MIXTURE SYNTHESIS AND SPECTROSCOPIC ANALYSIS OF A STEREOISOMER LIBRARY OF THE PHYTOPHTHORA MATING HORMONE α1 AND THE CORRESPONDING BIS-MTPA ESTERS

by

Reena Bajpai

Master of Science, Indian Institute of Technology, Kanpur, 2004

Submitted to the Graduate Faculty of

Art and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2010

UNIVERSITY OF PITTSBURGH

Art and Sciences

This dissertation was presented

by

Reena Bajpai

It was defended on

May 21, 2010

and approved by

Professor Paul E. Floreancig, Department of Chemistry

Professor Craig S. Wilcox, Department of Chemistry

Professor Alexander Doemling, Department of Pharmaceutical Sciences

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

MIXTURE SYNTHESIS AND SPECTROSCOPIC ANALYSIS OF THE PHYTOPHTHORA MATING HORMONE α1 AND THE CORRESPONDING BIS-MTPA esters

Reena Bajpai, PhD

University of Pittsburgh, 2010

Phytophthora are parasitic fungi like species that attack the roots and stems of plants. The heterothallic species of *phytophthora* consist of two mating types A1 and A2. A hormone α1 secreted by the A1 mating type induces the formation of sexual oospores in the A2 mating type. In 2005 by Ojika and coworkers reported the isolation and constitutional characterization of the hormone α1. The absolute configuration of the hormone α1 was later assigned by comparison of the hormonal activity of a synthetic sample with the natural sample. Assignment of absolute configuration on the basis of hormonal activity can however be error prone because the activity of any particular sample will depend on its isomeric purity.

In order to provide a spectroscopic method to assign the absolute configuration of hormone α1, we have synthesized eight stereoisomers of hormone α1 by Fluorous Mixture Synthesis. During the FMS, stereoisomeric starting materials were tagged with different fluorous PMB 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 hydrogenolysis to provide pure products. The NMR spectra of the eight isomers of hormone α1 provided only limited information about their absolute configuration.

The synthetic isomers of hormone α1 were subsequently converted to the corresponding bis-*R* and *S* Mosher ester derivatives. By comparison of the ^{1}H NMR spectra of the sixteen bis-Mosher ester derivatives with the bis-Mosher ester derivatives of the natural product, we confirmed the partial configuration of hormone α1 as (3*R*,7*R*,15*R*).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
*t*Bu	*tert*-butyl
CDI	carbonyl diimidazole
COSY	correlation spectroscopy
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutyl aluminum hydride
DMAP	4-dimethylamino pyridine
DMF	dimethylformamide
DMP	Dess–Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
EDA	ethylenediamine
EI	electron ionization
equiv	equivalents

ESI	electrospray ionization
Et	ethyl
FMS	fluorous mixture synthesis
GC	gas chromatography
HMPA	hexamethylphosphoramide
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infrared spectrometry
LAB	lithiumamidotrihydroborate
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
MCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MOM	methoxymethyl
MS	mass spectrometry
MTPA	α-methoxytrifluorophenylacetic acid
NaHMDS	sodium hexamethyldisilazide
NMR	nuclear magnetic resonance
Ph	phenyl
PMB	*p*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate

*i*Pr	isopropyl
PTSA	*p*-toluenesulfonic acid
PTSH	1-phenyl-1*H*- tetrazole-5-thiol
Py	pyridine
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl

PREFACE

My first and foremost thanks to my research advisor and mentor Professor Dennis P. Curran for giving me the opportunity to grow both professionally and personally in his group. I am extremely fortunate to have studied under a person who demonstrates not only immeasurable scientific knowledge, but also impeccable professionalism. I would like to thank Professors Alexander Doemling, Paul E. Floreancig and Craig S. Wilcox for being a part of my thesis committee and Professor Theodore Cohen for being my proposal mentor.

I also want to thank the Curran group members, both past and present. I appreciate both the technical and theoretical help as well as the good times we had daily on the eleventh floor. My especial thanks to two most wonderful lab mates I have had the privilege to work with, Dr. Eveline Kumli and Dr. Maria Hopkins. Their friendships will be cherished for lifetime. Also thanks to Dr. Fanglong Yang for his contribution to this project.

I appreciate the help provided by Dr Damodaran Krishnan and Dr. John Williams for NMR spectroscopy and mass spectroscopy respectively. I also extend my gratitude towards Dr. Ojika and Dr. Yajima for providing us with the NMR spectra of the natural product derivatives of their synthetic bis-MTPA ester derivatives respectively.

Lastly, I am grateful to my parents for the immense sacrifices they have made to ensure that I reach this stage of my career and for their unconditional love, support and encouragement. I take this opportunity to thank my husband, Manu for being my idol, strength and best friend,

my brother and my sister for always being there through thick and thin, and my parents in-law for their understanding and patience. Last but not the least a sincere thanks to all my friends in Pittsburgh for being a family away from home.

1.0 MIXTURE SYNTHESIS AND SPECTROSCOPIC ANALYSIS OF THE PHYTOPHTHORA MATING HORMONE α1 AND THE CORRESPONDING BIS-MTPA ESTERS

1.1 INTRODUCTION

1.1.1 Fluorous mixture synthesis (FMS)

Natural products are small molecules isolated from living organisms. They generally have interesting pharmacological and biological activities and play a highly significant role in the drug discovery and development process.[1] A natural product is often chemically synthesized because of its challenging and complex molecular architecture. Such syntheses also provide opportunities for discovery of new synthetic methods, which could be used in a wider range of applications. At times, chemical synthesis is pursued to produce a scarce but intriguing natural product in larger quantities for more extensive biological analysis. Chemical syntheses of natural products also serve as absolute proof of their assigned structures.

Assigning the constitutional structure and absolute configuration of complex natural products with multiple stereocenters is not only laborious but also error prone.[2] Total synthesis of all of the stereoisomers of the natural products can be used to prove or disprove a structural assignment by comparison of various physical and spectral data of a natural product with the

synthetic samples.[3] The recent proofs of structures of natural products like murisolins,[3] cytostatin[4] and petrocortyne A[5] by comparison of a natural sample with a library of their stereoisomers shows the power of having multiple stereoisomers for comparison. Furthermore, the syntheses of stereoisomer libraries of natural products also provide valuable samples for biological testing.

However, synthesis of multiple stereoisomers of a natural product one at a time by traditional solution phase synthesis is a time consuming and labor intensive process. For example, in order to assign the complete stereochemistry of the natural product khafrefungin, Kobayashi and coworkers had to synthesize five stereoisomers one by one.[6]

Mixture synthesis, wherein one reaction sequence leads to multiple products, is emerging as an efficient tool for synthesis of stereoisomer libraries of natural products. Recently, Waldmann and coworkers reported the synthesis of a complete stereoisomer library of cryptocarya diacetate using polymer-bound mixture synthesis.[7] Takahashi and coworkers have also reported the combinatorial synthesis of a 122-membered macrosphelide library on polymer-support.[8]

In solid-phase or polymer-bound mixture synthesis, each bead contains a single compound and can be physically separated from every other bead providing individual products at the end of the synthesis. However, in comparison to the conventional solution-phase synthesis, solid-phase synthesis sacrifices the reactivity of the solid supported substrates because of unfavorable kinetics of heterogeneous reactions. The polymer-bound substrates are also difficult to characterize.

Fluorous mixture synthesis (FMS) is the first mixture synthesis technique which provides the benefits of solution phase mixture synthesis while maintaining the predictable isolation and

identification of individual pure products at the end.[9] A typical FMS consists of three stages: premix, mixture synthesis, and postmix. In the premix stage, individual substrates are prepared and tagged (protected) with homologous fluorous groups, then the tagged compounds are mixed together. During the mixture synthesis stage, the mixture of fluorous-tagged precursors is taken through the desired multiple-step synthesis. It is during this stage that the benefits of FMS are reaped because the number of reactions and separations required is divided by the number of tagged compounds present in the mixture. The mixture synthesis stage ends with demixing, where the fluorous mixture is separated into the individual tagged compounds by preparative HPLC over fluorous silica gel (silica gel with a fluorocarbon bonded phase). The fluorous HLPC separates the compounds based on their fluorine content with molecules of higher fluorine content having longer retention time.[10] In the final postmix stage, the tags are removed to produce the target molecules.

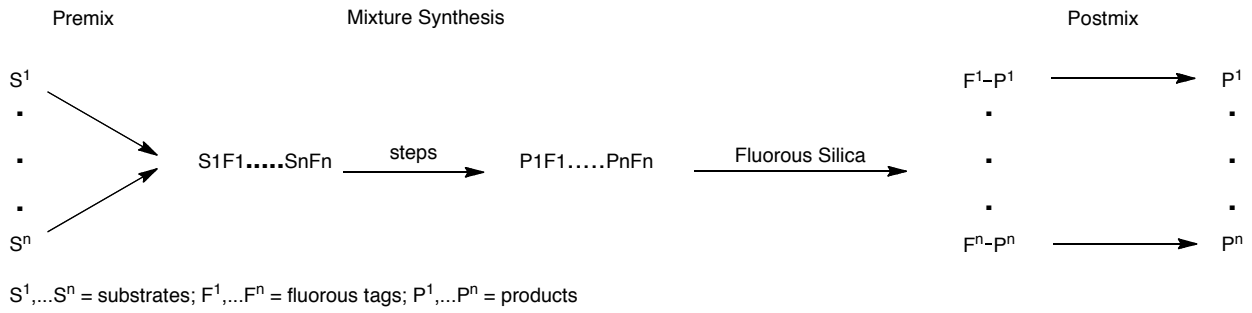


Figure 1. Schematic representation of a typical FMS.

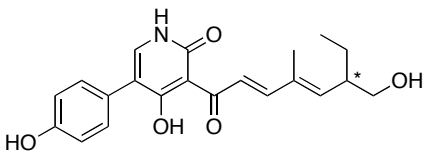
FMS has been successfully applied to synthesis of enantiomers, diastereomers, and natural product analogs. For synthesis of enantiomeric products by FMS, the two enantiomers of the starting substrate are tagged with different fluorous tags to obtain the two quasienantiomers. According to Curran and coworkers, quasienantiomers are pair of compounds that can be turned

into true enantiomers by simple changes in the chemical composition of one or two substituents.[11] The quasienantiomers are mixed in equimolar amount to obtain a quasiracemic[11] mixture, which is carried though the entire synthesis. Although not true racemates, the components of the quasiracemic mixtures usually have effectively identical physical and spectroscopic properties and chemical reactivities towards achiral reagents. Finally, the two target enantiomers are obtained after demixing and detagging. Both the enantiomers of pyridovercin and mappicine have been synthesized by this quasiracemic synthesis approach.[12]

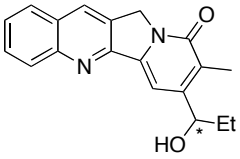
For synthesis of diastereomeric products by FMS, diastereomers of the starting material are attached to different fluorous tags to obtain quasidiastereomers. Like quasienantiomers, quasidiastereomers are compounds that can be converted into true diastereomers by simple changes in one or two substituents.[11] These quasidiastereomers are mixed in equimolar ratio and carried through a synthetic sequence. Individual diastereomers are obtained after final demixing and detagging. This approach has been applied towards synthesis of sixteen isomers of pine sawfly sex pheromone,[13] sixteen isomers of passifloricin,[14] twenty eight isomers of murisolin,[15] four isomers of cytostatin[4] and four stereoisomers of lagunapyrone B.[16]

FMS is also useful to generate a library of structurally diverse analogs of a natural product. Here, nonisomeric starting materials of a common structure with different substituents are tagged with different fluorous tags and mixed together. The mixture is carried through the entire synthetic sequence, final demixing and detagging provides the target natural product analogs. A 560-compound library of mappicine analogs has been synthesized by FMS.[17]

(a) FMS of enantiomers

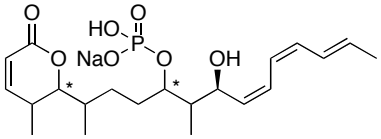


pyridovericin
two enantiomers

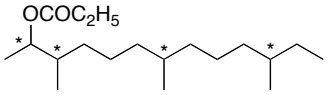


mappicine
two enantiomers

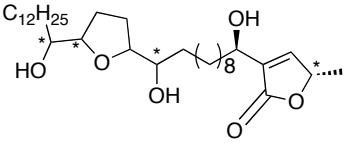
(b) FMS of diastereomers



cytostatin
four isomers

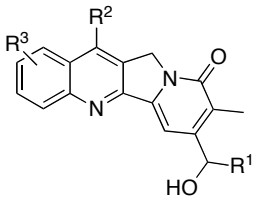


pinesaw fly pheromone
sixteen isomers



murisolin
sixteen isomers

(c) FMS of natural product analogs



mappicine
560 analogs

Figure 2. Representative examples of natural products and their stereoisomers synthesized by FMS.

Expanding the use of FMS to rapidly obtain the stereoisomer libraries of natural products, we aim to synthesize a stereoisomer library of the recently isolated *phytophthora* mating hormone α1.[18] The principle goal is to compare the spectroscopic data of the synthetic stereoisomers of the hormone α1 with the natural sample and to provide rigorous prove of its stereochemical configuration.

1.1.2 *Phytophthora* mating hormone α1

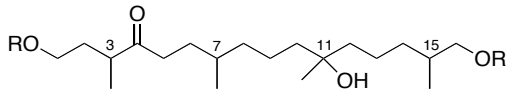
Phytophthora, derived from Greek 'the plant destroyer', are parasitic fungi-like species that live in the soil and attack the roots and basal stems of plants.[19] The members of this genus are among the most destructive plant pathogens, causing plant diseases of worldwide importance. For example, the late blight of potato, caused by *Phytophthora infestans*, resulted in the Irish potato famine during the mid-19th century.[19] Among the other diseases caused by *phytophthora* species are the black pod of cacao, caused by *Phytophthora palmivora*, the sudden oak death, caused by *Phytophthora ramorum*, and the root rot of avocado, caused by *Phytophthora cinnamoni*. The control of these organisms by use of fungicides remains difficult.

Sexual reproduction is an important event in the life cycle of *phytophthora* because it provides a means of propagation and enhances the fitness of the progenies by spawning recombinant genotypes that may be more pathogenic or resistant to fungicides compared to their parents. *Phytophthora* are classified as homothallic and heterothallic depending on whether they reproduce asexually or sexually. The heterothallic species consist of two mating types, A1 and A2. Although each individual can produce both male (anthenidia) and female (oogonia) organs, geographical proximity of the two mating types is essential for sexual reproduction.[20] After sexual reproduction, the oogonia develops into sexual spores called oospores, which can survive for months without a living host.[21] The sexual behavior of heterothallic species of *phytophthora* is different from all other known organisms in that sexual reproduction readily occurs between morphologically and physiologically distinct species, for example between the *P. cinnamomi* and the *P. infestans*.[19]

In 1929, Ashby proposed that sexual reproduction in *phytophthora* is regulated by a hormone-like compound.[22] Later, Galloway and Kouyears reported data supporting a mechanism

of chemical stimulation for oospore formation.[23] A factor secreted by the A1 mating type induces the formation of oospores in the A2 mating type, while a factor secreted by A2 induces the formation of oospores in A1. These factors are known as hormones α1 and α2 respectively. Although extensive studies have been conducted with the aim of isolating and characterizing these hormones, their structures remained obscure until recently due to their scarcity.[24]

In 2005, Ojika and coworkers finally succeeded in isolating 1.2 mg of hormone α1 from a 1830 L of cultural broth of the A1 mating type of *P. nicotianae*.[18] The two-dimensional structure of the hormone α1 was elucidated through 1D and 2D NMR spectroscopy, mass spectroscopy and infrared analysis of the natural product and its bis-*p*-bromobenzoate derivative. Based on these data, the constitutional structure of hormone α1 was assigned to be 1,11,16-trihydroxy-3,7,11,15-tetramethylhexadecan-4-one (Figure 3). Thus, hormone α1 is a novel acyclic diterpene with an array of 1,5-stereocenters. The hormone α1 was also found to induce oospore formation in the A2 mating types of three other *phytophthora* species (*P. capsici*, *P. cambivora*, and *P. infestans*), indicating that this hormone is not specific to *P. nicotianane* but is a common mating hormone in all heterothallic *phytophthora.*



R = H; Hormone α1 (**1**)
R = 4-BrC_6H_5CO (**2**)

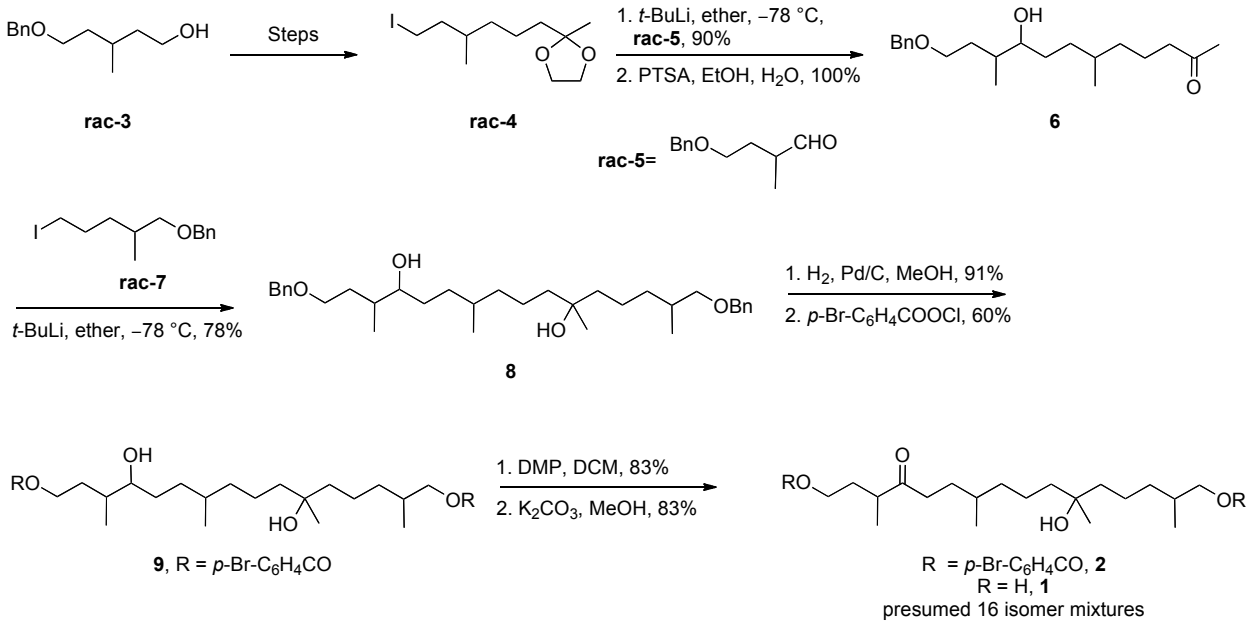
Figure 3. 2D structures of the *phytophthora* mating hormone α1 (**1**) and its bis-*p*-bromobenzoate **2**.

The constitutional structure of hormone α1 was confirmed when Yajima and co-workers reported its first synthesis as a stereoisomeric mixture, presumably containing all 16 stereoisomers.[25] Their racemic synthesis of all stereoisomers of **1** started from the known alcohol

rac-3 and is summarized in Scheme 1. The alcohol **rac-3** was converted to the iodide **rac-4** through a series of functional group transformations. Halogen-metal exchange of **rac-4** with *t*-BuLi followed by addition of aldehyde **rac-5**, afforded the coupled product, which upon acid hydrolysis of the ketal provided the ketone **6**. Addition of the ketone **6** to lithiated iodide **rac-7** gave the diol **8**. Deprotection of the two benzyl groups by hydrogenolysis and protection of the resulting primary alcohols with *p*-bromobenzoyl group provided the compound **9**. Oxidation of the remaining secondary hydroxy group afforded the racemic bis-*p*-bromobenzoate **2**. Hydrolysis of the *p*-bromobenzoyl groups gave the stereoisomeric mixture of **1**, presumably containing all sixteen isomers in an equimolar ratio.

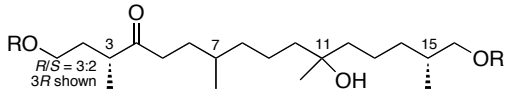
Both the synthetic samples of **1** and **2** were reported to exhibit simple ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra, as though they contained only a single diastereomer. These spectra were in good agreement with those reported for the natural product and its bis-*p*-bromobenzoyl derivative. Hence, the 2D structure of the hormone α1 was confirmed. At that time, these results indicated that differentiation between the diastereomers of **1** and **2** by NMR analysis alone would be difficult. However, later it was found that there are differences in the ^{1}H NMR spectra of the sixteen isomers of hormone α1. But, because the isolated natural product itself is a mixture of isomers, the ^{1}H NMR spectrum of the stereoisomeric mixture of **1** matched the ^{1}H NMR spectrum of the natural product. The oospore-inducing activity of this synthetic sample of **1** was about five times weaker than that of the natural product, indicating that all stereoisomers of **1** do not exhibit identical hormonal activity.

Scheme 1. Yajima's synthesis of a stereoisomeric mixture of hormone α1.



To gain insight into the absolute configuration of hormone α1, Ojika and coworkers converted the natural sample of hormone α1 to the corresponding (*R*) and (*S*) bis-α-methoxy-α-trifluoromethylphenylacetates (bis-MTPA esters) **10**.[26] The analysis of ^{1}H NMR spectra of the two bis-MTPA esters elucidated the C15 configuration of hormone α1 as (*R*) and C3 configuration as a 3:2 mixture of (*R*) and (*S*). Although natural products are not always isomerically pure,[27] Ojika and coworkers suggested that the natural hormone α1 originally has a (3*R*,15*R*) configuration corresponding to the major isomers in the two bis-MTPA esters. Because the C3 stereocenter is adjacent to a carbonyl group, epimerization can occur during isolation or esterification of the natural product. However, the 3:2 *R*:*S* composition of the C3 stereocenter mixture may represent the equilibrium composition and it is possible that the actual configuration at the C3 stereocenter in the hormone α1 is the minor 3*S* isomer.

If Ojika's assumption that the C3 configuration of hormone α1 is *R* is true, this stereochemical analysis reduced the number of unassigned stereocenters of hormone α1 from four to two. The structures of the two bis-MTPA esters obtained from hormone α1 are shown in Figure 4.



(***R***)**-10**, R = (*R*)-MTPA
(***S***)**-10**, R = (*S*)-MTPA
MTPA = α-methoxy-α-trifluoromethylphenylacetate

Figure 4. Structures of the two bis-MTPA esters obtained from the natural hormone α1.

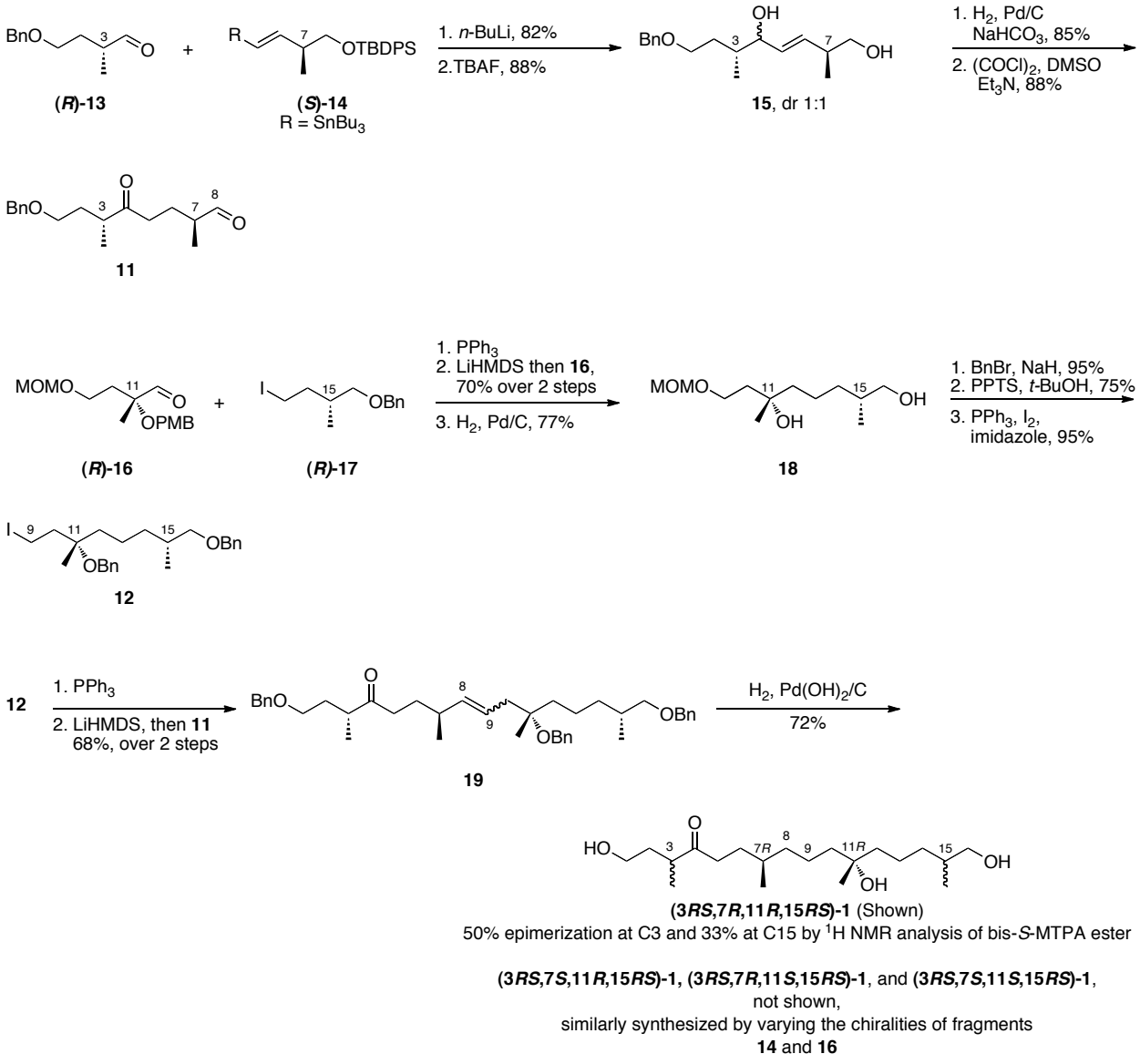
Following upon Ojika's partial assignment of hormone α1,[26] Yajima and coworkers attempted the asymmetric synthesis of the four stereoisomers of hormone α1 with fixed (3*R*,15*R*) configuration.[28] Their approach towards the synthesis of **(3*R*,7*R*,11*R*,15*R*)-1** is summarized in Scheme 2. They disconnected the C8-C9 bond of hormone α1 to divide it into fragments **11** and **12**. The synthesis of the aldehyde **11** commenced with addition of the organotin compound **(*S*)-14** to the aldehyde **(*R*)-13** to obtain the alcohol **15** as a diastereomeric mixture. Removal of the *t*-butyldiphenylsilyl (TBDPS) protecting group, saturation of the double bond and subsequent Swern oxidation provided the aldehyde **11**.

The synthesis of fragment **12** was achieved by a Wittig reaction between aldehyde **(*R*)-16** and iodide **(*R*)-17**. Reduction of the resulting double bond and simultaneous removal of both *p*-methoxybenzyl and benzyl protecting groups by hydrogenolysis provided the diol **18**. Reprotection of the C11 and C16 hydroxyl groups as benzyl ethers, removal of the MOM group under acidic conditions, and subsequent iodination provided the fragment **12**.

The coupling of the fragments **11** and **12** was achieved by a Wittig reaction. Removal of the three benzyl groups and simultaneous saturation of the double bond by hydrogenolysis afforded the final product. The ^{1}H NMR analysis of the bis-(*R*)-MTPA ester from this synthetic isomers of **1** showed about 50% epimerization at the C3 stereocenter and 33% epimerization at the C15 stereocenter. The final product **(3*RS*,7*R*,11*R*,15*RS*)-1** was thus a mixture of four isomers. They suggested that epimerization at C3 must have occurred during Wittig coupling of fragment **11** and **12** under strongly basic conditions and at C15 during simultaneous hydrogenation and hydrogenolysis to obtain alcohol **18**.[29] The four-isomer mixtures **(3*RS*,7*R*,11*S*,15*RS*)-1**, **(3*RS*,7*S*,11*S*,15*RS*)-1** and **(3*RS*,7*S*,11*R*,15*RS*)-1** were analogously synthesized by changing the configurations of the fragments **14** and **16**.

