FLUOROUS MIXTURE SYNTHESIS AND STRUCTURE ASSIGNMENT OF PETROCORTYNE A AND ITS STEREOISOMERS

by

Bin Sui

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MS, Nanjing University, 2004

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This dissertation was presented

by

Bin Sui

It was defended on

Nov 30, 2009

and approved by

Professor Theodore Cohen, Department of Chemistry

Professor Craig S. Wilcox, Department of Chemistry

Professor Barry Gold, Department of Pharmaceutical Sciences

Dissertation Advisor: Professor Dennis P. Curran, Department of Chemistry

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Petrocortyne A was isolated from the marine sponge *Petrosia* sp. by Shin and Jung in 1998 and 1999, respectively. Both groups assigned the absolute configuration of the natural product, but the assignments do not consistent with the reported optical rotations. Using the fluorous mixture synthesis (FMS), we have synthesized four stereoisomers of petrocortyne A to determine the absolute configuration. In the FMS, the stereoisomeric starting materials were tagged with different fluorous TIPS groups and mixed together. The resulting mixture was taken through a series of steps to make the fluorous-tagged products, which were separated by fluorous HPLC followed by desilylation to provide four pure products.

Second-generation fluorous TIPS tags were synthesized and used in the FMS. Both Mosher and NMA ester methods were studied during the synthesis. The study showed that NMA ester method is superior to Mosher method for the assignment of absolute configuration of stereocenter C14.

Comparison of optical rotations of the four synthetic and two natural samples showed that both natural samples had the C3-*S* configuration. Comparison of spectra of Mosher derivatives of the synthetic and natural samples showed that both natural samples had the 3*S*,14*S* configuration. At the same time, the use of the Mosher rule has been validated for assigning the challenging C14 stereocenter of petrocortyne A. A "shortcut" variant in which only one Mosher ester is made was developed and can also be used for assignment of this stereocenter.

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LIST OF ABBREVIATIONS

BINOL	1,1′-bi-2-naphthol
^{t}Bu	*tert*-butyl
CAN	ceric ammonium nitrate
COSY	correlation spectroscopy
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
	DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutyl aluminum hydride
DMAP	4-dimethylamino pyridine
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMPS	dimethylphenylsilyl
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EI	electron ionization
equiv	equivalents
ESI	electrospray ionization
Et	ethyl
FMS	fluorous mixture synthesis
HETCOR	heteronuclear correlation
HGF	hepatocyte growth factor
HMBC	heteronuclear multiple bond coherence
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
INF	interferon
IR	infrared spectrometry
LPS	lipopolysaccharide
Me	methyl
MS	mass spectrometry
MTM	methylthiomethyl
MTPA	α-methoxytrifluorophenylacetic acid
2-NMA	α-methoxy-2-naphthylacetic acid
NaHMDS	sodium bis(trimethylsilyl)amide
NMR	nuclear magnetic resonance

Ph	phenyl
PMA	phorbol 12-myristate 12-acetate
PMB	*p*-methoxybenzyl
^{i}Pr	isopropyl
PTSA	*p*-toluenesulfonic acid
Py	pyridine
rt	room temperature
SF	scatter factor
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TOCSY	total correlation spectroscopy
TLC	thin layer chromatography
TMS	trimethylsilyl
TfO	triflate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TNF	tumor necrosis factor

PREFACE

I don't think I would be proud of my degree if I had not worked for a person like Professor Dennis P. Curran, my research advisor. I thank him for his steadfast support, encouragement, and patience. I appreciate all his efforts on my behalf, both in the realm of my graduate studies and in preparation for my life in the future.

I would like to thank Professors Theodore Cohen, Craig S. Wilcox, and Barry Gold for serving on the thesis committee. I would like to thank Professor Paul F. Floreancig for being the mentor of my proposal.

The Curran group is where I have learned so much outside of chemistry. There are some people that have had a major impact on me as a scientist and also as a person at the same time. I would like to thank all the Curran group members, past and presents, for help and encouragement. Special thanks to Mr. Edmund A.-H. Yeh for his contribution in this project.

I am very appreciative of the help provided to me by Drs Damodaran Krishnan and John Williams for NMR spectroscopy and mass spectroscopy.

Finally, I would like to thank my parents and my wife Mingjian for their love, support, encouragement, and sacrifice in dealing with me through my graduate study.

1.0 FLUOROUS MIXTURE SYNTHESIS AND STRUCTURE ASSIGNMENT OF PETROCORTYNE A AND ITS STEREOISOMERS

1.1 INTRODUCTION

1.1.1 Fluorous Mixture Synthesis (FMS)

Natural products are chemical compounds isolated from living organisms, and they usually have pharmacological and biological activities. Natural products play an important role in drug discovery and drug design.[1] Recent reviews showed that natural products and their derivatives are significant sources of new drugs.[2,3] The syntheses of libraries of biologically active natural product stereoisomers are important because they allow the unambiguous structural assignments of natural products whose stereoisomers may have similar or even identical spectra. Establishing the correct stereostructure is a prerequisite for the study of structure-activity relationships (SAR) in drug discovery. Furthermore, the syntheses of stereoisomer libraries provide samples for biological tests that help establish an SAR.

As the complexity of isolated natural products increases, the structure assignment, especially the stereochemistry assignment, becomes more challenging. Total synthesis of all of the stereoisomers can provide enough samples that can be used to prove or disprove the structure assignment by comparison of various physical and spectral data of a natural product with

synthetic products. The recent proof of structure of murisolin by its comparison with a library of its stereoisomers shows the power of having multiple isomers for comparison.[4]

Synthetic chemists have always constructed compounds one at a time. It is time-consuming work to synthesize multiple stereoisomers of natural products by traditional solution phase synthesis. For instance, in order to elucidate the structure of khafrefungin, Kobayashi and coworkers had to synthesize five stereoisomers of khafrefungin one by one.[5]

The situation of synthesizing one stereoisomer at a time began to change in the 1990s as the revolution of solid-phase and combinatorial chemistry spread through synthetic laboratories.[6] Recently, Waldmann and coworkers reported the total syntheses of all isomers of cryptocarya diacetate on a polymeric carrier.[7] Takahashi and coworkers also reported the combinatorial synthesis of a macrosphelide library on polymer support.[8] However, compared to conventional solution-phase methods, solid-phase synthesis sacrifices the reactivity of the supported substrates because of unfavorable kinetics of heterogeneous reaction.[9] To date, the scope of reactions developed for solid phase synthesis is still limited.

Fluorous mixture synthesis (FMS), introduced in 2001, is the first solution phase technique that captures the efficiency inherent in mixing compounds yet still allows the reliable separation of the mixtures to provide individual pure target products in the end.[10] A typical fluorous mixture synthesis consists of four stages: premix, mixture synthesis, demix, and detag, as shown in Figure 1.1.

During the premix stage, a set of isomeric substrates (S^1–S^n) is prepared individually by traditional methods. The configuration of each isomer is encoded with a corresponding set of homologous fluorous tags (F^1–F^n) with increasing fluorine content. The fluorous-tagged precursors (S^1F^1–S^nF^n) are mixed together (M1) and taken through a multi-step synthesis

(mixture stage) in one-pot reactions or split-parallel fashion. At the end of synthesis, the final mixture (M2) is demixed based on fluorine content by preparative fluorous HPLC. Molecules (F^1P^1–F^nP^n) with longer fluorous chains have longer retention time on the fluorous HPLC column. The order of elucidation of products can be predicted in advance by the original tag/substrate pairs (SF) based on the fluorine content. In the final stage, detagging is conducted to release the final products (P^1–P^n).

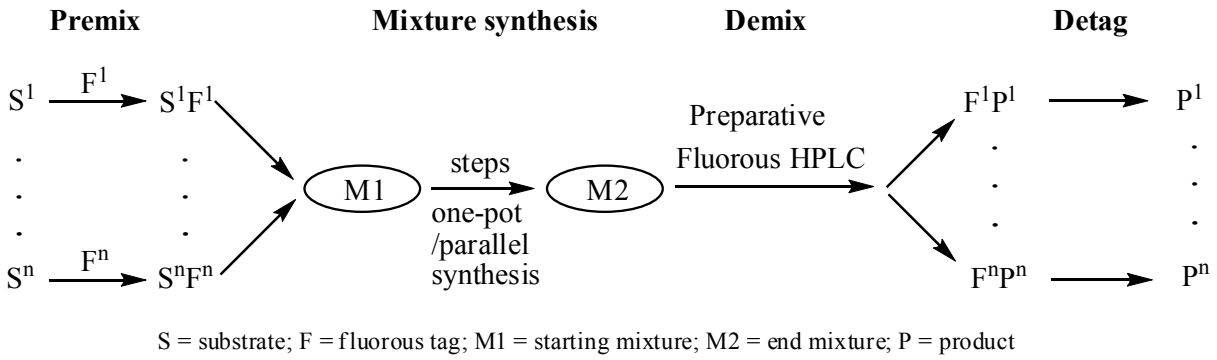
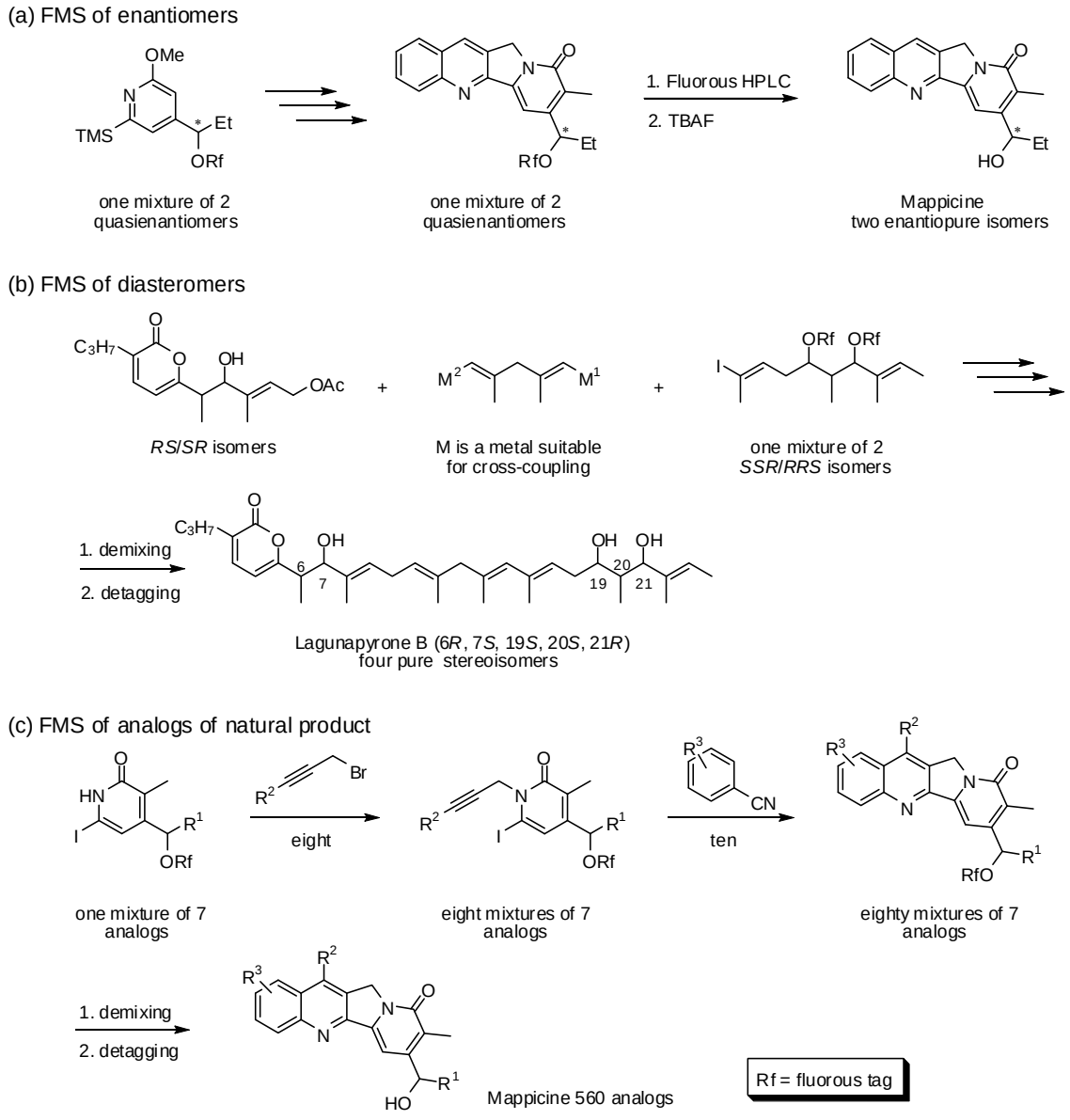


Figure 1.1. Schematic diagram of the concept of FMS

Based on the nature of target, fluorous mixture synthesis has been applied to three different categories of compounds: enantiomers, diastereomers, and analogs (Scheme 1.1). When both enantiomers of a compound are needed, two enantiomeric precursors are tagged with different tags to make quasienantiomers, which are mixed together. The resulting mixture is conducted in the whole synthesis. After the steps of demixing and detagging, the two target enantiomers are obtained as pure compounds. The synthesis of both mappicine enantiomers highlights this application, which is called quasi-racemic synthesis (Scheme 1.1a).[11] The synthesis of diastereomers of natural product is sometimes necessary for elucidation of structure. Fluorous mixture synthesis is a powerful tool to synthesize some or all diastereomers for

comparisons with an isolated natural product. This approach was taken in the synthesis and structure assignment of lagunapyrone B[12] (Scheme 1.1b) and murisolin.[4,13] Fluorous mixture synthesis can also be used to generate a library of analogs of a natural product with varying substituents. Recently, the syntheses of a 560-member library of mappicine analogs (Scheme 1.1c) has been reported by Zhang and coworkers.[14]

Scheme 1.1. Representative natural products synthesized by FMS



FMS has been proved to be a powerful tool to synthesize natural products, their isomers, and libraries. We now want to solve more challenging problem of stereocenter assignment for natural products with local symmetry.

1.1.2 Petrocortyne A

Many natural products with unique molecular architectures have been isolated from marine sponges.[15] These natural products often display remarkable biological activities, making them lead structures for the development of new chemotherapeutic agents. Polyacetylenes have been revealed as abundant sources of marine sponge metabolites, which possess great novel and diverse long chain and functionalities. More than 50 biologically active polyacetylenes characterized by unbranched long alkyl chains were isolated from the marine sponge *Petrosia* sp.. Borrowing from the name of the sponge, the compounds were named like petrocortynes,[16] petroformynes,[17] and petrosiacetylenes.[16a,c] One example of each type of substrate is shown in Figure 1.2. Most of these compounds modulate various biological activities such as anti-inflammatory, antimicrobial, antitumor, antiviral, and antifungal effects. The compounds typically consist of a linear carbon skeleton of 30 to 47 carbons interspersed with functional groups including alkynes, *E*- and *Z*-alkenes, and hydroxyl groups.

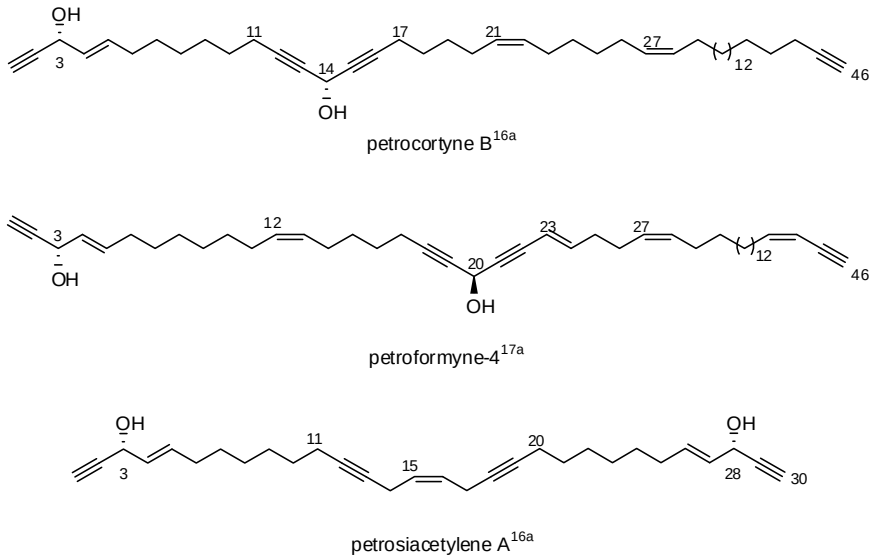
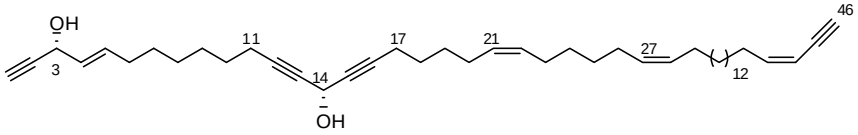


Figure 1.2. Representative polyacetylenes isolated from marine sponge *Petrosia* sp.

Petrocortyne A, a novel lipid compound, was first isolated from the marine sponge *Petrosia* sp. collected in 1994 at Komun Island, Korea by Shin and coworkers in 1998.[16a] Approximately 70 mg of a linear tetraacetylene assigned as (3*R*,14*R*)-petrocortyne A **1.1RR** (Figure 1.3) was isolated. The compound exhibited a modest inhibitory activity against the enzyme phospholipase A2 (PLA_2) (31% at 50 μg/mL).



1.1RR, 3*R*,14*R* (3*R*,14*R*)-petrocortyne A
1.1SS, 3*S*,14*S* (3*S*,14*S*)-petrocortyne A (not shown)

Figure 1.3. Structure of petrocortyne A

In 1999, Jung and coworkers reported another petrocortyne A, assigned as (3*S*,14*S*)-petrocortyne A **1.1SS** (Figure 1.3), isolated from sponge *Petrosia* sp. collected in 1995 again off

Komun Island.[16c] This time, about 142 mg of (3*S*,14*S*)-petrocortyne A **1.1SS** was obtained. Jung's petrocortyne **1.1SS** inhibited the production of tumor necrosis factor (TNF)-α from lipopolysaccharide (LPS)-stimulated murine macrophages RAW264.7 in a concentration-dependent manner with an IC_{50} of 2.35 μM. Similarly, it inhibited the production of TNF-α from phorbol 12-myristate 13-acetate (PMA)/LPS treated U937 cells at the transcriptional level (46% inhibition at 5 μM). (3*S*,14*S*)-Petrocortyne A **1.1SS** also blocked NO release from either LPS- or interferon (INF)-γ-treated RAW267.4 cells. It selectively blocked the expression of hepatocyte growth factor/scatter factor (HGF/SF), which plays an important role in regulating infiltration of immune or inflammatory cells into inflamed tissue. Compound **1.1SS** also induced U937 homotypic aggregation. Since homotypic aggregation is considered a potential tool for negative modulation of inflammatory cell migration,[18b] the pro-aggregative effect of this compound may reinforce its anti-inflammatory function. Therefore, (3*S*,14*S*)-petrocortyne A **1.1SS** inhibits cellular inflammatory processes and immune cell migration to inflamed tissue, which makes it a potential anti-inflammatory drug.[18]

The constitutions of these two samples **1.1RR** and **1.1SS** were assigned by a battery of spectroscopic methods. By the combination of HRMS, IR, ^{1}H NMR, and ^{13}C NMR analysis, petrocortyne A **1.1RR** or **1.1SS** consists of four isolated double bonds and a long alkyl chain without methyl groups or other branches. Several partial structures (Figure 1.4) were identified based on the study of 2D NMR spectra (COSY, HETCOR, HMQC, and HMBC). The COSY data revealed that none of the partial structures was directly connected to another, so the partial structures were considered to be linked by linear alkyl chains. The lengths of alkyl chains and connectivities of partial structures were determined by the combination of chemical degradation, detailed NMR analysis with the addition of $Eu(fod)_3$, a lanthanide-induced shift reagent, and

EIMS analysis. The geometry of four isolated double bonds was determined by NMR spectroscopy. The double bonds at C4 and C43 were assigned as *E* and *Z*, based on the coupling constants between the olefinic protons. However, the geometry of those at C21 and C27 were unable to be determined by coupling constants, because signals of the olefinic protons overlapped. However, the geometry of both double bonds was assigned as *Z* on the basis of chemical shift of allylic carbons in the ^{13}C NMR spectrum.[19]

Figure 1.4. Partial structures of petrocortyne A

The absolute configurations of the two remote stereocenters at C3 and C14 were assigned by the advanced Mosher ester method.[20] The configurations were assigned as 3*R*,14*R* for Shin's petrocortyne A **1.1RR**, and 3*S*,14*S* for Jung's petrocortyne A **1.1SS**, respectively. Thus, these two natural products are enantiomers. However, the values of optical rotations of petrocortyne A **1.1RR** (+ 6.4, MeOH, *c* = 0.25) and (3*S*,14*S*)-petrocortyne A **1.1SS** (+ 10.8, MeOH, *c* = 1.9) do not meet the expectation that enantiomers should give optical rotations with opposite sign and equal magnitude. Accordingly, the assignment of the absolute configuration of one or even both of these two natural products may be incorrect.

In the murisolin family of acetogenins with very remote stereocenters, we have found the diastereomers exhibit substantially identical spectra.[4] Similarly, petrocortynes also have remote stereocenters. Would the (3*S*,14*S*)/(3*R*,14*R*) pair of enantiomers (*syn* diastereomer) exhibit the same spectra as the (3*R*,14*S*)/(3*S*,14*R*) pair (*anti* diastereomer)? If the spectra are the same, then how can the diastereomers be differentiated? The configuration of the stereocenter at C3 can be

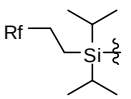
assigned by making a pair of diastereomeric Mosher esters and analyzing their ^{1}H NMR spectra by the advanced Mosher method. But, is the application of the advanced Mosher analysis a reliable tactic for assigning the configuration of the stereocenter at C14 of petrocortyne A? This center is difficult to assign because there is a local symmetry plane at C14 and because there are no protons directly attached to the carbons adjacent to the stereocenter.

Despite the novel skeleton and uncertain configuration, there have not been any reports of synthetic efforts toward the petrocortynes and similar compounds. Our goals of this project are to prepare all four individual pure stereoisomers of petrocortyne A by fluorous mixture synthesis, to compare the data of synthetic and natural samples and their Mosher derivatives, and thereby to prove the assignment of absolute configuration of these natural products.

1.2 RESULTS AND DISCUSSION

1.2.1 Retrosynthetic analysis of petrocortyne A

In the fluorous mixture synthesis, diisopropyl(perfluoroalkylethyl)silyl groups ($TIPS^F$) and triisopropylsilyl group are used as tags because they are stable under most reaction conditions and easily deprotected.[12,21] $TIPS^F$ group is not a "true" TIPS group because it has a 1°-alkyl(diisopropyl)silyl group while TIPS group has a triisopropylsilyl group. In the following schemes, $TIPS^{Fn}$ is used as an abbreviation of fluorous TIPS group; n is the number of certain fluorine content (the regular TIPS group is displayed as $TIPS^{F0}$). The structures of $TIPS^{F0}$ group and two fluorous tags, $C_3F_7(CH_2)_2(^iPr)_2Si–$ ($TIPS^{F7}$) and $C_4F_9(CH_2)_2(^iPr)_2Si–$ ($TIPS^{F9}$), used in the following synthesis are shown in Figure 1.5. Compounds bearing different $TIPS^F$ groups will be mixed, and in the numbering the following text, all samples bearing the "M" prefix are mixtures of fluorous-tagged quasiisomers.



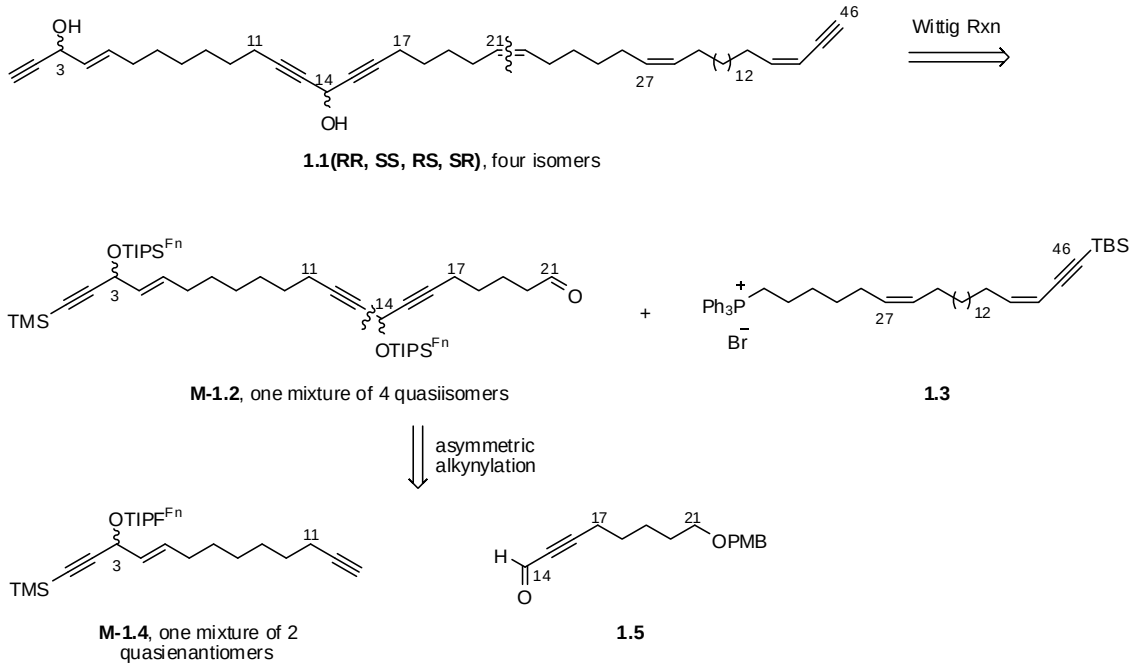
$TIPS^{F7}$ (Rf = C_3F_7): diisopropyl(3,3,4,4,5,5,5-heptafluoropentyl)silyl
$TIPS^{F9}$ (Rf = C_4F_9): diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyl

$TIPS^{F0}$: triisopropylsilyl

Figure 1.5. The structure of $TIPS^F$ groups used in the following synthesis

The retrosynthesis and tagging strategy of FMS to assemble the backbone of the target structure **1.1** are shown in Scheme 1.2. Petrocortyne A **1.1** can be constructed from the two large fragments, aldehyde **M-1.2** and triphenylphosphonium salt **1.3**, by Wittig reaction[22] followed by demixing over fluorous HPLC and desilylation. Because fragment **M-1.2** has two stereocenters, we planned to make **M-1.2** as quasiisomer mixture of four stereoisomers with configurations encoded by fluorous tags in the protecting group ($TIPS^F$). Fragment **M-1.2** can be assembled from alkyne **M-1.4** and aldehyde **1.5** by asymmetric alkynylation under Carreira's condition.[23]

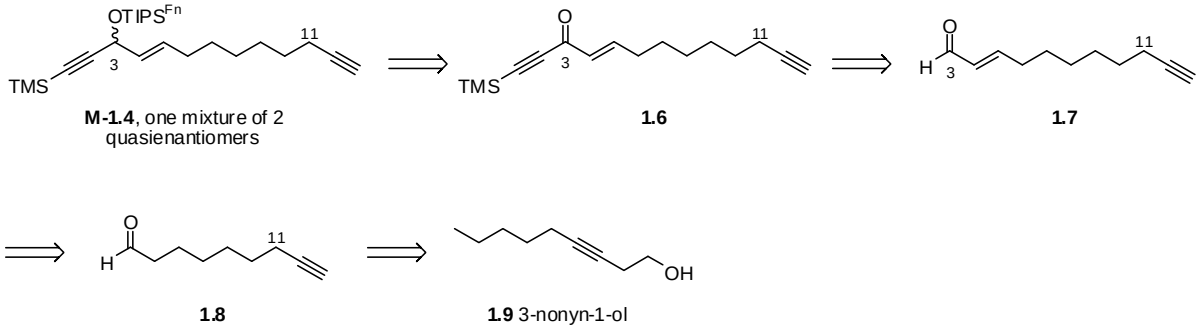
Scheme 1.2. The retrosynthesis of petrocortyne A 1.1



As shown in Scheme 1.3, both enantiomers of fragment **M-1.4** at C3 can be formed by enantioselective reduction of α,β-unsaturated ketone **1.6** using Alpine–Borane,[24] followed by silylation with different fluorous tags. Ketone **1.6** can be constructed from aldehyde **1.7** by alkynylation followed by oxidation. Aldehyde **1.7** can be synthesized from aldehyde **1.8** by

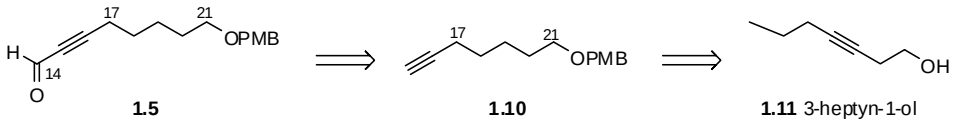
Wittig olefination[22] followed by reduction of ester to alcohol and oxidation of alcohol to corresponding aldehyde. Finally, we plan to prepare aldehyde **1.8** from commercially available 3-nonyn-1-ol **1.9** by a zipper reaction,[25] followed by Swern oxidation.[26]

Scheme 1.3. The retrosynthesis of M-1.4



Aldehyde **1.5** can be constructed from the reaction between DMF and alkyne **1.10**, which can be derived from commercially available 3-heptyn-1-ol **1.11** by another zipper reaction followed by PMB protection (Scheme 1.4).

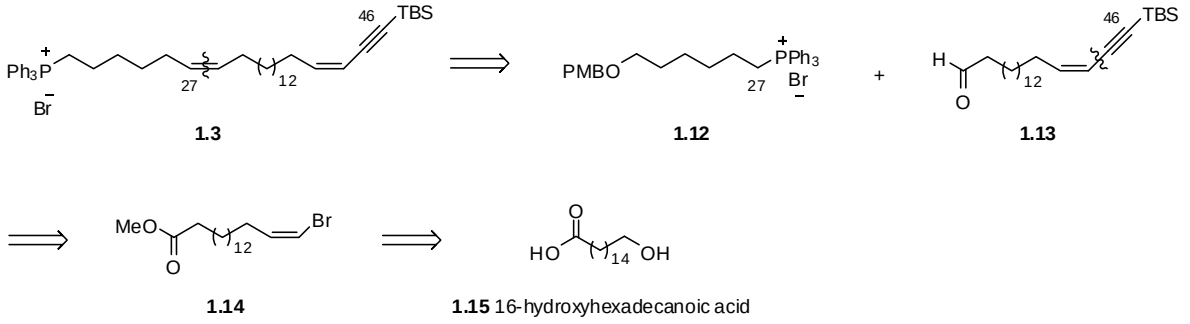
Scheme 1.4. The retrosynthesis of aldehyde 1.5



The synthesis of triphenylphosphonium salt **1.3** can start from a smaller triphenylphosphonium salt **1.12** and aldehyde **1.13** by Wittig reaction followed by deprotection, halogenation, and reaction with triphenylphosphine (Scheme 3). Aldehyde **1.13** can be obtained from a Sonagashira coupling reaction[27] between commercially available *tert*-

butyldimethylsilylacetylene and vinyl bromide **1.14**, which will be synthesized from 16-hydroxyhexadecanoic acid **1.15**.

Scheme 1.5. The retrosynthesis of triphenylphosphonium salt 1.3



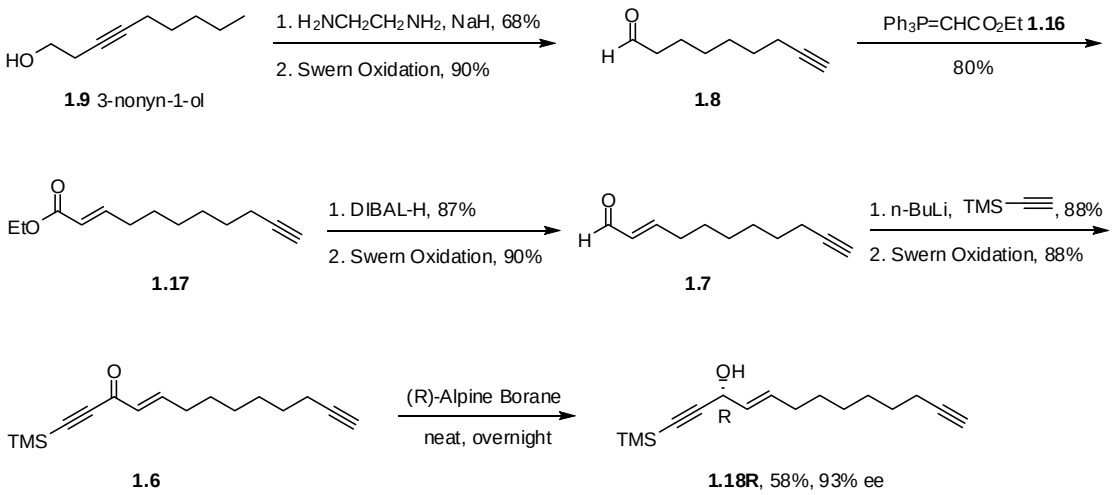
1.2.2 Synthesis of C1–C13 fragment 1.4R

Prior to starting the FMS of petrocortyne A, the partial synthesis of one isomer was performed. The first aim for this synthesis was to validate that every step could work for FMS. The second aim was to provide some fragments of petrocortynes with known configurations to validate that the Mosher method is a reliable tactic for assigning the absolute configurations at C3 and C14 of petrocortynes.

The work began with the preparation of propargylic alcohol **1.18R** (C1–C13), as summarized in Scheme 1.6. Internal alkyne **1.9** was first subjected to an acetylene zipper reaction with sodium hydride in warm ethylene diamine to provide a terminal alkyne[28] in 68% yield. Subsequent Swern oxidation of the primary alcohol of the above alkynol afforded aldehyde **1.8**[29] in 90% yield. This intermediate is unstable toward oxygen and can only be stored for prolonged periods when kept under argon. Aldehyde **1.8** was reacted with commercially

available Wittig reagent **1.16** to give (*E*)-α,β-unsaturated ester **1.17** as a single isomer in 80% isolated yield after flash chromatography. Reduction of ester **1.17** with DIBAL-H cleanly provided the alcohol in 87% yield. This was oxidized to α,β-unsaturated aldehyde **1.7** in 90% yield by Swern oxidation.

Scheme 1.6. Synthesis of propargylic alcohol 1.18R

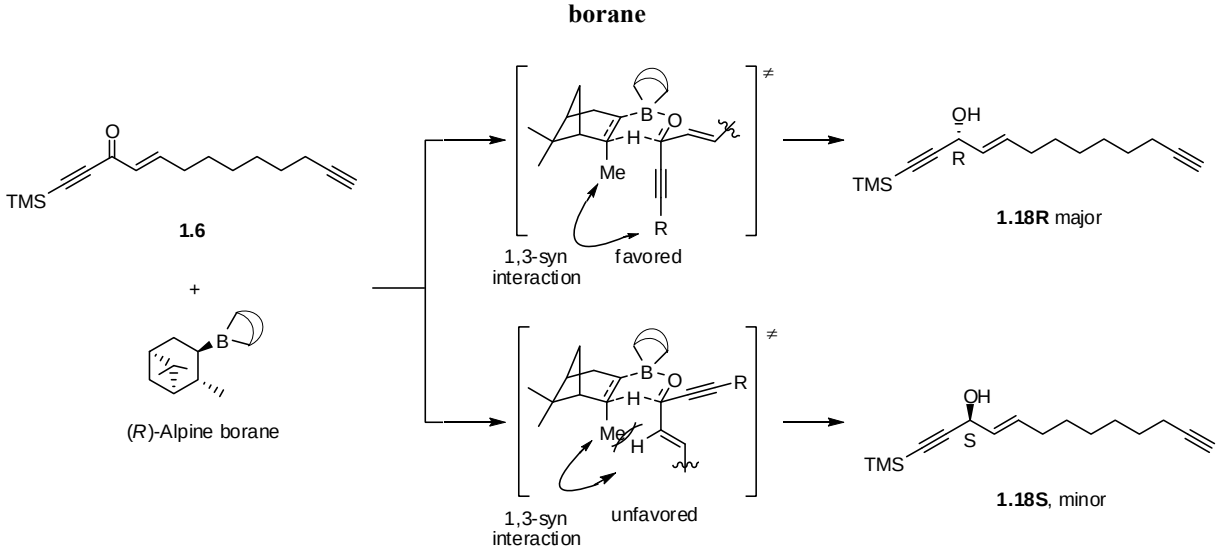


Trimethylsilylacetylene was treated with n-BuLi to generate ((trimethylsilyl)ethynyl)lithium, which was reacted with aldehyde **1.7** to give the racemic alcohol in 88% yield. Swern oxidation of this alcohol provided ketone **1.6**, which was isolated as yellow oil in 88% yield after rapid chromatographic purification. This ketone could only be stored for a short time; hence, it was used as quickly as possible. Ketone **1.6** was treated with neat (*R*)-Alpine–Borane at room temperature overnight to generate (*R*)-propargylic alcohol **1.18R** in 58% yield. The ee of compound **1.18R** was determined by ^{19}F NMR analysis of the crude Mosher esters (see following text for synthesis). Each crude Mosher ester exhibited three peaks in its ^{19}F NMR spectrum, one from excess MTPA acid (α-methoxytrifluorophenylacetic acid) (−71.0

ppm), and the others from two diastereomeric MTPA esters of −72.1 (major peak for **1.19RR** and minor peak for **1.19RS**) and −72.3 ppm (minor peak for **1.19RR** and major peak in **1.19RS**). Integration of the latter pair of peaks provided the ee of alcohol **1.18R** as 93%.

The absolute configuration of major compound **1.18R** could be predicted based on the model provided by Midland and coworkers (Scheme 1.7).[30] They proposed that the high enantioselectivity in this reduction originated from a cyclic, boat-like transition state due to the preferential *syn*-1,3-steric interaction between 2-methyl group of Alpine-Borane and the smaller group of the approaching ketone. In the case of reduction of ketone **1.6**, the acetylene acts as the smaller group, and the alcohol **1.18R** is predicted to form through the favored transition state. The configuration of compound **1.18R** can be confidently assigned from Midland model, so alcohol **1.18R** is a suitable substrate to validate the advanced Mosher method.

Scheme 1.7. Midland's transition state model for the asymmetric reduction of ketone 1.6 with (*R*)-alpine borane



The advanced Mosher method was developed by Kusumi and Kakisawa in 1991.[20] They proposed that the carbinyl proton, ester carbonyl and trifluoromethyl groups of MTPA moiety lie in the same plane. This idealized conformation is depicted in Figure 1.6a. Due to the anisotropic effect of the benzene ring, the resonances of protons H^A, H^B, H^C of the (*R*)-MTPA ester should appear upfield relative to those of the (*S*)-MTPA ester. The reverse should be true for protons H^X, H^Y, H^Z. Therefore, for the differences in chemical shifts as defined $\Delta\delta_H = \delta_S - \delta_R$, protons on the right side of the MTPA plane (Figure 1.6b) will have positive values ($\Delta\delta_H > 0$) and protons on the left side of the MTPA plane will have negative values ($\Delta\delta_H < 0$). The magnitude of $\Delta\delta_H$ will be proportional to the distance of the protons from MTPA moiety, with closer protons exhibit bigger $\Delta\delta_H$. Consequently, based on this model, the absolute configuration of the compound can be assigned.

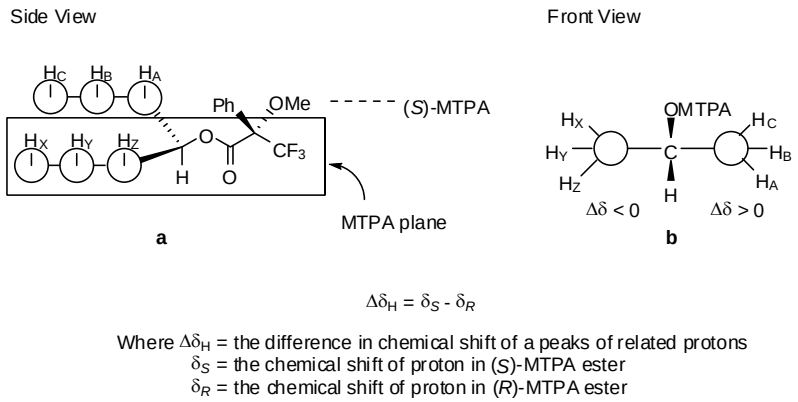


Figure 1.6. (a) An ideal conformation of an (*S*)-MTPA ester of a secondary alcohol. (b) Advanced Mosher model for assigning the absolute configuration of a secondary alcohol from $\Delta\delta_H$ values of Mosher ester.[20]

The Mosher esters of alcohol **1.18R** were then synthesized by treatment with (*S*)- and (*R*)-MTPA acid in CH_2Cl_2 in the presence of DCC and DMAP (Scheme 1.8). After removing the

solid byproducts by filtration, the corresponding crude esters **1.19RS** and **1.19RR** were obtained by solvent evaporation. These crude esters were used for assignment of absolute configuration of **1.18R** without further purification. Relevant chemical shifts of protons of esters **1.19RS**, **1.19RR** and their differences are listed in Table 1.1 in parts per million (ppm). The remote protons (H1') of the TMS group on one side of the stereocenter exhibited a small negative Δδ, while the protons H4, H5 and H6 on the other side exhibited a substantial positive Δδ. According to the advanced Mosher rule, the absolute configuration of C3 is *R*, as expected from the Midland transition state model.

Scheme 1.8. Synthesis of Mosher esters 1.19RS and 1.19RR

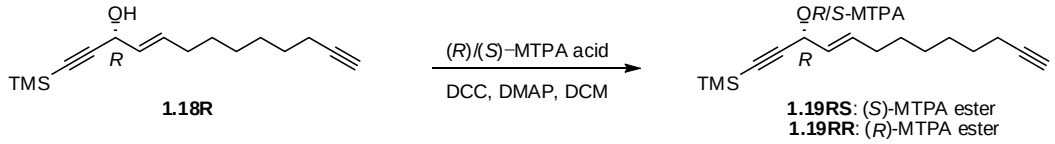
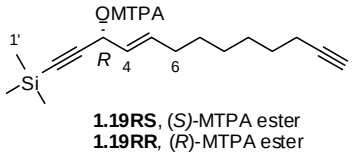


Table 1.1. Δδ ($\delta_{1.19RS} - \delta_{1.19RR}$) values (ppm) obtained from the MTPA esters of 1.19RS and 1.19RR

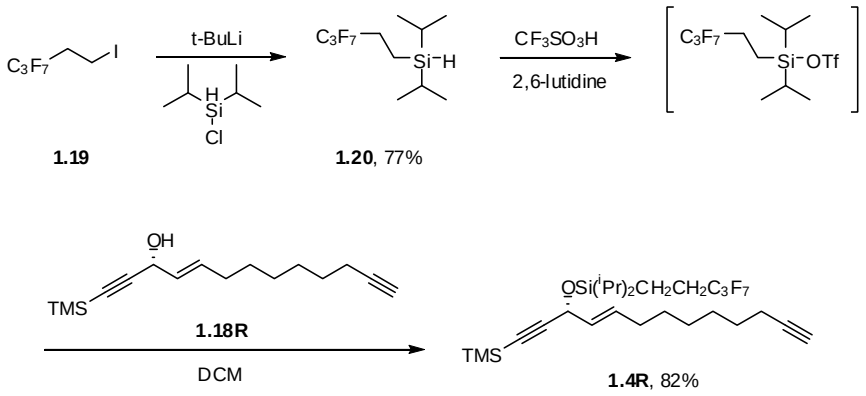


proton (H)	1'	4	5	6
$\delta_{1.19RS}$	0.154	5.569	6.018	2.080
$\delta_{1.19RR}$	0.174	5.472	5.960	2.045
$\Delta\delta$ ($\delta_{1.19RS} - \delta_{1.19RR}$)	−0.020	0.097	0.058	0.035

Alcohol **1.18R** was then tagged with fluorous tag **1.21** bearing a C_3F_7 group. The tag was synthesized from the corresponding perfluoroalkyl iodide **1.20** and chlorodiisopropylsilane in

77% yield.[11] Fluorous silane **1.21** was reacted with trifluoromethansulfonic acid at 0 °C to generate the fluorous TIPSOTf reagent in situ,[14] then alcohol **1.18R** in the solution of CH_2Cl_2 and 2,6-lutidine was slowly added at 0 °C. After stirring 2 h at room temperature followed by aqueous work up and flash chromatography, the desired product **1.4R** was obtained in 82% yield (Scheme 1.9).

Scheme 1.9. Synthesis of fluorous tagged ether 1.4R

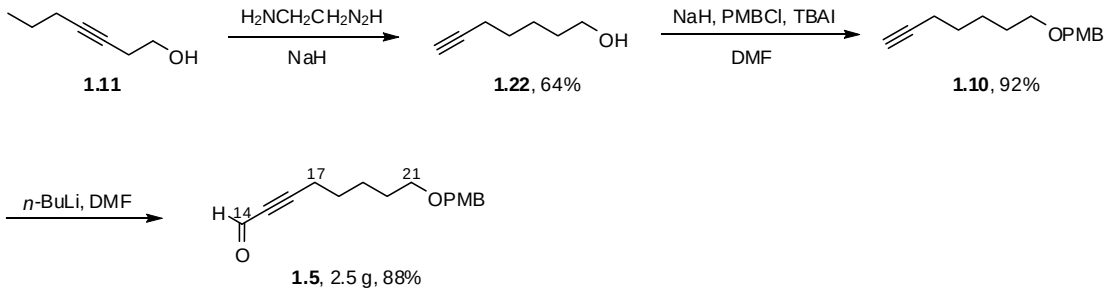


1.2.3 Synthesis of aldehyde 1.5 (C14–C21 fragment)

Aldehyde **1.5** was readily made in three steps (Scheme 1.10). Commercially available 3-heptyn-1-ol **1.11** was treated with sodium hydride in warm ethylenediamine to provide alkynol **1.22**[28] by a zipper reaction in 64% yield. Alkynol **1.22** was protected by *para*-methoxybenzyl chloride (PMBCl) in the presence of NaH and tetrabutylammonium iodide (TBAI) in DMF to generate the alkyne **1.10** in 92% yield. According to the procedure of Journet and Cai,[32] alkyne **1.10** was metallated with *n*-BuLi in THF, and the resulting lithium acetylide was formylated by DMF. Workup under mild acidic conditions (10% aqueous $KHPO_4$) followed by flash

chromatography provided aldehyde **1.5** in 88% yield. Thus, about 2.5 g of aldehyde **1.5** was made by this sequence.

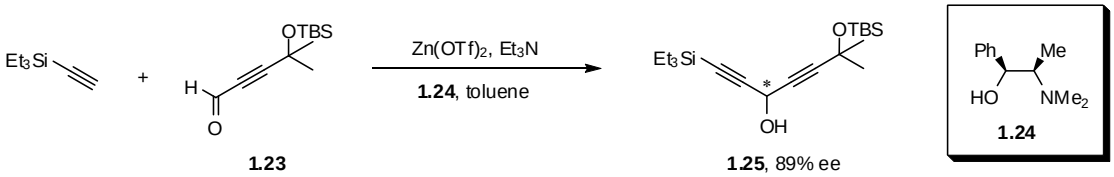
Scheme 1.10. Synthesis of aldehyde 1.5



1.2.4 Model reaction towards the synthesis of fragment M-1.2

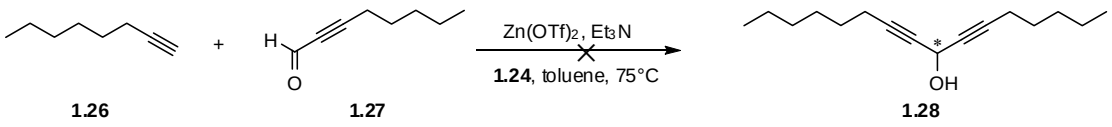
Assorted methods have been described to make enantioenriched secondary alcohols with one alkynyl and one alkyl, vinyl or aryl substituent.[32] However, very few methods to make enantioenriched dialkynyl carbinols have been reported. Carreira and co-workers reported one example of synthesizing enantioenriched dialkynyl methanol **1.25** by the asymmetric alkynylation of aldehyde **1.23** using chiral ligand (+)-*N*-methyl-ephedrine **1.24** (Scheme 1.10).[23] The product was obtained in 89% ee, but its configuration was not assigned.

Scheme 1.11. Carreira's approach to synthesize dialkynyl methanol 1.25



With the alkyne **1.4** and aldehyde **1.5** in hand, we initially investigated the Carreria method for asymmetric addition of alkynlides to alkynals by studying the reaction of 1-octyne **1.26** with 2-octynal **1.27** (Scheme 1.12). Following the general procedure reported by Carreira and coworkers, a mixture of dried $Zn(OTf)_2$, (+)-*N*-methyl-ephedrine **1.24** and Et_3N in toluene was stirred at 23 °C for 2 h. The alkyne **1.26** was then added in one portion, and the resulting mixture was stirred at 23 °C for 15 min. A solution of aldehyde **1.27** in toluene was then added by syringe pump over 2.5 h, followed by stirring at 75 °C for 20 h. Unfortunately, no product **1.28** was detected by ^{1}H NMR spectroscopy.

Scheme 1.12. Unsuccessful model reaction between 1-octyne 1.26 with 2-octynal 1.27



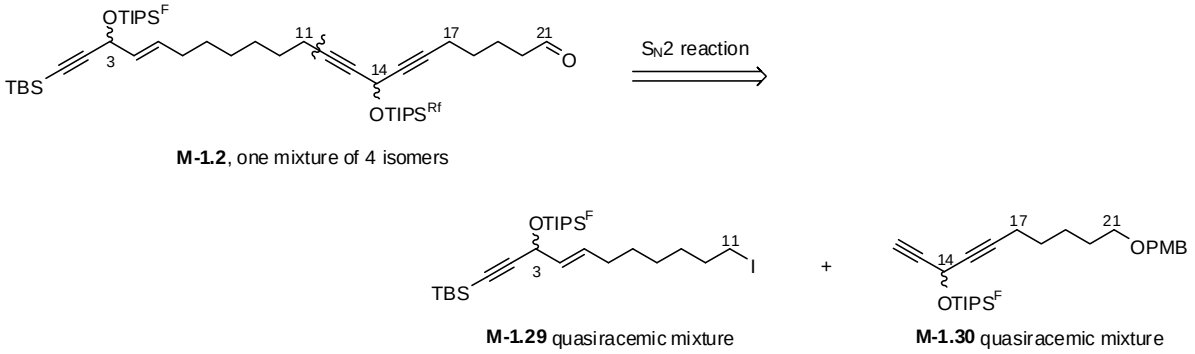
We also found several other examples of failed Carreira reactions on aliphatic aldehydes,[33] which suggested that this type of chiral zinc acetylide addition reaction is sensitive to substrate structure.[34] Due to the failure of Carreira asymmetric alkynylation, we had to revise the synthetic route for fragment **M-1.2**.

1.2.5 Revised synthetic route of C1–C21 fragment M-1.2

The revised retrosynthetic analysis of C1–C21 fragment **M-1.2** is shown in Scheme 1.13. We divide fragment **M-1.2** into two parts, iodide **M-1.29** and dialkynyl methanol **M-1.30**, which can be made as quasiracemic mixtures with configurations encoded by fluorous tags in the

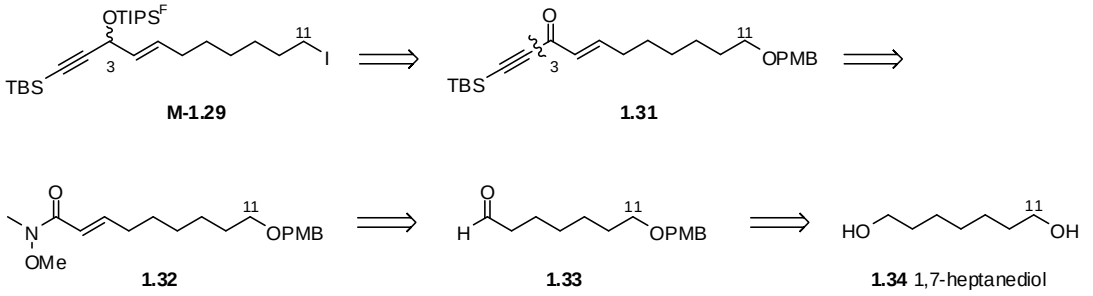
protecting groups ($TIPS^F$). These two fragments then can be connected by a S_N2 reaction to provide a mixture of four fluorous-tagged quasiisomers. This kind of double tagging strategy was recently reported in the synthesis of passifloricin A[21] and lagunapyrone B.[12]

Scheme 1.13. Revised retrosynthesis of fragment M-1.2



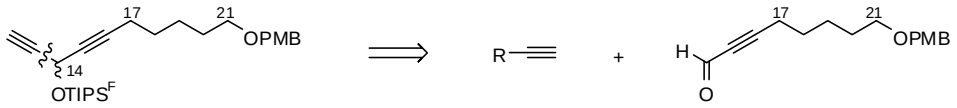
Iodide **M-1.29** can be constructed from ketone **1.31** by performing enantioselective reduction of α,β-unsaturated ketone **1.31** with chiral oxazaborolidine (CBS) catalyst (Scheme 1.14).[35] Ketone **1.31** can be synthesized from the addition of commercially available *tert*-butyldimethylsilylacetylene to Weinreb amide **1.32**, which can be obtained from aldehyde **1.33** by Horner-Wadsworth-Emmons (HWE) olefination.[36] Aldehyde **1.33** can be prepared from commercially available 1,7-heptanediol **1.34**.

Scheme 1.14. The retrosynthesis of iodide M-1.29



Dialkynyl methanol **M-1.30** can be synthesized by enantioselective addition of terminal alkyne to aldehyde **1.5** followed by protection and encoding with $TIPS^F$ groups.

Scheme 1.15. The retrosynthesis of fragment M-1.30

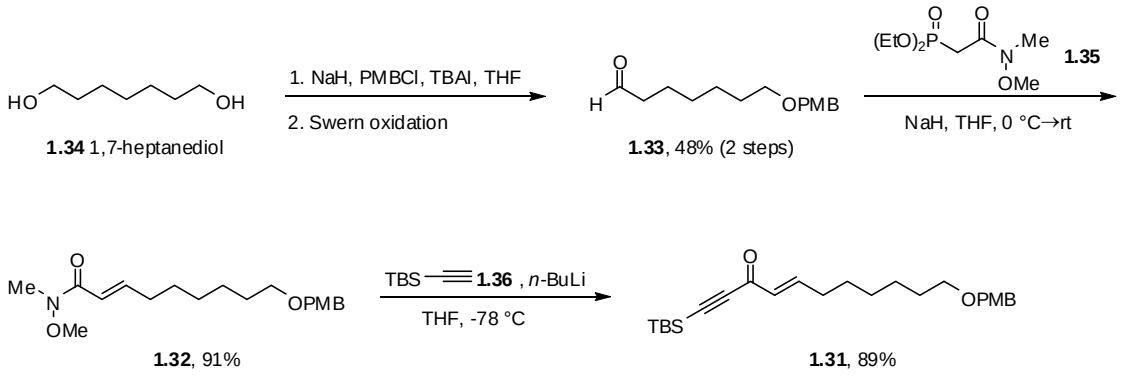


M-1.30 terminal alkyne **1.5**

1.2.6 Synthesis of iodide M-1.29 (fragment C1–C11)

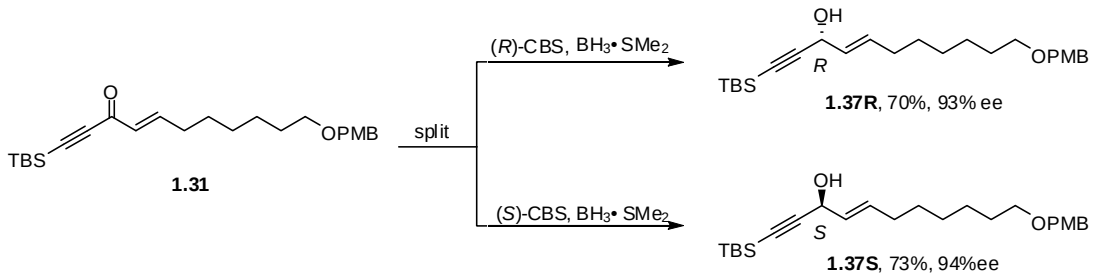
The synthesis of iodide **M-1.29** begins with the preparation of common intermediate ketone **1.31** (Scheme 1.16). Commercially available 1,7-heptanediol **1.34** was treated with sodium hydride (1.0 equiv) and PMBCl (1.0 equiv) in THF to provide the mono-PMB ether[37] in 49% yield after isolation by flash chromatography. Swern oxidation of the remaining primary alcohol afforded aldehyde **1.33**[37] in 98% yield. Weinreb amide **1.32** was accessed by a Horner-Wadsworth-Emmons (HWE) olefination of aldehyde **1.33** with commercially available phosphonate **1.35** in THF with 91 % yield. Nucleophilic addition of *tert*-butyldimethylsilylacetylene **1.36** to Weinreb amide **1.32** gave the ketone **1.31** in 89% yield. Conveniently, ketone **1.31** is stable and could be stored in refrigerator for 2 weeks without any decomposition.

Scheme 1.16. Synthesis of ketone 1.31



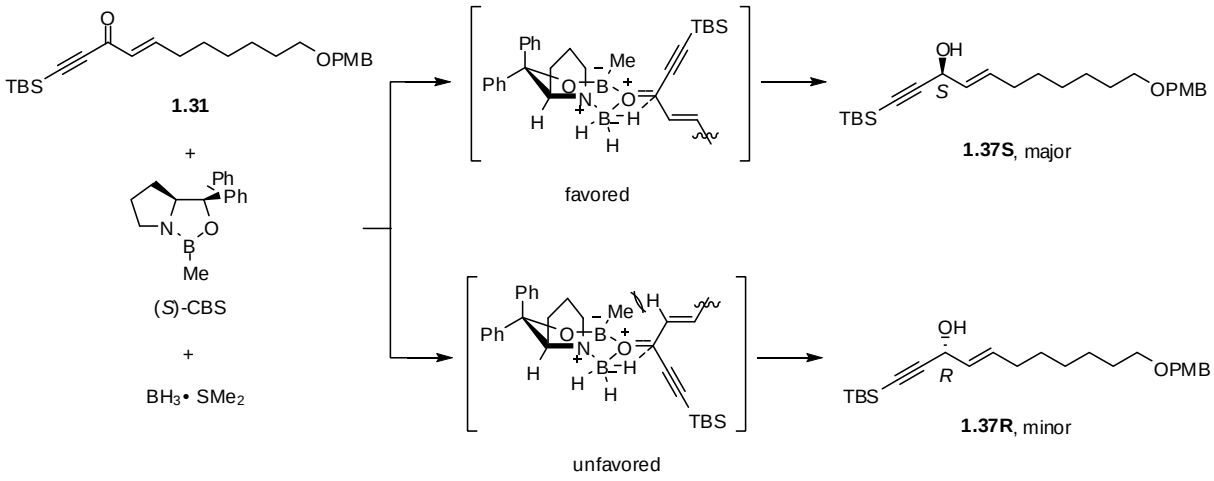
The sample of ketone **1.31** was split into half and each portion was subjected to CBS asymmetric reduction (Scheme 1.17).[35] Reduction with BH_3 in the presence of the catalyst (*R*)-CBS was proceeded to provide (*R*)-alcohol **1.37R** in 70% yield. Similarly, (*S*)-alcohol **1.37S** was generated by the reduction of alkynyl ketone **1.31** using (*S*)-CBS in 73% yield.

Scheme 1.17. Synthesis of alcohols 1.37R/S by CBS asymmetrical reduction



According to the mechanism proposed by Corey and coworkers for analogous oxazaborolidine-mediated reactions,[35b] the absolute configurations of alcohols **1.37R** and **1.37S** were confidently assigned based on the transition state models in which the acetylenic moiety acts as the smaller group (scheme 1.18).

Scheme 1.18. Corey's transition state model for the CBS asymmetric reduction of ketone 1.31



The corresponding Mosher esters of alcohols **1.37R** and **1.37S** were then synthesized for three reasons: 1) to determine the ees for the two alcohols; 2) to validate the Mosher method again, although we have done it using alcohol **1.18**; 3) to compare the Mosher method and NMA (α-methoxy-2-naphthylacetic acid) ester method in the configuration assignment of secondary alcohol. After removal of the TBS group by TBAF in DCM, the corresponding alcohols **1.38R** and **1.38S** were obtained. Alcohol **1.38S** was reacted with the *R*- and *S*-Mosher acid chloride (MTPACl = α-methoxy-α-trifluoromethylphenylacetic acid chloride) in dry pyridine to give the corresponding crude esters **1.39SS** and **1.39SR** after removing organic solvent under reduced pressure. Integration of the respective signals in ^{1}H and ^{19}F NMR spectra of the resulting crude samples provides the indicated ees (93% for **1.37R** and 94% for **1.37S**) for the CBS asymmetric reduction. After flash chromatography, the pure esters **1.39SS** and **1.39SR** were obtained and used in NMR experiments. All of the key protons of both compounds were assigned by a combination of ^{1}H NMR and COSY data. Relevant chemical shifts of protons of esters **1.39SS**/**SR** and the differences of resonances of corresponding pairs ($\delta_S - \delta_R$) are listed in Table 2. The proton (H1) on the left side of stereocenter exhibited a positive Δδ, while the protons H4–

H10 on the other side showed the substantial negative Δδs. According to the advanced Mosher rule, the absolute configuration of C3 is *S*, as expected from the Corey transition state model.

