5.3, 1.8$ Hz)^{*}, $1.59 - 1.53$ (m, 1H)^{*}, 1.44 (ddd, 1H, $J=14.5, 9.5, 7.4$ Hz)[#], 1.01 (dd, 3H, $J=6.9, 4.4$ Hz), 0.89 (s, 10H), 0.89 (s, 10H), $0.10 - 0.08$ (m, 6H), 0.06 (d, 6H, $J=3.9$ Hz) ppm.

$^{13}\text{C NMR}$ (CD_2Cl_2 , 176 MHz): $\delta = 141.9^{\#}$, 141.9^* , 114.7^* , $114.6^{\#}$, $73.5^{\#}$, $73.2^{\#}$, 72.5^* , 71.7^* , $67.9^{\#}$, 66.8^* , 44.8^* , $44.4^{\#}$, $39.1^{\#}$, 38.0^* , 26.1^* , $26.1^{\#}$, $26.0^{\#}$, 26.0^* , $18.6^{\#}$, 18.6^* , 18.3^* , $18.3^{\#}$, 15.4^* , $15.1^{\#}$, $-4.0^{\#}$, -4.4^* , $-4.7^{\#}$, -4.9^* , -5.3^* , $-5.3^{\#}$, -5.3^* ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 389.2902; found: 389.2898.

5.3.4 (3*R*,4*R*,6*R*)-6,7-Bis((*tert*-butyldimethylsilyl)oxy)-3-methylhept-1-en-4-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**149**)



(*R*)-(-)-MTPA-Cl (8.4 μL , 45 μmol , 5.0 equiv.) was added to a solution of alcohol **148** (3.5 mg, 9.0 μmol , 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO_3 (1 mL) was added, the aqueous phase was extracted with Et_2O (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO_4 . The residue was purified by flash column chromatography over silica gel (CH/EA 50:1) to yield ester **149** (4.0 mg, 6.6 μmol , 73%, $dr = 5:1$) as a colourless oil.

$R_f = 0.60$ (CH/EA 50:1).

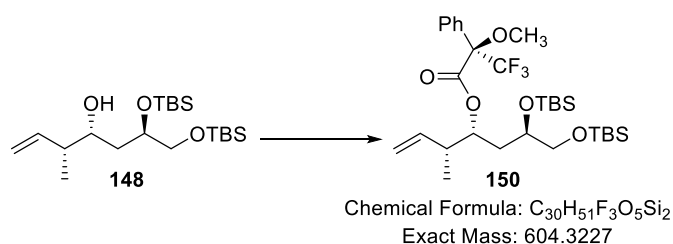
$[\alpha]_D^{20} = +2.0$ (DCM, $c = 1.0$).

^1H NMR (CDCl_3 , 700 MHz): $\delta = 7.61 - 7.56$ (m, 2H), 7.39 (qd, 4H, $J=3.1, 1.4$ Hz), 5.80 (ddd, 1H, $J=17.2, 10.5, 6.6$ Hz)[#], 5.66 (ddd, 1H, $J=17.3, 10.5, 6.8$ Hz)^{*}, 5.27 (ddd, 1H, $J=9.4, 4.3, 2.2$ Hz), 5.10 – 5.03 (m, 2H)[#], 4.99 – 4.87 (m, 2H)^{*}, 3.70 (p, 1H, $J=5.7$ Hz)[#], 3.65 (dddd, 1H, $J=9.8, 7.0, 5.0, 2.1$ Hz)^{*}, 3.56 – 3.55 (m, 3H), 3.55 – 3.53 (m, 1H), 3.45 (dd, 1H, $J=10.1, 4.6$ Hz)[#], 3.32 (dd, 1H, $J=9.9, 6.9$ Hz)^j, 2.61 – 2.57 (m, 1H)[#], 2.54 (tdt, 1H, $J=6.9, 4.3, 1.3$ Hz)^{*}, 1.96 – 1.93 (m, 1H)[#], 1.90 (ddd, 1H, $J=14.7, 9.4, 2.1$ Hz)^{*}, 1.70 (dddd, 1H, $J=32.8, 14.1, 8.1, 5.8$ Hz)[#], 1.56 (ddd, 1H, $J=14.8, 9.8, 2.2$ Hz)^{*}, 1.03 (d, 3H, $J=7.0$ Hz)[#], 0.99 (d, 3H, $J=7.0$ Hz)^{*}, 0.91 – 0.86 (m, 18H)^{*}, 0.85 (d, 18H, $J=2.7$ Hz)[#], 0.05 – 0.02 (m, 12H)^{*}, -0.03 (d, 12H, $J=8.3$ Hz)[#] ppm.

^{13}C NMR (CDCl_3 , 176 MHz): $\delta = 166.2, 139.3^{\#}, 138.8^*, 132.5^*, 132.3^{\#}, 129.7^{\#}, 129.6^*, 128.5^{\#}, 128.4^*, 127.7^{\#}, 127.6^*, 115.9^{\#}, 115.8^*, 84.6^{\#}, 84.5^*, 70.3^*, 70.0^{\#}, 67.7^*, 67.0^{\#}, 55.6^*, 55.6^{\#}, 41.1^*, 40.2^{\#}, 36.2^*, 35.4^{\#}, 26.1^{\#}, 26.0^*, 26.0^*, 26.0^{\#}, 18.5^{\#}, 18.4^*, 18.2^*, 18.2^{\#}, 14.6^*, 14.4^{\#}, -3.8^*, -4.3^{\#}, -4.8^*, -4.8^{\#}, -5.2^*, -5.3^{\#}, -5.3^*$ ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 605.3300; found: 605.3301.

5.3.5 (3*R*,4*R*,6*R*)-6,7-Bis((*tert*-butyldimethylsilyl)oxy)-3-methylhept-1-en-4-yl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**150**)



(*S*)-(+)-MTPA-Cl (9.6 μL , 51 μmol , 5.0 equiv.) was added to a solution of alcohol **148** (4.0 mg, 10 μmol , 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO_3 (1 mL) was added, the aqueous phase was extracted with Et_2O (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO_4 . The residue was purified by flash column chromatography over silica gel (CH/EA 50:1) to yield ester **150** (6.2 mg, 10 μmol , quant., $dr = 5:1$) as a colourless oil.

$R_f = 0.60$ (CH/EA 50:1).

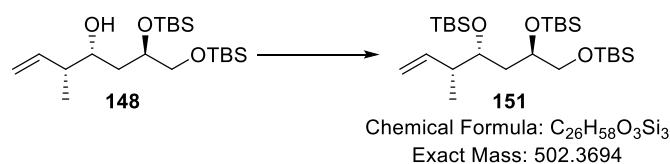
$[\alpha]_D^{20} = +27.0$ (DCM, $c = 1.0$).

^1H NMR (CDCl_3 , 700 MHz): $\delta = 7.57$ (dd, 2H, $J=7.7, 2.0$ Hz)^{*}, 7.55 – 7.51 (m, 2H)[#], 7.40 – 7.37 (m, 3H), 5.77 (ddd, 1H, $J=17.2, 10.5, 6.7$ Hz)^{*}, 5.68 (ddd, 0H, $J=17.3, 10.5, 6.9$ Hz)[#], 5.30 – 5.27 (m, 1H)[#], 5.27 – 5.23 (m, 1H)^{*}, 5.08 – 5.00 (m, 2H)^{*}, 4.99 – 4.94 (m, 2H)[#], 3.72 – 3.68 (m, 1H)[#], 3.61 (dd, 1H, $J=10.3, 4.7$ Hz)[#], 3.59 – 3.54 (m, 1H)^{*}, 3.52 (dd, 3H, $J=2.5, 1.3$ Hz), 3.51 – 3.47 (m, 1H)^{*}, 3.46 – 3.43 (m, 1H)[#], 3.30 (dd, 1H, $J=10.0, 6.5$ Hz)^{*}, 2.66 – 2.58 (m, 1H)^{*}, 2.55 (tdq, 1H, $J=6.6, 4.0, 1.4$ Hz)[#], 2.00 (ddd, 1H, $J=14.2, 6.8, 5.7$ Hz)[#], 1.83 (ddd, 1H, $J=14.7, 9.4, 2.1$ Hz)^{*}, 1.72 (ddd, 1H, $J=14.0, 7.7, 6.1$ Hz)[#], 1.54 (ddd, 1H, $J=14.7, 9.8, 2.2$ Hz)^{*}, 1.03 (d, 3H, $J=7.0$ Hz)^{*}, 0.99 (d, 1H, $J=6.9$ Hz)[#], 0.89 (d, 9H, $J=1.1$ Hz)^{*}, 0.87 (s, 18H)[#], 0.86 (s, 9H)^{*}, 0.07 (d, 6H, $J=22.5$ Hz)^{*}, 0.04 – 0.02 (m, 6H)[#], -0.00 (d, 6H, $J=12.1$ Hz)^{*}, -0.03 (d, 6H, $J=8.3$ Hz)[#] ppm.

^{13}C NMR (CDCl_3 , 176 MHz): $\delta = 166.3^*$, 166.1[#], 139.2[#], 138.9^{*}, 132.4[#], 132.3^{*}, 129.7[#], 129.7^{*}, 128.5, 127.8^{*}, 127.7[#], 124.4, 122.8, 115.9^{*}, 115.7[#], 84.7[#], 84.6^{*}, 78.1, 70.3^{*}, 70.2[#], 67.7^{*}, 67.1[#], 55.5[#], 55.4^{*}, 41.0^{*}, 40.2[#], 36.0^{*}, 35.8[#], 26.1[#], 26.0^{*}, 26.0[#], 26.0^{*}, 18.5[#], 18.4^{*}, 18.2^{*}, 18.2[#], 14.7^{*}, 13.7[#], -3.7^{*}, -4.2[#], -4.7^{*}, -4.7[#], -5.2[#], -5.3^{*}, -5.3[#] ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 605.3300; found: 605.3300.

5.3.6 (5*R*,7*R*)-5-((*R*)-But-3-en-2-yl)-7-((*tert*-butyldimethylsilyl)oxy)-2,2,3,3,10,10,11,11-octamethyl-4,9-dioxa-3,10-disiladodecane (**151**)



2,6-Lutidine (9.25 mL, 80.3 mmol, 10.0 equiv.) was added to a solution of alcohol **148** (3.12 g, 8.03 mmol, 1.00 equiv.) in DCM (8 mL) and the reaction stirred for 5 min at r.t. before it was cooled to 0 °C and TBSOTf (5.58 mL, 24.1 mmol, 3.00 equiv.) was added over a period of 10 min. The reaction was allowed to warm to r.t. and stirred for additional 2 h. Aq. sat. NH_4Cl (50 mL) was added and the aqueous phase was extracted with DCM (3x 20 mL). The combined

organic layers were washed with brine (20 mL) and dried over MgSO_4 . Removal of the solvent *in vacuo* and purification by flash column chromatography over silica gel (CH 100%) yielded silyl ether **151** (3.47 g, 6.89 mmol, 86%) as a colourless oil.

$R_f = 0.70$ (CH 100%).

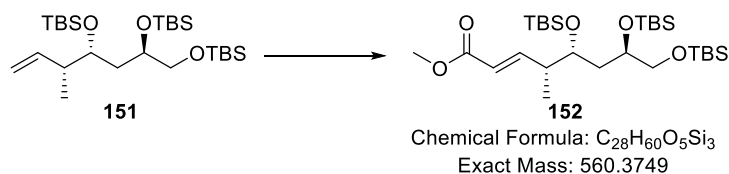
$[\alpha]_D^{20} = +13.0$ (DCM, $c = 1.0$).

$^1\text{H NMR}$ (CD_2Cl_2 , 700 MHz): $\delta = 5.93$ (ddd, 1H, $J=17.2, 10.7, 6.4$ Hz), 5.02 – 4.96 (m, 2H), 3.81 (dt, 1H, $J=7.5, 3.7$ Hz), 3.78 – 3.74 (m, 1H), 3.52 (dd, 1H, $J=10.2, 5.5$ Hz), 3.43 (dd, 1H, $J=10.2, 5.5$ Hz), 2.35 (ddtt, 1H, $J=10.1, 4.9, 3.5, 1.7$ Hz), 1.54 (ddd, 1H, $J=14.2, 7.7, 3.8$ Hz), 1.46 (ddd, 1H, $J=14.2, 8.1, 3.9$ Hz), 0.96 (d, 3H, $J=6.9$ Hz), 0.91 – 0.86 (m, 27H), 0.10 – 0.03 (m, 17H) ppm.

$^{13}\text{C NMR}$ (CD_2Cl_2 , 176 MHz): $\delta = 141.6, 114.0, 73.9, 72.0, 68.5, 43.6, 39.6, 26.2, 26.1, 26.1, 18.7, 18.5, 18.4, 14.3, -3.5, -3.9, -4.0, -4.3, -5.2, -5.2$ ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 503.3767; found: 503.3766.

5.3.7 Methyl (4*R*,5*R*,7*R*,*E*)-5,7,8-tris((*tert*-butyldimethylsilyl)oxy)-4-methyloct-2-enoate (**152**)



Hoveyda-Grubbs-II (100 mg, 159 μmol , 0.03 equiv.) was added to a solution of alkene **151** (2.50 mg, 4.97 mmol, 1.00 equiv., dried with 3x Freeze-Pump-Thaw cycles) and methyl acrylate (2.14 g, 24.9 mmol, 5.00 equiv.) in toluene (25 mL) and the reaction was refluxed (120 $^\circ\text{C}$) for 20 h. Celite[®] (~20 g) was added to the mixture and the solvent was reduced under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 30:1) yielded methyl ester **152** (2.22 g, 3.96 mmol, 80%, *E/Z* >20:1) as a yellowish oil.

$R_f = 0.22$ (CH/EA 30:1).

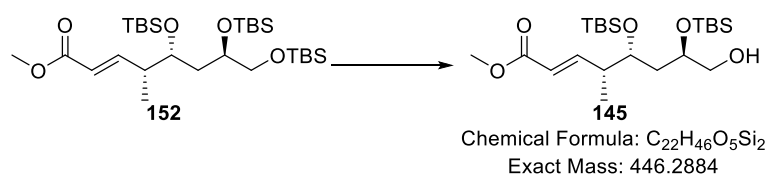
$[\alpha]_D^{20} = +31.0$ (DCM, $c = 1.0$).

^1H NMR (CD_2Cl_2 , 700 MHz): δ = 7.03 (dd, 1H, J =15.9, 6.7 Hz), 5.79 (dd, 1H, J =15.9, 1.5 Hz), 3.88 (dt, 1H, J =7.5, 3.8 Hz), 3.76 (dtd, 1H, J =8.1, 5.5, 3.6 Hz), 3.69 (s, 3H), 3.53 (dd, 1H, J =10.2, 5.4 Hz), 3.42 (dd, 1H, J =10.2, 5.7 Hz), 2.52 (pdd, 1H, J =6.8, 3.4, 1.6 Hz), 1.57 (ddd, 1H, J =14.1, 7.6, 3.6 Hz), 1.49 (ddd, 1H, J =14.1, 8.1, 4.1 Hz), 1.02 (d, 3H, J =6.9 Hz), 0.92 – 0.87 (m, 28H), 0.12 – 0.01 (m, 17H) ppm.

^{13}C NMR (CD_2Cl_2 , 176 MHz): δ = 167.2, 152.2, 120.9, 73.3, 71.8, 68.4, 51.6, 42.7, 39.9, 26.2, 26.1, 26.1, 18.7, 18.4, 18.4, 13.6, -3.5, -4.0, -4.1, -4.3, -5.2, -5.2 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 561.3821; found: 561.3822.

5.3.8 Methyl (4*R*,5*R*,7*R*,*E*)-5,7-bis((*tert*-butyldimethylsilyl)oxy)-8-hydroxy-4-methyloct-2-enoate (**145**)



CSA (479 mg, 2.06 mmol, 0.50 equiv., solved in 10 mL MeOH) was added over a period of 10 min to a solution of silyl ether **152** (2.31 g, 4.12 mmol, 1.00 equiv.) in DCM (80 mL) and MeOH (20 mL) at 0 °C. After 30 min of stirring, the reaction was allowed to warm to r.t. and stirred for additional 3 h. The reaction was quenched with aq. sat. NaHCO_3 (20 mL) and the aqueous phase was extracted with DCM (3x 20 mL) and EA (3x 20 mL). The combined organic layers were dried over MgSO_4 and the solvent was removed *in vacuo*. Purification of the residue by flash column chromatography over silica gel (CH/EA 2:1) yielded primary alcohol **145** (460 mg, 1.03 mmol, 25%) and 1,2 deprotected **153** (441 mg, 1.33 mmol, 32%) both as a colourless oil.

R_f = 0.20 (CH/EA 6:1).

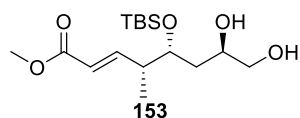
$[\alpha]_D^{20}$ = +26.0 (DCM, c = 1.0).

^1H NMR (CD_2Cl_2 , 700 MHz): δ = 7.02 (dd, 1H, J =15.9, 6.7 Hz), 5.80 (dd, 1H, J =15.9, 1.5 Hz), 3.80 (dddd, 2H, J =11.5, 9.1, 5.7, 4.4 Hz), 3.69 (s, 3H), 3.56 (dt, 1H, J =11.5, 3.8 Hz), 3.42 (dt, 1H, J =11.0, 5.4 Hz), 2.50 (dtddd, 1H, J =8.7, 6.8, 5.2, 3.5, 1.8 Hz), 1.75 (d, 1H, J =6.1 Hz), 1.63 (ddd,

^1H , $J=14.2$, 6.6, 4.8 Hz), 1.55 – 1.49 (m, 1H), 1.03 (d, 3H, $J=6.8$ Hz), 0.90 (s, 9H), 0.89 (s, 9H), 0.11 (d, 6H, $J=5.5$ Hz), 0.08 (d, 6H, $J=13.0$ Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 176 MHz): δ = 167.2, 151.7, 121.2, 73.4, 71.6, 67.3, 51.6, 42.3, 39.1, 26.0, 26.0, 18.4, 18.4, 13.7, -4.0, -4.1, -4.2 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 447.2957; found: 447.2954.



Chemical Formula: $\text{C}_{16}\text{H}_{32}\text{O}_5\text{Si}$
Exact Mass: 332.2019

R_f = 0.04 (CH/EA 6:1).

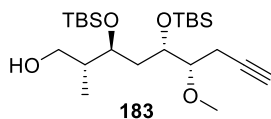
$[\alpha]_D^{20}$ = +18.0 (DCM, c = 1.0).

^1H NMR (CD_2Cl_2 , 700 MHz): δ = 6.99 (dd, 1H, $J=15.9$, 7.2 Hz), 5.83 (dd, 1H, $J=15.8$, 1.4 Hz), 3.95 (ddd, 1H, $J=8.2$, 5.5, 3.0 Hz), 3.89 – 3.83 (m, 1H), 3.70 (s, 3H), 3.56 (ddd, 1H, $J=11.0$, 5.8, 3.3 Hz), 3.35 (ddd, 1H, $J=10.9$, 6.9, 5.6 Hz), 2.66 (d, 1H, $J=3.6$ Hz), 2.62 (qdd, 1H, $J=6.9$, 5.4, 1.5 Hz), 1.93 (t, 1H, $J=5.8$ Hz), 1.53 (ddd, 1H, $J=14.3$, 10.4, 3.0 Hz), 1.37 (ddd, 1H, $J=14.3$, 7.9, 2.4 Hz), 1.06 (d, 3H, $J=6.9$ Hz), 0.91 (s, 9H), 0.11 (d, 6H, $J=11.7$ Hz) ppm.

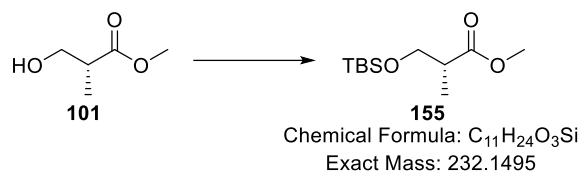
^{13}C NMR (CD_2Cl_2 , 176 MHz): δ = 167.2, 151.0, 121.5, 73.4, 68.9, 67.7, 51.7, 42.5, 36.3, 26.0, 18.3, 15.4, -4.3, -4.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 333.2092; found: 333.2094.

5.4 Experimental Details for Chapter 3.3.3: Synthesis of Alcohol 183



5.4.1 Methyl **(R)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropanoate (155)**



Imidazole (6.98 g, 103 mmol, 1.50 equiv.) was added to a solution of alcohol **101** (7.55 mL, 68.4 mmol, 1.00 equiv.) in DCM (70 mL) at 0 °C. Then TBSCl (15.5 g, 103 mmol, 1.50 equiv.) was added and the reaction was stirred for 1 h at 0 °C, before the reaction was allowed to warm to r.t. and stirred for additional 30 min. The reaction was quenched by adding aq. sat. NH₄Cl (100 mL). The aqueous phase was extracted with DCM (2x 50 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. Purification by flash column chromatography over silica gel (CH/EA 30:1) yielded silyl ether **155** (15.9 g, 68.4 mmol, quant.) as a colourless oil.

$R_f = 0.26$ (CH/EA 30:1).

$[\alpha]_D^{20} = -19.2$ (DCM, $c = 1.2$).

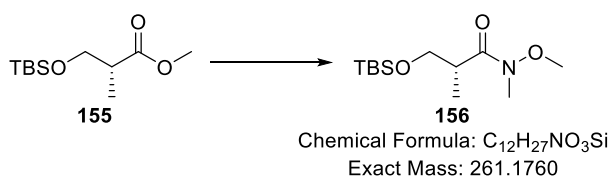
¹H NMR (CD₂Cl₂, 499 MHz): $\delta = 3.75$ (dd, 1H, $J=9.7, 6.9$ Hz), 3.68 – 3.65 (m, 1H), 3.64 (s, 3H), 2.65 – 2.57 (m, 1H), 1.11 (d, 3H, $J=7.0$ Hz), 0.87 (s, 9H), 0.04 (d, 6H, $J=1.9$ Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): $\delta = 175.6, 65.7, 51.7, 42.9, 27.3, 25.9, 18.5, 13.6, -5.4, -5.4$ ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 233.1567; found: 233.1566.

The experimental data are in agreement with those previously published.^[184]

5.4.2 **(R)-3-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-*N*,2-dimethylpropanamide (156)**



i-PrMgCl (2 M in THF, 240 mL, 480 mmol, 4.00 equiv.) was added slowly to a solution of ester **155** (27.9 g, 120 mmol, 1.00 equiv.) and *N,O*-dimethylhydroxylamine hydrochloride (14.7 g, 240 mmol, 2.00 equiv.) in THF (200 mL) at 0 °C and the reaction was stirred for 2 h. Aq. sat. NH₄Cl (200 mL) was added, the aqueous phase extracted with Et₂O (3x 300 mL) and the combined organic layers were dried over MgSO₄. Removal of the solvent under reduced pressure and purification of the residue by flash column chromatography over silica gel (CH/EA 4:1) yielded amide **156** (30.1 g, 115 mmol, 96%) as a colourless oil.

$R_f = 0.24$ (CH/EA 4:1).

$[\alpha]_D^{20} = -18.0$ (DCM, $c = 1.0$).

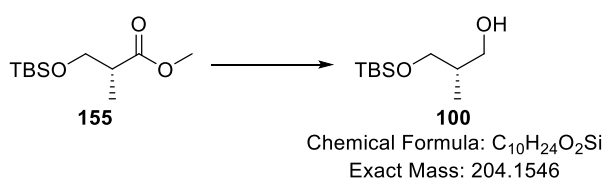
¹H NMR (CD₂Cl₂, 500 MHz): $\delta = 3.79$ (dd, 1H, $J=9.5, 8.2$ Hz), 3.69 (s, 3H), 3.51 (dd, 1H, $J=9.5, 6.0$ Hz), 3.15 (s, 3H), 1.02 (d, 3H, $J=6.9$ Hz), 0.87 (s, 9H), 0.04 (d, 6H, $J=4.9$ Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): $\delta = 176.2, 66.1, 61.9, 38.4, 27.3, 26.0, 18.6, -5.4$ ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 262.1833; found: 262.1830.

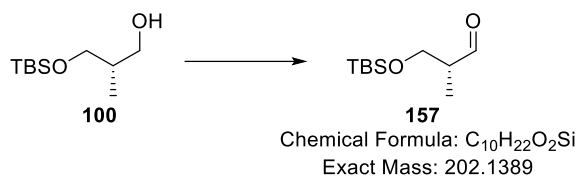
The experimental data are in agreement with those previously published.^[185]

5.4.3 (*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropan-1-ol (100)



DIBAL-H (1 M in THF, 86.0 mL, 86.0 mmol, 3.00 equiv.) was added over a period of 20 min to a solution of Ester **155** (6.66 g, 28.7 mmol, 1.00 equiv.) in DCM (100 mL) at -78 °C and the reaction was stirred for 2.5 h. The reaction was allowed to warm to 0 °C and Et₂O (80 mL), H₂O (10 mL) and NaOH (3 M, 10 mL) were added, followed by H₂O (30 mL). The reaction was allowed to warm to r.t. and stirred for 15 min. MgSO₄ was added, and the suspension was stirred for an additional 15 min before being filtered and the solvent removed under reduced

Procedure b:



DIPEA (375 μ L, 2.15 mmol, 4.00 equiv.) was added to a solution of alcohol **100** (110 mg, 538 μ mol, 1.00 equiv.) in DCM (3 mL) and DMSO (382 μ L, 5.38 mmol, 10.0 equiv.) at 0 °C. After stirring for 5 min, sulfur trioxide pyridine complex (257 mg, 1.61 mmol, 3.00 equiv.) was added and the reaction was allowed to warm to r.t. and stirred for 60 min. The solvent was removed under reduced pressure and the residue purified by flash column chromatography over silica gel (CH/EA 20:1) to yield aldehyde **157** (101 mg, 499 μ mol, 93%) as a colourless liquid.

R_f = 0.28 (CH/EA 20:1).

$[\alpha]_D^{20}$ = -29.0 (DCM, c = 1.0).

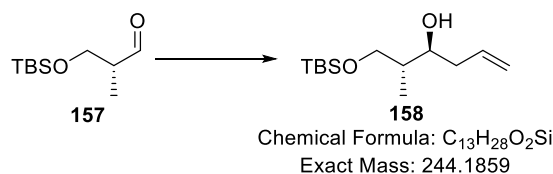
¹H NMR (CD₂Cl₂, 499 MHz): δ = 9.70 (d, 1H, J =1.6 Hz), 3.89 – 3.77 (m, 2H), 2.55 – 2.43 (m, 1H), 1.06 (d, 3H, J =7.0 Hz), 0.88 (s, 10H), 0.06 (s, 6H) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 204.8, 63.8, 49.2, 25.9, 18.5, 10.4, -5.4, -5.5 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 203.1462; found: 203.1467.

The experimental data are in agreement with those previously published.^[184]

5.4.5 (2R,3S)-1-((*tert*-Butyldimethylsilyl)oxy)-2-methylhex-5-en-3-ol (**158**)



Allylmagnesium chloride (1 M in THF, 12.0 mL, 12.0 mmol, 1.20 equiv.) was added over a period of 30 min to a solution of (–)-*B*-Methoxydiisopinocampheylboran (3.97 g, 12.5 mmol, 1.25 equiv.) in Et₂O (30 mL) at 0 °C. The reaction was stirred for 45 min and then cooled to –

78 °C. At this temperature, aldehyde **157** (2.03 g, 10.0 mmol, 1.00 equiv., dried 14 h over 3 Å molecular sieve in 12 mL Et₂O) was added over a period of 20 min. The reaction was stirred for an additional 1.5 h, followed by the addition of MeOH (20 mL), NaOH (3 M, 30 mL) and H₂O₂ (35%, 20 mL). The reaction mixture was then refluxed (70 °C) for 1.5 h. After cooling to r.t., the aqueous phase was extracted with Et₂O (3x 50 mL), the solvent removed under reduced pressure and the residue solved in Et₂O (20 mL) and H₂O (20 mL). FeSO₄ (~10 g) was added and the mixture stirred overnight (14 h). The aqueous phase was extracted with Et₂O (3x 20 mL), the combined organic layers washed with brine (10 mL) and dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 15:1) yielded title compound **158** (1.92 g, 7.86 mmol, 78%, *dr* = 14:1) as a colourless liquid.

R_f = 0.22 (CH/EA 15:1).

$[\alpha]_D^{20}$ = -15.0 (DCM, *c* = 0.8).

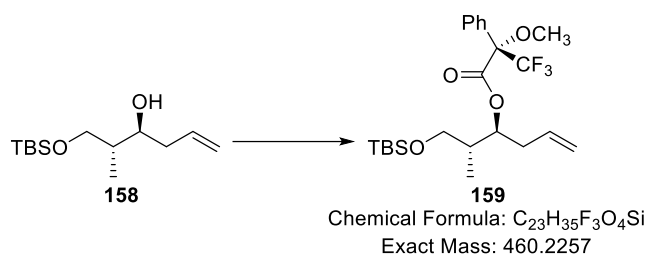
¹H NMR (Acetone, 700 MHz): δ = 5.94 (ddt, 1H, *J*=17.2, 10.2, 7.0 Hz), 5.06 (ddt, 1H, *J*=17.2, 2.3, 1.5 Hz), 5.00 (ddt, 1H, *J*=10.2, 2.4, 1.2 Hz), 3.74 (dd, 1H, *J*=9.9, 5.6 Hz), 3.65 (dd, 1H, *J*=9.9, 6.0 Hz), 3.59 – 3.52 (m, 2H), 2.32 (dt, 1H, *J*=5.5, 1.8 Hz), 2.30 (ddt, 1H, *J*=6.8, 3.6, 1.4 Hz), 2.16 (dtt, 1H, *J*=15.4, 7.2, 1.3 Hz), 1.74 – 1.66 (m, 1H), 0.91 (d, 9H, *J*=2.5 Hz), 0.90 (d, 3H, *J*=2.0 Hz), 0.07 (d, 6H, *J*=0.6 Hz) ppm.

¹³C NMR (Acetone, 176 MHz): δ = 137.1, 116.5, 73.7, 66.6, 41.6, 39.9, 26.3, 18.8, 13.7, -5.3, -5.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 245.1931; found: 245.1934.

The experimental data are in agreement with those previously published.^[186]

5.4.6 (2*R*,3*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-methylhex-5-en-3-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**159**)



(*R*)-(-)-MTPA-Cl (15 μ L, 81 μ mol, 3.0 equiv.) was added to a solution of alcohol **158** (6.6 mg, 27 μ mol, 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO₃ (1 mL) was added, the aqueous phase was extracted with EA (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO₄. The residue was purified by flash column chromatography over silica gel (CH/EA 50:1) to yield ester **159** (3.3 mg, 7.2 μ mol, 27%) as a colourless oil.

R_f = 0.14 (CH/EA 50:1).

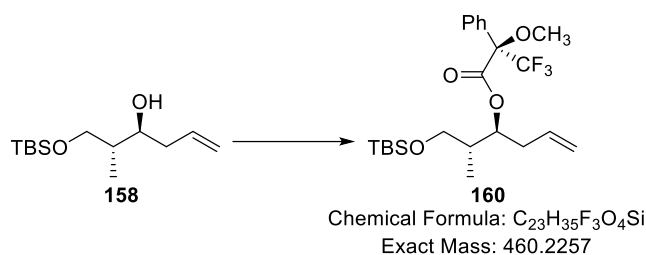
$[\alpha]_D^{20}$ = -1.4 (DCM, c = 0.6).

¹H NMR (CD₂Cl₂, 400 MHz): δ = 7.55 – 7.50 (m, 2H), 7.45 – 7.37 (m, 3H), 5.71 – 5.58 (m, 1H), 5.25 (ddd, 1H, J =7.7, 6.0, 3.9 Hz), 5.04 – 4.96 (m, 2H), 3.60 – 3.53 (m, 2H), 3.52 (p, 3H, J =1.4 Hz), 2.52 – 2.41 (m, 1H), 2.33 (dt, 1H, J =14.8, 7.8, 1.1 Hz), 2.04 (dddd, 1H, J =13.4, 7.6, 6.2, 1.4 Hz), 0.94 (d, 3H, J =6.9 Hz), 0.90 (s, 9H), 0.04 (s, 6H) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 166.3, 133.8, 132.7, 130.0, 128.7, 125.1, 122.8, 118.2, 85.2, 85.0, 78.1, 64.7, 55.8, 38.8, 35.1, 26.0, 18.5, 12.8, -5.4, -5.5 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 461.2329; found: 461.2311.

5.4.7 (2*R*,3*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-methylhex-5-en-3-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**160**)



(*S*)-(+)-MTPA-Cl (12 μ l, 64 μ mol, 3.0 equiv.) was added to a solution of alcohol **158** (5.2 mg, 21 μ mol, 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO₃ (1 mL) was added, the aqueous phase was extracted with EA (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO₄. The residue was purified by flash column chromatography over silica gel (CH/EA 50:1) to yield ester **160** (3.6 mg, 7.8 μ mol, 37%) as a colourless oil.

R_f = 0.14 (CH/EA 50:1).

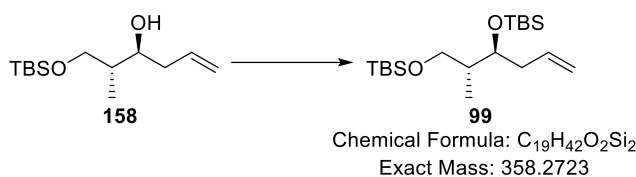
$[\alpha]_D^{20}$ = +40.0 (DCM, c = 0.6).

¹H NMR (CD₂Cl₂, 500 MHz): δ = 7.57 – 7.50 (m, 1H), 7.43 – 7.37 (m, 3H), 5.80 (dddd, 1H, J =17.1, 10.2, 7.9, 6.0 Hz), 5.26 (ddd, 1H, J =7.9, 5.8, 4.0 Hz), 5.16 – 5.08 (m, 2H), 3.54 (q, 3H, J =1.3 Hz), 3.51 – 3.46 (m, 1H), 3.41 (dd, 1H, J =10.1, 6.1 Hz), 2.55 – 2.48 (m, 1H), 2.40 (dt, 1H, J =15.0, 7.9, 1.1 Hz), 2.05 – 1.96 (m, 1H), 0.89 (s, 9H), 0.82 (d, 3H, J =7.0 Hz), 0.01 (d, 6H, J =3.3 Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 166.3, 134.3, 132.9, 130.0, 128.7, 127.8, 125.1, 122.8, 118.3, 85.0, 84.8, 78.3, 64.6, 55.9, 38.7, 35.2, 26.0, 18.5, 12.6, -5.4, -5.5 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 461.2329; found: 461.2334.

5.4.8 (5*S*,6*R*)-5-Allyl-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane (**99**)



TBSOTf (2.14 mL, 10.9 mmol, 2.00 equiv.) was added to a solution of alcohol **158** (1.33 g, 5.42 mmol, 1.00 equiv.) and 2,6-lutidine (2.50 mL, 21.8 mmol, 4.00 equiv.) in DCM (10 mL) at 0 °C. The reaction was then allowed to warm to r.t. and stirred for 45 min before it was quenched by adding aq. sat. NH₄Cl (20 mL). The aqueous phase was extracted with DCM (3x 5 mL) and the combined organic layers were dried over MgSO₄. Removal of the solvent under reduced pressure and purification of the residue by flash column chromatography over silica gel (CH/EA 50:1) yielded silyl ether **99** (1.47 g, 4.11 mmol, 76%) as a colourless oil.

R_f = 0.50 (CH/EA 50:1).

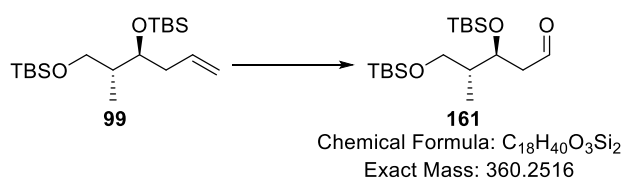
$[\alpha]_D^{20}$ = +15.6 (DCM, c = 0.9).

¹H NMR (CD₂Cl₂, 400 MHz): δ = 5.81 (ddt, 1H, J =17.3, 10.2, 7.1 Hz), 5.12 – 5.00 (m, 2H), 3.89 (ddd, 1H, J =7.2, 6.0, 3.0 Hz), 3.57 (dd, 1H, J =9.8, 7.0 Hz), 3.45 (dd, 1H, J =9.8, 6.6 Hz), 2.34 – 2.22 (m, 2H), 1.72 (qd, 1H, J =6.8, 3.1 Hz), 0.93 (d, 19H, J =0.9 Hz), 0.86 (d, 3H, J =6.8 Hz), 0.09 (d, 7H, J =1.3 Hz), 0.07 (s, 6H) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 136.1, 116.6, 71.9, 65.8, 40.3, 40.0, 26.1, 18.5, 18.4, 10.4, -4.0, -4.6, -5.2, -5.2 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 359.2796; found: 359.2797.

5.4.9 (3*S*,4*R*)-3,5-bis((*tert*-Butyldimethylsilyl)oxy)-4-methylpentanal (**161**)



Alkene **99** (6.50 g, 18.1 mmol, 1.00 equiv.) was solved in MeOH (50 mL) and DCM (50 mL) together with a tip of a spatula NaHCO₃ (~10 mg) and cooled to -78 °C. The reaction vessel was filled with ozone and stirred for 90 min. PPh₃ (7.13 g, 27.2 mmol, 1.50 equiv.) was added and the reaction mixture was stirred for 10 min at -78 °C. The reaction was then allowed to warm to r.t. and stirred for additional 2 h. Celite[®] (50 g) was added and the solvent was removed under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 30:1) yielded aldehyde **161** (6.54 g, 18.1 mmol, quant.) as a colourless oil.

$R_f = 0.16$ (CH/EA 30:1).

$[\alpha]_D^{20} = -3.0$ (DCM, $c = 1.0$).

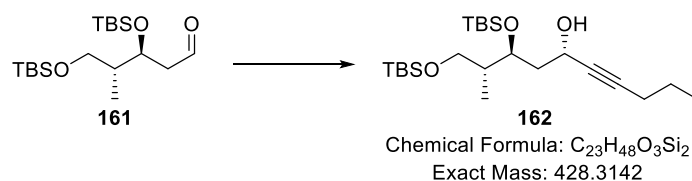
¹H NMR (CD₂Cl₂, 700 MHz): $\delta = 9.78$ (dd, 1H, $J=3.0, 2.0$ Hz), 4.37 (dt, 1H, $J=7.1, 4.7$ Hz), 3.50 (qd, 2H, $J=10.2, 6.4$ Hz), 2.55 – 2.41 (m, 2H), 1.92 (pdd, 1H, $J=7.0, 5.6, 4.8$ Hz), 0.89 (s, 9H), 0.86 (d, 3H, $J=7.0$ Hz), 0.07 (d, 6H, $J=22.9$ Hz), 0.04 (d, 6H, $J=2.6$ Hz) ppm.

¹³C NMR (CD₂Cl₂, 176 MHz): $\delta = 202.8, 69.3, 65.3, 47.3, 42.1, 26.0, 25.9, 18.5, 18.3, 11.6, -4.4, -4.5, -5.3, -5.4$ ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 361.2589; found: 361.2591.

The experimental data are in agreement with those previously published.^[187]

5.4.10 (2*R*,3*S*,5*S*)-1,3-bis((*tert*-Butyldimethylsilyl)oxy)-2-methyldec-6-yn-5-ol (**162**)



NEt₃ (158 μ L, 1.13 mmol, 2.40 equiv.) was added to a solution of Zn(OTf)₂ (377 mg, 1.04 mmol, 2.20 equiv.) and (1*R*,2*S*)-(-)-*N*-methylephedrine (203 mg, 1.13 mmol, 2.40 equiv.) in toluene (2 mL) and the mixture was stirred for 2 h. 1-Pentyne (112 μ L, 1.13 mmol, 2.40 equiv.) was added and the reaction was stirred for 15 min, followed by addition of aldehyde **161** (170 mg,

471 μmol , 1.00 equiv.). After 2 h of stirring, the reaction was quenched by adding aq. sat. NH_4Cl (5 mL). The aqueous phase was extracted with DCM (3x 5 mL), the combined organic layers dried over MgSO_4 and the solvent removed under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 20:1) to yield alkyne **162** (135 mg, 314 μmol , 67%, $dr > 20:1$) as a colourless oil.

$R_f = 0.25$ (CH/EA 20:1).

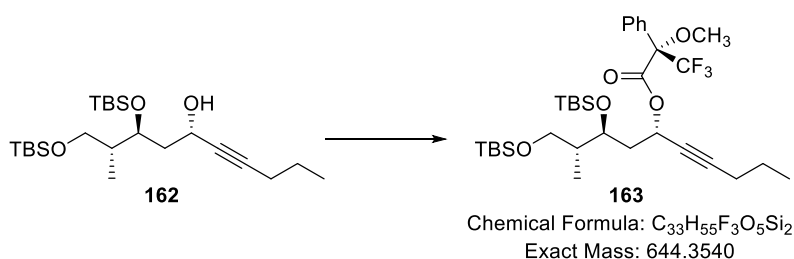
$[\alpha]_D^{20} = -13.0$ (DCM, $c = 1.0$).

$^1\text{H NMR}$ (CD_2Cl_2 , 500 MHz): $\delta = 4.51$ (dddt, 1H, $J=8.0, 5.8, 3.8, 2.0$ Hz), 4.21 (ddd, 1H, $J=8.3, 4.6, 3.8$ Hz), 3.47 (qd, 2H, $J=10.1, 6.6$ Hz), 2.73 (d, 1H, $J=6.1$ Hz), 2.17 (td, 2H, $J=7.1, 2.0$ Hz), 1.99 – 1.89 (m, 1H), 1.75 (qdd, 2H, $J=14.3, 8.2, 3.6$ Hz), 1.56 – 1.48 (m, 1H), 0.97 (t, 3H, $J=7.4$ Hz), 0.90 (d, 19H, $J=3.2$ Hz), 0.85 (d, 3H, $J=7.0$ Hz), 0.11 (d, 5H, $J=13.1$ Hz), 0.05 (s, 6H) ppm.

$^{13}\text{C NMR}$ (CD_2Cl_2 , 126 MHz): $\delta = 85.0, 82.2, 71.2, 65.4, 60.3, 41.6, 39.6, 26.1, 22.6, 21.0, 18.3, 13.7, 11.5, -4.3, -4.4, -5.4, -5.4$ ppm.

HRMS (ESI +), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 429.3215; found: 429.3236.

5.4.11 (2*R*,3*S*,5*S*)-1,3-Bis((*tert*-butyldimethylsilyl)oxy)-2-methyldec-6-yn-5-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**163**)



(*R*)-(-)-MTPA-Cl (9.9 μL , 52 μmol , 5.0 equiv.) was added to a solution of alcohol **162** (4.5 mg, 10 μmol , 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO_3 (1 mL) was added, the aqueous phase was extracted with EA (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO_4 . The residue was purified by flash column

chromatography over silica gel (CH/EA 50:1) to yield ester **163** (6.7 mg, 10 μ mol, quant.) as a colourless oil.

R_f = 0.21 (CH/EA 50:1).

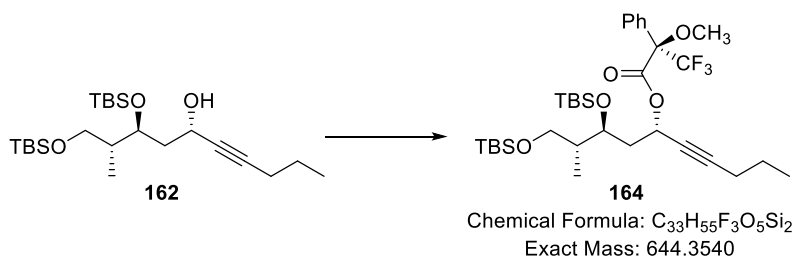
$[\alpha]_D^{20}$ = -30.0 (DCM, c = 1.0).

^1H NMR (CD_2Cl_2 , 700 MHz): δ = 7.58 (dd, 2H, J =6.7, 2.5 Hz), 7.47 – 7.35 (m, 5H), 5.55 (ddt, 1H, J =9.4, 4.1, 2.0 Hz), 3.80 – 3.70 (m, 1H), 3.56 (q, 4H, J =4.2 Hz), 3.48 (ddd, 1H, J =9.7, 5.7, 4.0 Hz), 3.35 (dd, 1H, J =10.1, 5.9 Hz), 2.21 (tt, 2H, J =7.0, 2.3 Hz), 2.04 (ddd, 1H, J =14.4, 9.4, 3.2 Hz), 1.85 (ddtd, 2H, J =24.2, 13.2, 7.6, 3.6 Hz), 1.55 – 1.48 (m, 2H), 1.00 – 0.93 (m, 3H), 0.89 (d, 9H, J =4.7 Hz), 0.87 (d, 9H, J =4.7 Hz), 0.86 (s, 3H), 0.00 (d, 12H, J =3.3 Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 176 MHz): δ = 166.0, 132.9, 130.1, 128.8, 127.9, 87.7, 85.3, 77.6, 70.1, 65.3, 64.8, 60.6, 55.6, 41.9, 39.3, 26.1, 26.0, 22.3, 20.9, 18.5, 18.3, 13.6, 11.5, -4.3, -4.6, -5.4, -5.5 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 645.3613; found: 645.3621.

5.4.12 (2*R*,3*S*,5*S*)-1,3-Bis((*tert*-butyldimethylsilyl)oxy)-2-methyldec-6-yn-5-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**164**)



(*S*)-(+)-MTPA-Cl (11 μ L, 58 μ mol, 5.0 equiv.) was added to a solution of alcohol **162** (5.0 mg, 12 μ mol, 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO_3 (1 mL) was added, the aqueous phase was extracted with EA (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO_4 . The residue was purified by flash column chromatography over silica gel (CH/EA 50:1) to yield ester **164** (7.5 mg, 12 μ mol, quant) as a colourless oil.

$R_f = 0.21$ (CH/EA 50:1).

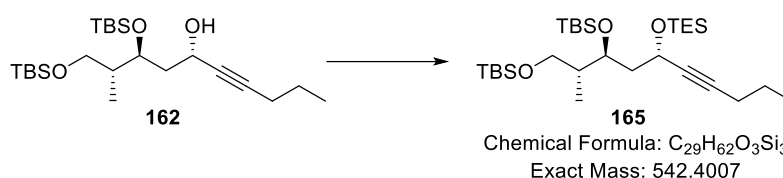
$[\alpha]_D^{20} = -6.0$ (DCM, $c = 1.0$).

$^1\text{H NMR}$ (CD_2Cl_2 , 700 MHz): $\delta = 7.54$ (dd, 2H, $J=6.9, 2.0$ Hz), 7.45 – 7.39 (m, 3H), 5.57 (ddt, 1H, $J=8.8, 4.3, 2.0$ Hz), 3.90 (dt, 1H, $J=8.7, 3.8$ Hz), 3.59 (d, 1H, $J=1.2$ Hz), 3.55 (d, 3H, $J=1.1$ Hz), 3.53 (dd, 1H, $J=10.2, 6.9$ Hz), 3.43 (ddd, 1H, $J=10.2, 5.5, 3.7$ Hz), 2.17 (td, 2H, $J=7.0, 2.0$ Hz), 2.06 (ddd, 1H, $J=14.3, 9.1, 3.6$ Hz), 1.94 – 1.90 (m, 1H), 1.90 – 1.86 (m, 1H), 1.49 (p, 2H, $J=7.2$ Hz), 0.95 (t, 3H, $J=7.4$ Hz), 0.90 (s, 9H), 0.89 – 0.86 (m, 12H), 0.04 (d, 6H, $J=19.9$ Hz), 0.02 (d, 6H, $J=1.1$ Hz) ppm.

$^{13}\text{C NMR}$ (CD_2Cl_2 , 176 MHz): $\delta = 166.0, 132.3, 130.0, 128.7, 128.0, 87.5, 85.1, 77.5, 70.1, 65.3, 65.0, 55.9, 41.8, 38.9, 27.3, 26.1, 26.0, 22.3, 20.9, 18.6, 18.4, 13.6, 11.7, -4.2, -4.5, -5.3, -5.4$ ppm.

HRMS (ESI +), 6.0 eV: calculated for $[\text{M}+\text{H}]^+$: 645.3613; found: 645.3617.

5.4.13 (6*R*,7*S*,9*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-11,11-diethyl-2,2,3,3,6-pentamethyl-9-(pent-1-yn-1-yl)-4,10-dioxo-3,11-disilatridecane (**165**)



TESCl (520 mg, 3.45 mmol, 2.00 equiv.) was added to a solution of alcohol **162** (740 mg, 1.73 mmol, 1.00 equiv.) and imidazole (470 mg, 6.90 mmol, 4.00 equiv.) in DCM (4 mL) at 0 °C. After 5 min of stirring, the reaction was allowed to warm to r.t. and stirred for additional 2 h. The reaction was quenched with aq. sat. NH_4Cl (20 mL), the aqueous phase extracted with DCM (3x 10 mL) and the combined organic layers were washed with brine (5 mL) and dried over MgSO_4 . Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 100:1) yielded silyl ether **165** (866 mg, 1.59 mmol, 92%) as a colourless oil.

$R_f = 0.11$ (CH/EA 100:1).

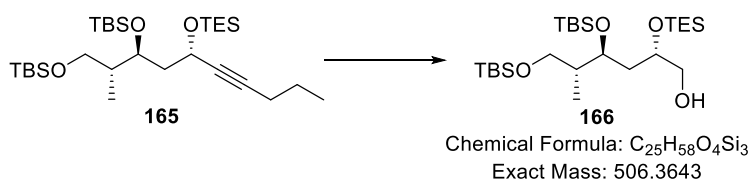
$[\alpha]_D^{20} = -33.0$ (DCM, $c = 1.0$).

$^1\text{H NMR}$ (CD_2Cl_2 , 700 MHz): $\delta = 4.48$ (ddt, 1H, $J=8.7, 4.4, 2.0$ Hz), 4.00 (dt, 1H, $J=7.9, 3.9$ Hz), 3.55 (dd, 1H, $J=10.1, 6.8$ Hz), 3.40 (dd, 1H, $J=10.1, 6.5$ Hz), 2.16 (td, 2H, $J=7.1, 2.0$ Hz), 1.86 (ddt, 1H, $J=10.5, 6.9, 3.7$ Hz), 1.77 (ddd, 1H, $J=13.7, 8.8, 4.0$ Hz), 1.64 (ddd, 1H, $J=13.7, 8.2, 4.6$ Hz), 1.52 (h, 2H, $J=7.2$ Hz), 0.97 (t, 11H, $J=8.0$ Hz), 0.89 (s, 9H), 0.89 (s, 10H), 0.86 (d, 6H, $J=6.9$ Hz), 0.72 – 0.60 (m, 6H), 0.07 (d, 6H, $J=8.0$ Hz), 0.04 (d, 6H, $J=2.3$ Hz) ppm.

$^{13}\text{C NMR}$ (CD_2Cl_2 , 176 MHz): $\delta = 84.9, 82.8, 70.3, 65.4, 60.1, 43.2, 42.0, 26.1$ (d, $J=1.5$ Hz), 22.5, 21.1, 18.6, 18.4, 13.7, 12.1, -4.3, -4.3, -5.3, -5.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 543.4080; found: 543.4084.

5.4.14 (2*S*,4*S*,5*R*)-4,6-Bis((*tert*-butyldimethylsilyl)oxy)-5-methyl-2-((triethylsilyl)oxy)hexan-1-ol (**166**)



Lindlar catalyst (923 mg, Pd-600%) was added to a solution of alkyne **165** (790 mg, 1.45 mmol, 1.00 equiv.) and quinoline (34.4 μL , 291 μmol , 0.20 equiv.) in hexane (20 mL). The reaction vessel was then filled with hydrogen. After stirring for 16 h, the suspension was filtered over a plug of celite[®] and washed with CH/EA (100:1, 50 mL). The solvent was removed under reduced pressure and the residue was solved in DCM/MeOH (1:1, 50 mL). A tip of a spatula NaHCO_3 (~10 mg) was added and the reaction vessel was filled with ozone at -78°C . After 30 min, NaBH_4 (275 mg, 7.27 mmol, 5.00 equiv.) was added and the mixture was stirred for 30 min before it was allowed to warm to r.t. and stir for an additional 2 h, followed by addition of H_2O (10 mL). The aqueous phase was extracted with DCM (3x 10 mL) and the combined organic layers were dried over MgSO_4 . Purification of the residue by flash column chromatography over silica gel (CH/EA 15:1) yielded alcohol **166** (457 mg, 902 μmol , 62%, 2 step) as a colourless oil.

$R_f = 0.42$ (CH/EA 15:1).

$[\alpha]_D^{20} = -6.7$ (DCM, $c = 0.6$).

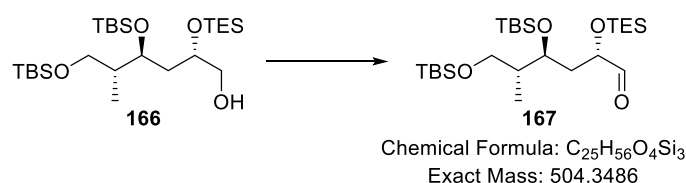
$^1\text{H NMR}$ (CD_2Cl_2 , 400 MHz): $\delta = 3.96$ (ddd, 1H, $J=7.9, 4.7, 3.5$ Hz), 3.82 (dtd, 1H, $J=6.4, 5.2, 3.8$ Hz), 3.58 (ddd, 1H, $J=11.1, 6.2, 3.8$ Hz), 3.51 (dd, 1H, $J=10.1, 7.3$ Hz), 3.47 – 3.37 (m, 2H), 1.95 (t, 1H, $J=6.4$ Hz), 1.88 (ddt, 1H, $J=10.4, 7.0, 3.5$ Hz), 1.59 – 1.55 (m, 2H), 0.90 (d, 20H, $J=2.1$ Hz), 0.84 (d, 3H, $J=7.0$ Hz), 0.68 – 0.58 (m, 6H), 0.08 (d, 6H, $J=0.6$ Hz), 0.05 (d, 6H, $J=1.5$ Hz) ppm.

$^{13}\text{C NMR}$ (CD_2Cl_2 , 126 MHz): $\delta = 72.1, 71.6, 67.6, 65.5, 42.4, 37.4, 26.1, 26.1, 18.6, 18.4, 11.5, 7.1, 5.5, -4.0, -4.2, -5.3, -5.4$ ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 507.3716; found: 507.3715.

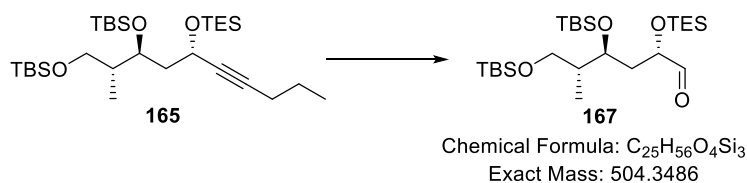
5.4.15 (2*S*,4*S*,5*R*)-4,6-Bis(*tert*-butyldimethylsilyl)oxy)-5-methyl-2-((triethylsilyl)oxy)hexanal (**167**)

Procedure a:



DIPEA (304 μL , 1.74 mmol, 4.00 equiv.) was added to a solution of alcohol **166** (221 mg, 436 μmol , 1.00 equiv.) in DCM (2 mL) and DMSO (310 μL , 4.36 mmol, 10.0 equiv.) at 0 °C. After stirring for 5 min, sulfur trioxide pyridine complex (208 mg, 1.31 mmol, 3.00 equiv.) was added and the reaction was stirred for 30 min. The solvent was removed under reduced pressure and the residue purified by flash column chromatography over silica gel (CH/EA 50:1) to yield aldehyde **167** (205 mg, 406 μmol , 93%) as a colourless oil.

Procedure b:



Lindlar catalyst (923 mg, Pd-600%) was added to a solution of alkyne **165** (790 mg, 1.45 mmol, 1.00 equiv.) and quinoline (34.4 μ L, 291 μ mol, 0.20 equiv.) in hexane (20 mL). The reaction vessel was then filled with hydrogen. After stirring for 16 h, the suspension was filtered over a plug of celite[®] and washed with CH/EA (100:1, 50 mL). The solvent was removed under reduced pressure and a part of the residue (3.5 mg) was solved in DCM/MeOH (1:1, 2 mL). A tip of a spatula NaHCO₃ (~3 mg) was added and the reaction vessel was filled with ozone at –78 °C. After 15 min, PPh₃ (3.4 mg, 13 μ mol, 2.0 equiv.) was added and the mixture was allowed to warm to r.t. and stir for 2 h. The solvent was removed under reduced pressure and the residue purified by flash column chromatography over silica gel (CH/EA 50:1) yielded aldehyde **167** (3.0 mg, 5.9 μ mol, 93%, 2 step) as a colourless oil.

R_f = 0.20 (CH/EA 50:1).

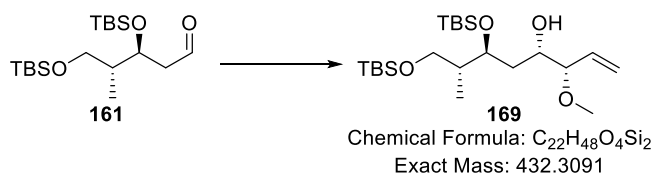
$[\alpha]_D^{20}$ = –17.0 (DCM, c = 1.0).

¹H NMR (CD₂Cl₂, 700 MHz): δ = 9.56 (d, 1H, J =1.5 Hz), 4.19 (ddd, 1H, J =8.2, 4.1, 1.6 Hz), 4.05 (ddd, 1H, J =8.7, 3.9, 3.0 Hz), 3.52 – 3.41 (m, 2H), 1.98 – 1.90 (m, 1H), 1.75 (ddd, 1H, J =14.1, 8.7, 4.1 Hz), 1.60 (ddd, 1H, J =14.1, 8.3, 3.0 Hz), 0.96 (t, 9H, J =8.0 Hz), 0.89 (d, 18H, J =1.6 Hz), 0.85 (d, 3H, J =7.0 Hz), 0.63 (q, 6H, J =8.0 Hz), 0.08 (d, 6H, J =7.6 Hz), 0.04 (d, 6H, J =2.4 Hz) ppm.

¹³C NMR (CD₂Cl₂, 176 MHz): δ = 203.1, 76.5, 70.3, 65.5, 42.3, 36.0, 26.1, 26.1, 18.6, 18.4, 11.3, 7.0, 5.6, –4.0, –4.2, –5.3, –5.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 505.3559; found: 505.3558.

5.4.16 (3*S*,4*S*,6*S*,7*R*)-6,8-Bis((*tert*-butyldimethylsilyl)oxy)-3-methoxy-7-methyloct-1-en-4-ol (**169**)



s-BuLi (1.4 M, 1.34 mL, 1.87 mmol, 1.30 equiv.) was added slowly over a period of 10 min to a solution of 3-methoxy-1-propene (203 μ L, 2.16 mmol, 1.50 equiv.) in THF (5 mL) at –78 °C and the reaction was stirred for 10 min. Then (+)-*B*-Methoxydiisopinocampheylboran (593 mg,

1.87 mmol, 1.30 equiv.) was to the reaction mixture along with THF (2x 2.5 mL). The reaction was stirred for an additional 30 min before boron trifluoride etherate (244 μ L, 1.95 mmol, 1.35 equiv.) and aldehyde **161** (520 mg, 1.44 mmol, 1.00 equiv., dried 2 h over 3 Å molecular sieve in 2 mL THF) were added, with the aldehyde being added gradually. The reaction was stirred for 2 h. Subsequently, MeOH (5 mL), NaOH (3 M, 50 mL) and H₂O₂ (35%, 30 mL) were cautiously added and the reaction mixture was refluxed (70 °C) for 45 min. Aq. sat. Na₂S₂O₃ (100 mL) was added to quench the reaction, the aqueous phase extracted with Et₂O (3x 50 mL), the combined organic layers dried over MgSO₄ and the solvent removed under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 15:1) yielded title compound **169** (362 mg, 836 μ mol, 58%, *dr* >20:1) as a colourless oil.

R_f = 0.24 (CH/EA 15:1).

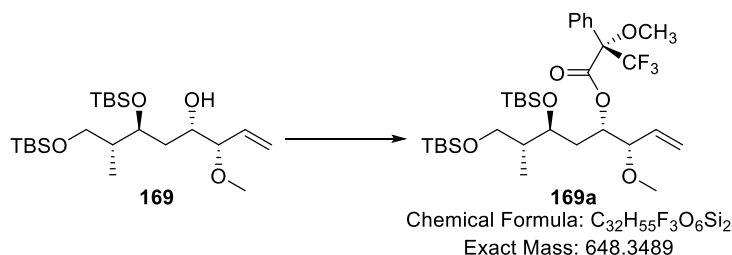
$[\alpha]_D^{20}$ = -9.0 (DCM, *c* = 1.0).

¹H NMR (CD₂Cl₂, 700 MHz): δ = 5.63 (ddd, 1H, *J*=17.3, 10.4, 8.0 Hz), 5.31 – 5.25 (m, 2H), 4.06 (ddd, 1H, *J*=9.1, 4.4, 2.6 Hz), 3.64 (dddd, 1H, *J*=10.6, 7.0, 2.9, 2.0 Hz), 3.54 (dd, 1H, *J*=10.1, 6.7 Hz), 3.41 (dd, 1H, *J*=10.0, 6.3 Hz), 3.32 (ddt, 1H, *J*=7.9, 7.0, 0.8 Hz), 3.29 (s, 3H), 2.72 (dd, 1H, *J*=2.9, 1.1 Hz), 1.88 (pd, 1H, *J*=6.8, 4.4 Hz), 1.48 (dddd, 1H, *J*=14.1, 9.1, 2.0, 1.1 Hz), 1.35 (ddd, 1H, *J*=14.1, 10.6, 2.6 Hz), 0.89 (s, 9H), 0.89 (s, 9H), 0.83 (d, 3H, *J*=7.0 Hz), 0.07 (d, 6H, *J*=6.5 Hz), 0.04 (s, 6H) ppm.

¹³C NMR (CD₂Cl₂, 176 MHz): δ = 135.7, 119.8, 87.7, 70.4, 70.3, 65.6, 56.7, 42.2, 35.5, 26.1, 26.1, 18.5, 18.4, 11.7, -4.3, -4.5, -5.3, -5.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 433.3164; found: 433.3161.

5.4.17 (3*S*,4*S*,6*S*,7*R*)-6,8-Bis((*tert*-butyldimethylsilyl)oxy)-3-methoxy-7-methyloct-1-en-4-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (169a**)**



(*R*)-(-)-MTPA-Cl (5.5 μ L, 30 μ mol, 2.0 equiv.) was added to a solution of alcohol **169** (6.4 mg, 15 μ mol, 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO₃ (1 mL) was added, the aqueous phase was extracted with EA (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO₄. The residue was purified by flash column chromatography over silica gel (CH/EA 50:1) to yield ester **169a** (2.6 mg, 4.0 μ mol, 27%) as a colourless oil.

R_f = 0.16 (CH/EA 50:1).

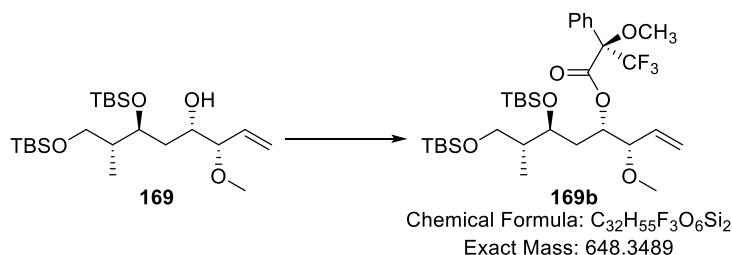
$[\alpha]_D^{20}$ = -150 (DCM, c = 0.1).

¹H NMR (CDCl₃, 700 MHz): δ = 7.63 (dt, 3H, J =9.9, 3.5 Hz), 7.44 – 7.34 (m, 4H), 5.62 (ddd, 1H, J =17.2, 10.4, 7.8 Hz), 5.36 – 5.33 (m, 1H), 5.33 – 5.30 (m, 1H), 5.28 (ddd, 1H, J =17.2, 1.6, 0.9 Hz), 3.64 – 3.62 (m, 1H), 3.62 – 3.59 (m, 1H), 3.55 (t, 3H, J =1.2 Hz), 3.39 (dd, 1H, J =10.1, 5.6 Hz), 3.28 (s, 3H), 3.22 – 3.18 (m, 1H), 1.75 (dddd, 1H, J =10.3, 6.8, 5.0, 2.2 Hz), 1.70 – 1.64 (m, 1H), 1.60 – 1.56 (m, 1H), 0.90 (d, 9H, J =4.0 Hz), 0.86 (s, 9H), 0.81 (d, 3H, J =7.0 Hz), 0.12 – 0.04 (m, 6H), -0.01 (d, 6H, J =2.5 Hz) ppm.

¹³C NMR (CDCl₃, 176 MHz): δ = 166.3, 134.0, 132.5, 129.6, 128.4, 127.9, 120.7, 84.0, 75.3, 70.4, 65.1, 56.5, 55.4, 42.5, 34.2, 26.1, 26.0, 18.4, 18.3, 11.0, -4.0, -4.4, -5.3, -5.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 649.3562; found: 649.3559.

5.4.18 (3*S*,4*S*,6*S*,7*R*)-6,8-Bis((*tert*-butyldimethylsilyl)oxy)-3-methoxy-7-methyloct-1-en-4-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (169b**)**



(*S*)-(+)-MTPA-Cl (3.5 μ l, 18.5 μ mol, 2.0 equiv.) was added to a solution of alcohol **169** (4.0 mg, 9.2 μ mol, 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO₃ (1 mL) was added, the aqueous phase was extracted with EA (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO₄. The residue was purified by flash column chromatography over silica gel (CH/EA 50:1) to yield ester **169b** (3.7 mg, 5.7 μ mol, 62%) as a colourless oil.

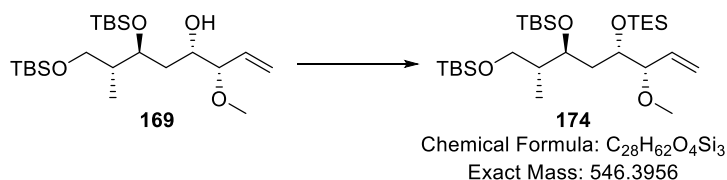
R_f = 0.16 (CH/EA 50:1).

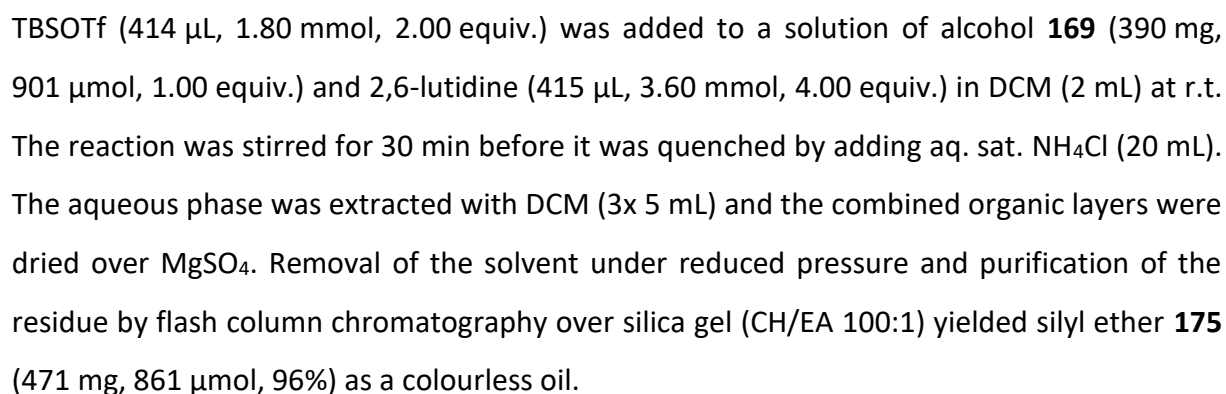
$[\alpha]_D^{20}$ = +0.0 (DCM, c = 0.8).

¹H NMR (CDCl₃, 700 MHz): δ = 7.62 (dd, 2H, J =7.1, 2.8 Hz), 7.41 – 7.37 (m, 3H), 5.55 – 5.48 (m, 1H), 5.34 – 5.28 (m, 1H), 5.26 – 5.23 (m, 1H), 5.16 (ddd, 1H, J =17.2, 1.7, 1.0 Hz), 3.78 (ddd, 1H, J =9.8, 3.5, 2.1 Hz), 3.60 – 3.57 (m, 1H), 3.56 (d, 3H, J =1.2 Hz), 3.55 – 3.52 (m, 1H), 3.48 (dd, 1H, J =10.2, 6.3 Hz), 3.37 – 3.33 (m, 1H), 3.20 (s, 2H), 1.86 – 1.80 (m, 1H), 1.73 – 1.63 (m, 2H), 0.90 (s, 9H), 0.88 (s, 9H), 0.85 – 0.83 (m, 3H), 0.11 – 0.05 (m, 6H), 0.03 – -0.00 (m, 6H) ppm.

¹³C NMR (CDCl₃, 176 MHz): δ = 166.2, 133.9, 129.6, 128.4, 127.8, 120.2, 83.6, 75.2, 70.2, 65.3, 56.7, 55.7, 42.5, 33.5, 26.1, 26.1, 18.5, 18.3, 11.1, -4.1, -4.5, -5.3, -5.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 649.3562; found: 649.3561.



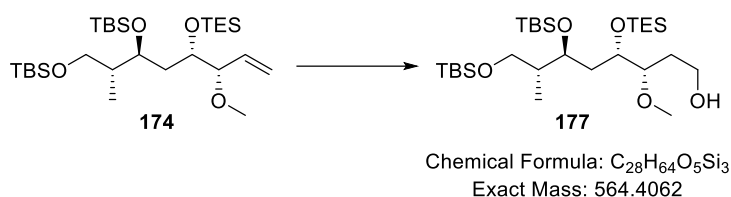

$$[\alpha]_D^{20} = -20.0 \text{ (DCM, } c = 1.0\text{)}.$$

¹H NMR (CDCl₃, 700 MHz): δ = 5.68 (ddd, 1H, *J*=17.5, 10.6, 7.3 Hz), 5.30 – 5.17 (m, 2H), 3.91 (dt, 1H, *J*=8.7, 3.1 Hz), 3.83 (ddd, 1H, *J*=8.5, 5.7, 2.8 Hz), 3.56 (dd, 1H, *J*=10.1, 5.8 Hz), 3.42 (ddt, 1H, *J*=6.9, 5.8, 1.1 Hz), 3.34 (dd, 1H, *J*=10.1, 7.2 Hz), 3.26 (s, 3H), 1.82 (tqd, 1H, *J*=9.1, 6.6, 4.5 Hz), 1.61 (ddd, 1H, *J*=14.1, 8.7, 2.8 Hz), 1.34 (ddd, 1H, *J*=14.2, 8.6, 2.8 Hz), 0.89 – 0.88 (m, 27H), 0.85 (d, 3H, *J*=6.9 Hz), 0.09 (d, 6H, *J*=13.2 Hz), 0.06 (d, 5H, *J*=6.6 Hz), 0.03 (d, 6H, *J*=3.4 Hz) ppm.

¹³C NMR (CDCl₃, 176 MHz): δ = 135.5, 118.3, 86.5, 72.0, 71.3, 65.4, 56.6, 42.7, 37.5, 26.3, 26.2, 26.1, 18.5, 18.5, 18.3, 12.0, -3.6, -3.8, -3.9, -4.2, -5.2, -5.2 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 547.4029; found: 547.4038.

5.4.22 (3*S*,4*S*,6*S*,7*R*)-6,8-Bis((*tert*-butyldimethylsilyl)oxy)-3-methoxy-7-methyl-4-((triethylsilyl)oxy)octan-1-ol (**177**)



9-BBN (0.5 M in THF, 978 μ L, 384 μ mol, 2.00 equiv.) was added slowly to a solution of alkene **174** (105 mg, 192 μ mol, 1.00 equiv., dried 30 min over 3 Å molecular sieve in 0.5 mL THF) in THF (1 mL) at 0 °C and the reaction was stirred for 2.5 h. MeOH (1 mL), NaOH (3 M, 5 mL) and H₂O₂ (35%, 5 mL) were added and the mixture was stirred for 1 h at r.t., followed by addition of aq. sat. Na₂S₂O₃ (20 mL). The aqueous phase was extracted with EA (3x 10 mL), the combined organic layers washed with brine (5 mL) and dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/Ea 3:1) yielded alcohol **177** (29.0 mg, 51.3 μ mol, 25%) as a colourless oil.

R_f = 0.41 (CH/Ea 3:1).

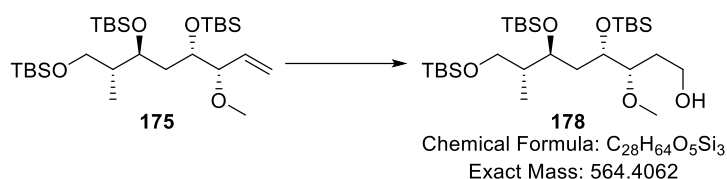
$[\alpha]_D^{20}$ = -35.0 (DCM, c = 0.6).

¹H NMR (CD₂Cl₂, 400 MHz): δ = 4.11 – 4.03 (m, 1H), 3.95 (dt, 1H, J =9.0, 2.8 Hz), 3.70 (qd, 2H, J =5.3, 3.1 Hz), 3.53 (dd, 1H, J =10.1, 6.5 Hz), 3.43 – 3.39 (m, 1H), 3.38 (s, 3H), 3.33 (ddd, 1H, J =9.4, 4.1, 3.3 Hz), 2.40 – 2.34 (m, 2H), 1.95 – 1.74 (m, 3H), 1.66 – 1.54 (m, 2H), 1.41 – 1.31 (m, 1H), 1.00 – 0.94 (m, 9H), 0.90 (d, 18H, J =1.5 Hz), 0.86 (d, 3H, J =6.9 Hz), 0.64 (qd, 6H, J =7.9, 0.7 Hz), 0.10 (d, 6H, J =1.2 Hz), 0.04 (d, 6H, J =1.4 Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 84.3, 71.7, 69.1, 65.8, 61.9, 57.8, 42.9, 35.2, 31.6, 29.6, 26.2, 26.2, 18.7, 18.5, 11.5, 7.2, 5.8, 1.2, -3.7, -4.0, -5.3, -5.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 565.4134; found: 565.4135.

5.4.23 (3*S*,4*S*,6*S*,7*R*)-4,6,8-Tris(*tert*-butyldimethylsilyl)oxy)-3-methoxy-7-methyloctan-1-ol (**178**)



Borane dimethyl sulfide complex (565 μ L, 6.03 mmol, 7.00 equiv.) was added to a solution of cyclohexene (1.22 mL, 12.05 mmol, 14.0 equiv.) in Et₂O (12 mL) at 0 °C and the reaction was stirred for 1 h. Then alkene **175** (471 mg, 861 μ mol, 1.00 equiv. dried 16 h over 3 Å molecular sieve in 10 mL Et₂O) was added and the reaction was allowed to warm to r.t. After stirring for 1 h, MeOH (10 mL), NaOH (3 M, 50 mL) and H₂O₂ (35%, 30 mL) were added. The reaction mixture was then gradually heated to 50 °C and stirred for an additional hour. Aq. sat. Na₂S₂O₃ (20 mL) was added, the aqueous phase extracted with EA (3x 30 mL), the combined organic layers dried over MgSO₄ and the solvent removed *in vacuo*. Purification of the residue by flash column chromatography over silica gel (CH/EA 6:1) yielded alcohol **178** (459 mg, 812 μ mol, 94%) as a colourless oil.

R_f = 0.28 (CH/EA 6:1).

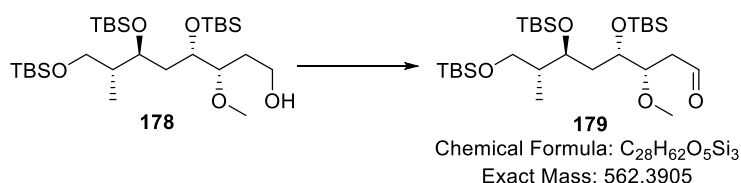
$[\alpha]_D^{20}$ = -40.0 (DCM, c = 0.6).

¹H NMR (CD₂Cl₂, 700 MHz): δ = 4.06 (ddd, 1H, J =9.3, 4.2, 1.7 Hz), 3.97 – 3.93 (m, 1H), 3.74 – 3.65 (m, 2H), 3.53 (dd, 1H, J =10.2, 6.4 Hz), 3.40 – 3.38 (m, 1H), 3.38 (s, 4H), 3.34 (ddd, 1H, J =9.9, 4.1, 2.9 Hz), 2.30 (dd, 1H, J =6.8, 4.3 Hz), 1.89 (dtq, 1H, J =10.4, 6.8, 3.4 Hz), 1.82 (dddd, 1H, J =14.1, 6.5, 4.8, 2.9 Hz), 1.58 (dddd, 2H, J =12.4, 7.3, 6.0, 4.1 Hz), 1.36 (ddd, 1H, J =14.1, 9.3, 2.2 Hz), 0.90 – 0.88 (m, 27H), 0.87 (d, 3H, J =7.0 Hz), 0.14 – 0.09 (m, 12H), 0.04 (d, 6H, J =2.9 Hz) ppm.

¹³C NMR (CD₂Cl₂, 176 MHz): δ = 84.2, 71.5, 68.8, 65.8, 62.0, 57.7, 43.1, 34.8, 31.2, 26.2, 26.1, 26.1, 18.6, 18.4, 18.3, 11.2, -3.8, -3.8, -3.9, -4.0, -5.2, -5.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 587.3954; found: 587.3938.

5.4.24 (3*S*,4*S*,6*S*,7*R*)-4,6,8-Tris(*tert*-butyldimethylsilyl)oxy)-3-methoxy-7-methyloctanal (**179**)



DIPEA (149 μ L, 857 μ mol, 2.00 equiv.) was added to a solution of alcohol **178** (242 mg, 428 μ mol, 1.00 equiv.) in DCM (2 mL) and DMSO (304 μ L, 4.28 mmol, 10.0 equiv.) at 0 °C. After stirring for 5 min, sulfur trioxide pyridine complex (204 mg, 1.28 mmol, 3.00 equiv.) was added and the reaction was stirred for 1 h. The solvent was removed under reduced pressure and the residue purified by flash column chromatography over silica gel (CH/EA 20:1) to yield aldehyde **179** (222 mg, 395 μ mol, 92%) as a colourless oil.

R_f = 0.26 (CH/EA 20:1).

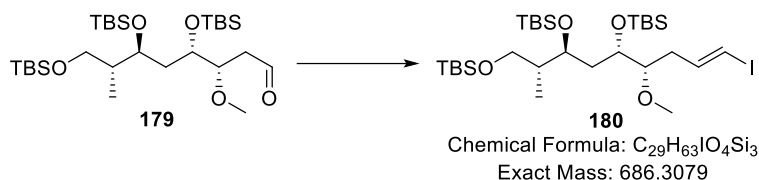
$[\alpha]_D^{20}$ = -26.0 (DCM, c = 0.5).

¹H NMR (CD₂Cl₂, 700 MHz): δ = 9.77 (dd, 1H, J =2.8, 1.3 Hz), 4.09 (ddd, 1H, J =9.1, 4.2, 1.9 Hz), 3.97 – 3.92 (m, 1H), 3.75 (ddd, 1H, J =9.7, 4.2, 2.7 Hz), 3.54 – 3.50 (m, 1H), 3.40 (dd, 1H, J =10.2, 6.4 Hz), 3.36 (d, 3H, J =2.7 Hz), 2.62 (ddd, 1H, J =16.7, 2.7, 1.4 Hz), 2.44 (ddd, 1H, J =16.7, 9.7, 2.8 Hz), 1.89 (hd, 1H, J =6.4, 2.8 Hz), 1.60 (ddd, 1H, J =14.0, 9.2, 1.9 Hz), 1.29 (ddd, 1H, J =14.0, 9.1, 2.3 Hz), 0.91 – 0.87 (m, 23H), 0.86 (d, 3H, J =6.9 Hz), 0.14 – 0.09 (m, 12H), 0.04 (d, 7H, J =2.8 Hz) ppm.

¹³C NMR (CD₂Cl₂, 176 MHz): δ = 201.9, 78.9, 71.4, 68.7, 65.7, 57.9, 43.9, 43.0, 41.5, 34.9, 26.2, 26.1, 26.1, 18.6, 18.4, 18.3, 11.3, -3.8, -3.8, -4.0, -4.0, -5.3, -5.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+Na]⁺: 585.3797; found: 585.3798.

5.4.25 (5*S*,7*S*,8*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-((*S*,*E*)-4-iodo-1-methoxybut-3-en-1-yl)-2,2,3,3,8,11,11,12,12-nonamethyl-4,10-dioxo-3,11-disilatridecane (**180**)



The following reaction was implemented in the dark.

Aldehyde **179** (220 mg, 394 μ mol, 1.00 equiv., dried 2 h over 3 Å molecular sieve in 1 mL THF) was added to a mixture of CrCl₂ (291 mg, 2.37 mmol, 6.00 equiv.) and iodoform (310 mg, 789 μ mol, 2.00 equiv.) in THF (1 mL) at 0 °C. The reaction was stirred for overnight (16 h). H₂O (2 mL) was added, the aqueous phase extracted with EA (3x 5 mL), the combined organic layers dried over MgSO₄ and the solvent removed *in vacuo*. Purification of the residue by flash column chromatography over silica gel (CH/EA 100:1) yielded vinyl iodide **180** (159 mg, 231 μ mol, 59%, *dr* = 5:1) as a colourless oil.

R_f = 0.16 (CH/EA 100:1).

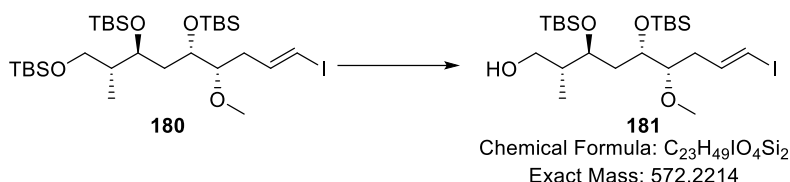
$[\alpha]_D^{20}$ = -24.0 (DCM, *c* = 0.5).

¹H NMR (CDCl₃, 700 MHz): δ = 6.59 – 6.54 (m, 1H)^{*}, 6.31 (td, 1H, *J*=7.2, 6.0 Hz)[#], 6.25 (dt, 1H, *J*=7.4, 1.5 Hz)[#], 6.06 (dt, 1H, *J*=14.4, 1.4 Hz)^{*}, 4.01 (dtd, 1H, *J*=9.8, 4.9, 2.0 Hz), 3.92 (ddd, 1H, *J*=9.2, 3.2, 2.1 Hz), 3.57 – 3.52 (m, 1H)[#], 3.52 – 3.48 (m, 1H)^{*}, 3.39 – 3.36 (m, 1H), 3.36 (s, 3H), 3.21 (dt, 1H, *J*=9.1, 3.7 Hz)[#], 3.14 (ddd, 1H, *J*=9.6, 4.1, 2.7 Hz)^{*}, 2.49 – 2.42 (m, 1H)[#], 2.35 (dddd, 1H, *J*=14.8, 7.6, 2.7, 1.4 Hz)^{*}, 2.20 (dddd, 1H, *J*=15.3, 9.1, 6.0, 1.6 Hz)[#], 2.09 – 2.03 (m, 1H)^{*}, 1.86 (ddh, 1H, *J*=10.1, 6.7, 3.3 Hz), 1.66 – 1.61 (m, 1H)[#], 1.57 (ddd, 1H, *J*=14.1, 9.3, 1.9 Hz)^{*}, 1.33 – 1.26 (m, 1H), 0.90 – 0.88 (m, 27H), 0.85 (d, 3H, *J*=6.9 Hz), 0.13 – 0.08 (m, 6H), 0.08 – 0.07 (m, 6H), 0.04 – 0.02 (m, 6H) ppm.

¹³C NMR (CDCl₃, 176 MHz): δ = 144.0^{*}, 139.0[#], 83.0^{*}, 83.0[#], 75.9, 71.2[#], 71.0^{*}, 69.3[#], 68.8^{*}, 65.4^{*}, 64.8[#], 57.9^{*}, 57.8[#], 42.6^{*}, 42.6[#], 35.4^{*}, 35.0[#], 34.5[#], 34.5^{*}, 26.0, 26.0, 25.9, 18.3, 18.1, 18.1, 11.3[#], 11.1^{*}, -3.9, -4.1, -4.1, -5.3, -5.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 687.3152; found: 687.3156.

5.4.26 (2*R*,3*S*,5*S*,6*S*,*E*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-9-iodo-6-methoxy-2-methylnon-8-en-1-ol (**181**)



CSA (8.23 mg, 35.4 μ mol, 0.50 equiv.) was added to a solution of silyl ether **180** (48.7 mg, 70.9 μ mol, 1.00 equiv.) in DCM (3 mL) and MeOH (1 mL). The reaction was stirred for 1 h. Aq. sat. $NaHCO_3$ (2 mL) was added, the aqueous phase extracted with DCM (3x 2 mL) and the combined organic layers dried over $MgSO_4$. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/Ea 3:1) yielded alcohol **181** (14.4 mg, 25.1 μ mol, 35%) as a colourless oil.

R_f = 0.26 (CH/Ea 9:1).

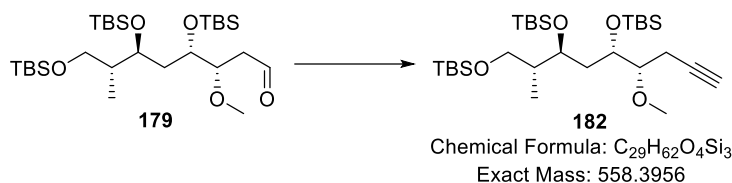
$[\alpha]_D^{20}$ = -23.0 (DCM, c = 1.0).

1H NMR ($CDCl_3$, 700 MHz): δ = 6.57 (dt, 1H, J =14.6, 7.4 Hz), 6.08 (dt, 1H, J =14.4, 1.3 Hz), 3.95 – 3.91 (m, 1H), 3.89 (td, 1H, J =5.9, 2.6 Hz), 3.80 (dd, 1H, J =11.0, 4.4 Hz), 3.51 (dd, 1H, J =11.0, 5.2 Hz), 3.36 (s, 3H), 3.13 (ddd, 1H, J =9.4, 4.1, 3.0 Hz), 2.35 (dddd, 1H, J =14.7, 7.5, 3.0, 1.4 Hz), 2.11 (dddd, 1H, J =14.8, 8.9, 7.3, 1.3 Hz), 1.80 (tqd, 1H, J =7.2, 4.6, 2.4 Hz), 1.73 (ddd, 1H, J =14.2, 6.2, 3.5 Hz), 1.56 (ddd, 1H, J =14.1, 8.5, 5.5 Hz), 1.01 (d, 3H, J =7.1 Hz), 0.89 (d, 19H, J =10.6 Hz), 0.11 – 0.08 (m, 12H) ppm.

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 143.8, 83.0, 76.4, 74.4, 69.5, 65.0, 58.2, 39.9, 36.5, 35.4, 26.0, 26.0, 18.2, 18.1, 13.7, 2.0, -3.8, -4.0, -4.2, -4.2 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 573.2287; found: 573.2292.

5.4.27 (5*S*,7*S*,8*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-5-((*S*)-1-methoxybut-3-yn-1-yl)-2,2,3,3,8,11,11,12,12-nonamethyl-4,10-dioxo-3,11-disilatridecane (182**)**



Dimethyl (1-diazo-2-oxopropyl)phosphonate (250 μ L, 1.66 mmol, 2.00 equiv.) was added to a solution of aldehyde **179** (468 mg, 831 μ mol, 1.00 equiv., dried 1 h over 3 Å molecular sieve in 6 mL MeOH) and K₂CO₃ (230 mg, 1.66 mmol, 2.00 equiv.) in MeOH (8 mL). The reaction was stirred for 72 h in a sealed pressure tube. H₂O (5 mL) was added, the aqueous phase extracted with EA (3x 10 mL) and the combined organic layers dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 50:1) yielded alkyne **182** (398 mg, 712 μ mol, 86%) as a colourless oil.

R_f = 0.18 (CH/EA 50:1).

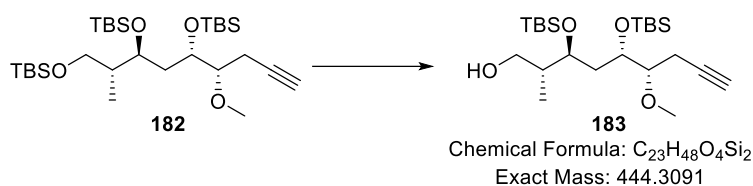
$[\alpha]_D^{20}$ = -20.0 (DCM, c = 0.8).

¹H NMR (CD₂Cl₂, 500 MHz): δ = 4.00 (dt, 1H, J =8.2, 3.5 Hz), 3.92 (dt, 1H, J =9.0, 3.0 Hz), 3.53 (dd, 1H, J =10.2, 6.5 Hz), 3.42 (s, 3H), 3.39 (dd, 1H, J =10.2, 6.6 Hz), 3.33 (dt, 1H, J =8.1, 4.0 Hz), 2.49 (ddd, 1H, J =17.0, 4.1, 2.7 Hz), 2.24 (ddd, 1H, J =17.0, 8.1, 2.6 Hz), 1.97 (t, 1H, J =2.7 Hz), 1.86 (hd, 1H, J =6.9, 3.3 Hz), 1.64 (ddd, 1H, J =14.0, 9.0, 3.2 Hz), 1.33 (ddd, 1H, J =14.0, 8.2, 2.9 Hz), 0.90 – 0.89 (m, 27H), 0.86 (d, 3H, J =7.0 Hz), 0.12 (d, 6H, J =1.0 Hz), 0.09 (d, 6H, J =4.2 Hz), 0.04 (d, 6H, J =1.9 Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 83.2, 83.1, 71.6, 70.0, 69.1, 65.6, 58.4, 42.8, 35.3, 26.2, 26.1, 26.1, 19.3, 18.6, 18.4, 18.4, 11.6, -3.8, -3.9, -4.0, -4.0, -5.3, -5.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 559.4029; found: 559.4037.

5.4.28 (2*R*,3*S*,5*S*,6*S*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-6-methoxy-2-methylnon-8-yn-1-ol (**183**)



CSA (2.74 mg, 11.8 μ mol, 0.10 equiv.) was added to a solution of silyl ether **182** (66.0 mg, 118 μ mol, 1.00 equiv.) in DCM (5 mL) and MeOH (5 mL). The reaction was stirred for 2 h. Aq. sat. NaHCO₃ (2 mL) was added, the aqueous phase extracted with DCM (3x 5 mL) and the combined organic layers dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 9:1) yielded alcohol **183** (34.3 mg, 77.1 μ mol, 65%, brsm: quant.) as a colourless oil.

R_f = 0.20 (CH/EA 9:1).

$[\alpha]_D^{20}$ = -6.0 (DCM, c = 1.0).

¹H NMR (CD₂Cl₂, 700 MHz): δ = 3.94 (ddd, 1H, J =7.7, 5.0, 3.7 Hz), 3.87 (td, 1H, J =6.3, 2.7 Hz), 3.75 (ddd, 1H, J =10.9, 4.6, 3.4 Hz), 3.48 (ddd, 1H, J =10.9, 7.4, 5.2 Hz), 3.43 (s, 3H), 3.29 (ddd, 1H, J =7.6, 4.7, 3.6 Hz), 2.50 (ddd, 1H, J =16.9, 4.7, 2.7 Hz), 2.31 (ddd, 1H, J =16.9, 7.6, 2.7 Hz), 2.16 (dd, 1H, J =7.5, 3.5 Hz), 1.99 (t, 1H, J =2.7 Hz), 1.80 (ddd, 1H, J =13.9, 6.3, 4.9 Hz), 1.76 (ddq, 1H, J =9.6, 4.9, 2.3 Hz), 1.58 (ddd, 1H, J =14.0, 7.7, 6.2 Hz), 1.01 (d, 3H, J =7.1 Hz), 0.89 (d, 18H, J =4.7 Hz), 0.12 – 0.10 (m, 12H) ppm.

¹³C NMR (CD₂Cl₂, 176 MHz): δ = 82.7, 82.6, 74.3, 70.2, 69.5, 64.8, 58.3, 39.9, 37.2, 26.0, 19.1, 18.4, 18.3, 13.8, -4.1, -4.1, -4.1, -4.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 445.3164; found: 445.3163.

Alcohol **321** (1.02 mL, 7.14 mmol, 1.40 equiv.) was added to a solution of diethylphosphonoacetic acid (8.20 μ L, 5.10 mmol, 1.00 equiv.) in THF (20 mL) followed by DCC (1 M in DCM, 8.16 mL, 8.16 mmol, 1.60 equiv.) and DMAP (93.4 mg, 764 μ mol, 0.15 equiv.). The reaction was stirred overnight (14 h). Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 1:2 $\rightarrow$ 100% EA) yielded phosphonate **195** (1.51 g, 5.10 mmol, quant.) as a colourless oil.

R_f = 0.25 (CH/EA 1:2).

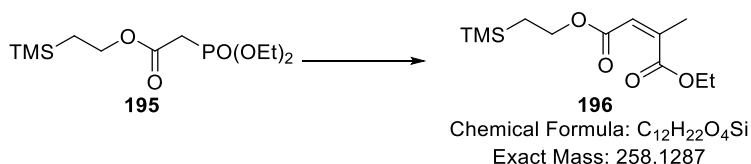
$^1\text{H NMR}$ (CDCl_3 , 500 MHz): δ = 4.25 – 4.12 (m, 6H), 2.94 (d, 2H, J =21.5 Hz), 1.34 (td, 6H, J =7.0, 0.5 Hz), 1.04 – 0.99 (m, 2H), 0.04 (s, 9H) ppm.

$^{13}\text{C NMR}$ (CDCl_3 , 126 MHz): δ = 166.1 (d, J =6.0 Hz), 64.1, 62.8, 62.8, 35.2, 34.1, 17.4, 16.5, 16.5, -1.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 297.1286; found: 297.1281.

The experimental data are in agreement with those previously published.^[189]

5.5.3 1-Ethyl 4-(2-(trimethylsilyl)ethyl) 2-methylmaleate (**196**)



$\text{Ba}(\text{OH})_2$ (860 mg, 5.02 mmol, 3.00 equiv.) was added to a solution of phosphonate **195** (1.24 g, 4.18 mmol, 2.50 equiv.) in THF (14 mL) and the mixture was stirred for 1 h. Then THF/ H_2O (40:1, 0.5 mL) was added followed by ethyl 2-oxopropanoate (185 μ L, 1.67 mmol, 1.00 equiv.) and the reaction was stirred for 2 h. Aq. sat. NH_4Cl (20 mL) was added, the aqueous phase extracted with Et_2O (3x 30 mL) and the combined organic layers dried over MgSO_4 . Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 9:1) yielded olefin **196** (233 mg, 902 μ mol, 54%, E/Z : <1:20) as a colourless oil.

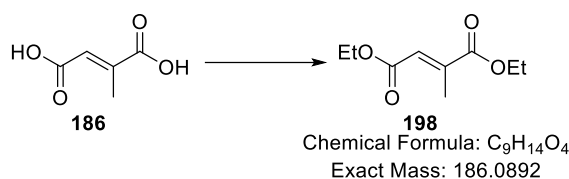
R_f = 0.28 (CH/EA 9:1).

^1H NMR (CDCl_3 , 700 MHz): δ = 5.82 (q, 1H, J =1.6 Hz), 4.28 (q, 2H, J =7.1 Hz), 4.23 – 4.17 (m, 2H), 2.04 (d, 3H, J =1.7 Hz), 1.32 (t, 3H, J =7.2 Hz), 1.02 – 0.95 (m, 2H), 0.03 (s, 9H) ppm.

^{13}C NMR (CDCl_3 , 176 MHz): δ = 169.1, 165.2, 145.4, 121.2, 63.1, 61.5, 20.6, 17.4, 14.1, -1.4 ppm.

HRMS (APCI (+), 5.0 eV): calculated for $[\text{M}+\text{H}]^+$: 259.1360; found: 259.1356.

5.5.4 Diethyl 2-methylfumarate (198)



EtOH (2.72 mL, 46.1 mmol, 30.0 equiv.) was added to a solution of acid **186** (200 mg, 1.54 mmol, 1.00 equiv.) and conc. HCl (5 drops) in a pressure tube. The tube was sealed and heated to 100 °C for 1 h. H_2O (5 mL) was added at r.t. and the aqueous phase extracted with EA (3x 5 mL). The combined organic layers were dried over MgSO_4 and the solvent removed under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 9:1) yielded ester **198** (286 mg, 1.54 mmol, quant.) as a colourless oil.

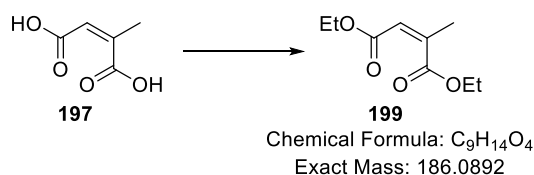
R_f = 0.35 (CH/EA 9:1).

^1H NMR (CDCl_3 , 400 MHz): δ = 6.77 (q, 1H, J =1.6 Hz), 4.24 (dq, 4H, J =9.4, 7.1 Hz), 2.28 (d, 3H, J =1.6 Hz), 1.31 (td, 6H, J =7.1, 4.0 Hz) ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 187.0965; found: 187.0964.

The experimental data are in agreement with those previously published.^[190]

5.5.5 Diethyl 2-methylmaleate (199)



EtOH (2.72 mL, 46.1 mmol, 30.0 equiv.) was added to a solution of acid **197** (200 mg, 1.54 mmol, 1.00 equiv.) and conc. HCl (5 drops) in a pressure tube. The tube was sealed and heated to 100 °C for 1 h. H₂O (5 mL) was added at r.t. and the aqueous phase extracted with EA (3x 5 mL). The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 9:1) yielded ester **199** (286 mg, 1.54 mmol, quant.) as a colourless oil.

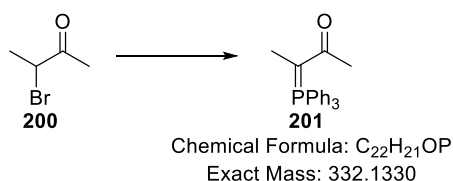
R_f = 0.22 (CH/EA 9:1).

¹H NMR (CDCl₃, 400 MHz): δ = 5.84 (q, 1H, J =1.6 Hz), 4.28 (q, 2H, J =7.2 Hz), 4.17 (q, 2H, J =7.1 Hz), 2.05 (d, 3H, J =1.6 Hz), 1.32 (t, 3H, J =7.2 Hz), 1.29 – 1.24 (m, 3H) ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+Na]⁺: 209.0784; found: 209.0785.

The experimental data are in agreement with those previously published.^[191]

5.5.6 3-(Triphenyl- λ^5 -phosphanylidene)butan-2-one (**201**)



PPh₃ (2.14 g, 8.16 mmol, 1.10 equiv.) was added to a solution of bromide **200** (1.12 g, 7.42 mmol, 1.00 equiv.) in toluene (40 mL). The reaction was stirred for 72 h. The mixture was filtered and washed with toluene (100 mL). The filter cake was solved in DCM (100 mL) and transferred to a solution of aq. NaOH (1 M, 50 mL). The mixture was stirred for 1 h before the aqueous phase was extracted with DCM (3x 100 mL). The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure to yield ylen **201** (1.28 g, 3.85 mmol, 52%) as a white solid with a slight yellowish tint.

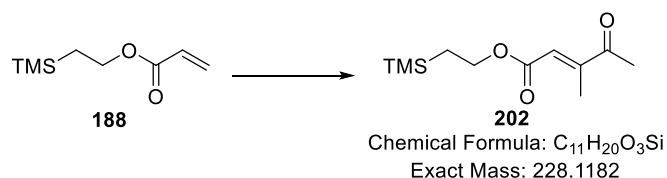
¹H NMR (CD₂Cl₂, 500 MHz): δ = 7.70 – 7.61 (m, 2H), 7.60 – 7.51 (m, 9H), 7.47 (dddd, 7H, J =12.3, 11.0, 5.3, 2.9 Hz), 2.05 (s, 3H), 1.63 (d, 3H, J =15.5 Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 188.0, 133.9, 133.9, 132.4, 132.3, 132.3, 132.2, 131.8, 128.9, 128.9, 128.8, 128.8, 25.0, 23.6, 14.2, 14.1 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 333.1403; found: 333.1398.

The experimental data are in agreement with those previously published.^[192]

5.5.7 2-(Trimethylsilyl)ethyl (E)-3-methyl-4-oxopent-2-enoate (202)



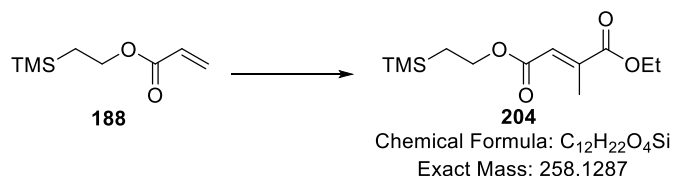
Alkene **188** (127 mg, 737 μ mol, 1.00 equiv.) was solved in MeOH (4 mL) and DCM (4 mL) together with a tip of a spatula $NaHCO_3$ (~10 mg) and cooled to $-78^\circ C$. The reaction vessel was filled with ozone and stirred for 15 min. PPh_3 (290 mg, 1.11 mmol, 1.50 equiv.) was added and the reaction mixture was stirred for 10 min at $-78^\circ C$. The reaction was allowed to warm to r.t. and stirred for additional 2 h. The solvent was removed under reduced pressure and the residue was put on a plug of silica gel and washed with CH (50 mL) and rinsed with CH/EA (3:1 30 mL). The solvent was removed *in vacuo* and the residue was added to a solution of ylen **201** (366 mg, 1.10 mmol, 1.50 equiv.) in DCM (2 mL) and the mixture was stirred overnight (12 h). The solvent was removed under reduced pressure and the residue purified by flash column chromatography over silica gel (CH/EA 15:1) yielded olefin **202** (140 mg, 613 μ mol, 83%, *E/Z*: >20:1) as a colourless oil.

R_f = 0.22 (CH/EA 15:1).

1H NMR ($CDCl_3$, 500 MHz): δ = 6.55 (q, 1H, J =1.5 Hz), 4.30 – 4.24 (m, 2H), 2.38 (s, 3H), 2.20 (d, 3H, J =1.5 Hz), 1.08 – 1.02 (m, 2H), 0.06 (s, 9H) ppm.

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 200.1, 166.5, 150.4, 126.9, 63.3, 26.3, 17.5, 13.2, -1.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 333.1403; found: 333.1398.

5.5.8 1-Ethyl 4-(2-(trimethylsilyl)ethyl) 2-methylfumarate (**204**)

Alkene **188** (969 mg, 5.62 mmol, 1.00 equiv.) was solved in MeOH (25 mL) and DCM (25 mL) together with a tip of a spatula NaHCO₃ (~10 mg) and cooled to –78 °C. The reaction vessel was filled with ozone and stirred for 15 min. PPh₃ (2.21 g, 8.44 mmol, 1.50 equiv.) was added and the reaction mixture was stirred for 10 min at –78 °C. The reaction was allowed to warm to r.t. and stirred for additional 2 h. The solvent was removed under reduced pressure and the residue was put on a plug of silica gel and washed with CH (200 mL) and rinsed with CH/EA (3:1 100 mL). The solvent was removed *in vacuo* and the residue was added to a solution of ethyl 2-(triphenylphosphoranylidene)propionate (4.08 g, 11.3 mmol, 2.00 equiv.) in toluene (5 mL). The reaction mixture was heated to 60 °C and stirred overnight (14 h). The solvent was removed under reduced pressure and the residue purified by flash column chromatography over silica gel (CH/EA 15:1) yielded olefin **204** (934 mg, 3.61 mmol, 64%, *E/Z*: >20:1) as a colourless oil.

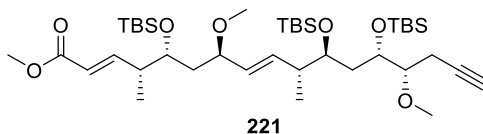
R_f = 0.37 (CH/EA 15:1).

¹H NMR (CDCl₃, 500 MHz): δ = 6.76 (q, 1H, *J*=1.6 Hz), 4.32 – 4.21 (m, 4H), 2.28 (d, 3H, *J*=1.6 Hz), 1.32 (t, 3H, *J*=7.1 Hz), 1.08 – 1.00 (m, 2H), 0.06 (s, 9H) ppm.

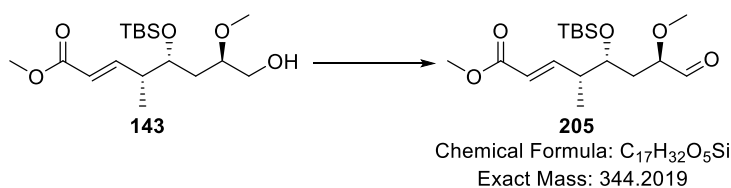
¹³C NMR (CDCl₃, 126 MHz): δ = 167.4, 166.3, 143.7, 127.0, 63.1, 61.7, 27.1, 17.5, 14.4, 14.3, -1.4 ppm.

HRMS (APCI (+), 5.0 eV): calculated for [M+H]⁺ : 259.1360; found: 259.1356.

5.6 Experimental Details for Chapter 3.3.5: Julia-Kocienski Olefination to 221 and Synthesis of Test Systems



5.6.1 Methyl (4*R*,5*R*,7*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-4-methyl-8-oxooct-2-enoate (**205**)



DIPEA (46.2 μ L, 265 μ mol, 4.00 equiv.) was added to a solution of alcohol **143** (23.0 mg, 66.4 μ mol, 1.00 equiv.) in DCM (1 mL) and DMSO (651 μ L, 9.17 mmol, 10.0 equiv.) in a pressure tube. After stirring for 5 min, sulfur trioxide pyridine complex (31.7 mg, 199 μ mol, 3.00 equiv.) was added, the pressure tube was sealed and heated to 50 °C for 3 h. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 6:1) yielded aldehyde **205** (18.0 mg, 52.3 μ mol, 79%) as a colourless oil.

R_f = 0.25 (CH/EA 6:1).

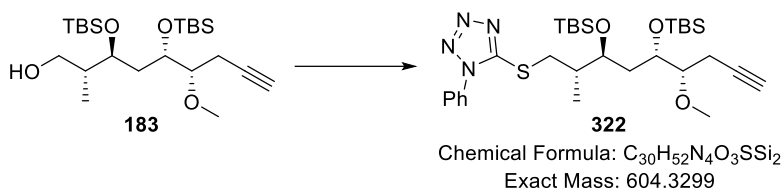
$[\alpha]_D^{20}$ = +89.0 (DCM, c = 1.0).

¹H NMR (Acetone, 700 MHz): δ = 9.65 (d, 1H, J =1.7 Hz), 7.08 (dd, 1H, J =15.9, 6.6 Hz), 5.86 (dd, 1H, J =15.9, 1.6 Hz), 4.02 (ddd, 1H, J =9.2, 4.0, 3.0 Hz), 3.81 (ddd, 1H, J =10.3, 3.0, 1.6 Hz), 3.68 (s, 3H), 3.44 (s, 3H), 2.77 – 2.76 (m, 1H), 2.67 (dddd, 1H, J =9.2, 6.9, 3.5, 1.8 Hz), 1.63 (ddd, 1H, J =14.3, 10.3, 3.1 Hz), 1.57 (ddd, 1H, J =14.3, 9.2, 3.0 Hz), 1.06 (d, 3H, J =7.0 Hz), 0.93 (s, 11H), 0.14 (s, 6H) ppm.

¹³C NMR (Acetone, 176 MHz): δ = 204.1, 167.0, 151.2, 122.1, 83.1, 72.3, 58.0, 51.5, 42.8, 34.0, 26.3, 18.7, 14.3, -3.9, -4.5 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 345.2092; found: 345.2085.

5.6.2 5-(((2*S*,3*S*,5*S*,6*S*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-6-methoxy-2-methylnon-8-yn-1-yl)thio)-1-phenyl-1*H*-tetrazole (322)



DIAD (266 μ L, 506 μ mol, 2.50 equiv.) was added dropwise to a solution of alcohol **183** (90.0 mg, 202 μ mol, 1.00 equiv.), PPh₃ (133 mg, 506 μ mol, 2.50 equiv.) and 1-Phenyl-1*H*-tetrazole-5-thiol (46.9 mg, 263 μ mol, 1.30 equiv.) in THF (1 mL) at 0 °C. The reaction was allowed to warm to r.t. and stirred overnight (14 h). Celite[®] (2 g) was added and the solvent was removed under reduced pressure. Purification by flash column chromatography over silica gel (CH/EA 20:1) yielded sulfide **322** (109 mg, 180 μ mol, 89%) as a colourless oil.

R_f = 0.17 (CH/EA 20:1).

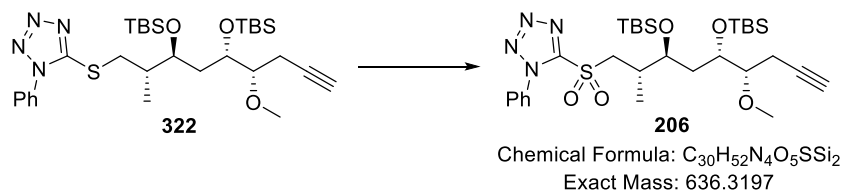
$[\alpha]_D^{20}$ = -10.0 (DCM, c = 0.3).

¹H NMR (CD₂Cl₂, 700 MHz): δ = 7.62 – 7.54 (m, 5H), 4.05 (dt, 1H, J =8.0, 3.9 Hz), 3.90 (ddd, 1H, J =7.4, 4.4, 2.7 Hz), 3.43 (s, 3H), 3.42 – 3.38 (m, 1H), 3.32 (dt, 1H, J =8.0, 3.9 Hz), 3.23 (dd, 1H, J =13.2, 7.8 Hz), 2.55 – 2.48 (m, 1H), 2.28 (ddd, 1H, J =17.0, 8.1, 2.7 Hz), 2.22 – 2.15 (m, 1H), 1.99 (t, 1H, J =2.7 Hz), 1.72 (ddd, 1H, J =14.0, 7.6, 3.8 Hz), 1.45 (ddd, 1H, J =14.0, 8.3, 4.4 Hz), 1.05 (d, 3H, J =6.9 Hz), 0.88 (s, 9H), 0.86 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H) ppm.

¹³C NMR (CD₂Cl₂, 176 MHz): δ = 155.1, 134.2, 130.5, 130.2, 124.3, 82.9, 82.8, 72.8, 69.7, 69.4, 58.4, 38.6, 36.0, 35.9, 26.0, 19.1, 18.4, 18.3, 15.0, -4.0, -4.0, -4.1, -4.1 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 605.3371; found: 605.3386.

5.6.3 5-(((2*S*,3*S*,5*S*,6*S*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-6-methoxy-2-methylnon-8-yn-1-yl)sulfonyl)-1-phenyl-1*H*-tetrazole (**206**)



H₂O₂ (35%, 1 mL) was added to a solution of sulfide **322** (25.8 mg, 42.6 μmol, 1.00 equiv.) and ammonium heptamolybdate (105 mg, 85.3 μmol, 2.00 equiv.) in EtOH (2 mL) and the reaction mixture was heated to 40 °C and stirred overnight (14 h) in a pressure tube. Aq. sat. Na₂S₂O₃ (2 mL) was added and the aqueous phase was extracted with EA (3x 2 mL). The combined organic layers were washed with brine (1 mL) and dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 30:1) yielded sulfone **206** (26.3 mg, 41.3 μmol, 97%) as a colourless oil.

R_f = 0.07 (CH/EA 30:1).

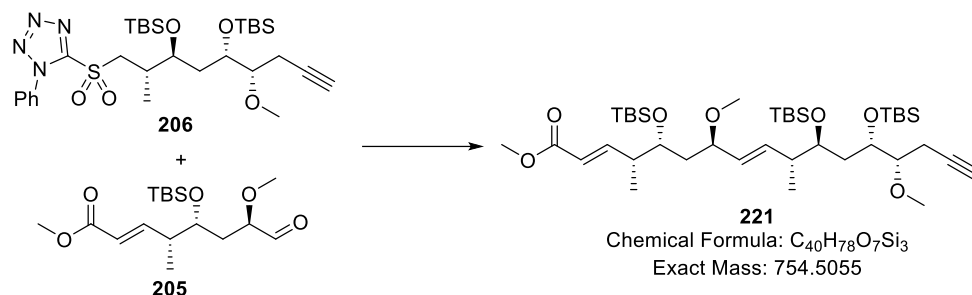
[α]_D²⁰ = −12.0 (DCM, *c* = 1.0).

¹H NMR (CD₂Cl₂, 700 MHz): δ = 7.69 – 7.60 (m, 5H), 4.00 (dt, 1H, *J*=8.2, 4.0 Hz), 3.86 (dd, 1H, *J*=14.8, 2.7 Hz), 3.84 – 3.82 (m, 1H), 3.43 – 3.40 (m, 1H), 3.32 (dt, 1H, *J*=8.0, 3.9 Hz), 2.54 (ddd, 1H, *J*=17.0, 3.9, 2.7 Hz), 2.46 – 2.40 (m, 1H), 2.27 (ddd, 1H, *J*=17.0, 8.1, 2.6 Hz), 2.00 (t, 1H, *J*=2.7 Hz), 1.73 (ddd, 1H, *J*=14.1, 6.3, 4.0 Hz), 1.17 (d, 3H, *J*=6.9 Hz), 0.89 (s, 9H), 0.87 (s, 9H), 0.12 – 0.06 (m, 12H) ppm.

¹³C NMR (CD₂Cl₂, 176 MHz): δ = 154.4, 133.5, 131.9, 130.1, 125.7, 82.9, 82.7, 74.0, 70.0, 69.5, 58.5, 58.5, 36.9, 34.2, 26.0, 26.0, 19.0, 18.3, 18.3, 16.8, −3.9, −4.0, −4.1, −4.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+Na]⁺: 659.3089; found: 659.3081.

5.6.4 Methyl (2*E*,4*R*,5*R*,7*R*,8*E*,10*R*,11*S*,13*S*,14*S*)-5,11,13-tris((*tert*-butyldimethylsilyl)oxy)-7,14-dimethoxy-4,10-dimethylheptadeca-2,8-dien-16-ynoate (**221**)



NaHMDS (1 M in THF, 41.5 μ L, 41.5 μ mol, 1.30 equiv.) was added to a mixture of sulfone **206** (24.4 mg, 38.3 μ mol, 1.20 equiv., dried 14 h over 3 Å molecular sieve in 0.1 mL THF) in DME (2 mL, freshly distilled) and 3 Å ground molecular sieve at -78 °C. The reaction was stirred for 1 h before aldehyde **205** (11.0 mg, 31.9 μ mol, 1.00 equiv., dried 14 h over 3 Å molecular sieve in 0.1 mL THF) was added and the reaction was allowed to warm to r.t. and stirred for an additional 72 h. H₂O (2 mL) was added and the aqueous phase extracted with EA (3x 2 mL), the combined organic layers dried over MgSO₄ and the solvent removed under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 9:1) yielded olefin **221** (0.5 mg, 0.7 μ mol, 2%, *E/Z* = 1:10) as a colourless oil.

R_f = 0.41 (CH/EA 9:1).

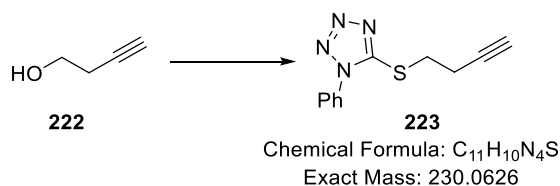
$[\alpha]_D^{20}$ = -10.0 (DCM, c = 0.2).

¹H NMR (CDCl₃, 700 MHz): δ = 7.13 – 7.08 (m, 1H), 5.79 (dd, 1H, J =16.0, 1.7 Hz), 5.50 (ddd, 1H, J =11.3, 10.1, 1.0 Hz), 5.18 (ddd, 1H, J =11.3, 9.1, 1.0 Hz), 4.08 – 4.03 (m, 2H), 3.93 (ddd, 1H, J =8.7, 4.1, 3.0 Hz), 3.71 (s, 3H), 3.68 (dt, 1H, J =8.5, 2.9 Hz), 3.45 (s, 4H), 3.29 (dt, 1H, J =8.1, 4.1 Hz), 3.22 (s, 3H), 2.56 – 2.51 (m, 3H), 2.51 (dd, 0H, J =4.1, 2.7 Hz), 2.31 – 2.21 (m, 1H), 1.97 (t, 1H, J =2.7 Hz), 1.66 (ddd, 1H, J =14.0, 8.4, 3.1 Hz), 1.52 – 1.48 (m, 2H), 1.37 – 1.27 (m, 2H), 1.01 (d, 3H, J =6.9 Hz), 0.97 (d, 3H, J =6.9 Hz), 0.92 (s, 9H), 0.90 (s, 9H), 0.87 (s, 9H), 0.10 – 0.06 (m, 18H) ppm.

^{13}C NMR (CDCl_3 , 176 MHz): δ = 167.0, 151.3, 134.7, 131.2, 121.0, 82.9, 82.8, 72.9, 72.4, 71.5, 70.0, 69.4, 58.4, 55.7, 51.5, 42.6, 39.5, 38.6, 36.6, 26.2, 26.1, 26.1, 19.1, 18.4, 18.3, 18.3, 14.2, -3.5, -3.7, -3.8, -4.0, -4.2, -4.2 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{Na}]^+$: 777.4948; found: 777.4948.

5.6.5 5-(But-3-yn-1-ylthio)-1-phenyl-1H-tetrazole (223)



DIAD (3.29 mL, 6.24 mmol, 1.25 equiv.) was added dropwise to a solution of alcohol **222** (380 μL , 4.99 mmol, 1.00 equiv.), PPh_3 (1.64 g, 6.24 mmol, 1.25 equiv.) and 1-phenyl-1H-tetrazole-5-thiol (979 mg, 5.49 mmol, 1.10 equiv.) in THF (25 mL) at 0 °C. The reaction was allowed to warm to r.t. and stirred overnight (14 h). Celite[®] (50 g) was added and the solvent was removed under reduced pressure. Purification by flash column chromatography over silica gel (CH/EA 6:1) yielded sulfide **223** (1.15 g, 5.08 mmol, quant.) as a colourless oil.

R_f = 0.23 (CH/EA 6:1).

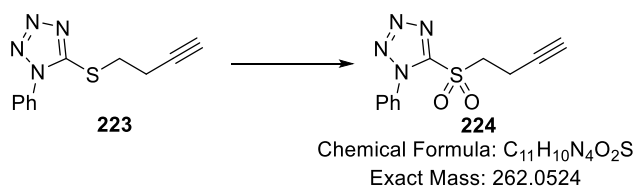
^1H NMR (CDCl_3 , 700 MHz): δ = 7.62 – 7.51 (m, 5H), 3.54 (t, 2H, J =6.8 Hz), 2.82 (td, 2H, J =6.8, 2.6 Hz), 2.06 (t, 1H, J =2.6 Hz) ppm.

^{13}C NMR (CDCl_3 , 176 MHz): δ = 153.8, 133.7, 130.3, 130.0, 124.0, 81.3, 70.8, 32.3, 19.5 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 231.0699; found: 231.0695.

The experimental data are in agreement with those previously published.^[193]

5.6.6 5-(But-3-yn-1-ylsulfonyl)-1-phenyl-1H-tetrazole (224)



H₂O₂ (35%, 40 mL) was added to a solution of sulfide **223** (1.20 g, 5.21 mmol, 1.00 equiv.) and ammonium heptamolybdate (12.1 g, 10.4 mmol, 2.00 equiv.) in EtOH (50 mL) and the reaction mixture was heated to 50 °C and stirred overnight (16 h). Aq. sat. Na₂S₂O₃ (100 mL) was added and the aqueous phase was extracted with EA (3x 50 mL). The combined organic layers were washed with brine (20 mL) and dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 6:1) yielded sulfone **224** (1.12 g, 4.26 mmol, 82%) as a yellowish solid.

R_f = 0.07 (CH/EA 6:1).

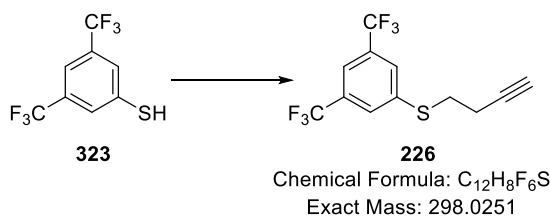
¹H NMR (CDCl₃, 700 MHz): δ = 7.70 – 7.58 (m, 5H), 3.94 – 3.90 (m, 2H), 2.93 – 2.88 (m, 2H), 2.07 (t, 1H, J =2.7 Hz) ppm.

¹³C NMR (CDCl₃, 176 MHz): δ = 153.2, 133.0, 131.7, 129.9, 125.3, 78.2, 71.7, 54.6, 13.5 ppm.

HRMS (APCI (+), 5.0 eV): calculated for [M+H]⁺: 263.0597; found: 263.0592.

The experimental data are in agreement with those previously published.^[194]

5.6.7 (3,5-Bis(trifluoromethyl)phenyl)(but-3-yn-1-yl)sulfane (**226**)



4-Bromobut-1-yne (292 mg, 2.19 mmol, 1.20 equiv.) was added to a stirring solution of thiol **323** (450 mg, 1.83 mmol, 1.00 equiv.) and NaH (146 mg, 3.66 mmol, 2.00 equiv., 60% dispersion in mineral oil) in acetonitrile (4 mL) and the reaction was stirred for 72 h. H₂O (5 mL) was added to quench the reaction, the aqueous phase extracted with EA (3x 5 mL) and the combined organic layers dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 50:1) yielded sulfide **226** (486 mg, 1.63 mmol, 89%) as a colourless oil.

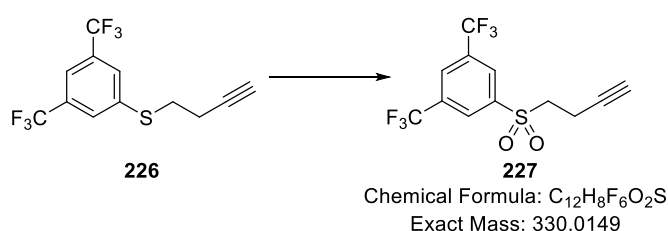
R_f = 0.31 (CH/EA 50:1).

^1H NMR (CDCl_3 , 500 MHz): δ = 7.75 (dt, 2H, J =1.5, 0.7 Hz), 7.67 (tt, 1H, J =1.6, 0.8 Hz), 3.19 (t, 2H, J =7.2 Hz), 2.58 (td, 2H, J =7.2, 2.6 Hz), 2.08 (t, 1H, J =2.6 Hz) ppm.

^{13}C NMR (CDCl_3 , 126 MHz): δ = 139.8, 132.4 (q, J =33.4 Hz), 128.5 (q, J =3.8 Hz), 126.4, 124.2, 122.1, 119.9 (hept, J =4.0 Hz), 81.3, 70.7, 32.3, 19.3 ppm.

HRMS (APCI (+), 5.0 eV): calculated for $[\text{M}+\text{H}]^+$: 299.0324; found: 299.0321.

5.6.8 1-(But-3-yn-1-ylsulfonyl)-3,5-bis(trifluoromethyl)benzene (227)



H_2O_2 (35%, 30 mL) was added to a solution of sulfide **226** (377 mg, 1.26 mmol, 1.00 equiv.) and ammonium heptamolybdate (2.94 g, 2.53 mmol, 2.00 equiv.) in EtOH (20 mL) and the reaction mixture was stirred at r.t. for 1 h before it was heated to 60 °C and stirred for an additional 72 h. Aq. sat. $\text{Na}_2\text{S}_2\text{O}_3$ (100 mL) was added and the aqueous phase was extracted with EA (3x 50 mL). The combined organic layers were washed with brine (20 mL) and dried over MgSO_4 . Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 6:1) yielded sulfone **227** (372 mg, 1.13 mmol, 89%) as a white solid.

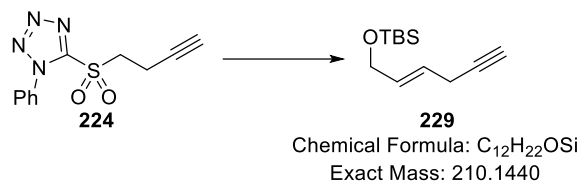
R_f = 0.26 (CH/EA 6:1).

^1H NMR (CDCl_3 , 500 MHz): δ = 8.44 – 8.38 (m, 2H), 8.18 (dp, 1H, J =1.7, 0.8 Hz), 3.40 (t, 2H, J =7.2 Hz), 2.74 (td, 2H, J =7.2, 2.7 Hz), 1.88 (t, 1H, J =2.7 Hz) ppm.

^{13}C NMR (CDCl_3 , 126 MHz): δ = 141.8, 133.5 (q, J =34.7 Hz), 129.2 (d, J =3.8 Hz), 128.0 – 127.6 (m), 125.7, 123.5, 121.4, 119.2, 78.6, 71.5, 54.8, 13.4 ppm.

HRMS (APCI (+), 5.0 eV): calculated for $[\text{M}+\text{H}]^+$: 331.0222; found: 331.0221.

5.6.9 (*E*)-*tert*-Butyl(hex-2-en-5-yn-1-yloxy)dimethylsilane (**229**)



2-((*tert*-Butyldimethylsilyl)oxy)acetaldehyde (1 M in THF, 57.2 μ L, 57.2 μ L, 1.00 equiv.) was added to a stirring solution of sulfone **224** (15.0 mg, 57.2 μ mol, 1.00 equiv.) and Cs₂CO₃ (18.6 mg, 57.2 μ mol, 1.00 equiv.) in THF (0.3 mL) and the reaction mixture was heated to 80 °C and stirred overnight (16 h). H₂O (0.2 mL) was added, the aqueous phase extracted with EA (3x 1 mL) and the combined organic layers dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/Ea 50:1) yielded olefin **229** (5.3 mg, 25 μ mol, 44%, *E/Z*: 3:1) as a colourless oil.