The four-isomer mixture **(3*RS*,7*R*,11*R*,15*RS*)-1** induced significant oospore formation in the A2 mating type of *P. nicotianae*. The other three four-isomer mixtures **(3*RS*,7*R*,11*S*,15*RS*)-1**, **(3*RS*,7*S*,11*R*,*15RS*)-1** and **(3*RS*,7*S*,11*S*,15*RS*)-1** did not show any considerable hormonal activity.

Scheme 2. Yajima's synthesis of four four-isomer mixtures of hormone α1.

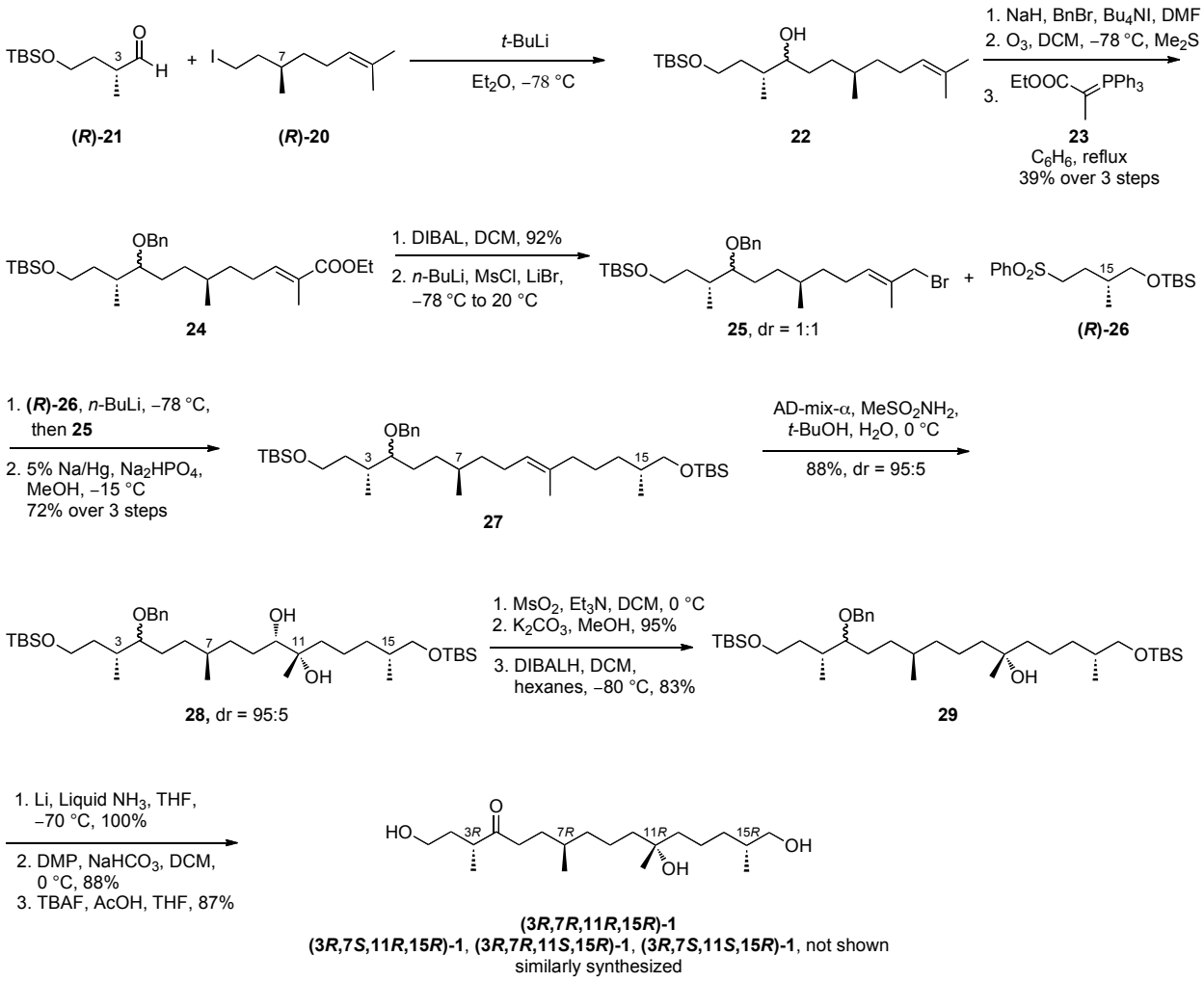


After obtaining the four four-isomer mixtures of hormone α1, Yajima and coworkers reattempted the synthesis of four isomers of **1** with fixed 3*R* and 15*R* configuration.[28] Their revised synthetic route to obtain **(3*R*,7*R*,11*R*,15*R*)-1** is shown in Scheme 3. Halogen-metal exchange of (*R*)-citronellyl iodide (***R*-20**) with *t*-BuLi, followed by coupling with aldehyde **(*R*)-21**, afforded **22** as an inconsequential diastereomeric mixture. Protection of the free hydroxyl

group of **22** with a benzyl group, oxidative cleavage of double bond, and Wittig condensation of the resulting aldehyde with (carbethoxyethylidene)triphenylphosphorane **23** afforded **24**. The ester **24** was reduced with DIBAL and the resulting primary alcohol was converted to allylic bromide **25**. Coupling of **25** with sulfone **26**, followed by desulfonation, afforded **27** with the full carbon skeleton of **1**.

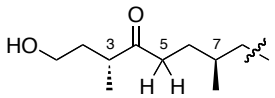
Stereoselective dihydroxylation of **27** with AD-mix-α gave diol **28** with a 95:5 diastereomeric ratio. Monomesylation of **28**, demesylation with K_2CO_3 and regioselective reduction of the epoxide with DIBAL gave the tertiary alcohol **29**. Removal of the benzyl group, followed by Dess-Martin oxidation of the resulting alcohol and removal of the two *t*-butyldimethylsilyl (TBS) groups afforded **(3*R*,7*R*,11*R*,15*R*)-1**. Diastereomers **(3*R*,7*R*,11*S*,15*R*)-1**, **(3*R*,7*S*,11*S*,15*R*)-1** and **(3*R*,7*S*,11*R*,15*R*)-1** were also successively prepared in a similar fashion. The stereochemical purities of the four isomers at C3 and C15 stereocenters were confirmed by ^{1}H NMR analysis of their corresponding bis-(*R*)-MTPA esters.

Scheme 3. Yajima's asymmetric synthesis of four stereoisomers of **1**.

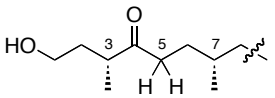


A comparison of the 400 MHz ^{1}H NMR spectra of the four isomerically pure compounds **(3*R*,7*R*,11*R*,15*R*)-1**, **(3*R*,7*S*,11*R*,15*R*)-1**, **(3*R*,7*R*,11*S*,15*R*)-1** and **(3*R*,7*S*,11*S*,15*R*)-1** with each other revealed significant differences for the signals of the C5 methylene protons at around 2.5 ppm. For C3,C7-anti isomers **(3*R*,7*R*,11*S*,15*R*)-1** and **(3*R*,7*R*,11*R*,15*R*)-1**, the resonances of the two C5 methylene protons overlapped and they appeared as a triplet at δ 2.53. For C3,C7-syn isomers **(3*R*,7*S*,11*R*,15*R*)-1** and **(3*R*,7*S*,11*S*,15*R*)-1**, the two C5 methylene protons were

observed as multiplets between δ 2.61–2.47. These results are summarized in Figure 5. A comparison of the ^{1}H NMR spectra of these four isomers with the ^{1}H NMR spectrum of the natural product revealed that the natural product spectrum showed mixed syn and anti isomer signals for the two C5 methylene protons. This is consistent with the natural hormone α1 being a mixture of isomers at the C3 stereocenter



C3,C7-anti isomers
(**3*R*,7*R*,11*R*,15*R*)-1** and (**3*R*,7*R*,11*S*,15*R*)-1**
the C5 methylene protons appear as a triplet at δ 2.53



C3,C7-syn isomers
(**3*R*,7*S*,11*R*,15*R*)-1** and (**3*R*,7*S*,11*S*,15*R*)-1**
the C5 methylene protons appear as multiplet between δ 2.61–2.47

Figure 5. Partial structures of the C3,C7-anti and syn isomers of **1** synthesized by Yajima and coworkers and the appearance of the C5 methylene protons in their ^{1}H NMR spectra.

No other differences were seen in the ^{1}H NMR spectra of the four isomers. Because the stereoisomeric mixture of hormone α1 synthesized earlier by Yajima and coworkers (Scheme 1) was also a mixture of C3,C7-syn and anti isomers (as is the natural hormone α1) its ^{1}H NMR spectrum matched the ^{1}H NMR spectrum of the natural product. The ^{13}C NMR spectra of **(3*R*,7*R*,11*R*,15*R*)-1**, **(3*R*,7*S*,11*R*,15*R*)-1**, **(3*R*,7*S*,11*R*,15*R*)-1** and **(3*R*,7*S*,11*S*,15*R*)-1** were reported to show very small insignificant differences.

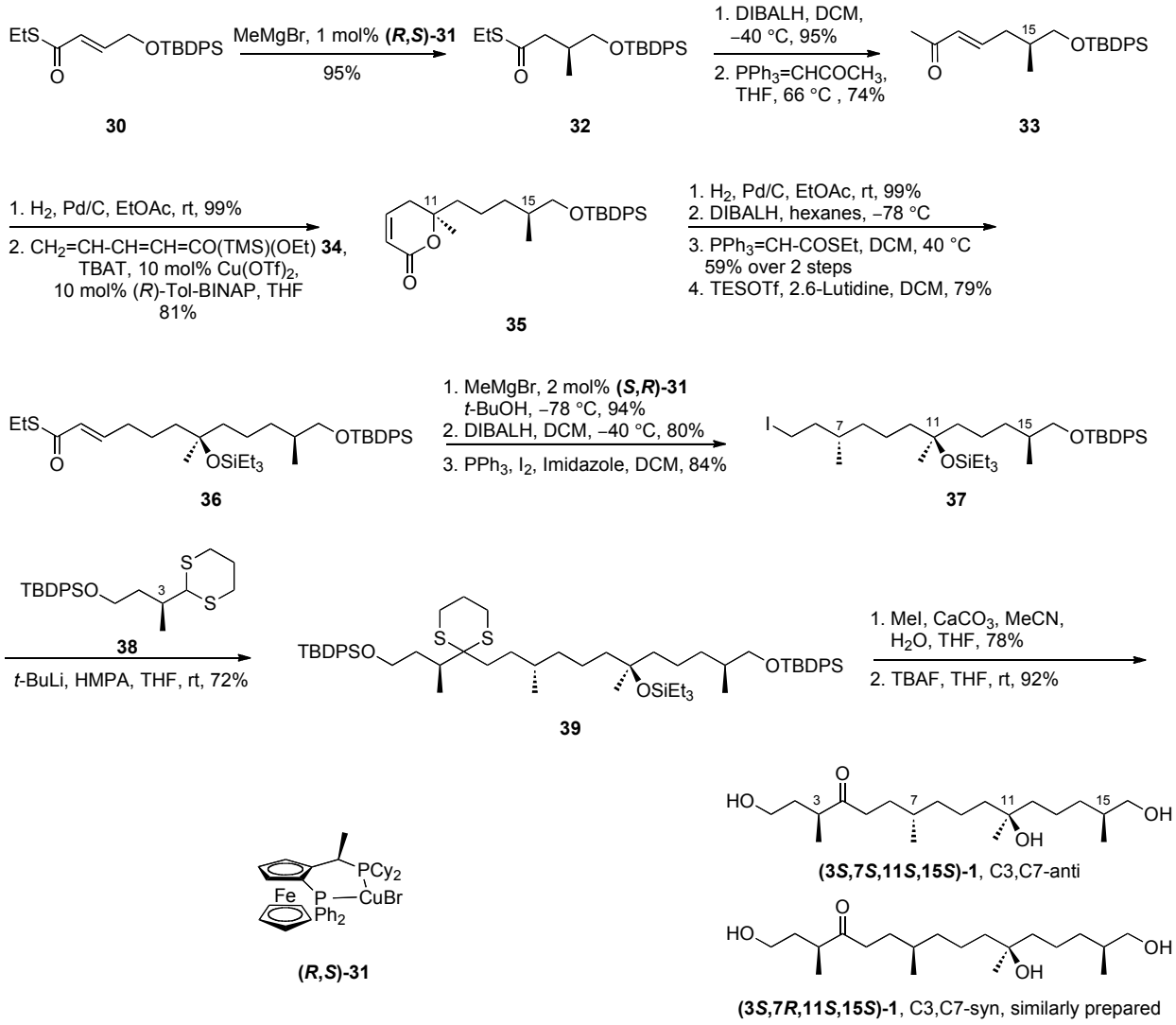
The oospore-inducing activities of the four synthetic isomers were also compared to that of the natural hormone α1. Similar to the behavior of natural hormone α1, the diastereomer **(3*R*,7*R*,11*R*,15*R*)-1** induced significant oospore formation in the A2 mating type of P. *nicotinane*. No noteworthy oospore formation was induced by the other three isomers. Based on these results, the absolute configuration of hormone α1 was assigned as (3*R*,7*R*,11*R*,15*R*). Also,

because only **(3*R*,7*R*,11*R*,15*R*)-1** and the four-isomer mixture **(3*RS*,7*R*,11*R*,15*RS*)-1** exhibited hormonal activity similar to that of the natural product, Yajima and coworkers concluded that (7*R*,11*R*) configuration is essential for hormonal activity of **1**.

Around the same time, Feringa and coworkers reported catalytic enantioselective synthesis of the (3*S*,7*S*,11*S*,15*S*) and (3*S*,7*R*,11*S*,15*S*) stereoisomers of **1**. Their synthetic approach involved iterative catalytic enantioselective conjugate addition of MeMgBr to the corresponding α,β-unsaturated thioesters to install the C3, C7 and C15 stereocenters, as summarized in Scheme 4.[30] Conjugate addition of MeMgBr to **30** catalyzed by **(*R*,*S*)-31** resulted in thioester **32**. DIBALH reduction of ester **32** to aldehyde, followed by a Wittig reaction provided ketone **33**. Hydrogenation of **33** with Pd/C resulted in the corresponding saturated ketone. The chiral tertiary alcohol was installed through catalytic asymmetric vinylogous Mukaiyama aldol condensation of the aliphatic ketone with **34** to obtain lactone **35**. After hydrogenation of the alkene moiety, the lactone was reduced with DIBALH to the corresponding lactol. A Wittig reaction on this lactol and protection of the resulting tertiary alcohol as triethylsilyl (TES) ether yielded α,β-unsaturated thioester **36**. The C7 stereocenter was installed through conjugate addition of MeMgBr to **36** in presence of **(*S*,*R*)-31**. The resulting thioester was converted efficiently to the corresponding alcohol and subsequently to the iodide **37**.

The iodide **37** was reacted with lithiated dithiane **38** to obtain the product **39**. Unmasking the ketone, using MeI in presence of $CaCO_3$ and desilylation with TBAF provided **(3*S*,7*S*,11*S*,15*S*)-1**. Diastereomer **(3*S*,7*R*,11*S*,15*S*)-1**, differing at C7 configuration, was prepared in a similar manner by employing (*R*,*S*)-enantiomer of the catalyst **31** during the conjugate addition of MeMgBr to **36**.

Scheme 4. Feringa's enantioselective synthesis of two stereoisomers of **1**.



Both **(3*S*,7*S*,11*S*,15*S*)-1** (C3,C7-syn isomer) and **(3*S*,7*R*,11*S*,15*S*)-1** (C3,C7-anti isomer) were reported to show identical ^{1}H and ^{13}C NMR spectra, which were in good accordance to that of the natural product. Considering that Yajima and coworkers saw significant differences in the ^{1}H NMR spectra of the C3,C7-syn and anti isomers of hormone α1,[28] we suspect that the two isomers synthesized by Feringa and coworkers may not have been isomerically pure. Both stereoisomers **(3*S*,7*S*,11*S*,15*S*)-1** and **(3*S*,7*R*,11*S*,15*S*)-1** also induced oospore formation in the

A2 mating type stains of *P. infestans*, *P. capsici*, and *P. nicotianae*. This is also in contradiction to Yajima's conclusion that (7*R*,11*R*) configuration is necessary for biological activity of **1**. Because Yajima's and Feringa's papers appeared almost simultaneously, Feringa and coworkers were not aware of the difference in the ^{1}H NMR spectra of the C3,C7-syn and anti stereoisomers of hormone α1. Also neither of them knew about the oospore-inducing activity of the stereoisomers of hormone α1 synthesized by the others.

The synthesis of enantiopure hormone α1 and its stereoisomers is challenging especially due to the presence of an easily epimerizable C3 stereocenter. Also, assignment of the complete stereochemistry of hormone α1 by NMR analysis appears to be difficult. Assignment of its configuration by comparison of biological activity of synthetic isomers with each other and with that of the natural product is also problematic, because the hormonal activity of any particular sample will depend on its isomeric purity (as evident by the contradicting results of biological activity of isomers of **1** reported by Yajima and Feringa).

We envisioned that it would be useful to have a reliable spectroscopic method to assign the complete stereochemistry of hormone α1 and its stereoisomers. We plan to employ FMS to synthesize a stereoisomer library of hormone α1 and the corresponding bis-MTPA esters. The spectroscopic data of the synthetic isomers of **1** and the bis-MTPA esters will then be compared with each other and with the data reported for the natural product.

1.1.3 Mosher ester analysis for the determination of enantiomeric composition of chiral alcohols

Establishment of the absolute configuration of a chiral molecule or determination of its enantiomeric composition is a difficult task because enantiomers have identical physical and

spectral properties. In many cases, this can be achieved by reacting the molecule with a chiral derivatizing agent (CDA) of known absolute configuration.[31] This converts the mixture of enantiomers into a mixture of diastereomers, with different physical and spectroscopic properties.

The requirement of such derivatizing methods to determine the enantiomeric ratio of chiral molecules is that neither kinetic resolution nor racemization of the reactants occurs during the derivatization reaction. This is usually achieved by using excess of the enantiopure derivatizing reagents and reactions that are fast and irreversible.

Mosher acid or α-methoxy-α-trifluoromethylphenylacetic acid (MTPA; Figure 6) is the most commonly used derivatizing reagent for the determination of the absolute configuration of chiral secondary alcohols.[32] In the standard approach known as advanced Mosher ester analysis,[33] a secondary alcohol with unknown configuration is coupled with both *R* and *S* Mosher acid. This acylation reaction can be performed by using either MTPA acid or MTPA acid chloride and results in the formation of two diastereomeric MTPA esters. Subtraction of the chemical shifts of the protons of the *R*-MTPA ester from the *S*-MTPA ester in the vicinity of the ester-bearing stereocenter then provides differences (Δδ), the signs of which are used to assign the configuration of the secondary alcohols. The Mosher ester method has also been extended to facilitate the assignment of the primary alcohols with β stereocenters.[34]

It is important to note that while the *R*-MTPA acid gives rise to the *R*-MTPA ester, it is the *S*-MTPA acid chloride that gives rise to the *R*-MTPA ester. This is because of a change in the relative CIP priority of the groups in going from the acid chloride to the ester: the CIP priority of the CF_3 group is lower than the COCl in MTPA acid chloride but is higher than the COOR in the MTPA ester.

Figure 6. Structures of (*R*) and (*S*)-MTPA acid and chloride.

Mosher esters can also be used to determine the enantiomeric ratio in the given alcohol by measuring the relative intensities of analogous resonances (^{19}F and/or ^{1}H) in each of the diastereomeric MTPA esters derivative. MTPA is a useful CDA for analyzing enantiomeric excess of chiral alcohols for several reasons. First, both enantiomers are available in high enantiomeric purity either as acid or chloride. Second, the stereocenter is adjacent to the carboxyl bringing it in close proximity to the stereocenter of the alcohol when the ester is prepared. Also, the stereocenter is not able to be racemized as it is quaternary and thus contains no acidic protons. Finally, the presence of the trifluoromethyl group allows for straightforward analysis of diastereomeric excess by ^{19}F NMR spectroscopy,[32b] which is uncomplicated by signals from the chiral alcohol. However, ^{1}H NMR spectroscopy can also be used if the signals are sufficiently resolved.[32a,33,35]

The MTPA ester derivatives have been widely used to determine the absolute configuration of a number of natural products.[36] The MTPA esters of the synthetic natural products and their stereoisomers have also been used prove or disprove the assigned structures of the natural products.[3,5] We plan to make a stereoisomer library of the hormone α1 by FMS and to convert these isomers to the corresponding bis-*R* and *S*-MTPA esters. A comparison of the spectroscopic data from these isomers of hormone α1 and the bis-MTPA esters with the data reported for the natural product and its bis-*R* and *S* MTPA esters might facilitate a rigorous

stereochemical assignment of the hormone α1.

1.2 FIRST-GENERATION MIXTURE SYNTHESIS AND COMPARISON OF FOUR STEREOISOMERS OF HORMONE α1

We started pursuing the synthesis of hormone α1 soon after Ojika's report on isolation. At that time only its 2D structure was assigned. As a prelude to employing the technique of FMS to make a library of hormone α1, we decided to first execute a traditional synthesis of one isomer of hormone α1. The goals of this synthesis were: (1) to put in place a route for subsequent FMS, (2) to prove the constitution of hormone α1, and (3) to gather preliminary information about the configuration of hormone α1.

1.2.1 Retrosynthetic analysis of hormone α1

The retrosynthetic analysis to assemble the backbone of the target structure **1** is shown in Scheme 5. Cleavage of the C5–C6 bond provides the ketoalcohol **40** (C1–C5 fragment) and aldehyde **41** (C6–C16 fragment). The aldehyde **41** can be derived from the symmetrical protected triol **42**.

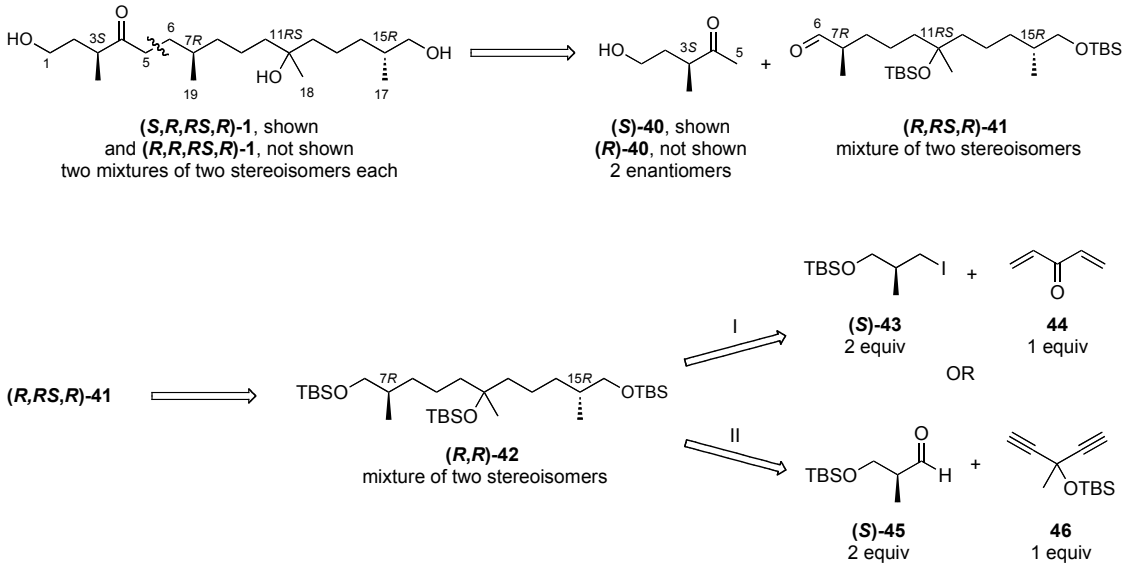
The triol **42** has four stereoisomers, two of these have a mirror plane of symmetry and the other two have a pseudo-C2 symmetry. The syntheses of these stereoisomers are facilitated by their symmetry. However, in order to take advantage of the symmetry towards their synthesis, the symmetry of fragment **42** must be broken prior to the union of the two fragments.[37] Purposefully refusing to do that, we decided to generate a two-compound mixture during the

symmetry-breaking step and to see if it would be possible to differentiate and/or separate the two stereoisomers at any stage of the synthesis.

The aldehyde **41** will thus be prepared as a mixture of diastereomers at C11. With no information available about the absolute configuration of hormone α1, we decided to keep the configuration at C7 and C15 as *R*. The two compound mixture **(*R*,*RS*,*R*)-41** will be coupled separately with both enantiomeric ketoalcohols **(*R*)-40** and **(*S*)-40** to obtain two two-isomer mixtures **(*S*,*R*,*RS*,*R*)-1** and **(*R*,*R*,*RS*,*R*)-1**.

We envisioned two different routes to synthesize the triol **(*R*,*R*)-42**. First, **(*R*,*R*)-42** can be prepared by a double conjugate addition of 2 equiv of iodide **(*S*)-43** to the divinyl ketone **44**, followed by methylation at the carbonyl carbon and TBS protection of the resulting tertiary alcohol. Second, trisilyl ether **(*R*,*R*)-42** can also be prepared by addition of 2 equiv of aldehyde **(*S*)-45** to the dialkyne **46**, followed by deoxygenation of the resulting free hydroxy groups and saturation of the two triple bonds.

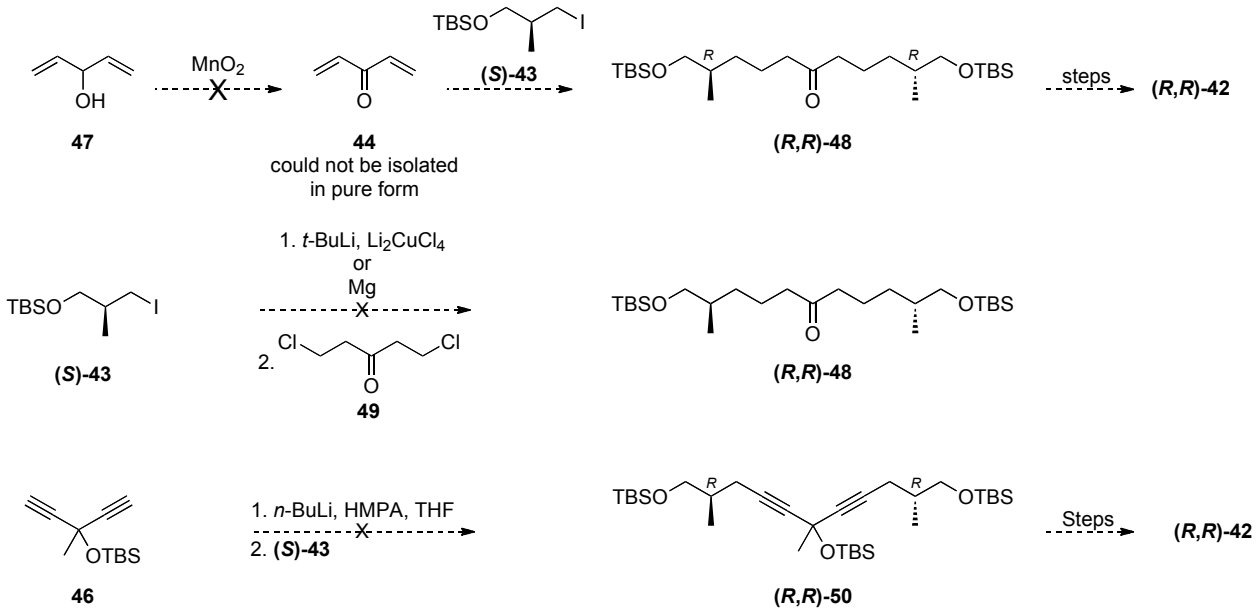
Scheme 5. Retrosynthesis of hormone α1.