Scheme 1.19. Synthesis of Mosher esters 1.39SS and 1.39SR

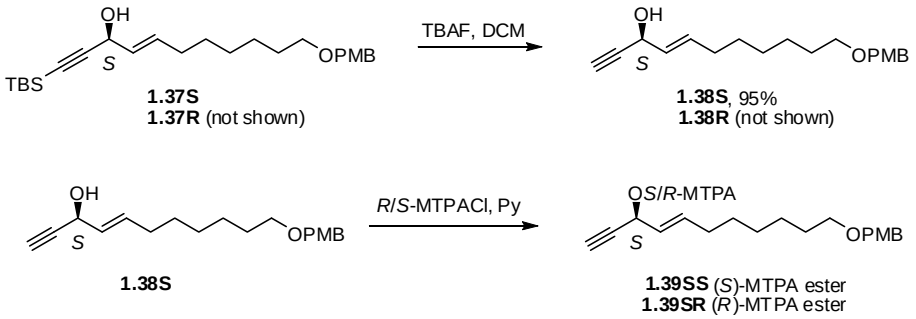
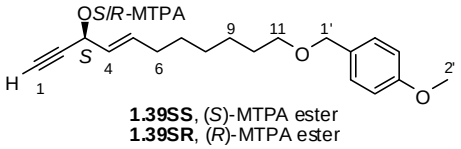


Table 1.2. Δδ ($\delta_{1.39SS} - \delta_{1.39SR}$) values (ppm) obtained from the MTPA esters of 1.39SS and 1.39SR



position	1	4	5	6	7	8	9	10
$\delta_{1.39SS}$	2.629	5.496	6.002	2.044	1.368	1.260	1.338	1.578
$\delta_{1.39SR}$	2.589	5.606	6.063	2.085	1.400	1.312	1.364	1.589
$\Delta\delta$ ($\delta_{1.39SS} - \delta_{1.39SR}$)	0.040	−0.110	−0.061	−0.041	−0.032	−0.052	−0.026	−0.011

During the model studies for the C14 stereocenter (see below), we needed to make α-methoxy-2-naphthylacetic acid (2-NMA) esters to validate the Mosher results, so we also made the NMA ester with alcohols **1.38S** and **1.38R**. The use of α-methoxy-2-naphthylacetic acid as a chiral anisotropic reagent for determining the absolute configuration of long chain secondary alcohols was developed simultaneously by several groups in mid-1990s.[38] Because the

anisotropic effect of 2-NMA is much greater than that of MTPA, Δδ values of 2-NMA esters are larger than those of MTPA esters. This makes assignment of absolute configuration both easier and more reliable.[39]

Since we only had (*S*)-2-NMA in hand, our strategy was to synthesize the corresponding (*S*)-2-NMA esters **1.40SS** and **1.40RS** by the reaction of two enantiomers **1.38S** and **1.38R** with (*S*)-2-NMA in the presence of DCC and DMAP (Scheme 1.20). Ester **1.40RS** is the enantiomer of ester **1.40SR** obtained from the reaction of **1.38S** with (*R*)-2-NMA acid. Consequently, $\Delta\delta_H$ between esters **1.40SR** and **1.40SS** were obtained from ^{1}H NMR data of esters **1.40RS** and **1.40SS**. For NMA ester, the subtraction formula is reversed,[39] $\Delta\delta_H = \delta_R - \delta_S$, due to the inverted CIP (Cahn–Ingold–Prelog) priority order of NMA ester compared to MTPA ester (δ_R is the ^{1}H chemical shift of (*R*)-2-NMA ester, δ_S is the ^{1}H chemical shift of (*S*)-2-NMA ester.). After purification by flash chromatography, esters **1.40SS** and **1.40RS** were studied by ^{1}H NMR spectroscopy. All of the key protons of both compounds were unambiguously assigned by a combination of ^{1}H NMR and COSY data. Relevant chemical shifts of protons of esters **1.40SS**, **1.40RS** and their differences are listed in Table 1.3. For comparison, the Δδ values for the Mosher esters were also listed in the last row in Table 1.3.

Scheme 1.20. Synthesis of (S)-2-NMA esters 1.40SS and 1.40RS

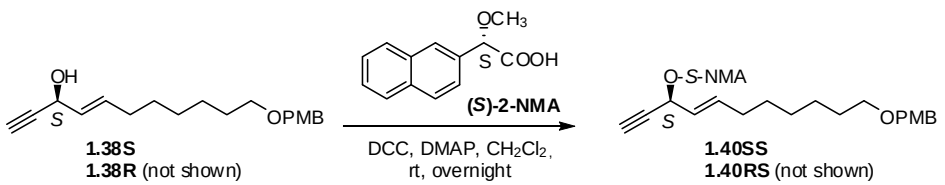
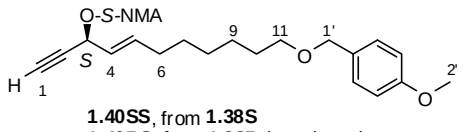


Table 1.3. Δδ ($\delta_{1.40RS} - \delta_{1.40SS}$) values (ppm) obtained from the (*S*)-2-NMA esters of 1.40RS and 1.40SS



1.40SS, from **1.38S**
1.40RS, from **1.38R** (not shown)

protons	1	4	5	6	7	8	9	10	11
$\delta_{1.40RS}$	2.558	5.335	5.798	1.886	1.173	1.149	1.237	1.515	3.393
$\delta_{1.40SS}$	2.444	5.534	5.981	2.038	1.356	1.267	1.329	1.569	3.420
$\Delta\delta$ ($\delta_{1.40RS} - \delta_{1.40SS}$)	0.114	−0.199	−0.183	−0.152	−0.183	−0.118	−0.092	−0.054	−0.027
$\Delta\delta$ ($\delta_{1.39SS} - \delta_{1.39SR}$)*	0.040	−0.110	−0.061	−0.041	−0.032	−0.052	−0.026	−0.011	0.000

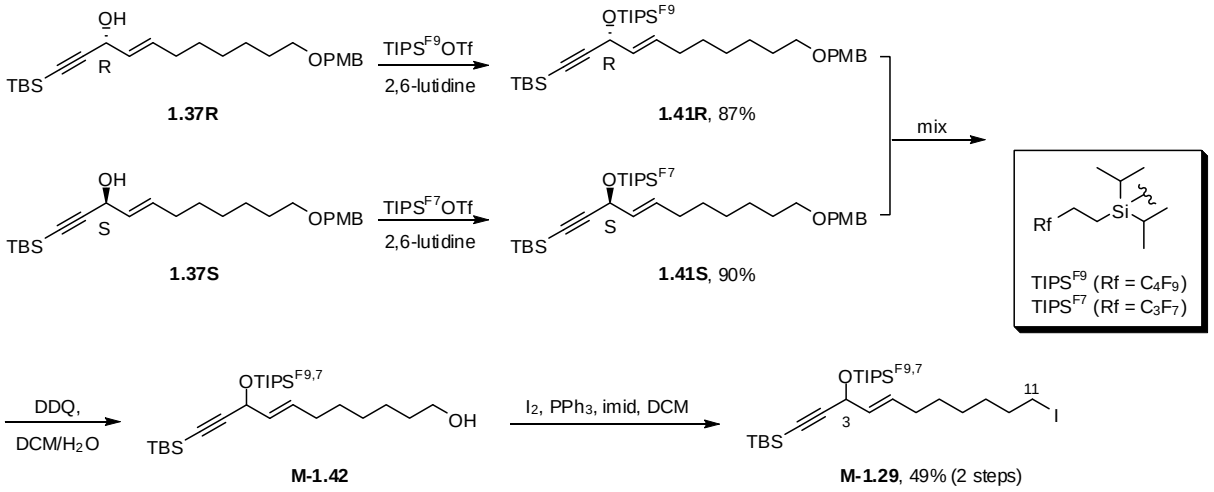
*MTPA ester

First, the results showed that the NMA ester method works for configuration assignment of secondary alcohol. The results also showed that the differences of chemical shifts obtained with NMA esters are much larger than those obtained with MTPA esters. For instance, the difference of chemical shift of NMA esters at H6 is −0.152, but that of MTPA esters is only −0.041. The large $\Delta\delta_H$ allowed us to confirm the C3 absolute configuration of alcohol **1.38S** without ambiguity. The results also showed the long-range anisotropic effect of NMA. For NMA esters, the difference of chemical shift for H11 (nine atoms away from the stereocenter) is −0.027, but for MTPA esters, there is no measurable difference for this proton. Taken together, the results show that NMA esters are superior to MTPA esters for the assignment of absolute configuration.

Alcohols **1.37R** and **1.37S** were then individually tagged with two different tags (Scheme 1.21). The hydroxyl group of **1.37R** was protected by silylation with in situ generated fluorous TIPS triflate bearing the C_4F_9 (F9) group to encode the 3*R* configuration in **1.41R**. Likewise,

silylation of **1.37S** with fluorous TIPS triflate bearing the C_3F_7 (F7) provided the quasienantiomer **1.41S** with the 3*S* configuration encoded. Quasienantiomers **1.41R** and **1.41S** were weighed and mixed with 1:1 molar ratio to generate the first quasiracemate. Although not true racemates, the components of quasiracemates usually have nearly identical physical and spectroscopic properties and chemical reactivities toward achiral reagents.[40] The quasiracemic mixture was deprotected by DDQ to afford alcohol **M-1.42**, which was then converted to iodide **M-1.29** with iodine in the presence of triphenylphosphine and imidazole in CH_2Cl_2 with 49% yield over two steps.

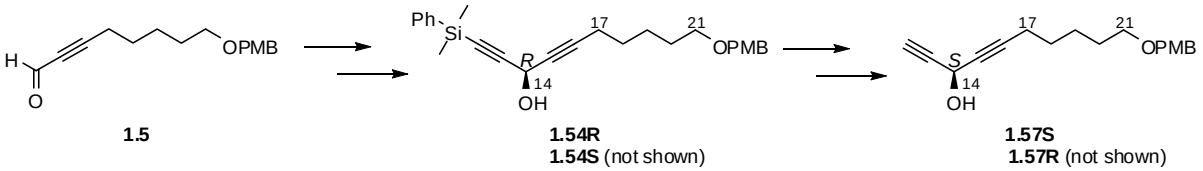
Scheme 1.21. Synthesis of iodide M-1.29



1.2.7 Synthesis of dialkynyl carbinols 1.57R and 1.57S

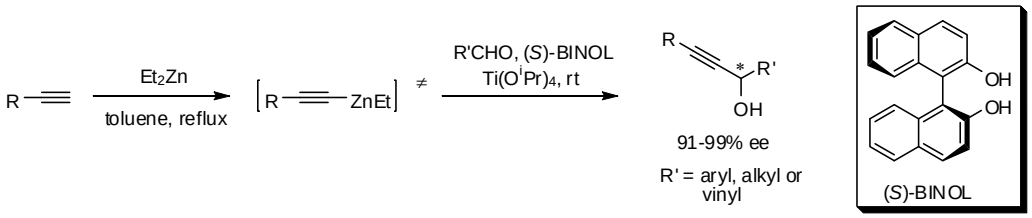
The precursors for synthesis of fragment **M-1.30**, dialkynyl carbinols **1.54R** and **1.54S**, can be synthesized from aldehyde **1.5** and terminal alkyne by asymmetric alkynylation (Scheme 1.22).

Scheme 1.22. Proposed synthetic route for 1.57R/S



The key reaction in this transformation is constructing the stereocenter C14 enantioselectively. After the failure of Carreira's asymmetric alkynylation, we were attracted by a literature report published by Pu and co-workers.[41] They described the asymmetric alkynylations of aldehydes (aromatic, alkyl and vinyl, but no alkynyl aldehyde) using chiral ligand (*S*)-BINOL with $Ti(O^iPr)_4$ in excellent yields and enantioselectivities. In Pu's reaction (Scheme 1.23), a terminal alkyne is first reacted with Et_2Zn to generate an alkynylzinc intermediate. This is then added to the aldehyde and the catalyst to form the chiral propargyl alcohol.

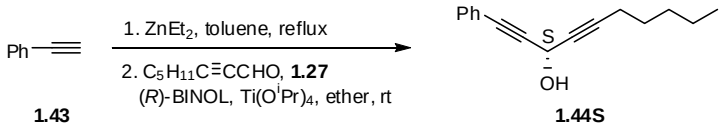
Scheme 1.23. Enantioselective synthesis of propargyl alcohols reported by Pu and coworkers



We set out to find whether Pu's asymmetric addition was applicable to alkynals. We first studied the asymmetric reaction of phenylacetylene **1.43** with 2-octynal **1.27**. A solution phenylacetylene **1.43** and diethylzinc in toluene was heated under argon atmosphere at reflux for

1 h. After the solution had cooled to room temperature, (*R*)-BINOL, Et_2O, and $Ti(O^iPr)_4$ were added sequentially, and the resulting mixture was stirred for 1 h. 2-Octynal **1.27** was added and stirring was continued for an additional 4 h. After purification on silica gel, alcohol **1.44S** was obtained (90–96% yield, Table 1.4). The absolute configuration of this alcohol was tentatively assigned as *S* by analogy to Pu's results with other types of aldehydes.[41]

Table 1.4. Yields and ees of reactions of phenylacetylene 1.43 with 2-octynal 1.27 to give propargyl alcohol 1.44S



1.43 **1.44S**

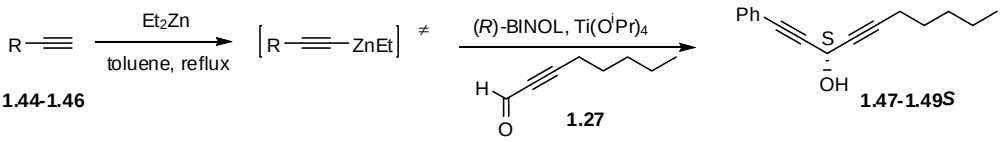
entry	alkyne (equiv)	Et_2Zn (equiv)	[Et_2Zn] (mol/L)	$Ti(O^iPr)_4$ (equiv)	BINOL (equiv)	yield[a] (%)	ee[b] (%)
1	4.0	4.0[c]	1.1	1.0	0.4	96	57
2	4.0	4.0[d]	3.0	1.0	0.4	94	63
3	6.0	6.0[d]	4.5	2.5	1.0	90	78
4	8.0	8.0[d]	6.0	2.5	1.0	92	67

[a]Isolated yield. [b]ee determined by chiral HPLC (Chiralcel OD column, 4.6 × 200 mm, hexane/^{i}PrOH = 9:1, 1.0 mL/min). [c]15 % wt Et_2Zn (1.1 M) in toluene was used. [d]95 % Et_2Zn was used.

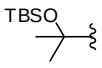
Various conditions were explored for the reaction to optimizing enantioselectivity (Table 1.4). The ee of propargyl alcohol **1.44S** was determined by chiral HPLC. We first used commercially available Et_2Zn solution (15 wt% in toluene ≈ 1.1 M) as source of zinc, but the ee of alcohol **1.44S** was only 57% (entry 1). When 95% Et_2Zn was used, the ee improved to 63% (entry 2). To further increase the ee, we increased the amount of all reagents. This increased the ee to 78% and provided a high yield (90%) (entry 3). In entry 4, we further increased the

amounts of diethylzinc and phenylacetylene **1.43** compared to the aldehyde **1.27**. This decreased the ee to 67%, but still gave an excellent yield (92%). Finally, we chose the conditions of entry 3 as the optimized conditions for this reaction.

Table 1.5. Enantioselective addition of alkynes and aldehyde 1.27



1.44-1.46 **1.27** **1.47-1.49S**

entry	R-	SM	product	yield (%)[a]	ee (%)[b]
1		**1.45**	**1.48S**	90[c]	78
2		**1.46**	**1.49S**	85[c]	80
3		**1.47**	**1.50S**	86	90

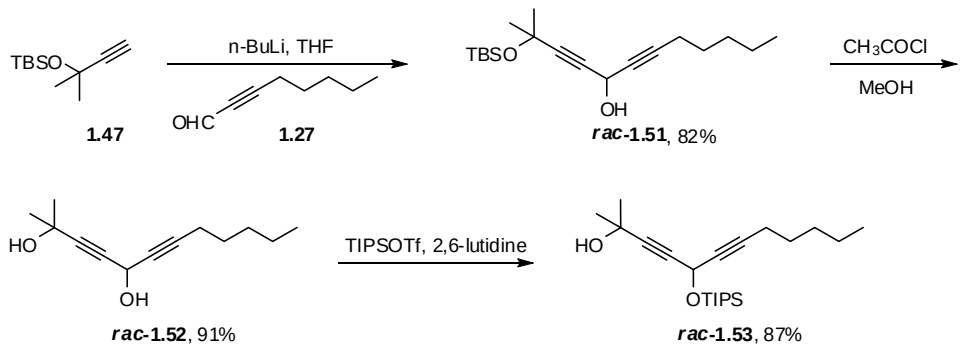
[a]Isolated yield. [b]ee determined by chiral HPLC (Chiralcel OD column, 4.6 × 200 mm, hexane/^{i}PrOH = 49:1, 0.6 mL/min). [c]Product was contaminated with BINOL.

The optimized procedure was then applied to the reactions of several terminal alkynes with 2-octynal **1.27**, and the results of this series of reactions are shown in Table 1.5. The ees of the products were again measured by chiral HPLC. Silylacetylenes generate products that can be easily converted to terminal alkynes by desilylation, so these were tested first. Reaction of dimethylphenylsilylacetylene **1.45** with aldehyde **1.27** gave alcohol **1.48S** in 90% yield and 78% ee (entry 1). When methyldiphenylsilylacetylene **1.46** was used, the yield was 85% and the ee of product **1.49S** was only increased to 80%. We rationalized this small increase due to the relatively long bond length of carbon-silicon bond (1.86 Å). Increasing the size of the silyl group had little impact on enantioselectivity. If an alkyne with shorter bond length between carbon and

R group is used in the reaction, then the enantioselectivity should be improved. 2-Methyl-3-butyn-2-o1 **1.47** is a suitable alkyne, because the bond length of carbon-carbon bonds (1.46 Å) is shorter than carbon-silicon bonds. The addition reaction followed by a facile fragmentation reaction provides an access to the enantioenriched terminal acetylene that could be a useful building block for synthesis of petrocortyne A. When alkyne **1.47** was subjected to this asymmetric addition reaction (entry 3), the product **1.50S** was isolated in 90% ee and 86% yield.

The next goal was to convert the compound **1.50S** to the corresponding terminal acetylene. As a prelude, the model reaction using racemic alcohol ***rac*-1.53** was performed. Compound ***rac*-1.53** was prepared in three steps (Scheme 1.24). Alkyne **1.47** was treated with *n*-BuLi to generate lithium acetylene in situ. This was reacted with aldehyde **1.27** to afford racemic propargylic alcohol ***rac*-1.51** in 82% yield. Alcohol ***rac*-1.51** was then converted to diol ***rac*-1.52** with acetyl chloride in MeOH in 91% yield. TIPS protection of the secondary alcohol of diol ***rac*-1.52** afforded alcohol ***rac*-1.53** in 87% yield.

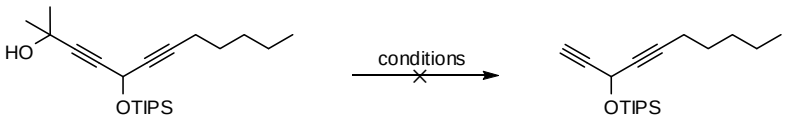
Scheme 1.24. Synthesis of racemic alcohol *rac*-1.53



The fragmentation reaction of alcohol ***rac*-1.53** was conducted under a variety of conditions (Scheme 1.25). Reaction with 40 mol % of 18-crown-6 and K_2CO_3 in refluxing

toluene[42] or under microwave irradiation resulted in decomposition. When the base was changed to KOH, no desired product was detected by TLC analysis and starting material was recovered. This reaction was then carried out in the KH solution of toluene with or without 18-crown-6 at room temperature, but only starting material was obtained.

Scheme 1.25. Unsuccessful fragmentation reaction of alcohol *rac*-1.53



***rac*-1.53**

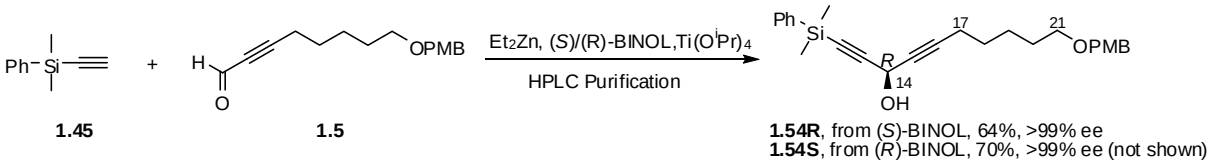
1. 40 mol % 18-crown-6, K_2CO_3, toluene reflux, decomposition
2. 40 mol % 18-crown-6, K_2CO_3, toluene microwave (30 min, 150 °C), decomposition
3. 40 mol % 18-crown-6, KOH, toluene reflux, recovered starting material
4. 40 mol % 18-crown-6, KH, toluene rt, recovered starting material
5. KH, toluene rt, recovered starting material

Because of the difficulty of performing a fragmentation reaction of ***rac*-1.53**, the product generated from dimethylphenylsilylacetylene **1.45** was chosen as the precursor to synthesize fragment **M-1.30**. Alcohol **1.54R** was synthesized according to the optimized version of Pu's procedure (Table 1.4 entry 3). Commercially available dimethylphenylsilylacetylene **1.45** was treated with Et_2Zn in refluxing toluene for 1 h to afford the alkynylzinc intermediate. Aldehyde **1.5** was then added with (*S*)-BINOL and $Ti(O^iPr)_4$ to form (*R*)-dialkynyl methanol **1.54R** (Scheme 1.26). Alcohol **1.54R** was contaminated with residual (*S*)-BINOL, which was difficult to remove by flash chromatography. Furthermore the ee of alcohol **1.54R**, while a substantial (83% determined by chiral HPLC: Chiralcel OD column, 4.6 × 200 mm hexane:^{i}PrOH = 9:1, 1.0 mL/min), did not meet our target level of ee >90%. Enantiomeric impurities at this stage would

produce diastereomeric impurities downstream, and we did not know whether or how the impurities could be either separated or identified.

In order to increase the ee and get rid of BINOL in alcohol **1.54R**, purification by preparative HPLC was undertaken. The enantiomerically pure (>99% ee) alcohol **1.54R** was obtained in 64% yield (269.3 mg) by using semi-preparative Chiralcel OD column (20 × 250 mm, hexane:^{i}PrOH = 19 : 1, 8.0 mL/min, 1.0 mL (0.1 M in hexane)/injection, 320 mg of crude product). Similarly, (*S*)-dialkynyl methanol **1.54S** (not shown) was obtained by addition of alkynylzinc to aldehyde **1.5** in the presence of (*R*)-BINOL and Ti($O^{i}Pr$)$_4$ in 83% ee too. After purification by HPLC (350 mg of crude product), the enantiomerically pure alcohol (>99% ee) **1.54S** was obtained in 70% yield (294.6 mg).

Scheme 1.26. Synthesis of alcohols 1.54R and 1.54S



1.45 **1.5**

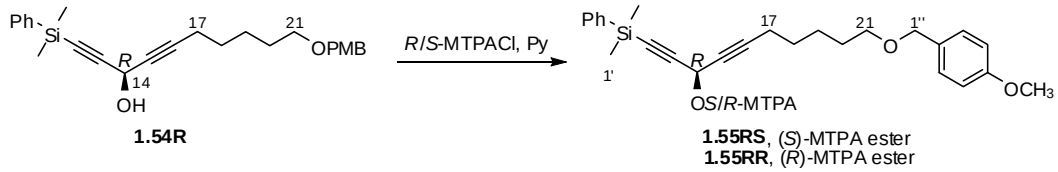
1.54R, from (*S*)-BINOL, 64%, >99% ee
1.54S, from (*R*)-BINOL, 70%, >99% ee (not shown)

With alcohols **1.54R/S** in hand, we next used them as models to validate the Mosher method for assigning the configuration at C14. It is more difficult to assign the C14 stereocenter than C3 for two reasons. First, there are no protons directly attached to the carbons adjacent to the C14 stereocenter. Second, because there is a local plane symmetry, the peaks of protons at C10 and C17 in ^{1}H NMR are overlap. Making the Mosher esters breaks this local symmetry and differentiates the protons at C10 and C17. It is essential to correctly assign the resonances for protons at C10 and C17 before applying the Mosher method. If the resonances are mis-assigned, then the stereocenter configuration will be mis-assigned.

To unambiguously assign pairs of propargylic methylene protons, we chose dialkynyl carbinol **1.54R** and/or **1.54S** as a model system with only one propargylic methylene group. We then made both MTPA and 2-NMA esters of alcohol **1.54**. Each of the pair of enantiomeric MTPA acid chlorides was reacted with **1.54R** in dry pyridine to provide the pair of Mosher esters **1.55RS** and **1.55RR**, while the single (*S*)-2-NMA acid was reacted with the pair of enantiomers **1.54R** and **1.54S** to give the NMA esters pair **1.56RS** and **1.56SS**. All of key protons of two pairs of esters were assigned by a combination of ^{1}H NMR and COSY spectra. The relevant chemical shifts of protons of Mosher esters **1.55RS**/**RR** and NMA esters **1.56RS**/**SS** and the differences of resonances of corresponding pairs ($\delta_S - \delta_R$ for Mosher esters and $\delta_R - \delta_S$ for NMA esters) are listed in Table 1.6 and 1.7, respectively. The configuration of stereocenter C14 at alcohol **1.54R** was assigned as *R* by applying either the Mosher method or NMA ester method.

Although the differences of proton resonances of both Mosher ester pairs and NMA ester pairs have negative sign on one side of the stereocenter and positive sign on the other side, the magnitudes are very different. For example, the largest chemical shift difference in the Mosher esters is only 0.029 ppm for the protons at the C17, while in NMA esters, this difference is 0.158 ppm. The large $\Delta\delta_H$ allowed us to confirm the C14 absolute configuration of alcohol **1.54S** without ambiguity. Besides the larger chemical shift differences, the NMA esters have a longer anistropic effect. No difference was measured for the benzylic protons H1" (10 atoms away from the stereocenter) in Mosher esters, but the difference of 0.022 ppm was measured in NMA esters. Taken together, NMA esters are superior to MTPA esters for the assignment of configuration of stereocenters with local symmetry.

Table 1.6. Δδ ($\delta_{1.55RS} - \delta_{1.55SS}$) values (ppm) obtained from the MTPA esters of 1.55RS and 1.55RR

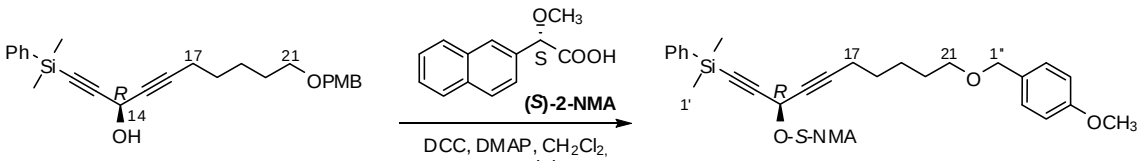


1.54R

1.55RS, (*S*)-MTPA ester
1.55RR, (*R*)-MTPA ester

position	1'	17	18	19	20	21	1"
$\delta_{1.55RS}$	0.405	2.242	1.534	1.444	1.598	3.415	4.410
$\delta_{1.55RR}$	0.428	2.213	1.511	1.420	1.587	3.413	4.410
$\Delta\delta$ ($\delta_{1.55RS} - \delta_{1.55RR}$)	−0.023	0.029	0.023	0.024	0.011	0.002	0.000

Table 1.7. Δδ ($\delta_{1.56SS} - \delta_{1.56RS}$) values (ppm) obtained from the MTPA esters of 1.56SS and 1.56RS



1.54R
1.54S (not shown)

1.56RS, (*S*)-NMA ester
1.56SS, (*S*)-NMA ester (not shown)

position	1'	17	18	19	20	21	1"
$\delta_{1.56SS}$	0.249	2.212	1.510	1.429	1.587	3.413	4.414
$\delta_{1.56RS}$	0.400	2.054	1.335	1.277	1.484	3.349	4.392
$\Delta\delta$ ($\delta_{1.56SS} - \delta_{1.56RS}$)	–0.151	0.158	0.175	0.152	0.103	0.064	0.022

From the above results, we validated the use of the Mosher method and the NMA ester method to assign the configuration at C14. Because of larger and longer anistropic effect of the NMA group, the NMA ester method is easier and more reliable to assign the configuration of the stereocenter, especially in a compound with local symmetry, such as petrocortyne A.

Continuing the synthesis of **1.57S**/**R**, silylacetylenes **1.54R** and **1.54S** were then treated with TBAF to generate terminal alkynes **1.57S** and **1.57R** in 85% and 89% yield, respectively (Scheme 1.27).

Scheme 1.27. Synthesis terminal alkynes 1.57S and 1.57R

1.54R
1.54S (not shown)

1.57S, 85%
1.57R, 89% (not shown)

Before the alcohols **1.57S** and **1.57R** were individually tagged with different fluorous tags, several model reactions were carried out to make sure that every step could work for the synthesis of fragment **M-1.2**.

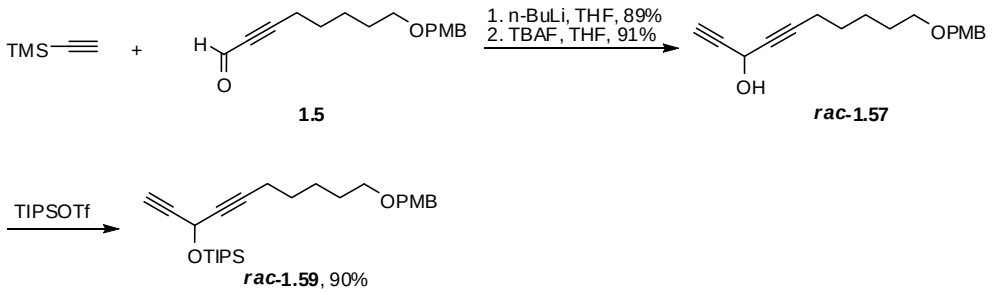
1.2.8 Towards the synthesis of fragment M-1.2 with silyl ether *rac*-1.59

After completing the syntheses of iodide **M-1.29** and alcohols **1.57R**/**S**, we initiated our task for the coupling reaction of iodide **M-1.29** with alkyne **M-1.30** derived from alcohols **1.57R** and **1.57S**. A model coupling reaction between commercially available iodide **1.58** and alkyne ***rac*-1.59** was first conducted before the iodide **M-1.29** and alcohol **1.57R**/**S** were used in the coupling reaction.

Terminal alkyne ***rac*-1.59** was easily prepared in a three-step procedure (Scheme 1.28). Trimethylsilylacetylene was treated with *n*-BuLi to generate ((trimethylsilyl)ethynyl)lithium, which was reacted with aldehyde **1.5** to give a racemic alcohol in 89% yield. After removal of

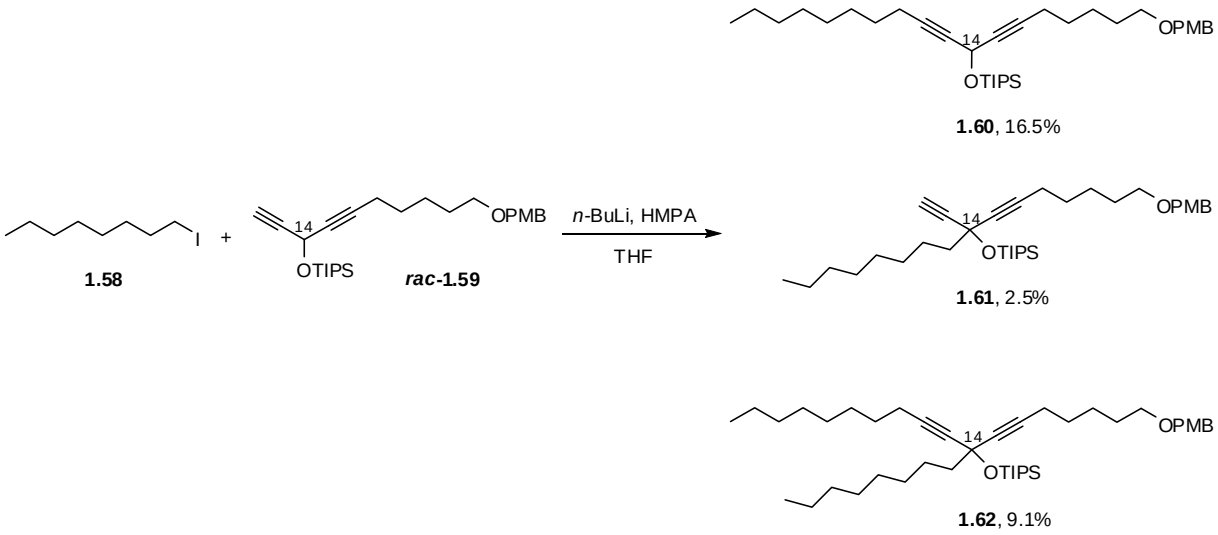
the TMS group with TBAF, the secondary alcohol ***rac*-1.57** was protected with TIPS group to afford alkyne ***rac*-1.59** in 90% yield.

Scheme 1.28. Synthesis terminal alkyne *rac*-1.59



The results of the model coupling reaction of iodide **1.58** (model for C1–C10 fragment) and alkyne ***rac*-1.59** were shown in Scheme 1.29. After treatment of ***rac*-1.59** with *n*-BuLi in THF at −78 °C for 1 h, a solution of iodide **1.58** in THF and HMPA was added. After workup and flash chromatography purification, three major products were isolated. The desired coupling product **1.60** was isolated in 16.5% yield along with the two undesired products **1.61** (2.5%) and **1.62** (9.1%) (Structures were determinated by ^{1}H NMR). The side products arrived from the deprotonation of the protected dialkynylcarbonol proton (proton at C14). Even if the alkylation at C14 could be prevented, this deprotonation still cause epimerization at C14 of substrates (***rac*-1.59**).

Scheme 1.29. Model coupling reaction of iodide 1.58 and alkyne *rac*-1.59



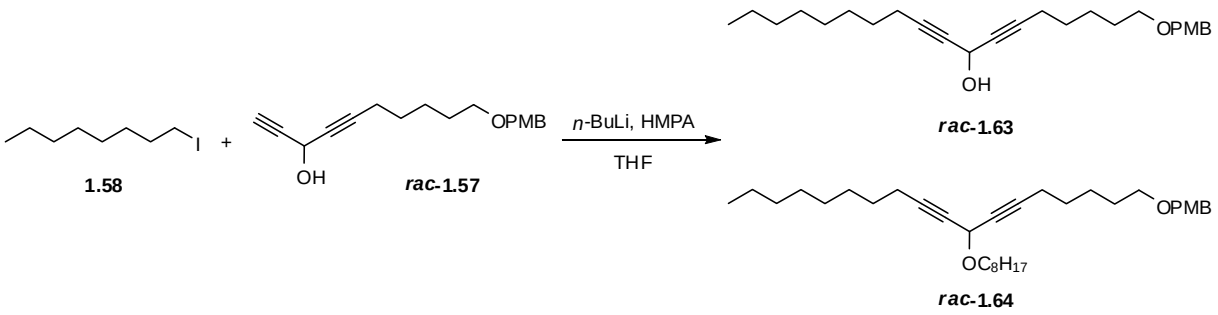
To suppress the undesired products and avoid the epimerization at the C14 stereocenter, we decided to conduct the coupling reaction on a dianion derived from free alcohol ***rac*-1.57**. Under the conditions for formation of dianion of ***rac*-1.57** by its treatment with *n*-BuLi, there should be no anion formation at C14 to give a trianion.[43]

1.2.9 Towards the synthesis of fragment M-1.2 by using dianion strategy

The model dianion alkylation was performed between iodide **1.58** and free alcohol ***rac*-1.57** (Scheme 1.30). Alcohol ***rac*-1.57** was treated with 2 equiv of *n*-BuLi to generate dianion in situ, which was then reacted with 2 equiv of iodide **1.58**. In addition to the desired product ***rac*-1.63** (26% yield), O-alkylated product ***rac*-1.64** was also isolated in 25% yield and its structure was confirmed by ^{1}H NMR. The 19% of alcohol ***rac*-1.57** was recovered (entry 1). In entry 2, 1:1 ratio of alkyne and iodide were subjected to the reaction also gave byproduct ***rac*-1.64** (10%) in addition to desired product ***rac*-1.63** (13%). The starting material ***rac*-1.57** was recovered in 51%.

When a 2:1 ratio of alkyne and iodide were used, only product ***rac*-1.63** was obtained in 59% yield with 65% recovered ***rac*-1.57** (entry 3).

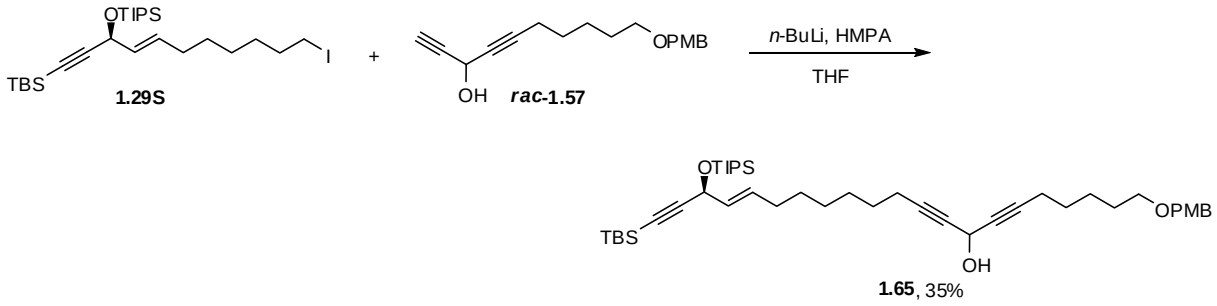
Scheme 1.30. Model reaction of iodide 1.58 and alkyne *rac*-1.57



entry	**1.58**/equiv	***rac*-1.57**/equiv	*n*-BuLi/equiv	***rac*-1.63**/%	***rac*-1.64**/%	***rac*-1.57**/%
1	2.0	1.0	2.2	25	26	19
2	1.0	1.0	2.2	13	10	51
3	1.0	2.0	4.4	59	0	65

We then carried out the coupling reaction of iodide **1.29S** with dialkynol ***rac*-1.57** (Scheme 1.31). Dialkynol ***rac*-1.57** was treated with 2 equiv of *n*-BuLi to generate dianion in situ, then iodide **1.29*S*** was added. Standard workup and chromatography provided coupled product **1.65** in 35% yield. Substantial starting material ***rac*-1.57** remained, and **1.65** was the only new product of the reaction.

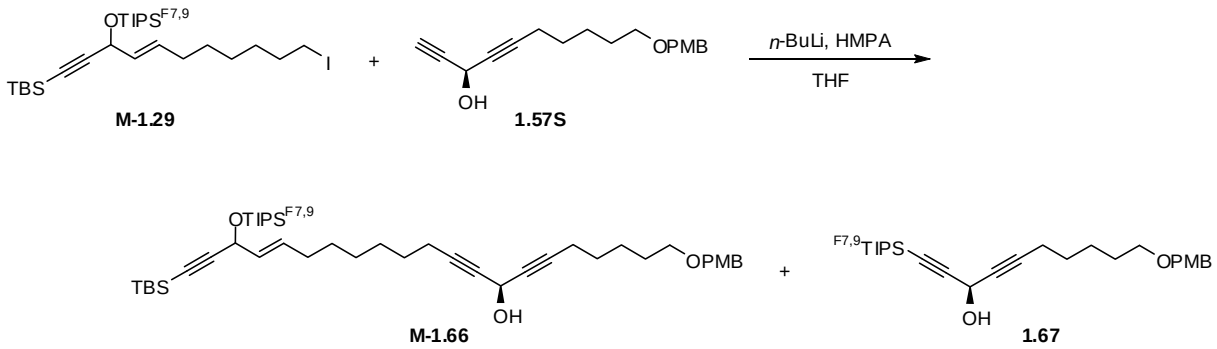
Scheme 1.31. Coupling reaction of iodide 1.29S and dialkynol *rac*-1.57



The coupling reaction of the iodide **M-1.29** and dialkynol **1.57S** was then performed (Scheme 1.32). The quasiracemate **M-1.29** was added to the dianion derived from **1.57S**. Again, a single new spot appeared on TLC analysis. However, this time the chromographically isolated product (30% yield) was not the pure quasiracemate **M-1.66**. Instead, this was contaminated by a substantial amount (about 50%) of a second component **1.67** resulting from transfer of the fluorous TIPS groups of **M-1.29** to the terminal acetylide of **1.57S**. These compounds were not separable, but the structure of **1.67** was secured by MS (*m*/*z* = 596.7 and 646.7) and NMR analysis of mixture. In particular, the ^{1}H NMR spectrum of the mixture exhibited no terminal acetylide proton resonance, so the TIPS^{F} group in alcohol **1.67** must be connected to the terminal acetylide and not to the alcohol.

Suspecting that this reaction provided the byproduct because of liability of the TIPS^{F} under the nucleophilic environment, we conspired to block this side reaction by applying the new second-generation TIPS^{F} tags with a propylene spacer, $Rf(CH_2)_3Si(iPr)_2$, to reduce the electrophilic reactivity of TIPS^{F} tags.[44]

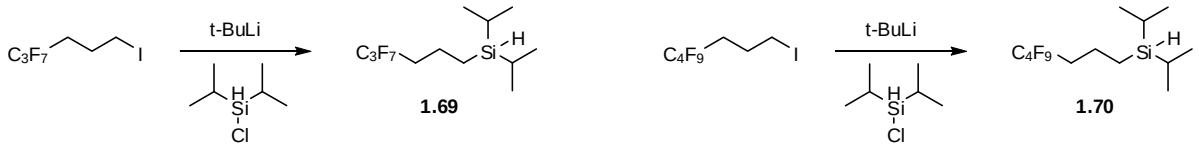
Scheme 1.32. Coupling reaction of iodide M-1.29 and dialkynol 1.57S



1.2.10 Synthesis of the second-generation TIPS^{F} tags and new iodide M-1.68

The second-generation TIPS^{F} tags **1.69** and **1.70** were synthesized from the corresponding perfluoroalkyl iodides and chlorodiisopropylsilane (Scheme 1.33).[44] The perfluoro carbon units in the two fluorous tags are C_3F_7 (TIPS$^{F7'}$) and C_4F_9 (TIPS$^{F9'}$). The "prime(′)" in the formula represents the propylene spacer.

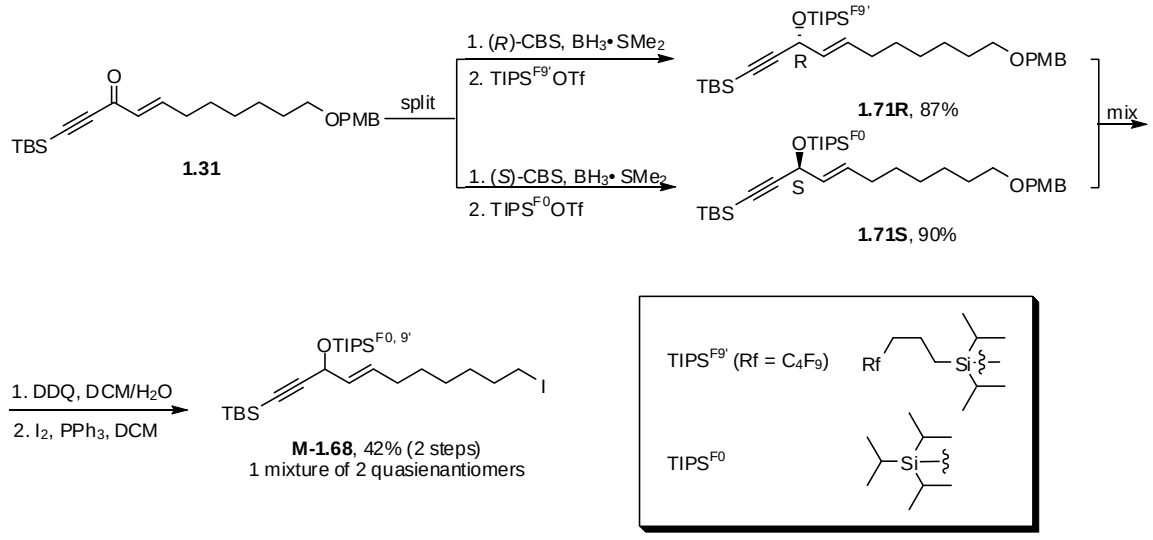
Scheme 1.33. Synthesis of the second-generation TIPSF 1.69 and 1.70



The synthesis of new iodide **M-1.68** starts from the common intermediate ketone **1.31** (Scheme 1.34). Asymmetric reduction of ketone **1.31** using BH_3 in the presence of the catalyst (*R*)-CBS proceeded in 70% yield with high enantiomeric selectivity (93%) to provide (*R*)-alcohol **1.37R**. Similarly, (*S*)-alcohol **1.37S** was generated by the reduction of alkynyl ketone **1.31** using (*S*)-CBS in 73% yield with 94% ee. Fluorosilane **1.70** bearing C_4F_9 (TIPS$^{F9'}$) group was treated

trifluoromethansulfonic acid at −78 °C to generate $TIPS^{F9'}OTf$ in situ. This was then reacted with the hydroxy group of **1.37R** to encode the 3*R* configuration in **1.71R**. Likewise, silylation of **1.37S** with general TIPS triflate provided the quasienantiomer **1.71S** with the 3*S* configuration encoded by TIPS ($TIPS^{F0}$) group. Quasienantiomers **1.71R** and **1.71S** were weighed and mixed with 1:1 molar ratio to generate the starting mixture. The mixture was deprotected by DDQ to afford alcohol, which was then converted to iodide **M-1.68** with iodine in the presence of triphenylphosphine and imidazole in CH_2Cl_2 with 42% yield (5.62 g) over two steps.

Scheme 1.34. Synthesis of new iodide M-1.68

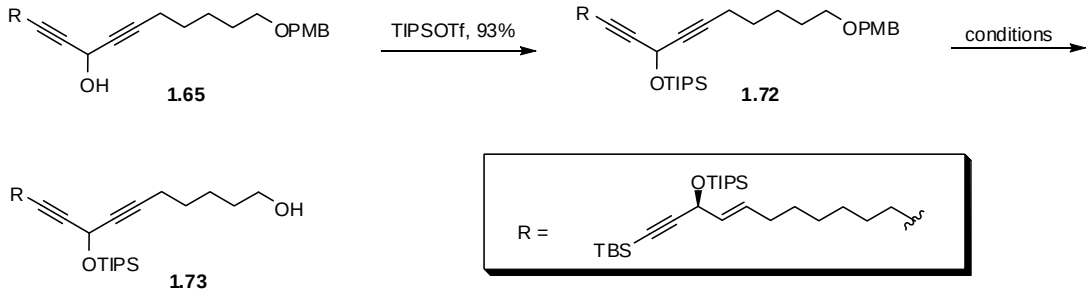


1.2.11 Unexpected difficulty of removal of PMB group in compound 1.65

In parallel with the syntheses of the second-generation $TIPS^F$ tags and new iodide **M-1.68**, we also continued the pilot synthesis from compound **1.65**. After protection of the hydroxyl group by TIPS, the resulting TIPS ether **1.72** was subjected to various conditions to remove the

PMB group (Scheme 1.35). We first tried DDQ deprotection in DCM with the pH 7 buffer, but many spots appeared on TLC analysis (entry 1). When the 3 equiv of ceric ammonium nitrate (CAN) was used in acetonitrile with pH 7 buffer, only 28% of desired alcohol **1.73** was obtained and 50% starting material was recovered (entry 2). When the amount of CAN was increased to 5 equiv, the yield of product **1.73** did not change, but the recovered PMB ether **1.72** decreased to 37% (entry 3). We suspected that the substrate, especially the alkynyl alkenyl carbinol unit, was not stable under oxidative cleavage conditions. We then turned to Lewis acids. When $MgBr_2 \cdot Et_2O$ and Me_2S were used,[45] only starting material was recovered (room temperature) or decomposition occurred (refluxing) (entry 4). Sonication of a solution of PMB ether **1.72** in DCM at rt for 5 min also gave nothing but starting material (entry 5).

Scheme 1.35. Unsuccessful removal of PMB group



entry	conditions	yield	comments
1	DDQ (1.2 + 0.3 equiv), pH7 buffer, DCM, rt	/	complex TLC
2	CAN (3.0 equiv), pH7 buffer, CH_3CN, rt	28%	recovered SM 50%
3	CAN (5.0 equiv), pH7 buffer, CH_3CN, rt	27%	recovered SM 37%
4	$MgBr_2 \cdot Et_2O$, Me_2S, DCM, rt/reflux	/	NR (rt), decomposition (reflux)
5	Sonication 5 min, DCM, rt	/	NR

Faced with difficulty of removal of the PMB group in compound **1.72**, we considered other protecting group options. The protecting group should be easily removed after the precursor of fragment **M-1.2** was obtained. In order to circumvent this issue, we chose to protect the hydroxyl group as MTM (methylthiomethyl) ether.[46] So it was necessary to synthesize the new middle fragment as an MTM ether.

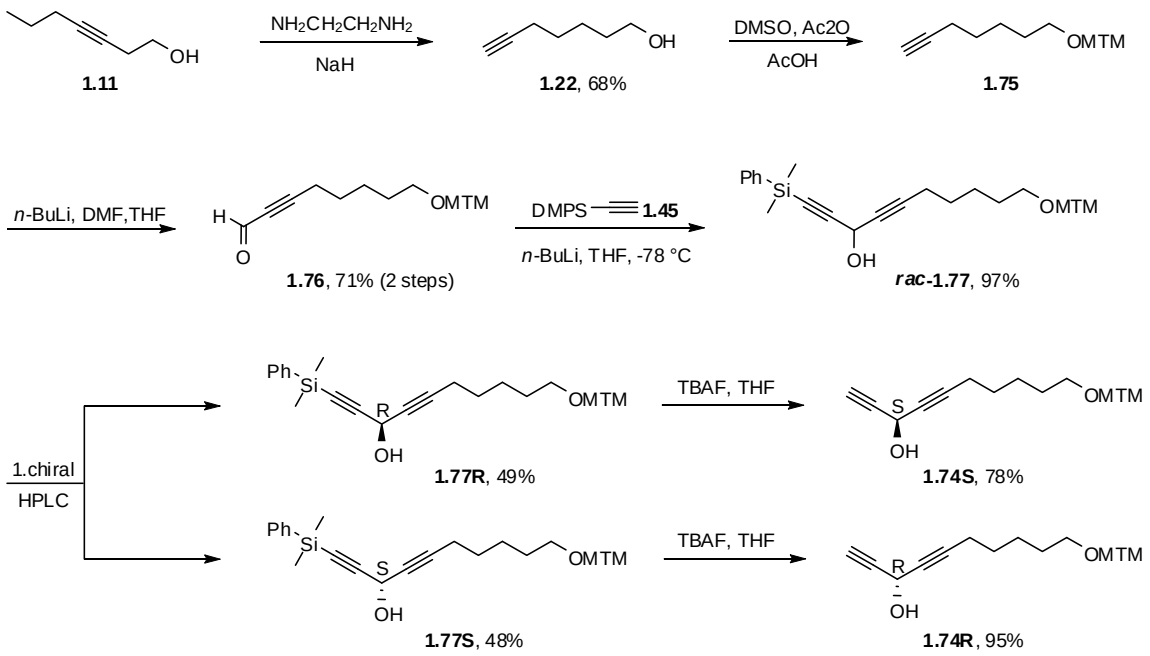
1.2.12 Synthesis of middle fragment MTM ethers 1.74S and 1.74R

The synthesis of alcohol **1.74S** and **1.74R** started from the commercially available 3-heptyn-1-ol **1.11** (Scheme 1.36), which was treated with sodium hydride in warm ethylenediamine to provide alkynol **1.22** by a zipper reaction in 68% yield. Alcohol **1.22** was protected by reacting with DSMO in the presence of AcOH in Ac_2O to generate MTM ether **1.75**.[46b] This was used directly in next step. According to the procedure of Journet and Cai,[32] MTM ether **1.75** was metallated with *n*-BuLi in THF, and resulting lithium acetylide was formylated by DMF. Workup under mild acidic conditions (10% aqueous $KHPO_4$) provided aldehyde **1.76** in 71% yield over two steps. Treatment of aldehyde **1.76** with the lithium (dimethylphenylsilyl)alkynide **1.45** afforded racemic alcohol ***rac*-1.77** in 97% yield.

In analyzing the ees from Pu reactions, we have found that the enantiomers of products like ***rac*-1.77** were well separated on a Chiralcel OD chiral column. Thus, instead doing two asymmetric alkyne additions and upgrading the ees of those enantiomeric products, we simply made racemic ***rac*-1.77** on gram scale and resolved it. The racemic alcohol ***rac*-1.77** was preparatively resolved by chiral HPLC to provide two enantiomerically pure alcohols **1.77R** in

49% yield and **1.77S** in 48% yield. Both samples had ees ≥ 99% by chiral HPLC analysis. The absolute configurations of two alcohols were assigned by advanced Mosher method. The terminal dimethylphenylsilyl group in **1.75R** was removed by TBAF in THF to afford **1.74S** in 78% yield. Likewise, alcohol **1.74R** was obtained in 95% yield from **1.75S**.

Scheme 1.36. Synthesis of MTM ether 1.74S and 1.74R



1.2.13 Successful synthesis of fragment M-1.2

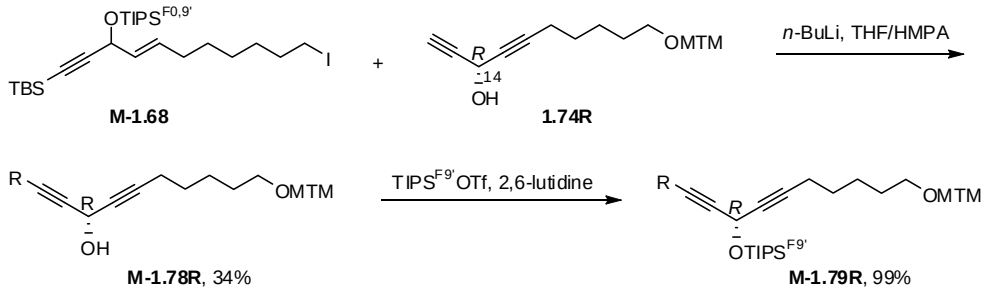
We envisioned an S_N2 nucleophilic addition to an iodide as the key coupling step to combine fragments **M-1.68** and **1.74S/R** (Scheme 1.37). In order to avoid racemization at C14 of **1.74S/R**, we decided to employ the dianion derived from **1.74S/R** for its alkylation with iodide **M-1.68** based on the results of the model reaction in Scheme 1.30. Formation of dianion of

1.74S/R by its treatment with *n*-BuLi should be clean and there should be no deprotonation at C14 of **1.74S/R** to give a trianion. We therefore prepared two quasi-diastereomeric compounds by dianion alkylation. Treatment of alcohol **1.74R** in THF/HMPA with 2.2 equiv of *n*-BuLi generated the dinaion. This was alkylated with **M-1.68** to provide the first quasi-diastereomeric product **M-1.78R** in 34% yield. The sample of **M-1.78R** was then tagged with a second-generation fluorous TIPS triflate bearing the C_4F_9 group ($TIPS^{F9'}$) to afford **M-1.79R** in 99% yield. Similarly, we prepared **M-1.79S** by alkylation of **1.74S** with **M-1.68** in 33% yield and tagged this with C_3F_7 variant of second-generation fluorous TIPS group ($TIPS^{F7'}$) in 85% yield. Although the yields of alkylations were moderate, there was no evidence of silyl transfer from the **M-1.68** to terminal acetylide of **1.74R**/**S**. Thus, the propylene spacer did its job.

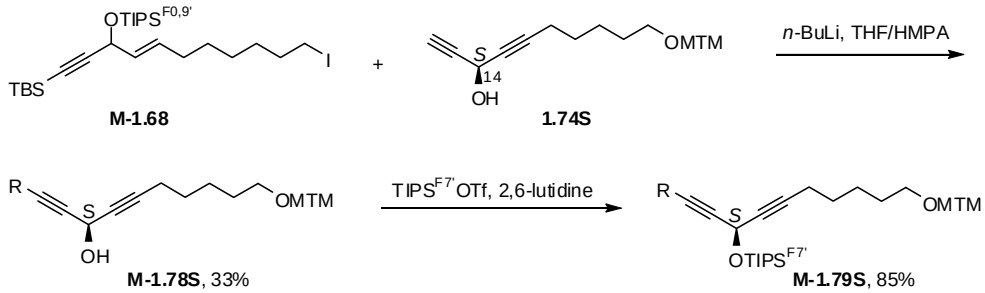
Quasidiastereomers **M-1.79R** and **M-1.79S** were then mixed in a 1/1 ratio to provide the mixtures of four quasiisomers. MTM deprotection was accomplished under mild alkylation conditions (MeI, $NaHCO_3$, aqueous acetone)[46a] to give alcohol **M-1.80** in 90% yield, and subsequent treatment with Dess-Martin periodinane gave the aldehyde **M-1.2** (338.5 mg) in 74% yield.

Scheme 1.37. Synthesis of fragment M-1.2

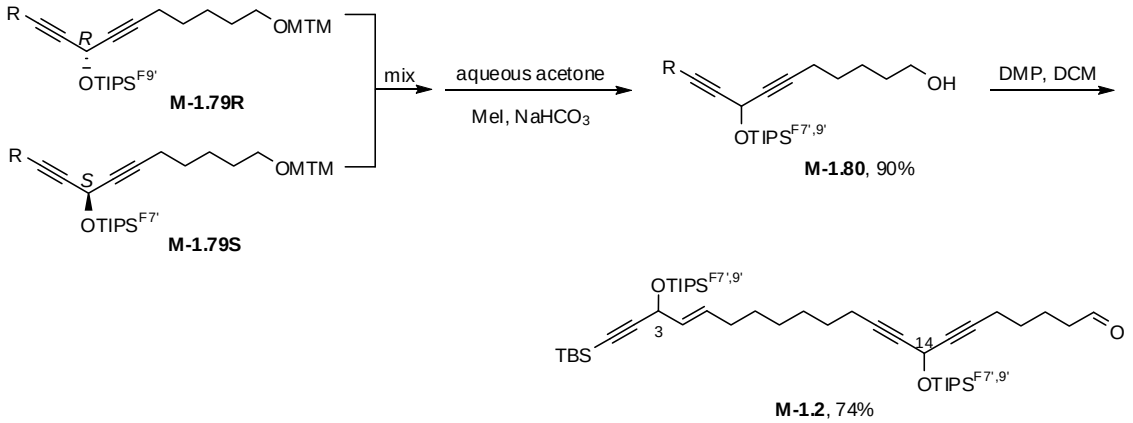
Synthesis of **M-1.79R**

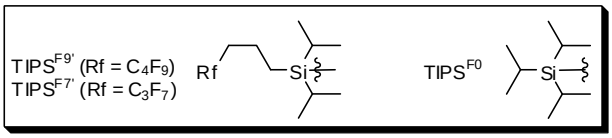


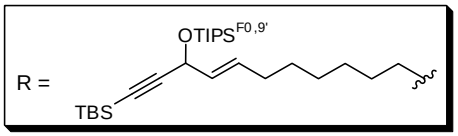
Synthesis of **M-1.79S**



Synthesis of **M-1.2**





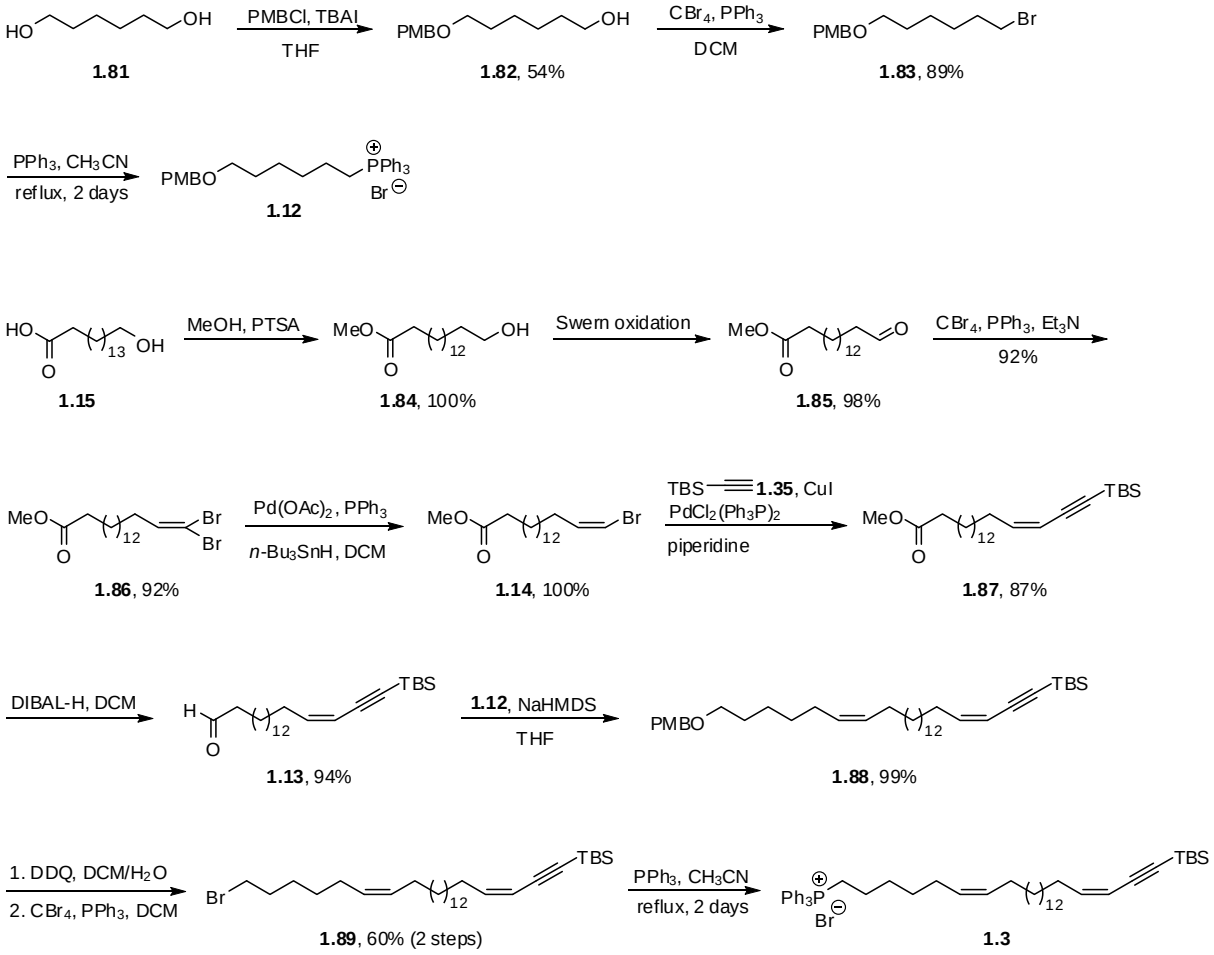


1.2.14 Synthesis of C22–C46 fragment 1.3

The synthesis of fragment **1.3** is summarized in Scheme 1.38. Commercially available 1,6-hexanediol **1.81** was treated with sodium hydride (1.0 equiv) and PMBCl (1.0 equiv) in the presence of TBAI in THF to provide the mono-PMB ether **1.82** in 54% yield. Alcohol **1.82** was converted to bromide **1.83** with CBr_4 in 89% yield.[47] The corresponding phosphonium salt **1.12** was derived from bromide **1.83** with triphenylphosphine in refluxing acetonitrile for 2 days.[47] Ester **1.84** was obtained from 16-hydroxyhexadecanoic acid **1.15** by the reaction with MeOH in the presence of *p*-toluenesulfonic acid with quantitative yield.[48] Swern oxidation of ester **1.84** provided aldehyde **1.85** in 98% yield.[49] The gem-dibromoalkene **1.86** was obtained, in excellent yield (92%) by Wittig homologation of aldehyde **1.85** in the presence of PPh_3 and CBr_4.