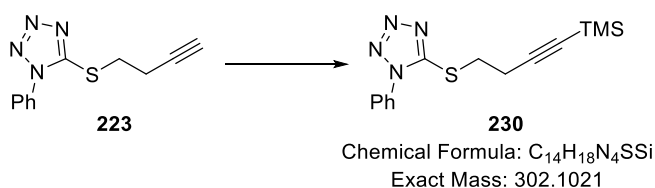
R_f = 0.29 (CH/Ea 50:1).

¹H NMR (CDCl₃, 400 MHz): δ = 5.85 (dtt, 1H, J =15.2, 4.8, 1.7 Hz)*, 5.66 (dtt, 1H, J =15.3, 5.6, 1.7 Hz)*, 5.60 (dt, 1H, J =5.9, 1.6 Hz)#, 5.49 (dtt, 1H, J =10.5, 7.0, 1.7 Hz)#, 4.25 (ddt, 2H, J =6.0, 1.7, 0.8 Hz)#, 4.17 (dq, 2H, J =5.0, 1.7 Hz)*, 2.99 (ddd, 2H, J =3.5, 1.7, 0.8 Hz)#, 2.96 (dtd, 2H, J =5.4, 1.7, 1.0 Hz)*, 2.10 (t, 1H, J =2.7 Hz)*, 1.98 (t, 1H, J =2.7 Hz)#, 0.91 (d, 9H, J =3.0 Hz), 0.07 (d, 6H, J =2.0 Hz) ppm.

¹³C NMR (CDCl₃, 101 MHz): δ = 131.8#, 131.4*, 124.6#, 123.9*, 81.7, 70.3*, 68.5#, 63.4*, 59.4#, 26.1*, 26.1#, 21.5, 18.6, -5.1 ppm.

HRMS (APCI (+), 5.0 eV): calculated for [M+H]⁺: 211.1513; found: 211.1506.

5.6.10 1-Phenyl-5-((4-(trimethylsilyl)but-3-yn-1-yl)thio)-1H-tetrazole (**230**)



Alkyne **223** (1.15 g, 4.99 mmol, 1.00 equiv.) was solved in Et₂O (10 mL) and then cooled to -78 °C before LHMDS (1 M in THF, 5.99 mL, 5.99 mmol, 1.20 equiv.) was added over a period of 10 min. After 1 h of stirring, TMSCl (908 µL, 6.99 mmol, 1.40 equiv.) was added over a period of 30 min and then the reaction was allowed to warm to r.t. and stirred for an additional 1 h. Aq. sat. NH₄Cl (20 mL) was added, the aqueous phase extracted with Et₂O (3x 15 mL) and the combined organic layers dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 9:1) yielded silyl ether **230** (1.48 g, 4.88 mmol, 98%) as a colourless paste.

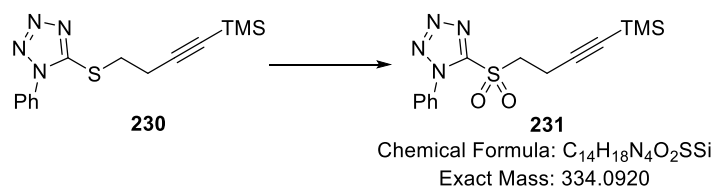
R_f = 0.26 (CH/EA 9:1).

¹H NMR (CDCl₃, 500 MHz): δ = 7.61 – 7.53 (m, 5H), 3.53 (t, 2H, J =7.0 Hz), 2.82 (t, 2H, J =7.0 Hz), 0.13 (s, 9H) ppm.

¹³C NMR (CDCl₃, 126 MHz): δ = 153.9, 133.8, 130.3, 130.0, 124.0, 103.5, 87.4, 32.3, 20.8, 0.1 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 303.1094; found: 303.1093.

5.6.11 1-Phenyl-5-((4-(trimethylsilyl)but-3-yn-1-yl)sulfonyl)-1H-tetrazole (**231**)



H₂O₂ (35%, 50 mL) was added to a solution of sulfide **230** (1.46 mg, 4.83 mmol, 1.00 equiv.) and ammonium heptamolybdate (1.12 g, 965 µmol, 0.20 equiv.) in EtOH (30 mL) and the reaction mixture was stirred at r.t. for 1 h before it was heated to 50 °C and stirred for an additional 16 h. Aq. sat. Na₂S₂O₃ (100 mL) was added and the aqueous phase was extracted with EA (3x 50 mL). The combined organic layers were washed with brine (20 mL) and dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 9:1) yielded sulfone **231** (1.33 g, 3.98 mmol, 83%) as a white solid.

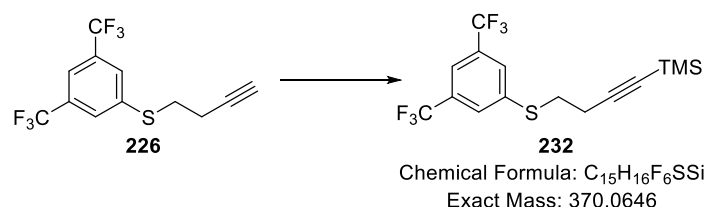
$R_f = 0.18$ (CH/EA 9:1).

$^1\text{H NMR}$ (CDCl_3 , 700 MHz): $\delta = 7.69 - 7.67$ (m, 2H), $7.65 - 7.58$ (m, 3H), $3.94 - 3.88$ (m, 2H), $2.96 - 2.90$ (m, 2H), 0.14 (s, 9H) ppm.

$^{13}\text{C NMR}$ (CDCl_3 , 176 MHz): $\delta = 153.3, 133.1, 131.7, 129.9, 125.3, 99.9, 88.7, 54.8, 27.1, 14.8, -0.0$ ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{Na}]^+$: 357.0812; found: 357.0809.

5.6.12 (4-((3,5-Bis(trifluoromethyl)phenyl)thio)but-1-yn-1-yl)trimethylsilane (**232**)



Alkyne **226** (462 mg, 1.55 mmol, 1.00 equiv.) was solved in Et_2O (3 mL) and then cooled to -78°C before LHMDS (1 M in THF, 1.86 mL, 1.86 mmol, 1.20 equiv.) was added over a period of 10 min. After 1 h of stirring, TMSCl (282 μL , 2.17 mmol, 1.40 equiv.) was added over a period of 30 min and then the reaction was allowed to warm to r.t. and stirred overnight (14 h). Aq. sat. NH_4Cl (10 mL) was added, the aqueous phase extracted with EA (3x 5 mL) and the combined organic layers dried over MgSO_4 . Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 100:1) yielded silyl ether **232** (537 mg, 1.45 mmol, 94%) as a colourless oil.

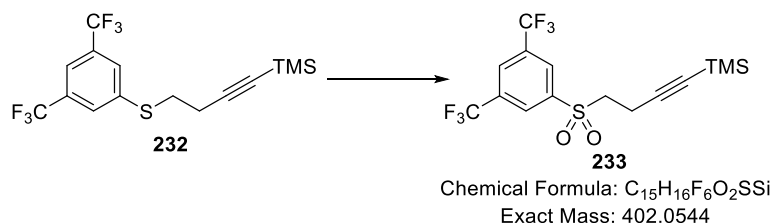
$R_f = 0.26$ (CH/EA 100:1).

$^1\text{H NMR}$ (CDCl_3 , 700 MHz): $\delta = 7.74 - 7.72$ (m, 2H), 7.66 (td, 1H, $J=1.7, 0.9$ Hz), 3.17 (t, 2H, $J=7.4$ Hz), 2.59 (t, 2H, $J=7.4$ Hz), 0.14 (s, 9H) ppm.

$^{13}\text{C NMR}$ (CDCl_3 , 176 MHz): $\delta = 140.1, 132.4$ (q, $J=33.4$ Hz), 128.4 (q, $J=3.9$ Hz), $125.5, 123.9, 122.4, 120.8, 119.8$ (p, $J=3.9$ Hz), $103.5, 87.3, 32.3, 20.7, 0.1$ ppm.

HRMS (APCI (+), 5.0 eV): calculated for $[\text{M}+\text{H}]^+$: 371.0719; found: 371.0719.

5.6.13 (4-((3,5-Bis(trifluoromethyl)phenyl)sulfonyl)but-1-yn-1-yl)trimethylsilane (**233**)



H_2O_2 (35%, 20 mL) was added to a solution of sulfide **232** (362 mg, 977 μ mol, 1.00 equiv.) and ammonium heptamolybdate (227 mg, 195 μ mol, 0.20 equiv.) in EtOH (10 mL) and the reaction mixture was heated to 60 °C and stirred for 72 h. Aq. sat. $Na_2S_2O_3$ (50 mL) was added and the aqueous phase was extracted with EA (3x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 15:1) yielded sulfone **233** (356 mg, 885 μ mol, 91%) as a colourless oil.

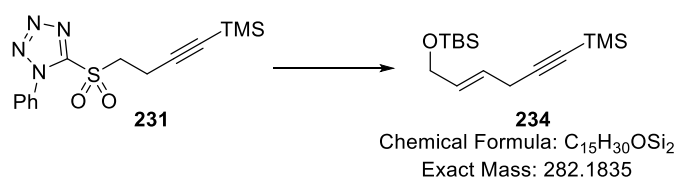
R_f = 0.26 (CH/EA 15:1).

1H NMR ($CDCl_3$, 700 MHz): δ = 8.39 – 8.37 (m, 2H), 8.18 (td, 1H, J =1.7, 0.9 Hz), 3.41 – 3.37 (m, 2H), 2.75 (dd, 2H, J =8.0, 7.2 Hz), 0.05 (s, 9H) ppm.

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 141.8, 133.5 (q, J =34.7 Hz), 129.0 (q, J =3.6 Hz), 127.9 (hept, J =3.5 Hz), 124.8, 123.2, 121.7, 120.1, 100.4, 88.3, 54.9, 14.6, -0.2 ppm.

HRMS (ESI (-), 6.0 eV): calculated for $[M+Na]^+$: 401.0472; found: 401.0473.

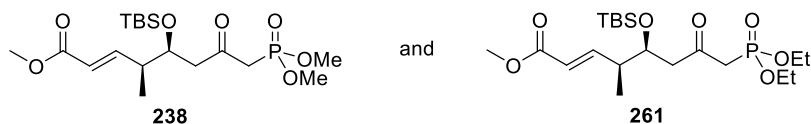
5.6.14 (*E*)-*tert*-Butyldimethyl((6-(trimethylsilyl)hex-2-en-5-yn-1-yl)oxy)silane (**234**)



¹H NMR (CDCl₃, 500 MHz): δ = 5.82 (dtt, 1H, *J*=15.2, 5.0, 1.7 Hz)^{*}, 5.67 – 5.61 (m, 1H)^{*}, 5.60 – 5.57 (m, 1H)[#], 5.51 – 5.44 (m, 1H)[#], 4.25 (ddt, 2H, *J*=6.0, 1.8, 0.9 Hz)[#], 4.18 (dq, 2H, *J*=5.0, 1.6 Hz)^{*}, 3.01 (dt, 2H, *J*=1.7, 0.9 Hz)[#], 2.99 (dq, 2H, *J*=5.2, 1.7 Hz)^{*}, 0.91 (s, 9H), 0.16 (s, 9H), 0.07 (s, 6H) ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 283.1908; found: 283.1905.

5.7 Experimental Details for Chapter 3.6.1: Synthesis of Phosphate 238 and 261



244 **251**

 Chemical Formula: $C_{11}H_{16}O_3$

 Exact Mass: 196.1099

Amberlyst[®] 15 hydrogen form (10% w/w, 1 g) was added to a solution of alcohol **244** (10.0 g, 131 mmol, 1.50 equiv.), 4-methoxybenzyl alcohol (12.1 g, 87.6 mmol, 1.00 equiv.) and DCM (100 mL) in a pressure tube. The tube was sealed and heated to 45 °C and the reaction stirred for 96 h. The mixture was filtered over a plug of silica gel, the solvent removed under reduced pressure and the residue purified by flash column chromatography over silica gel (CH/EA 2:1) to yield PMB alcohol **251** (16.9 g, 85.8 mmol, 98%) as a colourless liquid.

R_f = 0.16 (CH/EA 2:1).

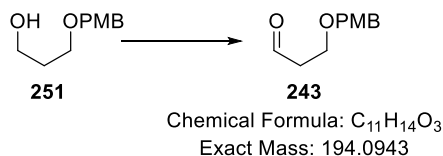
¹H NMR (CD₂Cl₂, 500 MHz): δ = 7.27 – 7.22 (m, 2H), 6.90 – 6.85 (m, 2H), 4.43 (s, 2H), 3.79 (s, 3H), 3.71 (t, 2H, J =5.8 Hz), 3.64 – 3.57 (m, 2H), 2.11 (s, 1H), 1.81 (p, 2H, J =5.9 Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 159.7, 131.0, 129.6, 114.1, 73.2, 69.4, 62.0, 55.6, 32.8 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+Na]⁺ : 219.0992; found: 219.0991.

The experimental data are in agreement with those previously published.^[196]

5.7.2 3-((4-Methoxybenzyl)oxy)propanal (**243**)



Oxalyl chloride (1.07 mL, 12.2 mmol, 1.20 equiv.) was added to a solution of DCM (20 mL) and DMSO (1.88 mL, 26.5 mmol, 2.60 equiv.) at –78 °C and the reaction was stirred for 30 min. Alcohol **251** (2.00 g, 10.2 mmol, 1.00 equiv., solved in 5 mL DCM) was added over a period of 5 min and the reaction stirred for 45 min. NEt₃ (7.06 mL, 51.0 mmol, 5.00 equiv.) was added and the reaction was allowed to warm to r.t. over a period of 30 min. Then H₂O (20 mL) was added and after 10 min the aqueous phase was extracted with DCM (3x 20 mL). The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 2:1) yielded aldehyde **243** (1.79 g, 9.24 mmol, 91%) as a colourless oil.

R_f = 0.36 (CH/EA 2:1).

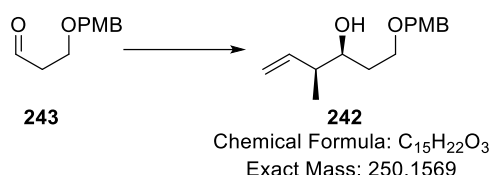
^1H NMR (CDCl_3 , 400 MHz): δ = 9.81 (t, 1H, J =1.8 Hz), 7.30 – 7.25 (m, 2H), 6.93 – 6.87 (m, 2H), 4.48 (s, 2H), 3.83 (s, 3H), 3.81 (t, 2H, J =6.1 Hz), 2.70 (td, 2H, J =6.1, 1.8 Hz) ppm.

^{13}C NMR (CDCl_3 , 101 MHz): δ = 201.4, 159.4, 130.1, 129.5, 114.0, 73.1, 63.6, 55.4, 44.0 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{NH}_4]^+$: 212.1281; found: 212.1280.

The experimental data are in agreement with those previously published.^[196]

5.7.3 (3*S*,4*S*)-1-((4-Methoxybenzyl)oxy)-4-methylhex-5-en-3-ol (242)



Cis-2-buten (~5 mL, ~5 equiv.) was condensed at $-78\text{ }^{\circ}\text{C}$ in the reaction vessel. Potassium *tert*-butoxide (1.32 mg, 11.8 mmol, 1.30 equiv.) was added together with THF (100 mL). *n*-BuLi (2.5 M in hexanes, 7.36 mL, 11.8 mmol, 1.30 equiv.) was added over a period of 20 min at $-40\text{ }^{\circ}\text{C}$ and the reaction stirred for additional 15 min before it was recooled to $-78\text{ }^{\circ}\text{C}$. (+)-*B*-Methoxydiisopinocampheylboran (3.73 g, 11.8 mmol, 1.30 equiv., solved in 10 mL Et_2O) was added over a period of 20 min and the reaction was allowed to stir for additional 60 min before boron trifluoride etherate (1.54 mL, 12.2 mmol, 1.35 equiv.) was added over a period of 20 min. Aldehyde **243** (1.76 g, 9.06 mmol, 1.00 equiv., dried 2 h over 3 Å molecular sieve in 20 mL THF) was added and the reaction mixture was stirred for 3 h before MeOH (50 mL), NaOH (3 M, 200 mL) and H_2O_2 (35%, 50 mL) were added and the reaction mixture was refluxed ($70\text{ }^{\circ}\text{C}$) overnight (14 h). Aq. sat. $\text{Na}_2\text{S}_2\text{O}_3$ (200 mL) was added to quench the reaction, the aqueous phase was extracted with Et_2O (3x 50 mL), the combined organic layers were washed with aq. sat. NH_4Cl (20 mL) and brine (20 mL). Drying the organic layer over MgSO_4 , removal of the solvents *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/Ea 6:1) yielded title compound **242** (1.19 g, 4.74 mmol, 52%, *dr* >20:1,) with additional 2,6,6-trimethylbicyclo[3.1.1]heptan-3-ol as impurity (285 mg, 1.85 mmol, 20%) as a colourless oil.

$R_f = 0.14$ (CH/EA 6:1).

$[\alpha]_D^{20} = -2.0$ (DCM, $c = 1.0$).

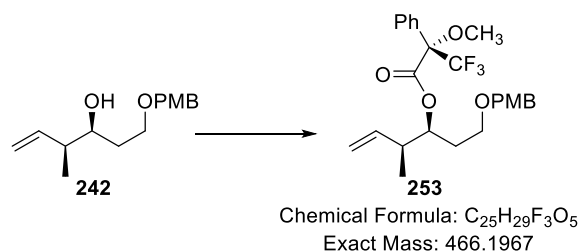
$^1\text{H NMR}$ (CD_2Cl_2 , 500 MHz): $\delta = 7.3 - 7.2$ (m, 2H), 6.9 – 6.9 (m, 2H), 5.8 (ddd, 1H, $J=17.3, 10.4, 7.6$ Hz), 5.1 – 5.0 (m, 2H), 4.4 (s, 2H), 4.0 (dt, 0H, $J=9.6, 5.0$ Hz), 3.8 (s, 3H), 3.7 (ddd, 1H, $J=9.3, 6.0, 4.7$ Hz), 3.6 – 3.6 (m, 2H), 2.7 (d, 1H, $J=3.4$ Hz), 2.5 – 2.5 (m, 0H), 2.4 (dtd, 0H, $J=9.7, 6.2, 2.3$ Hz), 2.3 – 2.2 (m, 1H), 1.9 (dddd, 1H, $J=14.7, 7.4, 5.6, 2.6$ Hz), 1.8 – 1.7 (m, 1H), 1.7 – 1.6 (m, 2H), 1.2 (s, 1H), 1.1 (d, 1H, $J=7.4$ Hz), 1.0 (d, 3H, $J=6.8$ Hz), 0.9 (s, 1H) ppm.

$^{13}\text{C NMR}$ (CD_2Cl_2 , 126 MHz): $\delta = 159.8, 141.8, 130.8, 129.7, 114.8, 114.2, 74.7, 73.3, 71.9, 69.6, 55.7, 48.4, 44.4, 42.4, 39.5, 34.7, 34.2, 23.8, 20.9, 15.3$ ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{Na}]^+$: 273.1461; found: 273.1457.

The experimental data are in agreement with those previously published.^[197]

5.7.4 (3*S*,4*S*)-1-((4-Methoxybenzyl)oxy)-4-methylhex-5-en-3-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**253**)



(*R*)-(-)-MTPA-Cl (7.5 μL , 40 μmol , 2.0 equiv.) was added to a solution of alcohol **242** (5.0 mg, 20 μmol , 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO_3 (1 mL) was added, the aqueous phase was extracted with EA (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO_4 . The residue was purified by flash column chromatography over silica gel (CH/EA 15:1) to yield ester **253** (3.8 mg, 8.2 μmol , 41%) as a colourless oil.

$R_f = 0.18$ (CH/EA 15:1).

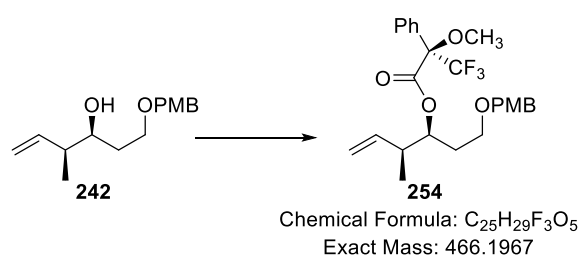
$[\alpha]_D^{20} = -84.0$ (DCM, $c = 1.0$).

¹H NMR (CD₂Cl₂, 500 MHz): δ = 7.54 (ddq, 2H, J =7.5, 1.8, 0.8 Hz), 7.44 – 7.36 (m, 3H), 7.24 – 7.19 (m, 2H), 6.89 – 6.84 (m, 2H), 5.82 (ddd, 1H, J =17.1, 10.7, 6.9 Hz), 5.26 (ddd, 1H, J =8.7, 4.8, 3.8 Hz), 5.11 – 5.05 (m, 2H), 4.35 – 4.27 (m, 2H), 3.79 (s, 3H), 3.51 (q, 3H, J =1.3 Hz), 3.35 (ddd, 1H, J =9.5, 6.6, 5.0 Hz), 3.27 (ddd, 1H, J =9.4, 8.1, 5.9 Hz), 2.57 (tdt, 1H, J =7.0, 4.7, 1.3 Hz), 1.90 (dddd, 1H, J =14.7, 8.1, 6.7, 3.8 Hz), 1.81 (dddd, 1H, J =14.7, 8.9, 5.9, 5.0 Hz), 1.05 (d, 3H, J =6.9 Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 166.5, 159.7, 139.6, 132.8, 131.0, 130.0, 129.6, 128.8, 128.0 (d, J =1.4 Hz), 125.1, 122.8, 116.1, 114.1, 77.9, 73.0, 66.4, 55.9, 55.6, 41.2, 31.5, 14.8 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+Na]⁺: 489.1859; found: 489.1855.

5.7.5 (3*S*,4*S*)-1-((4-Methoxybenzyl)oxy)-4-methylhex-5-en-3-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**254**)



(*S*)-(-)-MTPA-Cl (10 μ l, 56 μ mol, 2.0 equiv.) was added to a solution of alcohol **242** (7.0 mg, 28 μ mol, 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO₃ (1 mL) was added, the aqueous phase was extracted with EA (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO₄. The residue was purified by flash column chromatography over silica gel (CH/EA 15:1) to yield ester **254** (2.2 mg, 4.7 μ mol, 17%) as a colourless oil.

R_f = 0.18 (CH/EA 15:1).

$[\alpha]_D^{20}$ = -15.0 (DCM, c = 1.0).

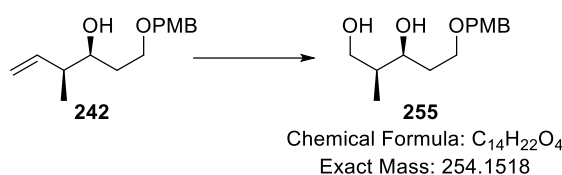
¹H NMR (CD₂Cl₂, 500 MHz): δ = 7.53 (dtd, 2H, J =6.6, 1.6, 0.8 Hz), 7.43 – 7.37 (m, 3H), 7.26 – 7.21 (m, 2H), 6.89 – 6.83 (m, 2H), 5.66 (ddd, 1H, J =17.4, 10.5, 7.1 Hz), 5.23 (ddd, 1H, J =8.7, 5.0, 3.9 Hz), 5.01 – 4.90 (m, 2H), 4.37 (s, 2H), 3.79 (s, 3H), 3.49 (q, 3H, J =1.2 Hz), 3.47 – 3.37 (m,

2H), 2.50 (tdt, 1H, $J=7.1, 4.9, 1.3$ Hz), 1.95 (dddd, 1H, $J=14.5, 7.9, 6.6, 3.8$ Hz), 1.87 (dddd, 1H, $J=14.6, 8.7, 5.9, 5.3$ Hz), 0.97 (d, 3H, $J=6.9$ Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): $\delta = 166.5, 159.7, 139.4, 132.8, 131.0, 130.0, 129.7, 128.8, 125.1, 122.8, 116.0, 114.1, 77.9, 73.1, 66.5, 55.8, 55.8, 55.6, 41.2, 31.7, 14.7$ ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{Na}]^+$: 489.1859; found: 489.1859.

5.7.6 (2*S*,3*S*)-5-((4-Methoxybenzyl)oxy)-2-methylpentane-1,3-diol (255)



Alkene **242** (70.0 mg, 280 μmol , 1.00 equiv.) was solved in MeOH (1 mL) and DCM (1 mL) together with a tip of a spatula NaHCO_3 (~3 mg) and cooled to -78°C . 1 drop of sudan III solution (0.1 M in MeOH) was added and the reaction vessel was filled with ozone until the mixture turned colourless (~1 min). NaBH_4 (52.9 mg, 1.40 mmol, 5.00 equiv.) was added and the reaction mixture was stirred for 10 min at -78°C . The reaction was allowed to warm to r.t. and stirred for additional 2 h. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography over silica gel (CH/EA 1:2) to get 1,3-diol **255** (49.2 mg, 193 μmol , 69%) as a colourless liquid.

$R_f = 0.19$ (CH/EA 1:2).

$[\alpha]_D^{20} = +13.0$ (DCM, $c = 1.0$).

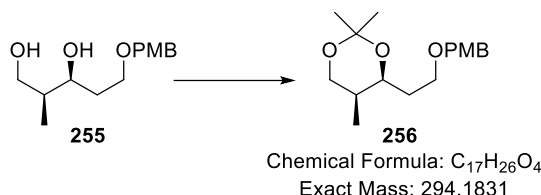
^1H NMR (CD_2Cl_2 , 500 MHz): $\delta = 7.28 - 7.22$ (m, 2H), 6.90 – 6.86 (m, 2H), 4.44 (s, 2H), 4.00 – 3.94 (m, 1H), 3.79 (s, 3H), 3.72 (dt, 1H, $J=9.5, 4.9$ Hz), 3.66 – 3.56 (m, 3H), 3.22 (s, 1H), 2.46 (s, 1H), 1.89 – 1.80 (m, 1H), 1.78 (ddtd, 1H, $J=10.1, 6.9, 3.6, 1.2$ Hz), 1.61 (dddd, 1H, $J=14.5, 5.0, 4.0, 2.3$ Hz), 0.88 (d, 3H, $J=7.1$ Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): $\delta = 159.8, 130.7, 129.7, 114.2, 75.0, 73.4, 70.0, 67.0, 55.7, 40.2, 33.5, 11.0$ ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+Na]^+$: 277.1410; found: 277.1406.

The experimental data are in agreement with those previously published.^[198]

5.7.7 (4*S*,5*S*)-4-(2-((4-Methoxybenzyl)oxy)ethyl)-2,2,5-trimethyl-1,3-dioxane (**256**)



Pyridinium *p*-toluenesulfonate (2.96 mg, 11.8 μ mol, 0.10 equiv.) was added to a solution of alcohol **255** (30.0 mg, 118 μ mol, 1.00 equiv.) and 2-methoxypropene (22.6 μ L, 236 μ mol, 2.00 equiv.) in DCM (1 mL) and the reaction was stirred overnight (16 h). The mixture was concentrated *in vacuo* and the residue purified by flash column chromatography over silica gel (CH/EA 9:1) to yield acetonide **256** (28.9 mg, 98.2 μ mol, 83%) as a colourless oil.

R_f = 0.13 (CH/EA 9:1).

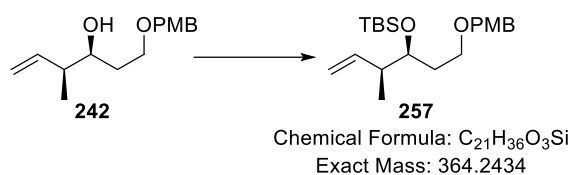
$[\alpha]_D^{20}$ = -22.0 (DCM, c = 1.0).

^1H NMR (CD_2Cl_2 , 500 MHz): δ = 7.28 – 7.20 (m, 2H), 6.92 – 6.84 (m, 2H), 4.43 – 4.36 (m, 2H), 4.11 (ddd, 1H, J =8.8, 4.5, 2.6 Hz), 4.09 – 4.04 (m, 1H), 3.79 (s, 3H), 3.55 – 3.44 (m, 3H), 1.69 (ddt, 1H, J =14.2, 8.7, 5.5 Hz), 1.42 (ddd, 1H, J =4.4, 2.7, 1.7 Hz), 1.59 (dddd, 1H, J =14.1, 7.8, 6.5, 4.5 Hz), 1.03 (dd, 3H, J =7.0, 0.5 Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): δ = 159.7, 131.4, 129.6, 114.1, 98.9, 73.0, 67.2, 66.9, 55.7, 33.9, 32.4, 29.9, 19.4, 10.9 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 295.1904; found: 295.1905.

5.7.8 *tert*-Butyl(((3*S*,4*S*)-1-((4-methoxybenzyl)oxy)-4-methylhex-5-en-3-yl)oxy)dimethylsilane (**257**)



TBSOTf (10.4 mL, 44.7 mmol, 2.00 equiv.) was added to a solution of alcohol **242** (5.60 g, 22.4 mmol, 1.00 equiv.) and 2,6-lutidine (12.9 mL, 112 mmol, 5.00 equiv.) in DCM (20 mL) at 0 °C and the reaction was allowed to stir for 30 min. Then the reaction was allowed to warm to r.t. and stirred for additional 2 h before the reaction was quenched with aq. sat. NH₄Cl (100 mL). The aqueous phase was extracted with DCM (3x 50 mL) and the combined organic layers were washed with brine (10 mL) and dried over MgSO₄. Removal of the solvent under reduced pressure and purification of the residue by flash column chromatography over silica gel (CH/EA 50:1) yielded silyl ether **257** (7.95 g, 21.8 mmol, 97%) as a colourless oil.

R_f = 0.12 (CH/EA 50:1).

$[\alpha]_D^{20}$ = -32.0 (DCM, c = 1.0).

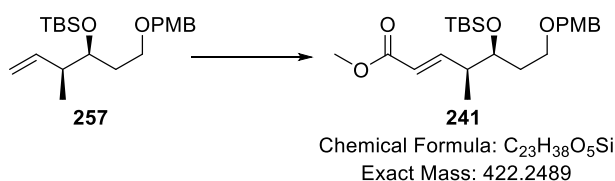
¹H NMR (CD₂Cl₂, 500 MHz): δ = 7.33 – 7.17 (m, 2H), 6.90 – 6.83 (m, 2H), 5.97 – 5.83 (m, 1H), 5.03 – 4.98 (m, 2H), 4.45 – 4.31 (m, 2H), 3.79 (s, 3H), 3.74 (dt, 1H, J =7.7, 4.4 Hz), 3.50 (dd, 2H, J =7.3, 6.0 Hz), 2.39 – 2.24 (m, 1H), 1.74 (dtd, 1H, J =13.9, 7.4, 4.1 Hz), 1.62 (ddt, 1H, J =13.9, 7.8, 6.0 Hz), 0.96 (d, 3H, J =6.9 Hz), 0.89 (s, 10H), 0.05 (d, 6H, J =3.0 Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 159.6, 141.6, 131.5, 129.6, 114.3, 114.1, 73.5, 72.9, 67.3, 55.6, 43.5, 34.0, 26.1, 18.5, 15.1, -4.2, -4.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 365.2506; found: 365.2506.

The experimental data are in agreement with those previously published.^[199]

5.7.9 Methyl (4*S*,5*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-4-methylhept-2-enoate (**241**)



Alkene **257** (7.80 g, 21.4 mmol, 1.00 equiv., dried with 3x Freeze-Pump-Thaw cycles) and methyl acrylate (9.69 mL, 107 mmol, 5.00 equiv.) in toluene (40 mL) were refluxed (120 °C) for 30 min. Hoveyda-Grubbs-II (268 mg, 428 μmol, 0.02 equiv.) was added and the reaction was allowed to stir overnight (22 h). Celite[®] (~100 g) was added to the mixture and the solvent was reduced under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 15:1) yielded methyl ester **241** (7.60 g, 18.0 mmol, 84%, *E/Z* >20:1) as a colourless oil.

R_f = 0.12 (CH/EA 15:1).

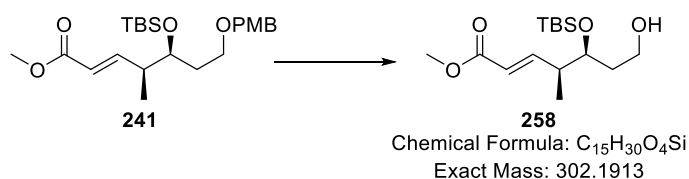
$[\alpha]_D^{20}$ = -39.0 (DCM, *c* = 1.0).

¹H NMR (CD₂Cl₂, 400 MHz): δ = 7.28 – 7.19 (m, 2H), 7.01 (dd, 1H, *J*=15.9, 7.0 Hz), 6.90 – 6.83 (m, 2H), 5.79 (dd, 1H, *J*=15.8, 1.5 Hz), 4.44 – 4.31 (m, 2H), 3.83 (dt, 1H, *J*=8.3, 4.3 Hz), 3.79 (s, 3H), 3.69 (s, 3H), 3.51 – 3.45 (m, 2H), 2.54 – 2.43 (m, 1H), 1.74 (dtd, 1H, *J*=14.3, 7.2, 4.2 Hz), 1.64 – 1.55 (m, 1H), 1.53 (d, 1H, *J*=0.7 Hz), 1.02 (d, 3H, *J*=6.9 Hz), 0.89 (s, 9H), 0.05 (d, 6H, *J*=0.9 Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 167.3, 159.7, 152.0, 131.3, 129.6, 121.2, 114.1, 72.9, 72.9, 67.0, 55.6, 51.6, 42.5, 34.2, 26.1, 18.4, 14.3, -4.3, -4.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+NH₄]⁺: 440.2827; found: 440.2830.

5.7.10 Methyl (4*S*,5*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-7-hydroxy-4-methylhept-2-enoate (**258**)



DDQ (5.64 g, 24.8 mmol, 1.40 equiv.) was added to a solution of PMB ether **241** (7.50 g, 17.8 mmol, 1.00 equiv.) and H₂O (1.8 mL, 97.6 mmol, 5.50 equiv.) in DCM (40 mL) and the reaction was allowed to stir for 2 h at r.t. Aq. sat. NaHCO₃ (50 mL) and H₂O (50 mL) was added, the aqueous phase extracted with DCM (3x 50 mL) and the combined organic layers were dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 6:1) yielded primary alcohol **258** (5.03 g, 16.6 mmol, 94%) as a colourless oil.

R_f = 0.06 (CH/EA 6:1).

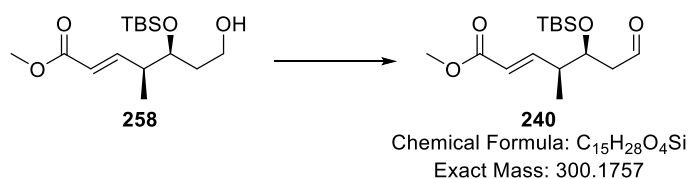
$[\alpha]_D^{20}$ = -67.0 (DCM, c = 1.0).

¹H NMR (CD₂Cl₂, 400 MHz): δ = 7.01 (dd, 1H, J =15.9, 7.1 Hz), 5.83 (dd, 1H, J =15.9, 1.5 Hz), 3.85 (ddd, 1H, J =7.8, 5.0, 3.9 Hz), 3.69 (s, 3H), 3.68 (s, 2H), 2.60 – 2.50 (m, 1H), 1.71 (dtd, 1H, J =14.1, 7.0, 4.0 Hz), 1.66 – 1.62 (m, 1H), 1.61 – 1.55 (m, 1H), 1.04 (d, 3H, J =6.9 Hz), 0.90 (s, 8H), 0.09 (d, 5H, J =5.8 Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 167.2, 151.4, 121.4, 73.8, 60.1, 51.6, 42.5, 36.3, 26.1, 18.4, 14.9, -4.3, -4.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+NH₄]⁺: 303.1986; found: 303.1987.

5.7.11 Methyl (4*S*,5*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-7-oxohept-2-enoate (**240**)



H₂O (296 μ L, 16.5 mmol, 1.20 equiv.) was added to a solution of alcohol **258** (4.15 g, 13.7 mmol, 1.00 equiv.) and DMP (11.6 g, 27.4 mmol, 2.00 equiv.) in DCM (70 mL) at 0 °C. The reaction was allowed to warm to r.t. and stirred for 4 h. Aq. sat. Na₂S₂O₃ (50 mL) and aq. sat. NaHCO₃ (50 mL) were added to the solution and the aqueous phase was extracted with DCM (3x 50 mL). The combined organic layers were dried over MgSO₄ and the solvent removed under reduced pressure. Purification of the residue by flash column chromatography over silica gel (Pentane/Et₂O 4:1) yielded volatile aldehyde **240** (4.48 g, 12.7 mmol, 92%) as a colourless liquid.

R_f = 0.21 (Pentane/Et₂O 4:1).

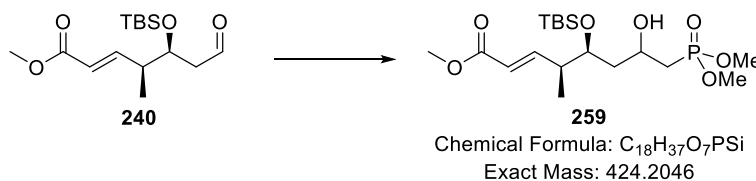
$[\alpha]_D^{20}$ = -40.0 (DCM, c = 1.0).

¹H NMR (CD₂Cl₂, 500 MHz): δ = 9.76 (t, 1H, J =2.2 Hz), 6.97 (dd, 1H, J =15.9, 7.2 Hz), 5.84 (dd, 1H, J =15.9, 1.5 Hz), 4.22 (dt, 1H, J =6.2, 5.2 Hz), 3.71 (s, 3H), 2.56 (tdd, 1H, J =7.1, 5.0, 1.5 Hz), 2.51 – 2.48 (m, 2H), 1.06 (d, 3H, J =6.8 Hz), 0.88 (s, 9H), 0.08 (d, 6H, J =17.7 Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 201.5, 167.0, 150.4, 122.1, 71.3, 51.7, 48.5, 43.0, 26.0, 18.3, 14.7, -4.4, -4.5 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+NH₄]⁺: 318.2095; found: 318.2095.

5.7.12 Methyl (4*S*,5*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-8-(dimethoxyphosphoryl)-7-hydroxy-4-methyloct-2-enoate (**259**)



n-BuLi (2 M in cyclohexane, 638 μ L, 1.60 mmol, 1.15 equiv.) was added to a solution of dimethyl methylphosphonate (193 μ L, 1.80 mmol, 1.30 equiv.) in THF (3 mL) at -78 °C and the reaction was stirred for 30 min. Aldehyde **240** (417 mg, 1.39 mmol, 1.00 equiv.) was added over a period of 2 min and the reaction was allowed to stir for further 30 min before it was

quenched by adding aq. sat. NH_4Cl (10 mL). The aqueous phase was extracted with EA (3x 5 mL), the combined organic layers dried over MgSO_4 and the solvent was removed *in vacuo*. Purification of the residue by flash column chromatography over silica gel (100% EA) yielded alcohol **259** (214 mg, 503 μmol , 36%, containing both diastereomers and impurities) as a yellowish oil.

$R_f = 0.14$ (100% EA).

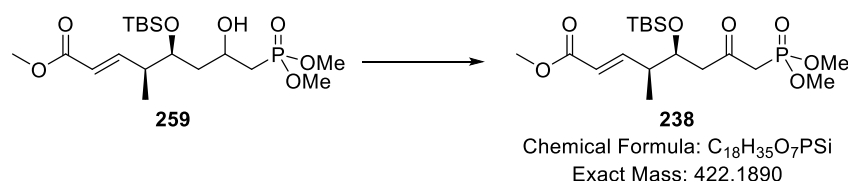
$[\alpha]_D^{20} = -21.0$ (DCM, $c = 1.0$).

$^1\text{H NMR}$ (CD_2Cl_2 , 500 MHz): $\delta = 7.03$ (ddd, 1H, $J=15.9, 6.9, 1.8$ Hz), 5.83 (ddd, 1H, $J=15.9, 2.6, 1.5$ Hz), 4.40 (dt, 0H, $J=9.7, 4.8$ Hz), 4.15 – 3.95 (m, 2H), 3.89 (td, 1H, $J=6.4, 4.2$ Hz), 3.76 – 3.63 (m, 13H), 3.49 (d, 1H, $J=2.7$ Hz), 2.64 – 2.53 (m, 1H), 2.40 (dd, 0H, $J=15.0, 4.9$ Hz), 2.10 (dd, 1H, $J=18.4, 6.5$ Hz), 2.03 – 1.97 (m, 1H), 1.96 – 1.82 (m, 2H), 1.66 (td, 2H, $J=6.6, 1.0$ Hz), 1.44 – 1.35 (m, 0H), 1.03 (d, 3H, $J=6.8$ Hz), 0.92 – 0.88 (m, 14H), 0.10 – 0.06 (m, 8H) ppm.

$^{13}\text{C NMR}$ (CD_2Cl_2 , 126 MHz): $\delta = 172.1, 167.2, 151.7, 151.3, 121.5, 121.4, 73.7, 73.7, 72.7, 70.6, 66.0, 64.8, 64.7, 63.2, 63.2, 52.8 - 52.6$ (m), 52.0, 51.6, 42.7, 42.2, 42.1, 42.0, 41.9, 41.6, 40.7, 34.6, 34.1, 33.8, 33.0, 32.7, 32.4, 31.3, 18.4, 18.3, 14.8, 13.9, 13.1, -4.2, -4.4, -4.5, -4.7 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 425.2119; found: 425.2119.

5.7.13 Methyl (4*S*,5*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-8-(dimethoxyphosphoryl)-4-methyl-7-oxooct-2-enoate (**238**)



H_2O (9.7 μL , 0.54 mmol, 1.2 equiv.) was added to a solution of alcohol **259** (190 mg, 448 μmol , 1.00 equiv.) and DMP (285 mg, 671 μmol , 1.50 equiv.) in DCM (3 mL) and the reaction was stirred for 2 h. Aq. sat. $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) and aq. sat. NaHCO_3 (5 mL) were added to the solution and the aqueous phase was extracted with DCM (3x 5 mL). The combined organic layers were dried over MgSO_4 and the solvent removed under reduced pressure. Purification of the

residue by flash column chromatography over silica gel (CH/EA 3:7) to yield ketone **238** (105 mg, 249 μ mol, 56%) as a colourless oil.

R_f = 0.17 (CH/EA 3:7).

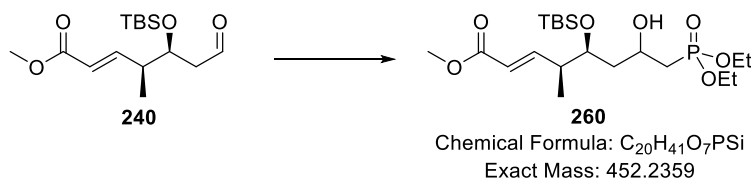
$[\alpha]_D^{20}$ = -78.0 (DCM, c = 1.0).

^1H NMR (CD_2Cl_2 , 500 MHz): δ = 6.99 (dd, 1H, J =15.9, 6.9 Hz), 5.83 (dd, 1H, J =15.9, 1.5 Hz), 4.22 (td, 1H, J =5.9, 4.2 Hz), 3.75 (d, 3H, J =1.4 Hz), 3.73 (d, 3H, J =1.4 Hz), 3.71 (s, 3H), 3.12 – 3.05 (m, 1H), 3.05 – 2.98 (m, 1H), 2.71 (s, 1H), 2.69 (d, 1H, J =0.7 Hz), 2.52 (tdd, 1H, J =6.9, 4.1, 1.5 Hz), 1.02 (d, 3H, J =6.9 Hz), 0.87 (s, 9H), 0.05 (d, 6H, J =26.0 Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): δ = 200.5 (d, J =6.4 Hz), 167.1, 151.0, 121.7, 71.5, 51.7, 48.7, 48.7, 43.3, 42.4, 42.3, 26.0, 18.3, 14.0, -4.6, -4.6 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 423.1962; found: 423.1958.

5.7.14 Methyl (4*S*,5*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-8-(diethoxyphosphoryl)-7-hydroxy-4-methyloct-2-enoate (**260**)



n-BuLi (2 M in cyclohexane, 4.92 mL, 9.84 mmol, 1.20 equiv.) was added to a solution of diethyl methylphosphonate (1.80 mL, 12.3 mmol, 1.50 equiv.) in THF (200 mL) at -78 °C and the reaction was stirred for 30 min before the reaction was cooled to -90 °C. Aldehyde **240** (2.90 g, 8.20 mmol, 1.00 equiv., solved in 10 mL THF) was added quickly and the reaction was allowed to stir for 15 min. The reaction was warmed to -40 °C and stirred for further 40 min before it was quenched by adding aq. sat. NH_4Cl (100 mL) and allowed to warm to r.t. The aqueous phase was extracted with EA (3x 50 mL), the combined organic layers dried over MgSO_4 and the solvent was removed *in vacuo*. Purification of the residue by flash column chromatography over silica gel (100% EA) yielded alcohol **260** (1.96 g, 4.33 mmol, 53%, containing both diastereomers) as a yellowish oil.

$R_f = 0.17$ (100% EA).

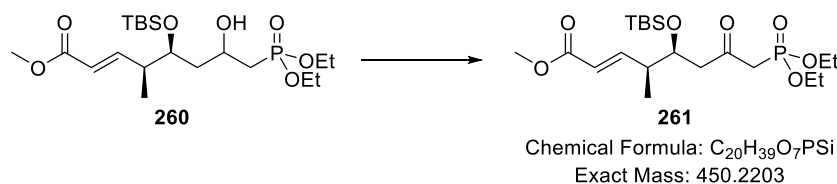
$[\alpha]_D^{20} = -27.0$ (DCM, $c = 1.0$).

$^1\text{H NMR}$ (CDCl_3 , 500 MHz): $\delta = 7.06$ (ddd, 1H, $J=15.9, 11.8, 6.7$ Hz), 5.83 (ddd, 1H, $J=15.9, 4.9, 1.5$ Hz), 4.18 – 4.05 (m, 5H), 4.03 – 3.86 (m, 1H), 3.73 (s, 3H), 3.70 – 3.60 (m, 1H), 3.58 (d, 1H, $J=2.3$ Hz), 2.63 – 2.52 (m, 1H), 2.00 – 1.84 (m, 2H), 1.68 (t, 1H, $J=6.3$ Hz), 1.36 – 1.31 (m, 6H), 1.03 (dd, 3H, $J=6.9, 5.6$ Hz), 0.90 (d, 9H, $J=4.6$ Hz), 0.13 – 0.06 (m, 6H) ppm.

$^{13}\text{C NMR}$ (CDCl_3 , 126 MHz): $\delta = 167.2, 167.1, 151.4, 151.1, 121.2, 121.2, 73.5$ (d, $J=1.7$ Hz), 72.2 (d, $J=2.6$ Hz), 64.7 (d, $J=4.3$ Hz), 63.0 (d, $J=5.1$ Hz), 62.1 – 61.9 (m), 51.5, 42.5, 41.6 (dd, $J=15.5, 6.8$ Hz), 41.4, 35.0, 34.7, 33.9, 33.6, 26.1, 26.0, 18.3, 18.2, 16.7 – 16.5 (m), 14.7, 13.9, -4.2, -4.2, -4.3, -4.5 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 453.2432; found: 453.2426.

5.7.15 Methyl (4*S*,5*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-8-(diethoxyphosphoryl)-4-methyl-7-oxooct-2-enoate (**261**)



H_2O (11 μL , 0.61 mmol, 1.2 equiv.) was added to a solution of alcohol **260** (230 mg, 508 μmol , 1.00 equiv.) and DMP (431 mg, 1.02 mmol, 2.00 equiv.) in DCM (3 mL) and the reaction was stirred for 2 h. Aq. sat. $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) and aq. sat. NaHCO_3 (5 mL) were added to the solution and the aqueous phase was extracted with DCM (3x 5 mL). The combined organic layers were dried over MgSO_4 and the solvent removed under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 3:7) to yield ketone **261** (166 mg, 368 μmol , 73%) as a colourless oil.

$R_f = 0.26$ (CH/EA 3:7).

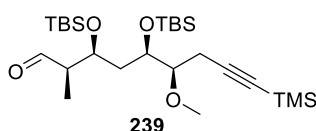
$[\alpha]_D^{20} = -66.0$ (DCM, $c = 0.5$).

^1H NMR (CDCl_3 , 500 MHz): δ = 7.02 (dd, 1H, J =15.9, 6.8 Hz), 5.83 (dd, 1H, J =15.9, 1.5 Hz), 4.22 (ddd, 1H, J =6.8, 5.1, 4.1 Hz), 4.18 – 4.09 (m, 4H), 3.73 (s, 3H), 3.15 – 2.97 (m, 2H), 2.76 – 2.64 (m, 2H), 2.52 (tdd, 1H, J =6.8, 4.1, 1.6 Hz), 1.33 (tdd, 6H, J =7.1, 1.0, 0.5 Hz), 1.02 (d, 3H, J =6.9 Hz), 0.86 (s, 9H), 0.04 (d, 6H, J =27.5 Hz) ppm.

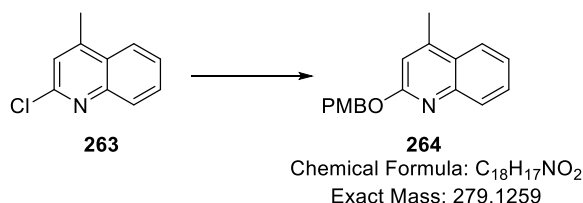
^{13}C NMR (CDCl_3 , 126 MHz): δ = 200.6 (d, J =6.3 Hz), 167.0, 150.8, 121.4, 71.2, 62.7 (dd, J =12.1, 6.4 Hz), 51.6, 48.2, 44.3, 43.3, 42.1, 26.0, 18.2, 16.5, 16.4, 13.9, -4.5, -4.6 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 451.2275; found: 451.2268.

5.8 Experimental Details for Chapter 3.6.2: Synthesis of Aldehyde 239



5.8.1 2-((4-methoxybenzyl)oxy)-4-methylquinoline (264)



p-Anisyl alcohol (18.7 g, 135 mmol, 1.20 equiv.) was added to a stirring solution of 2-chloro-4-methylquinoline (**263**, 20.0 g, 113 mmol, 1.00 equiv.), 18-crown-6 (1.49 g, 5.63 mmol, 0.05 equiv.) and KOH (25.3 g, 450 mmol, 4.00 equiv., ground with mortar and pestle) in toluene (225 mL). The mixture was heated to 140 °C for 1.5 h with azeotropic removal of water (Dean-Stark trap). The reaction mixture was allowed to cool to r.t. and H_2O (100 mL) and EA (200 mL) were added. The aqueous phase was extracted with EA (3x 100 mL), the combined organic layers washed with brine (50 mL) and dried over MgSO_4 . Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 20:1) yielded PMB ether **264** (27.6 g, 98.9 mmol, 88%) as a white solid.

$R_f = 0.22$ (CH/EA 20:1).

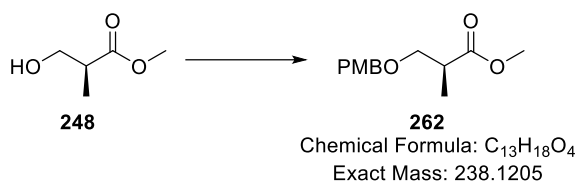
$^1\text{H NMR}$ (CDCl_3 , 400 MHz): $\delta = 7.93 - 7.85$ (m, 2H), 7.64 (ddd, 1H, $J=8.4, 7.0, 1.5$ Hz), 7.51 – 7.45 (m, 2H), 7.41 (ddd, 1H, $J=8.2, 6.9, 1.3$ Hz), 6.98 – 6.91 (m, 2H), 6.81 (q, 1H, $J=1.1$ Hz), 5.49 (s, 2H), 3.82 (s, 3H), 2.62 (d, 3H, $J=1.1$ Hz) ppm.

$^{13}\text{C NMR}$ (CDCl_3 , 126 MHz): $\delta = 161.9, 159.5, 146.9, 146.6, 130.2, 129.7, 129.3, 127.9, 125.6, 123.9, 123.8, 114.0, 113.3, 67.3, 55.4, 18.8$ ppm.

HRMS (EI (+), 70.0 eV): calculated for $[\text{M}]^+$: 279.1254; found: 279.1252.

The experimental data are in agreement with those previously published.^[200]

5.8.2 Methyl (S)-3-((4-methoxybenzyl)oxy)-2-methylpropanoate (262)



CSA (816 mg, 3.51 mmol, 0.10 equiv.) was added to a solution of 2-((4-methoxybenzyl)oxy)-4-methylquinoline (19.6 g, 70.3 mmol, 2.00 equiv.) and methyl (S)-3-hydroxy-2-methylpropanoate (**248**, 4.15 g, 35.1 mmol, 1.00 equiv.) in DCM (70 mL) and the reaction mixture was stirred for 72 h. The solvent was removed in vacuo and the residue was purified by flash column chromatography over silica gel (CH/EA 9:1) to yield PMB ether **262** (7.15 g, 30.0 mmol, 85%) as a colourless oil.

$R_f = 0.18$ (CH/EA 9:1).

$[\alpha]_D^{20} = +14.0$ (DCM, $c = 1.0$).

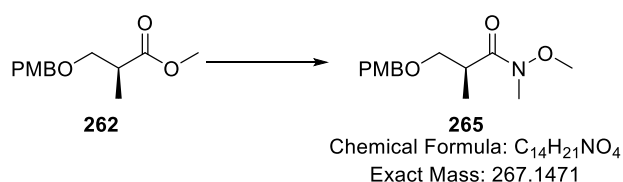
$^1\text{H NMR}$ (CDCl_3 , 400 MHz): $\delta = 7.26 - 7.20$ (m, 2H), 6.91 – 6.84 (m, 2H), 4.45 (d, 2H, $J=1.5$ Hz), 3.80 (s, 3H), 3.69 (s, 3H), 3.63 (dd, 1H, $J=9.2, 7.2$ Hz), 3.46 (dd, 1H, $J=9.2, 5.9$ Hz), 2.77 (pd, 1H, $J=7.1, 5.9$ Hz), 1.17 (d, 3H, $J=7.1$ Hz) ppm.

^{13}C NMR (CDCl_3 , 101 MHz): δ = 175.5, 159.3, 130.4, 129.3, 113.9, 72.9, 71.8, 55.4, 51.8, 40.3, 14.1 ppm.

HRMS (EI (+), 70.0 eV): calculated for $[\text{M}]^+$: 238.1200; found: 238.1200.

The experimental data are in agreement with those previously published.^[201]

5.8.3 (*S*)-*N*-Methoxy-3-((4-methoxybenzyl)oxy)-*N*,2-dimethylpropanamide (**265**)



Isopropylmagnesium chloride (2 M in THF, 38.4 mL, 76.8 mmol, 3.00 equiv.) was added over a period of 20 min to a solution of ester **262** (6.10 g, 25.6 mmol, 1.00 equiv.) and *N*-methoxymethylamine hydrochloride (3.87 g, 39.7 mmol, 1.55 equiv.) in THF (50 mL) at $-20\text{ }^{\circ}\text{C}$ and the solution was stirred for 40 min before it was allowed to warm to r.t. and stirred for an additional 2 h. Aq. sat. NH_4Cl (200 mL) and H_2O (100 mL) were added and the aqueous phase extracted with EA (3x 100 mL). The combined organic layers were dried over MgSO_4 and the solvent removed *in vacuo*. Purification of the residue by flash column chromatography over silica gel (CH/EA 2:1) yielded amide **265** (6.65 g, 24.9 mmol, 97%) as colourless oil.

R_f = 0.15 (CH/EA 2:1).

$[\alpha]_D^{20}$ = +5.0 (DCM, c = 1.0).

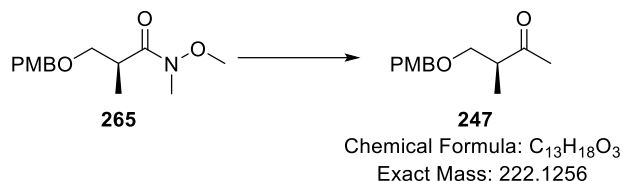
^1H NMR (CDCl_3 , 400 MHz): δ = 7.25 – 7.21 (m, 2H), 6.88 – 6.83 (m, 2H), 4.53 – 4.36 (m, 2H), 3.79 (s, 3H), 3.69 (s, 3H), 3.68 – 3.65 (m, 1H), 3.39 (dd, 1H, J =8.9, 5.9 Hz), 3.30 – 3.21 (m, 1H), 3.20 (s, 3H), 1.10 (d, 3H, J =6.9 Hz) ppm.

^{13}C NMR (CDCl_3 , 101 MHz): δ = 159.2, 130.6, 129.3, 113.8, 73.0, 72.5, 61.6, 55.4, 36.0, 14.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 268.1543; found: 268.1539.

The experimental data are in agreement with those previously published.^[202]

5.8.4 (S)-4-((4-Methoxybenzyl)oxy)-3-methylbutan-2-one (247)



Methylmagnesium chloride (3 M in THF, 24.7 mL, 74.1 mmol, 3.00 equiv.) was added over a period of 15 min to a solution of amide **265** (6.60 g, 24.7 mmol, 1.00 equiv.) in THF (120 mL) at 0 °C and the reaction mixture was stirred for 30 min before it was allowed to warm to r.t. and stirred for an additional 2 h. Aq. sat. NH₄Cl (150 mL) was added, the aqueous phase extracted with Et₂O (3x 100 mL) and the combined organic layers dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 6:1) yielded ketone **247** (4.88 g, 22.0 mmol, 89%) as a colourless oil.

R_f = 0.16 (CH/EA 6:1).

$[\alpha]_D^{20}$ = +66.0 (DCM, c = 0.5).

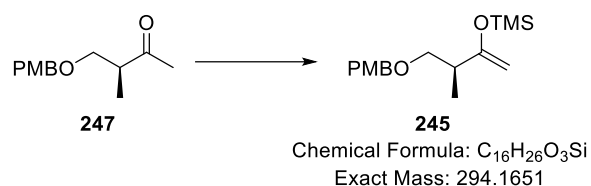
¹H NMR (CDCl₃, 400 MHz): δ = 7.27 – 7.18 (m, 2H), 6.90 – 6.85 (m, 2H), 4.42 (d, 2H, J =1.9 Hz), 3.80 (s, 3H), 3.59 (dd, 1H, J =9.2, 7.5 Hz), 3.45 (dd, 1H, J =9.2, 5.5 Hz), 2.83 (td, 1H, J =7.2, 5.4 Hz), 2.17 (s, 3H), 1.08 (d, 3H, J =7.1 Hz) ppm.

¹³C NMR (CDCl₃, 101 MHz): δ = 211.3, 159.4, 130.3, 129.4, 113.9, 73.0, 71.9, 55.4, 47.4, 29.2, 13.6 ppm.

HRMS (EI (+), 70.0 eV): calculated for [M]⁺: 222.1256; found: 222.1256.

The experimental data are in agreement with those previously published.^[202]

5.8.5 (S)-((4-((4-Methoxybenzyl)oxy)-3-methylbut-1-en-2-yl)oxy)trimethylsilane (**245**)



NEt₃ (8.04 mL, 58.0 mmol, 3.00 equiv.) was added to TMSCl (7.38 mL, 58.0 mmol, 3.00 equiv.) and the mixture was transferred after 5 min to a solution of ketone **247** (4.30 g, 19.3 mmol, 1.00 equiv.) in THF (65 mL) at –78 °C. LHMDs (1 M in THF, 32.9 mmol, 32.9 mmol, 1.70 equiv.) was added and the reaction mixture was stirred for 3 h before it was quenched by adding aq. sat. NaHCO₃ (100 mL). The aqueous phase was extracted with pentane (2x 100 mL), the combined organic layers were washed with aq. sat. CuSO₄ (2x 100 mL), brine (50 mL) and dried over NaSO₄. Removal of the solvent and impurities by using a short-path vacuum distillation (70 °C, 100 mbar) yielded silyl enol ether **245** (5.70 g, 19.3 mmol, quant.) as a colourless liquid.

$R_f = 0.55$ (CH/EA 6:1).

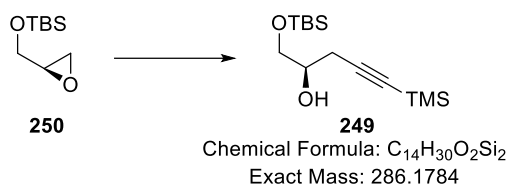
$[\alpha]_D^{20} = +1.0$ (DCM, $c = 1.0$).

¹H NMR (CD₂Cl₂, 700 MHz): δ = 7.26 – 7.22 (m, 2H), 6.89 – 6.84 (m, 2H), 4.40 (d, 2H, $J=1.1$ Hz), 4.08 (dd, 1H, $J=1.2, 0.5$ Hz), 4.04 (d, 1H, $J=1.2$ Hz), 3.79 (s, 3H), 3.50 (dd, 1H, $J=9.1, 6.6$ Hz), 3.27 (dd, 1H, $J=9.1, 6.8$ Hz), 2.40 (h, 1H, $J=6.8$ Hz), 1.03 (d, 3H, $J=6.9$ Hz), 0.19 (d, 9H, $J=7.5$ Hz) ppm.

¹³C NMR (CD₂Cl₂, 176 MHz): δ = 161.3, 159.5, 131.4, 129.5, 114.0, 89.5, 73.3, 72.9, 55.6, 41.1, 15.8, 5.5, 0.2 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 295.1724; found: 295.1728.

5.8.6 (R)-1-((*tert*-Butyldimethylsilyl)oxy)-5-(trimethylsilyl)pent-4-yn-2-ol (**249**)



t-Buli (1.7 M in pentane, 20.8 mL, 35.3 mmol, 1.40 equiv.) was added over a period of 5 min to a stirring solution of ethynyltrimethylsilane (4.54 mL, 32.8 mmol, 1.30 equiv.) in THF (50 mL) at -78°C . The reaction mixture was stirred for 30 min before epoxide **250** (95%, 5.00 g, 25.2 mmol, 1.00 equiv.) and boron trifluoride etherate (6.55 mL, 32.8 mmol, 1.30 equiv.) were added, the latter over a period of 15 min. The reaction mixture was allowed to warm to r.t. and stirred for an additional 3 h. pH 7 Buffer (100 mL) was added and the aqueous phase extracted with EA (3x 50 mL). The organic layers were combined and washed with brine (20 mL), dried over MgSO₄ and the solvent was removed under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 15:1) yielded alcohol **249** (6.59 g, 23.0 mmol, 91%) as a colourless oil.

$R_f = 0.21$ (CH/EA 15:1).

$[\alpha]_D^{20} = -13.0$ (DCM, $c = 1.0$).

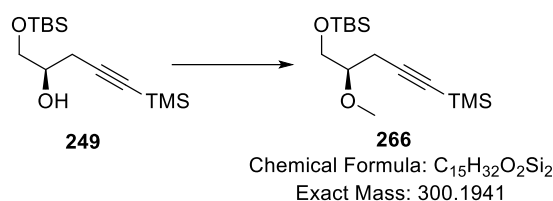
¹H NMR (CDCl₃, 700 MHz): $\delta = 3.79$ (dtd, 1H, $J=7.1, 5.7, 4.3$ Hz), 3.72 (dd, 1H, $J=10.0, 4.2$ Hz), 3.64 (dd, 1H, $J=10.0, 5.7$ Hz), 2.51 – 2.40 (m, 3H), 0.91 (s, 10H), 0.15 (s, 9H), 0.09 (d, 6H, $J=0.9$ Hz) ppm.

¹³C NMR (CDCl₃, 176 MHz): $\delta = 103.0, 87.2, 70.3, 65.6, 26.0, 24.7, 18.5, 0.2, -5.2, -5.3$ ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 309.1677; found: 309.1674.

The experimental data are in agreement with those previously published.^[203]

5.8.7 (R)-tert-Butyl((2-methoxy-5-(trimethylsilyl)pent-4-yn-1-yl)oxy)dimethylsilane (**266**)



Proton-sponge[®] (17.8 g, 83.8 mmol, 4.00 equiv.) was added to a solution of alcohol **249** (6.00 g, 20.9 mmol, 1.00 equiv.) in DCM (40 mL) at 0 °C. After 30 min of stirring, trimethyloxonium tetrafluoroborate (9.29 g, 62.8 mmol, 3.00 equiv.) was added. The reaction was allowed to warm to r.t. and stirred overnight (16 h). Aq. HCl (1 M, 100 mL) was added and the aqueous phase was extracted with DCM (3x 50 mL), the combined organic layers were washed with brine (50 mL) and dried over MgSO₄. Celite[®] (100 g) was added before the mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography over silica gel (Pentane/Et₂O 20:1) yielded volatile methyl ether **266** (6.07 g, 20.2 mmol, 96%) as a colourless oil.

$R_f = 0.29$ (Pentane/Et₂O 20:1).

$[\alpha]_D^{20} = -10.0$ (DCM, c = 1.0).

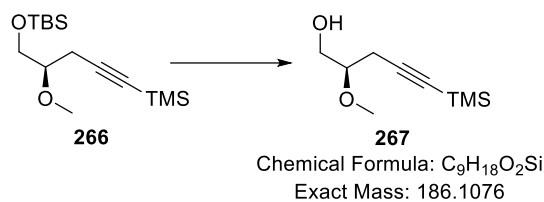
¹H NMR (CD₂Cl₂, 499 MHz): δ = 3.69 (qd, 2H, $J=10.6, 5.0$ Hz), 3.40 (s, 3H), 3.34 (dq, 1H, $J=6.3, 5.1$ Hz), 2.49 – 2.38 (m, 2H), 0.90 (s, 9H), 0.13 (s, 9H), 0.07 (s, 6H) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 104.2, 86.2, 80.7, 64.1, 58.0, 26.1, 22.2, 18.6 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+Na]⁺ : 323.1833; found: 323.1825.

The experimental data are in agreement with those previously published.^[203]

5.8.8 (*R*)-2-Methoxy-5-(trimethylsilyl)pent-4-yn-1-ol (**267**)



Aq. HCl (3 M, 2.00 mL, 5.99 mmol, 0.30 equiv.) was added to a solution of silyl ether **266** (6.00 g, 20.0 mmol, 1.00 equiv.) in methanol (40 mL) and the reaction was stirred for 45 min at r.t. Aq. sat. NaHCO₃ (15 mL) was added, the aqueous phase extracted with Et₂O (3x 30 mL). The combined organic layers were washed with brine (10 mL) and dried over MgSO₄. Removal of the solvent under reduced pressure (130 mbar, 40 °C) and purification of the residue by flash column chromatography over silica gel (Pentane/Et₂O 2:1) yielded primary alcohol **267** (3.35 g, 18.0 mmol, 90%) as a colourless liquid.

R_f = 0.31 (Pentane/Et₂O 2:1).

$[\alpha]_D^{20}$ = -46.0 (DCM, c = 1.0).

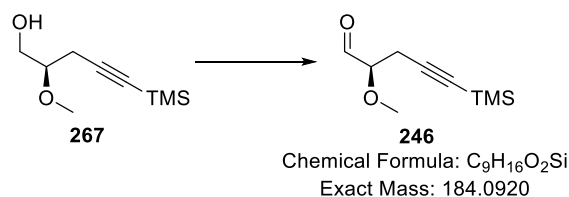
¹H NMR (CD₂Cl₂, 500 MHz): δ = 3.73 (ddd, 1H, J =11.6, 7.0, 3.6 Hz), 3.57 (dt, 1H, J =11.6, 5.8 Hz), 3.42 (s, 3H), 3.42 – 3.38 (m, 1H), 2.51 (dd, 1H, J =17.0, 5.2 Hz), 2.38 (dd, 1H, J =17.0, 7.5 Hz), 1.89 (dd, 1H, J =7.0, 5.8 Hz), 0.14 (s, 9H) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 103.4, 86.9, 80.4, 63.9, 57.8, 21.8, 0.1 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+Na]⁺: 209.0968; found: 209.0969.

The experimental data are in agreement with those previously published.^[203]

5.8.9 (*R*)-2-Methoxy-5-(trimethylsilyl)pent-4-ynal (**246**)



H₂O (11.2 μ L, 644 μ mol, 1.20 equiv.) was added to a mixture of alcohol **267** (100 mg, 537 μ mol, 1.00 equiv.), pyridine (130 μ L, 1.61 mmol, 3.00 equiv.) and DMP (455 mg, 1.07 mmol, 2.00 equiv.) in DCM (2 mL) at 0 °C. The reaction was stirred for 3 h before it was allowed to warm to r.t. and stirred for an additional 3 h. Aq. sat. NaHCO₃ (5 mL) and aq. sat. Na₂S₂O₃ (5 mL) were added to the solution and the aqueous phase was extracted with DCM (2x 5 mL). The combined organic layers were washed with aq. sat. CuSO₄ (2x 4 mL), aq. sat. NaHCO₃ (1x 4 mL), brine (1x 3 mL) and dried over NaSO₄ before the solvent was removed under reduced pressure (40 °C, 900 mbar). Purification of the residue by flash column chromatography over silica gel (Pentane/Et₂O 3:1) yielded volatile aldehyde **246** (after accounting for Et₂O as impurity, 69.9 mg, 379 μ mol, 71%) as a colourless liquid.

R_f = 0.14 (Pentane/Et₂O 3:1).

$[\alpha]_D^{20}$ = +3.0 (DCM, c = 1.0).

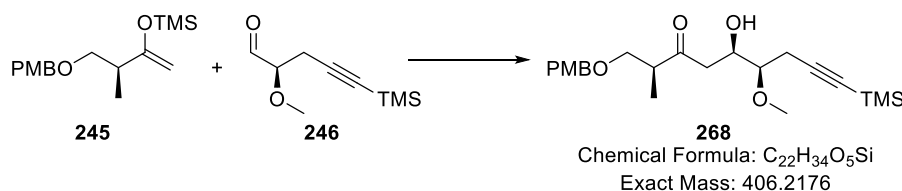
¹H NMR (CD₂Cl₂, 500 MHz): δ = 9.67 (d, 1H, J =1.4 Hz), 3.71 (ddd, 1H, J =6.5, 6.0, 1.4 Hz), 3.50 (s, 3H), 2.61 (qd, 2H, J =17.2, 6.2 Hz), 0.14 (s, 9H) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 201.8, 101.5, 87.8, 83.7, 58.9, 21.8, -0.0 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 185.0992; found: 185.0993.

The experimental data are in agreement with those previously published.^[203]

5.8.10 (2*S*,5*R*,6*R*)-5-Hydroxy-6-methoxy-1-((4-methoxybenzyl)oxy)-2-methyl-9-(trimethylsilyl)non-8-yn-3-one (**268**)



Silyl enol ether **245** (5.40 g, 18.3 mmol, 3.00 equiv.) was added to a mixture of aldehyde **246** (1.13 g, 6.11 mmol, 1.00 equiv.) and magnesium bromide ethyl etherate (4.74 g, 18.3 mmol, 3.00 equiv.) in DCM (15 mL) at -78 °C and the reaction was stirred for 3 h before Et₂O (20 mL) and aq. sat. NaHCO₃ (40 mL) were added. Subsequently, the reaction mixture

was allowed to warm to r.t. and stirred for 1 h. The aqueous phase was extracted with Et₂O (3x 50 mL), the combined organic layers were washed with aq. sat. NH₄Cl (20 mL) and dried over NaSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 6:1 → 3:1) yielded coupling product **268** (2.29 g, 5.64 mmol, 92%) as a colourless oil and recovered methyl ketone **247** (2.68g, 12.1 mmol, 66% of starting material).

$R_f = 0.13$ (CH/EA 3:1).

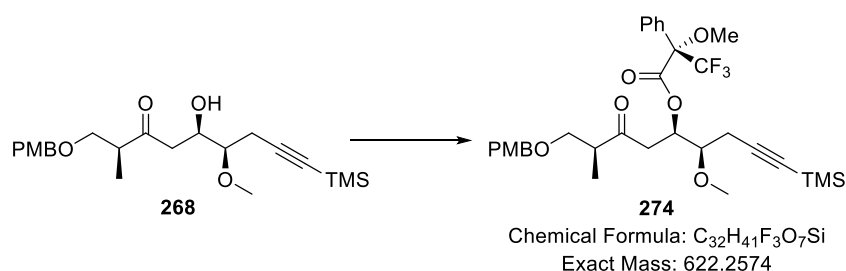
$[\alpha]_D^{20} = +14.0$ (DCM, $c = 1.0$).

¹H NMR (CD₂Cl₂, 700 MHz): δ = 7.22 (td, 2H, $J=5.3, 2.0$ Hz), 6.88 – 6.82 (m, 2H), 4.45 – 4.34 (m, 2H), 4.17 (ddt, 1H, $J=7.6, 5.4, 3.8$ Hz), 3.79 (d, 3H, $J=1.5$ Hz), 3.63 – 3.54 (m, 1H), 3.51 – 3.44 (m, 1H), 3.41 (d, 3H, $J=1.4$ Hz), 3.29 – 3.18 (m, 1H), 2.93 – 2.83 (m, 1H), 2.78 – 2.74 (m, 1H), 2.74 – 2.60 (m, 2H), 2.54 – 2.41 (m, 2H), 1.05 (dd, 3H, $J=8.1, 3.2$ Hz), 0.20 – 0.09 (m, 9H) ppm.

¹³C NMR (CD₂Cl₂, 176 MHz): δ = 213.1, 159.7, 130.6, 129.7, 114.1, 104.3, 86.7, 82.0, 73.3, 72.3, 68.7, 58.8, 55.6, 47.3, 45.3, 21.4, 13.4, 0.1 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 407.2248; found: 407.2248.

5.8.11 (4*R*,5*R*,8*S*)-4-Methoxy-9-((4-methoxybenzyl)oxy)-8-methyl-7-oxo-1-(trimethylsilyl)non-1-yn-5-yl (S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**274**)



(*R*)-(-)-MTPA-Cl (18 μ L, 98 μ mol, 4.0 equiv.) was added to a solution of alcohol **268** (10 mg, 25 μ mol, 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO₃ (1 mL) was added, the aqueous phase was extracted with EA (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO₄. The residue was purified by flash column

chromatography over silica gel (CH/EA 6:1) to yield ester **274** (10 mg, 16 μ mol, 65%) as a colourless oil.

R_f = 0.20 (CH/EA 6:1).

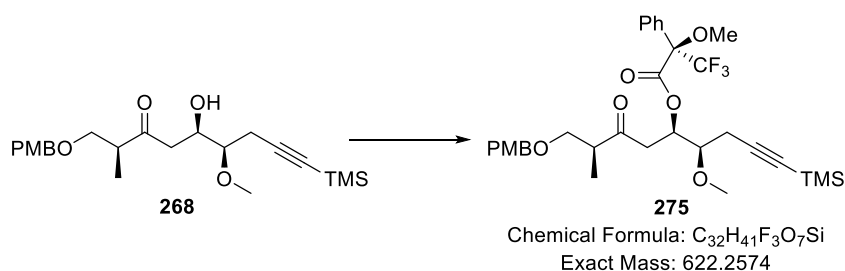
$[\alpha]_D^{20}$ = -41.0 (DCM, c = 1.0).

^1H NMR (CD_2Cl_2 , 700 MHz): δ = 7.52 – 7.48 (m, 2H), 7.43 – 7.38 (m, 3H), 7.23 – 7.18 (m, 2H), 6.87 – 6.83 (m, 2H), 5.69 (ddd, 1H, J =7.4, 5.3, 3.9 Hz), 4.39 (s, 2H), 3.78 (s, 3H), 3.57 – 3.52 (m, 2H), 3.50 (d, 3H, J =1.2 Hz), 3.46 (dd, 1H, J =9.2, 5.1 Hz), 3.33 (s, 3H), 3.03 (dd, 1H, J =18.0, 5.2 Hz), 2.86 – 2.79 (m, 2H), 2.26 (dd, 1H, J =17.0, 7.0 Hz), 2.04 (dd, 1H, J =17.0, 5.9 Hz), 1.03 (d, 3H, J =7.0 Hz), 0.16 (s, 9H) ppm.

^{13}C NMR (CD_2Cl_2 , 176 MHz): δ = 209.5, 165.9, 159.7, 132.8, 130.6, 130.0, 129.7, 128.8, 127.7, 114.1, 103.2, 87.4, 78.9, 73.3, 72.1, 72.1, 59.0, 56.0, 55.6, 47.3, 41.3, 21.2, 13.3, 0.0 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{Na}]^+$: 645.2466; found: 645.2463.

5.8.12 (4*R*,5*R*,8*S*)-4-Methoxy-9-((4-methoxybenzyl)oxy)-8-methyl-7-oxo-1-(trimethylsilyl)non-1-yn-5-yl (R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (**275**)



(*S*)-(+)-MTPA-Cl (17 μ L, 89 μ mol, 4.0 equiv.) was added to a solution of alcohol **268** (9 mg, 22 μ mol, 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO_3 (1 mL) was added, the aqueous phase was extracted with EA (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO_4 . The residue was purified by flash column chromatography over silica gel (CH/EA 6:1) to yield ester **275** (9 mg, 14 μ mol, 65%) as a colourless oil.

R_f = 0.24 (CH/EA 6:1).

$[\alpha]_D^{20} = +6.0$ (DCM, $c = 1.0$).

$^1\text{H NMR}$ (CD_2Cl_2 , 499 MHz): $\delta = 7.53 - 7.48$ (m, 2H), 7.41 (tdd, 3H, $J=3.2, 2.1, 1.2$ Hz), 7.24 – 7.18 (m, 2H), 6.90 – 6.84 (m, 2H), 5.71 (ddd, 1H, $J=7.2, 5.5, 4.2$ Hz), 4.43 – 4.33 (m, 2H), 3.78 (s, 3H), 3.59 (td, 1H, $J=6.4, 4.2$ Hz), 3.53 – 3.51 (m, 4H), 3.41 (dd, 1H, $J=9.2, 5.2$ Hz), 3.36 (s, 3H), 2.93 (dd, 1H, $J=17.9, 5.5$ Hz), 2.81 (dd, 1H, $J=18.0, 7.2$ Hz), 2.78 – 2.69 (m, 1H), 2.47 (dd, 1H, $J=17.1, 6.6$ Hz), 2.37 (dd, 1H, $J=17.1, 6.2$ Hz), 0.96 (d, 3H, $J=7.0$ Hz), 0.15 (s, 9H) ppm.

$^{13}\text{C NMR}$ (CD_2Cl_2 , 126 MHz): $\delta = 209.1, 166.0, 159.7, 132.6, 130.6, 130.0, 129.7, 128.8, 127.9, 114.1, 102.9, 87.7, 79.2, 73.3, 72.5, 72.0, 58.8, 55.8, 55.6, 47.2, 41.6, 21.6, 13.2, -0.0$ ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{Na}]^+$: 645.2466; found: 645.2463.

5.8.13 (2*S*,3*S*,5*R*,6*R*)-6-Methoxy-1-((4-methoxybenzyl)oxy)-2-methyl-9-(trimethylsilyl)non-8-yne-3,5-diol (**276**)



Diethyl(methoxy)borane (1 M in THF, 10.8 mL, 10.8 mmol, 2.00 equiv.) was added to a solution of alcohol **268** (2.20 g, 5.41 mmol, 1.00 equiv.) in THF/MeOH (4:1, 50 mL) at -78°C . The reaction was stirred for 15 min before NaBH_4 (225 mg, 5.95 mmol, 1.10 equiv.) was added. After 3 h of stirring, acetic acid (6 mL) and EA (30 mL) were added before the mixture was washed with NaHCO_3 (20 mL). The aqueous phase was extracted with EA (3x 20 mL), the combined organic layers dried over MgSO_4 and the solvent removed *in vacuo*. The residue was azeotroped three times with methanol until hydrolysis of boronate was complete. The residue was then purified by flash column chromatography over silica gel (CH/EA 2:1) to yield diol **276** (2.07 g, 5.06 mmol, 93%) as a colourless oil.

$R_f = 0.21$ (CH/EA 2:1).

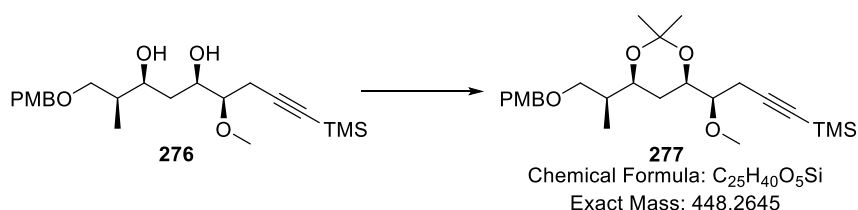
$[\alpha]_D^{20} = -10.0$ (DCM, $c = 0.5$).

¹H NMR (CD₂Cl₂, 500 MHz): δ = 7.27 – 7.22 (m, 2H), 6.91 – 6.85 (m, 2H), 4.45 – 4.38 (m, 2H), 4.01 – 3.94 (m, 1H), 3.89 (dtd, 1H, J =8.2, 4.7, 3.3 Hz), 3.79 (s, 3H), 3.53 – 3.46 (m, 2H), 3.45 (s, 3H), 3.40 (d, 1H, J =3.1 Hz), 3.29 (d, 1H, J =3.2 Hz), 3.21 (td, 1H, J =5.8, 4.7 Hz), 2.52 (dd, 1H, J =17.2, 5.6 Hz), 2.41 (dd, 1H, J =17.2, 5.9 Hz), 1.87 (pdd, 1H, J =7.0, 5.1, 2.9 Hz), 1.59 – 1.56 (m, 2H), 0.92 (d, 3H, J =7.0 Hz), 0.14 (s, 9H) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 159.8, 130.9, 129.7, 114.2, 104.4, 86.6, 82.9, 74.5, 74.2, 73.7, 73.4, 58.8, 55.6, 39.1, 36.1, 21.3, 11.5, 0.1 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 409.2405; found: 409.2401.

5.8.14 ((*R*)-4-Methoxy-4-((4*R*,6*S*)-6-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)but-1-yn-1-yl)trimethylsilane (**277**)



2-Methoxypropen (4.7 μ L, 49 μ mol, 2.0 equiv.) was added to a solution of alcohol **276** (10 mg, 24 μ mol, 1.00 equiv.) and PPTS (0.6 mg, 2.5 μ mol, 0.1 equiv.) in DCM (1 mL). The reaction was stirred overnight (14 h) before H₂O (1 mL) was added. The aqueous phase was extracted with DCM (3x 1 mL) and the combined organic layers were dried over MgSO₄. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 9:1) yielded acetonide **277** (7.2 mg, 16 μ mol, 66%) as a colourless oil.

R_f = 0.25 (CH/EA 9:1).

$[\alpha]_D^{20}$ = –14.0 (DCM, c = 1.0).

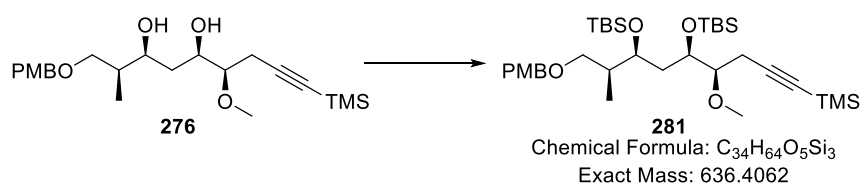
¹H NMR (CD₂Cl₂, 400 MHz): δ = 7.28 – 7.21 (m, 2H), 6.90 – 6.83 (m, 2H), 4.39 (d, 2H, J =1.8 Hz), 4.05 (ddd, 1H, J =11.7, 3.9, 2.5 Hz), 3.89 (ddd, 1H, J =11.7, 5.1, 2.5 Hz), 3.79 (s, 3H), 3.46 – 3.42 (m, 1H), 3.40 (s, 3H), 3.31 (dd, 1H, J =9.1, 5.9 Hz), 3.21 (td, 1H, J =6.4, 3.9 Hz), 2.54 – 2.37 (m,

2H), 1.81 – 1.68 (m, 1H), 1.51 – 1.41 (m, 1H), 1.41 – 1.38 (m, 3H), 1.32 (d, 3H, $J=0.8$ Hz), 1.28 (dt, 1H, $J=12.6$, 2.5 Hz), 0.94 (d, 3H, $J=6.9$ Hz), 0.14 (s, 9H) ppm.

^{13}C NMR (CD_2Cl_2 , 101 MHz): δ = 159.5, 131.3, 129.6, 114.0, 104.6, 99.0, 86.2, 82.1, 73.0, 72.2, 70.1, 70.1, 58.9, 55.6, 39.1, 30.2, 29.8, 21.0, 19.7, 12.5, 0.1 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{Na}]^+$: 471.2537; found: 471.2527.

5.8.15 (5*R*,7*S*)-5-((*R*)-1-Methoxy-4-(trimethylsilyl)but-3-yn-1-yl)-7-((*S*)-1-((4-methoxybenzyl)oxy)propan-2-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (**281**)



N,N-Dimethylpyridin-4-amine (26.4 mg, 216 μmol , 0.05 equiv.) was added to a stirring solution of alcohol **276** (1.76 g, 4.31 mmol, 1.00 equiv.), TBSCl (1.95 g, 12.9 mmol, 3.00 equiv.) and imidazole (1.17 g, 17.3 mmol, 4.00 equiv.) in DMF/DCM (1:1, 16 mL). The reaction was stirred overnight (14 h) at r.t. before it was quenched by adding aq. sat. NH_4Cl (20 mL). The aqueous phase was extracted with DCM (3x 20 mL) and the combined organic layers were dried over MgSO_4 . Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 30:1) yielded silyl ether **281** (2.71 g, 4.26 mmol, 99%) as a colourless oil.

R_f = 0.18 (CH/EA 30:1).

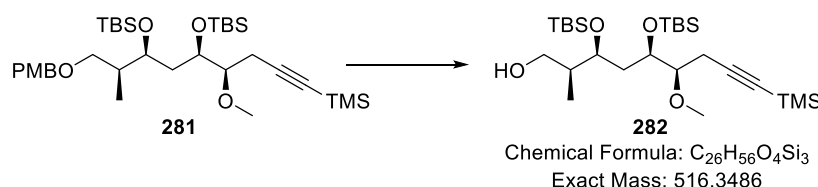
$[\alpha]_D^{20}$ = -2.0 (DCM, c = 1.0).

^1H NMR (CD_2Cl_2 , 500 MHz): δ = 7.26 – 7.22 (m, 2H), 6.87 – 6.83 (m, 2H), 4.44 – 4.33 (m, 2H), 3.94 (ddd, 1H, $J=8.0$, 5.6, 2.3 Hz), 3.86 – 3.81 (m, 1H), 3.79 (s, 3H), 3.45 (dd, 1H, $J=8.8$, 6.4 Hz), 3.41 (s, 2H), 3.31 – 3.24 (m, 2H), 2.56 (dd, 1H, $J=17.1$, 4.6 Hz), 2.34 (dd, 1H, $J=17.1$, 7.1 Hz), 1.93 – 1.81 (m, 2H), 1.38 (ddd, 1H, $J=13.8$, 8.1, 5.6 Hz), 0.88 (d, 18H, $J=0.9$ Hz), 0.14 (s, 9H), 0.06 (t, 12H, $J=14.2$ Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): δ = 159.6, 131.6, 129.6, 114.0, 105.5, 85.9, 82.7, 73.3, 73.1, 70.0, 69.7, 58.6, 55.6, 38.0, 37.0, 26.2, 20.7, 18.4, 10.8, 0.2, -3.7, -4.2, -4.2, -4.5 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 637.4134; found: 637.4138.

5.8.16 (2*S*,3*S*,5*R*,6*R*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-6-methoxy-2-methyl-9-(trimethylsilyl)non-8-yn-1-ol (**282**)



Magnesium bromide ethyl etherate (17.3 g, 67.1 mmol, 15.0 equiv.) was added to a solution of PMB ether **281** (2.85 g, 4.47 mmol, 1.00 equiv.) and DMS (16.4 mL, 224 mmol, 50.0 equiv.) in DCM (50 mL). The reaction vessel was sealed and stirred for 96 h. H_2O (50 mL) was added and the aqueous phase extracted with DCM (3x 50 mL). The organic layers were combined and dried over MgSO_4 . Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 9:1) yielded primary alcohol **282** (1.77 g, 3.42 mmol, 77%, 97% brsm) as a colourless oil.

R_f = 0.08 (CH/EA 9:1).

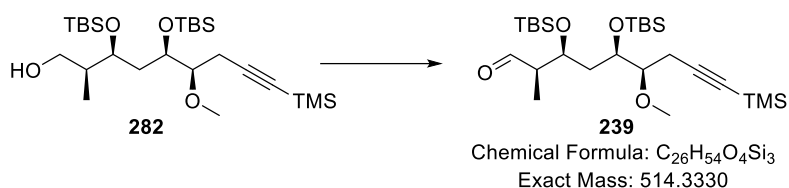
$[\alpha]_D^{20}$ = -3.0 (DCM, c = 1.0).

^1H NMR (CD_2Cl_2 , 500 MHz): δ = 3.96 – 3.92 (m, 1H), 3.90 (ddd, 1H, J =7.1, 5.9, 4.0 Hz), 3.65 (ddd, 1H, J =10.4, 7.4, 4.3 Hz), 3.50 (dt, 1H, J =10.8, 5.7 Hz), 3.41 (s, 3H), 3.30 (ddd, 1H, J =6.7, 5.3, 4.0 Hz), 2.57 (dd, 1H, J =17.0, 5.3 Hz), 2.40 (dd, 1H, J =17.0, 6.7 Hz), 2.01 (t, 1H, J =5.2 Hz), 1.95 – 1.83 (m, 2H), 1.50 (dt, 1H, J =13.8, 6.9 Hz), 0.91 (s, 9H), 0.90 (s, 9H), 0.85 (d, 3H, J =6.9 Hz), 0.14 (s, 9H), 0.11 (d, 6H, J =5.3 Hz), 0.10 (d, 6H, J =1.5 Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): δ = 105.2, 86.2, 82.2, 71.9, 70.2, 66.2, 58.5, 39.9, 36.3, 26.2, 26.2, 20.7, 18.4, 18.3, 11.3, 0.2, -3.7, -4.1, -4.2, -4.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 517.3559; found: 517.3552.

5.8.17 (2*R*,3*S*,5*R*,6*R*)-3,5-Bis((*tert*-butyldimethylsilyl)oxy)-6-methoxy-2-methyl-9-(trimethylsilyl)non-8-ynal (**239**)



DIPEA (215 μ L, 1.20 mmol, 4.00 equiv.) was added to a solution of alcohol **282** (155 mg, 300 μ mol, 1.00 equiv.) in DCM (2 mL) and DMSO (213 μ L, 3.00 mmol, 10.0 equiv.) at 0 °C. After stirring for 5 min, sulfur trioxide pyridine complex (286 mg, 1.80 mmol, 6.00 equiv.) was added and the reaction was stirred for 1 h. The solvent was removed under reduced pressure and the residue purified by flash column chromatography over silica gel (CH/Ea 30:1) to yield aldehyde **239** (135 mg, 262 μ mol, 87%) as a colourless oil.

R_f = 0.21 (CH/Ea 30:1).

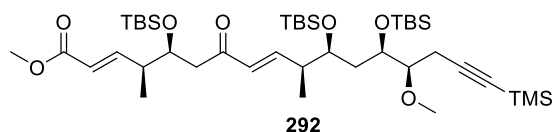
$[\alpha]_D^{20}$ = -31.0 (DCM, c = 1.0).

¹H NMR (CDCl₃, 500 MHz): δ = 9.75 (d, 1H, J =0.8 Hz), 4.37 (ddd, 1H, J =8.3, 5.6, 2.8 Hz), 3.81 (dt, 1H, J =8.6, 4.4 Hz), 3.44 (s, 3H), 3.30 (dt, 1H, J =6.8, 4.6 Hz), 2.61 (dd, 1H, J =17.2, 4.6 Hz), 2.45 (dtd, 1H, J =7.7, 6.5, 2.7 Hz), 2.37 (dd, 1H, J =17.2, 6.8 Hz), 1.92 (ddd, 1H, J =13.8, 8.1, 4.4 Hz), 1.52 – 1.48 (m, 1H), 1.09 (d, 3H, J =7.0 Hz), 0.91 (s, 9H), 0.85 (s, 9H), 0.14 (s, 9H), 0.10 (d, 6H, J =11.7 Hz), 0.06 (d, 6H, J =23.3 Hz) ppm.

¹³C NMR (CDCl₃, 126 MHz): δ = 205.0, 104.5, 86.3, 82.3, 69.9, 68.8, 58.5, 50.6, 37.0, 26.1, 25.9, 20.4, 18.3, 18.1, 7.1, 0.2, -3.7, -4.1, -4.3, -4.5 ppm.

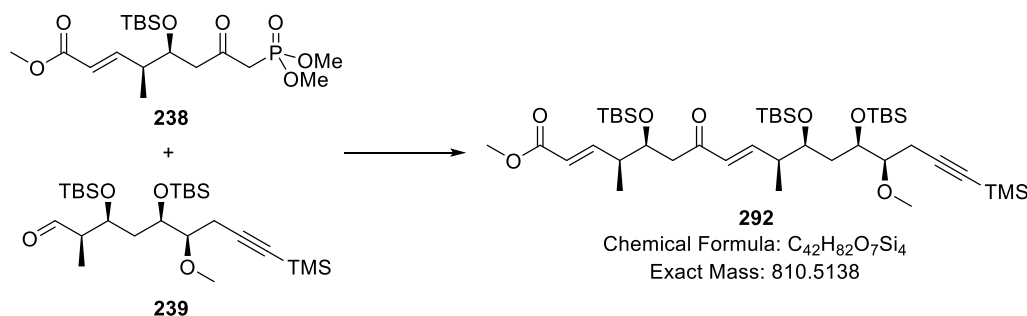
HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 515.3403; found: 515.3399.

5.9 Experimental Details for Chapter 3.6.3: HWE and Grubbs Coupling to olefin **292**



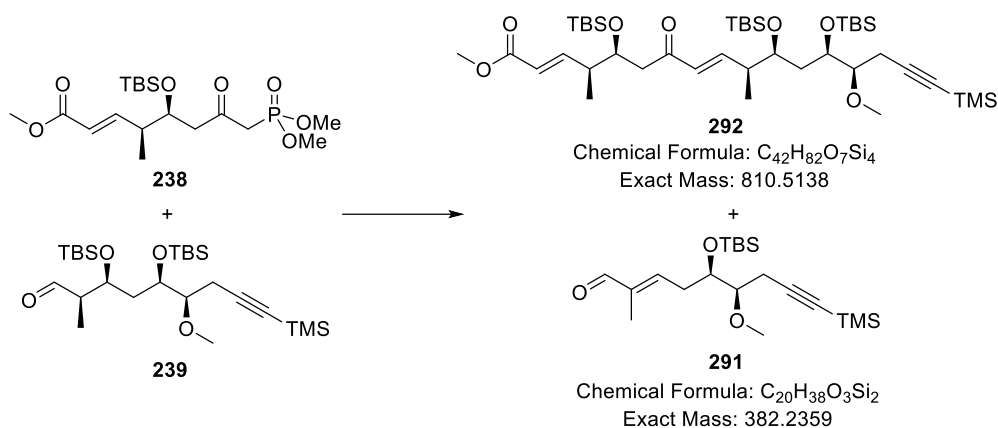
5.9.1 Methyl (2*E*,4*S*,5*S*,8*E*,10*S*,11*S*,13*R*,14*R*)-5,11,13-tris((*tert*-butyldimethylsilyl)oxy)-14-methoxy-4,10-dimethyl-7-oxo-17-(trimethylsilyl)heptadeca-2,8-dien-16-ynoate (**292**)

Procedure a:



NaHMDS (41.2 μ L, 41.2 μ mol, 1.10 equiv.) was added to a solution of phosphonate **238** (19.0 mg, 45.0 μ mol, 1.20 equiv., dried with 3x Freeze-Pump-Thaw cycles) in THF (1.5 mL) at -78 $^{\circ}$ C and the reaction was stirred for 20 min. Aldehyde **239** (19.3 mg, 37.5 μ mol, 1.00 equiv.) was added and the reaction was allowed to warm to 0 $^{\circ}$ C overnight (13 h). Aq. sat. NH₄Cl (2 mL) was added and the aqueous phase was extracted with EA (3x 5 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. Purification of the residue by flash column chromatography over silica gel (CH/EA 20:1) yielded title compound **292** (6.3 mg, 7.8 μ mol, 18%, and 3% of **291** as impurity) as a colourless oil.

Procedure b:



Ba(OH)₂ (11.1 mg, 65.1 μmol, 1.10 equiv.) was added to a solution of phosphonate **238** (30.0 mg, 71.0 μmol, 1.20 equiv.) in THF (1 mL) at r.t. and the reaction was stirred for 1 h. Aldehyde **239** (30.5 mg, 59.2 μmol, 1.00 equiv.) was added to the suspension together with THF/H₂O (40:1, 0.6 mL) and the reaction was warmed to 40 °C and stirred overnight (21 h). Aq. sat. NH₄Cl (2 mL) was added and the aqueous phase was extracted with EA (3x 5 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. Purification of the residue by flash column chromatography over silica gel (CH/EA 20:1) and HPLC (H₂O/MeOH 15:85 → 100% MeOH, KNAUER Eurospher II 100-5 C8; 5 μm, flow: 16 mL/min, pressure 194-117 bar, retention time 25 min) yielded title compound **292** (5.7 mg, 7.0 μmol, 12%) and elimination product **291** (14.6 mg, 38.2 μmol, 65%, partially decomposed while HPLC separation) both as a colourless oil.

Analytical data of **292**:

R_f = 0.21 (CH/EA 20:1).

$[\alpha]_D^{20}$ = -56.0 (DCM, c = 1.0).

¹H NMR (CDCl₃, 700 MHz): δ = 7.05 (dd, 1H, J =15.9, 6.8 Hz), 6.91 (dd, 1H, J =16.2, 6.8 Hz), 6.05 (dd, 1H, J =16.2, 1.4 Hz), 5.82 (dd, 1H, J =15.9, 1.5 Hz), 4.32 (dt, 1H, J =7.4, 4.3 Hz), 3.87 (ddd, 1H, J =7.1, 5.8, 4.1 Hz), 3.83 (td, 1H, J =6.5, 3.1 Hz), 3.73 (s, 3H), 3.43 (s, 3H), 3.29 (ddd, 1H, J =6.7, 5.3, 4.0 Hz), 2.71 (dd, 1H, J =16.1, 7.4 Hz), 2.58 (dd, 1H, J =17.0, 5.3 Hz), 2.54 – 2.46 (m, 3H), 2.40 (dd, 1H, J =17.0, 6.6 Hz), 1.86 (dt, 1H, J =13.9, 6.1 Hz), 1.39 (dt, 1H, J =13.8, 6.9 Hz),

1.02 (dd, 6H, $J=6.8, 1.1$ Hz), 0.88 (d, 18H, $J=3.7$ Hz), 0.84 (s, 9H), 0.14 (s, 9H), 0.08 (d, 6H, $J=20.0$ Hz), 0.05 (d, 6H, $J=0.9$ Hz), -0.00 (d, 6H, $J=43.7$ Hz) ppm.

^{13}C NMR (CDCl_3 , 176 MHz): δ = 198.7, 167.1, 151.4, 150.7, 130.9, 121.1, 104.6, 86.2, 81.8, 71.7, 71.5, 69.8, 58.5, 51.6, 43.9, 42.3, 41.3, 36.6, 26.1, 26.0, 26.0, 20.4, 18.2, 18.2, 18.1, 13.7, 12.9, 0.2, -3.8, -4.2, -4.3, -4.4, -4.6 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{NH}_4]^+$: 828.5476; found: 828.5460.

Analytical data of **291**:

R_f = 0.21 (CH/EA 20:1).

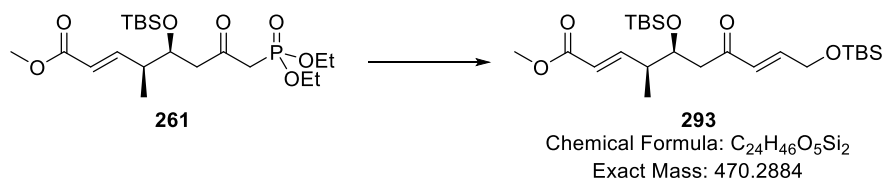
$[\alpha]_D^{20}$ = +6.0 (DCM, c = 1.0).

^1H NMR (CDCl_3 , 700 MHz): δ = 9.42 (s, 1H), 6.57 (tq, 1H, $J=7.5, 1.4$ Hz), 4.01 (ddd, 1H, $J=6.8, 5.6, 4.1$ Hz), 3.42 (d, 3H, $J=5.6$ Hz), 3.25 (td, 1H, $J=6.1, 4.1$ Hz), 2.73 – 2.67 (m, 1H), 2.56 (ddd, 1H, $J=17.0, 5.7, 2.1$ Hz), 2.51 – 2.45 (m, 1H), 2.45 – 2.38 (m, 1H), 1.76 (q, 2H, $J=1.0$ Hz), 0.89 (d, 8H, $J=1.5$ Hz), 0.14 (s, 9H), 0.12 – 0.05 (m, 6H) ppm.

^{13}C NMR (CDCl_3 , 176 MHz): δ = 195.3, 151.2, 140.6, 104.1, 86.7, 82.4, 71.8, 58.6, 32.8, 26.0, 20.6, 18.2, 9.6, 0.1, -4.4, -4.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 383.2432; found: 383.2429.

5.9.2 Methyl (2*E*,4*S*,5*S*,8*E*)-5,10-bis((*tert*-butyldimethylsilyl)oxy)-4-methyl-7-oxodeca-2,8-dienoate (**293**)



NaHMDS (1 M in THF, 6.7 μL , 6.7 μmol , 1.1 equiv.) was added to a solution of phosphonate **261** (3.0 mg, 6.7 μmol , 1.1 equiv., dried with 3x Freeze-Pump-Thaw cycles) in THF (1 mL) and 3 Å ground molecular sieve at -78°C and the reaction was stirred for 15 min. 2-((*Tert*-butyldimethylsilyl)oxy)acetaldehyde (1.1 mg, 6.1 μmol , 1.0 equiv.) was added and the reaction was allowed to warm to r.t. and stir for 2 h. Aq. sat. NH_4Cl (2 mL) was added and the

aqueous phase was extracted with EA (3x 5 mL). The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. Purification of the residue by flash column chromatography over silica gel (CH/EA 15:1) yielded silyl ether **293** (1.5 mg, 3.2 μmol , 53%, *dr* >20:1) as a colourless oil.

$R_f = 0.23$ (CH/EA 15:1).

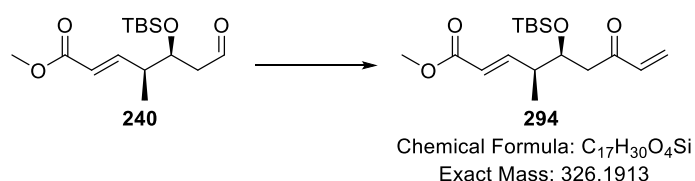
$[\alpha]_D^{20} = -90.0$ (DCM, $c = 0.2$).

$^1\text{H NMR}$ (CDCl_3 , 400 MHz): $\delta = 7.06$ (dd, 1H, $J=15.9, 6.8$ Hz), 6.84 (dt, 1H, $J=15.8, 3.5$ Hz), 6.36 (dt, 1H, $J=15.7, 2.2$ Hz), 5.83 (dd, 1H, $J=15.9, 1.5$ Hz), 4.36 (dd, 2H, $J=3.5, 2.2$ Hz), 4.29 (dt, 1H, $J=7.5, 4.4$ Hz), 3.74 (s, 3H), 2.72 (dd, 1H, $J=15.7, 7.5$ Hz), 2.56 – 2.47 (m, 2H), 1.04 (d, 3H, $J=6.9$ Hz), 0.92 (s, 9H), 0.85 (s, 9H), 0.08 (s, 6H), 0.02 (d, 6H, $J=33.9$ Hz) ppm.

$^{13}\text{C NMR}$ (101 MHz, CDCl_3): $\delta = 198.8, 168.9, 167.2, 151.2, 128.7, 121.3, 90.1, 71.9, 62.4, 51.6, 44.6, 42.5, 26.0, 26.0, 18.2, 14.0, -5.3$.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{NH}_4]^+$: 502.3379; found: 502.3373.

5.9.3 Methyl (4*S*,5*S*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-7-oxonona-2,8-dienoate (**294**)



Vinylmagnesium bromide (125 mg, 949 μmol , 1.50 equiv.) was added to a solution of aldehyde **240** (190 mg, 632 μmol , 1.00 equiv.) in THF (4 mL) at -78°C and the reaction was stirred for 1 h before it was warmed to -30°C and stirred for further 45 min. Aq. sat. NH_4Cl (5 mL) was added and the aqueous phase extracted with EA (3x 5 mL). The combined organic layers were dried over MgSO_4 and concentrated *in vacuo*. The residue was solved in DCM (4 mL) and DMP (804 mg, 1.90 mmol, 3.00 equiv.) was added at r.t. and the reaction was stirred for 1 h. Aq. sat. $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) and aq. sat. NaHCO_3 (5 mL) were added and the aqueous phase was extracted with DCM (3x 5 mL). The combined organic layers were dried over MgSO_4 and the solvent removed under reduced pressure. Purification of the residue by flash column

chromatography over silica gel (CH/EA 6:1) to yield vinyl ketone **294** (158 mg, 485 μ mol, 77%) as a colourless oil.

R_f = 0.24 (CH/EA 6:1).

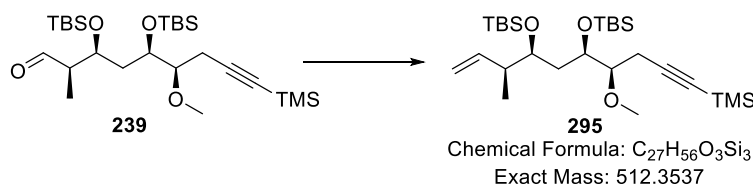
$[\alpha]_D^{20}$ = -62.0 (DCM, c = 0.5).

^1H NMR (CD_2Cl_2 , 700 MHz): δ = 7.02 (dd, 1H, J =15.8, 6.9 Hz), 6.33 (dd, 1H, J =17.7, 10.7 Hz), 6.18 (dd, 1H, J =17.7, 1.0 Hz), 5.85 – 5.81 (m, 2H), 4.29 (dt, 1H, J =7.4, 4.4 Hz), 3.70 (s, 3H), 3.70 (s, 1H), 2.74 (dd, 1H, J =15.9, 7.5 Hz), 2.56 (dd, 1H, J =16.0, 4.5 Hz), 2.54 (s, 0H), 1.04 (d, 3H, J =6.9 Hz), 0.91 – 0.86 (m, 2H), 0.86 (s, 10H), 0.07 (s, 3H), -0.02 (s, 3H) ppm.

^{13}C NMR (CD_2Cl_2 , 176 MHz): δ = 199.2, 167.1, 151.2, 137.7, 128.7, 121.6, 72.1, 51.7, 44.2, 42.8, 26.0, 18.4, 14.2, -4.5, -4.6 ppm.

HRMS (ESI +), 6.0 eV: calculated for $[\text{M}+\text{H}]^+$: 327.1986; found: 327.1979.

5.9.4 (5*S*,7*R*)-5-((*S*)-But-3-en-2-yl)-7-((*R*)-1-methoxy-4-(trimethylsilyl)but-3-yn-1-yl)-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane (**295**)



n -BuLi (2 M in cyclohexane, 699 μ L, 1.40 mmol, 1.20 equiv.) was added to a solution of methyltriphenylphosphonium bromide (624 mg, 1.75 mmol, 1.50 equiv.) and 3 Å ground molecular sieve in THF (12 mL) at -78 °C. The reaction was stirred at this temperature for 30 min, then allowed to warm to r.t. and stirred for an additional 10 min. The mixture was subsequently cooled back to -78 °C, and aldehyde **239** (600 mg, 1.17 mmol, 1.00 equiv.) was added. The reaction was then allowed to warm to r.t. and stirred overnight (14 h). Aq. sat. NH_4Cl (10 mL) was added, the aqueous phase extracted with EA (3x 10 mL) and the combined organic layers dried over MgSO_4 . Removal of the solvent *in vacuo* and purification of the

residue by flash column chromatography over silica gel (CH/EA 30:1) yielded alkene **295** (553 mg, 1.08 mmol, 93%) as a colourless oil.

$R_f = 0.32$ (CH/EA 30:1).

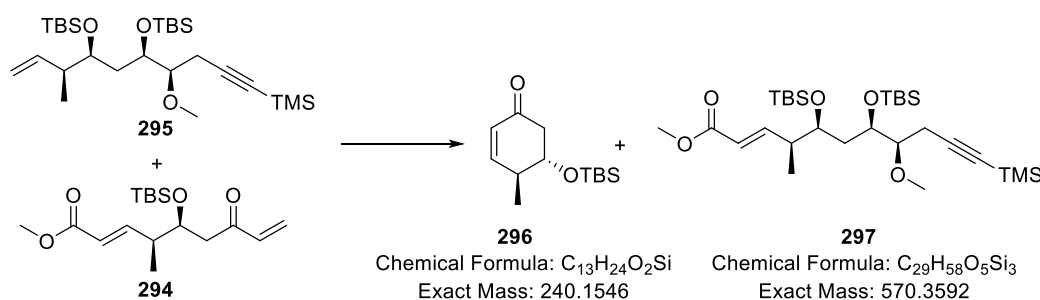
$[\alpha]_D^{20} = -34.0$ (DCM, $c = 1.0$).

^1H NMR (CD_2Cl_2 , 500 MHz): $\delta = 5.99 - 5.89$ (m, 1H), 5.03 (dd, 1H, $J=1.4, 0.8$ Hz), 5.00 (ddd, 1H, $J=8.8, 2.0, 1.4$ Hz), 3.91 (td, 1H, $J=6.6, 3.9$ Hz), 3.74 (ddd, 1H, $J=7.1, 5.7, 3.3$ Hz), 3.40 (s, 3H), 3.30 (ddd, 1H, $J=6.6, 5.6, 3.9$ Hz), 2.55 (dd, 1H, $J=16.9, 5.6$ Hz), 2.41 (dd, 1H, $J=16.9, 6.6$ Hz), 2.35 (tddt, 1H, $J=6.9, 5.5, 3.5, 1.5$ Hz), 1.81 (ddd, 1H, $J=13.9, 6.5, 5.7$ Hz), 1.41 (dt, 1H, $J=13.8, 6.8$ Hz), 0.96 (d, 3H, $J=6.9$ Hz), 0.89 (s, 9H), 0.89 (s, 9H), 0.13 (s, 9H), 0.09 (d, 6H, $J=11.5$ Hz), 0.07 (d, 6H, $J=9.2$ Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): $\delta = 141.6, 114.1, 105.1, 86.0, 81.9, 72.7, 70.3, 58.5, 42.5, 36.6, 26.1, 26.1, 20.8, 18.4, 18.3, 13.7, 0.1, -3.8, -4.2, -4.2, -4.4$ ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 513.3610; found: 513.3617.

5.9.5 (4*S*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-methylcyclohex-2-en-1-one (296) and Methyl (4*S*,5*S*,7*R*,8*R*,*E*)-5,7-bis((*tert*-butyldimethylsilyl)oxy)-8-methoxy-4-methyl-11-(trimethylsilyl)undec-2-en-10-ynoate (297)



Hoveyda-Grubbs-II (1.9 mg, 3.1 μmol , 0.1 equiv.) was added to a solution of alkene **295** (15.7 mg, 30.6 μmol , 1.00 equiv.) and alkene **294** (10.0 mg, 30.6 μmol , 1.00 equiv.) in toluene (5 mL) and the reaction was refluxed (120 $^\circ\text{C}$) overnight (20 h). Celite[®] (~2 g) was added to

the mixture and the solvent was reduced under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 30:1) yielded cyclisation product **296** (4.0 mg, 17 μ mol, 54%) and olefin **297** (2.8 mg, 4.9 μ mol, 16%) both as a colourless oil.

Analytical data of **296**:

R_f = 0.16 (CH/EA 30:1).

$[\alpha]_D^{20}$ = +87.1 (DCM, c = 0.7).

^1H NMR (CD_2Cl_2 , 700 MHz): δ = 6.71 (dd, 1H, J =10.0, 2.7 Hz), 5.93 (ddd, 1H, J =10.1, 2.5, 0.8 Hz), 3.79 (ddd, 1H, J =10.3, 7.4, 4.1 Hz), 2.64 (ddd, 1H, J =16.1, 4.1, 0.8 Hz), 2.46 (pt, 1H, J =7.3, 2.6 Hz), 2.41 (dd, 1H, J =16.1, 10.3 Hz), 1.19 (d, 3H, J =7.2 Hz), 0.90 (s, 9H), 0.08 (s, 6H) ppm.

^{13}C NMR (CD_2Cl_2 , 176 MHz): δ = 198.7, 153.8, 129.1, 73.9, 47.4, 40.5, 25.9, 18.3, 17.5, -4.2, -4.7 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 241.1618; found: 241.1616.

Analytical data of **297**:

R_f = 0.31 (CH/EA 30:1).

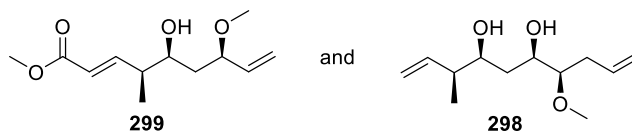
$[\alpha]_D^{20}$ = -20.0 (DCM, c = 0.5).

^1H NMR (CD_2Cl_2 , 700 MHz): δ = 7.03 (dd, 1H, J =15.9, 7.0 Hz), 5.81 (dd, 1H, J =15.9, 1.4 Hz), 3.89 (ddd, 1H, J =7.2, 5.7, 4.1 Hz), 3.84 (td, 1H, J =6.5, 3.3 Hz), 3.70 (s, 3H), 3.41 (s, 3H), 3.30 (ddd, 1H, J =6.6, 5.1, 4.1 Hz), 2.56 (dd, 1H, J =17.0, 5.2 Hz), 2.52 (tdd, 1H, J =6.9, 3.3, 1.5 Hz), 2.39 (dd, 1H, J =17.0, 6.7 Hz), 1.86 (dt, 1H, J =13.9, 6.1 Hz), 1.03 (d, 3H, J =6.9 Hz), 0.90 (d, 18H, J =1.4 Hz), 0.13 (s, 9H), 0.11 – 0.04 (m, 12H) ppm.

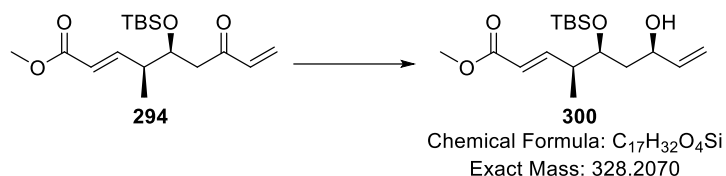
^{13}C NMR (CD_2Cl_2 , 176 MHz): δ = 167.2, 152.4, 121.0, 105.1, 86.2, 82.2, 72.1, 70.2, 58.6, 51.6, 41.4, 37.1, 26.2, 26.1, 20.7, 18.4, 18.4, 13.0, 0.1, -3.8, -4.2, -4.2, -4.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{Na}]^+$: 593.3484; found: 593.3487.

5.10 Experimental Details for Chapter 3.6.4: Synthesis of Authentic Fragment 298 and 299



5.10.1 Methyl (4*S*,5*S*,7*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-7-hydroxy-4-methylnona-2,8-dienoate (**300**)



BH₃·THF (1 M in THF, 574 μ L, 574 μ mol, 1.50 equiv.) was added to a solution of vinyl ketone **294** (125 mg, 383 μ mol, 1.00 equiv.) and (*S*)-2-methyl-CBS-oxazaborolidine (1 M in toluene, 421 μ L, 421 μ mol, 1.10 equiv.) in THF (2 mL) at -20 °C and the reaction was stirred for 2.5 h. MeOH (3 mL) and aq. sat. NaHCO₃ (3 mL) were added and the aqueous phase was extracted with EA (4x 5 mL). The combined organic layers were dried over MgSO₄ and concentrated *in vacuo*. Purification of the residue by flash column chromatography over silica gel (CH/EA 6:1) to yield alcohol **300** (94 mg, 286 μ mol, 75%, *dr* = 19:1) as a colourless oil.

R_f = 0.20 (CH/EA 6:1).

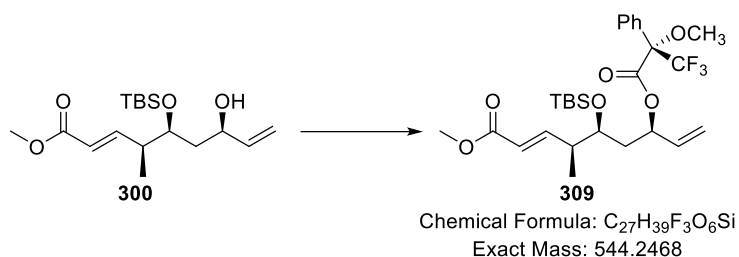
$[\alpha]_D^{20}$ = -42.0 (DCM, c = 0.5).

¹H NMR (CD₂Cl₂, 400 MHz): δ = 7.06 (dd, 1H, J =15.9, 6.5 Hz), 5.88 – 5.83 (m, 1H), 5.82 – 5.79 (m, 1H), 5.23 (dt, 1H, J =17.2, 1.6 Hz), 5.08 (dt, 1H, J =10.5, 1.5 Hz), 4.25 – 4.16 (m, 1H), 3.90 (dt, 1H, J =8.2, 4.5 Hz), 3.70 (s, 3H), 2.61 (pdd, 1H, J =6.9, 4.1, 1.6 Hz), 2.38 (d, 1H, J =2.7 Hz), 1.67 – 1.48 (m, 3H), 1.02 (d, 3H, J =6.9 Hz), 0.91 (s, 9H), 0.10 (d, 6H, J =5.9 Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 167.1, 151.1, 141.4, 121.5, 114.5, 74.8, 71.4, 51.6, 42.0, 40.2, 26.0, 18.3, 14.2, -4.1 , -4.5 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+H]^+$: 329.2143; found: 329.2141.

5.10.2 Methyl (4*S*,5*S*,7*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-7-(((*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)nona-2,8-dienoate (309**)**



(*R*)-(-)-MTPA-Cl (4.6 μ L, 25 μ mol, 2.0 equiv.) was added to a solution of alcohol **300** (4.0 mg, 12 μ mol, 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. $NaHCO_3$ (1 mL) was added, the aqueous phase was extracted with EA (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over $MgSO_4$. The residue was purified by flash column chromatography over silica gel (CH/EA 15:1) to yield ester **309** (4.6 mg, 8.5 μ mol, 69%) as a colourless oil.

R_f = 0.19 (CH/EA 15:1).

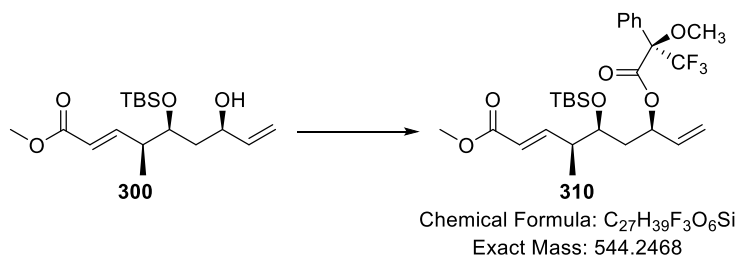
$[\alpha]_D^{20}$ = -47.0 (DCM, c = 1.0).

1H NMR (CD_2Cl_2 , 500 MHz): δ = 7.50 – 7.37 (m, 5H), 6.96 (dd, 1H, J =15.9, 7.0 Hz), 5.79 (dd, 1H, J =15.8, 1.5 Hz), 5.73 (ddd, 1H, J =17.4, 10.5, 7.2 Hz), 5.52 (qt, 1H, J =7.1, 0.9 Hz), 5.37 – 5.25 (m, 2H), 3.72 (dd, 1H, J =6.3, 4.0 Hz), 3.70 (s, 3H), 3.50 (q, 3H, J =1.2 Hz), 2.53 (pdd, 1H, J =6.8, 4.0, 1.5 Hz), 1.82 (dd, 2H, J =7.0, 6.3 Hz), 1.00 (d, 3H, J =6.8 Hz), 0.90 (s, 9H), 0.04 (d, 6H, J =12.3 Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): δ = 167.1, 165.8, 151.3, 135.2, 132.5, 130.1, 128.8, 127.8, 125.0, 122.7, 121.5, 119.8, 84.9 (d, J =27.5 Hz), 75.3, 71.9, 55.7, 51.7, 41.4, 38.6, 26.0, 18.3, 13.5, -4.3, -4.4 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[M+Na]^+$: 567.2360; found: 567.2358.

5.10.3 Methyl (4*S*,5*S*,7*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-7-(((*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl)oxy)nona-2,8-dienoate (**310**)



(*S*)-(+)-MTPA-Cl (4.6 μ l, 25 μ mol, 2.0 equiv.) was added to a solution of alcohol **300** (4.0 mg, 12 μ mol, 1.0 equiv.) in pyridine (0.2 mL). After 2 h of stirring, aq. sat. NaHCO₃ (1 mL) was added, the aqueous phase was extracted with EA (3x 1 mL), the combined organic layers were washed with brine (1 mL) and dried over MgSO₄. The residue was purified by flash column chromatography over silica gel (CH/EA 15:1) to yield ester **310** (4.0 mg, 7.3 μ mol, 60%) as a colourless oil.

R_f = 0.17 (CH/EA 15:1).

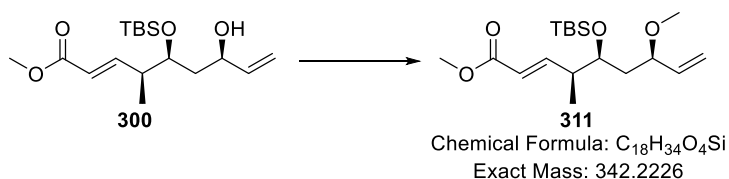
$[\alpha]_D^{20}$ = +37.5 (DCM, c = 0.8).

¹H NMR (CD₂Cl₂, 500 MHz): δ = 7.52 – 7.48 (m, 2H), 7.44 – 7.37 (m, 3H), 6.86 (dd, 1H, J =15.8, 7.2 Hz), 5.83 (ddd, 1H, J =17.2, 10.4, 7.5 Hz), 5.77 (dd, 1H, J =15.8, 1.4 Hz), 5.58 – 5.49 (m, 1H), 5.44 – 5.33 (m, 2H), 3.71 (s, 3H), 3.59 – 3.55 (m, 1H), 3.55 (q, 3H, J =1.3 Hz), 2.37 (pdd, 1H, J =6.7, 4.0, 1.4 Hz), 1.77 (td, 2H, J =6.3, 0.9 Hz), 0.92 (d, 3H, J =6.8 Hz), 0.88 (s, 9H), -0.04 (d, 6H, J =14.5 Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 167.1, 166.0, 151.6, 135.4, 132.8, 130.1, 128.8, 127.5, 125.0, 122.7, 121.3, 120.1, 84.8, 84.6, 75.2, 71.5, 55.9, 51.6, 41.1, 38.6, 25.9, 18.2, 13.3, -4.5, -4.5 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+Na]⁺: 567.2360; found: 567.2360.

5.10.4 Methyl (4*S*,5*S*,7*R*,*E*)-5-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-4-methylnona-2,8-dienoate (**311**)



Proton-sponge[®] (243 mg, 1.13 mmol, 6.00 equiv.) was added to a solution of alcohol **300** (62 mg, 189 μ mol, 1.00 equiv., dried with 3x Freeze-Pump-Thaw cycles) in DCM (2 mL) at r.t. After 30 min of stirring, trimethyloxonium tetrafluoroborate (112 mg, 755 μ mol, 4.00 equiv.) was added and the reaction was stirred overnight (20 h). 1 M HCl (2 mL) was added and the aqueous phase was extracted with DCM (3x 2 mL). The combined organic layers were dried over MgSO₄ and celite[®] (2 g) was added before the mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 6:1) yielded methyl ether **311** (52.0 mg, 152 μ mol, 80%) as a colourless oil.

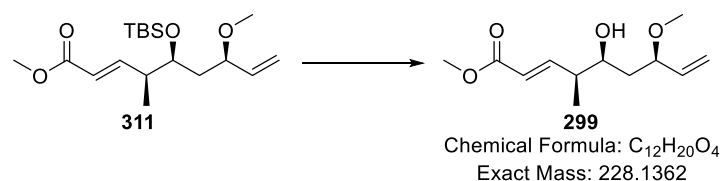
R_f = 0.42 (CH/EA 6:1).

$[\alpha]_D^{20}$ = -30.0 (DCM, c = 1.0).

¹H NMR (CD₂Cl₂, 500 MHz): δ = 7.02 (dd, 1H, J =15.9, 6.9 Hz), 5.80 (dd, 1H, J =15.9, 1.5 Hz), 5.61 (ddd, 1H, J =17.1, 10.5, 7.8 Hz), 5.24 – 5.17 (m, 2H), 3.77 (ddd, 1H, J =6.4, 5.8, 4.1 Hz), 3.69 (s, 3H), 3.60 (dddt, 1H, J =8.0, 7.1, 6.3, 0.9 Hz), 3.20 (s, 3H), 2.53 (pdd, 1H, J =6.9, 4.1, 1.5 Hz), 1.69 (ddd, 1H, J =13.7, 7.2, 6.4 Hz), 1.60 – 1.53 (m, 1H), 1.01 (d, 3H, J =6.9 Hz), 0.89 (s, 9H), 0.04 (d, 6H, J =6.3 Hz) ppm.

¹³C NMR (CD₂Cl₂, 126 MHz): δ = 167.3, 152.4, 138.9, 121.0, 117.7, 80.3, 72.5, 56.1, 51.6, 41.7, 40.3, 26.0, 18.3, 13.6, -4.2, -4.3 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+H]⁺: 343.2299; found: 343.2299.