1.2.2 Initial efforts towards synthesis of triol (*R*,*R*)-42 by Dr. Yang

Initial efforts towards the synthesis of triol **(*R*,*R*)-42** were carried out by Dr. Fanglong Yang as summarized in Scheme 6. The synthesis of trisilyl ether **(*R*,*R*)-42** was first targeted by double conjugate addition of 2 equiv of the known iodide **(*S*)-43**[50] to divinyl ketone **44**. However, the literature synthesis of ketone **44**[38] by oxidation of divinylcarbinol **47**, proved to be challenging due to its high volatility (lit bp = 90 °C) and tendency to polymerize. All attempts to synthesize **44** in reasonable quantity and purity were unsatisfactory. Accordingly, this route towards the synthesis of **(*R*,*R*)-42** was abandoned. Attempts to synthesize the carbon skeleton of **(*R*,*R*)-42** by metal mediated addition of iodide **(*S*)-43** to the dichloride **49** or by alkylation of one equiv of diyne **46** with 2 equiv of the iodide **(*S*)-43** were also unsuccessful.

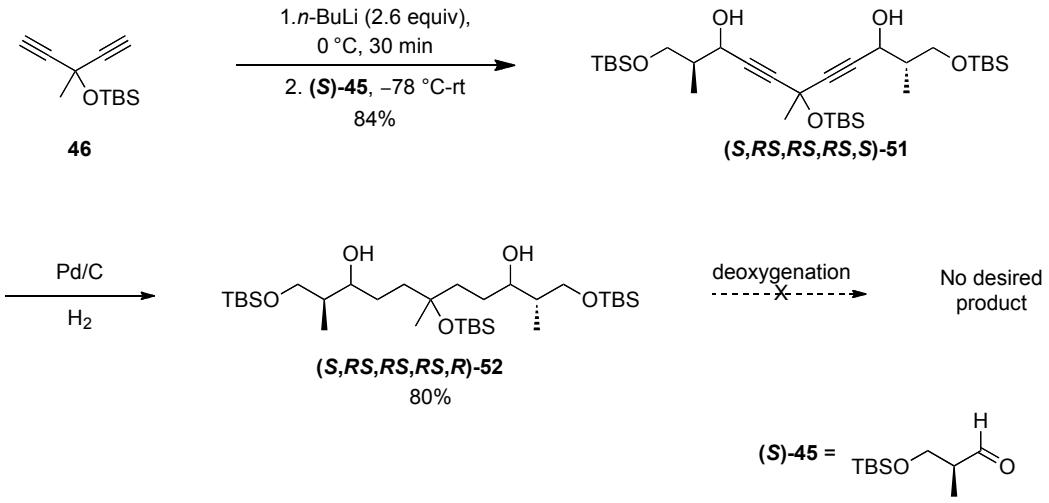
Scheme 6. Dr. Yang's initial attempts towards synthesis of the **(*R*,*R*)-42**.



Further efforts towards the synthesis of **(*R*,*R*)-42** are summarized in Scheme 7. Deprotonation of dialkyne **46** with *n*-BuLi and reaction with 2 equiv of aldehyde **(*S*)-45** provided the desired diol **51** in 84% yield. Hydrogenation of the diol **51** with Pd/C under hydrogen atmosphere gave the saturated diol **52** in 80% yield. Unfortunately, all attempts to effect radical deoxygenation on either **52** or **51** were unsuccessful.

Although, these efforts towards the synthesis of trisilyl ether **(*R*,*R*)-42** were unsuccessful, they did lead us to a successful synthesis of a C6–C16 fragment. The further synthesis was carried out by me.

Scheme 7. Dr. Yang's final attempts towards synthesis of **(*R*,*R*)-42**.

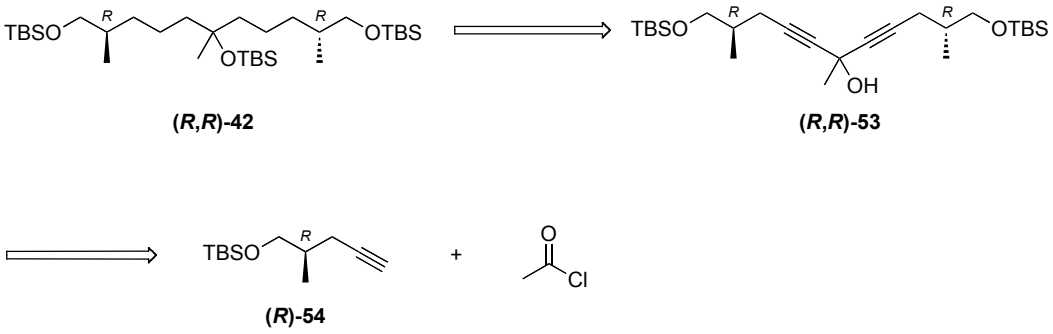


1.2.3 Successful synthesis of C6–C16 aldehyde fragment

The revised retrosynthesis of triol **(*R*,*R*)-42** is summarized in Scheme 8. Triol **(*R*,*R*)-42** can be obtained by hydrogenation of the two alkynes and protection of the free alcohol in the

diyne **(*R*,*R*)-53**, which in turn can be synthesized by the addition of 2 equiv of alkyne **(*R*)-54** to one equiv of acetyl chloride (CH_3COCl).

Scheme 8. Revised retrosynthesis of the triol **(*R*,*R*)-42**.

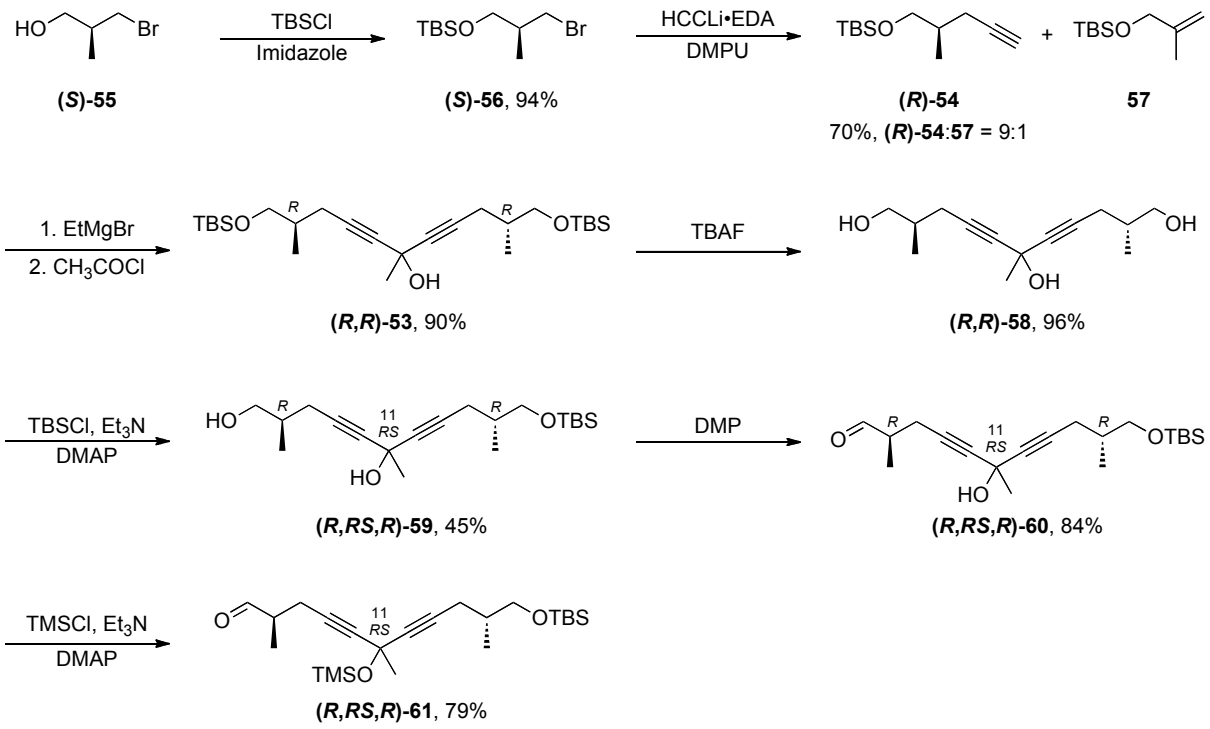


The forward synthesis of triol **(*R*,*R*)-53** starts from the commercially available (*S*)-3-bromo-2-methyl propanol **(*S*)-55** as summarized in Scheme 9. Protection of the hydroxyl group of **(*S*)-55** as a TBS ether provided the bromide **(*S*)-56** in 94% yield. Treatment of **(*S*)-56** with 2 equiv lithium acetylide-ethylenediamine complex afforded alkyne **(*R*)-54**, but only as an inseparable mixture with the elimination product **57** (alkyne:alkene ratio = 9:1, based on ^{1}H NMR spectroscopic analysis). This mixture was carried forward to the next step without further purification. Deprotonation of 2 equiv of **(*R*)-54** with 2 equiv EtMgBr and addition of 1 equiv of acetyl chloride provided pseudo-C2 symmetric alcohol **(*R*,*R*)-53**. At this point we decided to postpone the hydrogenation of the two triple bonds until after the coupling with ketoalcohol **40**.

Removal of both the TBS groups in **(*R*,*R*)-53** with TBAF provided the triol **(*R*,*R*)-58** in 96% yield. The symmetry of **(*R*,*R*)-58** was broken in a non-selective fashion by statistical monosilylation with TBSCl in presence of triethylamine and DMAP.[39] This reaction provided an inseparable mixture of two compounds **59** whose configurations differed at C11 in 45% yield. Oxidation of the free primary alcohol of **59** with Dess-Martin periodinane[40] followed by

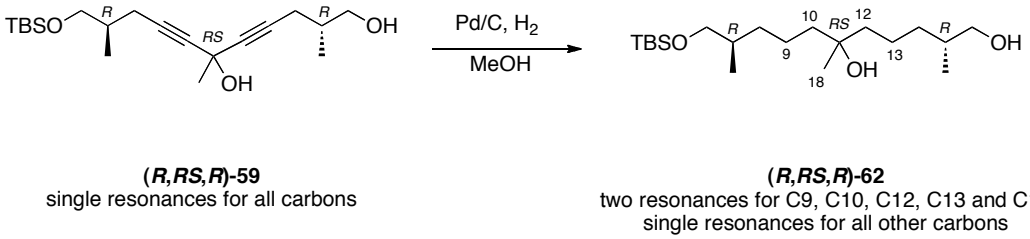
silylation of the remaining tertiary alcohol with TMSCl provided the C6-C16 fragment **(*R*,*RS*,*R*)-61**, again as an inseparable mixture of epimers at the C11 stereocenter.

Scheme 9. Synthesis of C6–C16 fragment aldehyde **(*R*,*RS*,*R*)-61**.



The spectra of the two mixed isomers in compounds **(*R*,*RS*,*R*)-59**, **(*R*,*RS*,*R*)-60** and **(*R*,*RS*,*R*)-61** were substantially identical, and no doubling of resonances was observed in the ^{1}H or ^{13}C NMR spectra of these compounds. (In a related compound **(*R*,*RS*,*R*)-62** with saturated alkynes (Scheme 10), the ^{13}C NMR spectra of the two mixed isomers were resolved and two resonances were observed in its ^{13}C NMR spectrum for the C9, C10, C12, C13 and C18 carbons.)

Scheme 10. Hydrogenation of **(*R*,*RS*,*R*)-59**.



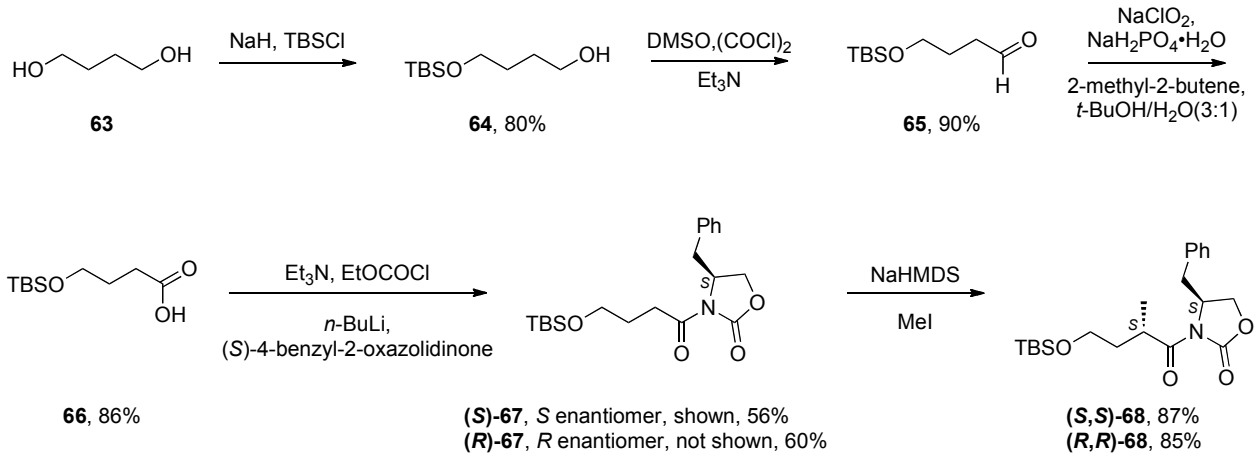
(*R*,*RS*,*R*)-59
single resonances for all carbons

(*R*,*RS*,*R*)-62
two resonances for C9, C10, C12, C13 and C18
single resonances for all other carbons

1.2.4 Synthesis of C1–C5 fragment, ketoalcohol 40

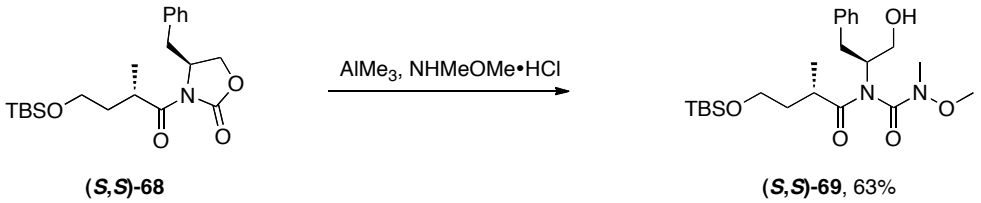
The two enantiomers of ketoalcohol **40** were synthesized by standard Evans aldol methods[41] as summarized in Scheme 11. Monosilylation of 1,4-butanediol **63** was affected in 80% yield by reaction with sodium hydride and TBSCl.[42] The monosilylated ether **64** was converted to the corresponding carboxylic acid **66** by using a two step procedure: a Swern oxidation[43] of alcohol **64**, followed by Pinnick oxidation[44] of the resulting aldehyde **65**. Conversion of acid **66** to the mixed anhydride and treatment with lithiated *R*-4-benzyl-2-oxazolidinone furnished **(*S*)-67**.[41] Alkylation of **(*S*)-67** with NaHMDS and CH_3I gave **(*S*,*S*)-68** in 87% yield.[45]

Scheme 11. Synthesis of the oxazolidinone derivatives **68**.



Conversion of the oxazolidinone derivative **(*S*,*S*)-68** to the corresponding Weinreb amide[36b] was next attempted by reaction with trimethylaluminium and *N*,*O*-dimethylhydroxyl-amine hydrochloride (Scheme 12).[46] However, this reaction gave urea **(*S*,*S*)-69**, resulting from the attack on the oxazolidinone carbonyl, as the only product in 63% yield.[47]

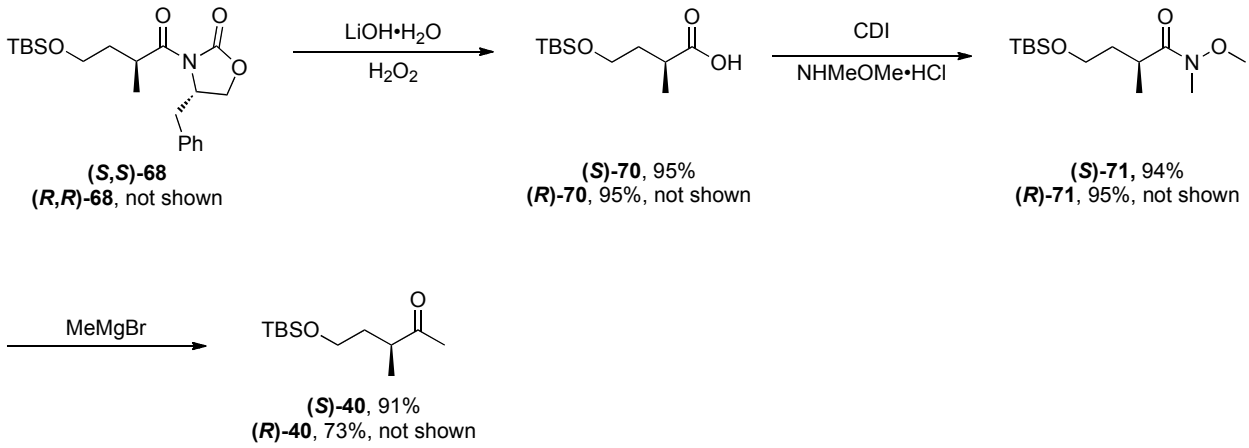
Scheme 12. Attempted conversion of **(*S*,*S*)-68** to the corresponding Weinreb amide.



Weinreb amides **71** were obtained by a two-step protocol shown in Scheme 13. Basic hydrolysis of the oxazolidinone derivatives **68** with lithium hydroperoxide gave the corresponding carboxylic acids **70** in 95% yield.[48] Reactions of carboxylic acids with *N*,*O*-

dimethylhydroxylamine hydrochloride in presence of carbonyl diimidazole (CDI) afforded the Weinreb amides **71**.[49] Addition of CH_3MgBr to the Weinreb amides provided the C1–C5 fragment **40** in good overall yield.[50]

Scheme 13. Completion of the synthesis of fragment **(*S*)-40**.



(*S*,*S*)-68
(*R*,*R*)-68, not shown

(*S*)-70, 95%
(*R*)-70, 95%, not shown

(*S*)-71, 94%
(*R*)-71, 95%, not shown

(*S*)-40, 91%
(*R*)-40, 73%, not shown

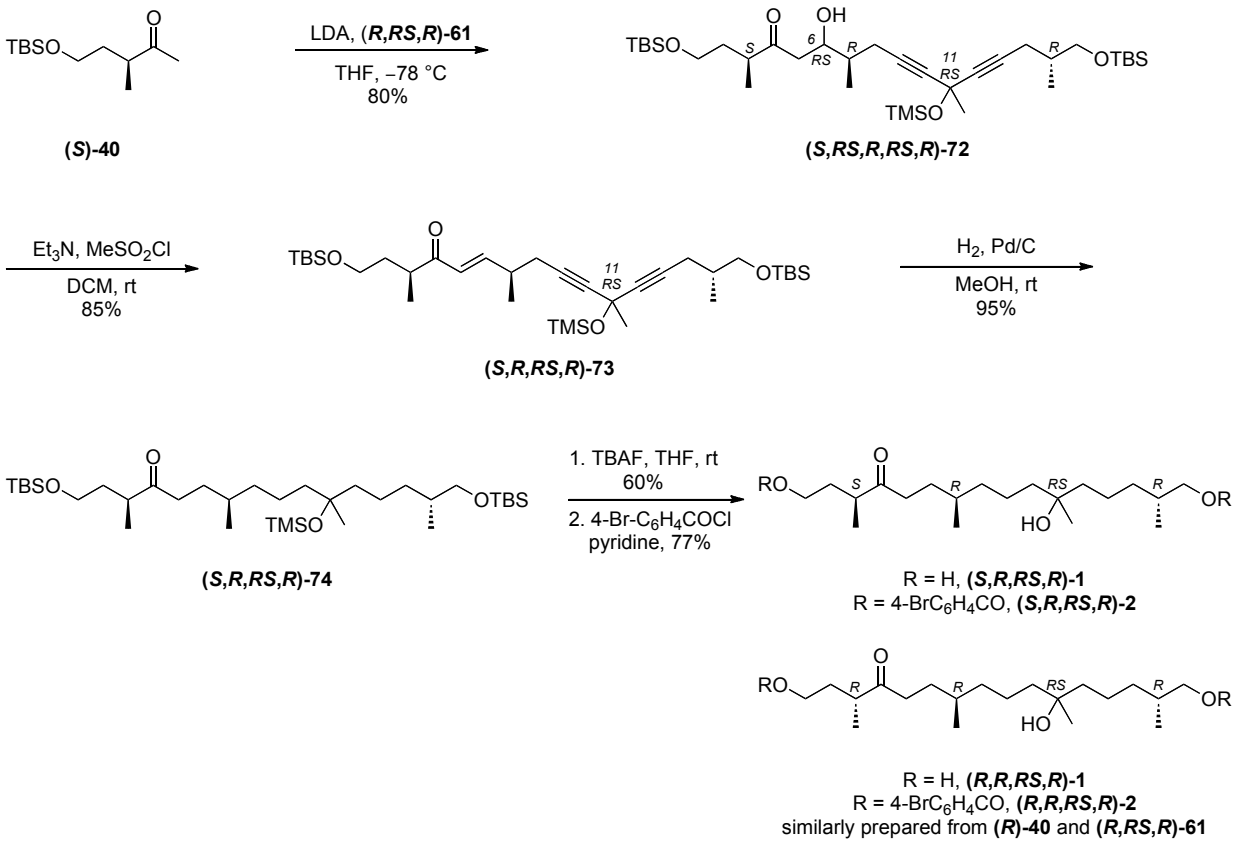
The enantiopurities of the ketones **(*S*)-40** and **(*R*)-40** were confirmed by GC analysis using chiral capillary column, chiraldex GTA. The chromatogram of the racemic ketone **rac-40** showed two equal intensity peaks at 49.5 and 50.2 min, the GC chromatogram of ketone **(*R*)-40** showed a single peak corresponding to the first peak of **rac-40** and the GC chromatogram of ketone **(*S*)-40** showed a single peak corresponding to the second peak of **rac-40**.

1.2.5 Coupling of ketoalcohol 40 with aldehyde 61 and completion of the synthesis of 1

The coupling of the two fragments was accomplished by an aldol reaction of the ketone **(*S*)-40** and aldehyde **(*R*,*RS*,*R*)-61** with LDA as base to obtain **72** as a mixture of diastereomers at C6 and C11, in 80% yield (Scheme 14).[51] Mesylation of the free secondary alcohol with MsCl

and triethylamine and in situ elimination provided the ene-diyne **73** in 85% yield. The ene-diyne **73** must again be a mixture of two isomers with different configuration at C11. The alkene and alkynes were reduced by catalytic hydrogenation to afford the protected ketotriol **74**.[52] Deprotection of **74** with TBAF in THF provided the first two compound mixture **(*S*,*R*,*RS*,*R*)-1** in 65% yield. The second two compound mixture **(*R*,*R*,*RS*,*R*)-1** was similarly prepared by coupling **(*R*)-40** with **(*R*,*RS*,*R*)-61**, then carrying the coupled product through the same sequence of steps. Both the samples of **1** were also converted to the corresponding bis-*p*-bromobenzoate derivatives **(*S*,*R*,*RS*,*R*)-2** and **(*R*,*R*,*RS*,*R*)-2** by acylation with *p*-bromobenzoyl chloride in pyridine for comparison with the bis-*p*-bromobenzoate of the natural product.[18]

Scheme 14. Fragment coupling and completion of the synthesis of **1**.



The 500 MHz ^{1}H NMR spectra of **(*S*,*R*,*RS*,*R*)-1** and **(*R*,*R*,*RS*,*R*)-1** were substantially identical, and there was no indication that these samples were a mixture of two isomers. Both these spectra were also identical to that of the natural product. The 150 MHz ^{13}C NMR spectra of the two samples did show doubling of a few resonances indicating small differences in the ^{13}C resonances of the isomers of **1**. The ^{1}H NMR spectra of **(*S*,*R*,*RS*,*R*)-1** and **(*R*,*R*,*RS*,*R*)-1** are shown in Figure 7. The Table 1 summarizes the ^{1}H and ^{13}C NMR spectral data of the natural hormone α1 and the two synthetic isomers of **1**.

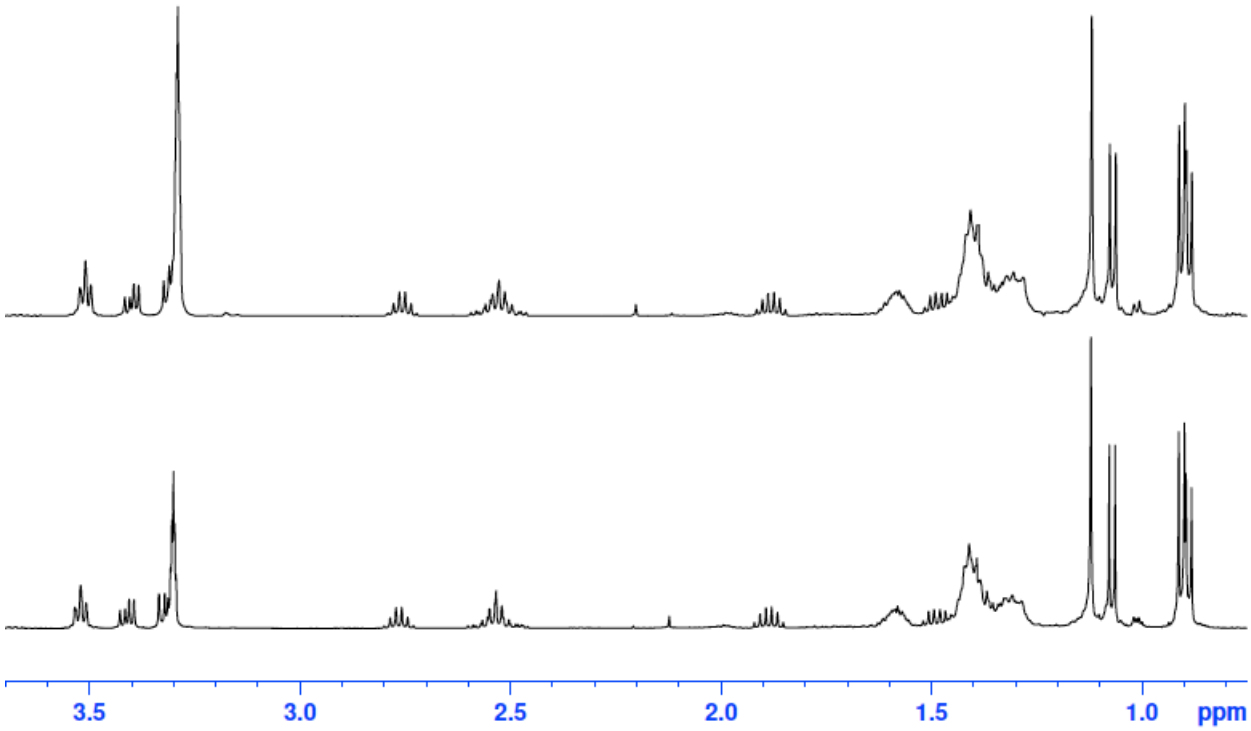


Figure 7. ^{1}H (500 MHz) NMR spectra of **(*S*,*R*,*RS*,*R*)-1** (top) and **(*R*,*R*,*RS*,*R*)-1** (bottom).

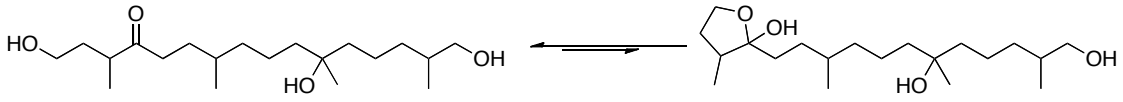
Table 1. ^{1}H and ^{13}C NMR data for hormone α1[18] (600 MHz and 150 MHz) and the two synthetic isomers **(*S*,*R*,*RS*,*R*)-1** and **(*R*,*R*,*RS*,*R*)-1** (500 MHz and 125 MHz).