Stereoselective palladium-catalyzed hydrogenolysis of **1.86** with *n*-Bu_3SnH was then performed, yielding the desired *Z*-vinyl bromide **1.14** quantitatively. Sonogashira cross-coupling reaction of **1.14** with *tert*-butyldimethylsilylacetylene **1.35** was successfully carried out with $Pd(PPh_3)_2Cl_2$ and CuI in piperidine to furnish ester **1.87** in 87% yield. Conversion of ester **1.87** to aldehyde **1.13** was effected by DIBAL reduction in 94% yield. Wittig olefination reaction of **1.13** with the ylide derived from triphenylphosphonium salt **1.12** (NaHMDS, THF, −78 °C to rt) afforded olefin **1.88** in 99% yield with complete *Z*-selectivity. Deprotection of PMB ether **1.88** with DDQ in DCM/H_2O provided alcohol, which was directly brominated by CBr_4 in the presence of PPh_3 to furnish bromide **1.89** in 60% yield over two steps. The bromide **1.89** was then treated with excess PPh_3 in refluxing acetonitrile for 2 days to provide corresponding triphenylphosphonium salt **1.3** (6.8 g).

Scheme 1.38. Synthesis of triphenylphosphonium salt 1.3



1.2.15 Synthesis of four isomers of petrocortyne A

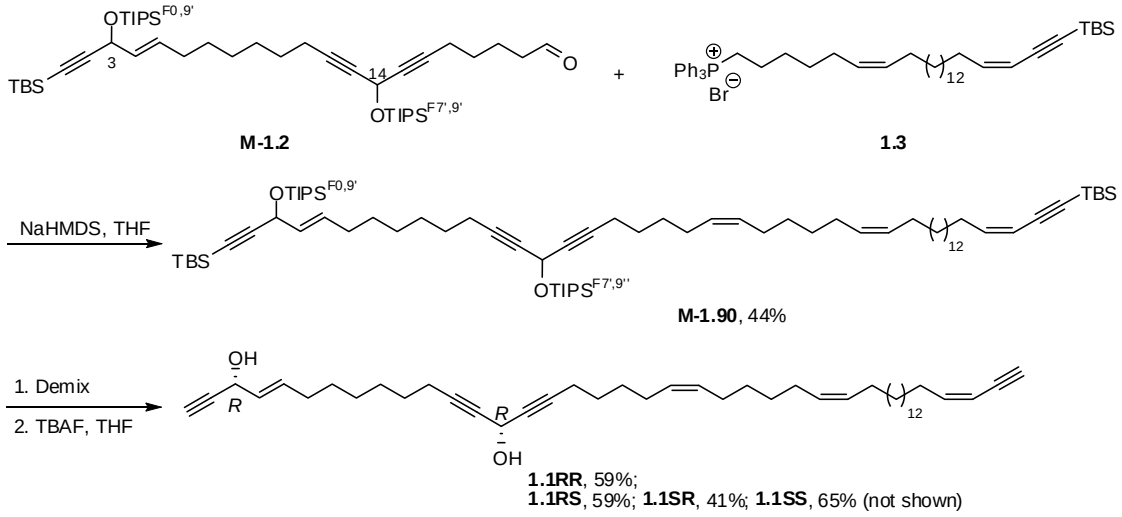
With the two large fragments **M-1.2** and **1.3** in hand, we finished the synthesis of four isomers of petrocortyne A as shown in Scheme 1.39. The mixture of four aldehydes **M-1.2** was subjected to Wittig olefination with phosphonium salt **1.3** to afford final mixture **M-1.90** in 44% isolated yield. The low yield of this reaction was caused by instability of **M-1.90**, which slowly

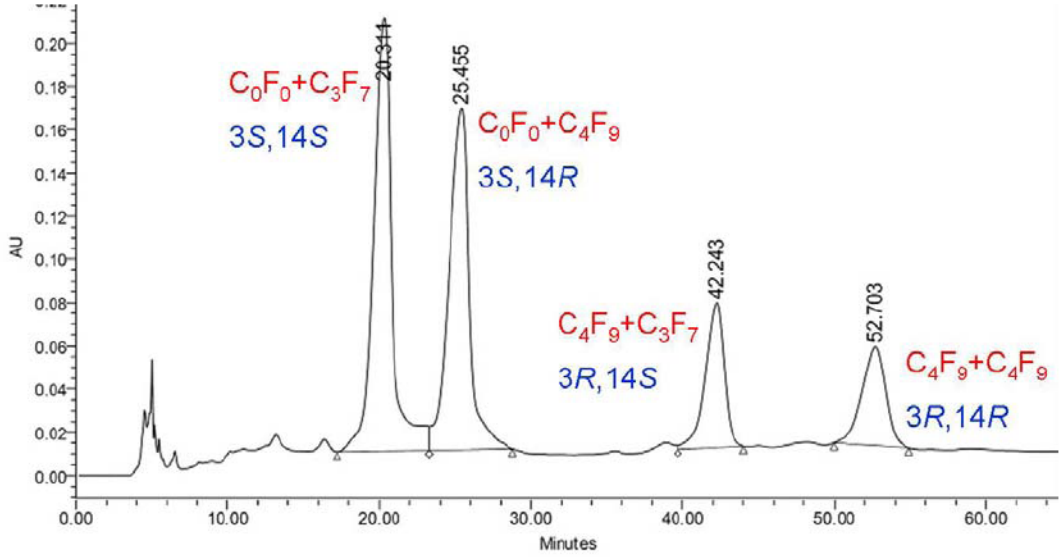
decomposed during the purification. The 1H NMR of **M-1.90** showed that about 50% of the compound **M-1.90** decomposed in one week at −20 °C.

The mixture **M-1.90** was quickly demixed into four individual quasiisomers by preparative fluorous HPLC. Demixing was conducted on a Waters high-performance liquid chromatograph by fluorous chromatography over a *FluoroFlash*^{TM} PFC8 column (10 mL/min) with the following gradient: 0 to 45 min, 100% CH_3CN up to 85% CH_3CN/15% THF; 45 to 65 min, keep 85% CH_3CN/15% THF. A representative preparative HPLC demixing chromatogram of mixture **M-1.90** is shown in Figure 1.7. The four mixture compounds (137.2 mg) were well separated and eluted in order of increasing fluorine content to give the four quaiisomers **1.90[F0,7′]** (41.3 mg) (represents the quasiisomer bearing $TIPS^{F0}$ and $TIPS^{F7'}$ groups), **1.90[F0,9′]** (39.5 mg), **1.90[F9′,7′]** (16.0 mg) and **1.90[F9′,9′]** (19.7 mg). The combined recovery of demixing was 85%. All four quaiisomers decomposed slightly during the demixing, so the compounds were subjected to the next step immediately.

All four quasiisomers were then deprotected individually by exposure to TBAF in THF to provide four final products **1.1SS** (11.4 mg), **1.1SR** (10.4 mg), **1.1RS** (2.1 mg) and **1.1RR** (5.1 mg) in 59%, 59%, 41% and 65% yields, respectively. The complete structures of these final products are shown in Figure 1.8 along with their optical rotations and the fluorous tagging scheme for reference.

Scheme 1.39. Synthesis of petrocortyne A 1.1





Conditions: *FluoroFlash*™ PFC8 column, 10 mL/min, 0 to 45 min, 100% CH_3CN up to 85% CH_3CN/15% THF; 45 to 65 min, keep 85% CH_3CN/15% THF.

Figure 1.7. Representative HPLC demixing chromatogram

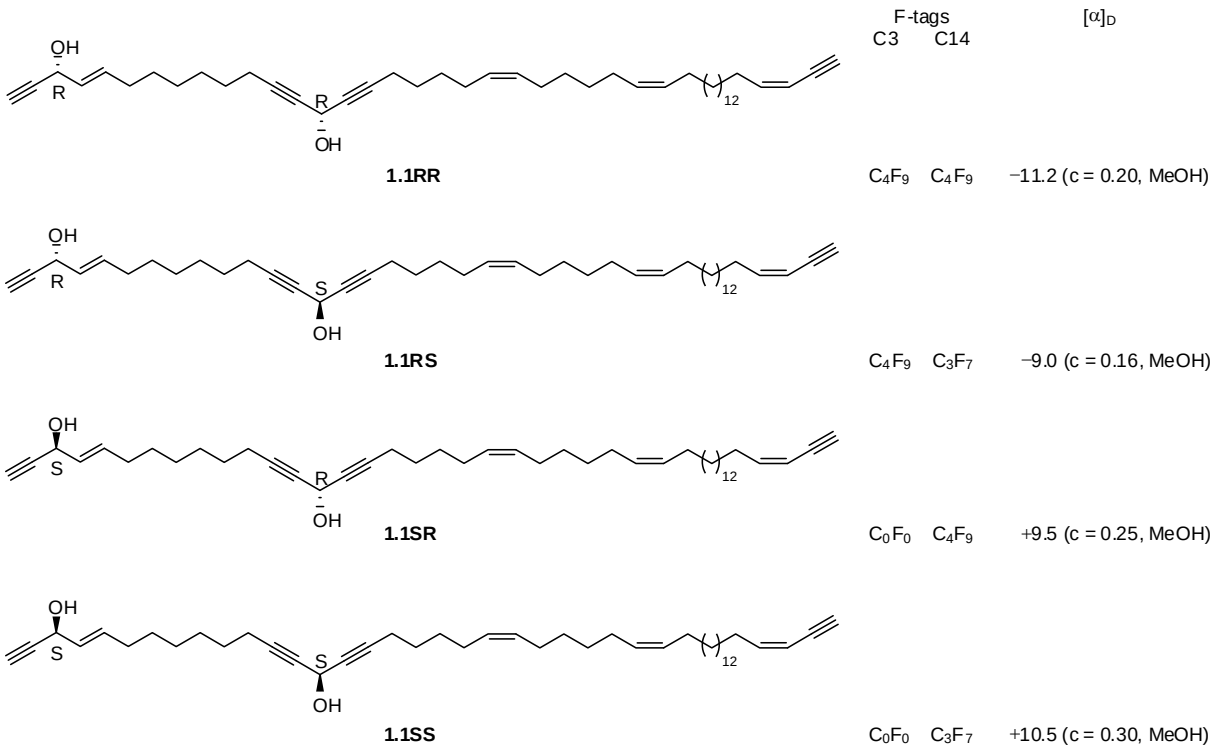


Figure 1.8. Four isomer of petrocortyne A with optical rotations

In a parallel, Mr. Edmund Yeh in our lab also finished the non-selective synthesis of a mixture of all four petrocortyne A isomers **1.1Mix**. He used a strategy that somewhat similar to that outlined here, but there were no fluorous protecting groups and the stereocenters were generated non-selectively.

We then compared four pure isomers of **1.1** with mixture **1.1Mix**. ^{1}H and ^{13}C NMR spectra (600 and 151 MHz) of all four stereoisomers of **1.1** and mixture **1.1Mix** were identical (Figure 1.9, only differences come from the peaks of free alcohols). This is expected for two pairs of compounds, **1.1SS**/**1.1RR** and **1.1SR**/**1.1RS**, because they are enantiomers. However, the spectra of the diastereomeric compounds were also identical, indicating that the long spacer between the two remote stereocenters C3 and C14 prohibits their communication, at least under these standard NMR recording conditions. This phenomenon was also observed in the syntheses

of libraries of murisolin[4b] and lagunapyrone B.[12] Importantly, all of the spectra also matched very well with spectra for (3*R*,14*R*)-petrocortyne A (The ^{1}H and ^{13}C NMR data ($CDCl_3$) were listed in Table 1.8 and 1.9, respectively) and (3*S*,14*S*)-petrocortyne A (The ^{1}H and ^{13}C NMR data (CD_3OD) were listed in Table 1.10 and 1.11, respectively). Thus, based on the NMR spectra, we cannot assign the relative configuration of the natural products.

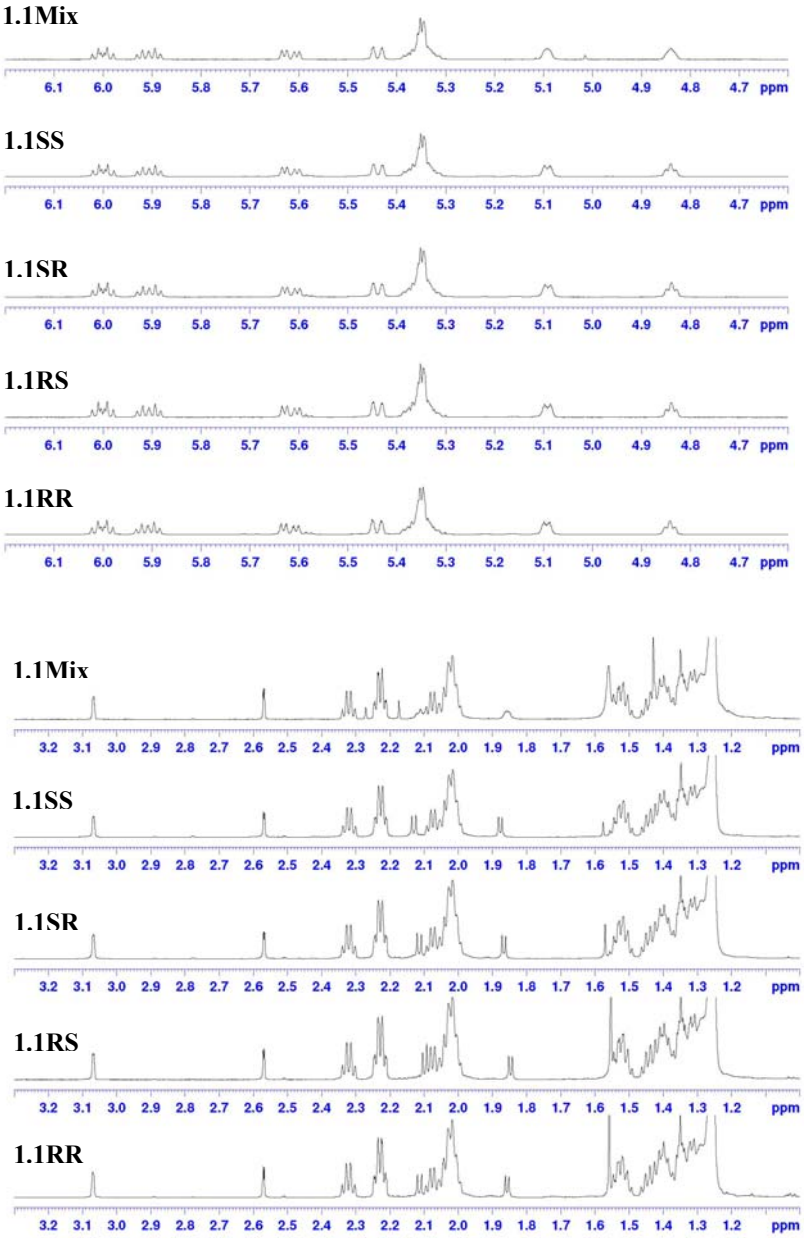


Figure 1.9. ^{1}H NMR spectra of mixture 1.1Mix and four pure stereoisomers of 1.1 ($CDCl_3$)

Table 1.8. ^{1}H NMR data of 3*R*,14*R*-petrocortyne A, 1.1SS/SR and 1.1Mix ($CDCl_3$)

H	**3*R*,14*R*-1.1**[a]	**1.1SS**[b]	**1.1SR**[b]	**1.1-Mix**[c]
1	2.56 (dd, 2.0, 1.0)	2.57 (d, 2.4)	2.57 (d, 2.4)	2.57 (d, 2.4)
3	4.83 (br d, 5.9)	4.84 (t, 6.0)	4.84 (t, 6.0)	4.84 (br s)
4	5.61 (dd, 15.6, 5.9)	5.62 (dd, 15.0, 6.0)	5.62 (dd, 15.0, 6.0)	5.62 (dd, 15.0, 6.0)
5	5.90 (dt, 15.6, 7.0)	5.91 (dt, 15.0, 7.0)	5.91 (dt, 15.0, 7.0)	5.91 (dt, 15.6, 6.6)
6	2.07 (dt, 7.0, 6.7)	2.08 (q, 7.2)	2.08 (q, 7.2)	2.08 (q, 7.2)
7	1.39 (m)	1.46–1.25 (m)	1.46–1.25 (m)	1.46–1.25 (m)
8	1.32 (m)	1.46–1.25 (m)	1.46–1.25 (m)	1.46–1.25 (m)
9	1.37 (m)	1.46–1.25 (m)	1.46–1.25 (m)	1.46–1.25 (m)
10	1.50 (m)	1.52 (m)	1.52 (m)	1.52 (m)
11	2.22 (br t, 6.3)	2.23 (qd, 6.0, 1.2)	2.23 (qd, 6.0, 1.2)	2.23 (qd, 6.6, 1.2)
14	5.09 (br s)	5.09 (dt, 7.2, 1.8)	5.09 (dt, 7.2, 1.8)	5.09 (br s)
17	2.23 (br t, 6.3)	2.23 (qd, 6.0, 1.2)	2.23 (qd, 6.0, 1.2)	2.23 (qd, 6.6, 1.2)
18	1.53 (m)	1.52 (m)	1.52 (m)	1.52 (m)
19	1.43 (m)	1.46–1.25 (m)	1.46–1.25 (m)	1.46–1.25 (m)
20	2.04 (m)	2.05–1.99 (m)	2.05–1.99 (m)	2.05–1.99 (m)
21,22	5.36–5.32 (m)	5.39–5.31 (m)	5.38–5.32 (m)	5.39–5.31 (m)
23	2.03 (m)	2.05–1.99 (m)	2.05–1.99 (m)	2.05–1.99 (m)
24,25	1.35 (m)	1.46–1.25 (m)	1.46–1.25 (m)	1.46–1.25 (m)
26	2.02 (m)	2.05–1.99 (m)	2.05–1.99 (m)	2.05–1.99 (m)
27,28	5.36–5.32 (m)	5.39–5.31 (m)	5.39–5.31 (m)	5.39–5.31 (m)
29	2.02 (m)	2.05–1.99 (m)	2.05–1.99 (m)	2.05–1.99 (m)
30–41	1.46–1.25 (m)	1.46–1.25 (m)	1.46–1.25 (m)	1.46–1.25 (m)
42	2.32 (dt, 7.3, 7.3)	2.32 (q, 7.2)	2.32 (q, 7.2)	2.32 (q, 7.2)
43	5.99 (dt, 10.7, 7.3)	6.00 (dt, 10.8, 7.2)	6.00 (dt, 10.8, 7.2)	6.00 (dt, 10.8, 7.8)
44	5.43 (ddt, 10.7, 2.4, 1.0)	5.44 (dd, 10.8, 1.2)	5.44 (dd, 10.8, 1.2)	5.44 (dd, 10.8, 1.2)
46	3.06 (d, 2.4)	3.07 (d, 1.8)	3.07 (d, 1.8)	3.07 (d, 1.2)

[a]Reported by Shin (500MHz), [16a] [b]This work (600 MHz), [c]Mr. Yeh's work (600 MHz).

Table 1.9. ^{13}C NMR data of 3*R*,14*R*-petrocortyne A, 1.1SS/SR and 1.1Mix ($CDCl_3$)

C	**3*R*,14*R*-1.1**[a]	**1.1SS**[b]	**1.1SR**[b]	**1.1-Mix**[c]
1	73.99	74.01	74.01	74.00
2	83.29	83.26	83.26	83.27
3	62.78	62.77	62.78	62.79
4	128.54	128.52	128.51	128.55
5	134.29	134.32	134.33	134.32
6	31.77	31.76	31.77	31.77
7	28.56	28.54	28.54	28.55
8	29.70–28.51	29.68–28.49	29.68–28.50	29.60–28.50
9	28.58	28.56	28.56	28.57
10	28.22	28.19	28.20	28.21
11[d]	18.67	18.64	18.65	18.64
12[e]	85.02	85.02	85.03	85.03
13[f]	78.14	78.10	78.09	78.13
14	52.56	52.54	52.54	52.56
15[j]	78.13	78.10	78.08	78.10
16[e]	84.96	84.97	84.98	84.98
17[d]	18.65	18.63	18.63	18.63
18	27.95	27.92	27.91	27.93
19	28.90	28.87	28.87	28.88
20[g]	26.68	26.65	26.65	26.66
21[h]	129.64	129.65	129.65	129.66
22[h]	130.20	130.21	130.21	130.22
23[g]	27.11	27.09	27.09	27.10
24	29.40	29.37	29.37	29.38
25	29.70–28.51	29.68–28.49	29.68–28.50	29.68–28.50
26[i]	27.25	27.23	27.23	27.24
27[j]	130.06	130.07	130.07	130.07
28[j]	129.30	129.31	129.31	129.31
29[i]	27.15	27.13	27.13	27.14
30–38	29.70–28.51	29.68–28.49	29.68–28.50	29.68–28.50
39	29.45	29.44	29.44	29.44
40	29.19	29.17	29.17	29.18
41	29.70–28.51	29.68–28.49	29.68–28.50	29.68–28.50
42	30.28	30.26	30.26	30.27
43	146.27	146.31	146.32	146.31
44	107.88	107.88	107.87	107.89
45	80.58	80.58	80.58	80.58
46	81.12	81.13	81.12	81.12

[a] Reported by Shin (125MHz), [16a] [b]This work (151 MHz), [c]Mr. Yeh's work (151 MHz), [d–j]Assignments with the same superscript in the same column may be interchanged.

Table 1.10. ^{1}H NMR data of 3*S*,14*S*-petrocortyne A and 1.1SS/SR (CD_3OD)

H	**3*S*,14*S*-1.1**[a]	**1.1SS**[b]	**1.1SR**[b]
1	2.83 (d, 2.2)	2.86 (d, 2.4)	2.87 (d, 2.4)
3	4.74 (br d, 5.9)	4.74 (br d, 6.0)	4.75 (br d, 6.0)
4	5.55 (ddt, 15.2, 5.9, 1.3)	5.55 (ddt, 15.0, 6.0, 1.2)	5.56 (ddt, 15.0, 6.0, 1.2)
5	5.85 (dtd, 15.2, 6.0, 1.0)	5.84 (dtd, 15.6, 6.6, 1.2)	5.84 (dtd, 15.0, 6.6, 1.2)
6	2.05–2.02 (m)	2.08–2.02 (m)	2.09–2.03 (m)
7–10	1.51–1.30 (m)	1.53–1.29 (m)	1.54–1.30 (m)
11	2.21 (td, 7.0, 2.0)	2.21 (td, 7.2, 2.4)	2.22 (td, 6.6, 1.8)
14	5.01 (quint, 2.0)	5.00 (quint, 2.1)	5.01 (quint, 1.8)
17	2.21 (td, 7.0, 2.0)	2.21 (td, 7.2, 2.4)	2.21 (td, 6.6, 1.8)
18,19	1.51–1.30 (m)	1.53–1.29 (m)	1.54–1.30 (m)
20	2.05–2.02 (m)	2.08–2.02 (m)	2.09–2.03 (m)
21,22	5.38–5.33 (m)	5.38–5.32 (m)	5.39–5.33 (m)
23	2.05–2.02 (m)	2.08–2.02 (m)	2.09–2.03 (m)
24,25	1.51–1.30 (m)	1.53–1.29 (m)	1.54–1.30 (m)
26	2.05–2.02 (m)	2.08–2.02 (m)	2.09–2.03 (m)
27,28	5.38–5.33 (m)	5.38–5.32 (m)	5.39–5.33 (m)
29	2.05–2.02 (m)	2.08–2.02 (m)	2.09–2.03 (m)
30–41	1.51–1.30 (m)	1.53–1.29 (m)	1.54–1.30 (m)
42	2.32 (q, 6.6)	2.31 (qd, 7.2, 1.2)	2.32 (qd, 7.2, 1.2)
43	5.98 (dtd, 10.8, 7.4, 1.0)	5.99 (dtd, 10.8, 7.2, 0.6)	6.00 (dt, 10.2, 7.2)
44	5.43 (ddt, 10.8, 2.0, 1.3)	5.44 (ddt, 10.8, 1.8, 1.2)	5.44 (ddt, 10.2, 1.8, 1.2)
46	3.36 (d, 2.0)	3.39 (d, 2.4)	3.41 (d, 1.8)

[a]Reported by Jung (200 MHz),[16c] [b]This work (600 MHz).

Table 1.11. ^{13}C NMR data of 3*S*,14*S*-petrocortyne A and 1.1SS/SR (CD_3OD)

C	**3*S*,14*S*-1.1**[a]	**1.1SS**[b]	**1.1SR**[b]
1	74.5	74.53	74.52
2	84.8	84.77	84.77
3	63.1	63.16	63.16
4	130.5	130.56	130.56
5	134.0	134.05	134.06
6	32.9	32.93	32.93
7–10	30.9–29.2	30.93–29.21	30.93–29.21
11[c]	19.2	19.21	19.21
12[d]	84.5	84.48	84.48
13[e]	79.9	79.94	79.94
14	52.6	52.62	52.61
15[e]	79.8	79.86	79.86
16[d]	84.3	84.36	84.36
17[c]	19.3	19.28	19.28
18,19	30.9–29.2	30.93–29.21	30.93–29.21
20[f]	27.8	27.72	27.71
21[g]	130.7	130.74	130.74
22[g]	131.1	131.10	131.10
23[f]	28.22	28.06	28.04
24,25	30.9–29.2	30.93–29.21	30.93–29.21
26[h]	28.2	28.04	28.02
27[i]	131.0	130.99	130.99
28[i]	130.7	130.76	130.76
29[h]	28.1	28.15	28.14
30–41	30.9–29.2	30.93–29.21	30.93–29.21
42	31.2	31.14	31.13
43	146.3	146.41	146.42
44	109.4	109.34	109.34
45	81.2	81.23	81.24
46	82.8	82.72	82.72

[a]Reported by Jung (50 MHz),[16c] [b]This work (151 MHz), [c–i]Assignments with the same superscript in the same column may be interchanged.

Furthermore, we could not obtain a natural sample of (3*R*,14*R*)- or (3*S*,14*S*)-petrocortyne A to do chiral HPLC analysis to assign the structure of the natural product. Accordingly, chiral HPLC analysis, such as used to assign the murisolin, was not possible.

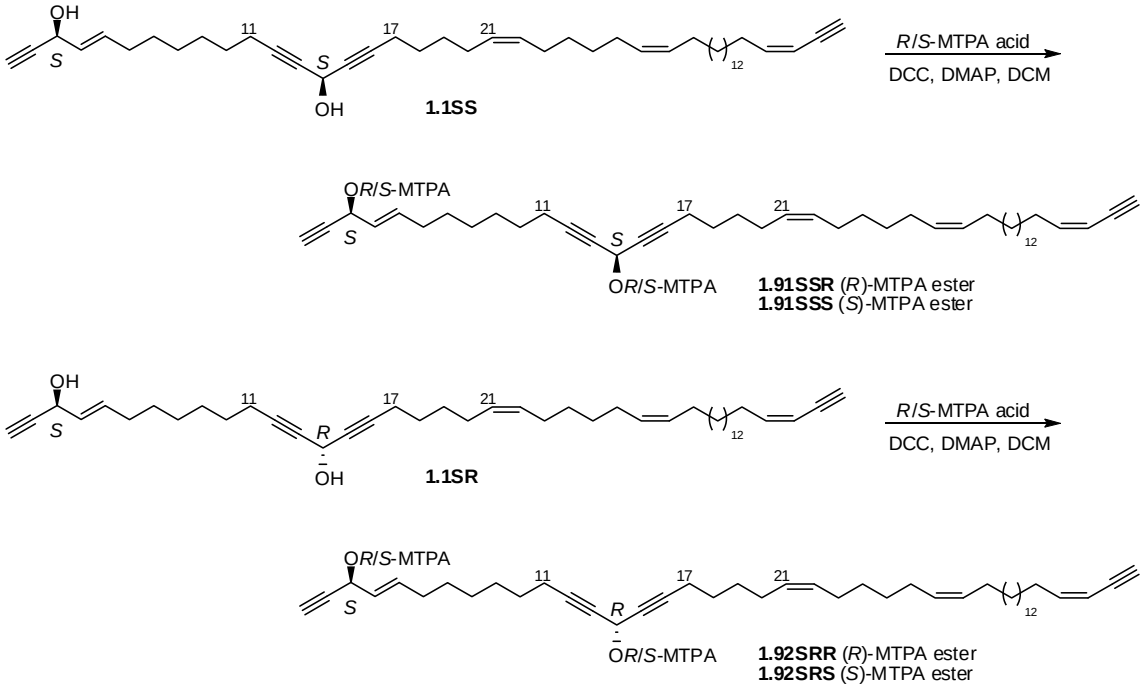
1.2.16 Structure assignment of petrocortyne A

In order to assign the stereo structure of petrocortyne A, we first looked at optical rotations. The optical rotations of these isomers are shown in Figure 1.8. Two pairs of diastereomer, **1.1RR/1.1RS** and **1.1SS/1.1SR**, have rotations that are too close to be differentiated in practice. So for the structure assignment purposes, the sign of the optical rotation can be used to assign the configuration of C3, but no information is provided about C14. Contributions to rotation from remote stereocenters are often approximately additive, so at this wavelength the C14 stereocenter apparently contributes an almost negligible amount to the total rotation. Thus, the four isomers could be partly differentiated by optical rotation.

The optical rotations of Shin's petrocortyne A (+6.4, *c* = 0.25 MeOH) and Jung's sample (+10.8, *c* = 1.9 MeOH) match the measure optical rotations of either (3*S*,14*R*)-petrocrotyne A **1.1SR** (+9.5, *c* = 0.25 MeOH) or (3*S*,14*S*)-petrocortyne A **1.1SS** (+10.5, *c* = 0.30 MeOH). The optical rotation of Jung's sample happens to match that of the (3*S*,14*S*)-petrocortyne A very well, but as mentioned above, the magnitudes of the rotations of the two diastereomers **1.1SR/1.1SS** are too close to be differentiated. So after the comparison of optical rotations, we can only assign the configuration of C3 as *S*. Accordingly, Jung's assignment of this stereocenter is correct and Shin's is incorrect. But we still cannot assign the absolute configuration of stereocenter at C14.

Since we have individual samples of all four isomers and have validated the Mosher ester analysis, in order to assign the absolute configuration of petrocortyne A, we turned to advanced Mosher ester derivatives. This was possible because Shin reported full ^{1}H NMR data for Mosher esters of his samples and Jung did not report the full Mosher esters' spectra, but he did report the differences of chemical shifts of the corresponding Mosher ester derivatives. After comparison of the reported and synthetic Mosher esters, we will confirm the assignment of the natural product. We then converted the pair of petrocortyne A diastereomers with the 3S configuration **1.1SS**, **1.1SR** to both the *bis*-(*R*)- and *bis*-(*S*)-Mosher esters **1.91SSR**, **1.91SSS**, **1.92SRR**, and **1.92SRS**, respectively (Scheme 1.40).

Scheme 1.40. Synthesis of Mosher esters of 1.1SS and 1.1SR



A set of 1D and 2D ^{1}H NMR spectra of these esters were recorded for assignment and analysis. The expansions of the spectra of **1.91SSR/SSS** and **1.92SRR/SRS** along with their precursors **1.1SS** and **1.1SR** are shown in Figure 1.10. Our expectations that all the 1D Mosher esters' spectra might be substantially identical in the region of the C14 stereocenter (H11 and H17) proved to be wrong; there were small yet clear differences.

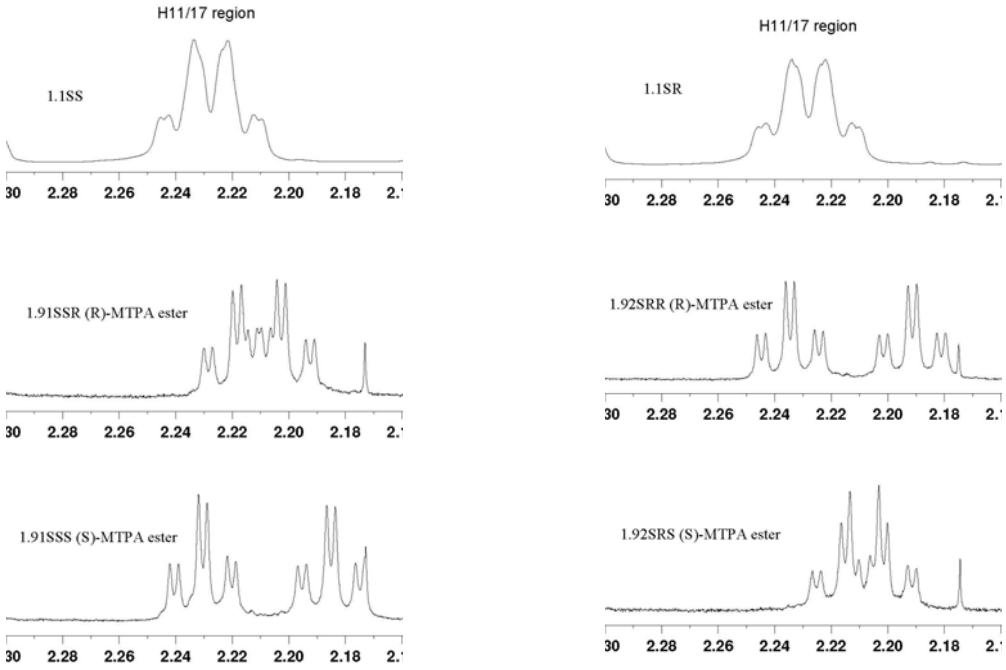


Figure 1.10. Expansions of the H11/H17 region of the ^{1}H NMR spectra of 1.1SS/SR (top) Mosher esters of 1.1SS/SR (middle and bottom)

Although the differences of the 1D ^{1}H NMR spectra of each pair of Mosher esters, **1.91SSR/SSS** and **1.92SRR/SRS**, were observed in Figure 1.10, how can we assign H11 and H17? The proper assignments of H11 and H17 are crucial for comparison of ^{1}H NMR data of reported and synthetic Mosher esters. These assignments were made by TOCSY experiments. The expansions of the TOCSY spectra of **1.91SSS/SSR** and **1.92SRS/SRR** are shown in Figure

1.12 and 1.13, respectively. Accordingly, H11, H17 and related protons were assigned unambiguously. Only one cross-coupling peak between H21 and one of the two resonances in the H11 and H17 region was observed. H11 is too far away to communicate with H21, so this cross peak must be the result of interaction between protons H21 and H17.

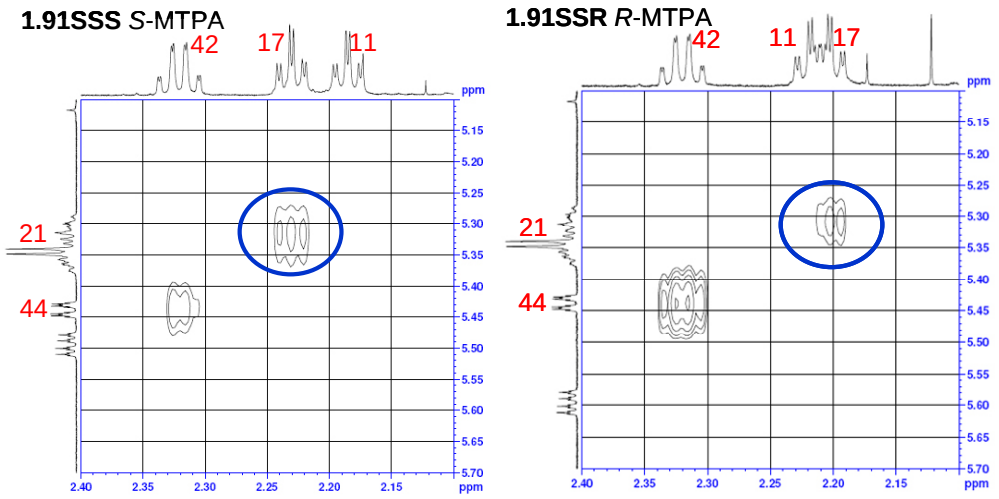


Figure 1.11. Expansions of portions of the TOCSY spectra of Mosher esters 1.91SSS/SSR

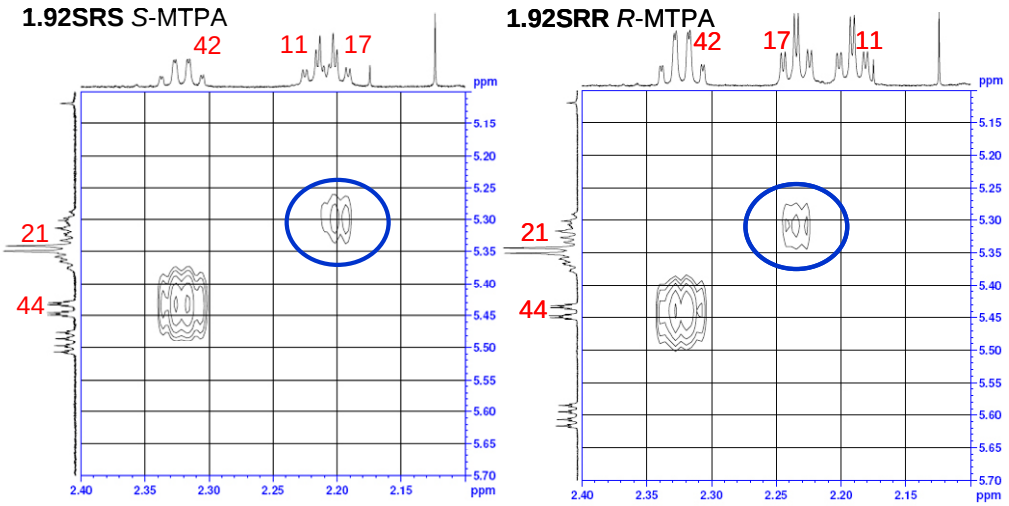


Figure 1.12. Expansions of portions of the TOCSY spectra of Mosher esters 1.92SRS/SRR

All four Mosher esters spectra of the petrocortyne A isomers were unique. To assign the natural product configuration, we do not need to apply the Mosher rule and just simply compared the 1D ^{1}H NMR spectra of the synthetic Mosher esters with those reported by Shin and the differences of chemical shifts of the Mosher ester derivatives reported by Jung. The data of the Mosher esters **1.91SSS/SSR** of synthetic product **1.1SS**, 3*S*,14*S*-petrocortyne A, uniquely matched the data reported by both groups (Table 1.12, 1.13). We also disproved the compound **1.1SR** is the natural product by comparison of the data obtained from the Mosher ester **1.92SRS**/**SRR** with the reported data (Table 1.12, 1.13). All results showed that Shin's and Jung's samples are identical, not enantiomers, and that Jung's assignment of the 3*S*,14*S* configuration is correct. Jung assigned H11 and H17 in the Mosher esters and applied the advanced Mosher method to assign the natural product correctly. Shin also assigned H11 and H17 correctly, but unfortunately, Shin and coworker forgot to reverse CIP priority of order of Mosher esters when using Mosher chlorides to synthesize Mosher esters. So their assignment of natural product is reversed.

Table 1.12. ^{1}H NMR data of reported and synthetic Mosher ester derivatives

H	**(R)-MTPA ester**[a]	**1.91SSR**[b]	**1.92SRR**[b]
1	2.59 (d, 2.0)	2.59 (d, 2.1)	2.59 (d, 2.1)
3	6.01 (br dd, 6.8, 2.0)	6.01 (m)	6.01 (m)
4	5.60 (br dd, 15.6, 6.8)	5.60 (ddt, 15.4, 7.0, 1.4)	5.60 (ddt, 15.4, 7.0, 1.4)
5	6.06 (dt, 15.6, 6.8)	6.05 (dtd, 15.4, 7.0, 1.4)	6.06 (dtd, 15.4, 7.0, 1.4)
6	2.08 (td, 7.3, 6.8))	2.07 (q, 7.0)	2.08 (q, 7.0)
11	**2.22 (td, 7.3, 2.0)**	**2.22 (td, 7.0, 2.1)**	**2.19 (td, 7.0, 2.1)**
14	6.21 (t, 2.0)	6.21 (t, 2.1)	6.21 (t, 2.1)
17	**2.21 (td, 7.3, 2.0)**	**2.21 (td, 7.0, 2.1)**	**2.23 (td, 7.0, 2.1)**
42	2.33 (q, 7.3)	2.32 (qd, 7.7, 1.4)	2.32 (qd, 7.2, 1.2)
43	6.00 (br dt, 10.7, 7.3)	6.01 (m)	6.00 (m)
44	5.44 (ddt, 10.7, 2.0, 1.5)	5.44 (ddt, 10.5, 2.8, 1.4)	5.44 (ddt, 10.5, 2.8, 1.4)
46	3.07 (d, 2.0)	3.06 (d, 2.1)	3.07 (d, 1.8)

[a]Reported by Shin (500 MHz),[16a] [b]This is work (700 MHz)

Table 1.13. $\Delta\delta_{S\text{-MTPA ester} - R\text{-MTPA ester}}$ value (ppm) of reported and synthetic Mosher ester derivatives

H	1	4	5	6	11	17	18
$\Delta\delta_{S-R}$[a]	0.04	−0.10	−0.06	−0.04	−0.03	0.03	NA
$\Delta\delta_{\mathbf{1.91SSS - 1.91SSR}}$	0.04	−0.10	−0.06	−0.04	−0.03	0.03	0.02
$\Delta\delta_{\mathbf{1.92SRS - 1.92SRR}}$	0.04	−0.11	−0.06	−0.04	0.02	−0.03	−0.03

[a]Reported by Jung [16c]

With the optical rotations and Mosher esters spectra, we can confirm that the 3*S*,14*S* configuration of petrocortyne A is correct. This assignment of the 3*S*,14*S*-petrocortyne A is rigorous and is based solely on comparison of data derived from natural and synthetic samples and Mosher ester derivatives; it does not depend on applying Mosher rules.

1.2.17 "Shortcut" Mosher Ester Method[50]

Because the local symmetry at C14, the pairs of methylene protons (H11, H17) in the alcohols **1.1SS/SR** are chemical equivalent but can be differentiated in the Mosher ester derivatives **1.91SSS/SSR** and **1.92SRS/SRR**. Subtraction of the pair of resonances from each other in one Mosher ester (rather than from the corresponding resonances in the two Mosher esters as advanced Mosher method mentioned) will provide the absolute configuration of the alcohol. We call this "shortcut" Mosher ester method.

Since we have synthesized and unambiguously assigned Mosher esters **1.91SSS/SSR** for alcohol **1.1SS** and Mosher esters **1.92SRS/SRR** for **1.1SR**. We next analyzed the Mosher esters spectra by applying the standard advanced method and the shortcut method. In the advanced Mosher method, the differences of chemical shifts of corresponding protons ($\delta_S - \delta_R$) in (*R*)- and

(*S*)-Mosher esters need to be used. The chemical shift of key protons and their differences between two Mosher esters are listed in Table 1.14. The differences of chemical shift of protons at both sides of the stereocenters have the opposite sign, based on the advanced Mosher method, and the absolute configurations of stereocenters at C3 and C14 were assigned as 3*S*,14*S* for **1.1SS** and 3*S*,14*R* for **1.1SR**, respectively.

In the shortcut Mosher method, we only use the difference of a symmetry-related pairs of protons ($\delta_{H11} - \delta_{H17}$ or $\delta_{H17} - \delta_{H11}$) in one single Mosher ester. Here we use subtraction ($\delta_{H11} - \delta_{H17}$) to assign the absolute configuration of stereocenter at C14. The subtraction data of Mosher esters of **1.1SS** and **1.1SR** are listed in Table 1.4. The signs of the subtractions are the opposite for stereocenters 14*R* and 14*S*, so both analyses correctly indicate the known configuration of the compounds. This validates the applicability of the shortcut Mosher method.

The shortcut Mosher method can be used to assign the petrocortyne A like natural products with local symmetry dialkynyl carbinol unit (other petrocortynes). Only one Mosher ester derivative is needed, after comparison of the natural product derivative with our results, the absolute configuration of the carbinol can be assigned. The shortcut method can also be generally applicable to assign any stereocenters with local symmetry. The method conserves valuable natural product, especially when only small amounts of natural product are isolated.

Table 1.14. Selective chemical shifts in Mosher esters and application of the advanced and shortcut Mosher methods

config.	H#	$\delta_{S\text{-MTPA}}$	$\delta_{R\text{-MTPA}}$	$\delta_S - \delta_R$ [a]	$\delta_{H11} - \delta_{H17}$ [b]
3*S*,14*R* (**1.1SR**)	1	2.632	2.591	+0.041[c]	
	4	5.490	5.601	−0.111[c]	
	11	2.214	2.190	+0.024[d]	−0.043[d]
	17	2.204	2.233	−0.029[d]	
3*S*,14*S* (**1.1SS**)	1	2.628	2.590	+0.038[c]	
	4	5.494	5.594	−0.100[c]	
	11	2.185	2.219	−0.034[e]	+0.015[e]
	17	2.220	2.204	+0.026[e]	

[a]The standard advanced Mosher method. [b]The shortcut Mosher method with the *R*-MTPA ester. [c]Indicates 3*S*. [d]Indicates 14*R*. [e]Indicates 14*S*.

1.3 CONCLUSIONS

Fluorous mixture synthesis was applied to the total synthesis of petrocortyne A and its isomers. This technique features the tagging and mixing of enantiomers of the chiral starting material with different fluorous TIPS groups. The resulting mixture is taken through a series of steps to make the fluorous-tagged products, which are separated by fluorous HPLC in the demixing stage to provide the final enantiomerically pure products. The extra effort in making precursors in enantiopure form and tagging them with fluorous tags paid dividends in the end with easy separation and identification by fluorous dimixing.

The second-generation fluorous TIPS tags were synthesized and used in the synthesis. Both Mosher and NMA derivatization methods were developed during the synthesis. Because the Mosher esters of petrocortyne A are known, we used Mosher method to assign the absolute

configuration of the natural product. However, the study showed that NMA ester method is superior to Mosher method for the assignment of absolute configuration of stereocenter C17. NMA ester method should be a better choice for future natural product isolation work.

Comparison of optical rotations of the four synthetic and two natural samples showed that both natural samples had the C3-*S* configuration. Comparison of spectra of Mosher derivatives of the synthetic and natural samples showed that both natural samples had the 3*S*,14*S* configuration. At the same time, the use of the Mosher rule has been validated for assigning the challenging C14 stereocenter of petrocortyne A. As we showed above, a "shortcut" variant in which only one Mosher ester is made can also be used for assignment of this stereocenter.

In summary, the petrocortyne A and its isomers were synthesized and the two natural products were proved to be the same compound, 3*S*,14*S*-petrocortyne A.

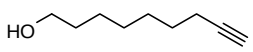
1.4 EXPERIMENTAL

General Information:

All reactions were performed under an atmosphere of argon unless otherwise noted. Reaction solvents were freshly dried either by distillation or by passing through an activated alumina column. THF and toluene were freshly distilled from Na/benzophenone. Methylene chloride and Et_2O were dried by activated alumina according to literature.[51] All other reagents were purchased commercially and used without further purification unless stated otherwise. Reaction mixtures were magnetically stirred and reaction progress was monitored by TLC with

0.25 mm E. Merck precoated silica gel plates. Flash chromatography was performed with silica gel 60 (particle size 0.040 – 0.063 mm) supplied by Sorbent Technologies.

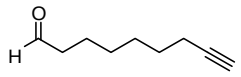
Products and reactions were analyzed by ^{1}H NMR, ^{13}C NMR, COSY, ^{19}F NMR, FT-IR, high and low resolution mass spectroscopy, and HPLC. NMR spectra were taken on a Bruker WH-300, IBM AF-300, a Bruker Avance™ 500 NMR, a Bruker Avance™ 600 NMR, and a Bruker Avance™ 700 NMR spectrometer. Spectra were recorded at room temperature in the indicated deuteriated solvents and chemical shifts were reported in parts per million (ppm) downfield relative to TMS using the residual solvent proton resonance of $CDCl_3$ (7.26 ppm) or central $CDCl_3$ carbon peak (77.0 ppm) as the internal standard. In reporting spectral data, the following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintuplet, m = multiplet, dd = doublet doublet, dt = doublet triplet, td = triplet doublet, qd = quartet doublet, ddt = doublet doublet triplet, dtd = doublet triplet double. Infrared spectra were taken on a Mattson Genesis Series FTIR using thin film on NaCl plate. Peaks are reported in wavenumbers (cm^{-1}). Low resolution mass spectra were obtained on Fision Autospec. High resolution mass spectra were obtained on a V/G 70/70 double focusing machine and were reported in units of *m/e*. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at the Na D-line (λ = 589 nm) using a 1 dm cell. HPLC analyses were performed on a Waters 600 E system with a Waters 2487 dual λ absorption detector.



Non-8-yn-1-ol:[29]

NaH (2.85 g, 60 wt% in mineral oil, 71.3 mmol) was added to a 250 ml of three-neck flask containing ethylenediamine (35 mL) at 0 °C. The resulting suspension was stirred at room

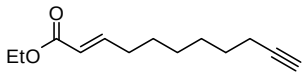
temperature for 1 h and then warmed to 60 °C. After being stirred at 60 °C for 1 h, the deep blue-black mixture was cooled to 45 °C and 3-nonyn-1-ol **1.9** (2.5 g, 17.8 mmol) was added dropwise. After complete addition, the resulting mixture was warmed back to 60 °C and was stirred for further 1 h. Upon slowly cooling to 0 °C, 1 M HCl (15 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (pentane/Et_2O = 1:3 followed by 1:1) to afford title compound (1.71 g, 68%) as the colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (t, *J* = 6.5 Hz, 2 H), 2.18 (td, *J* = 6.8, 2.6 Hz, 2 H), 1.92 (t, *J* = 2.6 Hz, 1 H), 1.63–1.48 (m, 4 H), 1.45–1.28 (m, 6 H).



Non-8-ynal (1.8):[30]

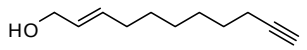
A solution of DMSO (2.13 mL, 30 mmol) in CH_2Cl_2 (17 mL) was slowly added to a solution of oxalyl chloride (1.72 mL, 20 mmol) in CH_2Cl_2 (85 mL) at –78 °C. After 15 min at the same temperature, a solution of non-8-yn-1-ol (1.40 g, 10 mmol) in CH_2Cl_2 (17 mL) was then added dropwise. The resulting mixture was stirred for 15 min and Et_3N (6.97 mL, 50 mmol) was added slowly. The reaction was maintained at –78 °C for 15 min, then allowed to warm to 0 °C, the stirring continued for further 30 min. Water was added and the mixture was diluted with Et_2O. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (pentane/Et_2O = 9:1) to afford the title compound **1.8** (1.24 g, 90%) as colorless oil: ^{1}H NMR

(300 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.8 Hz, 1 H), 2.42 (td, *J* = 7.3, 1.8 Hz, 2 H), 2.17 (td, *J* = 6.8, 2.6 Hz, 2 H), 1.93 (t, *J* = 2.6 Hz, 1 H), 1.68–1.27 (m, 8 H).



(*E*)-Ethyl undec-2-en-10-ynoate (1.17):

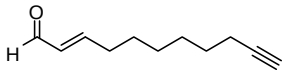
Ethyl (triphenylphosphoranylidene)acetate **1.16** (3.21 g, 9.2 mmol) was added to a solution of aldehyde **1.8** (1.06 g, 7.7 mmol) in CH_2Cl_2 (20 mL) at room temperature. After being stirred overnight, the organic solvent was removed *in vacuo*, the residue was washed with petane and filtered through Celite®. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (pentane/Et_2O = 30:1) to afford the title compound **1.17** as (1.27 g, 80%) colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (dt, *J* = 15.6, 6.9 Hz, 1 H), 5.80 (dt, *J* = 15.6, 1.6 Hz, 1 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 2.23–2.14 (m, 4 H), 1.93 (t, *J* = 2.6 Hz, 1 H), 1.56–1.23 (m, 8 H) 1.28 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 149.2, 121.3, 84.5, 68.2, 60.1, 32.1, 28.5, 28.4, 28.3, 18.3, 14.2.



(*E*)-Undec-2-en-10-yn-1-ol:

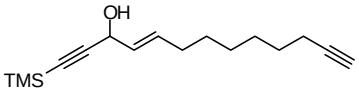
DIABL-H (12.5 mL, 1.0 M solution in hexane, 12.5 mmol) was added to a solution of ester **1.17** (1.04 g, 5.0 mmol) in CH_2Cl_2 (50 mL) over 10 min at –78 °C. After 30 min at the same temperature, the mixture was poured into a solution of saturated aqueous sodium potassium tartrate (125 mL) and Et_2O (125 mL), the resultant cloudy mixture was then vigorously stirred for 1 h, at which time the organic layer cleared. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with Et_2O (2 × 25 mL). Then the

combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (pentane/Et_2O = 3:1) to afford the title compound (0.82 g, 99%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71–5.55 (m, 2 H), 4.05 (t, *J* = 5.1, 2 H), 2.16 (td, *J* = 6.9, 2.6 Hz, 2 H), 2.02 (q, *J* = 6.3 Hz, 2 H), 1.92 (t, *J* = 2.6 Hz, 1 H), 1.65 (t, *J* = 5.7 Hz, 1 H), 1.57–1.23 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.1, 128.9, 84.6, 68.1, 63.6, 32.0, 28.9, 28.5, 28.4, 28.3, 18.3.



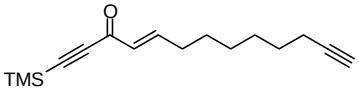
(*E*)-Undec-2-en-10-ynal (1.7):

A solution of DMSO (0.96 mL, 13.5 mmol) in CH_2Cl_2 (7.5 mL) was slowly added to a solution of oxalyl chloride (0.77 mL, 9 mmol) in CH_2Cl_2 (42 mL) at –78 °C. After 15 min at the same temperature, a solution of (*E*)-undec-2-en-10-yn-1-ol (0.75 g, 4.5 mmol) in CH_2Cl_2 (7.5 mL) was then added dropwise. The resulting mixture was stirred for 15 min and Et_3N (3.14 mL, 22.5 mmol) was added slowly. The reaction was maintained at –78 °C for 15 min, then allowed to warm to 0 °C, the stirring continued for further 30 min. Water was added and the mixture was diluted with Et_2O. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (pentane/Et_2O = 9:1) to afford the title compound **1.7** (0.66 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (d, *J* = 7.9 Hz, 1 H), 6.83 (dt *J* = 15.6, 6.8 Hz, 1 H), 6.09 (ddt, *J* = 15.6, 7.9, 1.4 Hz, 1 H), 2.33 (qd, *J* = 7.1, 1.4 Hz, 2 H), 2.17 (td, *J* = 6.8, 2.6 Hz, 2 H), 1.93 (t, *J* = 2.6 Hz, 1 H), 1.56–1.28 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 158.5, 133.0, 84.4, 68.2, 32.5, 28.5, 28.3, 28.3, 27.6, 18.3.



(*E*)-1-(Trimethylsilyl)trideca-4-en-1,12-diyn-3-ol:

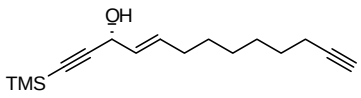
A solution of *n*-BuLi (3.15 mL, 1.6 M solution in hexane, 5.0 mmol) was added to a solution of trimethylsilylacetylene (0.8 mL, 5.5 mmol) in THF (20 mL) at –78 °C. After 10 min, a solution of aldehyde **1.7** (554 mg, 3.4 mmol) in THF (5 mL) was added dropwise. The resulting mixture was stirred for further 10 min at this temperature and allowed to warm to room temperature. The mixture was poured into pH 7 phosphate buffer (20 mL) and extracted with Et_2O (3 × 20mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/CH_2Cl_2 = 1:2) to afford the title compound as pale yellow oil (775 mg, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (dtd *J* = 15.2, 6.7, 1.0 Hz, 1 H), 5.59 (ddt, *J* = 15.3, 6.2, 1.4 Hz, 1 H), 4.82 (t, *J* = 6.1 Hz, 1 H), 2.19 (td, *J* = 6.9, 2.6 Hz, 2 H), 2.07 (q, *J* = 7.0 Hz, 2 H), 1.94 (t, *J* = 2.6 Hz, 1 H), 1.79 (d, *J* = 6.0 Hz, 1 H), 1.55–1.26 (m, 8H), 0.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.3, 129.1, 105.3, 90.9, 84.9, 68.4, 63.6, 32.1, 29.0, 28.9, 28.8, 28.7, 18.7, 0.14.



(E)-1-(trimethylsilyl)trideca-4-en-1,12-diyn-3-one (1.6):

To a solution of oxalyl chloride (0.26 mL, 3 mmol) in CH_2Cl_2 (14 mL) was slowly added a solution of DMSO (0.32 mL, 4.5 mmol) in CH_2Cl_2 (2.5 mL) at –78 °C. After 15 min at the same temperature, a solution of (*E*)-1-(trimethylsilyl)trideca-4-en-1,12-diyn-3-ol (0.40 g, 1.5 mmol) in CH_2Cl_2 (2.5 mL) was then added dropwise. The resulting mixture was stirred for 15

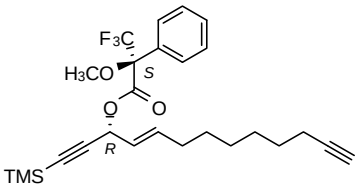
min and Et_3N (1.05 mL, 7.5 mmol) was added slowly. The reaction was maintained at –78 °C for 15 min, then allowed to warm to 0 °C, the stirring continued for further 30 min. Water was added and the mixture was diluted with Et_2O. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/CH_2Cl_2 = 1:1) to afford the title compound **1.6** (347.8 mg, 88%) as pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (dt, *J* = 15.7, 6.8 Hz, 1H), 6.15, (dt, *J* = 15.7, 1.4 Hz, 1H), 2.30 (qd, *J* = 6.6, 1.4 Hz, 2H), 2.19 (td, *J* = 6.8, 2.6 Hz, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.55–1.36 (m, 8H), 0.26 (s, 9H).



(*R*,*E*)-1-(Trimethylsilyl)trideca-4-en-1,12-diyn-3-ol (1.18R):

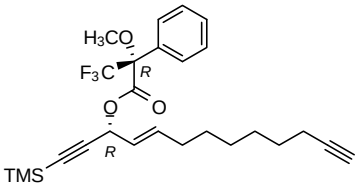
(*R*)-Alpine borane (7.2 mL, 0.5 M solution in THF, 3.6 mmol) was placed in a round bottle flask, the solvent was removed under vacuum and the flask was refilled with Ar. To it ketone **1.6** (315.0 mg, 1.2 mmol) was added slowly at 0 °C. After stirring at room temperature for 15 h, a solution of acetaldehyde (1.15 mL, 20 mmol)) in THF (2.4 mL) was added and the mixture was then stirred at room temperature for 6 h before removing the solvent *in vacuo*. To the residue a solution of ethanolamine (0.16 mL) in Et_2O (2.4 mL) was added. After 1 h, the white precipitate was filtered and washed with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude compound was purified by column chromatography (hexane/CH_2Cl_2 = 1:2) to afford the title compound **1.18R** (183.6 mg, 58%, 93% ee): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (dtd, *J* = 15.3, 7.4, 0.9 Hz, 1H), 5.58, (dd, *J* = 15.3, 6.2 Hz, 1H), 4.82 (t, *J* = 5.9 Hz, 1H), 2.18 (td, *J* = 7.0, 2.6 Hz, 2H), 2.07 (q, *J* = 7.2 Hz, 2H), 1.94

(t, *J* = 2.6 Hz, 1H), 1.83 (d, *J* = 6.0 Hz, 1H), 1.55–1.49 (m, 2H), 1.44–1.37 (m, 4H), 1.34–1.28 (m, 2H), 0.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.1, 128.7, 104.9, 90.9, 84.9, 68.1, 63.4, 31.8, 29.6, 28.6, 28.5, 28.4, 18.4, –0.16; MS (EI) *m/z* 262 (M^+); HRMS (EI) *m/z* (M^+) calcd for $C_{16}H_{26}OSi$ 262.1753, found 262.1747.