TBAF (1 M in THF, 701 μ L, 701 μ mol, 10.0 equiv.) was added to a solution of silyl ether **311** (24.0 mg, 70.1 μ mol, 1.00 equiv.) in THF (2 mL) at r.t. and the reaction was stirred for 2 h. H₂O (5 mL) was added and the aqueous phase was extracted with EA (3x 5 mL). The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure. Purification of the residue by flash column chromatography over silica gel (CH/EA 3:1) yielded alcohol **299** (8.5 mg, 37 μ mol, 53%) as a colourless oil.

CSA (8.1 mg, 35 μ mol, 1.50 equiv.) was added to a solution of silyl ether **311** (8.0 mg, 23 μ mol, 1.00 equiv.) in DCM (1 mL) and MeOH (1 mL) and the reaction was stirred overnight (18 h). Aq. sat. NaHCO_3 (2 mL) was added, the aqueous phase extracted with DCM (3x 2 mL) and the combined organic layers dried over MgSO_4 . Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 3:1) yielded alcohol **299** (5.3 mg, 23 μ mol, quant.) as a colourless oil.

$$[\alpha]_D^{20} = +19.0 \text{ (DCM, } c = 1.0).$$

¹H NMR (CDCl₃, 700 MHz): δ = 6.97 (dd, 1H, *J*=15.8, 7.8 Hz), 5.85 (dd, 1H, *J*=15.8, 1.2 Hz), 5.66 – 5.59 (m, 1H), 5.23 (ddd, 1H, *J*=6.6, 1.5, 0.8 Hz), 5.21 (d, 1H, *J*=0.8 Hz), 3.79 – 3.75 (m, 2H), 3.72 (d, 3H, *J*=0.8 Hz), 3.29 (d, 3H, *J*=0.8 Hz), 2.41 (dddd, 1H, *J*=8.0, 6.9, 5.8, 1.3 Hz), 1.61 (dt, 1H, *J*=14.6, 9.9 Hz), 1.56 (ddd, 1H, *J*=14.6, 3.7, 2.0 Hz), 1.09 (d, 3H, *J*=6.9 Hz) ppm.

^{13}C NMR (CDCl_3 , 176 MHz): δ = 167.2, 151.3, 137.6, 121.2, 118.0, 84.3, 74.6, 56.2, 51.6, 42.9, 39.5, 14.7 ppm.

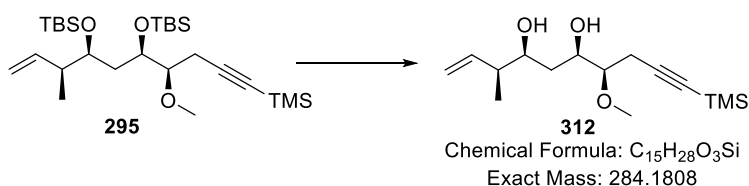
NMR measured in DCM:

^1H NMR (CD_2Cl_2 , 700 MHz): δ = 6.93 (dd, 1H, J =15.8, 7.8 Hz), 5.83 (dd, 1H, J =15.8, 1.3 Hz), 5.68 – 5.61 (m, 1H), 5.24 – 5.19 (m, 2H), 3.81 – 3.77 (m, 1H), 3.77 – 3.72 (m, 1H), 3.69 (s, 3H), 3.62 (d, 1H, J =1.6 Hz), 3.28 (s, 3H), 2.38 (dddd, 1H, J =8.2, 7.0, 5.7, 1.3 Hz), 1.60 – 1.53 (m, 2H), 1.06 (d, 3H, J =6.8 Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 176 MHz): δ = 167.2, 151.7, 138.2, 121.3, 117.8, 84.4, 74.6, 56.3, 51.6, 43.1, 39.9, 14.6 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 229.1434; found: 229.1432.

5.10.6 (3*S*,4*S*,6*R*,7*R*)-7-Methoxy-3-methyl-10-(trimethylsilyl)dec-1-en-9-yne-4,6-diol (**312**)



HF-Pyridine (70% HF, 481 μL , 5.34 mmol, 50.0 equiv.) was added to a solution of silyl ether **295** (55 mg, 107 μmol , 1.00 equiv.) in THF (1 mL) and the reaction was stirred for 2 h. Pyridine (5 mL) and aq. sat. CaCl_2 (5 mL) were added and the mixture was stirred for an additional 1 h before the aqueous phase was extracted with EA (3x 5 mL) and the combined organic layers dried over MgSO_4 . Removal of the solvent and purification of the residue by flash column chromatography over silica gel (CH/EA 3:1) yielded diol **312** (after accounting for H_2O as impurity: 30.5 mg, 107 μmol , quant.) as colourless oil.

R_f = 0.17 (CH/EA 3:1).

$[\alpha]_D^{20}$ = -20.0 (DCM, c = 0.3).

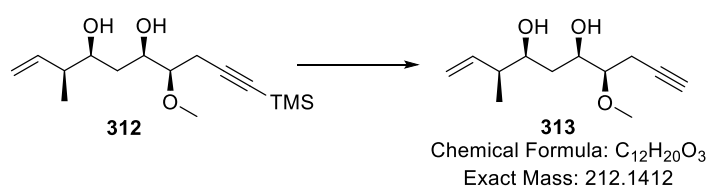
^1H NMR (CD_2Cl_2 , 500 MHz): δ = 5.82 (ddd, 1H, J =17.2, 10.4, 7.5 Hz), 5.11 – 4.97 (m, 2H), 3.90 – 3.83 (m, 1H), 3.75 – 3.66 (m, 1H), 3.45 (s, 3H), 3.24 (d, 1H, J =2.1 Hz), 3.17 (q, 1H, J =5.4 Hz),

3.01 (d, 1H, $J=4.0$ Hz), 2.56 – 2.38 (m, 2H), 2.25 (dddt, 1H, $J=7.9, 6.8, 5.6, 1.1$ Hz), 1.70 (dt, 1H, $J=14.4, 2.3$ Hz), 1.47 (dt, 1H, $J=14.4, 10.2$ Hz), 1.03 (d, 3H, $J=6.8$ Hz), 0.14 (s, 9H) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): δ = 141.5, 115.0, 103.6, 86.9, 82.8, 75.6, 74.3, 58.6, 44.4, 36.4, 21.2, 14.9, 0.0 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{Na}]^+$: 307.1700; found: 307.1697.

5.10.7 (3*S*,4*S*,6*R*,7*R*)-7-Methoxy-3-methyldec-1-en-9-yne-4,6-diol (313)



K_2CO_3 (80.2 mg, 580 μmol , 10.0 equiv.) was added to a solution of alkyne **312** (16.5 mg, 58.0 μmol , 1.00 equiv.) in MeOH (1 mL) and the reaction was stirred for 2 h. Removal of the solvent *in vacuo* and purification of the residue by flash column chromatography over silica gel (CH/EA 3:1) yielded alkyne **313** (9.3 mg, 44 μmol , 76%) as a colourless oil.

R_f = 0.20 (CH/EA 3:1).

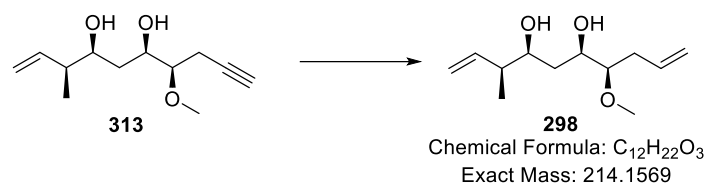
$[\alpha]_D^{20}$ = -20.0 (DCM, c = 0.5).

^1H NMR (CD_2Cl_2 , 500 MHz): δ = 5.81 (ddd, 1H, $J=17.2, 10.5, 7.5$ Hz), 5.10 – 5.02 (m, 2H), 3.91 (dddd, 1H, $J=10.3, 5.1, 3.8, 2.6$ Hz), 3.72 (ddt, 1H, $J=9.9, 5.6, 2.0$ Hz), 3.44 (s, 3H), 3.21 – 3.17 (m, 2H), 3.04 (d, 1H, $J=3.9$ Hz), 2.52 (ddd, 1H, $J=17.2, 6.0, 2.7$ Hz), 2.40 (ddd, 1H, $J=17.2, 5.2, 2.7$ Hz), 2.25 (dddt, 1H, $J=7.8, 6.8, 5.6, 1.2$ Hz), 2.03 (t, 1H, $J=2.7$ Hz), 1.69 (dt, 1H, $J=14.4, 2.3$ Hz), 1.48 (dt, 1H, $J=14.4, 10.2$ Hz), 1.03 (d, 3H, $J=6.9$ Hz) ppm.

^{13}C NMR (CD_2Cl_2 , 126 MHz): δ = 141.5, 115.1, 82.5, 81.0, 75.5, 73.8, 70.3, 58.5, 44.5, 36.4, 19.6, 14.9 ppm.

HRMS (ESI (+), 6.0 eV): calculated for $[\text{M}+\text{H}]^+$: 213.1485; found: 213.1485.

5.10.8 (3*S*,4*S*,6*R*,7*R*)-7-Methoxy-3-methyldeca-1,9-diene-4,6-diol (298)



Lindlar catalyst (25 mg, Pd-50%) was added to a solution of alkyne **313** (100 mg, 471 μ mol, 1.00 equiv.) and quinoline (112 μ L, 942 μ mol, 2.00 equiv.) in hexane (2 mL). The reaction vessel was then filled with hydrogen. After stirring for 30 min, the suspension was filtered over a plug of silica gel and washed with CH (200 mL) and subsequently rinsed with CH/EA (1:1, 50 mL). The solvent was removed under reduced pressure and the residue was purified by HPLC (H₃CCN/H₂O 33:67, MACHEREY-NAGEL Nucleodur 100-5 Gravity C18; 5 μ m, flow: 16 mL/min, pressure 224 bar, retention time 30 min) yielded title compound **298** (68.6 mg, 320 μ mol, 68%) as a colourless oil.

R_f = 0.20 (CH/EA 1:1).

$[\alpha]_D^{20}$ = -21.0 (DCM, c = 1.0).

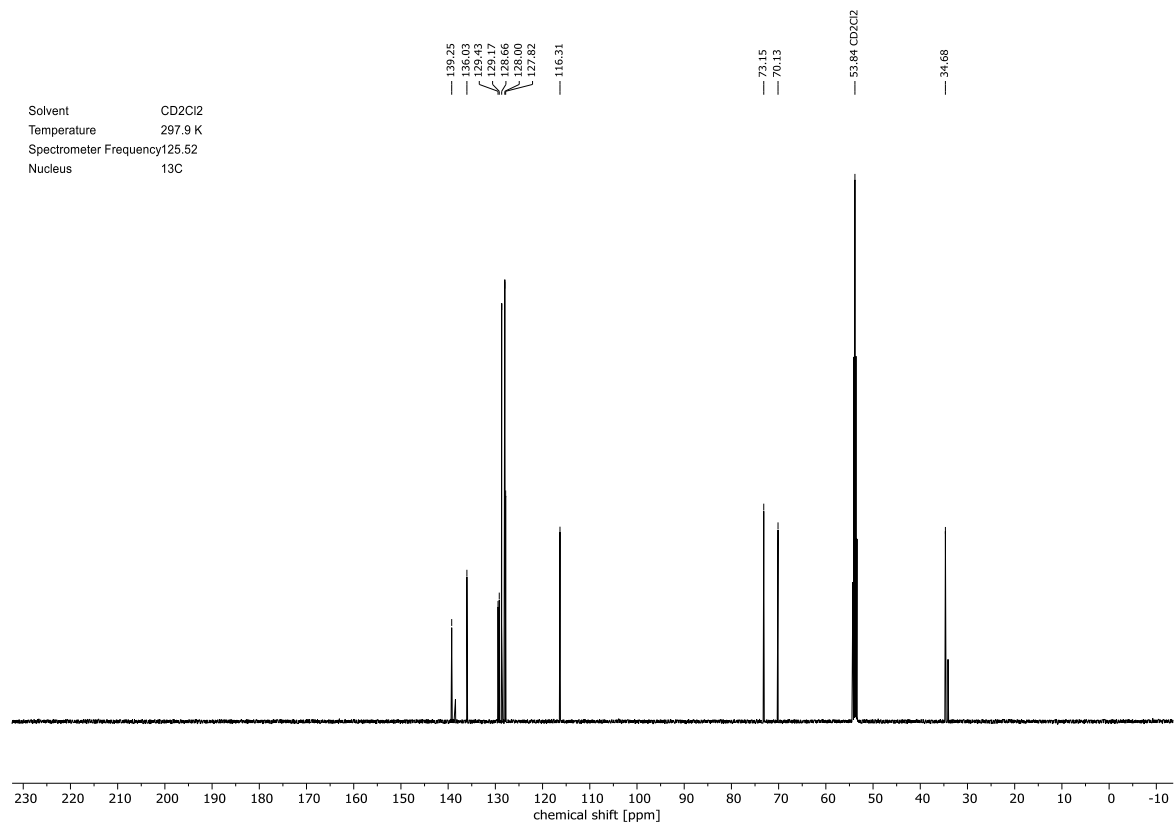
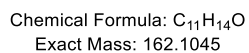
¹H NMR (CDCl₃, 700 MHz): δ = 5.85 – 5.80 (m, 1H), 5.80 – 5.77 (m, 1H), 5.13 – 5.08 (m, 2H), 5.08 – 5.04 (m, 2H), 3.77 (ddd, 1H, J =10.5, 5.8, 2.4 Hz), 3.72 (ddd, 1H, J =10.1, 5.8, 1.9 Hz), 3.42 (s, 3H), 3.09 (p, 3H, J =6.0 Hz), 2.42 (dddt, 1H, J =14.9, 6.8, 5.4, 1.4 Hz), 2.30 – 2.25 (m, 1H), 2.25 – 2.21 (m, 1H), 1.68 (dt, 1H, J =14.3, 2.2 Hz), 1.46 (dt, 1H, J =14.4, 10.3 Hz), 1.05 (d, 3H, J =6.9 Hz) ppm.

¹³C NMR (CDCl₃, 176 MHz): δ = 141.0, 134.1, 117.7, 115.3, 83.7, 75.5, 73.9, 58.2, 44.1, 35.9, 34.0, 15.0 ppm.

HRMS (ESI (+), 6.0 eV): calculated for [M+Na]⁺: 237.1461; found: 237.1461.

6 Copies of NMR Spectra

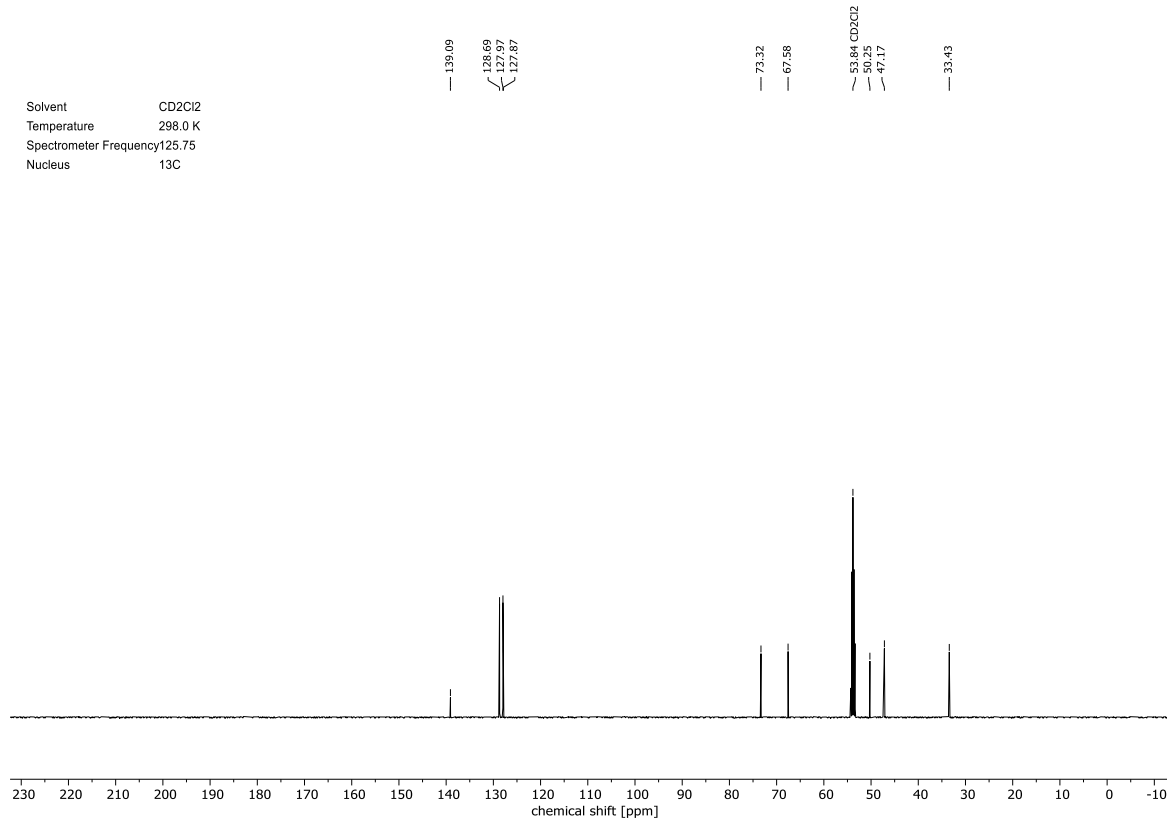
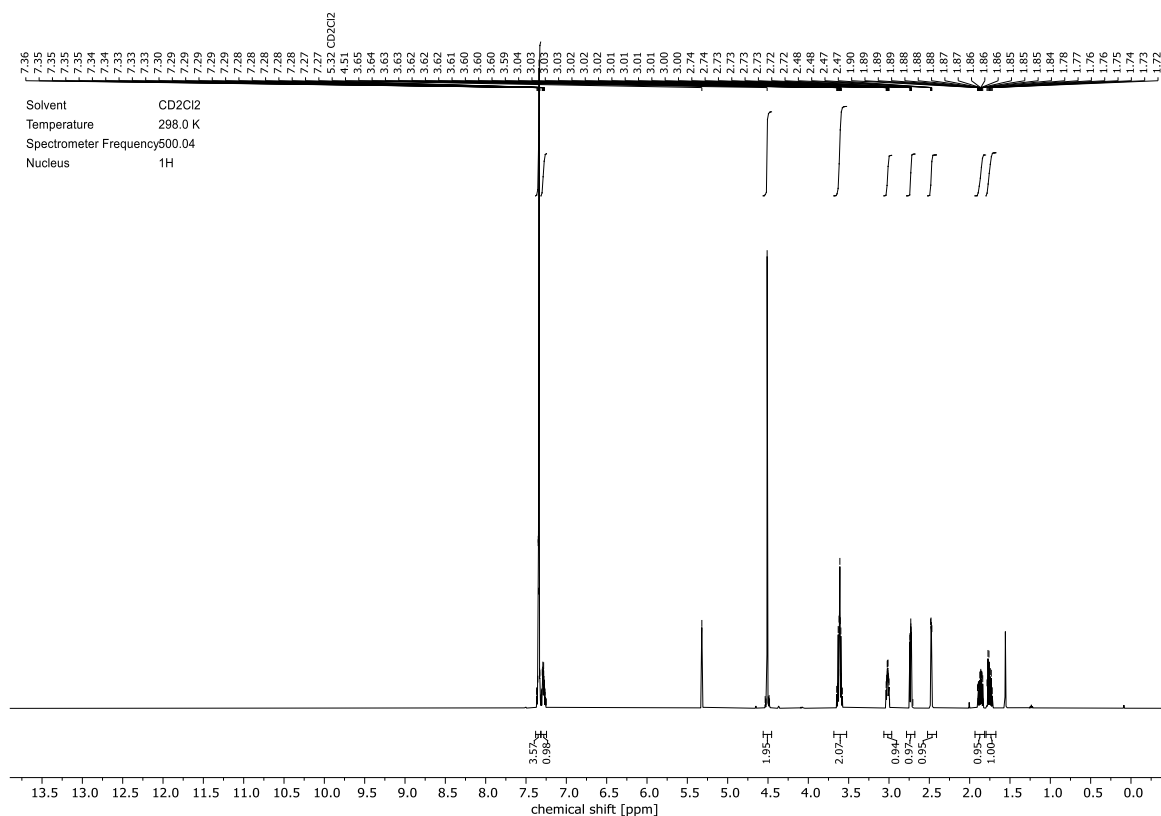
– NMR Spectra of the synthesised compounds starting at the next page –



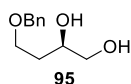
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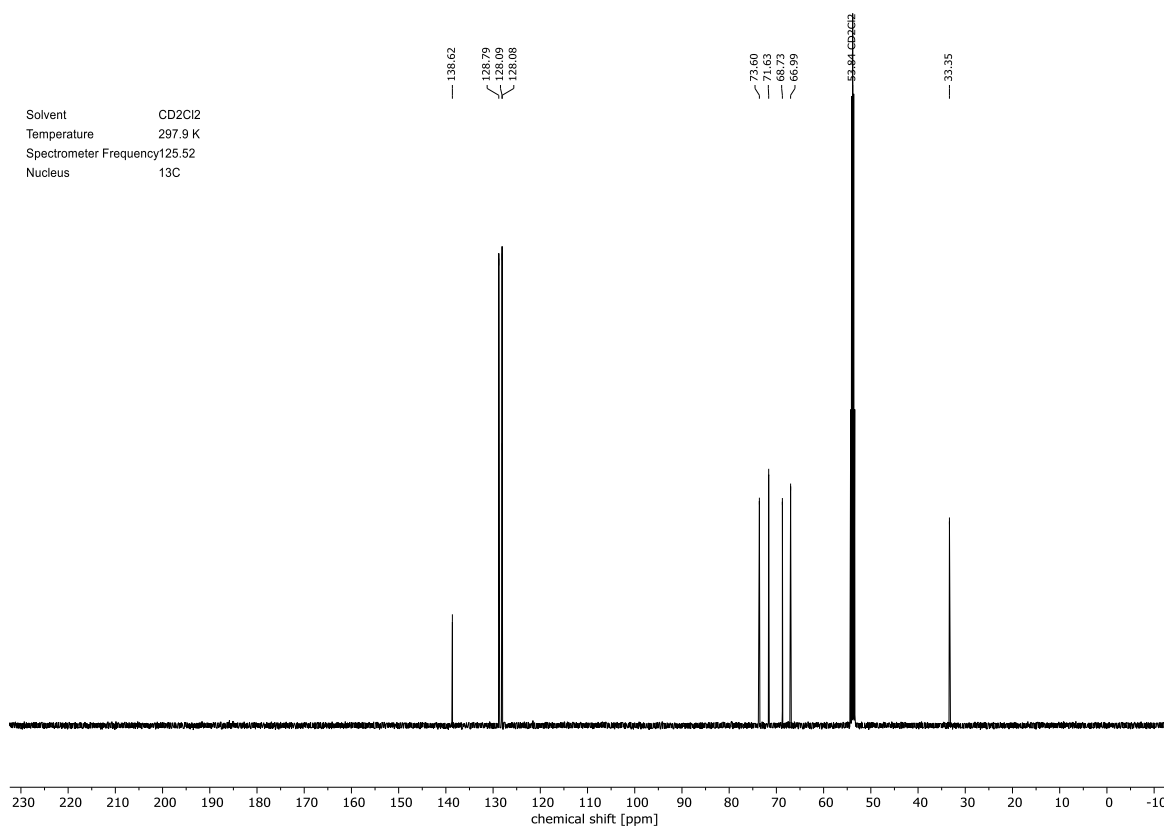
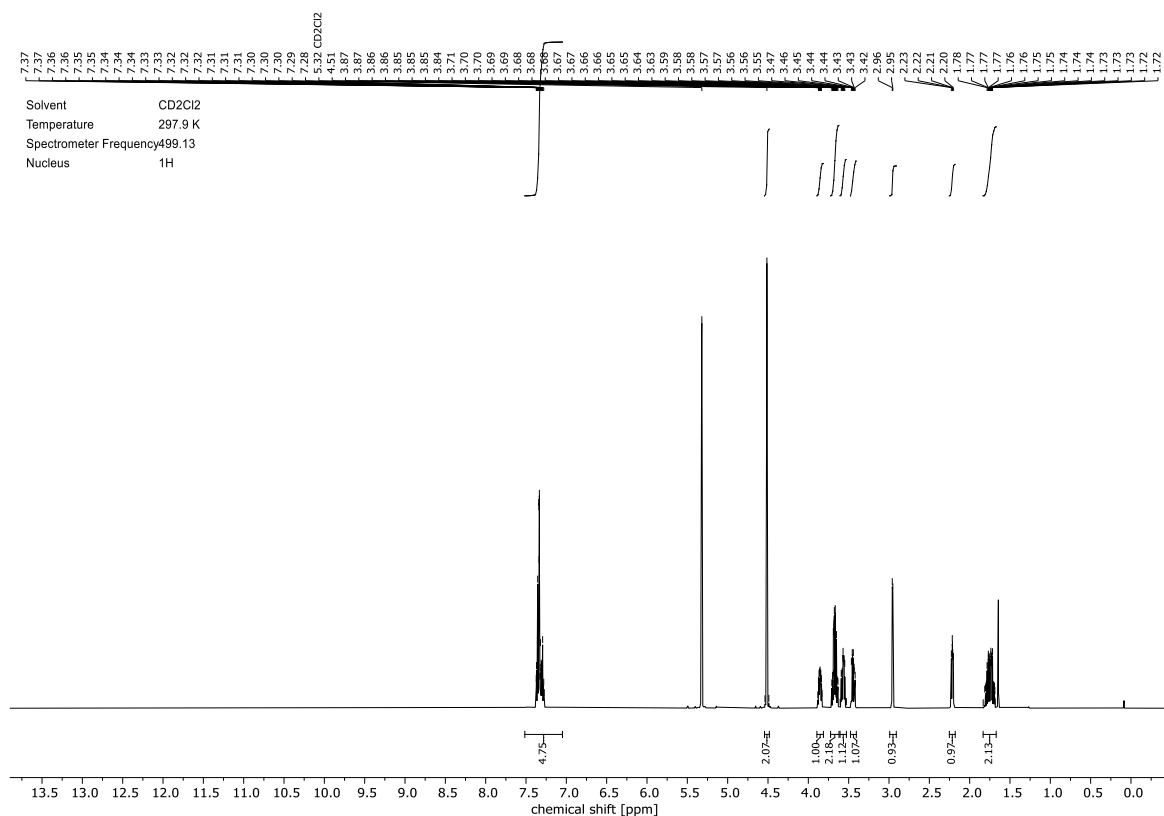
Chemical Formula: $C_{11}H_{14}O_2$
Exact Mass: 178.0994

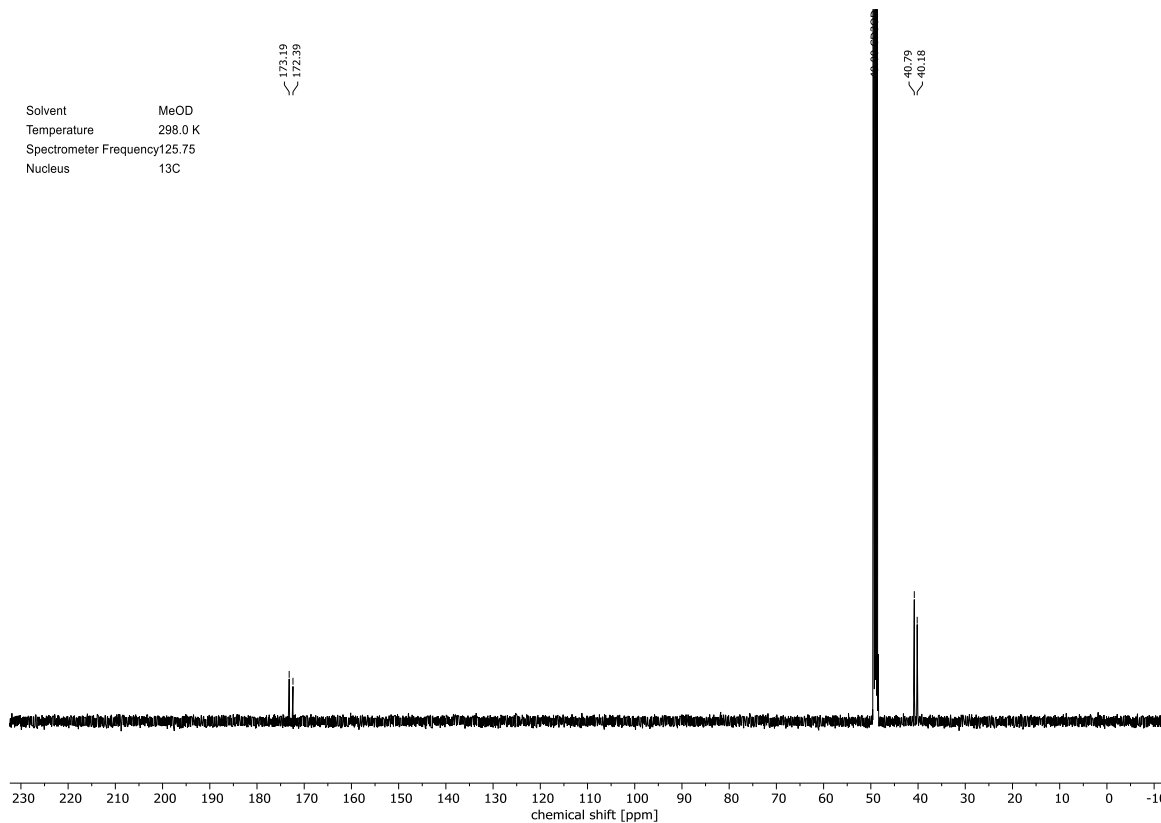
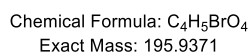


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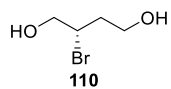


Chemical Formula: $C_{11}H_{16}O_3$
Exact Mass: 196.1099



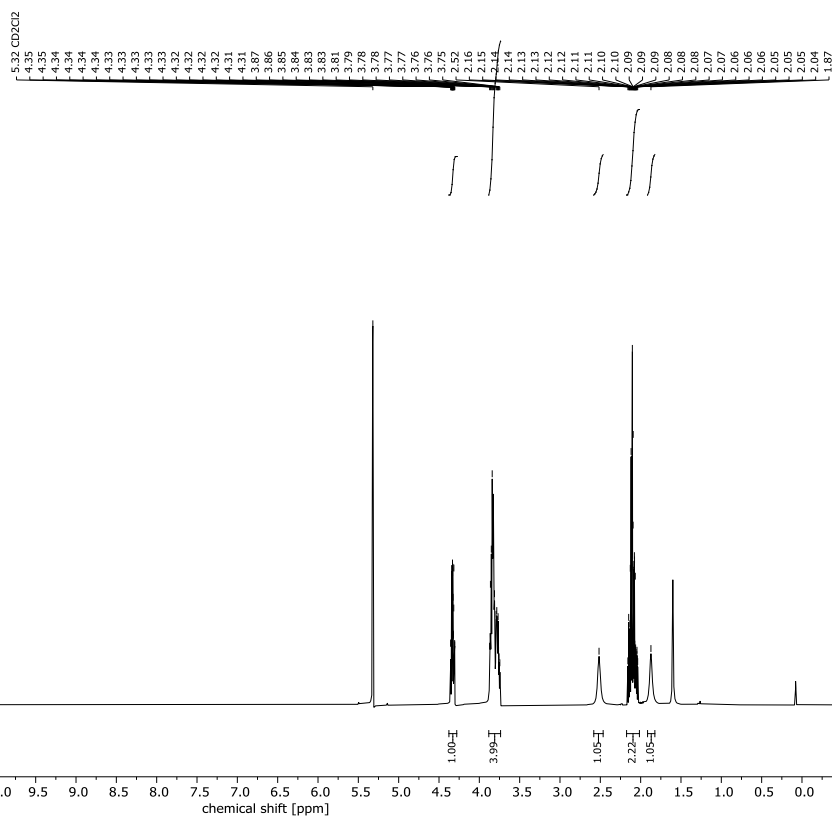


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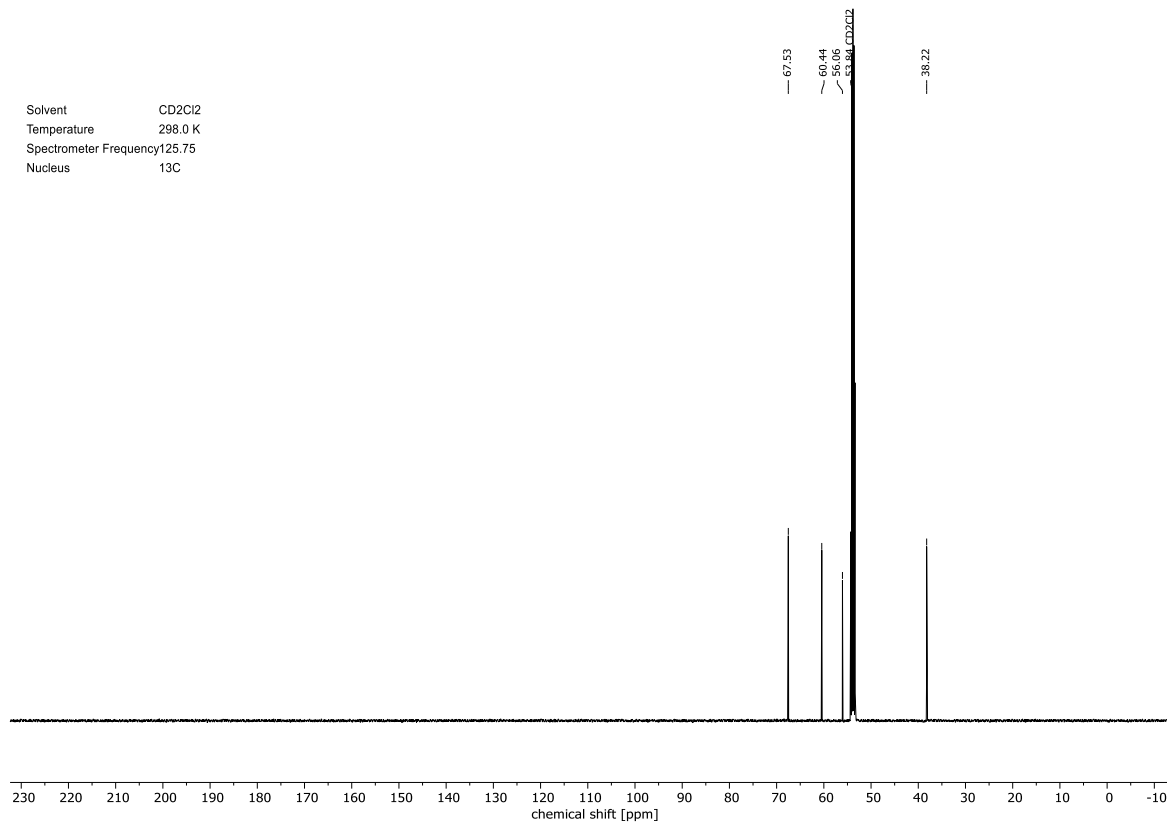


Chemical Formula: C₄H₉BrO₂
Exact Mass: 167.9786

Solvent CD₂Cl₂
Temperature 298.0 K
Spectrometer Frequency 500.04
Nucleus ¹H



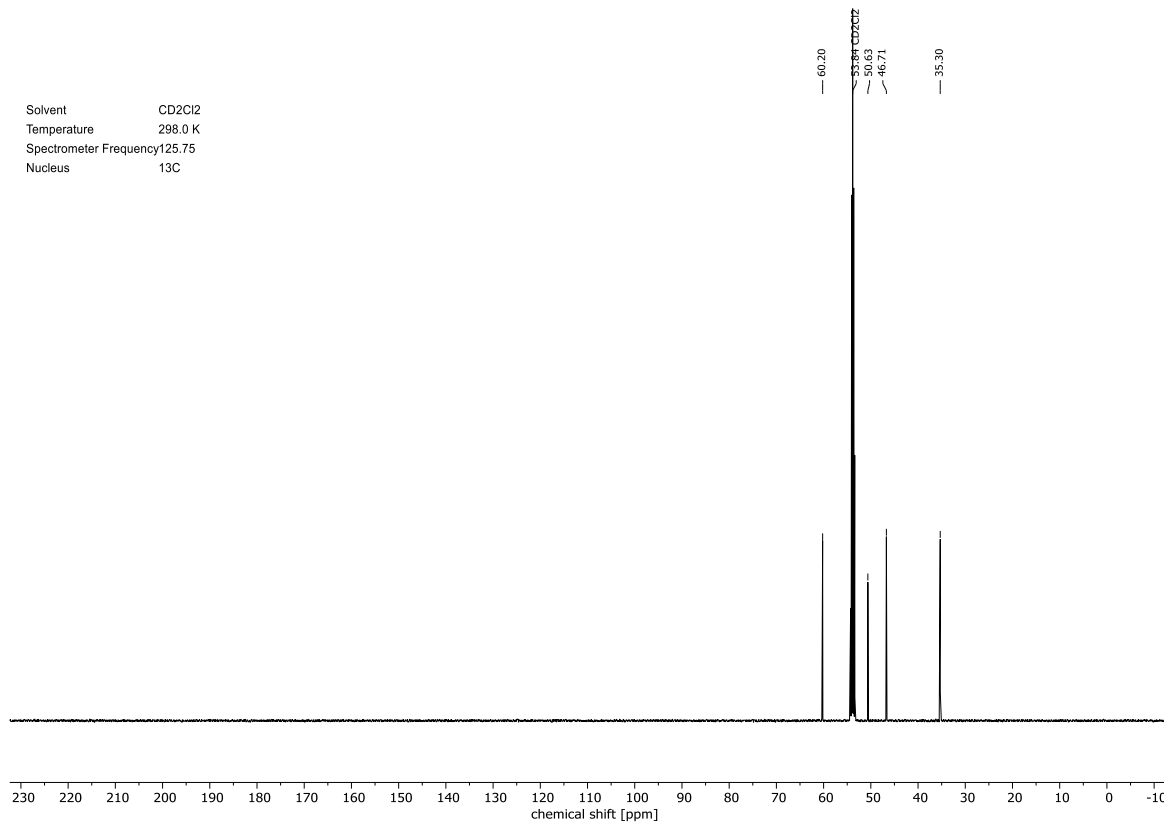
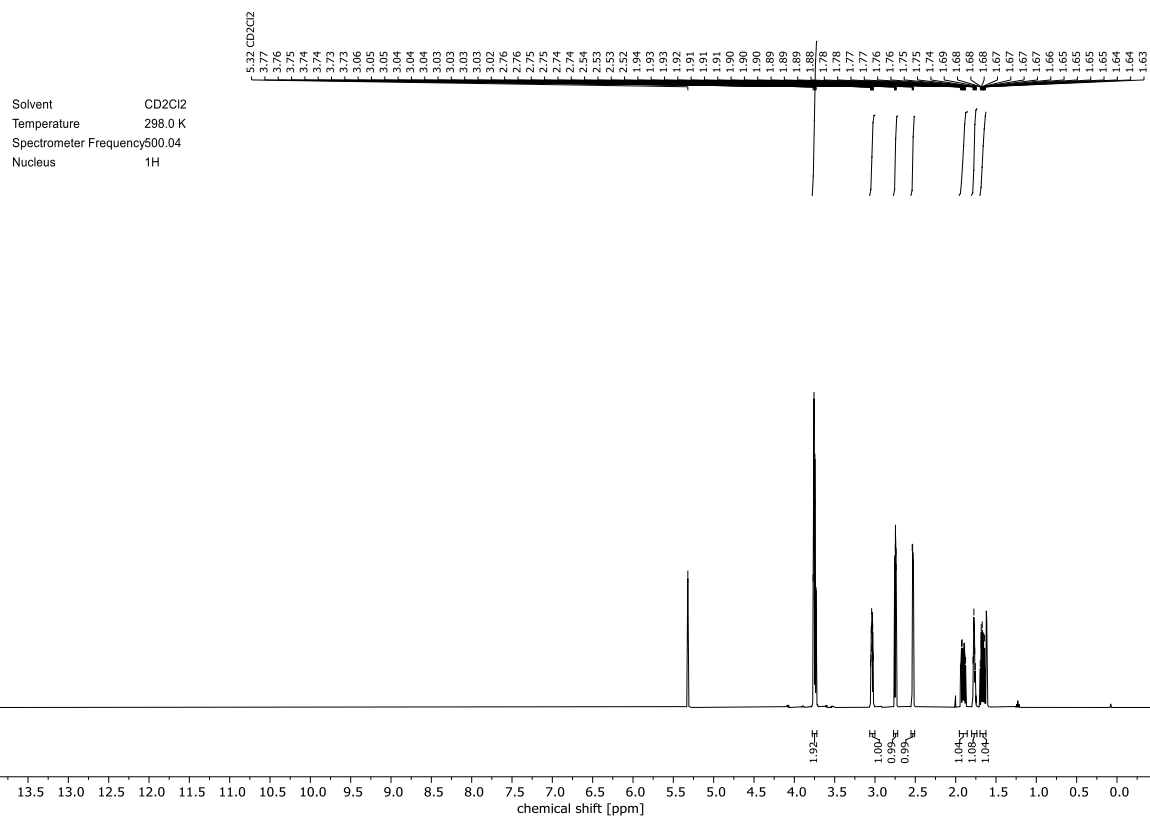
Solvent CD₂Cl₂
Temperature 298.0 K
Spectrometer Frequency 125.75
Nucleus ¹³C



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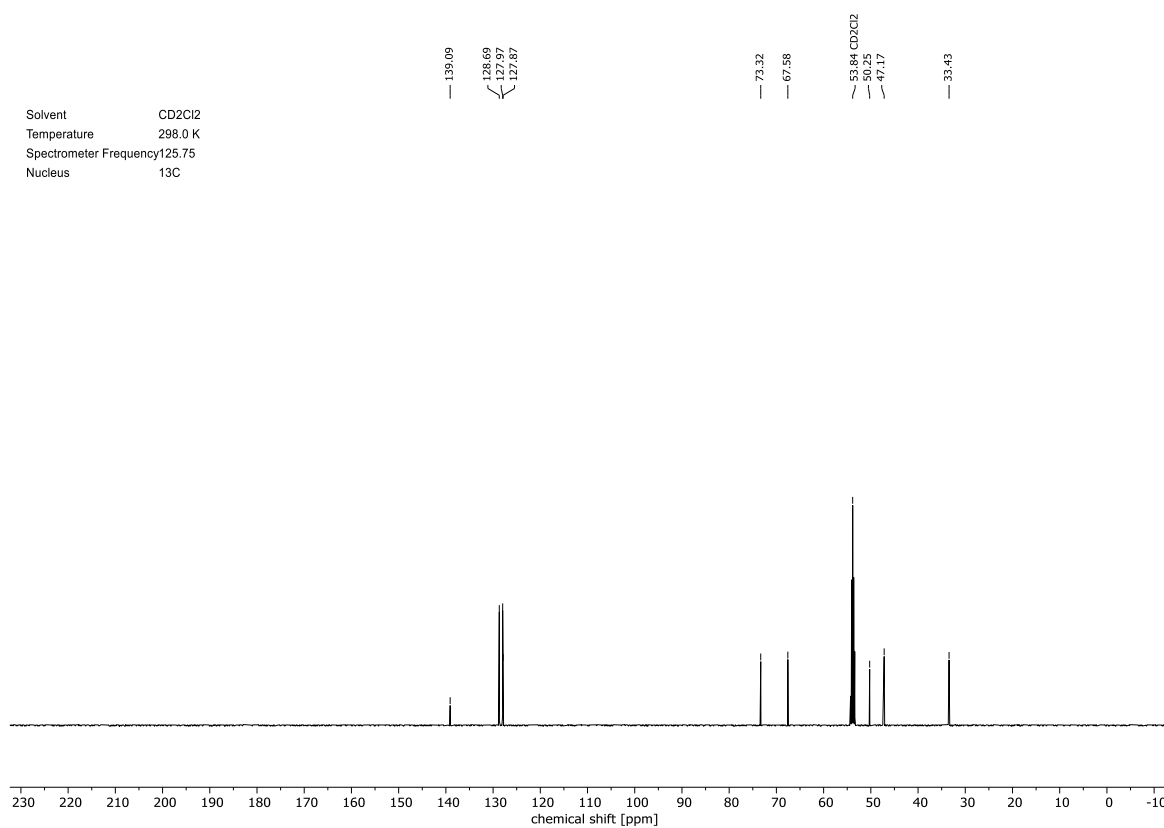
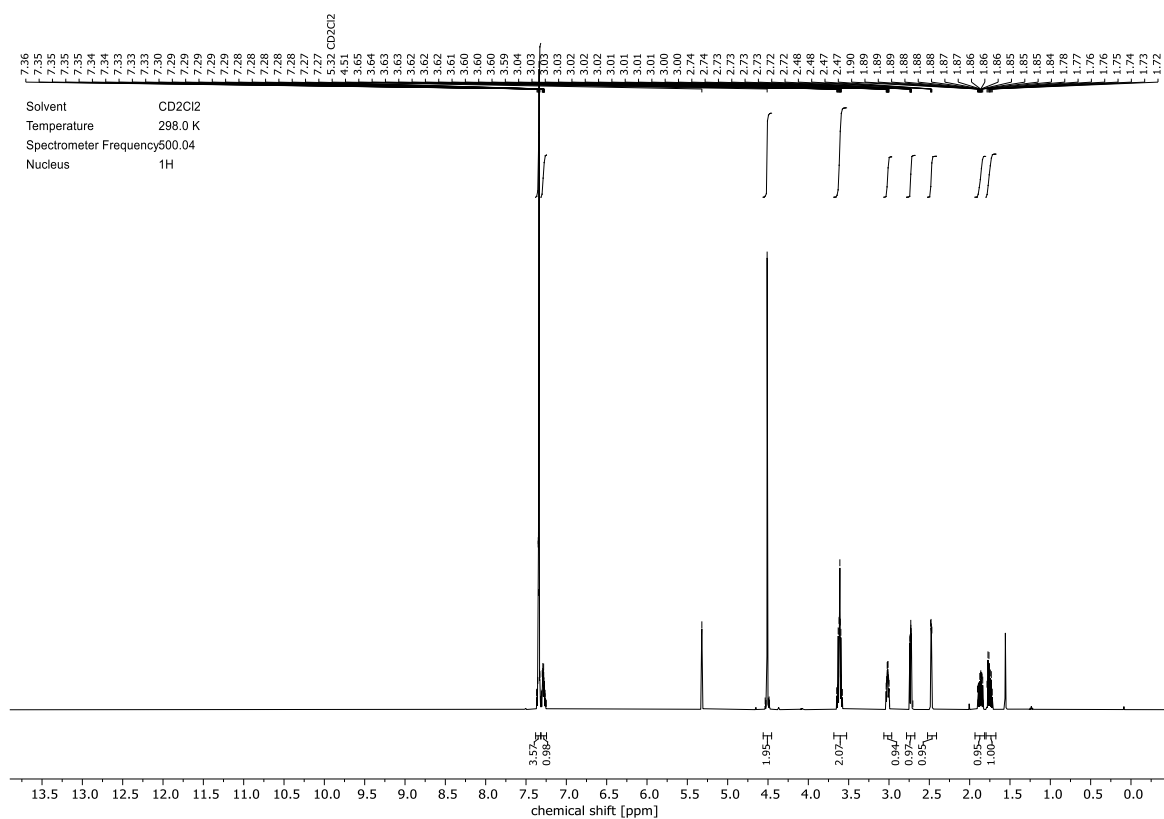
Chemical Formula: $C_4H_8O_2$
Exact Mass: 88.0524



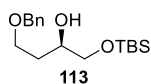
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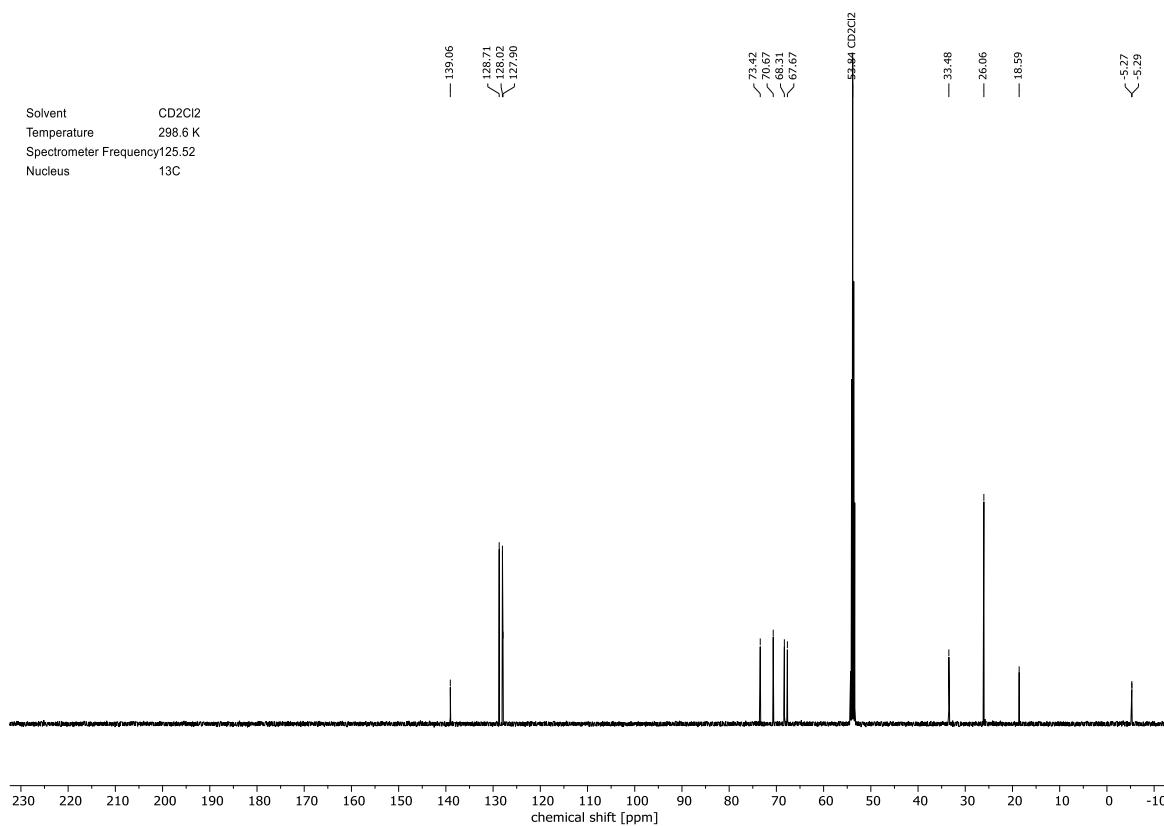
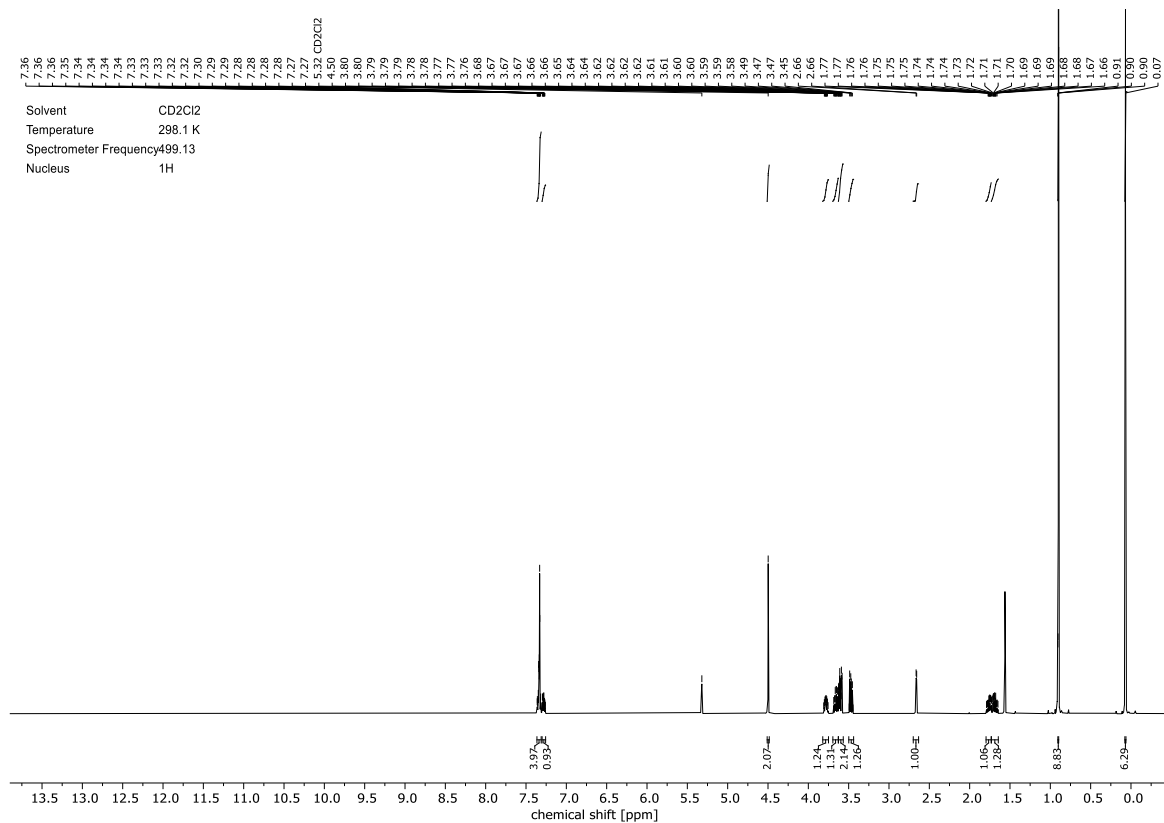
Chemical Formula: $C_{11}H_{14}O_2$
Exact Mass: 178.0994



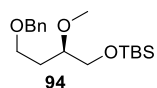
6 Copies of NMR Spectra



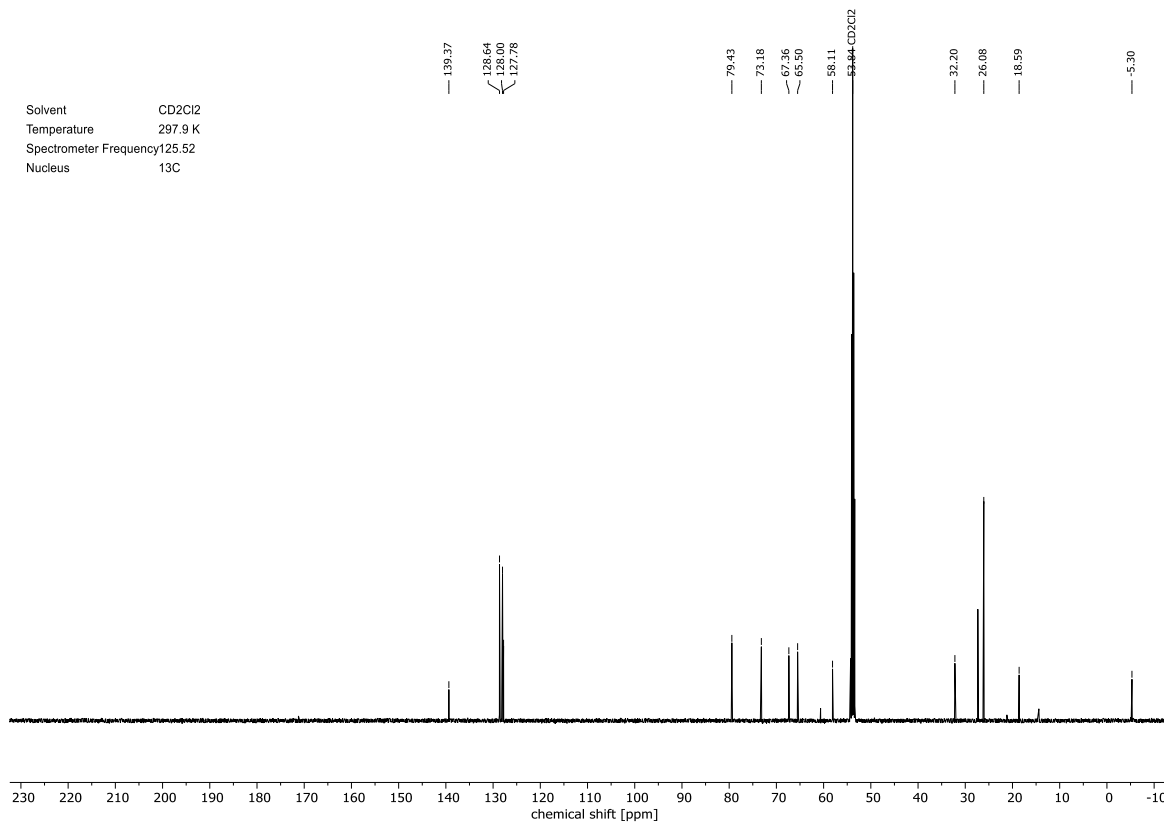
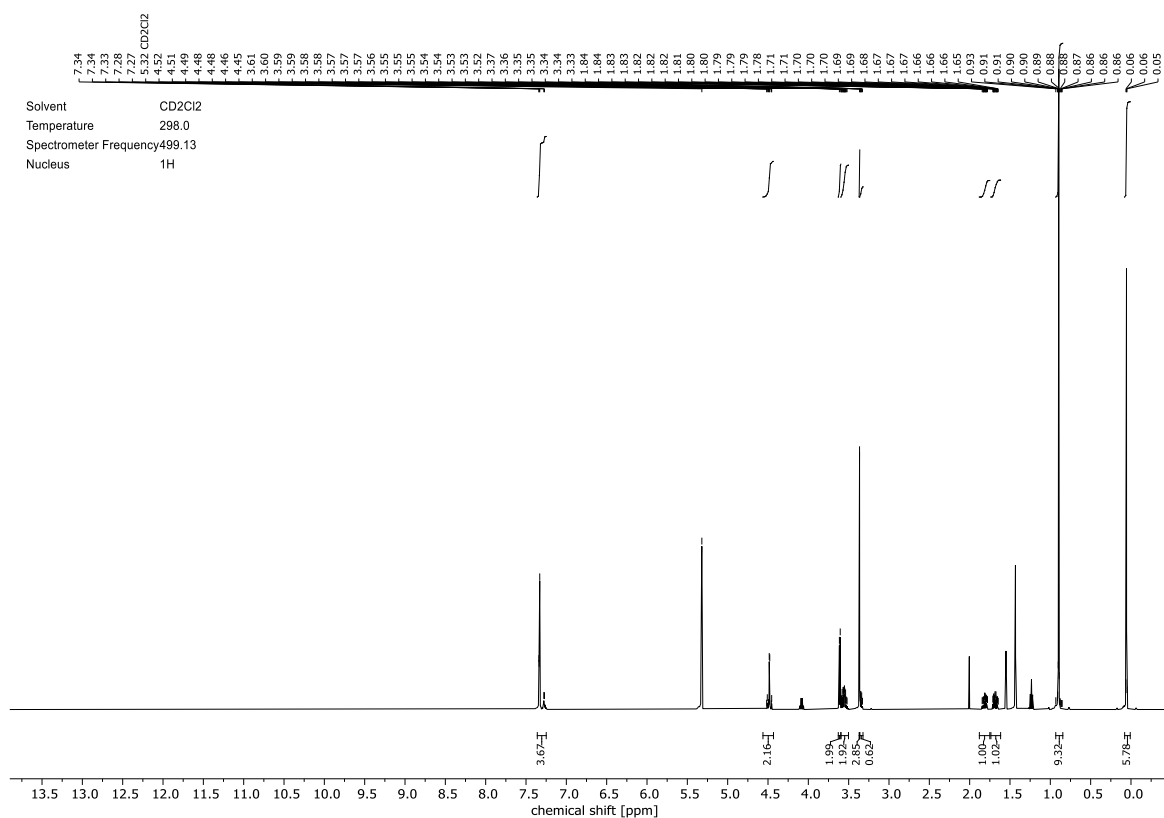
Chemical Formula: $C_{17}H_{30}O_3Si$
Exact Mass: 310.1964



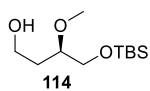
6 Copies of NMR Spectra



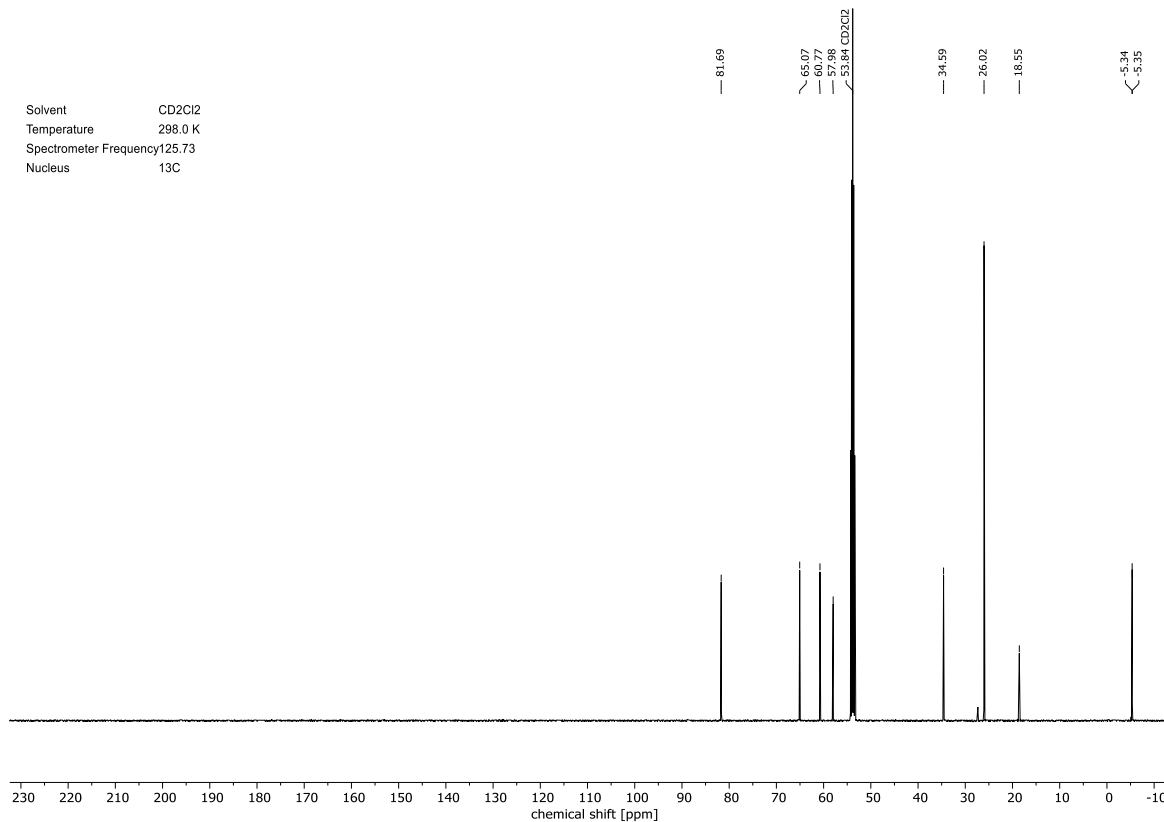
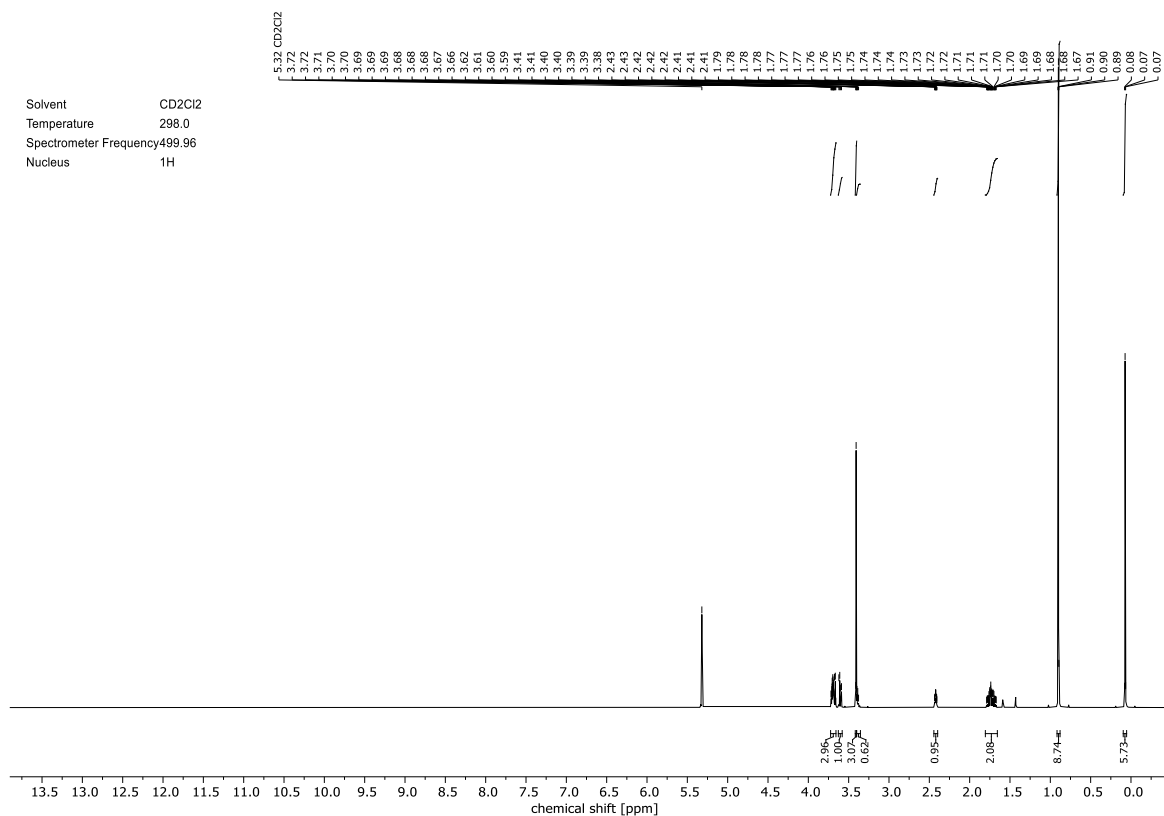
Chemical Formula: $C_{18}H_{32}O_3Si$
Exact Mass: 324.2121

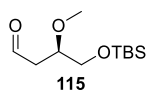


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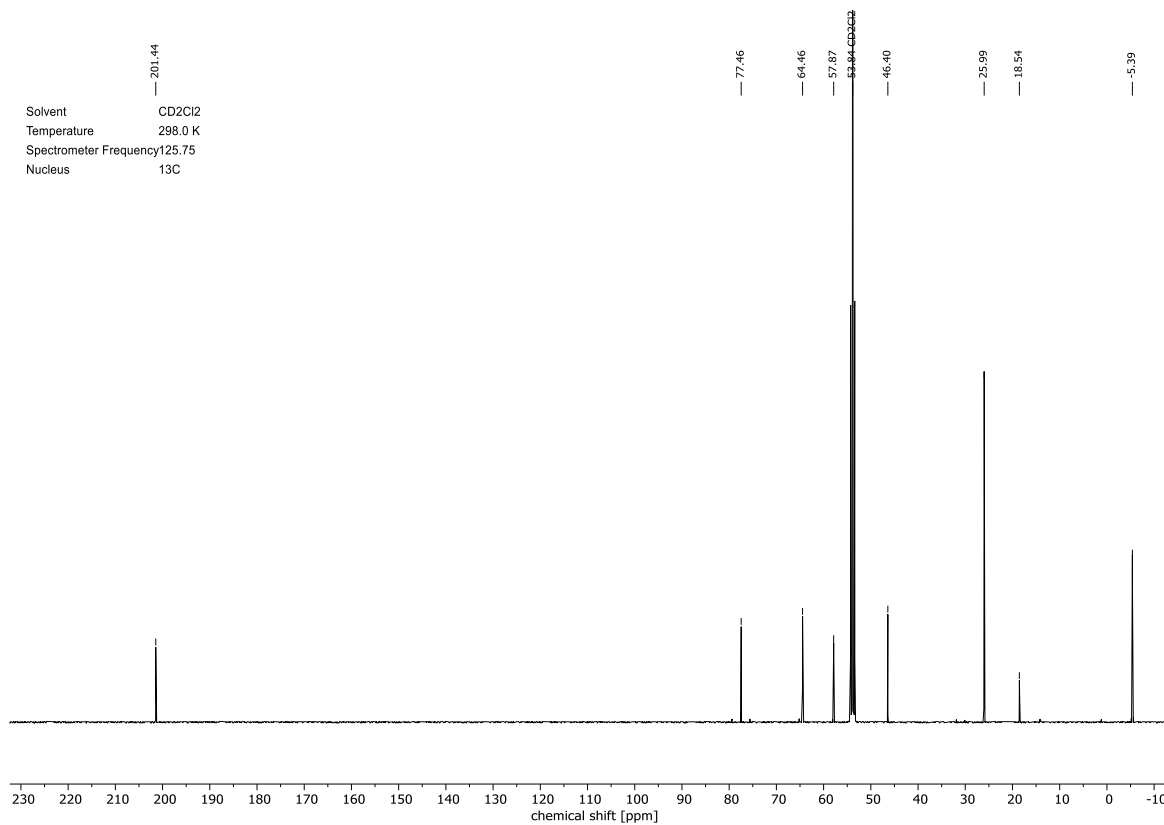
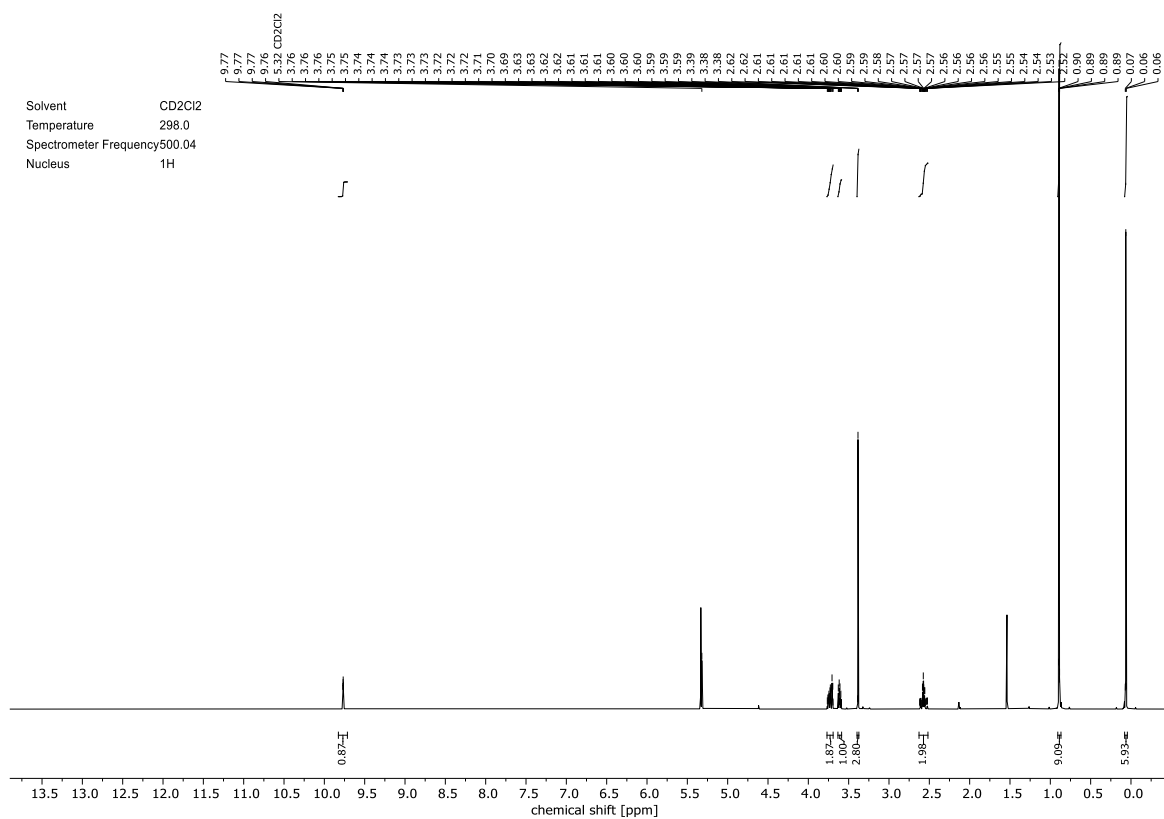


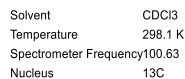
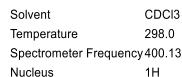
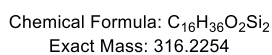
Chemical Formula: $C_{11}H_{26}O_3Si$
Exact Mass: 234.1651



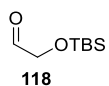


Chemical Formula: C₁₁H₂₄O₃Si
Exact Mass: 232.1495

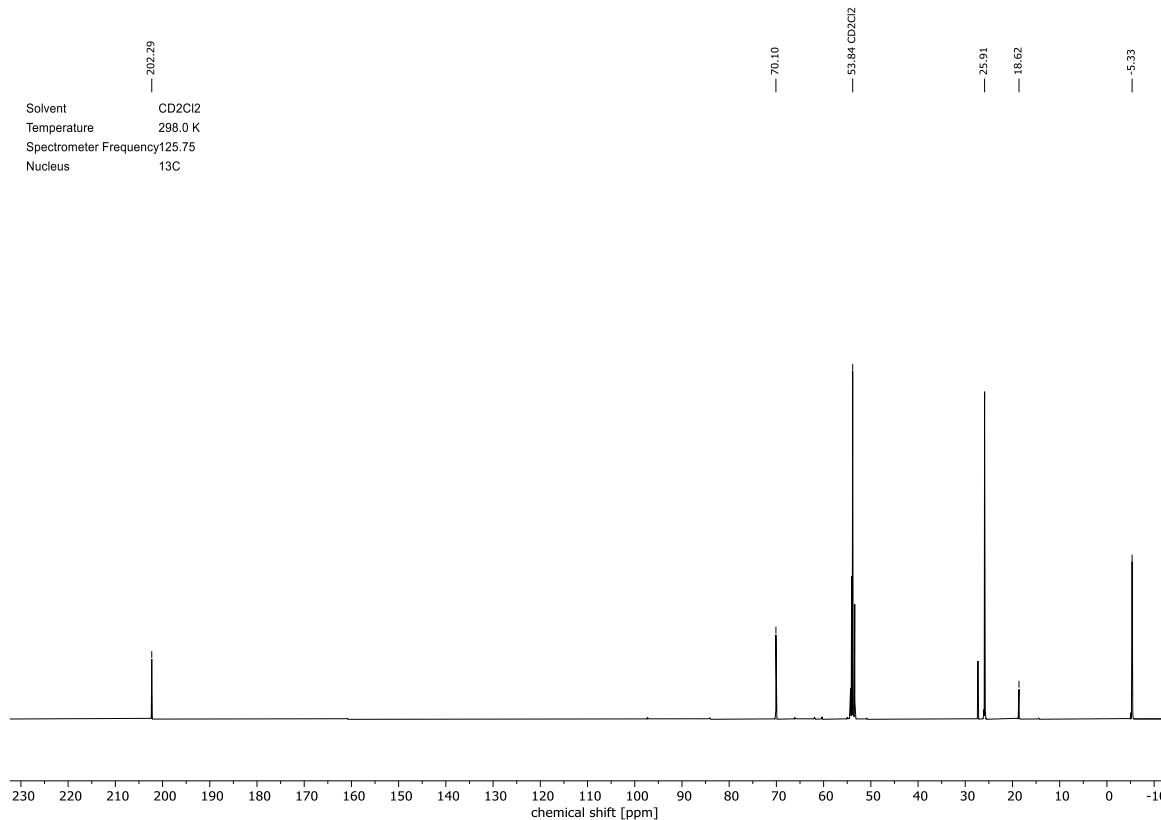
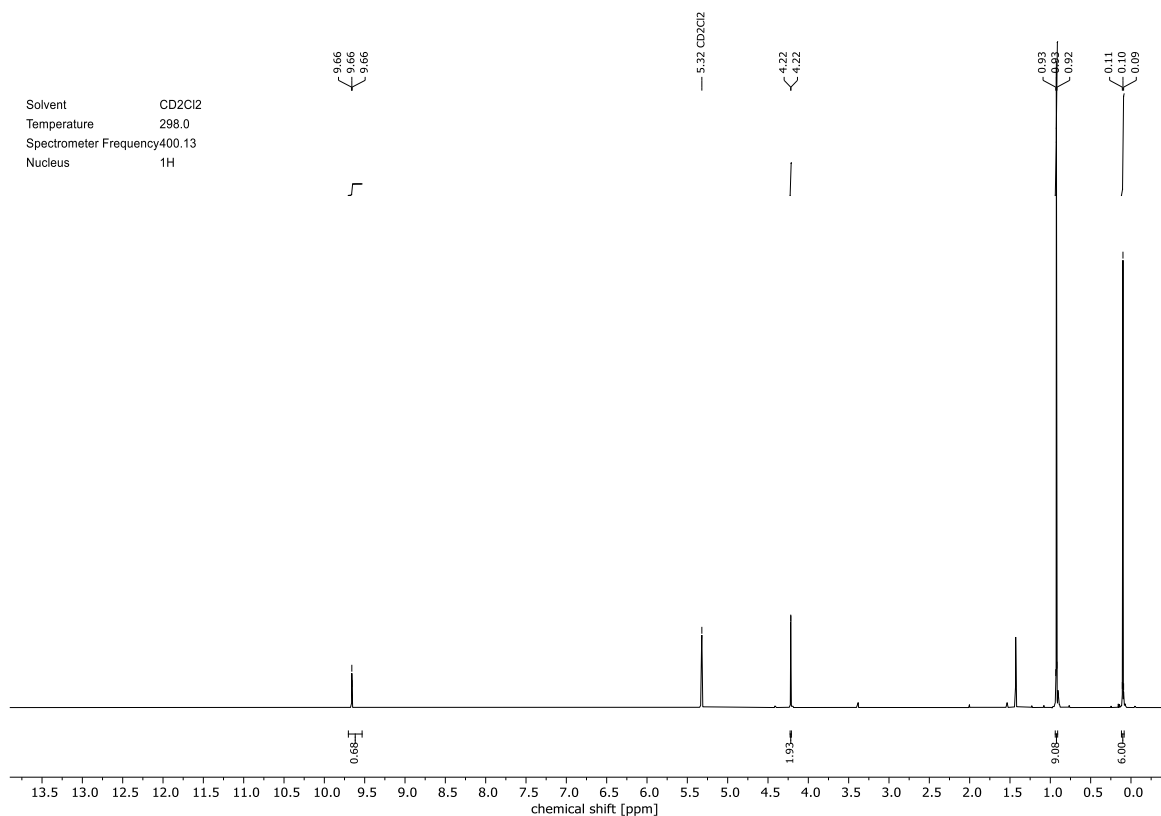


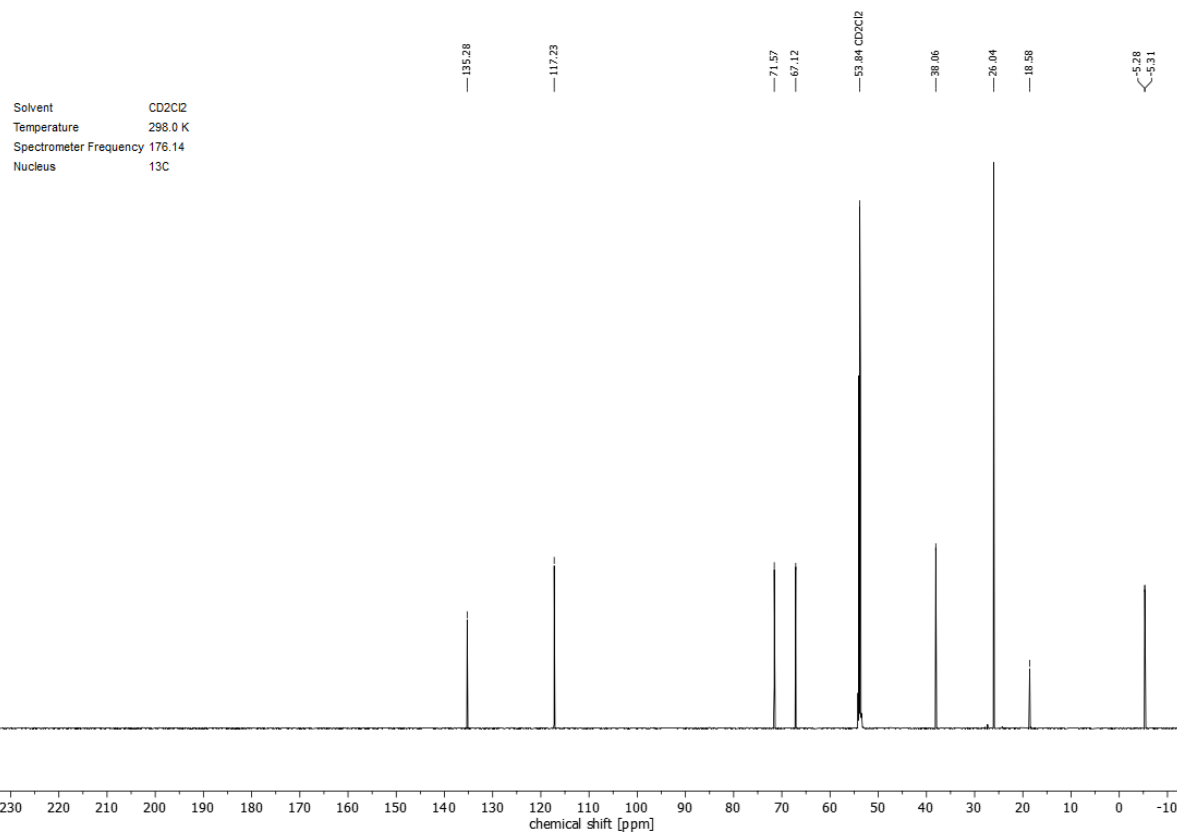
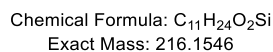


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Chemical Formula: C₈H₁₈O₂Si
Exact Mass: 174.1076

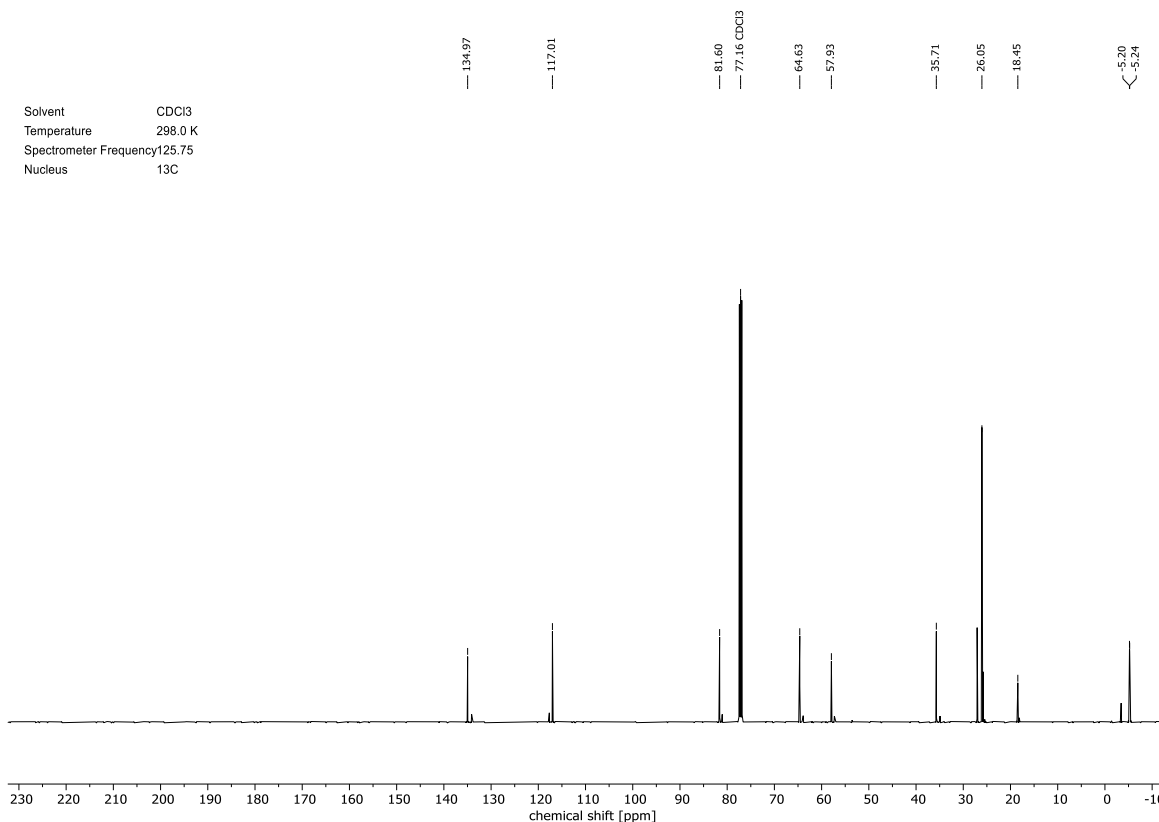
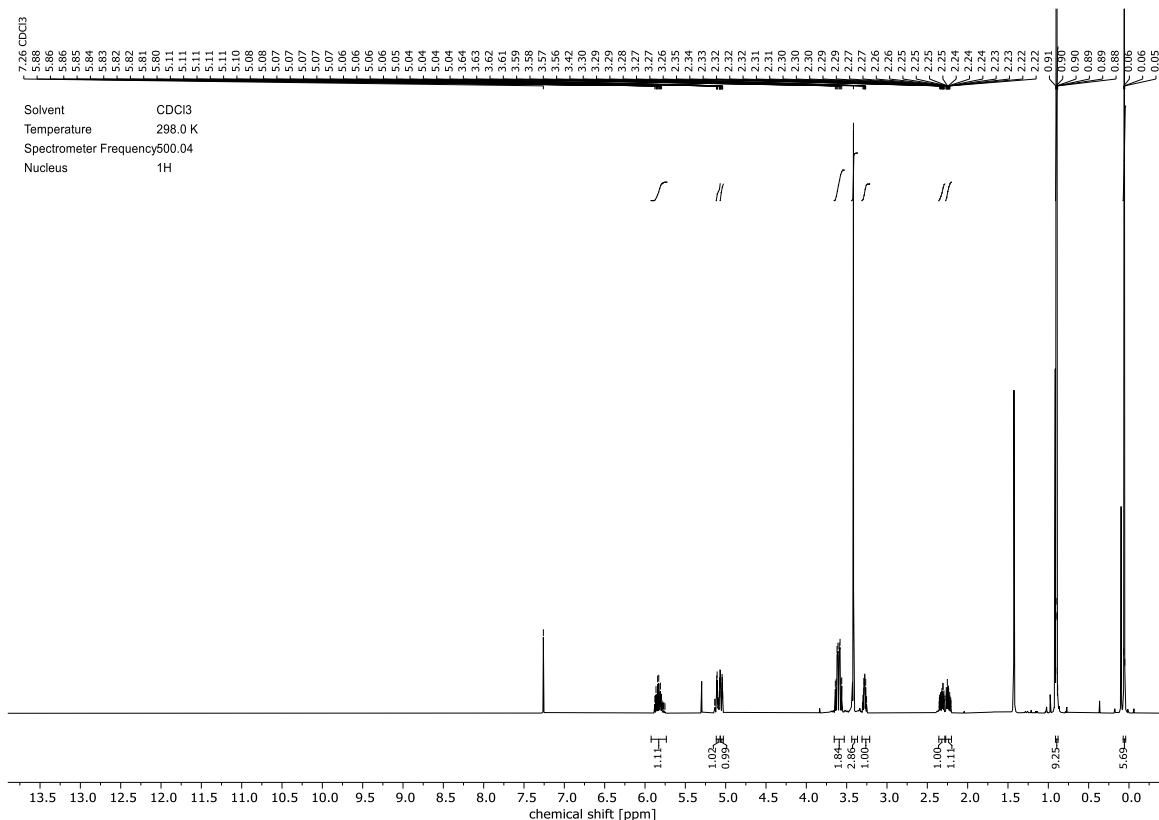




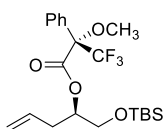
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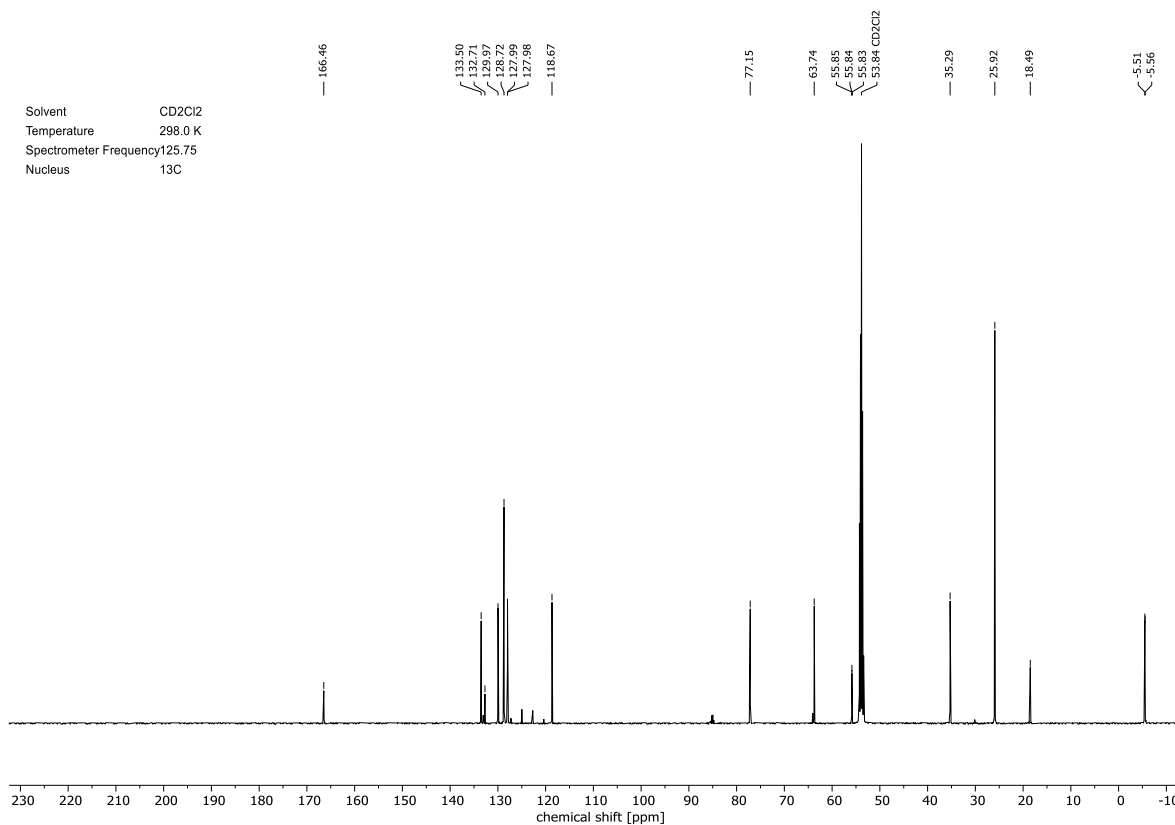
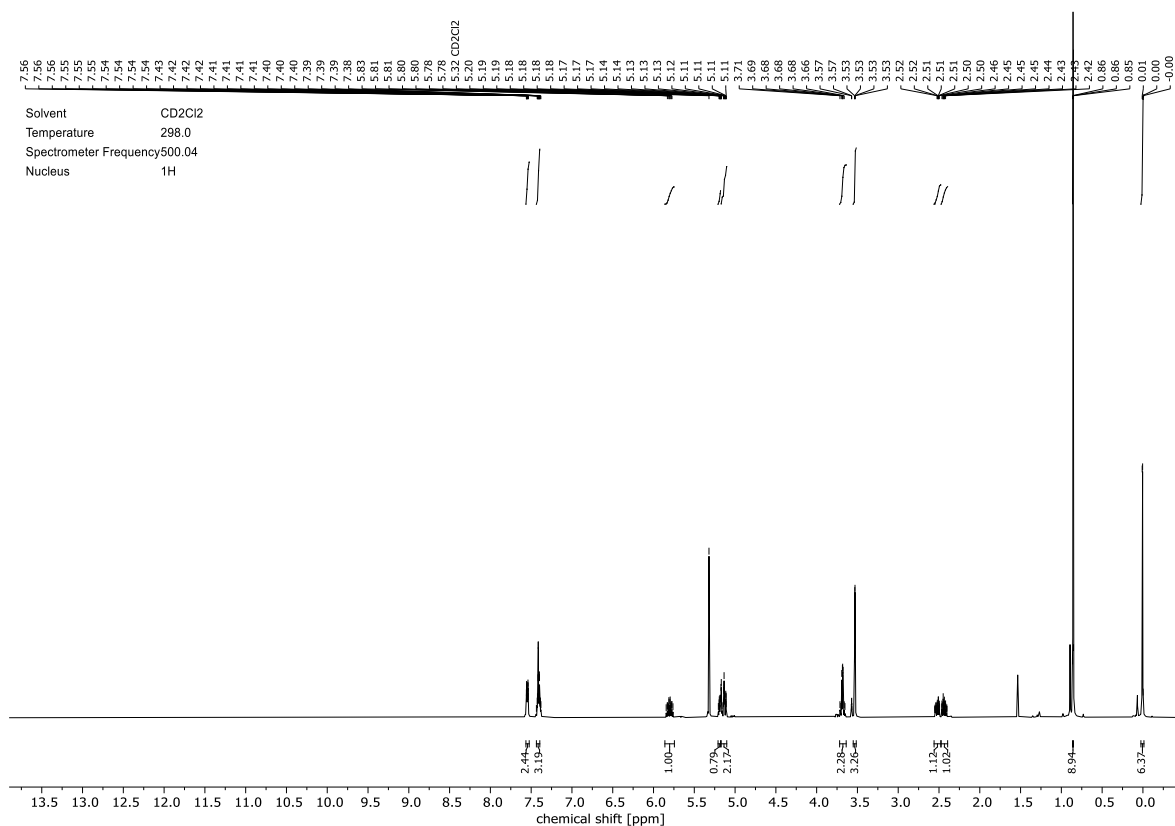
Chemical Formula: $C_{12}H_{26}O_2Si$
Exact Mass: 230.1702



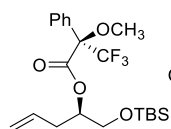
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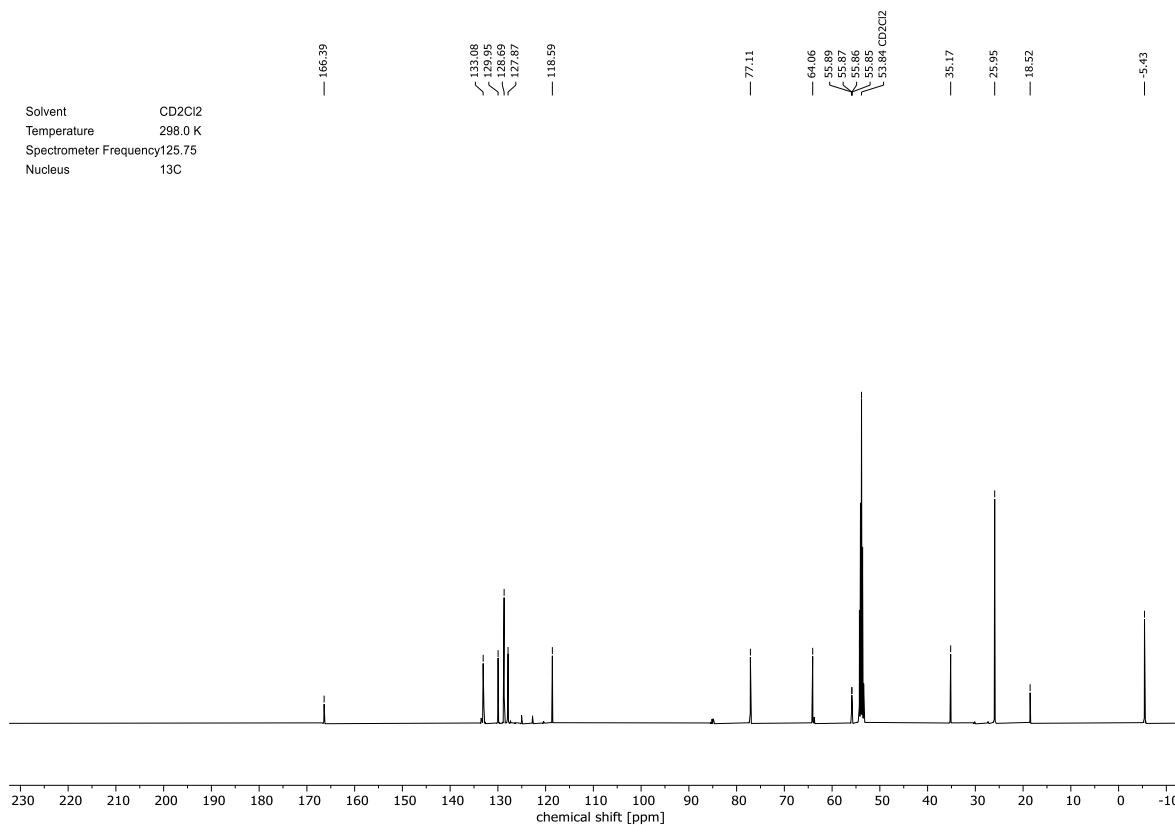
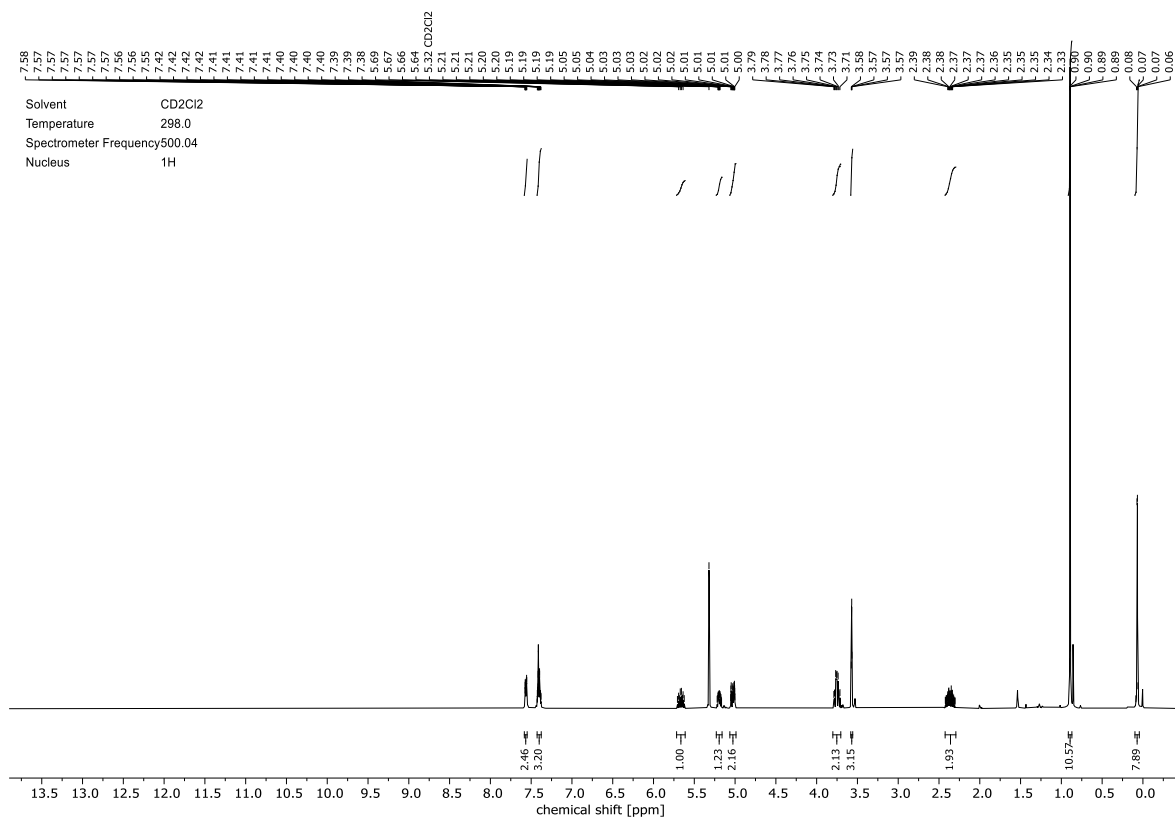
124
Chemical Formula: $C_{21}H_{31}F_3O_4Si$
Exact Mass: 432.1944



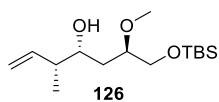
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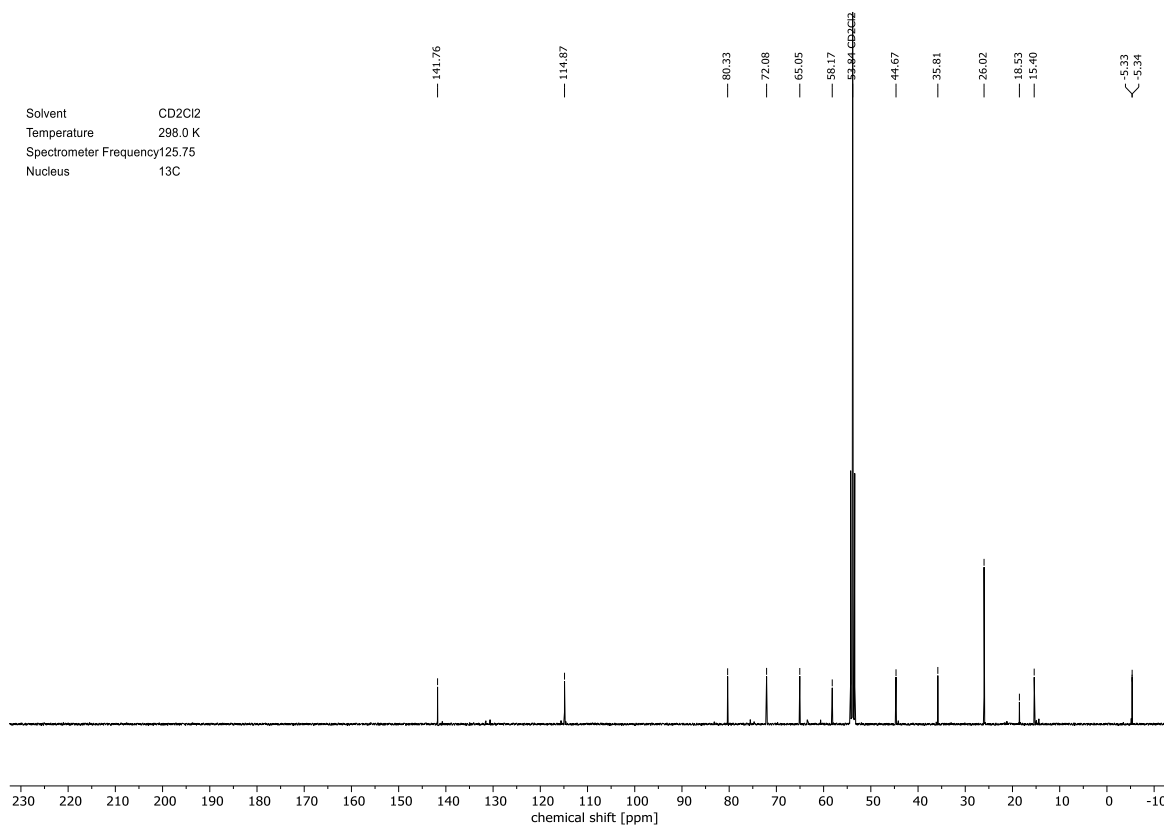
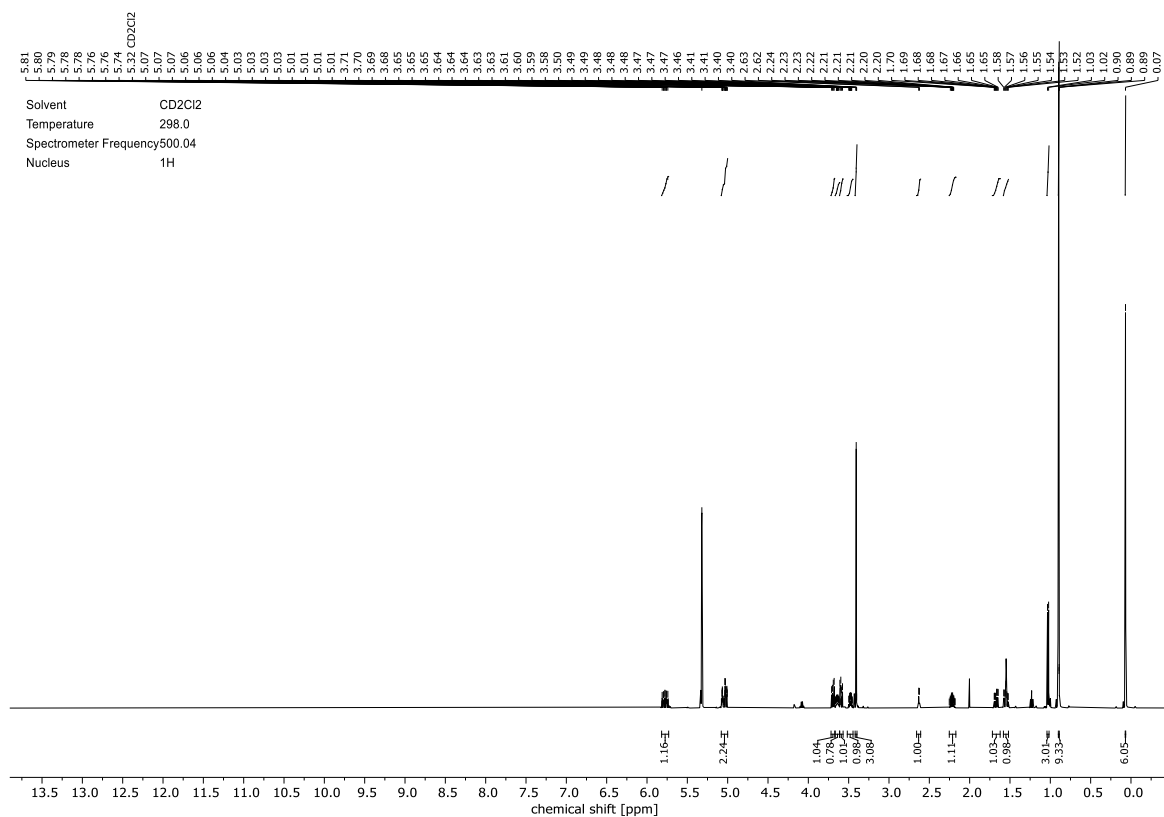
125
Chemical Formula: $C_{21}H_{31}F_3O_4Si$
Exact Mass: 432.1944



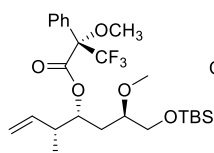
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Chemical Formula: $C_{15}H_{32}O_3Si$
Exact Mass: 288.2121



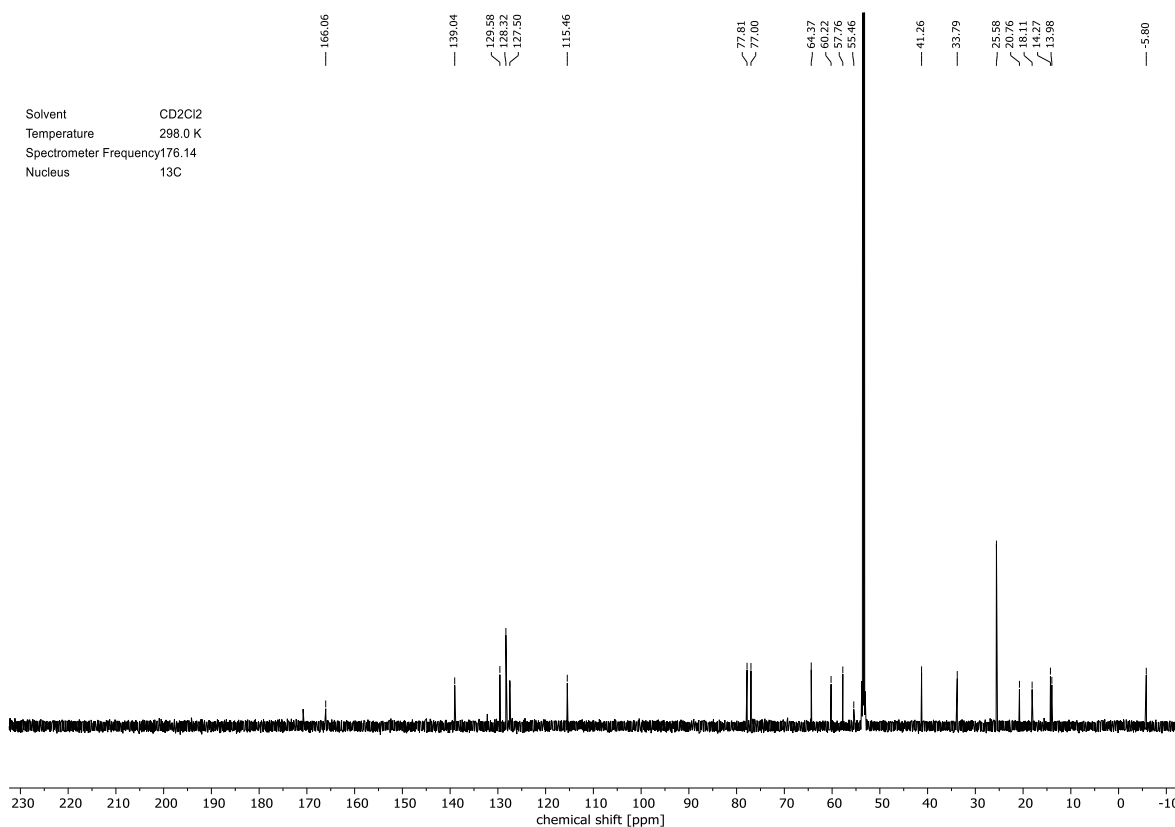
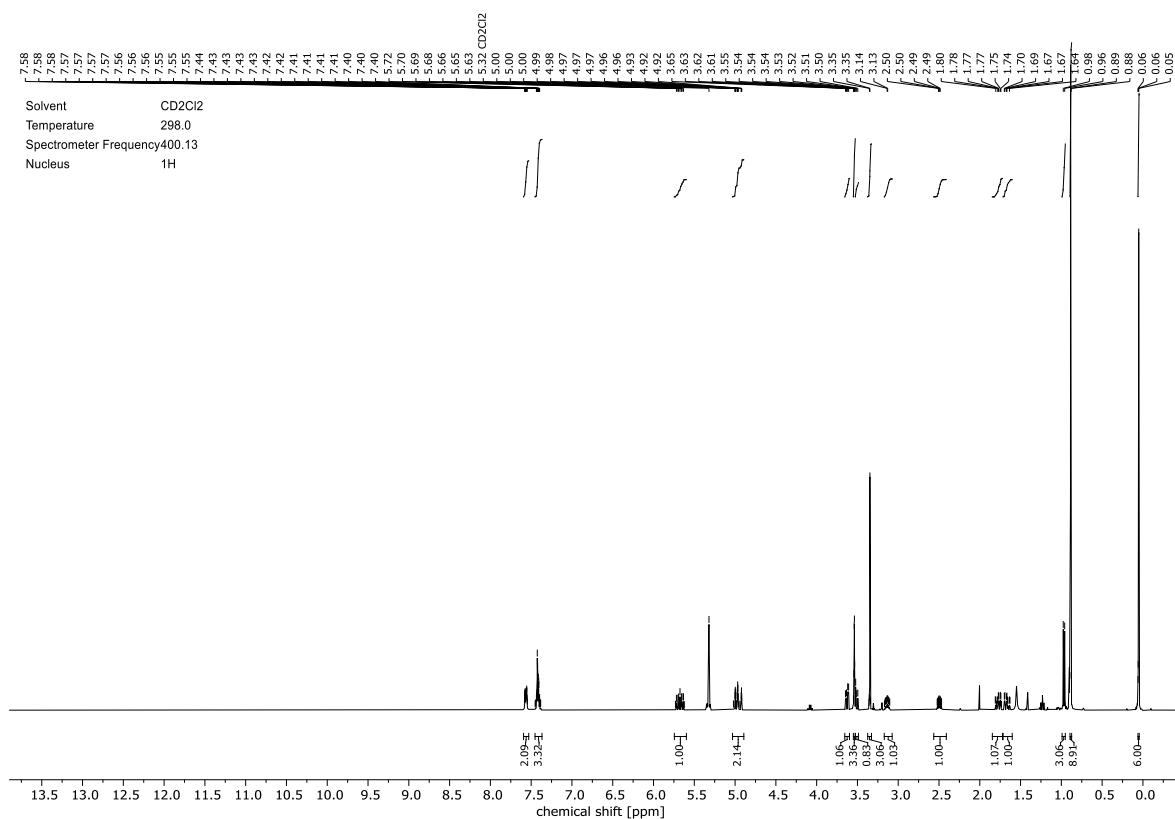
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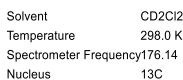
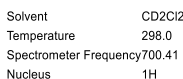
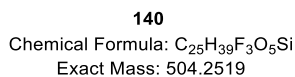


139

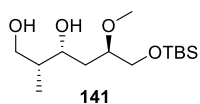
Chemical Formula: $C_{25}H_{36}F_3O_5Si$

Exact Mass: 504.2519

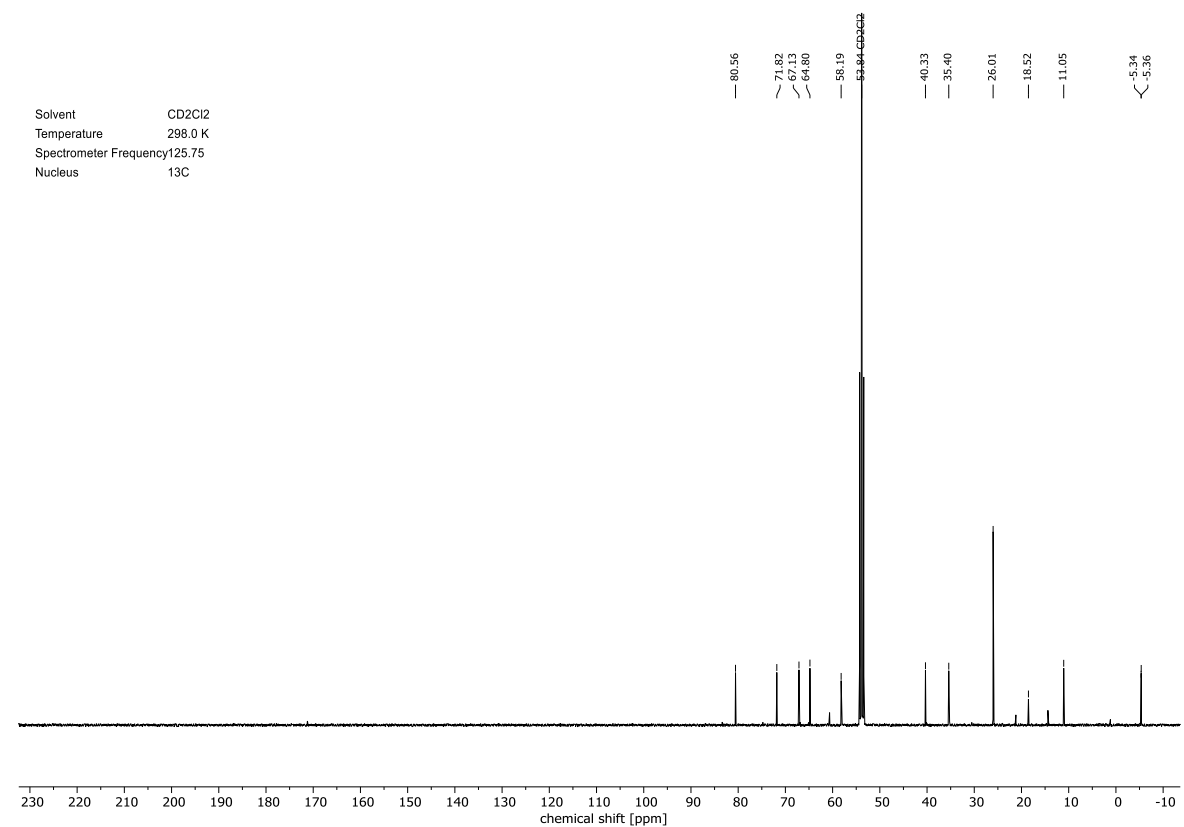
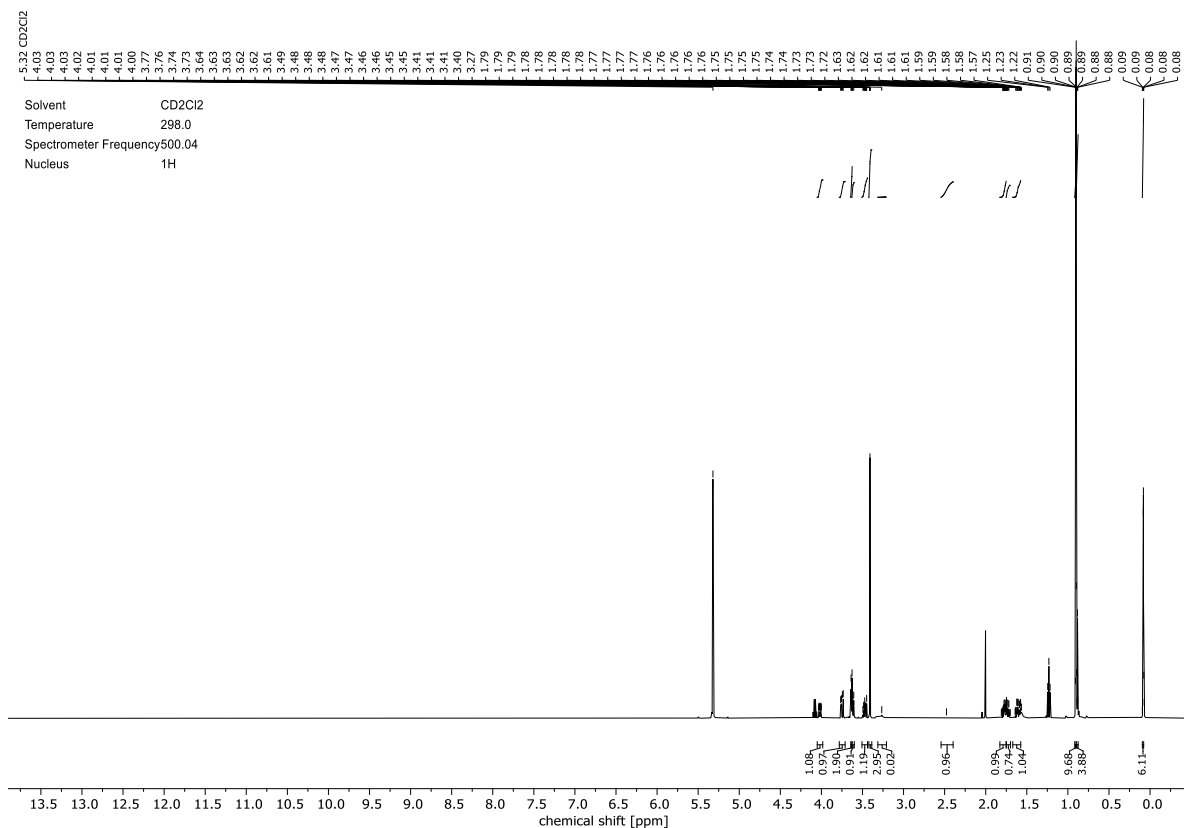




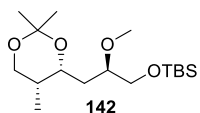
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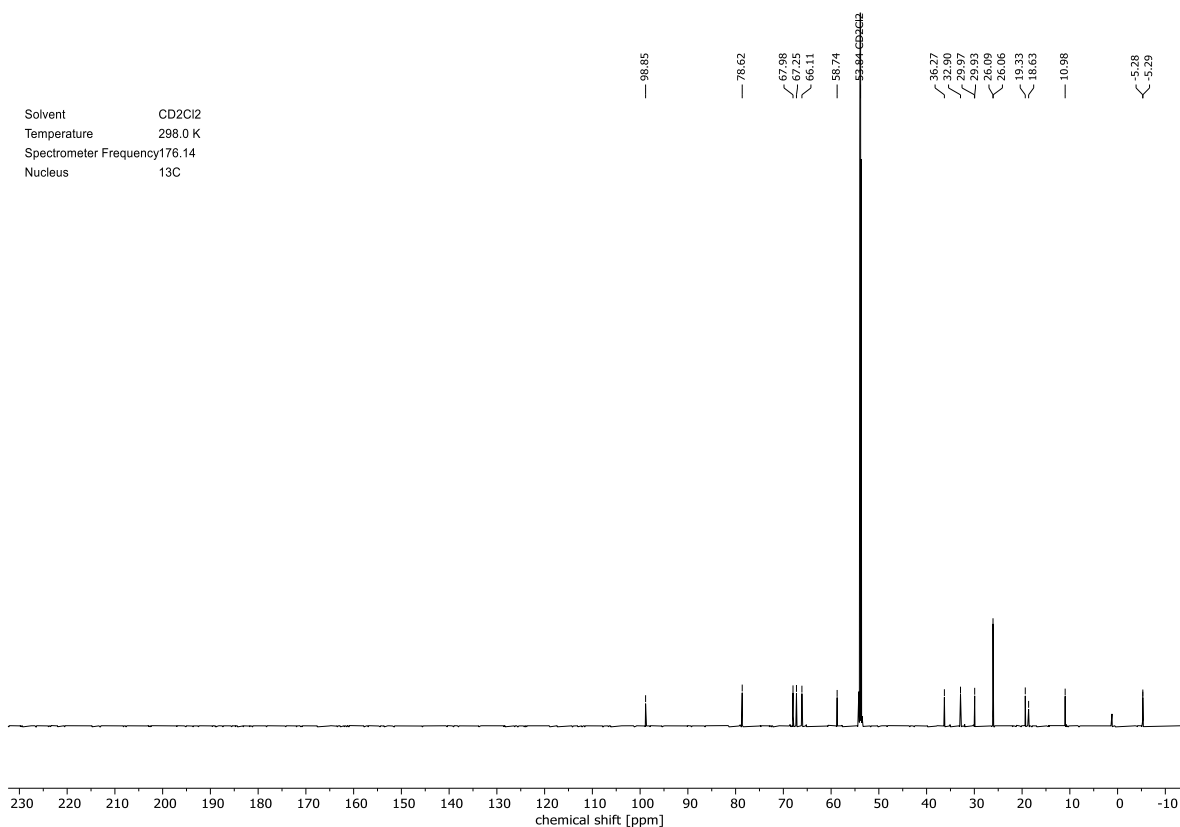
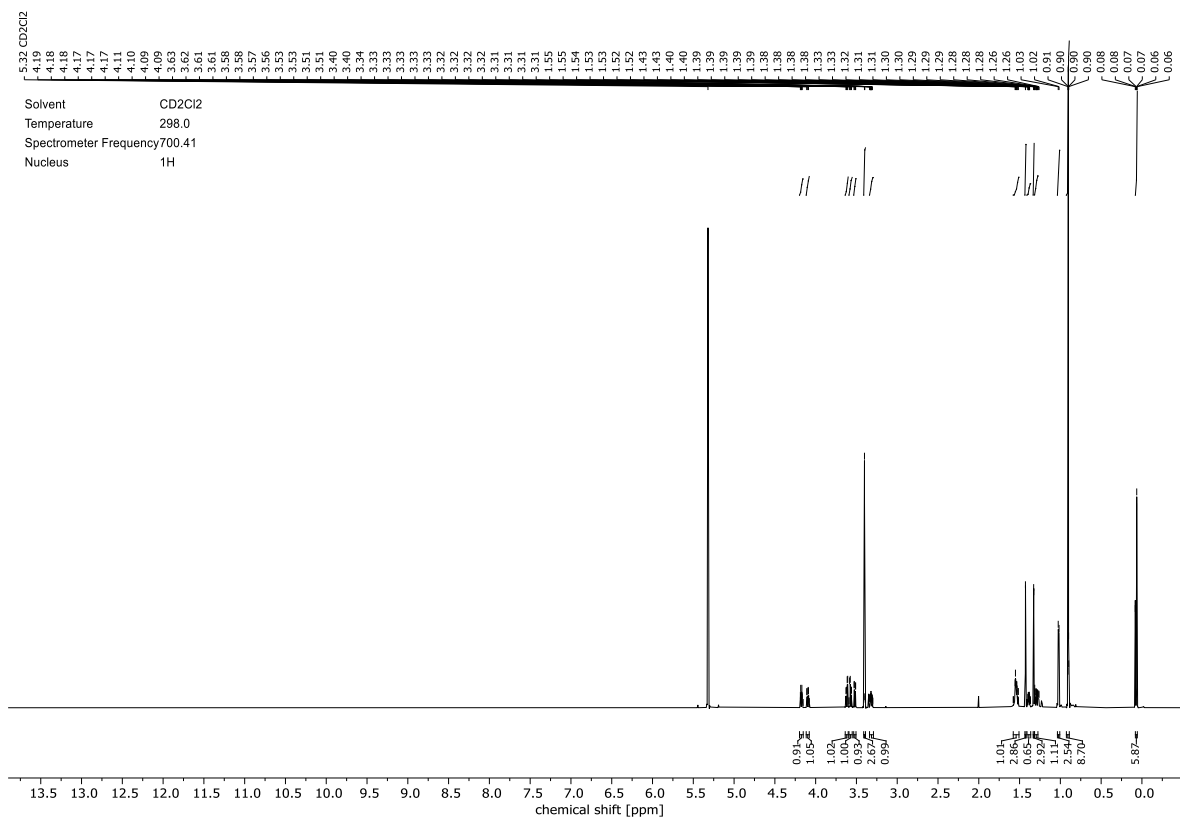
Chemical Formula: $C_{14}H_{32}O_4Si$
Exact Mass: 292.2070