C No.	δ Hormone α1		δ **(*S*,*R*,*RS*,*R*)-1**		δ **(*R*,*R*,*RS*,*R*)-1**	
	^{1}H (*J* Hz)	^{13}C	^{1}H (*J* Hz)	^{13}C	^{1}H (*J* Hz)	^{13}C
1	3.52 br t (6.6)	60.6	3.52 t (6.0)	60.63	3.53 t (6.0)	60.63
2	1.48, 1.88 m	36.7	1.89 sxt (7.0)	36.75	1.88 sxt (7.0)	36.75
			1.52–1.46 m	36.72	1.52–1.45 m	36.72
3	2.77 sxt (6.9)	44.0	2.77 sxt (6.9)	43.97	2.77 sxt (6.9)	43.98
4	-	217.6	-	217.49	-	217.48
5	2.53 m	40.0	2.60–2.46 m	39.97	2.60-2.47 m	39.97
6	1.35, 1.60 m	31.7	1.62–1.55 m	31.74	1.62–1.56 m	31.74
			1.46–1.28 m		1.45–1.25 m	
7	1.42 m	33.6	1.46–1.28 m	33.58	1.45–1.25 m	33.59
8	1.13, 1,31 m	38.6	1.46–1.28 m	38.62	1.45–1.25 m	38.62
			1.15–1.05 m	38.60	1.15–1.05 m	
9*	1.41 m	22.3	1.46–1.28 m	22.37	1.45–1.25 m	22.36
				22.34		22.34
10#	1.41 m	43.0	1.46–1.28 m	42.93	1.45–1.25 m	42.91
				42.89		
11	-	73.4	-	73.38	-	73.37
12#	1.41 m	43.0	1.46–1.28 m	43.00	1.45–1.25 m	43.02
				42.97		42.98
13*	1.31, 1.41 m	22.4	1.46–1.28 m	22.32	1.45–1.25 m	22.32
				22.30		22.30
14	1.08, 1.42 m	35.1	1.46–1.28 m	35.04	1.15–1.05 m	35.05
			1.15–1.05 m		1.45–1.25 m	
15	1.58 m	36.9	1.62-1.55 m	36.88	1.62–1.56 m	36.88
16	3.41 dd (6.0, 10.8)	68.5	3.41 dd (6.0, 10.5)	68.45	3.41 dd (6.0, 10.5)	68.45
	3.33 dd (10.8, 4.2)		3.33 dd (7.0, 11.0)		3.33 dd (6.5, 11.0)	
17	0.91 d (7.2)	17.7	0.91 d (7.0)	17.09	0.91 d (6.5)	17.11
18	1.12 s	26.9	1.12 s	26.96	1.12 s	26.97
				26.94		26.94
				26.91		26.92
19	0.89 d (6.6)	19.9	0.89 d (6.5)	19.89	0.89 d (6.5)	19.90
20	1.07 d (6.6)	16.9	1.07 d (7.0)	16.90	1.07 d (6.5)	16.90

The assignments of peaks marked with * and # are interchangeable.

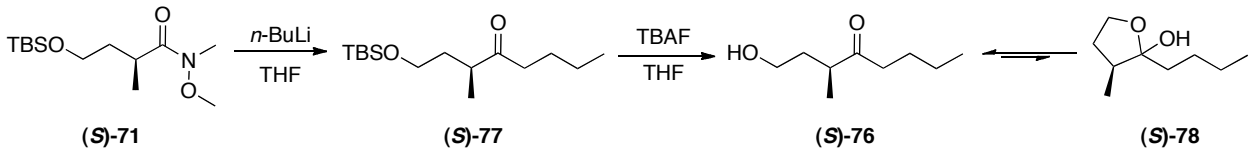
Ojika and coworkers had reported that the spectra of the natural product showed the presence of trace amounts of unknown impurities[18] and we saw similar small peaks (<10%) in the ^{1}H NMR spectra of the two synthetic samples **(*S*,*R*,*RS*,*R*)-1** and **(*R*,*R*,*RS*,*R*)-1**. We suspected that these small peaks might be arising from the hemiacetal **75** (addition of OH at C1 to ketone at C4) present at equilibrium (Scheme 15).[53]

Scheme 15. Proposed ketoalcohol–hemiacetal equilibrium.



To support this assumption, we synthesized ketoalcohol **76**, a structural analog of **1** (Scheme 16) to see if its ^{1}H NMR spectrum would show similar hemiacetal peaks. Treatment of the Weinreb amide **(*S*)-71** with *n*-BuLi afforded the silylether **(*S*)-77**, which was deprotected with TBAF in THF to obtain the target compound **(*S*)-76**. The ^{1}H NMR spectrum of ketoalcohol **(*S*)-76** did show small peaks corresponding to the hemiacetal **78**. These additional hemiacetal peaks were similar to the small 'impurity' peaks present in the natural product ^{1}H NMR spectrum (Figure 8). Accordingly, we concluded that the natural product **1** exists in equilibrium with the hemiacetal **75**.

Scheme 16. Synthesis of **(*S*)-76**, a structural analog of **1**.



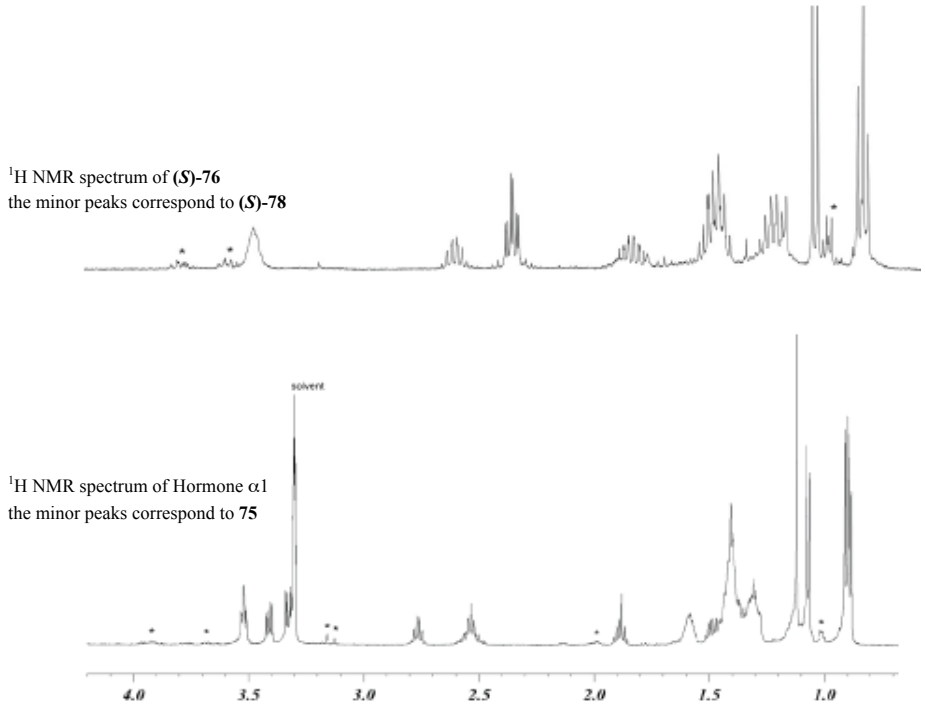


Figure 8. A comparison of the ^{1}H NMR spectra of the hormone α1 (bottom, taken from *Science* **2005**, *309*, 1828) and **(*S*)-76** (top), the peaks marked with asterisk correspond to the hemiacetal **75** and **(*S*)-78** present in equilibrium with **1** and **(*S*)-76** respectively.

Both the purified bis-*p*-bromobenzoate samples **(*S*,*R*,*RS*,*R*)-2** and **(*R*,*R*,*RS*,*R*)-2** exhibited a single spot on the standard silica gel TLC plate and showed a single peak on reverse phase HPLC analysis. However, the ^{1}H NMR spectra of these benzoates suggested that they were not single compounds. The ^{1}H NMR spectra of the two synthetic samples of **2** and were substantially identical and showed single resonances for all non-overlapping protons, with an important exception. The methyl group at C19 (bonded to C7) appeared as an apparent triplet. We interpreted this triplet as two overlapping doublets (δ 0.83 and 0.82 ppm), each arising from a different diastereomer. Surprisingly, the ^{1}H NMR spectrum of the bis-*p*-bromobenzoate of the natural sample also showed this feature, suggesting that the natural sample of **1** was not

isomerically pure. The ^{1}H NMR spectra of the two synthetic bis-*p*-bromobenzoates **2** along with an expansion of the C19 methyl peak are shown in are shown in Figure 9.

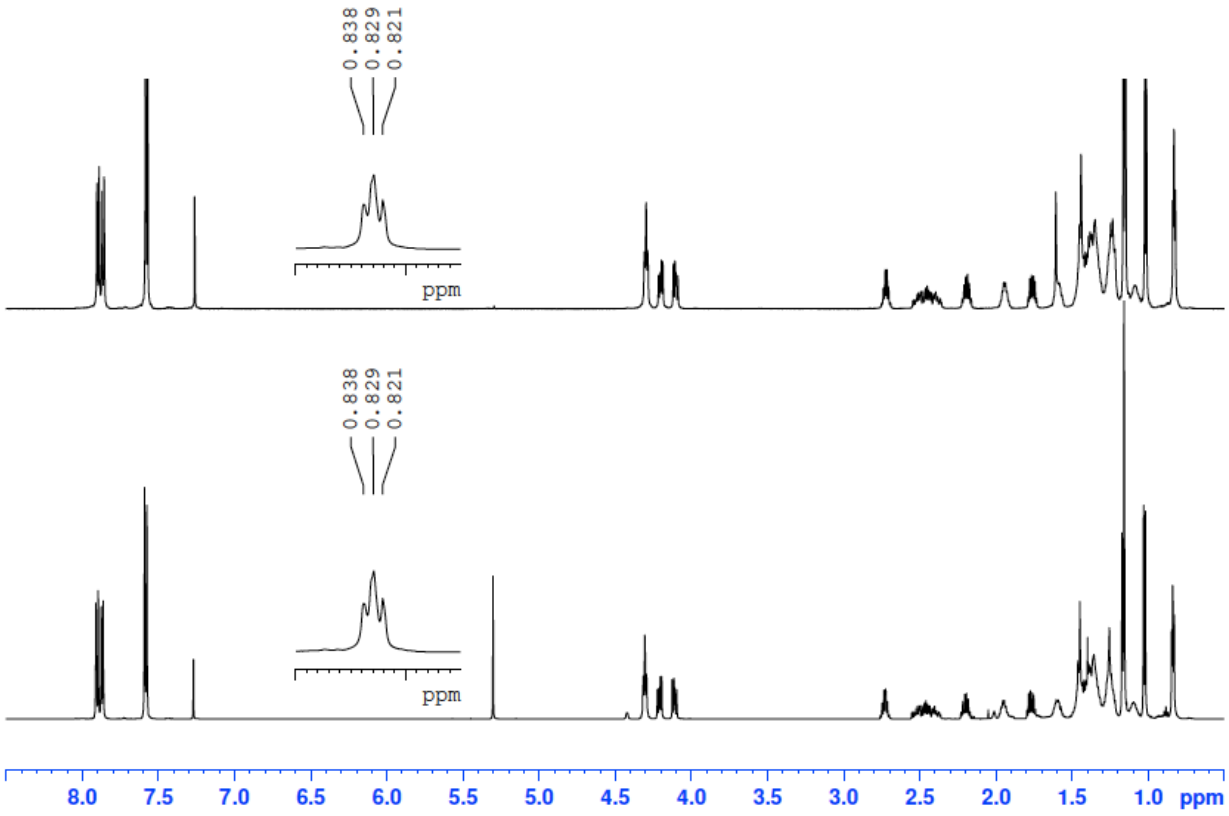


Figure 9. ^{1}H NMR (500 MHz) spectra of the bis-*p*-bromobenzoates **(*S*,*R*,*RS*,*R*)**-2 (top) and **(*R*,*R*,*RS*,*R*)-2** (bottom) along with a expansion of the C19 methyl peak.

The ^{13}C spectra of the two synthetic samples of **2** showed single resonances for many of the carbons. However, some of the resonances were doubled, and the C18 resonance was even quadrupled. Figure 10 summarizes the doubled and quadrupled resonances. The ^{13}C NMR spectra **(*S*,*R*,*RS*,*R*)-2** and **(*R*,*R*,*RS*,*R*)-2** are shown on page 198 and 199 of the Appendix. HPLC analysis of **(*S*,*R*,*RS*,*R*)-2** and **(*R*,*R*,*RS*,*R*)-2** on a chiralcel OD column showed four overlapping

peaks for both the samples. These results suggested that the two samples of **2** were a mixture of more than two isomers.

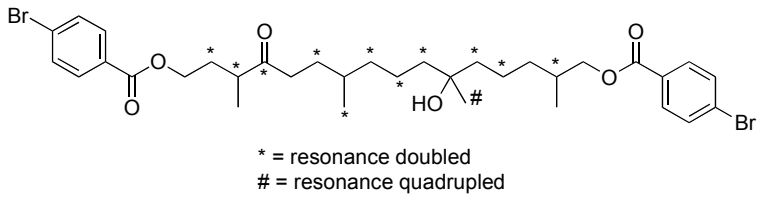


Figure 10. Doubled and quadrupled ^{13}C NMR resonances of the two samples of **2**.

The fact that both the sample of **1** and **2** were identical and that they both were a mixture of more than two isomers each suggested that epimerization occurred at some point during the synthesis and that the final products **1** and **2** are four-isomer mixtures rather than the expected two-isomer mixtures. We speculated that epimerization at C3 occurred either during the aldol/elimination sequence or during hydrogenation of the ene diyne **73**.

1.2.6 Conclusions from the first-generation mixture synthesis of hormone α1

This mixture synthesis of **1** helps to advance the understanding of the hormone α1. We confirmed the constitutional structure of the natural hormone α1. The ^{1}H NMR spectra of the four isomers that we made are identical, while the ^{13}C spectra are very similar but not identical. The ^{1}H spectra of the bis-*p*-bromobenzoate derivatives are better resolved and both ^{1}H and ^{13}C NMR spectra show small differences for stereoisomers. Some of these differences also appear in the bis-*p*-bromobenzoate derived from the natural sample, indicating that the natural product is also a mixture of stereoisomers, probably at the C3 stereocenter. This was confirmed at about the

same time by Ojika and coworkers by Mosher ester analysis of the natural product.[26] We also learned that **1** exists in equilibrium with the hemiacetal form **75**.

Finally, although this purposeful synthesis of **1** as a mixture of epimers at C11 did prove helpful in looking for differences in spectra, it is not a good strategy for an expanded synthesis of a stereoisomer library of **1**. It did not prove practical to separate the C11 epimers at any stage of the synthesis. The results were further complicated by the observed epimerization at the C3 stereocenter. Our further efforts were directed towards FMS of an isomerically pure stereoisomer library of hormone α1 by a revised synthetic route.

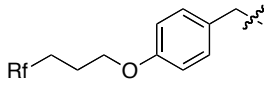
1.3 FLUOROUS MIXTURE SYNTHESIS OF EIGHT ISOMERS OF HORMONE α1

1.3.1 Fluorous *para*-methoxybenzyl groups as fluorous tags

Before deciding the retrosynthetic strategy for synthesis of a stereoisomer library of hormone α1, we had to decide the fluorous tags to be used in its FMS. Our group has previously reported the use of fluorous triisopropylsilyl ($TIPS^F$)[4-5,14,16,54] and fluorous *para*-methoxybenzyl (PMB^F)[13,55] groups as fluorous tags for syntheses of stereoisomer libraries of natural products. We choose to use the PMB^F groups as the fluorous tags. PMB^F groups are a fluorous analogue of the popular *para*-methoxybenzyl (PMB) protecting group. Instead of a methoxy substituent at the *para* position of the benzyl ring they have a (perfluoroalkyl)propyl ($–O(CH_2)_3Rf$) substituent, Rf being a perfluoroalkyl chain of varying length. The structures of the various PMB^F groups used in the FMS of hormone α1 are shown in Figure 11.

Throughout this document, PMB^{F} or PMB^{Fn} will be used as an abbreviation of fluorous PMB group, with n being the number of fluorine atoms present in the given tag. During the course of this synthesis, the compounds bearing different PMB^{F} groups will be mixed, the PMB^{F} groups of such mixtures will be depicted as $PMB^{Fm,n}$, where m and n are the number of fluorine atoms in the fluorous tags of the mixed compounds. Also, the letter "**M**" before any compound number will indicate that the particular compound is a mixture of fluorous-tagged quasiisomers. For example, compound **M79** in Scheme 17 is a mixture of four fluorous-tagged quasiisomers. When same compounds have different fluorous-tags suffix **a**, **b** or **c** has been used to indicate C_4F_9, C_6F_{13} and CF_3 bearing PMB^{F} group respectively. For example $PMB^{F9}OH$, $PMB^{F13}OH$ and $PMB^{F3}OH$ have been named as **95a**, **95b** and **95c** respectively.

The reactivity of the PMB^{F} groups is very similar to the reactivity of the conventional PMB protecting group. They are stable to a wide range of reaction conditions and provide for easy protection and deprotection.[55a,56] The fluorous PMB^{F} groups also provide a chromophore for the UV detection of compounds during preparative HPLC demixing of the fluorous-tagged products before detagging.



Rf	Abbreviation	Name
C_6F_{13}	PMB^{F13}	4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzyl
C_4F_9	PMB^{F9}	4-(4,4,5,5,6,6,7,7-nonafluoroheptyloxy)benzyl
CF_3	PMB^{F3}	4-(4,4,4-trifluorobutoxy)benzyl

Figure 11. Structures, abbreviations and names of the PMB^{F} groups used in the FMS of hormone α1.

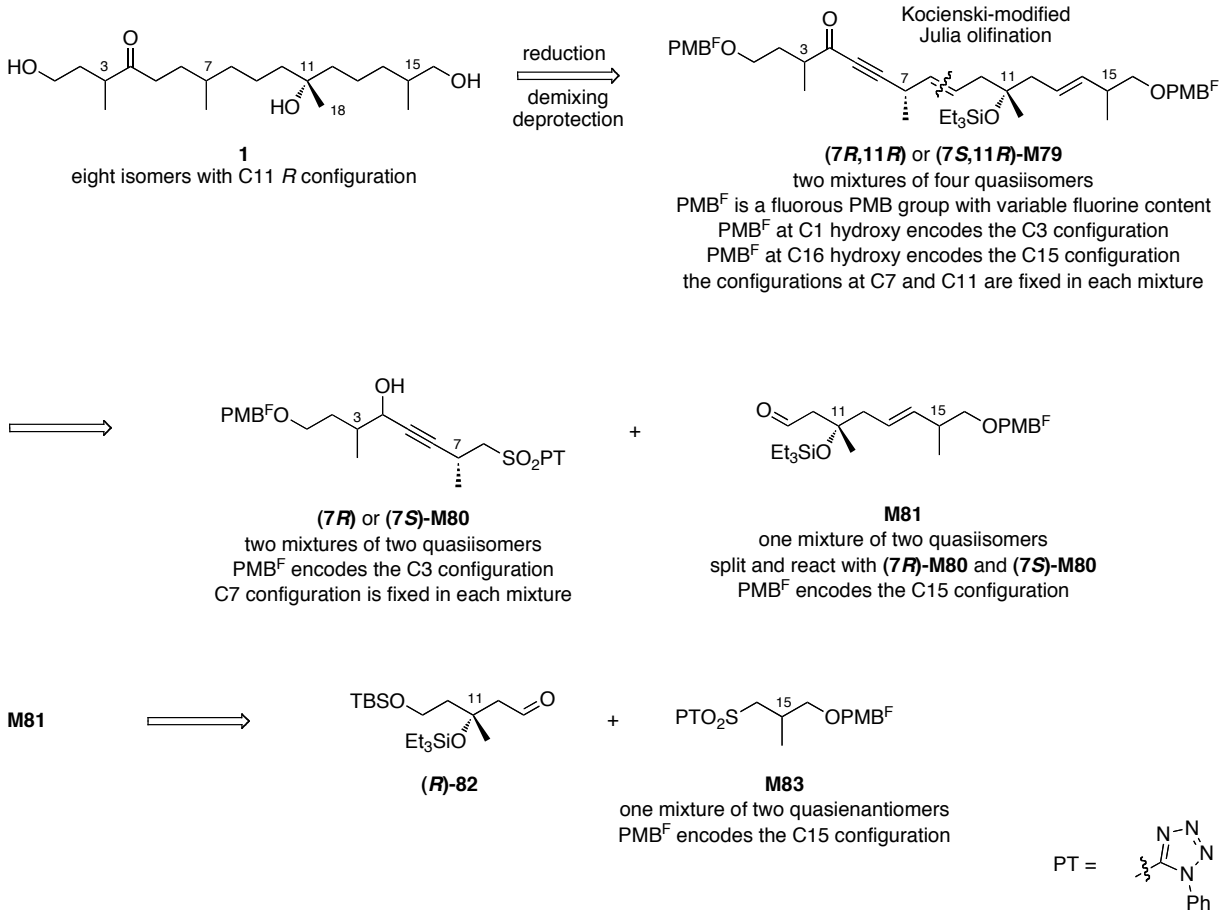
1.3.2 Retrosynthetic analysis for FMS of hormone α1

The hormone α1 has four stereocenters, so its complete stereoisomer library will have 16 members, grouped as eight pairs of enantiomers. Since enantiomers have same physical, chemical and spectroscopic properties, the 16 isomers of hormone α1 will give up to eight unique ^{1}H and ^{13}C NMR spectra. We targeted the synthesis of eight isomers of **1** with fixed C11 *R* configuration and all possible configurations at C3, C7 and C15. Because all eight synthetic isomers will have same configuration at C11, they will be diastereomers of each other. Thus, by synthesizing these eight isomers we will have access to all the possible ^{1}H and ^{13}C NMR spectra from the stereoisomers of hormone α1. We choose to fix the C11 configuration as *R* because the configuration of the natural hormone α1 at C11 has been assigned as *R*.[28]

Our retrosynthesis and tagging strategy to synthesize the target isomers of **1** is shown in Scheme 17. We envisioned that **1** can be readily obtained from the diene **M79** by reduction, demixing over fluorous HPLC, and deprotection. We plan to prepare two mixtures of diene **M79** each containing four quasiisomers. The two mixtures **M79** will have fixed configurations at C7 (*R* or *S*) and C11 (*R*) and all possible configurations at C3 and C15. The PMB^{F} groups in the mixture **M79** at the C1 and C16 hydroxy groups will encode the C3 and C15 configuration, respectively.

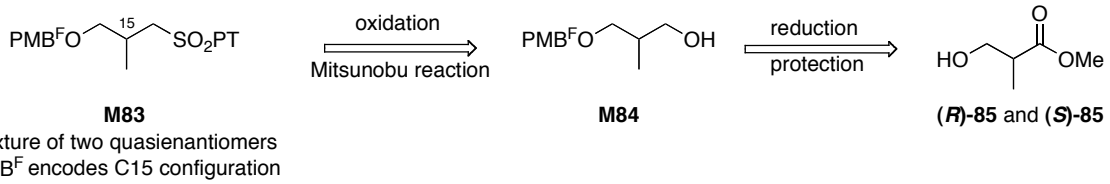
Now the two mixtures **M79** can be obtained by a Kocienski-modified Julia olefination[57] of one two-compound mixture aldehyde **M81** with two two-compound mixtures sulfones **M80**. The synthesis of the two-compound mixture aldehyde **M81** can be accomplished by another Kocienski-modified Julia olefination[57] of the aldehyde **(*R*)-82** with a two-compound mixture sulfone **M83**.

Scheme 17. Retrosynthesis for FMS of eight stereoisomers of hormone α1.



The planned synthesis of C16-C14 fragment **M83** as a mixture of two quasienantiomers with different fluorous tags is shown Scheme 18. The PMB^F groups here will encode the C15 configuration of the final products. The quasiracemate **M83** will be obtained by a Mitsunobu reaction[58] of alcohol **M84** with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH),[59] followed by oxidation of the sulfide to sulfone. The quasiracemic alcohol **M84** can be prepared by protection of commercially available (*R*) and (*S*) methyl 3-hydroxy-2-methylpropionate **85** with two different PMB^F groups, followed by mixing and reduction of the ester to the alcohol.

Scheme 18. Retrosynthesis of fragment **M83**.



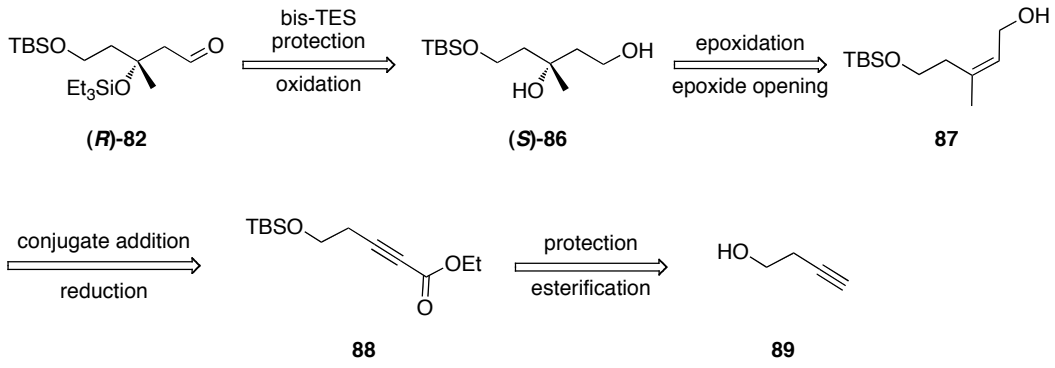
M83
mixture of two quasienantiomers
PMB^F encodes C15 configuration

M84

(***R***)**-85** and (***S***)**-85**

As shown in Scheme19, the aldehyde **(*R*)-82** can be obtained by bis-triethylsilyl (TES) protection of the diol **(*S*)-86** followed by oxidation of the primary TES ether to the corresponding aldehyde under Swern conditions.[43] The diol **(*S*)-86** will be synthesized by Sharpless asymmetric epoxidation[60] and subsequent ring opening of the allylic alcohol **87**. The alcohol **87** will be obtained from ester **88**, which in turn will be prepared from the commercially available 3-butyn-1-ol **89.**

Scheme 19. Retrosynthesis of aldehyde **(*R*)-82**.



(***R***)**-82**

(***S***)**-86**

87

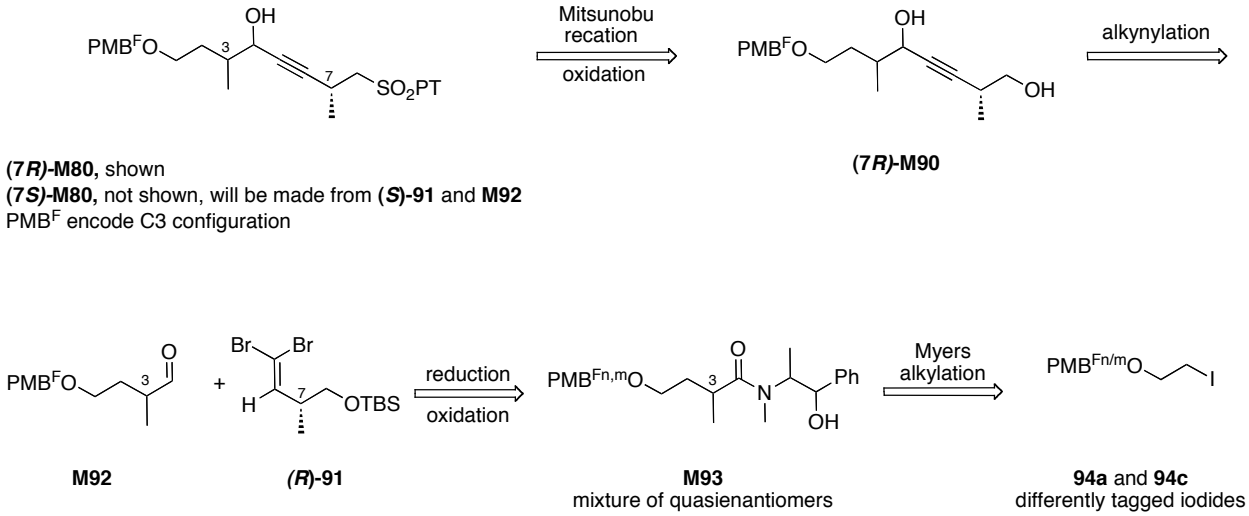
88

89

The sulfone **M80** will be synthesized as two mixtures of two quasidiastereomers each. The two quasidiastereomers in each mixture will have same configuration at the C7 stereocenter (*R* or *S*) and different configuration at the C3 stereocenter, which will be encoded by the PMB^F

group. The retrosynthesis of **(7*R*)-M80** is summarized in Scheme 20. The sulfone **(7*R*)-M80** can be obtained by a Mitsunobu reaction[58] of diol **(7*R*)-M90** with PTSH and subsequent oxidation of the sulfide to the corresponding sulfone. The diol **(7*R*)-M90** can be synthesized by alkynylation[61] of aldehyde **M92** with the known dibromide **(*R*)-91**[62]. The quasiracemic aldehyde **M92** can be prepared from the mixture of differently protected quasienantiomeric amides **M93**. The PMB^F groups in the amides **93** encode the C3 configuration. The amides **93** can be obtained by the Myers alkylation[63] of the (1*R*,2*R*)- and (1*S*,2*S*)-pseudoephedrine propionamide with two differentially tagged 2-iodoethanols **94a** and **94c**. The second mixture **(7*S*)-M80** will be similarly prepared by coupling of quasiracemic aldehyde **M92** with bromide **(*S*)-91**[64].