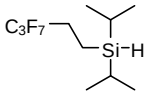
(*S*)-((*R*,*E*)-1-(Trimethylsilyl)trideca-4-en-1,12-diyn-3-yl) 3,3,3-trifluoro-2-methoxy-2-phenyl propanoate (1.19RS):

(*S*)-MTPA acid (23.5 mg, 0.10 mmol), DCC (24.8 mg, 0.12 mmol), and DMAP (0.6 mg, 0.005mmol) was added to a solution of alcohol **1.18R** (13.1 mg, 0.05 mmol) in CH_2Cl_2 (0.7 ml) at room temperature. The resulting mixture was stirred at the same temperature overnight. The mixture was then filtered through a pad of Celite ®, the filtrate was concentrated *in vacuo*. The crude product **1.19RS** was obtained: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.43-7.36 (m, 3H), 6.02 (dtd, *J* = 15.7, 7.1, 0.7 Hz, 1H), 6.00 (d, *J* = 6.8 Hz, 1H), 5.57 (ddt, J = 15.3, 6.9, 1.2 Hz, 1H), 3.54 (s, 3H), 2.17 (td, *J* = 6.8, 2.6 Hz, 2H), 2.08 (q, *J* = 6.6 Hz, 2H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.58–1.23 (m, 8H), 0.15 (s, 9H).



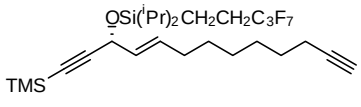
(*R*)-((*R*,*E*)-1-(Trimethylsilyl)trideca-4-en-1,12-diyn-3-yl)3,3,3-trifluoro-2-methoxy-2-phenyl propanoate (1.19RR):

Following the same procedure as above, except for using (*R*)-MTPA acid rather than (*S*)-MTPA acid, the title compound **1.19RR** was obtained: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.43-7.36 (m, 3H), 6.02 (dtd, *J* = 15.7, 7.1, 0.7 Hz, 1H), 6.00 (d, *J* = 6.8 Hz, 1H), 5.57 (ddt, J = 15.3, 6.9, 1.2 Hz, 1H), 3.54 (s, 3H), 2.17 (td, *J* = 6.8, 2.6 Hz, 2H), 2.08 (q, *J* = 6.6 Hz, 2H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.58–1.23 (m, 8H), 0.15 (s, 9H).



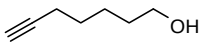
(3,3,4,4,5,5,5-Heptafluoropentyl)diisopropylsilane (1.21):

t-BuLi (10.4 mL, 1.7 M solution in pentane, 17.6 mmol) was added by syringe pump in 40 min to a solution of iodide **1.20** (3.80 g, 11.7 mmol) in Et_2O (20 mL) at –78 °C. After 10 min at the same temperature, the mixture was warmed to –15 °C and stirred for further 10 min. The mixture was recooled to –78 °C. Chlorodiisopropylsilane (1.10 mL, 6.5 mmol) was added to the above solution in 15 min. The resulting mixture was then warmed to room temperature and stirred overnight. Water (2 mL) was added at 0 °C, followed by 1 M HCl (20 mL). The mixture was extracted with Et_2O (3 × 30 mL). The organic layer was washed with water (2 × 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (100% hexane) to afford the title compound **25** (1.56 g, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.49 (s, 1H), 2.20–2.04 (m, 2H), 1.05 (s, 14H), 0.88–0.82 (m, 2H).



(*R*,*E*)-(3,3,4,4,5,5,5-Heptafluoropentyl)diisopropyl(1-(trimethylsilyl)trideca-4-en-1,12- diyn-3-yloxy)silane (1.4R):

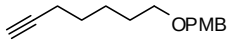
Trifluoromethanesulfonic acid (neat, 75.0 mg, 0.50 mmol) was slowly added to silane **25** (neat, 203.0 mg, 0.65 mmol) at 0 °C. After being stirred for 5 min at the same temperature, the mixture was warmed to room temperature and stirred for 15 h. To it a solution of alcohol **23** (131.2 mg, 0.50 mmol) in CH_2Cl_2 and 2,6-lutidine (116.0 μL, 1.00 mmol) were added at 0 °C. The resulting mixture was warmed to room temperature and stirred for further 2 h. Saturated aqueous NH_4Cl (1 mL) was then added to quench the reaction at 0 °C. The mixture was extracted with Et_2O (3 × 10 mL), the organic layers were combined and washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (100% hexane) to afford the title compound **1.4R** (135.9 mg, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (dtd, *J* = 15.2, 6.7, 1.1 Hz, 1H), 5.34 (ddt, *J* = 15.2, 5.7, 1.3 Hz, 1H), 4.88 (dd, *J* = 5.7, 1.0 Hz, 1H), 2.18 (td, *J* = 6.9, 2.6 Hz, 2H), 2.05 (q, *J* = 6.9 Hz, 2H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.55-1.25 (m, 10H), 1.10–1.03 (m, 12H), 0.93–0.87 (m, 2H), 0.15 (s, 9H); MS (EI) *m/z* 572 (M^+); HRMS (EI) *m/z* (M^+) calcd for $C_{27}H_{43}F_7OSi_2$ 572.2741, found 572.2744.



Hept-6-yn-1-ol (1.22):[29]

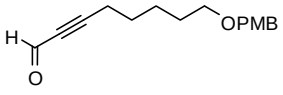
NaH (3.75g, 60 wt% in mineral oil, 93.8 mmol) was added to a 250 ml of three-neck flask containing ethylenediamine (37.5 mL) at 0 °C. The resulting suspension was stirred at room temperature for 1 h and then warmed to 60 °C. After being stirred at 60 °C for 1 h, the deep blue-black mixture was cooled to 45 °C and 3-heptyn-1-ol **1.10** (2.1 g, 18.8 mmol) was added dropwise. After complete addition, the resulting mixture was warmed back to 60 °C and was

stirred for further 1 h. Upon slowly cooling to 0 °C, 1 M HCl (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (pentane/Et_2O = 1:3) to afford compound **1.22** (1.35 g, 64%) as the colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (t, *J* = 6.2 Hz, 2H), 2.20 (td, *J* = 6.7, 2.6 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.63–1.41 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.3, 68.2, 62.4, 32.0, 28.1, 24.8, 18.2.



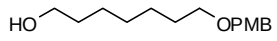
1-((Hept-6-ynyloxy)methyl)-4-methoxybenzene (1.10)

Alcohol 1.22 (1.34 g, 12 mmol) was added dropwise to a suspension of NaH (0.60 g, 60 wt% in mineral oil, 15 mmol) in DMF (25 mL) at 0 °C. After being stirred for 30 min at the same temperature, PMBCl (2.06 g, 13 mmol) was slowly added followed by addition of TBAI (44 mg, 0.12 mmol). The resulting mixture was stirred at room temperature for 18 h. Cold water (20 mL) was added to quench the reaction. The resulting mixture was extracted with Et_2O (3 × 30 mL). The organic layer was washed with brine, dried over MgSO4, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/Et_2O = 9:1) to afford the title compound **1.10** (2.55 g, 92%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.46 (s,2H), 3.80 (s, 3H), 3.44 (t, *J* = 6.4 Hz, 2H), 2.19 (td, *J* = 6.8, 2.6 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.66–1.41 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 130.7, 129.2, 113.7, 84.5, 72.5, 69.9, 68.2, 55.2, 29.2, 28.3, 25.4, 18.4.



8-(4-Methoxybenzyloxy)oct-2-ynal (1.5)

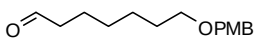
n-BuLi (6.8 mL, 1.6 M solution in hexane, 10.8 mmol) was slowly added to a solution of alkyne **1.10** (2.50 g, 10.8 mmol) in THF (27 mL) at –40 °C. After completion of addition, DMF (1.67 mL, 21.6 mmol) was added. The mixture was then warmed to room temperature. After being stirred for 30 min at the same temperature, the resulting mixture was poured into a solution of 10% acquous solution KH_2PO_4 (58 mL) and methyl *tert*-butyl ether (MTBE) (54mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted with MTBE (3 × 40 mL). The combined organic layers was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/Et2O = 3:1) to afford the title compound **1.5** (2.46 g, 88%) as pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.43 (s,2H), 3.81 (s, 3H), 3.45 (t, *J* = 6.2 Hz, 2H), 2.42 (t, *J* = 6.5 Hz, 2H), 1.67–1.46 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 159.0, 130.5, 129.1, 113.7, 99.0, 81.6, 72.5, 69.6, 55.2, 29.1, 27.3, 25.5, 19.0; IR (film) 2935, 2858, 2279, 1667, 1612, 1512, 1462, 1246, 1173, 1095, 1033, 817 cm^{-1}; MS (EI) *m/z* 260 (M^+); HRMS (EI) *m/z* (M^+) calcd for $C_{16}H_{20}O_3$ 260.1412, found 260.1410.



7-(4-Methoxybenzyloxy)heptan-1-ol:[37]

1,7 – Heptanediol **1.34** (17.00 g, 128.6 mmol) was added dropwise to a suspension of NaH (5.15 g, 60 wt% in mineral oil, 128.8 mmol) in THF (490 mL) at 0 °C. PMBCl (17.50 mL, 128.9 mmol) was then added dropwise followed by addition of TBAI (5.22 g, 14.1 mmol). After warm to room temperature and stirring for 1 h, the reaction mixture was heated to 60 °C for 15 h. After being cooled to room temperature, the resulting mixture was poured into a solution of

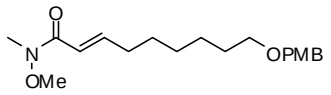
saturated $NaHCO_3$ and vigorously stirred. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/EtOAc = 7:3) to afford the title compound (15.93 g, 49%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 4.42 (s, 2 H), 3.80 (s, 3 H), 3.61 (t, *J* = 6.6 Hz, 2 H), 3.43 (t, *J* = 6.6 Hz, 2 H), 1.62–1.50 (m, 4 H), 1.40–1.33 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 130.7, 129.2, 113.7, 72.5, 70.1, 62.9, 55.2, 32.6, 29.6, 29.2, 26.1, 25.6; IR (film) 3428, 2935, 2859, 1612, 1513, 1465, 1247, 1092, 908, 734, 650 cm^{-1}; MS (EI) *m/z* 252 (M^+); HRMS (ESI) *m/z* (M^+) calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1730.



7-(4-Methoxybenzyloxy)heptanal (1.33):[37]

A solution of DMSO (13.0 mL, 183.0 mmol) in CH_2Cl_2 (76 mL) was slowly added to a solution of oxalyl chloride (10.5 mL, 122.0 mmol) in CH_2Cl_2 (350 ml) at –78 °C. After 15 min at the same temperature, a solution of 7-(4-Methoxybenzyloxy)heptan-1-ol (15.40 g, 61.0 mmol) in CH_2Cl_2 (76 mL) was then added dropwise. The resulting mixture was stirred for 15 min and Et_3N (42.6 mL, 305.6 mmol) was added slowly. The reaction was maintained at −78 °C for 15 min, then allowed to warm to 0 °C, the stirring continued for further 30 min. Water was added and the mixture was diluted with Et_2O. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with Et_2O (3 × 120 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (Hexane/EtOAc = 5:1) to afford the title compound **1.33** (15.01 g, 98%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.8 Hz, 1 H) 7.26 (d, *J*

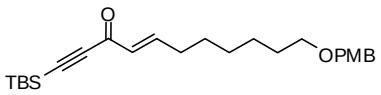
= 8.5 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.42 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, *J* = 6.5 Hz, 2 H), 2.42 (td, J = 7.3, 1.7 Hz, 2 H), 1.67–1.55 (m, 4 H), 1.44–1.28 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 159.0, 130.6, 129.1, 113.6, 72.4, 69.8, 55.1, 43.7, 29.4, 28.8, 25.9, 21.9; IR (film) 2937, 2860, 1722, 1612, 1512, 1464, 1248, 1093, 1036, 908, 731, 650 cm^{-1}; MS (EI) *m/z* 250 (M^+); HRMS (ESI) *m/z* (M^+) calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1572.



(*E*)-*N*-Methoxy-9-(4-methoxybenzyloxy)-*N*-methylnon-2-enamide (1.32):

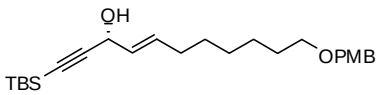
The diethyl *N*-methoxy-*N*-methylphosphonoacetamide **1.35** (15.1 mL, 73.2 mmol) was added to a suspension of NaH (3.30 g, 60 wt% in mineral oil, 82.5 mmol) in THF (400 mL) at 0 °C. The resulting mixture was stirred for 30 min, then a solution of aldehyde **1.33** (15.01 g, 60.0 mmol) in THF (100 mL) was added dropwise. The mixture was stirred for 1 h at room temperature before saturated aqueous NH_4Cl solution (120 mL) and Et_2O (120 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 120 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc = 6:4) to afford the title compound **1.32** (18.30 g, 91%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2 H), 6.97 (dt, *J* = 15.4, 7.0 Hz, 1 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 6.38 (dt, *J* = 15.4, 1.3 Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.69 (s, 3 H), 3.43 (t, *J* = 6.6 Hz, 2 H), 3.23 (s, 3 H), 2.23 (qd, J = 7.0, 1.3 Hz, 2 H), 1.64–1.55 (m, 4 H), 1.50–1.25 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 159.0, 147.8, 130.7, 129.1, 118.6, 113.7, 72.4, 70.0, 61.6, 55.2, 32.3, 32.2, 29.6, 28.9, 28.2, 25.9; IR (film) 2932, 2855, 1664, 1633, 1613, 1513, 1463, 1442, 1413, 1380, 1247,

1173, 1097, 1053, 998, 820 cm^{-1}; MS (EI) *m/z* 335 (M^+); HRMS (ESI) *m/z* (M^+) calcd for $C_{19}H_{29}NO_4$ 335.2097, found 335.2099.



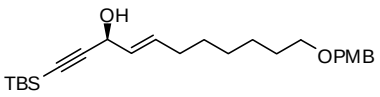
(*E*)-1-(*tert*-Butyldimethylsilyl)-11-(4-methoxybenzyloxy)undec-4-en-1-yn-3-one (1.31):

n-BuLi (72.0 mL, 1.6 M solution in hexane, 115.2 mmol) was added to a solution of *tert*-butyldimethylsilylacetylene **1.36** (20.5 mL, 109.8 mmol) in THF (300 ml) at –78 °C. After 20 min, the solution of amide **1.32** (18.30 g, 54.6 mmol) in THF (100 mL) was added. The resulting mixture was stirred for further 1 h at –78 °C. The mixture was poured into a saturated aqueous NH_4Cl solution and extracted with Et_2O (3 × 150 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 10:1) to afford the title compounds **1.31** (20.17 g, 89%) as pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2 H), 7.19 (dt, *J* = 15.5, 7.0 Hz, 1 H), 6.88 (d, *J* = 8.5 Hz, 2 H), 6.15 (dt, *J* = 15.5, 1.3 Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, *J* = 6.5 Hz, 2 H), 2.29 (qd, *J* = 7.0, 1.0 Hz, 2 H), 1.60 (quin, *J* = 6.9 Hz, 2 H), 1.50 (quin, *J* = 7.4 Hz, 2 H), 1.4–1.34 (m, 4 H), 0.98 (s, 9 H), 0.20 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 159.0, 154.6, 132.1, 130.6, 129.1, 113.6, 101.1, 96.7, 72.4, 69.9, 55.1, 32.4, 29.5, 28.9, 27.8, 25.9, 25.8, 16.5, –5.2; IR (film) 2933, 2859, 1641, 1620, 1513, 1465, 1363, 1301, 1248, 1174, 1095, 1037, 1008, 976, 910, 841, 780, 734 cm^{-1}; MS (EI) *m/z* 437 (M^+ + Na); HRMS (ESI) *m/z* (M^+) calcd for $C_{25}H_{39}O_3Si$ 415.2668, found 415.2669.



(*R*,*E*)-1-(*tert*-Butyldimethylsilyl)-11-(4-methoxybenzyloxy)undec-4-en-1-yn-3-ol (1.37R):

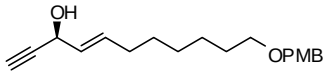
A solution of compound **1.31** (10.62 g, 25.6 mmol) in THF (90 ml) was added dropwise in 10 min to a solution of (*R*)-CBS (7.10 g, 25.6 mmol) and $BH_3 \cdot SMe_2$ (2.8 mL, 29.5 mmol) in THF (30 mL) at 0 °C under Ar. Upon completion of addition, reaction was cautiously quenched by slow addition of MeOH (30 mL) at 0 °C. The resulting solution was stirred for 15 min at room temperature and most organic solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 17:3) to afford the title compound **1.37R** (7.48 g, 70%, 93% ee), $[\alpha]_D^{25}$ = –21.7 (*c* = 1.30, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 5.90 (dtd, *J* = 15.3, 6.6，0.9 Hz, 1 H), 5.59 (ddt, *J* = 15.3, 5.7, 1.4 Hz, 1 H), 4.82 (t, *J* = 6.0 Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, *J* = 6.6 Hz, 2 H), 2.06 (q, *J* = 6.6 Hz, 2 H), 1.80 (d, *J* = 6.3 Hz, 1 H), 1.63–1.55 (m, 2 H), 1.45 - 1.28 (m, 6 H), 0.94 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 133.7, 130.6, 129.1, 128.8, 113.6, 105.8, 88.4, 72.3, 69.9, 63.0, 55.1, 31.7, 29.5, 28.8, 28.7, 26.0, 25.9, 16.4, –4.8; IR (film) 3593, 3419, 2932, 2858, 1612, 1513, 1465, 1363, 1301, 1249, 1091, 1034, 909, 827, 777, 734 cm^{-1}; HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{25}H_{40}O_3NaSi$ 439.2644, found 439.2620.



(*S*,*E*)-1-(*tert*-Butyldimethylsilyl)-11-(4-methoxybenzyloxy)undec-4-en-1-yn-3-ol (1.37S):

Following the same procedure for **1.37R**, ketone **1.31** (9.50 g, 22.9 mmol) was reacted with (*S*)-CBS (6.35 g, 22.9 mmol), $BH_3 \cdot SMe_2$ (2.5 mL, 26.4 mmol), the title compound **1.37S** (6.99 g, 73%, 94% ee) was obtained. $[\alpha]_D^{25}$ = +22.1 (*c* = 1.17, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.1 Hz, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 5.89 (dt, *J* = 15.0, 6.9 Hz, 1 H),

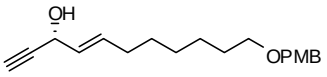
5.59 (dd, *J* = 15.0, 5.7 Hz, 1 H), 4.82 (t, *J* = 6.0 Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, *J* = 6.6 Hz, 2 H), 2.05 (q, *J* = 6.6 Hz, 2 H), 1.86 (d, *J* = 6.3 Hz, 1 H), 1.63–1.54 (m, 2 H), 1.45–1.28 (m, 6 H), 0.94 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 133.9, 130.7, 129.2, 128.8, 113.7, 105.7, 88.7, 72.4, 70.0, 63.2, 55.2, 31.8, 29.6, 28.9, 28.7, 26.0(2C), 16.4, –4.7; IR (film) 3405, 2931, 2857, 1613, 1513, 1464, 1362, 1302, 1249, 1091, 1035, 910, 828, 776, 733 cm^{-1}; MS (EI) *m/z* 439 (M^+ + Na); HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{25}H_{40}O_3NaSi$ 439.2644, found 439.2640.



(*S*,*E*)-11-(4-methoxybenzyloxy)undec-4-en-1-yn-3-ol (1.38S):

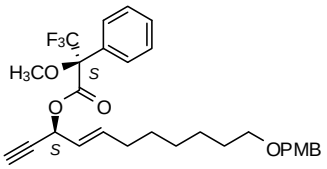
TBAF (0.77 mL, 1.0 M solution in THF, 0.77 mmol) was added to a solution of **43b** (216.3 mg, 0.52 mmol) in THF (10 mL) at –20 °C. The mixture then was stirred for 30 min at this temperature and quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 9 : 1) to give compound **1.38S** (149.1 mg, 95%) as pale yellow oil. $[\alpha]_D^{25}$ = +17.9 (*c* = 1.14, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.90 (dtd, *J* = 15.3, 6.7，1.1 Hz, 1H), 5.60 (ddt, *J* = 15.3, 6.1, 1.4 Hz), 4.83 (m, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.43 (t, *J* = 6.5 Hz, 2H), 2.56 (d, *J* = 2.2 Hz, 1H), 2.06 (q, *J* = 6.5 Hz, 2H), 1.89 (d, *J* = 6.2 Hz, 1H), 1.64–1.54 (m, 2H), 1.45–1.23 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 134.1, 130.6, 129.2, 128.5, 113.7, 83.4, 73.8, 72.4, 69.9, 62.5, 55.2, 31.7, 29.5, 28.9, 28.6, 25.9; IR (film) 3591, 3416, 3306, 3004, 2935, 2858, 1613, 1513,

1465, 1248, 1090, 908, 732, 650 cm^{-1}; MS (EI) *m/z* 302 (M^+); HRMS (EI) *m/z* (M^+) calcd for $C_{19}H_{26}O_3$ 302.1882, found 302.1872.



(*R,E*)-11-(4-methoxybenzyloxy)undec-4-en-1-yn-3-ol (1.38R):

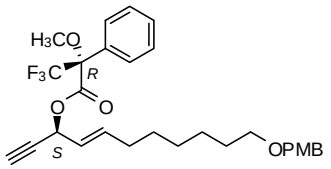
Following the same procedure for **1.38S**, alcohol **1.37R** (207.6 mg, 0.50 mmol) was reacted with TBAF (0.75 mL, 1.0 M solution in THF, 0.75 mmol), the title compound **1.38R** (150.2 mg, 95%) was obtained. $[\alpha]_D^{25}$ = –18.1 (*c* = 1.37, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.90 (dtd, *J* = 15.2, 6.7， 1.1 Hz, 1H), 5.60 (ddt, *J* = 15.3, 6.1, 1.4 Hz), 4.83 (m, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.43 (t, *J* = 6.6 Hz, 2H), 2.56 (d, *J* = 2.2 Hz, 1H), 2.06 (q, *J* = 6.7 Hz, 2H), 1.89 (d, *J* = 6.2 Hz, 1H), 1.63–1.55 (m, 2H), 1.45–1.23 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 133.9, 130.5, 129.1, 128.5, 113.6, 83.4, 73.7, 72.3, 69.9, 62.4, 55.1, 31.7, 29.4, 28.8, 28.6, 25.8; IR (film) 3591, 3417, 3306, 3004, 2934, 2858, 1613, 1513, 1465, 1248, 1090, 905, 731, 650 cm^{-1}; MS (EI) *m/z* 302 (M^+); HRMS (EI) *m/z* (M^+) calcd for $C_{19}H_{26}O_3$ 302.1882, found 302.1871.



(*S*)-((*S,E*)-11-(4-Methoxybenzyloxy)undec-4-en-1-yn-3-yl)3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (1.39SS):

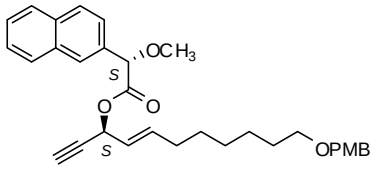
Alcohol **1.38S** (11.0 mg, 0.04 mmol) was added to a solution of (*R*)-MTPA-Cl (20.4 μL, 0.11 mmol) in pyridine (0.4 mL) at room temperature. After 4 h, the organic solvent was

removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 19:1) to afford the title compound **1.39SS** (14.5 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.41-7.36 (m, 3H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.00 (d, J = 6.8 Hz, 1H), 6.03 (dtd, *J* = 15.3, 6.9, 0.9 Hz, 1H), 5.49 (ddt, *J* = 15.1, 6.9, 1.4 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.59 (s, 3H), 3.42 (t, *J* = 6.6 Hz, 2H), 2.63 (d, *J* = 2.2 Hz, 1H), 2.04 (q, *J* = 7.0 Hz, 2H), 1.63–1.53 (m, 2H), 1.41–1.23 (m, 6H).



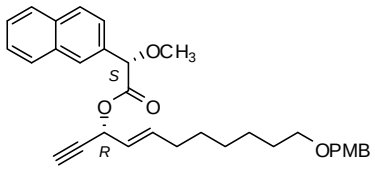
(*R*)-((*S*,*E*)-11-(4-Methoxybenzyloxy)undec-4-en-1-yn-3-yl)3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (1.39SR)

Following the same procedure as above, except for using (*S*)-MTPA-Cl rather than (*R*)-MTPA-Cl, the title compound **1.39SR** (15.0 mg, 80%) was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.52 (m, 2H), 7.43-7.37 (m, 3H), 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.07 (dt, *J* = 15.3, 6.9 Hz, 1H), 6.00 (d, J = 6.8 Hz, 1H), 5.60 (ddt, *J* = 15.4, 6.9, 1.2 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.55 (s, 3H), 3.43 (t, *J* = 6.5 Hz, 2H), 2.59 (d, *J* = 2.2 Hz, 1H), 2.09 (q, *J* = 6.9 Hz, 2H), 1.64–1.54 (m, 2H), 1.45–1.23 (m, 6H).



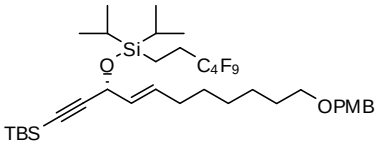
(*S*)-((*S*,*E*)-11-(4-Methoxybenzyloxy)undec-4-en-1-yn-3-yl)2-methoxy-2-(naphthalen-2-yl) acetate (1.40SS):

(*S*)-NMA acid (16.0 mg, 0.07 mmol), DCC (18.3, 0.09 mmol), and DMAP (0.9 mg, 0.007mmol) was added to a solution of alcohol **43a** (11.2 mg, 0.04 mmol) in CH_2Cl_2 (0.7 ml) at room temperature. The resulting mixture was stirred at the same temperature overnight. The mixture was then filtered through a pad of Celite ®, the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc = 17:3) to afford the tiltle compound **1.40SS** (14.2 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.86-7.82 (m, 3H), 7.56 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.51-7.47 (m, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.98 (dtd, *J* = 15.0, 7.0, 1,0 Hz, 1H), 5.87 (dd, *J* = 6.5, 1.0 Hz, 1H), 5.53 (ddt, *J* = 15.0, 6.5, 1.5 Hz, 1H), 4.96 (s, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.46 (s, 3H), 3.42 (t, *J* = 6.5 Hz, 2H), 2.45 (d, *J* = 2.0 Hz, 1H), 2.04 (q, *J* = 7.0 Hz, 2H), 1.61–1.55 (m, 2H), 1.39–1.23 (m, 6H).



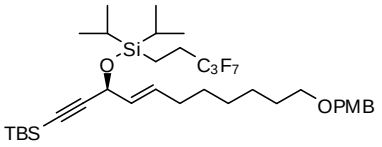
(*S*)-((*R*,*E*)-11-(4-Methoxybenzyloxy)undec-4-en-1-yn-3-yl) 2-methoxy-2-(naphthalen-2-yl) acetate (1.40RS):

Following the same procedure as above, except for using alcohol **1.38R** rather than **1.38S**, the title compound **1.40RS** (15.7 mg, 85%) was obtained. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.86-7.81 (m, 3H), 7.54 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.50-7.47 (m, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.89 (dd, *J* = 6.5, 1.0 Hz, 1H), 5.79 (dtd, *J* = 15.0, 7.0, 1.0 Hz, 1H), 5.34 (ddt, *J* = 15.0, 6.5, 1.5 Hz, 1H), 4.97 (s, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.47 (s, 3H), 3.39 (t, *J* = 7.0 Hz, 2H), 2.56 (d, *J* = 2.5 Hz, 1H), 1.89 (q, *J* = 6.5 Hz, 2H), 1.52 (m, 2H), 1.27–1.12 (m, 6H).



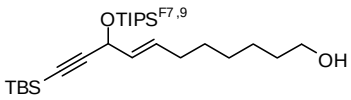
(*R*,*E*)-*tert*-Butyl(3-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-11-(4-methoxybenzyloxy)undec-4-en-1-ynyl)dimethylsilane (1.41R):

Trifluoromethanesulfonic acid (neat, 2.9 mL, 33.2 mmol) was slowly added to silane $C_4F_9(CH_2)_2(^iPr)_2SiH$ (neat, 15.1 g, 41.5 mmol) at 0 °C. After being stirred for 20 min at the same temperature, the mixture was warmed to room temperature and stirred for 15 h. CH_2Cl_2 (30 mL) was added to above mixture at –60 °C, followed by a solution of alcohol **1.37R** (6.92 g, 16.6 mmol) in CH_2Cl_2 (42 mL) and 2,6-lutidine (5.8 mL, 49.8 mmol). The resulting mixture was warmed to room temperature and stirred for further 2 h. Saturated aqueous NH_4Cl (100 mL) was then added to quench the reaction at 0 °C. The mixture was extracted with Et_2O (3 × 150 mL), the organic layers were combined and washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc = 19:1) to afford the title compound **1.41R** (11.23 g, 87%) as colorless oil. $[\alpha]_D^{25}$ = +1.13 (*c* = 1.20, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 5.79 (dtd, *J* = 15.3, 6.6, 0.9 Hz, 1 H), 5.51 (dd, *J* = 15.0, 5.7 Hz, 1 H), 4.89 (d, *J* = 5.4 Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, *J* = 6.3 Hz, 2 H), 2.23–2.01 (m, 4 H), 1.61–1.54 (m, 2 H), 1.43–1.28 (m, 6 H), 1.06 (br s, 14 H), 0.93–0.86 (m, 11 H), 0.09 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 132.5, 130.8, 129.4, 129.2, 113.8, 106.0, 88.4, 72.5, 70.2, 64.1, 55.3, 31.7, 29.7, 29.0, 28.9, 26.0, 25.9, 25.4 (t, J_{CF} = 23.2 Hz, 1 C), 17.5 (2 C), 17.4 (2 C) 16.5, 12.7, 12.6, 0.3 –4.9; IR (film) 3020, 2934, 1640, 1514, 1474, 1424, 1216, 1133, 1036, 929, 755 cm^{-1}; HRMS (ESI) *m/z* (M^+ + H) calcd for $C_{37}H_{58}O_3Si_2F_9$ 777.3793, found 777.3781.



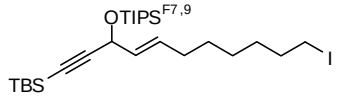
(*S*,*E*)-*tert*-Butyl(3-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-11-(4-methoxybenzyloxy)undec-4-en-1-ynyl)dimethylsilane (1.41S):

Trifluoromethanesulfonic acid (neat, 2.7 mL, 30.8 mmol) was slowly added to silane $C_3F_7(CH_2)_2(^iPr)_2SiH$ (neat, 12.1 g, 39.5 mmol) at 0 °C. After being stirred for 20 min at the same temperature, the mixture was warmed to room temperature and stirred for 15 h. CH_2Cl_2 (23 mL) was added to above mixture at –60 °C, followed by a solution of alcohol **1.37R** (6.44 g, 15.4 mmol) in CH_2Cl_2 (39 mL) and 2,6-lutidine (5.4 mL, 46.2 mmol). The resulting mixture was warmed to room temperature and stirred for further 2 h. Saturated aqueous NH_4Cl (90 mL) was then added to quench the reaction at 0 °C. The mixture was extracted with Et_2O (3 × 150 mL), the organic layers were combined and washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc = 19:1) to afford the title compound **1.41S** (10.11 g, 90%) as colorless oil. $[\alpha]_D^{25} = -1.09$ (*c* = 0.92, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 5.79 (dtd, *J* = 15.3, 6.9, 0.6 Hz, 1 H), 5.51 (dd, *J* = 15.3, 5.7 Hz, 1 H), 4.89 (d, *J* = 5.7 Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, *J* = 6.6 Hz, 2 H), 2.23–2.01 (m, 4 H), 1.61–1.53 (m, 2 H), 1.43–1.28 (m, 6 H), 1.06 (br s, 14 H), 0.93–0.86 (m, 11 H), 0.09 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 132.5, 130.8, 129.4, 129.2, 113.8, 106.0, 88.4, 72.5, 70.2, 64.1, 55.2, , 31.7, 29.7, 29.0, 28.9, 26.0, 25.9, 25.3 (t, J_{CF} = 23.2 Hz, 1 C), 17.5 (2 C), 17.4 (2 C) 16.5, 12.7, 12.6, 0.3 –4.9; IR (film) 3020, 2934, 1640, 1514, 1474, 1424, 1216, 1133, 1037, 929, 755 cm^{-1}; HRMS (ESI) *m/z* (M^+ + Na + H) calcd for $C_{37}H_{58}O_3NaSi_2F_7$ 749.3634, found 749.3632.



(*R*/*S*,*E*)-11-(*tert*-Butyldimethylsilyl)-9-((perfluoroalkylethyl)diisopropylsilyloxy)undec-7-en-10-yn-1-ol (M-1.42):

DDQ (5.90 g, 26.0 mmol) was added to the mixture of compound **1.41R** (7.77 g, 10.0 mmol) and compound **1.41S** (7.25 g, 10.0 mmol) in CH_2Cl_2 (200 mL) and H_2O (22.3 mL) at room temperature. The reaction was monitored by TLC until completion, and then saturated $NaHCO_3$ aqueous solution was added. The mixture was extracted with CH_2Cl_2 (3 × 150 mL), the organic layers were combined, washed with saturated $NaHCO_3$ aqueous solution, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/Et_2O = 85:15) to afford the title compound **M-41**, which was contaminated with tiny 4-(methoxymethyl)benzaldehyde and was used in the following step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (dtd, *J* = 15.3, 7.8, 0.9 Hz, 1H), 5.54 (dd, *J* = 15.3, 5.7, 1H), 4.89 (d, *J* = 5.7 Hz, 1H), 3.64 (q, *J* = 6.2 Hz, 2H), 2.23–2.03 (m, 2H), 2.06 (q, *J* = 6.6 Hz, 2H), 1.61–1.52 (m, 2H), 1.45–1.33 (m, 6H), 1.18 (t, *J* = 5.4 Hz, 1H), 1.08–1.06 (m, 14H), 0.95–0.85 (m, 11H), 0.09 (s, 6H).



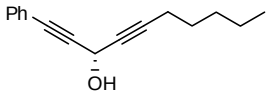
(*R*/*S*,*E*)-*tert*-Butyl(3-(perfluoroalkylethyl)diisopropylsilyloxy)-11-iodoundec-4-en-1-ynyl)dimethylsilane (M-1.29):

A solution of iodine (5.74 g, 22.6 mmol) in CH_2Cl_2 (85 mL) was slowly added to a solution of triphenylphosphine (5.93 g, 22.6 mmol) in CH_2Cl_2 (28 mL), followed by a mixture of imidazole (1.69 g, 24.8 mmol) and alcohol **M-1.42** (crude, 7.14 g, 11.3 mmol) in CH_2Cl_2 (28 mL)

at room temperature. After 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (150 mL). The mixture was extracted with Et_2O (3 × 100 mL) and organic layer was washed with saturated aqueous $Na_2S_2O_3$ (100 mL), water, brine, dried over $MgSO_4$, and concentrated *in vacuuo*. The crude product was purified by column chromatography (hexane/Et_2O = 99.5:0.5) to afford the title comound **M-40** (7.33 g, 49%) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (dtd, *J* = 15.3, 7.5, 0.9 Hz, 1H), 5.52 (dd, *J* = 15.3, 5.7 Hz, 1H), 4.90 (d, *J* = 5.7 Hz, 1H), 3.18 (t, *J* = 6.9 Hz, 2 H), 2.28–2.06 (m, 2H), 2.06 (q, *J* = 6.6 Hz, 2H), 1.86–1.77 (m, 2H), 1.43–1.26 (m, 6H), 1.19–1.02 (m, 14H), 1.06 (m, 11H), 0.09 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.2, 129.6, 105.9, 88.4, 87.6, 64.1, 33.5, 31.6, 30.3, 28.7, 28.0, 26.0, 17.5 (2C), 17.4 (2C), 16.5, 12.7, 12.6, 7.0, 0.3, −4.9.

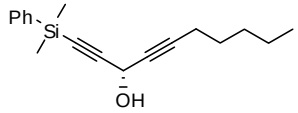
General procedure: asymmetric alkynylation to alkynyl aldehyde.

In a 25mL round bottle flask, a solution of alkyne (3.0 mmol) and diethylzinc (323.4 μL, 3.0 mmol) in toluene (1.0 mL) was heated under argon atmosphere to reflux for 1 h. After the solution cooled to room temperature, (*R*)-BINOL (143.2 mg, 0.5 mmol), Et_2O (8.0 mL), and $Ti(O^iPr)_4$ (370.0 μL, 1.25 mmol) were added sequentially, the resulting mixture was stirred for 1 h. Aldehyde (0.5 mmol) was added to the above mixture and stirring continued for additional 4 h. Saturated aqueous NH_4Cl was added to quench the reaction. The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography to afford the corresponding propargylic alcohol. The ee of product was determined by chiral HPLC (Chiralcel OD column, 4.6 × 200 mm, hexane/^{i}PrOH = 9:1, 1.0 mL/min)



(*S*)-1-Phenyldeca-1,4-diyn-3-ol (1.44S):

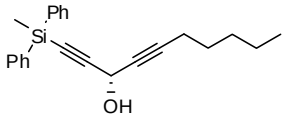
General procedure was followed employing phenylacetylene **1.43** (336.2 μL, 3.0 mmol), diethylzinc (323.4 μL, 3.0 mmol), (*R*)-BINOL (143.2 mg, 0.5 mmol), $Ti(O^iPr)_4$ (370.0 μL, 1.25 mmol), and 2-octynal **1.27** (73.5 μL, 0.5 mmol). Purification by column chromatography (hexane/EtOAc = 19:1) afforded the title compound **1.44S** (102.1 mg, 90%). 78% ee determined by HPLC analysis (t_{minor} = 6.16 min, t_{major} = 11.03 min), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.45 (m, 2H), 7.34–7.28 (m, 3H), 5.35 (dt, *J* = 6.9, 1.8 Hz, 1H), 2.35 (d, *J* = 7.0, 1H), 2.25 (td, *J* = 7.1 Hz, 2.0 Hz, 2H), 1.60–1.50 (m, 2H), 1.43–1.26 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.8, 128.7, 128.2, 122.1, 86.7, 86.0, 83.9, 77.4, 52.9, 31.0, 28.0, 22.1, 18.7, 13.9; IR (film) 3336, 3032, 2917, 1855, 2230, 1599, 1499, 1443, 1378, 1071, 1010, 996, 963, 942, 756, 691 cm^{-1}.



(*S*)-1-(Dimethyl(phenyl)silyl)deca-1,4-diyn-3-ol (1.48*S*):

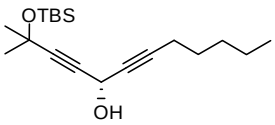
General procedure was followed employing dimethylphenylsilyacetylene **1.45** (540.1 μL, 3.0 mmol), diethylzinc (323.4 μL, 3.0 mmol), (*R*)-BINOL (143.2 mg, 0.5 mmol), $Ti(O^iPr)_4$ (370.0 μL, 1.25 mmol), and 2-octynal **1.27** (73.5 μL, 0.5 mmol). Purification by column chromatography (hexane/EtOAc = 19:1) afforded the title compound **1.48S** (127.1 mg, 90%) as yellow oil. 78% ee determined by HPLC analysis (hexane/^{i}PrOH = 49:1, 1mL/min, t_{minor} = 11.01 min, t_{major} = 13.25 min), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.61 (m, 2H), 7.39–7.35 (m, 3H), 5.14 (dt, *J* = 7.4, 1.9 Hz, 1H), 2.23 (td, *J* = 7.0, 1.9 Hz, 2H), 2.15 (d, *J* = 7.4 Hz, 1H), 1.58–1.49

(m, 2H), 1.42–1.26 (m, 4H), 0.90 (t, J =7.1 Hz, 3H), 0.44 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 133.7, 129.5, 127.9, 104.3, 86.9, 86.0, 77.2, 52.9, 31.0, 28.0, 22.2, 18.7, 13.9, −1.1; IR (film) 3368, 3070, 2958,2932, 2860, 2178, 1466, 1429, 1298,1250, 1115, 1034, 964, 838, 782, 732, 698; MS (EI) *m/z* 283 (M^+ − H); HRMS (EI) *m/z* (M^+ − H) calcd for $C_{18}H_{23}OSi$ 283.1518, found 283.1520.



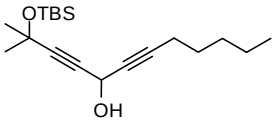
(*S*)-1-(Methyldiphenylsilyl)deca-1,4-diyn-3-ol (1.49S):

General procedure was followed employing methyldiphenylsilyacetylene **1.46** (660.5 μL, 3.0 mmol), diethylzinc (323.4 μL, 3.0 mmol), (*R*)-BINOL (143.2 mg, 0.5 mmol), $Ti(O^iPr)_4$ (370.0 μL, 1.25 mmol), and 2-octynal **1.27** (73.5 μL, 0.5 mmol). Purification by column chromatography (hexane/EtOAc = 33:1) afforded the title compound **1.49S** (147.3 mg, 85%) as a yellow oil. 80% ee determined by HPLC analysis (hexane/^{i}PrOH = 49:1, 1 mL/min, t_{minor} = 15.55 min, t_{major} = 20.78 min), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66–7.63 (m, 4H), 7.45–7.34 (m, 6H), 5.19 (dt, J = 7.6, 2.1 Hz, 1H), 2.24 (td, J = 7.0, 2.1 Hz, 2H), 2.20 (d, J = 7.5 Hz, 1H), 1.59-1.50 (m, 2H), 1.43–1.26 (m, 4H), 0.90 (t, J =6.9 Hz, 3H), 0.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.7 134.5, 129.8, 128.0, 105.9, 86.2, 85.3, 77.1, 53.0, 31.0, 28.0, 22.2, 18.7, 13.9, −–2.3; IR (film) 3398, 3069, 2957,2930, 2859, 2178, 1466, 1429, 1298,1252, 1114, 1034, 964, 793, 728, 698; MS (EI) *m/z* 346 (M^+); HRMS (EI) *m/z* (M^+) calcd for $C_{23}H_{26}OSi$ 346.1753, found 346.1736.



(*S*)-2-(*tert*-Butyldimethylsilyloxy)-2-methyldodeca-3,6-diyn-5-ol (1.50S):

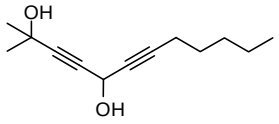
General procedure was followed employing alkyne **1.47** (679.2 mg, 3.0 mmol), diethylzinc (323.4 μL, 3.0 mmol), (*R*)-BINOL (143.2 mg, 0.5 mmol), $Ti(O^iPr)_4$ (370.0 μL, 1.25 mmol), and 2-octynal **1.27** (73.5 μL, 0.5 mmol). Purification by column chromatography (hexane/EtOAc = 33:1) afforded the title compound **1.50S** (150.6 mg, 86%) as a yellow oil. 90% ee determined by HPLC analysis (hexane/^{i}PrOH = 49:1, 0.6 mL/min, t_{minor} = 15.55 min, t_{major} = 20.78 min), ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (dt, *J* = 7.4, 2.1 Hz, 1H), 2.22 (td, *J* = 7.0, 2.0 Hz, 2H), 1.99 (d, *J* = 7.3 Hz, 1H), 1.57–1.50 (m, 2H), 1.46 (s, 6H), 1.39-1.25 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.19 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 89.3, 85.8, 80.1, 77.2, 66.2, 52.5, 32.7, 31.0, 28.0, 25.7, 22.2, 18.6, 17.9, 13.9, −3.0; IR (film) 3053, 2986, 2254, 1422, 1265, 1162, 1037, 909, 735, 650; MS (EI) *m/z* 307 ($M^+ - CH_3$); HRMS (EI) *m/z* ($M^+ - CH_3$) calcd for $C_{18}H_{31}O_2Si$ 307.2093, found 307.2089.



2-(*tert*-Butyldimethylsilyloxy)-2-methyldodeca-3,6-diyn-5-ol (*rac*-1.51):

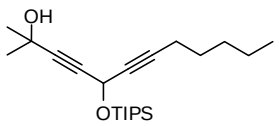
n-BuLi (4.1 mL, 1.6 M solution in hexane, 6.5 mmol) was slowly added to a solution of alkyne **1.47** (1.29 g, 6.5 mmol) in THF (30 mL) at −78 °C. The mixture was then warmed to room temperature and stirred for 1 h. 2-Octynal **1.27** (0.74 mL, 5.0 mmol) was added and the resulting mixture was then stirred overnight. Ice was added to quench reaction; the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, dried over $MgSO_4$, and

concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 97:3) to afford the racemic compound ***rac*-1.51** (1.32 g, 82%) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (dt, *J* = 7.3, 2.0 Hz, 1H), 2.21 (td, *J* = 7.0, 2.1 Hz, 2H), 2.12 (d, *J* = 7.4 Hz, 1H), 1.56–1.48 (m, 2H), 1.45 (s, 6H), 1.39–1.27 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H), 0.86 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 89.2, 85.7, 80.0, 77.3, 66.1, 52.4, 32.6, 31.0, 28.0, 25.7, 22.2, 18.6, 17.9, 13.9, −3.1.



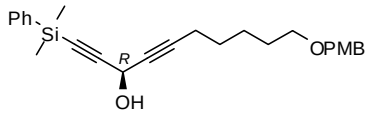
2-Methyldodeca-3,6-diyne-2,5-diol (*rac*-1.52):

Acetyl chloride (1 mL) was added to a solution of compound **37** (1.28 g, 4.0 mmol) in MeOH (40 mL) at room temperature. The mixture was then stirred for 10 min at the same temperature. The organic solvents were then removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 7:3) to afford the title compound **38** (0.75 g, 91%) as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (br s, 1H), 3.06 (d, *J* = 6.7 Hz, 1H), 2.80 (s, 1H), 2.21 (td, *J* = 7.1, 2.0 Hz, 2H), 1.58-1.45 (m, 2H), 1.52 (s, 6H), 1.39–1.24 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 88.4, 85.6, 80.0, 77.0, 65.1, 52.1, 31.0 (3C), 28.0, 22.1, 18.6, 13.9.



2-Methyl-5-(triisopropylsilyloxy)dodeca-3,6-diyn-2-ol (*rac*-1.53):

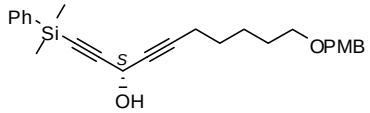
TIPSCl (0.66 mL, 3.1 mmol) and imidazole (279 mg, 4.1 mmol) was added to a solution of diol ***rac*-1.52** (533 mg, 2.6 mmol) in DMF (13 mL) at room temperature. The mixture was stirred overnight at the same temperature. Water (20 mL) was added to quench reaction. The organic layer was separated; the aqueous layer was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuuo*. The residue was purified by column chromatography (hexane/EtOAc = 97:3) to afford title compound **39** (813 mg, 87%) as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (t, J = 2.1 Hz, 1H), 2.20 (td, *J* = 6.9, 2.0 Hz, 2H), 1.96 (br s, 1H), 1.55-1.44 (m, 2H), 1.50 (s, 6H), 1.39–1.26 (m, 4H), 1.17–1.04 (m, 21H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 87.3, 84.4, 80.9, 78.2, 65.1, 53.3, 31.2, 31.1, 31.0, 28.0, 22.1, 18.6, 17.8, 13.9, 12.2.



(*R*)-1-(Dimethyl(phenyl)silyl)-10-(4-methoxybenzyloxy)deca-1,4-diyn-3-ol (1.54R):

In a 50 mL round bottle flask, a solution of dimethylphenylsilyacetylene **1.45** (6.0 mmol) and diethylzinc (646.8 μL, 6.0 mmol) in toluene (2.0 mL) was heated under argon atmosphere to reflux for 1 h. After the solution cooled to room temperature, (*S*)-BINOL (286.4 mg, 1.0 mmol), Et_2O (16.0 mL), and $Ti(O^iPr)_4$ (540.0 μL, 2.5 mmol) were added sequentially, the resulting mixture was stirred for 1 h. Aldehyde **1.5** (260.1 mg, 1.0 mmol) was added to the above mixture and stirring continued for additional 4 h. Saturated aqueous NH_4Cl (20 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 35 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by chiral HPLC (semi-preparation Chiracel OD column, hexane/^{i}PrOH = 19:1, 8.0 mL/min) to afford the optical pure compound

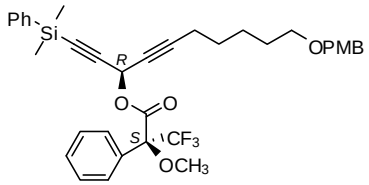
1.54R (269.3 mg, 64%), followed by **1.54S** (25.8 mg, 6%). $[\alpha]_D^{25}$ = +4.3 (*c* = 1.09, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.64–7.61 (m, 2H), 7.39–7.37 (m, 3H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.12 (dt, *J* = 7.5, 2.1 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.44 (t, *J* = 6.3 Hz, 2H), 2.24 (td, *J* = 6.9, 1.8 Hz, 2H), 2.22 (d, *J* = 7.5 Hz, 1H), 1.64–1.46 (m, 6H), 0.43 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 136.2, 133.6, 130.4, 129.4, 129.2, 127.8, 113.6, 104.5, 86.4, 85.2, 77.4, 72.3, 69.6, 55.1, 52.5, 29.0, 27.9, 25.3, 18.5, –1.2; IR (film) 3585, 3019, 2986, 2400, 1613, 1513, 1429, 1215, 1114, 1033, 929, 755; MS (EI) *m/z* 420 (M^+); HRMS (EI) *m/z* (M^+) calcd for $C_{26}H_{32}SiO_3$ 420.2121, found 420.2109.



(*S*)-1-(Dimethyl(phenyl)silyl)-10-(4-methoxybenzyloxy)deca-1,4-diyn-3-ol (1.54S):

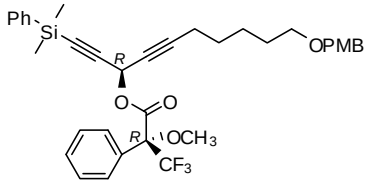
In a 50 mL round bottle flask, a solution of dimethylphenylsilyacetylene **1.45** (6.0 mmol) and diethylzinc (646.8 μL, 6.0 mmol) in toluene (2.0 mL) was heated under argon atmosphere to reflux for 1 h. After the solution cooled to room temperature, (*R*)-BINOL (286.4 mg, 1.0 mmol), Et_2O (16.0 mL), and $Ti(O^iPr)_4$ (540.0 μL, 2.5 mmol) were added sequentially, the resulting mixture was stirred for 1 h. Aldehyde **1.5** (260.1 mg, 1.0 mmol) was added to the above mixture and stirring continued for additional 4 h. Saturated aqueous NH_4Cl (20 mL) was added to quench the reaction. The mixture was extracted with CH_2Cl_2 (3 × 35 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by chiral HPLC (semi-preparation Chiracel OD column, hexane/^{i}PrOH = 19:1, 8.0 mL/min) to afford the optical pure compound **1.54R** (23.4 mg, 5%), followed by **1.54S** (294.6 mg, 70%). $[\alpha]_D^{25}$ = −4.2 (*c* = 0.96, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.65–7.61 (m, 2H), 7.40–7.35 (m, 3H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.88

(d, *J* = 8.7 Hz, 2H), 5.12 (dt, *J* = 7.2, 2.1 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.44 (t, *J* = 6.3 Hz, 2H), 2.28 (d, *J* = 7.5 Hz, 1H), 2.24 (td, *J* = 6.9, 2.1 Hz, 2H), 1.66–1.43 (m, 6H), 0.44 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 136.3, 133.6, 130.5, 129.4, 129.2, 127.8, 113.7, 104.4, 86.5, 85.4, 77.4, 72.4, 69.7, 55.2, 52.6, 29.1, 27.9, 25.3, 18.6, −1.2; IR (film) 3585, 3019, 2400, 1613, 1514, 1429, 1215, 1114, 1034, 929, 755; MS (EI) *m/z* 420 (M^+); HRMS (EI) *m/z* (M^+) calcd for $C_{26}H_{32}SiO_3$ 420.2121, found 420.2121.



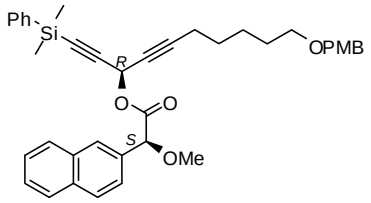
(*S*)-((*R*)-1-(Dimethyl(phenyl)silyl)-10-(4-methoxybenzyloxy)deca-1,4-diyn-3-yl)3,3,3-tri fluoro-2-methoxy-2-phenylpropanoate (1.55RS):

Alcohol **1.54R** (11.0 mg, 0.04 mmol) was added to a solution of (*R*)-MTPA-Cl (20.4 μL, 0.11 mmol) in pyridine (0.4 mL) at room temperature. After 4 h, the organic solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 19:1) to afford the title compound **1.55RS** (15.1 mg, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.56 (m, 2H), 7.53 (d, *J* = 7.3 Hz, 2H), 7.41–7.30 (m, 6H), 7.25 (d, *J* = 8.1Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.27 (t, *J* = 2.1 Hz, 1H), 4.41 (s, 2H), 3.80 (s, 3H), 3.57 (s, 3H), 3.41 (t, *J* = 6.4 Hz, 2H), 2.24 (td, J = 7.0, 2.1 Hz, 2H), 1.62–1.41 (m, 6H), 0.41 (s, 6H).



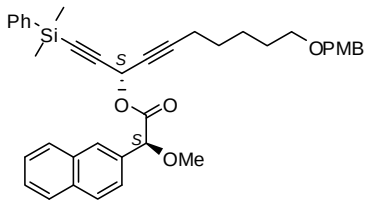
(*R*)-((*R*)-1-(Dimethyl(phenyl)silyl)-10-(4-methoxybenzyloxy)deca-1,4-diyn-3-yl)3,3,3-tri fluoro-2-methoxy-2-phenylpropanoate (1.55RR):

Following the same procedure as above, except for using (*S*)-MTPA-Cl rather than (*R*)-MTPA-Cl, the title compound **1.55RR** (14.5 mg, 78%) was obtained: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61–7.58 (m, 2H), 7.53 (d, *J* = 7.0 Hz, 2H), 7.42–7.31 (m, 6H), 7.25 (d, *J* = 7.5 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.29 (t, *J* = 2.1 Hz, 1H), 4.41 (s, 2H), 3.80 (s, 3H), 3.56 (s, 3H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.21 (td, *J* = 6.8, 2.0 Hz, 2H), 1.64–1.33 (m, 6H), 0.43 (s, 6H).



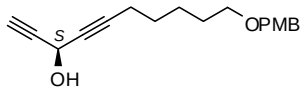
(*S*)-((*R*)-1-(Dimethyl(phenyl)silyl)-10-(4-methoxybenzyloxy)deca-1,4-diyn-3-yl) 2-methoxy-2-(naphthalen-2-yl)acetate (1.56RS):

(*S*)-NMA acid (7.8 mg, 0.04 mmol), DCC (8.9, 0.04 mmol), and DMAP (0.4 mg, 0.004mmol) was added to a solution of alcohol **1.54R** (7.6 mg, 0.02 mmol) in CH_2Cl_2 (0.3 ml) at room temperature. The resulting mixture was stirred at the same temperature overnight. The mixture was then filtered through a pad of Celite ®, the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc = 17:3) to afford the tiltle compound **1.56RS** (8.7 mg, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.85–7.80 (m, 3H), 7.60–7.55 (m, 3H), 7.49–7.46 (m, 2H), 7.37–7.32 (m, 3H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.13 (t, *J* = 2.1 Hz, 1H), 4.99 (s, 1H), 4.39 (s, 2H), 3.80 (s, 3H), 3.46 (s, 3H), 3.35 (t, *J* = 6.5 Hz, 2H), 2.05 (td, *J* = 6.8, 2.1 Hz, 2H), 1.51–1.44 (m, 2H), 1.38–1.23 (m, 4H), 0.40 (s, 6H).



(*S*)-((*S*)-1-(Dimethyl(phenyl)silyl)-10-(4-methoxybenzyloxy)deca-1,4-diyn-3-yl) 2- methoxy-2-(naphthalen-2-yl)acetate (1.56SS):

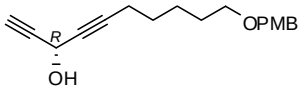
Following the same procedure as above, except for using alcohol **1.54S** rather than **1.54R**, the title compound **1.56SS** (8.2 mg, 74%) was obtained: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.85–7.76 (m, 3H), 7.60–7.45 (m, 4H), 7.37–7.24 (m, 6H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.13 (t, *J* = 2.0 Hz, 1H), 5.00 (s, 1H), 4.41 (s, 2H), 3.79 (s, 3H), 3.47 (s, 3H), 3.41 (t, *J* = 6.4 Hz, 2H), 2.21 (td, *J* = 6.6, 2.0 Hz, 2H), 1.70–1.37 (m, 6H), 0.25 (s, 6H).



(*S*)-10-(4-Methoxybenzyloxy)deca-1,4-diyn-3-ol (1.57S):

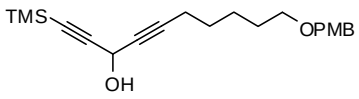
TBAF (9.2 mL, 1.0 M solution in THF, 9.2 mmol) was added to a solution of alcohol **1.54R** (1.93 g, 4.6 mmol) in THF (45 mL) at room temperature. The mixture then was stirred for 1 h at this temperature and quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with CH_2Cl_2 (3 × 70 mL). The organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 4 : 1) to give compound **1.57S** (1.12 g, 85%) as a pale yellow oil. $[\alpha]_D^{25}$ = +3.71 (*c* = 1.09, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.09 (dq, *J* = 7.5, 2.1 Hz, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.44 (t, *J* = 6.6

Hz, 2H), 2.53 (d, J = 2.1 Hz, 1H), 2.30–2.25(m, 1H), 2.24 (td, J = 6.6, 2.1 Hz, 2H), 1.66–1.40 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 130.6, 129.3, 113.8, 85.8, 81.5, 77.2, 72.5, 72.2, 69.8, 55.3, 52.1, 29.1, 28.0, 25.5, 18.6; IR (film) 3422, 3020, 1642, 1514, 1425, 1216, 1089, 1015, 928, 757.



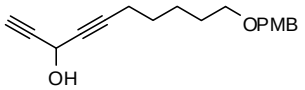
(*R*)-10-(4-Methoxybenzyloxy)deca-1,4-diyn-3-ol (1.57R):

TBAF (9.1 mL, 1.0 M solution in THF, 9.1 mmol) was added to a solution of alcohol **1.54R** (1.91 g, 4.5 mmol) in THF (45 mL) at room temperature. The mixture then was stirred for 1 h at this temperature and quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with CH_2Cl_2 (3 × 70 mL). The organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 4 : 1) to give compound **1.57S** (1.15 g, 85%) as a pale yellow oil. $[\alpha]_D^{25}$ = −3.29 (c = 1.25, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.09 (dq, J = 7.5, 2.1 Hz, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.44 (t, J = 6.6 Hz, 2H), 2.53 (d, J = 2.1 Hz, 1H), 2.30–2.25(m, 1H), 2.24 (td, J = 6.6, 2.1 Hz, 2H), 1.66–1.40 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 130.6, 129.3, 113.8, 85.8, 81.5, 77.2, 72.5, 72.2, 69.8, 55.3, 52.1, 29.1, 28.0, 25.5, 18.6; IR (film) 3422, 3020, 1642, 1514, 1425, 1216, 1089, 1015, 928, 757.