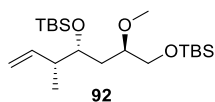
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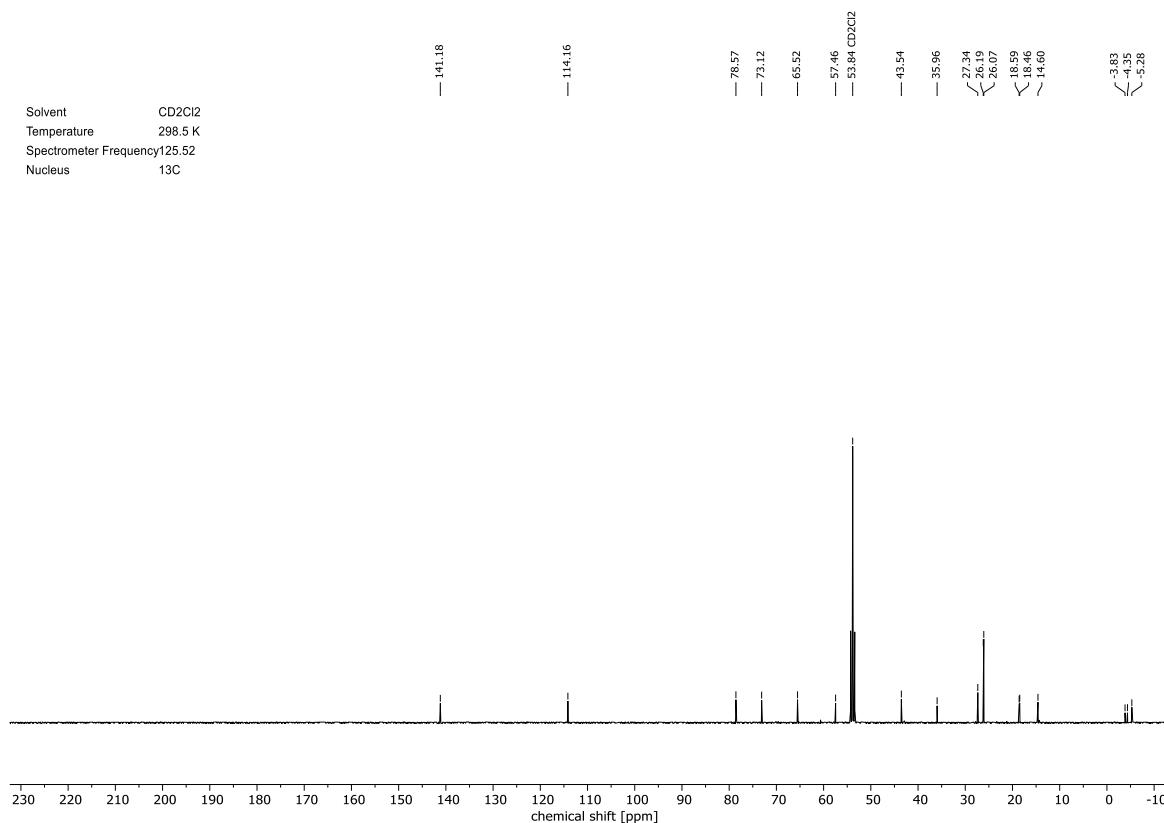
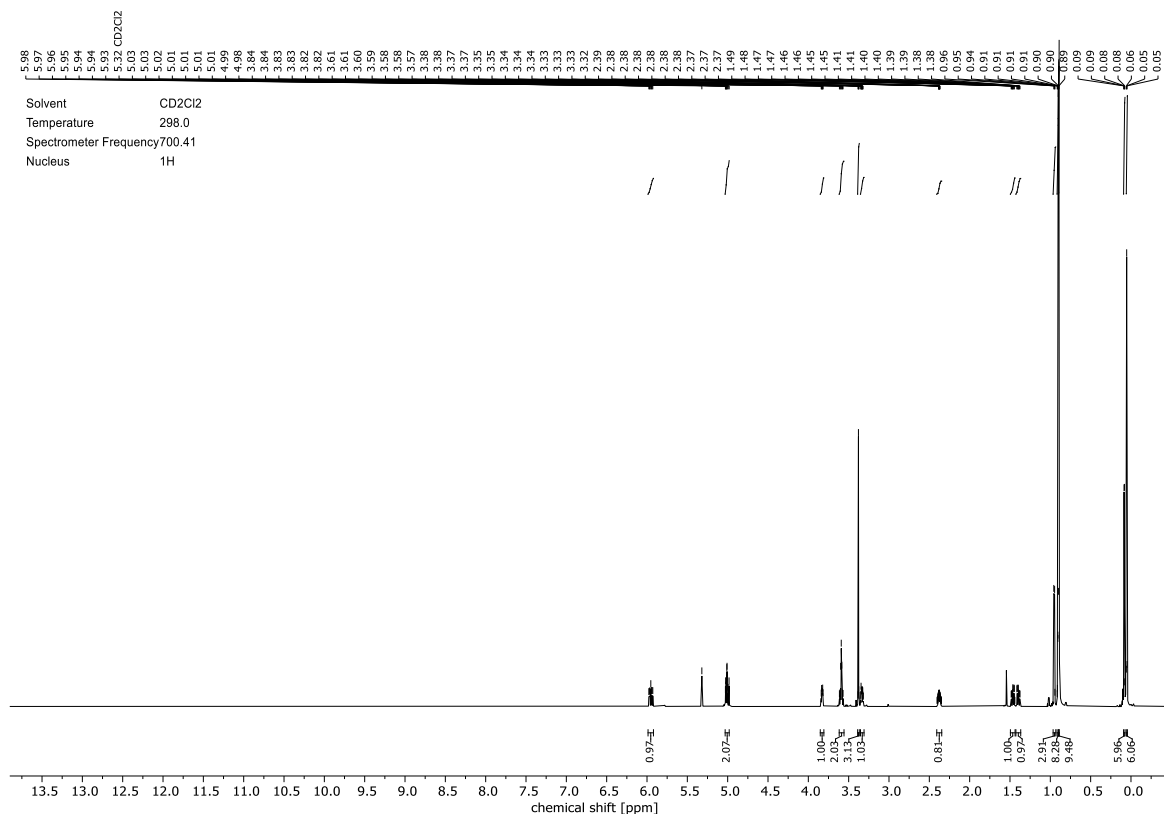
Chemical Formula: $C_{17}H_{36}O_4Si$
Exact Mass: 332.2383



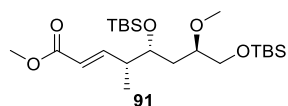
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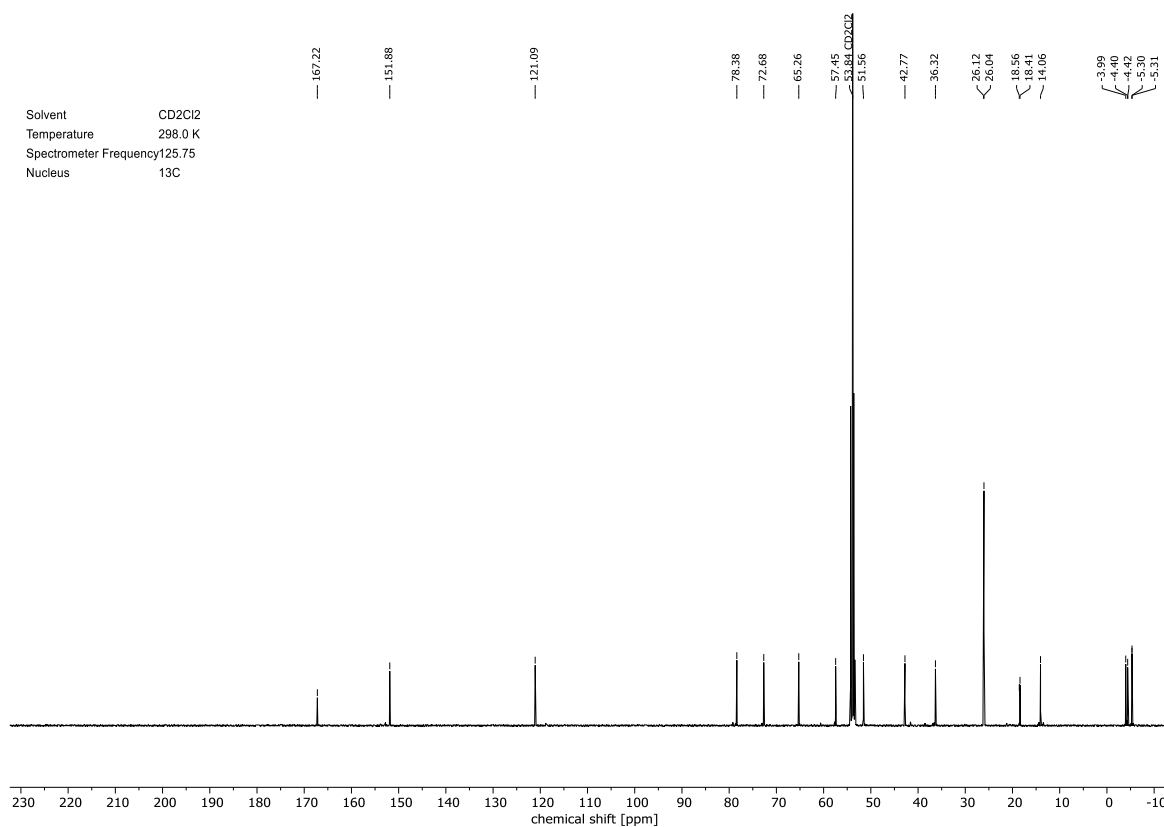
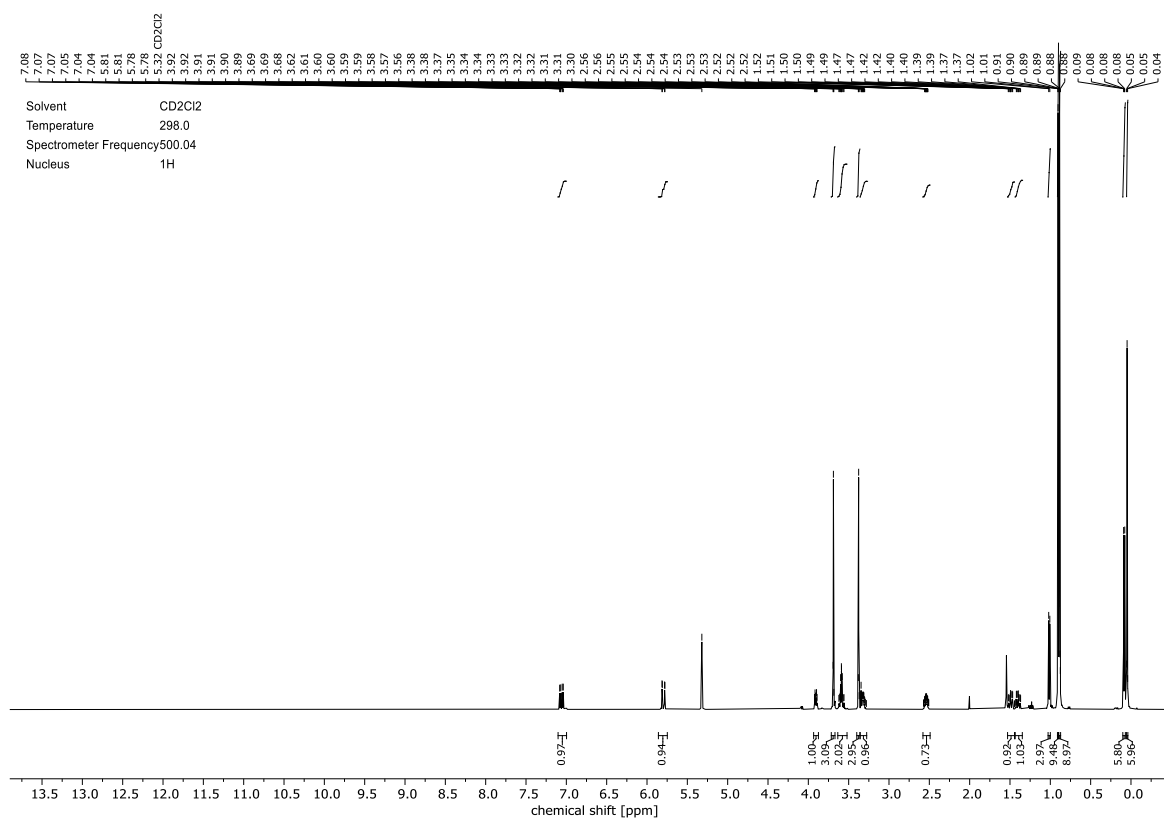
Chemical Formula: $C_{21}H_{46}O_3Si_2$
Exact Mass: 402.2985



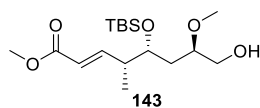
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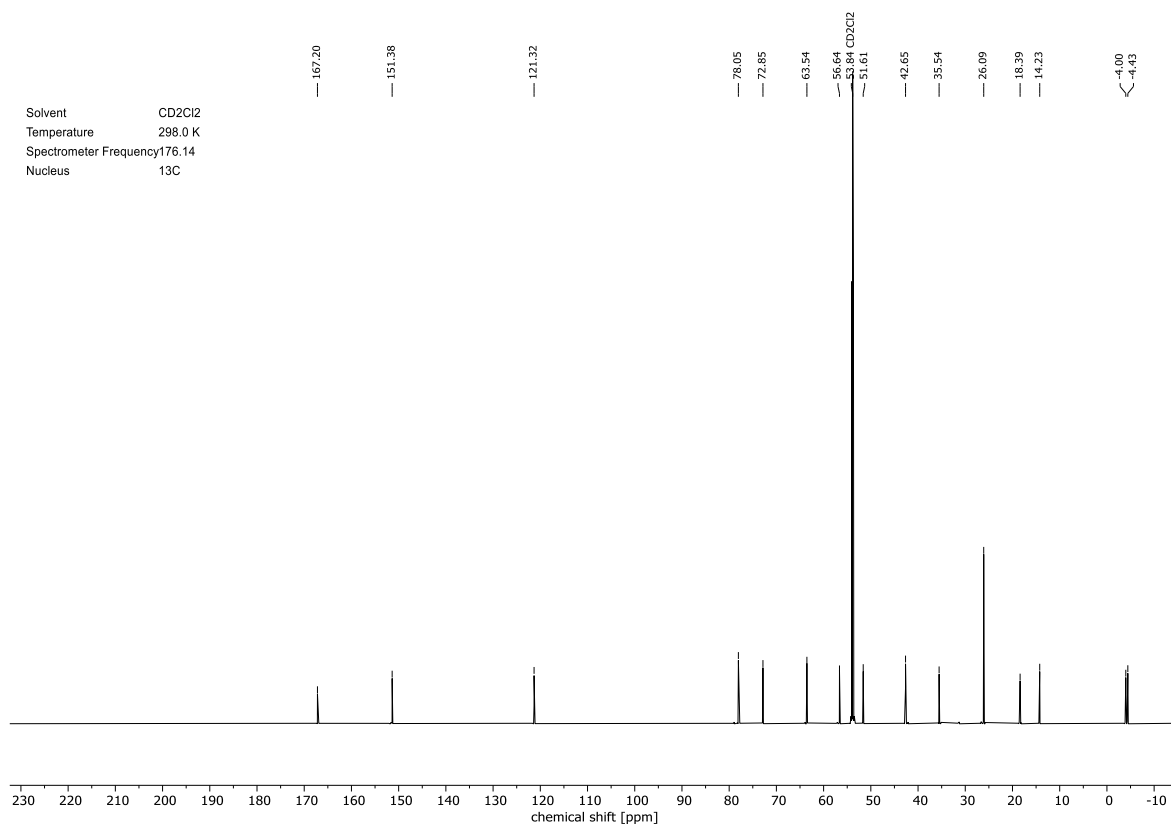
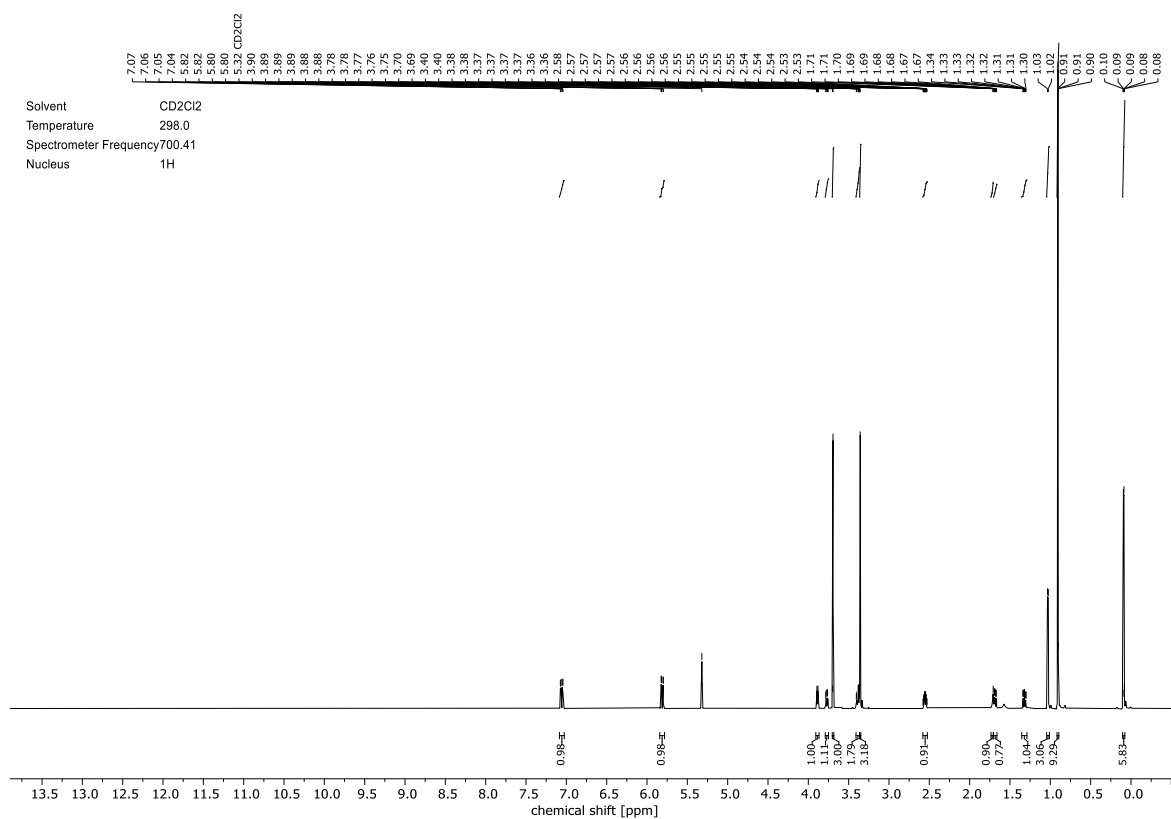
Chemical Formula: $C_{23}H_{48}O_5Si_2$
Exact Mass: 460.3040



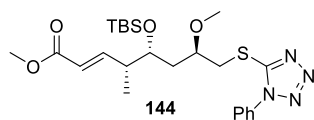
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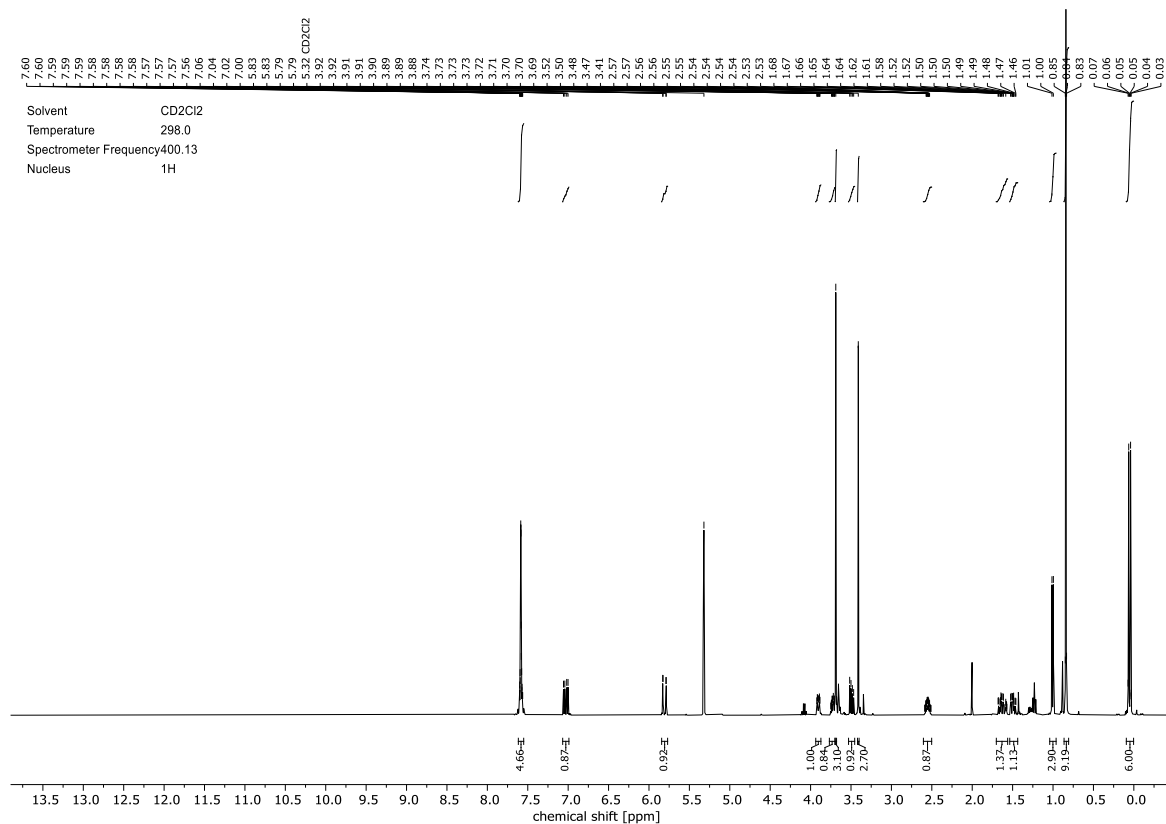
Chemical Formula: $C_{17}H_{34}O_5Si$
Exact Mass: 346.2176



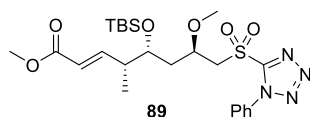
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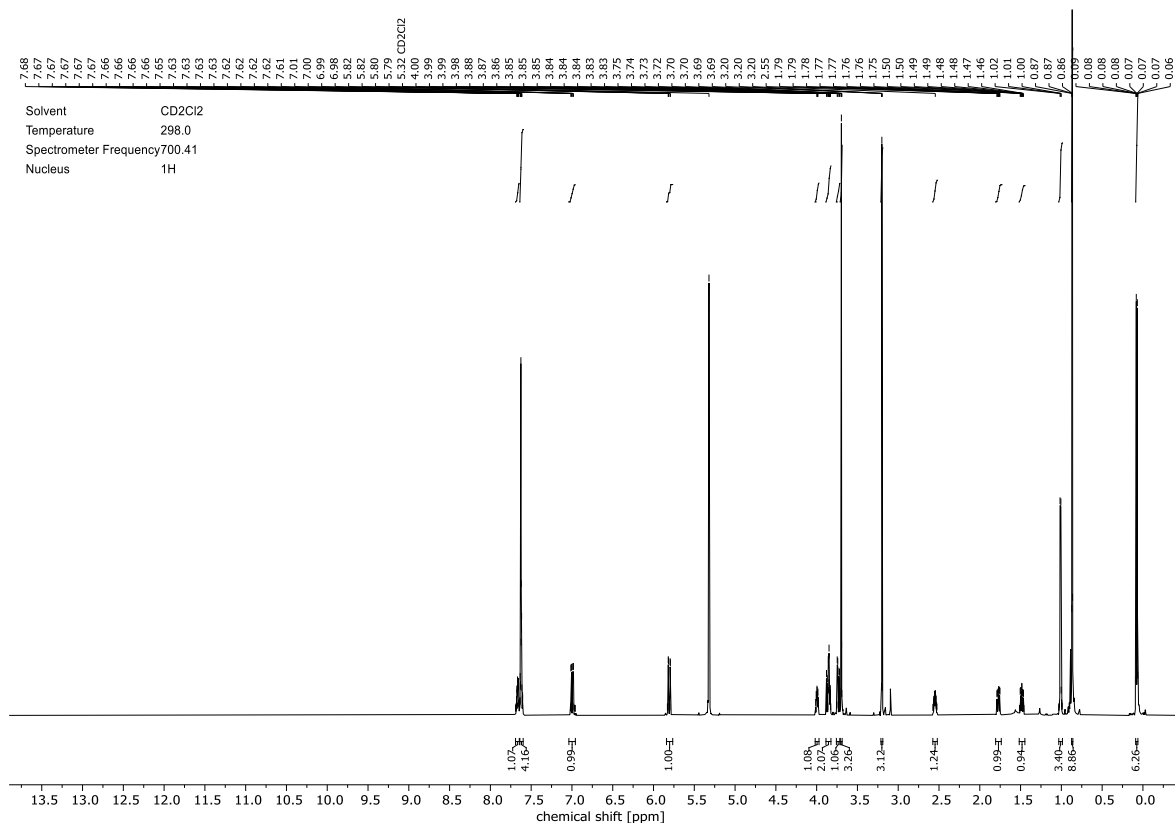
Chemical Formula: $C_{24}H_{38}N_4O_4Si$
Exact Mass: 506.2383



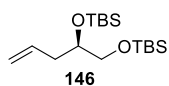
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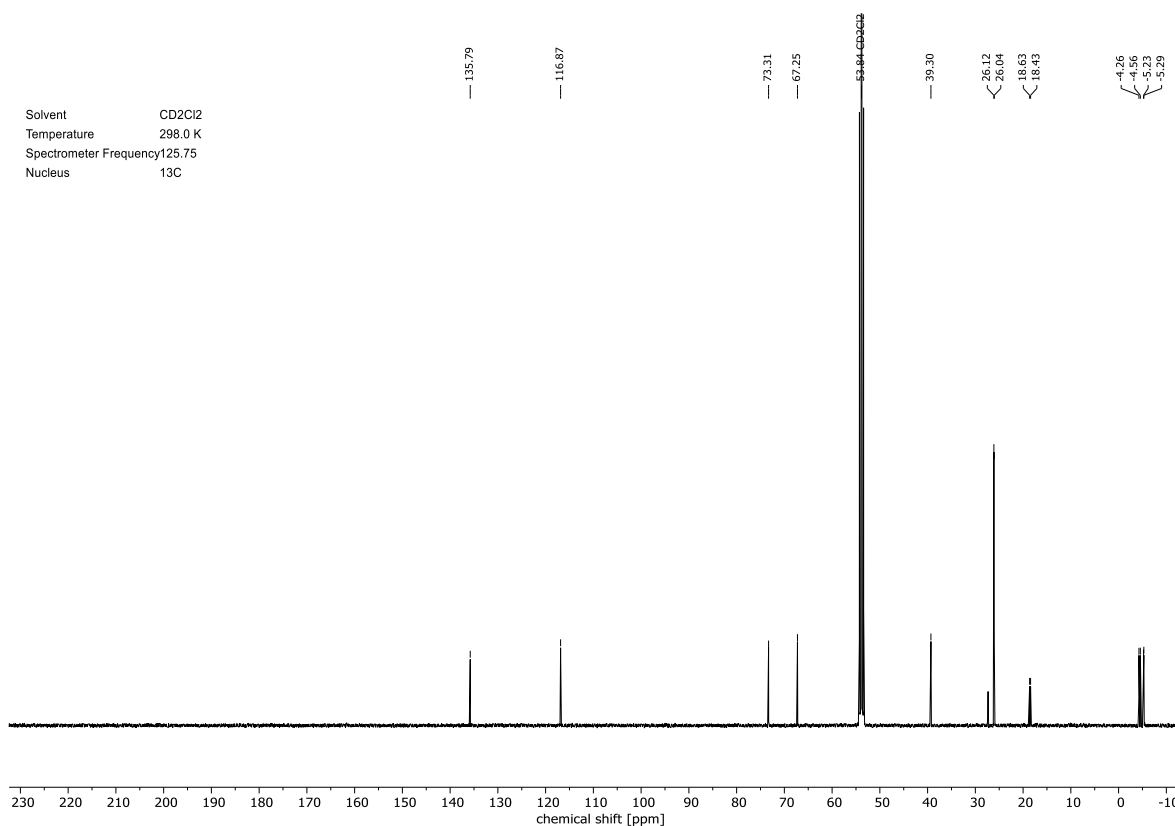
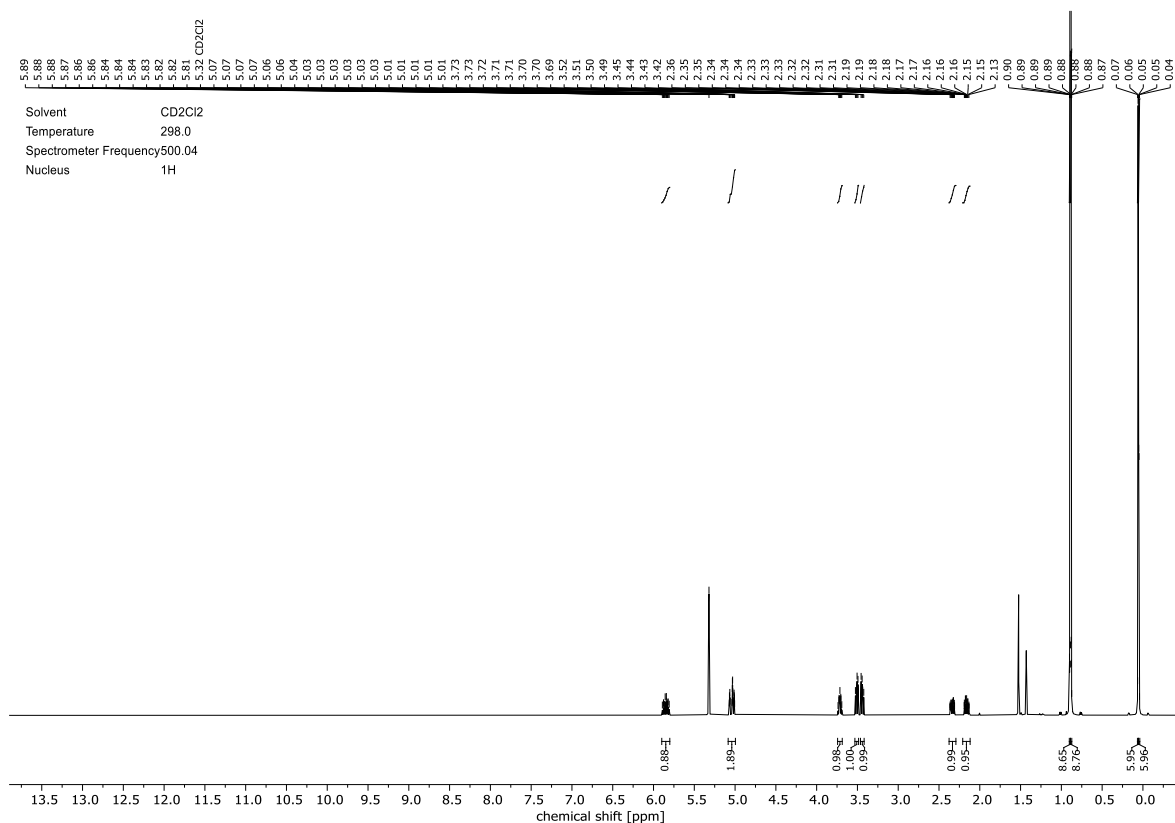
Chemical Formula: $C_{24}H_{38}N_4O_6SSi$
Exact Mass: 538.2281



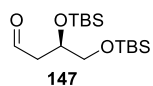
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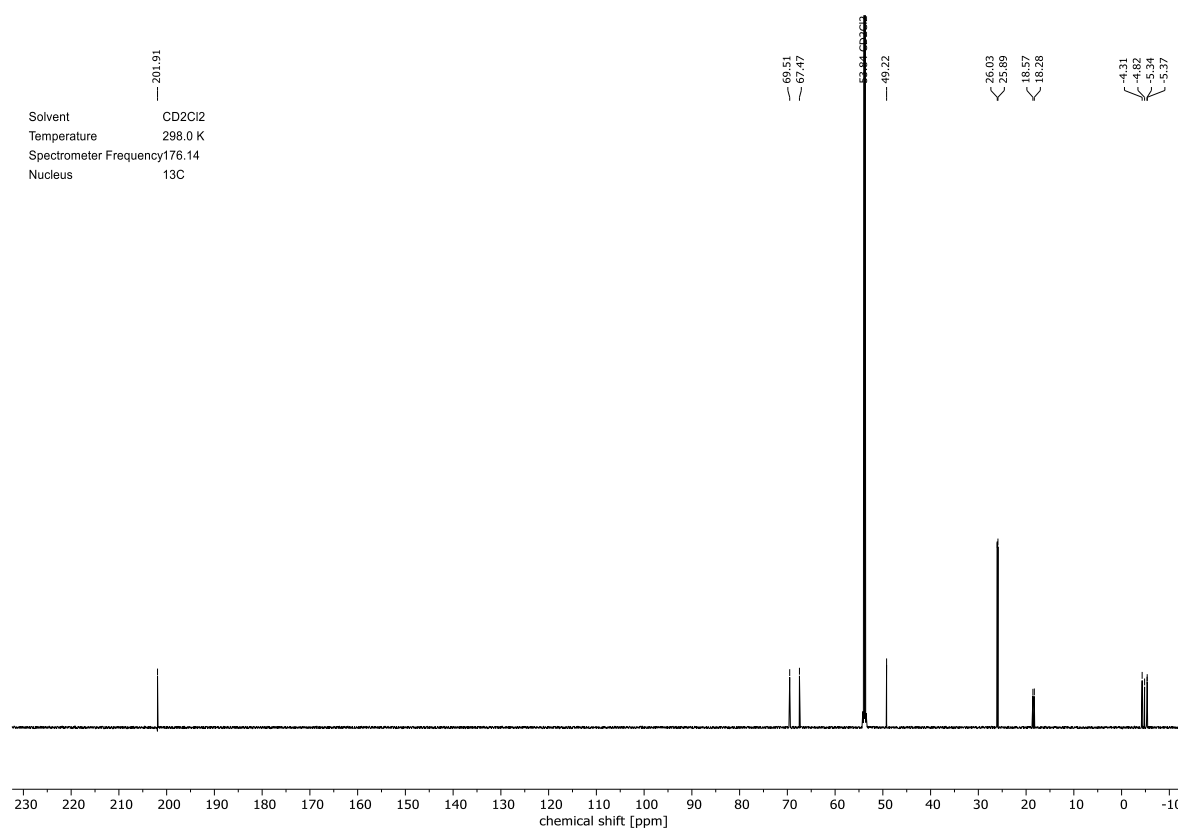
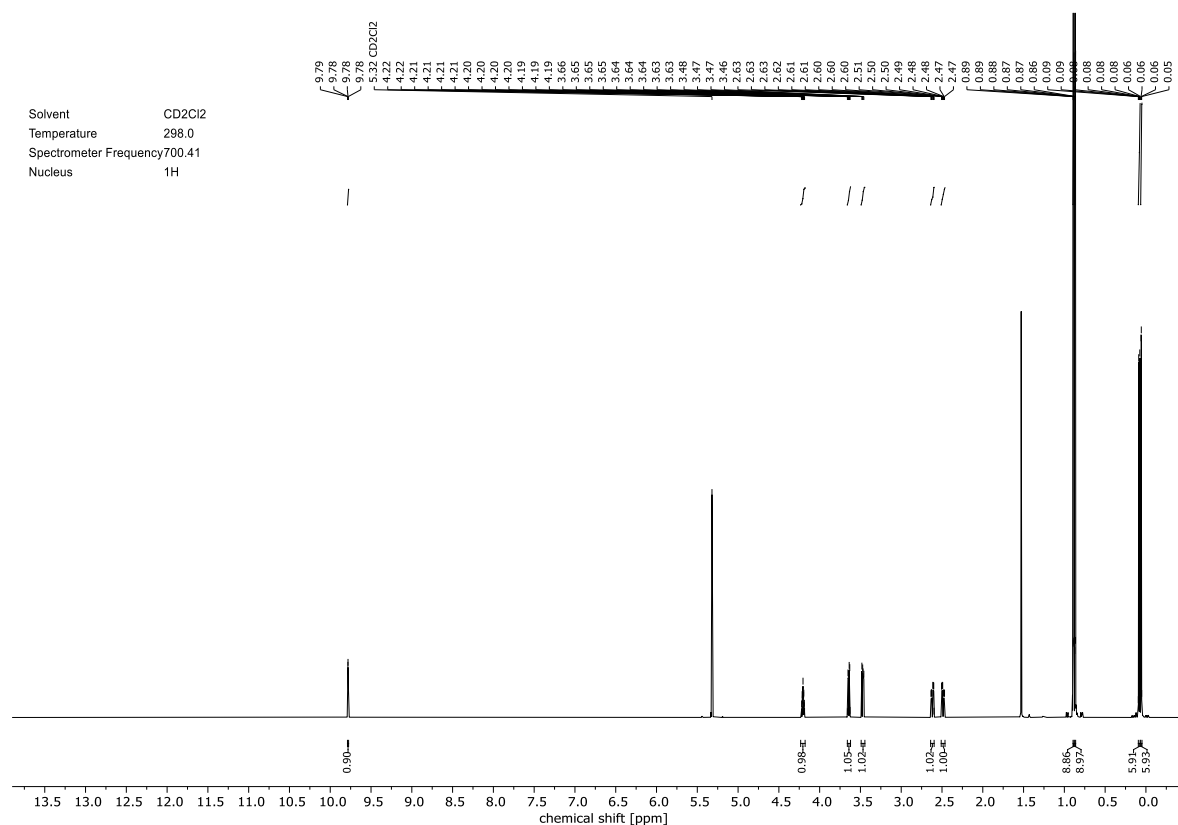
Chemical Formula: $C_{17}H_{38}O_2Si_2$
Exact Mass: 330.2410



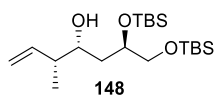
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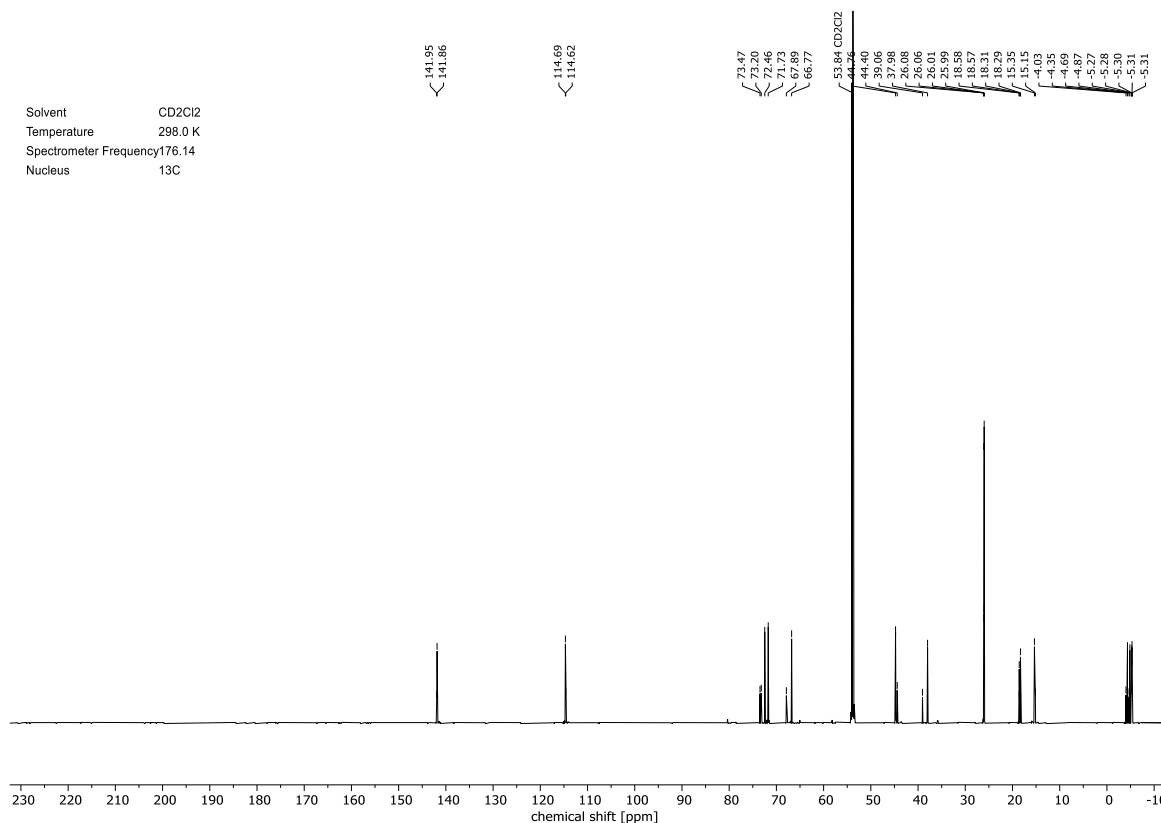
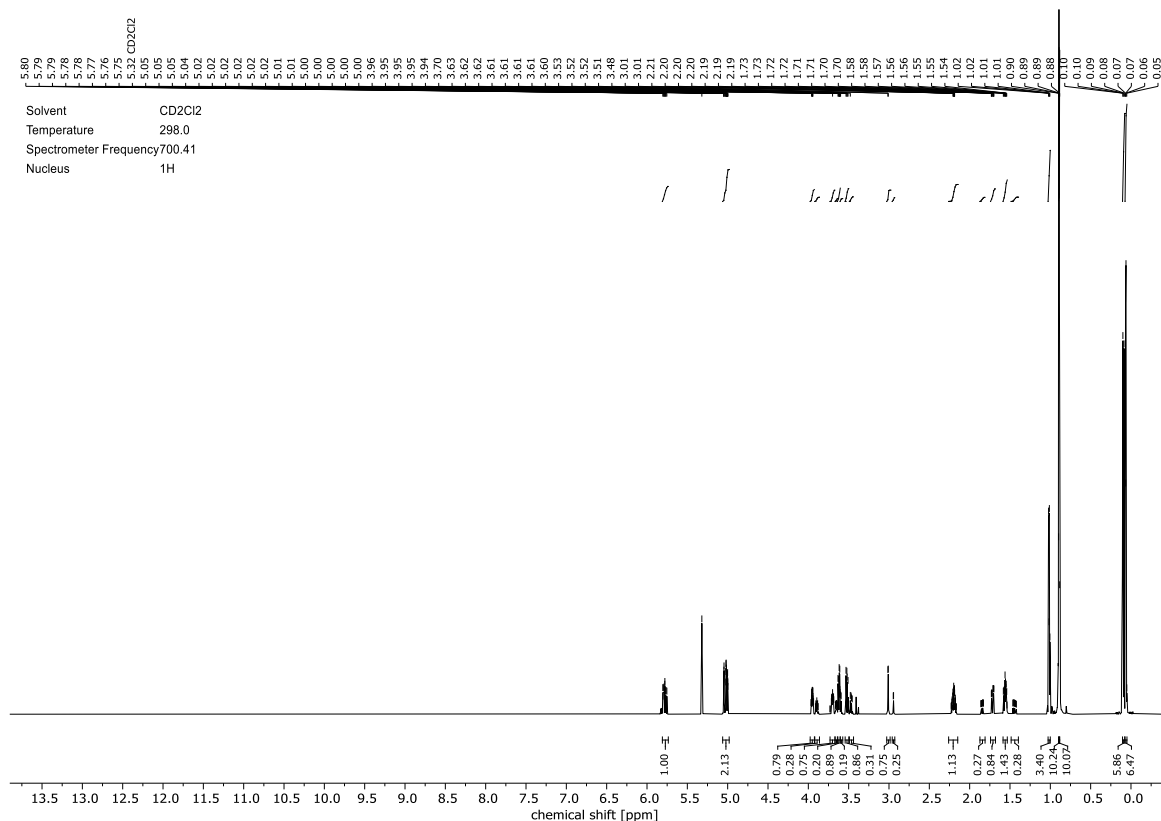
Chemical Formula: $C_{16}H_{36}O_3Si_2$
Exact Mass: 332.2203



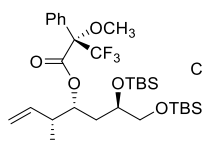
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Chemical Formula: $C_{20}H_{44}O_3Si_2$
Exact Mass: 388.2829



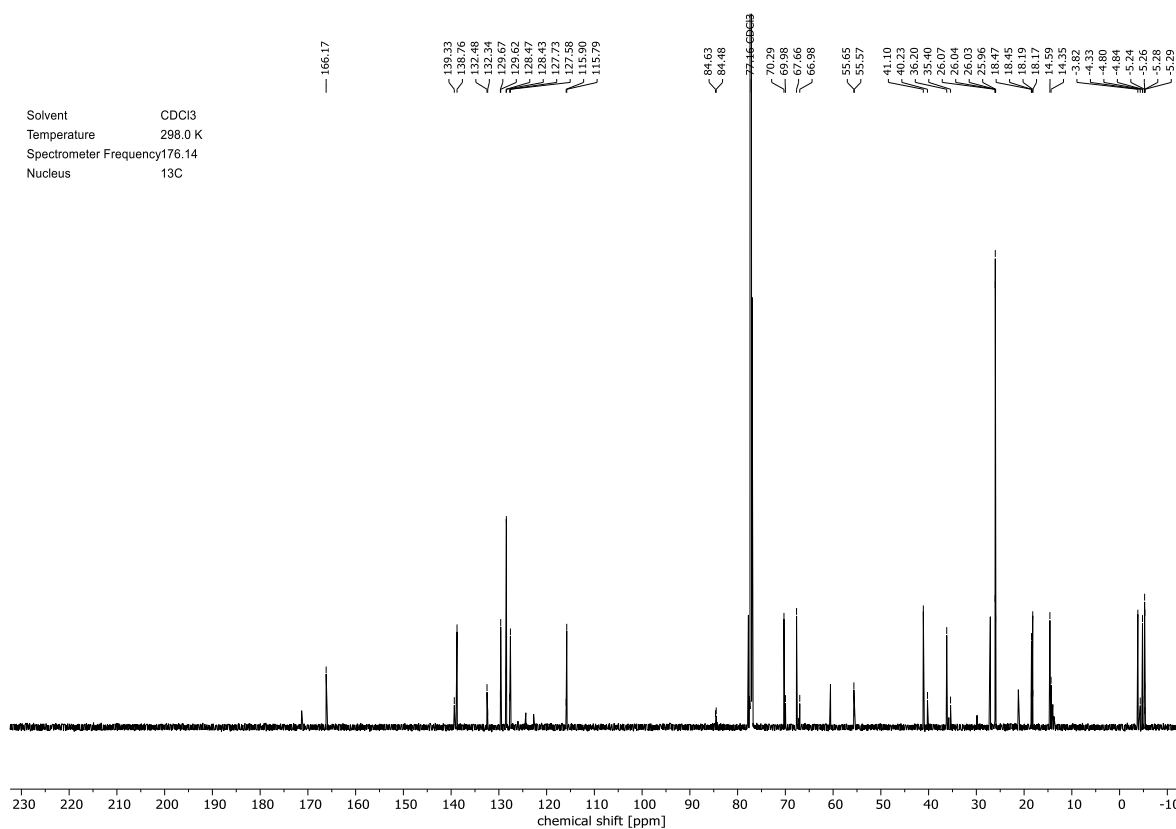
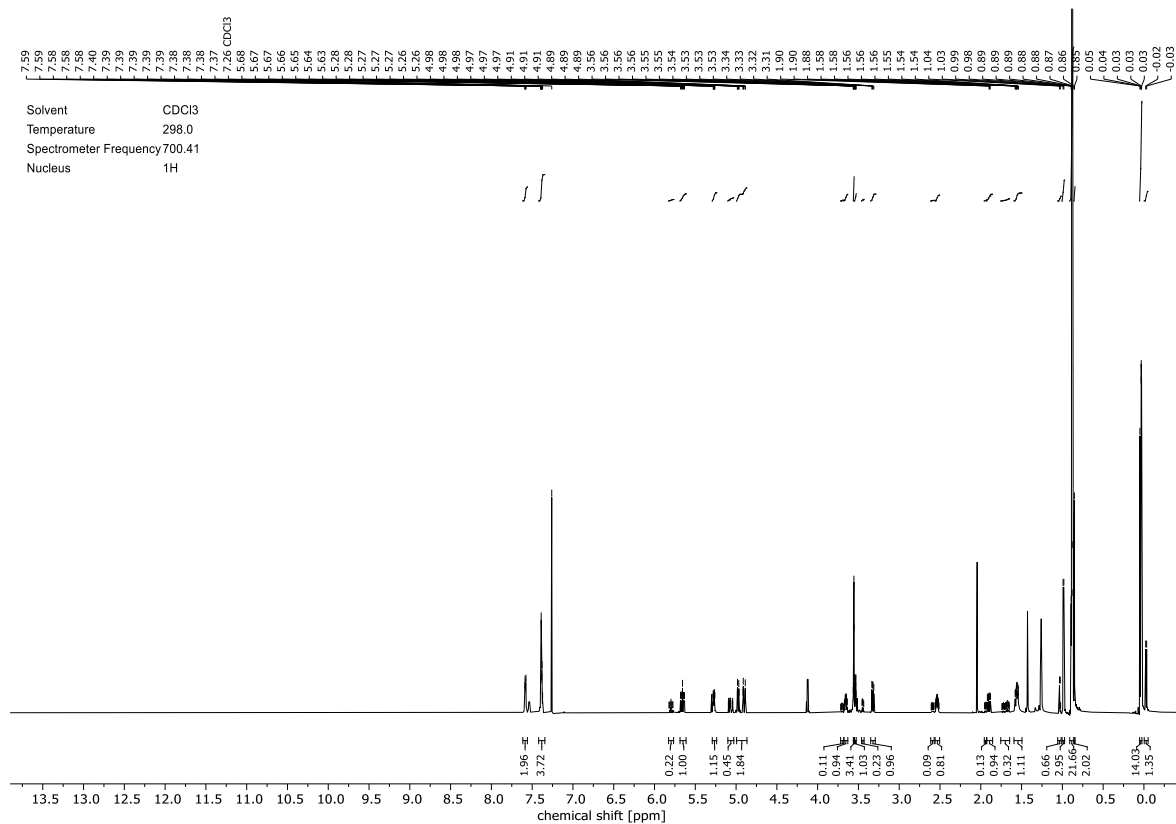
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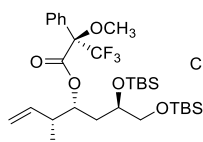
149

Chemical Formula: $C_{30}H_{51}F_3O_5Si_2$

Exact Mass: 604.3227



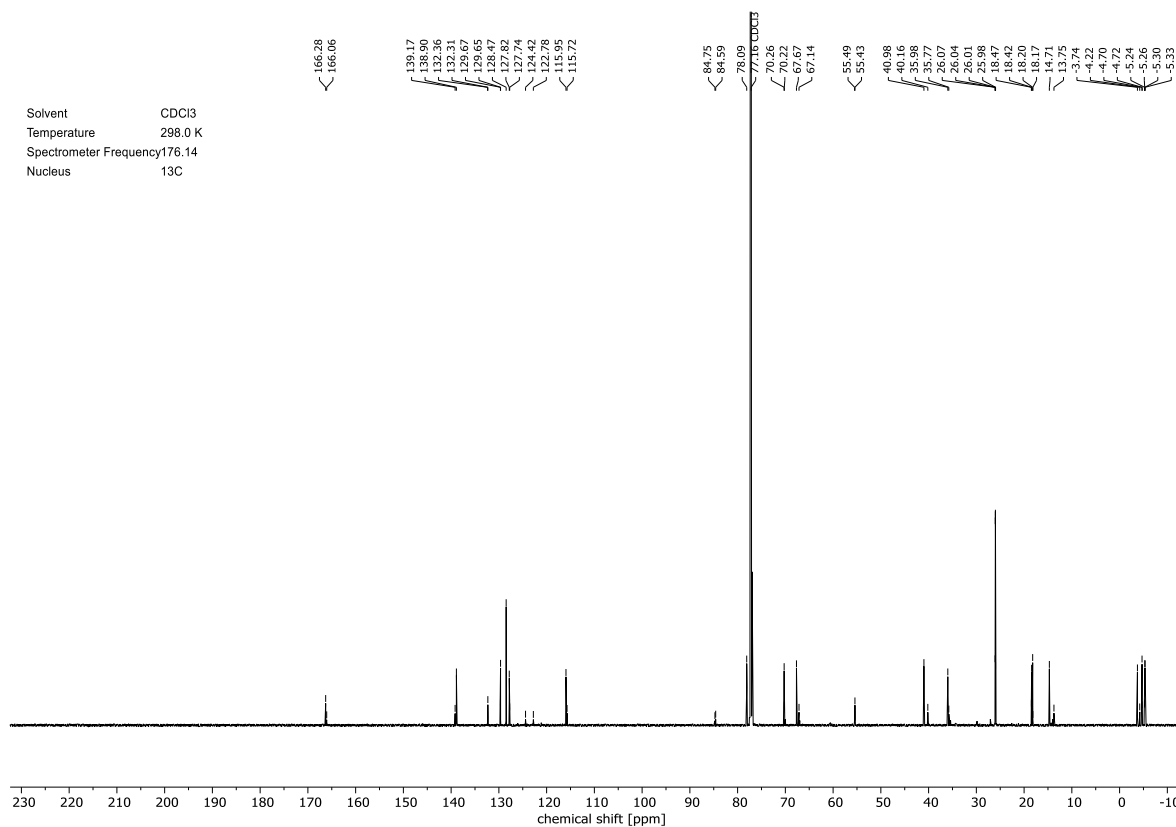
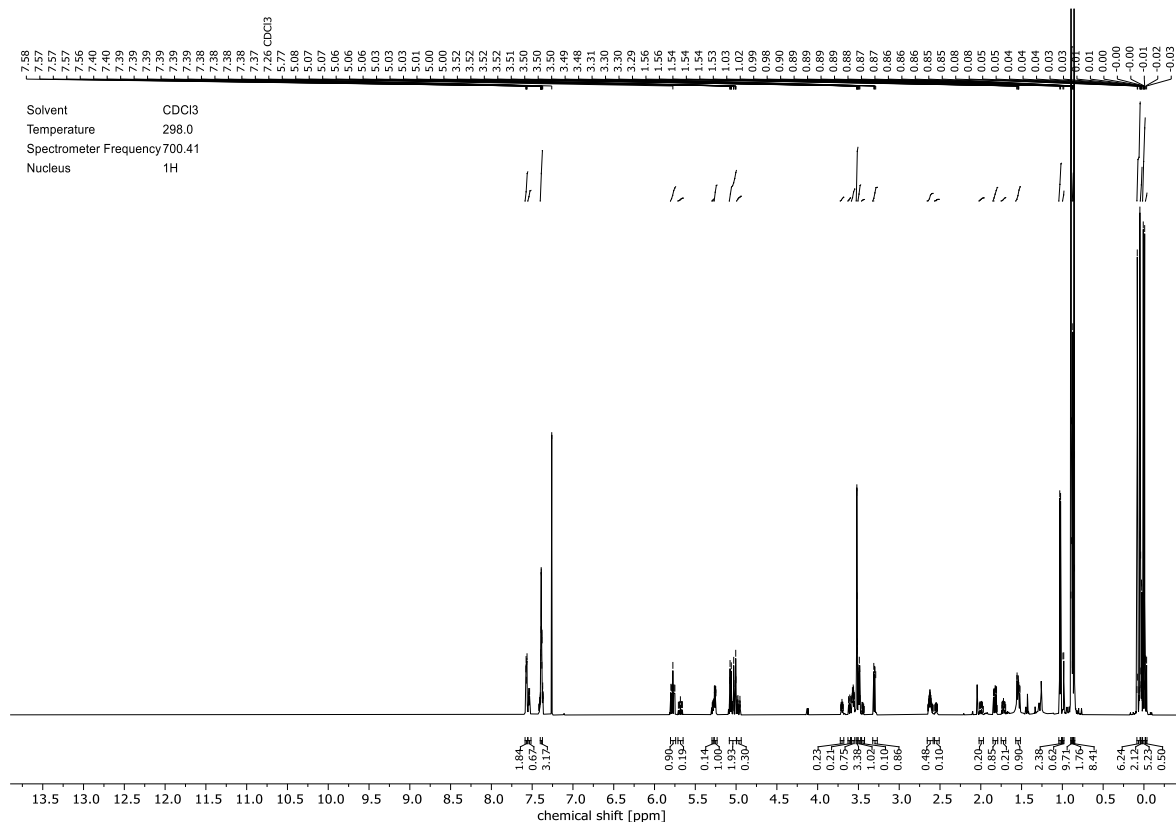
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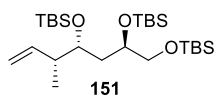
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Chemical Formula: $C_{30}H_{51}F_3O_5Si_2$

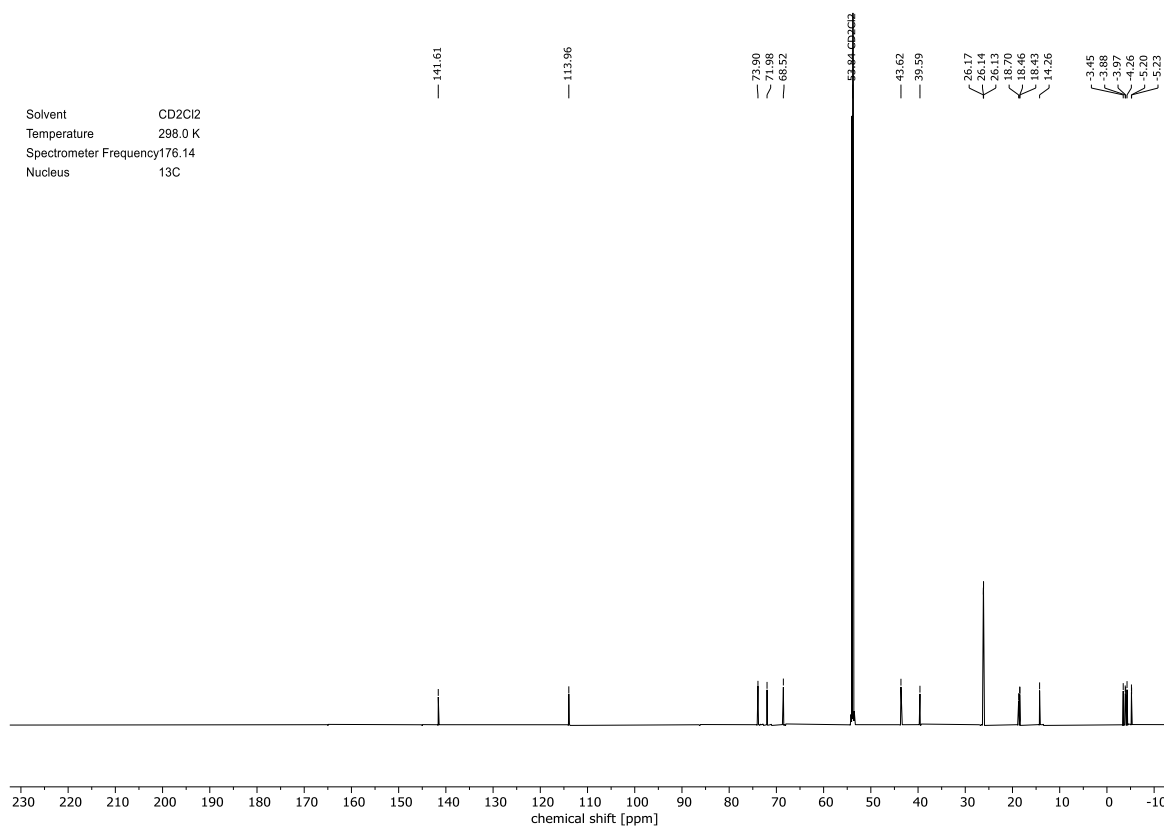
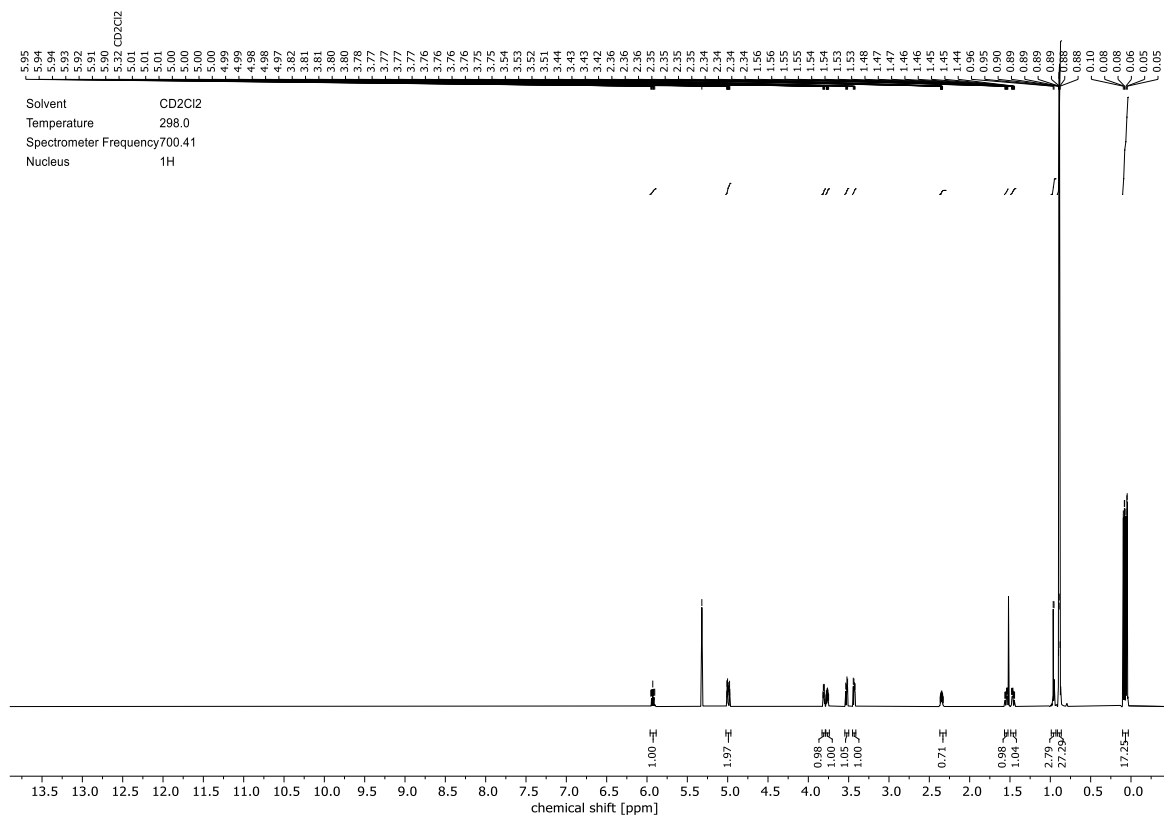
Exact Mass: 604.3227



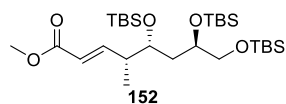
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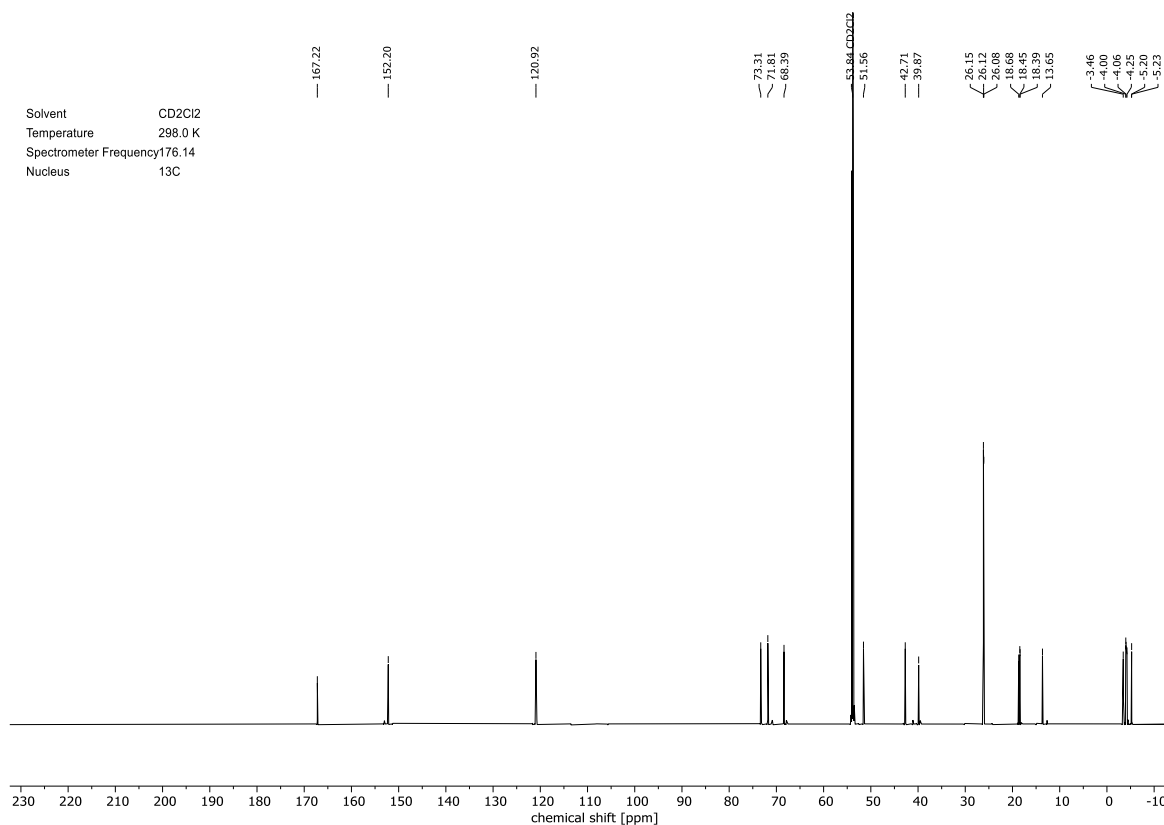
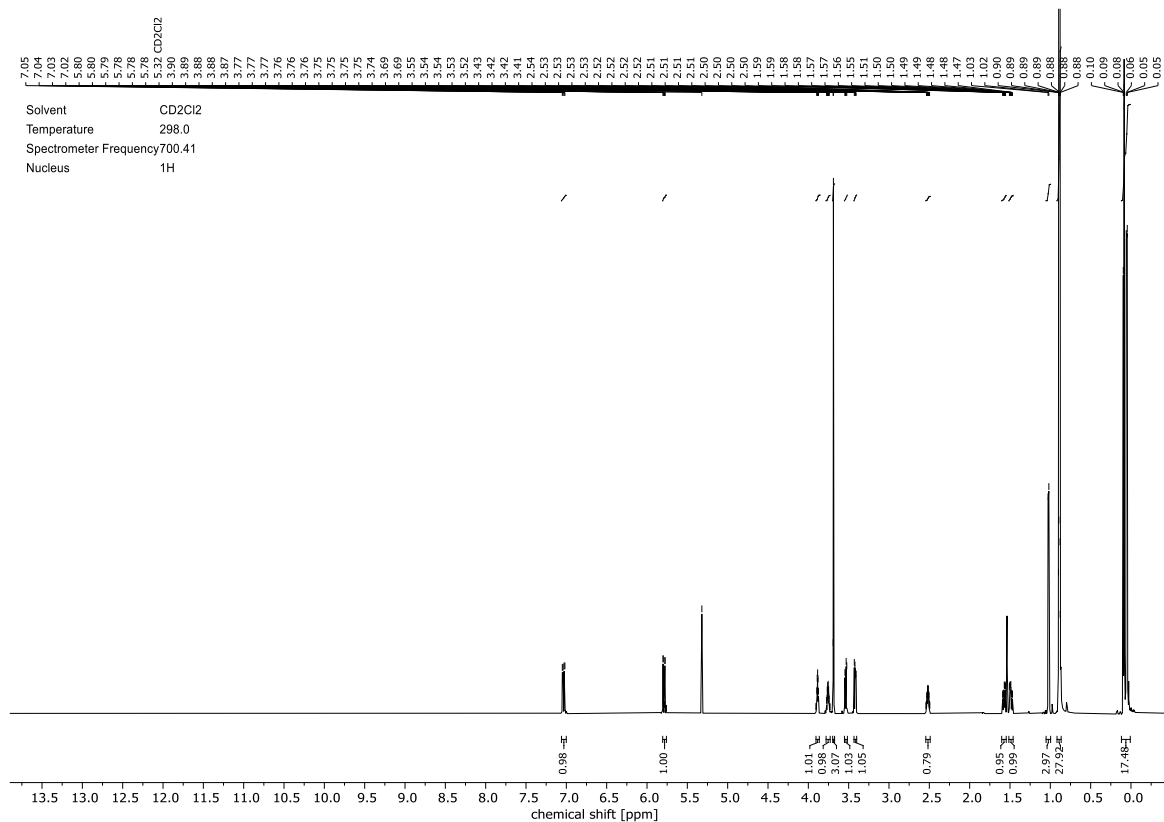
Chemical Formula: $C_{26}H_{58}O_3Si_3$
Exact Mass: 502.3694



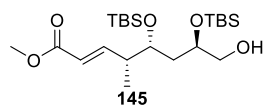
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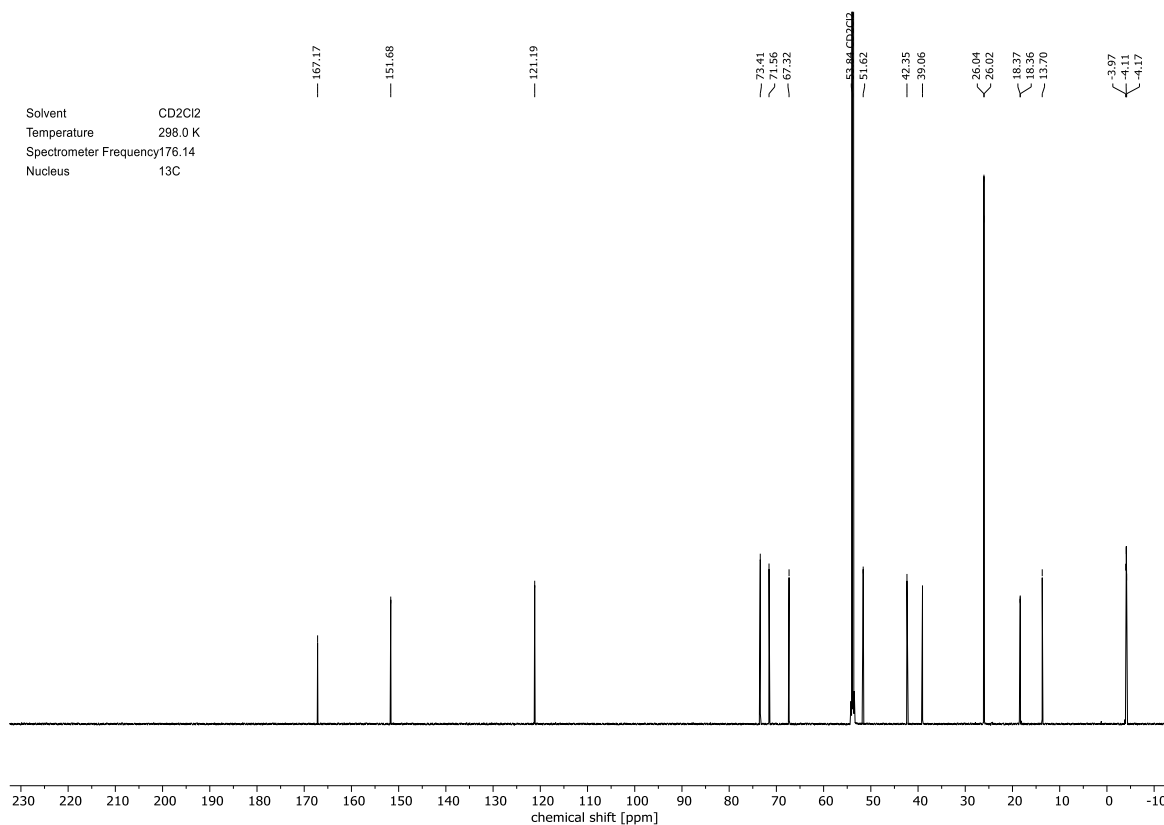
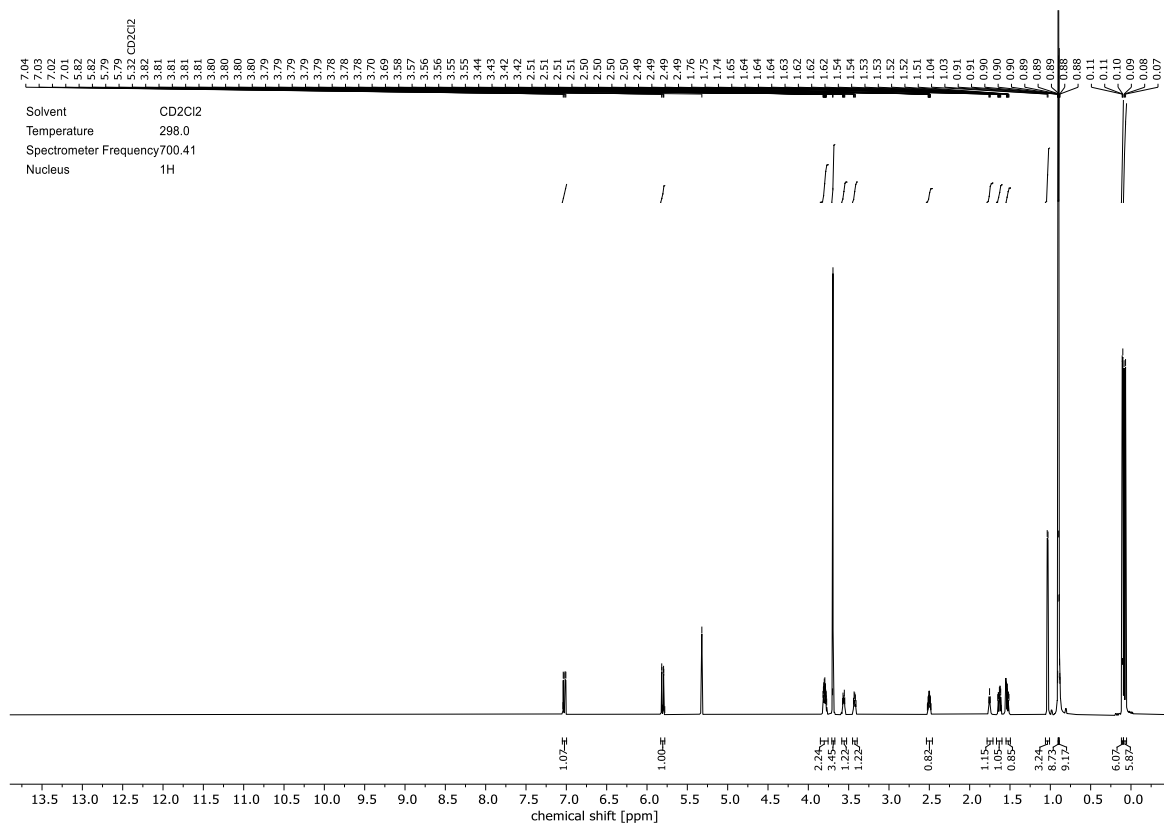
Chemical Formula: $C_{28}H_{60}O_5Si_3$
Exact Mass: 560.3749



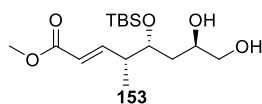
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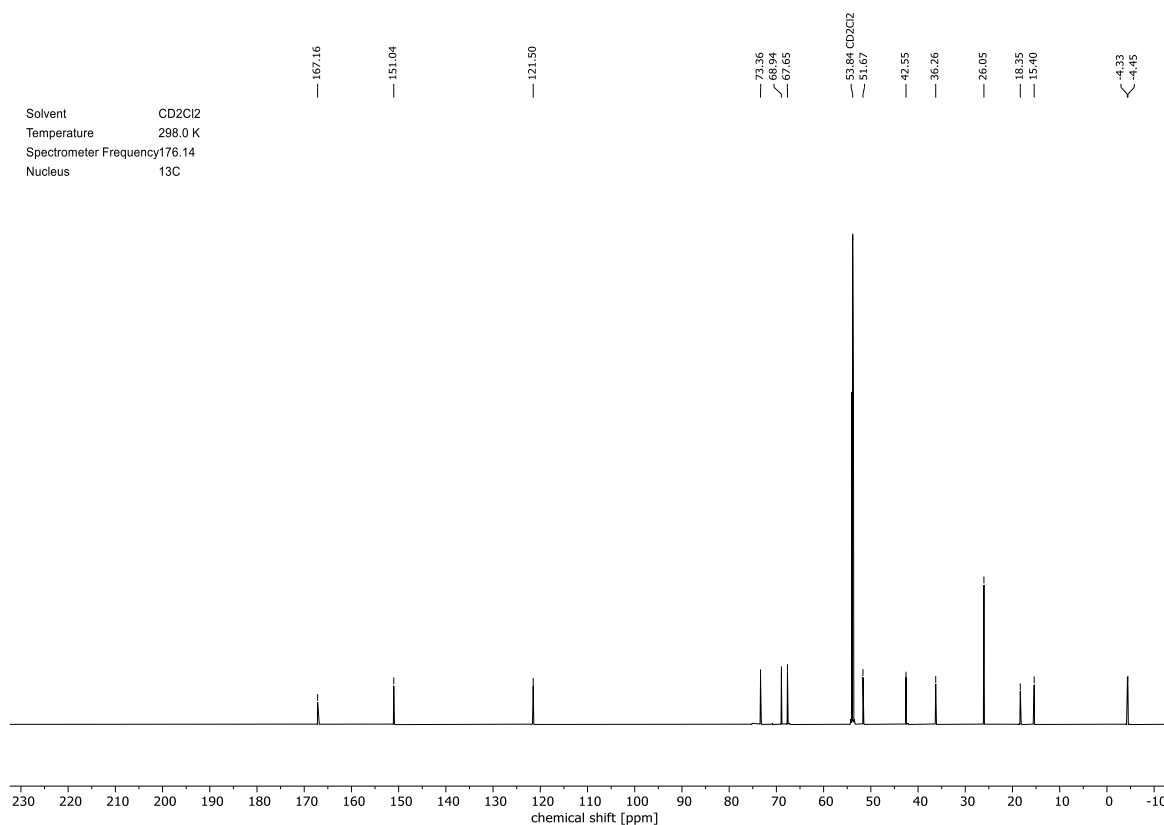
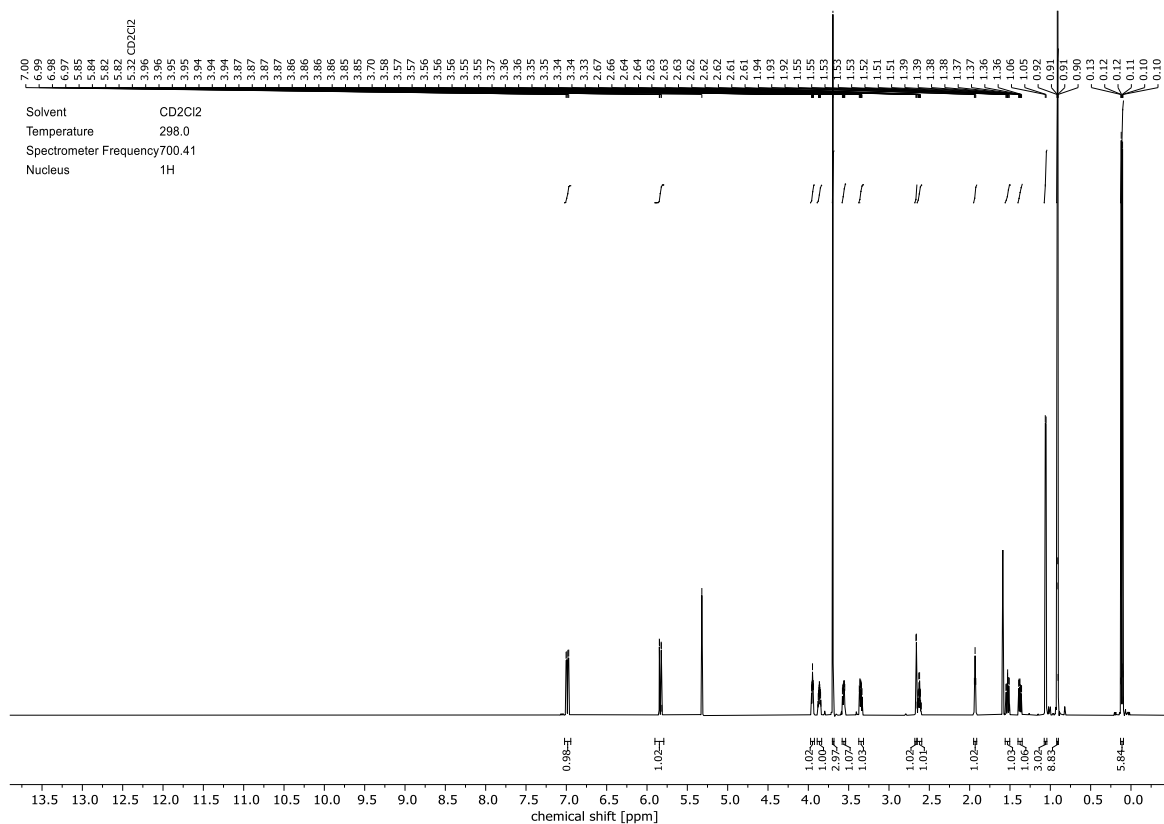
Chemical Formula: $C_{22}H_{46}O_5Si_2$
Exact Mass: 446.2884



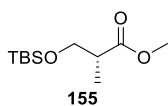
6 Copies of NMR Spectra



Chemical Formula: $C_{16}H_{32}O_5Si$
Exact Mass: 332.2019

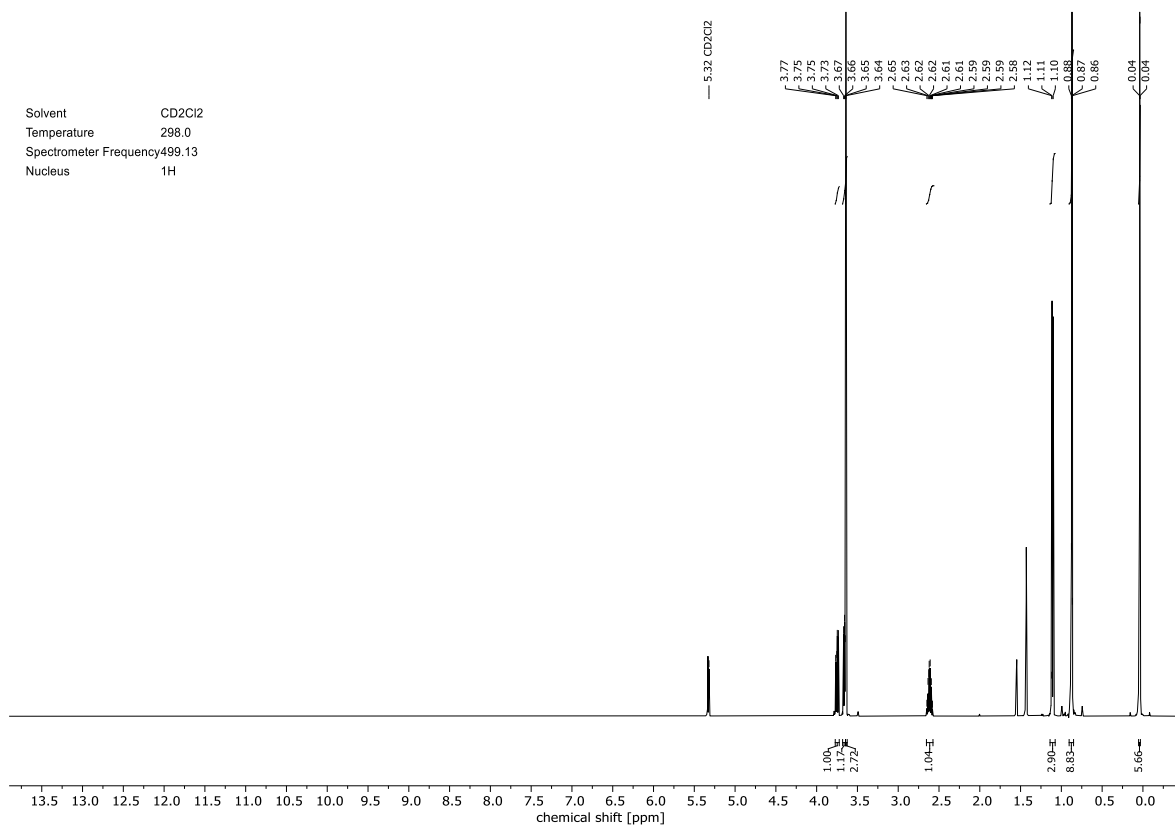


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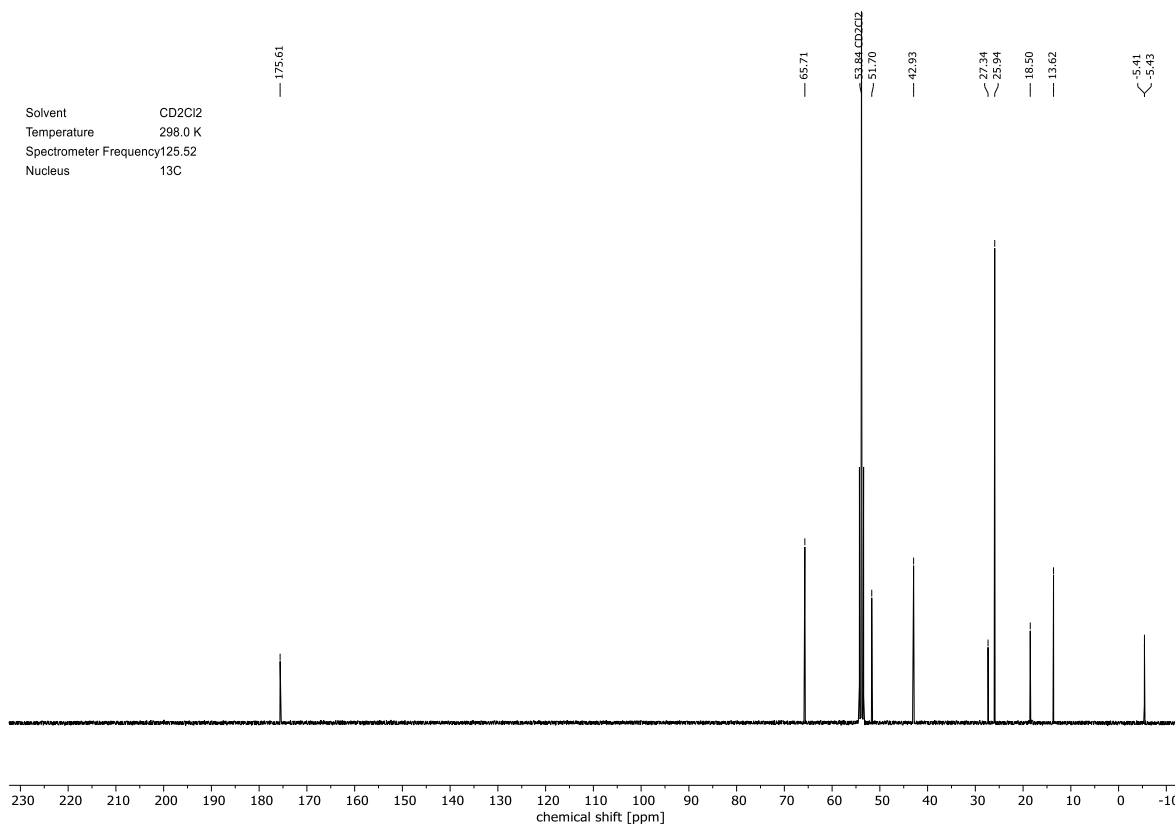


Chemical Formula: $C_{11}H_{24}O_3Si$
 Exact Mass: 232.1495

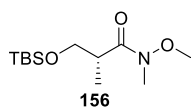
Solvent CD₂Cl₂
 Temperature 298.0
 Spectrometer Frequency 499.13
 Nucleus ¹H



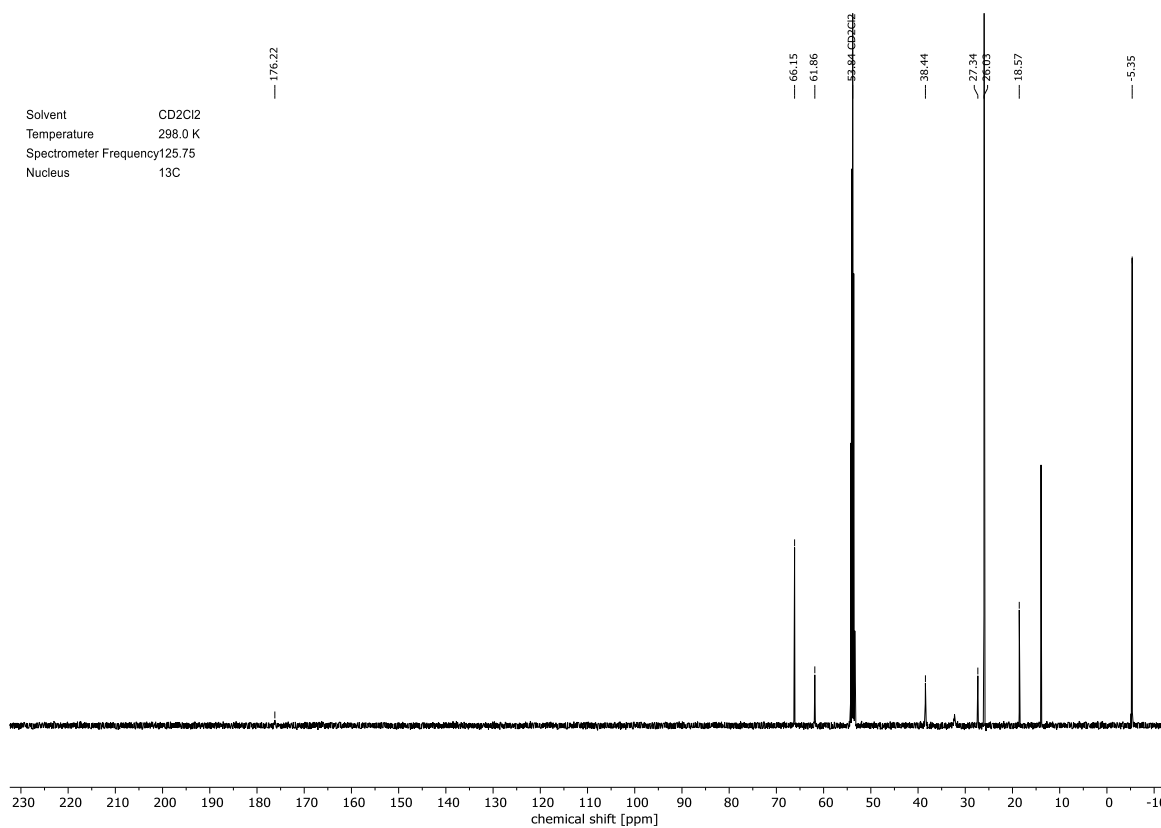
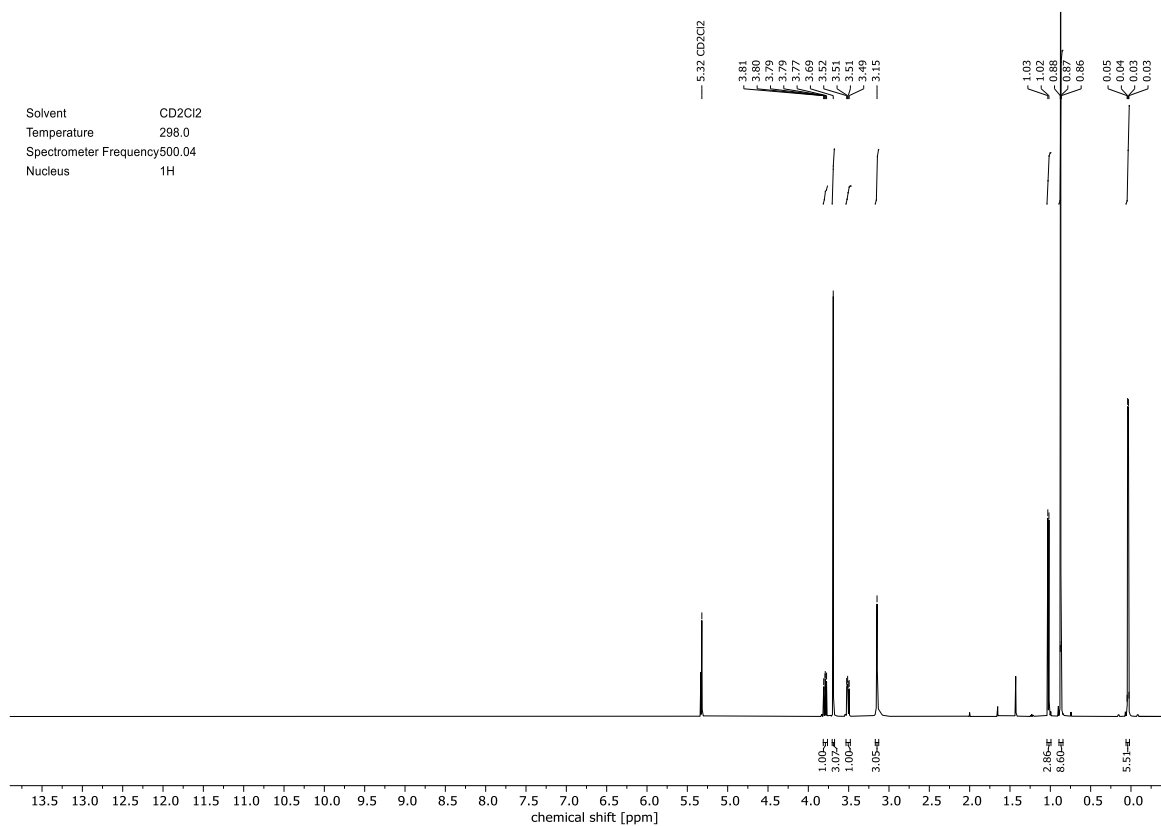
Solvent CD₂Cl₂
 Temperature 298.0 K
 Spectrometer Frequency 125.52
 Nucleus ¹³C



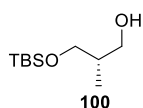
6 Copies of NMR Spectra



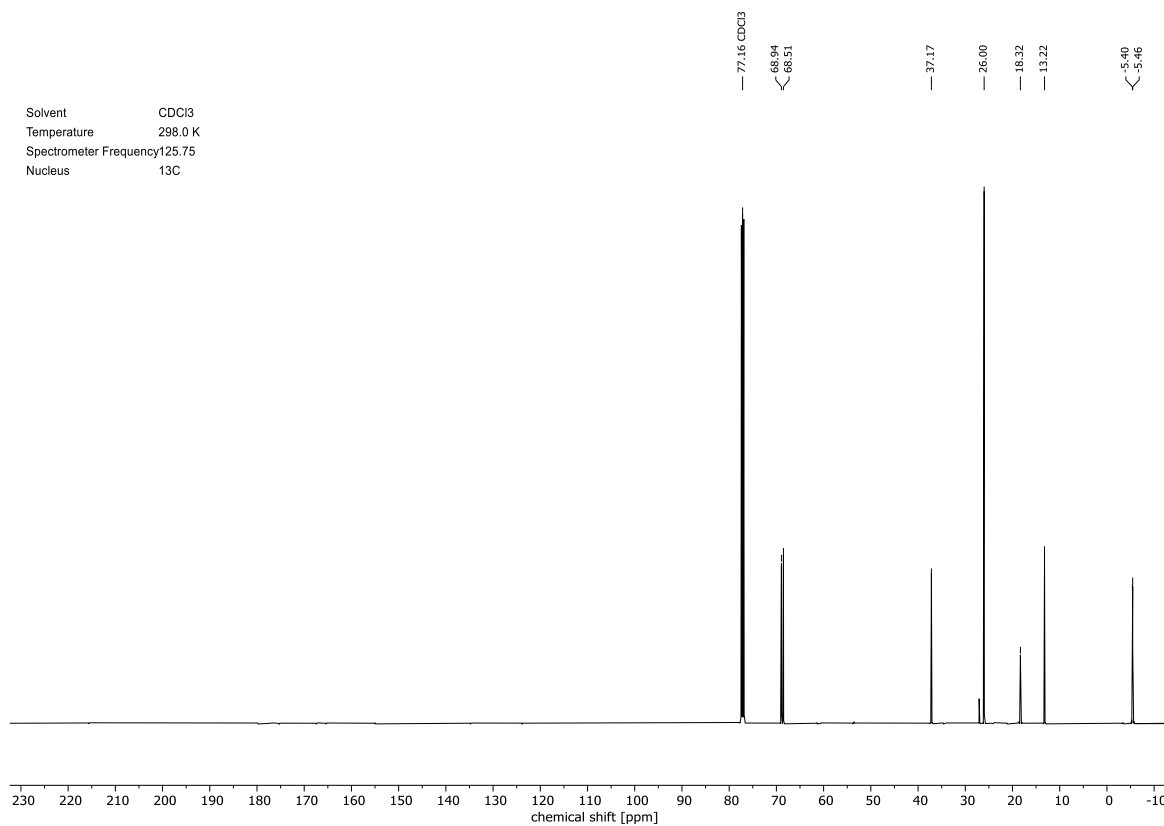
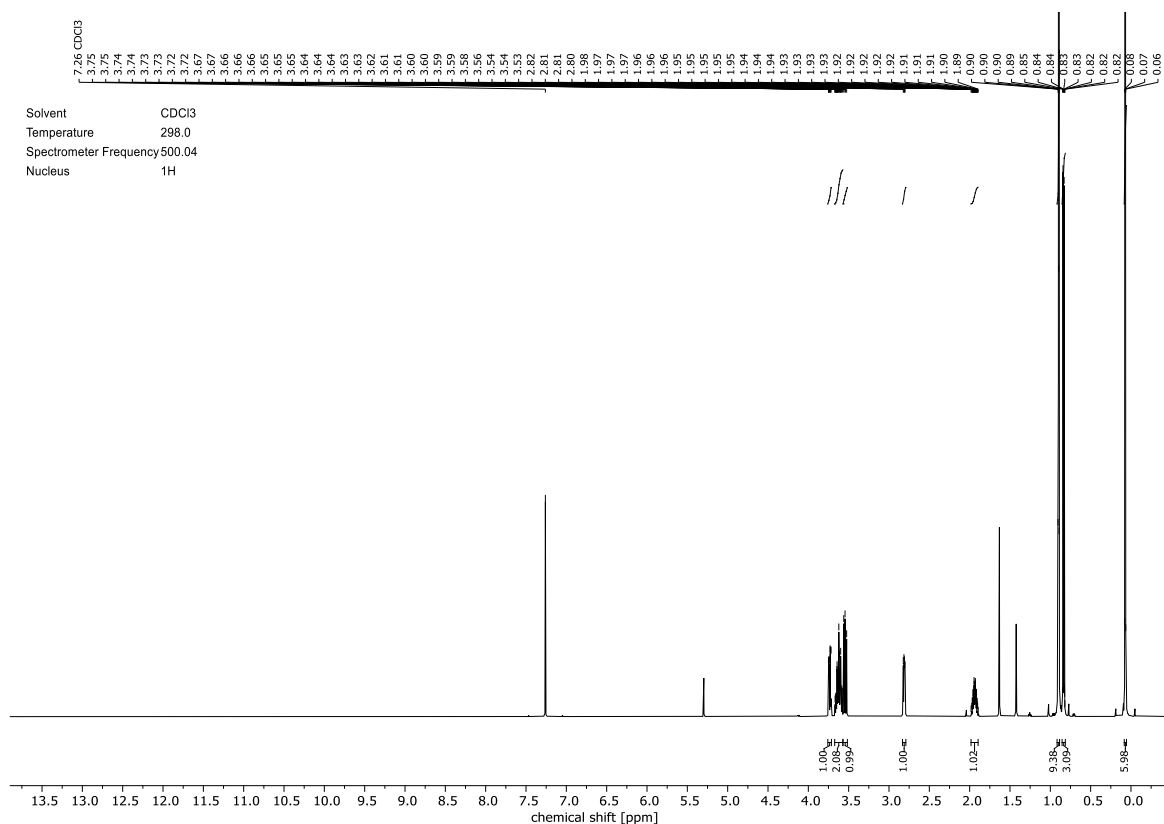
Chemical Formula: $C_{12}H_{27}NO_3Si$
 Exact Mass: 261.1760



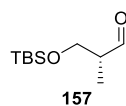
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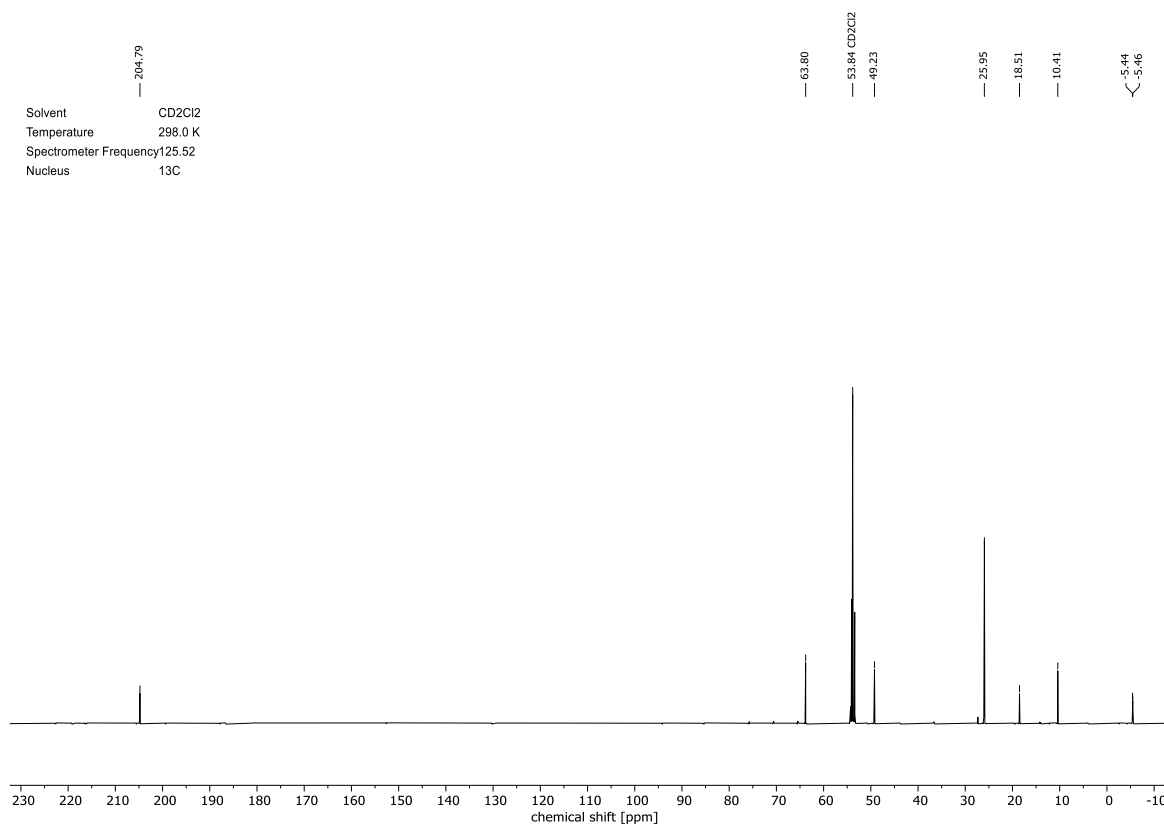
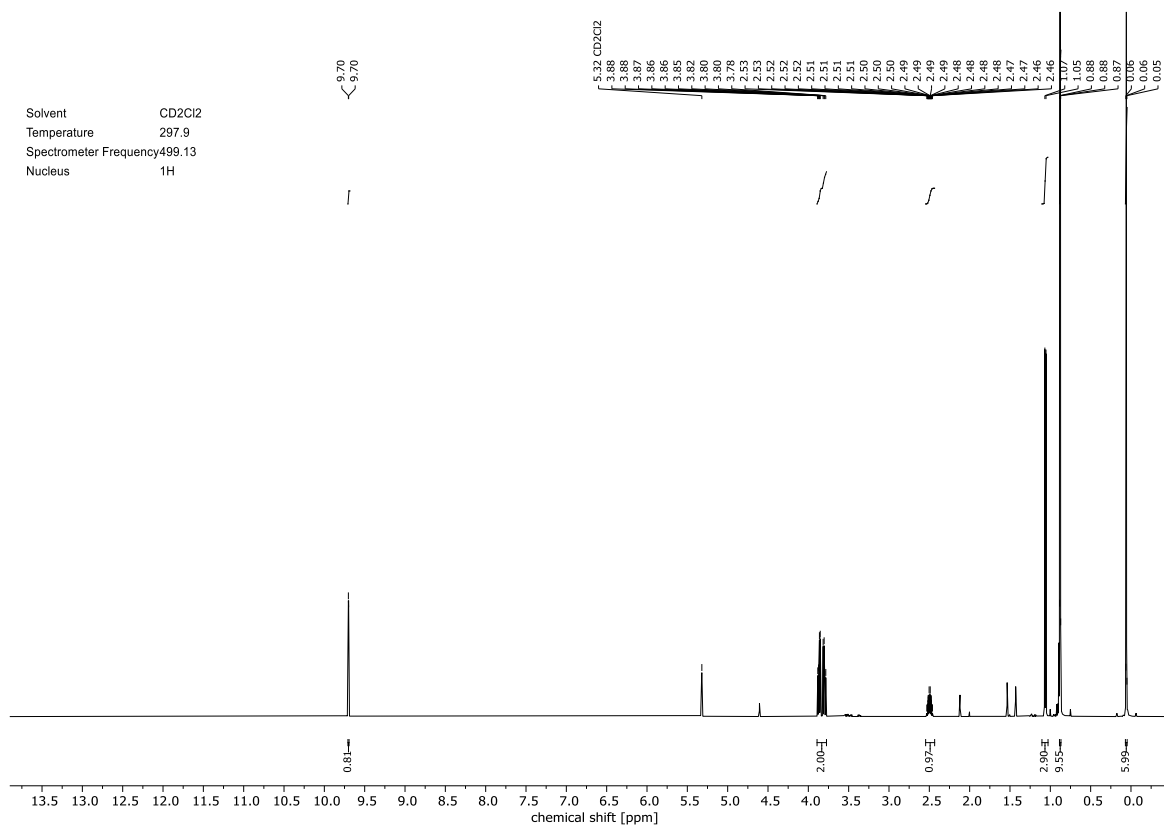
Chemical Formula: $C_{10}H_{24}O_2Si$
Exact Mass: 204.1546



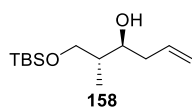
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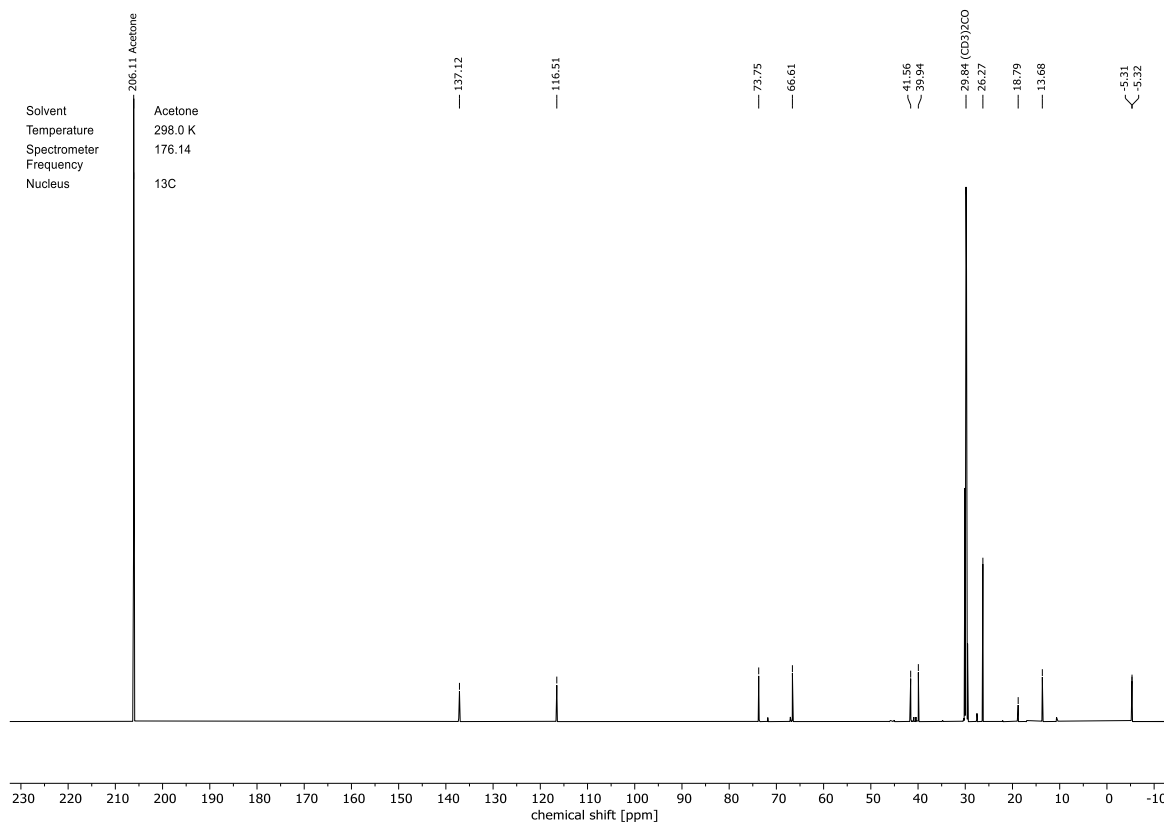
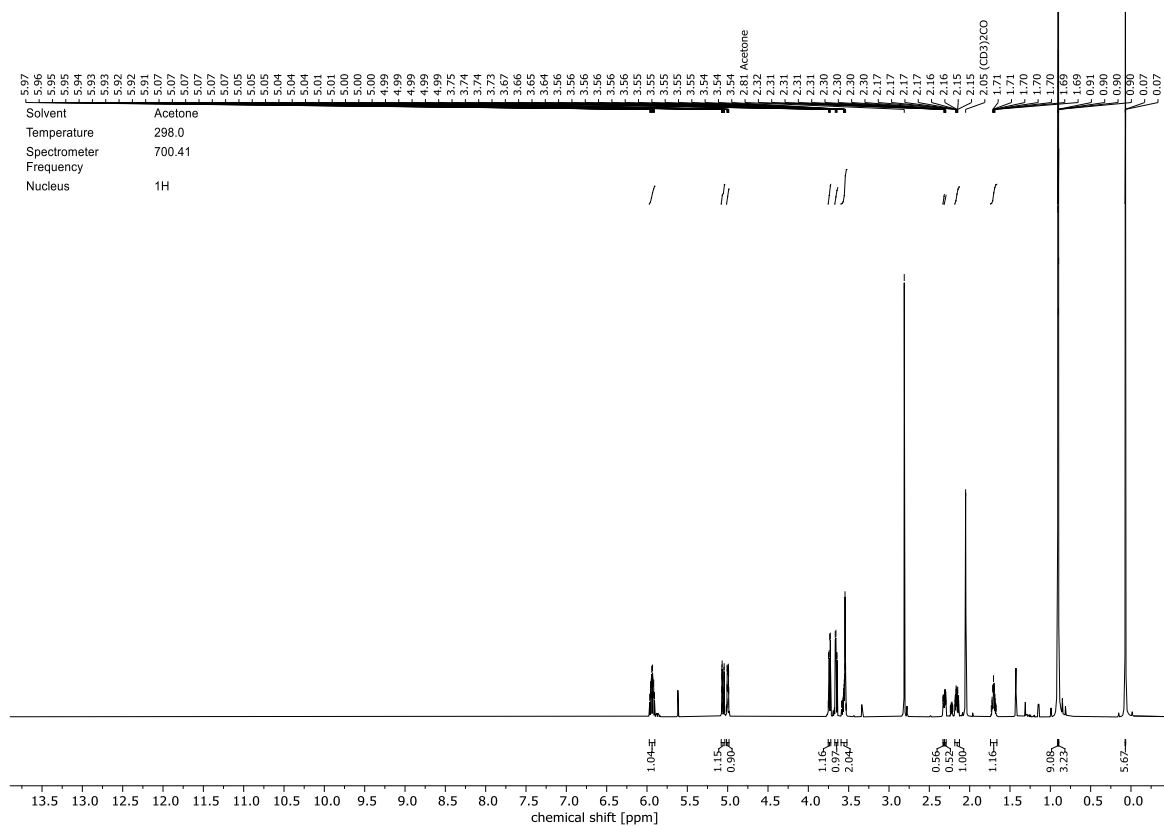
Chemical Formula: $C_{10}H_{22}O_2Si$
 Exact Mass: 202.1389



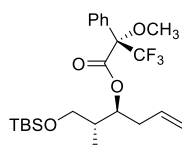
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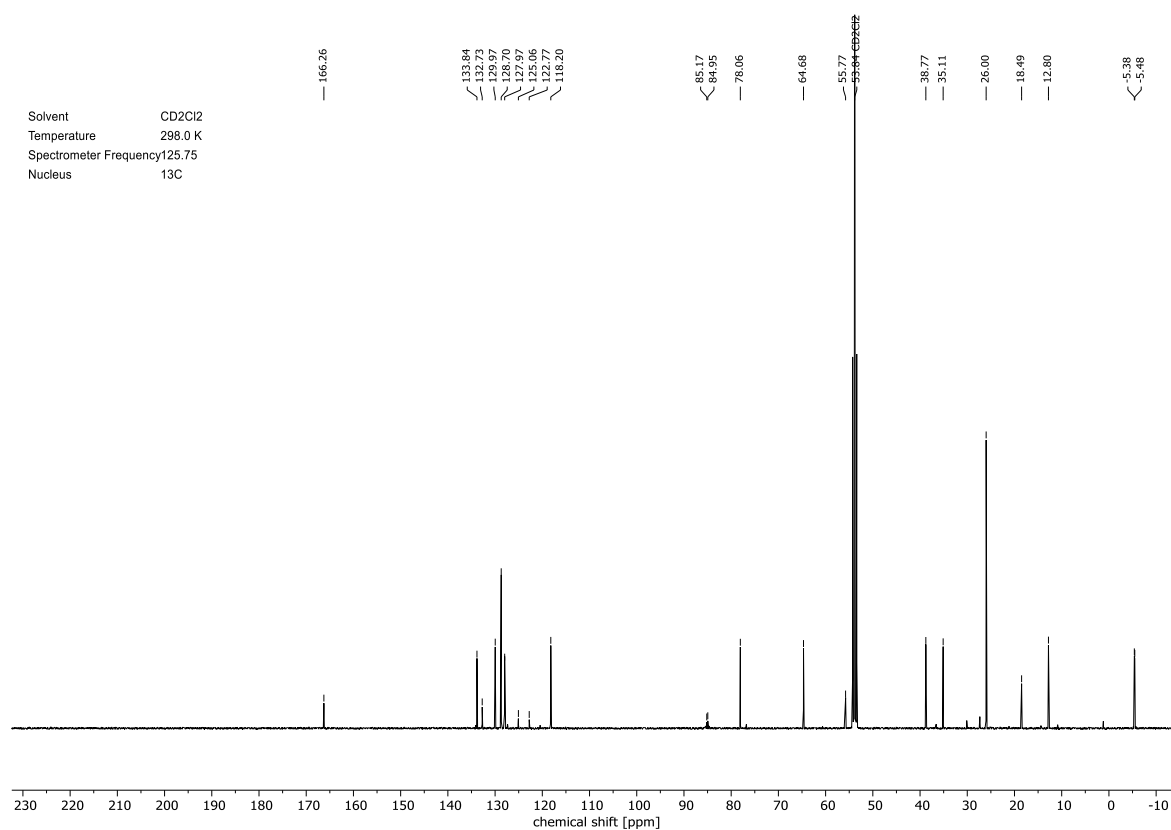
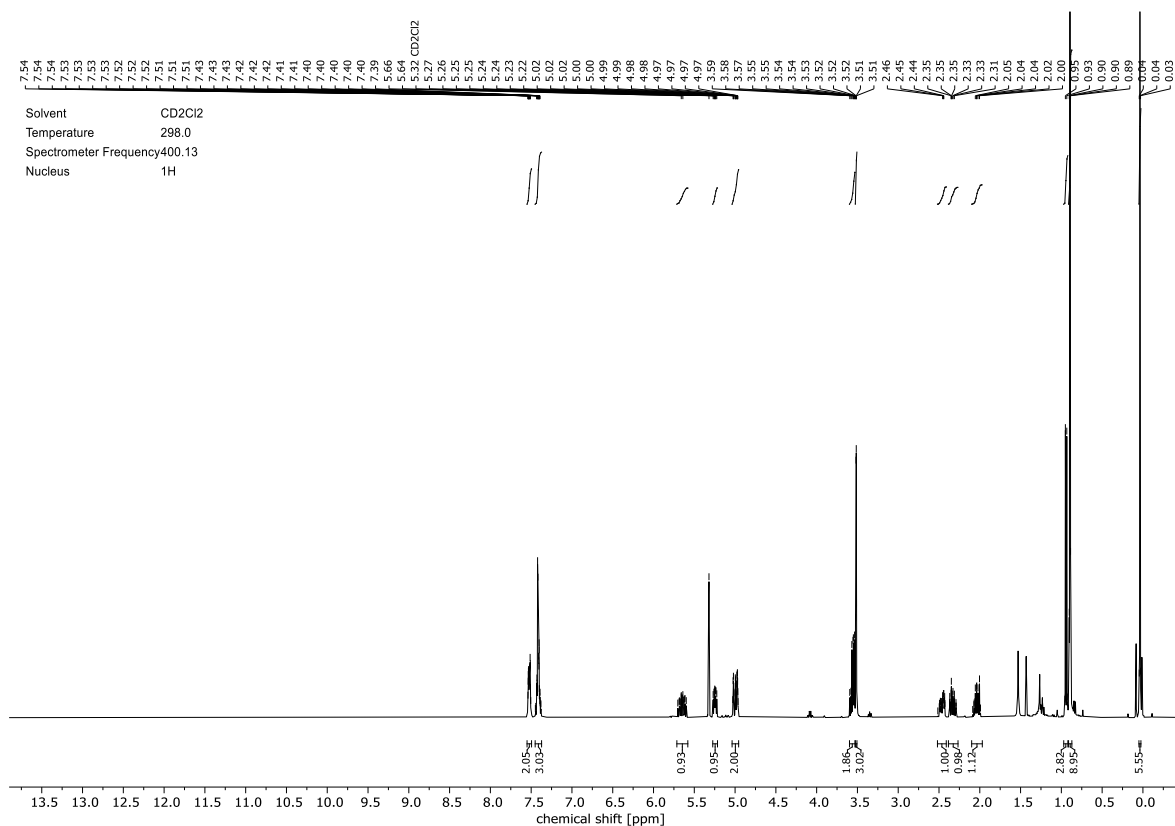
Chemical Formula: $C_{13}H_{28}O_2Si$
Exact Mass: 244.1859



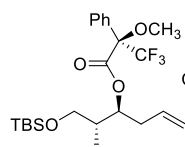
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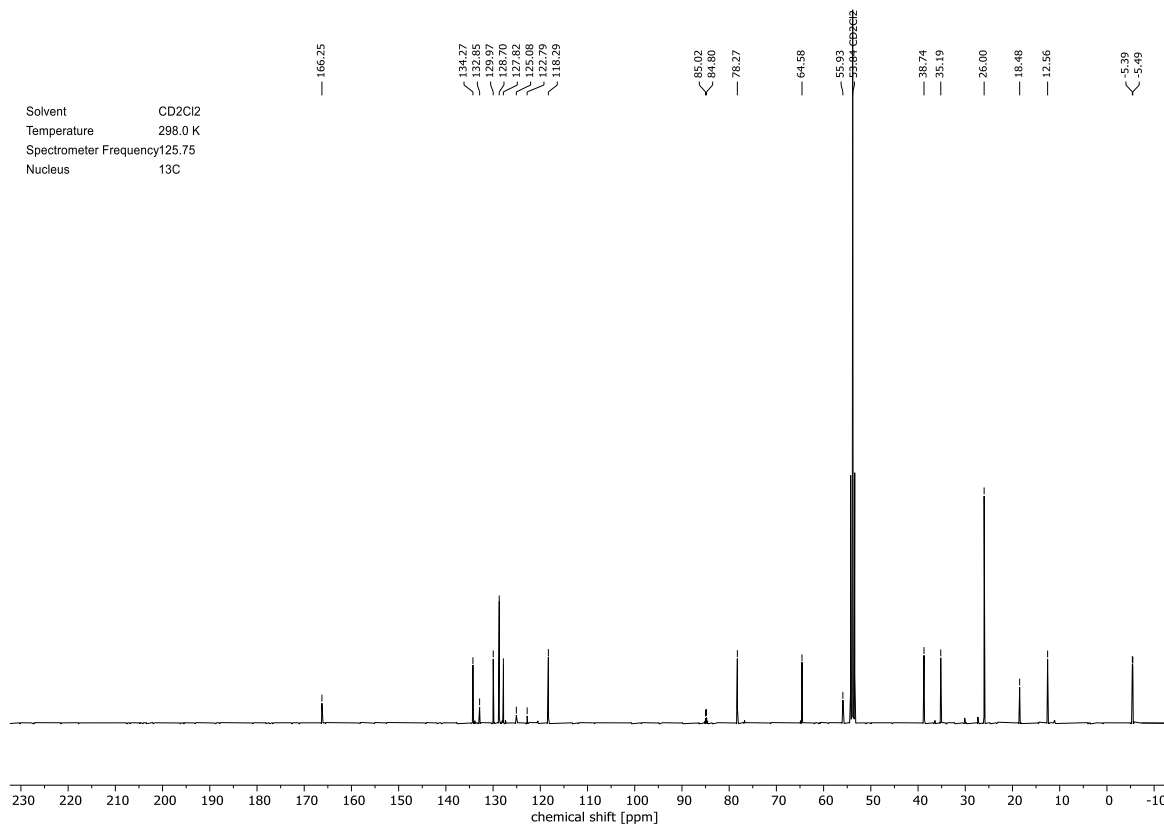
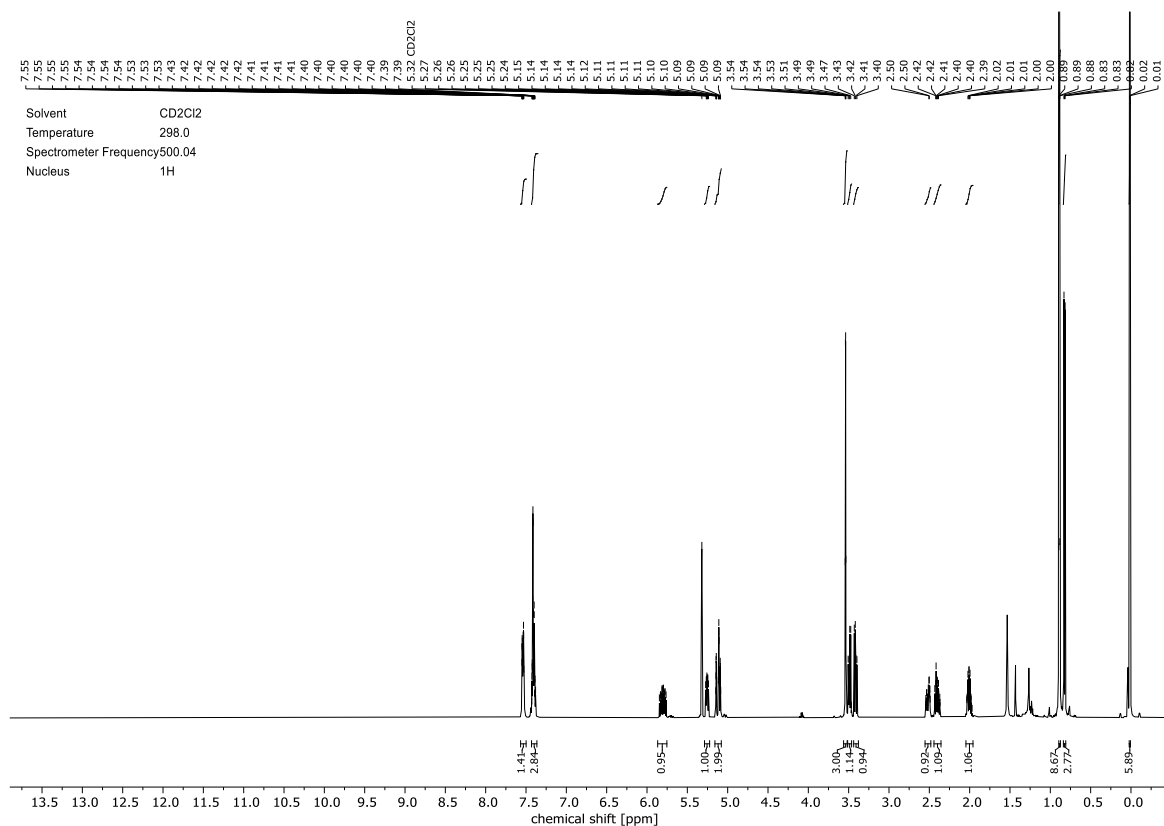
159
Chemical Formula: $C_{23}H_{35}F_3O_4Si$
Exact Mass: 460.2257