Scheme 20. Retrosynthesis of fragment **(7*R*)-M80**.

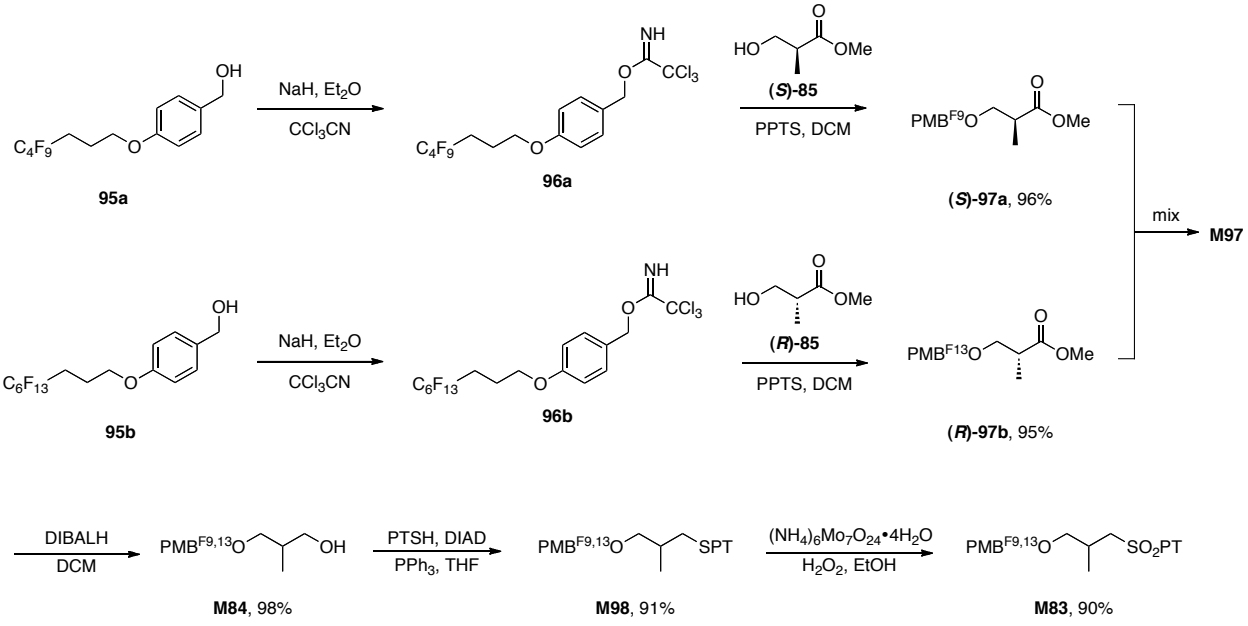


1.3.3 Synthesis of C14-C16 fragment M83

The synthesis of fragment **M83** starts from commercially available (*R*) and (*S*)-methyl 3-hydroxy-2-methylpropionate (**(*S*)-85** and **(*R*)-85**) as summarized in Scheme 21. The hydroxy groups in **(*S*)-85** and **(*R*)-85** were individually tagged with two different fluorous tags. The alcohol **(*S*)-85** was protected as a PMB^F ether bearing a perfluorobutyl (C_4F_9) group to encode the C15 *R* configuration in **M79**. The required PMB^{F9} trichloroacetimidate **96a** was prepared by reaction of commercially available $PMB^{F9}OH$ **95a** with sodium hydride and trichloroacetonitrile.[65] Reaction of crude **96a** with **(*S*)-85** in presence of pyridinium *p*-toulenesulfonate (PPTS) gave the ester **(*S*)-97a**.[65] Likewise, protection of the hydroxy group in **(*R*)-85** as a PMB^F ether bearing perfluorohexyl (C_6F_{13}) chain to encode the C15 *S* configuration in **M79**, provided **(*R*)-97b**.

Equimolar amounts of quasienantiomers **(*S*)-97a** (3.54 g, 7.32 mmol) and **(*R*)-97b** (4.28 g, 7.32 mmol) were weighed and mixed to generate the quasiracemic mixture **M97** (7.82 g, 14.64 mmol). The quasiracemate **M97** was reduced with DIBAL to afford **M84** in 98% yield. The alcohol **M84** was converted to the corresponding sulfide **M98** by a Mitsunobu reaction[58] with PTSH in the presence of triphenylphosphine and DIAD in 91% yield.[59] Oxidation of **M98** with ammonium molybdate/H_2O_2[66] in EtOH afforded the C14-C16 fragment **M83** in 90% yield.[59] A total of 8.01 g (11.50 mmol) of the **M83** was synthesized.

Scheme 21. Synthesis of C14-C16 fragment **M83**.



Throughout the FMS, the ^{19}F NMR spectra of the intermediates have been used to confirm that the 1:1 ratio of the tagged compounds is maintained. The ^{19}F NMR spectra of the esters **(*S*)-97a**, **(*R*)-97b** and the mixture **M84** are shown in Figure 12. The ^{19}F NMR spectrum of the PMB^{F9} protected ester **(*S*)-97a** shows a peak at δ –81.80 and three peaks at δ –114.55, –124.40, and –126.03. Based on the integration ratio, these peaks are assigned to the CF_3 group and to the three CF_2 groups in the PMB^{F9} tag respectively. The ^{19}F NMR spectrum of the PMB^{F13} protected ester **(*R*)-97b**, exhibits a peak at –80.85 for the CF_3 group and peaks at –114.26, –121.89, –122.86, –123.46, –126.13 for the five CF_2 groups in the PMB^{F13} tag. The ^{19}F NMR spectrum of the quasiracemic mixture **M84**, containing PMB^{F9} and PMB^{F13} tagged quasienantiomers, is effectively an addition of ^{19}F NMR spectra of PMB^{F9} tagged **(*S*)-97a** and PMB^{F13} tagged **(*R*)-97b**. The integration ratio of the two CF_3 peaks at –81.80 and –80.85 is 1:1, confirming that the two quasienantiomers in **M84** are present in 1:1 molar ratio. The ^{19}F NMR

spectra of the quasiracemates **M98** and **M83** were similar to that of **M84** and confirmed that the ratio of the quasienantiomers was maintained as 1:1 throughout the synthesis of fragment **M83**.

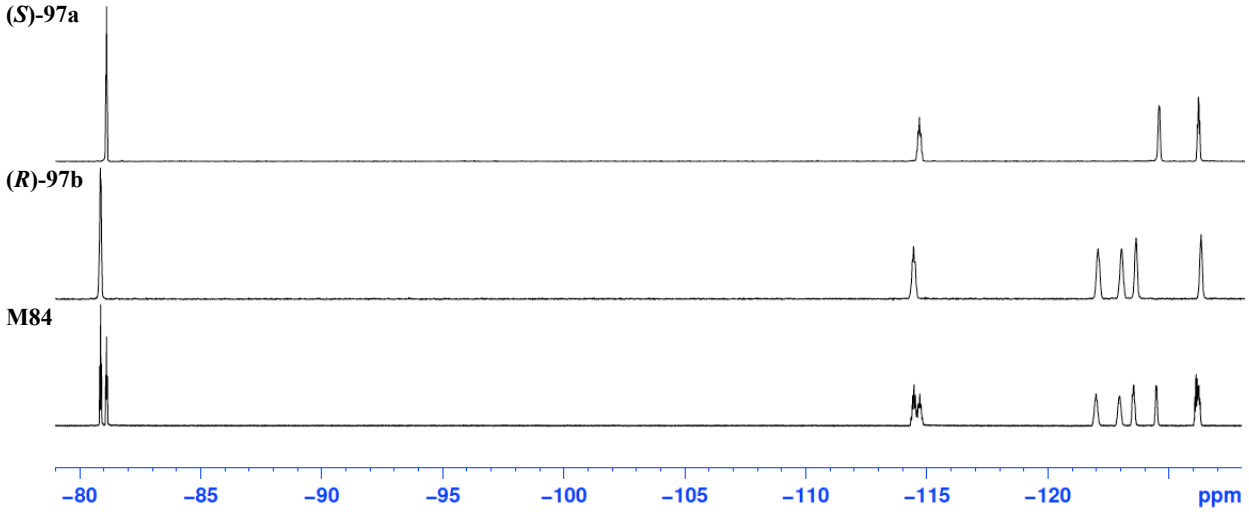
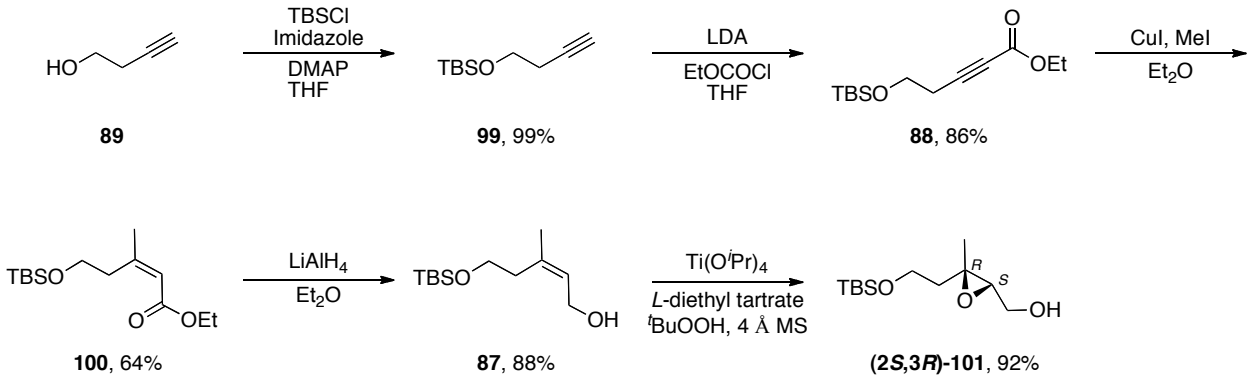


Figure 12. ^{19}F NMR spectra of PMB^{F9} tagged **(*S*)-97a**, PMB^{F13} tagged **(*R*)-97b** and **M84**.

1.3.4 Synthesis of C9-C13 aldehyde fragment (*R*)-82

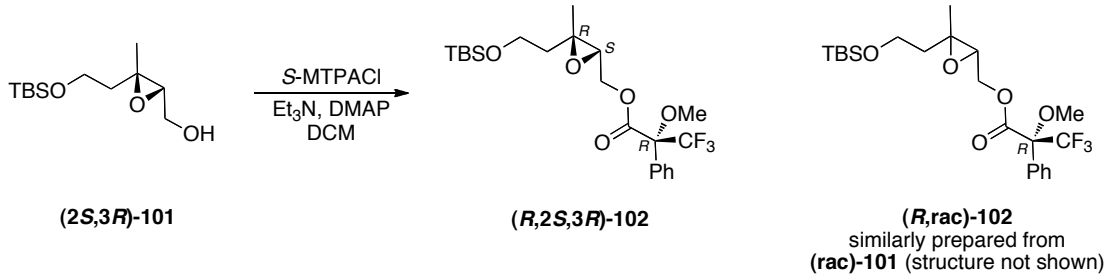
The synthesis of fragment **(*R*)-82** starts from 3-butyn-1-ol (**89**) and is shown in Scheme 22. Protection of the free alcohol group in **89** as a TBS ether by reaction with TBSCl, imidazole and DMAP afforded the alkyne **99**. Deprotonation of the terminal alkyne proton of **99** with LDA followed by addition of ethyl chloroformate afforded the acetylenic ester **88** in 86% yield. Conjugate addition of (dimethylcopper)lithium[67] (prepared by the reaction of copper iodide with methyllithium) furnished the known *Z* unsaturated ester **100**[68] in 64% isolated yield.[69] Reduction of the ester **100** with $LiAlH_4$ provided the allylic alcohol **87**,[68] which upon epoxidation by Sharpless method[60] using *L*(+)-diethyl tartrate yielded the epoxy alcohol **(2*S*,3*R*)-101**.[70]

Scheme 22. Synthesis of epoxide **(2*S*,3*R*)-101**.



The enantiopurity purity of epoxide **(2*S*,3*R*)-101** was determined by ^{1}H NMR analysis of the corresponding Mosher ester[32a,32d] (Scheme 23). The epoxy alcohol **(2*S*,3*R*)-101** was reacted with *S*-MTPA chloride to obtain the *R*-MTPA ester **(*R*,2*S*,3*R*)-102**. An authentic sample of racemic epoxide **(rac)-101** (synthesis and structure not shown) was prepared by the MCPBA epoxidation of alcohol **87** and converted to the *R*-MTPA ester **(*R*,rac)-102** under identical conditions. In the 300 MHz ^{1}H NMR spectrum of (***R*,rac)-102**, one of the C1 methylene protons appeared as two equal intensity doublets of doublets at δ 4.66 and δ 4.59. The ^{1}H NMR spectrum of **(*R*,2*S*,3*R*)-102** showed only a minor doublet of doublets at δ 4.66 and a major doublet of doublets at δ 4.59. Based on the integration ratio of the major peaks to minor peaks, the enantiomeric ratio of the epoxide **(2*S*,3*R*)-101** was calculated as 12:1.

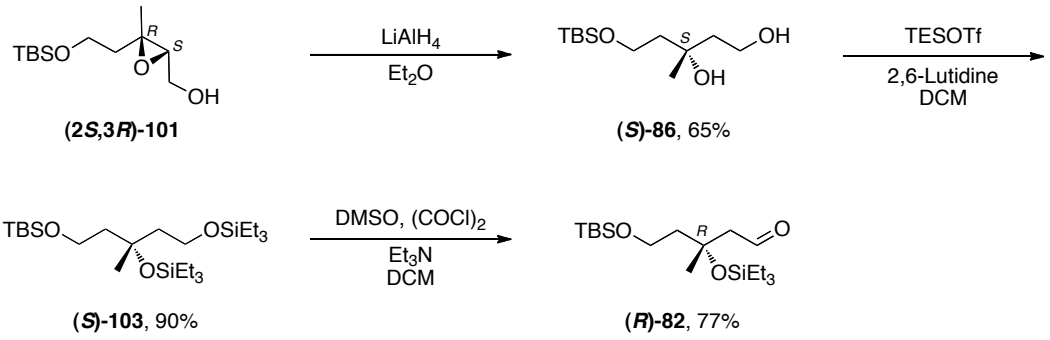
Scheme 23. Conversion of the epoxide **(2*S*,3*R*)-101** to the corresponding Mosher ester.



(2*S*,3*R*)-101 **(*R*,2*S*,3*R*)-102** **(*R*,rac)-102** similarly prepared from **(rac)-101** (structure not shown)

The epoxy alcohol **(2*S*,3*R*)-101** was subsequently reduced with $LiAlH_4$ to afford the diol **(*S*)-86**[70] in 65% yield after flash chromatography (Scheme 24). Silylation of the two free hydroxy groups as TES ethers afforded the protected triol **(*S*)-103**. Finally, selective oxidation of the primary TES ether to the corresponding aldehyde under Swern conditions afforded the C9-C13 fragment **(*R*)-82**.[71] About 4.8 g (10.23 mmol) of the triethylsilyl ether **(*S*)-103** was synthesized and stored. Only the required amount of aldehyde **(*R*)-82** was prepared before each use.

Scheme 24. Completion of the synthesis of **(*R*)-82**.



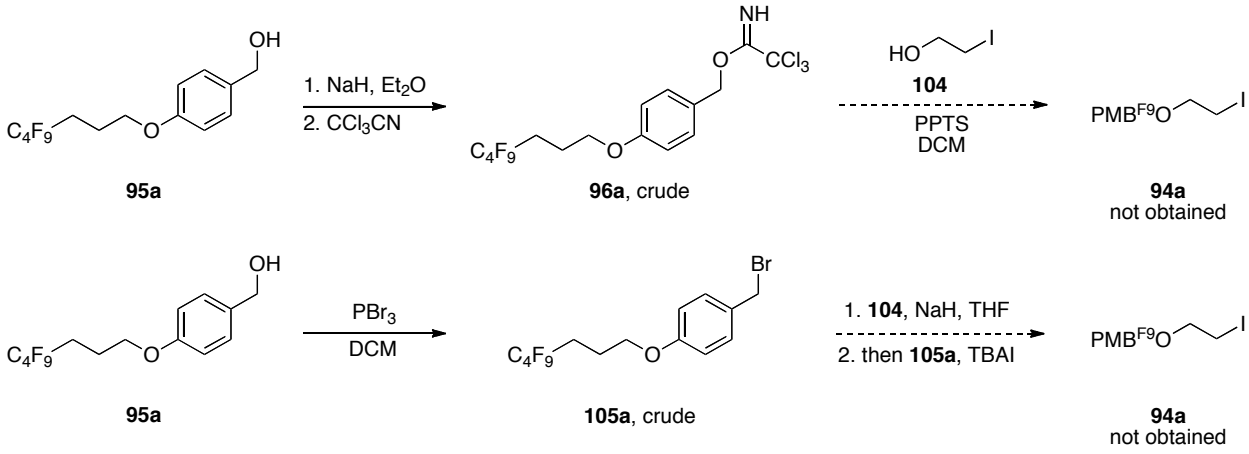
(2*S*,3*R*)-101 **(*S*)-86**, 65%

(*S*)-103, 90% **(*R*)-82**, 77%

1.3.5 Synthesis of iodides 94a and 94c

The preparation of iodide **94a** was initially attempted by protection of commercially available 2-iodoethanol **104** as a PMB^{F9} ether, and these results are summarized in Scheme 25. Protection by reaction of **104** with PMB^{F9} trichloroacetimidate **96a** in presence of PPTS was unsuccessful. Protection of alcohol **104** was also attempted by deprotonation with 1 equiv NaH and treatment with PMB^{F9} bromide **105a** (obtained by bromination of alcohol **95a** with phosphorous tribromide)[72] and tetrabutylammonium iodide (TBAI). The TLC of this reaction mixture indicated disappearance of the 2-iodoethanol, but no target product was obtained and only the bromide **105a** was recovered.

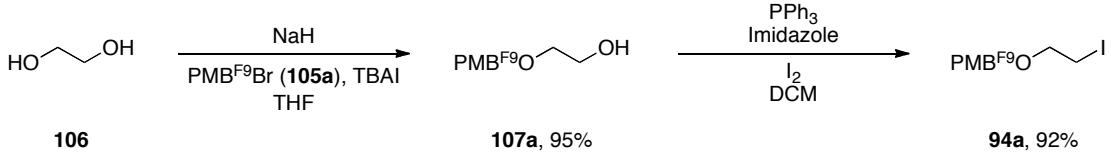
Scheme 25. Unsuccessful attempts towards the synthesis of PMB^{F9} protected iodide **94a**.



The iodide **94a** was successfully prepared in two steps starting from ethylene glycol **106** as shown in Scheme 26. Monoprotection of ethylene glycol with the PMB^{F9} group was affected in 95% yield by deprotonation of an excess of ethylene glycol (20 equiv) with 1 equiv NaH

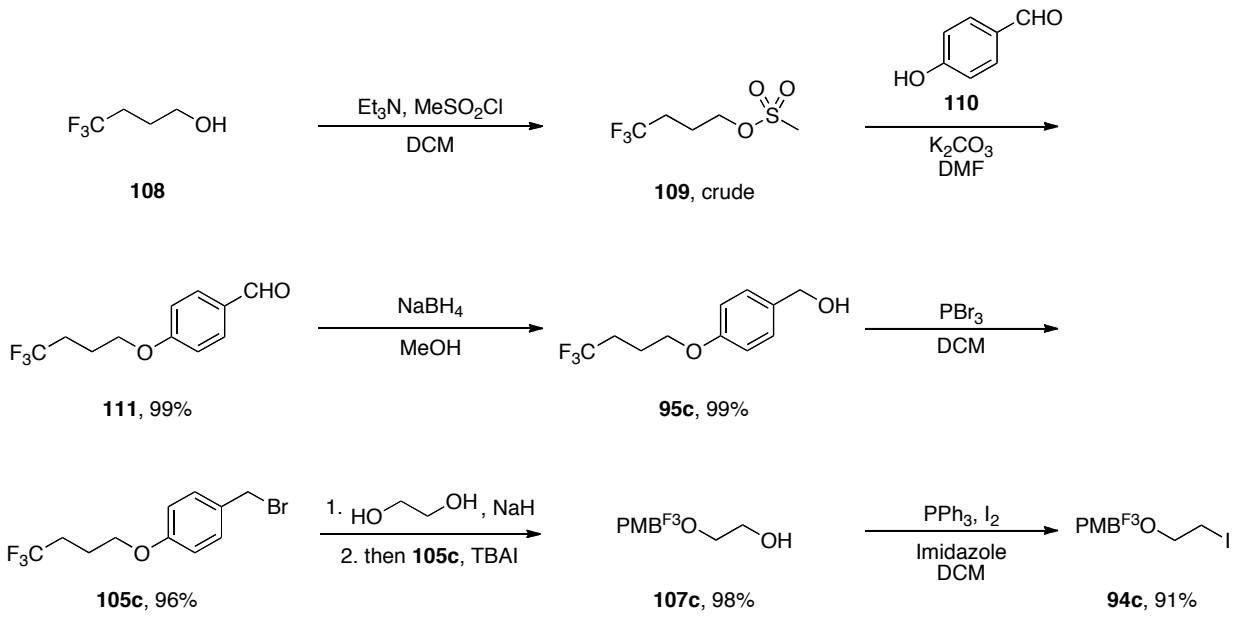
followed by the addition of 1 equiv of $PMB^{F9}Br$ **105a** and catalytic amount of TBAI.[73] The alcohol **107a** was converted to the iodide **94a** in 92% yield by reaction with triphenylphosphine, imidazole and iodine.[74]

Scheme 26. Alternate synthesis of the iodide **94a**.



We decided to use a PMB^{F} group bearing a trifluoromethyl (CF_3) chain as the second fluorous tag to encode the C3 stereocenter in **M79**. The PMB^{F3} alcohol **95c** is not commercially available and was synthesized in three steps from 4,4,4-trifluorobutanol **108** (Scheme 27). Mesylation of **108** followed by reaction with 4-hydroxybenzaldehyde in presence of K_2CO_3 provided the aldehyde **111**. Reduction of **111** with $NaBH_4$ in methanol provided the desired PMB^{F3} alcohol **95c** in 99% yield. This alcohol was converted to the corresponding bromide **105c** by reaction with PBr_3.[72] Once again, deprotonation of excess ethylene glycol with 1 equiv NaH followed by the addition of the bromide **105c** and TBAI provided the PMB^{F3} monoprotected alcohol **107c**.[73] Reaction of **107c** with triphenylphosphine, imidazole and iodine, provided the iodide **94c**.[74]

Scheme 27. Preparation of PMB^{F3} protected iodide **94c.**



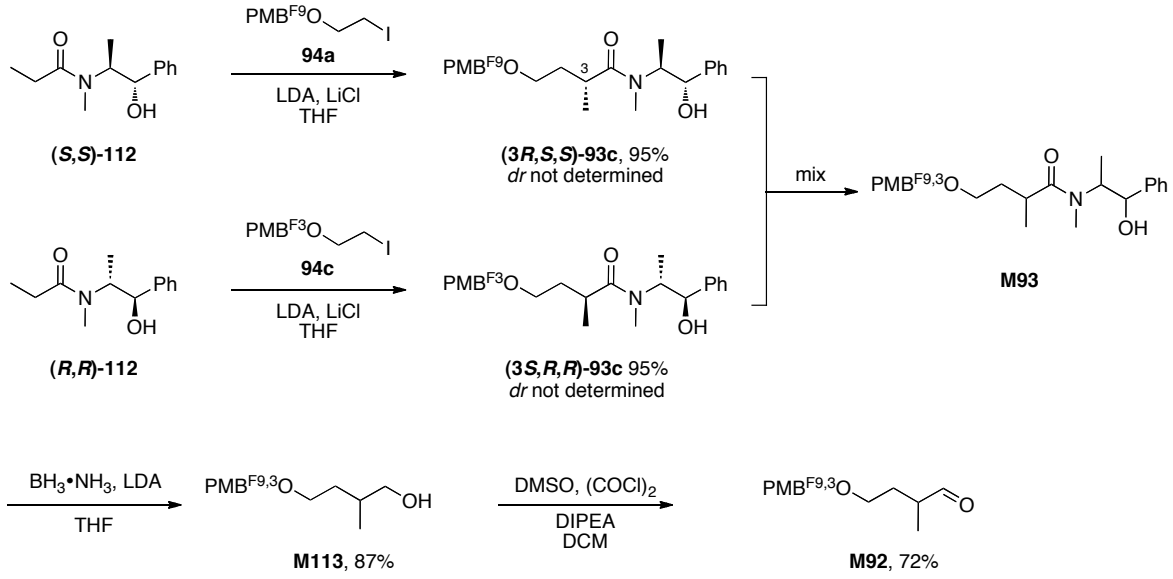
1.3.6 Synthesis of the aldehyde M92

The synthesis of aldehyde **M92** commenced with the Myers alkylation[63] of amides (*S*,*S*)- and (*R*,*R*)-pseudoephedrine propionamides **(*S*,*S*)-112** and **(*R*,*R*)-112** with iodides **94a** and **94c** respectively (Scheme 28). Enolization of **(*S*,*S*)-112** with LDA in the presence of anhydrous lithium chloride, followed by the addition of iodide **94a** led to the efficient formation of the alkylation product **(3*R*,*S*,*S*)-93a**.[75] Considering that alkylation of (*S*,*S*)-pseudoephedrine **(*S*,*S*)-112** will take place from the same face as the carbon-bound methyl group of the pseudoephedrine auxiliary (1,4-syn) as described by Myers,[63] we assigned the configuration of the C3 stereocenter of the amide **93a** as *R*. The amide **(3*S*,*R*,*R*)-93c** was similarly obtained by the alkylation of **(*R*,*R*)-112** with the CF_3 tagged iodide **94c**.

The ^{1}H and ^{13}C NMR spectra of the amides **(3*R*,*S*,*S*)-93a** and **(3*S*,*R*,*R*)-93c** were complicated because of the presence of the amide rotamer and it was not possible to determine their diastereomeric ratio by spectral analysis. We decided to postpone this analysis till after their conversion to the aldehyde **M92**.[76]

Equimolar amounts of the two quasienantiomeric amides **(3*R*,*S*,*S*)-93a** (3.40 g, 5.38 mmol) and **(3*S*,*R*,*R*)-93c** (2.59 g, 5.38 mmol) were mixed to obtain the quasiracemate **M93** (5.99 g, 10.76mmol). Reduction of **M93** with lithiumamidotrihydroborate (LAB),[77] prepared by deprotonation of commercial borane-ammonia complex with LDA, provided the alcohol **M113**.[78] Subsequent oxidation of **M113** under Swern conditions[43] provided the aldehyde **M92**. A total of 2.95 g (7.51 mmol) of **M92** was obtained.

Scheme 28. Synthesis of aldehyde **M92**.



The ^{19}F NMR spectrum of the PMB^{F9} tagged amide **(3*R*,*S*,*S*)-93a** was similar to the ^{19}F NMR spectra of the PMB^{F9} tagged compounds previously synthesized during the synthesis of

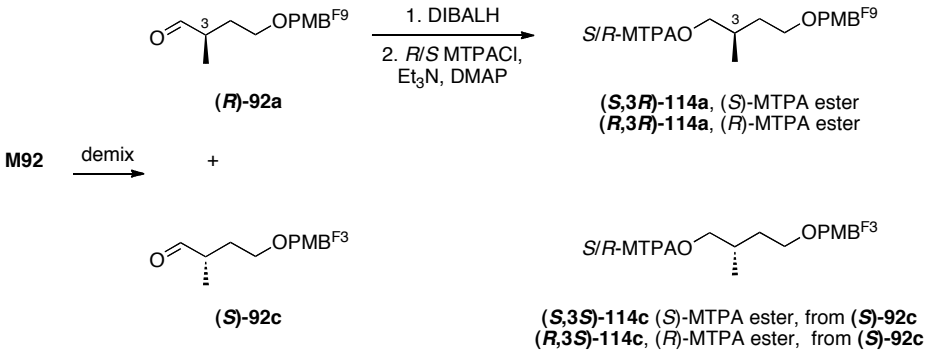
fragment **M83**. It showed a peak at δ −81.80 for the CF_3 group and peaks at δ –114.55, –124.40, and –126.03 for the three CF_2 groups. The ^{19}F NMR spectrum of amide **(3*S*,*R*,*R*)-93c**, showed a single resonance at −66.31 for the CF_3 in the PMB^{F3} tag. The ^{19}F NMR spectrum of the quasiracemic mixture **M113** showed a resonance at −66.31 for the CF_3 group in PMB^{F3}, at −81.80 for the CF_3 group in PMB^{F9}, and three peaks at δ –114.55, –124.40, and –126.03 for the three CF_2 groups in PMB^{F9}. The integration ratio of the two CF_3 peaks was 1:1, confirming that the two quasienantiomers in **M113** were present in 1:1 molar ratio. The ^{19}F NMR spectrum of **M92** was substantially identical to that of **M113** and confirmed that the ratio of the quasienantiomers was maintained as 1:1 in aldehyde **M92**.