10-(4-Methoxybenzyloxy)-1-(trimethylsilyl)deca-1,4-diyn-3-ol:

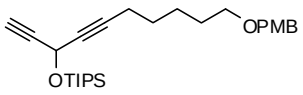
n-BuLi (7.5 mL, 1.6 M in hexane, 12.0 mmol) was added dropwise to a solution of trimethylsilylacetylene (1.70 mL, 12.0 mmol) in THF (50 mL) at −78 °C. After 30 min, a solution of aldehyde 1.5 (2.09 g, 8.0 mmol) in THF (14 mL) was added slowly. The resulting mixture was stirred for 45 min, and then allowed to warm to rt. The solution was poured into pH 7 phosphate buffer and extracted with Et_2O (3 × 50 mL). The organic layer was washed with brine. The aqueous layer was extracted with Et_2O (50 mL) again. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 85 : 15) to give the title compound (2.55 g, 89%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.08 (dq, *J* = 7.2, 2.1 Hz, 1H), 4.30 (s, 2H), 3.81 (s, 3H), 3.44 (t, *J* = 6.3 Hz, 2H), 2.23 (td, *J* = 6.9, 2.1 Hz, 2H), 2.21 (d, *J* = 7.5 Hz, 1H), 1.66–1.40 (m, 6H), 0.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 130.6, 129.2, 113.8, 102.7, 88.7, 85.4, 77.5, 72.5, 69.8, 55.2, 52.7, 29.2, 28.0, 25.4, 18.7, −0.3; IR (film) 3419, 2941, 1612, 1513, 1464, 1373, 1302, 1251, 1174, 1093, 1034, 907, 846, 732; MS (EI) *m/z* 358 (M^+)



10-(4-Methoxybenzyloxy)deca-1,4-diyn-3-ol (*rac*-1.57):

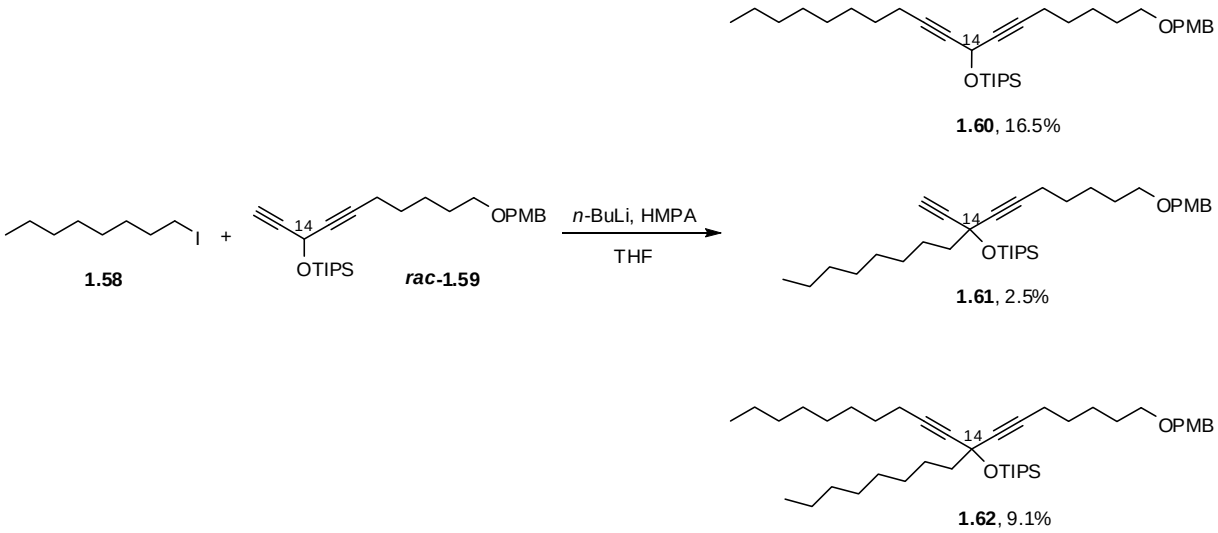
TBAF (14.4 mL, 1.0 M in THF, 14.4 mmol) was added to a solution of 10-(4-Methoxybenzyloxy)-1-(trimethylsilyl)deca-1,4-diyn-3-ol (2.50 g, 7.2 mmol) in THF (70 mL). The resulting mixture was stirred for 2 h at rt. The mixture was diluted with Et_2O (50 mL), washed with brine (3 × 50 mL), dried over MgSO4, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 3:1) to give the compound rac-1.57 (1.88 g, 91%) as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* =

8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.08 (dq, *J* = 7.5, 2.1 Hz, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.44 (t, *J* = 6.3 Hz, 2H), 2.54 (d, *J* = 2.4 Hz, 1H), 2.26 (d, *J* = 7.5 Hz, 1H), 2.23 (td, *J* = 6.6, 2.1 Hz, 2H), 1.66–1.40 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 130.6, 129.2, 113.8, 85.7, 81.6, 77.2, 72.5, 72.1, 69.8, 55.3, 52.1, 29.1, 28.0, 25.4, 18.6; IR (film) 3416, 2941, 1615, 1514, 1464, 1378, 1302, 1248, 1174, 1095, 1014, 907, 731; MS (EI) *m/z* 286 (M^+).



Triisopropyl(10-(4-methoxybenzyloxy)deca-1,4-diyn-3-yloxy)silane (*rac*-1.59):

2,6-Lutidine (1.5 mL, 13.1 mmol) and TIPSOTf (3.6 mL, 13.1 mmol) were sequentially added to a solution of alcohol ***rac*-1.57** (1.85 g, 6.5 mmol) in CH_2Cl_2 (65 mL) at 0 °C. The reaction was monitored by TLC until completion. Saturated NH_4Cl (aq) (50 mL) was then added to quench reaction. The reaction mixture was poured in a separatory funnel containing CH_2Cl_2 (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried over MgSO4, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 92:8) to afford the product ***rac*-1.59** (2.59 g, 90%) as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.23 (q, *J* = 2.1 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.43 (t, *J* = 6.3 Hz, 2H), 2.47 (d, *J* = 2.4 Hz, 1H), 2.22 (td, *J* = 6.9, 2.1 Hz, 2H), 1.66–1.40 (m, 6H), 1.18–1.04 (m, 21H).



n-BuLi (0.15 mL, 1.6 M in hexane, 0.24 mmol) was added to a solution of alkyne ***rac*-1.59** (88.5 mg, 0.2 mmol) in THF (2 mL) at −30 °C. After stirring at the same temperature for 1 h, the reaction mixture was cooled to −78 °C. HMPA (0.2 mL) was added to above solution, followed by a solution of iodide **1.58** (64.6 μL, 0.4 mmol) in THF (1 mL). The mixture was stirred at −78 °C for another 3 h and allowed to warm to rt for overnight stirring. The reaction was quenched with saturated NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/Et_2O = 98:2) to give three products shown below.

Triisopropyl(1-(4-methoxybenzyloxy)octadeca-6,9-diyn-8-yloxy)silane (1.60):

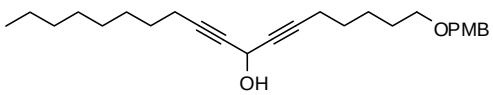
Yield: 18.3 mg, 16.5%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.22 (quint, *J* = 2.1 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.43 (t, *J* = 6.6 Hz, 2H), 2.25–2.16 (m, 2H), 1.62–1.41 (m, 8H), 1.26 (br s, 12H), 1.18–1.08 (m, 21H), 0.88 (t, *J* = 6.3 Hz, 3H).

(8-Ethynyl-1-(4-methoxybenzyloxy)hexadec-6-yn-8-yloxy)triisopropylsilane (1.61):

Yield: 2.8 mg, 2.5%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.43 (t, *J* = 6.6 Hz, 2H), 2.44 (s, 1H), 2.24–2.16 (m, 2H), 1.89–1.84 (m, 2H), 1.62–1.41 (m, 8H), 1.26 (br s, 12H), 1.10–1.06 (m, 21H), 0.88 (t, *J* = 6.3 Hz, 3H).

Triisopropyl(9-(7-(4-methoxybenzyloxy)hept-1-ynyl)nonadec-10-yn-9-yloxy)silane (1.62):

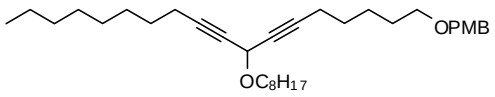
Yield: 12.2 mg, 9.1%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 3.43 (t, *J* = 6.6 Hz, 2H), 2.44 (s, 1H), 2.24–2.16 (m, 2H), 1.89–1.84 (m, 2H), 1.62–1.41 (m, 8H), 1.26 (br s, 12H), 1.10–1.06 (m, 21H), 0.88 (t, *J* = 6.3 Hz, 3H).



1-(4-Methoxybenzyloxy)octadeca-6,9-diyn-8-ol (*rac*-1.63):

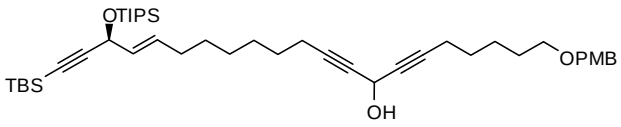
n-BuLi (0.28 mL, 1.6 M in hexane, 0.44 mmol) was added to a solution of alkyne ***rac*-1.57** (57.3 mg, 0.2 mmol) in THF (1 mL) at −30 °C. After stirring at the same temperature for 1 h, the reaction mixture was cooled to −78 °C. HMPA (0.1 mL) was added to above solution, followed by a solution of iodide **1.58** (16.2 μL, 0.1 mmol) in THF (0.5 mL). The mixture was stirred at −78 °C for another 3 h and allowed to warm to rt for overnight stirring. The reaction was quenched with saturated NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 95:5) to give the product ***rac*-1.63** (23.3

mg, 59%) as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.09 (dt, *J* = 3.0, 2.1 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.43 (t, *J* = 6.3 Hz, 2H), 2.25–2.19 (m, 2H), 2.14 (d, J = 7.2 Hz, 1H), 1.65–1.45 (m, 8H), 1.26 (br s, 12H), 0.88 (t, *J* = 6.3 Hz, 3H).



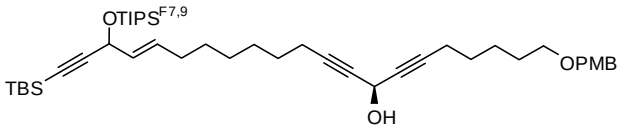
1-Methoxy-4-((8-(octyloxy)octadeca-6,9-diynyloxy)methyl)benzene (rac-1.64):

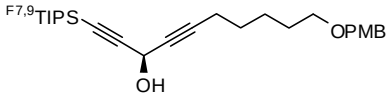
n-BuLi (0.28 mL, 1.6 M in hexane, 0.44 mmol) was added to a solution of alkyne ***rac*-1.57** (57.3 mg, 0.2 mmol) in THF (2 mL) at −30 °C. After stirring at the same temperature for 1 h, the reaction mixture was cooled to −78 °C. HMPA (0.2 mL) was added to above solution, followed by a solution of iodide **1.58** (64.6 μL, 0.4 mmol) in THF (1 mL). The mixture was stirred at −78 °C for another 3 h and allowed to warm to rt for overnight stirring. The reaction was quenched with saturated NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 95:5) to give the products ***rac*-1.64** (26.3 mg, 26%) and ***rac*-1.63** (20.0 mg, 25%) as pale yellow oils. ***rac*-1.64**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.92 (t, *J* = 2.1 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.56 (t, J = 6.6 Hz, 2 H), 3.43 (t, *J* = 6.3 Hz, 2H), 2.25–2.19 (m, 2H), 1.65–1.45 (m, 8H), 1.26 (br s, 24H), 0.88 (t, *J* = 6.3 Hz, 6H).



(19*S*,*E*)-21-(*tert*-Butyldimethylsilyl)-1-(4-methoxybenzyloxy)-19-(triisopropylsilyloxy) henicosa-17-en-6,9,20-triyn-8-ol (1.65):

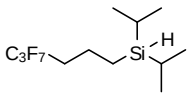
n-BuLi (0.28 mL, 1.6 M in hexane, 0.44 mmol) was added to a solution of alkyne ***rac*-1.57** (57.3 mg, 0.2 mmol) in THF (0.35 mL) at −30 °C. After stirring at the same temperature for 1 h, the reaction mixture was cooled to −78 °C. HMPA (0.1 mL) was added to above solution, followed by a solution of iodide **1.29S** (56.3 mg, 0.1 mmol) in THF (0.05 mL). The mixture was stirred at −78 °C for another 3 h and allowed to warm to rt for overnight stirring. The reaction was quenched with saturated NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 95:5) to give the products **1.65** (25.1 mg, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.79 (dtd, *J* = 15.0, 7.8, 0.9 Hz, 1H), 5.53 (dd, *J* = 15.3, 5.4 Hz, 1H), 5.08 (br s, 1H), 4.92 (d, *J* = 5.1 Hz, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.43 (t, *J* = 6.6 Hz, 2H), 2.25–2.16 (m, 4H), 2.04 (q, J = 6.6 Hz, 2H), 1.65–1.28 (m, 16H), 1.13–1.02 (m, 21H), 0.92 (s, 9H), 0.09 (s, 6H).





(8*S*,*E*)-21-(*tert*-butyldimethylsilyl)-19-((purfluoroethyl)diisopropylsilyloxy)-1-(4-methoxy benzyloxy)henicosa-17-en-6,9,20-triyn-8-ol (M-1.66) and (*R*)-1-((3,3,4,4,5,5,5-perfluoro ethyl)diisopropylsilyl)-10-(4-methoxybenzyloxy)deca-1,4-diyn-3-ol (1.67):

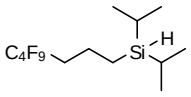
n-BuLi (0.27 mL, 1.6 M in hexane, 0.42 mmol) was added to a solution of alkyne **1.57S** (57.3 mg, 0.2 mmol) in THF (1.0 mL) at −30 °C. After stirring at the same temperature for 1 h, the reaction mixture was cooled to −78 °C. HMPA (0.1 mL) was added to above solution, followed by a solution of iodide **M-1.29** (74.2 mg, 0.1 mmol) in THF (0.5 mL). The mixture was stirred at −78 °C for another 3 h and allowed to warm to rt for overnight stirring. The reaction was quenched with saturated NH_4Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 95:5) to give the inseparable products **M-1.66** and **1.67** (24.7 mg, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 4H), 6.88 (d, *J* = 8.4 Hz, 4H), 5.79 (dtd, *J* = 15.0, 7.8, 0.9 Hz, 1H), 5.52 (dd, *J* = 15.3, 5.4 Hz, 1H), 5.08 (m, 2H), 4.89 (d, *J* = 6.0 Hz, 1H), 4.43 (s, 4H), 3.80 (s, 6H), 3.43 (td, *J* = 6.0, 0.9 Hz, 4H), 2.25–2.04 (m, 8H), 1.65–1.28 (m, 28H), 1.13–1.02 (m, 28H), 0.92 (s, 11H), 0.09 (s, 6H); MS (ESI) for **M-1.66-C_3F_7** *m/z* 913.3 (M^+ + K); **M-1.66-C_4F_9** *m/z* 963.4 (M^+ + K); **1.63-C_3F_7** *m/z* 635.2 (M^+ + K); **1.67-C_4F_9** *m/z* 685.2 (M^+ + K).



(4,4,5,5,6,6,6-Heptafluorohexyl)diisopropylsilane (1.69):

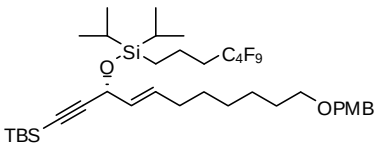
To a three-neck falsk equipped with adition funnel, thermometer, and Ar gas inlet, *t*-BuLi (14.7 mL, 1.7 M in hexane, 25.0 mmol) was added while cooling with −78 °C bath (a precipitate was observed). A solution of 1,1,1,2,2,3,3-heptafluoro-6-iodohexane (3.72 g, 11.0 mmol) in Et_2O (25 mL) was added dropwise, keeping the internal temperature below −50 °C. The mixture was

stirred for 45 min and allowed to warm to −25 °C (internal temperature) and maintained at this temperature until the solution became clear. After everything were into solution, the solution was cooled to −50 °C, chlorodiisopropylsilane (1.71 mL, 10.0 mmol) was added slowly. The mixture was stirred for overnight, during which time it was warmed to rt. The mixture was cooled to 0 °C, H_2O (12.5 mL) was added quickly and the mixture was stirred for 30 min. The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane 100%) to afford the title compound **1.69** (2.94 g, 90%) as colorless oil. 1H NMR (300 MHz, $CDCl_3$) 3.46 (s, 1H), 2.20–2.02 (m, 2H), 1.78–1.66 (m, 2H), 0.72–0.66 (m, 2H).



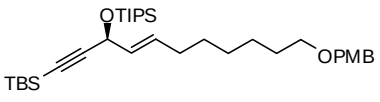
Diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silane (1.70):

Following the same procedure for **1.69**, 1,1,1,2,2,3,3,4,4-nonafluoro-7-iodoheptane (4.27 g, 11.0 mmol) was reacted with chlorodiisopropylsilane (1.71 mL, 10.0 mmol), the title compound **1.70** (3.34 g, 89%) was obtained as colorless oil. 1H NMR (300 MHz, $CDCl_3$) 3.46 (s, 1H), 2.20–2.02 (m, 2H), 1.78–1.66 (m, 2H), 0.72–0.66 (m, 2H).



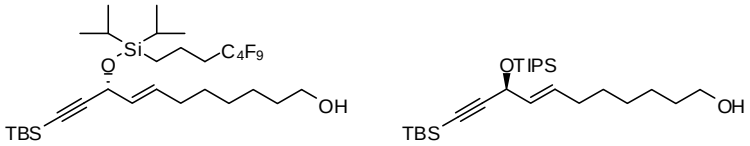
(*R,E*)-*tert*-Butyl(3-(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy)-11-(4-methoxy benzyloxy)undec-4-en-1-ynyl)dimethylsilane (1.71R):

Trifluoromethanesulfonic acid (neat, 1.9 mL, 21.7 mmol) was slowly added to silane **1.70** (neat, 8.67 g, 23.0 mmol) at 0 °C. After being stirred for 20 min at the same temperature, the mixture was warmed to room temperature and stirred for 15 h. To it CH_2Cl_2 (24 mL) was added at –60 °C, followed by a solution of alcohol **1.37R** (6.00 g, 14.4 mmol) in CH_2Cl_2 (36 mL) and 2,6-lutidine (3.3 mL, 28.7 mmol). The resulting mixture was warmed to room temperature and stirred for further 2 h. Saturated aqueous NH_4Cl (75 mL) was then added to quench the reaction at 0 °C. The mixture was extracted with Et_2O (3 × 150 mL), the organic layers were combined and washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc = 19:1) to afford the title compound **1.71R** (9.94 g, 87%). $[\alpha]_D^{25}$ = +1.1 (*c* = 1.20, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 5.79 (dtd, *J* = 15.0, 6.9, 0.9 Hz, 1 H), 5.51 (dd, *J* = 15.3, 5.7 Hz, 1 H), 4.88 (d, *J* = 6.0 Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, *J* = 6.6 Hz, 2 H), 2.19–2.00 (m, 4 H), 1.76–1.69 (m, 2 H), 1.61–1.53 (m, 2 H), 1.43–1.28 (m, 6 H), 1.06 (br s, 14 H), 0.93 (s, 9 H), 0.79–0.73 (m, 2 H), 0.09 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 132.2, 130.8, 129.6, 129.2, 113.8, 106.3, 88.0, 72.5, 70.2, 64.0, 55.3, 34.5 (t, J_{CF} = 21.8 Hz, 1 C), 31.8, 29.7, 29.0, 28.9, 26.0 (2 C), 17.6 (2 C), 17.5 (2 C) 16.5, 14.6, 12.7, 12.6, 11.0, −4.8; IR (film) 3020, 2933, 1514, 1423, 1215, 1133, 1044, 928, 755 cm^{-1}; HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{38}H_{59}O_3NaSi_2F_9$ 813.3757, found 813.3793.



(*S*,*E*)-*tert*-Butyl(11-(4-methoxybenzyloxy)-3-(triisopropylsilyloxy)undec-4-en-1-ynyl) dimethylsilane (1.71S):

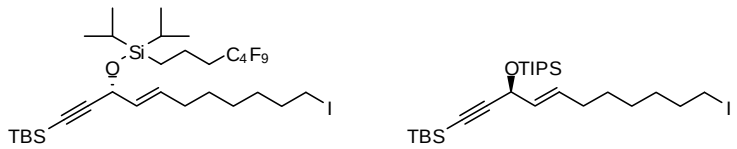
2,6-Lutidine (3.5 mL, 30.1 mmol) and TIPSOTf (7.9 mL, 29.4 mmol) were sequentially added to the solution of alcohol **1.37S** (6.90 g, 16.6 mmol) in CH_2Cl_2 (160 mL) at 0 °C. The resulting mixture was stirred for 2 h at the same temperature. Saturated aqueous NH_4Cl (80 mL) was then added to quench the reaction. The mixture was extracted with Et_2O (3 × 150 mL), the organic layers were combined and washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc = 19:1) to afford the title compound **1.71S** (8.53 g, 90%). $[\alpha]_D^{25} = -1.0$ (*c* = 0.92, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 5.80 (dtd, *J* = 15.3, 6.6, 0.9 Hz, 1 H), 5.52 (dd, *J* = 15.0, 5.4 Hz, 1 H), 4.92 (dd, *J* = 5.1, 0.6 Hz, 1 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.43 (t, *J* = 6.6 Hz, 2 H), 2.04 (q, *J* = 6.6 Hz, 2 H), 1.61–1.54 (m, 2 H), 1.43–1.28 (m, 6 H), 1.15–1.06 (m, 21 H), 0.92 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 131.7, 130.8, 129.9, 129.2, 113.7, 106.8, 87.5, 72.5, 70.2, 63.9, 55.3, 31.8, 29.7, 28.9 (2 C), 26.1 (2 C), 18.0, 16.5, 12.2, −4.7; IR (film) 3019, 2934, 2864, 1514, 1424, 1216, 1039, 928, 756 cm^{-1}; HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{34}H_{60}O_3NaSi_2$ 595.3979, found 595.3959.



(*R,E*)-11-(*tert*-Butyldimethylsilyl)-9-(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy) undec-7-en-10-yn-1-ol and (*S,E*)-11-(*tert*-butyldimethylsilyl)-9-(triisopropylsilyloxy) undec-7-en-10-yn-1-ol:

DDQ (7.88 g, 34.7 mmol) was added to the mixture of compound 1.71**R** (7.89 g, 10.0 mmol) and compound **1.71S** (5.75 g, 10.0 mmol) in CH_2Cl_2 (250 mL) and H_2O (13 mL) at room temperature. The reaction was monitored by TLC until completion, and then saturated $NaHCO_3$

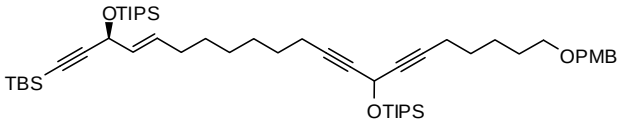
aqueous solution was added. The mixture was extracted with CH_2Cl_2 (3 × 150 mL), the organic layers were combined, washed with saturated $NaHCO_3$ aqueous solution, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/Et_2O = 4:1) to afford the title mixture, which was contaminated with tiny 4-(methoxymethyl)benzaldehyde and was used in the following step without further purification.



(*R,E*)-*tert*-Butyl(3-(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy)-11-iodoundec-4-en-1-ynyl)dimethylsilane and (*S,E*)-*tert*-butyl(11-iodo-3-(triisopropylsilyloxy)undec-4 -en-1-ynyl)dimethylsilane (M-1.68):

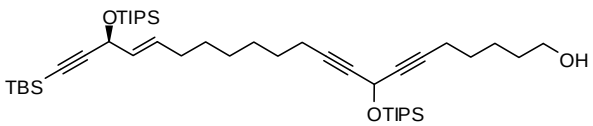
To a solution of triphenylphosphine (5.44 g, 20.7 mmol) in CH_2Cl_2 (27 mL) was slowly added a solution of iodine (5.26 g, 20.7 mmol) in CH_2Cl_2 (27 mL), followed by a mixture of imidazole (1.55 g, 22.8 mmol) and above alcohol (5.74 g, 10.2 mmol) in CH_2Cl_2 (80 mL) at room temperature. After 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (100 mL). The mixture was extracted with Et_2O (3 × 100 mL) and organic layer was washed with saturated aqueous $Na_2S_2O_3$ (100 mL), water, brine, dried over $MgSO_4$, and concentrated *in vacuuo*. The crude product was purified by column chromatography (hexane/EtOAc = 99:1) to afford the title comound **M-1.68** (5.62 g, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83–5.74 (m, 1 H), 5.52 (dd, *J* = 15.0, 5.1 Hz, 1 H), 4.94–4.88 (m, 1 H), 3.18 (t, *J* = 6.9 Hz, 2 H), 2.19–2.04 (m, 4H), 1.88–1.70 (m, 4H), 1.47–1.27 (m, 8 H), 1.19–1.02 (m, 17.5 H), 1.06 (s, 9 H), 0.79–0.73 (m, 2 H), 0.09 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.9, 131.4, 130.1, 129.8, 106.8, 106.2, 88.1, 87.6, 64.0, 63.8, 34.5 (t, J_{CF} = 21.8 Hz), 33.5, 31.6, 30.3, 28.7, 28.0, 26.0, 18.0, 17.6, 17.5, 16.5,

14.6, 12.7, 12.6, 12.2, 10.9, 7.1; IR (film) 2932, 2862, 1464, 1384, 1236, 1133, 1057, 908, 826, 733; MS (EI) for **M-1.68-C_4F_9** *m/z* 737 ($M^+ - C_3H_7$); **M-1.68-TIPS** *m/z* 519 ($M^+ - C_3H_7$); HRMS (ESI) **M-1.68-C_4F_9** *m/z* ($M^+ - C_3H_7$) calcd for $C_{27}H_{43}OF_9Si_2I$ 737.1753, found 737.1748; . **M-1.68-TIPS** *m/z* ($M^+ - C_3H_7$) calcd for $C_{23}H_{44}OSi_2I$ 519.1976, found 519. 1993.



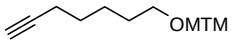
(5S,E)-5-((tert-butyldimethylsilyl)ethynyl)-3,3,18,18-tetraisopropyl-16-(7-(4-methoxy benzyloxy)hept-1-ynyl)-2,19-dimethyl-4,17-dioxa-3,18-disilaicos-6-en-14-yne (1.72):

2,6-Lutidine (27.2 μL, 0.24 mmol) and TIPSOTf (62.9 μL, 0.24 mmol) were sequentially added to the solution of alcohol **1.65** (84.4 mg, 0.12 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C. The resulting mixture was stirred for 2 h at the same temperature. Saturated aqueous NH_4Cl (5 mL) was then added to quench the reaction. The mixture was extracted with Et_2O (3 × 10 mL), the organic layers were combined and washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/EtOAc = 19:1) to afford the title compound **1.72** (95.6 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) 7.26 (d, *J* = 8.0 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2 H), 5.79 (dt, *J* = 15.0, 6.5 Hz, 1H), 5.53 (dd, *J* = 15.5, 5.5 Hz, 1H), 5.22 (d, *J* = 2.0 Hz, 1H), 4.92 (d, *J* = 5.5 Hz, 1H), 4.42 (s, 2H), 3.82 (s, 3H), 3.42 (t, *J* = 6.5 Hz, 2H), 2.21 (q, *J* = 7.5 Hz, 4H), 2.06 (q, *J* = 7.0 Hz, 2H), 1.63–1.21 (m, 14H), 1.20–1.10 (m, 42H), 0.93 (s, 9H), 0.09 (s, 6H).



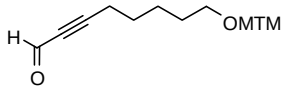
(19*S*,*E*)-21-(*tert*-Butyldimethylsilyl)-8,19-bis(triisopropylsilyloxy)henicosa-17-en-6,9,20-triyn-1-ol (1.73):

Ceric ammonium nitrate (CAN, 16.5 mg, 0.03 mmol) was added to a solution of PMB ether **1.72** (8.6 mg, 0.01 mmol) in CH_2Cl_2 (0.4 mL) and pH 7 phosphate buffer (0.04 mL) at rt. The orange mixture was stirred at rt for 30 min, CH_2Cl_2 (5 mL) was added to dilute the mixture. The organic layer was washed with saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentracted under reduced pressure. The crude product was purified by column chromatography (hexane/Et_2O = 7:3) to give the title compound **1.73** (2.1 mg, 28%) and strating material **1.72** (4.4 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) 5.80 (dt, *J* = 15.0, 6.9 Hz, 1H), 5.52 (dd, *J* = 15.0, 4.5 Hz, 1H), 5.22 (m, 1H), 4.92 (d, *J* = 5.1 Hz, 1H) 3.64 (t, *J* = 6.0 Hz, 2H), 2.27–2.21 (m, 4H), 2.05–2.03 (m, 2H), 1.63–1.21 (m, 14H), 1.20–1.10 (m, 42H), 0.93 (s, 9H), 0.09 (s, 6H).



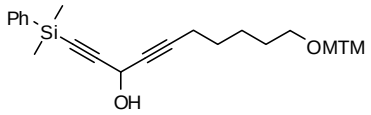
((Hept-6-ynyloxy)methyl)(methyl)sulfane (1.75):

A mixture of Ac_2O (71 mL) and AcOH (12.7 mL) was added to a solution of alcohol **1.22** (3.70 g, 33.0 mmol) in DMSO (102 mL) at room temperature. The resulting mixture was stirred at same temperature for 24 h. The mixture was poured into cold saturated $NaHCO_3$ aqueous solution. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The organic layer was washed with saturated $NaHCO_3$ aqueous solution, water, brine, dried over $MgSO_4$ concentrated *in vacuuo*. The curde product was used in next step without further purification.



8-(Methylthiomethoxy)oct-2-ynal (1.76):

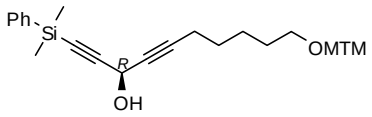
To a solution of alkyne **1.75** (4.98 g, 28.9 mmol) in THF (67 mL) was slowly added *n*-BuLi (21.7 mL, 1.6 M solution in hexane, 34.7 mmol) at −40 °C. After completion of addition, DMF (4.5 mL, 57.9 mmol) was added. The mixture was then warmed to room temperature. After being stirred for 30 min at the same temperature, the resulting mixture was poured into a solution of 10% acquous solution KH_2PO_4 (145 mL) and methyl *tert*-butyl ether (MTBE) (135 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted with MTBE (3 × 120 mL). The combined organic layers was washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/Et_2O = 17:3) to afford the title compound **1.76** (4.11 g, 71%) as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1H), 4.62 (s,2H), 3.53 (t, *J* = 6.0 Hz, 2H), 2.43 (t, *J* = 6.6 Hz, 2 H), 2.15 (s, 3H), 1.69–1.47 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 99.9, 81.7, 75.2, 67.6, 28.8, 27.3, 25.5, 19.1, 13.9; IR (film) 3054, 2987, 1666, 1423, 1265, 1139, 1077, 896, 740 cm^{-1}; MS (EI) *m/z* 185 (M^+ − CH_3); HRMS (EI) *m/z* (M^+ − CH_3) calcd for $C_9H_{13}O_2S$ 185.0636, found 185.0629.



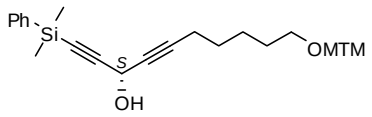
1-(Dimethyl(phenyl)silyl)-10-(methylthiomethoxy)deca-1,4-diyn-3-ol (*rac*-1.77):

n-BuLi (18.5 mL, 1.6 M solution in hexane, 29.7 mmol) was added to a solution of (dimethylphenylsilyl)acetylene **1.45** (5.2 mL, 29.7 mmol) in the THF (125 mL) at –78 °C. After stirring at same temperature for 30 min, a solution of aldehyde **1.76** (3.96 g, 19.8 mmol) in THF

(30 mL) was added slowly. The resulting mixture was stirred for additional 45 min at –78 °C, then allowed to warm to toom temperature. The mixture was poured into pH 7 phosphate buffer (100 mL) and extracted with Et_2O (3× 100 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/Et2O = 4:1) to afford the title compound ***rac*-1.77** (6.25 g, 97%) as pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 – 7.61 (m, 2H), 7.39 – 7.35 (m, 3H), 5.13 (dt, *J* = 7.5, 1.8 Hz, 1H), 4.62 (s, 2H), 3.52 (t, *J* = 6.3 Hz, 2H), 2.25 (td, *J* = 6.9, 2.1 Hz, 2H), 2.23 (d, *J* = 7.5 Hz, 1H), 2.14 (s, 3H), 1.66–1.43 (m, 6H), 0.44 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 133.7, 129.5, 127.9, 104.2, 86.9, 85.6, 77.2, 75.2, 67.9, 52.8, 28.8, 28.0, 25.5, 18.7, 14.0, −1.1; IR (film) 3585, 3399, 3070, 2942, 2864, 1644, 1429, 1300, 1253, 1113, 1077, 1033, 909, 820, 733; HRMS (ESI) *m/z* (M^+ + K) calcd for $C_{20}H_{28}O_2SiSK$ 399.1216, found 399.1215.



(*R*)-1-(Dimethyl(phenyl)silyl)-10-(methylthiomethoxy)deca-1,4-diyn-3-ol (1.77R):



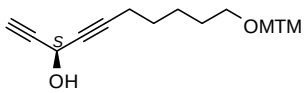
(*S*)-1-(Dimethyl(phenyl)silyl)-10-(methylthiomethoxy)deca-1,4-diyn-3-ol (1.77S):

The racemic alcohol ***rac*-1.77** (6.25 g, 17.3 mmol) was separated by chiral HPLC (Chiralcel OD semi-preparative column, hexane/^{i}PrOH = 93:7, 10.0 mL/min) to afford two optical pure compounds **1.77R** (3.04 g, 49%) and **1.77S** (2.99 g, 48%) as pale yellow oils.

1.77R: $[\alpha]_D^{25}$ = +5.0 (*c* = 1.03, $CHCl_3$)**,** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.61 (m, 2H), 7.39–7.35 (m, 3H), 5.13 (dt, *J* = 7.5, 2.1 Hz, 1H), 4.62 (s, 2H), 3.52 (t, *J* = 6.3 Hz, 2H), 2.25 (td, *J* =

6.9, 2.1 Hz, 2H), 2.22 (d, *J* = 7.5 Hz, 1H), 2.14 (s, 3H), 1.66–1.43 (m, 6H), 0.44 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 133.7, 129.5, 127.9, 104.3, 86.8, 85.5, 77.2, 75.2, 67.9, 52.8, 28.8, 28.0, 25.4, 18.7, 13.9, −1.1; IR (film) 3420, 3019, 2942, 2865, 1640, 1429, 1300, 1216, 1113, 1076, 1031, 956, 756; HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{20}H_{28}O_2NaSiS$ 383.1477, found 383.1461.

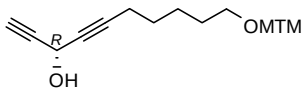
1.77S: $[\alpha]_D^{25}$ = −4.5 (*c* = 0.99, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.61 (m, 2H), 7.39–7.35 (m, 3H), 5.13 (dt, *J* = 7.2, 2.1 Hz, 1H), 4.62 (s, 2H), 3.52 (t, *J* = 6.3 Hz, 2H), 2.25 (td, *J* = 6.6, 1.8 Hz, 2H), 2.24 (d, *J* = 7.5 Hz, 1H), 2.14 (s, 3H), 1.66–1.43 (m, 6H), 0.44 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 133.7, 129.5, 127.9, 104.3, 86.8, 85.5, 77.2, 75.2, 67.9, 52.7, 28.8, 27.9, 25.4, 18.6, 13.9, −1.1; IR (film) 3440, 3019, 2973, 1637, 1427, 1382, 1216, 1159, 1076, 946, 755; HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{20}H_{28}O_2NaSiS$ 383.1477, found 383.1460.



(*S*)-10-(Methylthiomethoxy)deca-1,4-diyn-3-ol (1.74S):

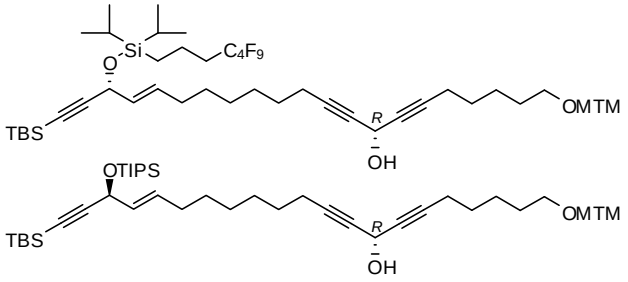
TBAF (12.5 mL, 1.0 M solution in THF, 12.5 mmol) was added to a solution of alcohol **1.77R** (3.00 g, 8.3 mmol) in THF (80 mL) at room temperature. The mixture then was stirred for 1 h at this temperature and quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/Et_2O = 4:1) to give compound **1.74S** (1.47 g, 78%) as pale yellow oil. $[\alpha]_D^{25}$ = +5.0 (*c* = 1.20, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (dq, *J* = 7.5, 2.1 Hz, 1H),

4.62 (s, 2H), 3.53 (t, *J* = 6.0 Hz, 2H), 2.54 (d, *J* = 2.4 Hz, 1H), 2.25 (td, *J* = 6.9, 2.1 Hz, 2H), 2.22 (d, *J* = 7.2 Hz, 1H), 2.15 (s, 3H), 1.66–1.43 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.7, 81.5, 77.3, 75.2, 72.1, 67.9, 52.1, 28.8, 27.9, 25.4, 18.6, 13.9; IR (film) 3422, 3020, 1647, 1429, 1216, 1015, 929, 757; MS (EI) *m/z* 249 (M^+ + Na); HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{12}H_{18}O_2NaS$ 249.0925, found 249.0945.



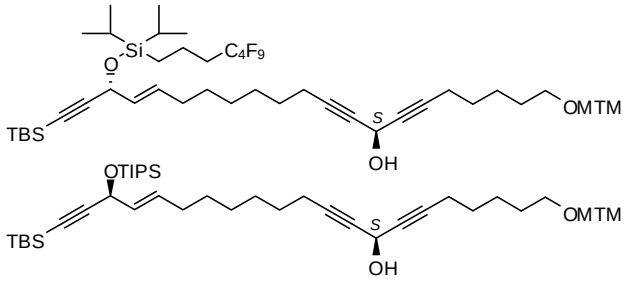
(*R*)-10-(Methylthiomethoxy)deca-1,4-diyn-3-ol (1.74R):

Following the same procedure for **1.74S**, alcohol **1.77R** (2.99 g, 8.3 mmol) was reacted with TBAF (12.5 mL, 1.0 M solution in THF, 12.5 mmol), the title compound **1.74R** (1.78 g, 95%) was obtained as pale yellow oil. $[\alpha]_D^{25}$ = −4.4 (*c* = 1.37, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10 (dq, *J* = 7.5, 2.1 Hz, 1H), 4.63 (s, 2 H), 3.53 (t, *J* = 6.3 Hz, 2H), 2.54 (d, *J* = 2.1 Hz, 1H), 2.25 (td, *J* = 6.6, 1.8 Hz, 2H), 2.24 (d, *J* = 7.5 Hz, 1H), 2.15 (s, 3H), 1.66–1.42 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.3, 81.5, 77.3, 75.0, 71.9, 67.8, 51.8, 28.6, 27.8, 25.3, 18.5, 13.8; IR (film) 3420, 3307, 3020, 2943, 1641, 1430, 1216, 1076, 1015, 928, 755; MS (EI) *m/z* 249 (M^+ + Na); HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{12}H_{18}O_2NaS$ 249.0925, found 249.0950.



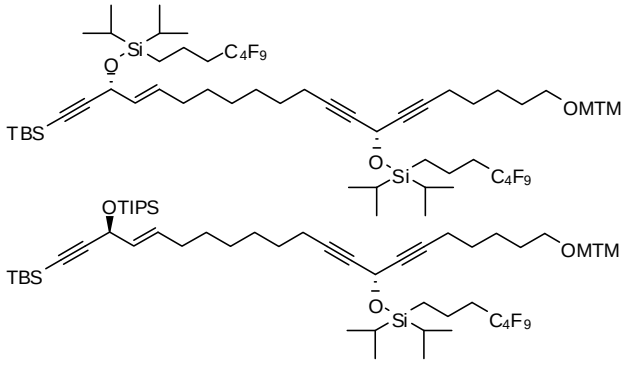
(12*R*,23*R*,*E*)-23-((*tert*-Butyldimethylsilyl)ethynyl)-29,29,30,30,31,31,32,32,32-nonafluoro-25,25-diisopropyl-4,24-dioxa-2-thia-25-siladotriaconta-21-en-10,13-diyn-12-ol and (12*R*,23*S*,*E*)-23-((*tert*-butyldimethylsilyl)ethynyl)-25,25-diisopropyl-26-methyl-4,24-dioxa-2-thia-25-silaheptacosa-21-en-10,13-diyn-12-ol (M-1.78R):

n-BuLi (4.0 mL, 1.6 M solution in THF, 6.4 mmol) was slowly added to the solution of alkyne **1.74R** (679.0 mg, 3.0 mmol) in THF (15 mL) at −30 °C. After stirring at the same temperature for 1 h, the mixture was cooled to −78 °C, HMPA (1.5 mL) was added followed by a solution of iodide **M-1.68** (1.01 g, 1.5 mmol) in THF (7.5 mL). The resulting mixture was stirred for 2 h at −78 °C and warmed to room temperature. After stirring at room temperature for overnight, saturated NH_4Cl aqueous solution (20 mL) was added, the organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/Et_2O = 4:1) to afford the mixture **M-1.78R** (370.7 mg, 34%), which was contaminated with some inseparable impurities and was used in the following step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80–5.76 (m, 1H), 5.55–5.49 (m, 1H), 5.10–5.08 (m, 1H), 4.93–4.88 (m, 1H), 4.63 (s, 2H), 3.52 (t, *J* = 6.5 Hz, 2H), 2.23 (quind, *J* = 7.0, 1.5 Hz, 4H), 2.15 (s, 3H), 2.12–2.06 (m, 1H), 2.05 (q, *J* = 6.5 Hz, 2H), 1.78–1.69 (m, 1H), 1.64–1.45 (m, 8H), 1.40–1.25 (m, 6H), 1.10–1.05 (m, 17.5H), 0.93 (s, 9H), 0.78–0.74 (m, 1H), 0.09 (s, 6H); HRMS (ESI) **M-1.78R-C_4F_9** *m/z* (M^+ + Na) calcd for $C_{42}H_{67}O_3F_9NaSi_2S$ 901.4103, found 901.4134; **M-1.78R-TIPS** *m/z* (M^+ + Na) calcd for $C_{38}H_{68}O_3NaSi_2S$ 683.4325, found 683.4340.



(12*S*,23*R*,*E*)-23-((*tert*-Butyldimethylsilyl)ethynyl)-29,29,30,30,31,31,32,32,32-nonafluoro-25,25-diisopropyl-4,24-dioxa-2-thia-25-siladotriaconta-21-en-10,13-diyn-12-ol and (12*S*,23*S*,*E*)-23-((*tert*-butyldimethylsilyl)ethynyl)-25,25-diisopropyl-26-methyl-4,24-dioxa-2-thia-25-silaheptacosa-21-en-10,13-diyn-12-ol (M-1.78S):

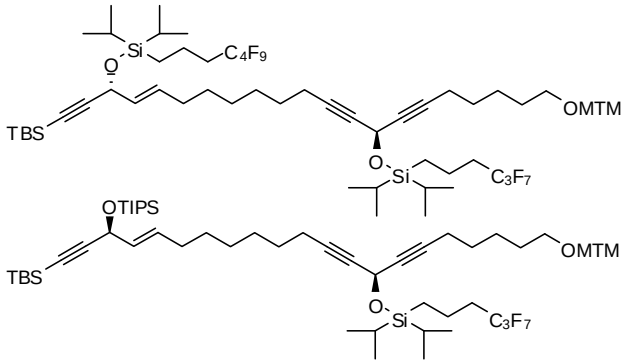
Following the same procedure for **M-1.78R**, alkyne **1.74S** (679.0 mg, 3.0 mmol) was reacted with *n*-BuLi (4.0 mL, 1.6 M solution in THF, 6.4 mmol), HMPA (1.5 mL), and iodide **M-1.68** (1.01 g, 1.5 mmol), the title mixture **M-1.78S** (356.2 mg, 33%) was obtained, which was contaminated with some inseparable impurities and was used in the following step without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.82–5.77 (m, 1H), 5.55–5.49 (m, 1H), 5.10–5.08 (m, 1H), 4.92–4.88 (m, 1H), 4.63 (s, 2H), 3.52 (t, *J* = 6.6 Hz, 2H), 2.23–2.20 (m, 4H), 2.15 (s, 3H), 2.14–2.09 (m, 1H), 2.05 (q, *J* = 6.6 Hz, 2H), 1.76–1.70 (m, 1H), 1.63–1.43 (m, 8H), 1.40–1.25 (m, 6H), 1.11–1.03 (m, 17.5H), 0.92 (s, 9H), 0.77–0.74 (m, 1H), 0.09 (s, 6H); HRMS (ESI) **M-1.78S-C_4F_9** *m/z* (M^+ + Na) calcd for $C_{42}H_{67}O_3F_9NaSi_2S$ 901.4103, found 901.4072; **M-1.78S-TIPS** *m/z* (M^+ + Na) calcd for $C_{38}H_{68}O_3NaSi_2S$ 683.4325, found 683.4296.



(12*R*,23*R*,*E*)-23-((*tert*-butyldimethylsilyl)ethynyl)-12-(diisopropyl(4,4,5,5,6,6,7,7,7-nona fluoroheptyl)silyloxy)-29,29,30,30,31,31,32,32,32-nonafluoro-25,25-diisopropyl-4,24-dioxa-2 -thia-25-siladotriaconta-21-en-10,13-diyne and (12*R*,23*S*,*E*)-23-((*tert*-butyldimethylsilyl) eth ynyl)-12-(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy)-25,25-diisopropyl-26-methyl-4,24-dioxa-2-thia-25-silaheptacosa-21-en-10,13-diyne (M-1.79R):

Trifluoromethanesulfonic acid (neat, 72.4 μL, 0.82 mmol) was slowly added to silane **1.70** (neat, 359.0 mg, 0.95 mmol) at 0 °C. After being stirred for 20 min at the same temperature, the mixture was warmed to room temperature and stirred for 15 h. To it CH_2Cl_2 (0.8 mL) was added at –60 °C, followed by a solution of alcohol **M-1.78R** (200.0 mg, 0.27 mmol) in CH_2Cl_2 (1.2 mL) and 2,6-lutidine (0.13 mL, 1.09 mmol). The resulting mixture was warmed to room temperature and stirred for further 2 h. Saturated aqueous NH_4Cl (10 mL) was then added to quench the reaction at 0 °C. The mixture was extracted with Et_2O (3 × 10 mL), the organic layers were combined and washed with water, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/Et_2O = 97:3) to afford the title mixture **M-1.79R** (272.5 g, 99%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.81–5.77 (m, 1H), 5.54–5.49 (m, 1H), 5.21 (s, 1H), 4.92–4.87 (m, 1H), 4.62 (s, 2H), 3.50 (t, *J* = 6.6 Hz, 2H), 2.23–2.18 (m, 4H), 2.14 (s, 3H), 2.12–2.03 (m, 5H), 1.80–1.73 (m, 3H), 1.62–1.41 (m, 8H), 1.40–1.33 (m, 4H), 1.31–1.25 (m, 2H), 1.12–1.05 (m, 31.5H), 0.92 (s, 9H), 0.79–0.75 (m, 3H), 0.09 (s, 6H); MS (EI) **M-1.79R-**

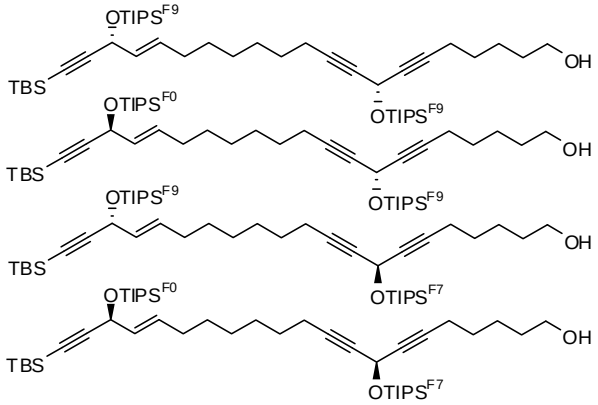
C_4F_9, C_4F_9 *m/z* 1275 (M^+ + Na); **M-1.79R-TIPS, C_4F_9** *m/z* 1057 (M^+ + Na); HRMS (ESI) **M-1.79R-C_4F_9, C_4F_9** *m/z* (M^+ + Na) calcd for $C_{55}H_{86}O_3F_{18}NaSi_3S$ 1275.5216, found 1275.5110; **M-1.79R-TIPS, C_4F_9** *m/z* (M^+ + Na) calcd for $C_{51}H_{87}O_3F_9NaSi_3S$ 1057.5438, found 1057.5507.



(12*S*,23*R*,*E*)-23-((*tert*-Butyldimethylsilyl)ethynyl)-29,29,30,30,31,31,32,32,32-nonafluoro-12-((4,4,5,5,6,6,6-heptafluorohexyl)diisopropylsilyloxy)-25,25-diisopropyl-4,24-dioxa-2-thia-25-siladotriaconta-21-en-10,13-diyne and (12*S*,23*S*,*E*)-23-((*tert*-butyldimethylsilyl)ethynyl)-12-((4,4,5,5,6,6,6-heptafluorohexyl)diisopropylsilyloxy)-25,25-diisopropyl-26-methyl-4,24-dioxa-2-thia-25-silaheptacosa-21-en-10,13-diyne (M-1.79S):

Following the same procedure for **M-1.79R**, the mixture **M-1.78S** (250.0 mg, 0.34 mmol) was reacted with Trifluoromethanesulfonic acid (neat, 79.6 μL, 0.90 mmol), silane **1.69** (neat, 333.6 mg, 1.02 mmol), and 2,6–lutidine (0.14 mL, 1.19 mmol), the title mixture **M-1.79S** (277.7 mg, 85%) was obtained. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.80–5.77 (m, 1 H), 5.54–5.50 (m, 1 H), 5.21 (s, 1 H), 4.92–4.87 (m, 1 H), 4.62 (s, 2 H), 3.50 (t, *J* = 6.6 Hz, 2 H), 2.23–2.18 (m, 4 H), 2.14 (s, 3 H), 2.12–2.03 (m, 5 H), 1.80–1.73 (m, 3 H), 1.62–1.43 (m, 8 H), 1.40–1.33 (m, 4 H), 1.31–1.25 (m, 2 H), 1.12–1.05 (m, 31.5 H), 0.92 (s, 9 H), 0.79–0.75 (m, 3 H), 0.09 (s, 6 H); MS (EI) **M-1.79S-C_4F_9, C_3F_7** *m/z* 1225 (M^+ + Na); **M-1.79S-TIPS, C_3F_7** *m/z* 1008 (M^+ + Na + H); HRMS (ESI) **M-1.79S-C_4F_9, C_3F_7** *m/z* (M^+ + Na) calcd for $C_{54}H_{86}O_3F_{16}NaSi_3S$ 1225.5248,

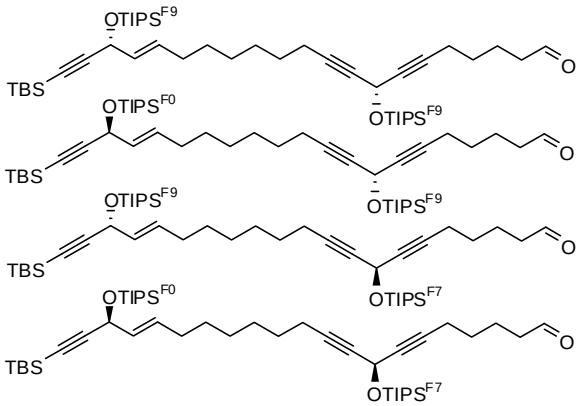
found 1225.5331; **M-1.79S-TIPS, C_3F_7** *m/z* (M^+ + Na) calcd for $C_{50}H_{87}O_3F_7NaSi_3S$ 1007.5470, found 1007.5438.



(8*R*,19*R*,*E*)-21-(*tert*-Butyldimethylsilyl)-8,19-bis(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoro heptyl)silyloxy)henicosa-17-en-6,9,20-triyn-1-ol, (8*R*,19*S*,*E*)-21-(*tert*-butyl dimethylsilyl)-8-(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy)-19-(triisopropyl silyloxy)henicosa-17-en-6,9,20-triyn-1-ol, (8*S*,19*R*,*E*)-21-(*tert*-butyldimethylsilyl)-19-(diisopropyl(4,4,5,5,6,6, 7,7,7-nonafluoroheptyl)silyloxy)-8-((4,4,5,5,6,6,6-heptafluorohexyl)diisopropylsilyloxy) henicosa-17-en-6,9,20-triyn-1-ol, and (8*S*,19*S*,*E*)-21-(*tert*-butyldimethyl silyl)-8-((4,4,5,5, 6,6,6-heptafluorohexyl)diisopropylsilyloxy)-19-(triisopropylsilyloxy) henicosa-17-en-6,9,20-triyn-1-ol (M-1.80):

Solid $NaHCO_3$ (324.4 mg, 3.86 mmol) and MeI (9.0 mL) were added to the solution of mixture **M-1.79R** (270.0 mg, 0.27 mmol) and **M-1.79S** (259.4 mg, 0.27 mmol) in mixture of acetone (16.0 mL) and water (0.86 mL). The resulting suspension was stirred in a sealed tube at 45 °C for 14 h. The mixture was diluted with water (20 mL) and EtOAc (30 mL). The organic layer was separated and the aqueous phase was extracted with EtOAC (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*.

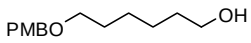
The crude product was purified by column chromatography (hexane/Et_2O = 3:1) to afford the mixture **M-1.80** (451.0 mg, 90%). ^1H NMR (600 MHz, $CDCl_3$) δ 5.82–5.76 (m, 1H), 5.54–5.49 (m, 1H), 5.20 (s, 1H), 4.92–4.87 (m, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.24–2.18 (m, 4H), 2.14–2.03 (m, 5H), 1.78–1.73 (m, 3H), 1.62–1.43 (m, 8H), 1.40–1.24 (m, 6H), 1.13–1.05 (m, 31.5H), 0.92 (s, 9H), 0.79–0.75 (m, 3H), 0.09 (s, 6H); MS (EI) **M-1.80-C_4F_9, C_4F_9** *m/z* 1215 (M^+ + Na); **M-1.80-TIPS, C_4F_9** *m/z* 998 (M^+ + Na + H); **M-1.80-C_4F_9, C_3F_7** *m/z* 1165 (M^+ + Na); **M-1.80-TIPS, C_3F_7** *m/z* 948 (M^+ + Na + H) HRMS (ESI) **M-1.80-C_4F_9, C_4F_9** *m/z* (M^+ + Na) calcd for $C_{53}H_{82}O_3F_{18}NaSi_3$ 1215.5182, found 1215.5067; **M-1.80-TIPS, C_4F_9** *m/z* (M^+ + Na) calcd for $C_{49}H_{83}O_3F_9NaSi_3$ 997.5404, found 997.5370; **M-1.80-C_4F_9, C_3F_7** *m/z* (M^+ + Na) calcd for $C_{52}H_{82}O_3F_{16}NaSi_3$ 1165.5214, found 1165.5240; **M-1.80-TIPS, C_3F_7** *m/z* (M^+ + Na) calcd for $C_{48}H_{83}O_3F_7NaSi_3$ 947.5436, found 947.5422.



(8*R*,19*R*,*E*)-21-(*tert*-Butyldimethylsilyl)-8,19-bis(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoro heptyl)silyloxy)henicosa-17-en-6,9,20-triynal, (8*R*,19*S*,*E*)-21-(*tert*-butyldimethylsilyl)-8-(di isopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy)-19-(triisopropylsilyloxy)henicosa-17-en-6,9,20-triynal, (8*S*,19*R*,*E*)-21-(*tert*-butyldimethylsilyl)-19-(diisopropyl(4,4,5,5,6,6,7,7,7-nonafluoroheptyl)silyloxy)-8-((4,4,5,5,6,6,6-heptafluorohexyl)diisopropylsilyloxy)henicosa-

17-en-6,9,20-triynal, and (8*S*,19*S*,*E*)-21-(*tert*-butyldimethylsilyl)-8-((4,4,5,5,6,6,6-hepta fluorohexyl)diisopropylsilyloxy)-19-(triisopropylsilyloxy)henicosa-17-en-6,9,20-triynal (M-1.2):

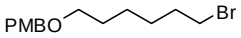
$NaHCO_3$ (196.2 mg, 2.34 mmol) was added followed by DMP (371.5 mg, 0.88 mmol) to the solution of mixture **M-1.80** (270.0 mg, 0.29 mmol) in CH_2Cl_2 (4.5 mL) at room temperature. The resulting mixture was stirred at the same temperature for 2 h. Saturated NH_4Cl aqueous solution (15 mL) was added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over MgSO4, and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/Et_2O = 9:1) to afford the mixture **M-1.2** (200.3 mg, 74%). ^1H NMR (600 MHz, $CDCl_3$) δ 9.76 (s, 1H), 5.82–5.76 (m, 1H), 5.54–5.49 (m, 1H), 5.20 (s, 1H), 4.92–4.87 (m, 1H), 2.44 (t, *J* = 7.2 Hz, 2H), 2.24 (t, *J* = 6.6 Hz, 2H), 2.19 (t, *J* = 7.2 Hz, 2H), 2.14–2.02 (m, 5H), 1.79–1.70 (m, 5H), 1.57–1.46 (m, 6H), 1.38–1.33 (m, 4H), 1.31–1.25 (m, 2H), 1.13–1.05 (m, 31.5H), 0.92 (s, 9H), 0.79–0.75 (m, 3H), 0.09 (s, 6H); HRMS (ESI) **M-1.2-C_4F_9, C_4F_9** *m/z* (M^+ + Na) calcd for $C_{53}H_{80}O_3F_{18}NaSi_3$ 1213.5026, found 1213.5062; **M-1.2-TIPS, C_4F_9** *m/z* (M^+ + Na) calcd for $C_{49}H_{81}O_3F_9NaSi_3$ 995.5248, found 995.5237; **M-1.2-C_4F_9, C_3F_7** *m/z* (M^+ + Na) calcd for $C_{52}H_{80}O_3F_{16}NaSi_3$ 1163.5058, found 1163.5133; **M-1.2-TIPS, C_3F_7** *m/z* (M^+ + Na) calcd for $C_{48}H_{81}O_3F_7NaSi_3$ 945.5279, found 945.5218.



6-(4-Methoxybenzyloxy)hexan-1-ol (1.82):[47]

1,6-Hexanediol **1.81** (14.19 g, 120 mmol) was added dropwise to a suspension of NaH (4.80 g, 60 wt% in mineral oil, 120 mmol) in THF (400 mL) at 0 °C. PMBCl (16.4 mL, 120

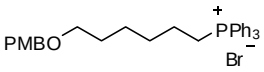
mmol) was then added dropwise followed by addition of TBAI (4.88 g, 13.2 mmol). After stirring at room temperature for 1 h, the reaction mixture was heated to 60 °C for 15 h. After being cooled to room temperature, the resulting mixture was poured into a solution of saturated $NaHCO_3$ and vigorously stirred. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/EtOAc = 3:2) to afford the title compound **1.82** (15.45 g, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.63 (q, *J* = 5.5 Hz, 2H), 3.44 (t, *J* = 6.5 Hz, 2H), 1.64–1.52 (m, 4 H), 1.39–1.36 (m, 4H), 1.23 (t, *J* = 5.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 130.4, 129.0, 113.5, 72.3, 69.8, 62.3, 55.0, 32.4, 29.5, 25.8, 25.4; IR (film) 3425, 2937, 2861, 1613, 1513, 1464, 1302, 1248, 1174, 1090, 1036, 907, 731, 650; MS (EI) *m/z* 238 (M^+); HRMS (ESI) *m/z* (M^+) calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1575.



1-((6-Bromohexyloxy)methyl)-4-methoxybenzene (1.83):[47]

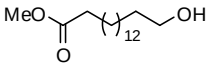
A solution of triphenylphosphine (18.5 g, 70.7 mmol) was added to a solution of alcohol **1.82** (11.23 g, 47.1 mmol) and CBr_4 (18.8 g, 56.5 mmol) in CH_2Cl_2 (175 mL) at 0 °C. After stirring at room temperature for 1 h, the organic solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 19:1) to afford the title compound **1.83** (12.65 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.44 (t, *J* = 6.5 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 1.86 (quin, *J* = 6.8 Hz, 2H), 1.66–1.57 (m, 2H), 1.50–1.37 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 130.7, 129.2, 113.8, 72.5, 69.9, 55.3, 33.8, 32.7, 29.6, 28.0, 25.4; IR (film) 3015, 2938,

2860, 1612, 1513, 1463, 1302, 1248, 1216, 1174, 1094, 1036, 756; MS (EI) *m/z* 300 (M^+); HRMS (ESI) *m/z* (M^+) calcd for $C_{14}H_{21}O_2Br$ 300.0725, found 300.0718.



(6-(4-Methoxybenzyloxy)hexyl)triphenylphosphonium bromide (1.12):[47]

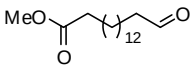
A mixture of bromide **1.83** (12.62 g, 41.9 mmol) and triphenylphosphine (22.03 g, 84.0 mmol) in CH_3CN (310 mL) was stirred at 90 °C for 2 days. The organic solvent was removed under reduced pressure, the residue was purified by column chromatography ($CHCl_3$/MeOH = 19:1) to afford the title compound **1.12** with tiny triphenylphosphine (21.23 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81–7.73 (m, 9H), 7.68–7.59 (m, 6H), 7.17 (d, *J* = 8.7 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 4.33 (s, 2H), 3.73 (s, 3H), 3.68 (m, 2H), 3.34 (t, *J* = 6.3 Hz, 2H), 1.60 (br s, 4H), 1.52–1.43 (m, 2H), 1.33–1.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 134.4 (d, J_{CP} = 2.2 Hz, 1C), 132.8 (d, J_{CP} = 9.8 Hz, 1C), 129.8 (d, J_{CP} = 12.8 Hz, 1C), 128.5, 127.6, 117.4 (d, J_{CP} = 85.5 Hz, 1C), 113.0, 71.7, 69.1, 54.6, 29.4 (d, J_{CP} = 15.8 Hz, 1C), 28.5, 25.0, 22.0 (d, J_{CP} = 49.5 Hz, 1C), 21.8 (d, J_{CP} = 3.8 Hz, 1C); IR (film) 3010, 2937, 2863, 2193, 1702, 1610, 1513, 1462, 1439, 1302, 1250, 1170, 1113, 1033, 910, 732; MS (EI) *m/z* 483 (M^+ − Br); HRMS (ESI) *m/z* (M^+) calcd for $C_{32}H_{36}O_2P$ 483.2453, found 483.2418.