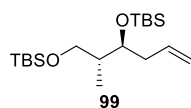
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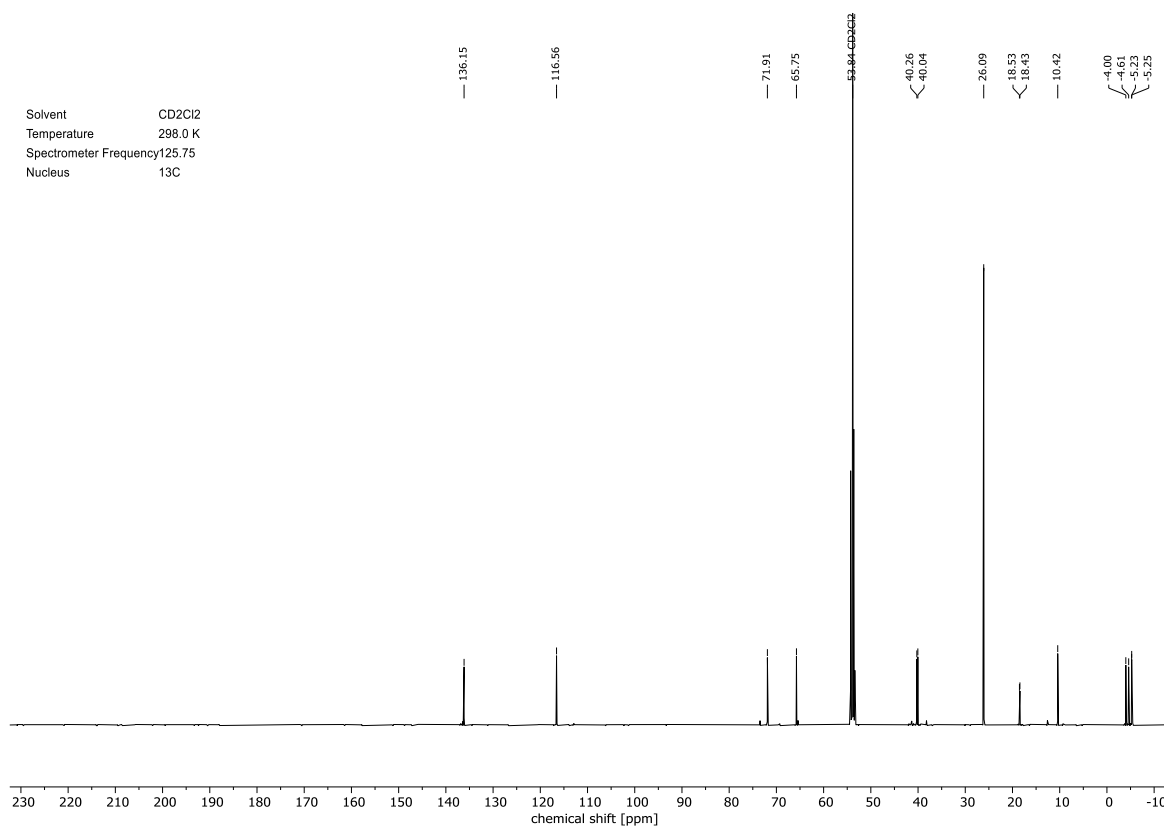
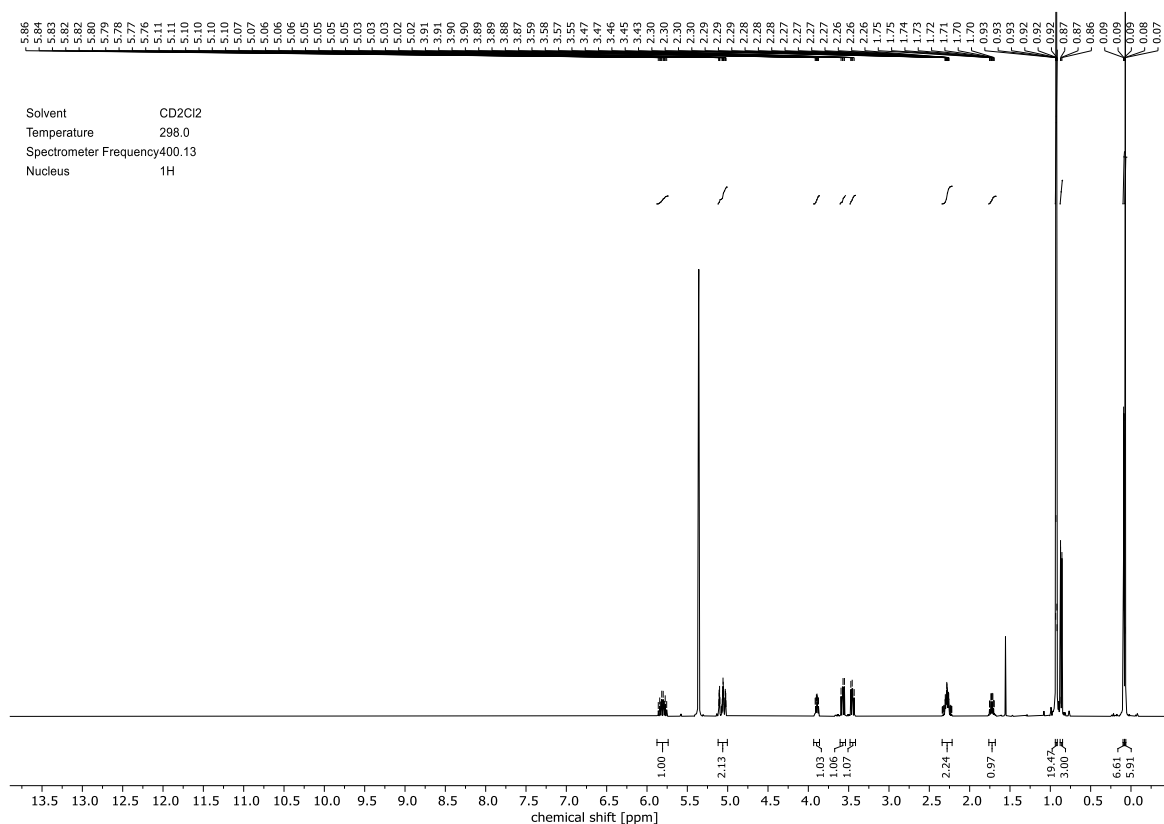
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Chemical Formula: $C_{23}H_{35}F_3O_4Si$
Exact Mass: 460.2257



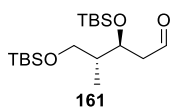
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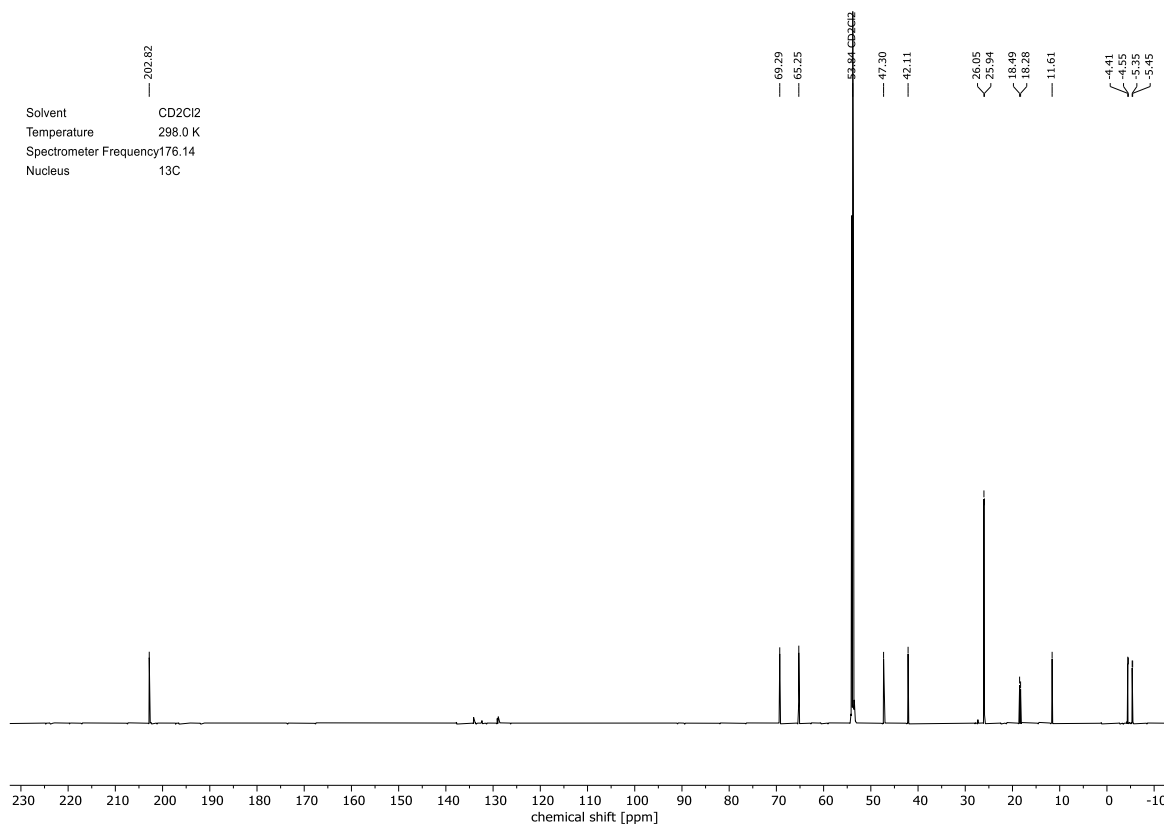
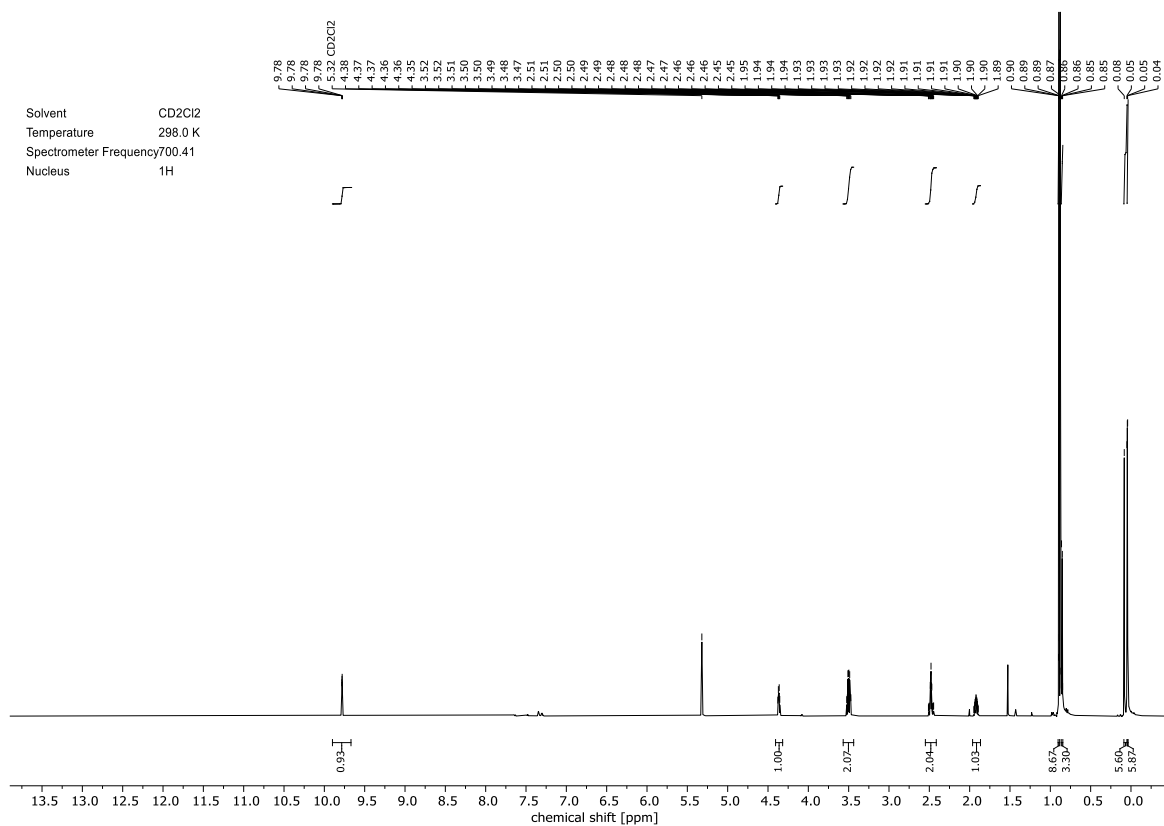
Chemical Formula: $C_{19}H_{42}O_2Si_2$
Exact Mass: 358.2723



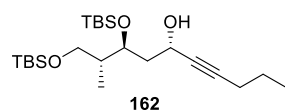
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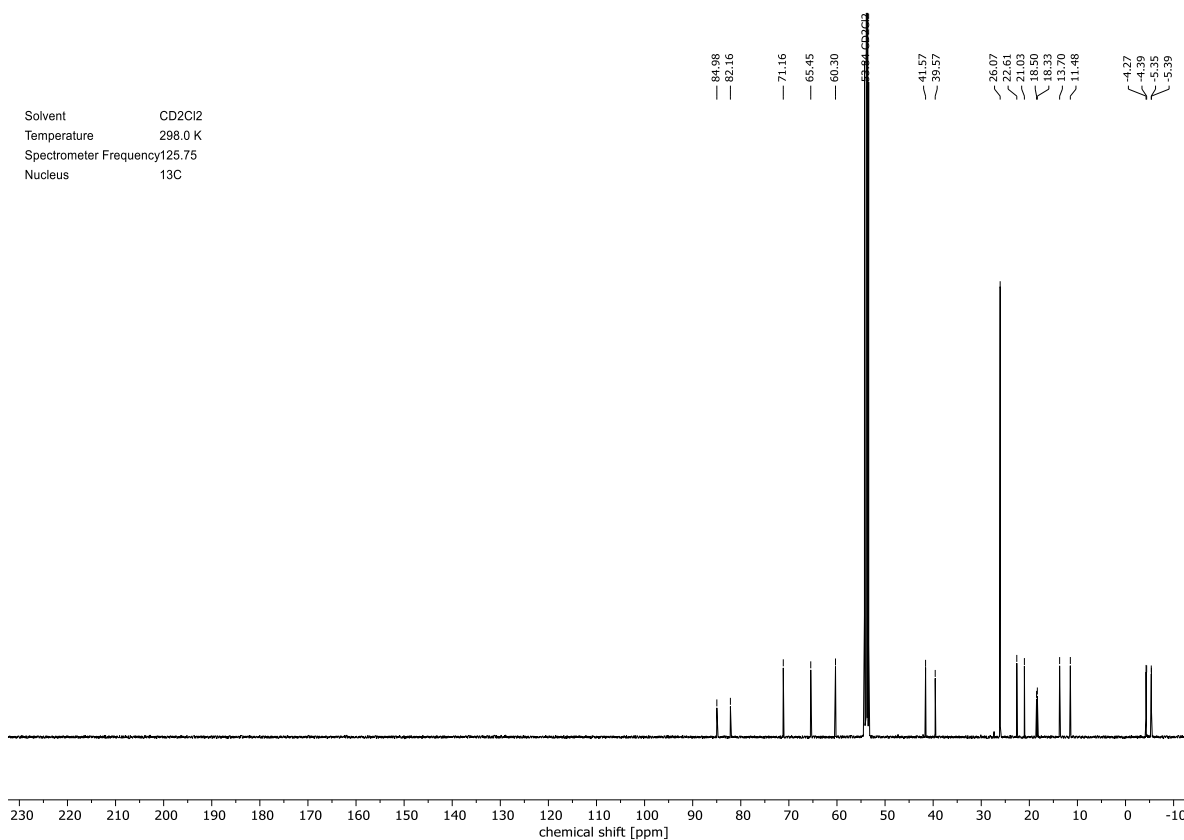
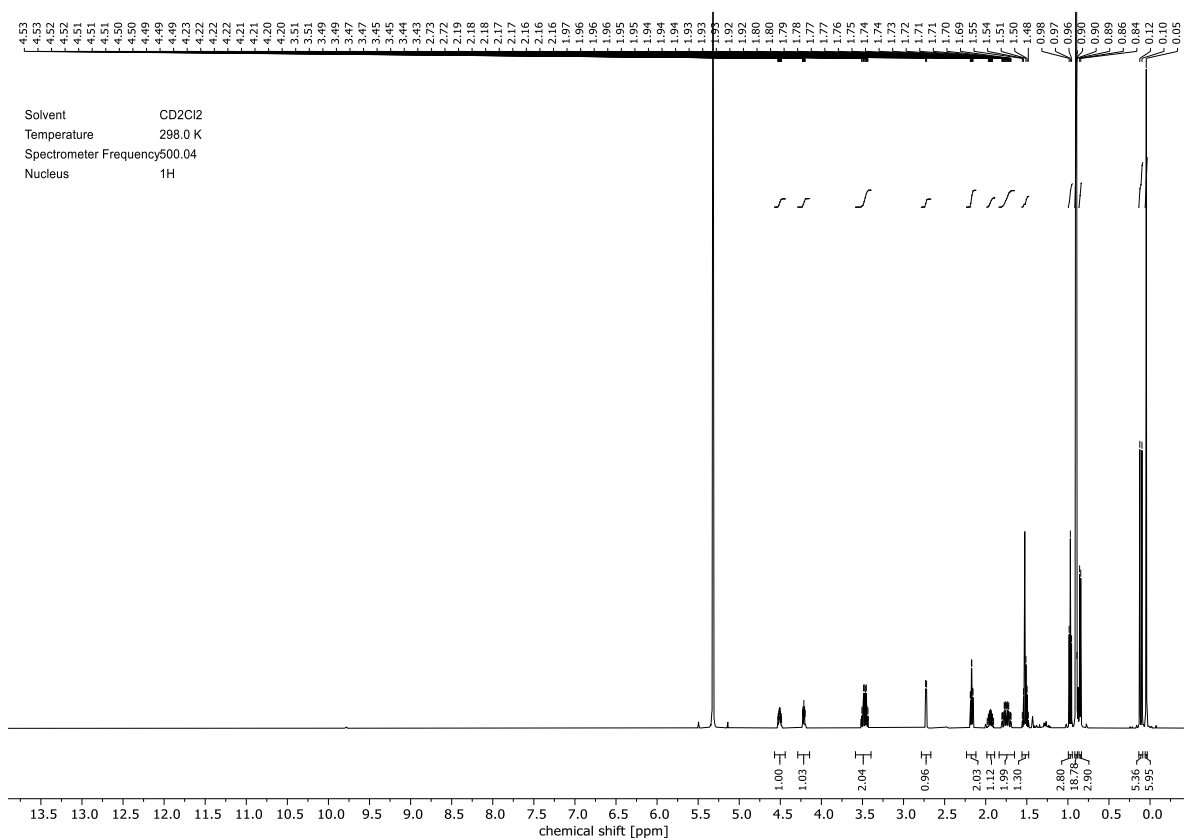
Chemical Formula: $C_{18}H_{40}O_3Si_2$
Exact Mass: 360.2516

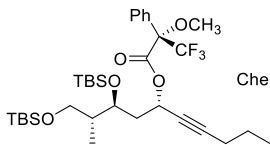


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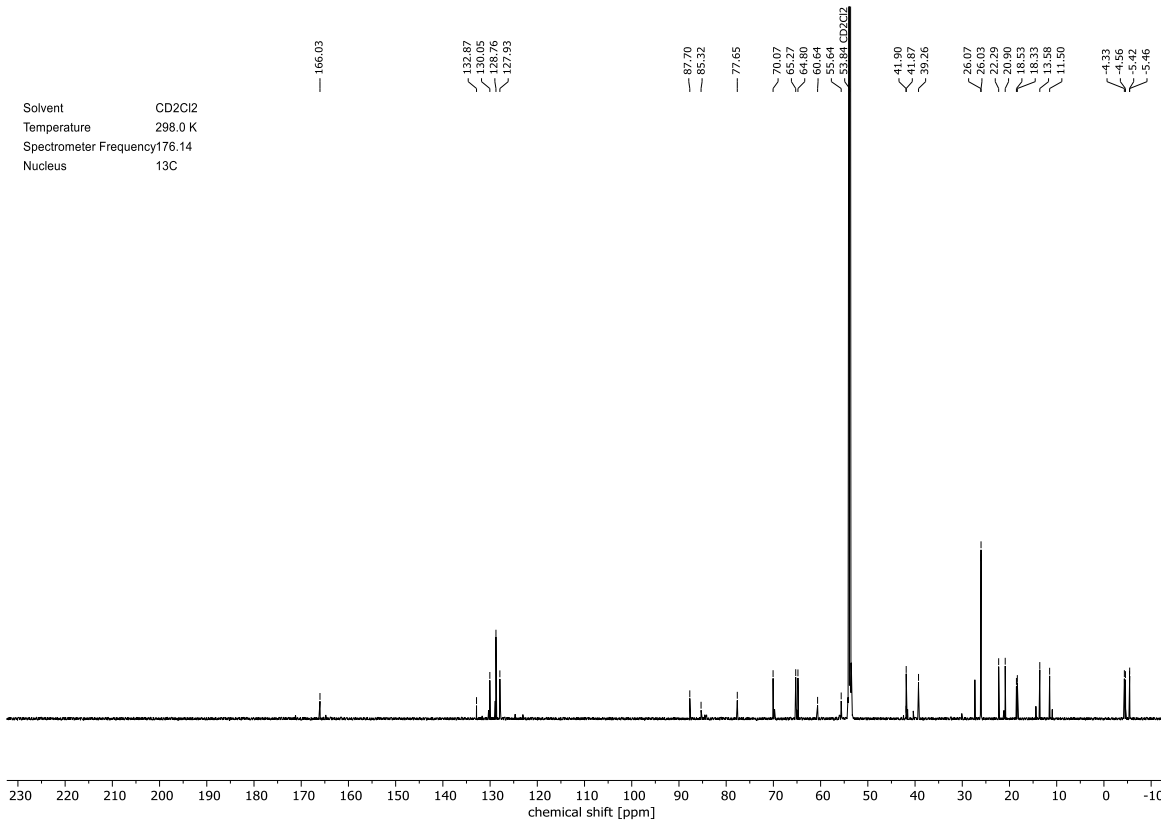
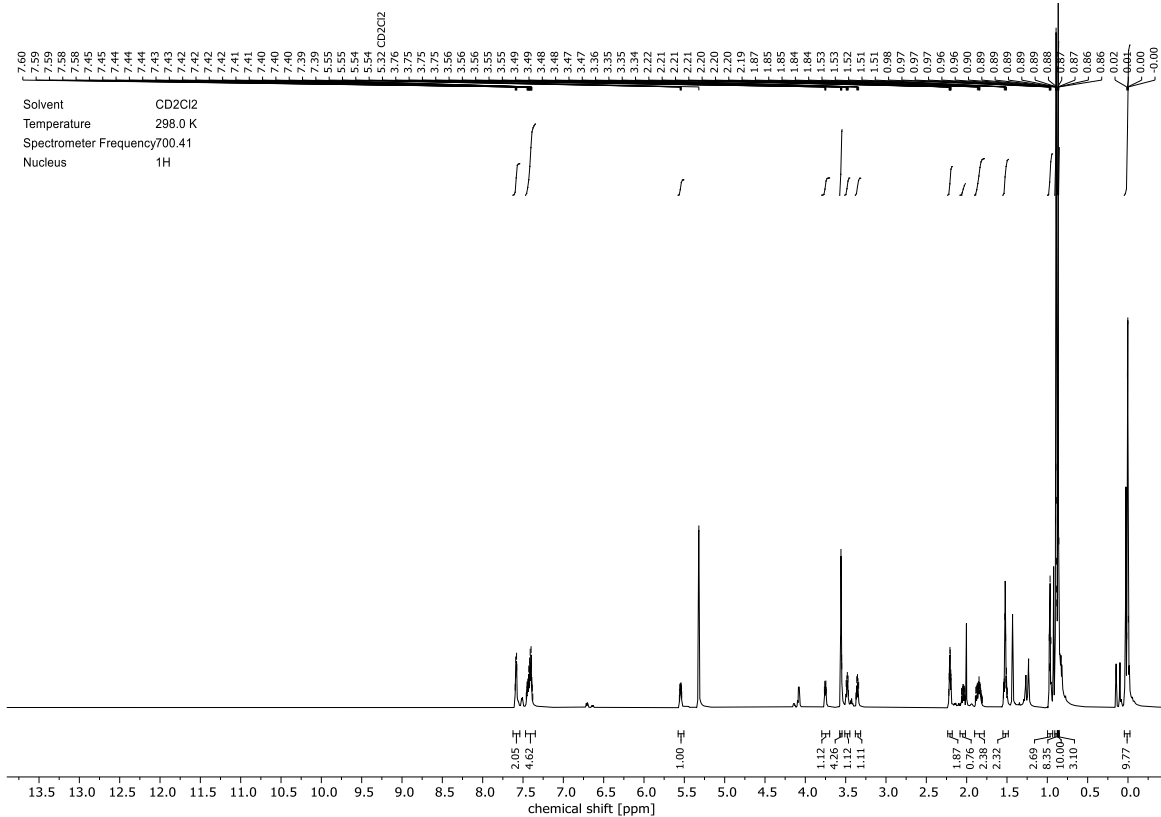
Chemical Formula: $C_{23}H_{48}O_3Si_2$
Exact Mass: 428.3142





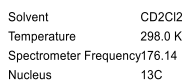
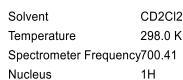
Chemical Formula: $C_{33}H_{55}F_3O_5Si_2$

Exact Mass: 644.3540

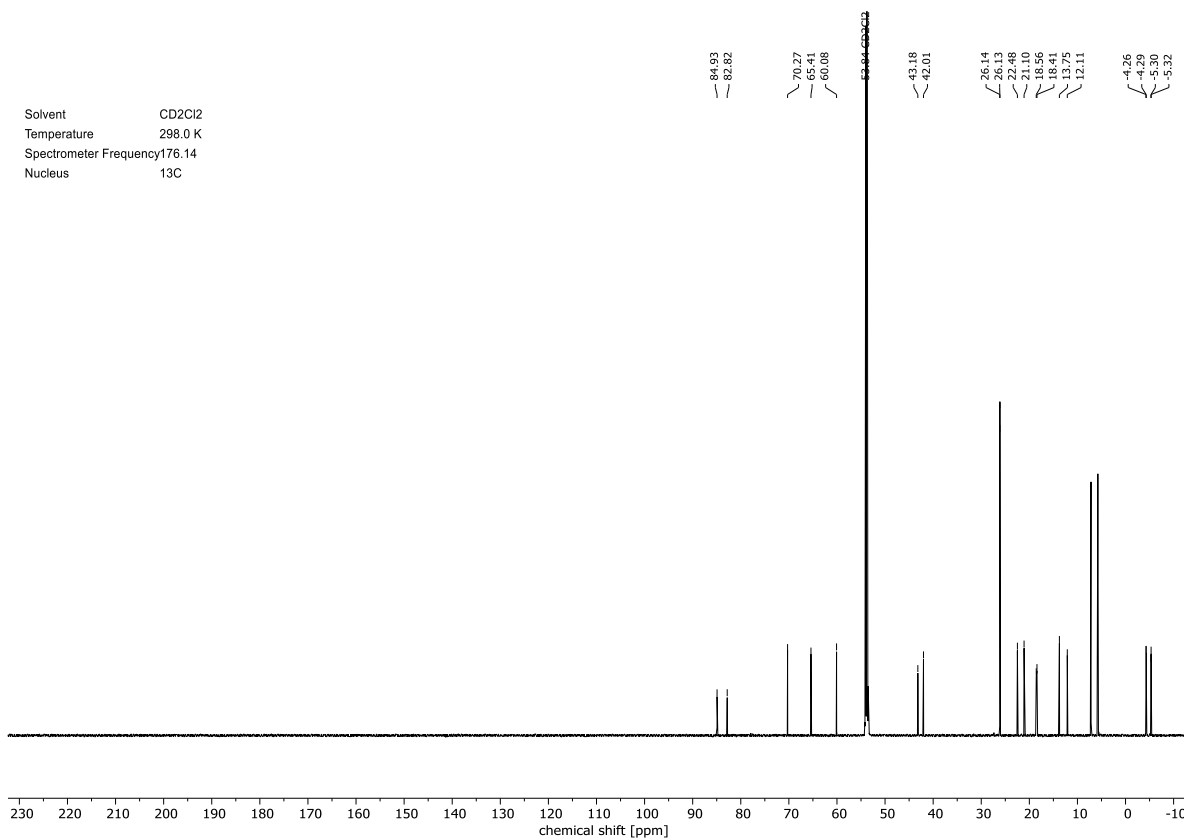
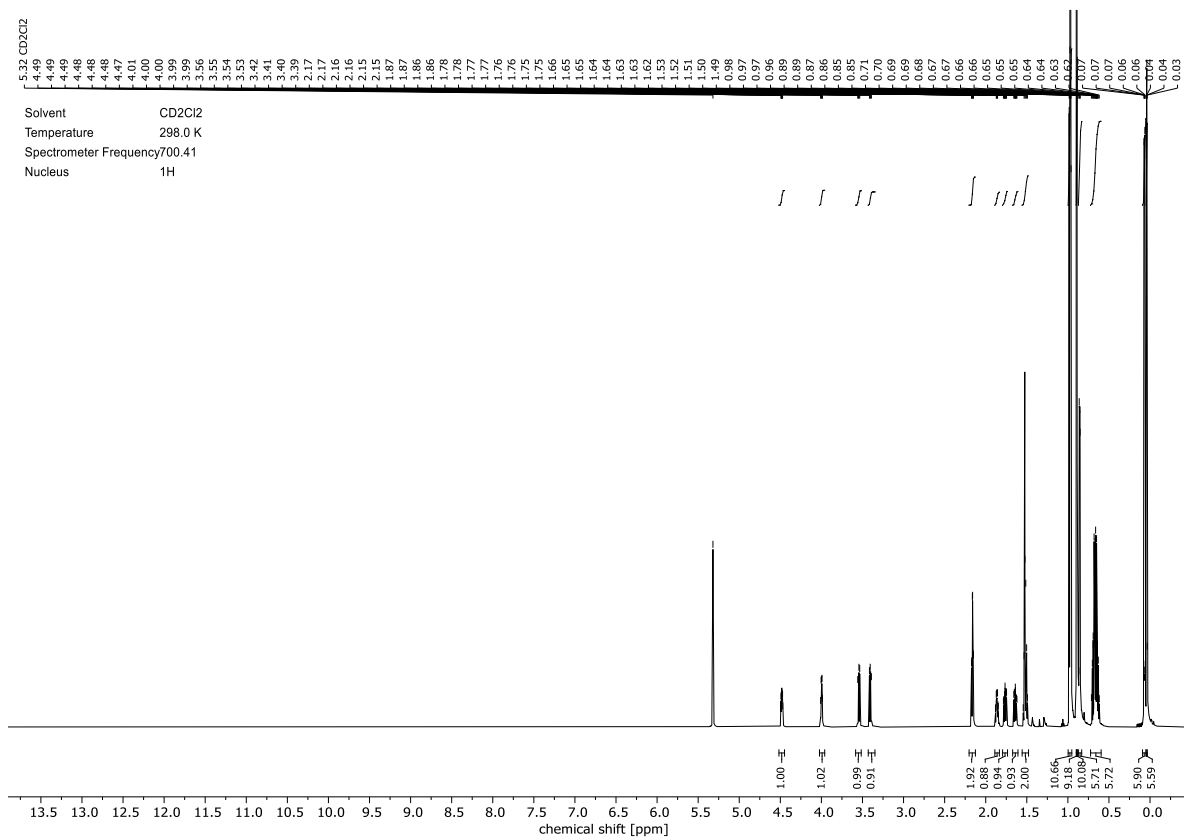
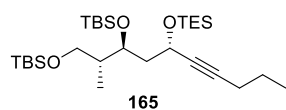




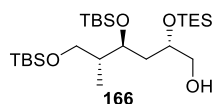
Exact Mass: 644.3540



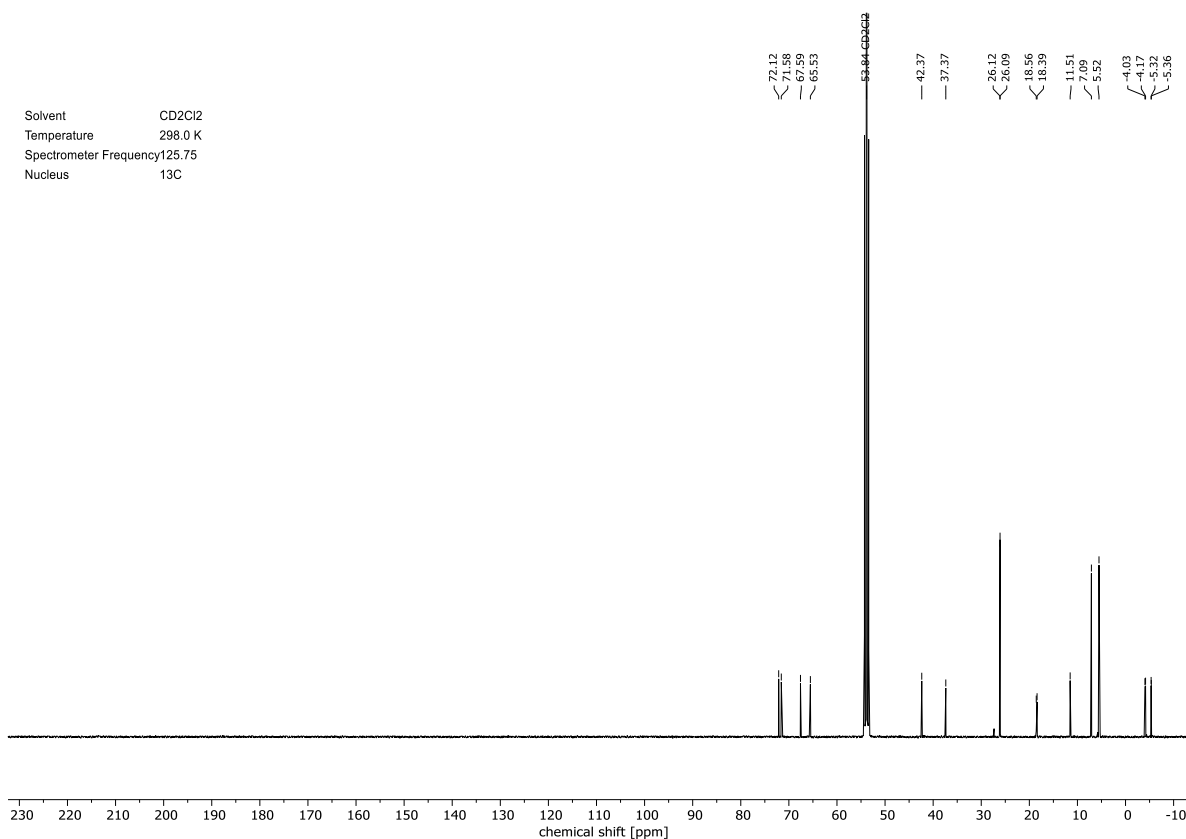
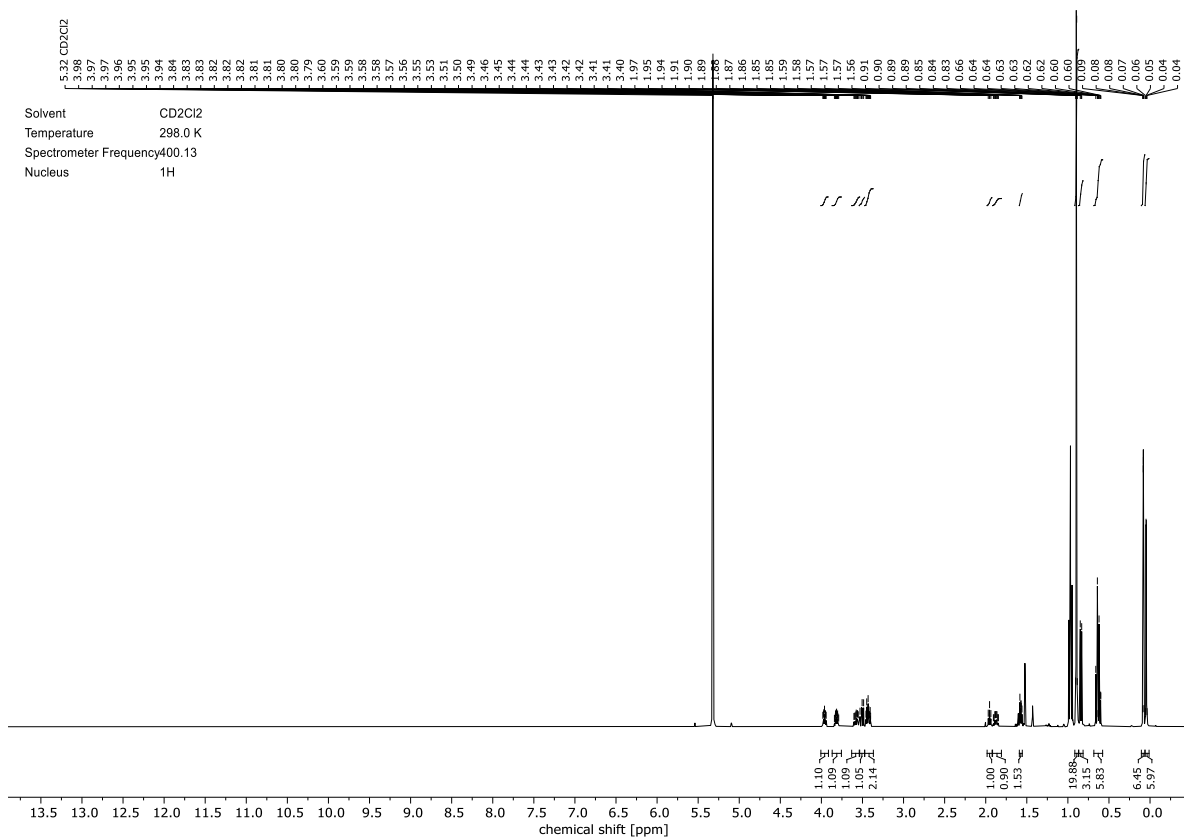
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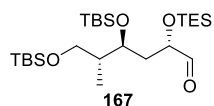
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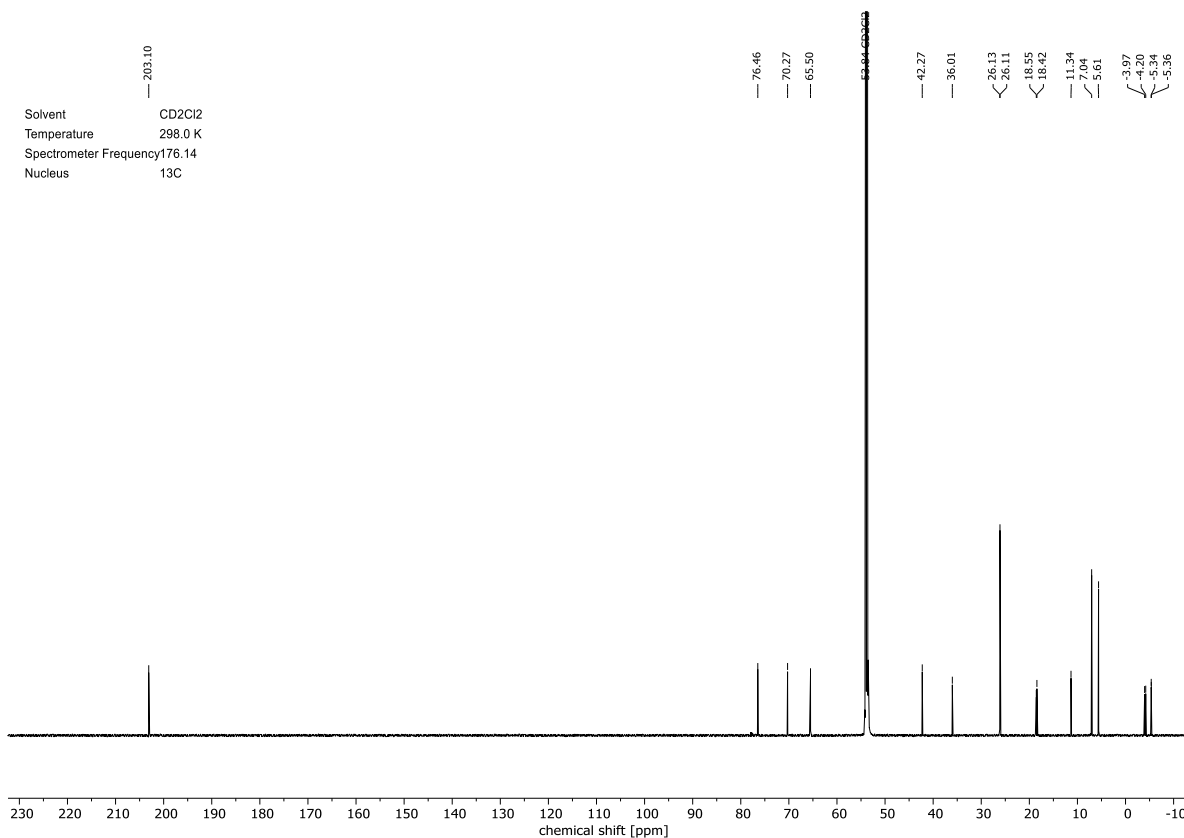
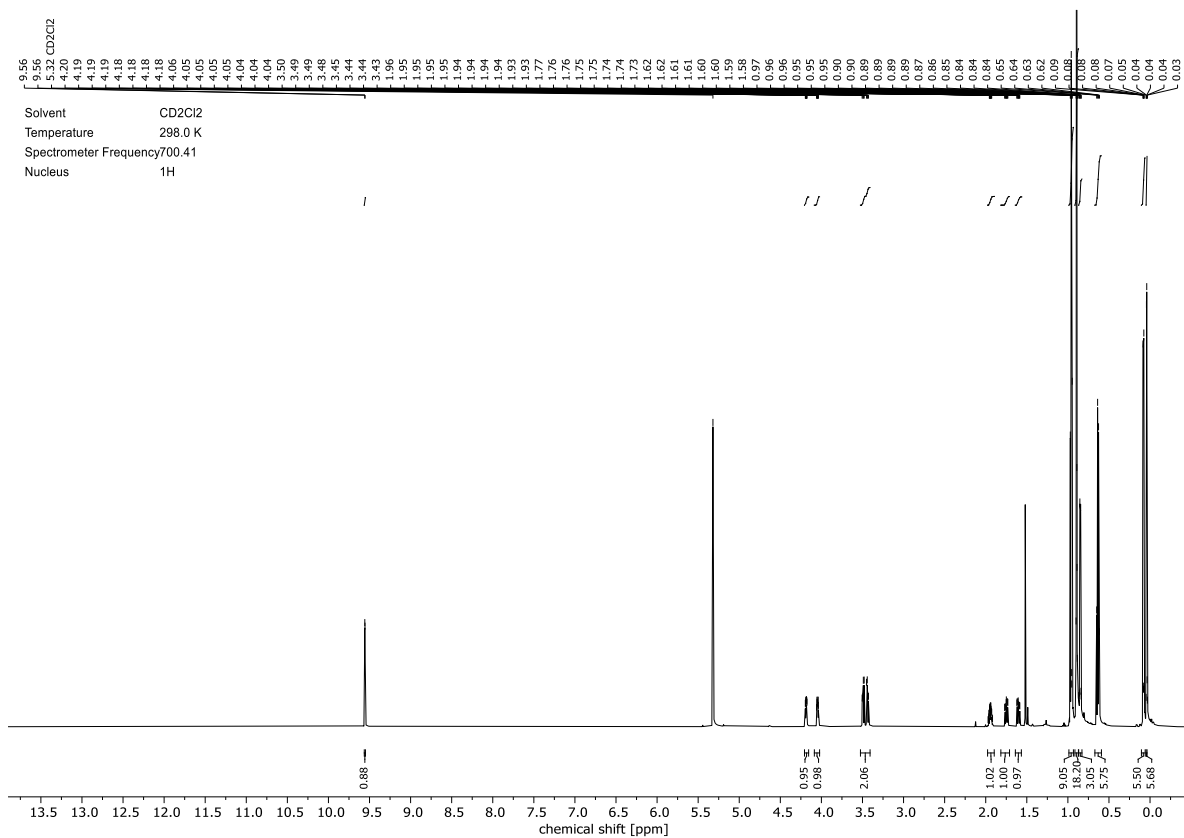
Chemical Formula: $C_{25}H_{58}O_4Si_3$
Exact Mass: 506.3643



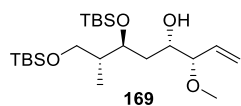
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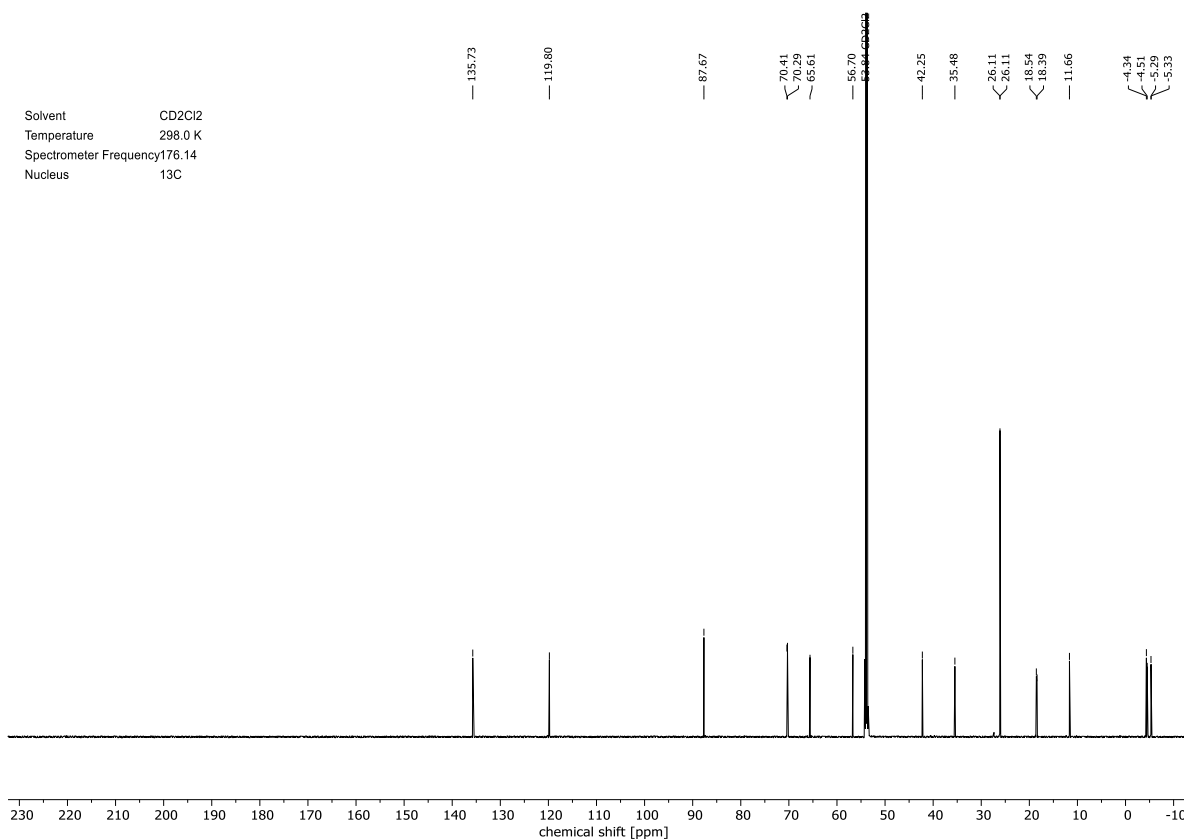
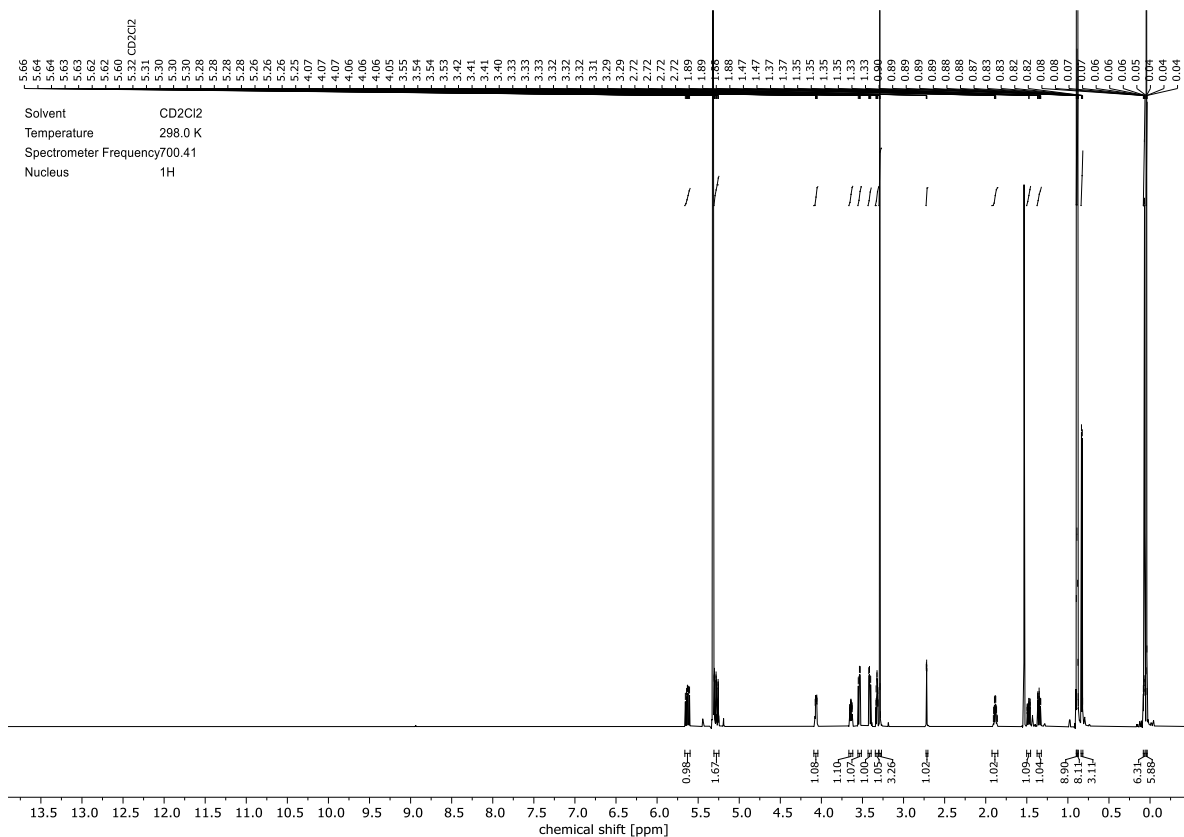
Chemical Formula: $C_{25}H_{56}O_4Si_3$
Exact Mass: 504.3486

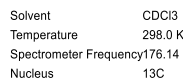
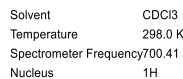
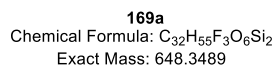


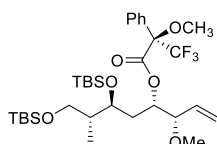
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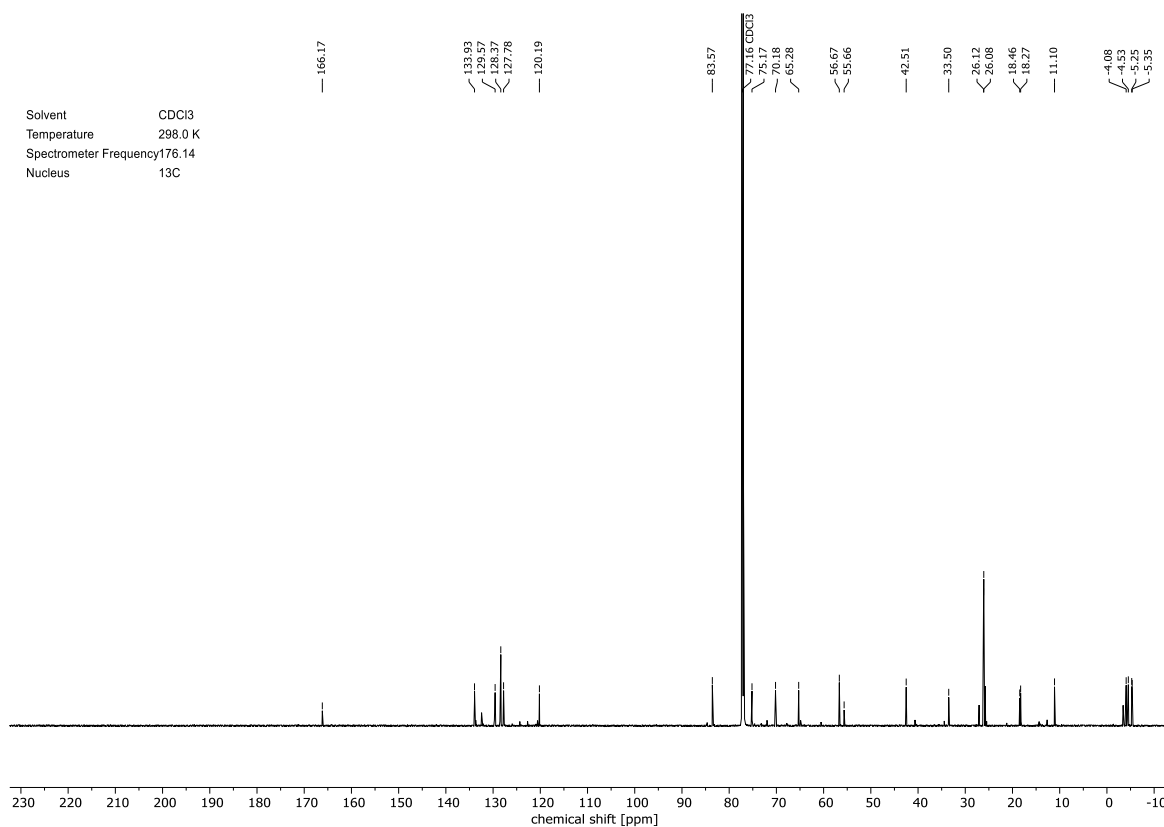
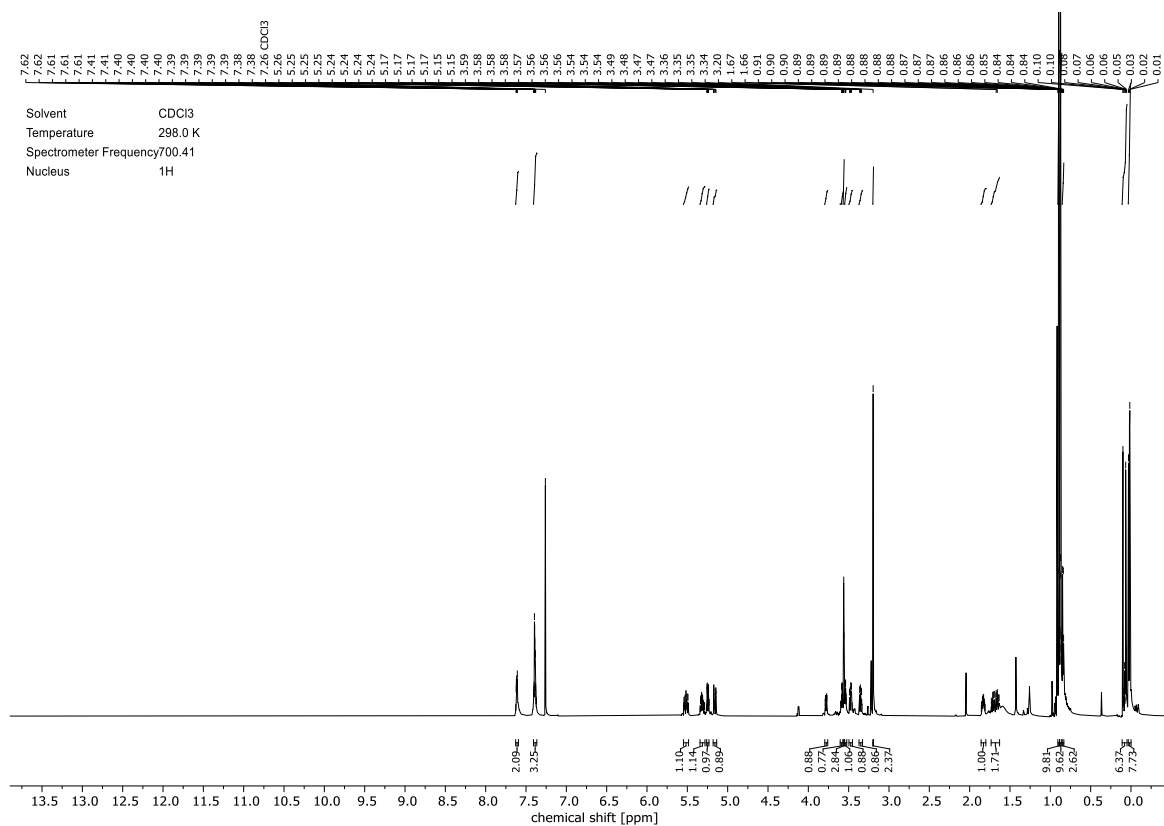
Chemical Formula: $C_{22}H_{48}O_4Si_2$
Exact Mass: 432.3091



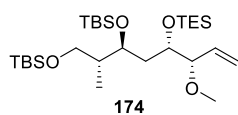




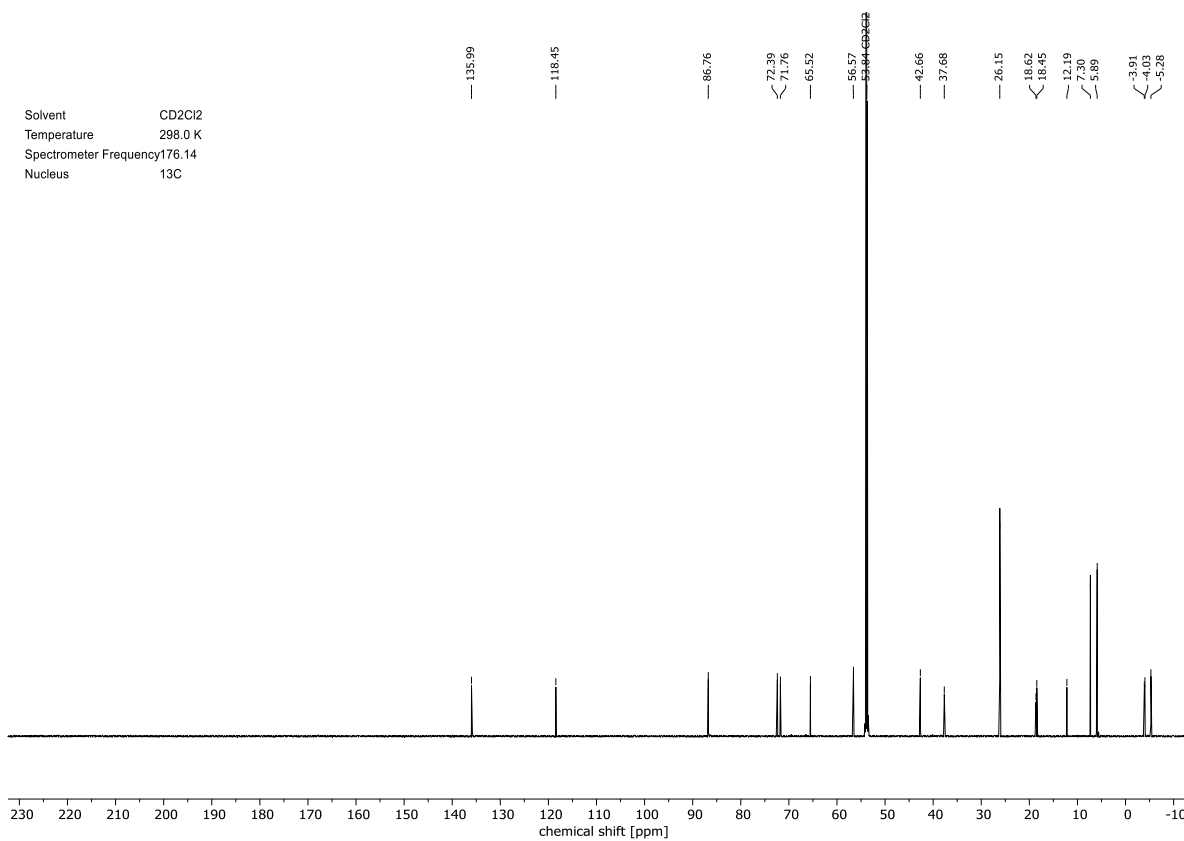
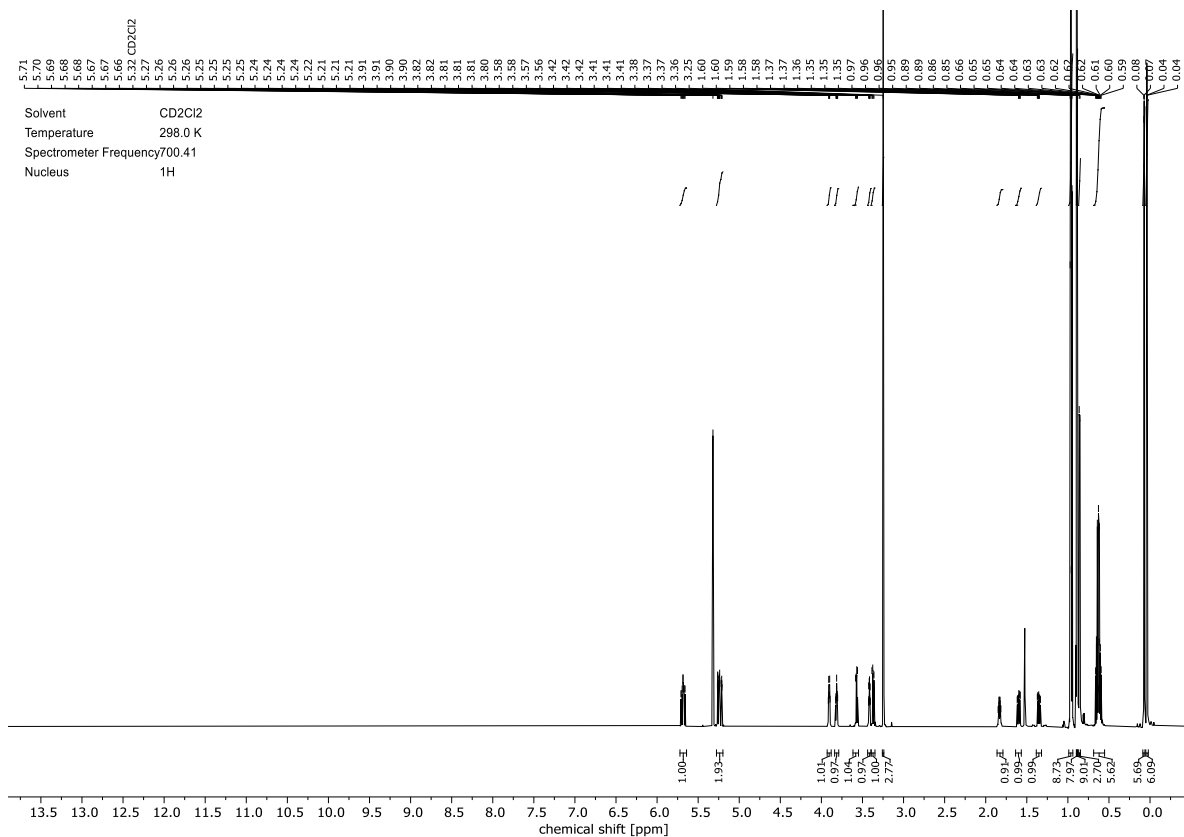
169b
Chemical Formula: $C_{32}H_{55}F_3O_6Si_2$
Exact Mass: 648.3489



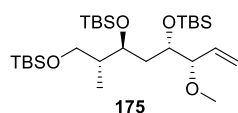
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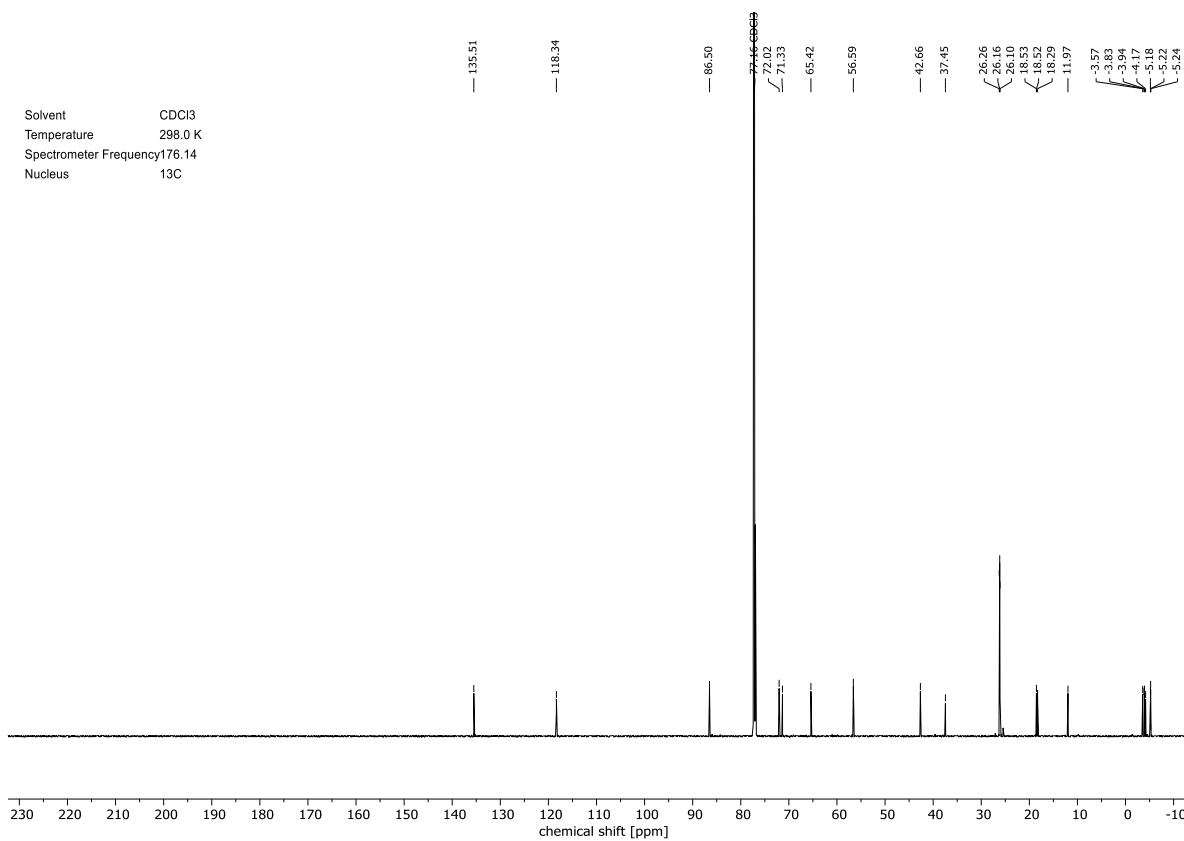
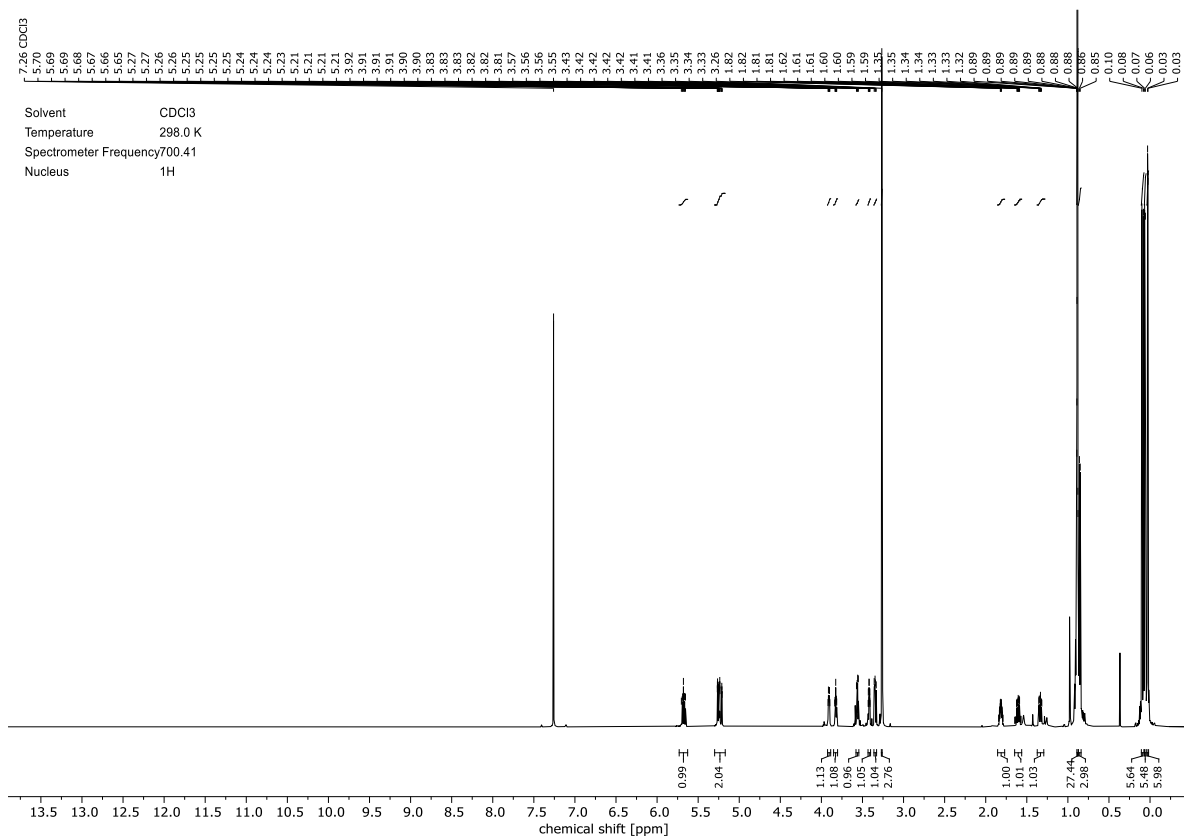
Chemical Formula: $C_{28}H_{62}O_4Si_3$
Exact Mass: 546.3956



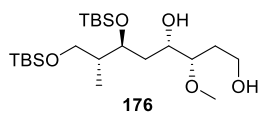
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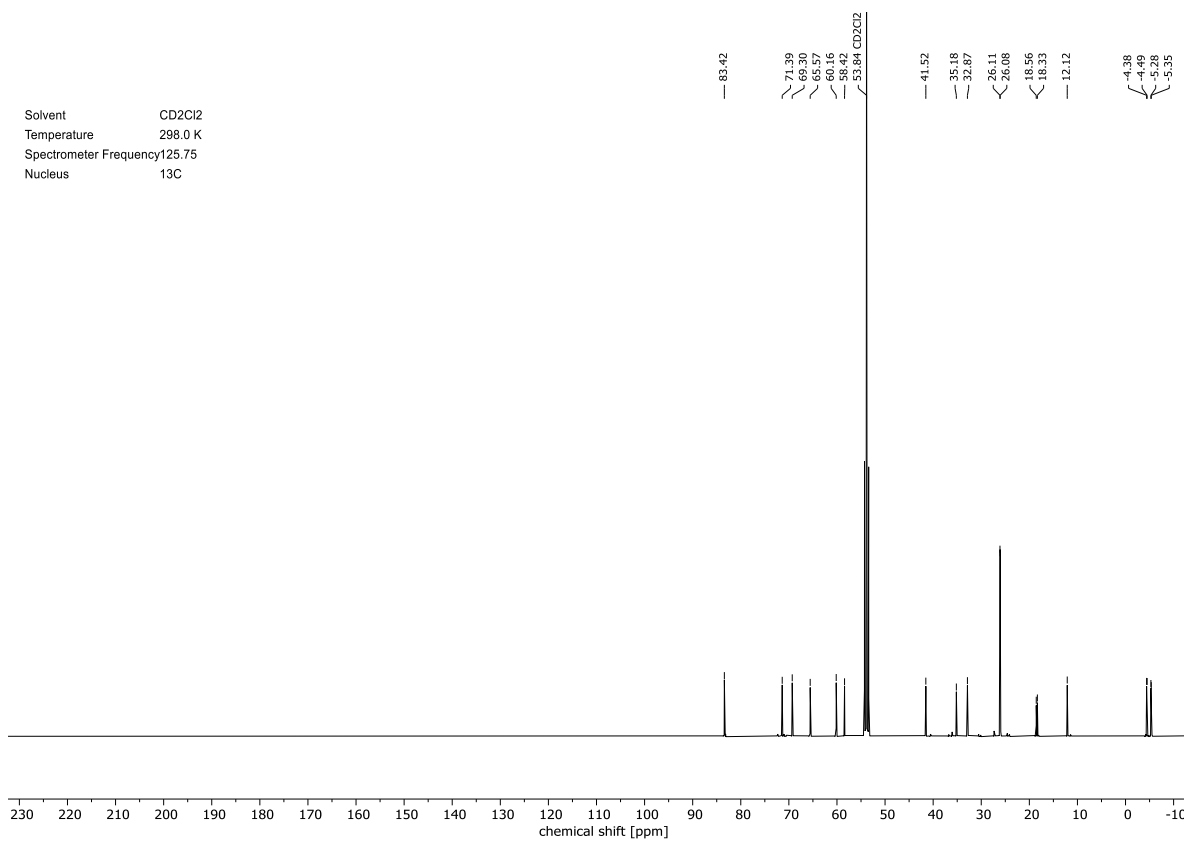
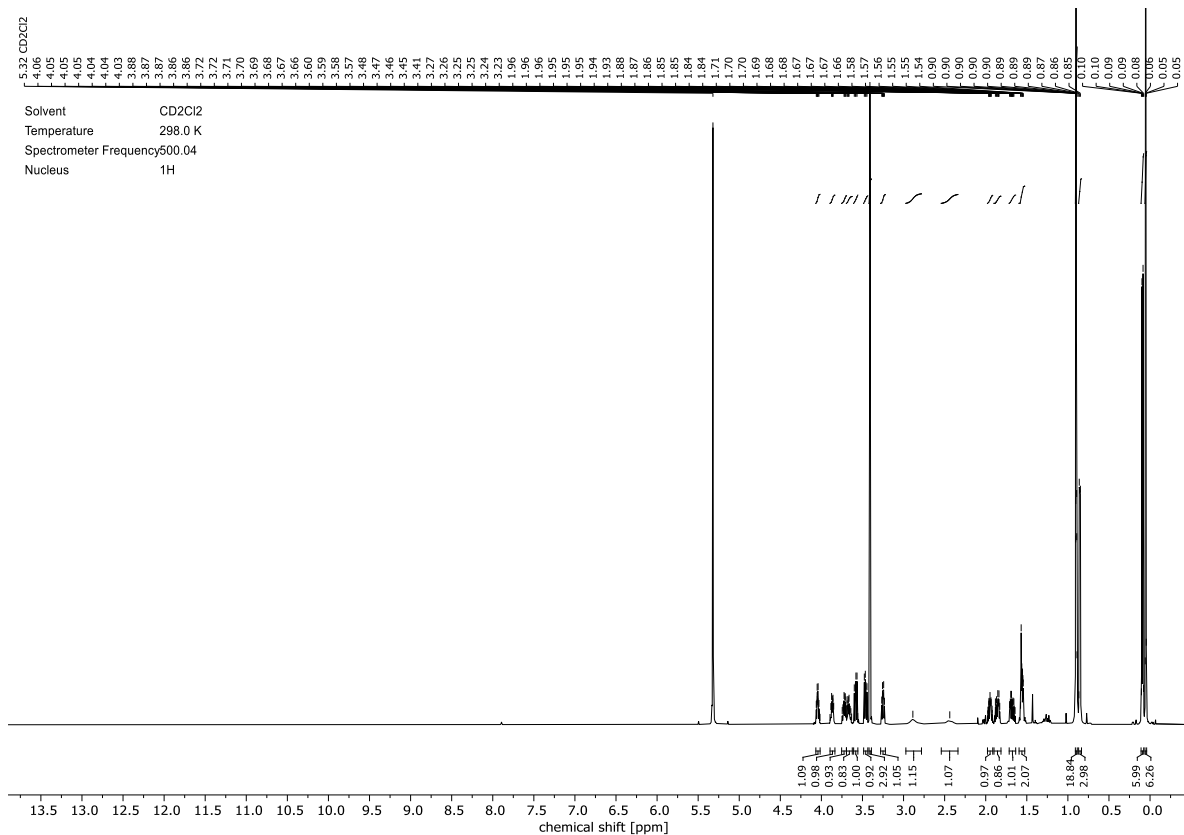
Chemical Formula: $C_{28}H_{62}O_4Si_3$
Exact Mass: 546.3956



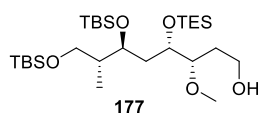
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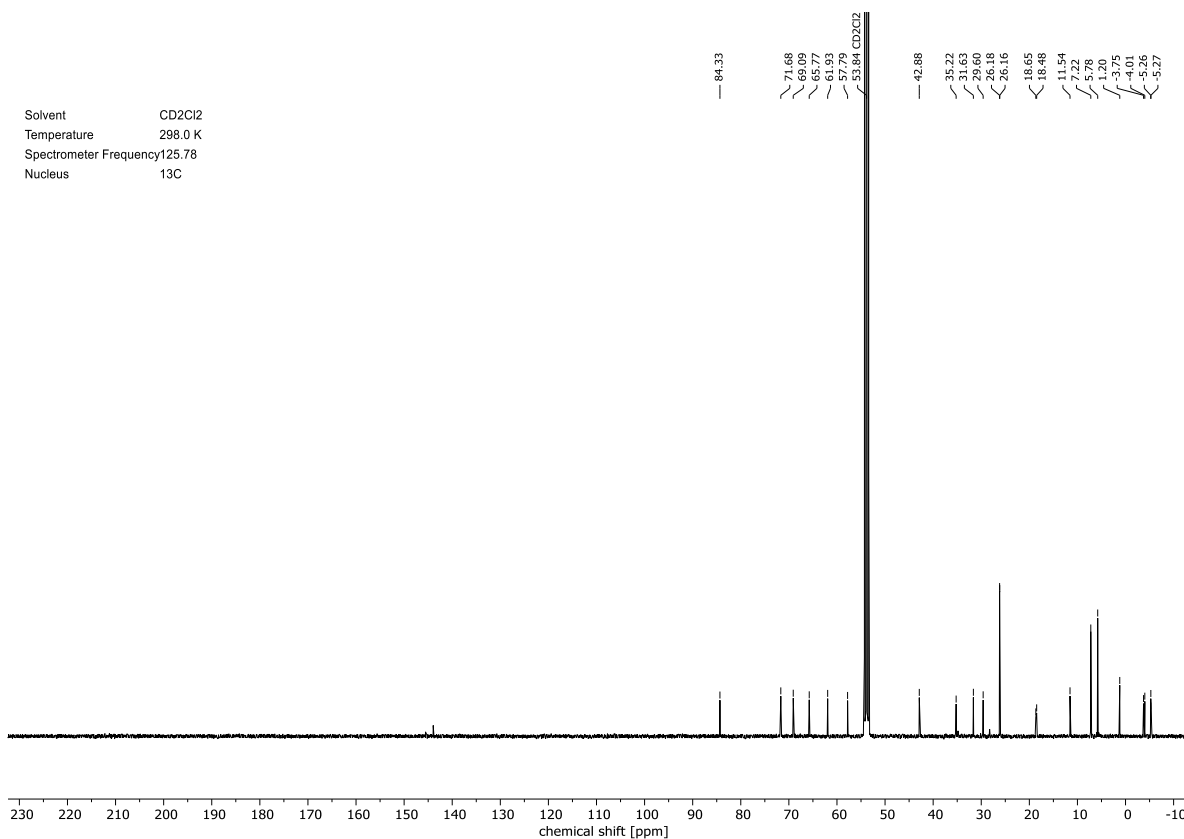
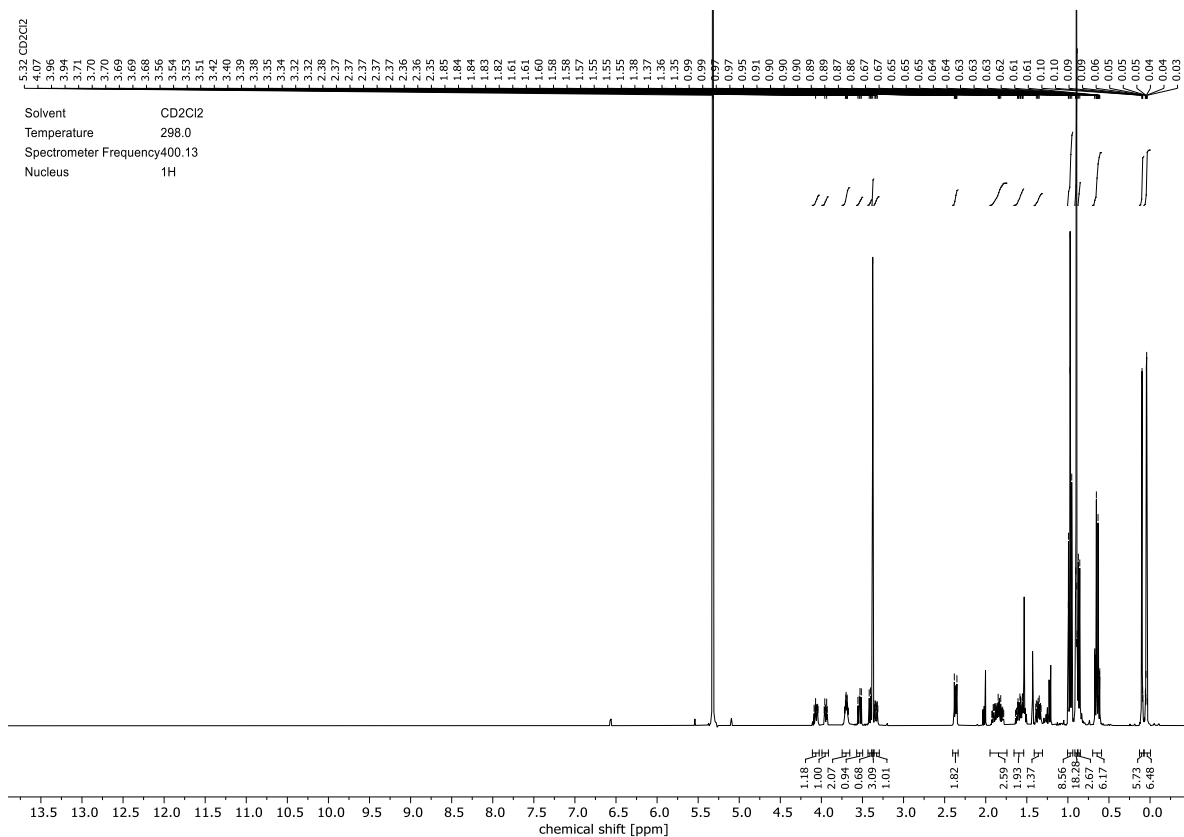
Chemical Formula: $C_{22}H_{50}O_5Si_2$
Exact Mass: 450.3197



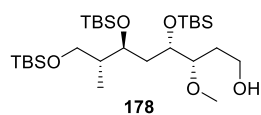
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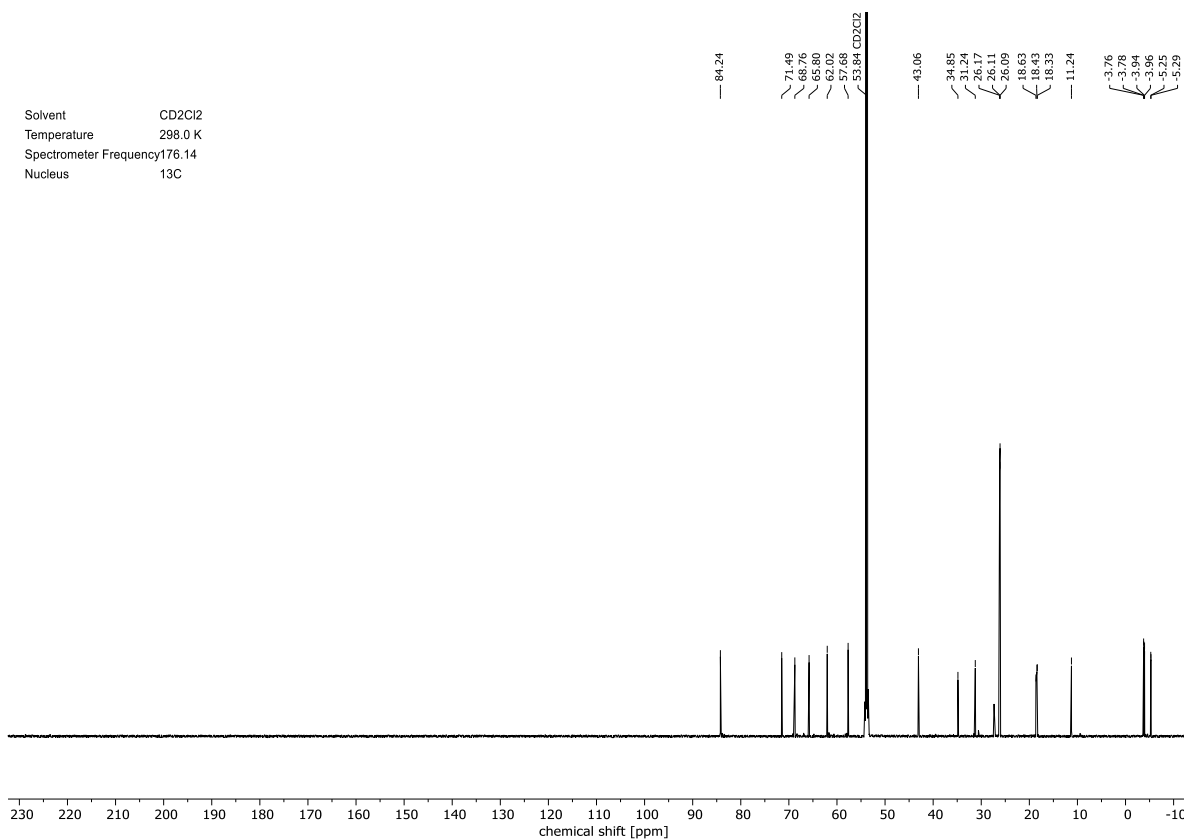
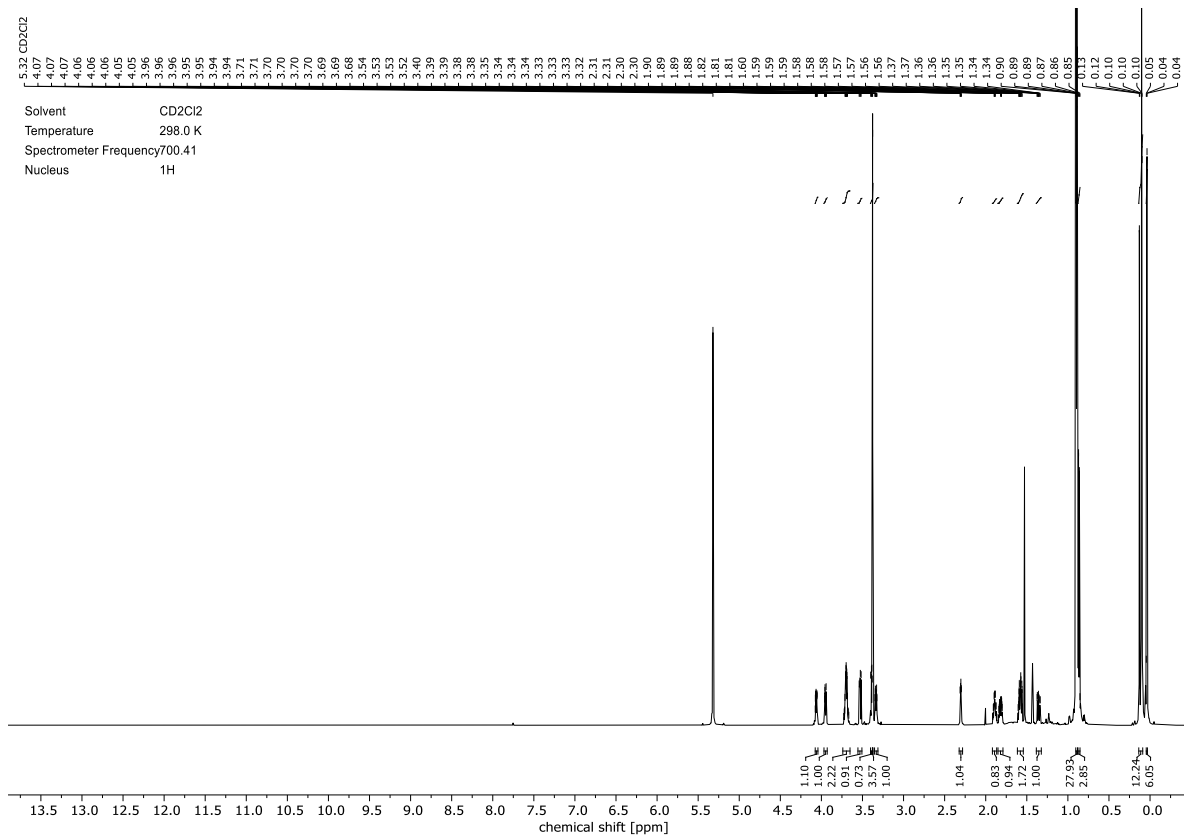
Chemical Formula: $C_{28}H_{64}O_5Si_3$
Exact Mass: 564.4062



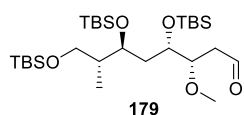
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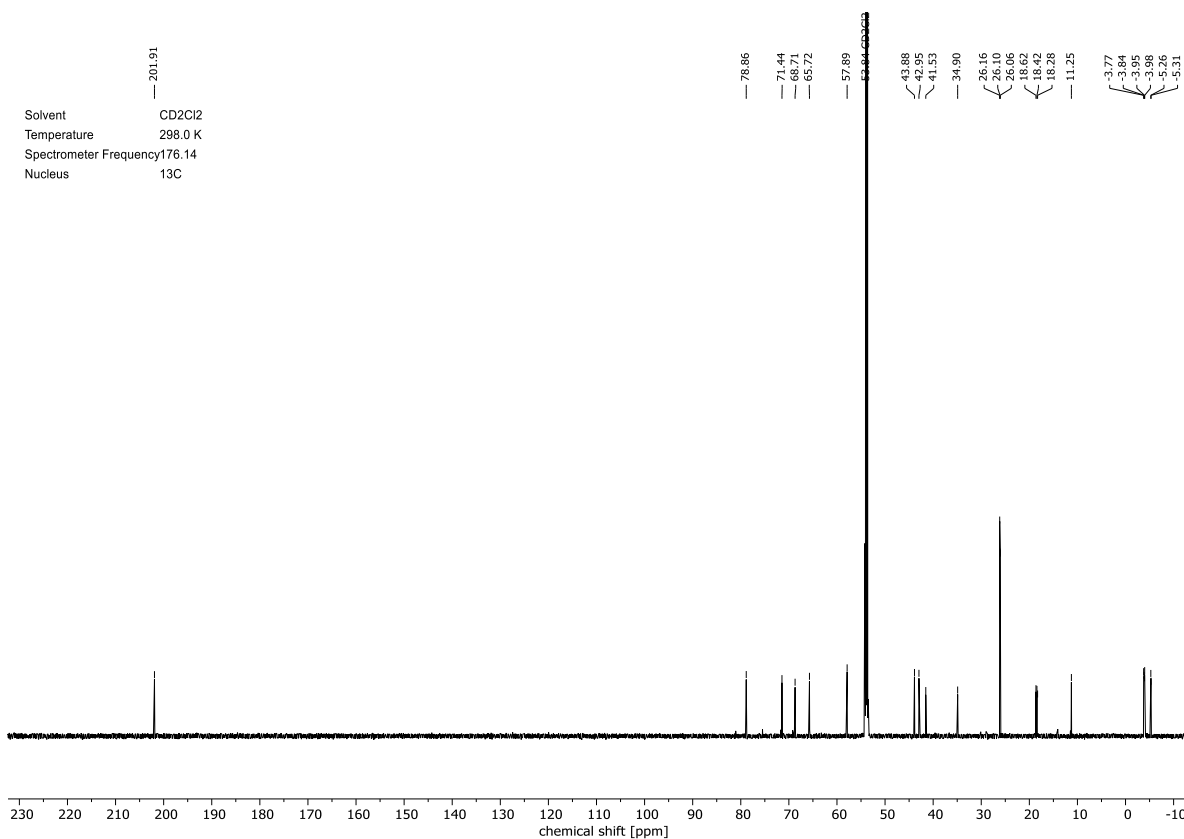
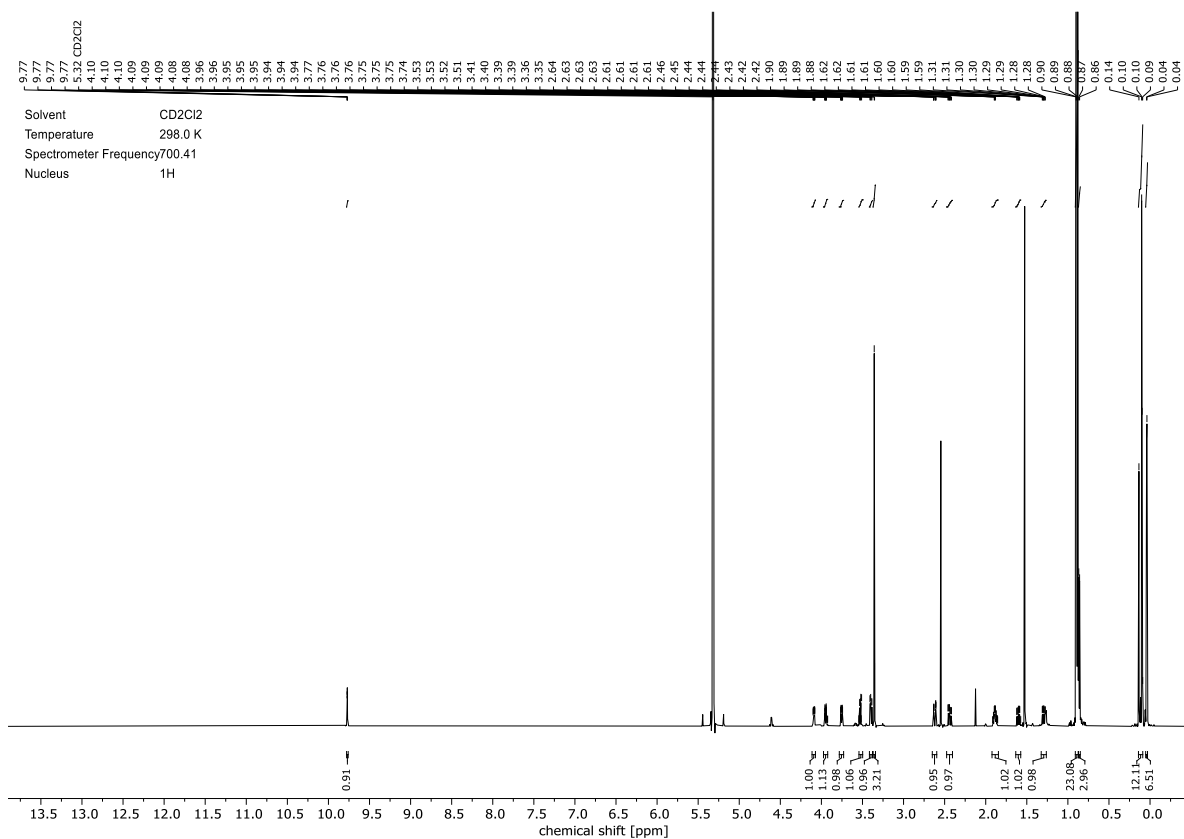
Chemical Formula: $C_{28}H_{64}O_5Si_3$
Exact Mass: 564.4062

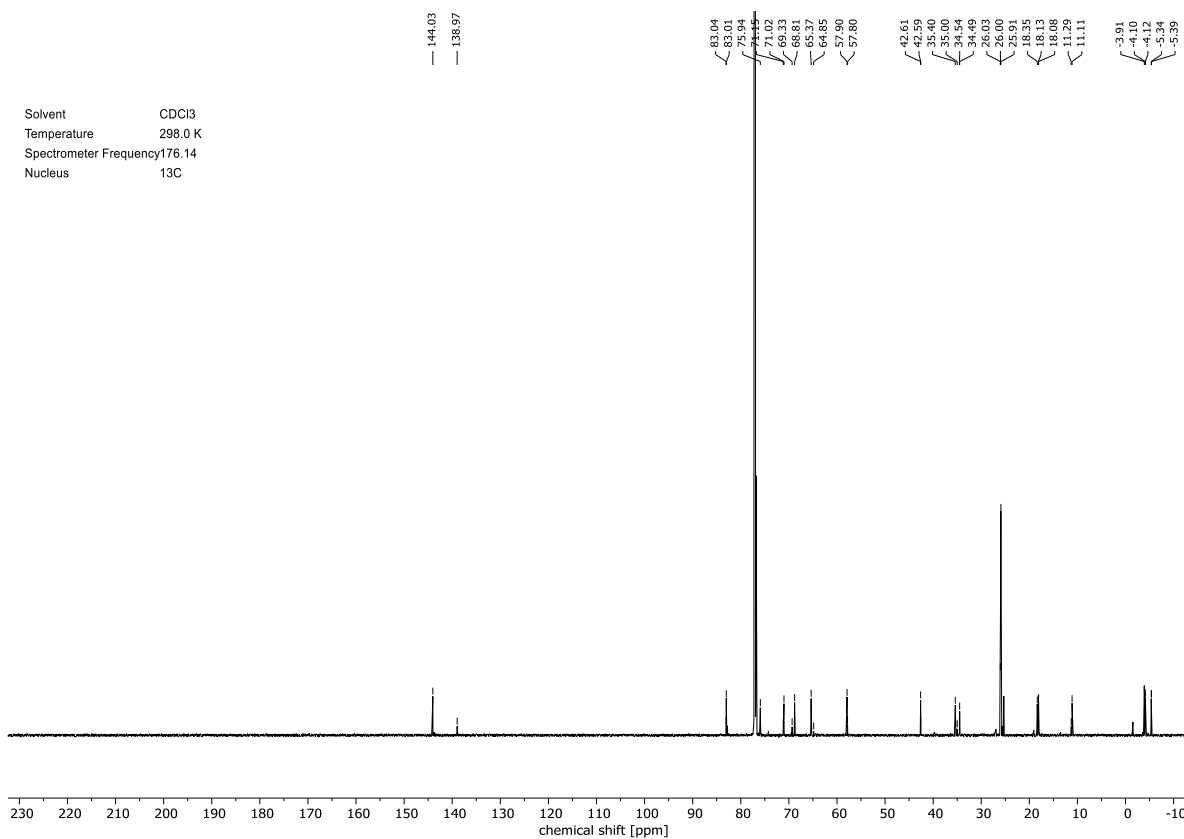
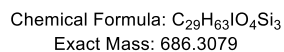


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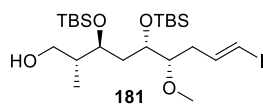


Chemical Formula: $C_{28}H_{62}O_5Si_3$
Exact Mass: 562.3905

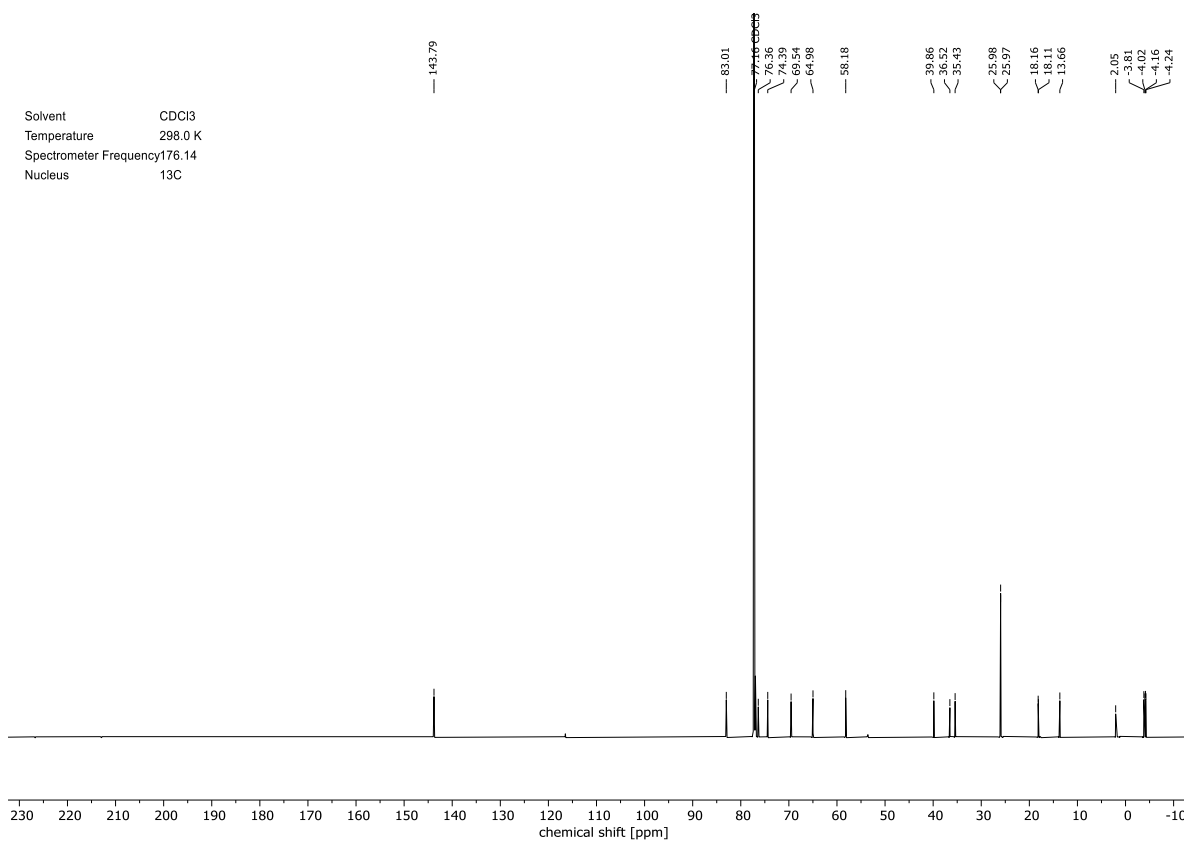
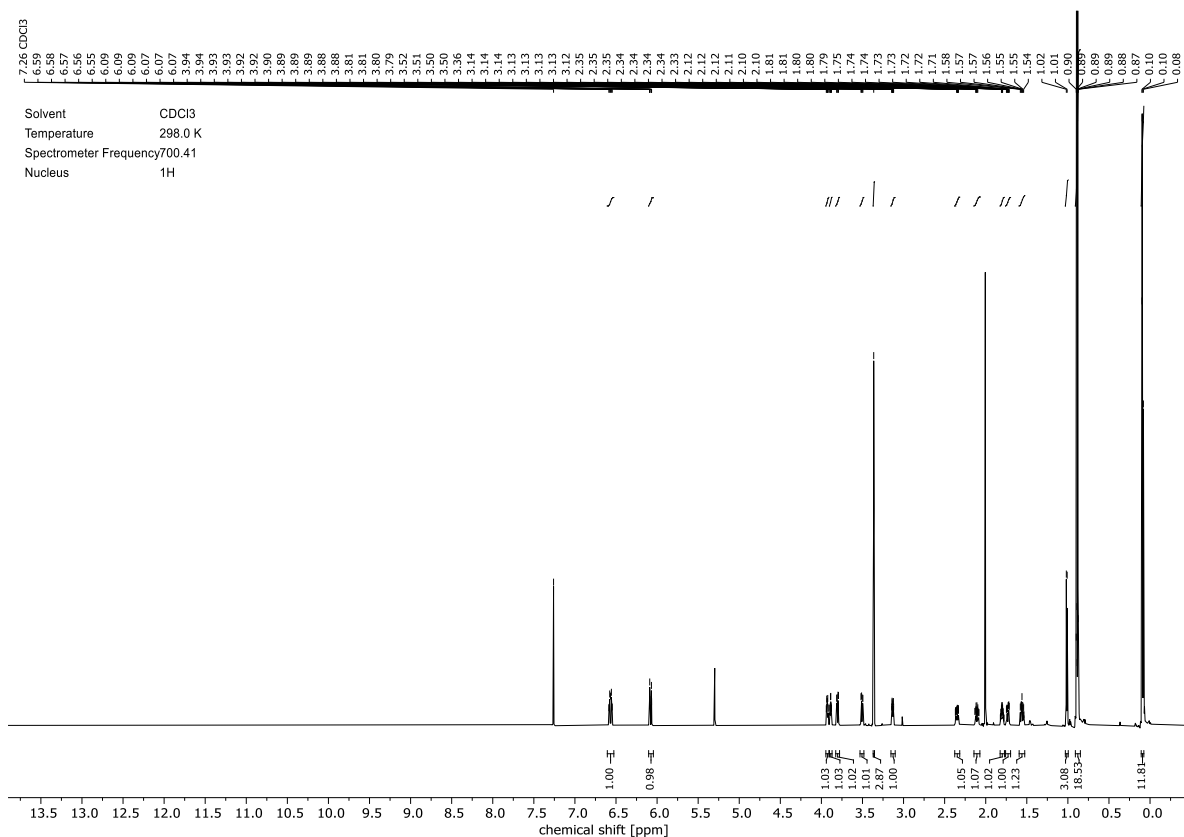




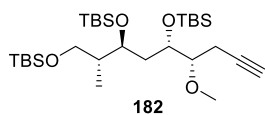
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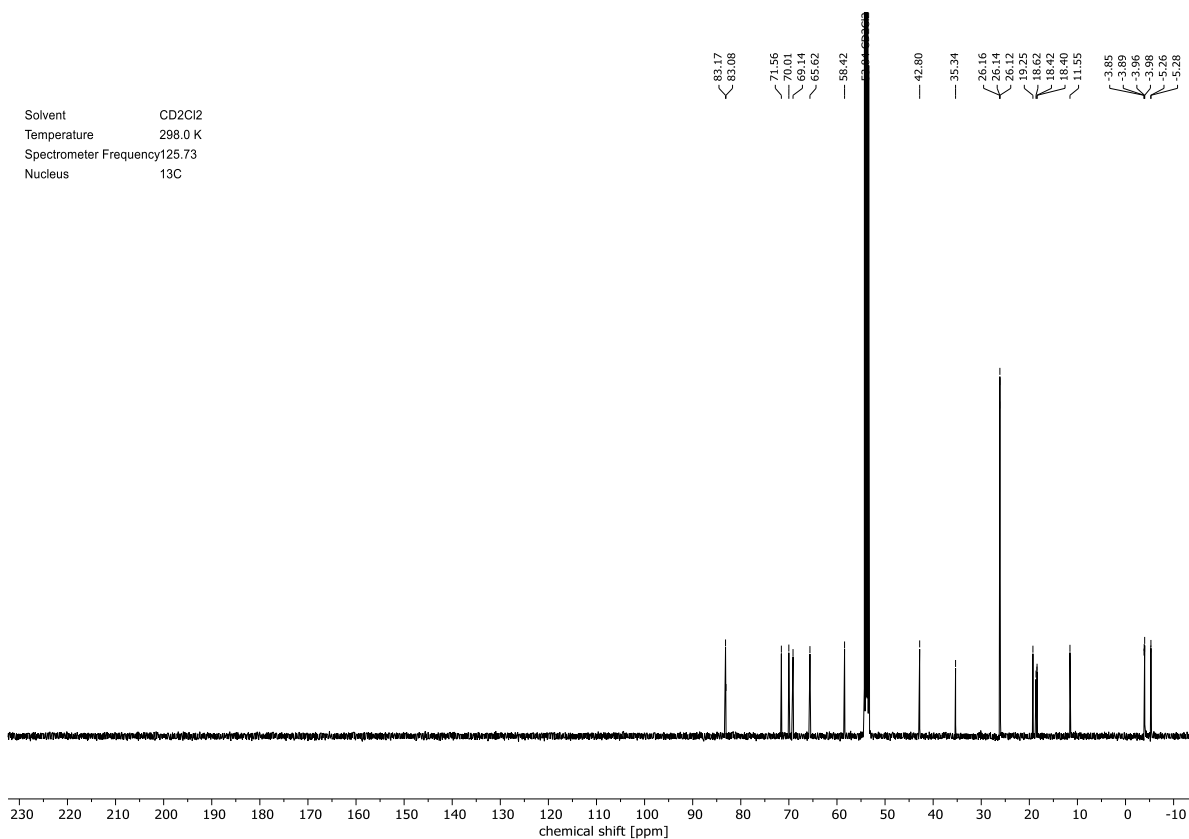
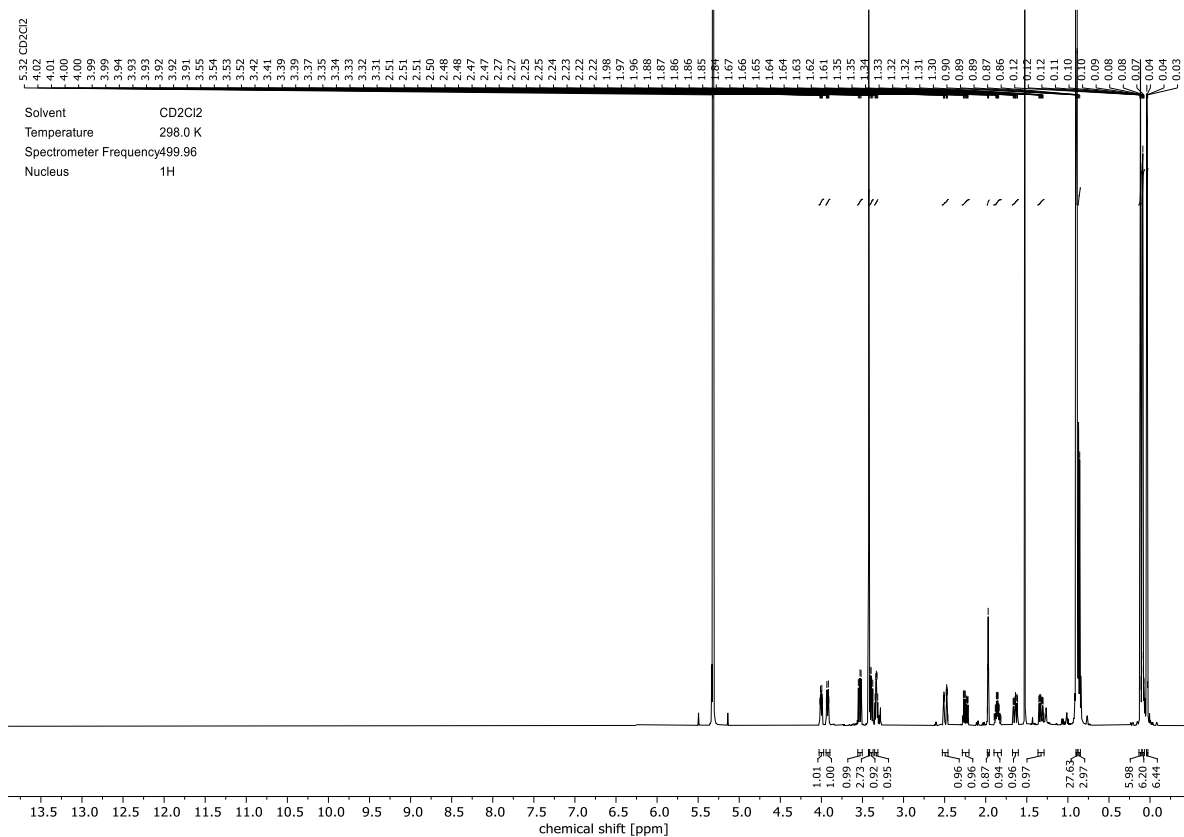
Chemical Formula: $C_{23}H_{49}IO_4Si_2$
Exact Mass: 572.2214



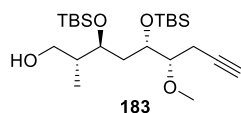
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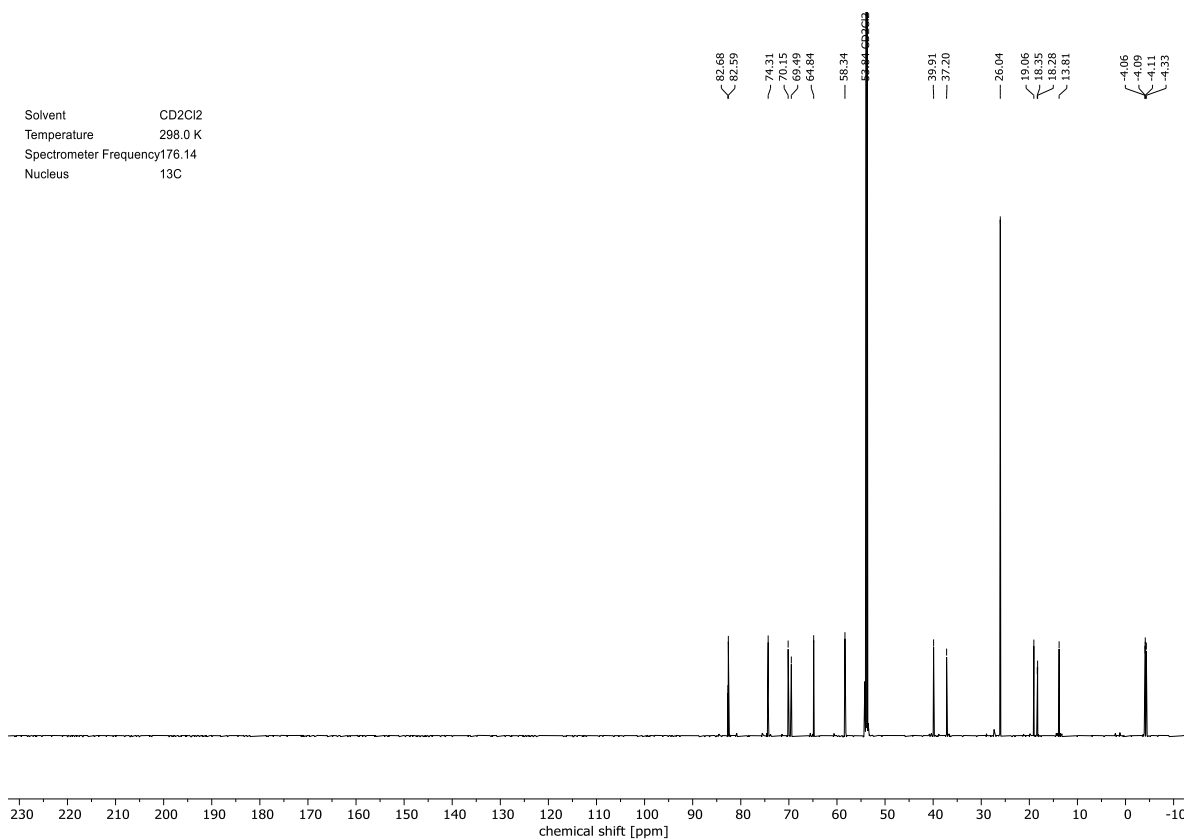
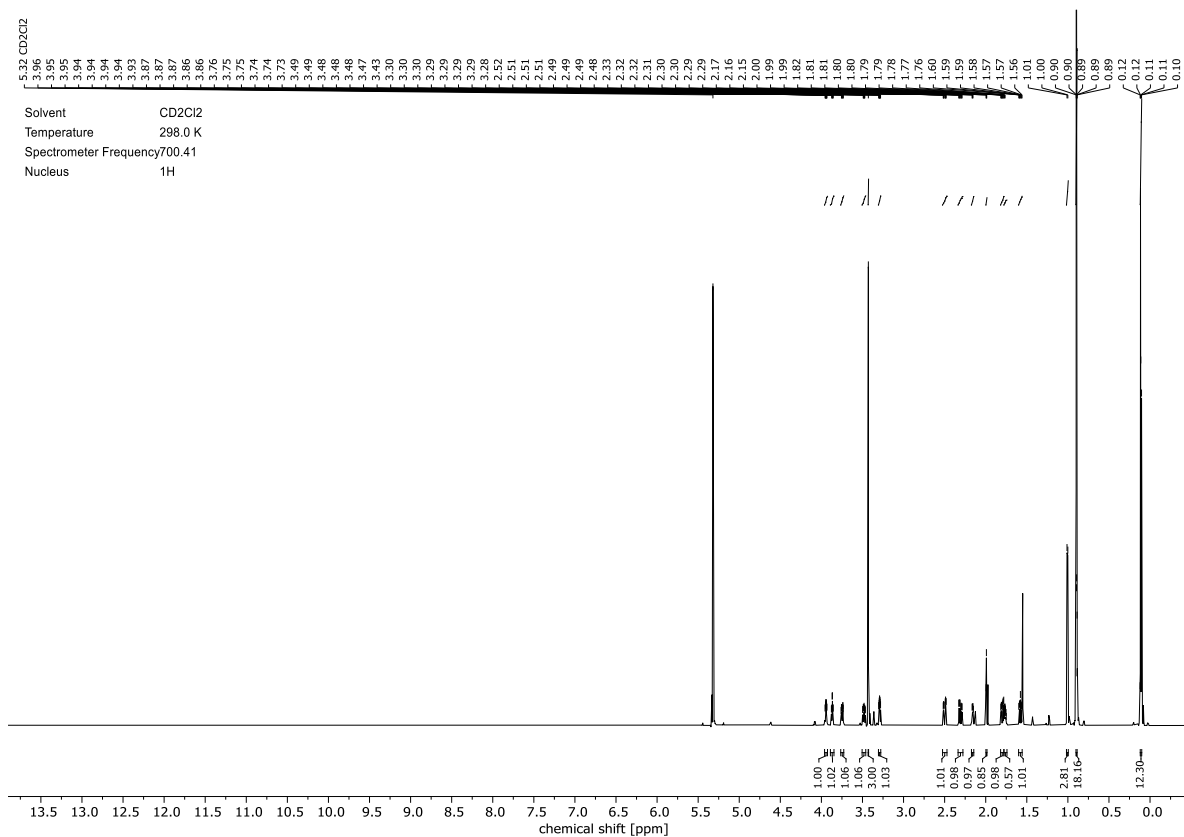
Chemical Formula: $C_{29}H_{62}O_4Si_3$
Exact Mass: 558.3956



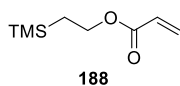
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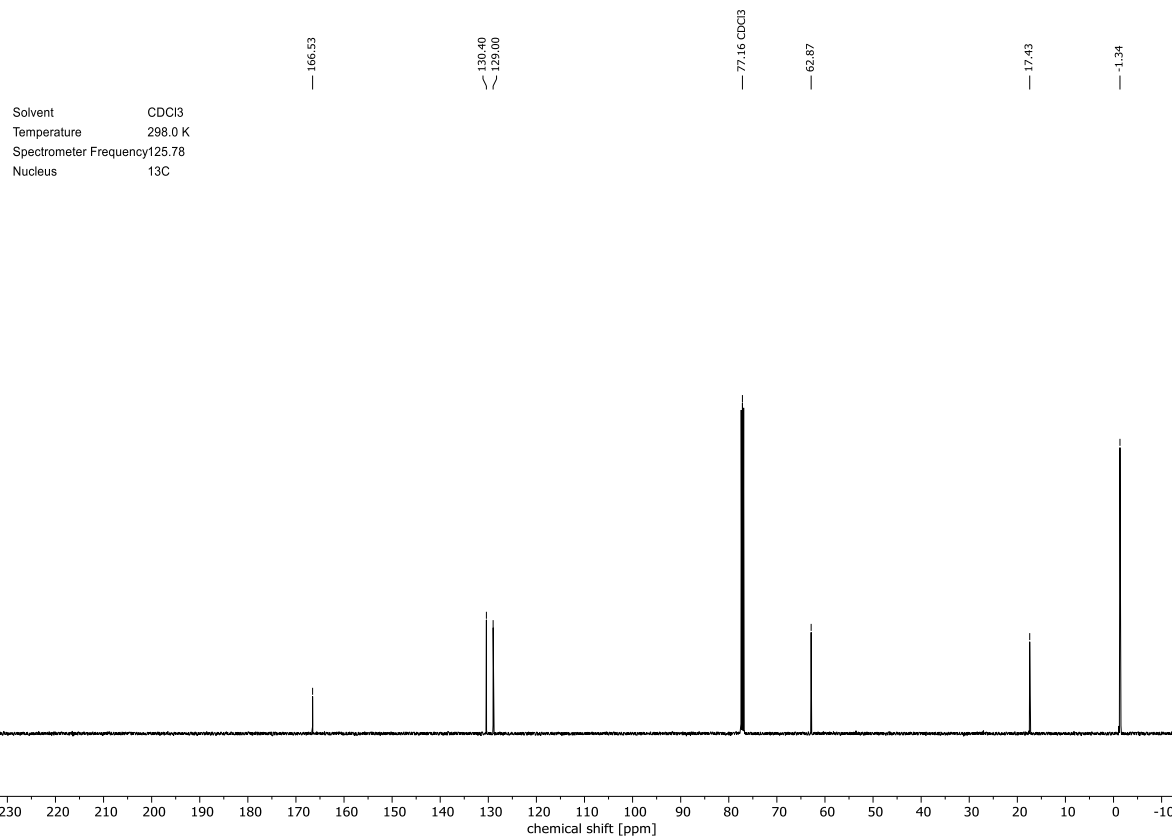
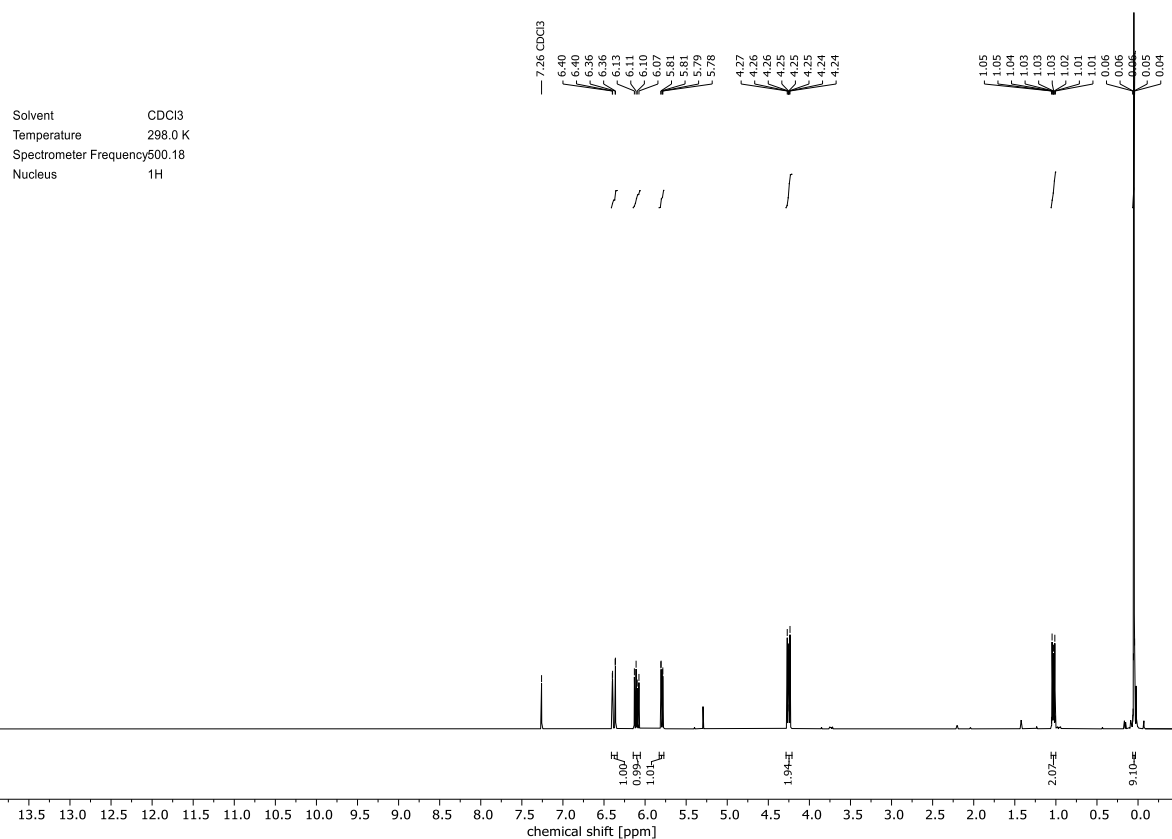
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Exact Mass: 444.3091