Because we did not determine the diastereomeric ratio of the amides **93a** and **93c**, we evaluated the enantiomeric purity of the two quasienantiomeric aldehydes in the mixture **M92**. These results are summarized in Scheme 29. About 40 mg of aldehyde **M92** was demixed into two individual quasienantiomers by preparative fluorous HPLC. Demixing was conducted on a Waters high-performance liquid chromatograph over a *FluoroFlash*TM PFC8 column (10 mL/min) under a gradient elution with 60:40 CH_3CN:H_2O to 100% CH_3CN in 30 min. The demixed quasienantiomeric aldehydes **(*R*)-92a** (15 mg) and **(*S*)-92c** (13 mg) were reduced with DIBAL, and the resulting primary alcohols were converted to the corresponding Mosher esters by treatment with (*R*)- and (*S*)-MTPA chloride in the presence of triethylamine and DMAP. Four crude esters **(*S*,3*R*)-114a**, **(*R*,3*R*)-114a**, **(*S*,3*S*)-114c** and **(*R*,3*S*)-114c** were obtained.

In the 500 MHz ^1H NMR spectrum of the *S*-MTPA ester **(*S*,3*R*)-114a**, the two C4 methylene protons were observed as two major doublets of doublets signals centered at δ 4.28 and 4.12 and two minor doublets of doublets δ 4.21 and 4.18. In the ^1H NMR spectrum of the *R*-MTPA ester **(*R*,3*R*)-114a** these two protons appeared as two minor doublets of doublets at δ 4.28

and 4.12 and two major doublets of doublets δ 4.21 and 4.18 (Figure 13). Based on the integration ratio of the respective major and the minor peaks in the ^{1}H NMR spectra of two the MTPA esters, the enantiomeric ratio of aldehyde **(*R*)-92a** was found to be 16:1. Similarly comparison of ^{1}H NMR spectra of **(*S*,3*S*)-114c** and **(*R*,3*S*)-114c** revealed an enantiomeric ratio of 13:1 for aldehyde **(*S*)-92c**. Because the enantiomeric ratio of the quasienantiomers in mixture **M92** is good, we can conclude that the diastereomeric ratio of their precursor amides **93a** and **93b** was high.

Scheme 29. Synthesis of Mosher esters **(*S*,3*R*)-114a**, **(*R*,3*R*)-114a**, **(*S*,3*S*)-114c**, **(*S*,3*S*)-114c**.



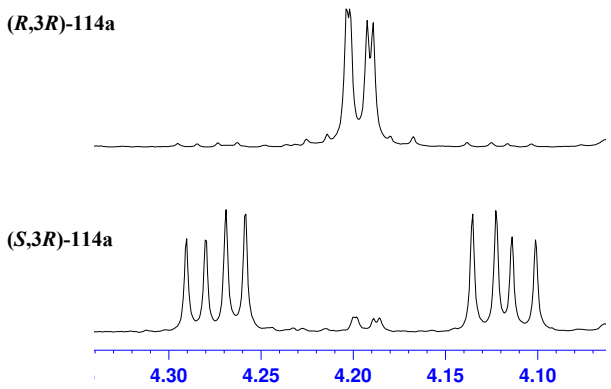
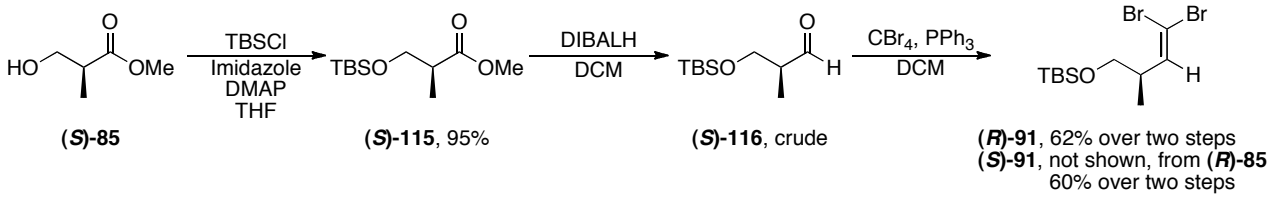


Figure 13. An expansion of the C4 methylene peaks in the ^{1}H NMR spectra (500 MHz) of the MTPA esters **(*S*,3*R*)-114a** (bottom) and **(*R*,3*R*)-114a** (top).

1.3.7 Synthesis of dibromides (*R*)-91 and (*S*)-91

The dibromides **(*R*)-91** and **(*S*)-91** were synthesized from commercially available (*R*) and (*S*)-methyl 3-hydroxy-isobutyrate (**(*S*)-85** and **(*R*)-85**) according to the procedure described by Schreiber and coworkers (Scheme 30).[79] TBS protection of the free hydroxyl group in **85** under standard conditions followed by DIBAL-H reduction of the ester afforded the aldehyde **116**, which was transformed to the corresponding dibromide **91** following the Corey-Fuchs protocol.[80]

Scheme 30. Synthesis of dibromides **(*R*)-91** and **(*S*)-91**.



1.3.8 Synthesis of C1-C8 fragment M80

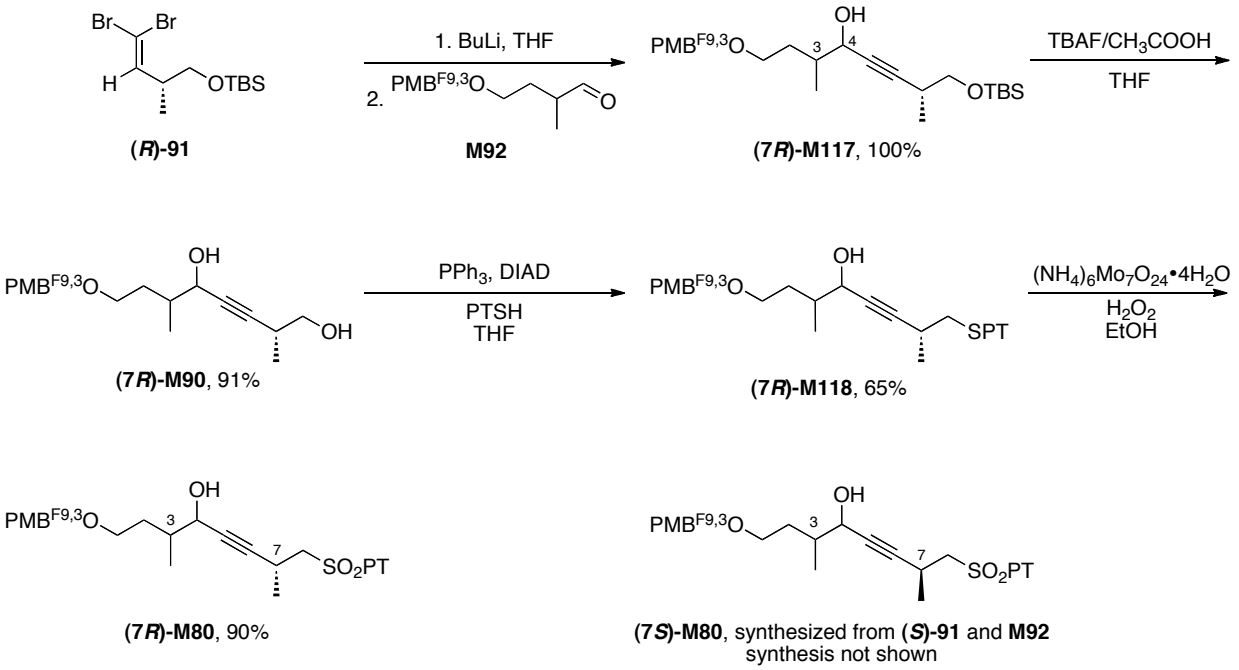
The fragment **M80** was prepared with both C7 *R* and *S* configuration and the synthesis of **(7*R*)-M80** is summarized in Scheme 31. Treatment of **(*R*)-91** with 2 equiv of *n*-BuLi followed by the addition of aldehyde **M92** provided the propargylic alcohol **(7*R*)-M117**. In the 300 MHz ^{1}H NMR spectrum of **(7*R*)-M117**, the C4 proton appears as two equal intensity multiplets between δ 4.32–4.27 and δ 4.25–4.21. This suggests that the product **(7*R*)-M117** may be a 1:1 mixture of diastereomers at C4. However, because **(7*R*)-M117** is also a mixture of quasidiastereomers (with different configurations at C3) these separate signals might also originate from the different

quasidiastereomers. Because the C4 hydroxy group will ultimately be oxidized to a ketone, its absolute configuration is not important and we did not further investigate it.

Deprotection of the TBS ether with TBAF buffered with acetic acid provided the diol **(7*R*)-M90**. Mitsunobu reaction of the primary hydroxyl group with PTSH in presence of DIAD and triphenylphosphine afforded the phenyltetrazolyl sulfide **(7*R*)-M118**.[81] On standard SiO_2 TLC plates, the sulfide **(7*R*)-M118** had very similar R_f as that of the hydrazine byproduct ($^{i}PrO_2CNHNHCO_2{}^{i}Pr$) from the Mitsunobu reaction.[58] Even after repeated column chromatography, sulfide **(7*R*)-M118** was contaminated with about 10–15% of the hydrazine byproduct. This impure sulfide was oxidized to the corresponding sulfone by reaction with hydrogen peroxide and ammonium molybdate[66] in ethanol to afford the desired C1–C8 fragment **(7*R*)-M80**.[59] At this stage, the hydrazine impurity was removed by flash column chromatography. A total of 1.35 g (2.11 mmol) of **(7*R*)-M80** was obtained for coupling with aldehyde **M81**. Fragment **(7*S*)-M80** (0.45 mg, 0.64 mmol) with C7 *S* configuration was analogously prepared by coupling the dibromide **(*S*)-91** with aldehyde **M92**, and carrying the coupled product through the same sequence of steps.

The ^{19}F NMR spectra of mixtures **M117**, **M90**, **M118** and **M80** were substantially identical to the ^{19}F NMR spectra of **M113** and **M92**, described previously and they confirmed that the ratio of the quasidiastereomers in all these mixtures was about 1:1.

Scheme 31. Synthesis of C1-C8 fragment **(7*R*)-M80**.



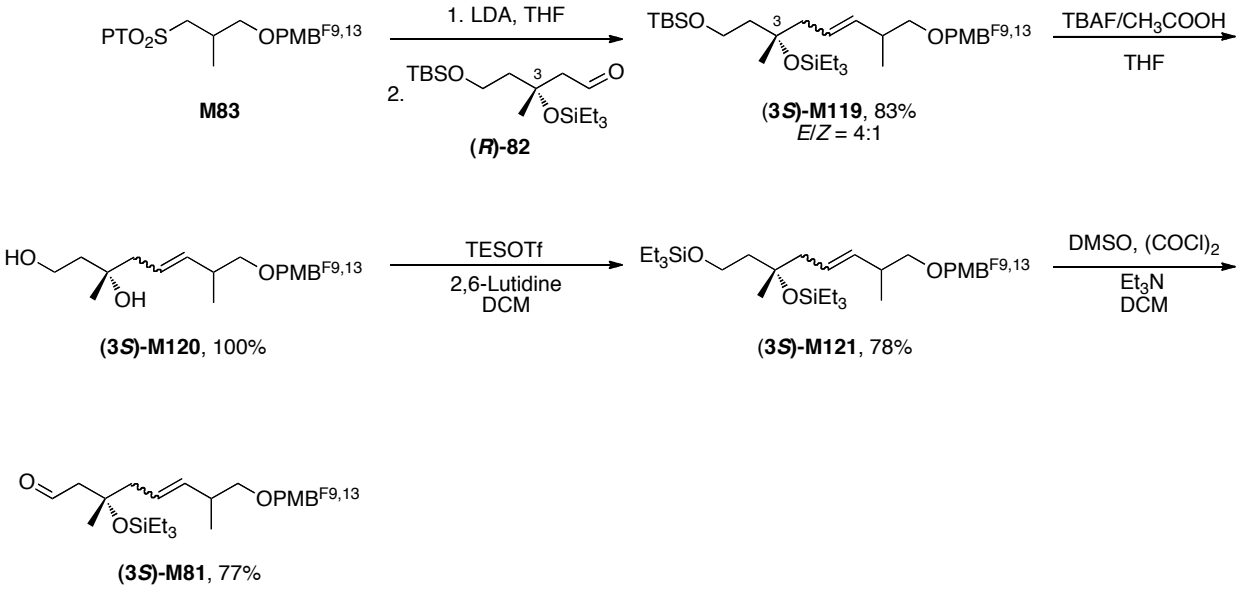
1.3.9 Synthesis of aldehyde M81 by coupling of fragments M83 and (*R*)-82

The quasiracemate **M83** was coupled to the aldehyde **(*R*)-82** by a Kocienski-Julia olefination (Scheme 32).[57,82] Deprotonation of sulfone **M83** with LDA in THF at −78 °C followed by the addition of aldehyde **(*R*)-82** provided the olefin **(3*S*)-M119** in 83% yield. The olefinic proton region of the 300 MHz ^{1}H NMR spectrum of **(3*S*)-M119** showed two major doublets of doublets at δ 5.40 (J = 6.6, 15.6 Hz) and 5.49 (J = 6.6, 15.6 Hz) along with two minor multiplets between δ 5.55–5.45 and 5.31–5.23. Because of the large coupling constant (15.6 Hz), we assigned the major peaks to the *E* alkene and the minor multiplets to the *Z* alekne. By calculating the ratio of integrations of the major and minor peaks the *E*:*Z* ratio of **(3*S*)-M119** was found to be 4:1.

The monodeprotection of the primary TBS group was next attempted by treatment of **(3*S*)-M119** with TBAF buffered with acetic acid. After 1 h, the TLC analysis of this reaction mixture showed three spots: a first very nonpolar spot corresponding to the unreacted starting material, a second moderately polar spot and a third very polar spot. After 24 h, both the non-polar spots were completely consumed and only the most polar spot remained. After workup and purification, this product was identified as the bis-desilylated diol **(3*S*)-M120** (100% isolated yield). Silylation of both the hydroxy groups in **(3*S*)-M120** with TESOTf and 2,6-lutidine gave **(3*S*)-M121** in 78% yield. Oxidation of the primary TES ether[71] under Swern conditions provided the aldehyde **(3*S*)-M81**, which was split into two parts for coupling with the sulfones **(7*R*)-M80** and **(7*S*)-M80**.

The ^{19}F NMR spectra of mixtures **M119, M120, M121** and **M81** were substantially identical to the ^{19}F NMR spectra of **M83, M84** and **M98**, described previously and they confirmed that the ratio of the quasidiastereomers in all these mixtures was about 1:1.

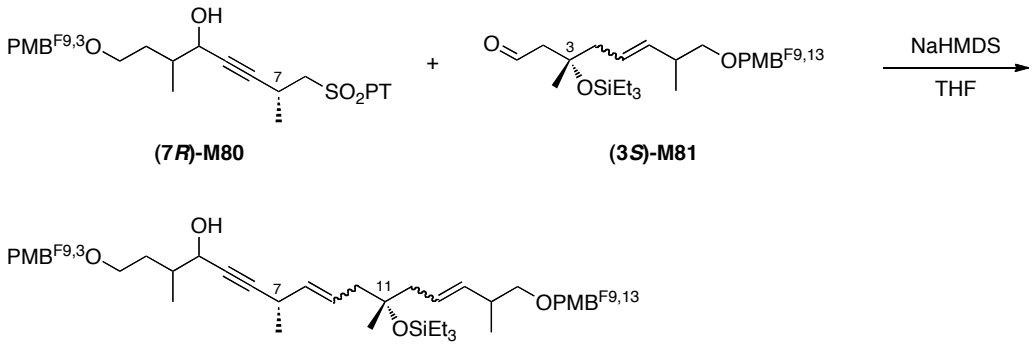
Scheme 32. Synthesis of aldehyde **(3*S*)-M81** by coupling of sulfone **M83** with aldehyde **(*R*)-82**.



1.3.10 Coupling of aldehyde (3*S*)-M81 with fragment (7*R*)-M80

The coupling of aldehyde **(3*S*)-M81** and sulfone **(7*R*)-M80** was affected by a Kocienski-Julia olefination.[57,82] Deprotonation of the sulfone **(7*R*)-M80** with 2 equiv of NaHMDS (to deprotonate both the free hydroxyl group and the sulfone) followed by addition of the aldehyde **(3*S*)-M81** provided the desired coupled product **(7*S*,11*R*)-M122** with full carbon skeleton of **1**, in an isolated yield of only 35% (Scheme 33).

Scheme 33. Coupling of aldehyde **(3*S*)-M81** with fragment **(7*R*)-M80**.

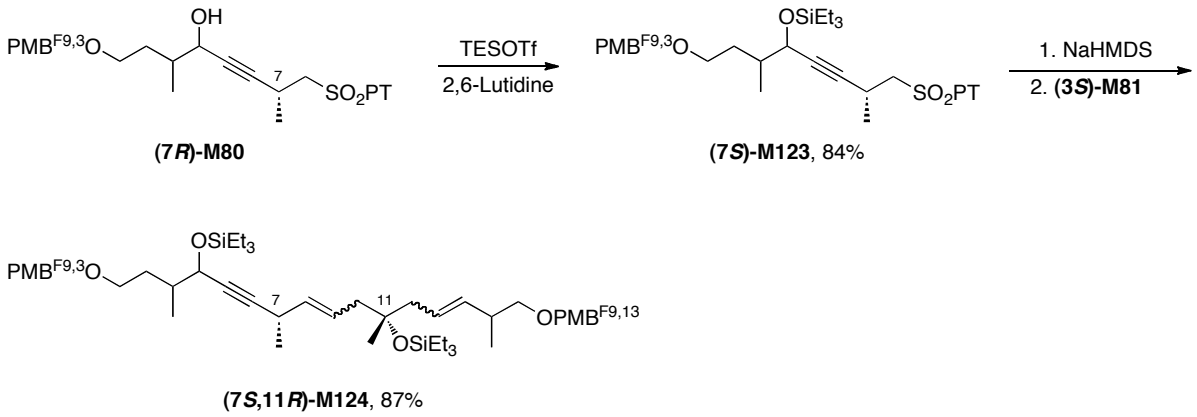


The yield of the coupling reaction was improved by protection of the free secondary hydroxyl group in sulfone **(7*R*)-M80** (Scheme 34). Silylation of **(7*R*)-M80** with TESOTf and 2,6-lutidine provided the sulfone **(7*R*)-M123**. Deprotonation of **(7*R*)-M123**, with 1 equiv of NaHMDS and addition of the aldehyde **(3*S*)-M81** afforded the coupled product **(7*S*,11*R*)-M124** in 87% isolated yield after column chromatography.

Due to significant overlap of the peaks due to the four olefinic protons in the ^{1}H NMR spectrum of the diene **(7*S*,11*R*)-M124**, it was not possible to determine the *E*/*Z* ratio of the diene

(7*S*,11*R*)-M124. Because the two alkenes will be soon reduced, we did not investigate their stereochemistry further. Although **(7*S*,11*R*)-M124** is a mixture of up to 32 compounds (four differently tagged fluorous compound, each of which is a mixture of diastereomers at C4 and also *E* and *Z* isomers of both alkenes), it showed a single spot on silica gel TLC plates and came as a single fraction during column chromatography.

Scheme 34. Coupling of modified **(7*R*)-M80** with aldehyde **(3*S*)-M81**.



(7*R*)-M80

(7*S*)-M123, 84%

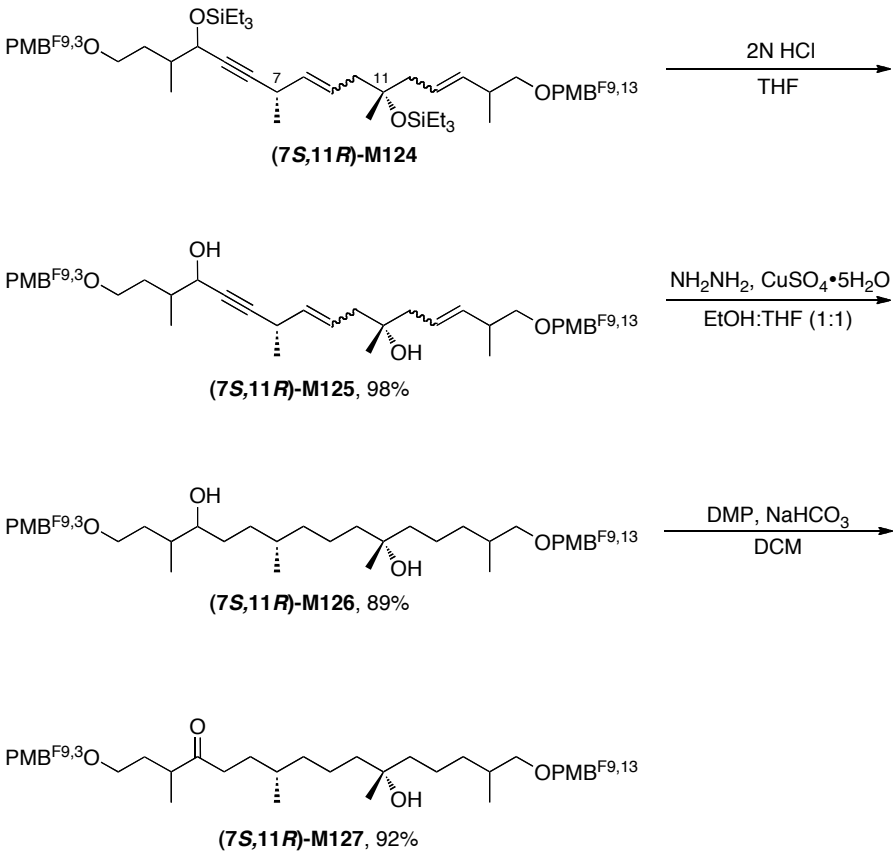
(7*S*,11*R*)-M124, 87%

1.3.11 Completion of the synthesis of first mixture of four fluorous tagged isomers of 1

The coupled product **(7*S*,11*R*)-M124** was desilylated under acidic conditions by treatment with 2 N aqueous HCl to obtain the diol **(7*S*,11*R*)-M125** in 98% (Scheme 35).[83] Because it is known that metal-catalyzed hydrogenations of an alkene can epimerize stereocenters at the allylic carbon through reversible hydrometalation,[84] diimide reduction[85] was the method of choice for reduction of the unsaturated bonds in diene yne **(7*S*,11*R*)-M125**.[55a] The secondary alcohol **(7*S*,11*R*)-M126** obtained after the diimide reduction, was oxidized to the corresponding ketone with Dess-Martin peridinone in presence of sodium bicarbonate buffer to

obtain the first mixture of four differently tagged isomers of **1 (7*S*,11*R*)-M127** in 92% yield. The four quasiisomers in mixture **(7*S*,11*R*)-M127** have fixed C7 *R* and C11 *S* configuration and all possible configurations at C3 and C15.

Scheme 35. Completion of the synthesis of the first mixture of four fluorous tagged isomers of **1**, with all four possible configurations at C3 and C15 and fixed (7*S*,11*R*) configuration.



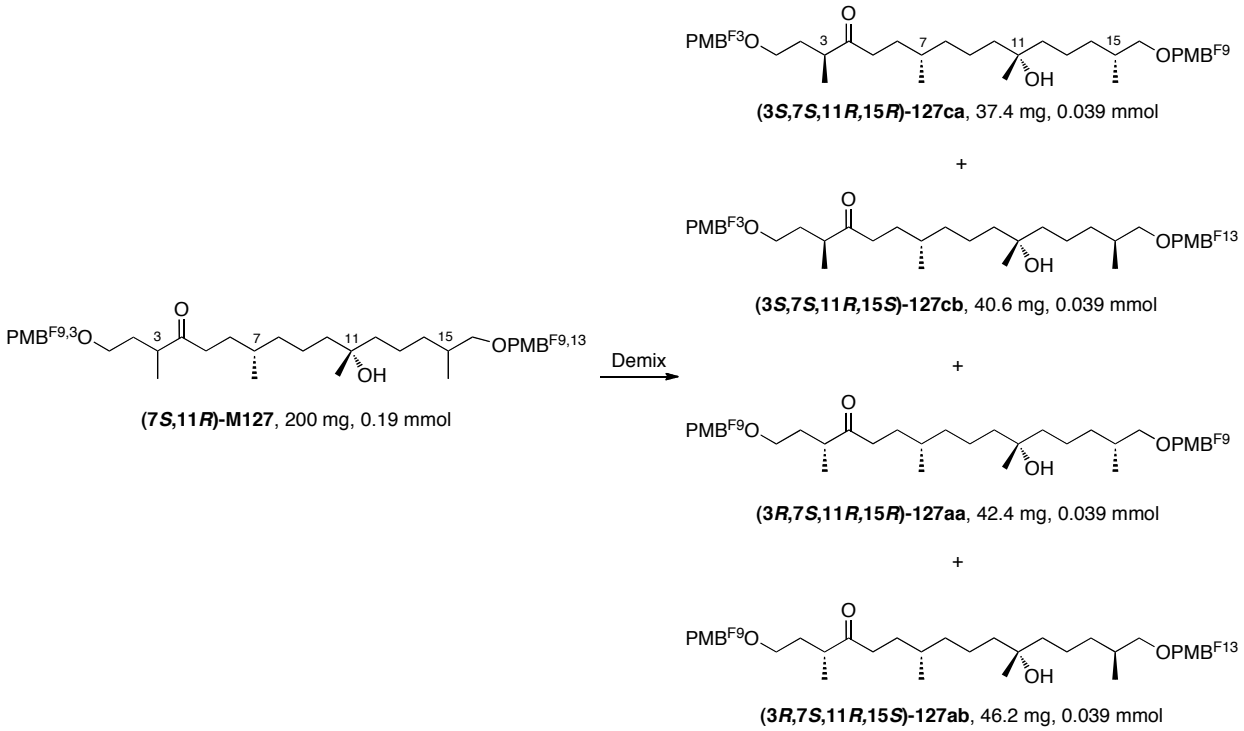
The ^{19}F NMR spectrum of the four compound mixture **M124** shows a peak at δ –66.4 for the CF_3 group in PMB^{F3}, a peak at δ –80.8 for the CF_3 group in PMB^{F13} and a peak at δ –81.1 for the CF_3 group in PMB^{F9}. The integration ratio of these peaks is 1:1:2 respectively. The integration of the peak corresponding to the PMB^{F9} CF_3 group is twice the integration of the CF_3

peaks of $PMBF^3$ and PMB^{F13} groups because the PMB^{F9} group has been used twice (both at C1 and C16 hydroxy group). Thus, the 1:1:2 integration ratio of the three CF_3 peaks confirmed that the four quasidiastereomers in mixture **M124** were present in 1:1:1:1 molar ratio. The ^{19}F NMR spectra of the other four-compound mixtures **M125**, **M126** and **M127** were substantially identical to that of **M124** and confirmed that the ratio of the four quasidiastereomers was maintained as 1:1:1:1 throughout the synthetic sequence.