Methyl 16-hydroxyhexadecanoate (1.84):[48]

16-Hydroxyhexadecanic acid **1.15** (5.60 g, 20.6 mmol) and *p*-toluenesulfonic acid monohydrate (1.25 g, 6.6 mmol) were dried under vacuum for 2 h. MeOH (300 mL) was added and the mixture was stirred at room temperature for 16 h. Solid $NaHCO_3$ (1.25 g) was added and

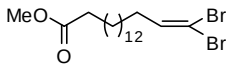
the resulting mixture was stirred for further 30 min, then filtered through a pad of Celite. The organic solvent was removed under reduced pressure. The crude product was purified by column chromatography (hexane/EtOAc = 3:1) to afford the title compound **1.84** (5.89 g, 100%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.64 (q, *J* = 6.5 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.64–1.54 (m, 4H), 1.25 (br s, 22H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 62.6, 51.3, 39.9, 32.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 25.6, 24.8; IR (film) 3435, 2927, 2855, 1731, 1465, 1438, 1202, 1175, 1054, 908, 735, 650; MS (EI) *m/z* 287 (M^+); HRMS (ESI) *m/z* (M^+) calcd for $C_{17}H_{35}O_3$ 287.2586, found 287.2594.



Methyl 16-oxohexadecanoate (1.85):[49]

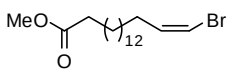
To a solution of oxalyl chloride (3.50 mL, 40.8 mmol) in CH_2Cl_2 (145 mL) was slowly added a solution of DMSO (4.35 mL, 61.2 mmol) in CH_2Cl_2 (30 mL) at –78 °C. After 15 min at the same temperature, a solution of alcohol **1.84** (5.85 g, 20.4 mmol) in CH_2Cl_2 (30 mL) was then added dropwise. The resulting mixture was stirred for 15 min and Et_3N (14.2 mL, 102.0 mmol) was added slowly. The reaction was maintained at –78 °C for 15 min, then allowed to warm to 0 °C, the stirring continued for further 30 min. Water was added and the mixture was diluted with Et_2O. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with Et_2O (3 × 90 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane/EtOAc = 9:1) to afford the title compound **1.85** (5.70 g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.0 Hz, 1H), 3.66 (s, 3H), 2.41 (td, *J* = 7.5, 2.0 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 1.69–1.58 (m, 4H), 1.25 (br s, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.7,

174.2, 51.3, 43.8, 34.0, 32.6, 29.5, 29.4, 29.3, 29.3, 29.2, 29.1, 29.0, 29.0, 24.8, 22.0; IR (film) 2928, 2855, 1725, 1644, 1465, 1438, 1201, 1175, 908, 735, 650; MS (EI) *m/z* 285 (M^+ + H); HRMS (ESI) *m/z* (M^+) calcd for $C_{17}H_{32}O_3$ 284.2351, found 284.2338.



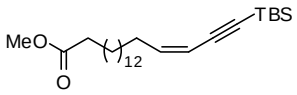
Methyl 17, 17-dibromoheptadec-16-enoate (1.86):

To a solution of triphenylphosphine (23.6 g, 90 mmol) in CH_2Cl_2 (60 mL) at 0 °C was slowly added a solution of CBr_4 (13.9 g, 42 mmol) in CH_2Cl_2 (12 mL) at a rate to maintain the temperature below 15 °C. Then a solution of aldehyde **1.85** (5.7 g, 20 mmol) and Et_3N (8.4 mL, 60 mmol) in CH_2Cl_2 (12 mL) was added dropwise at 0 °C. After stirring for 35 min at the same temperature, the mixture was poured into hexane (120 mL) and filtered through a pad of Celite. The solid was washed with hexane (2 × 50 mL) and the filtrate was concentrated under reduced pressure. Hexane (40 mL) was added and the mixture was filtered again. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/EtOAc = 49:1) to afford the title compound **1.86** (8.10 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (t, *J* = 7.2 Hz, 1 H), 3.66 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.08 (q, *J* = 7.2 Hz, 2H), 1.66–1.56 (m, 2H), 1.46–1.35 (m, 2H), 1.25 (br. s, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 138.8, 88.4, 51.3, 34.0, 33.0, 29.5, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 27.7, 24.9; IR (film) 2925, 2853, 1741, 1462, 1436, 1361, 1249, 1197, 1170, 1112, 1016, 911, 799; MS (EI) *m/z* 439 (M^+ + H); HRMS (ESI) *m/z* (M^+) calcd for $C_{18}H_{32}O_2Br_2$ 438.0769, found 438.0782.



(*Z*)-Methyl 17-bromoheptadec-16-enoate (1.14):

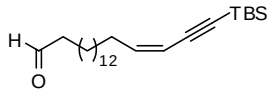
A mixture of triphenylphosphine (2.42 g, 9.2 mmol) and $Pd(OAc)_2$ (0.42 g, 1.9 mmol) in CH_2Cl_2 (95 mL) was stirred for 15 min at room temperature to generate a light yellow solution. Dibromide **1.86** (8.10 g, 18.4 mmol) and tributyltin hydride (12.9 mL, 47.8 mmol) were sequentially added and the mixture was stirred for 45 min at room temperature. After the reaction was completed, the mixture was diluted with Et_2O and washed with water (3 × 75 mL), brine (3 × 75 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/Et_2O = 49:1) to afford the title compound **1.14** (6.66 g, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15–6.04 (m, 2H), 3.65 (s, 3H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.18 (q, *J* = 6.9 Hz, 2H), 1.66–1.56 (m, 2H), 1.44–1.33 (m, 2H), 1.25 (br. s, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 134.9, 107.5, 51.3, 34.0, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.1, 24.9; IR (film) 2928, 2855, 1731, 1463, 1439, 1201, 1174, 908, 734; MS (EI) *m/z* 329 ($M^+ - CH_3O$); HRMS (ESI) *m/z* ($M^+ - CH_3O$) calcd for $C_{17}H_{30}OBr$ 329.1480, found 329.1480.



(*Z*)-Methyl 19-(tert-butyldimethylsilyl)nonadec-16-en-18-ynoate (1.87):

tert-Butyldimethylsilylacetylene **1.35** (8.4 mL, 45 mmol) was added to a solution of vinyl bormide **1.14** (6.60 g, 18.3 mmol), $PdCl_2(PPh_3)_2$ (1.52 g, 2.2 mmol), and CuI (0.34 g, 1.8 mmol) in degassed piperidine (180 mL) at room temperature. After stirring at the same temperature for 2 h, saturated NH_4Cl aqueous solution (90 mL) was added and extracted with Et_2O (3 × 75 mL). The organic layer was washed with brine (3 × 75 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/Et_2O = 49:1) to afford the title compound **1.87** (6.86 g, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (dt, *J* = 10.8,

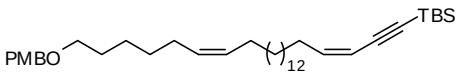
7.8 Hz, 1H), 5.48 (d, *J* = 10.8 Hz, 1H), 3.66 (s, 3H), 2.31 (q, *J* = 7.1 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.64–1.56 (m, 2H), 1.43–1.35 (m, 2H), 1.25 (br. s, 20H), 0.96 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 145.5, 109.2, 102.7, 96.6, 51.3, 34.1, 30.3, 29.6, 29.6, 29.4, 29.4, 29.2, 29.2, 29.1, 28.7, 26.1, 24.9, 16.6, −4.6; IR (film) 2928, 2855, 1731, 1465, 1439, 1251, 1201, 1174, 909, 838, 735; MS (EI) *m/z* 443 (M^+ + Na); HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{26}H_{48}O_2NaSi$ 443.3321, found 443.3309.



(*Z*)-19-(*tert*-Butyldimethylsilyl)nonadec-16-en-18-ynal (1.13):

DIBAL-H (22 mL, 1.0 M solution in hexane, 22 mmol) was added to a solution of ester **1.87** (6.85 g, 16.3 mmol) in CH_2Cl_2 (85 mL) at −78 °C. After stirring for 30 min at the same temperature, the mixture was poured into a rapidly stirred mixture of saturated aqueous sodium potassium tartrate (240 mL) and Et_2O (160 mL). The resulting mixture was stirred vigorously for 1 h, at which time the organic layer cleared. The organic layer was washed with brine (150 mL) and the combined aqueous layers were extracted with Et_2O (150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/Et_2O = 49:1) to afford the title compound **1.13** (5.98 g, 94%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.8 Hz, 1H), 5.95 (dt, *J* = 10.8, 7.5 Hz, 1H), 5.48 (d, *J* = 10.8 Hz, 1H), 2.42 (td, *J* = 7.5, 2.1 Hz, 2H), 2.32 (qd, *J* = 6.9, 0.6 Hz, 2H), 1.68–1.57 (m, 2H), 1.44–1.35 (m, 2H), 1.25 (br. s, 20H), 0.96 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 145.5, 109.2, 102.8, 96.7, 43.9, 30.4, 29.6, 29.6, 29.6, 29.4, 29.3, 29.2, 29.2, 28.7, 26.1,

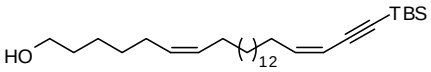
22.1, 16.6, −4.6; IR (film) 2928, 2855, 1721, 1641, 1466, 1389, 1251, 908, 810, 733; MS (EI) *m/z* 390 (M^+); HRMS (ESI) *m/z* (M^+) calcd for $C_{25}H_{46}OSi$ 390.3318, found 390.3316.



***tert*-Butyl((3*Z*,19*Z*)-25-(4-methoxybenzyloxy)pentacosa-3,19-dien-1-ynyl)dimethylsilane (1.88):**

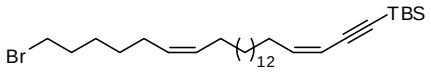
NaHMDS (30 mL, 1.0 M solution in THF, 30 mmol) was added to the solution of phosphonium bromide **1.12** (19.86 g, 35 mmol) in THF (120 mL) at 0 °C. The resulting orange solution was stirred at the same temperature for 30 min and then cooled to −78 °C. The solution of aldehyde **1.13** (5.86 g, 15 mmol) in THF (55 mL) was then added. The mixture was stirred at −78 °C for 2 h and warmed to room temperature for further 2 h stirring. Saturated NH_4Cl aqueous solution (75 mL) was added, the organic phase was separated and aqueous phase was extracted with Et_2O (3 × 75 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/Et_2O = 49:1) to afford the title compound **1.88** (8.85 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.88 (m, 2H), 5.96 (dt, *J* = 10.8, 7.5 Hz, 1H), 5.47 (d, *J* = 10.8 Hz, 1H), 5.37–5.28 (m, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.43 (t, *J* = 6.6 Hz, 2H), 2.32 (qd, *J* = 6.6, 0.6 Hz, 2H), 2.07–1.95 (m, 4H), 1.64–1.56 (m, 2H), 1.44–1.33 (m, 6H), 1.25 (br. s, 22H), 0.96 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 145.6, 130.8, 130.1, 129.6, 129.2, 113.7, 109.2, 102.8, 96.7, 72.5, 70.2, 55.2, 30.4, 29.8, 29.7, 29.6, 29.4, 29.3, 29.2, 28.8, 27.2, 27.1, 26.1, 25.9, 16.6, −4.5; IR (film) 3054, 2928, 2855, 1612, 1513, 1463, 1423, 1361, 1265,

1096, 1035, 895, 826, 740, 706; MS (EI) *m/z* 595 (M^+ + H); HRMS (ESI) *m/z* (M^+ + H) calcd for $C_{39}H_{47}O_2Si$ 595.4910, found 595.4912.



(6*Z*,22*Z*)-25-(*tert*-Butyldimethylsilyl)pentacosa-6,22-dien-24-yn-1-ol:

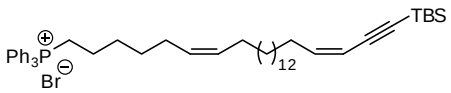
DDQ (5.03 g, 22.2 mmol) was added to the solution of compound **1.88** (8.80 g, 14.8 mmol) in CH_2Cl_2 (150 mL) and H_2O (16 mL) at room temperature. The reaction was monitored by TLC until completion, and then saturated $NaHCO_3$ aqueous solution was added. The mixture was extracted with CH_2Cl_2 (3 × 100 mL), the organic layers were combined, washed with saturated $NaHCO_3$ aqueous solution, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/Et_2O = 3:1) to afford the title compound, which was contaminated with tiny 4-(methoxymethyl)benzaldehyde and was used in the following step without further purification.



((3*Z*,19*Z*)-25-Bromopentacosa-3,19-dien-1-ynyl)(*tert*-butyl)dimethylsilane (1.89):

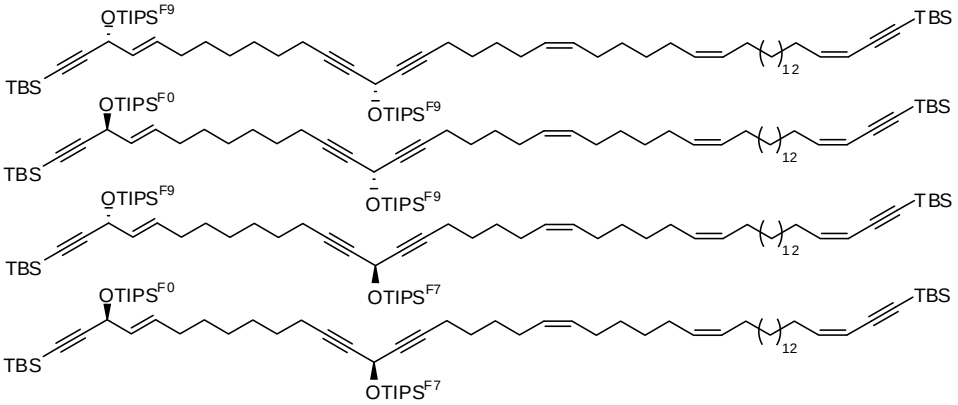
A solution of triphenylphosphine (14.0 g, 53.4 mmol) was added to a solution of (6*Z*,22*Z*)-25-(*tert*-Butyldimethylsilyl)pentacosa-6,22-dien-24-yn-1-ol (14.8 mmol) and CBr_4 (14.2 g, 42.8 mmol) in CH_2Cl_2 (70 mL) at 0 °C. After stirring at room temperature for 1 h, the organic solvent was removed under reduced pressure. The residue was purified by column chromatography (hexane/EtOAc = 99:1) to afford the title compound **1.89** (4.77 g, 60% for 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (dt, *J* = 10.8, 7.5 Hz, 1H), 5.48 (d, *J* = 10.8 Hz, 1H),

5.43–5.28 (m, 2H), 3.41 (t, *J* = 6.9 Hz, 2H), 2.32 (q, *J* = 7.2 Hz, 2H), 2.07–1.96 (m, 4H), 1.87 (quin, J = 6.9 Hz, 2H), 1.50–1.37 (m, 6H), 1.26 (br. s, 22H), 0.96 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 130.4, 129.2, 109.2, 102.8, 96.7, 33.9, 32.8, 30.4, 29.7, 29.7, 29.7, 29.6, 29.6, 29.4, 29.3, 29.2, 28.9, 28.8, 27.8, 27.2, 27.0, 26.1, 16.6, −4.5; IR (film) 2926, 2854, 1650, 1558, 1459, 1251, 1022, 910, 810, 736; MS (EI) *m/z* 536 (M^+); HRMS (ESI) *m/z* (M^+) calcd for $C_{31}H_{57}OSi$ 536.3413, found 536.3401.



((6*Z*,22*Z*)-25-(*tert*-butyldimethylsilyl)pentacosa-6,22-dien-24-ynyl)triphenylphosphonium bromide (1.3):

A mixture of bromide **1.89** (4.77 g, 8.9 mmol) and triphenylphosphine (5.82 g, 22.2 mmol) in CH_3CN (90 mL) was stirred at 90 °C for 2 days. The organic solvent was removed under reduced pressure, the residue was purified by column chromatography ($CHCl_3$/MeOH = 19:1) to afford the title compound **1.3** (6.78 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87–7.82 (m, 6H), 7.79–7.74 (m, 3H), 7.71–7.67 (m, 6H), 5.95 (dtd, *J* = 10.5, 7.5, 2.0 Hz, 1H), 5.46 (dt, *J* = 11.0, 1.3 Hz, 1H), 5.31–5.20 (m, 2H), 3.87–3.77 (m, 2H), 2.30 (q, *J* = 6.5 Hz, 2H), 1.96–1.89 (m, 4H), 1.68–1.58 (m, 4H), 1.43–1.35 (m, 4H), 1.23 (br. s, 22H), 0.94 (d, *J* = 2.0 Hz, 9H), 0.11 (d, *J* = 2.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.6, 134.9 (d, J_{CP} = 2.5 Hz), 133.6 (d, J_{CP} = 10.0 Hz), 133.4 (d, J_{CP} = 12.5 Hz), 130.3, 129.0, 118.3 (d, J_{CP} = 86.3 Hz), 109.1, 102.7, 96.6, 30.3, 30.0, 29.9, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.7, 27.2, 26.7, 26.0, 22.7 (d, J_{CP} = 45 Hz), 22.5, 16.5, −4.5; IR (film) 2925, 2854, 1650, 1558, 1458, 1437, 1112, 914; HRMS (ESI) *m/z* (M^+ − Br) calcd for $C_{49}H_{72}SiP$ 719.5141, found 719.5121.



(10*R*,21*R*,*E*)-21-((7*Z*,13*Z*,29*Z*)-32-(*tert*-Butyldimethylsilyl)dotriaconta-7,13,29-trien-1,31-diynyl)-10-((tert-butyldimethylsilyl)ethynyl)-1,1,1,2,2,3,3,4,4,27,27,28,28,29,29,30,30,30-octadecafluoro-8,8,23,23-tetraisopropyl-9,22-dioxa-8,23-disilatriacont-11-en-19-yne, (5*S*,16*R*,*E*)-16-((7*Z*,13*Z*,29*Z*)-32-(*tert*-butyldimethylsilyl)dotriaconta-7,13,29-trien-1,31-diynyl)-5-((tert-butyldimethylsilyl)ethynyl)-22,22,23,23,24,24,25,25,25-nonafluoro-3,3,18,18-tetraisopropyl-2-methyl-4,17-dioxa-3,18-disilapentacos-6-en-14-yne, (9*S*,20*R*,*E*)-9-((7*Z*,13*Z*,29*Z*)-32-(*tert*-butyldimethylsilyl)dotriaconta-7,13,29-trien-1,31-diynyl)-20-((tert-butyldimethylsilyl)ethynyl)-1,1,1,2,2,3,3,26,26,27,27,28,28,29,29,29-hexadecafluoro-7,7,22,22-tetraisopropyl-8,21-dioxa-7,22-disilanonacos-18-en-10-yne, and (5*S*,16*S*,*E*)-16-((7*Z*,13*Z*,29*Z*)-32-(*tert*-butyldimethylsilyl)dotriaconta-7,13,29-trien-1,31-diynyl)-5-((tert-butyldimethylsilyl)ethynyl)-22,22,23,23,24,24,24-heptafluoro-3,3,18,18-tetraisopropyl-2-methyl-4,17-dioxa-3,18-disilatetracos-6-en-14-yne (M-1.90):

NaHMDS (0.63 mL, 1.0 M solution in THF, 0.63 mmol) was added to the solution of phosphonium bromide **1.3** (658.9 mg, 0.82 mmol) in THF (2.1 mL) at 0 °C. The resulting orange solution was stirred at the same temperature for 10 min and then cooled to −78 °C. The solution of aldehyde **M-1.2** (190.0 mg, 0.21 mmol) in THF (1.4 mL) was then added. The mixture was

stirred at −78 °C for 2 h. Saturated NH_4Cl aqueous solution (10 mL) was added, the organic phase was separated and aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (hexane/CH_2Cl_2 = 9:1) to afford the title compound **M-1.90** (137.2 mg, 44%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.96 (dt, *J* = 10.8, 7.8 Hz, 1H), 5.83–5.76 (m, 1H), 5.54–5.47 (m, 2H), 5.38–5.30 (m, 4H), 5.21 (s, 1H), 4.92–4.87 (m, 1H), 2.32 (q, *J* = 7.2 Hz, 2H), 2.20 (q, *J* = 7.8 Hz, 2H), 2.15–2.08 (m, 3H), 2.06–1.98 (m, 10H), 1.79–1.72 (m, 3H), 1.53–1.47 (m, 4H), 1.44–1.25 (m, 36H), 1.13–1.05 (m, 31.5H), 0.96 (s, 9H), 0.92 (s, 9H), 0.79–0.75 (m, 3H), 0.13 (s, 6H), 0.09 (s, 6H).

Demix the mixture M-1.90:

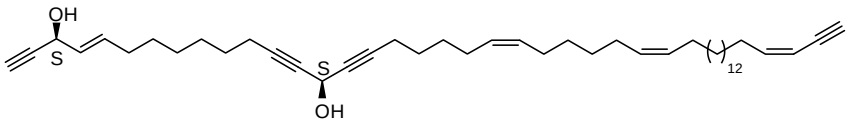
The mixture **M-1.90** (137.2 mg, 0.09 mmol) was dissolved in CH_3CN/THF (3:2) (6 mL) and demixed by semi-preparative fluorous HPLC (*FluorosFlash*^{TM} PFC8 column, CH_3CN:THF = 100:0 to 85:15 in 45 min, then 85:15 for further 20 min). The four desired compounds were obtained.

1.90SS: 41.3 mg, t = 20.3 min

1.90SR: 39.5 mg, t = 25.5 min

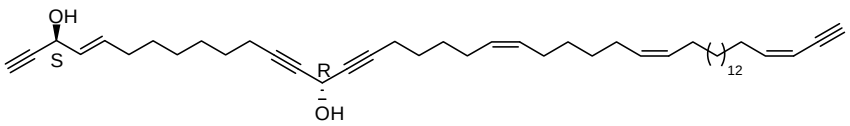
1.90RS: 16.0 mg, t = 42.2 min

1.90RR: 19.7 mg, t = 52.7 min



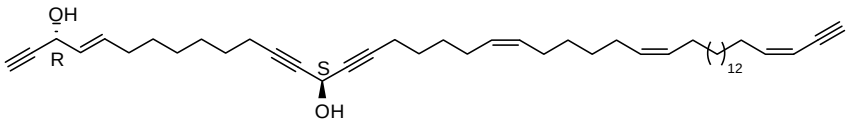
(3*S*,4*E*,14*S*,21*Z*,27*Z*,43*Z*)-Hexatetraconta-4,21,27,43-tetraen-1,12,15,45-tetrayne-3,14-diol (1.1SS):

TBAF (0.24 mL, 1.0 M solution in THF, 0.24 mmol) was added to a solution of compound **1.90SS** (40.0 mg, 0.29 mmol) in THF (0.6 mL) at room temperature. The mixture then was stirred for 1 h at this temperature and quenched with saturated aqueous NH_4Cl. The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography (hexane/Et_2O = 4:1) to give compound **1.1SS** (11.4 mg, 59%). $[\alpha]_D^{25}$ = +10.5 (*c* = 0.30, CH_3OH), ^1H NMR (600 MHz, $CDCl_3$) δ 6.00 (dt, *J* = 10.8, 7.2 Hz, 1H), 5.91 (dt, *J* = 15.0, 7.0 Hz, 1H), 5.62 (dd, *J* = 15.0, 6.0 Hz, 1H), 5.44 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.39–5.31 (m, 4H), 5.09 (dt, *J* = 7.2, 1.8 Hz, 1H), 4.84 (t, *J* = 6.0 Hz, 1H), 3.07 (d, *J* = 1.8 Hz, 1H), 2.57 (d, *J* = 2.4 Hz, 1H), 2.32 (q, *J* = 7.2 Hz, 2H), 2.23 (qd, *J* = 6.0, 1.2 Hz, 4H), 2.13 (d, *J* = 7.2 Hz, 1H), 2.08 (q, *J* = 7.2 Hz, 2H), 2.06–1.99 (m, 8H), 1.88 (d, *J* = 6.0 Hz, 1H), 1.55–1.49 (m, 4H), 1.46–1.25 (m, 36H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 146.31, 134.32, 130.21, 130.07, 129.65, 129.31, 128.52, 107.88, 85.02, 84.97, 83.26, 81.13, 80.58, 78.10, 78.10, 74.01, 62.77, 52.54, 31.76, 30.26, 29.76, 29.68 (3 C), 29.65 (3 C), 29.57, 29.44, 29.37, 29.33 (2 C), 29.17, 28.87, 28.72, 28.56, 28.54, 28.49, 28.19, 27.92, 27.23, 27.13, 27,09, 26.65, 18.64, 18.63; IR (film) 3054, 2986, 2929, 2855, 1422, 1265, 909, 740; MS (EI) *m/z* 678 (M^+ + Na + H); HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{46}H_{70}O_2Na$ 677.5274, found 677.5321.



(3*S*,4*E*,14*R*,21*Z*,27*Z*,43*Z*)-Hexatetraconta-4,21,27,43-tetraen-1,12,15,45-tetrayne-3,14-diol (1.1SR):

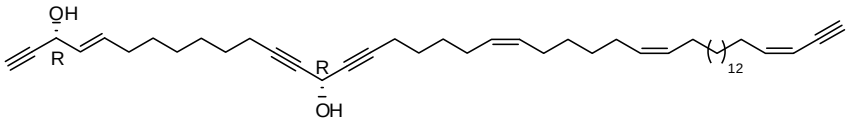
Following the same procedure for **1.1SS**, the compound **1.90SR** (38.0 mg, 0.027 mmol) was reacted with TBAF (0.22 mL, 1.0 M solution in THF, 0.22 mmol), the title compound **1.1SR** (10.4 mg, 59%) was obtained. $[\alpha]_D^{25}$ = +9.5 (*c* = 0.25, CH_3OH), ^1H NMR (600 MHz, $CDCl_3$) δ 6.00 (dt, *J* = 10.8, 7.2 Hz, 1H), 5.91 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.62 (ddd, *J* = 15.6, 6.0, 0.6 Hz, 1H), 5.44 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.39–5.31 (m, 4H), 5.09 (dt, *J* = 6.6, 1.2 Hz, 1H), 4.84 (t, *J* = 6.0 Hz, 1H), 3.07 (d, *J* = 1.8 Hz, 1H), 2.57 (d, *J* = 1.8 Hz, 1H), 2.32 (q, *J* = 7.2 Hz, 2H), 2.23 (qd, *J* = 6.5, 1.2 Hz, 4H), 2.11 (d, *J* = 7.2 Hz, 1H), 2.08 (q, *J* = 7.2 Hz, 2H), 2.06–1.99 (m, 8H), 1.87 (d, *J* = 6.0 Hz, 1H), 1.56–1.49 (m, 4H), 1.46–1.25 (m, 36H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 146.32, 134.33, 130.21, 130.07, 129.65, 129.31, 128.51, 107.87, 85.03, 84.98, 83.26, 81.12, 80.58, 78.09, 78.08, 74.02, 62.78, 52.54, 31.77, 30.26, 29.76, 29.68 (3 C), 29.66 (3 C), 29.58, 29.44, 29.37, 29.33 (2 C), 29.17, 28.87, 28.72, 28.56, 28.54, 28.50, 28.20, 27.91, 27.23, 27.13, 27,09, 26.65, 18.65, 18.63; IR (film) 3054, 2986, 2929, 2855, 1423, 1265, 909, 736; MS (EI) *m/z* 678 (M^+ + Na + H); HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{46}H_{70}O_2Na$ 677.5274, found 677.5267.



(3*R*,4*E*,14*S*,21*Z*,27*Z*,43*Z*)-Hexatetraconta-4,21,27,43-tetraen-1,12,15,45-tetrayne-3,14-diol (1.1RS):

Following the same procedure for **1.1SS**, the compound **1.90RS** (12.5 mg, 0.008 mmol) was reacted with TBAF (0.07 mL, 1.0 M solution in THF, 0.07 mmol), the title compound **1.1RS**

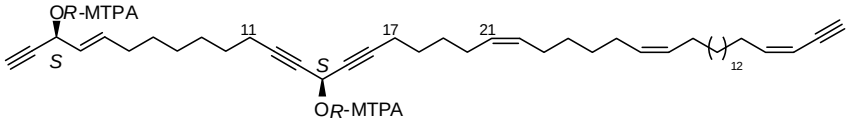
(2.1 mg, 41%) was obtained. $[\alpha]_D^{25} = -9.0$ (c = 0.16, CH_3OH), ^1H NMR (600 MHz, $CDCl_3$) δ 6.00 (dt, J = 10.8, 7.2 Hz, 1H), 5.91 (dt, J = 15.0, 7.2 Hz, 1H), 5.62 (dd, J = 15.6, 6.0 Hz, 1H), 5.44 (dd, J = 10.8, 1.2 Hz, 1H), 5.39–5.31 (m, 4H), 5.09 (dt, J = 7.2, 1.8 Hz, 1H), 4.84 (t, J = 6.0 Hz, 1H), 3.07 (d, J = 1.8 Hz, 1H), 2.57 (d, J = 1.8 Hz, 1H), 2.32 (q, J = 7.2 Hz, 2H), 2.23 (qd, J = 6.9, 1.8 Hz, 4H), 2.10 (d, J = 6.6 Hz, 1H), 2.08 (q, J = 7.2 Hz, 2H), 2.06–1.99 (m, 8H), 1.85 (d, J = 6.0 Hz, 1H), 1.56–1.49 (m, 4H), 1.46–1.25 (m, 36H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 146.33, 134.35, 130.22, 130.08, 129.66, 129.31, 128.52, 107.88, 85.05, 85.00, 83.26, 81.12, 80.58, 78.08 (2 C), 74.02, 62.80, 52.55, 31.77, 30.27, 29.77, 29.68 (3 C), 29.66 (3 C), 29.59, 29.45, 29.38, 29.34 (2 C), 29.18, 28.88, 28.73, 28.57, 28.55, 28.51, 28.21, 27.92, 27.24, 27.14, 27,09, 26.66, 18.65, 18.63; IR (film) 3053, 2986, 2929, 1423, 1265, 909, 736, 706; MS (EI) *m/z* 678 (M^+ + Na + H); HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{46}H_{70}O_2Na$ 677.5274, found 677.5307.



(3*R*,4*E*,14*R*,21*Z*,27*Z*,43*Z*)-Hexatetraconta-4,21,27,43-tetraen-1,12,15,45-tetrayne-3,14-diol (1.1RR):

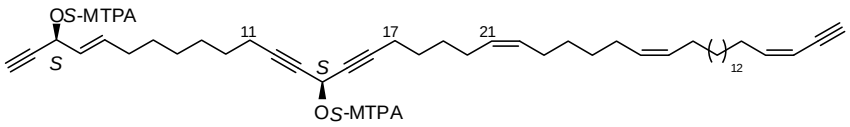
Following the same procedure for **1.1SS**, the compound **1.90RR** (18.5 mg, 0.011 mmol) was reacted with TBAF (0.09 mL, 1.0 M solution in THF, 0.09 mmol), the title compound **1.1RR** (5.1 mg, 69%) was obtained. $[\alpha]_D^{25} = -11.2$ (c = 0.20, CH_3OH), ^1H NMR (600 MHz, $CDCl_3$) δ 6.00 (dt, J = 10.8, 7.2 Hz, 1H), 5.91 (dt, J = 15.6, 6.6 Hz, 1H), 5.62 (ddd, J = 15.0, 6.0, 1.2 Hz, 1H), 5.44 (d, J = 10.8, 1H), 5.39–5.31 (m, 4H), 5.09 (dt, J = 7.2, 1.8 Hz, 1H), 4.84 (t, J = 6.0 Hz, 1H), 3.07 (d, J = 1.2 Hz, 1H), 2.57 (d, J = 1.8 Hz, 1H), 2.32 (q, J = 7.2 Hz, 2H), 2.23 (qd, J = 7.2, 1.8 Hz, 4H), 2.11 (d, J = 7.2 Hz, 1H), 2.08 (q, J = 7.2 Hz, 2H), 2.06–1.99 (m, 8H), 1.86

(d, J = 6.0 Hz, 1H), 1.56–1.49 (m, 4H), 1.46–1.25 (m, 36H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 146.33, 134.35, 130.22, 130.08, 129.66, 129.31, 128.52, 107.88, 85.04, 84.99, 83.26, 81.13, 80.58, 78.09 (2 C), 74.03, 62.79, 52.55, 31.77, 30.28, 29.77, 29.69 (3 C), 29.66 (3 C), 29.59, 29.45, 29.38, 29.34 (2 C), 29.18, 28.88, 28.73, 28.56, 28.54, 28.50, 28.20, 27.92, 27.24, 27.14, 27,09, 26.66, 18.65, 18.63; IR (film) 3054, 2986, 1423, 1265, 909, 735, 705; MS (EI) *m/z* 678 (M^+ + Na + H); HRMS (ESI) *m/z* (M^+ + Na) calcd for $C_{46}H_{70}O_2Na$ 677.5274, found 677.5295.



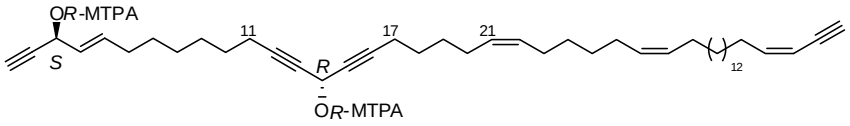
(2*R*,2'*R*)-((3*S*,4*E*,14*S*,21*Z*,27*Z*,43*Z*)-hexatetraconta-4,21,27,43-tetraen-1,12,15,45-tetrayne-3,14-diyl) bis(3,3,3-trifluoro-2-methoxy-2-phenylpropanoate) (1.91SSR):

To a solution of alcohol **1.1SS** (1.0 mg, 1.5×10^{-3} mmol) in CH_2Cl_2 (0.5 ml) was added (*R*)-MTPA acid (1.8 mg, 7.6×10^{-3} mmol), DCC (1.9 mg, 9.2×10^{-3} mmol), and DMAP (0.2 mg, 1.5×10^{-3} mmol) at room temperature. The resulting mixture was stirred at the same temperature overnight. The mixture was then filtered through a pad of Celite ®, the filtrate was concentrated *in vacuo*. The crude product **1.191SSR** was obtained: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.55 (d, J = 7.0 Hz, 2H), 7.52 (d, J = 7.0 Hz, 2H), 7.43–7.39 (m, 6H), 6.21 (t, J = 2.1 Hz, 1H), 6.05 (dtd, J = 15.4, 7.0, 1.4 Hz, 1H), 6.02–5.98 (m, 2H), 5.60 (ddt, J = 15.4, 7.0, 1.4 Hz, 1H), 5.44 (ddt, J = 10.5, 2.8, 1.4 Hz, 1H), 5.39–5.29 (m, 4H), 3.59 (s, 3H), 3.55 (s, 3H), 3.06 (d, J = 2.1 Hz, 1H), 2.59 (d, J = 2.1 Hz, 1H), 2.32 (qd, J = 7.7, 1.4 Hz, 2H), 2.22 (td, J = 7.0, 2.1 Hz, 2H), 2.20 (td, J = 7.0, 2.1 Hz, 2H), 2.07 (q, J = 7.0 Hz, 2H), 2.03–1.99 (m, 8H), 1.52–1.46 (m, 4H), 1.42–1.38 (m, 4H), 1.36–1.25 (m, 32H).



(2*S*,2'*S*)-((3*S*,4*E*,14*S*,21*Z*,27*Z*,43*Z*)-hexatetraconta-4,21,27,43-tetraen-1,12,15,45-tetrayne-3,14-diyl) bis(3,3,3-trifluoro-2-methoxy-2-phenylpropanoate) (1.91SSS):

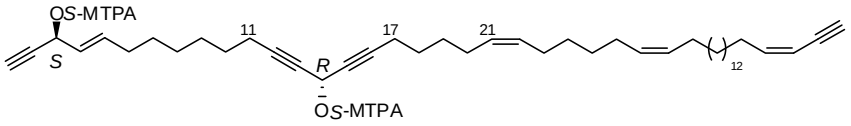
Following the same procedure for **1.91SSR**, the compound **1.1SS** (1.0 mg, 0.027 mmol) was reacted with (*S*)-MTPA acid (1.8 mg, 7.6×10^{-3} mmol), DCC (1.9 mg, 9.2×10^{-3} mmol), and DMAP (0.2 mg, 1.5×10^{-3} mmol), the title compound **1.91SSS** (10.4 mg, 59%) was obtained. ^{1}H NMR (700 MHz, $CDCl_3$) δ7.55 (d, *J* = 7.0 Hz, 2H), 7.52 (d, *J* = 7.0 Hz, 2H), 7.43–7.39 (m, 6H), 6.21 (t, *J* = 2.1 Hz, 1H), 6.03 (m, 1H), 6.00 (m, 1H), 5.99 (m, 1H), 5.49 (dd, *J* = 15.4, 7.0 Hz, 1H), 5.44 (d, *J* = 10.5 Hz, 1H), 5.37–5.29 (m, 4H), 3.59 (s, 3H), 3.58 (s, 3H), 3.06 (d, *J* = 1.4 Hz, 1H), 2.63 (d, *J* = 2.1 Hz, 1H), 2.32 (q, *J* = 7.0 Hz, 2H), 2.23 (td, *J* = 7.0, 2.1 Hz, 2H), 2.22 (td, *J* = 7.0, 2.1 Hz, 2H), 2.04 (m, 2H), 2.03–1.99 (m, 8H), 1.53–1.50 (m, 2H), 1.48–1.44 (m, 2H), 1.43–1.38 (m, 4H), 1.36–1.25 (m, 32H).



(2*R*,2'*R*)-((3*S*,4*E*,14*R*,21*Z*,27*Z*,43*Z*)-hexatetraconta-4,21,27,43-tetraen-1,12,15,45-tetrayne-3,14-diyl) bis(3,3,3-trifluoro-2-methoxy-2-phenylpropanoate) (1.92SRR):

Following the same procedure for **1.91SSR**, the compound **1.1SR** (1.0 mg, 0.027 mmol) was reacted with (*R*)-MTPA acid (1.8 mg, 7.6×10^{-3} mmol), DCC (1.9 mg, 9.2×10^{-3} mmol), and DMAP (0.2 mg, 1.5×10^{-3} mmol), the title compound **1.92SRR** (10.4 mg, 59%) was obtained. ^{1}H NMR (600 MHz, $CDCl_3$) δ7.55 (d, *J* = 7.0 Hz, 2H), 7.52 (d, *J* = 7.0 Hz, 2H), 7.43–7.39 (m, 6H), 6.21 (t, *J* = 2.1 Hz, 1H), 6.06 (dtd, *J* = 15.4, 7.0, 1.4 Hz, 1H), 6.01 (m, 1H), 6.00 (m, 2H), 5.60

(ddt, *J* = 15.4, 7.0, 1.4 Hz, 1H), 5.44 (ddt, *J* = 10.5, 2.8, 1.4 Hz, 1H), 5.38–5.29 (m, 4H), 3.59 (s, 3H), 3.55 (s, 3H), 3.07 (d, J = 1.4 Hz, 1H), 2.59 (d, J = 2.1 Hz, 1H), 2.32 (q, J = 7.0 Hz, 2H), 2.23 (td, J = 7.0, 2.1 Hz, 2H), 2.19 (td, J = 7.0, 2.1 Hz, 2H), 2.08 (q, *J* = 7.0Hz, 2H), 2.04–2.00 (m, 8H), 1.53–1.50 (m, 2H), 1.48–1.44 (m, 2H), 1.43–1.38 (m, 4H), 1.36–1.25 (m, 32H).



(2*S*,2'*S*)-((3*S*,4*E*,14*R*,21*Z*,27*Z*,43*Z*)-hexatetraconta-4,21,27,43-tetraen-1,12,15,45-tetrayne-3,14-diyl) bis(3,3,3-trifluoro-2-methoxy-2-phenylpropanoate) (1.92SRS):

Following the same procedure for **1.91SSR**, the compound **1.1SR** (1.0 mg, 0.027 mmol) was reacted with (*S*)-MTPA acid (1.8 mg, 7.6×10^{-3} mmol), DCC (1.9 mg, 9.2×10^{-3} mmol), and DMAP (0.2 mg, 1.5×10^{-3} mmol), the title compound **1.92SRS** (10.4 mg, 59%) was obtained. ^{1}H NMR (600 MHz, $CDCl_3$) δ7.55 (d, *J* = 7.0 Hz, 2H), 7.52 (d, *J* = 7.0 Hz, 2H), 7.43–7.39 (m, 6H), 6.21 (t, *J* = 2.1 Hz, 1H), 6.02 (m, 1H), 6.00 (m, 1H), 5.99 (m, 1H), 5.49 (ddt, *J* = 15.4, 7.0, 1.4 Hz, 1H), 5.44 (ddt, *J* = 10.5, 2.8, 1.4 Hz, 1H), 5.38–5.29 (m, 4H), 3.59 (s, 3H), 3.58 (s, 3H), 3.07 (d, *J* = 0.7 Hz, 1H), 2.63 (d, *J* = 1.4 Hz, 1H), 2.32 (qd, *J* = 7.0, 1.4 Hz, 2H), 2.21 (td, *J* = 7.7, 2.1 Hz, 2H), 2.20 (td, *J* = 7.0, 2.1 Hz, 2H), 2.04 (m, 2H), 2.03–1.99 (m, 8H), 1.52–1.46 (m, 4H), 1.42–1.38 (m, 4H), 1.36–1.25 (m, 32H).

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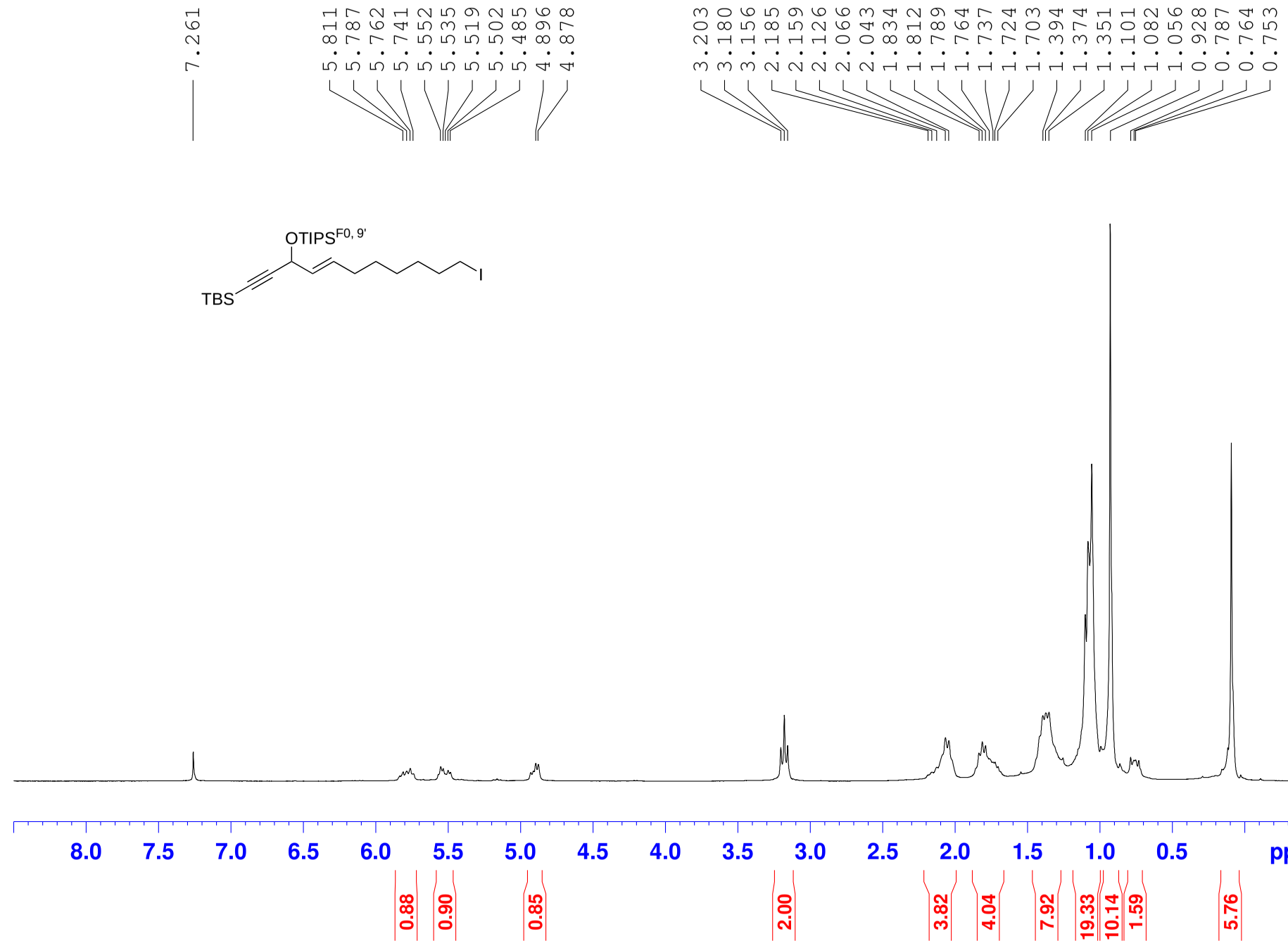
APPENDIX

NMR SPECTRA

1. ^{1}H and ^{13}C NMR spectra of **M-1.68**, **1.74R/S**, **M-1.78**–**M-1.80**, **M-1.2**, **1.3**, and **M-1.90**.
2. ^{1}H and ^{13}C NMR spectra of petrocortyne A four isomers **1.1** and COSY, HMQC, and HMBC spectra of **1.1SS**
3. ^{1}H, and TOCSY spectra of Mosher esters **1.91SSR**/**SSS** and **1.92SRS**/**SRR**

BS4P204 CDCl3 301b BinS 11/27/07



BS4P204 13CNMR CDC13 301a BinS 11/28/07
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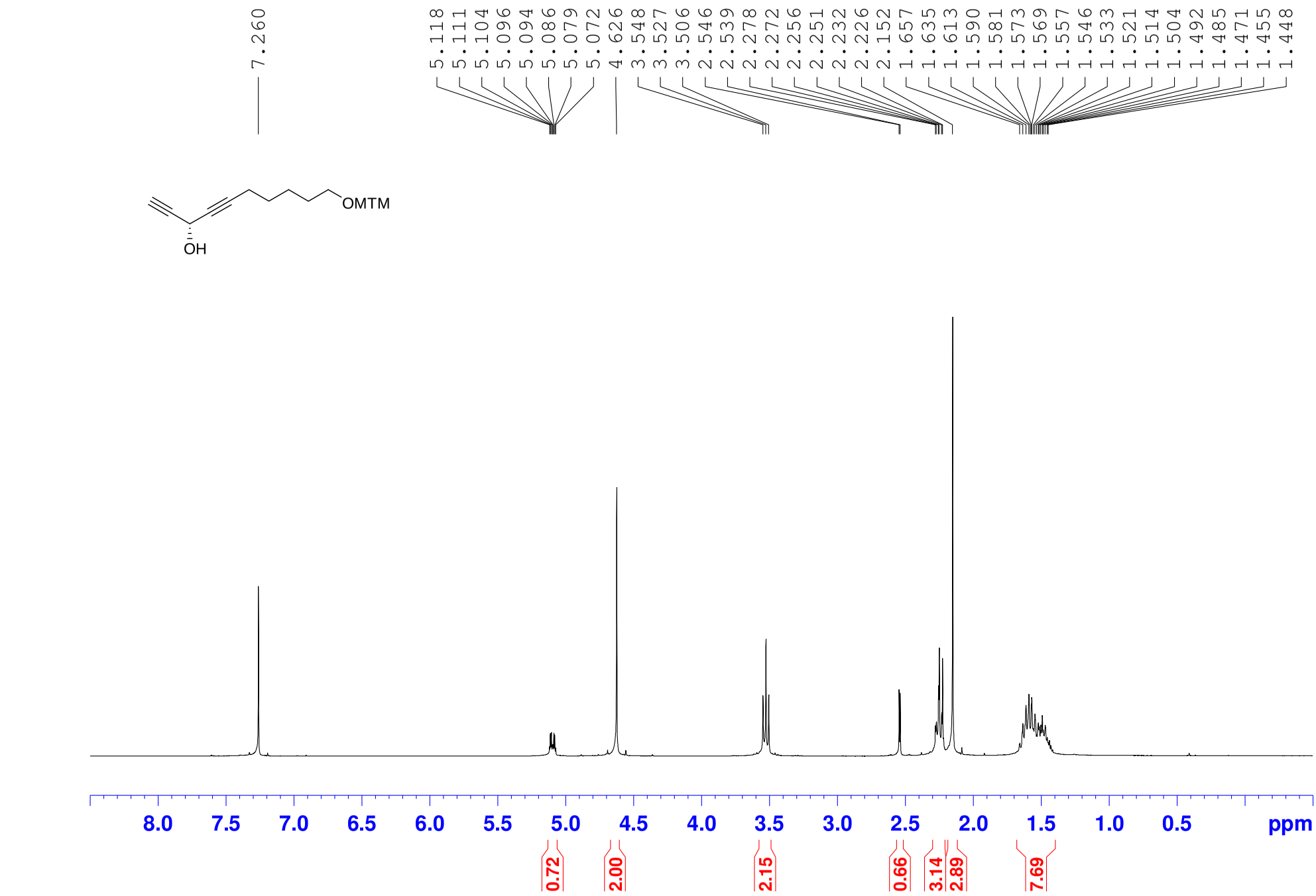
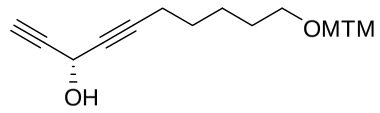
131.41
130.13
129.76
106.75
106.24
88.06
87.58
77.43
77.00
76.58
63.95
63.81
34.79
34.50
34.21
33.51
33.48
31.66
30.32
30.29
28.73
28.67
27.96
26.05
26.00
22.65
17.98
17.61
17.59
17.54
17.51
16.48
14.62
14.11
TBS
OTIPS
F0, 9'
I
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

BS4P198 CDCl3 301 BinS 11/16/07

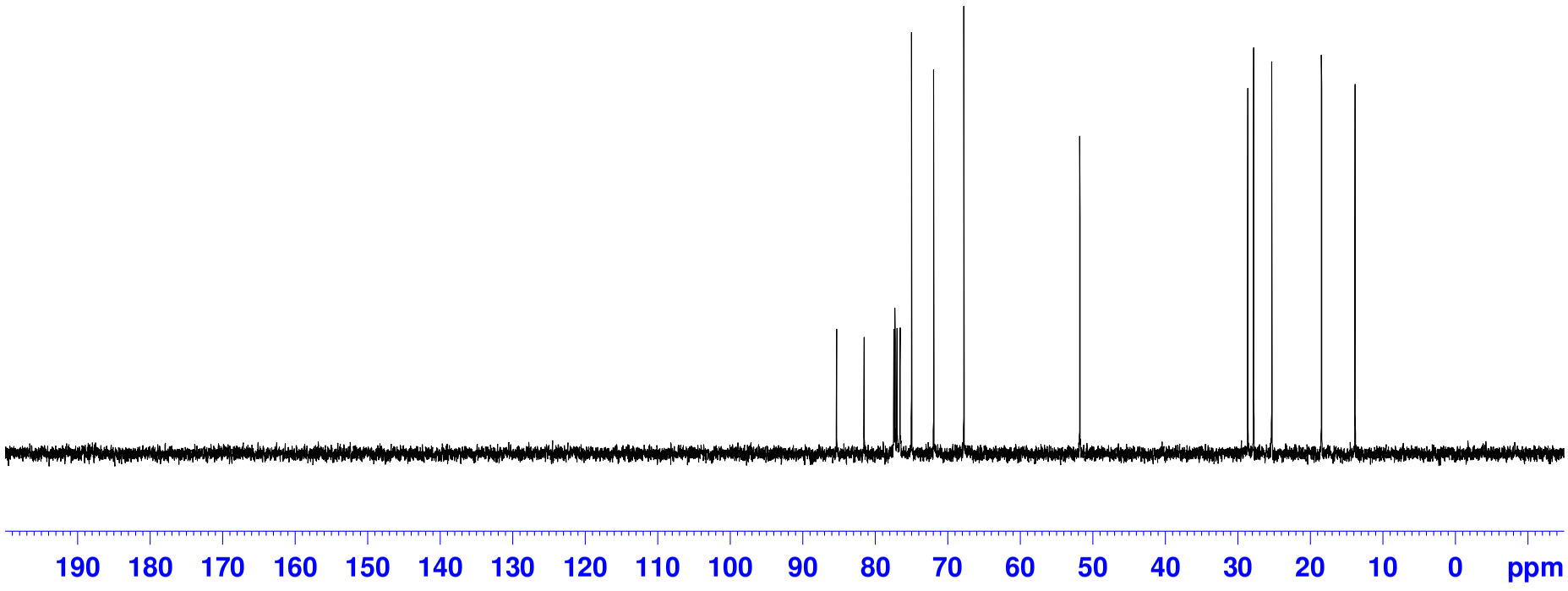


BS4P198 13CNMR CDCl3 301 BinS 11/16/07

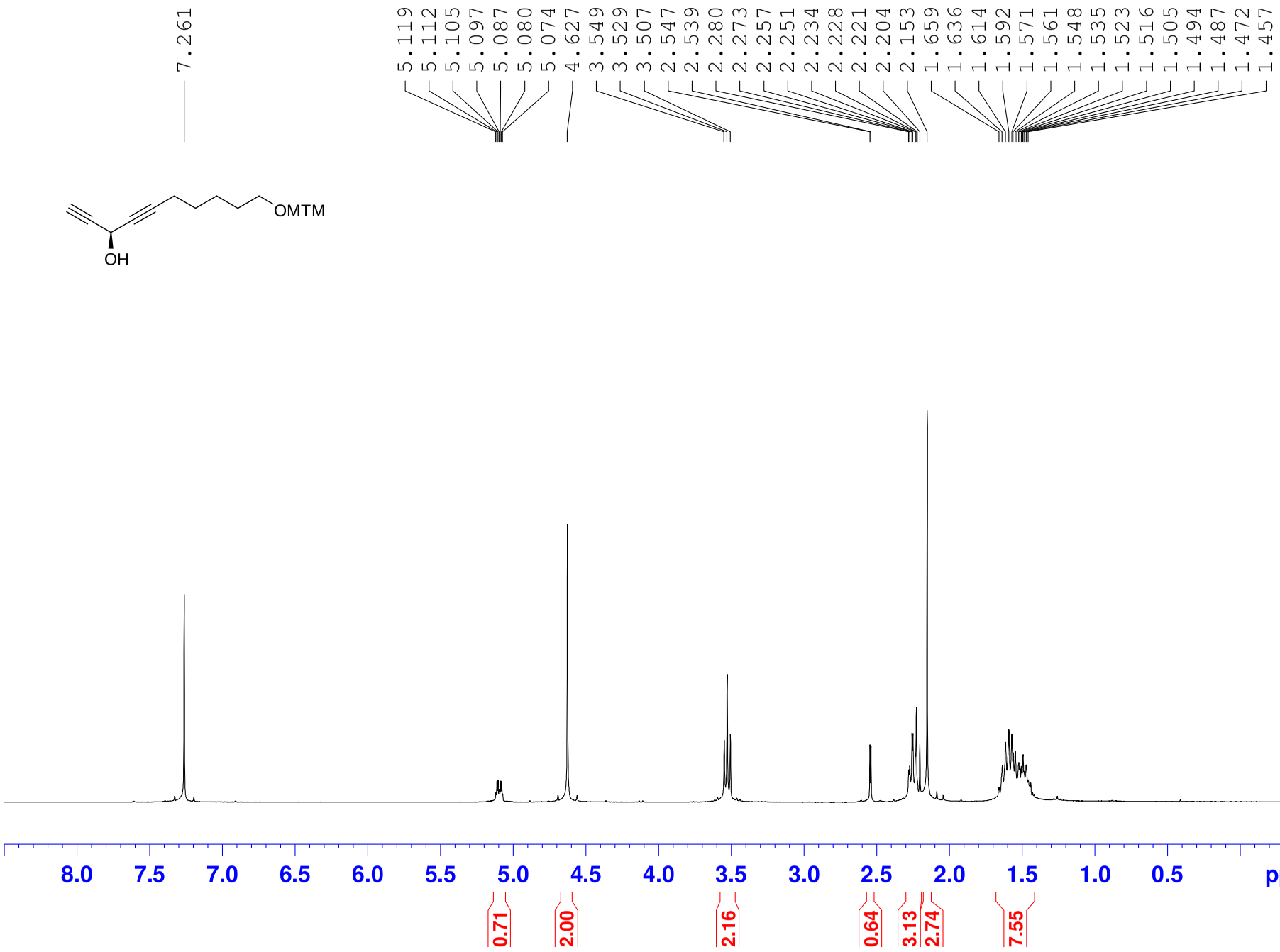
85.32
81.53
77.43
77.27
77.00
76.58
75.00
71.94
67.78
51.78
28.62
27.81
25.31
18.45
13.82



150

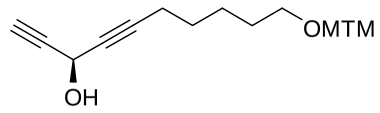


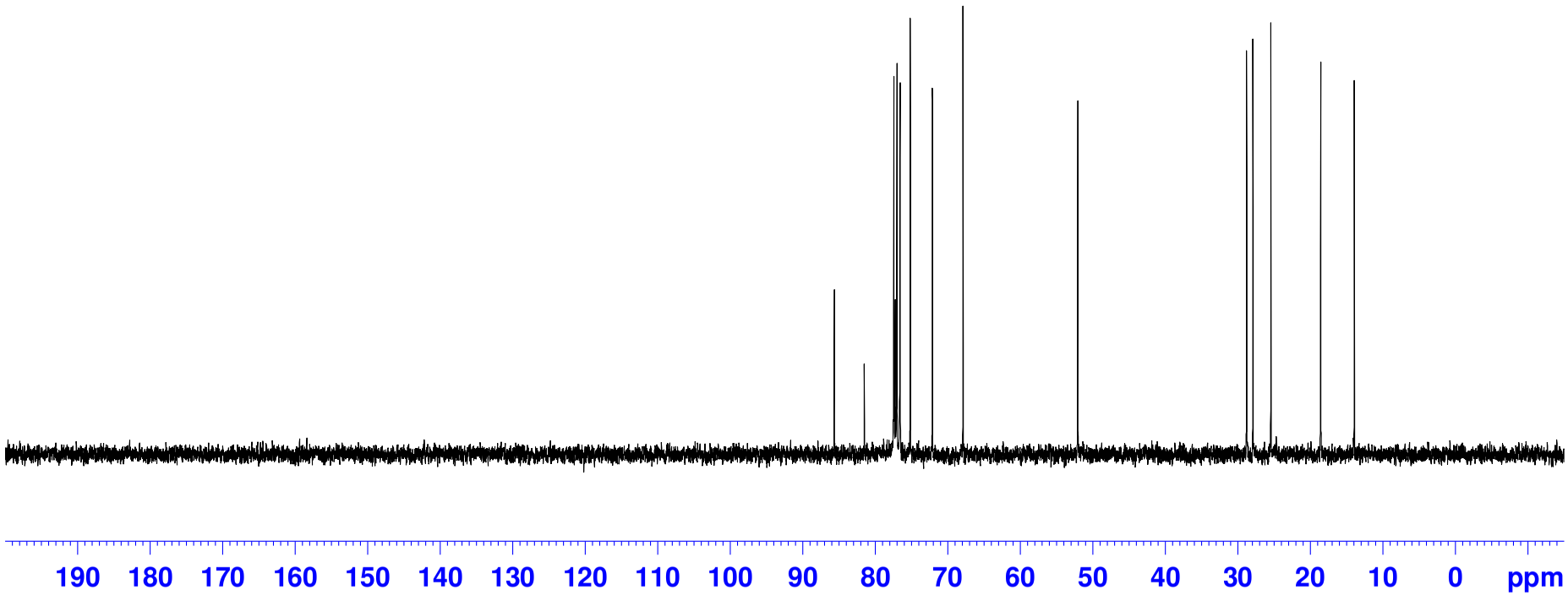
BS4P197 CDCl3 301 BinS 11/15/07



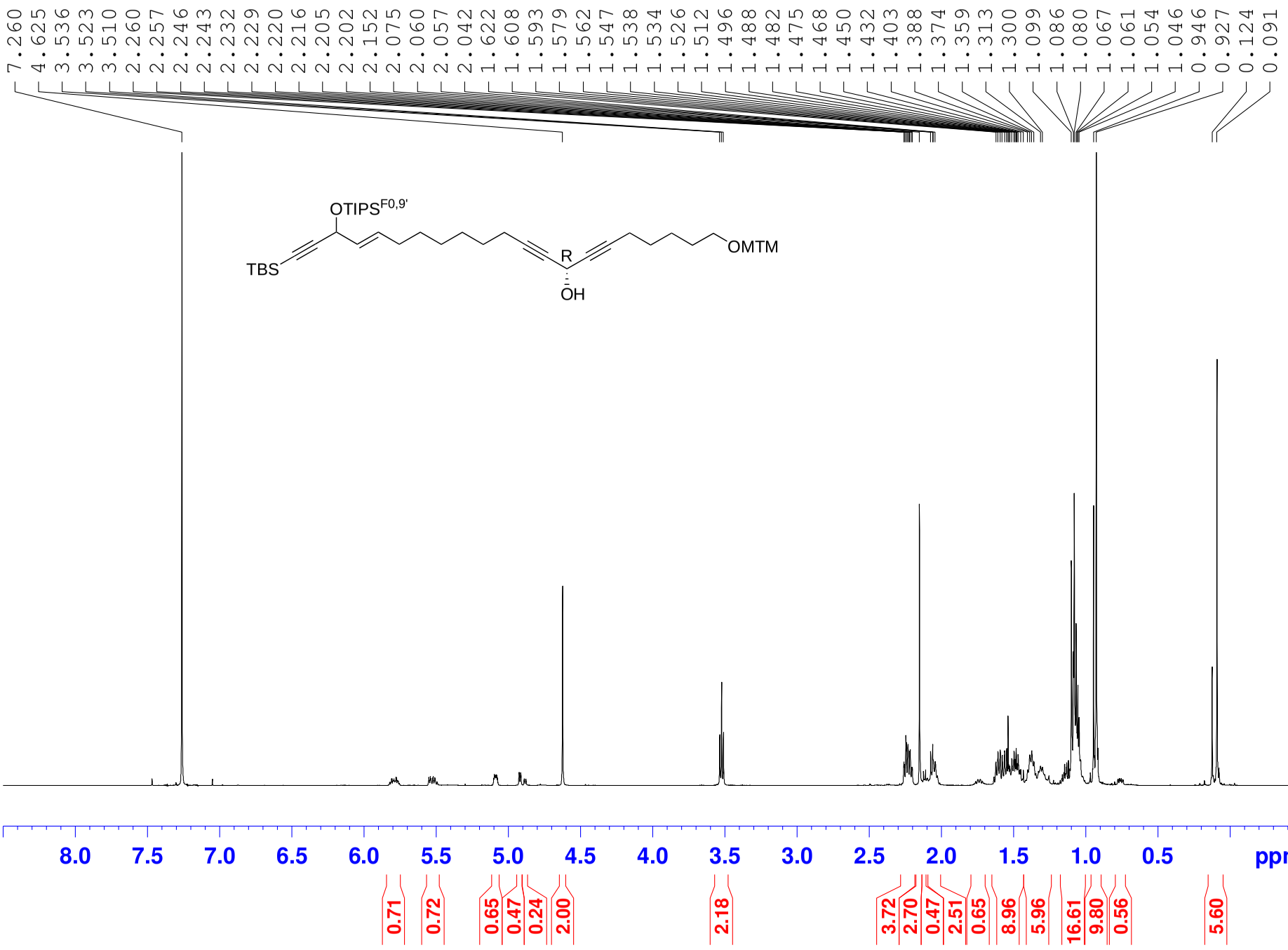
BS4P197 13CNMR CDCl3 301 BinS 11/15/07

85.65
81.50
77.43
77.25
77.00
76.58
75.16
72.10
67.89
52.06
28.78
27.90
25.44
18.57
13.93