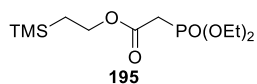
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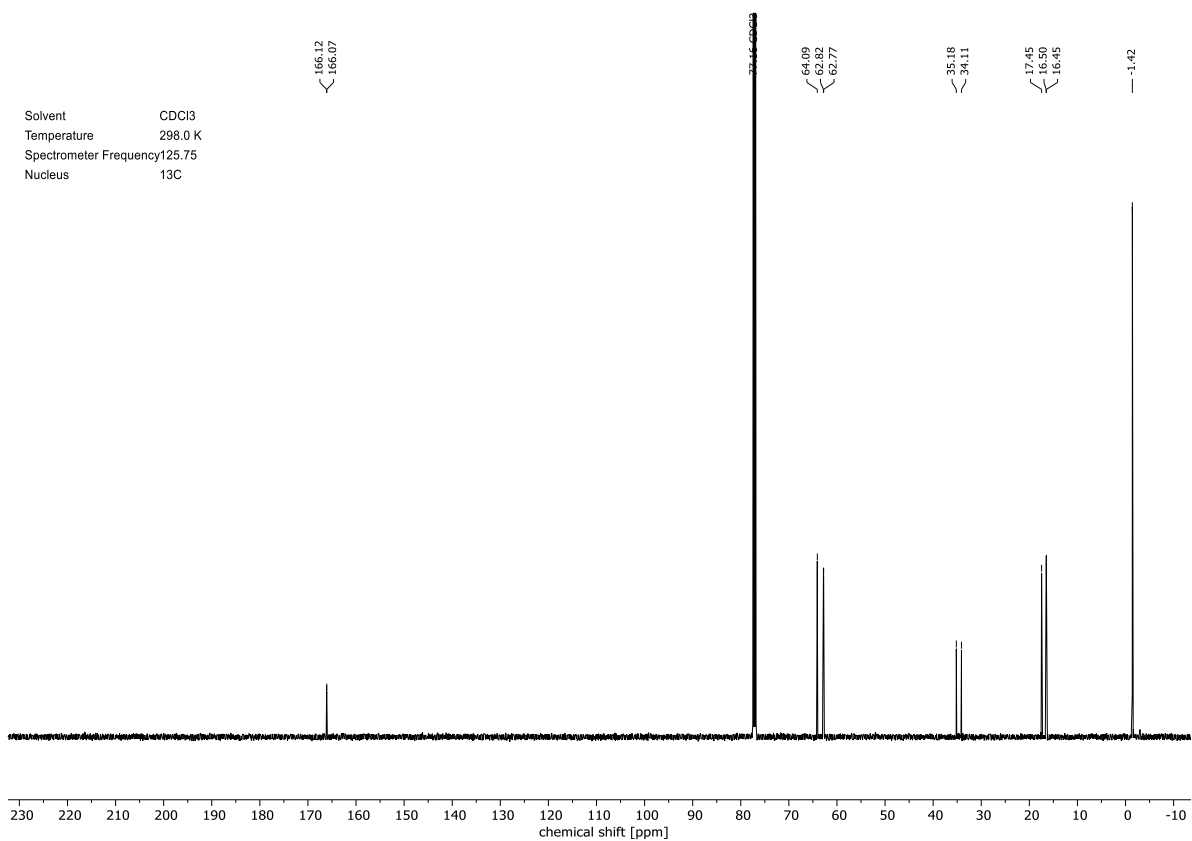
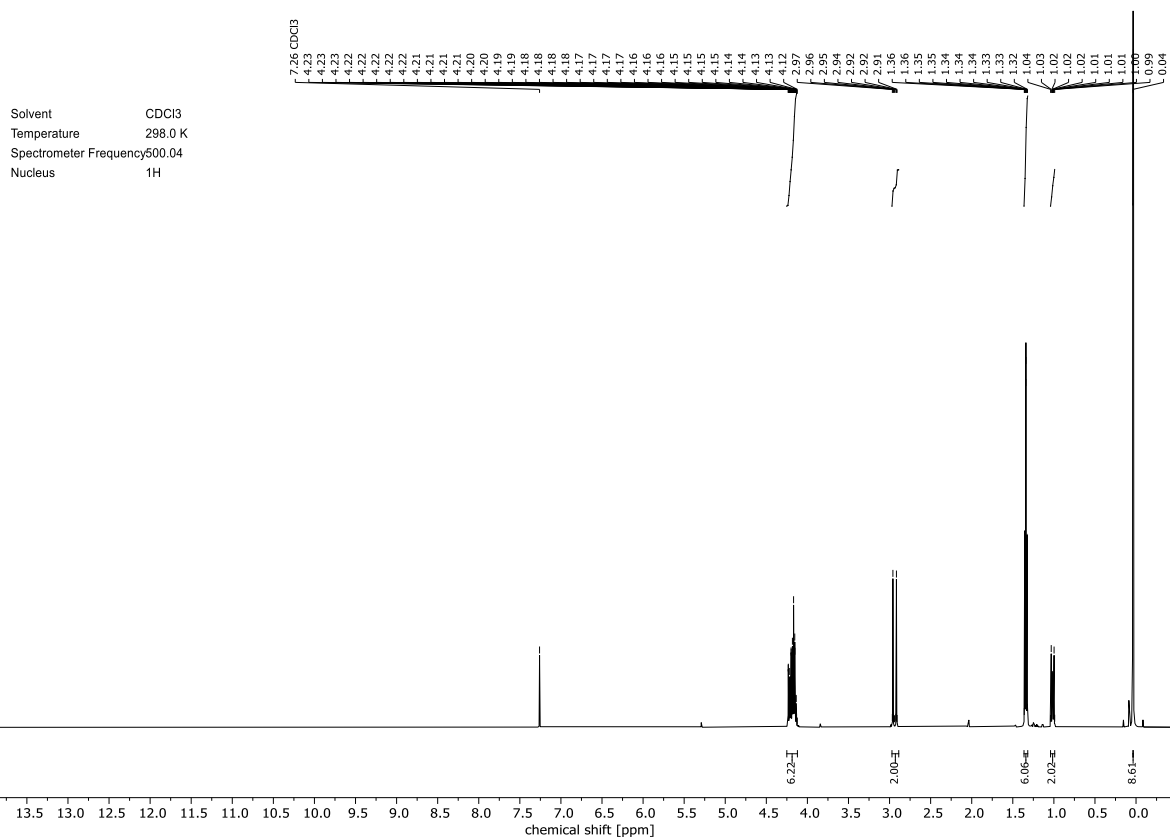
Chemical Formula: $C_8H_{16}O_2Si$
 Exact Mass: 172.0920



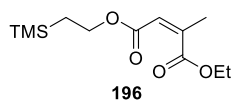
6 Copies of NMR Spectra



Chemical Formula: $C_{11}H_{25}O_5PSi$
 Exact Mass: 296.1209

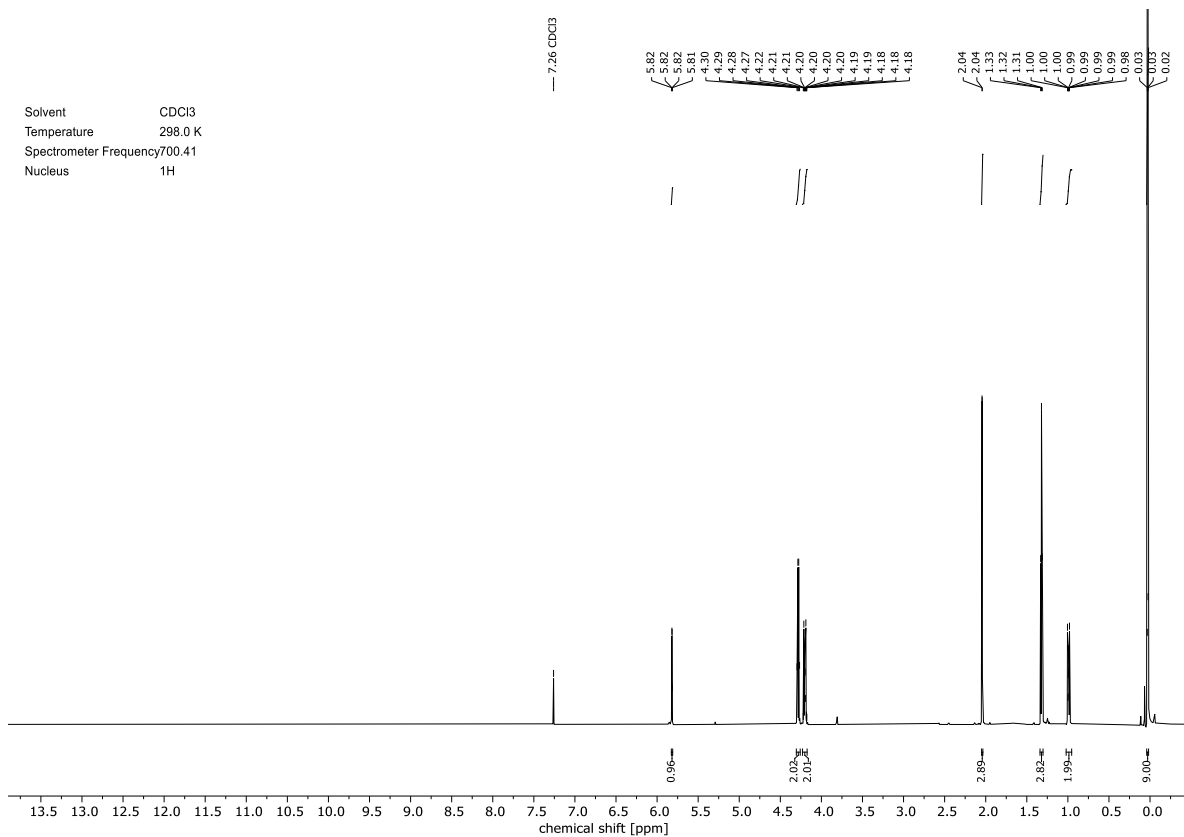


6 Copies of NMR Spectra

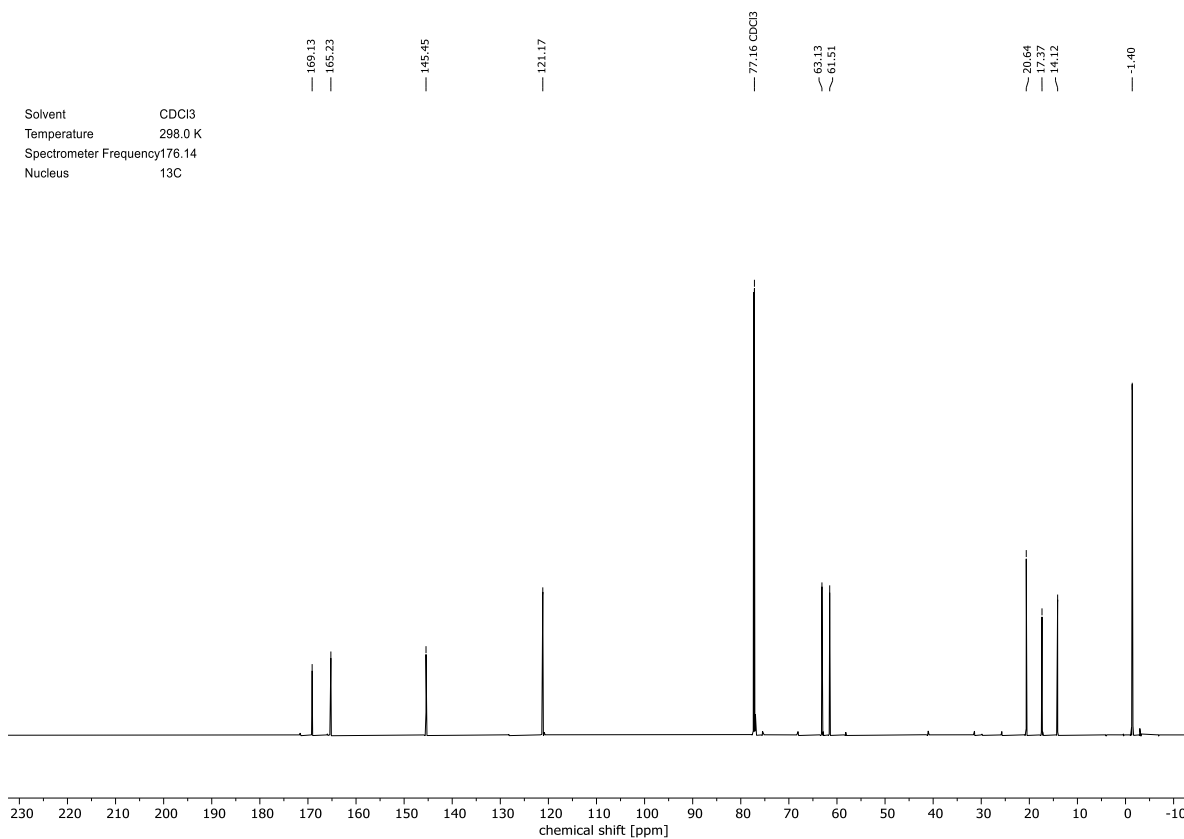


Chemical Formula: $C_{12}H_{22}O_4Si$
 Exact Mass: 258.1287

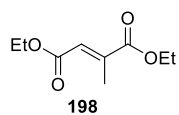
Solvent $CDCl_3$
 Temperature 298.0 K
 Spectrometer Frequency 700.41
 Nucleus 1H



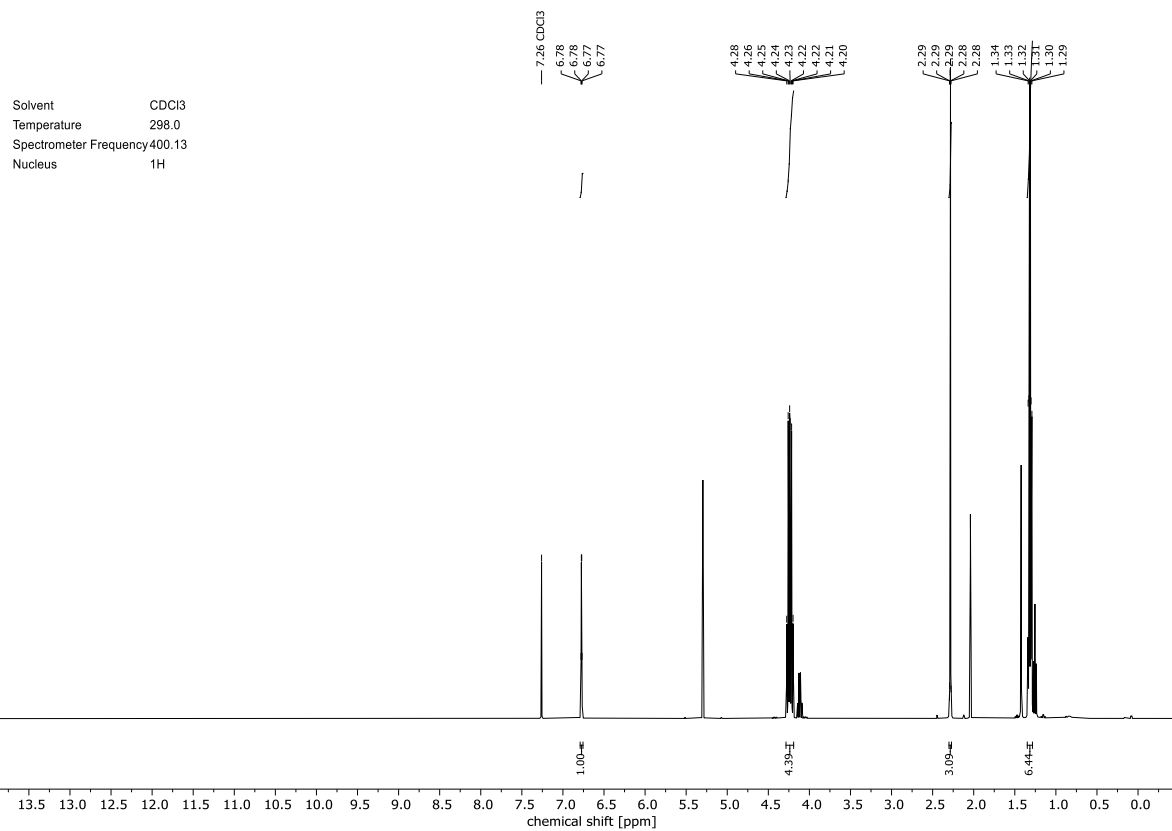
Solvent $CDCl_3$
 Temperature 298.0 K
 Spectrometer Frequency 176.14
 Nucleus ^{13}C



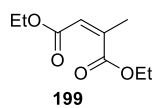
6 Copies of NMR Spectra



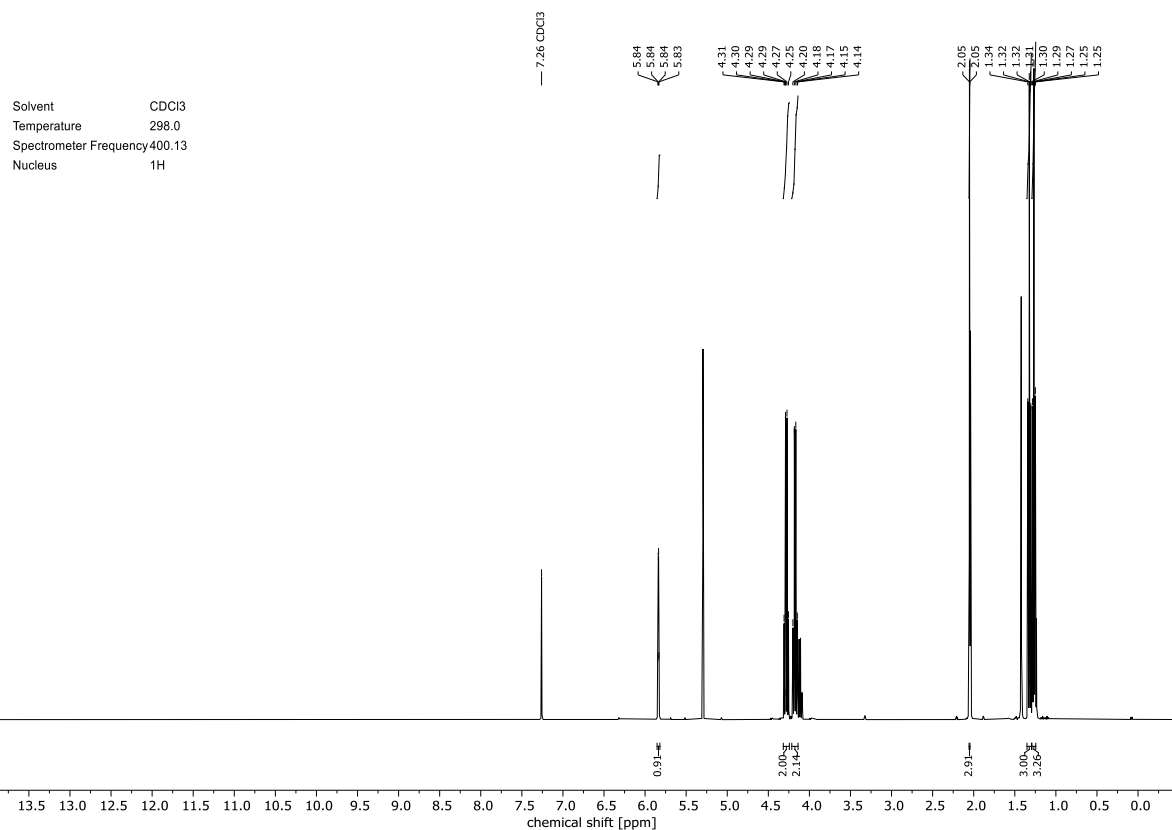
Chemical Formula: $C_9H_{14}O_4$
 Exact Mass: 186.0892



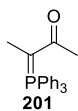
6 Copies of NMR Spectra



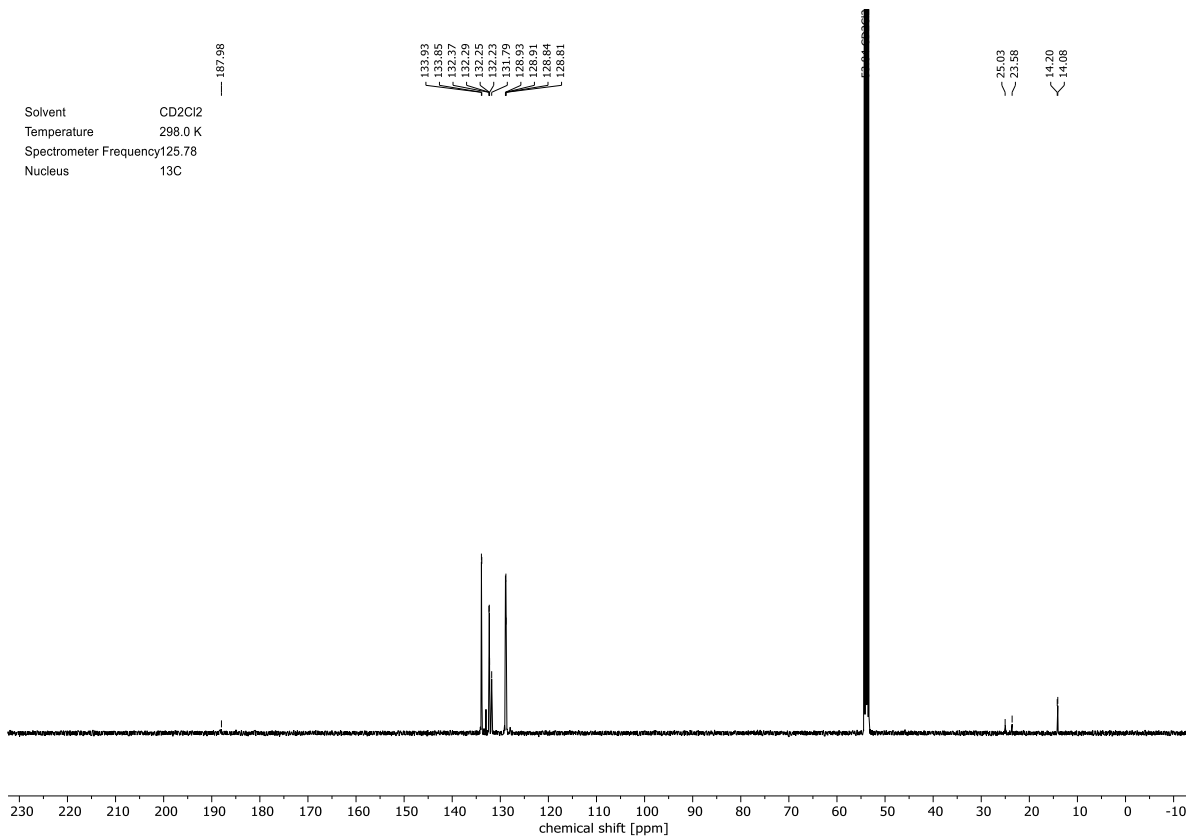
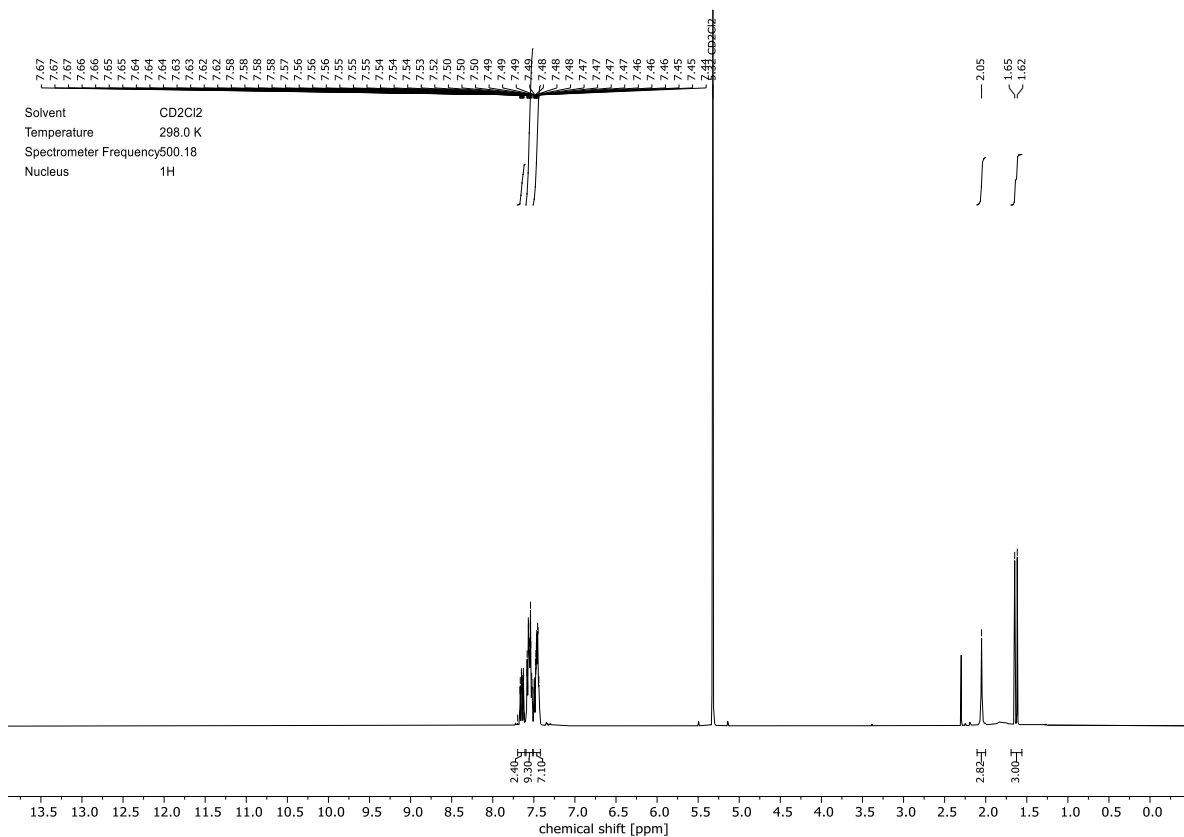
Chemical Formula: $C_9H_{14}O_4$
 Exact Mass: 186.0892



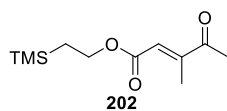
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Chemical Formula: $C_{22}H_{21}OP$
Exact Mass: 332.1330

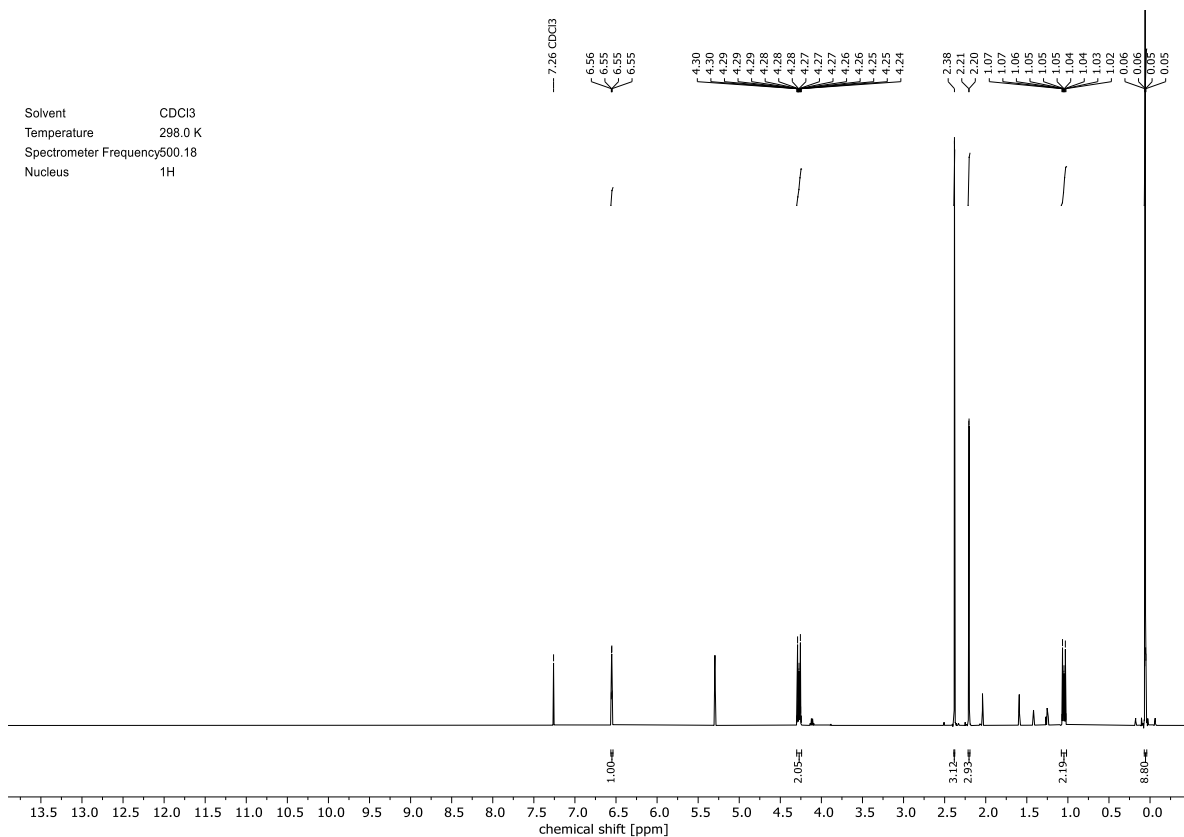


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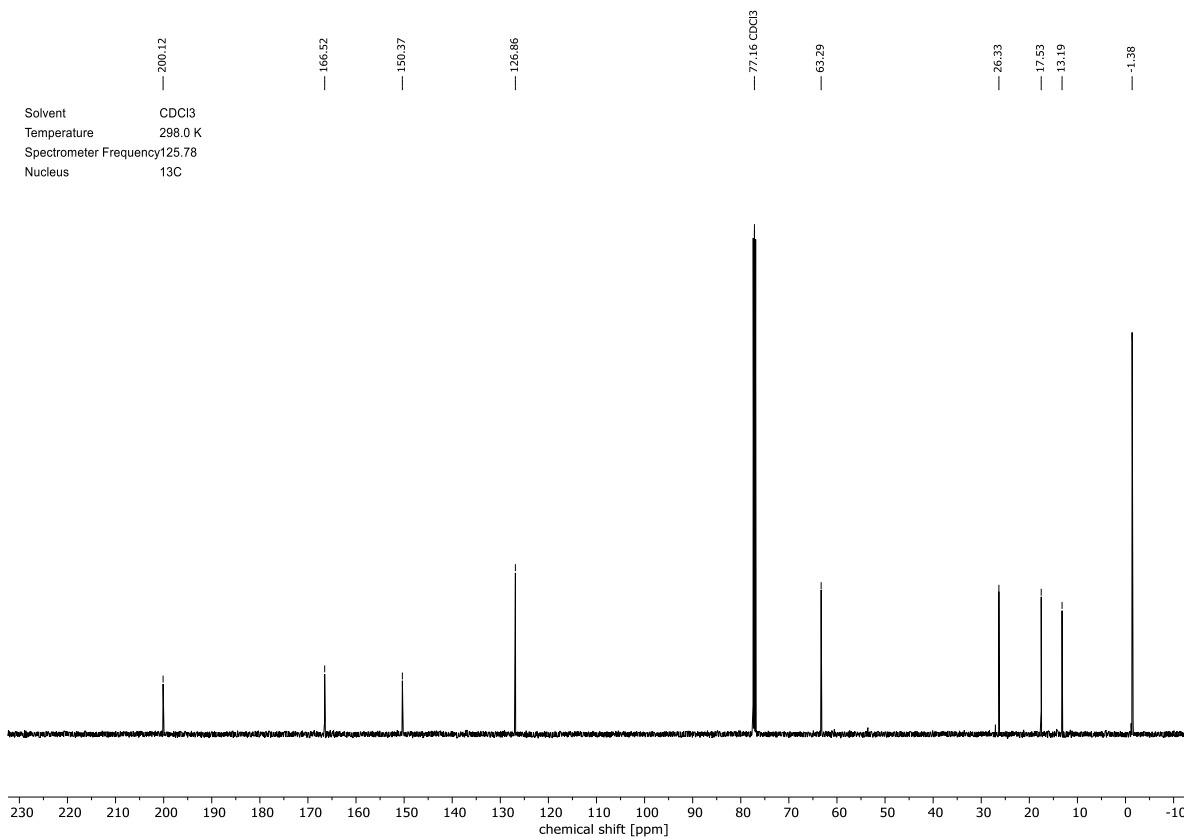


Chemical Formula: $C_{11}H_{20}O_3Si$
 Exact Mass: 228.1182

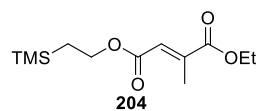
Solvent $CDCl_3$
 Temperature 298.0 K
 Spectrometer Frequency 500.18
 Nucleus 1H



Solvent $CDCl_3$
 Temperature 298.0 K
 Spectrometer Frequency 125.78
 Nucleus ^{13}C

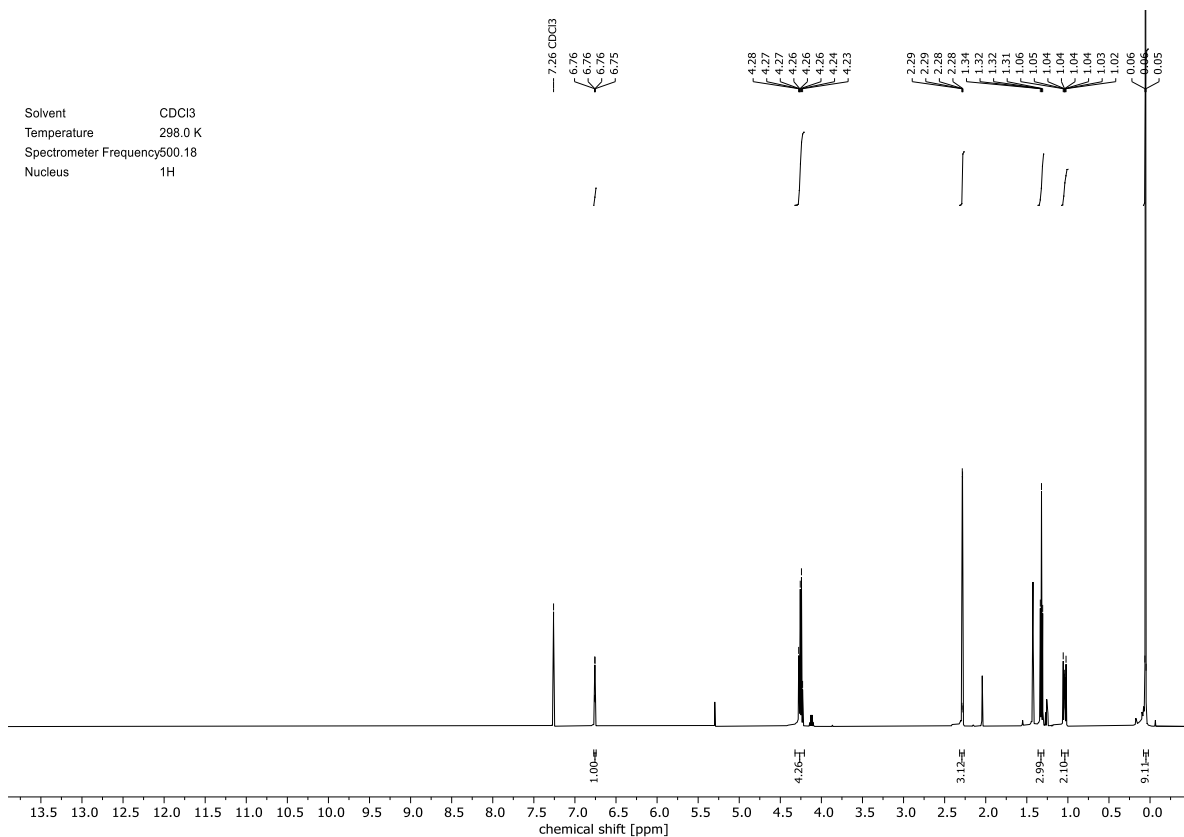


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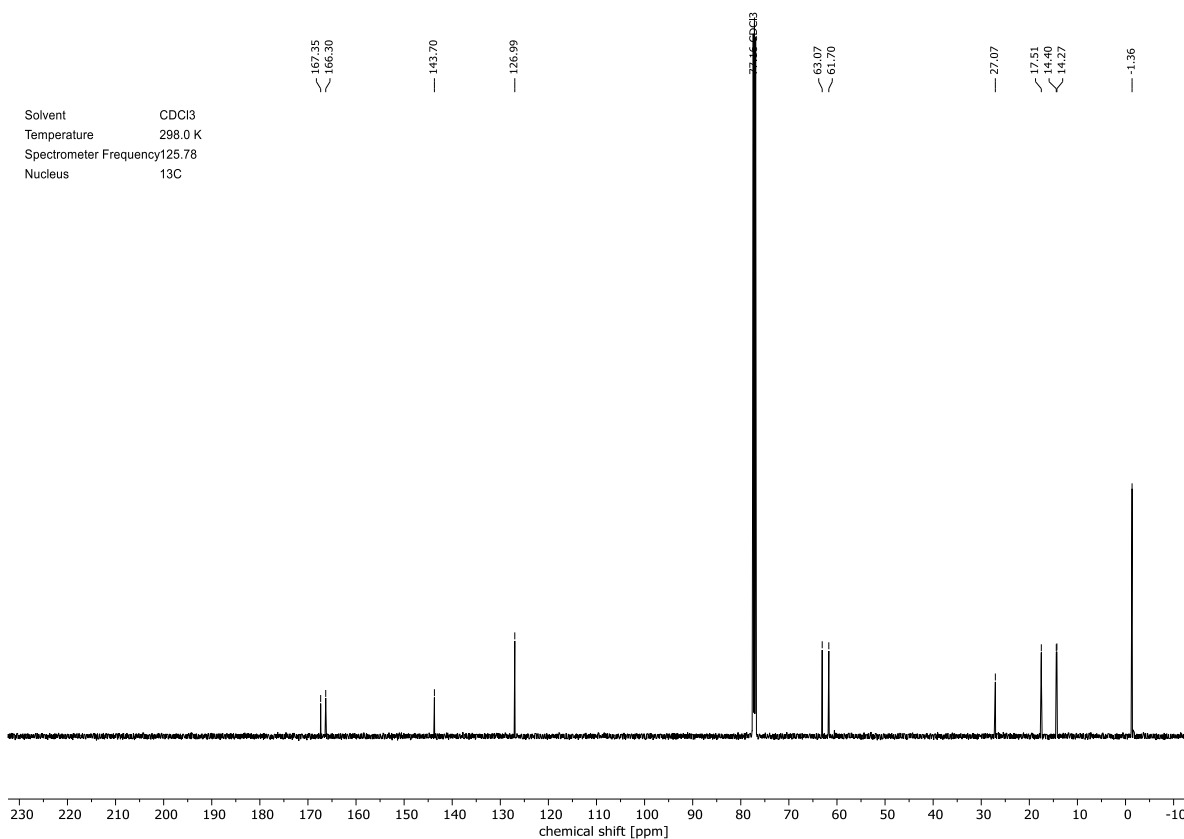


Chemical Formula: $C_{12}H_{22}O_4Si$
 Exact Mass: 258.1287

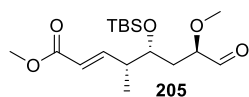
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 Spectrometer Frequency: 500.18
 Nucleus: 1H



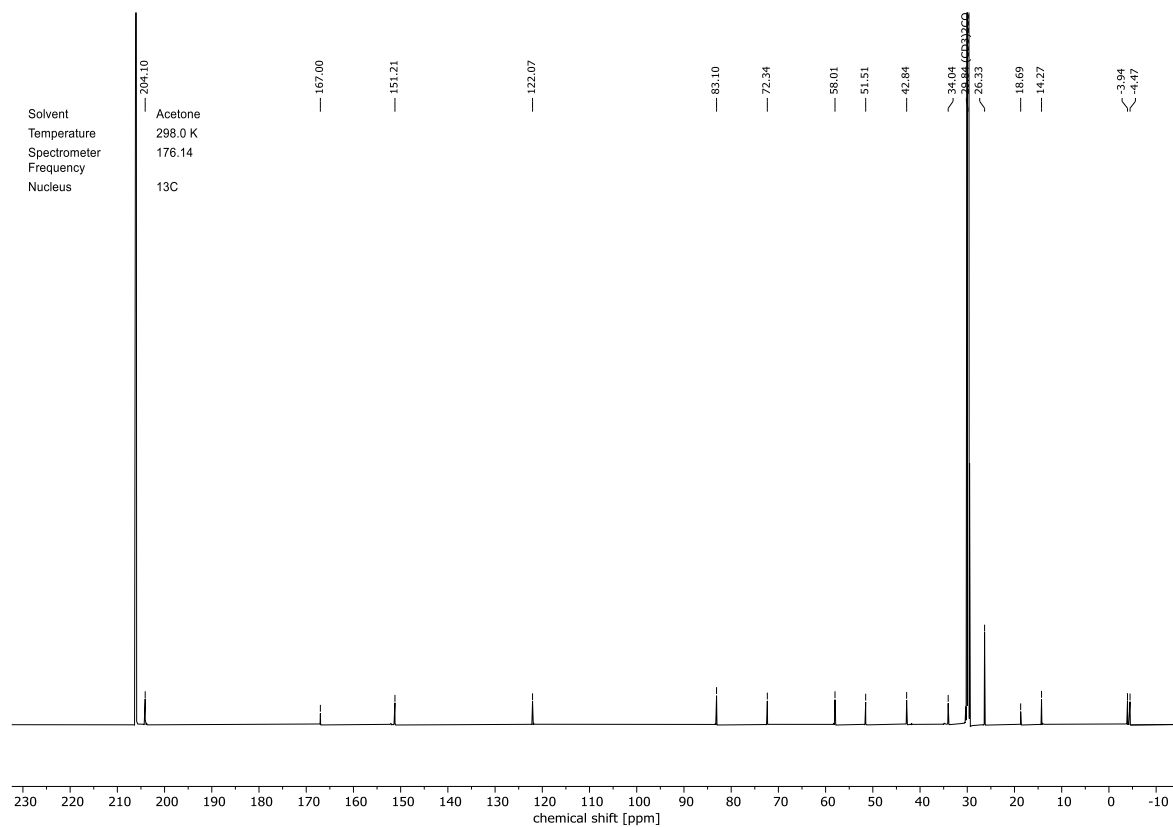
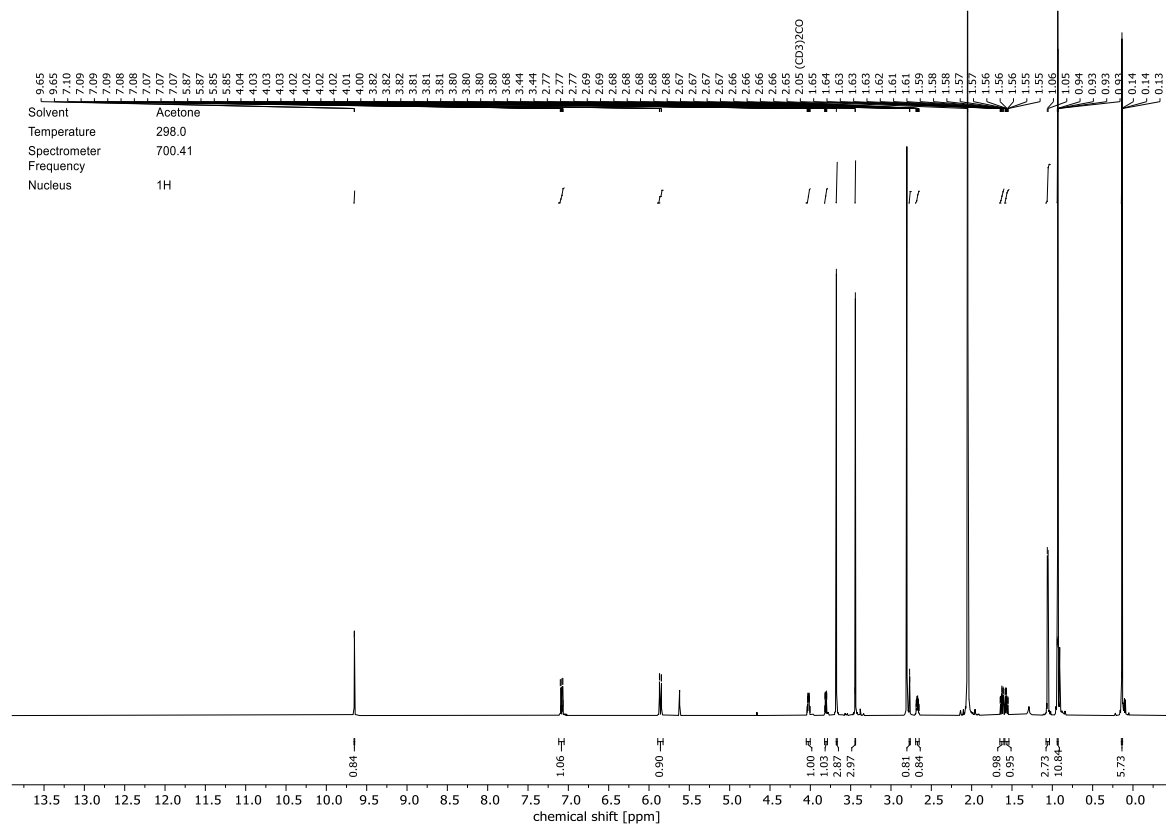
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 Temperature: 298.0 K
 Spectrometer Frequency: 125.78
 Nucleus: ^{13}C

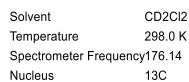
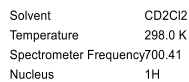
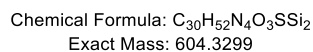


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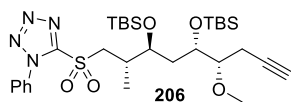


Chemical Formula: $C_{17}H_{32}O_5Si$
Exact Mass: 344.2019

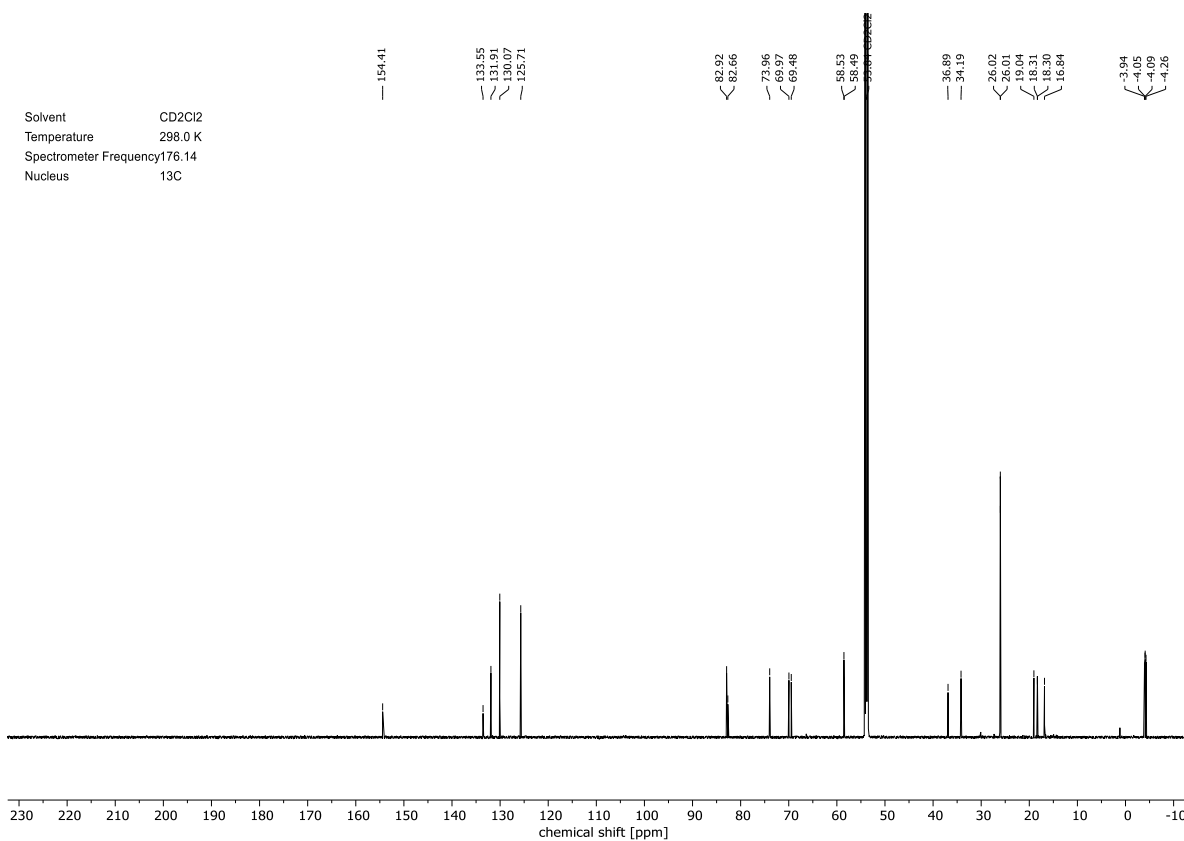
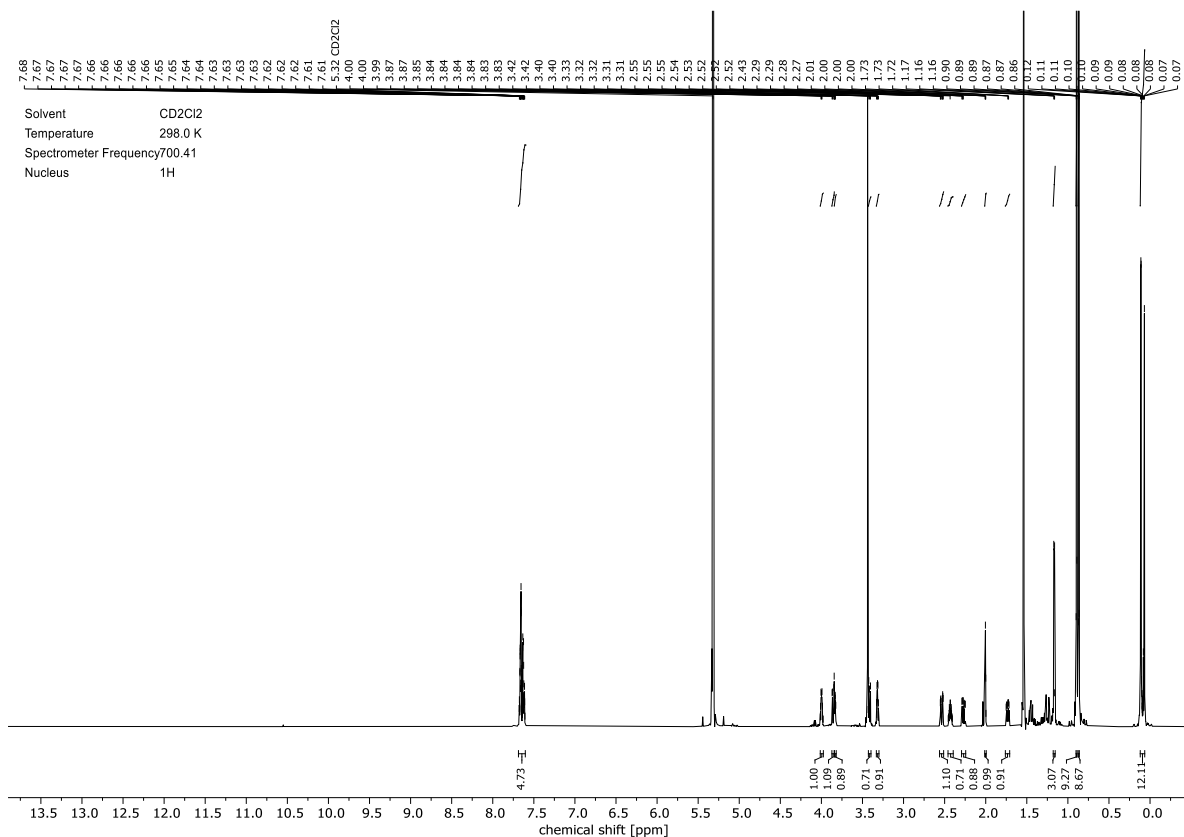


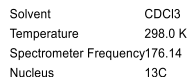
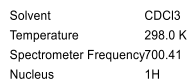
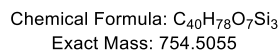


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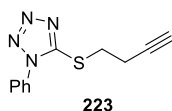


Chemical Formula: $C_{30}H_{52}N_4O_5SSi_2$
Exact Mass: 636.3197



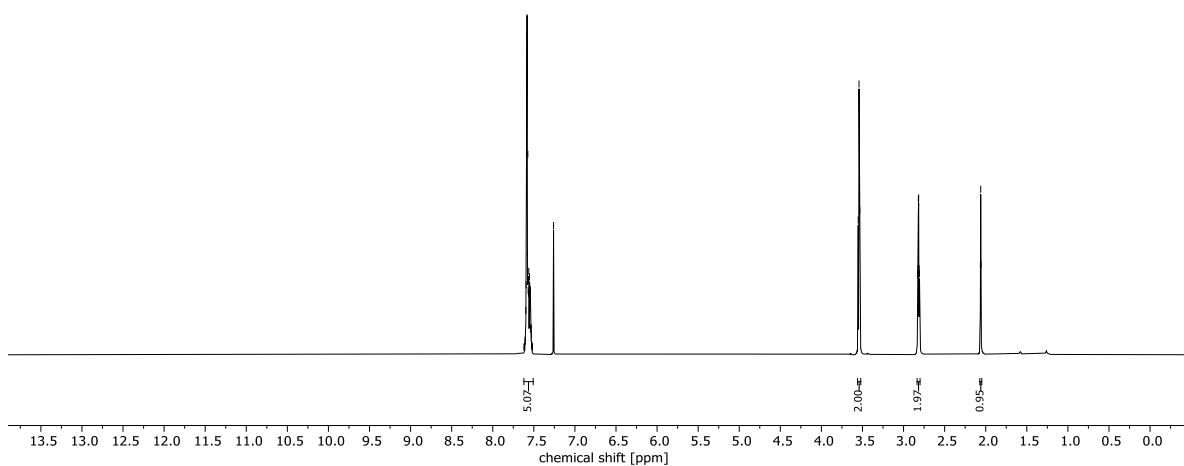
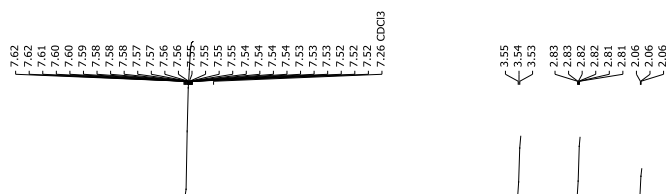


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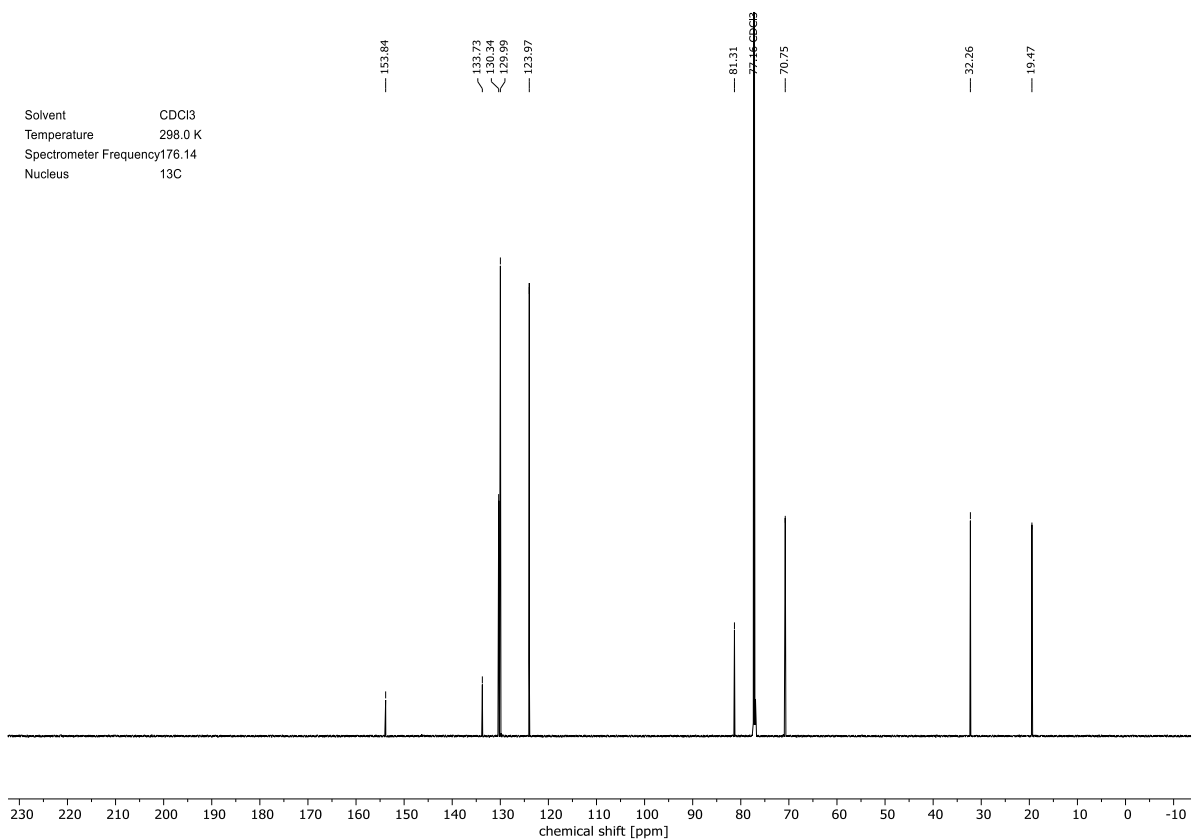


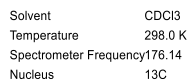
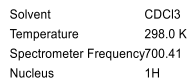
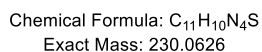
Chemical Formula: $C_{11}H_{10}N_4S$
Exact Mass: 230.0626

Solvent $CDCl_3$
Temperature 298.0 K
Spectrometer Frequency 700.41
Nucleus 1H

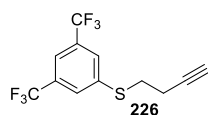


Solvent $CDCl_3$
Temperature 298.0 K
Spectrometer Frequency 176.14
Nucleus ^{13}C



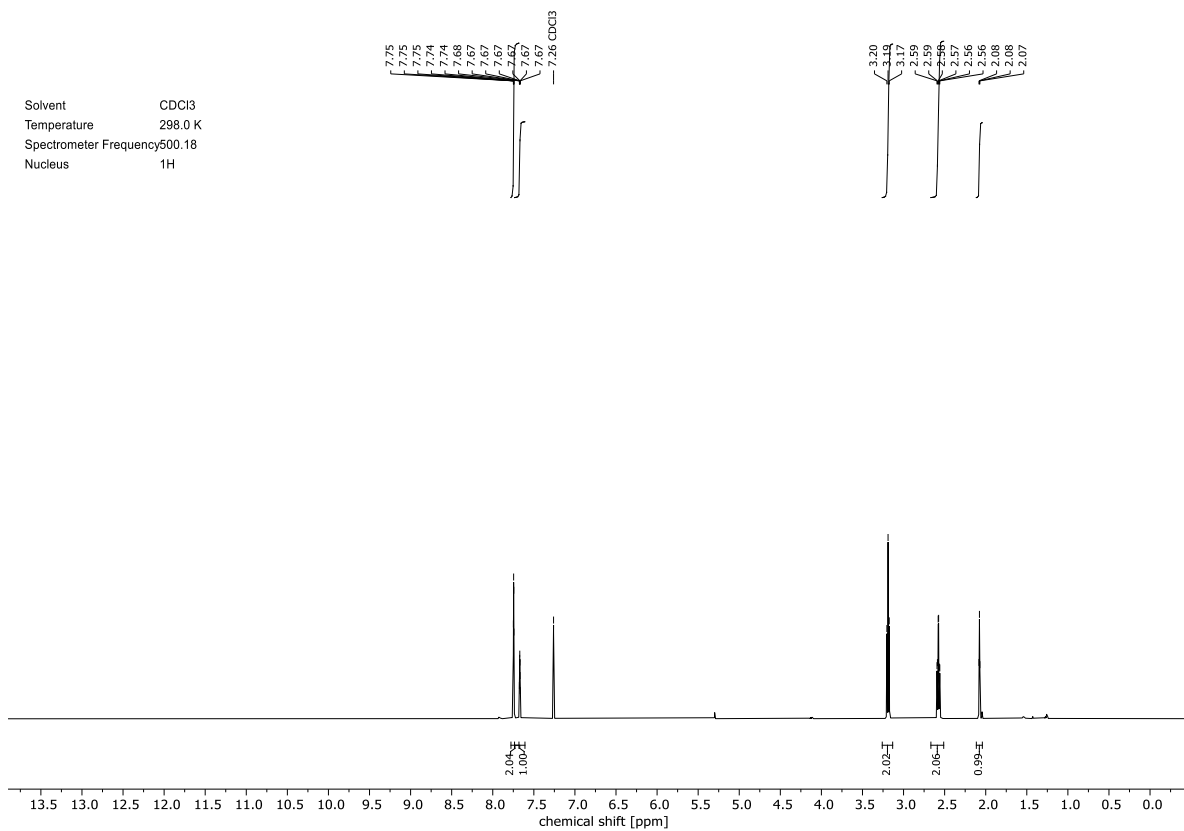


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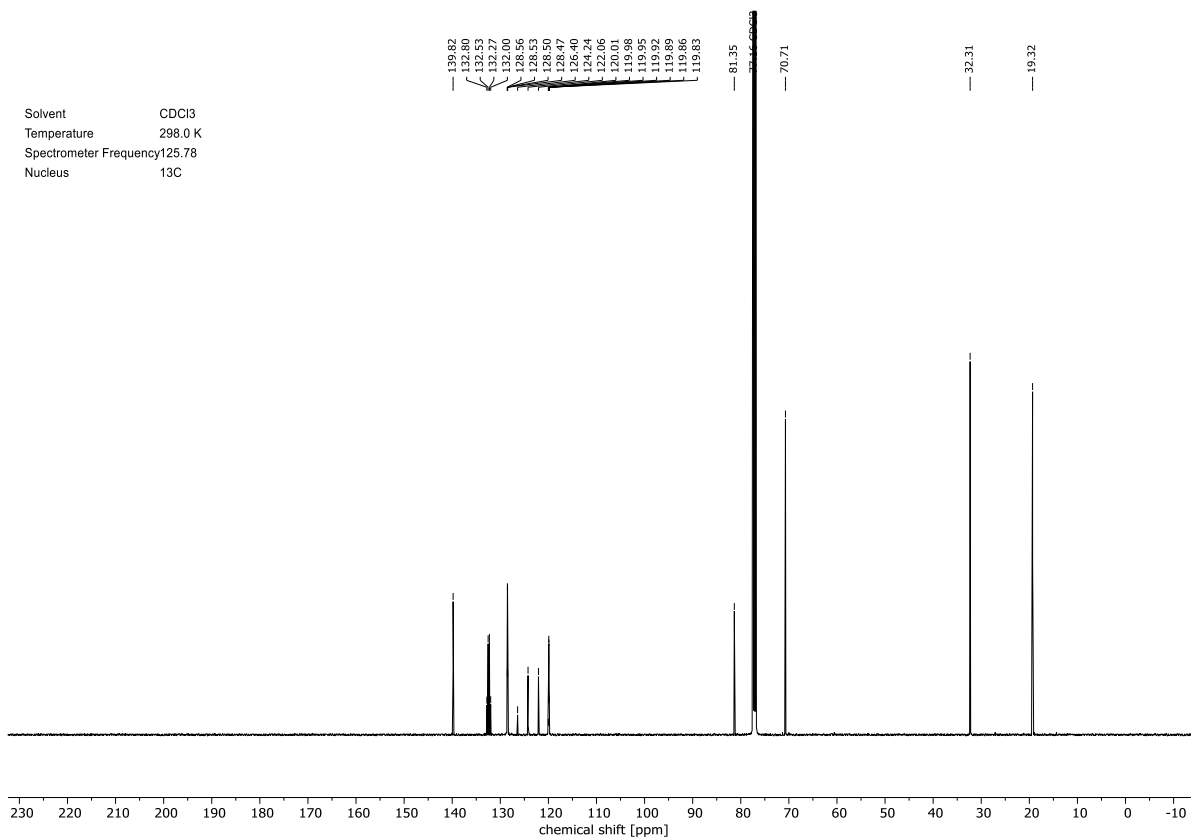


Chemical Formula: $C_{12}H_8F_6S$
Exact Mass: 298.0251

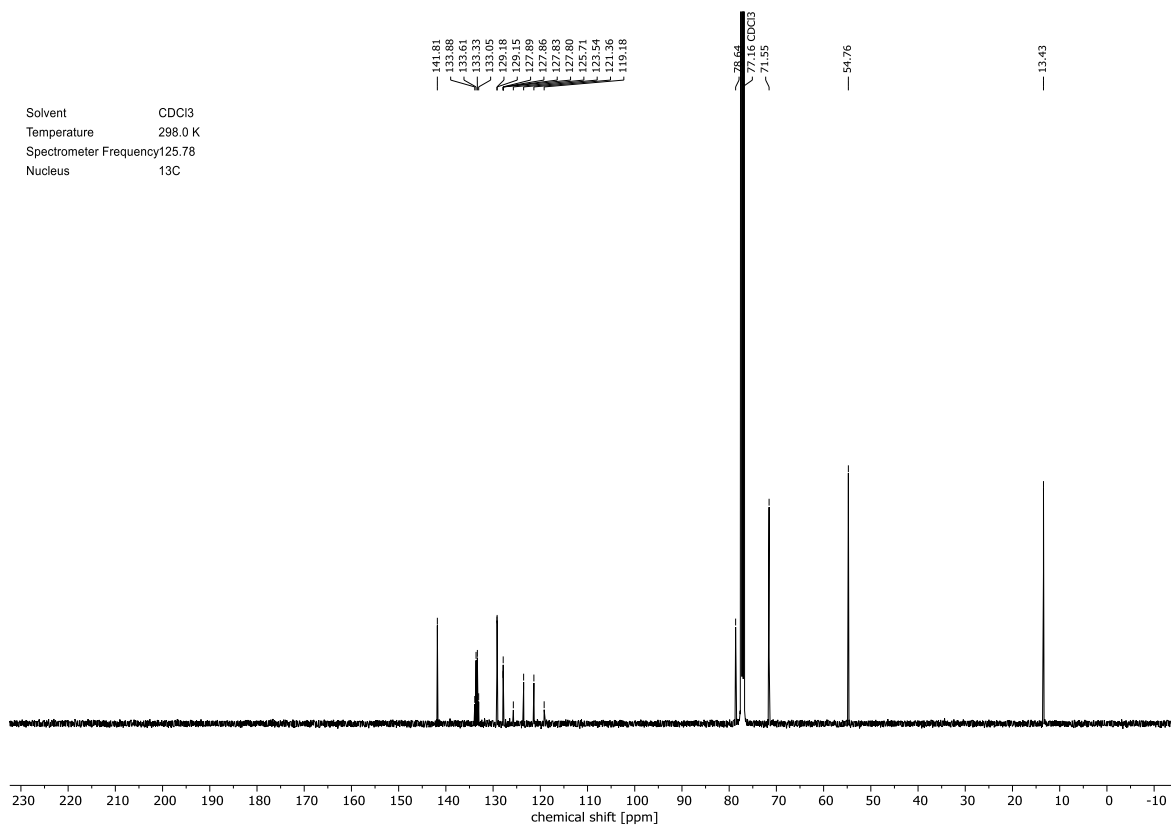
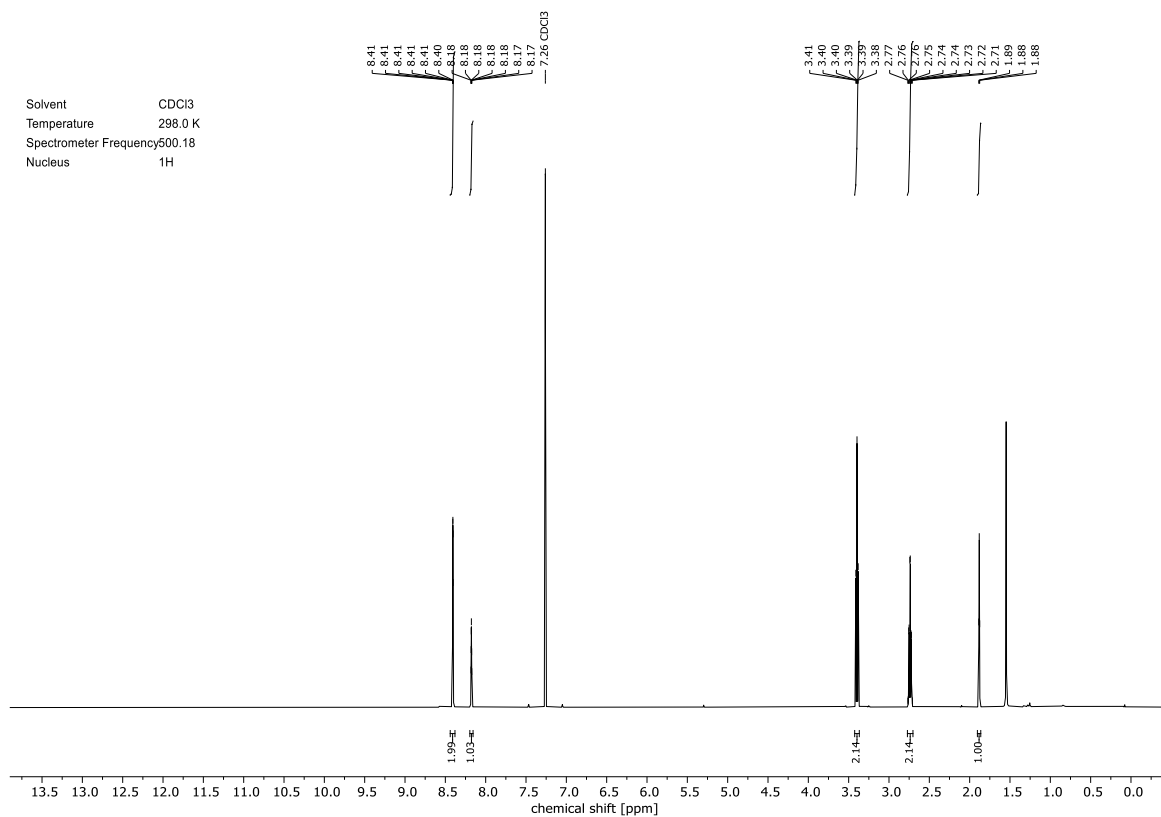
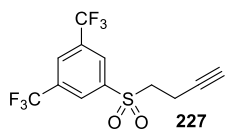
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Temperature: 298.0 K
Spectrometer Frequency: 500.18
Nucleus: 1H



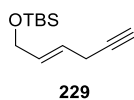
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Temperature: 298.0 K
Spectrometer Frequency: 125.78
Nucleus: ^{13}C



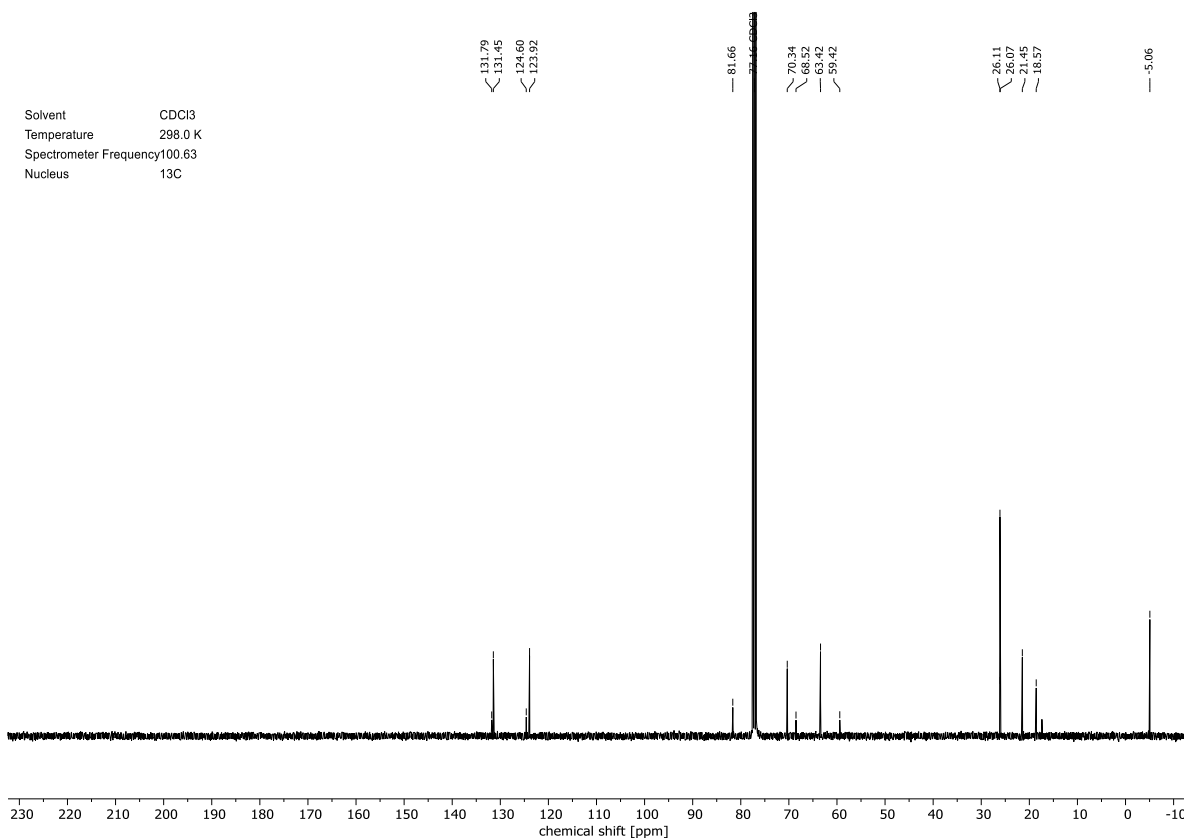
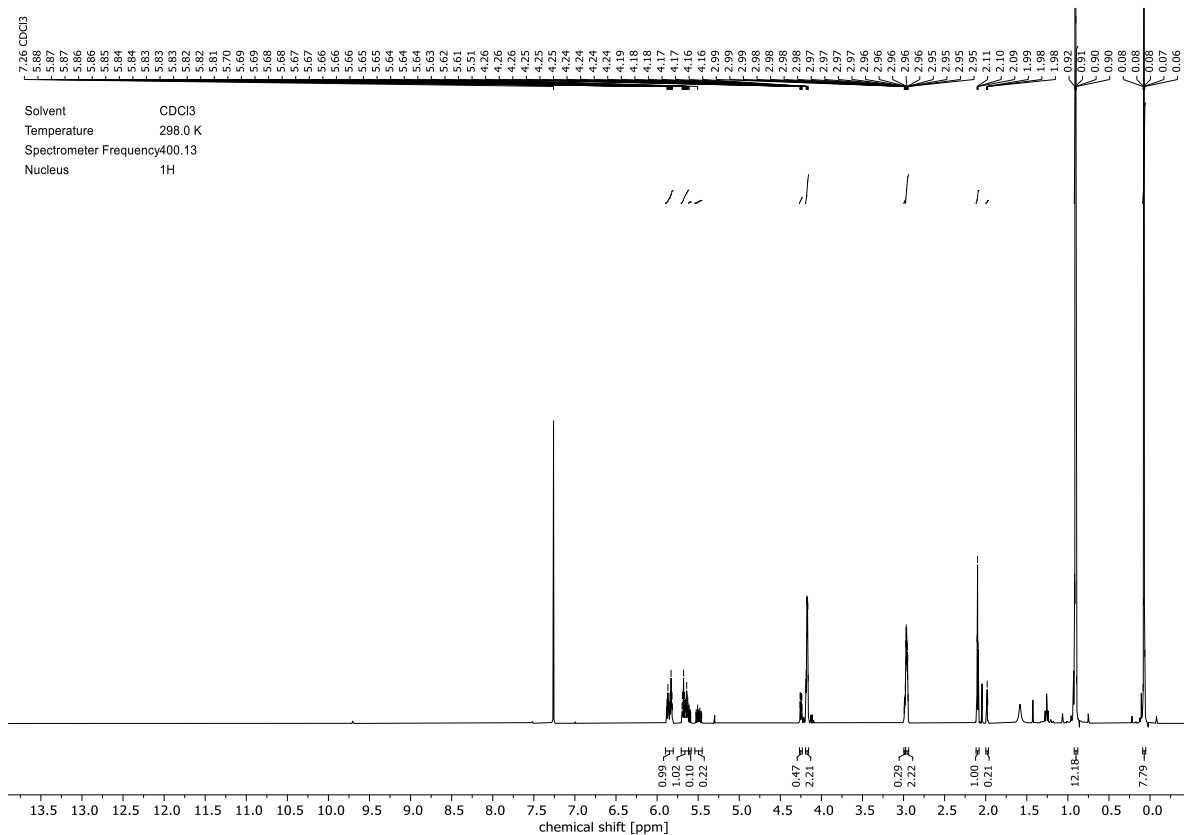
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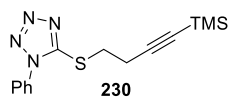
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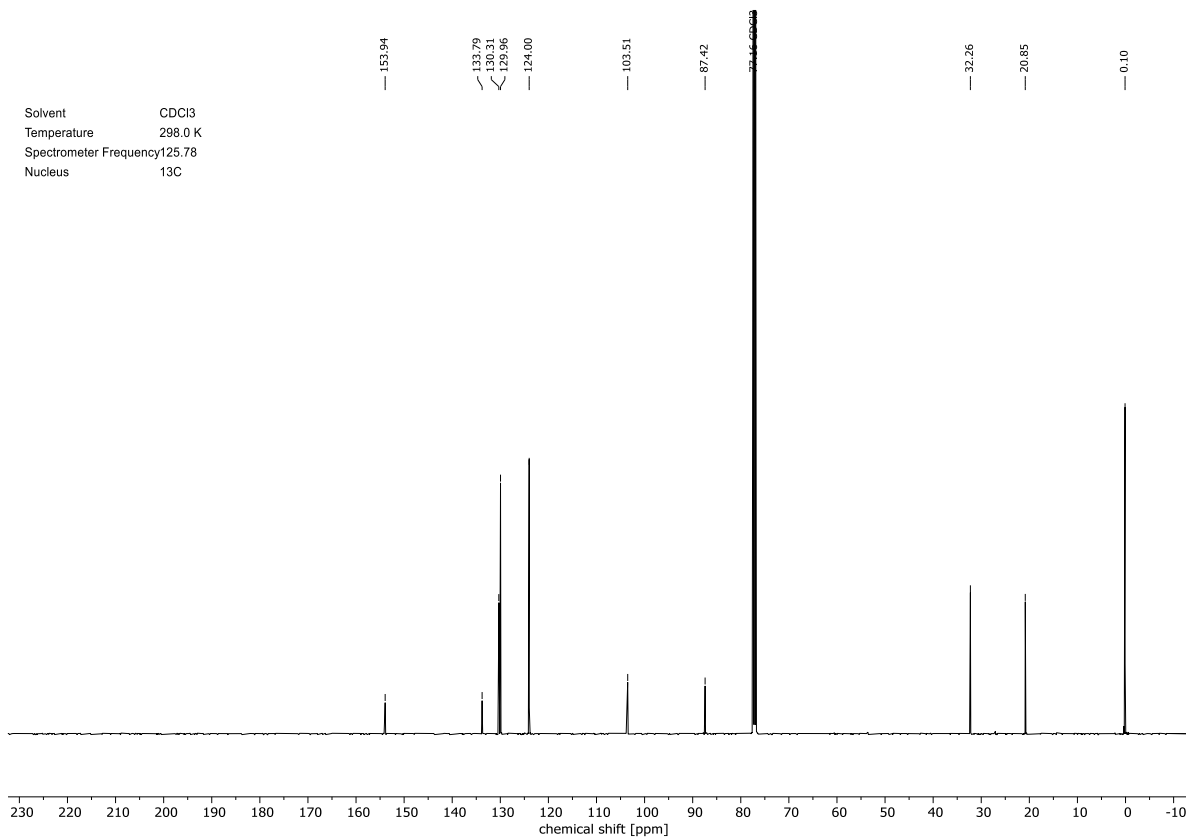
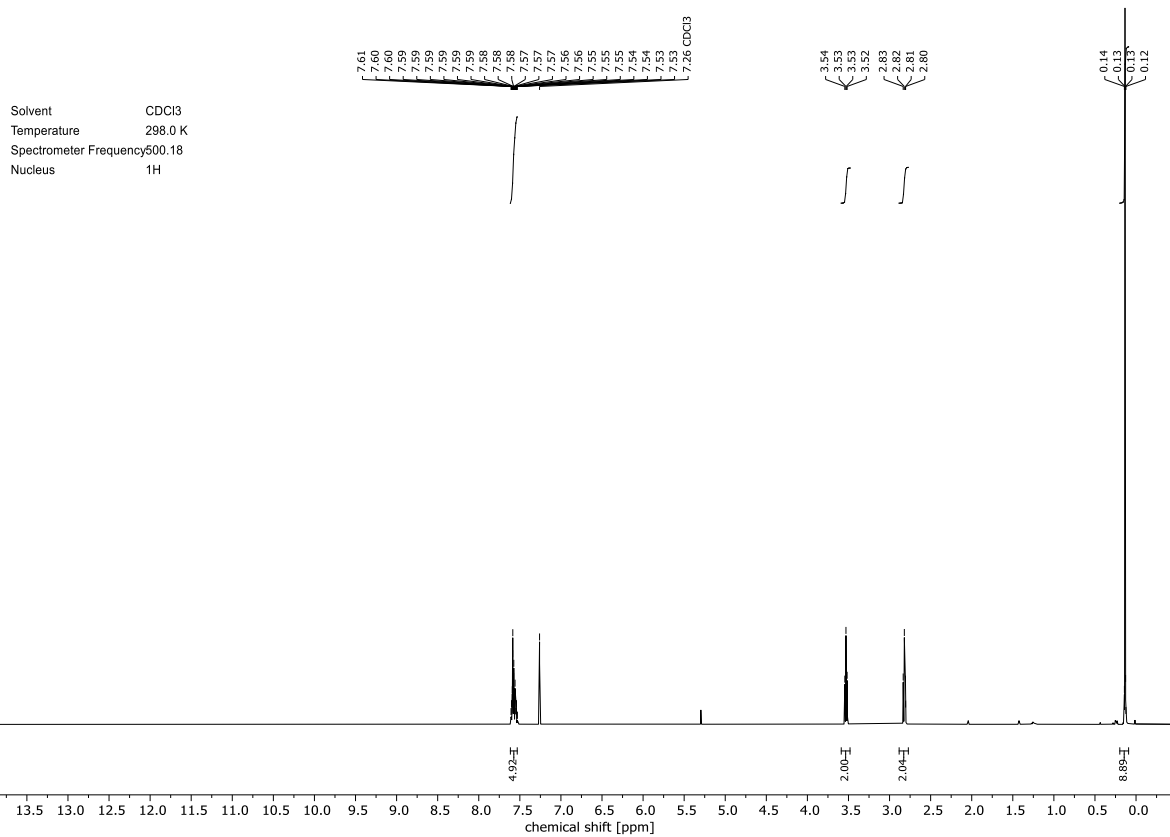
Chemical Formula: $C_{12}H_{22}OSi$
Exact Mass: 210.1440



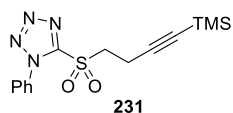
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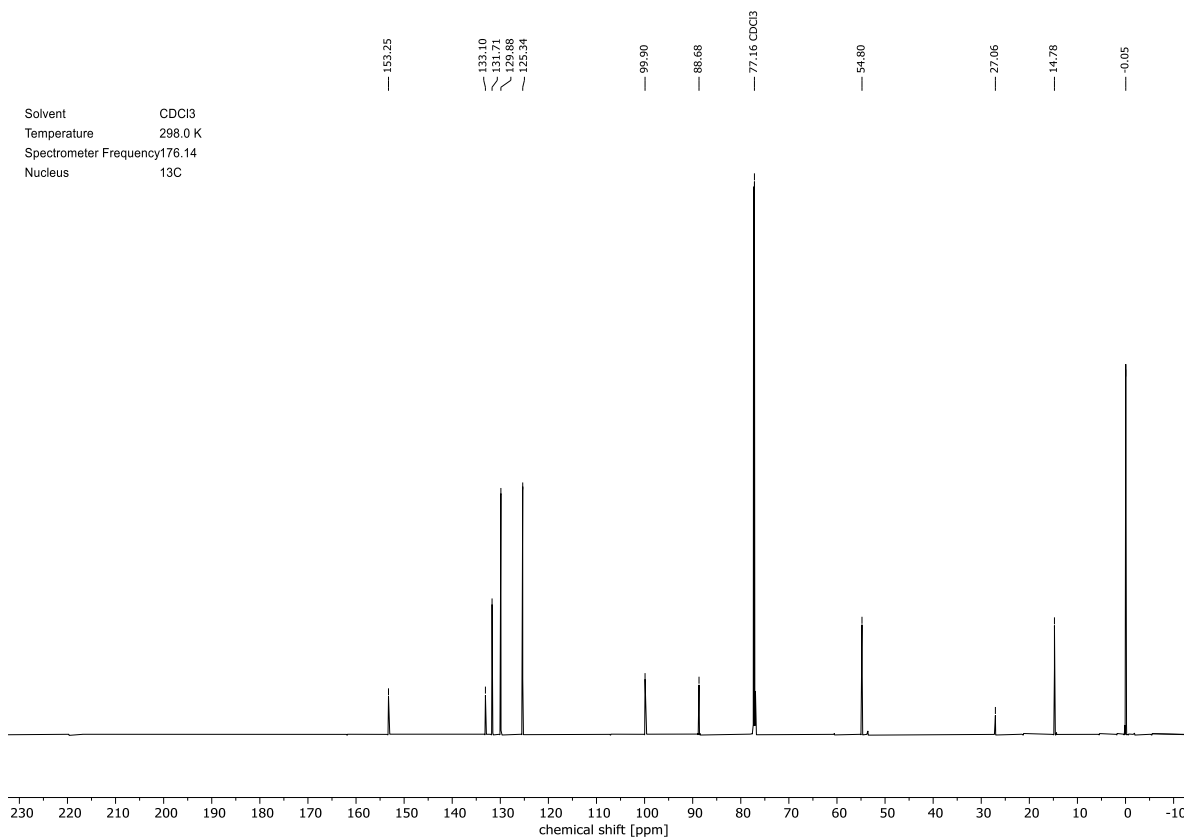
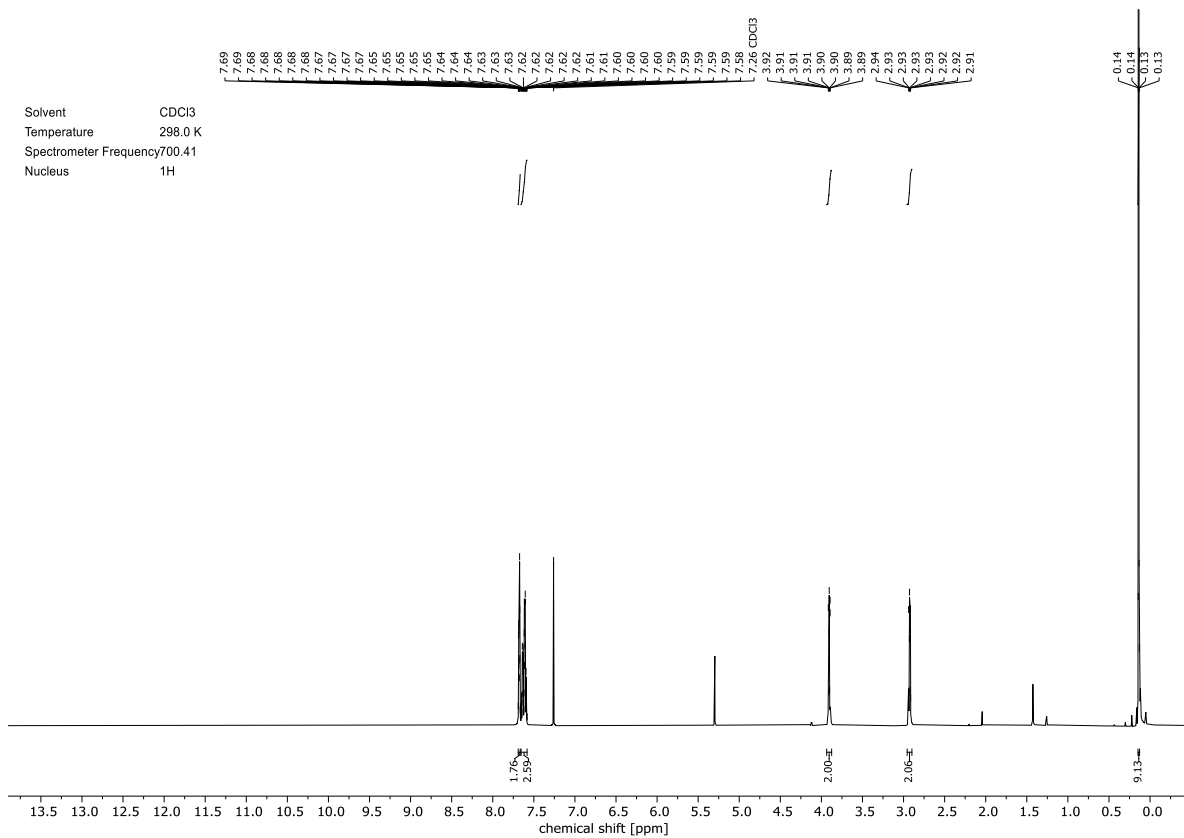
Chemical Formula: $C_{14}H_{18}N_4SSi$
Exact Mass: 302.1021



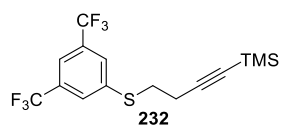
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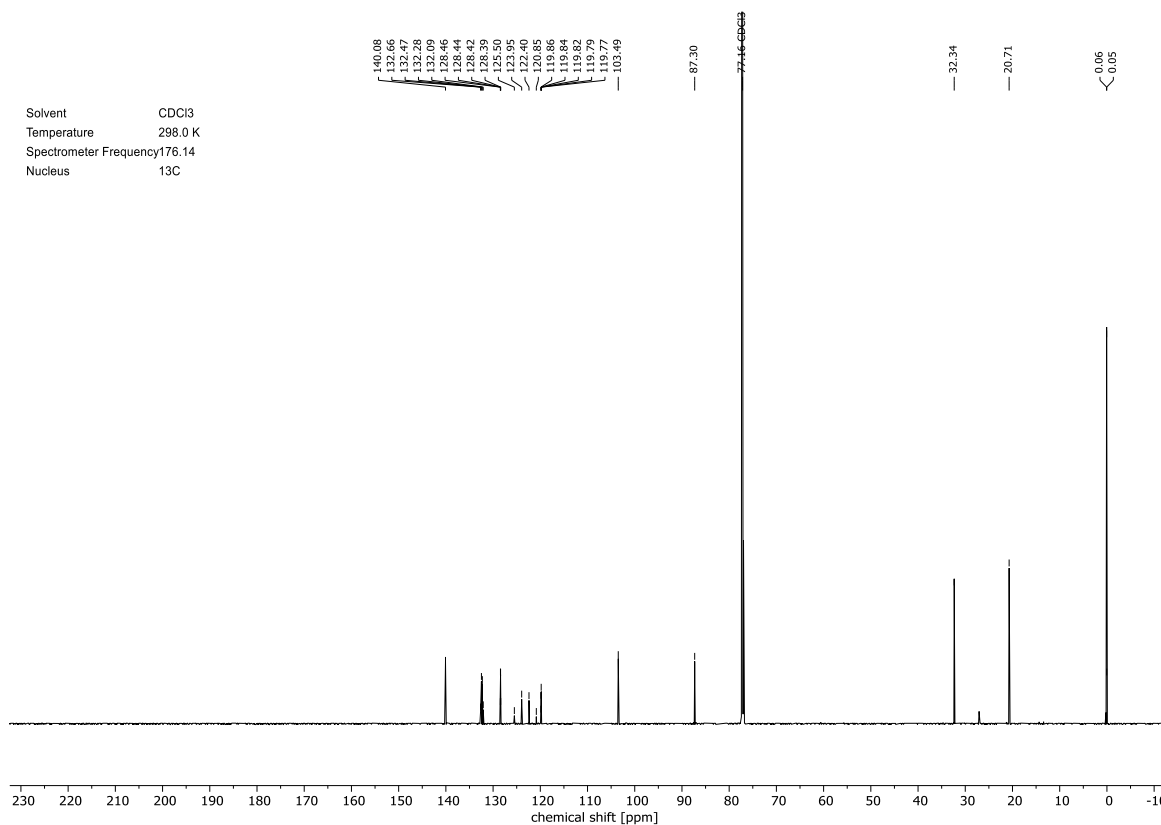
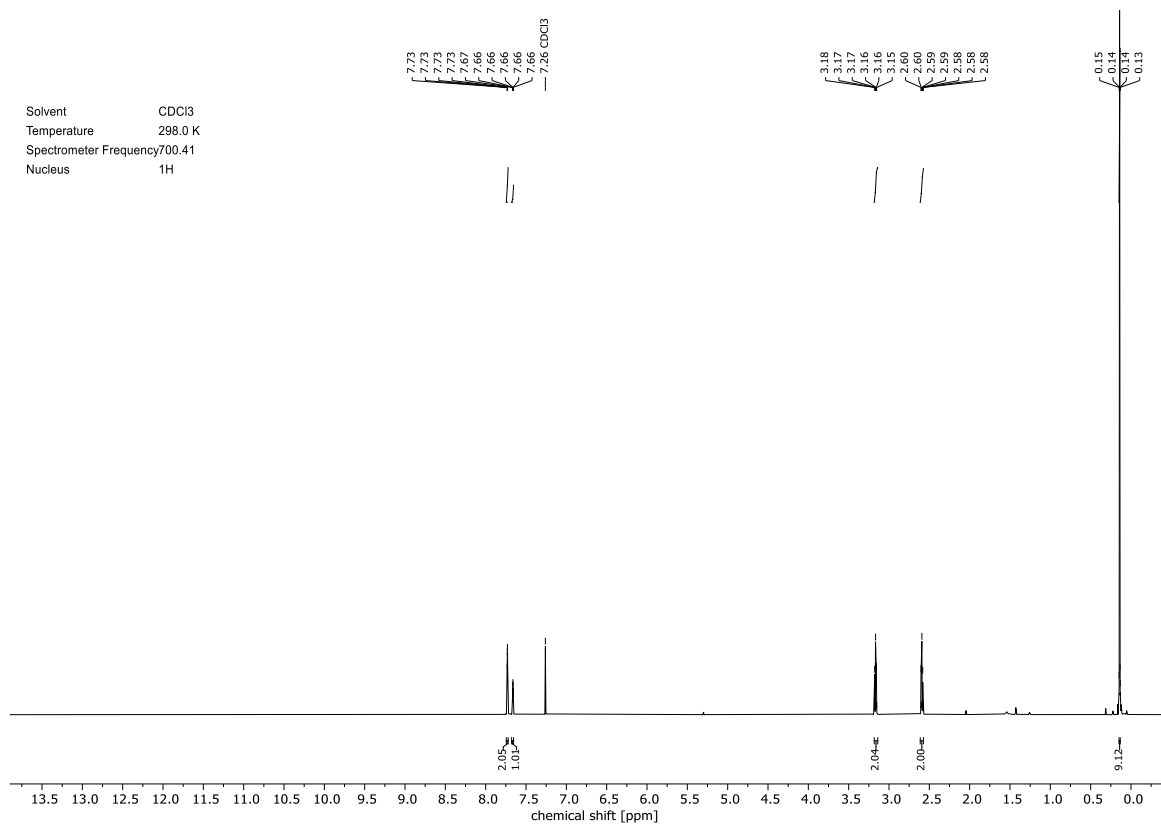
Chemical Formula: $C_{14}H_{18}N_4O_2SSi$
Exact Mass: 334.0920



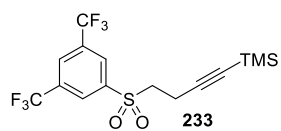
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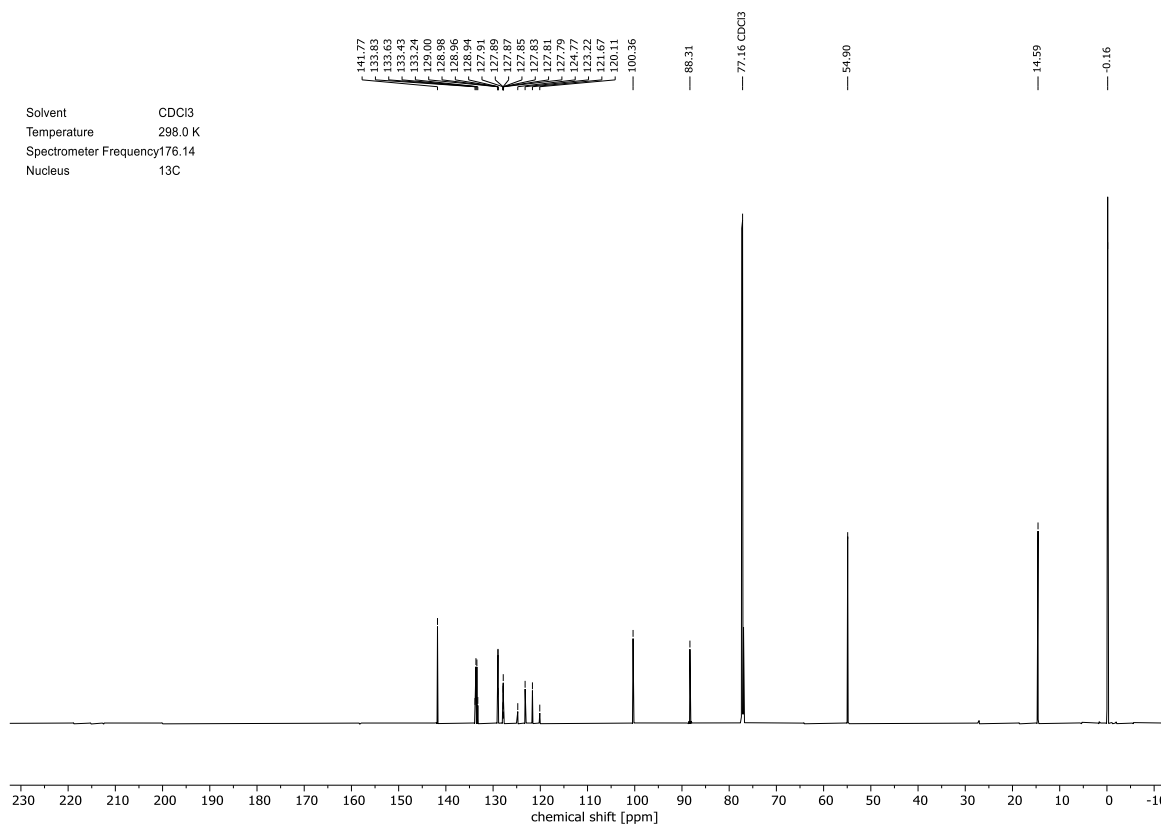
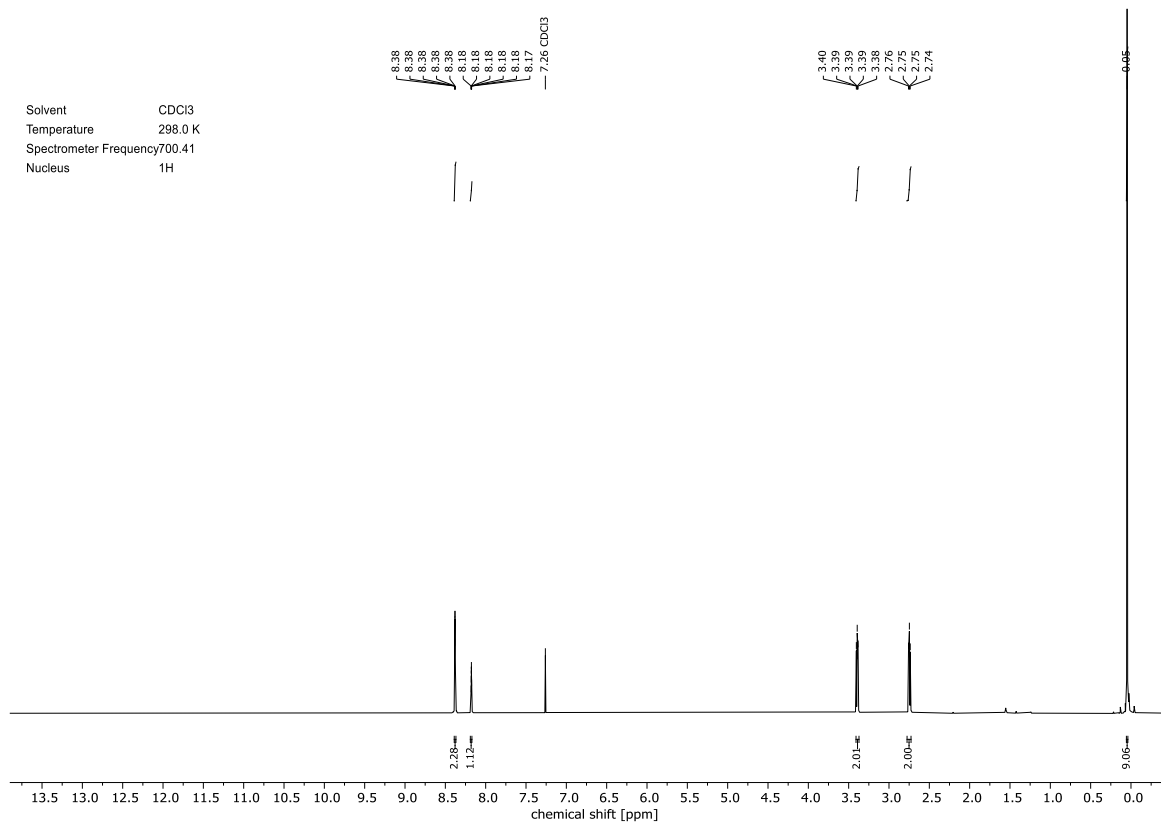
Chemical Formula: $C_{15}H_{16}F_6Si$
Exact Mass: 370.0646

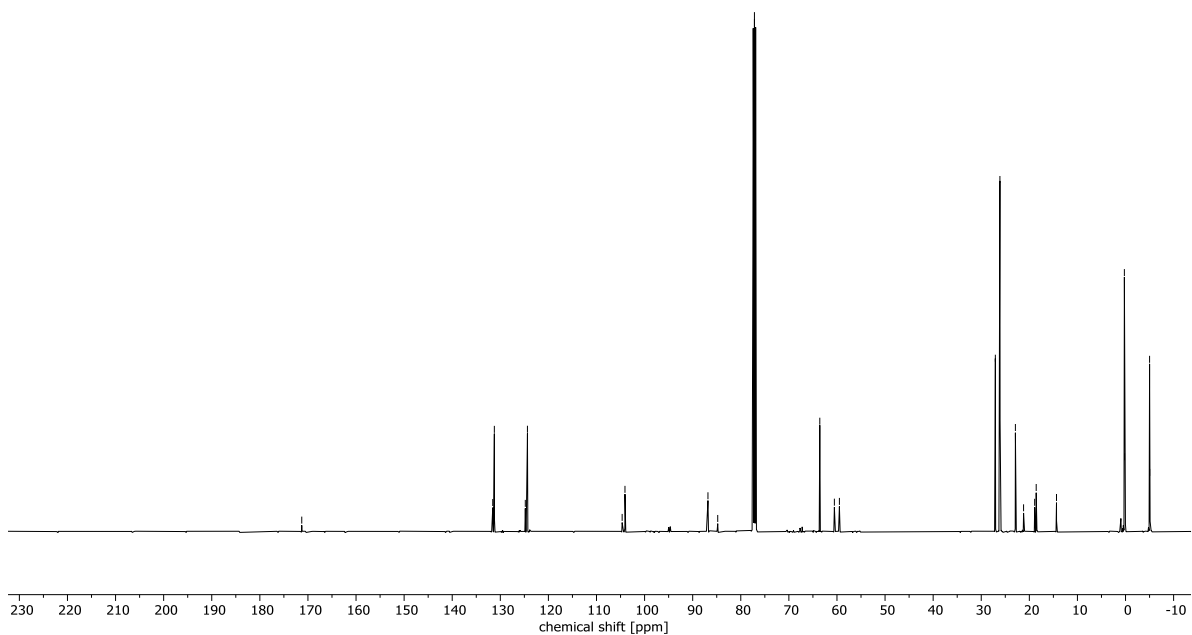
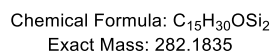


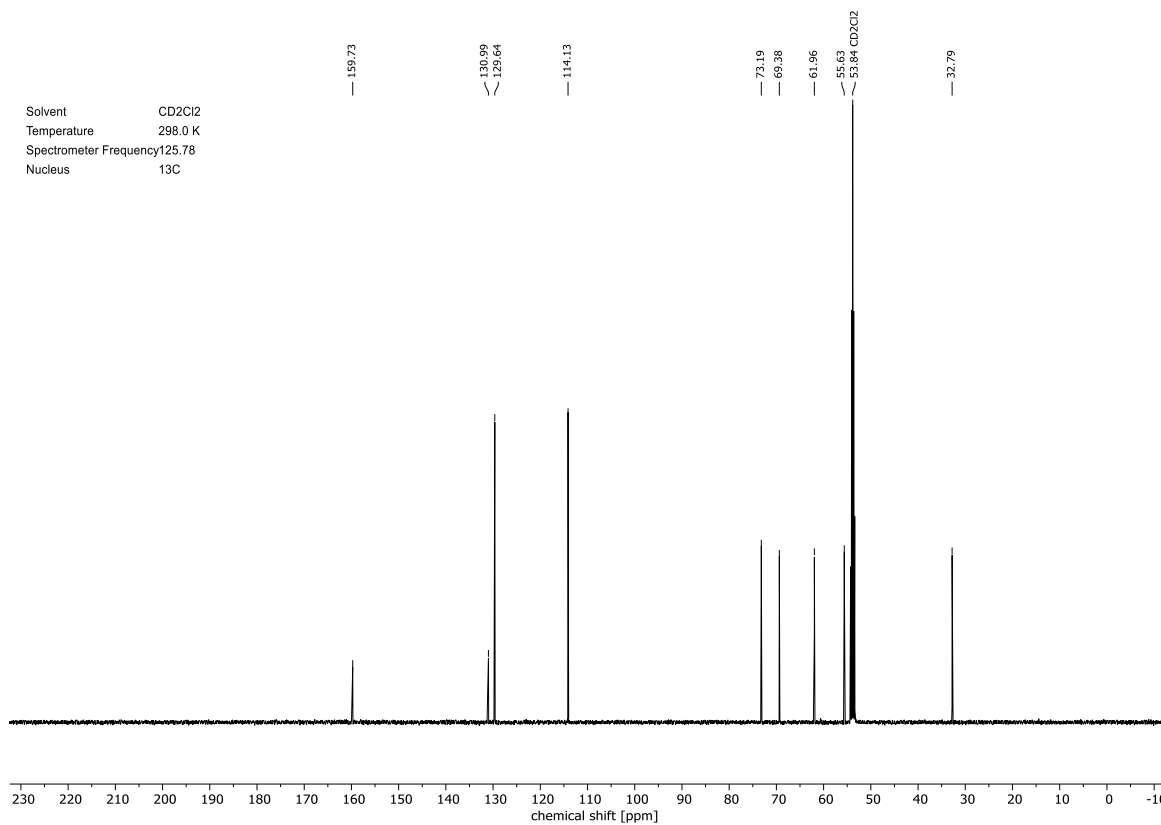
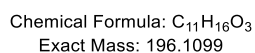
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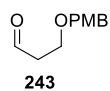
Chemical Formula: $C_{15}H_{16}F_6O_2SSi$
Exact Mass: 402.0544



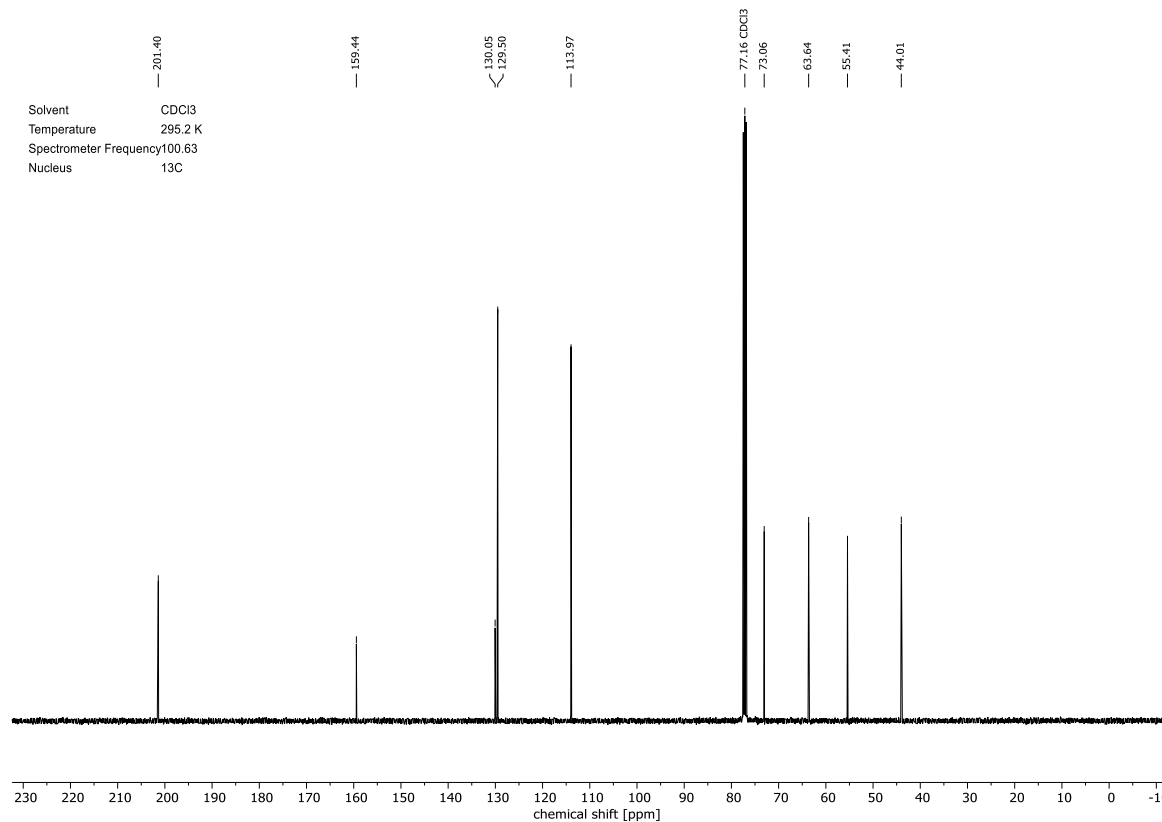
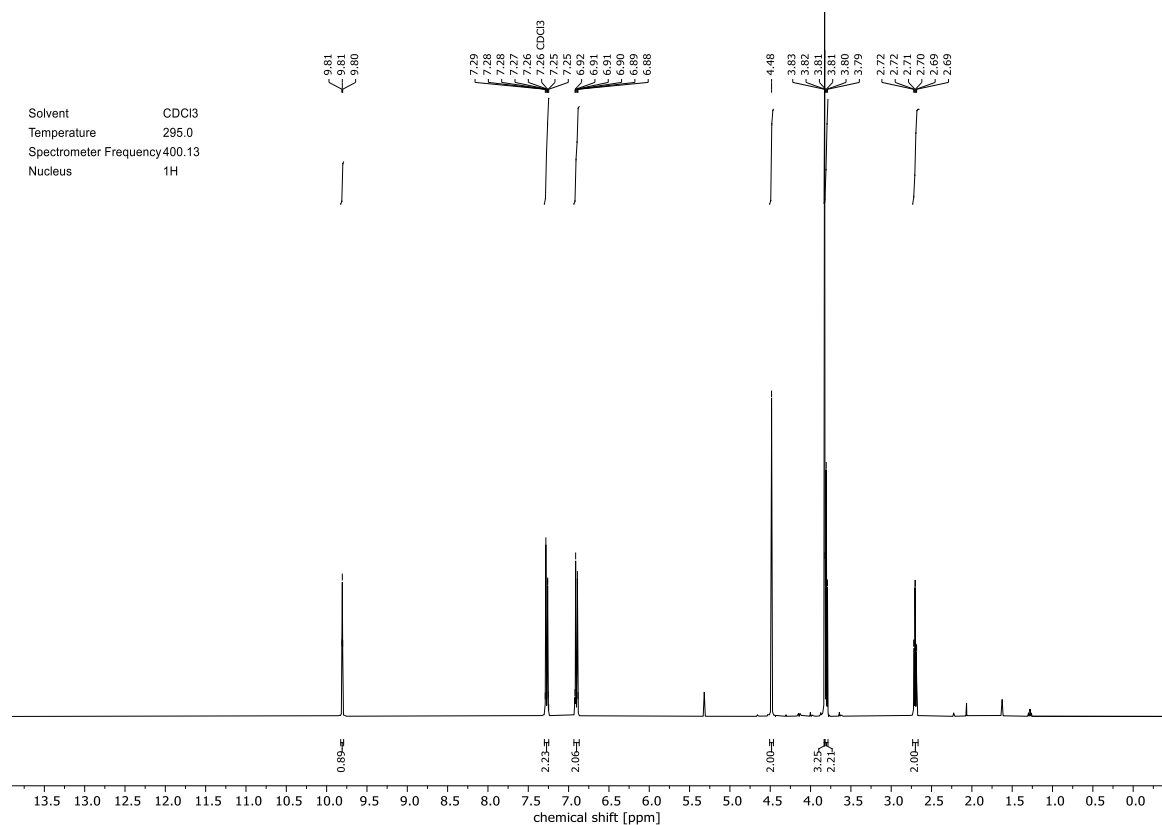




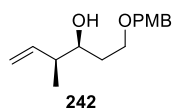
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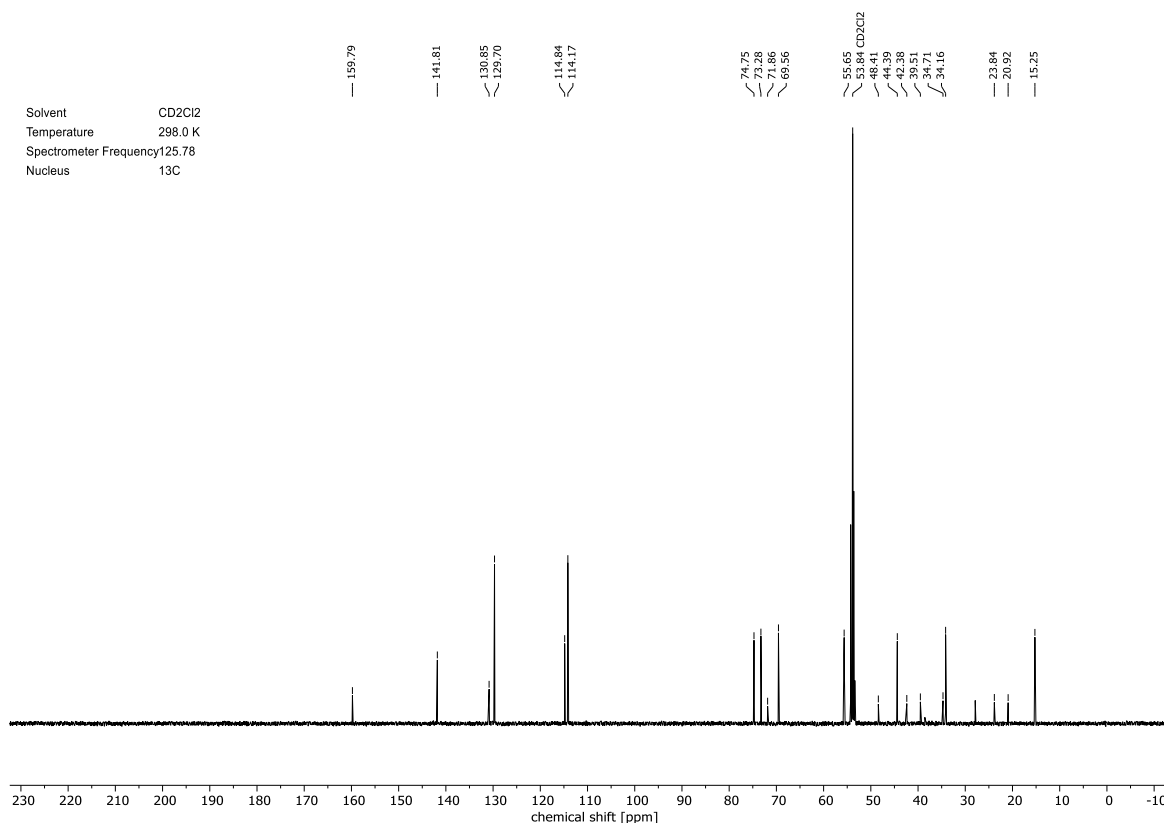
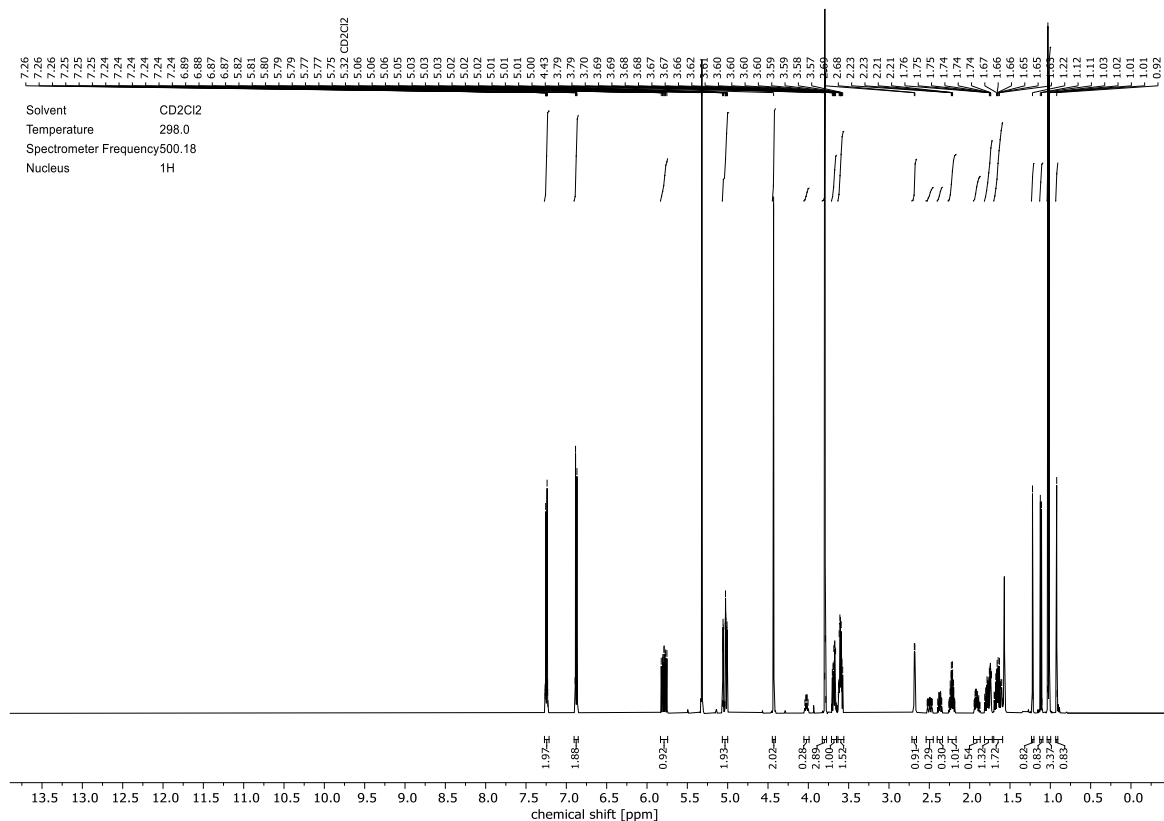
Chemical Formula: $C_{11}H_{14}O_3$
 Exact Mass: 194.0943



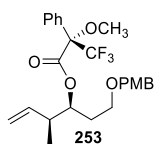
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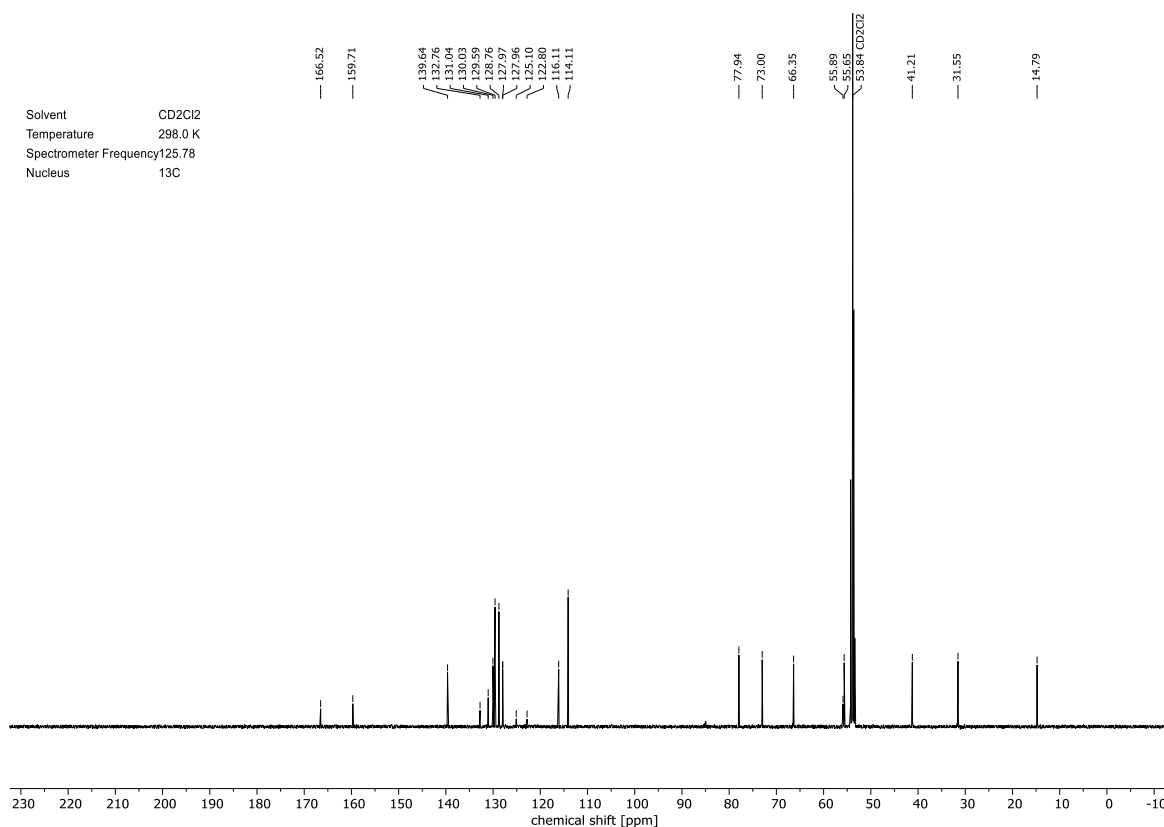
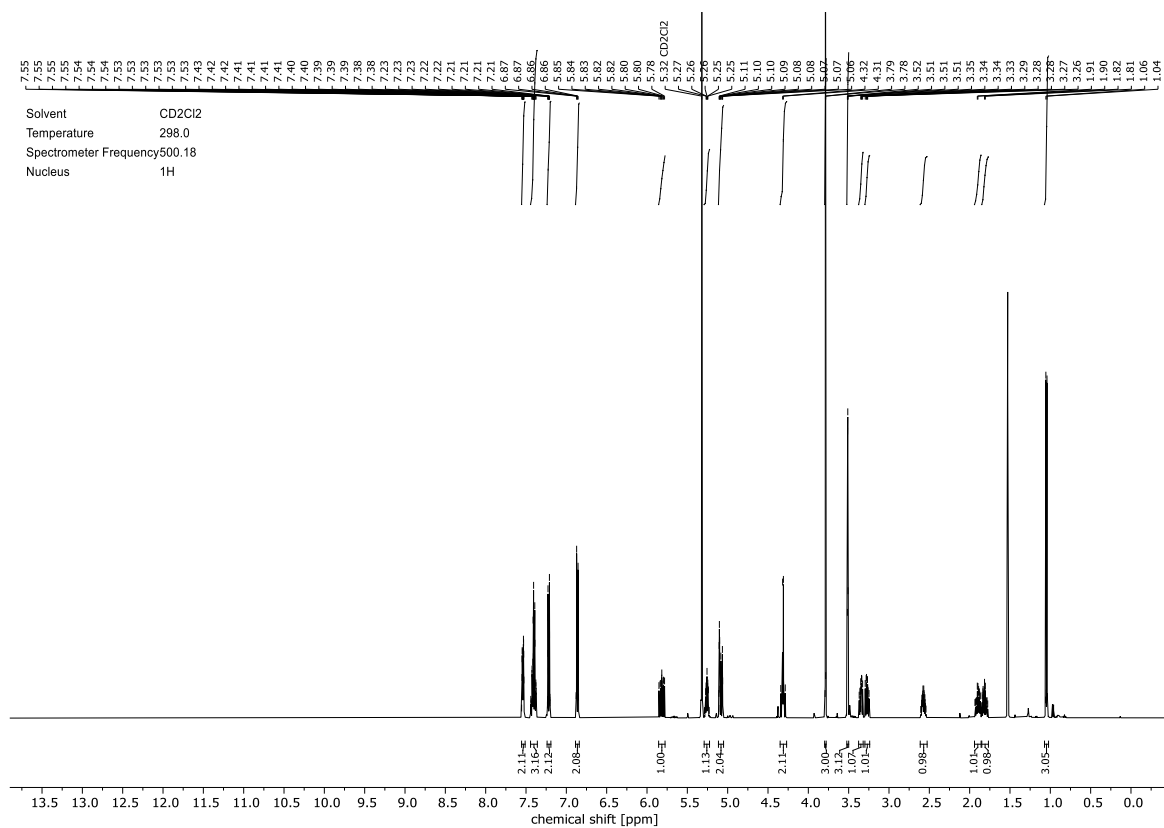
Chemical Formula: $C_{15}H_{22}O_3$
Exact Mass: 250.1569