1.3.12 Demixing of the mixture (7*S*,11*R*)-M127

The mixture **(7*S*,11*R*)-M127** was demixed into four individual quasiisomers by preparative fluorous HPLC. Demixing was conducted on a Waters high-performance liquid chromatograph over a FluoroFlash semiprep HPLC column (20 × 250 mm) under a gradient elution from 80:20 CH_3CN:H_2O to 100% CH_3CN in 30 min. The four fractions were well separated and eluted in order of increasing fluorine content to give the four quasiisomers **(3*S*,7*S*,11*R*,15*R*)-127ca**, **(3*S*,7*S*,11*R*,15*S*)-127cb**, **(3*R*,7*S*,11*R*,15*R*)-127aa** and **(3*R*,7*S*,11*R*,15*S*)-127ab**. The results of the demixing experiments are summarized in Scheme 36 and a representative preparative HPLC demixing chromatogram of mixture **(7*S*,11*R*)-M127** is shown in Figure 14. Up to 40 mg of the mixture was demixed in a single injection, and five injections were needed to demix 200 mg of **(7*S*,11*R*)-M127**. The overall mass recovery during the demixing of **(7*S*,11*R*)-M127** was 83% and the mole ratio of the four tagged compounds isolated after demixing (**127ca**:**127cb**:**127aa**:**127ab**) was about 1:1:1:1.

Scheme 36. Results of the HPLC demixing of the mixture **(7*S*,11*R*)-M127**.



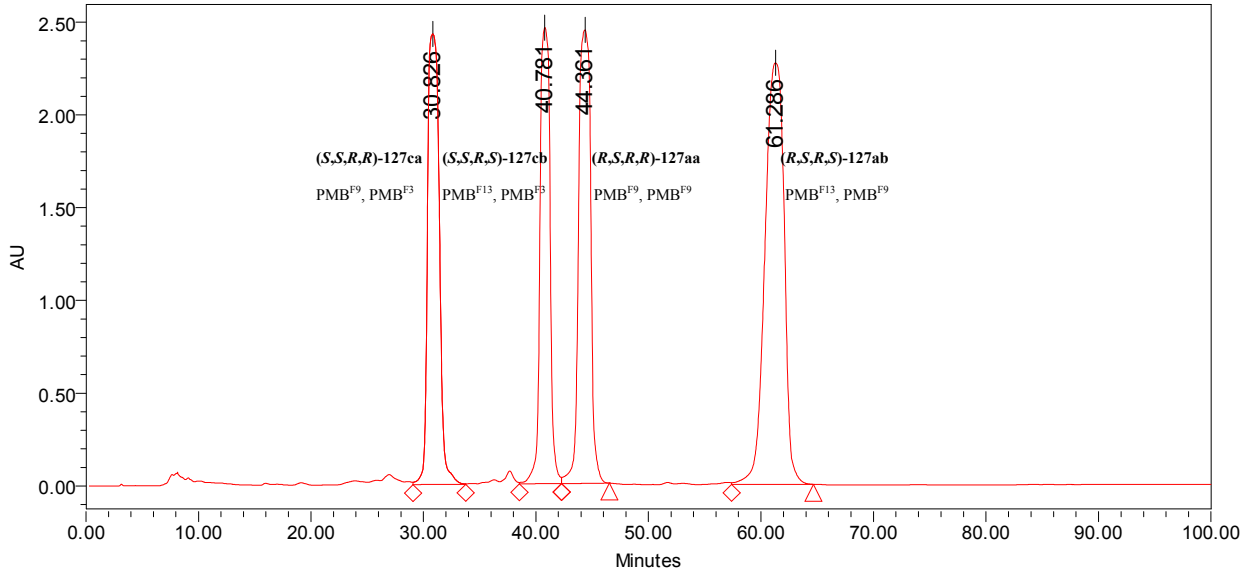


Figure 14. Representative semiprep HPLC chromatogram for demixing of **(7*S*,11*R*)-M127**; conditions: 80:20 CH_3CN:H_2O to 100% CH_3CN in 30 min, then 100% CH_3CN for 70 min at a flow rate of 7 mL/min.

The purities of the four individual PMB^F ethers were confirmed by spectroscopic methods. The ^{19}F NMR spectra of these four compounds showed the presence of only the relevant fluorous tags. Because each fluorous tag has a unique spectrum, this confirms that none of these PMB^F ethers were contaminated with any other.

The ^1H NMR spectra of the four PMB^F ethers were also informative about their isomeric purity. Yajima and coworkers have reported that it is possible to differentiate the C3,C7-syn and anti isomers of **1** by ^1H NMR spectroscopy.[28] We could see such differences in the ^1H NMR (600 MHz) spectra the four PMB^F ethers of **1** (Figure 15). In the spectra of the C3,C7-anti compounds **(3*S*,7*S*,11*R*,15*R*)-127ca** and **(3*S*,7*S*,11*R*,15*S*)-127cb**, the C5 methylene protons appear as triplet at δ 2.44. In the C3,C7-syn compounds **(3*R*,7*S*,11*R*,15*R*)-127aa** and **(3*R*,7*S*,11*R*,15*S*)-127ab**, the two C5 methylene protons appear as two separate multiplets between δ 2.51–2.45 and 2.44–2.37. The minor peaks between δ 2.51–2.45 and 2.44–2.37 in the ^1H NMR spectra of **(3*S*,7*S*,11*R*,15*R*)-127ca** and **(3*S*,7*S*,11*R*,15*S*)-127cb** and at δ 2.44 in the ^1H NMR spectra of **(3*R*,7*S*,11*R*,15*R*)-127aa** and **(3*R*,7*S*,11*R*,15*S*)-127ab** indicated some epimerization at the C3 stereocenter. By calculating the ratios of the integrations of major and the minor peaks we estimated about 10% epimerization for **(3*S*,7*S*,11*R*,15*R*)-127ca**, 12% for **(3*S*,7*S*,11*R*,15*S*)-127cb**, 7% for **(3*R*,7*S*,11*R*,15*R*)-127aa** and 6% for **(3*R*,7*S*,11*R*,15*S*)-127ab**. However, these estimates might have large error due to significant overlap of the major and minor C5 methylene proton peaks in these ^1H NMR spectra of the four PMB^F ethers.

The partial ^1H NMR spectra of the four PMB^F ethers shown in Figure 15, also exhibit minor differences in the multiplet pattern between δ 2.37–2.27. This multiplet is assigned to a CH_2 group in the PMB^F tags. So the difference in its pattern is due to the different PMB^F tags in **127ca**, **127cb**, **127aa** and **127ab** and not due to difference in their configurations.

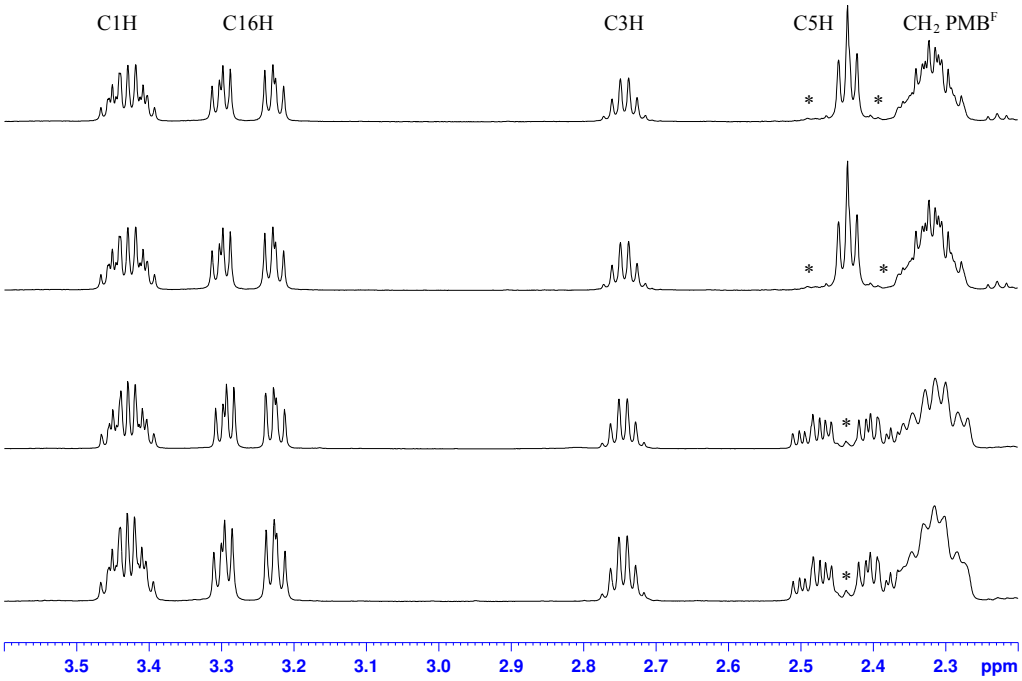


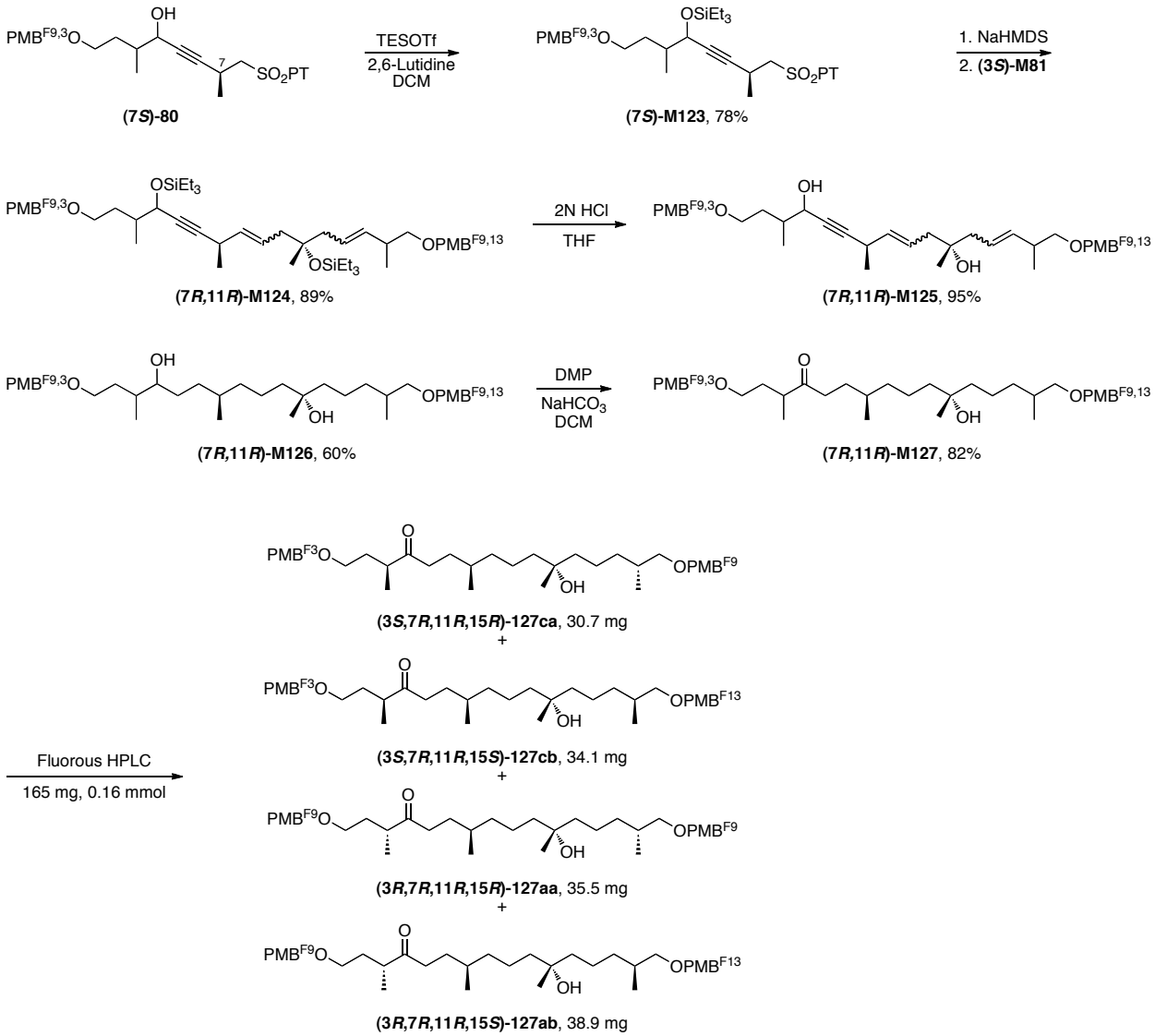
Figure 15. Partial ^{1}H NMR spectra (600 MHz) of **(3*S*,7*S*,11*R*,15*R*)-127ca**, **(3*S*,7*S*,11*R*,15*S*)-127cb**, **(3*R*,7*S*,11*R*, 15*R*)-127aa**, and **(3*R*,7*S*,11*R*,15*S*)-127ab** (top to bottom); peaks marked with asterisk correspond to the C3 epimerized minor diastereomer.

1.3.13 Synthesis of the second mixture of four fluorous tagged isomers of 1

The synthesis of the second mixture of four fluorous tagged quasiisomers of **1** is summarized in Scheme 37. The free hydroxy group in sulfone **(7*S*)-M80** was protected as the TES ether, and the resulting sulfone was coupled with aldehyde **(3*S*)-M81** by a Kocienski-Julia olefination[57,82] in 80% yield. The product **(7*R*,11*R*)-M124** was carried through the same sequence of steps as for the synthesis of **(7*S*,11*R*)-M127**. The final mixture **(7*R*,11*R*)-M127** was demixed by fluorous HPLC as before to obtain four PMB^{F} ethers **(3*S*,7*R*,11*R*,15*R*)-127ca**, **(3*S*,7*R*,11*R*,15*S*)-127cb**, **(3*R*,7*R*,11*R*,15*R*)-127aa** and **(3*R*,7*R*,11*R*,15*S*)-127ab**.

The purities of these PMB^F ethers were evaluated by ^{19}F and ^1H NMR spectroscopy. The ^{19}F NMR spectra of these four PMB^F ethers showed only the peaks corresponding to the relevant tags, implying that the demixing was successful. Their ^1H NMR spectra revealed the presence of about 10-15% of the C3 epimerized isomer. The overall mass recovery from this demixing was of 85% and the mole ratio of the four PMB^F ethers obtained was about 1:1:1:1. These results were similar to those described previously for the demixing of **(7*S*,11*R*)-M127**.

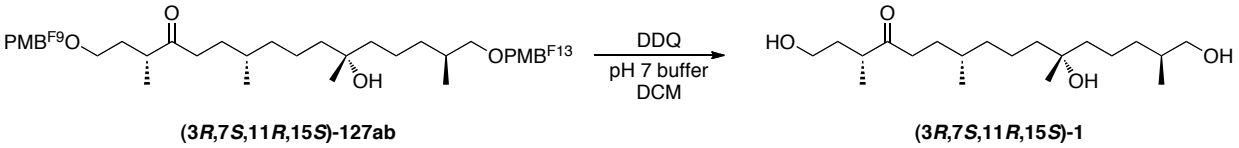
Scheme 37. Synthesis of a second mixture of four fluorous tagged isomers of **1**.



1.3.14 Global deprotection of the eight PMB^F ethers 127

The global deprotection of the PMB^F ethers **127** was first attempted with DDQ as summarized in Scheme 38. Addition of 2 equiv DDQ to a solution of **(3*R*,7*S*,11*R*,15*S*)-127ab** in DCM:pH 7 buffer (10:1) at 0 °C followed by warming to room temperature led to significant decomposition of the starting material as did reaction with of 5 equiv of DDQ at 0 °C. Addition of 2 equiv of DDQ to a solution of **(3*R*,7*S*,11*R*,15*S*)-127ab** in DCM:pH 7 buffer (10:1) at 0 °C for 4 h gave the desired product in 44% yield along with a mixture of recovered starting material and partially deprotected products. No increase in the isolated yield was observed if the reaction was allowed to stir at this temperature for longer time.

Scheme 38. Global deprotection of **(3*R*,7*S*,11*R*,15*S*)-127ab** with DDQ.



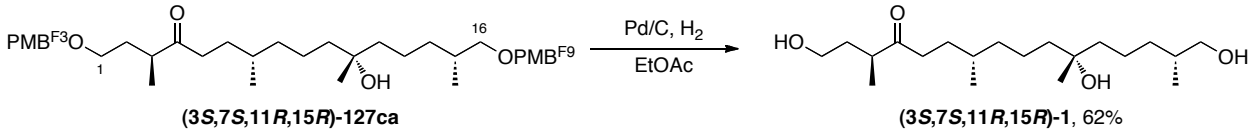
(3*R*,7*S*,11*R*,15*S*)-127ab **(3*R*,7*S*,11*R*,15*S*)-1**

Starting Material	Equiv of DDQ	Reaction temp/Time	Yield
(3*R*,7*S*,11*R*,15*S*)-127ab	2	0 °C, 2 h then rt, 2 h	-
(3*R*,7*S*,11*R*,15*S*)-127ab	5	0 °C, 4 h	-
(3*R*,7*S*,11*R*,15*S*)-127ab	2	0 °C, 4 h	44%

The PMB^F ethers **127** could be deprotected more efficiently by hydrogenolysis over catalytic palladium on carbon (Scheme 39). In a typical experiment, the PMB^F ether **(3*S*,7*S*,11*R*,15*R*)-127ca** (35.0 mg, 0.04 mmol) was dissolved in EtOAc (2.7 mL) and of Pd/C (10% wt by volume, 4.4 mg) was added. The resulting mixture was stirred under hydrogen from

balloon for 48 h followed by filtration through Celite. The final pure product **(3*S*,7*S*,11*R*,15*R*)-1** (8.0 mg, 0.03 mmol, 62%) was obtained after column chromatography of the concentrated filterate. The remaining 15 PMB^F ethers were also subjected to hydrogenolysis under similar conditions. The Table 2 summarizes the results of the hydrogenolysis reactions to obtain eight isomers of **1**, their amounts obtained and the percentage yields. The structures of the eight isomers of hormone α1 obtained are shown in Figure 16.

Scheme 39. Deprotection of the fluorous PMB^F **(3*S*,7*S*,11*R*,15*R*)-127ca** by hydrogenolysis with Pd/C.



(3*S*,7*S*,11*R*,15*R*)-127ca **(3*S*,7*S*,11*R*,15*R*)-1**, 62%

Table 2. The results of hydrogenolysis reactions of PMB^F ethers **127**, the amount of products isolated and the percentage yields.

Starting material	PMB^F at C1 hydroxy group	PMB^F at C16 hydroxy group	Product	Amount (mg)	% Yield
From the mixture **(7*S*,11*R*)-127**					
127ca	PMB^{F3}	PMB^{F9}	**(3*S*,7*S*,11*R*,15*R*)-1**	8.0	62
127cb	PMB^{F3}	PMB^{F13}	**(3*S*,7*S*,11*R*,15*S*)-1**	9.2	69
127aa	PMB^{F9}	PMB^{F9}	**(3*R*,7*S*,11*R*,15*R*)-1**	6.2	69
127ab	PMB^{F9}	PMB^{F13}	**(3*R*,7*S*,11*R*,15*S*)-1**	5.3	86
From the mixture **(7*R*,11*R*)-127**					
127ca	PMB^{F3}	PMB^{F9}	**(3*S*,7*R*,11*R*,15*R*)-1**	4.3	64
127cb	PMB^{F3}	PMB^{F13}	**(3*S*,7*R*,11*R*,15*S*)-1**	6.3	66
127aa	PMB^{F9}	PMB^{F9}	**(3*R*,7*R*,11*R*,15*R*)-1**	9.0	85
127ab	PMB^{F9}	PMB^{F13}	**(3*R*,7*R*,11*R*,15*S*)-1**	4.8	63

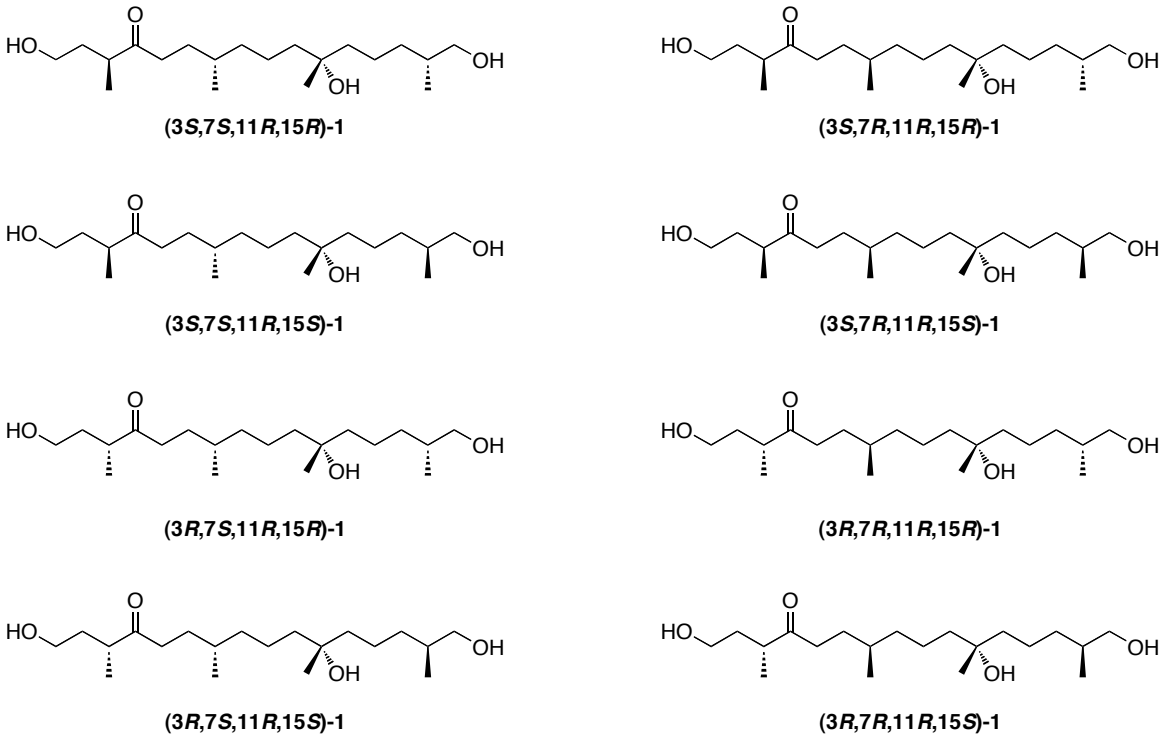


Figure 16. Structures of the eight isomers of **1** obtained after hydrogenolysis of PMB^F ethers **127**.

The ^{1}H NMR spectra of the eight isomers of **1** were obtained at the 700 MHz. These spectra exhibited significant differences at about δ 2.55, for the peaks corresponding to the C5 methylene protons. These differences were same as those noticed by Yajima and coworkers.[28] For the C7,C3-anti isomers, the two C5 methylene protons appeared as a triplet at δ 2.55, while for the C7,C3-syn compounds these proton came as multiplet at δ 2.60–2.48. Figure 17 shows the C5 methylene proton region in the ^{1}H NMR spectra of C3,C7-anti isomer **(3*S*,7*S*,11*R*,15*S*)-1** and C3,C7-syn isomer **(3*S*,7*R*,11*R*,15*S*)-1** as a representative example to highlight this difference in the ^{1}H NMR spectra of the isomers of **1**. The presence of the minor multiplets between δ 2.60–2.48 in the ^{1}H NMR spectra of the C3,C7-anti isomers (these peaks are marked with an asterisk in the Figure 17) indicated some epimerization at the C3 center during the

synthesis. Again the exact extent of epimerization could not be determined due to significant overlap, but we estimated about 15-20% epimerization of all eight isomers of **1**.

The ^{1}H NMR spectra of the eight isomers are shown in Figure 18 and the data is tabulated in Table 3 and 4. The ^{13}C NMR spectra of these eight isomers were also very similar and this data is summarized in Table 5.

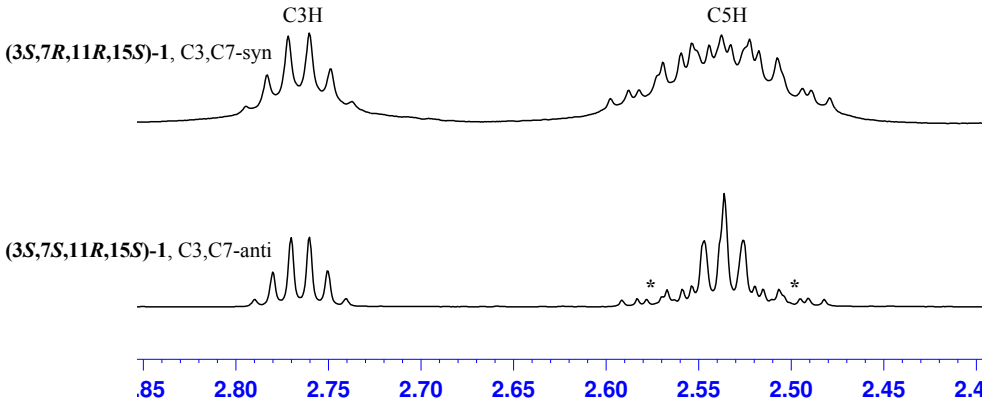


Figure 17. Partial ^{1}H NMR spectra of **(3*S*,7*S*,11*R*,15*S*)-1** (C3,C7-anti, bottom) and **(3*S*,7*R*,11*R*,15*S*)-1** (C3,C7-syn, top) showing the expansion of the C3 and C5 protons. The peaks due to the minor epimer are indicated by an asterisk.

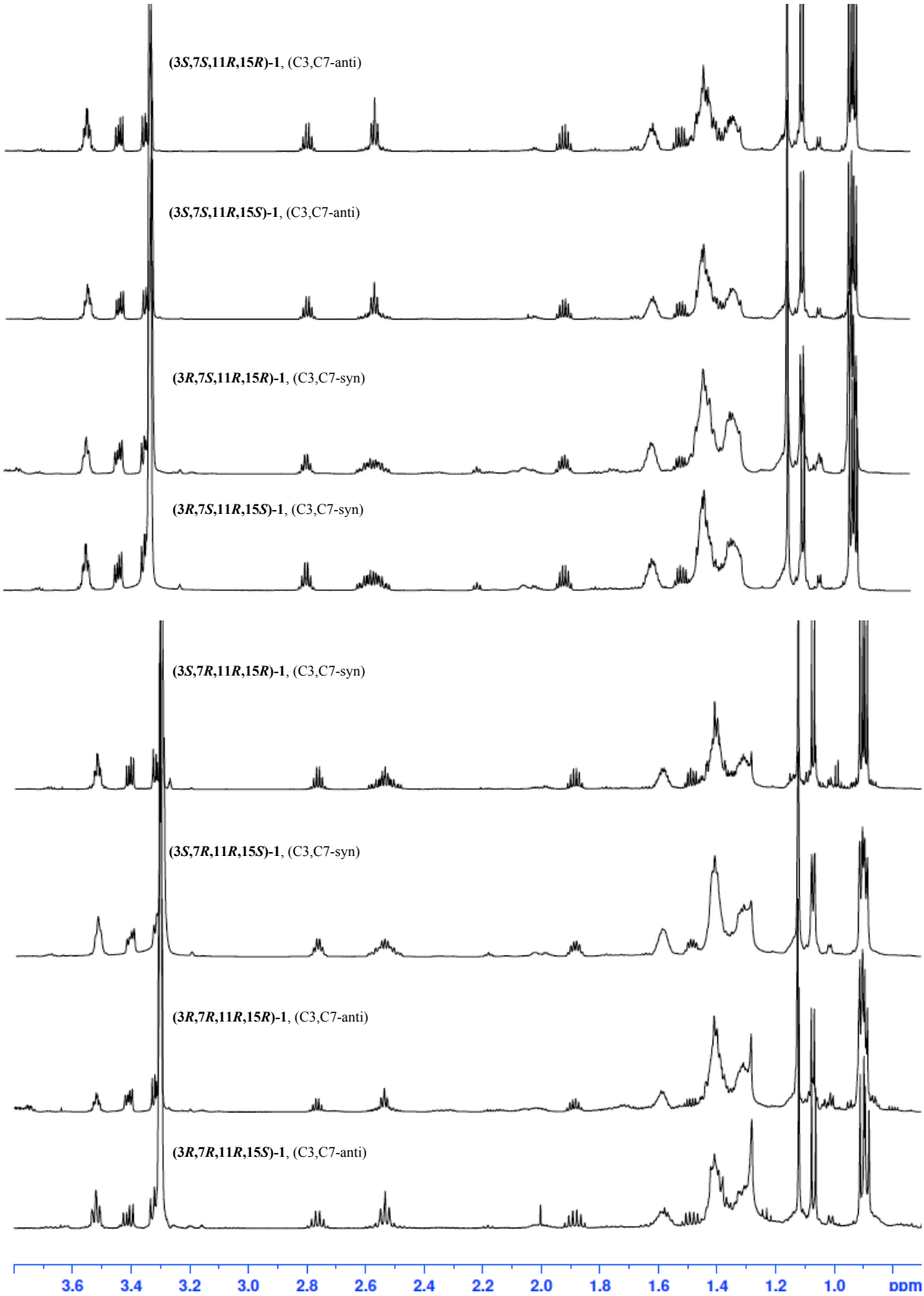


Figure 18. The ^{1}H NMR spectra (700 MHz) of the eight isomers of **1** in MeOD.