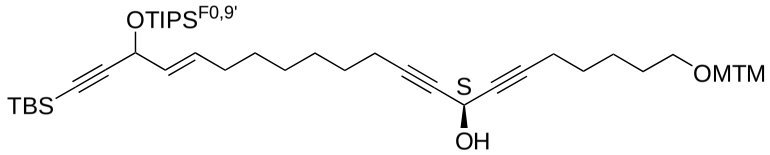


BS5P28 SM CDCl3 500 BinS 01/10/08



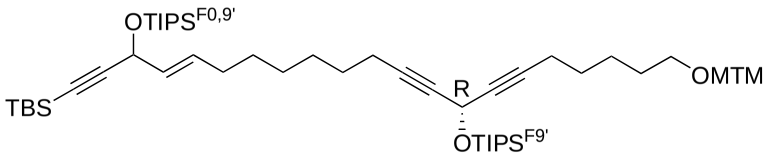
BS5P29 SM CDCl3 600 BinS 01/11/08

7.260 4.625 3.532 3.521 3.510 3.257 2.254 2.245 2.242 2.233 2.230 2.216 2.204 2.151 2.144 2.099 2.087 2.052 2.041 1.617 1.605 1.593 1.572 1.559 1.555 1.547 1.520 1.508 1.496 1.483 1.477 1.472 1.465 1.457 1.395 1.383 1.371 1.359 1.308 1.297 1.144 1.132 1.121 1.096 1.084 1.076 1.064 1.051 1.043 1.033 0.943 0.923 0.122 0.088

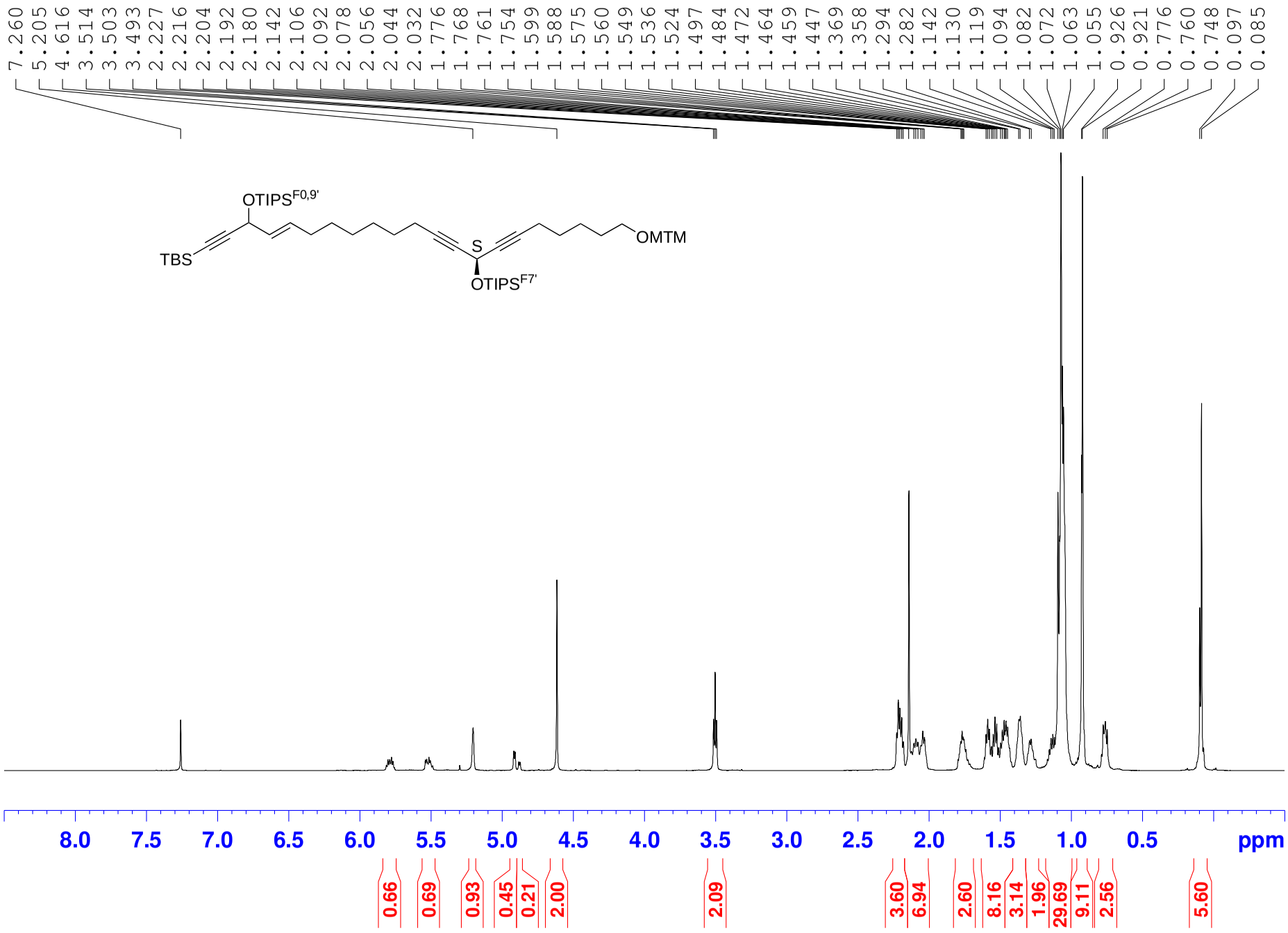


BS5P33 CDCl3 600 BinS 01/28/08

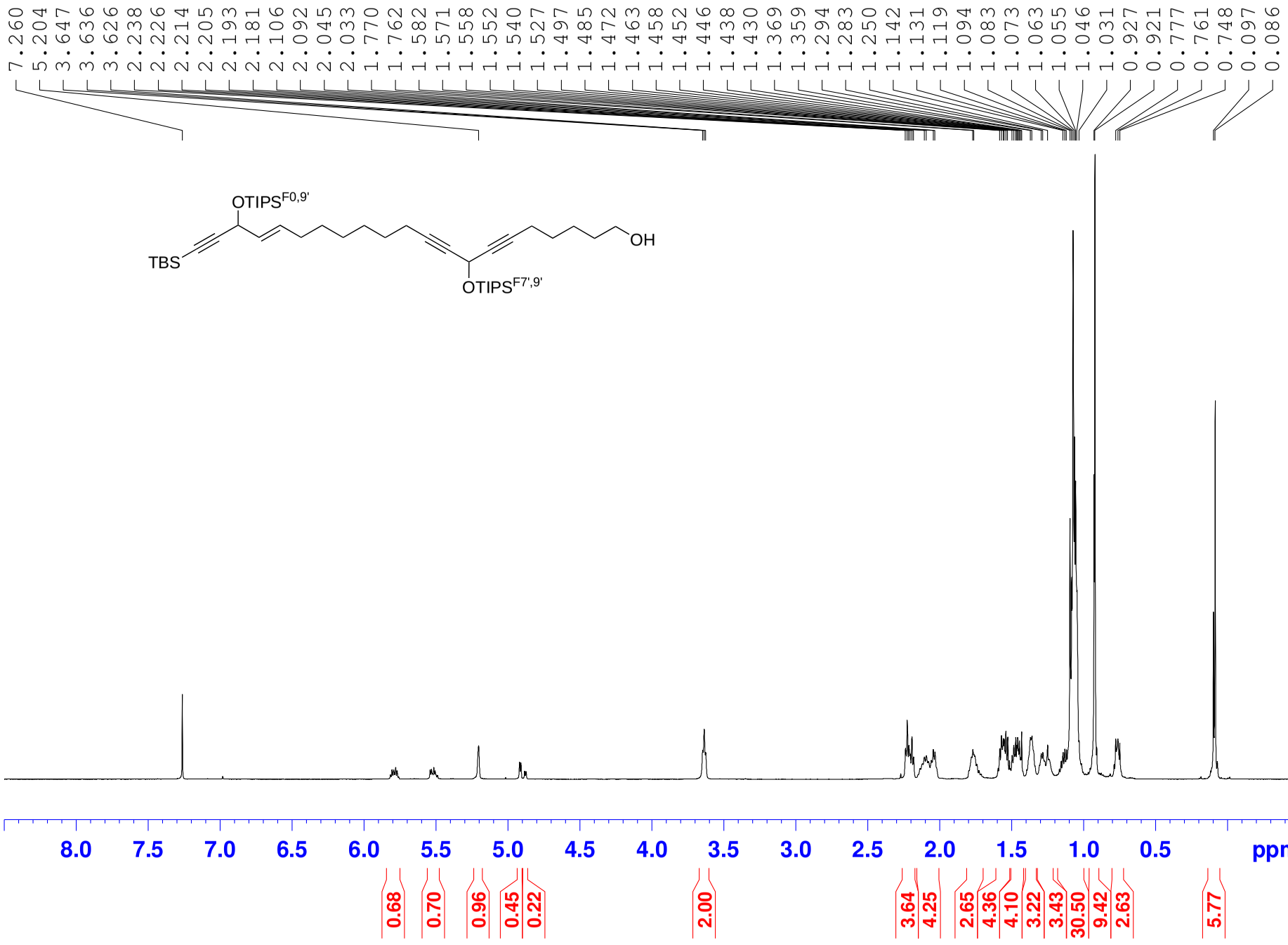
7.260 5.205 4.615 3.514 3.503 3.492 2.228 2.226 2.216 2.204 2.191 2.141 2.104 2.043 2.031 1.779 1.771 1.763 1.756 1.599 1.587 1.575 1.560 1.549 1.536 1.524 1.484 1.472 1.463 1.458 1.453 1.446 1.369 1.357 1.346 1.293 1.282 1.142 1.129 1.119 1.093 1.082 1.073 1.062 1.055 1.047 1.030 0.926 0.921 0.777 0.761 0.749 0.097 0.085

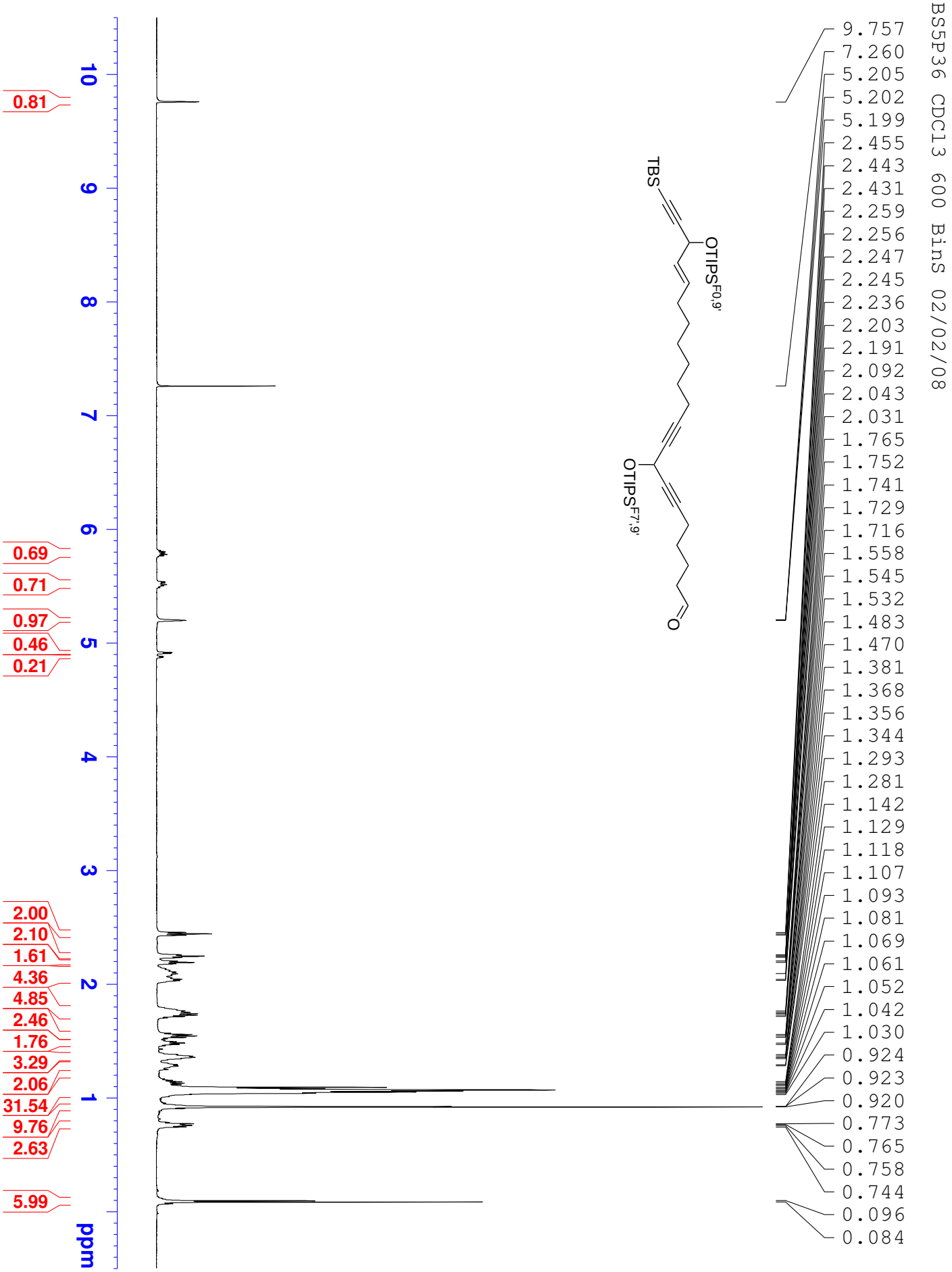


BS5P34 CDCl3 600 BinS 01/28/08



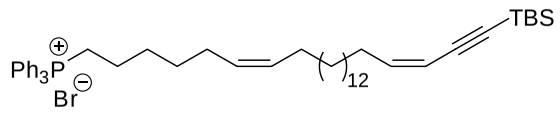
BS5P35 CDCl3 600 BinS 01/31/08

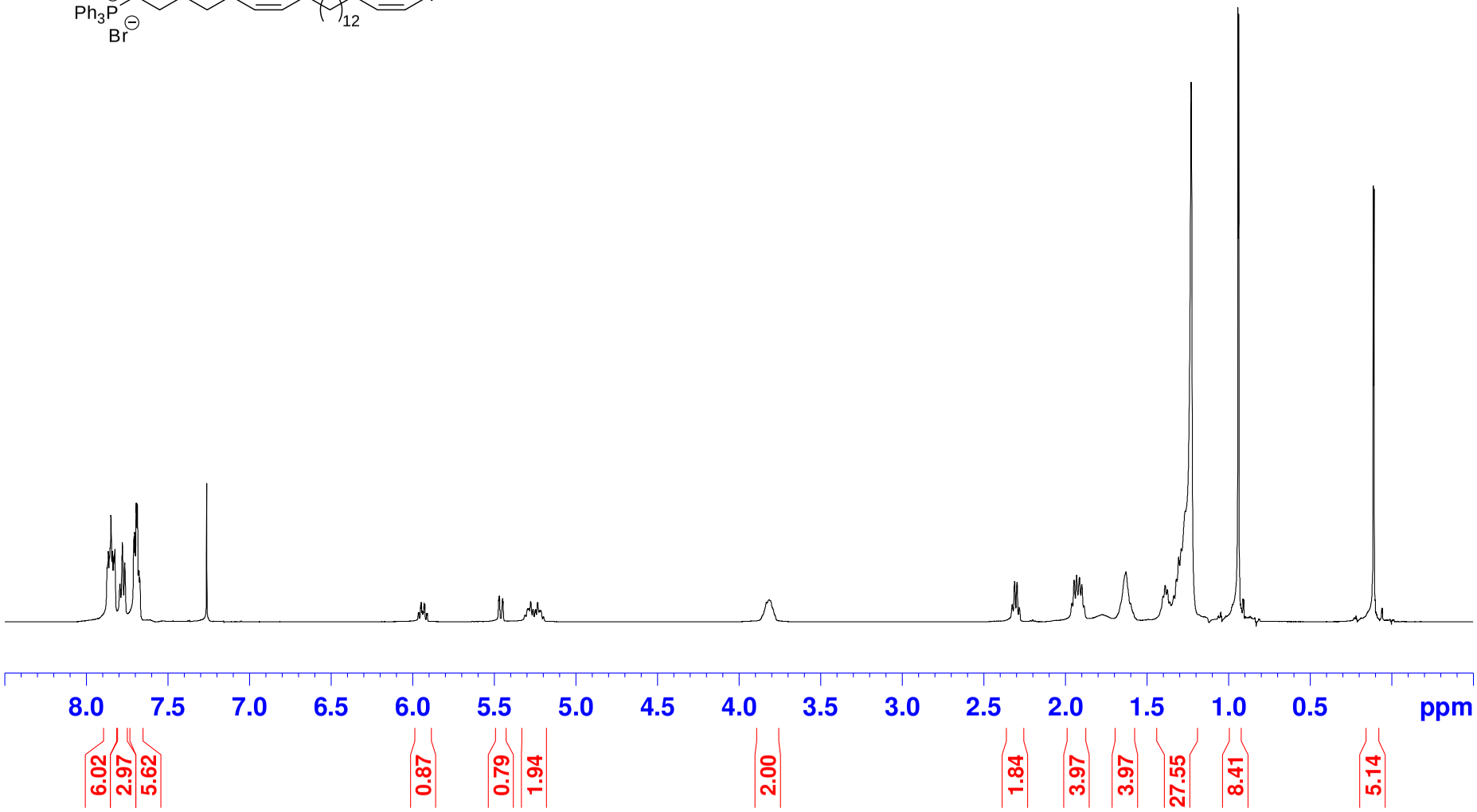



BS5P36 CDC13 600 BinS 02/02/08
9.757
7.260
5.205
5.202
5.199
2.455
2.443
2.431
2.259
2.256
2.247
2.245
2.236
2.203
2.191
2.092
2.043
2.031
1.765
1.752
1.741
1.729
1.716
1.558
1.545
1.532
1.483
1.470
1.381
1.368
1.356
1.344
1.293
1.281
1.142
1.129
1.118
1.107
1.093
1.081
1.069
1.061
1.052
1.042
1.030
0.924
0.923
0.920
0.773
0.765
0.758
0.744
0.096
0.084
TBS
OTIPS F0,9'
OTIPS F7,9'
O
0.81
0.69
0.71
0.97
0.46
0.21
2.00
2.10
1.61
4.36
4.85
2.46
1.76
3.29
2.06
31.54
9.76
2.63
5.99
10
9
8
7
6
5
4
3
2
1
ppm

BS4P42 CDCl3 500 BinS 05/01/07

7.871 7.868 7.864 7.857 7.854 7.848 7.845 7.839 7.832 7.829 7.823 7.820 7.777 7.763 7.706 7.702 7.700 7.693 7.690 7.686 7.678 7.675 7.261 5.473 5.471 5.468 5.452 5.449 5.277 3.816 3.808 2.312 2.297 1.947 1.932 1.914 1.899 1.629 1.402 1.389 1.376 1.335 1.320 1.306 1.291 1.266 1.230 0.942 0.941 0.938 0.912 0.907 0.113 0.108

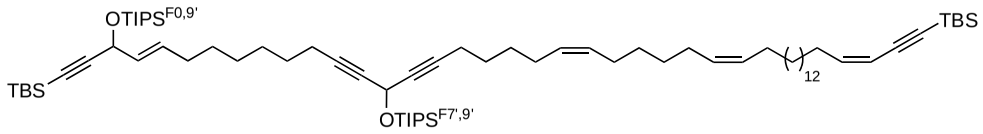




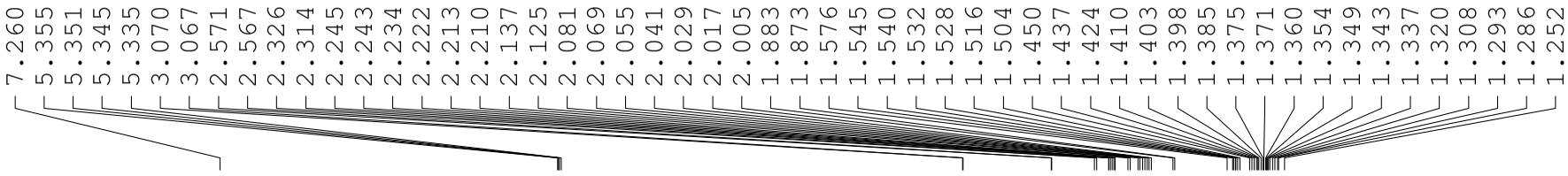
BS4P42 13CNMR CDCl3 500 BinS 05/01/07
145.55
134.93
134.91
133.65
133.57
130.46
130.36
130.28
128.98
118.66
117.97
109.11
102.71
96.59
77.26
77.00
76.75
30.29
29.97
29.85
29.67
29.61
29.58
29.53
29.35
29.27
29.19
29.14
28.67
27.16
26.65
26.03
22.90
22.54
22.50
16.53
-4.62
TBS
ppm

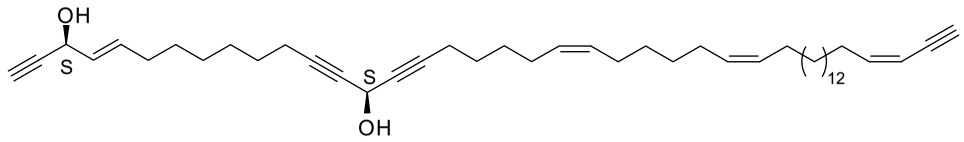
BS5P32 CDCl3 600 BinS 01/20/08

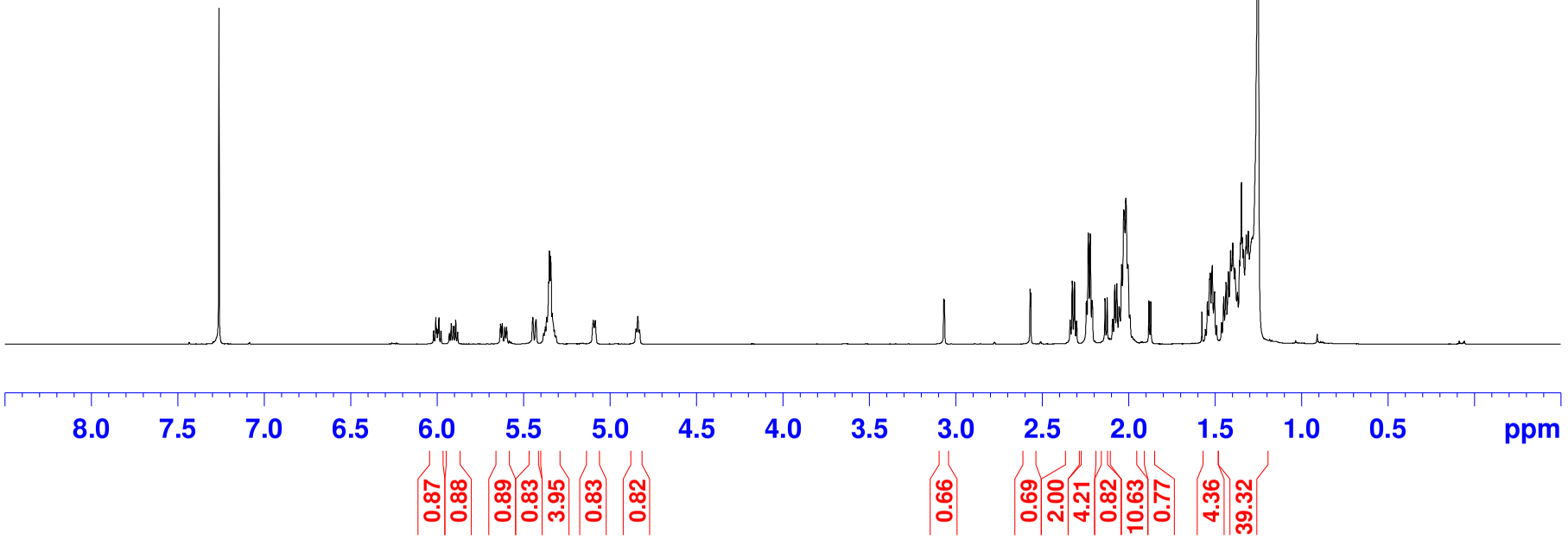
7.260 5.489 5.357 5.348 5.342 5.328 5.206 2.326 2.314 2.219 2.206 2.193 2.181 2.092 2.026 2.015 2.005 1.771 1.523 1.510 1.498 1.485 1.473 1.438 1.426 1.414 1.403 1.391 1.369 1.356 1.345 1.326 1.283 1.253 1.157 1.144 1.132 1.120 1.110 1.095 1.083 1.074 1.064 1.057 1.050 0.955 0.939 0.922 0.910 0.779 0.764 0.750 0.127 0.087



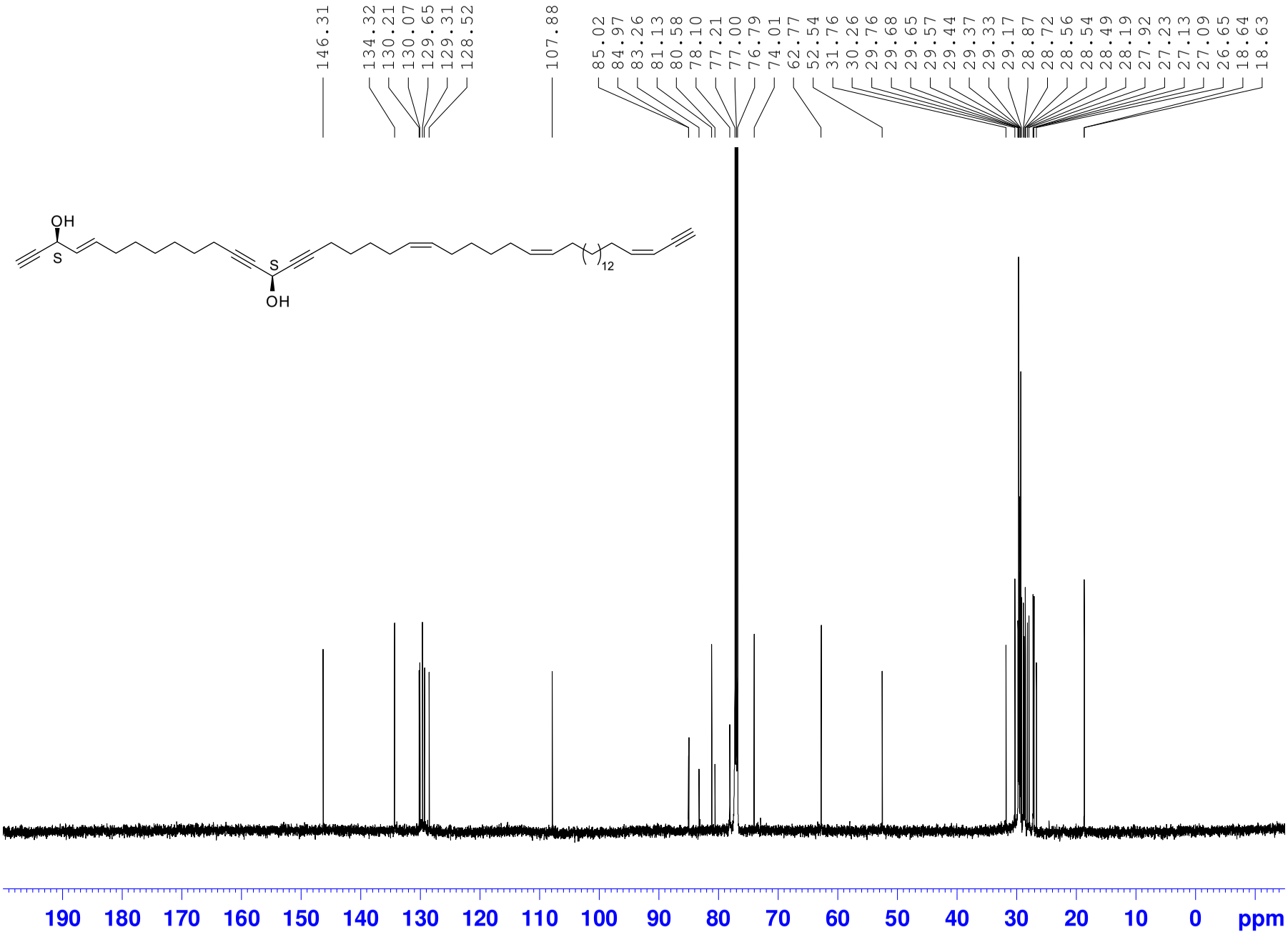
BS5P40 peak 1 Rf(0, 3) After deprotection CDCl3 600 BinS 02/16/08





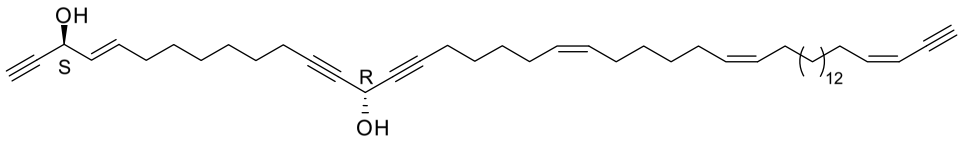


BS5P40 peak 1 Rf(0, 3) After deprotection 13CNMR CDCl3 600 BinS 02/16/08

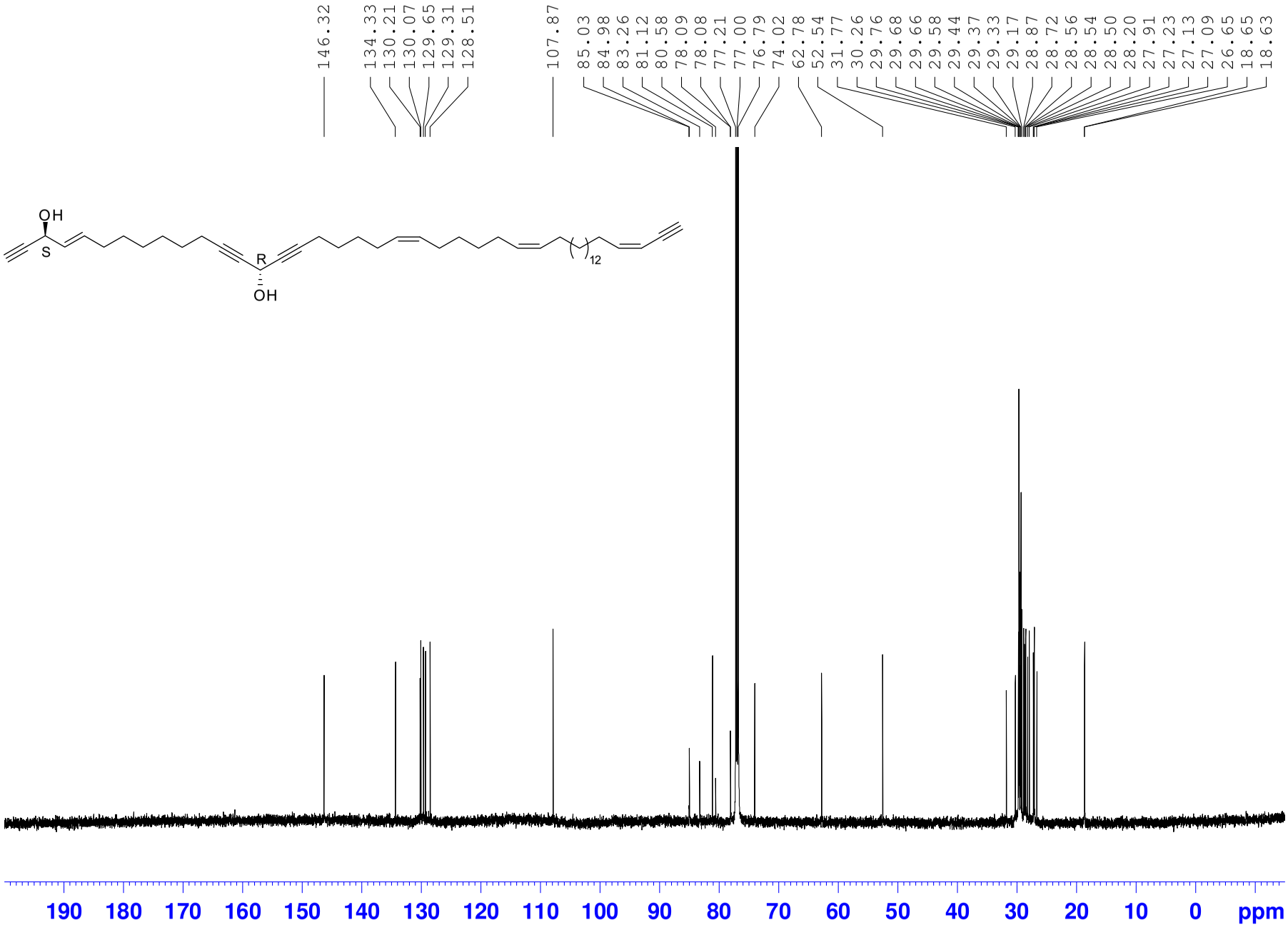


BS5P40 peak 2 Rf(0, 4) After deprotection CDCl3 600 BinS 02/19/08

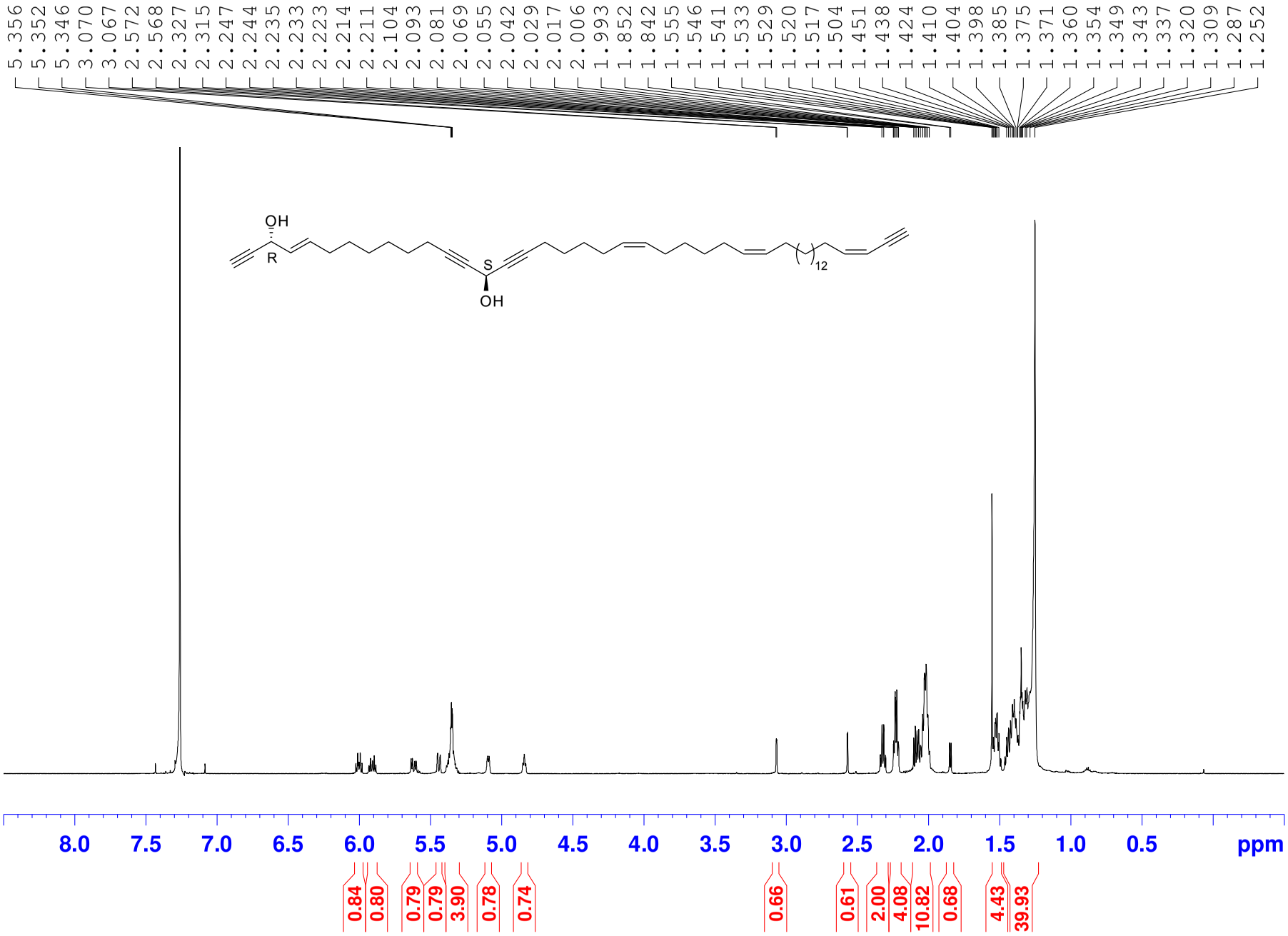
7.260 5.356 5.352 5.345 3.070 3.067 2.570 2.568 2.567 2.327 2.315 2.246 2.243 2.234 2.224 2.222 2.213 2.211 2.121 2.109 2.081 2.069 2.055 2.042 2.029 2.018 2.006 1.872 1.862 1.571 1.546 1.532 1.529 1.517 1.504 1.451 1.438 1.424 1.410 1.405 1.398 1.386 1.375 1.371 1.360 1.354 1.349 1.344 1.338 1.320 1.309 1.293 1.289 1.253



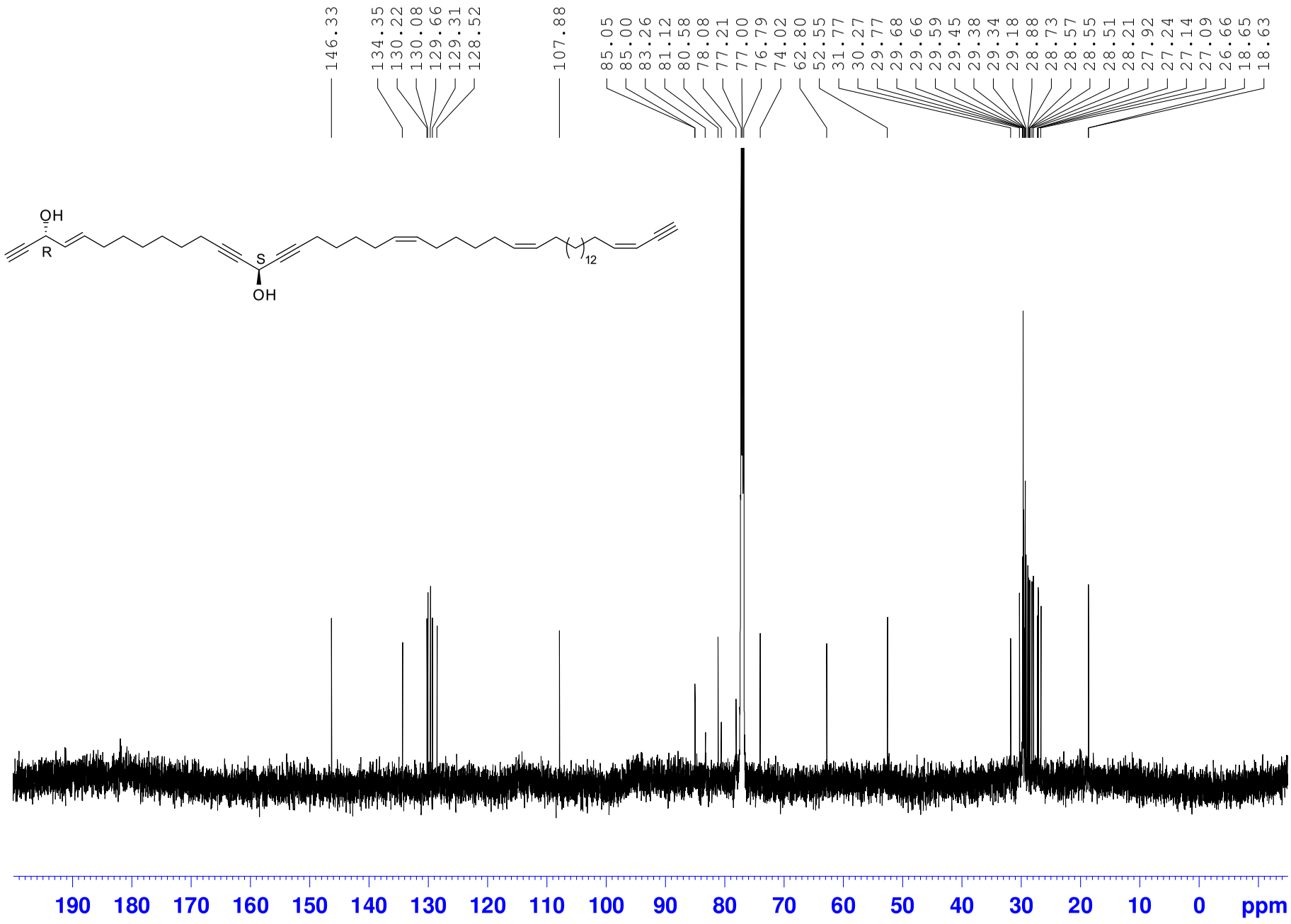
BS5P40 peak 2 Rf(0, 4) After deprotection 13CNMR CDCl3 600 BinS 02/19/08



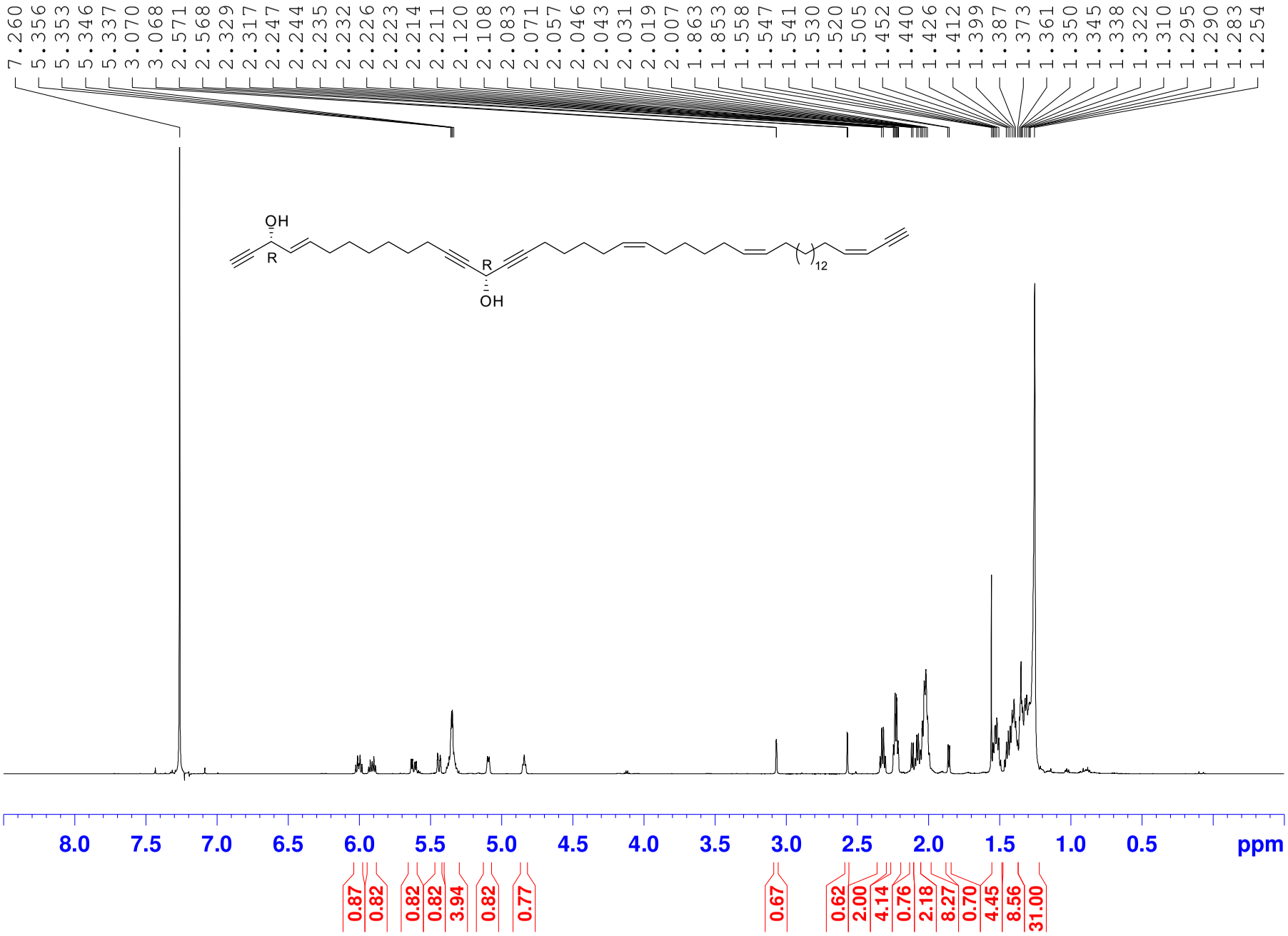
BS5P40 peak 3 Rf(4, 3) After deprotection CDCl3 600 BinS 02/17/08



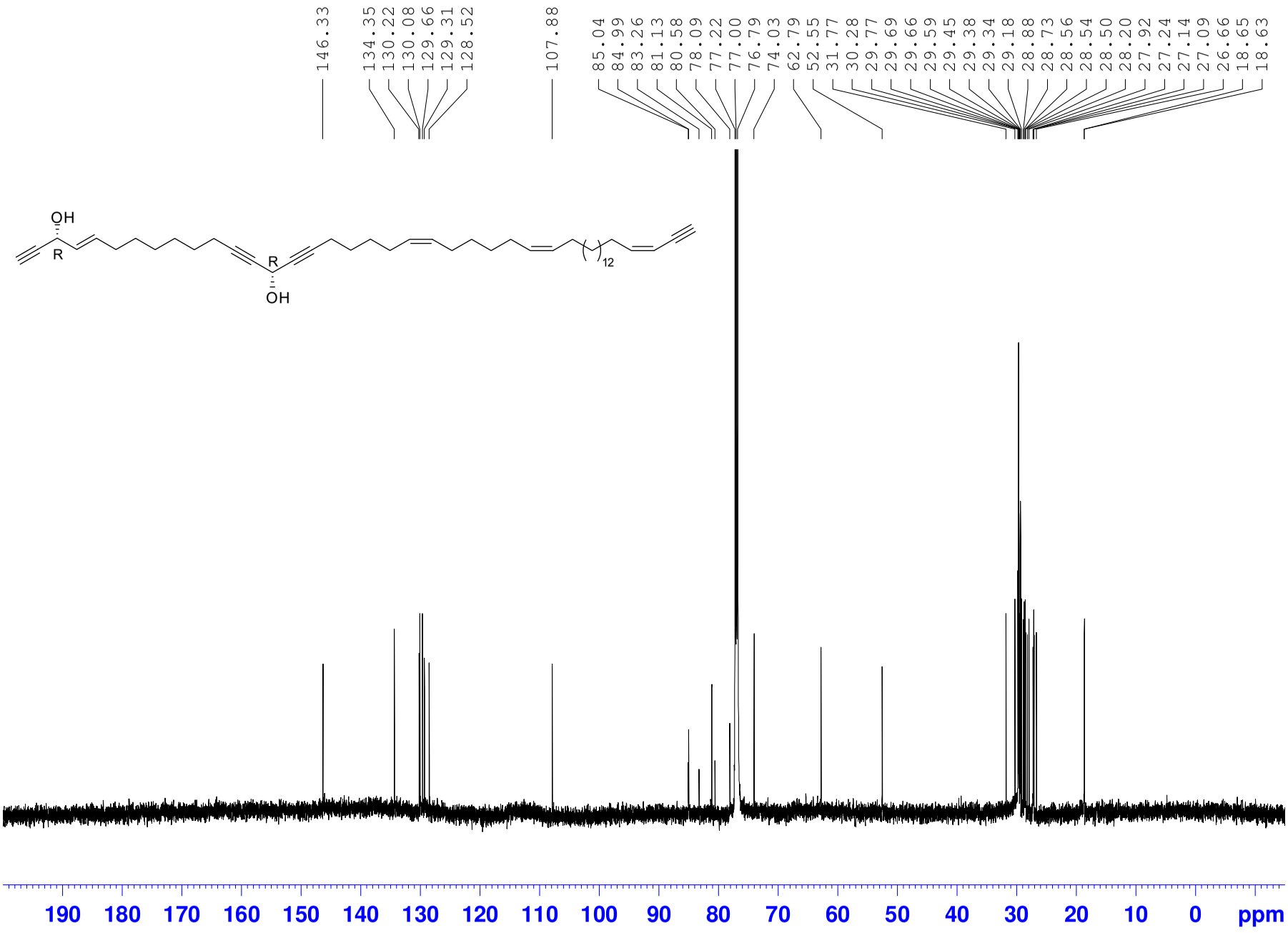
BS5P40 peak 3 Rf(4, 3) After deprotection 13CNMR CDCl3 600 BinS 02/17/08



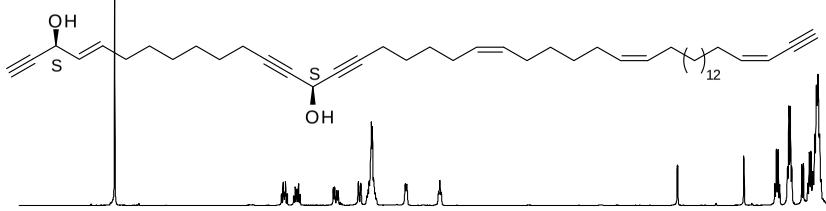
BS5P40 peak 4 Rf(4, 4) After deprotection 13CNMR CDCl3 600 BinS 02/18/08

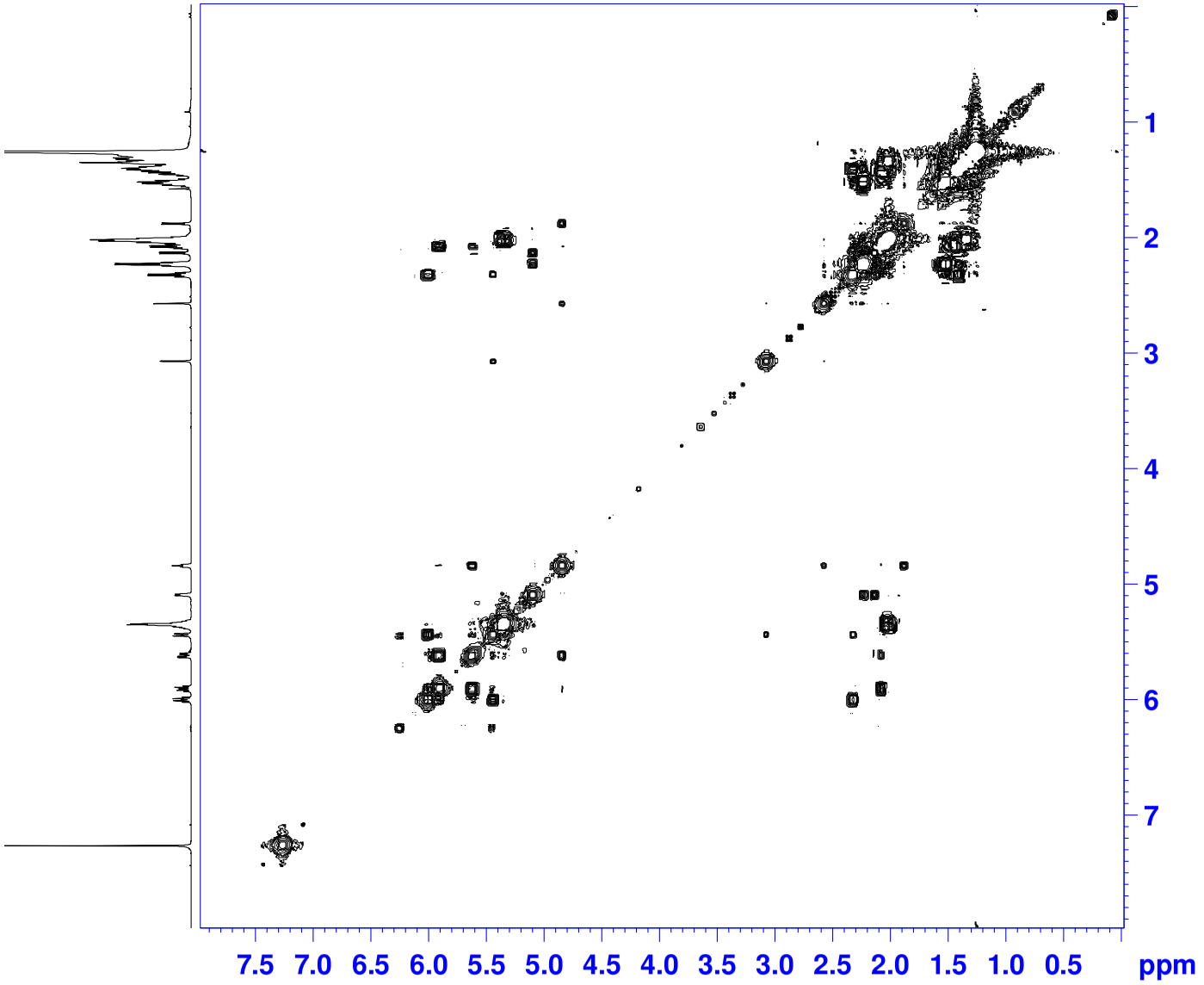


BS5P40 peak 4 Rf(4, 4) After deprotection 13CNMR CDCl3 600 BinS 02/18/08



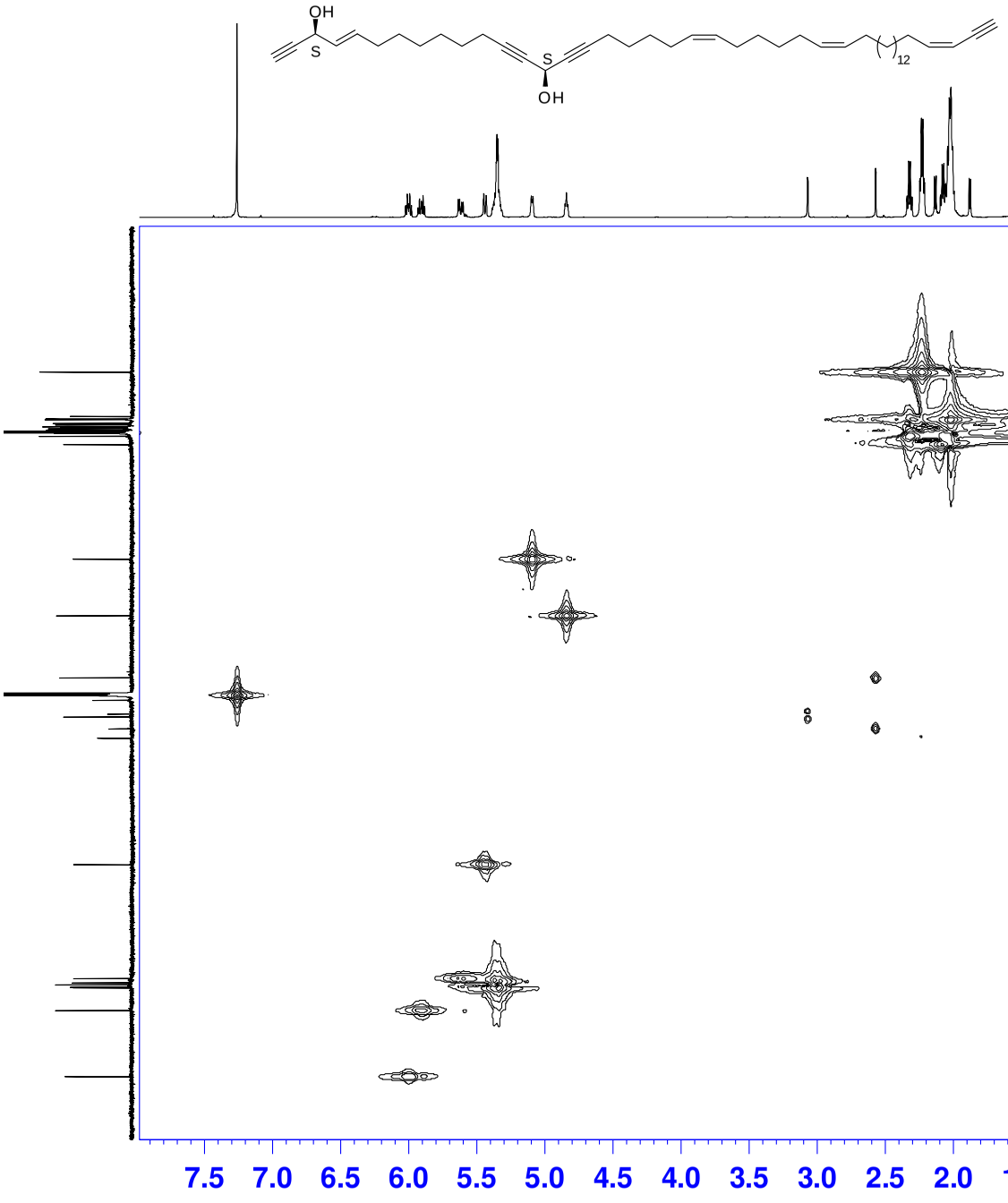
BS5P40 peak 1 Rf(0, 3) After deprotection COSY CDCl3 600 BinS 02/16/08





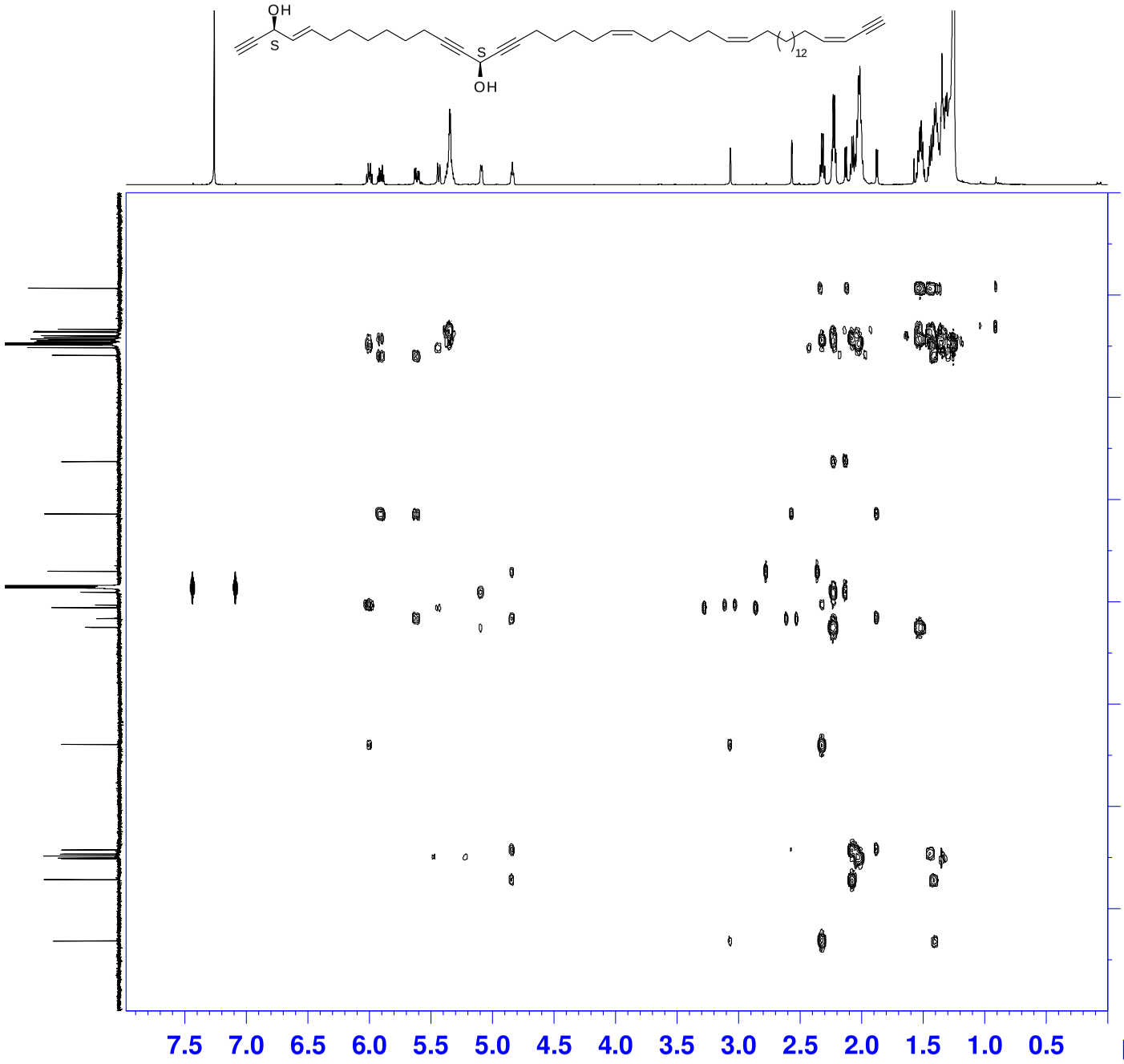

```
Current Data Parameters
NAME                  BS5P40
EXPNO                      8
PROCNO                     1

F2 - Acquisition Parameters
Date_              20080216
Time                  18.32
INSTRUM                spect
PROBHD    5 mm TBI 1H-BB
PULPROG          cosygpqf
TD                     2048
SOLVENT               CDCl3
NS                       32
DS                       16
SWH               4807.692 Hz
FIDRES            2.347506 Hz
AQ                0.2130420 sec
RG                    143.7
DW                  104.000 usec
DE                    6.00 usec
TE                   294.1 K
d0                0.00000300 sec
D1                1.48689198 sec
d13               0.00000400 sec
D16               0.00020000 sec
IN0               0.00020800 sec

======== CHANNEL f1 ========
NUC1                     1H
P0                    8.24 usec
P1                    8.24 usec
PL1                   8.00 dB
SFO1          600.8724034 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SMSQ10.100
GPNAM2          SMSQ10.100
GPX1                  0.00 %
GPX2                  0.00 %
GPY1                  0.00 %
GPY2                  0.00 %
GPZ1                 10.00 %
GPZ2                 10.00 %
P16                1000.00 usec

F1 - Acquisition parameters
ND0                       1
TD                       72
SFO1             600.8724 MHz
FIDRES          66.773506 Hz
SW                    8.001 ppm
FnMODE                   QF

F2 - Processing parameters
SI                     1024
SF            600.8700137 MHz
WDW                    SINE
SSB                       0
LB                    0.00 Hz
GB                        0
PC                    1.40

F1 - Processing parameters
SI                     1024
MC2                      QF
SF            600.8700137 MHz
WDW                    SINE
SSB                       0
LB                    0.00 Hz
GB                        0
```