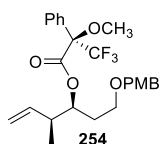
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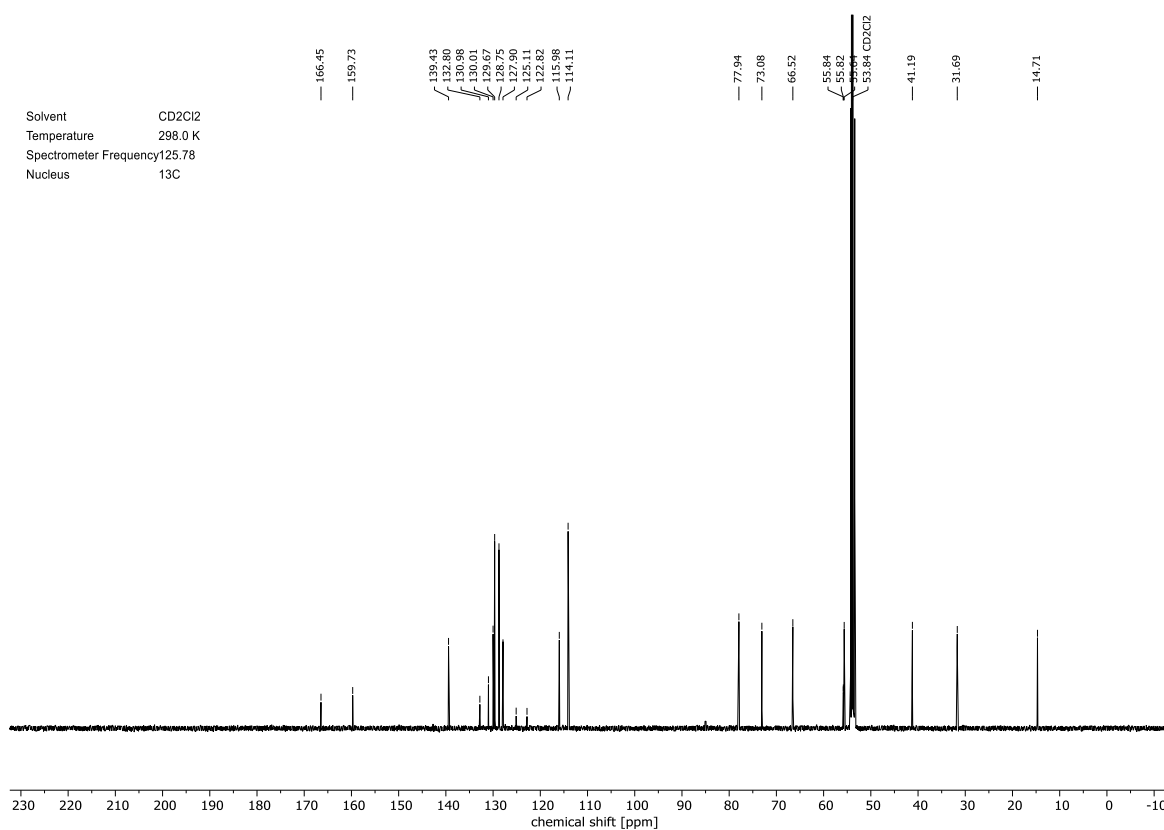
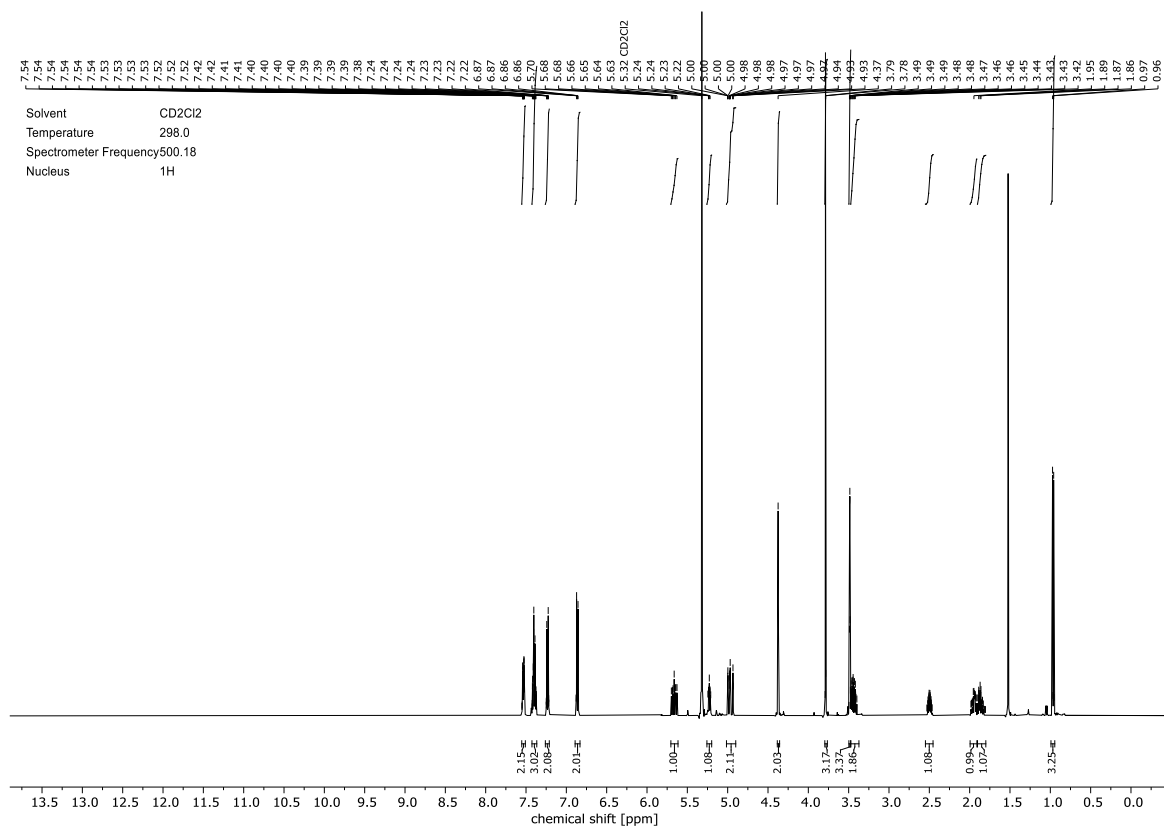
Chemical Formula: $C_{25}H_{29}F_3O_5$
Exact Mass: 466.1967

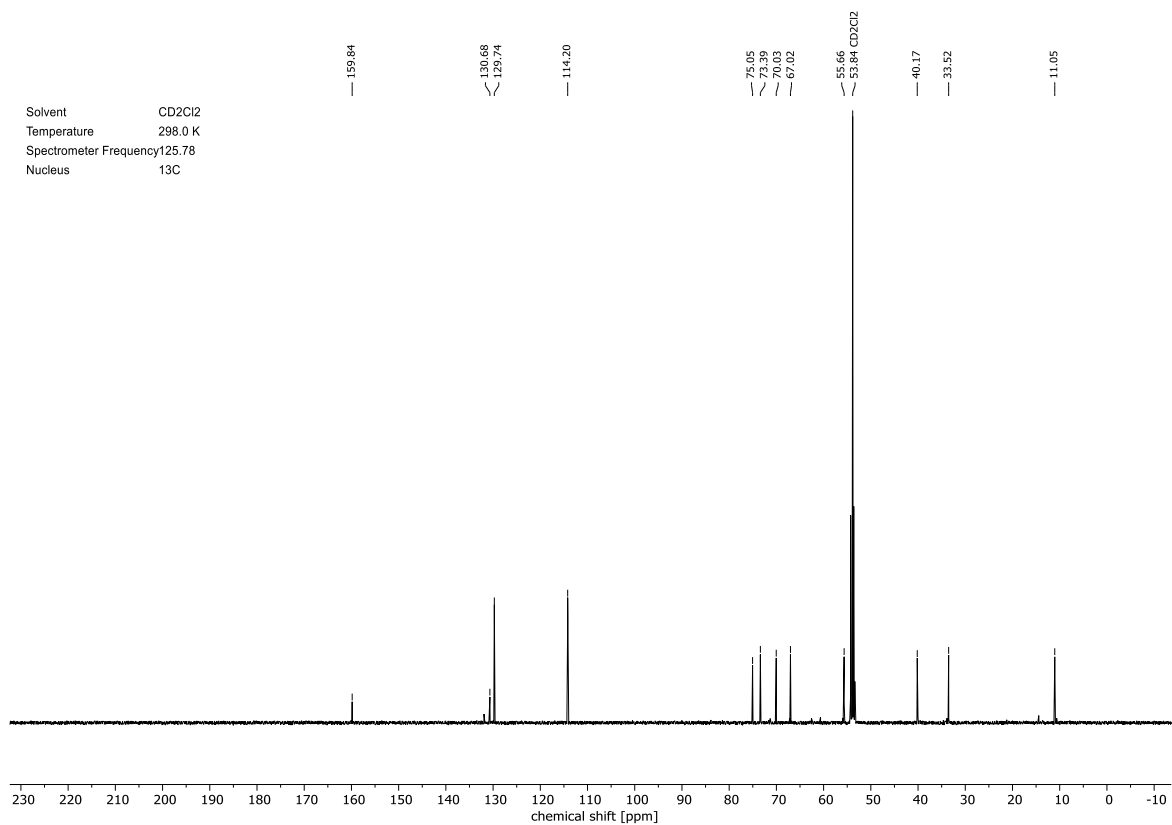
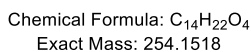


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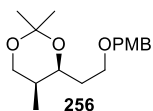


Chemical Formula: $C_{25}H_{29}F_3O_5$
Exact Mass: 466.1967

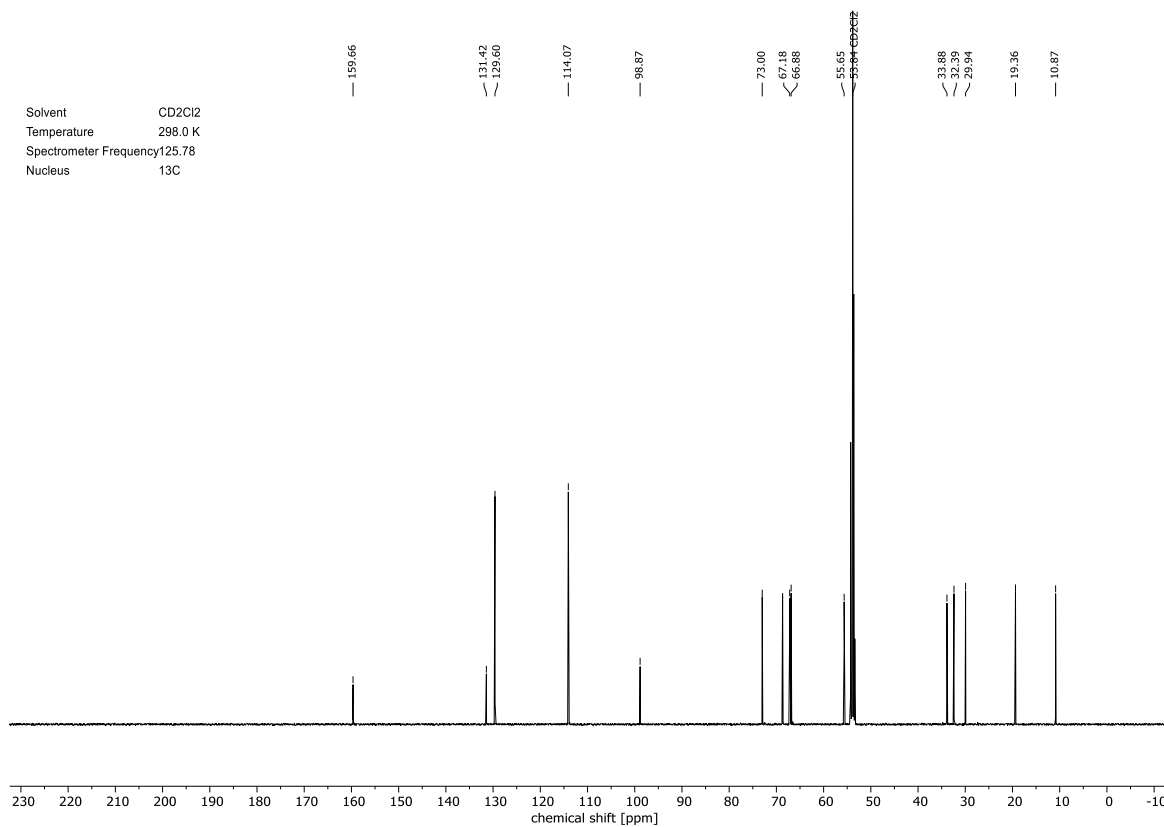
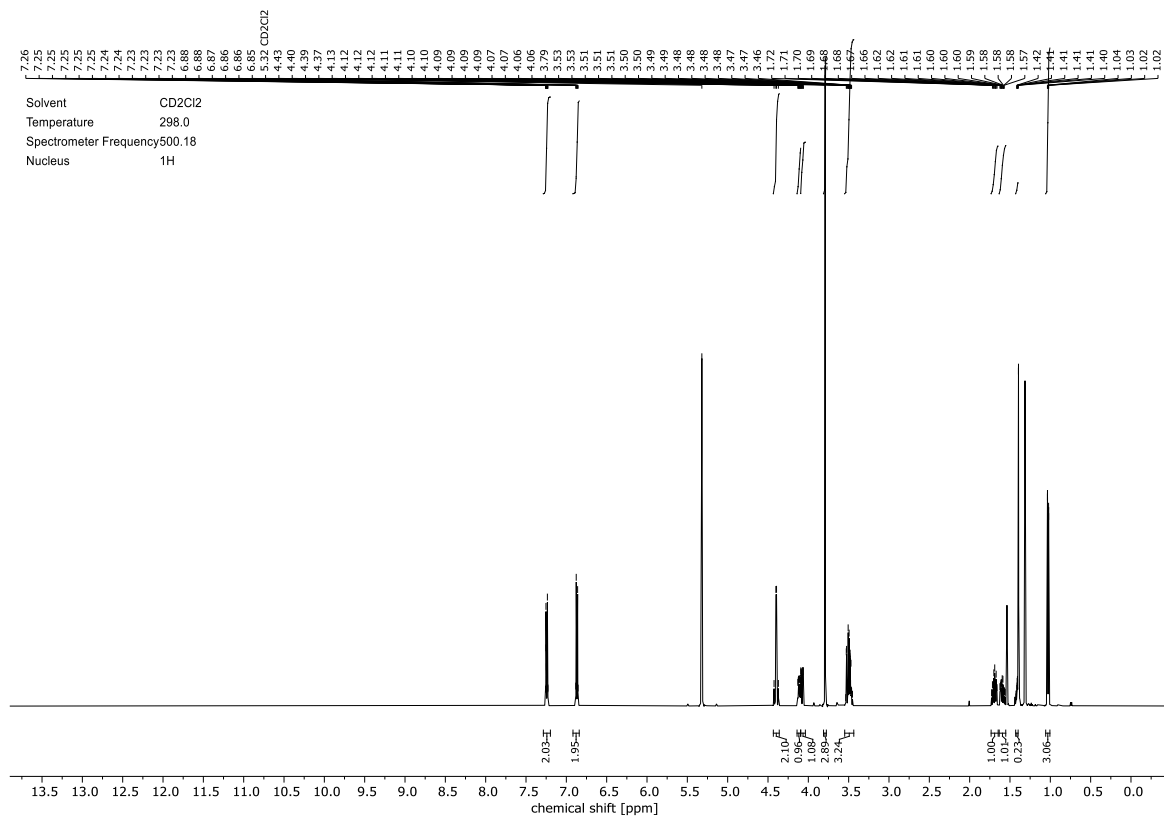




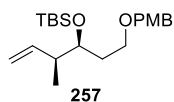
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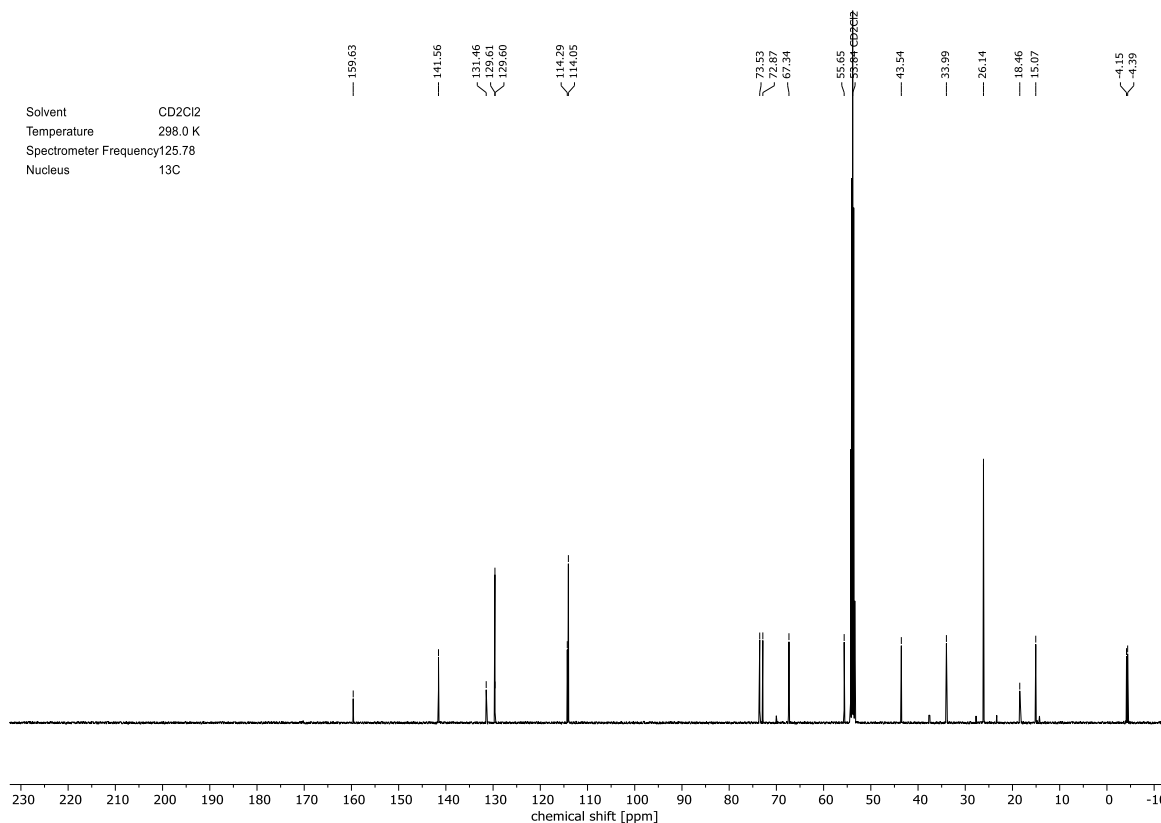
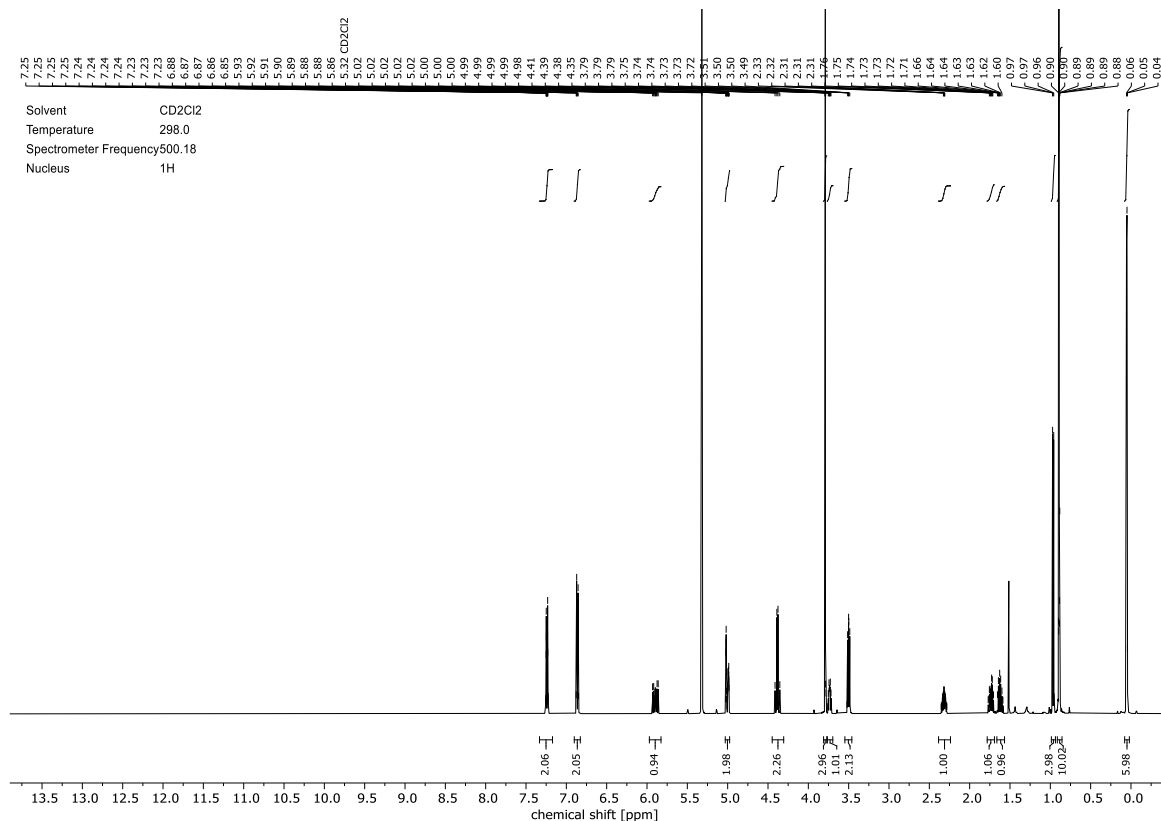
Chemical Formula: $C_{17}H_{26}O_4$
Exact Mass: 294.1831



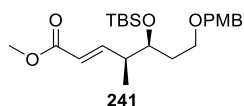
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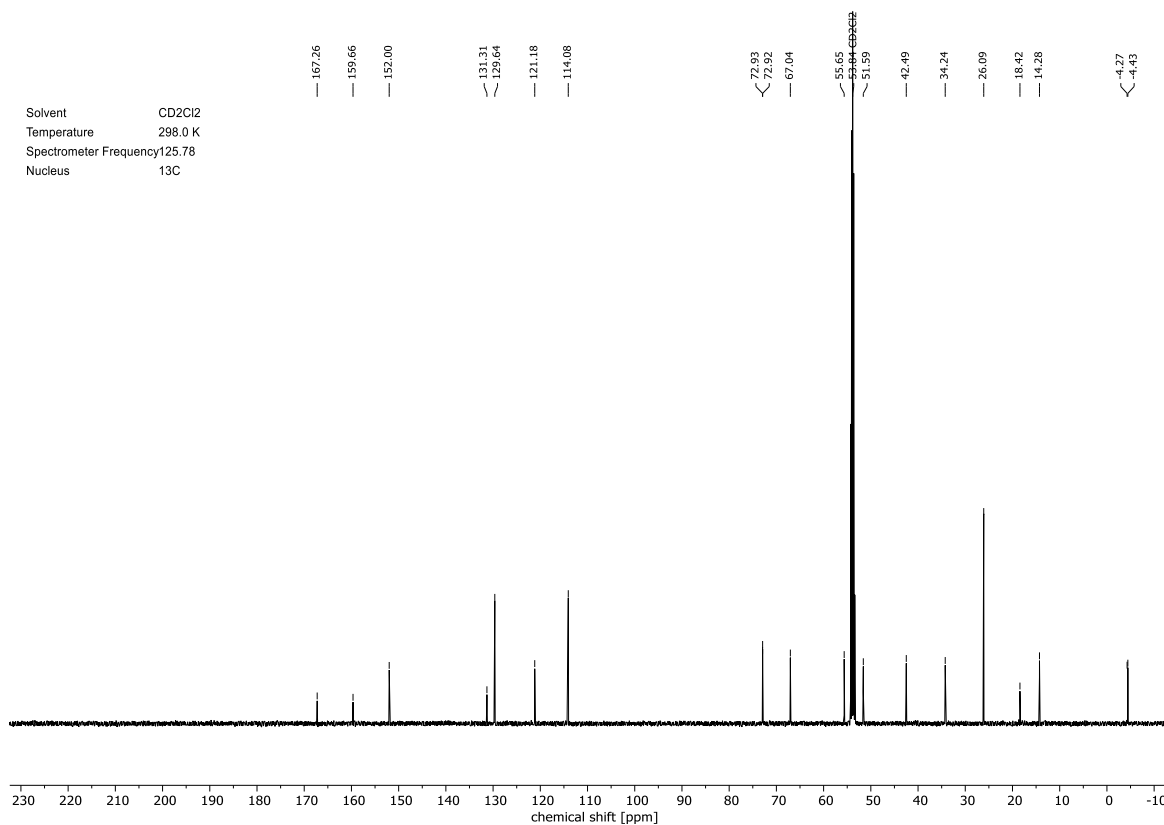
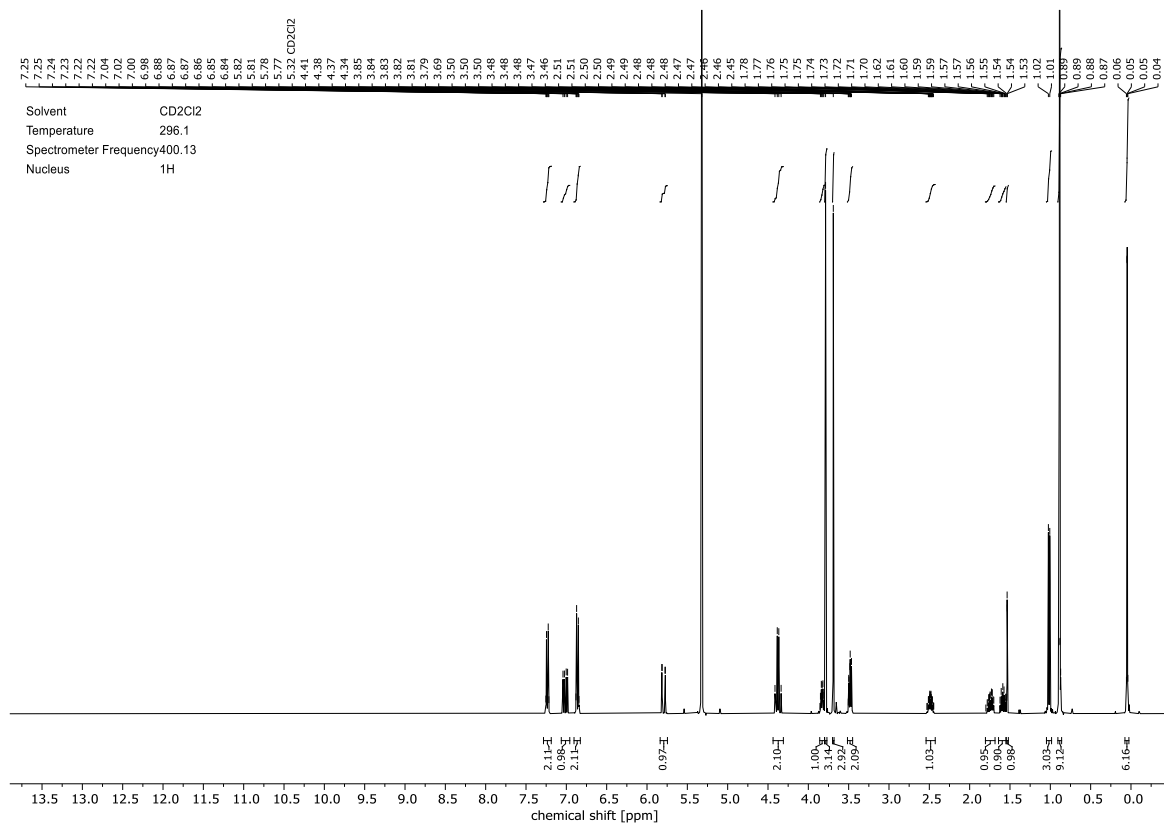
Chemical Formula: $C_{21}H_{36}O_3Si$
Exact Mass: 364.2434



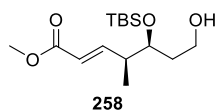
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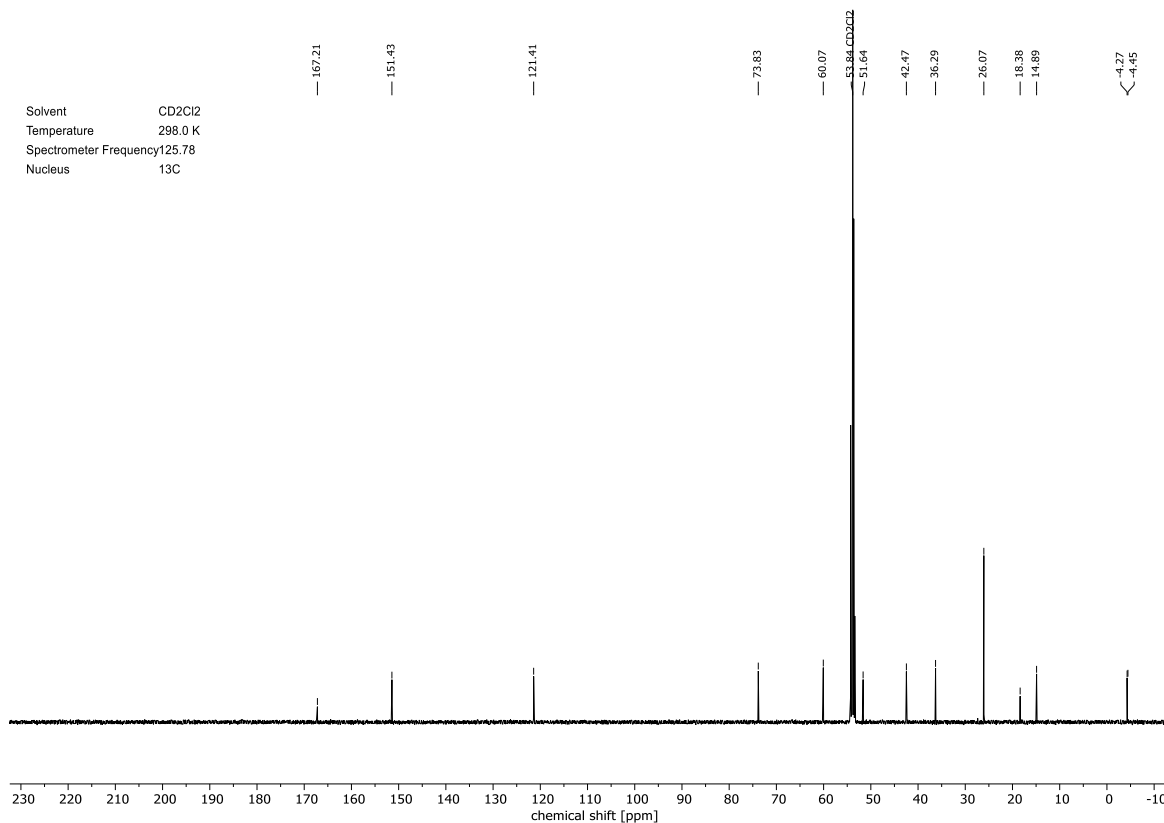
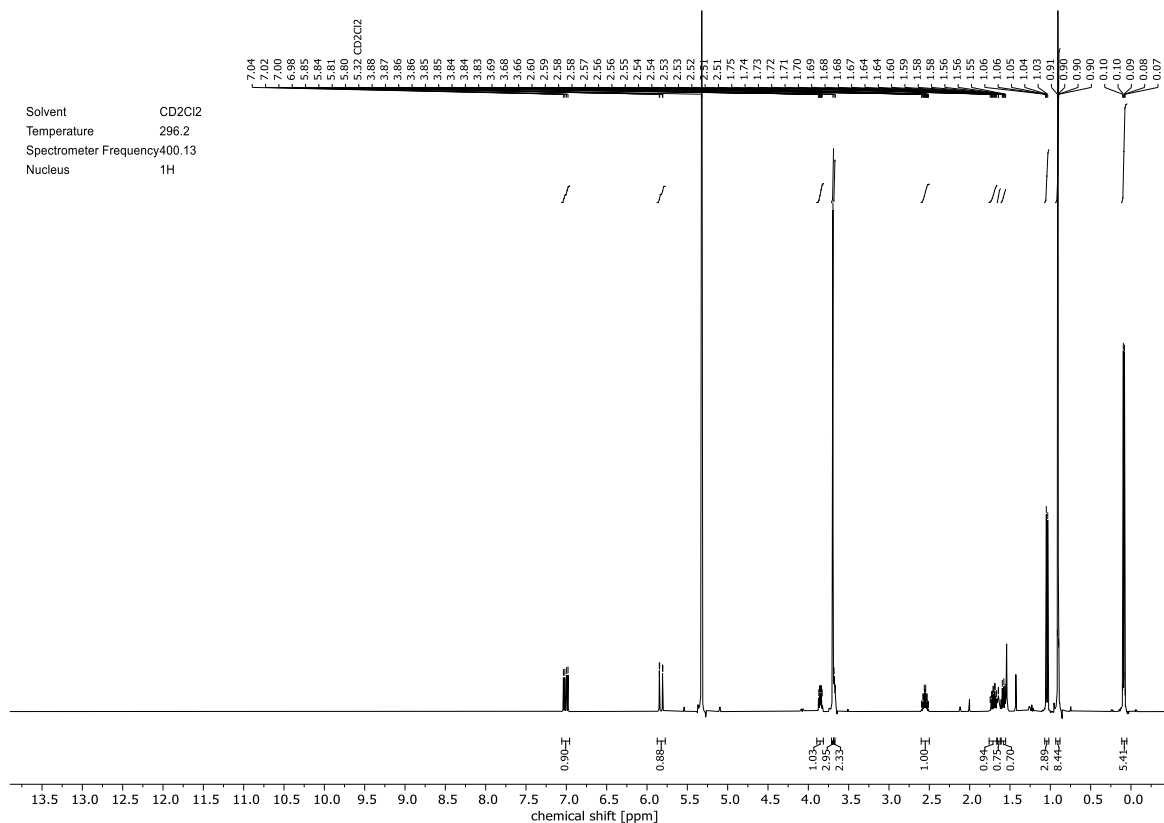
Chemical Formula: $C_{23}H_{38}O_5Si$
Exact Mass: 422.2489



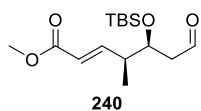
6 Copies of NMR Spectra



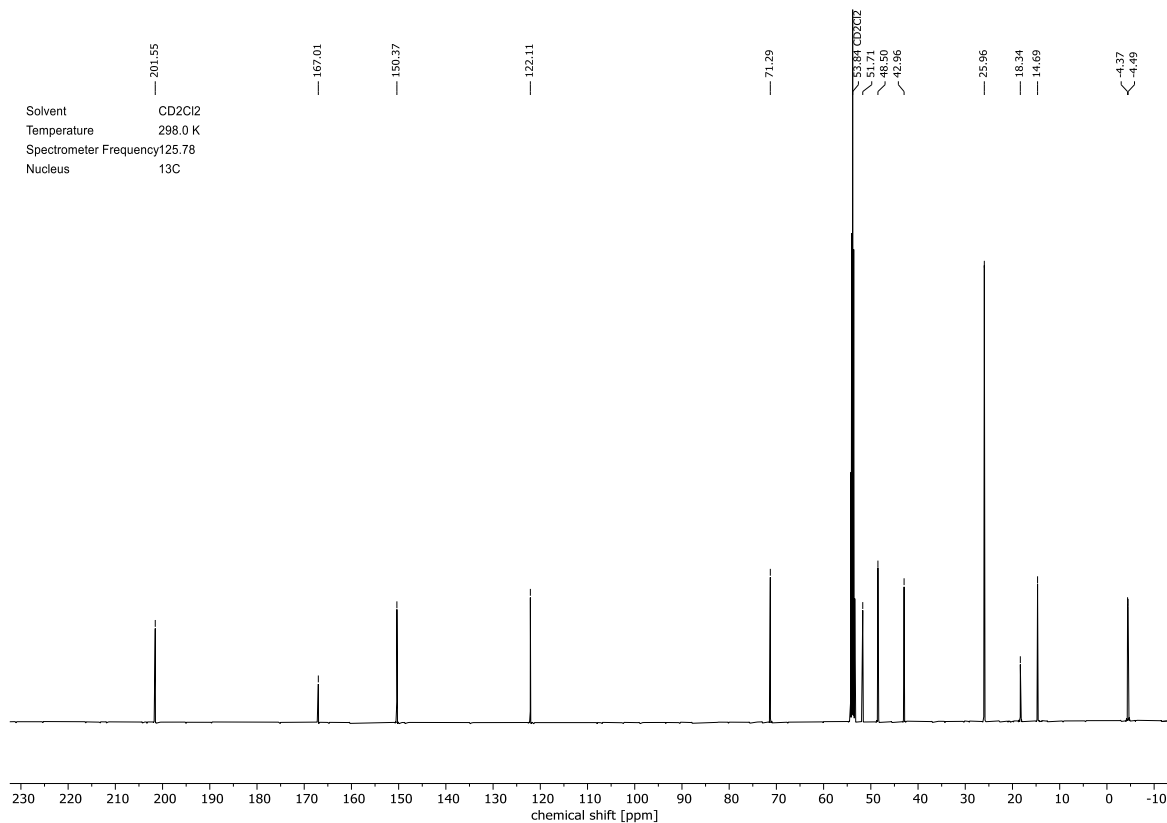
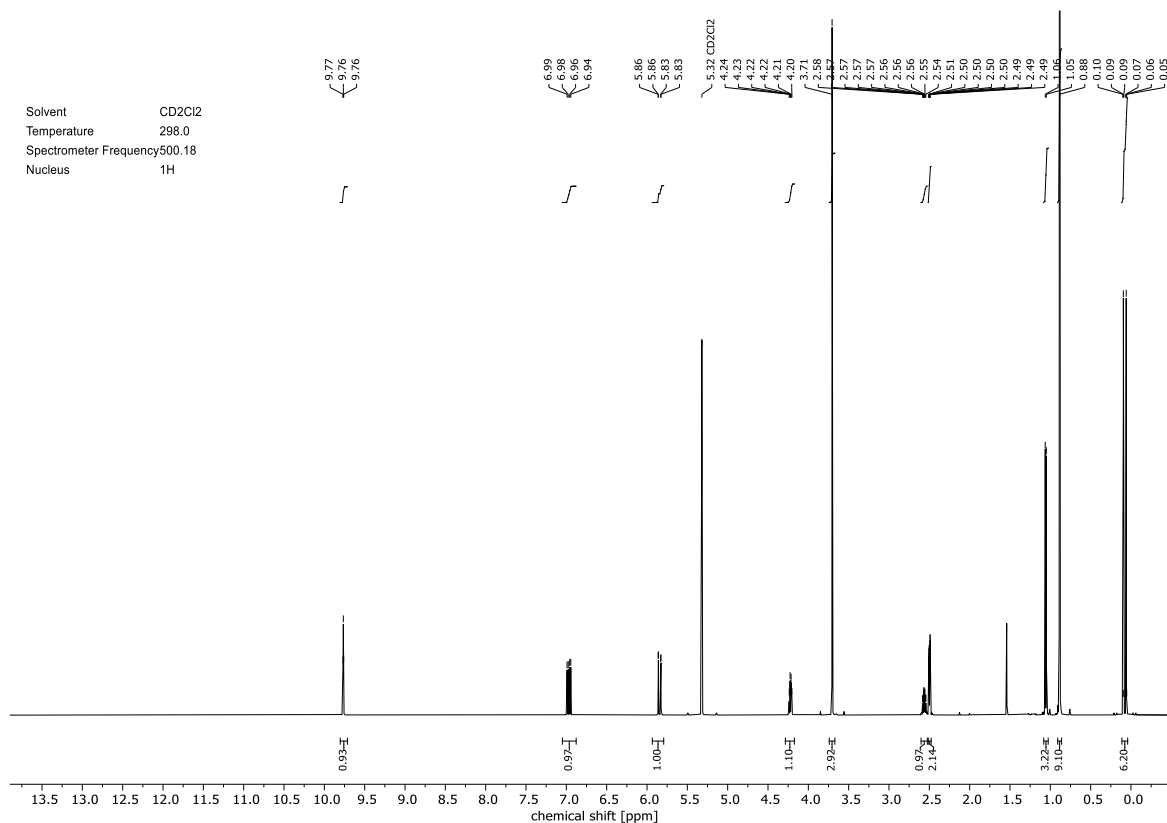
Chemical Formula: $C_{15}H_{30}O_4Si$
Exact Mass: 302.1913



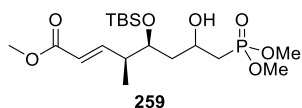
6 Copies of NMR Spectra



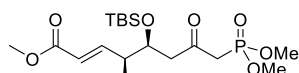
Chemical Formula: $C_{15}H_{28}O_4Si$
Exact Mass: 300.1757



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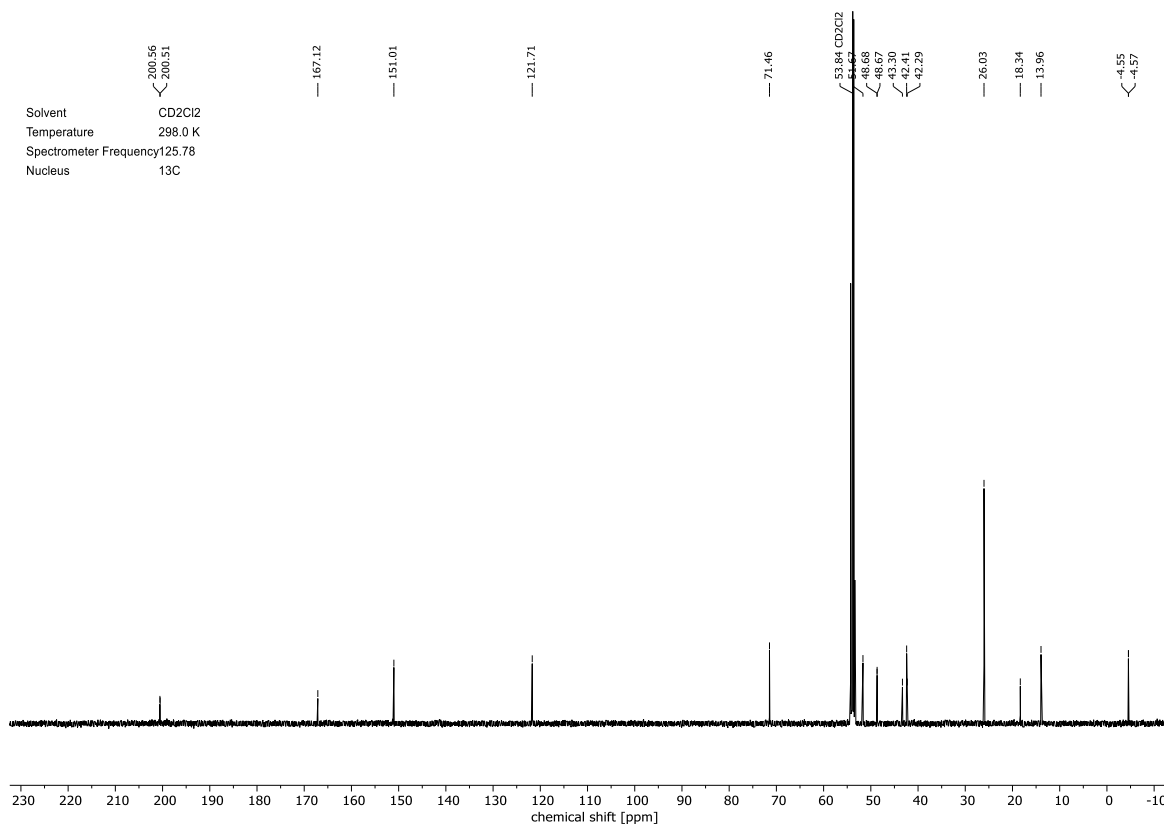
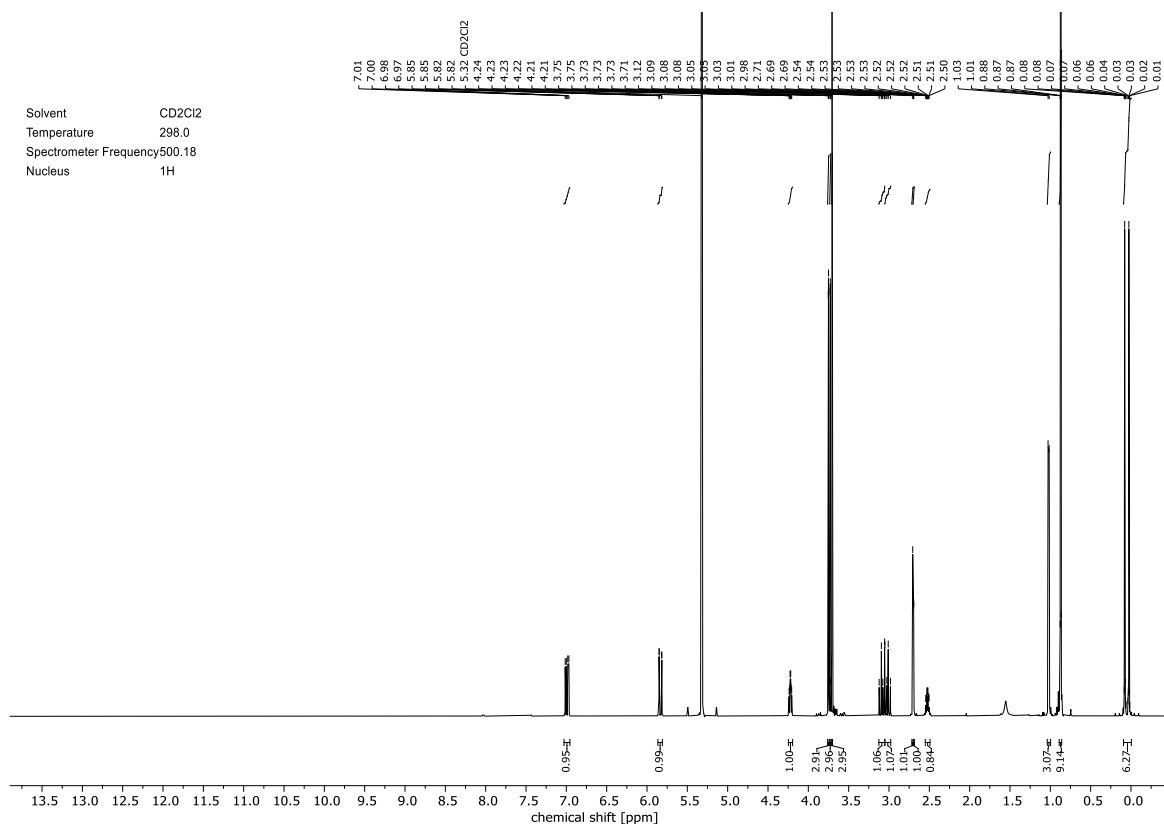
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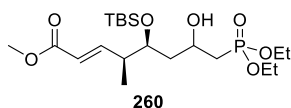


238

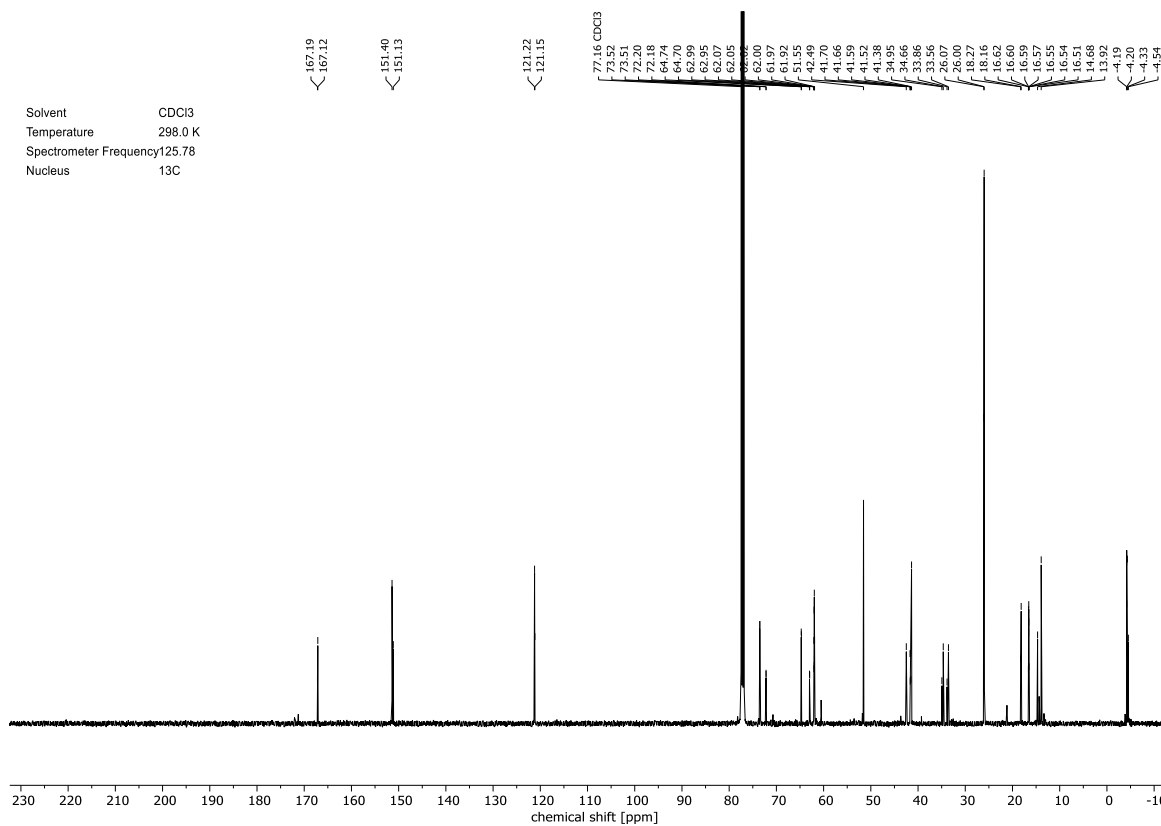
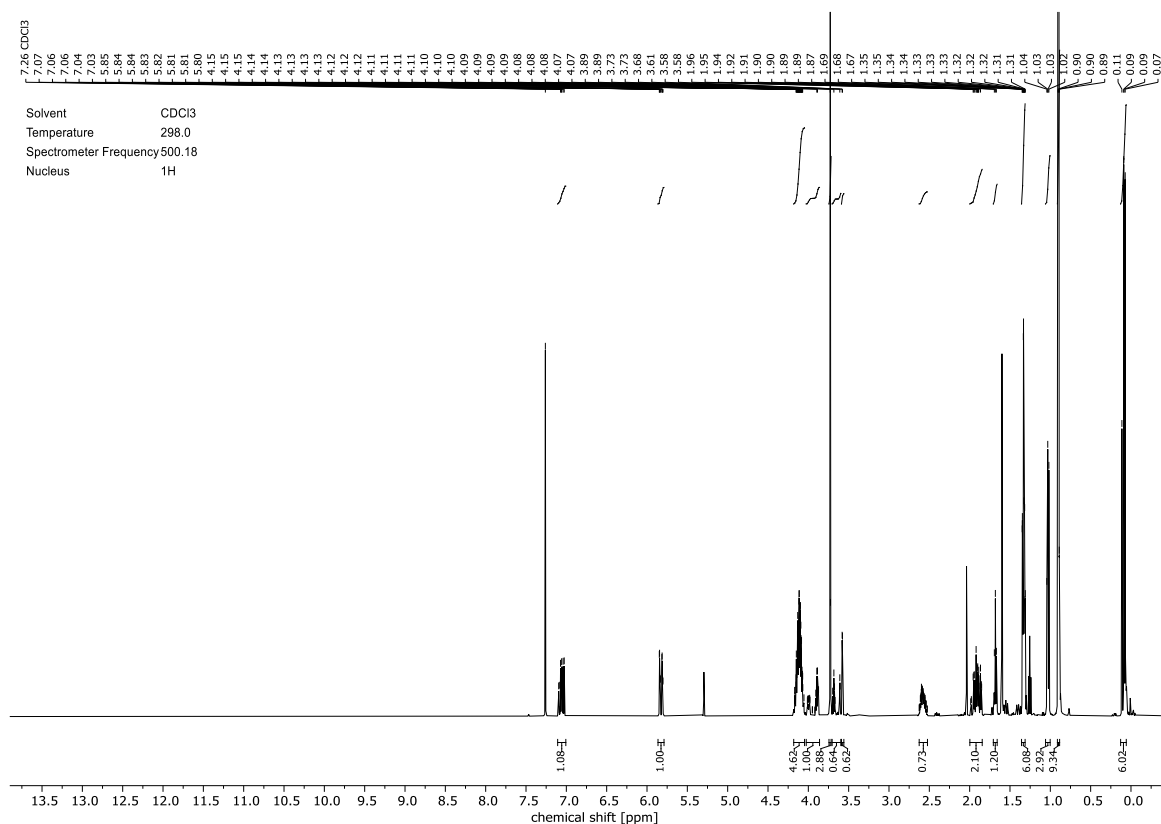
Chemical Formula: $C_{18}H_{35}O_7PSi$

Exact Mass: 422.1890

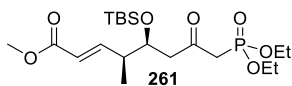




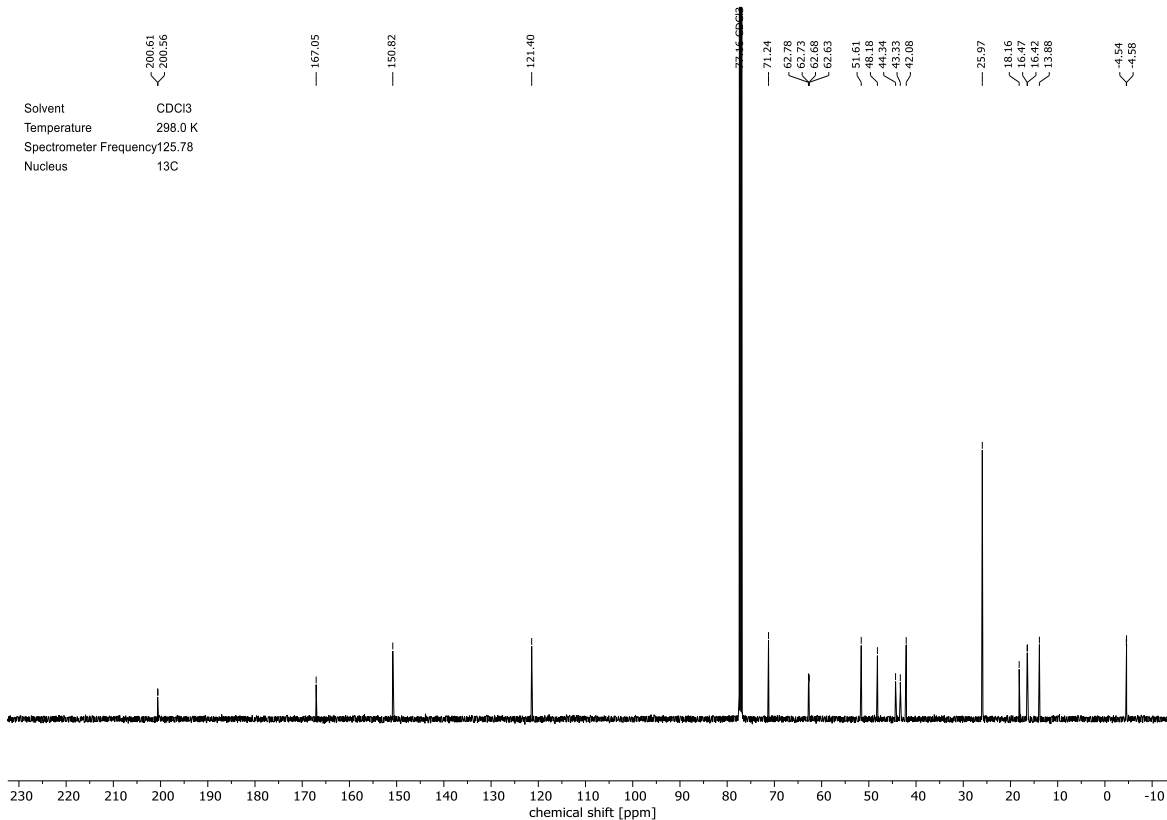
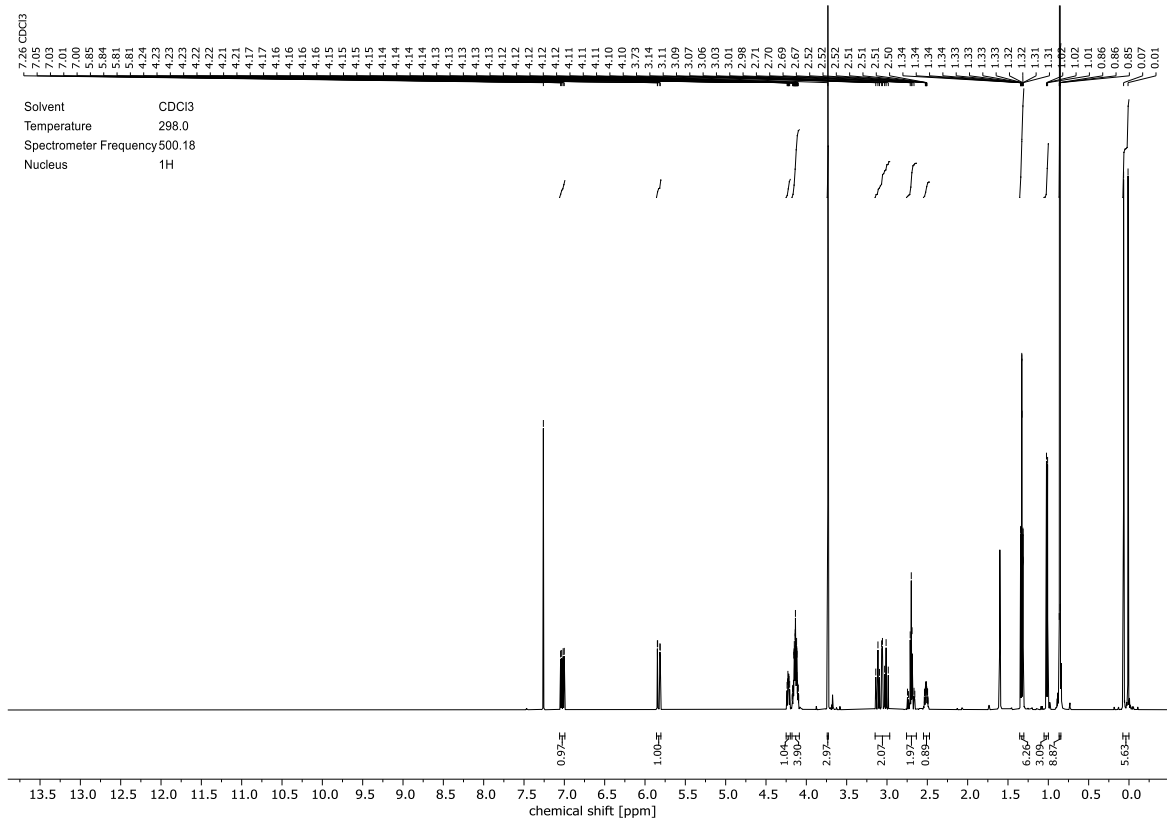
Chemical Formula: C₂₀H₄₁O₇PSi
Exact Mass: 452.2359

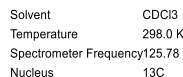
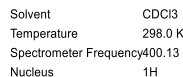
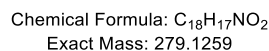


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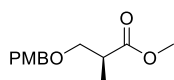


Chemical Formula: $C_{20}H_{39}O_7P$
Exact Mass: 450.2203



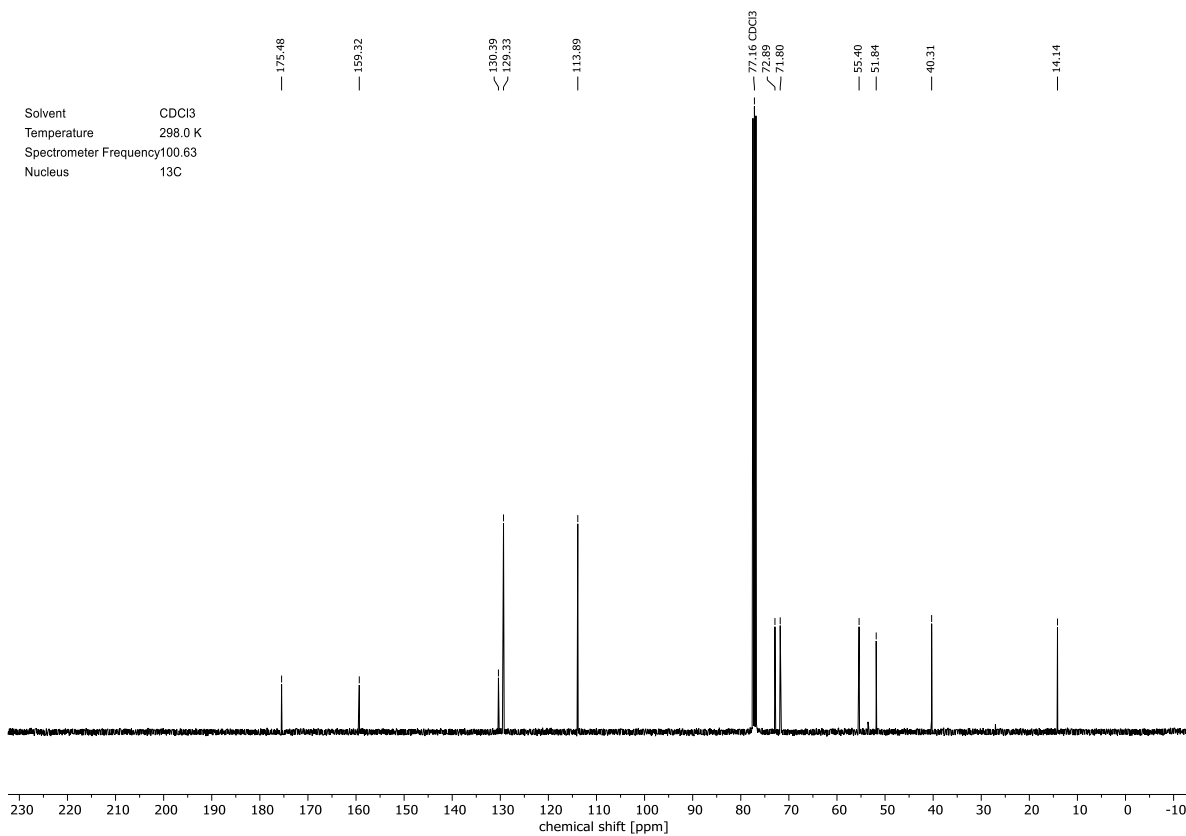
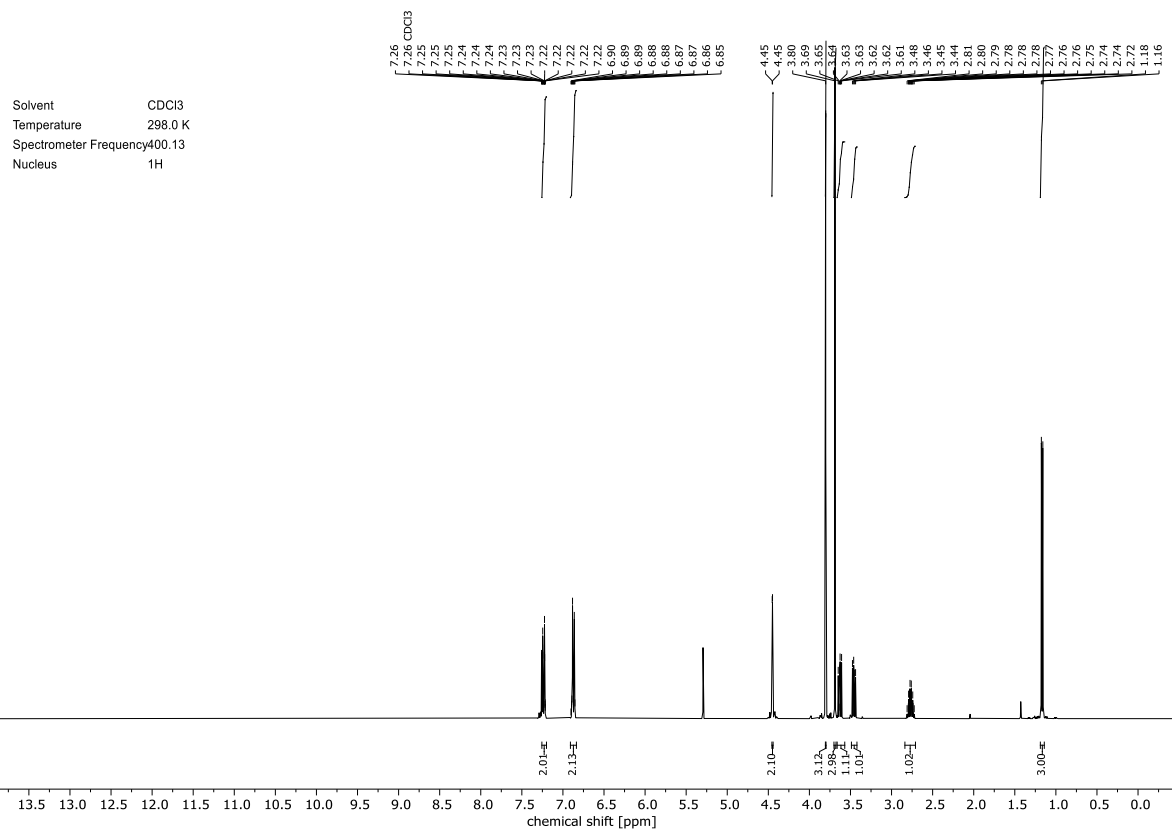


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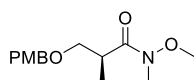


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Chemical Formula: $C_{13}H_{18}O_4$
Exact Mass: 238.1205

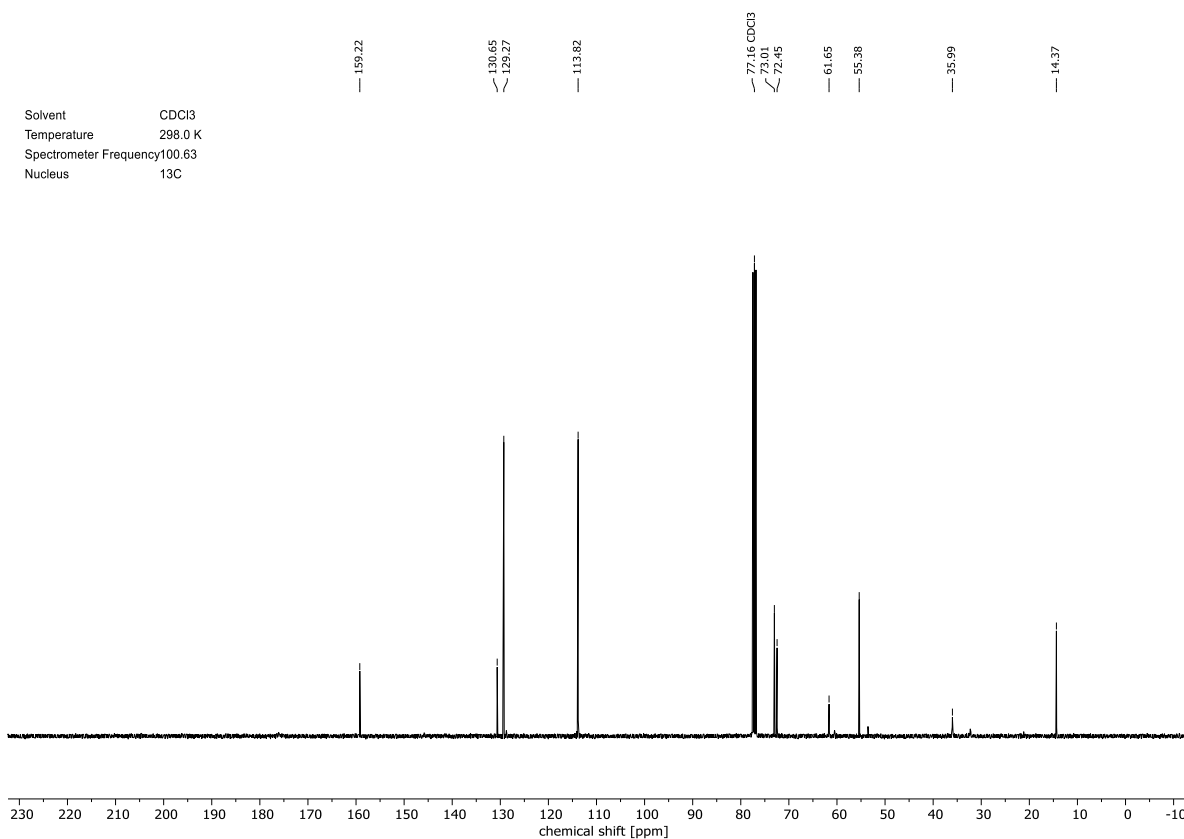
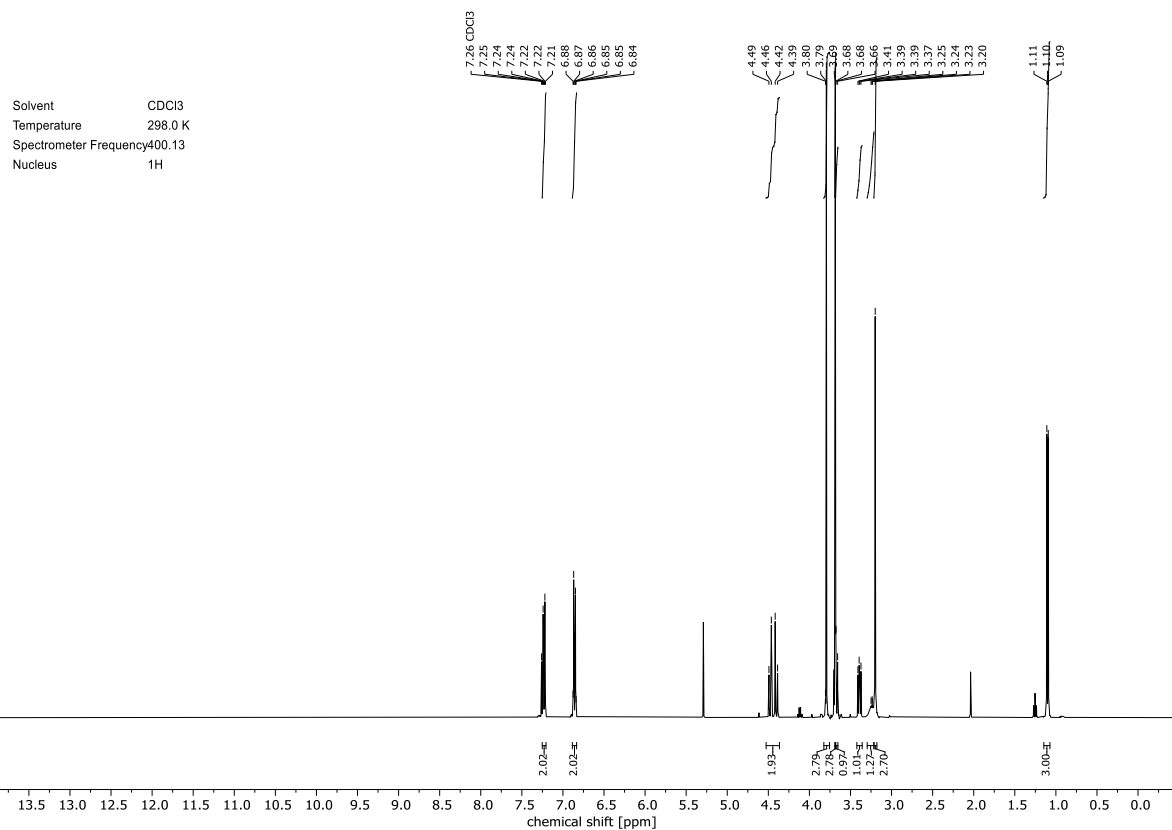


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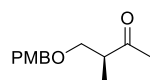


265

Chemical Formula: $C_{14}H_{21}NO_4$
Exact Mass: 267.1471

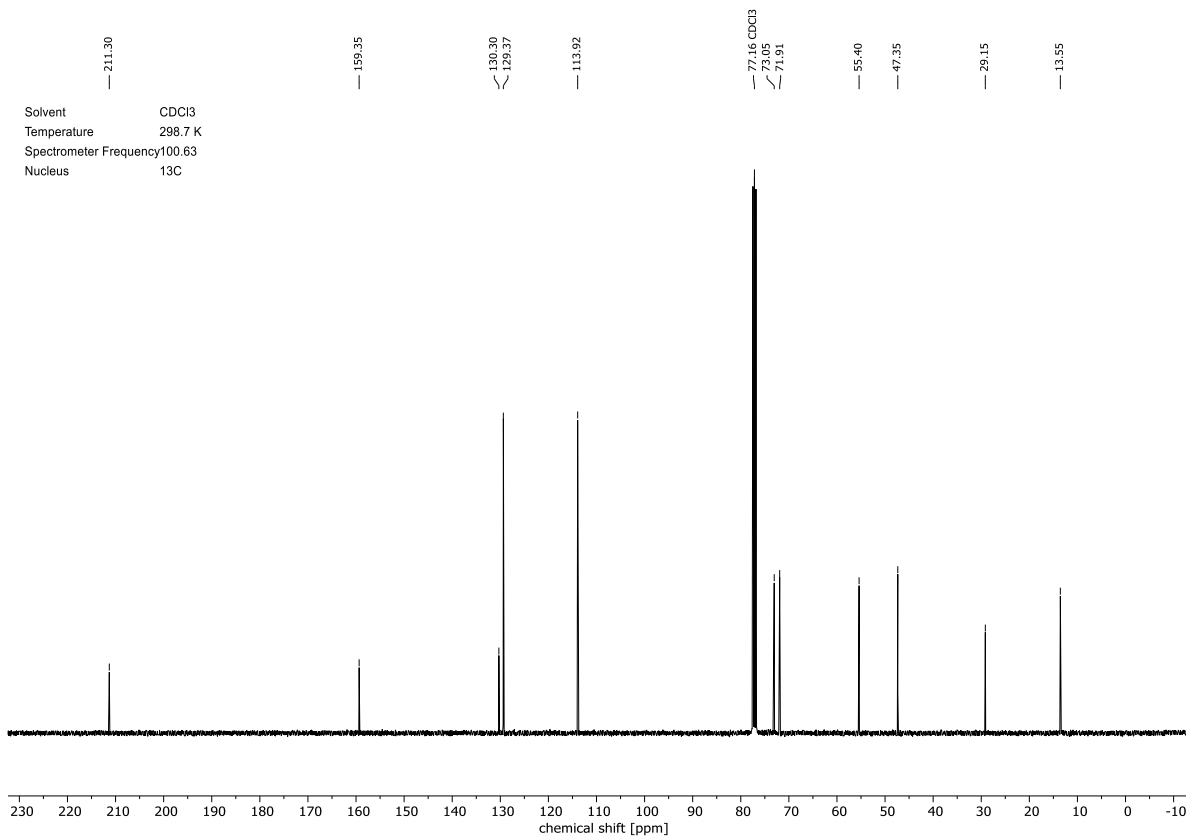
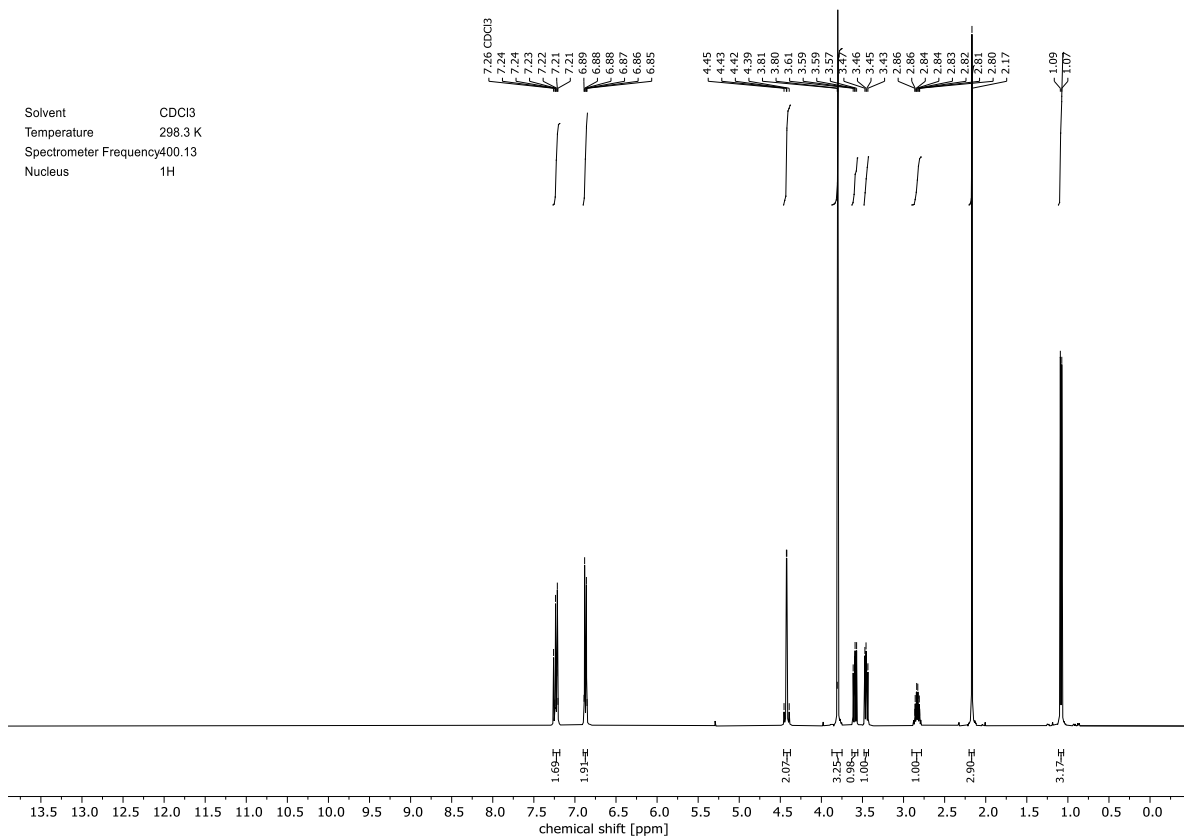


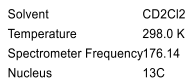
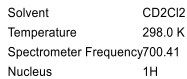
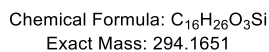
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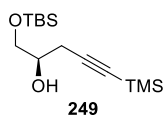
Chemical Formula: C₁₃H₁₈O₃
Exact Mass: 222.1256

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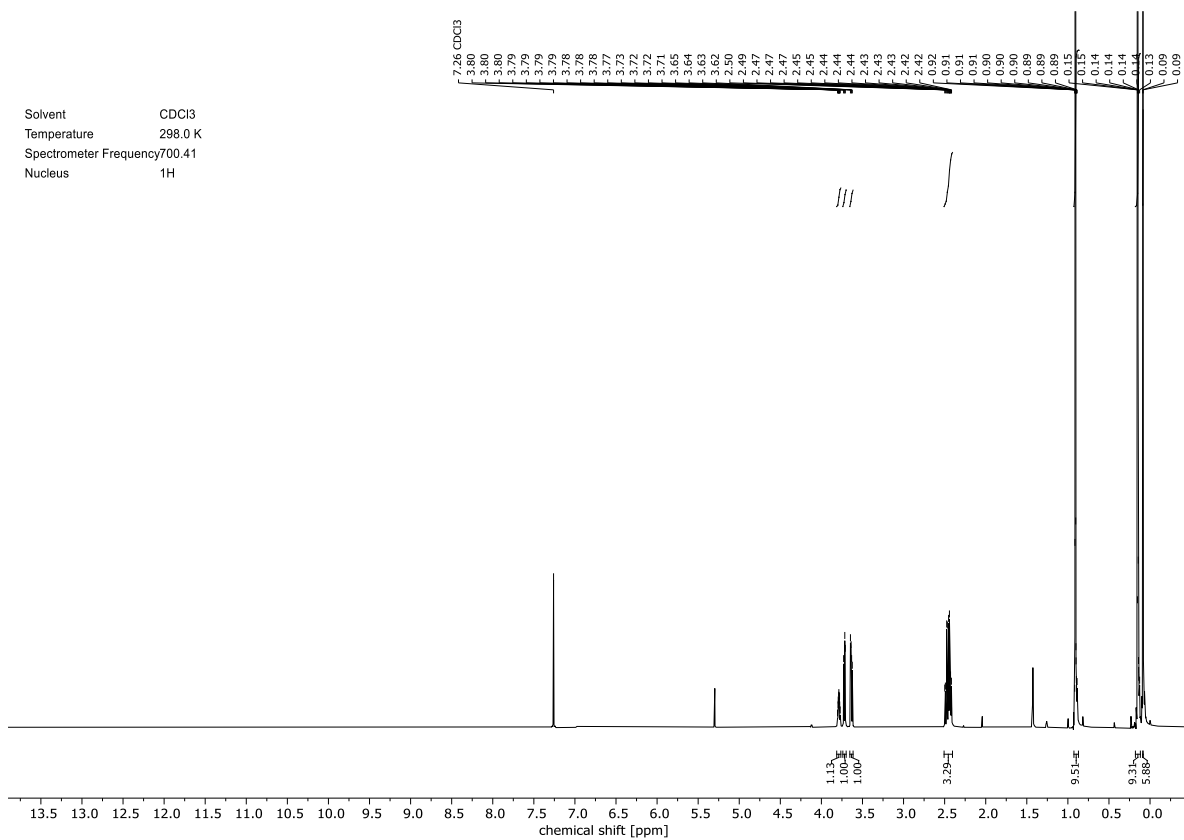


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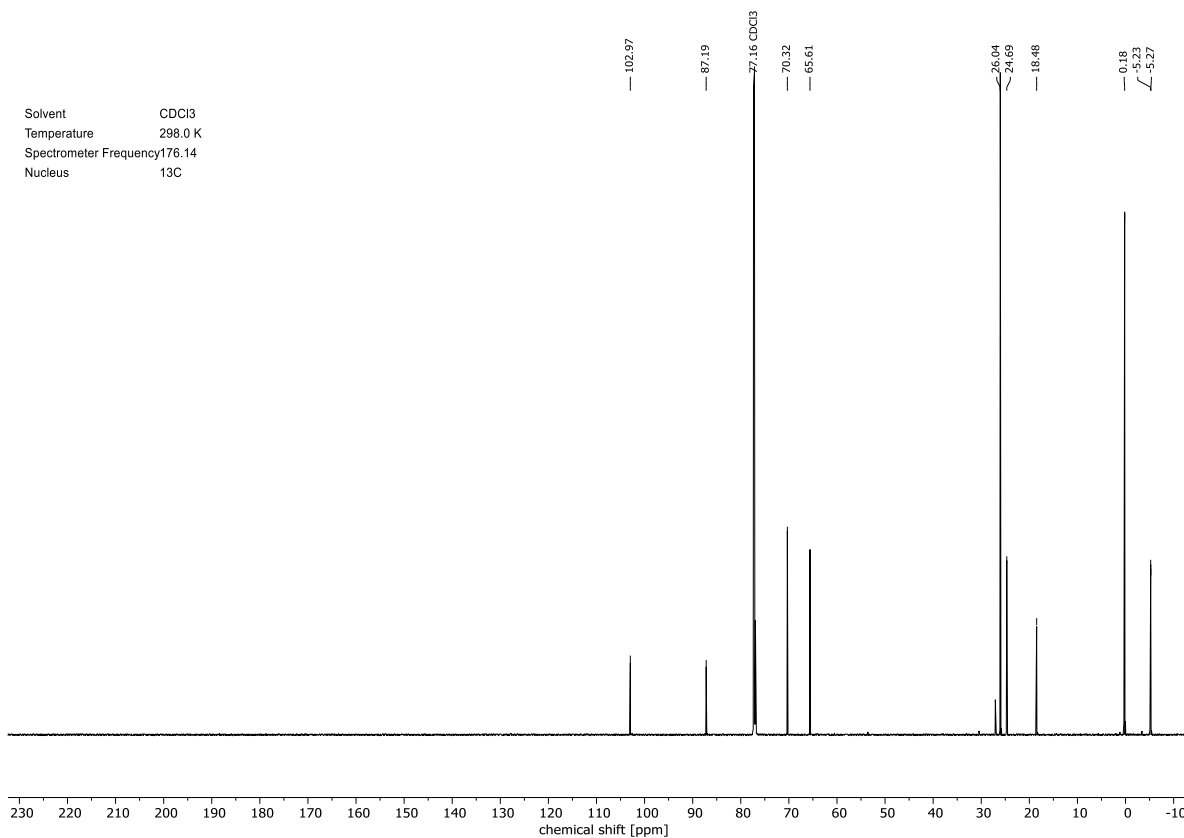


Chemical Formula: $C_{14}H_{30}O_2Si_2$
Exact Mass: 286.1784

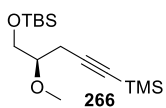
Solvent CDCl₃
Temperature 298.0 K
Spectrometer Frequency 700.41
Nucleus ¹H



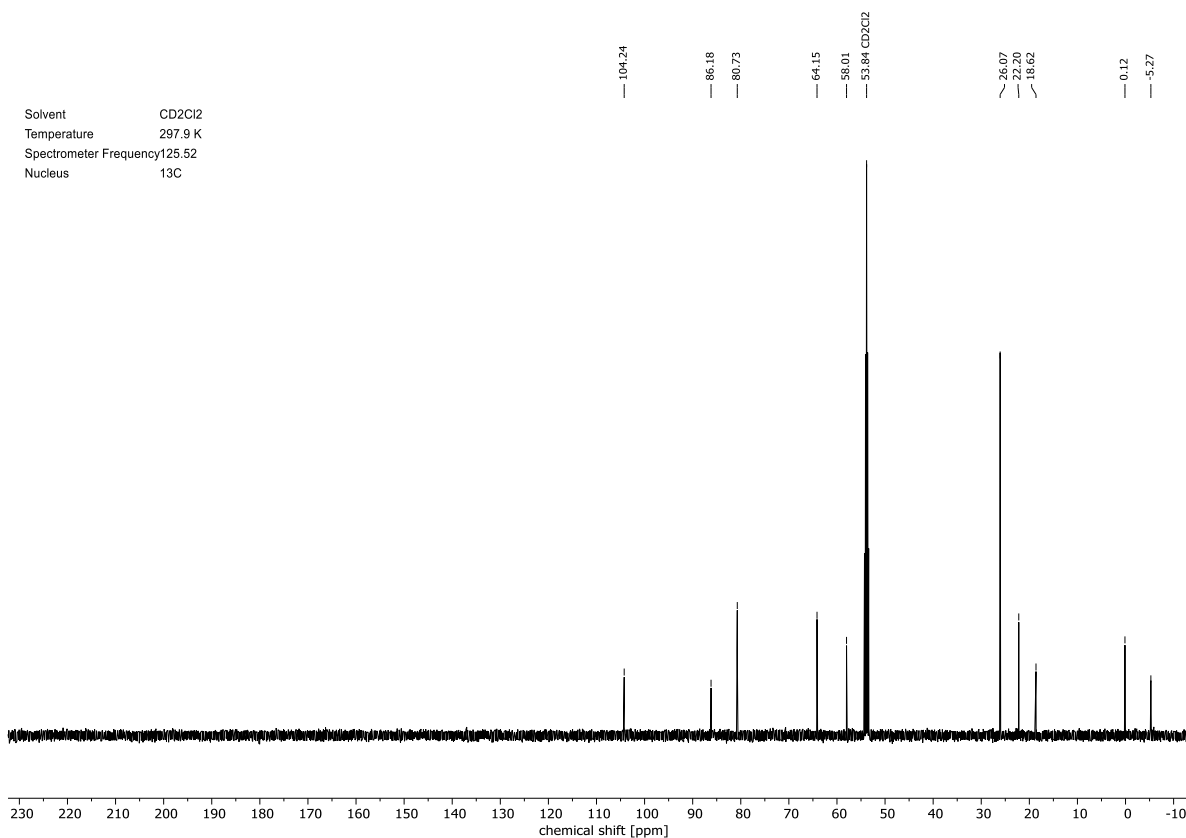
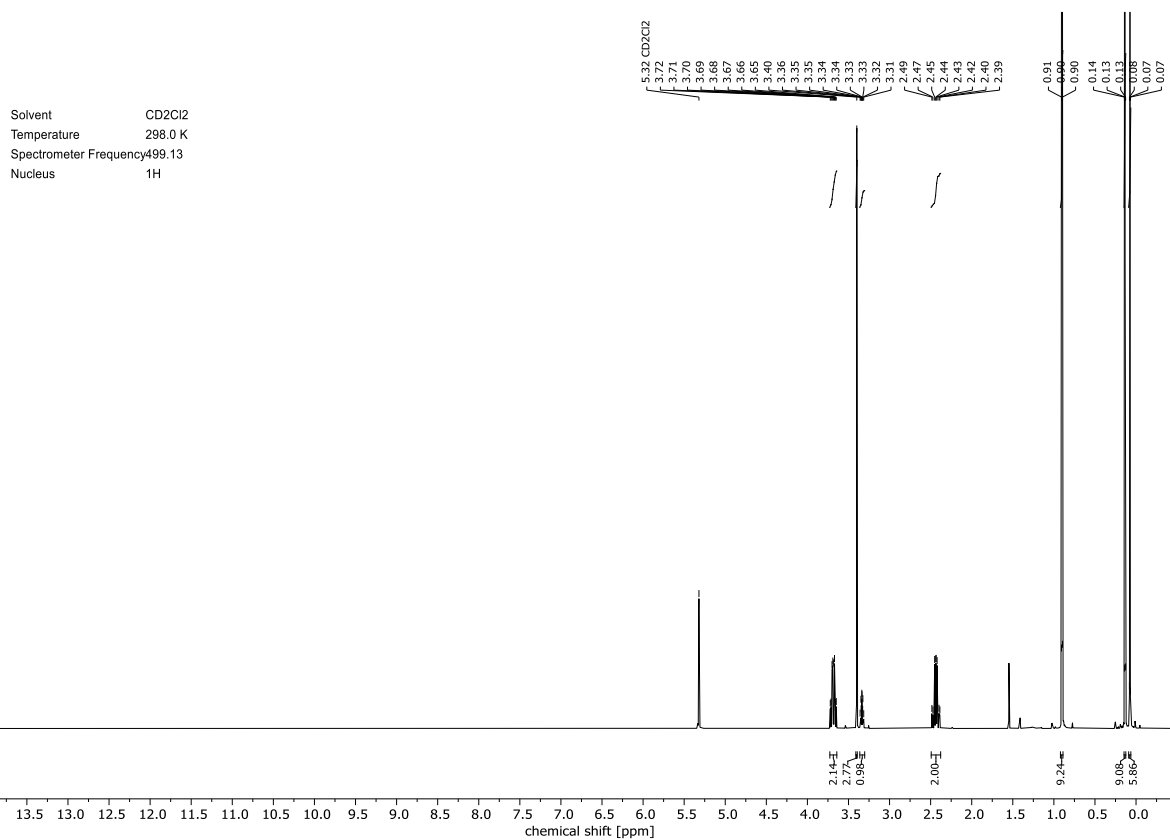
Solvent CDCl₃
Temperature 298.0 K
Spectrometer Frequency 176.14
Nucleus ¹³C



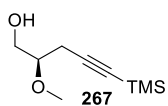
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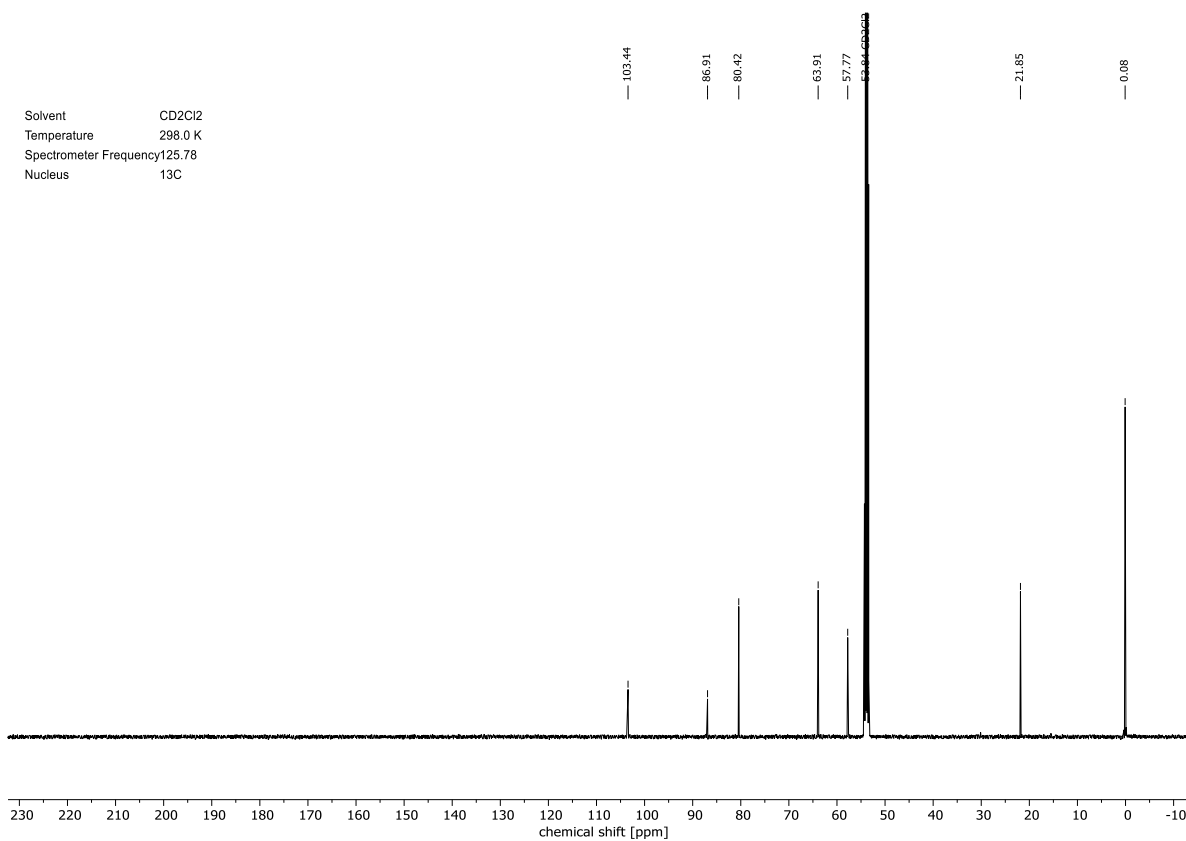
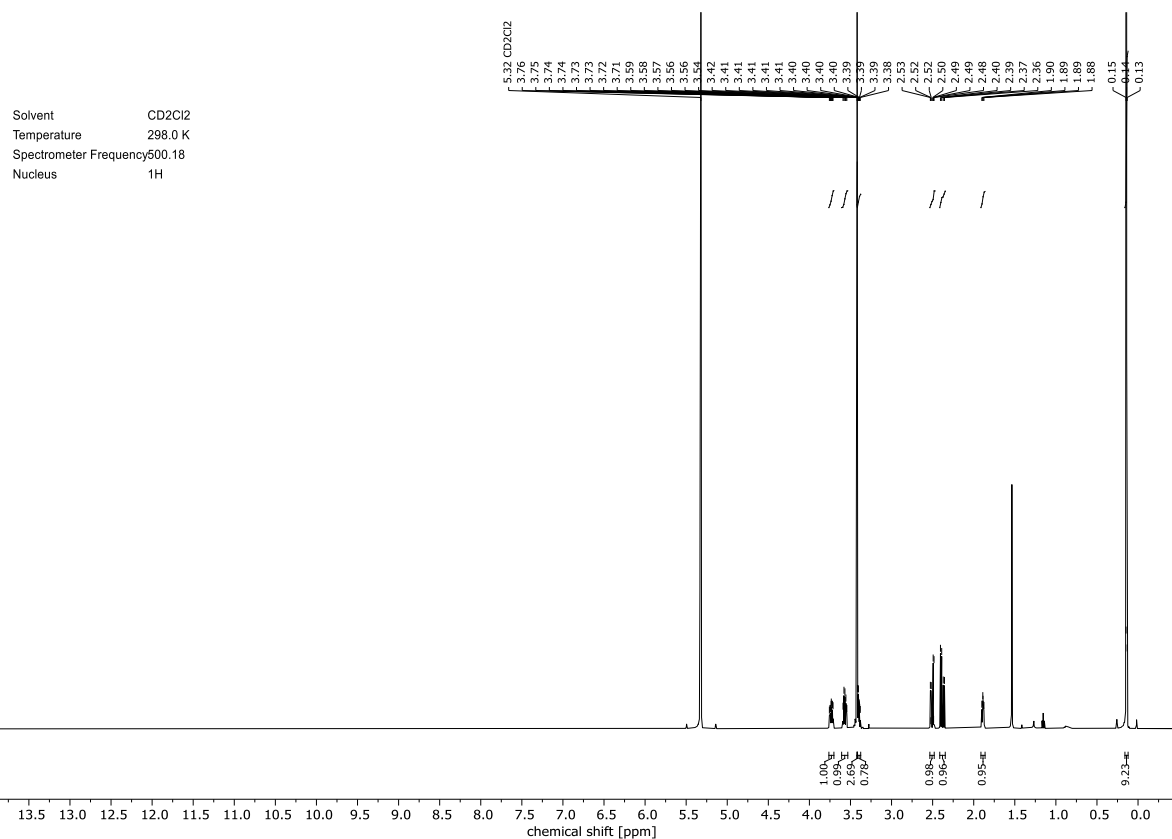
Chemical Formula: $C_{15}H_{32}O_2Si_2$
Exact Mass: 300.1941



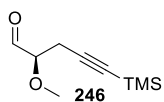
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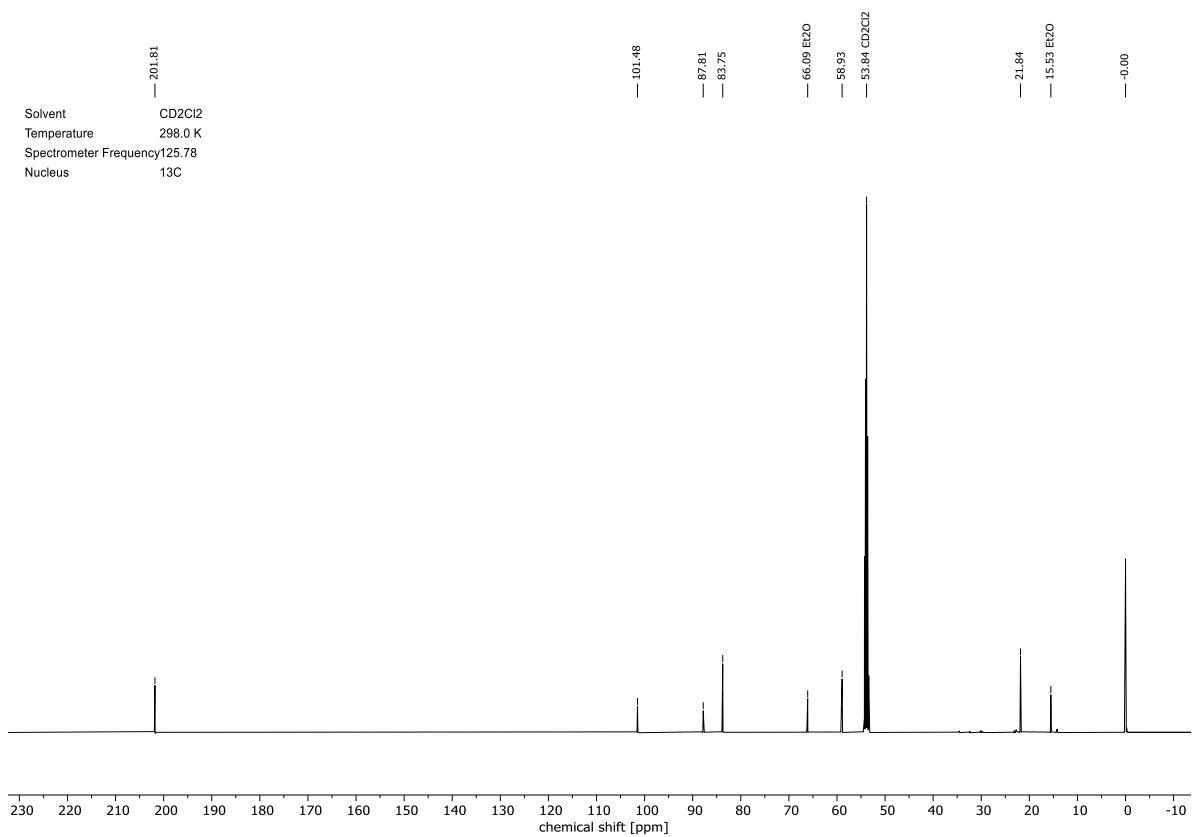
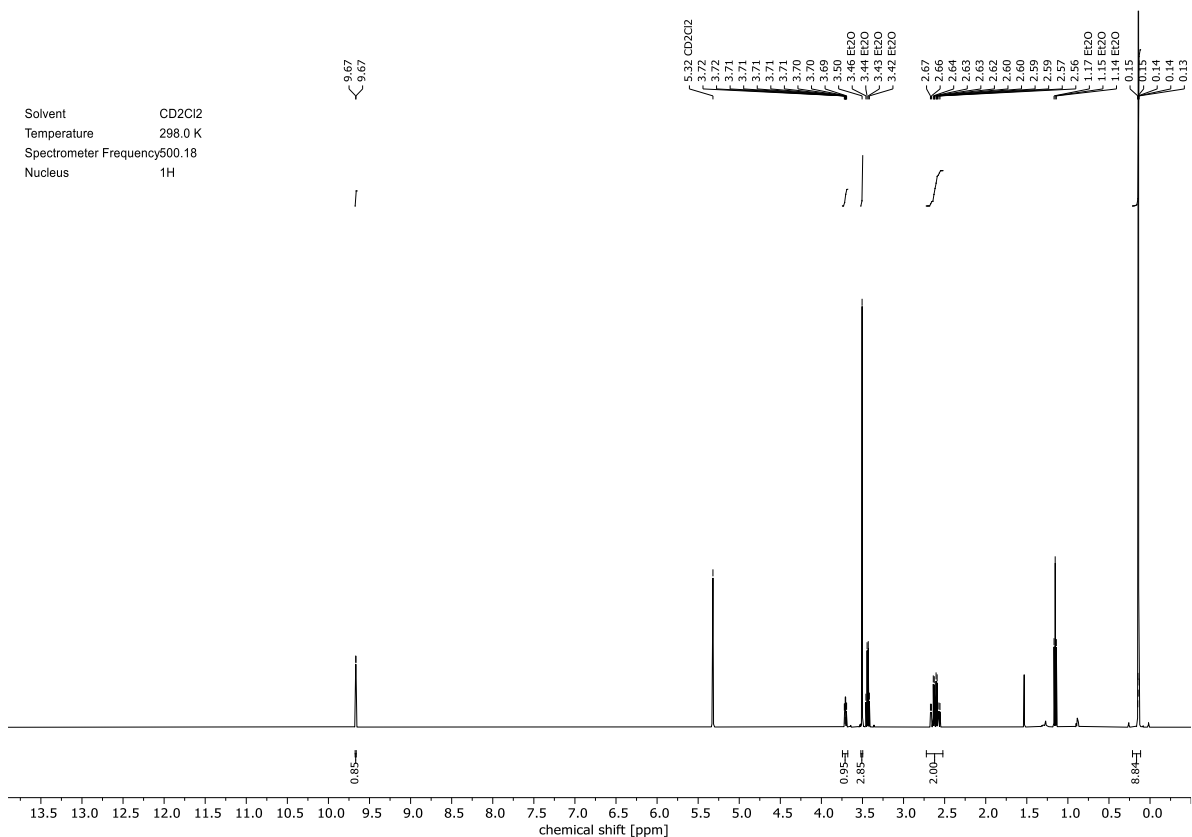
Chemical Formula: $C_9H_{18}O_2Si$
Exact Mass: 186.1076



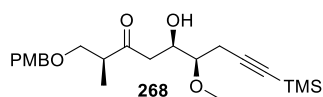
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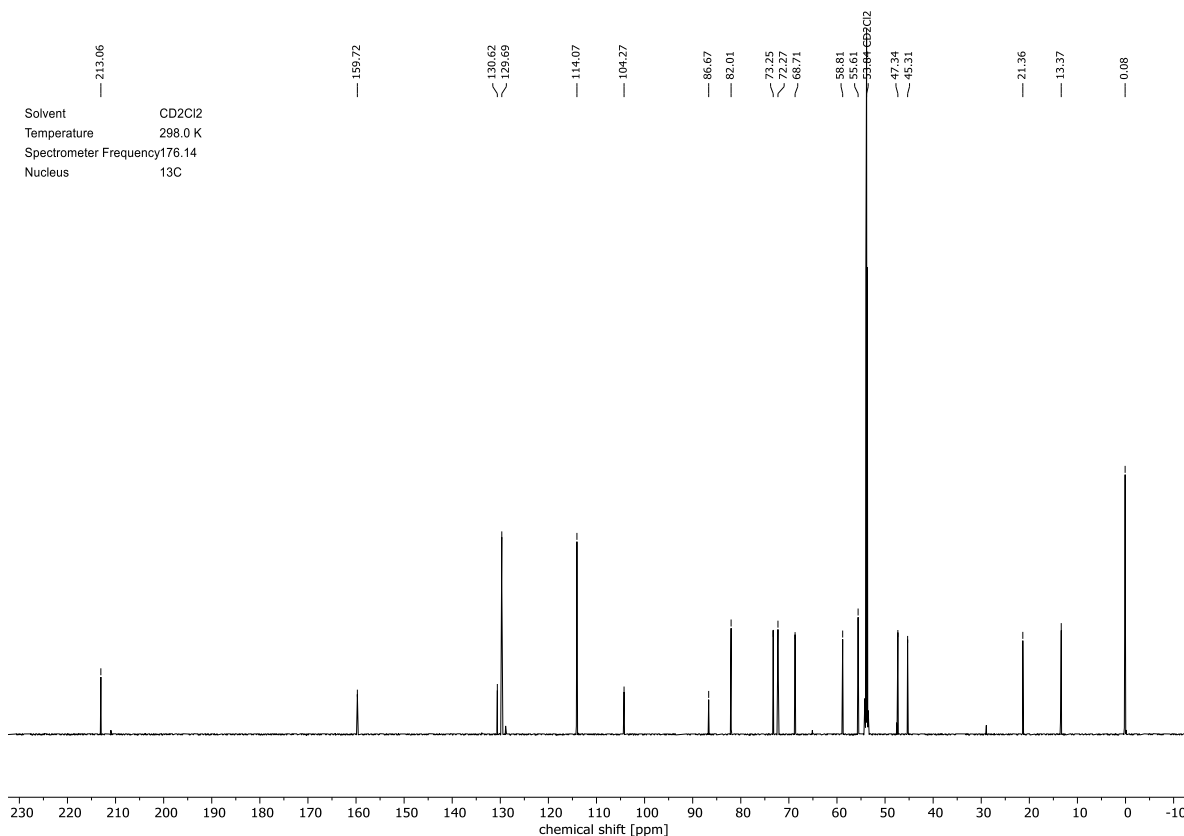
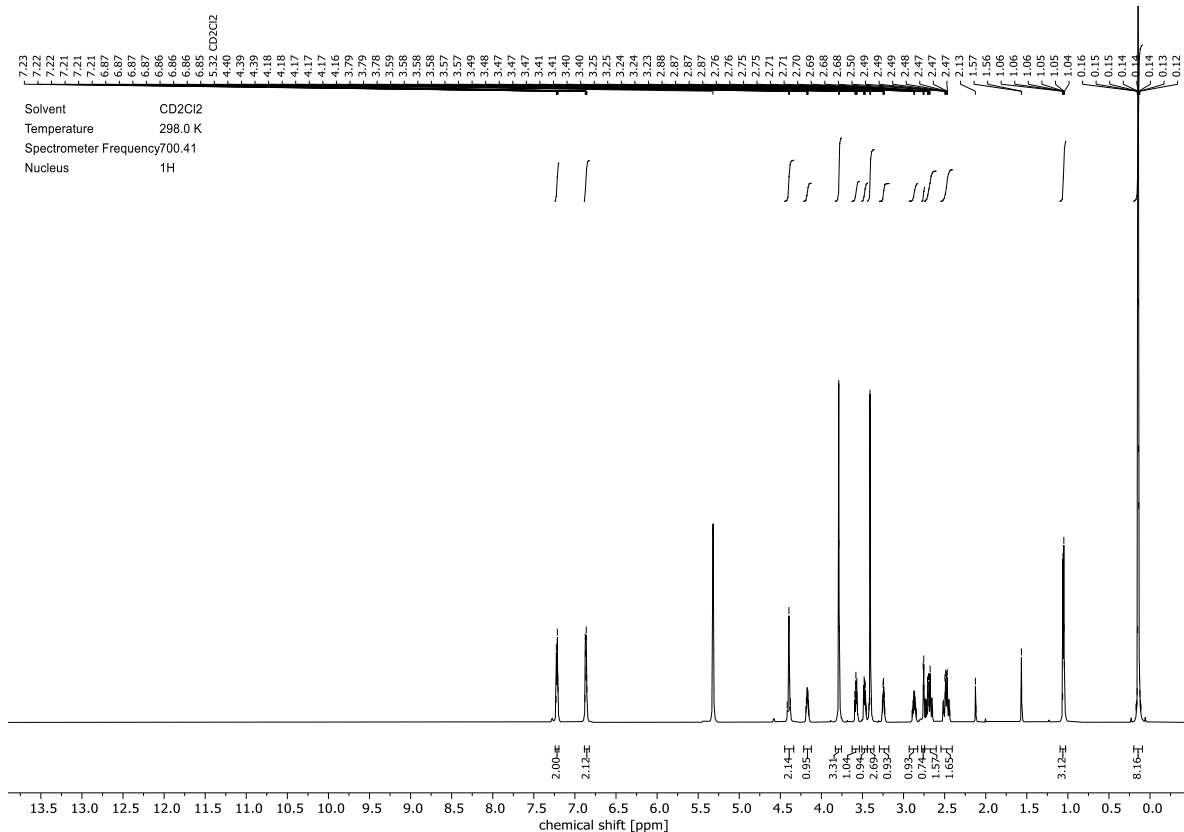
Chemical Formula: $C_9H_{16}O_2Si$
Exact Mass: 184.0920



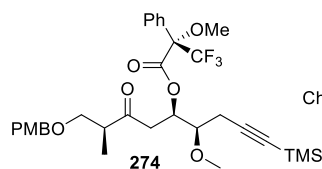
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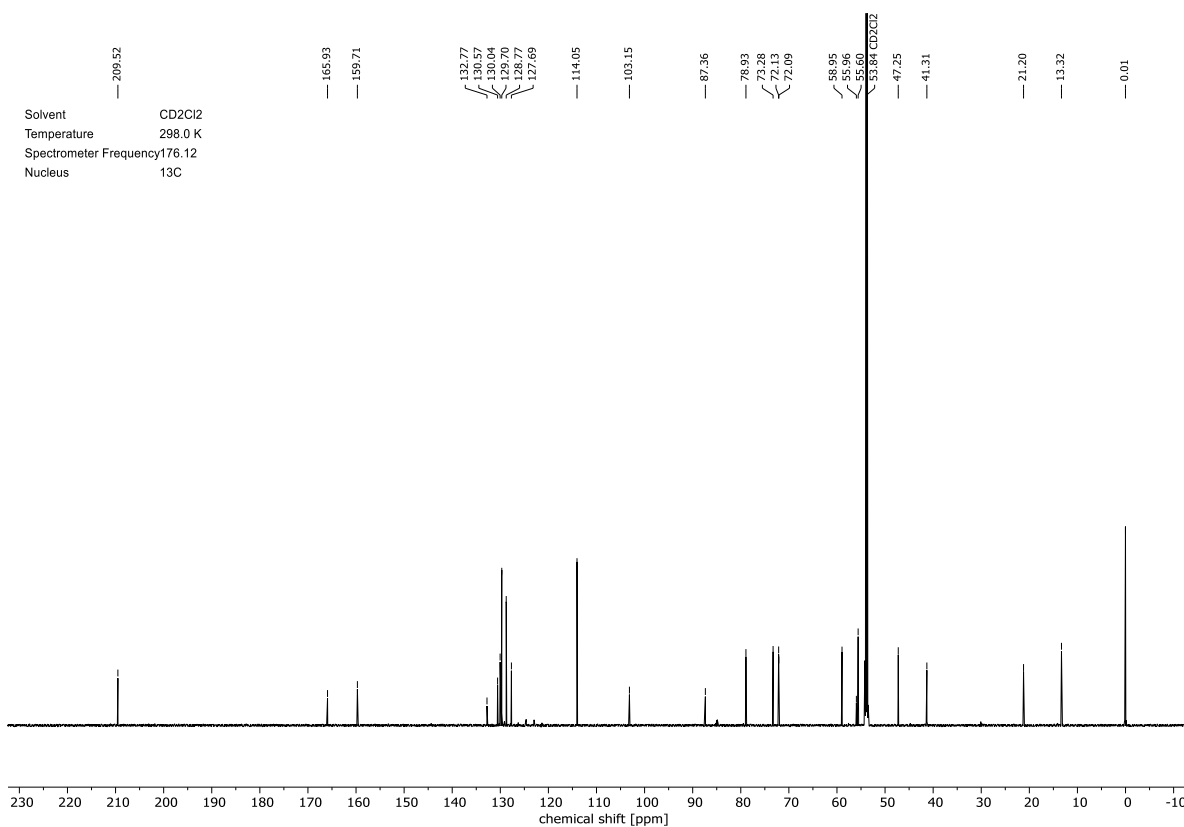
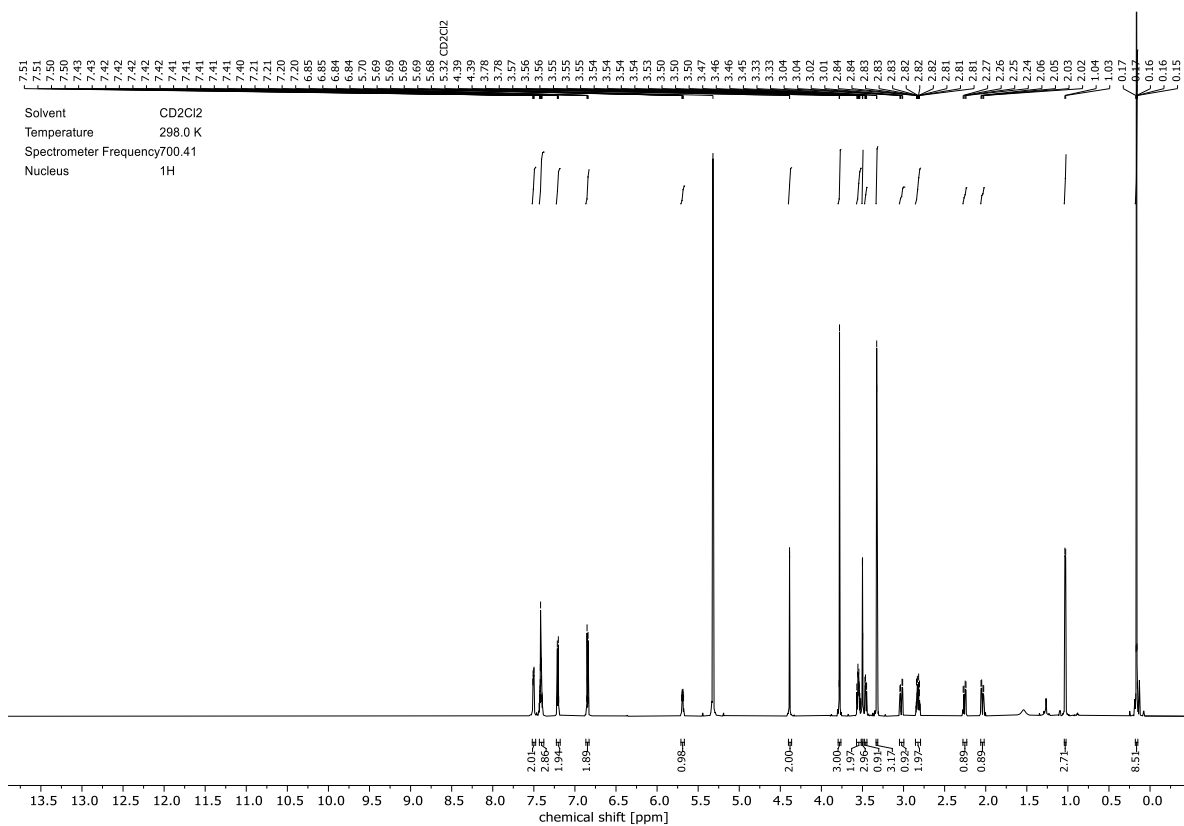
Chemical Formula: $C_{22}H_{34}O_5Si$
Exact Mass: 406.2176



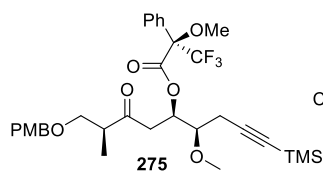
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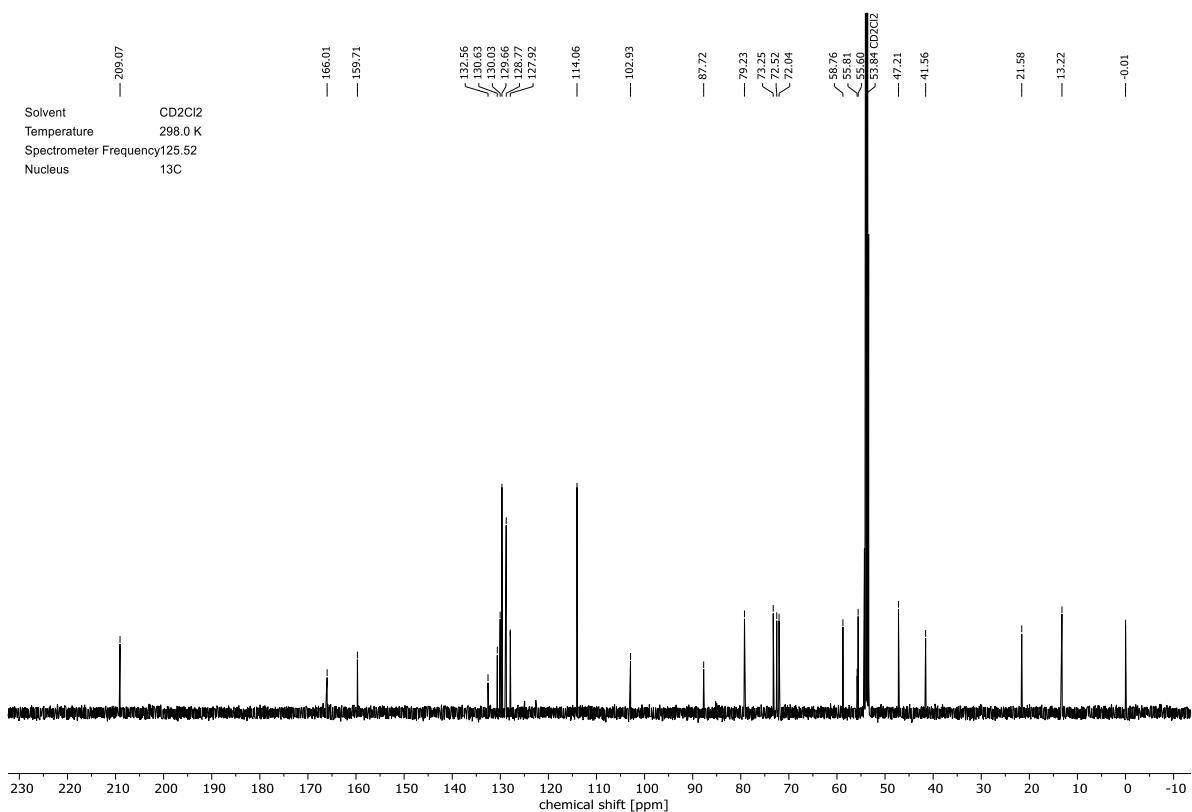
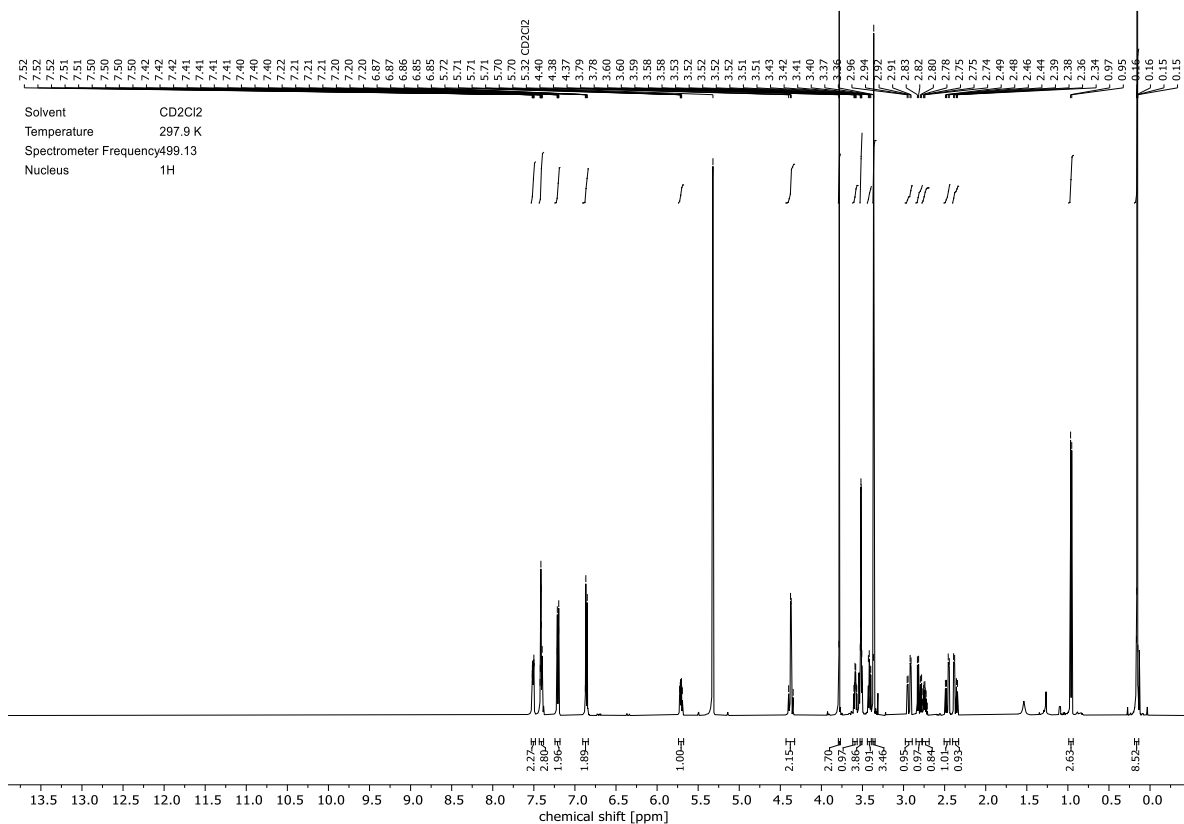
Chemical Formula: $C_{32}H_{41}F_3O_7Si$
Exact Mass: 622.2574