BS5P40 peak 1 Rf(0, 3) After deprotection HMQC CDCl3 600 BinS 02/17/08



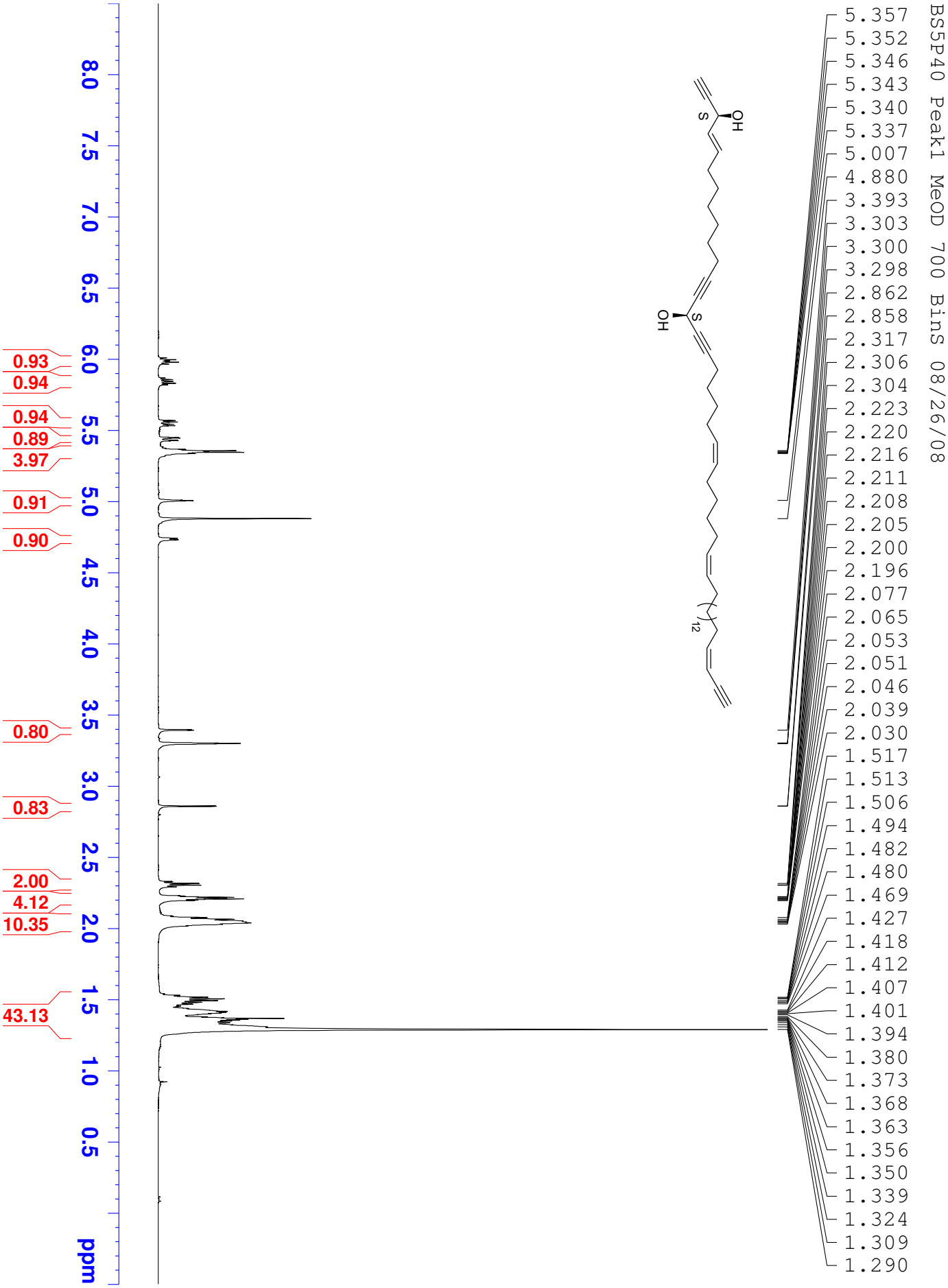

```
Current Data Parameters
NAME                 BS5P40
EXPNO                    10
PROCNO                    1

F2 - Acquisition Parameters
Date_              20080217
Time                  14.42
INSTRUM               spect
PROBHD    5 mm TBI 1H-BB
PULPROG           hmqcgpqf
TD                    1024
SOLVENT               CDCl3
NS                      96
DS                      16
SWH                4807.692 Hz
FIDRES             4.695012 Hz
AQ                 0.1065460 sec
RG                    16384
DW                  104.000 usec
DE                    6.00 usec
TE                   293.6 K
CNST2           145.0000000
d0                 0.00000300 sec
D1                 2.00000000 sec
d2                 0.00344828 sec
d12                0.00002000 sec
d13                0.00000400 sec
D16                0.00020000 sec
DELTA1             0.00222428 sec
IN0                0.00002000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                      8.24 usec
p2                     16.48 usec
PL1                     8.00 dB
SFO1            600.8724034 MHz

======== CHANNEL f2 ========
CPDPRG2                 garp
NUC2                     13C
P3                     13.00 usec
PCPD2                 100.00 usec
PL2                    -1.00 dB
PL12                   16.72 dB
SFO2            151.1002126 MHz

====== GRADIENT CHANNEL =====
GPNAM1              SINE.100
GPNAM2              SINE.100
GPNAM3              SINE.100
GPX1                    0.00 %
GPX2                    0.00 %
GPX3                    0.00 %
GPY1                    0.00 %
GPY2                    0.00 %
GPY3                    0.00 %
GPZ1                   50.00 %
GPZ2                   30.00 %
GPZ3                   40.10 %
P16                  1000.00 usec

F1 - Acquisition parameters
ND0                       2
TD                      128
SFO1             151.1002 MHz
FIDRES          195.312500 Hz
SW                 165.453 ppm
FnMODE                  QF

F2 - Processing parameters
SI                      1024
SF              600.8700137 MHz
WDW                  QSINE
SSB                       2
LB                     0.00 Hz
GB                        0
PC                     1.40

F1 - Processing parameters
SI                      1024
MC2                     QF
SF              151.0888820 MHz
WDW                  QSINE
SSB                       2
LB                     0.00 Hz
GB                        0
```

BS5P40 peak 1 Rf(0, 3) After deprotection HMBC CDCl3 600 BinS 02/16/08

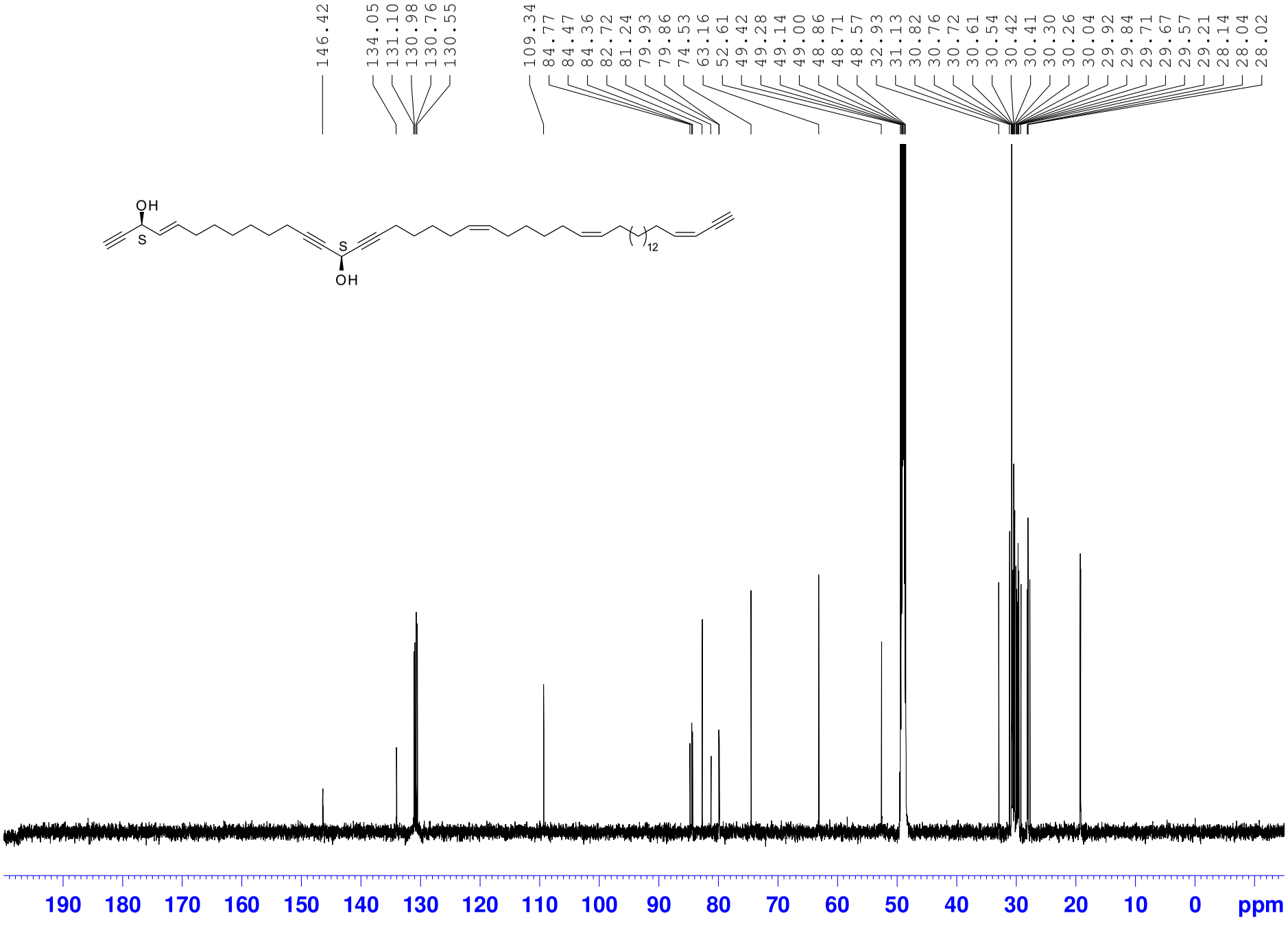


BRUKER

```
Current Data Parameters
NAME                  BS5P40
EXPNO                      9
PROCNO                     1

F2 - Acquisition Parameters
Date_              20080216
Time                  19.52
INSTRUM                spect
PROBHD    5 mm TBI 1H-BB
PULPROG     hmbcgplpndqf
TD                     4096
SOLVENT               CDCl3
NS                      240
DS                       16
SWH                4807.692 Hz
FIDRES             1.173753 Hz
AQ                 0.4260340 sec
RG                     16384
DW                   104.000 usec
DE                     6.00 usec
TE                    294.0 K
CNST2            145.0000000
CNST13            10.0000000
d0                 0.00000300 sec
D1                 2.00000000 sec
d2                 0.00344828 sec
d6                 0.05000000 sec
D16                0.00020000 sec
IN0                0.00001490 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                      8.24 usec
p2                     16.48 usec
PL1                     8.00 dB
SFO1             600.8724034 MHz

======== CHANNEL f2 ========
NUC2                     13C
P3                     13.00 usec
PL2                    -1.00 dB
SFO2             151.1039665 MHz

====== GRADIENT CHANNEL =====
GPNAM1               SINE.100
GPNAM2               SINE.100
GPNAM3               SINE.100
GPX1                    0.00 %
GPX2                    0.00 %
GPX3                    0.00 %
GPY1                    0.00 %
GPY2                    0.00 %
GPY3                    0.00 %
GPZ1                   50.00 %
GPZ2                   30.00 %
GPZ3                   40.10 %
P16                  1000.00 usec

F1 - Acquisition parameters
ND0                        2
TD                       113
SFO1                151.104 MHz
FIDRES           296.965027 Hz
SW                   222.079 ppm
FnMODE                    QF

F2 - Processing parameters
SI                      2048
SF               600.8700137 MHz
WDW                     SINE
SSB                        0
LB                      0.00 Hz
GB                         0
PC                      1.40

F1 - Processing parameters
SI                      1024
MC2                       QF
SF               151.0888820 MHz
WDW                     SINE
SSB                        0
LB                      0.00 Hz
GB                         0
```

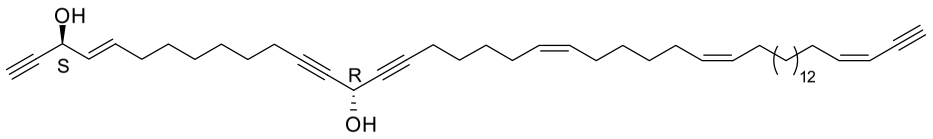

BS5P40 Peak1 MeOD 700 BinS 08/26/08
5.357
5.352
5.346
5.343
5.340
5.337
5.007
4.880
3.393
3.303
3.300
3.298
2.862
2.858
2.317
2.306
2.304
2.223
2.220
2.216
2.211
2.208
2.205
2.200
2.196
2.077
2.065
2.053
2.051
2.046
2.039
2.030
1.517
1.513
1.506
1.494
1.482
1.480
1.469
1.427
1.418
1.412
1.407
1.401
1.394
1.380
1.373
1.368
1.363
1.356
1.350
1.339
1.324
1.309
1.290
OH
S
S
OH
12
0.93
0.94
0.94
0.89
3.97
0.91
0.90
0.80
0.83
2.00
4.12
10.35
43.13
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

BS5P40 Peak1 13CNMR MeOD 600 BinS 01/26/09



BS5P40 peak 2 Rf(0, 4) After deprotection MeOD 600 BinS 01/24/09

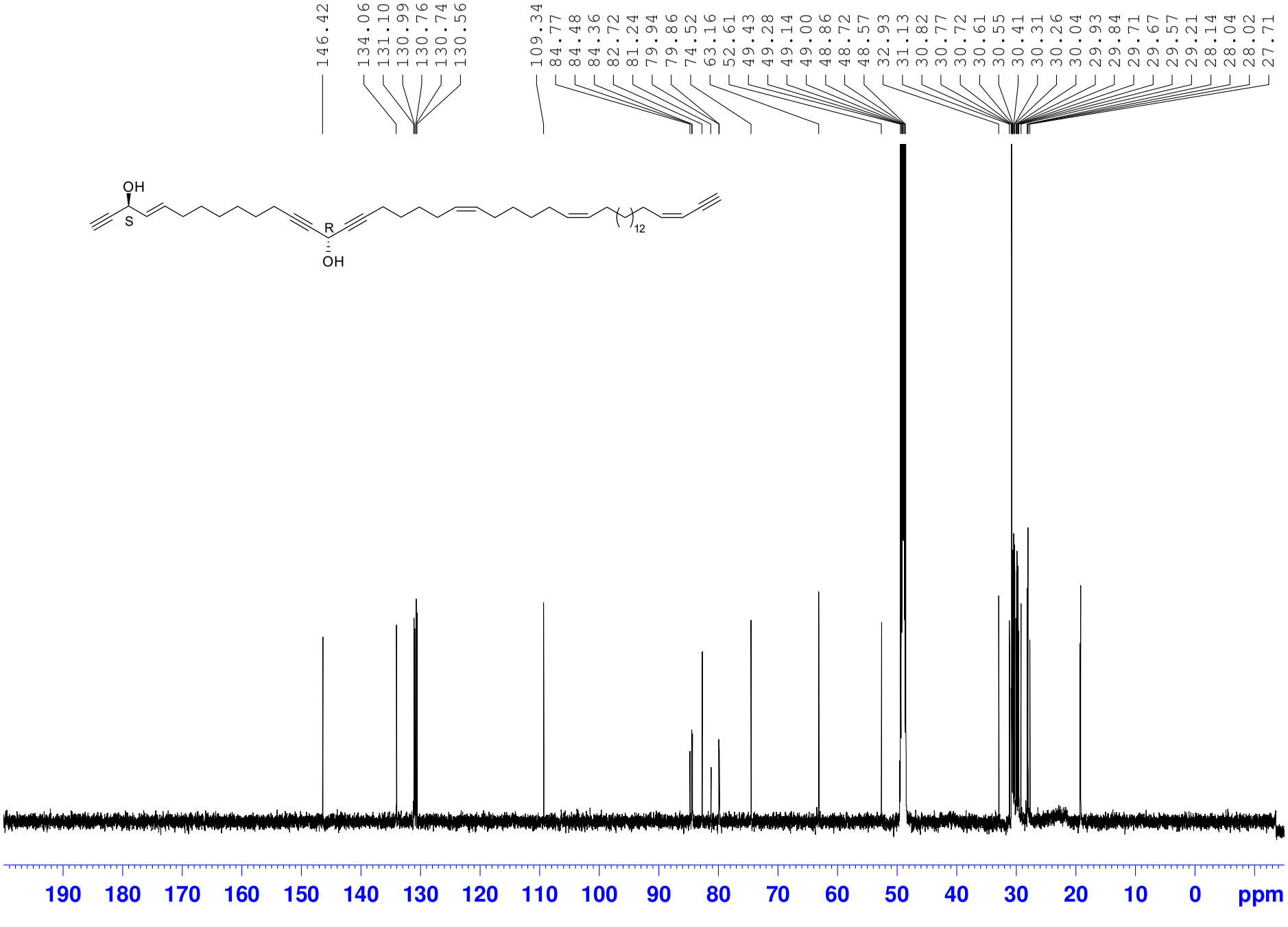
5.376 5.373 5.367 5.361 5.356 5.350 5.346 5.016 5.013 4.894 3.408 3.405 3.313 3.310 3.308 2.874 2.870 2.326 2.314 2.237 2.229 2.226 2.221 2.218 2.210 2.207 2.087 2.075 2.055 2.049 2.039 2.027 1.527 1.522 1.515 1.503 1.491 1.484 1.479 1.464 1.460 1.448 1.428 1.422 1.417 1.411 1.389 1.377 1.372 1.366 1.360 1.348 1.334 1.318 1.299

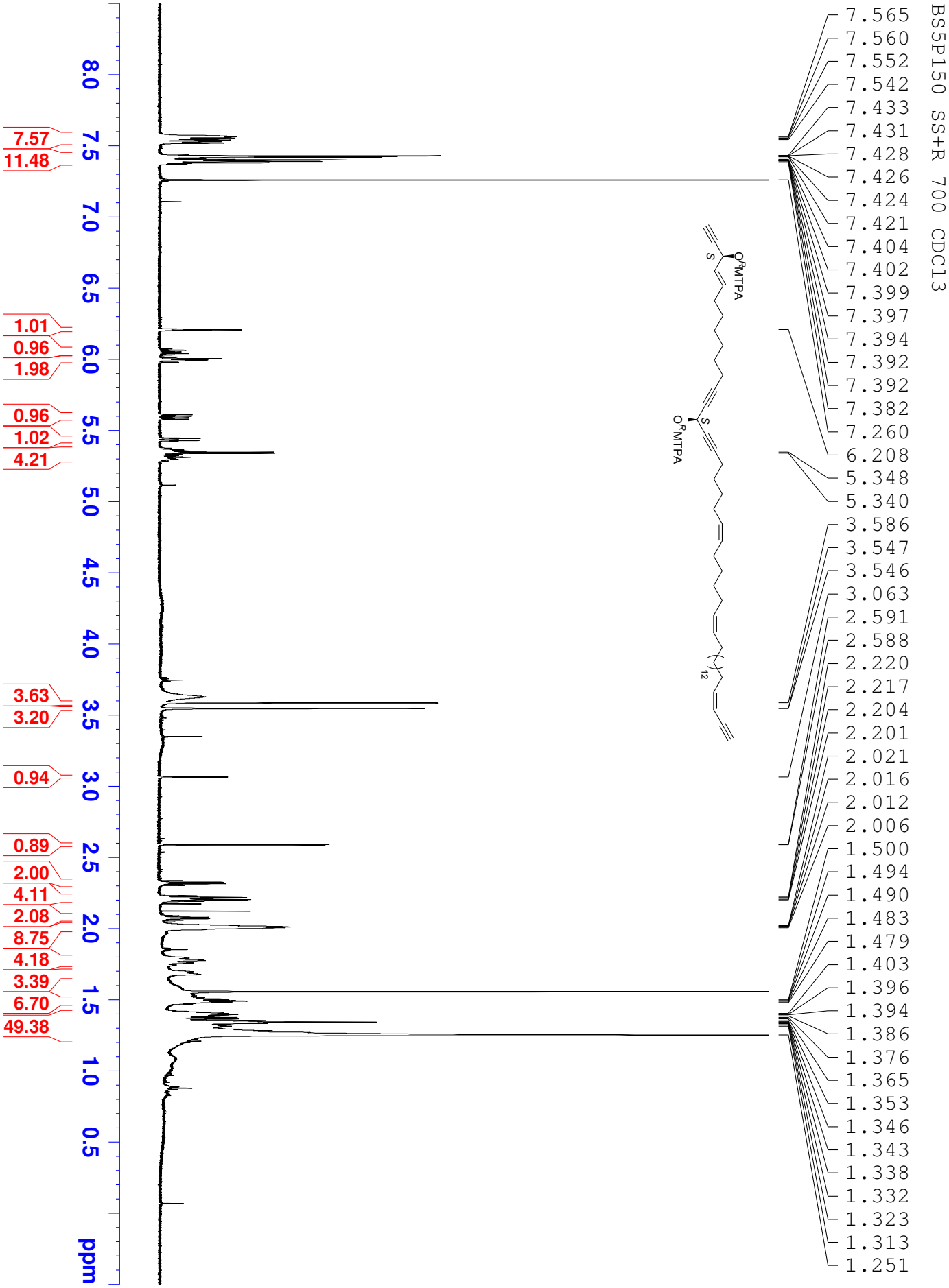


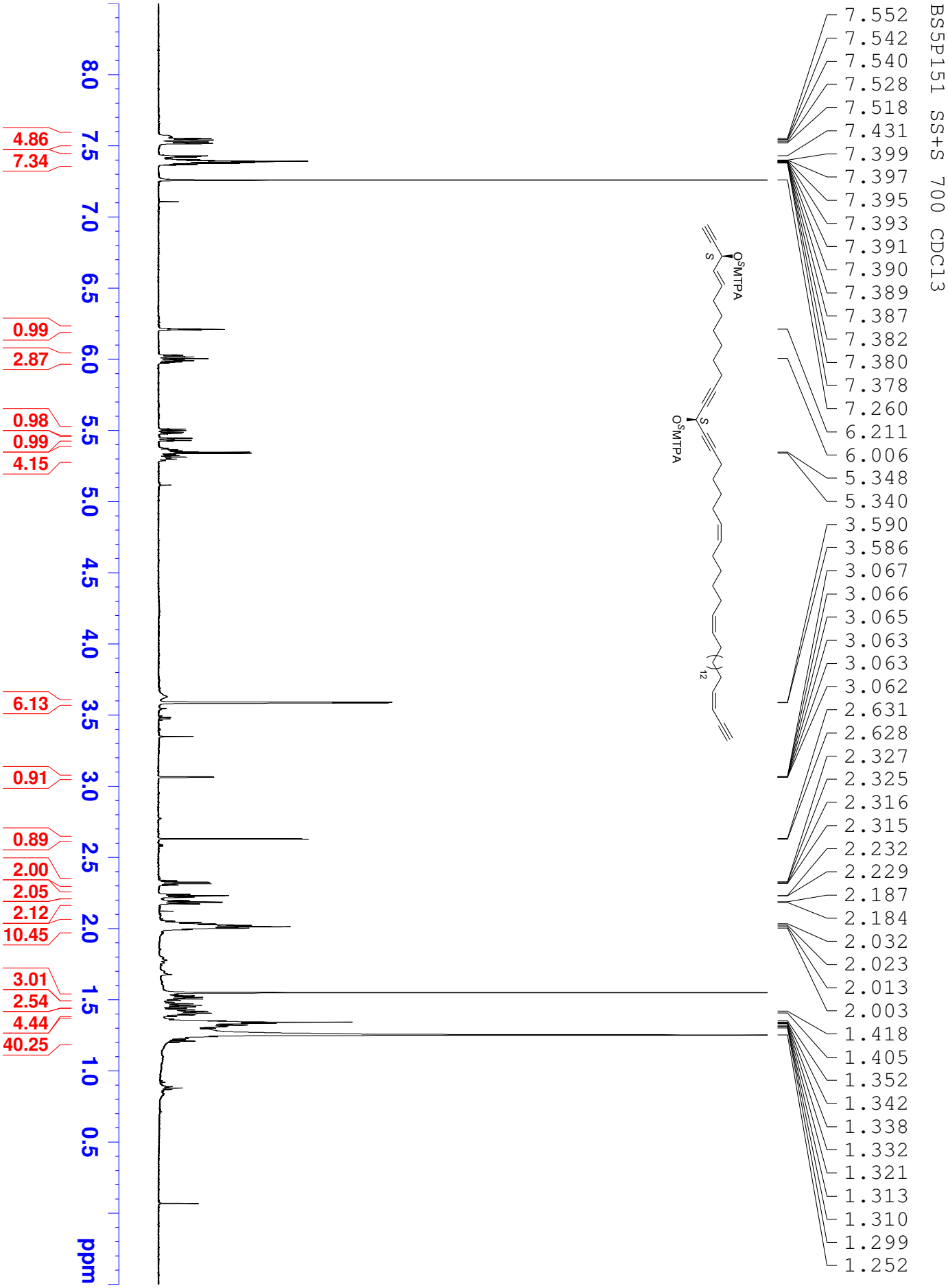
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm

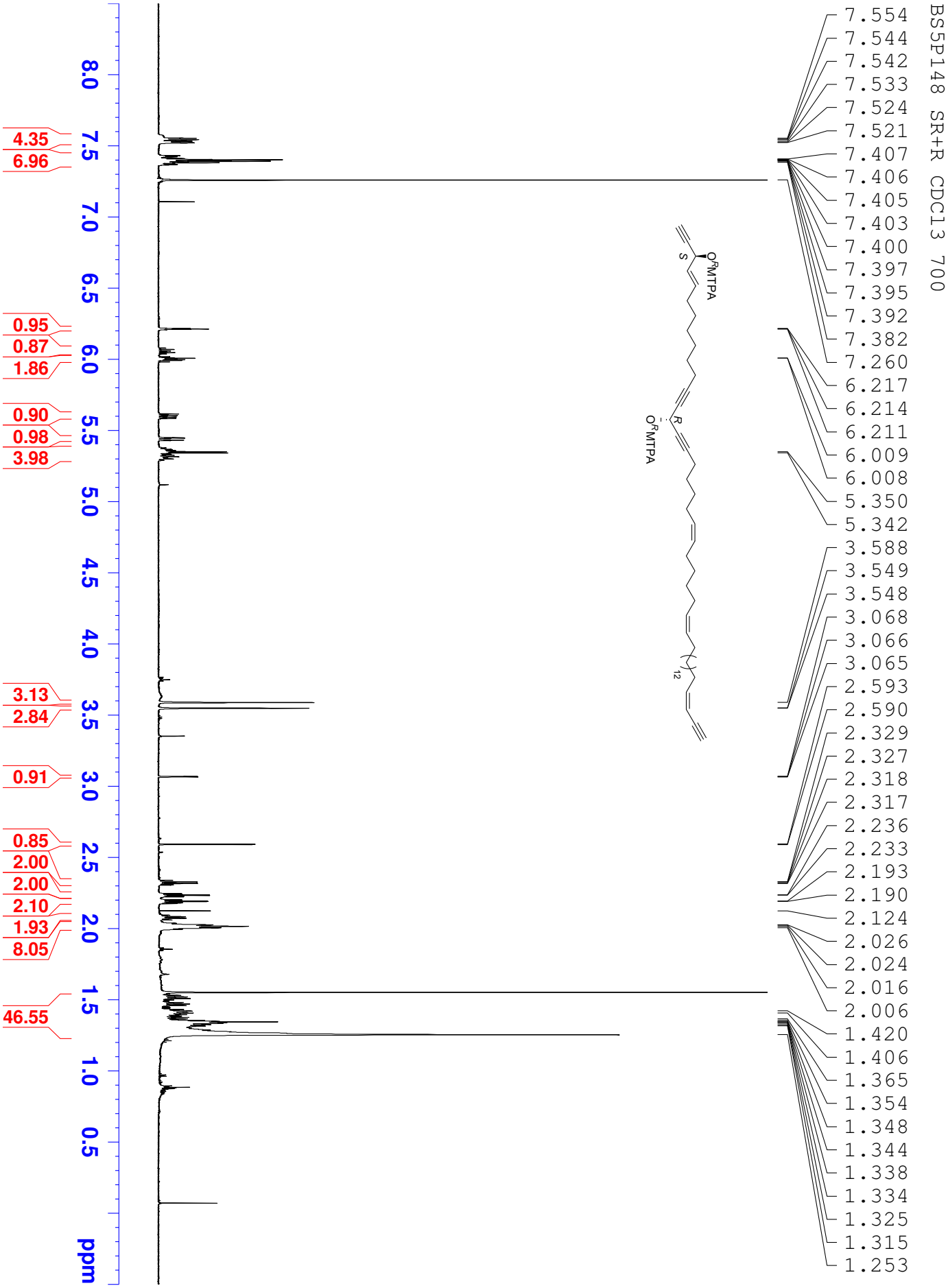
0.87 0.87 0.85 0.83 3.92 0.82 0.83 0.74 0.69 2.00 4.08 10.55 43.86

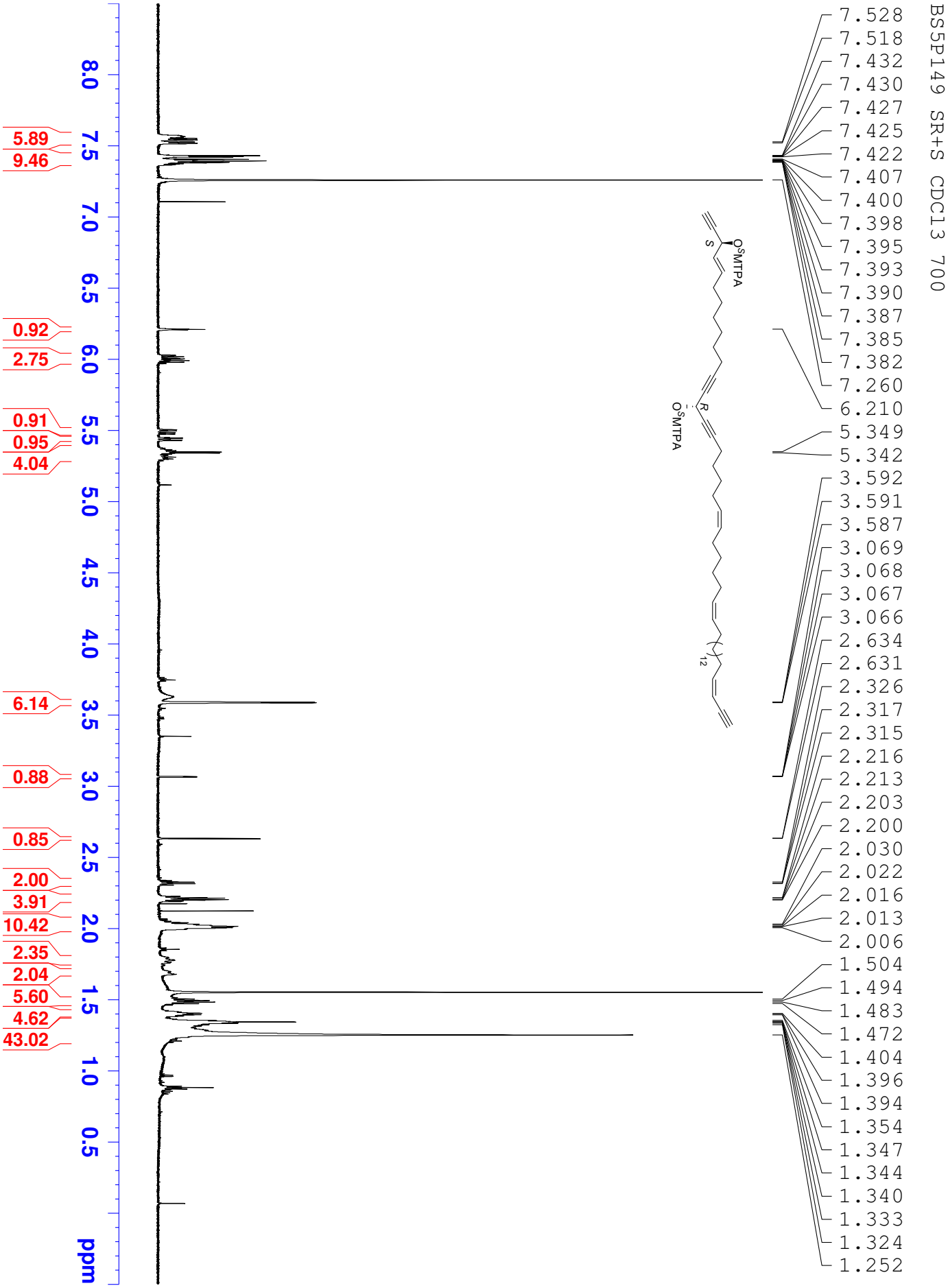
BS5P40 peak 2 Rf(0, 4) After deprotection 13CNMR MeOD 600 BinS 01/24/09

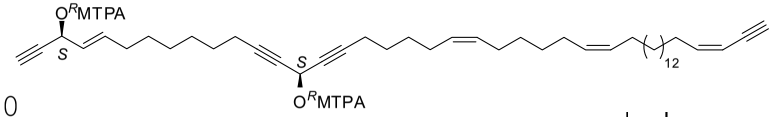



BS5P150 SS+R 700 CDC13
7.565
7.560
7.552
7.542
7.433
7.431
7.428
7.426
7.424
7.421
7.404
7.402
7.399
7.397
7.394
7.392
7.392
7.382
7.260
6.208
5.348
5.340
3.586
3.547
3.546
3.063
2.591
2.588
2.220
2.217
2.204
2.201
2.021
2.016
2.012
2.006
1.500
1.494
1.490
1.483
1.479
1.403
1.396
1.394
1.386
1.376
1.365
1.353
1.346
1.343
1.338
1.332
1.323
1.313
1.251
7.57
11.48
1.01
0.96
1.98
0.96
1.02
4.21
3.63
3.20
0.94
0.89
2.00
4.11
2.08
8.75
4.18
3.39
6.70
49.38
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
S
OR MTPA
S
OR MTPA
12

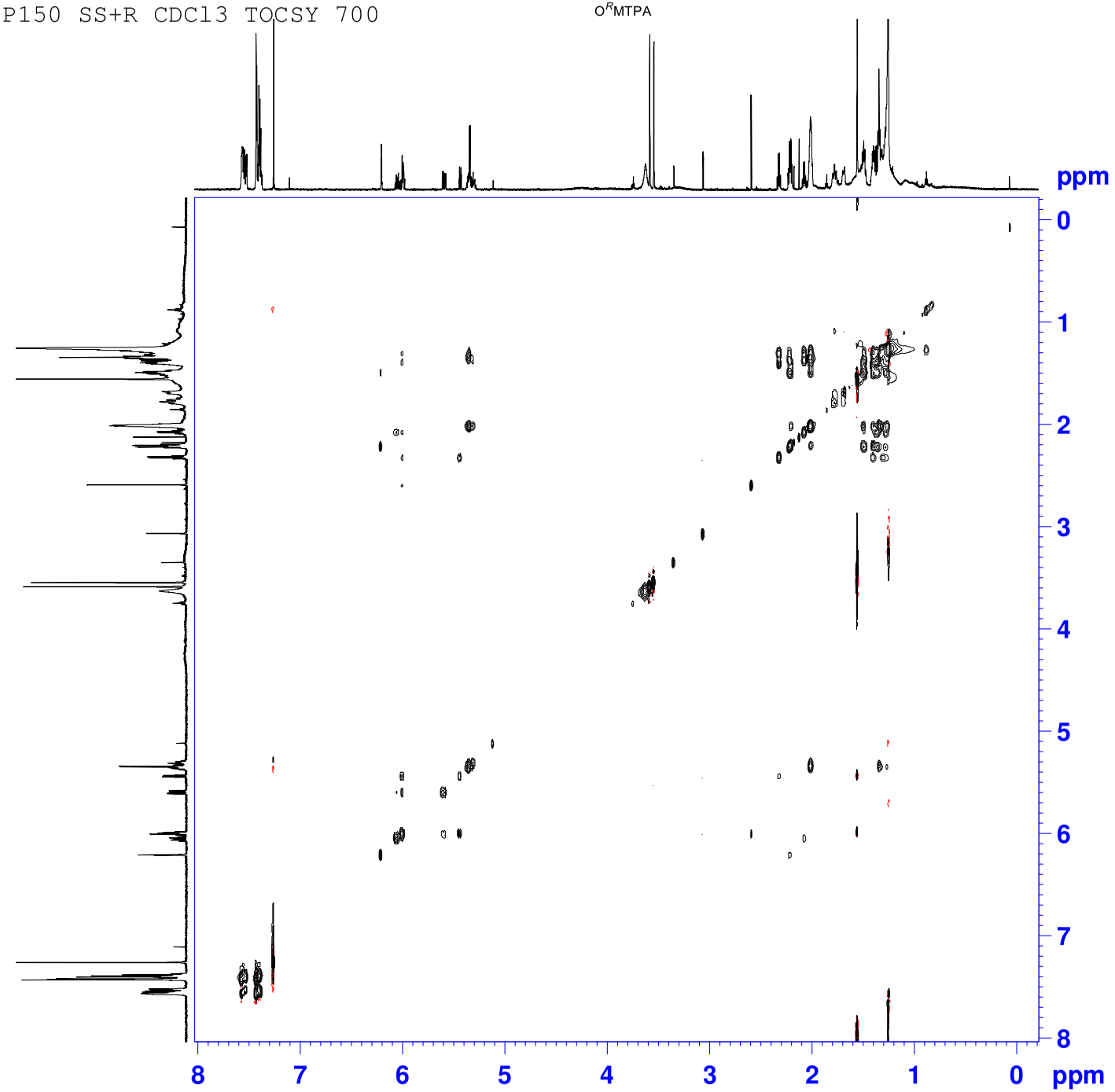

BS5P151 SS+S 700 CDC13
7.552
7.542
7.540
7.528
7.518
7.431
7.399
7.397
7.395
7.393
7.391
7.390
7.389
7.387
7.382
7.380
7.378
7.260
6.211
6.006
5.348
5.340
3.590
3.586
3.067
3.066
3.065
3.063
3.063
3.062
2.631
2.628
2.327
2.325
2.316
2.315
2.232
2.229
2.187
2.184
2.032
2.023
2.013
2.003
1.418
1.405
1.352
1.342
1.338
1.332
1.321
1.313
1.310
1.299
1.252
4.86
7.34
0.99
2.87
0.98
0.99
4.15
6.13
0.91
0.89
2.00
2.05
2.12
10.45
3.01
2.54
4.44
40.25
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
OSMTPA
OSMTPA
12


BS5P148 SR+R CDC13 700
7.554
7.544
7.542
7.533
7.524
7.521
7.407
7.406
7.405
7.403
7.400
7.397
7.395
7.392
7.382
7.260
6.217
6.214
6.211
6.009
6.008
5.350
5.342
3.588
3.549
3.548
3.068
3.066
3.065
2.593
2.590
2.329
2.327
2.318
2.317
2.236
2.233
2.193
2.190
2.124
2.026
2.024
2.016
2.006
1.420
1.406
1.365
1.354
1.348
1.344
1.338
1.334
1.325
1.315
1.253
4.35
6.96
0.95
0.87
1.86
0.90
0.98
3.98
3.13
2.84
0.91
0.85
2.00
2.00
2.10
1.93
8.05
46.55
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
S
OMTPA
R
OMTPA
12

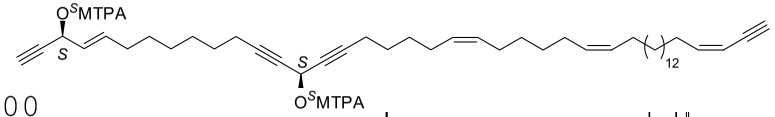

BS5P149 SR+S CDC13 700
7.528
7.518
7.432
7.430
7.427
7.425
7.422
7.407
7.400
7.398
7.395
7.393
7.390
7.387
7.385
7.382
7.260
6.210
5.349
5.342
3.592
3.591
3.587
3.069
3.068
3.067
3.066
2.634
2.631
2.326
2.317
2.315
2.216
2.213
2.203
2.200
2.030
2.022
2.016
2.013
2.006
1.504
1.494
1.483
1.472
1.404
1.396
1.394
1.354
1.347
1.344
1.340
1.333
1.324
1.252
OSMTPA
OSMTPA
S
R
12
5.89
9.46
0.92
2.75
0.91
0.95
4.04
6.14
0.88
0.85
2.00
3.91
10.42
2.35
2.04
5.60
4.62
43.02
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm



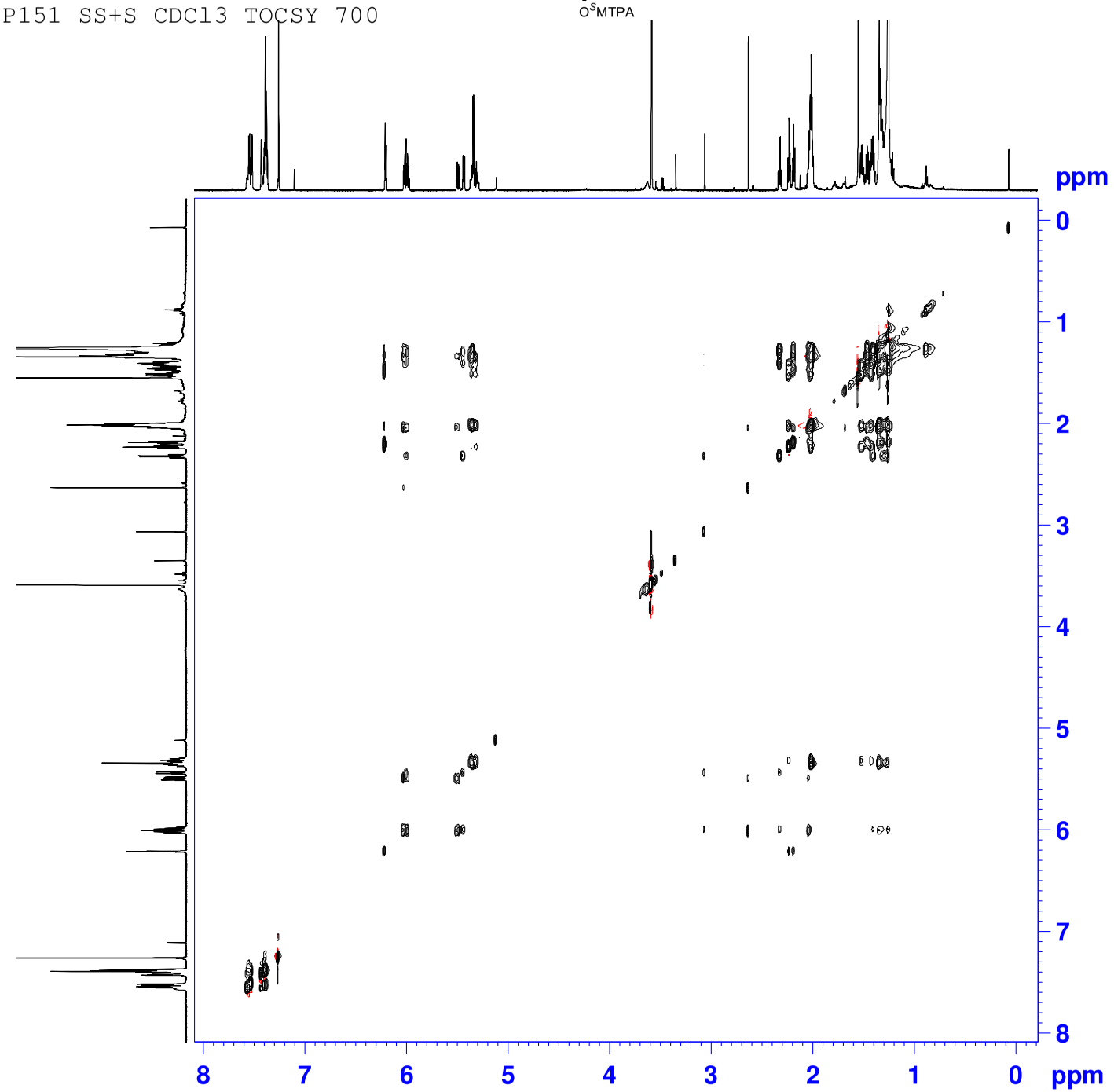
BS5P150 SS+R CDCl3 TOCSY 700




```
Current Data Parameters
NAME         Bin_BS5P150
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20081023
Time               11.19
INSTRUM            spect
PROBHD   5 mm PATXI 1H-
PULPROG         mlevetgp
TD                 4096
SOLVENT            CDCl3
NS                   16
DS                   16
SWH             5813.954 Hz
FIDRES          1.419422 Hz
AQ              0.3523060 sec
RG                  406
DW                86.000 usec
DE                 6.50 usec
TE                293.7 K
D0           0.00000300 sec
D1           2.00000000 sec
D9           0.06000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
D16          0.00020000 sec
IN0          0.00017200 sec
L1                   30

======== CHANNEL f1 ========
NUC1                 1H
P1                8.06 usec
P2               16.12 usec
P5               17.34 usec
P6               26.00 usec
P7               52.00 usec
P17            2500.00 usec
PL1               2.40 dB
PL10             12.57 dB
PL1W        13.05232048 W
PL10W        1.25512731 W
SFO1        700.1327375 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPZ1               30.00 %
GPZ2               30.00 %
P16              1000.00 usec

F1 - Acquisition parameters
ND0                  1
TD                 256
SFO1          700.1327 MHz
FIDRES       22.710829 Hz
SW                8.304 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 4096
SF          700.1300215 MHz
WDW               QSINE
SSB                   2
LB                 0.00 Hz
GB                    0
PC                 1.00

F1 - Processing parameters
SI                 1024
MC2        echo-antiecho
SF          700.1300176 MHz
WDW               QSINE
SSB                   2
LB                 0.00 Hz
GB                    0
```

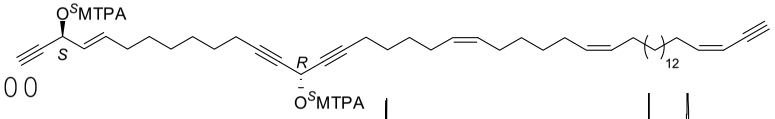


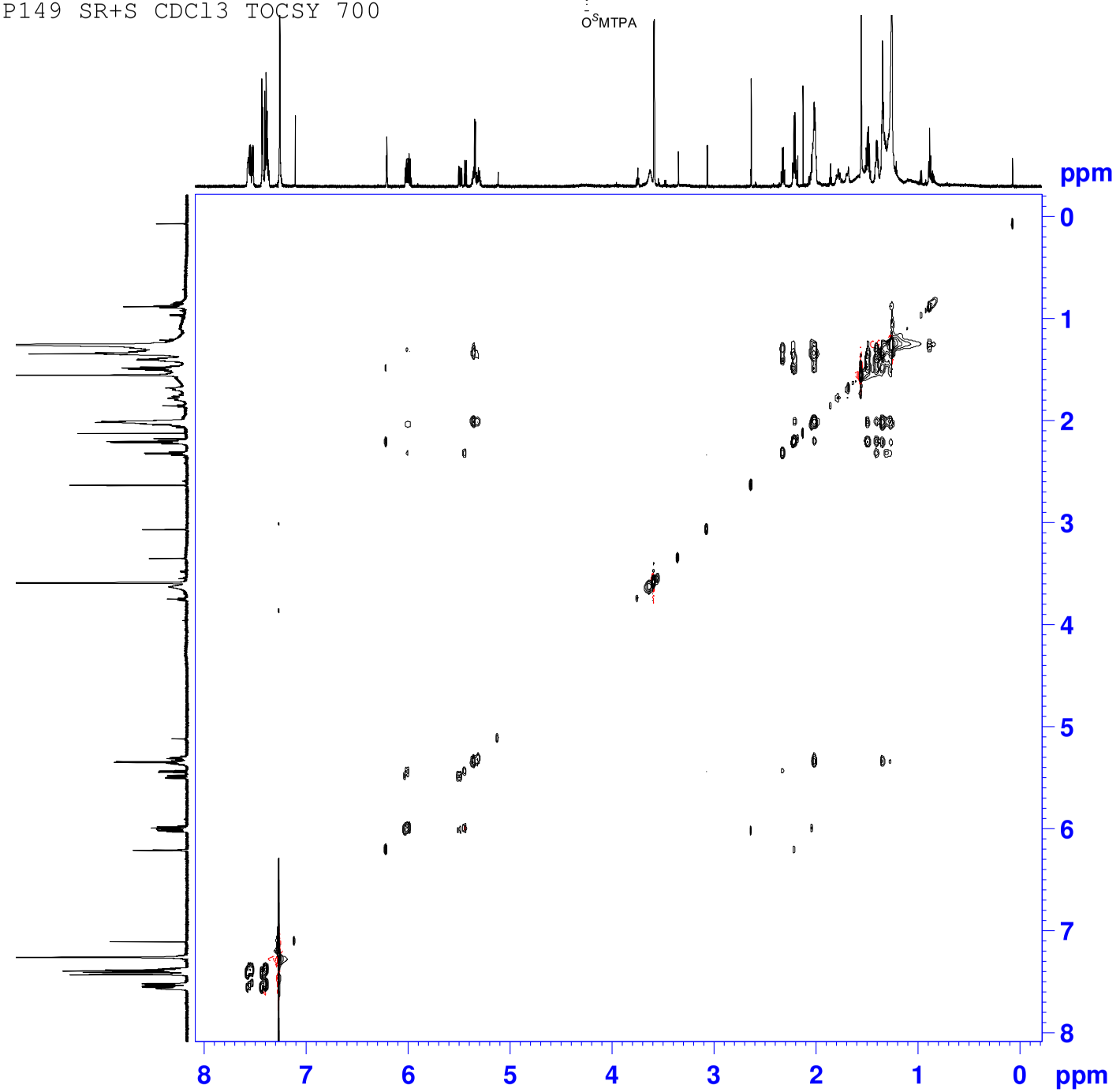
BS5P151 SS+S CDCl3 TOCSY 700




```
Current Data Parameters
NAME         Bin_BSSP151
EXPNO                  5
PROCNO                 1

F2 - Acquisition Parameters
Date_           20081008
Time               11.19
INSTRUM            spect
PROBHD   5 mm PATXI 1H-
PULPROG         mlevetgp
TD                 3072
SOLVENT            CDCl3
NS                   16
DS                   16
SWH             5933.544 Hz
FIDRES          1.931492 Hz
AQ              0.2589172 sec
RG                   645
DW                84.267 usec
DE                 6.50 usec
TE                295.0 K
D0           0.00000300 sec
D1           2.00000000 sec
D9           0.12000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
D16          0.00020000 sec
IN0          0.00016855 sec
L1                   66

======== CHANNEL f1 ========
NUC1                 1H
P1                6.89 usec
P2               13.78 usec
P5               17.34 usec
P6               26.00 usec
P7               52.00 usec
P17            2500.00 usec
PL1               2.40 dB
PL10             13.94 dB
PL1W        13.05232048 W
PL10W        0.91556209 W
SFO1        700.1327424 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPZ1              30.00 %
GPZ2              30.00 %
P16             1000.00 usec

F1 - Acquisition parameters
ND0                  1
TD                 256
SFO1          700.1327 MHz
FIDRES       23.177950 Hz
SW                8.475 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                4096
SF          700.1300209 MHz
WDW               QSINE
SSB                  2
LB                0.00 Hz
GB                   0
PC                1.00

F1 - Processing parameters
SI                1024
MC2       echo-antiecho
SF          700.1300201 MHz
WDW               QSINE
SSB                  2
LB                0.00 Hz
GB                   0
```

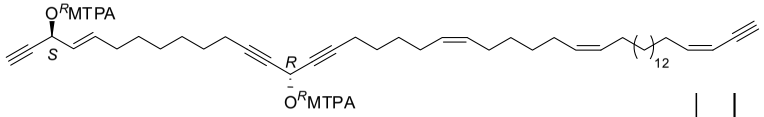
BS5P149 SR+S CDCl3 TOCSY 700

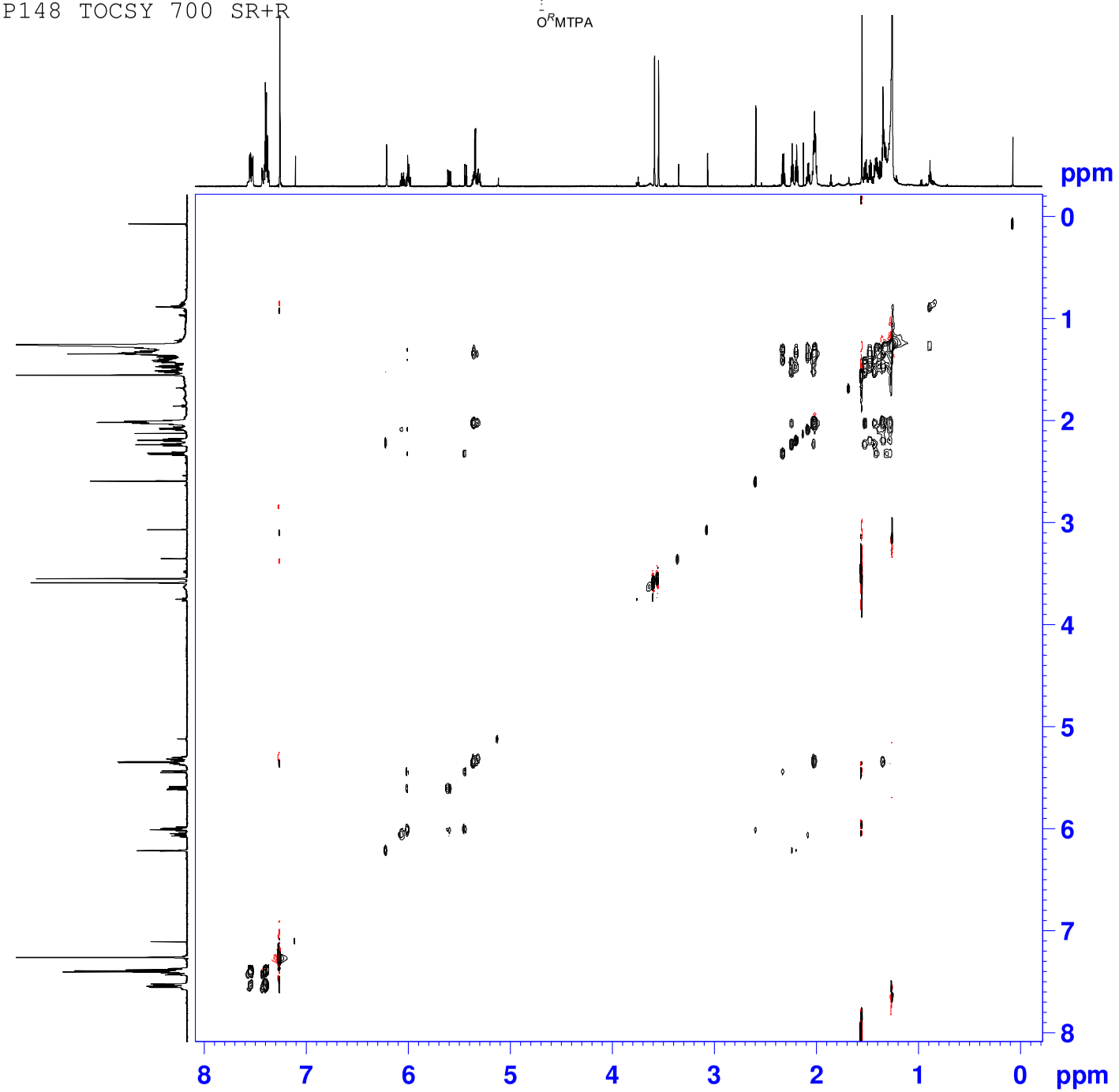





```
Current Data Parameters
NAME         Bin_BS5P149
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20081021
Time               17.44
INSTRUM            spect
PROBHD   5 mm PATXI 1H-
PULPROG         mlevetgp
TD                 4096
SOLVENT            CDCl3
NS                   16
DS                   16
SWH             5933.544 Hz
FIDRES          1.448619 Hz
AQ              0.3452063 sec
RG                   645
DW                84.267 usec
DE                 6.50 usec
TE                293.0 K
D0           0.00000300 sec
D1           2.00000000 sec
D9           0.06000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
D16          0.00020000 sec
IN0          0.00016855 sec
L1                   30

======== CHANNEL f1 ========
NUC1                 1H
P1                8.09 usec
P2               16.18 usec
P5               17.34 usec
P6               26.00 usec
P7               52.00 usec
P17            2500.00 usec
PL1               2.40 dB
PL10             12.54 dB
PL1W        13.05232048 W
PL10W        1.26382732 W
SFO1        700.1327585 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPZ1              30.00 %
GPZ2              30.00 %
P16             1000.00 usec

F1 - Acquisition parameters
ND0                  1
TD                 256
SFO1          700.1328 MHz
FIDRES        23.177950 Hz
SW                8.475 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                 4096
SF          700.1300215 MHz
WDW               QSINE
SSB                   2
LB                 0.00 Hz
GB                    0
PC                 1.00

F1 - Processing parameters
SI                 1024
MC2       echo-antiecho
SF          700.1300227 MHz
WDW               QSINE
SSB                   2
LB                 0.00 Hz
GB                    0
```

BS5P148 TOCSY 700 SR+R






```
Current Data Parameters
NAME         Bin_BS5P148
EXPNO                  2
PROCNO                 1

F2 - Acquisition Parameters
Date_           20081022
Time               13.45
INSTRUM            spect
PROBHD   5 mm PATXI 1H-
PULPROG         mlevetgp
TD                 4096
SOLVENT            CDCl3
NS                   16
DS                   16
SWH             5813.954 Hz
FIDRES          1.419422 Hz
AQ              0.3523060 sec
RG                   645
DW                86.000 usec
DE                 6.50 usec
TE                292.8 K
D0           0.00000300 sec
D1           2.00000000 sec
D9           0.06000000 sec
D11          0.03000000 sec
D12          0.00002000 sec
D16          0.00020000 sec
IN0          0.00017200 sec
L1                   30

======== CHANNEL f1 ========
NUC1                 1H
P1                6.85 usec
P2               13.70 usec
P5               17.34 usec
P6               26.00 usec
P7               52.00 usec
P17            2500.00 usec
PL1               2.40 dB
PL10             13.99 dB
PL1W        13.05232048 W
PL10W        0.90508169 W
SFO1        700.1327760 MHz

====== GRADIENT CHANNEL =====
GPNAM1          SINE.100
GPNAM2          SINE.100
GPZ1              30.00 %
GPZ2              30.00 %
P16             1000.00 usec

F1 - Acquisition parameters
ND0                  1
TD                 256
SFO1          700.1328 MHz
FIDRES         22.710831 Hz
SW                8.304 ppm
FnMODE    Echo-Antiecho

F2 - Processing parameters
SI                2048
SF          700.1300209 MHz
WDW               QSINE
SSB                  2
LB                0.00 Hz
GB                   0
PC                1.00

F1 - Processing parameters
SI                1024
MC2       echo-antiecho
SF          700.1300213 MHz
WDW               QSINE
SSB                  2
LB                0.00 Hz
GB                   0
```