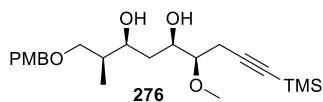
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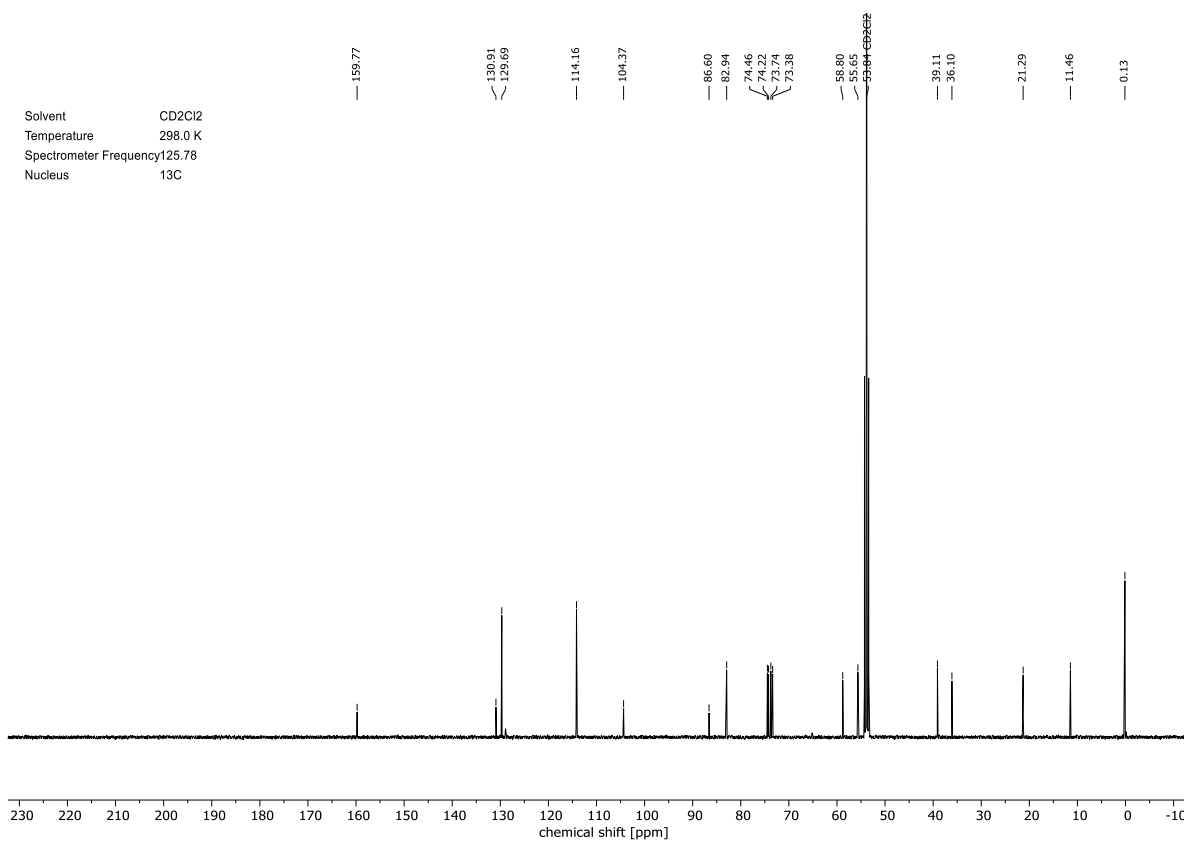
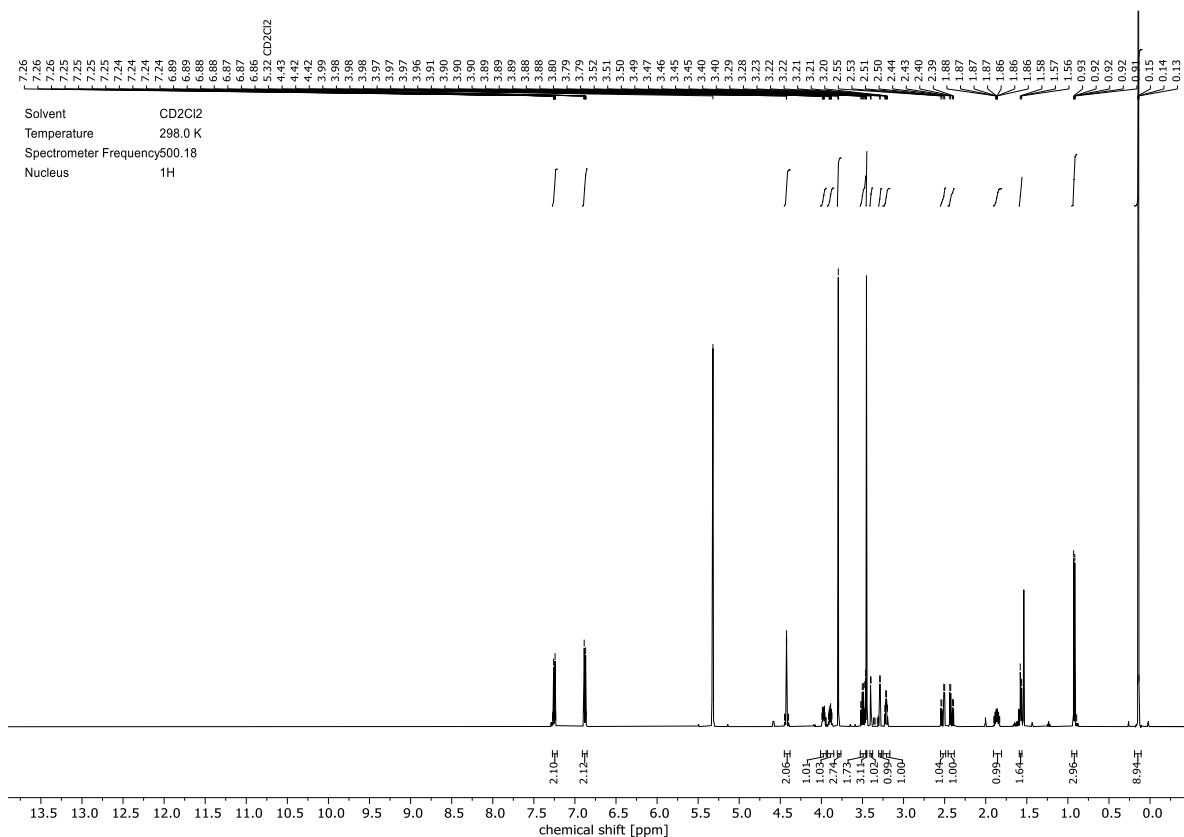
Chemical Formula: $C_{32}H_{41}F_3O_7Si$
Exact Mass: 622.2574



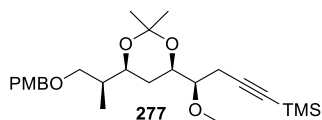
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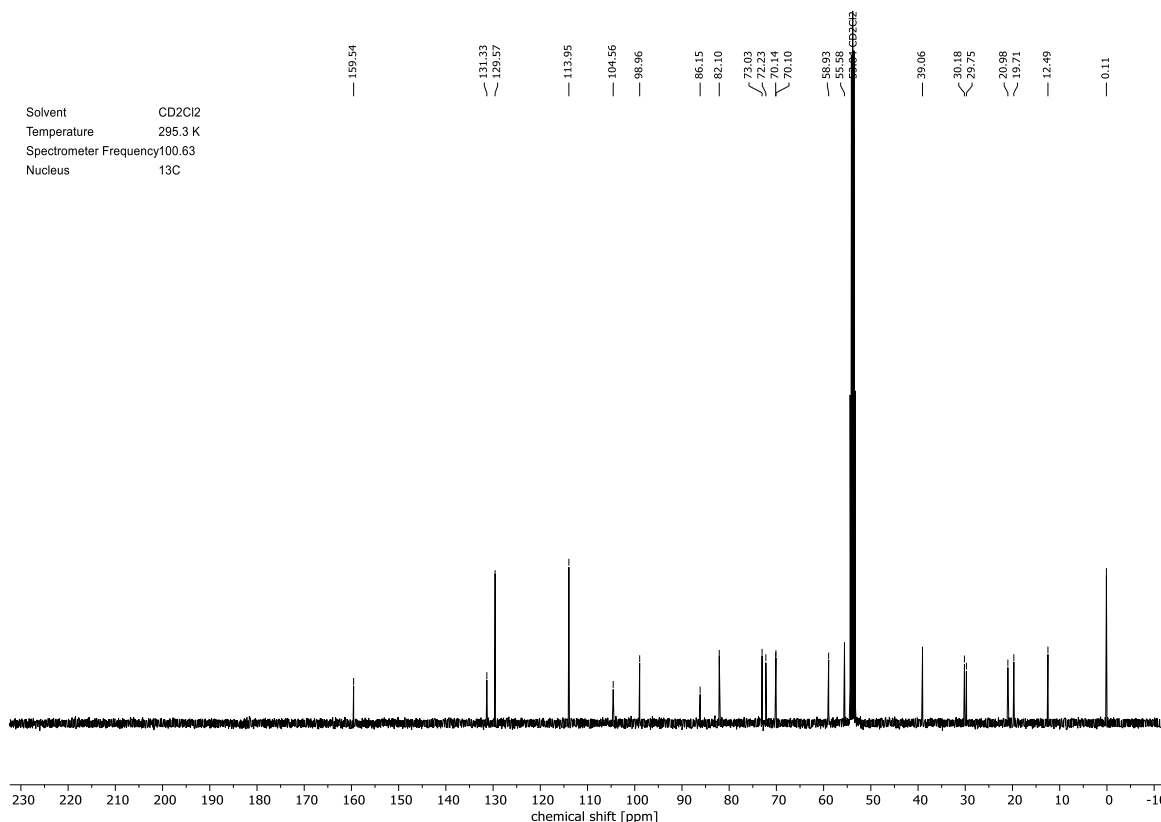
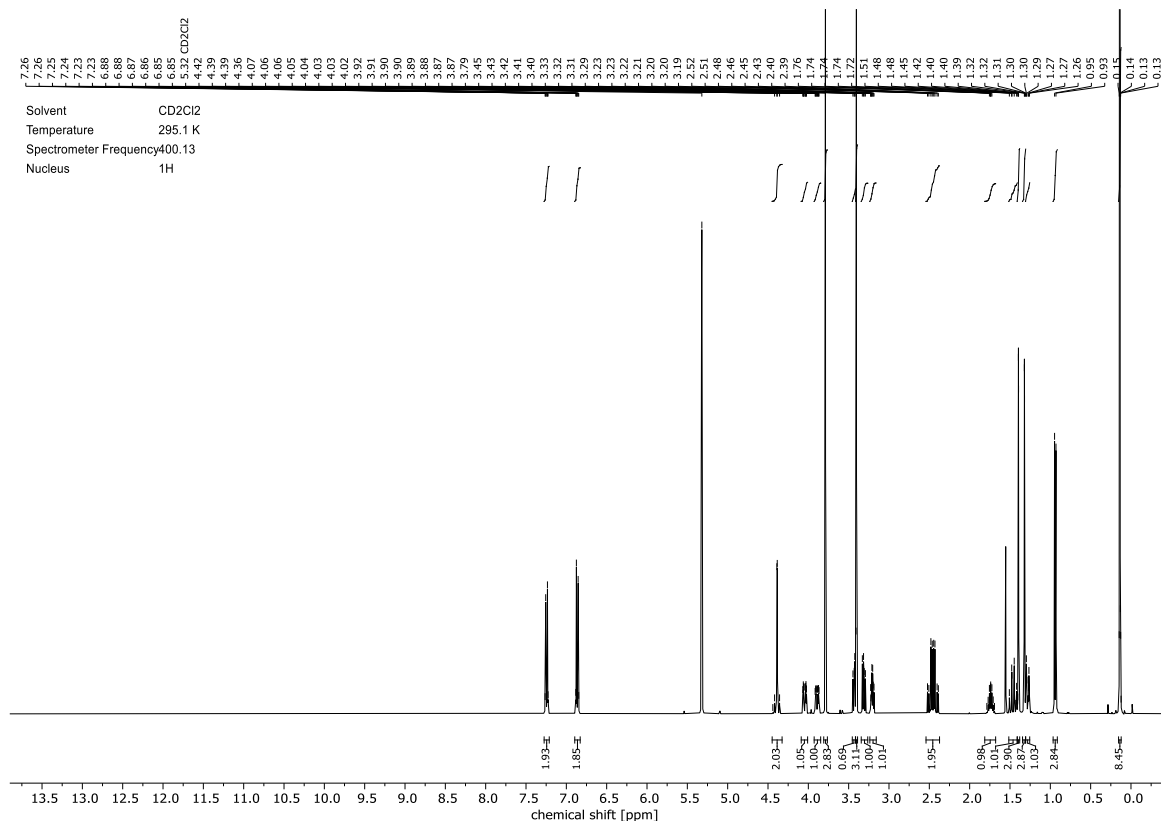
Chemical Formula: $C_{22}H_{36}O_5Si$
Exact Mass: 408.2332



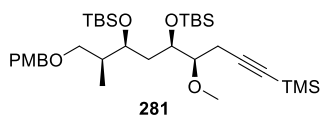
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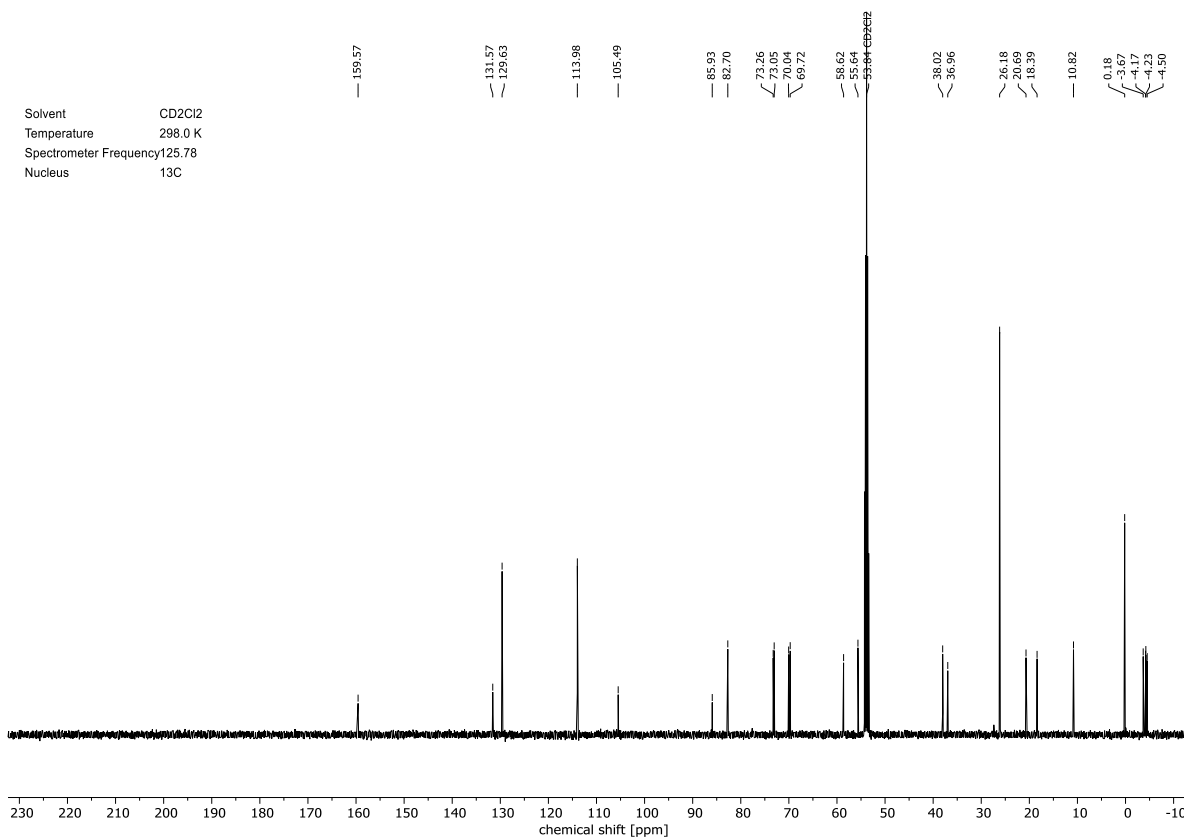
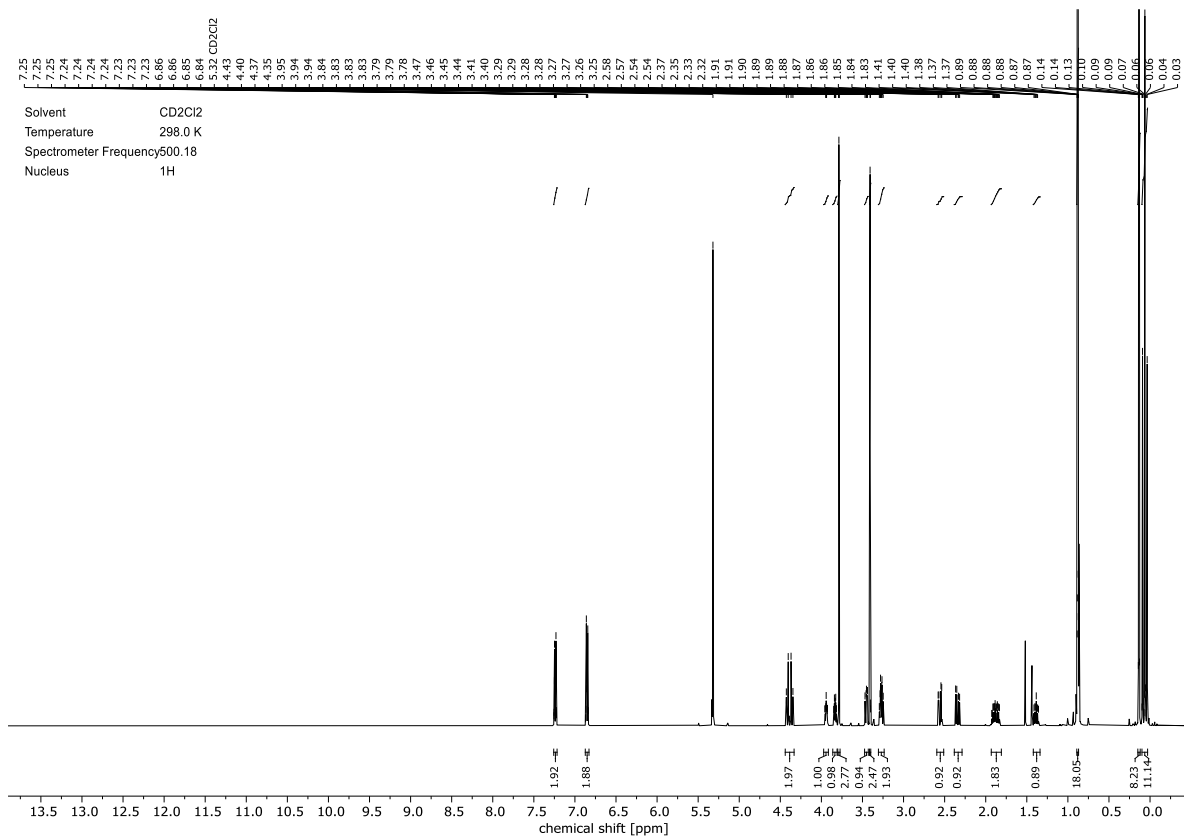
Chemical Formula: $C_{25}H_{40}O_5Si$
Exact Mass: 448.2645

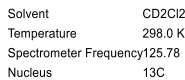
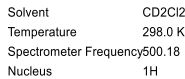
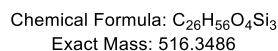


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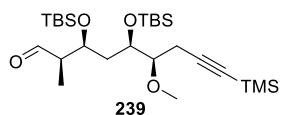


Chemical Formula: $C_{34}H_{64}O_5Si_3$
Exact Mass: 636.4062

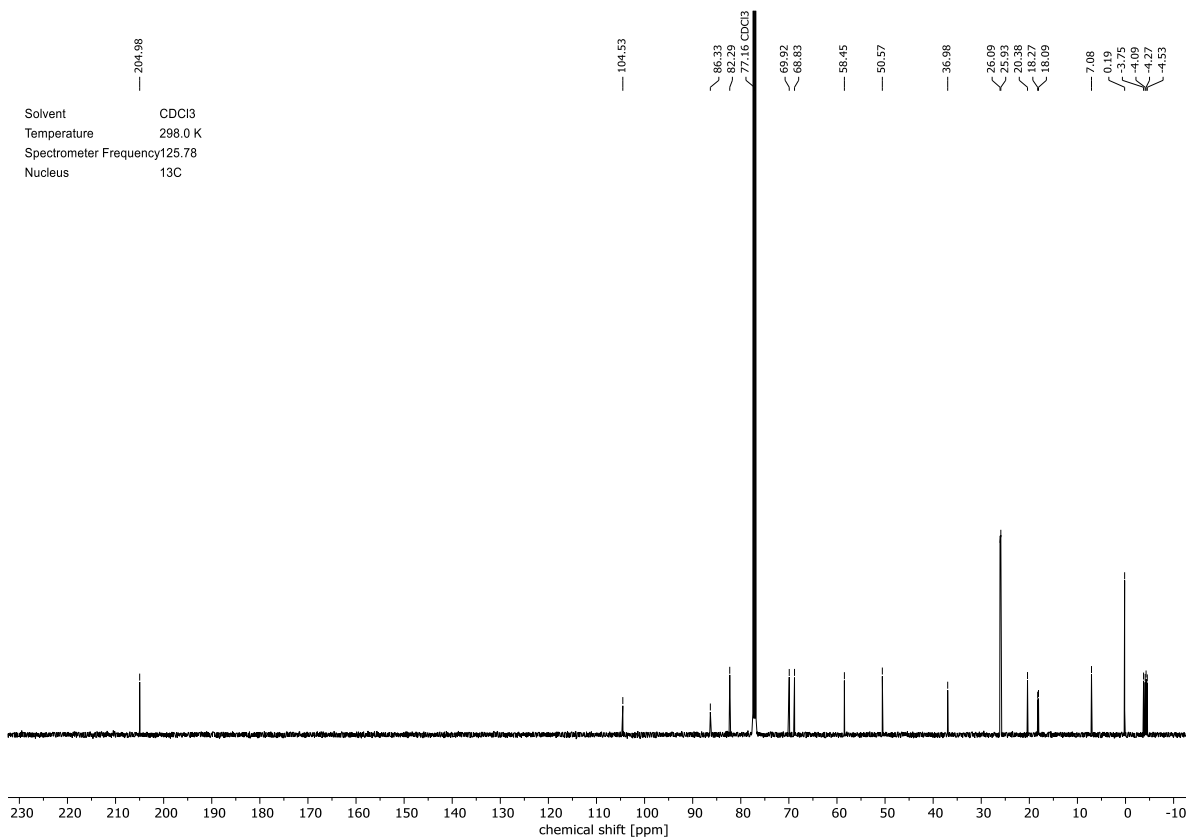
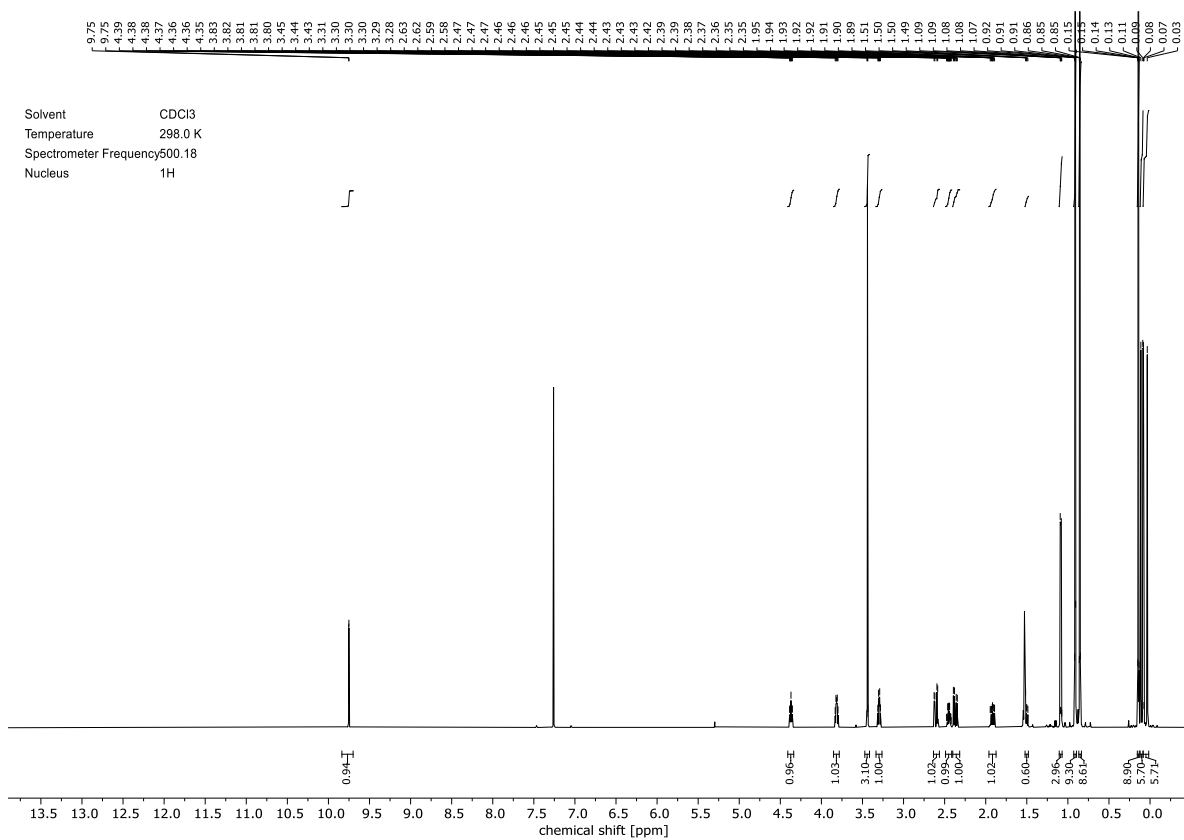




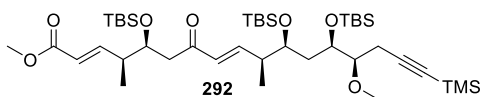
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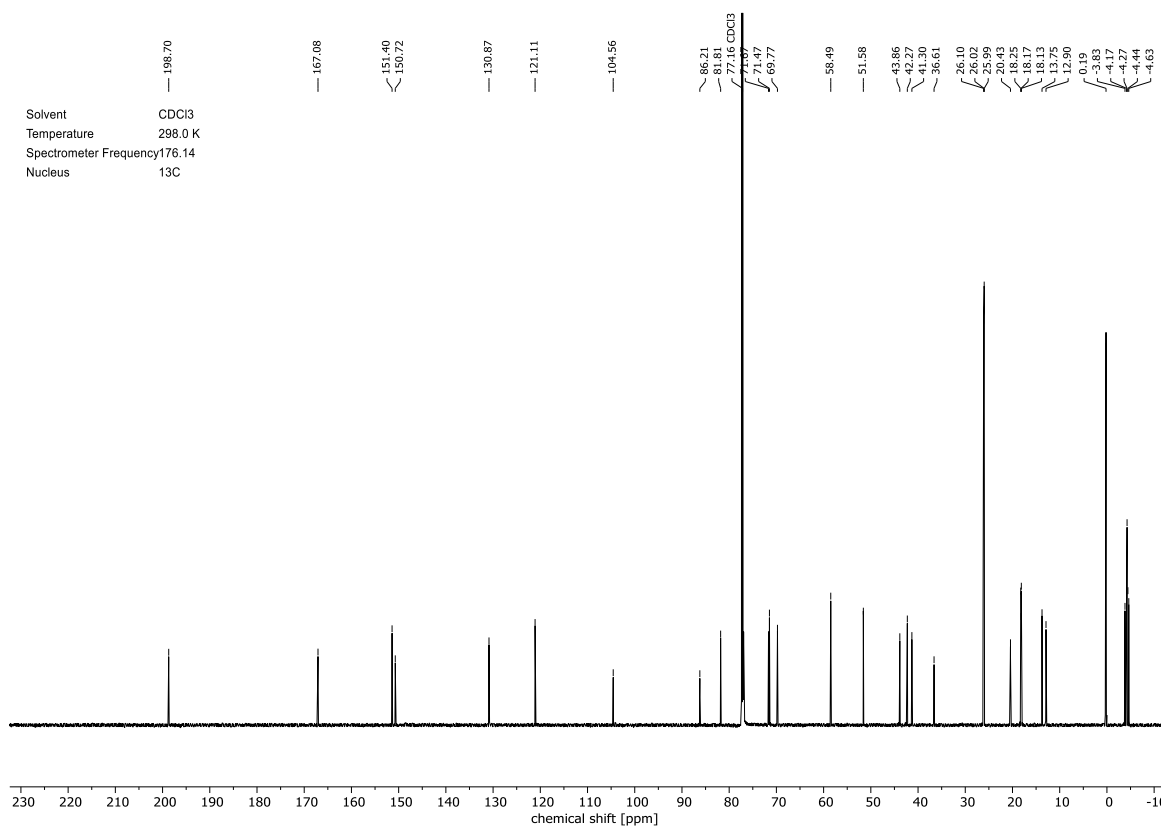
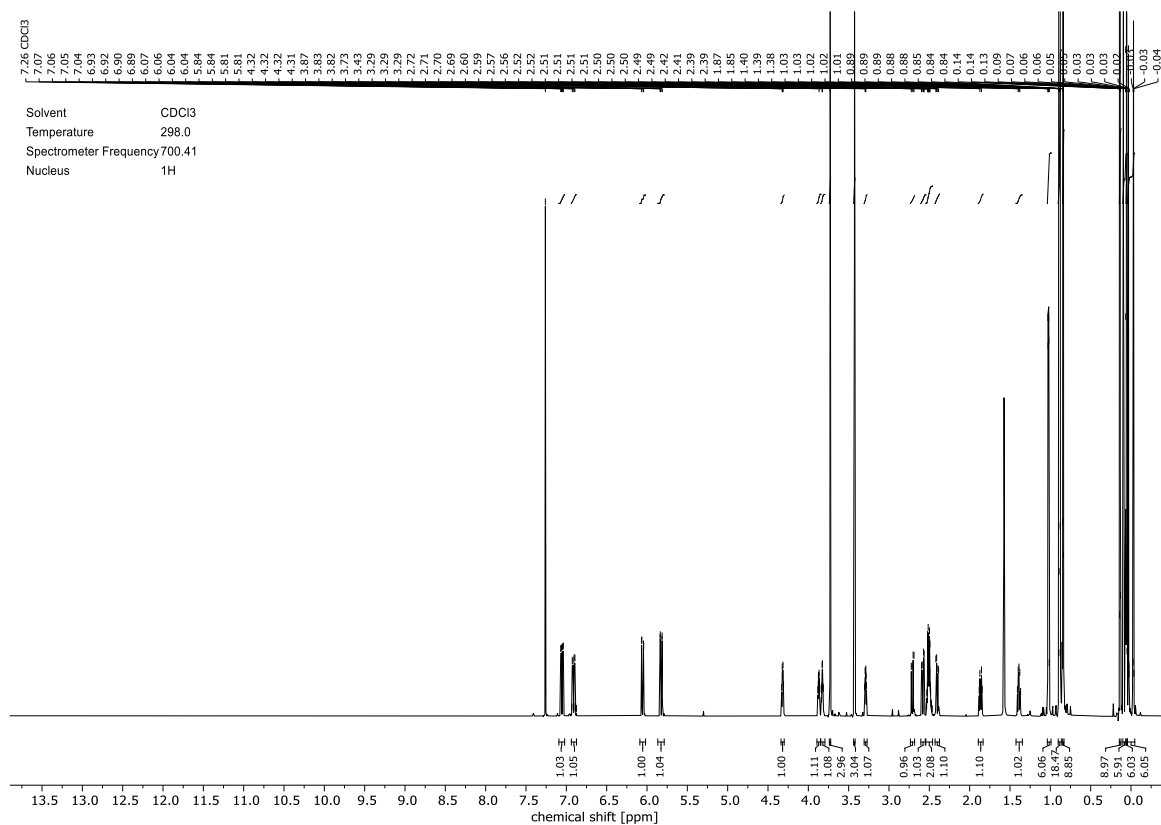
Chemical Formula: $C_{26}H_{54}O_4Si_3$
Exact Mass: 514.3330



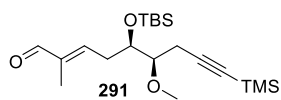
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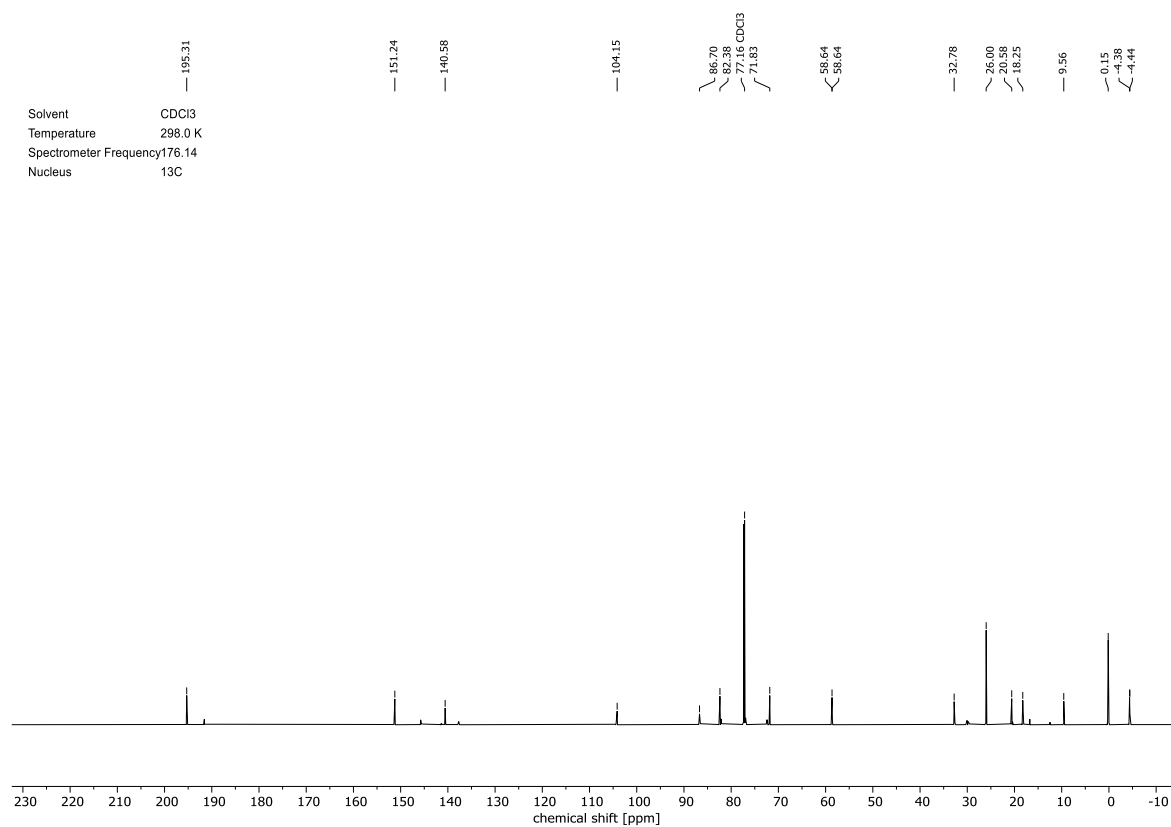
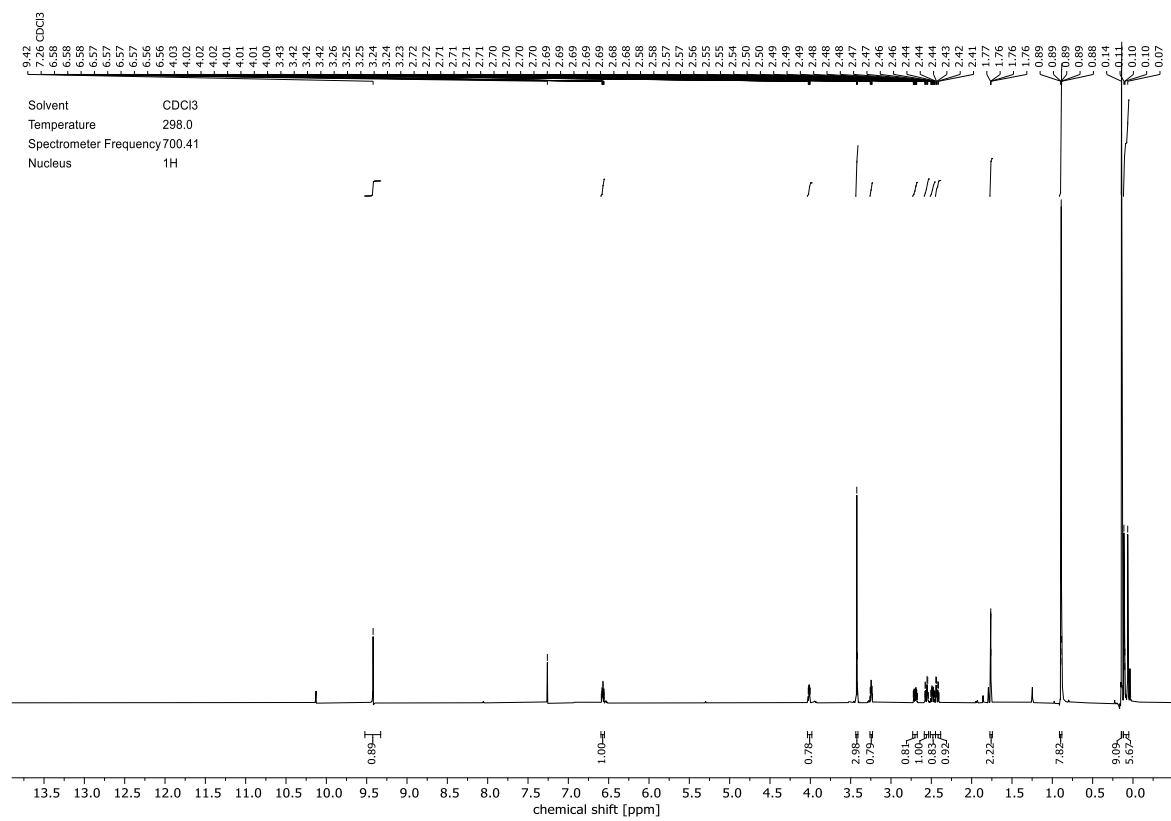
Chemical Formula: $C_{42}H_{82}O_7Si_4$
Exact Mass: 810.5138



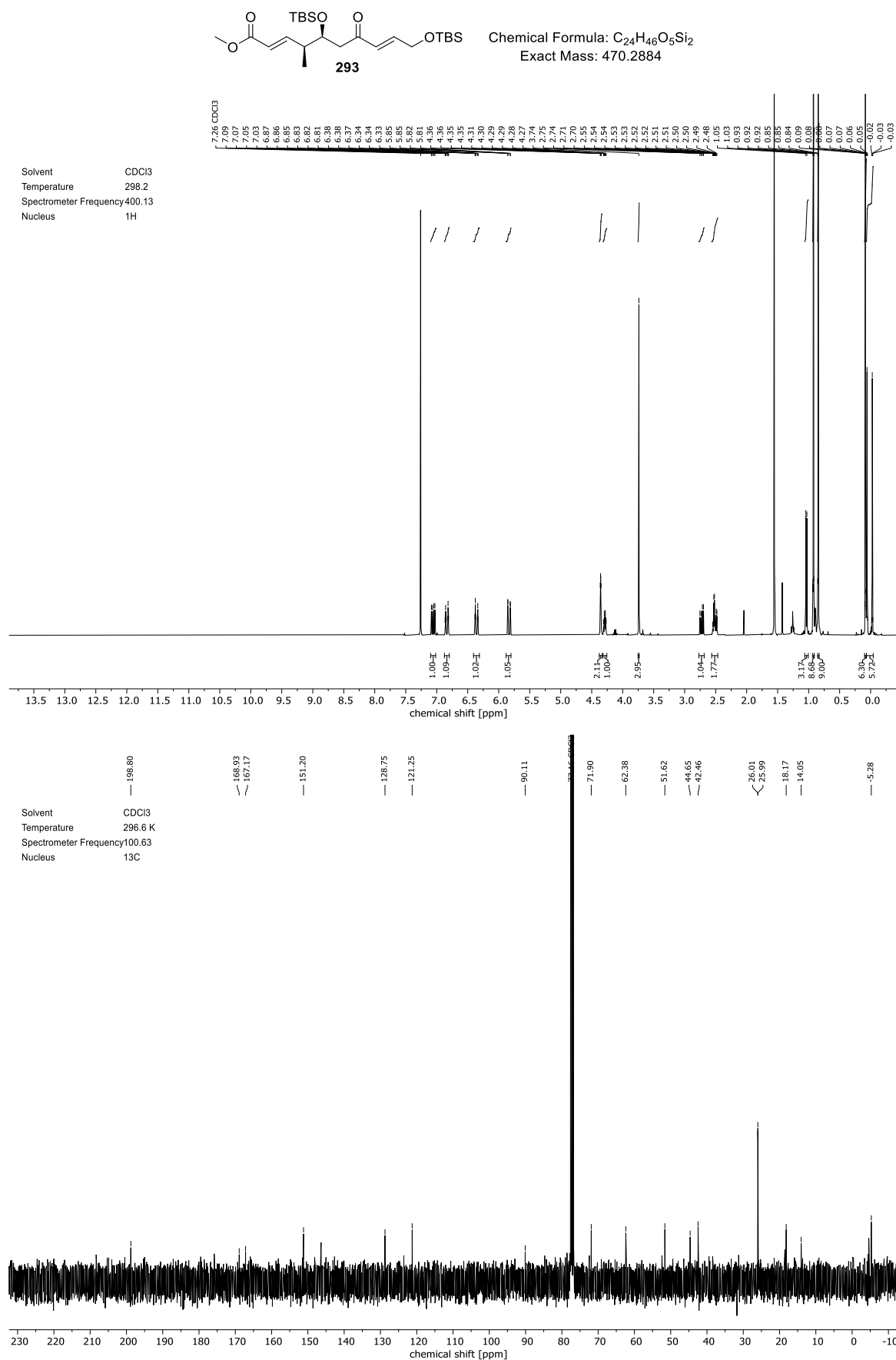
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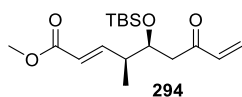
Chemical Formula: $C_{20}H_{38}O_3Si_2$
Exact Mass: 382.2359



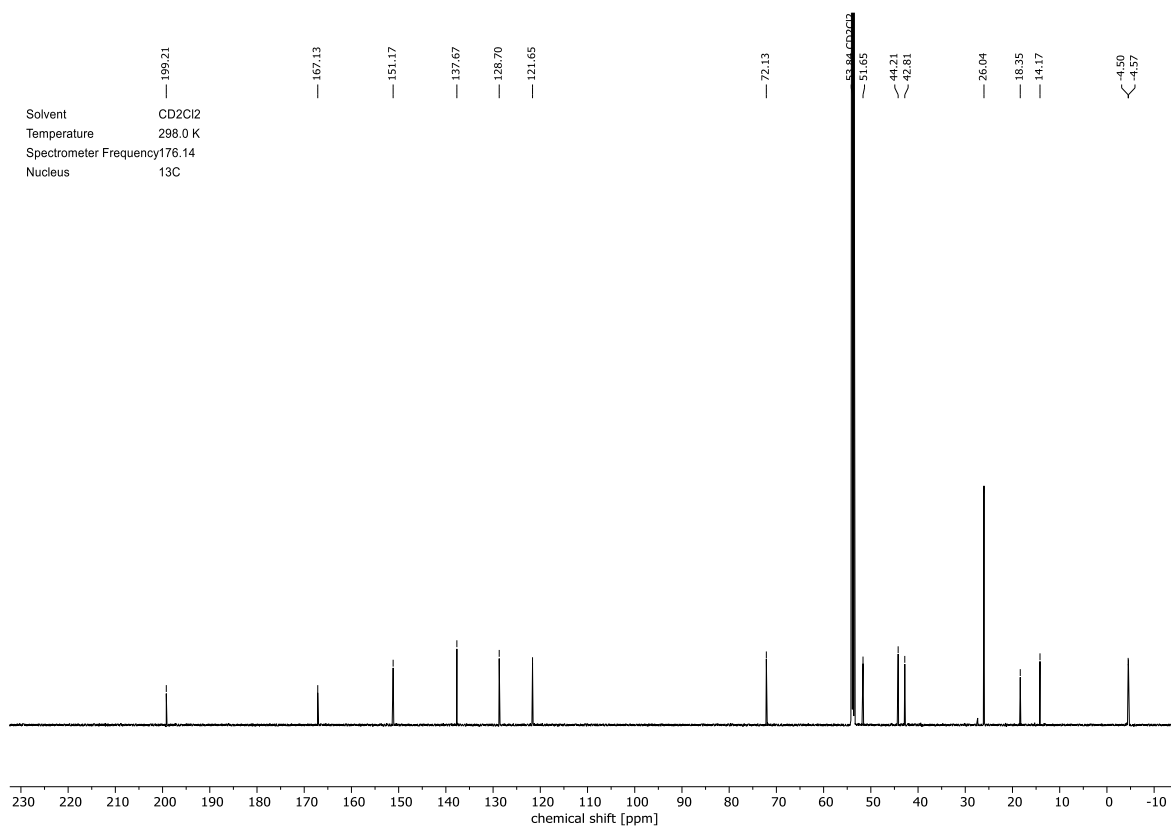
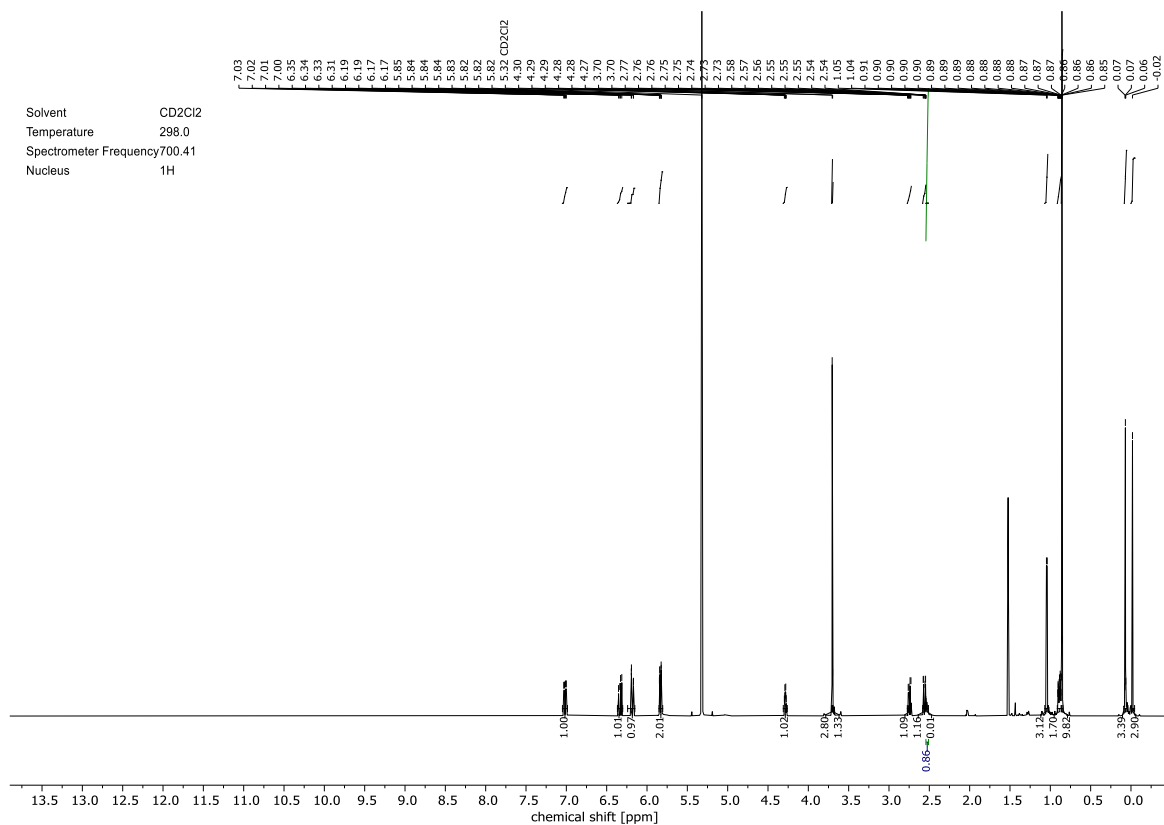
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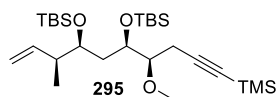
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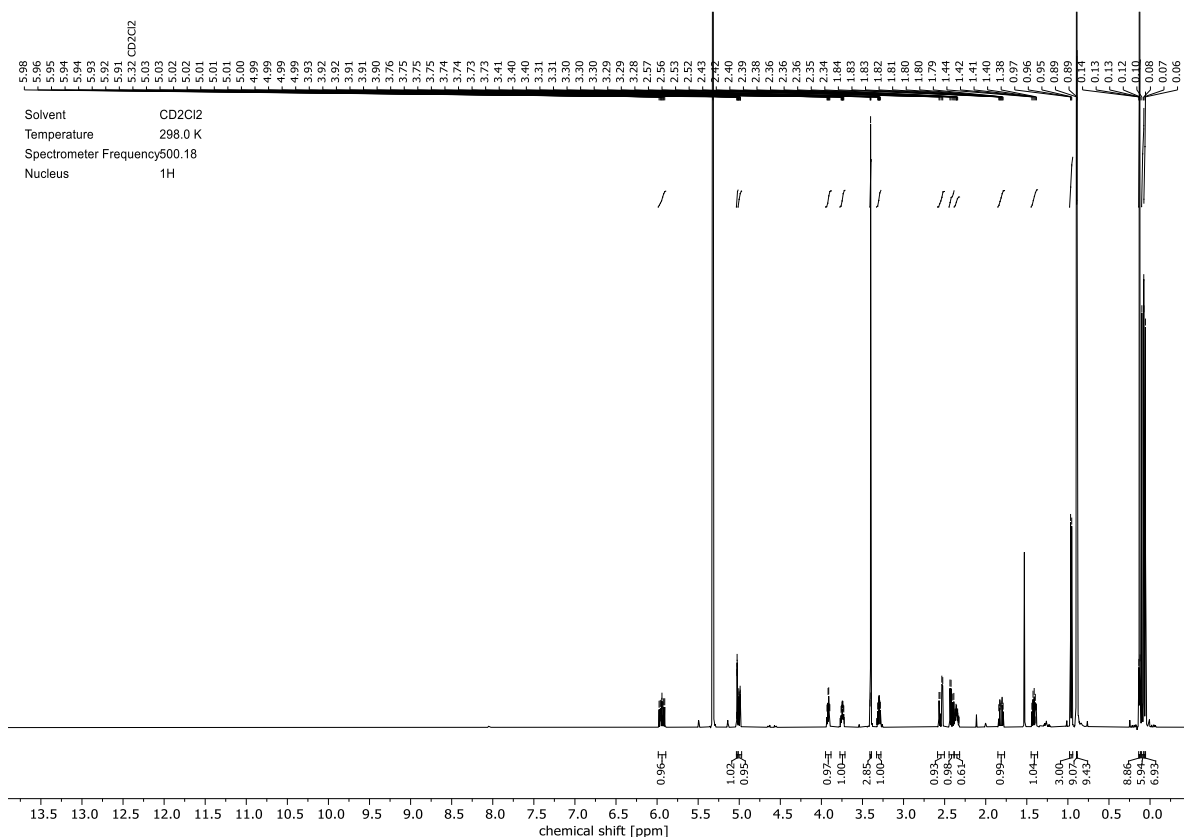
Chemical Formula: $C_{17}H_{30}O_4Si$
Exact Mass: 326.1913



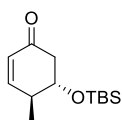
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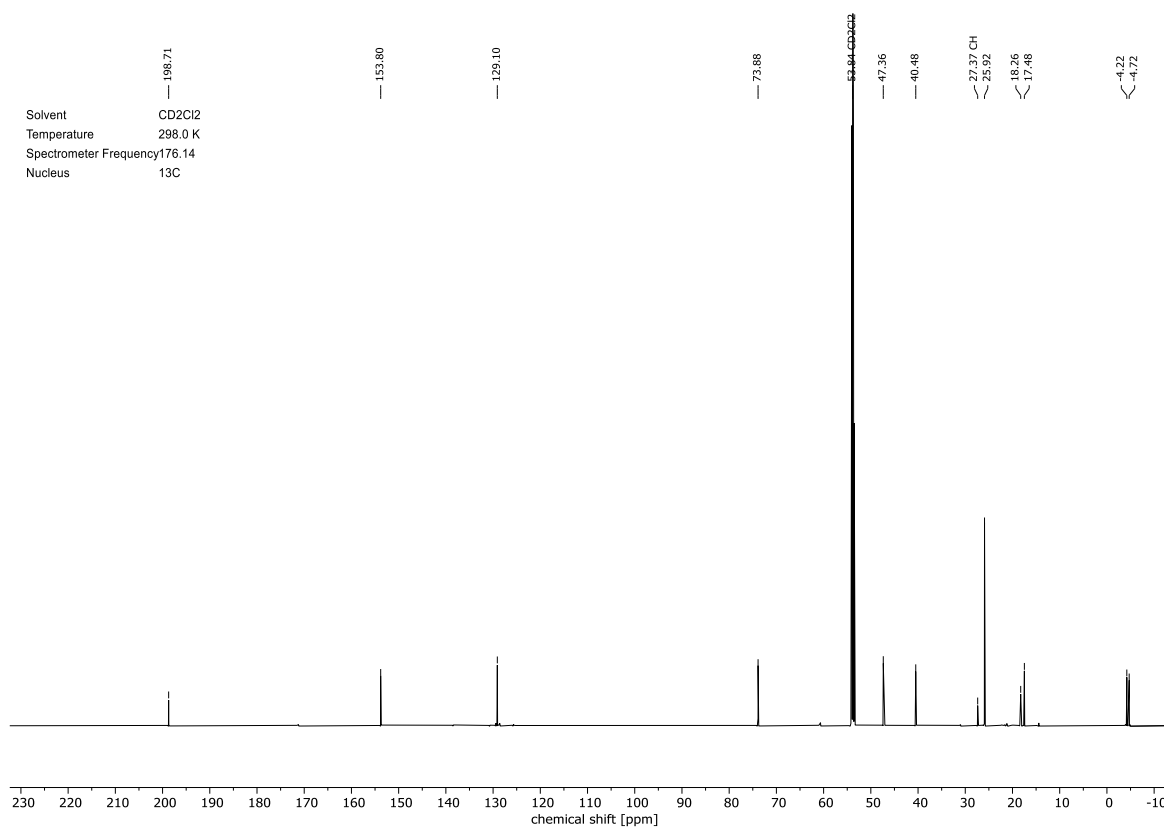
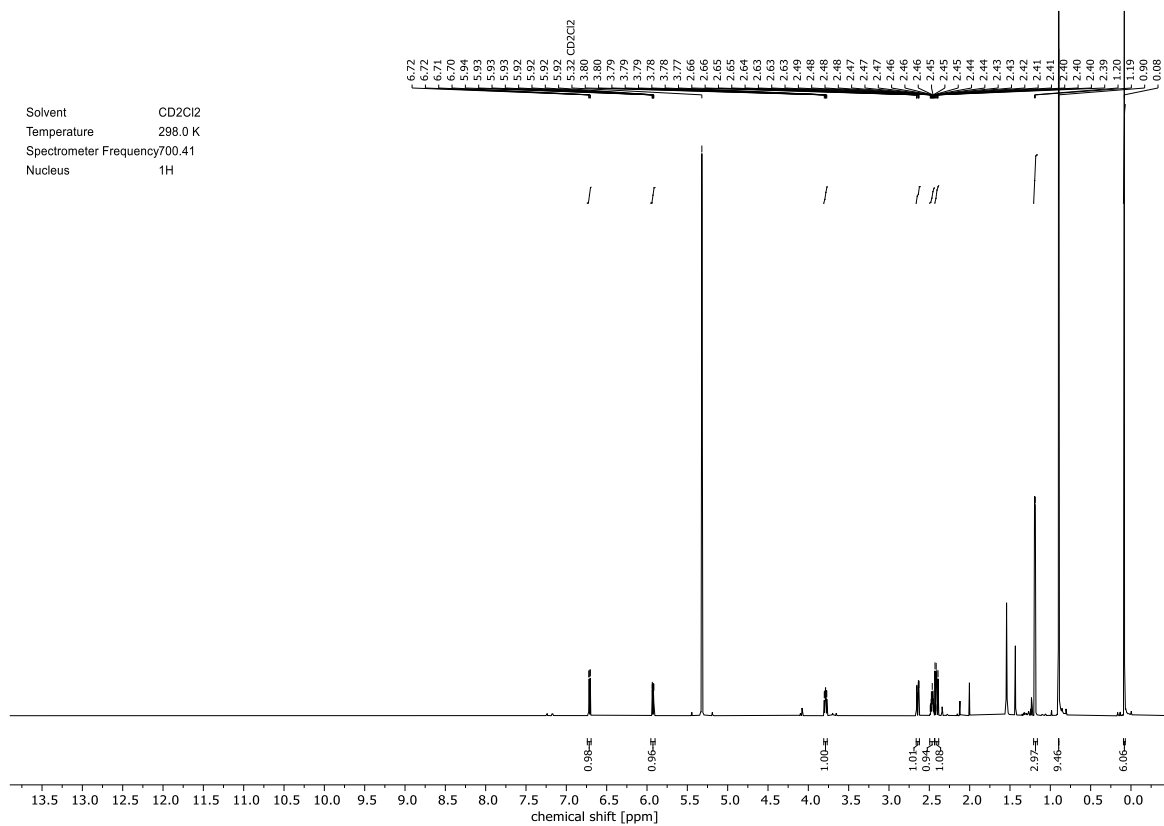
Chemical Formula: $C_{27}H_{56}O_3Si_3$
Exact Mass: 512.3537



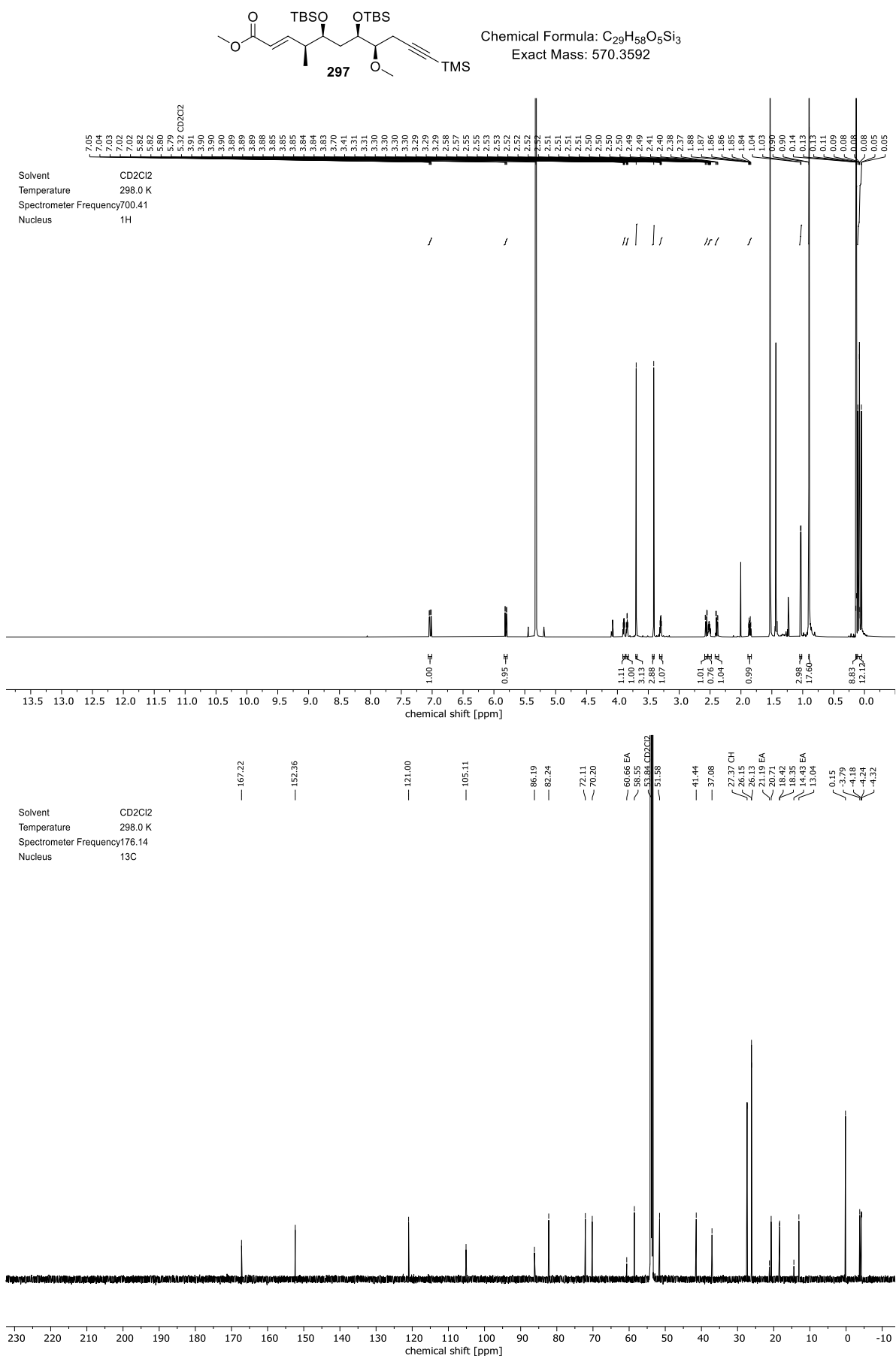
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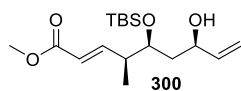
296
Chemical Formula: $C_{13}H_{24}O_2Si$
Exact Mass: 240.1546



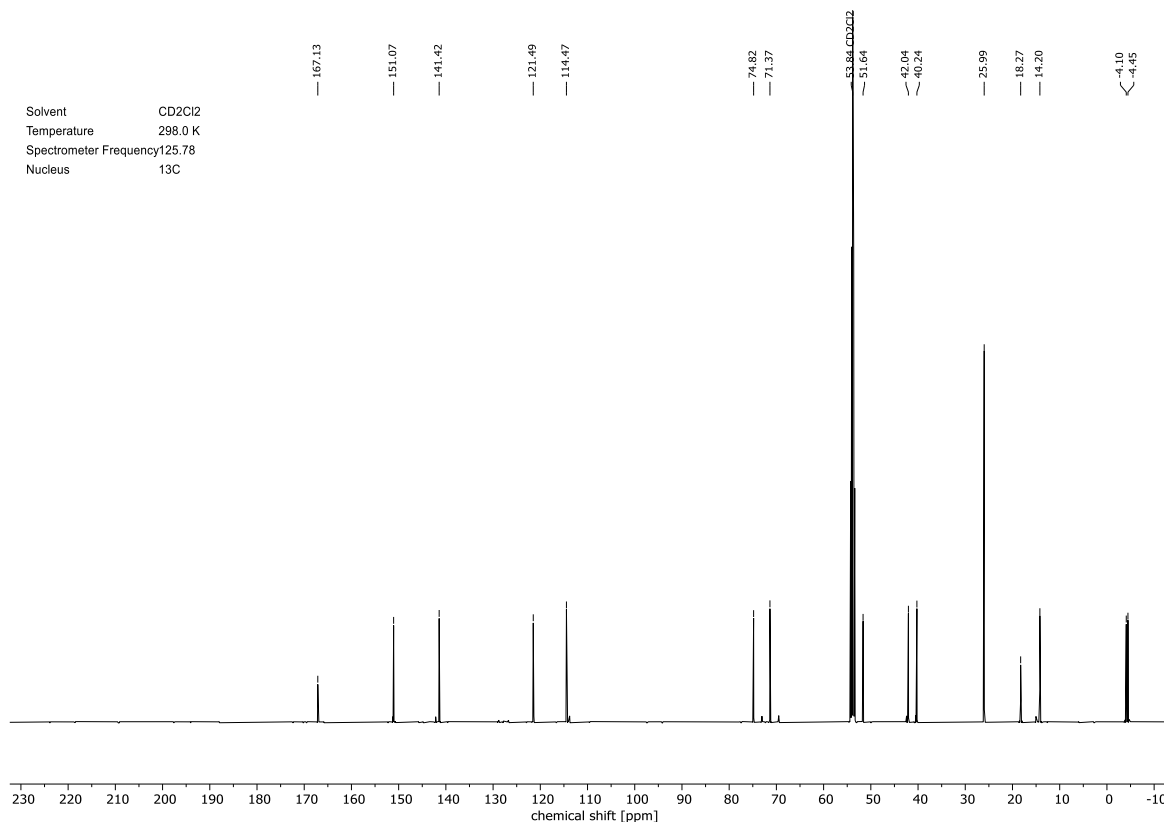
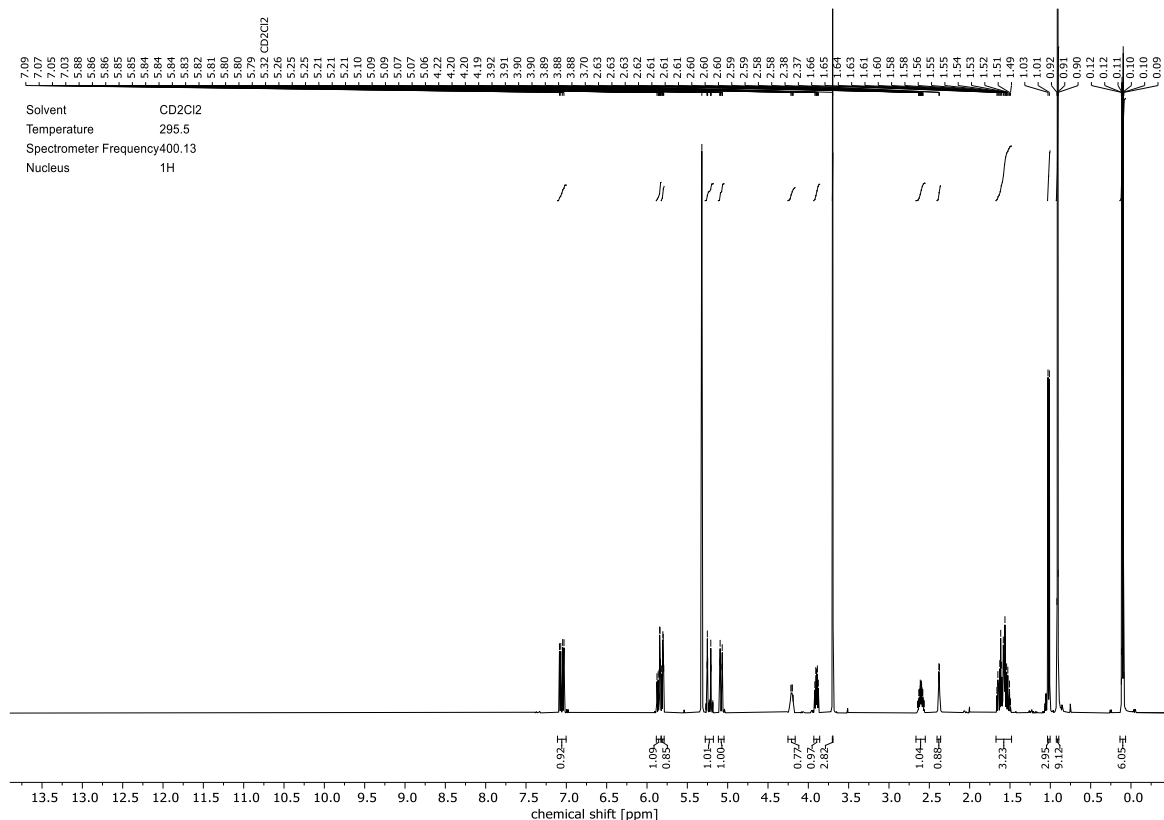
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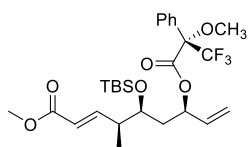
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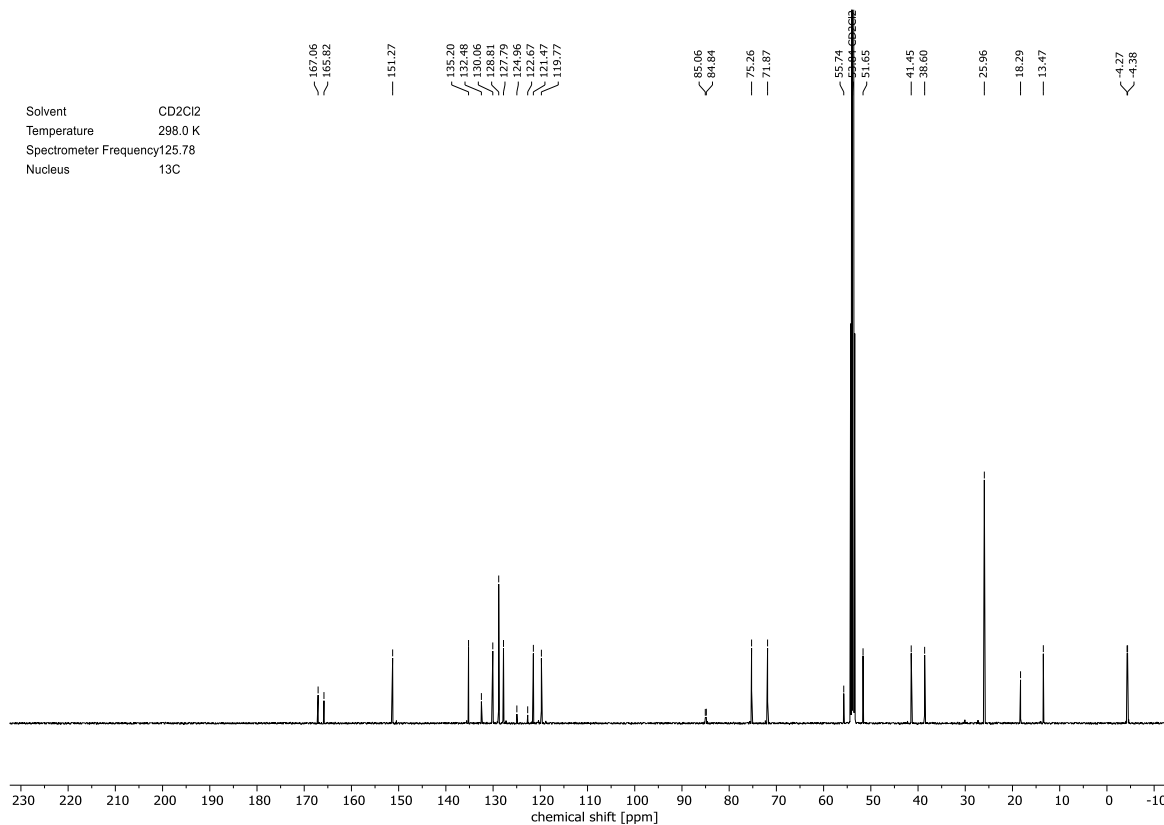
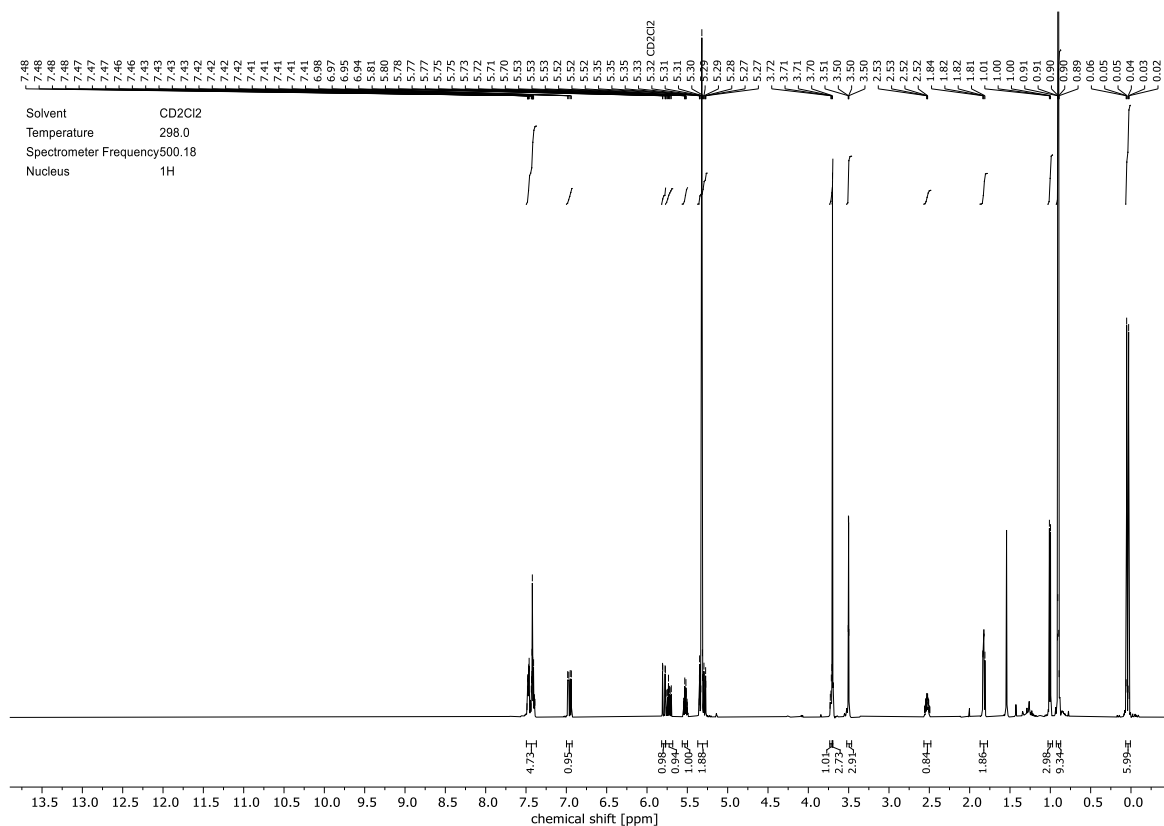
Chemical Formula: $C_{17}H_{32}O_4Si$
Exact Mass: 328.2070

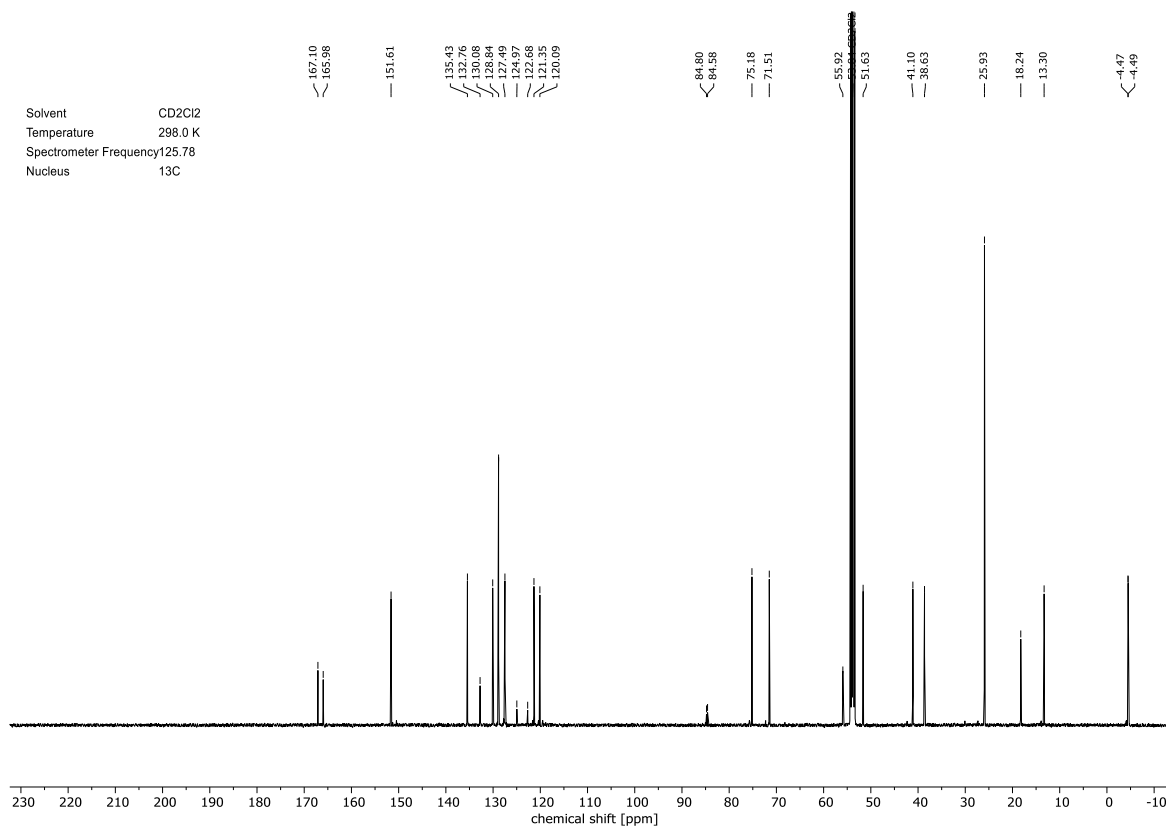
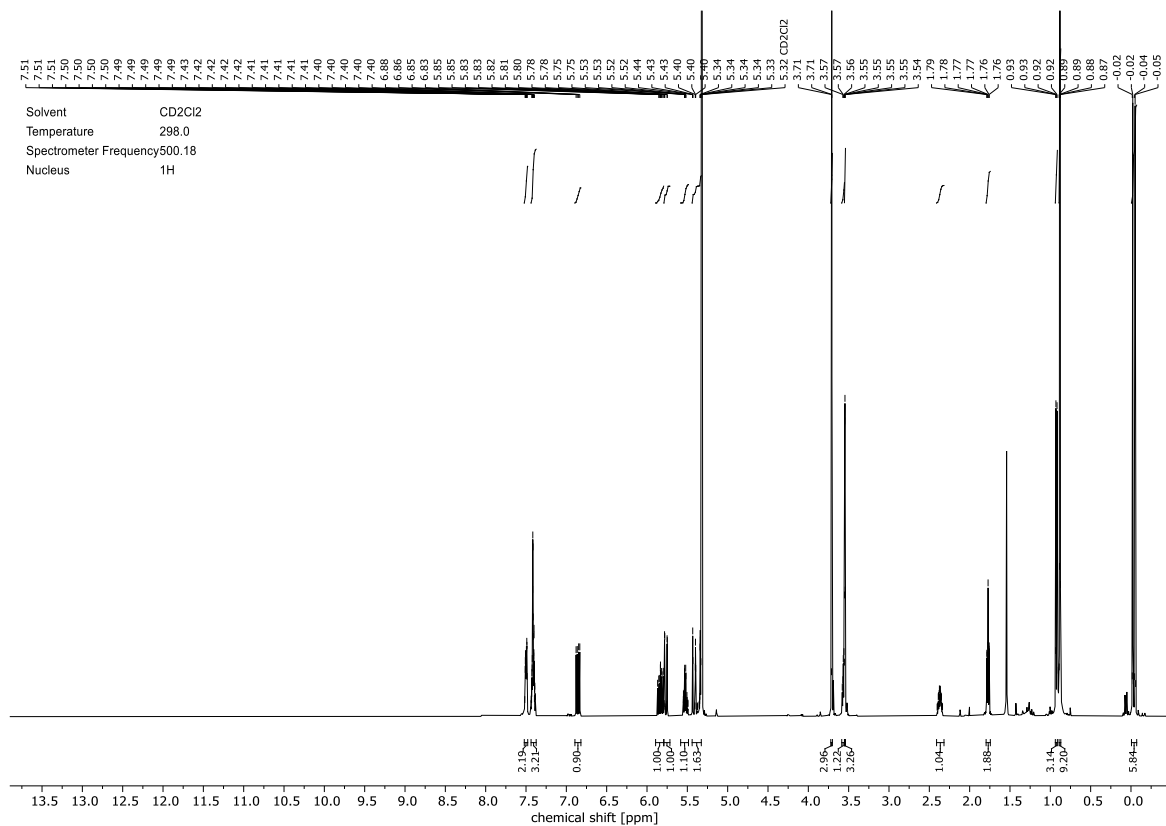
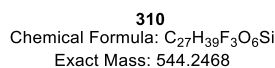


6 Copies of NMR Spectra

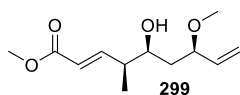


309
Chemical Formula: $C_{27}H_{39}F_3O_6Si$
Exact Mass: 544.2468

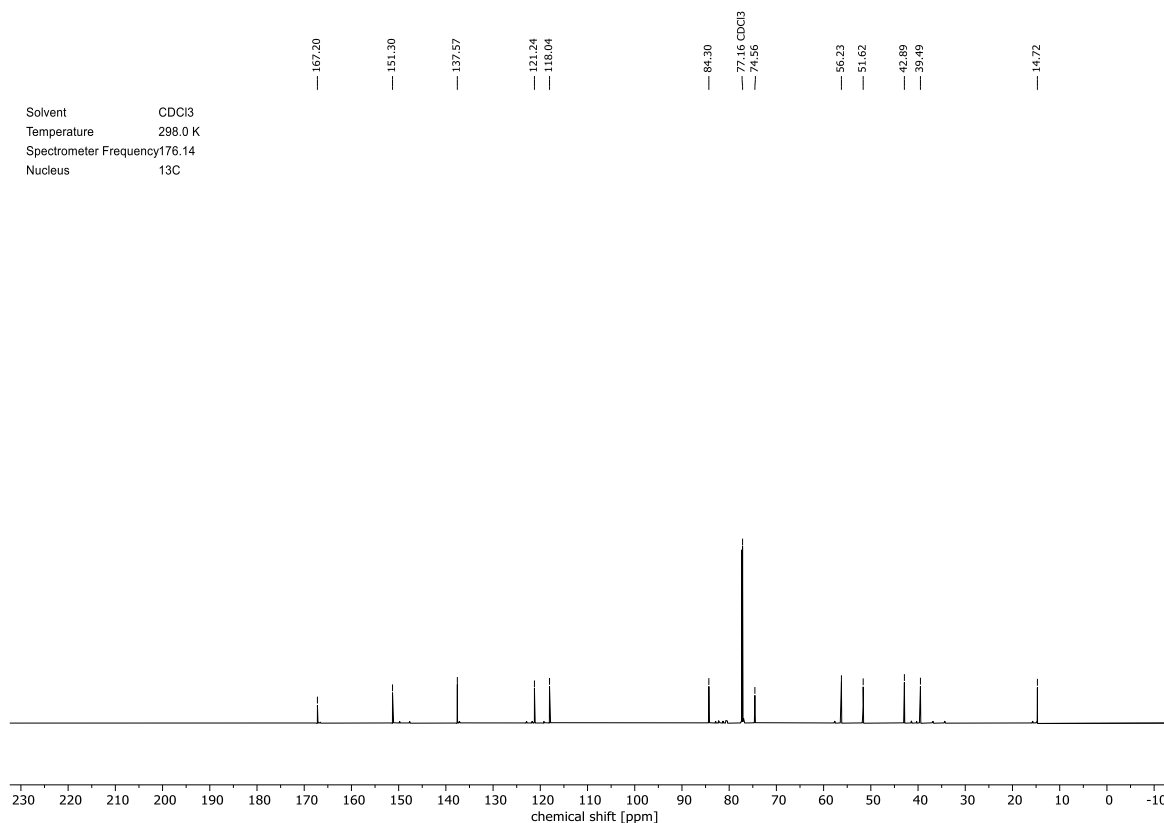
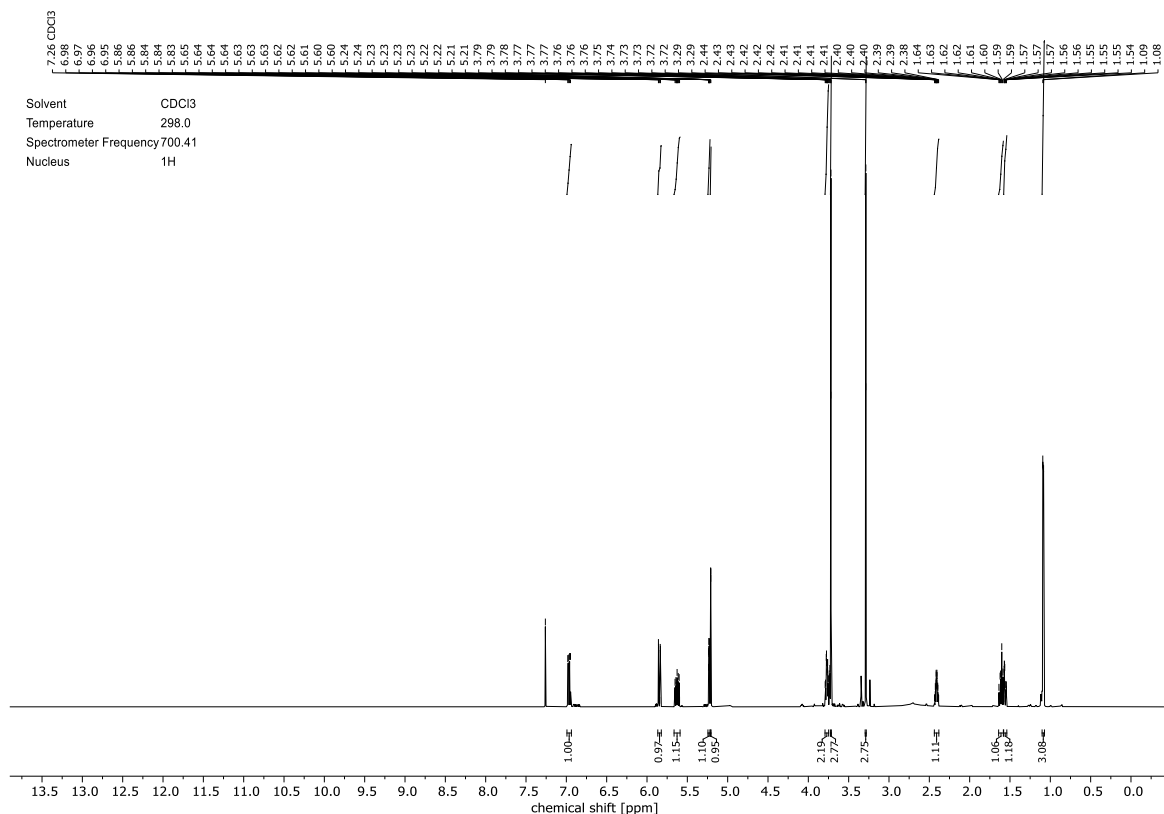




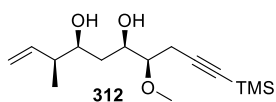
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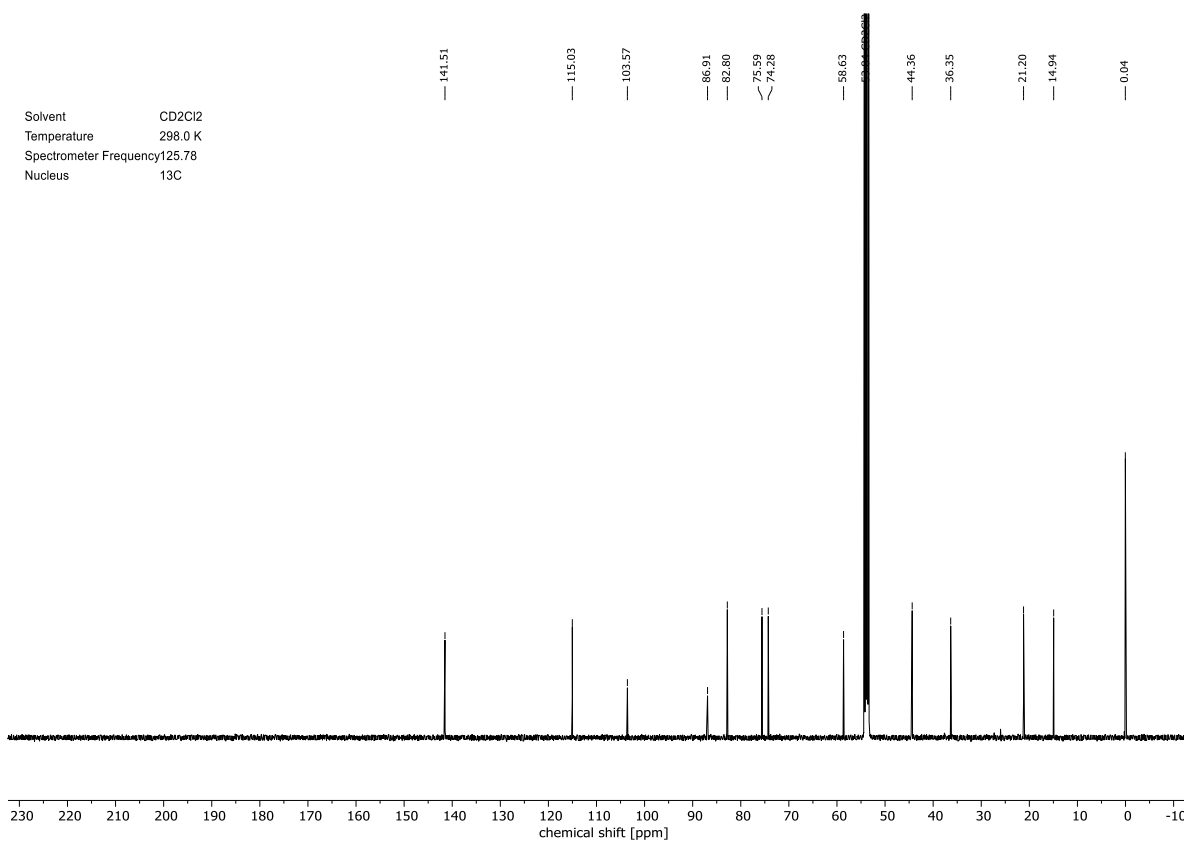
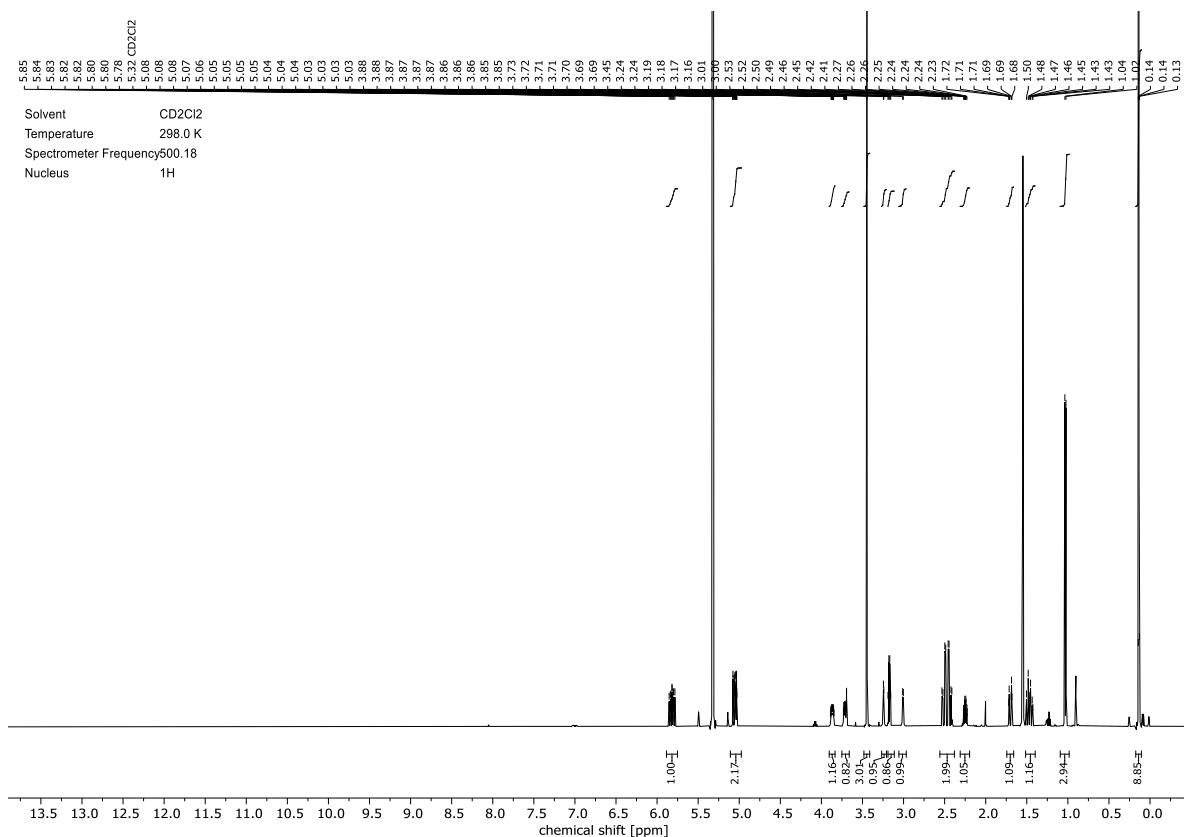
Chemical Formula: $C_{12}H_{20}O_4$
Exact Mass: 228.1362



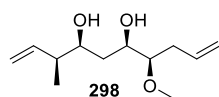
6 Copies of NMR Spectra



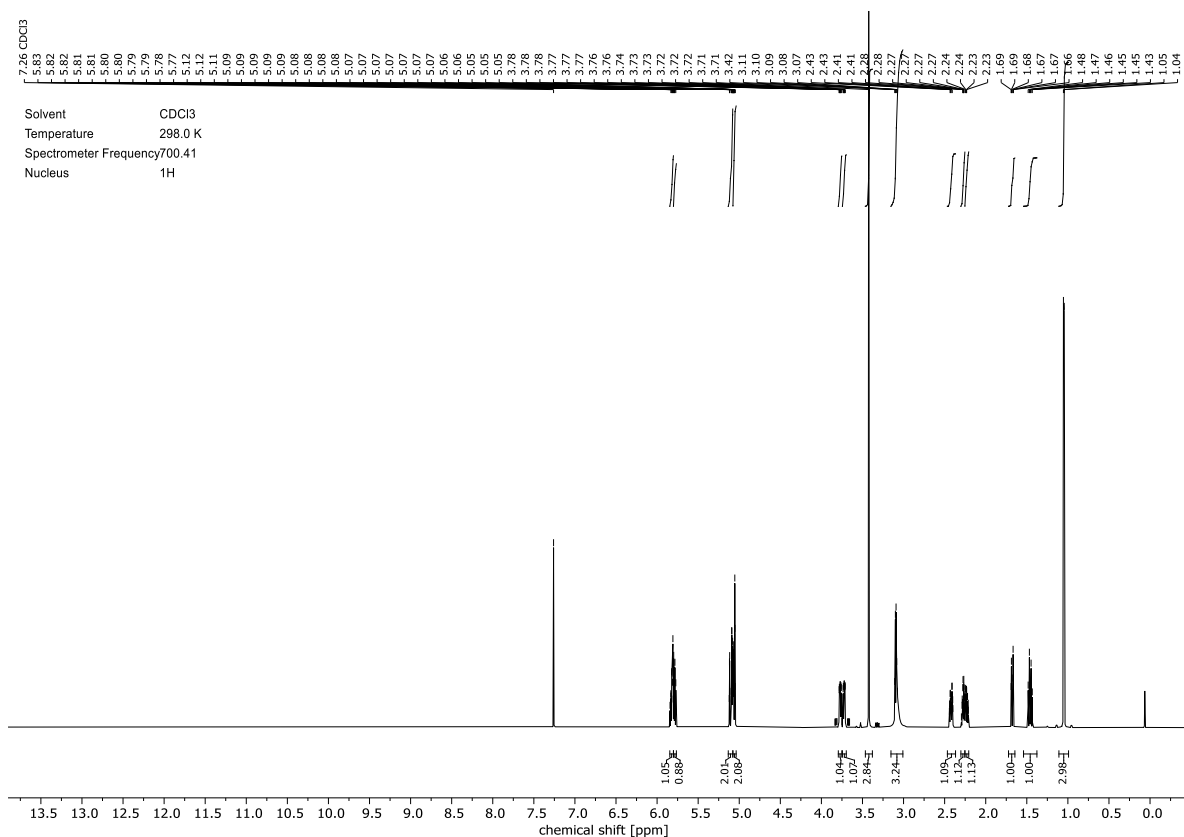
Chemical Formula: $C_{15}H_{28}O_3Si$
Exact Mass: 284.1808



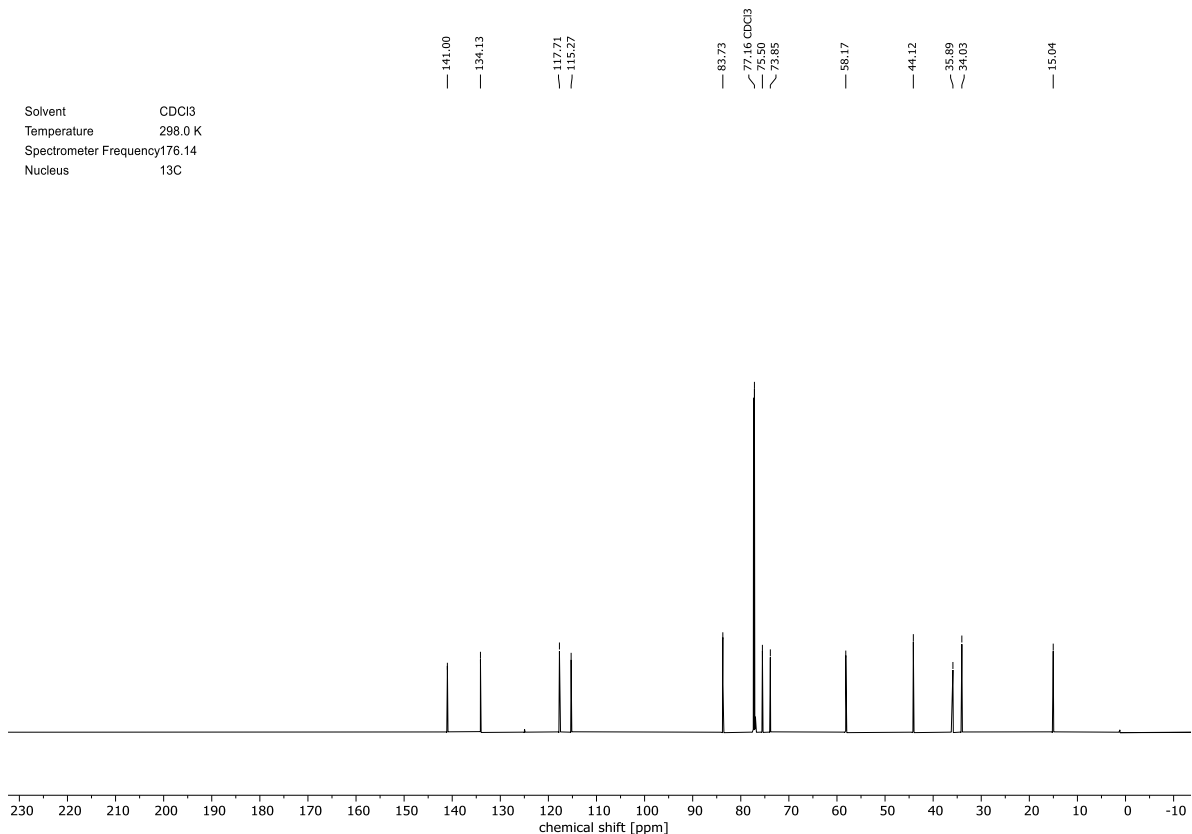
6 Copies of NMR Spectra



Chemical Formula: $C_{12}H_{22}O_3$
Exact Mass: 214.1569



Solvent: CDCl₃
Temperature: 298.0 K
Spectrometer Frequency: 176.14
Nucleus: ¹³C



7 References

- [1] G. M. Cragg, D. J. Newman, *Pure Appl. Chem.* **2005**, 77, 7.
- [2] M. Goerig, J. Schulte Am Esch, *Anästhesiol Intensivmed Notfallmed Schmerzther* **1991**, 26, 492.
- [3] J. R. Hanson, *Natural products: the secondary metabolites*, Royal Society of Chemistry, Cambridge, **2003**.
- [4] P. Karlovsky, *Secondary metabolites in soil ecology*, Springer, Berlin, **2008**.
- [5] D. J. Kliebenstein, *Plant Cell Environ.* **2004**, 27, 675.
- [6] A. L. Demain, A. Fang, in *History of Modern Biotechnology I*, Springer Berlin Heidelberg, **2000**, 69, 1–39.
- [7] K. C. Nicolaou, S. A. Snyder, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 11929.
- [8] F. Wöhler, *Annalen der Physik* **1828**, 88, 253.
- [9] R. Bade, H.-F. Chan, J. Reynisson, *Eur. J. Med. Chem.* **2010**, 45, 5646.
- [10] M. Simone, S. I. Maffioli, A. Tocchetti, S. Tretter, M. Cattaneo, I. Biunno, E. Gaspari, S. Donadio, *J. Antibiot.* **2015**, 68, 406.
- [11] M. C. Kim, H. Machado, K. H. Jang, L. Trzoss, P. R. Jensen, W. Fenical, *J. Am. Chem. Soc.* **2018**, 140, 10775.
- [12] J. Ding, A. B. Smith, *J. Am. Chem. Soc.* **2023**, 145, 18240.
- [13] S. Zhang, S. Zhang, Y. Fan, X. Zhang, J. Chen, C. Jin, S. Chen, L. Wang, Q. Zhang, Y. Chen, *Angew. Chem.* **2023**, 135, e202313186.
- [14] S.-X. Huang, X.-J. Wang, Y. Yan, J.-D. Wang, J. Zhang, C.-X. Liu, W.-S. Xiang, B. Shen, *Org. Lett.* **2012**, 14, 1254.
- [15] S. Ōmura, *Macrolide antibiotics: chemistry, biology, and practice*, Academic Press, Amsterdam Boston, 2nd ed., **2002**.
- [16] S. Qi, M. Gui, H. Li, C. Yu, H. Li, Z. Zeng, P. Sun, *Chem. Biodivers.* **2020**, 17, e2000024.

- [17] D. M. Citron, C. V. Merriam, K. L. Tyrrell, Y. A. Warren, H. Fernandez, E. J. C. Goldstein, *Antimicrob. Agents Chemother.* **2003**, *47*, 2334.
- [18] K. V. I. Rolston, N. Dholakia, D. H. Ho, B. LeBlanc, T. Dvorak, H. Streeter, *J. Antimicrob. Chemother.* **1996**, *38*, 265.
- [19] H. Takeshita, T. Sugai, H. Fuwa, *J. Org. Chem.* **2021**, *86*, 6787.
- [20] Y. M. Pyun, S. In Cho, S. J. Lee, D. H. Lee, *Bull. Korean Chem. Soc.* **2022**, *43*, 1364.
- [21] X. Liang, M. Yoo, T. Schempp, S. Maejima, M. J. Krische, *Angew. Chem. Int. Ed.* **2022**, *61*, e202214786.
- [22] D. S. Lee, S. Maejima, M. J. Krische, *Org. Lett.* **2023**, *25*, 6763.
- [23] E. G. Choi, E. B. Kim, D. H. Lee, *Bull. Korean Chem. Soc.* **2024**, *45*, 362.
- [24] H. Sharma, S. Paul, S. Ganguly, S. Shankar Auddy, R. Kumar Goswami, *Org. Biomol. Chem.* **2024**, *22*, 7203.
- [25] A. E. Healy, M. D. Van Engen, N. A. Cinti, P. E. Floreancig, *Org. Lett.* **2024**, *26*, 10774.
- [26] J. Hao, C. J. Forsyth, *Tetrahedron Lett.* **2002**, *43*, 1.
- [27] G. V. M. Sharma, G. Srikanth, P. P. Reddy, *Org. Biomol. Chem.* **2012**, *10*, 8119.
- [28] L. K. Geisler, S. Nguyen, C. J. Forsyth, *Org. Lett.* **2004**, *6*, 4159.
- [29] C. Raji Reddy, B. Srikanth, U. Dilipkumar, K. V. M. Rao, B. Jagadeesh, *Eur. J. Org. Chem.* **2013**, *2013*, 525.
- [30] G. Lefèbvre, J. Seyden-Penne, *J. Chem. Soc. D* **1970**, *0*, 1308.
- [31] C. A. LeClair, M. B. Boxer, C. J. Thomas, D. J. Maloney, *Tetrahedron Lett.* **2010**, *51*, 6852.
- [32] D. E. Frantz, R. Fässler, E. M. Carreira, *J. Am. Chem. Soc.* **2000**, *122*, 1806.
- [33] D. A. Evans, K. T. Chapman, E. M. Carreira, *J. Am. Chem. Soc.* **1988**, *110*, 3560.
- [34] A. K. Saksena, P. Mangiaracina, *Tetrahedron Lett.* **1983**, *24*, 273.
- [35] N. Gaida, *Studies towards the total synthesis of Neaumycin B*, Master Thesis, Rheinische Friedrich-Wilhelms-Universität Bonn, **2025**.

- [36] T. Suzuki, H. Saimoto, H. Tomioka, K. Oshima, H. Nozaki, *Tetrahedron Lett.* **1982**, 23, 3597.
- [37] D. A. Evans, J. Bartroli, T. L. Shih, *J. Am. Chem. Soc.* **1981**, 103, 2127.
- [38] K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repič, M. J. Shapiro, *Tetrahedron Lett.* **1987**, 28, 155.
- [39] K. Narasaka, F.-C. Pai, *Tetrahedron* **1984**, 40, 2233.
- [40] R. Appel, *Angew. Chem. Int. Ed.* **1975**, 14, 801.
- [41] Y. Ai, N. Ye, Q. Wang, K. Yahata, Y. Kishi, *Angew. Chem. Int. Ed.* **2017**, 56, 10791.
- [42] T. Itoh, K. Jitsukawa, K. Kaneda, S. Teranishi, *J. Am. Chem. Soc.* **1979**, 101, 159.
- [43] S. J. Lee, T. M. Anderson, M. D. Burke, *Angew. Chem. Int. Ed.* **2010**, 49, 8860.
- [44] F. David-Quillot, J. Thibonnet, D. Marsacq, M. Abarbri, A. Duchêne, *Tetrahedron Lett.* **2000**, 41, 9981.
- [45] F. David-Quillot, D. Marsacq, A. Balland, J. Thibonnet, M. Abarbri, A. Duchêne, *Synthesis* **2003**, 2003, 0448.
- [46] M. Y. H. Wong, G. R. Gray, *J. Am. Chem. Soc.* **1978**, 100, 3548.
- [47] B. Wang, T. M. Hansen, T. Wang, D. Wu, L. Weyer, L. Ying, M. M. Engler, M. Sanville, C. Leitheiser, M. Christmann, Y. Lu, J. Chen, N. Zunker, R. D. Cink, F. Ahmed, C.-S. Lee, C. J. Forsyth, *J. Am. Chem. Soc.* **2011**, 133, 1484.
- [48] J. A. Marshall, N. D. Adams, *J. Org. Chem.* **1999**, 64, 5201.
- [49] Z. Fang, M. Wills, *J. Org. Chem.* **2013**, 78, 8594.
- [50] X. Mo, A. Letort, D. Roşca, K. Higashida, A. Fürstner, *Chem. Euro. J.* **2018**, 24, 9667.
- [51] A. Fürstner, *J. Am. Chem. Soc.* **2019**, 141, 11.
- [52] J. K. Stille, *Angew. Chem. Int. Ed.* **1986**, 25, 508.
- [53] K. Narasaka, K. Maruyama, T. Mukaiyama, *Chemistry Lett.* **1978**, 7, 885.
- [54] X. Gao, H. Han, M. J. Krische, *J. Am. Chem. Soc.* **2011**, 133, 12795.

- [55] J. Moran, A. Preetz, R. A. Mesch, M. J. Krische, *Nature Chem.* **2011**, *3*, 287.
- [56] S. B. Han, A. Hassan, I. S. Kim, M. J. Krische, *J. Am. Chem. Soc.* **2010**, *132*, 15559.
- [57] D. J. Del Valle, M. J. Krische, *J. Am. Chem. Soc.* **2013**, *135*, 10986.
- [58] Y. Lu, S. K. Woo, M. J. Krische, *J. Am. Chem. Soc.* **2011**, *133*, 13876.
- [59] H. C. Brown, K. S. Bhat, *J. Am. Chem. Soc.* **1986**, *108*, 293.
- [60] P. R. Blakemore, W. J. Cole, P. J. Kocieński, A. Morley, *Synlett* **1998**, *1998*, 26.
- [61] C. Aïssa, *J. Org. Chem.* **2006**, *71*, 360.
- [62] K. A. Ouzounthanasis, S. R. Rizos, A. E. Koumbis, *Eur. J. Org. Chem.* **2023**, *26*, e202300626.
- [63] G. Sakaine, Z. Leitis, R. Ločmele, G. Smits, *Eur. J. Org. Chem.* **2023**, *26*, e202201217.
- [64] B. M. Trost, J. D. Chisholm, S. T. Wroblewski, M. Jung, *J. Am. Chem. Soc.* **2002**, *124*, 12420.
- [65] A. B. Smith, S. Dong, J. B. Brennen, R. J. Fox, *J. Am. Chem. Soc.* **2009**, *131*, 12109.
- [66] Haolun. Jin, Junichi. Uenishi, W. J. Christ, Yoshito. Kishi, *J. Am. Chem. Soc.* **1986**, *108*, 5644.
- [67] X. Liu, X. Li, Y. Chen, Y. Hu, Y. Kishi, *J. Am. Chem. Soc.* **2012**, *134*, 6136.
- [68] K. Takai, M. Tagashira, T. Kuroda, K. Oshima, K. Utimoto, H. Nozaki, *J. Am. Chem. Soc.* **1986**, *108*, 6048.
- [69] V. Praveen Kumar, Y. Kishi, *J. Am. Chem. Soc.* **2020**, *142*, 14743.
- [70] T. Q. Davies, J. J. Murphy, M. Dousset, A. Fürstner, *J. Am. Chem. Soc.* **2021**, *143*, 13489.
- [71] M. Kimura, A. Ezoe, M. Mori, K. Iwata, Y. Tamaru, *J. Am. Chem. Soc.* **2006**, *128*, 8559.
- [72] B. M. Trost, W.-J. Bai, C. E. Stivala, C. Hohn, C. Poock, M. Heinrich, S. Xu, J. Rey, *J. Am. Chem. Soc.* **2018**, *140*, 17316.
- [73] J. A. Marshall, H. R. Chobanian, M. M. Yanik, *Org. Lett.* **2001**, *3*, 3369.
- [74] J. A. Marshall, C. M. Grant, *J. Org. Chem.* **1999**, *64*, 8214.

- [75] X. Shen, A. S. Wasmuth, J. Zhao, C. Zhu, S. G. Nelson, *J. Am. Chem. Soc.* **2006**, *128*, 7438.
- [76] C. Zhu, X. Shen, S. G. Nelson, *J. Am. Chem. Soc.* **2004**, *126*, 5352.
- [77] K. Liu, J. W. Arico, R. E. Taylor, *J. Org. Chem.* **2010**, *75*, 3953.
- [78] K. Liu, R. E. Taylor, R. Kartika, *Org. Lett.* **2006**, *8*, 5393.
- [79] R. Kartika, R. E. Taylor, *Angew. Chem.* **2007**, *119*, 6998.
- [80] E. Stefan, R. E. Taylor, *Org. Lett.* **2012**, *14*, 3490.
- [81] E. Nakamura, T. Inubushi, S. Aoki, D. Machii, *J. Am. Chem. Soc.* **1991**, *113*, 8980.
- [82] A. L. Moure, R. Gómez Arrayás, D. J. Cárdenas, I. Alonso, J. C. Carretero, *J. Am. Chem. Soc.* **2012**, *134*, 7219.
- [83] D. V. Reddy, G. Sabitha, T. P. Rao, J. S. Yadav, *Org. Lett.* **2016**, *18*, 4202.
- [84] L. A. Wessjohann, G. Scheid, *Synthesis* **1999**, *1999*, 1.
- [85] K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408.
- [86] K. Takai, K. Nitta, K. Utimoto, *J. Am. Chem. Soc.* **1986**, *108*, 7408.
- [87] D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1978**, *100*, 3636-3638.
- [88] A. Fürstner, J.-A. Funel, M. Tremblay, L. C. Bouchez, C. Nevado, M. Waser, J. Ackerstaff, C. C. Stimson, *Chem. Commun.* **2008**, 2873.
- [89] A. B. Smith, S. M. Condon, J. A. McCauley, J. L. Leazer, J. W. Leahy, R. E. Maleczka, *J. Am. Chem. Soc.* **1995**, *117*, 5407.
- [90] H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodtt, J. Spille, *Chem. Ber.* **1956**, *89*, 2060.
- [91] D. W. Hart, J. Schwartz, *J. Am. Chem. Soc.* **1974**, *96*, 8115.
- [92] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
- [93] P. A. Wender, C. T. Hardman, S. Ho, M. S. Jeffreys, J. K. Maclaren, R. V. Quiroz, S. M. Ryckbosch, A. J. Shimizu, J. L. Sloane, M. C. Stevens, *Science* **2017**, *358*, 218.

- [94] M. H. Nguyen, M. Imanishi, T. Kurogi, A. B. Smith, *J. Am. Chem. Soc.* **2016**, *138*, 3675.
- [95] N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.* **1979**, *20*, 3437.
- [96] N. Miyaura, A. Suzuki, *J. Chem. Soc., Chem. Commun.* **1979**, 866.
- [97] K. C. Nicolaou, E. J. Sorensen, Eds., *Classics in total synthesis. 1: Targets, strategies, methods / K. C. Nicolaou and E. J. Sorensen*, VCH, Weinheim, 5. repr., **2008**.
- [98] B. Hong, T. Luo, X. Lei, *ACS Cent. Sci.* **2020**, *6*, 622.
- [99] E. J. Corey, *Pure Appl. Chem.* **1967**, *14*, 19.
- [100] A. F. Parsons, *J. Chem. Educ.* **2021**, *98*, 3390.
- [101] E. J. Corey, *Chem. Soc. Rev.* **1988**, *17*, 111.
- [102] E. J. Corey, *Angew. Chem. Int. Ed.* **1991**, *30*, 455.
- [103] C. Braun, *Total Synthesis of Farnesyl Lipid I/II Analogues and Contributions to the Total Synthesis of Neaumycin B*, PhD Thesis, Rheinische Friedrich-Wilhelms-Universität Bonn, **2025**.
- [104] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
- [105] D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1978**, *100*, 3636.
- [106] A. Babczyk, D. Menche, *J. Am. Chem. Soc.* **2023**, *145*, 10974.
- [107] J. B. Baudin, G. Hareau, S. A. Julia, O. Ruel, *Tetrahedron Lett.* **1991**, *32*, 1175.
- [108] N. Cramer, S. Laschat, A. Baro, H. Schwalbe, C. Richter, *Angew. Chem.* **2005**, *117*, 831.
- [109] S. M. J. DeChant, J. B. Hunt, *J. Am. Chem. Soc.* **1967**, *89*, 5988.
- [110] T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18.
- [111] N. N. Schwartz, J. H. Blumbergs, *J. Org. Chem.* **1964**, *29*, 1976.
- [112] H. Jacobsen, L. Cavallo, *Chem. Eur. J.* **2001**, *7*, 800.

- [113] S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307.
- [114] D. D. Ford, L. P. C. Nielsen, S. J. Zuend, C. B. Musgrave, E. N. Jacobsen, *J. Am. Chem. Soc.* **2013**, *135*, 15595.
- [115] L. P. C. Nielsen, C. P. Stevenson, D. G. Blackmond, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 1360.
- [116] H. C. Brown, B. C. S. Rao, *J. Am. Chem. Soc.* **1956**, *78*, 5694.
- [117] H. C. Brown, P. K. Jadhav, *J. Am. Chem. Soc.* **1983**, *105*, 2092.
- [118] S. Takano, T. Yoshimitsu, K. Ogasawara, *J. Org. Chem.* **1994**, *59*, 54.
- [119] M. G. Organ, Y. V. Bilokin, S. Bratovanov, *J. Org. Chem.* **2002**, *67*, 5176.
- [120] M. C. Noe, M. A. Letavic, S. L. Snow, in *Organic Reactions*, (Ed: S. E. Denmark), Wiley, 1st edn., **2005**, pp. 109–625.
- [121] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.
- [122] T. Göbel, K. B. Sharpless, *Angew. Chem. Int. Ed.* **1993**, *32*, 1329.
- [123] M. Akram, H. M. Asif, M. Uzair, N. Akhtar, A. Madni, S. M. A. Shah, *J. Med. Plants Res.* **2011**, *17*, 3997-4000.
- [124] L. E. Erickson, *J. Am. Chem. Soc.* **1965**, *87*, 1867.
- [125] R. A. Volkmann, P. R. Kelbaugh, D. M. Nason, V. J. Jasys, *J. Org. Chem.* **1992**, *57*, 4352.
- [126] J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734.
- [127] B. Holmberg, *J. Prakt. Chem.* **1913**, *88*, 553.
- [128] J. G. Buchanan, R. A. Diggie, G. D. Ruggiero, I. H. Williams, *Chem. Commun.* **2006**, 1106.
- [129] B. E. Rossiter, K. B. Sharpless, *J. Org. Chem.* **1984**, *49*, 3707.
- [130] R. Brückner, *Reaktionsmechanismen: organische Reaktionen, Stereochemie, Moderne Synthesemethoden*, Springer Spektrum, Berlin Heidelberg, 3. Aufl., Nachdruck., **2015**.
- [131] C. Schmuck, Ed., *Chemie für Mediziner*, Pearson Studium, München, Nachdr., **20**.

- [132] H. Meerwein, *Org. Synth.* **1966**, *46*, 113.
- [133] T. R. Hoye, C. S. Jeffrey, F. Shao, *Nat. Protoc.* **2007**, *2*, 2451.
- [134] R. W. Hoffmann, H. J. Zeiss, *J. Org. Chem.* **1981**, *46*, 1309.
- [135] M. Schlosser, *Pure Appl. Chem.* **1988**, *60*, 1627.
- [136] C. Brown, J. A. Sinclair, *J. Organomet. Chem.* **1977**, *131*, 163-169.
- [137] D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.* **1981**, *103*, 3099-3111.
- [138] Z. Boiarska, T. Braga, A. Silvani, D. Passarella, *Eur. J. Org. Chem.* **2021**, *2021*, 3214.
- [139] D. A. Evans, D. L. Rieger, J. R. Gage, *Tetrahedron Lett.* **1990**, *31*, 7099.
- [140] M. Karplus, *J. Chem. Phys.* **1959**, *30*, 11.
- [141] I. S. Kim, M.-Y. Ngai, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 6340.
- [142] J. M. Williams, R. B. Jobson, N. Yasuda, G. Marchesini, U.-H. Dolling, E. J. J. Grabowski, *Tetrahedron Lett.* **1995**, *36*, 5461.
- [143] J. R. Parikh, W. V. E. Doering, *J. Am. Chem. Soc.* **1967**, *89*, 5505.
- [144] H. C. Brown, P. K. Jadhav, K. S. Bhat, *J. Am. Chem. Soc.* **1988**, *110*, 1535.
- [145] D. Chrenko, J. Pospíšil, *Molecules* **2024**, *29*, 2719.
- [146] P. R. Blakemore, W. J. Cole, P. J. Kociński, A. Morley, *Synlett* **1998**, *1998*, 26.
- [147] C. Aïssa, *Eur. J. Org. Chem.* **2009**, *2009*, 1831.
- [148] A. A. Levy, H. C. Rains, S. Smiles, *J. Chem. Soc.* **1931**, *0*, 3264.
- [149] J. F. Bunnett, *Angew. Chem. Int. Ed.* **1962**, *1*, 225.
- [150] J. Pospíšil, *Tetrahedron Lett.* **2011**, *52*, 2348.
- [151] G. Sakaine, Z. Leitis, R. Ločmele, G. Smits, *Eur. J. Org. Chem.* **2023**, *26*, e202201217.
- [152] K. A. Ouzounthanasis, S. R. Rizos, A. E. Koumbis, *Eur. J. Org. Chem.* **2023**, *26*, e202300626.
- [153] P. R. Blakemore, W. J. Cole, P. J. Kociński, A. Morley, *Synlett* **1998**, *1998*, 26.

- [154] D. A. Alonso, C. Nájera, M. Varea, *Tetrahedron Lett.* **2004**, *45*, 573.
- [155] M. H. Medema, K. Blin, P. Cimermancic, V. De Jager, P. Zakrzewski, M. A. Fischbach, T. Weber, E. Takano, R. Breitling, *Nucleic Acids Res.* **2011**, *39*, W339.
- [156] A. Kitsche, M. Kalesse, *ChemBioChem* **2013**, *14*, 851.
- [157] L. M. Suen, M. L. Steigerwald, J. L. Leighton, *Chem. Sci.* **2013**, *4*, 2413.
- [158] T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett.* **1973**, *2*, 1011.
- [159] D. J. Cram, K. R. Kopecky, *J. Am. Chem. Soc.* **1959**, *81*, 2748.
- [160] T. J. Leitereg, D. J. Cram, *J. Am. Chem. Soc.* **1968**, *90*, 4019.
- [161] D. A. Evans, J. J. Beiger, J. D. Burch, P. H. Fuller, F. Glorius, E. Kattnig, D. A. Thaisrivongs, W. C. Trenkle, J. M. Young, J. Zhang, *J. Am. Chem. Soc.* **2022**, *144*, 19953.
- [162] K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repič, M. J. Shapiro, *Tetrahedron Lett.* **1987**, *28*, 155.
- [163] M. Squillacote, R. S. Sheridan, O. L. Chapman, F. A. L. Anet, *J. Am. Chem. Soc.* **1975**, *97*, 3244.
- [164] W. S. Wadsworth, in *Organic Reactions*, (Ed: S. E. Denmark), Wiley, 1st edn., **1977**, pp. 73–253.
- [165] J. Boutagy, R. Thomas, *Chem. Rev.* **1974**, *74*, 87.
- [166] S. K. Thompson, C. H. Heathcock, *J. Org. Chem.* **1990**, *55*, 3386.
- [167] R. O. Larsen, G. Aksnes, *Phosphorus Sulfur Rel. Elem.* **1983**, *15*, 219.
- [168] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essinfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183.
- [169] E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092.
- [170] H. Lindlar, *Helv. Chim. Acta* **1952**, *35*, 446.
- [171] S. Specklin, J. Cossy, *J. Org. Chem.* **2015**, *80*, 3302.
- [172] A. Darwish, J. M. Chong, *Tetrahedron* **2012**, *68*, 654.

- [173] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.
- [174] G. Helmchen, G. Nill, D. Flockerzi, M. S. K. Youssef, *Angew. Chem. Int. Ed.* **1979**, *18*, 63.
- [175] G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics* **2010**, *29*, 2176.
- [176] S. K. Murphy, D. A. Petrone, M. M. Coulter, V. M. Dong, *Org. Lett.* **2011**, *13*, 6216.
- [177] J. R. Cochrane, C. S. P. McErlean, K. A. Jolliffe, *Org. Lett.* **2010**, *12*, 3394.
- [178] C. Liu, J. K. Coward, *J. Org. Chem.* **1991**, *56*, 2262.
- [179] K. Jones, J. M. D. Storey, *Tetrahedron* **1993**, *49*, 4901.
- [180] J. Aszodi, A. Bonnet, G. Teutsch, *Tetrahedron* **1990**, *46*, 1579.
- [181] A. K. Ghosh, S. Gemma, A. Baldrige, Y.-F. Wang, A. Yu. Kovalevsky, Y. Koh, I. T. Weber, H. Mitsuya, *J. Med. Chem.* **2008**, *51*, 6021.
- [182] D. Enders, A. Lenzen, M. Müller, *Synthesis* **2004**, *2004*, 1486.
- [183] L. C. Dias, E. C. De Lucca, *J. Org. Chem.* **2017**, *82*, 3019.
- [184] C. Rink, V. Navickas, M. E. Maier, *Org. Lett.* **2011**, *13*, 2334.
- [185] B. Göricke, M. F. Bieber, K. E. Mohr, D. Menche, *Angew. Chem. Int. Ed.* **2019**, *58*, 13019.
- [186] T. J. Hoffman, A. Kolleth, J. H. Rigby, S. Arseniyadis, J. Cossy, *Org. Lett.* **2010**, *12*, 3348.
- [187] K. Suenaga, T. Kimura, T. Kuroda, K. Matsui, S. Miya, S. Kuribayashi, A. Sakakura, H. Kigoshi, *Tetrahedron* **2006**, *62*, 8278.
- [188] C. Caumes, T. Hjelmgaard, O. Roy, M. Reynaud, D. Servent, C. Taillefumier, S. Faure, *Med. Chem. Commun.* **2012**, *3*, 1531.
- [189] E. C. Taylor, H. M. L. Davies, *J. Org. Chem.* **1986**, *51*, 1537.
- [190] J. Maury, L. Feray, M. P. Bertrand, *Org. Lett.* **2011**, *13*, 1884.
- [191] E. Wenkert, K. J. Chou, R. P. Hatch, *Synth. Commun.* **1977**, *7*, 375.

- [192] H. J. Bestmann, A. B. Attygalle, J. Glasbrenner, R. Riemer, O. Vostrowsky, M. G. Constantino, G. Melikian, E. D. Morgan, *Liebigs Ann. Chem.* **1988**, 1988, 55.
- [193] T. Saito, H. Fuwa, M. Sasaki, *Tetrahedron* **2011**, 67, 429.
- [194] A. K. Ghosh, G. Gong, *Chem. Asian J.* **2008**, 3, 1811.
- [195] P. Sellès, R. Lett, *Tetrahedron Lett.* **2002**, 43, 4621.
- [196] B. Padhi, D. S. Reddy, D. K. Mohapatra, *RSC Adv.* **2015**, 5, 96758.
- [197] T. P. Stockdale, N. Y. S. Lam, I. Paterson, *Chem. Commun.* **2022**, 58, 5729.
- [198] T. K. Chakraborty, M. Sreekanth, K. K. Pulukuri, *Tetrahedron Lett.* **2011**, 52, 59.
- [199] D. P. Witter, Y. Chen, J. K. Rogel, G. E. Boldt, P. Wentworth, *ChemBioChem* **2009**, 10, 1344.
- [200] E. O. Nwoye, G. B. Dudley, *Chem. Commun.* **2007**, 1436.
- [201] K. C. Nicolaou, A. P. Patron, K. Ajito, P. K. Richter, H. Khatuya, P. Bertinato, R. A. Miller, M. J. Tomaszewski, *Chem. Eur. J.* **1996**, 2, 847.
- [202] A. B. Smith, V. A. Doughty, C. Sfougataakis, C. S. Bennett, J. Koyanagi, M. Takeuchi, *Org. Lett.* **2002**, 4, 783.
- [203] A. B. Smith, K. P. Minbiole, P. R. Verhoest, M. Schelhaas, *J. Am. Chem. Soc.* **2001**, 123, 10942.