Table 3. 700 MHz ^{1}H NMR data for **(3*S*,7*S*,11*R*,15*R*)-1**, **(3*S*,7*S*,11*R*,15*S*)-1**, **(3*R*,7*S*,11*R*,15*R*)-1**, **(3*R*,7*S*,11*R*,15*S*)-1**.

C No.	**(3*S*,7*S*,11*R*,15*R*)-1**	**(3*S*,7*S*,11*R*,15*S*)-1**	**(3*R*,7*S*,11*R*,15*R*)-1**	**(3*R*,7*S*,11*R*,15*S*)-1**
1	3.520 (m, 2H)	3.518 (m, 2H)	3.523 (m, 2H)	3.520 (m, 2H)
2	1.887 (sxt, 7.0, 1H)	1.885 (sxt, 6.9, 1H)	1.886 (sxt, 6.9, 1H)	1.885 (sxt, 7.0, 1H)
	1.511–1.464 (m, 1H)	1.508–1.462 (m, 1H)	1.508–1.470 (m, 1H)	1.507–1.460 (m, 1H)
3	2.764 (sxt, 7.0, 1H)	2.765 (sxt, 6.9, 1H)	2.766 (sxt, 6.8, 1H)	2.766 (sxt, 7.0, 1H)
5	2.534 (t, 7.0, 2H)	2.536 (t, 7.1, 2H)	2.593–2.483 (m, 2H)	2.592–2.482 (m, 2H)
6	1.621–1.562 (m, 1H)	1.615–1.549 (m, 1H)	1.620–1.550 (m, 1H)	1.621–1.552 (m, 1H)
	1.455–1.282 (m, 1H)	1.445–1.281 (m, 1H)	1.449–1.282 (m, 1H)	1.446–1.282 (m, 1H)
7	1.455–1.282 (m, 1H	1.445–1.281 (m, 1H)	1.449–1.282 (m, 1H)	1.451–1.280 (m, 1H)
8	1.455–1.282 (m, 1H)	1.445–1.281 (m, 1H)	1.449–1.282 (m, 1H)	1.451–1.280 (m, 1H)
	1.152–1.050 (m, 1H)	1.152–1.050 (m, 1H)	1.152–1.050 (m, 1H)	1.160–1.050 (m, 1H)
9	1.455–1.282 (m, 2H)	1.445–1.281 (m, 2H)	1.449–1.282 (m, 2H)	1.446–1.282 (m, 1H)
10	1.455–1.282 (m, 2H)	1.445–1.281 (m, 2H)	1.449–1.282 (m, 2H)	1.446–1.282 (m, 1H)
12	1.455–1.282 (m, 2H)	1.445–1.281 (m, 2H)	1.449–1.282 (m, 2H)	1.446–1.282 (m, 1H)
13	1.455–1.282 (m, 2H)	1.445–1.281 (m, 2H)	1.449–1.282 (m, 2H)	1.446–1.282 (m, 1H)
14	1.455–1.282 (m, 1H)	1.615–1.549 (m, 1H)	1.449–1.282 (m, 1H)	1.446–1.282 (m, 1H)
	1.152–1.050 (m, 1H)	1.152–1.050 (m, 1H)	1.152–1.050 (m, 1H)	1.160–1.050 (m, 1H)
15	1.621–1.562 (m, 1H)	1.615–1.549 (m, 1H)	1.620–1.550 (m, 1H)	1.621–1.552 (m, 1H)
16	3.409 (dd, 10.5, 6.3)	3.409 (dd, 10.6, 5.6)	3.409 (dd, 10.6, 5.9)	3.409 (dd, 10.5, 5.6)
	3.318 (dd, 10.5, 7.0)	3.316 (dd, 10.6, 6.7)	3.317 (dd, 10.6, 6.6)	3.316 (dd, 11.2, 7.0)
17	0.906 (d, 6.3, 3H)	0.905 (d, 6.7, 3H)	0.906 (d, 6.6, 3H)	0.905 (d, 7.0, 3H)
18	1.121 (s, 3H)	1.121 (s, 3H)	1.121 (s, 3H)	1.121 (s, 3H)
19	0.889 (d, 6.3, 3H)	0.888 (d, 6.6, 3H)	0.889 (d, 6.6, 3H)	0.889 (d, 6.3, 3H)
20	1.071 (d, 7.0, 3H)	1.070 (d, 7.0, 3H)	1.070 (d, 6.9, 3H)	1.070 (d, 6.3, 3H)

Table 4. 700 MHz ^{1}H NMR data for **(3*S*,7*R*,11*R*,15*R*)-1**, **(3*S*,7*R*,11*R*,15*S*)-1**, **(3*R*,7*R*,11*R*,15*R*)-1**, **(3*R*,7*R*,11*R*,15*S*)-1**.

C No.	**(3*S*,7*R*,11*R*,15*R*)-1**	**(3*S*,7*R*,11*R*,15*S*)-1**	**(3*R*,7*R*,11*R*,15*R*)-1**	**(3*R*,7*R*,11*R*,15*S*)-1**
1	3.519 (m, 2H)	3.519 (m, 2H)	3.519 (m, 2H)	3.520 (m, 2H)
2	1.885 (sxt, 6.7, 1H)	1.885 (sxt, 7.0, 1H)	1.886 (sxt, 6.9, 1H)	1.886 (sxt, 7.0, 1H)
	1.508–1.465 (m, 1H)	1.507–1.460 (m, 1H)	1.509–1.472 (m, 1H)	1.507–1.450 (m, 1H)
3	2.765 (sxt, 6.9, 1H)	2.765 (sxt, 7.0, 1H)	2.765 (sxt, 7.0 Hz)	2.764 (sxt, 7.0, 1H)
5	2.594–2.482 (m, 2H)	2.592–2.482 (m, 2H)	2.535 (t, 6.7, 2H)	2.534 (t, 6.5, 2H)
6	1.616–1.562 (m, 1H)	1.620–1.550 (m, 1H)	1.631–1.549 (m)	1.627–1.520 (m, 1H)
	1.462–1.281 (m, 1H)	1.450–1.280 (m, 1H)	1.455–1.281 (m, 1H)	1.450–1.281 (m, 1H)
7	1.462–1.281 (m, 1H)	1.450–1.280 (m, 1H)	1.455–1.281 (m, 1H)	1.450–1.281 (m, 1H)
8	1.462–1.281 (m, 1H)	1.450–1.280 (m, 1H)	1.455–1.281 (m, 1H)	1.450–1.281 (m, 1H)
	1.160–1.050 (m, 1H)	1.160–1.050 (m, 1H)	1.160–1.050 (m, 1H)	1.161–1.049 (m, 1H
9	1.462–1.281 (m, 2H)	1.450–1.280 (m, 2H)	1.455–1.281 (m, 2H)	1.450–1.281 (m, 2H)
10	1.462–1.281 (m, 2H)	1.450–1.280 (m, 2H)	1.455–1.281 (m, 2H)	1.450–1.281 (m, 2H)
12	1.462–1.281 (m, 2H)	1.450–1.280 (m, 2H)	1.455–1.281 (m, 2H)	1.450–1.281 (m, 2H)
13	1.462–1.281 (m, 2H)	1.450–1.280 (m, 2H)	1.455–1.281 (m, 2H)	1.450–1.281 (m, 2H)
14	1.462–1.281 (m, 1H)	1.450–1.280 (m, 1H)	1.455–1.281 (m, 1H)	1.450–1.281 (m, 1H)
	1.160–1.050 (m, 1H)	1.160–1.050 (m, 1H)	1.160–1.050 (m, 1H)	1.161–1.049 (m, 1H
15	1.616–1.562 (m, 1H)	1.620–1.550 (m, 1H)	1.631–1.549 (m)	1.627–1.520 (m, 1H)
16	3.408 (dd,10.6, 5.9)	3.408 (dd, 10.5, 5.6)	3.409 (dd, 10.6, 6.0)	3.405 (dd, 10.5, 6.0)
	3.322 (dd, 10.8, 6.5)	3.315 (dd, 11.2, 7.0)	3.322 (dd, 11.0, 6.7)	3.315 (dd, 11.2, 7.0)
17	0.905 (d, 6.7, 3H)	0.905 (d, 7.0, 3H)	0.905 (d, 6.7, 3H)	0.906 (d, 6.5, 3H)
18	1.121 (s, 3H)	1.121 (s, 3H)	1.121 (s, 3H)	1.121 (s, 3H)
19	0.889 (d, 6.6, 3H)	0.888 (d, 7.0, 3H)	0.888 (d, 6.5, 3H)	0.889 (d, 6.5, 3H)
20	1.070 (d, 7.0, 3H)	1.069 (d, 7.0, 3H)	1.070 (d, 7.0, 3H)	1.071 (d, 7.0, 3H)

Table 5. ^{13}C NMR data (175 MHz) for **(3*S*,7*S*,11*R*,15*R*)-1**, **(3*S*,7*S*,11*R*,15*S*)-1**, **(3*R*,7*S*,11*R*,15*R*)-1**, **(3*R*,7*S*,11*R*,15*S*)-1**, **(3*S*,7*R*,11*R*,15*R*)-1**, **(3*S*,7*R*,11*R*,15*S*)-1**, **(3*R*,7*R*,11*R*,15*R*)-1** and **(3*R*,7*R*,11*R*,15*S*)-1**.

C No	**(*S*,*S*,*R*,*R*-1**	**(*S*,*S*,*R*,*S*)-1**	**(*R*,*S*,*R*,*R*)-1**	**(*R*,*S*,*R*,*S*)-1**	**(*S*,*R*,*R*,*R*)-1**	**(*S*,*R*,*R*,*S*)-1**	**(*R*,*R*,*R*,*R*)-1**	**(*R*,*R*,*R*,*S*)-1**
1	60.62	60.61	60.61	60.61	60.62	60.63	60.61	60.61
2	36.88	36.88	36.88	36.87	36.88	36.89	36.88	36.82
3	43.97	43.95	43.95	43.95	43.96	43.97	43.95	43.97
4	217.48	217.48	217.50	217.50	217.51	217.52	217.47	217.48
5	39.97	39.98	39.99	39.98	39.98	39.99	39.97	39.97
6	31.74	31.71	31.73	31.72	31.72	31.74	31.71	31.74
7	33.57	33.56	33.58	33.57	33.59	33.59	33.57	33.57
8	38.62	38.62	38.60	38.60	38.61	38.61	38.62	38.62
9#	22.36	22.34	22.36	22.33	22.37	22.37	22.36	22.36
10*	43.00	43.00	42.99	43.00	42.96	42.97	42.95	43.00
11	73.37	73.37	73.37	73.37	73.38	73.38	73.36	73.37
12*	42.96	42.87	42.94	42.88	42.96	42.90	42.95	42.96
13#	22.29	22.32	22.30	22.33	22.30	22.33	22.30	22.30
14	35.03	35.02	35.02	35.02	35.03	35.04	35.02	35.03
15	36.71	36.70	36.74	36.74	36.74	36.75	36.70	36.71
16	68.45	68.42	68.44	68.42	68.44	68.45	68.43	68.45
17	17.08	17.10	17.08	17.11	17.09	17.10	17.09	17.09
18	26.88	26.93	26.88	26.94	26.91	26.97	26.91	26.88
19	19.86	19.87	19.88	19.89	19.88	19.89	19.88	19.86
20	16.90	16.91	16.91	16.91	16.90	16.91	16.91	16.90

The assignments of the peaks marked with # and * are interchangeable with each other.

We learned from this sequence of experiments that the ^{1}H NMR spectra of the eight isomers of **1** do not provide any information about the stereochemistry of **1** except for the relative configuration of the C3 and C7 stereocenters. The ^{13}C NMR spectra of the eight isomers show very small differences that are not a reliable indicator of the stereochemistry of **1**. Next, we decided to convert all the eight stereoisomers of **1** to the corresponding *R* and *S* bis-MTPA esters and compare the spectroscopic data of the synthetic bis-MTPA esters with each other and with the bis-MTPA ester of the natural product

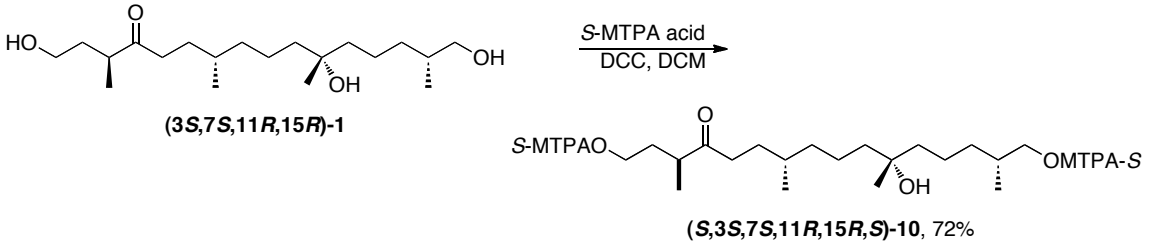
1.4 SYNTHESIS AND SPECTROSCOPIC ANALYSIS OF 16 BIS-MTPA ESTERS OF HORMONE α1

1.4.1 Synthesis and purification of the 16 bis-MTPA esters

Each of the eight isomers of **1** was converted to both bis-*R* and *S*-MTPA esters to obtain a 16-stereoisomer library of the bis-MTPA esters of hormone α1. In the typical esterification reaction,[32e] a solution of **(3*S*,7*S*,11*R*,15*R*)-1** (1.5 mg, 0.04 mmol) in DCM (0.33 mL) was treated with DCC (27.0 mg, 0.13 mmol) and *S*-MTPA acid (31.0 mg, 0.13 mmol). After 24 h, the reaction mixture was filtered and the filtrate was concentrated. The crude mixture was purified by flash column chromatography (SiO_2, 30% EtOAc in hexanes) to obtain 6.2 mg (72%) of the bis-MTPA ester **(*S*,3*S*,7*S*,11*R*,15*R*,*S*)-10** (Scheme 40). Although the bis-MTPA ester **(*S*,3*S*,7*S*,11*R*,15*R*,*S*)-10** showed a single spot on the standard silica gel TLC plate, its ^{1}H NMR spectrum indicated the presence of 19% of a minor isomer. This was expected since the precursor was partially epimerized. The remaining 15 bis-MTPA esters were similarly prepared

by esterification of the eight isomers of **1** with *R* or *S*-MTPA acid. The ^{1}H NMR spectra of all these 15 bis-MTPA esters also indicated the presence of 16–34% of a minor isomer.

Scheme 40. Synthesis of bis-MTPA ester **(*S*,3*S*,7*S*,11*R*,15*R*,*S*)-10**.



Because we have all diastereomers, the minor isomer from one sample should match the major isomer from the other sample. Accordingly, we compared the ^{1}H NMR spectra of all the bis-*S*-MTPA esters with each other and the bis-*R*-MTPA esters with each other. We found that the minor peaks in the ^{1}H NMR spectrum of **(*S*,3*S*,7*S*,11*R*,15*R*,*S*)-10** matched only the major peaks in the ^{1}H NMR spectrum of **(*S*,3*R*,7*S*,11*R*,15*R*,*S*)-10** and vice versa. The partial ^{1}H NMR spectra of these two bis-MTPA esters are shown in Figure 19. For example, the ^{1}H NMR spectrum of the bis-MTPA ester **(*S*,3*S*,7*S*,11*R*,15*R*,*S*)-10** shows two major doublets of doublets of doublets at δ 2.42 and 2.33 and two minor doublets of doublets of doublets at δ 2.47 and 2.31. While the ^{1}H NMR spectrum of the MTPA ester **(*S*,3*R*,7*S*,11*R*,15*R*,*S*)-10** shows two minor doublets of doublets of doublets at δ 2.42 and 2.33 and two major doublets of doublets of doublets at δ 2.47 and 2.31. The bis-MTPA esters, **(*S*,3*S*,7*S*,11*R*,15*R*,*S*)-10** and **(*S*,3*R*,7*S*,11*R*,15*R*,*S*)-10** differ only in their configuration at the C3 stereocenter. The major and minor peaks in the corresponding bis-*R*-MTPA esters **(*R*,3*S*,7*S*,11*R*,15*R*,*R*)-10** and **(*R*,3*R*,7*S*,11*R*,15*R*,*R*)-10** also matched. Thus, we assigned the minor peaks in the ^{1}H NMR spectrum of **(*S*,3*S*,7*S*,11*R*,15*R*,*S*)-10** to the C3 epimerized isomer. The minor peaks in the ^{1}H

NMR spectra of the remaining bis-MTPA esters were similarly assigned to the corresponding C3 epimers.

The Table 6 summarizes the results of the synthesis of the 16 bis-MTPA esters from the eight isomers of **1**, their amounts obtained, the percentage yields of the esterification reactions, the C3 epimer impurity, and the percentage of the C3 epimer present. The extent of the C3 epimerization in the 16 bis-MTPA esters ranged from 16–34%. As expected the pairs of the bis-MTPA esters obtained from the same isomer of **1** showed approximately equal epimerization. For example the two bis-MTPA esters **(*R*,3*S*,7*S*,11*R*,15*R*,*R*)-10** and **(*S*,3*S*,7*S*,11*R*,15*R*,*S*)-10** prepared by the esterification of **(3*S*,7*S*,11*R*,15*R*)-1** show 18% and 19% epimerization respectively.

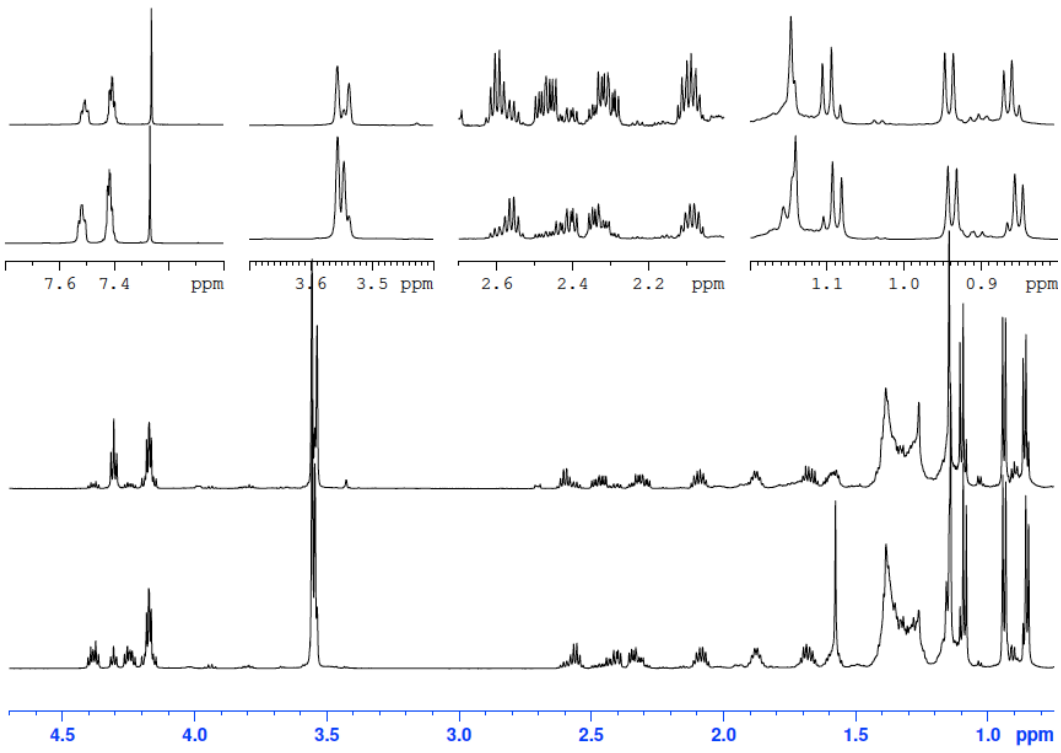


Figure 19. Partial ^{1}H NMR spectra of bis-MTPA esters **(*S*,3*S*,7*S*,11*R*,15*R*,*S*)-10** (bottom) and **(*S*,3*R*,7*S*,11*R*,15*R*,*S*)-10** (top).

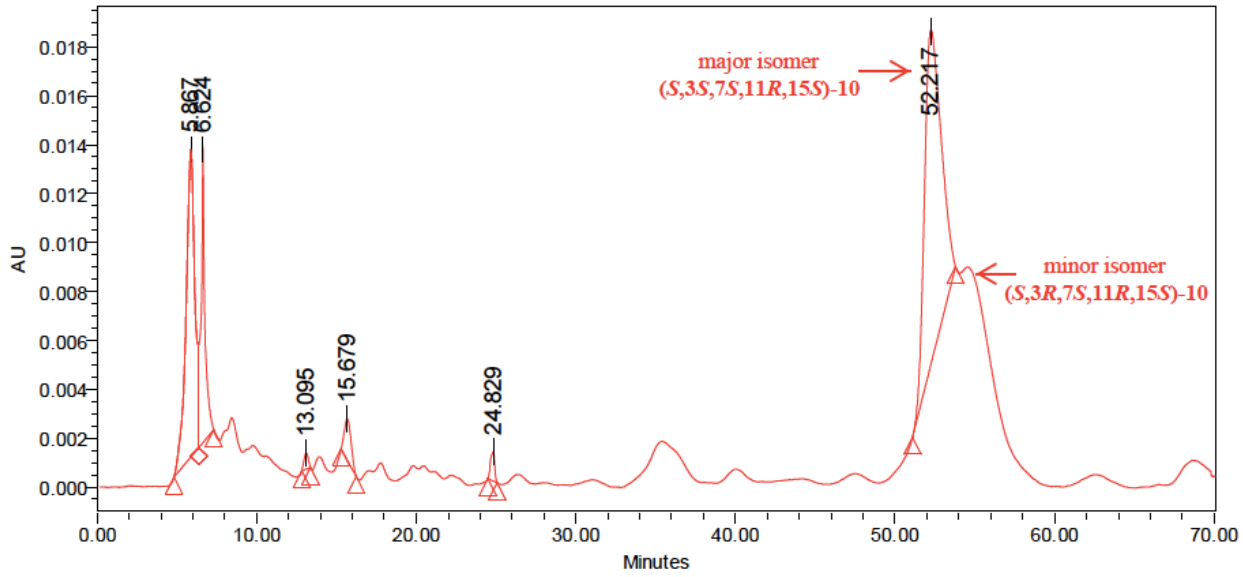
Table 6. The results of the esterification reactions of the eight isomers of **1**, the amount of bis-MTPA esters isolated, the percentage yield of the esterification reaction, the C3 epimer impurity in each bis-MTPA ester and the percentage of the C3 epimer present.

starting material	MTPA acid	product	amount (mg) (%)	C3 epimer, % epimerization
(3*S*,7*S*,11*R*,15*R*)-1	*R*	**(*R*,3*S*,7*S*,11*R*,15*R*,*R*)-10**	6.2 (72%)	**(*R*,3*R*,7*S*,11*R*,15*R*,*R*)-10**, 18%
(3*S*,7*S*,11*R*,15*R*)-1	*S*	**(*S*,3*S*,7*S*,11*R*,15*R*,*S*)-10**	6.4 (73%)	**(*S*,3*R*,7*S*,11*R*,15*R*,*S*)-10**, 19%
(3*S*,7*S*,11*R*,15*S*)-1	*R*	**(*R*,3*S*,7*S*,11*R*,15*S*,*R*)-10**	5.7 (63%)	**(*R*,3*R*,7*S*,11*R*,15*S*,*R*)-10**, 33%
(3*S*,7*S*,11*R*,15*S*)-1	*S*	**(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10**	5.5 (61%)	**(*S*,3*R*,7*S*,11*R*,15*S*,*S*)-10**, 34%
(3*R*,7*S*,11*R*,15*R*)-1	*R*	**(*R*,3*R*,7*S*,11*R*,15*R*,*R*)-10**	4.8 (82%)	**(*R*,3*S*,7*S*,11*R*,15*R*,*R*)-10**, 23%
(3*R*,7*S*,11*R*,15*R*)-1	*S*	**(*S*,3*R*,7*S*,11*R*,15*R*,*S*)-10**	6.1 (64%)	**(*S*,3*S*,7*S*,11*R*,15*R*,*S*)-10**, 21%
(3*R*,7*S*,11*R*,15*S*)-1	*R*	**(*R*,3*R*,7*S*,11*R*,15*S*,*R*)-10**	2.3 (68%)	**(*R*,3*S*,7*S*,11*R*,15*S*,*R*)-10**, 26%
(3*R*,7*S*,11*R*,15*S*)-1	*S*	**(*S*,3*R*,7*S*,11*R*,15*S*,*S*)-10**	2.6 (77%)	**(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10**, 26%
(3*S*,7*R*,11*R*,15*R*)-1	*R*	**(*R*,3*S*,7*R*,11*R*,15*R*,*R*)-10**	4.5 (79%)	**(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10**, 28%
(3*S*,7*R*,11*R*,15*R*)-1	*S*	**(*S*,3*S*,7*R*,11*R*,15*R*,*S*)-10**	4.8 (78%)	**(*S*,3*R*,7*R*,11*R*,15*R*,*S*)-10**, 28%
(3*S*,7*R*,11*R*,15*S*)-1	*R*	**(*R*,3*S*,7*R*,11*R*,15*S*,*R*)-10**	5.2 (77%)	**(*R*,3*R*,7*R*,11*R*,15*S*,*R*)-10**, 17%
(3*S*,7*R*,11*R*,15*S*)-1	*S*	**(*S*,3*S*,7*R*,11*R*,15*S*,*S*)-10**	3.3 (73%)	**(*S*,3*R*,7*R*,11*R*,15*S*,*S*)-10**, 16%
(3*R*,7*R*,11*R*,15*R*)-1	*R*	**(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10**	6.5 (64%)	**(*R*,3*S*,7*R*,11*R*,15*R*,*R*)-10**, 24%
(3*R*,7*R*,11*R*,15*R*)-1	*S*	**(*S*,3*R*,7*R*,11*R*,15*R*,*S*)-10**	5.4 (80%)	**(*S*,3*S*,7*R*,11*R*,15*R*,*S*)-10**, 25%
(3*R*,7*R*,11*R*,15*S*)-1	*R*	**(*R*,3*R*,7*R*,11*R*,15*S*,*R*)-10**	1.9 (77%)	**(*R*,3*S*,7*R*,11*R*,15*S*,*R*)-10**, 19%
(3*R*,7*R*,11*R*,15*S*)-1	*S*	**(*S*,3*R*,7*R*,11*R*,15*S*,*S*)-10**	3.7 (63%)	**(*S*,3*S*,7*R*,11*R*,15*S*,*S*)-10**, 20%

Mosher esters are usually used for spectroscopic analysis and not diastereomeric separation. Nonetheless, we subjected the bis-*S*-MTPA ester **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10** to purification with semi-prep HPLC with Chiral (*S*,*S*)-Whelk-O column (2 x 20 cm) in an attempt to remove the minor C3 epimer. The column was eluted under isocratic conditions with 97:3 hexanes/2-propanol. The flow rate was maintained at 3 mL/min. The HPLC chromatogram of

bis-*S*-MTPA ester **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10** under these conditions is shown in Figure 20. The major isomer eluted at 52.2 min and the minor C3 epimer eluted at about 52.5 min as a shoulder to the major peak. Because, of considerable overlap of the two peaks, peak shaving was necessary to obtain pure fractions.

The bis-*S*-MTPA ester **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10** (major peak in HPLC chromatogram) obtained after HPLC purification was found to be isomerically pure and the peaks corresponding to the corresponding C3 epimer were no longer seen in the ^{1}H NMR spectrum of the purified sample. Only 1.2 mg of pure **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10** was obtained by HPLC purification of 5.0 mg of the epimerized sample. Figure 21 shows a comparison of the ^{1}H NMR spectra of **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10** before and after HPLC purification.



Conditions: (*S*,*S*) Whelk-O column (2 x 20 cm), elution with 97:3 hexanes:2-propanol at a flow rate of 3 mL/min.

Figure 20. Semi prep HPLC chromatogram of the bis-MTPA ester **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10**.

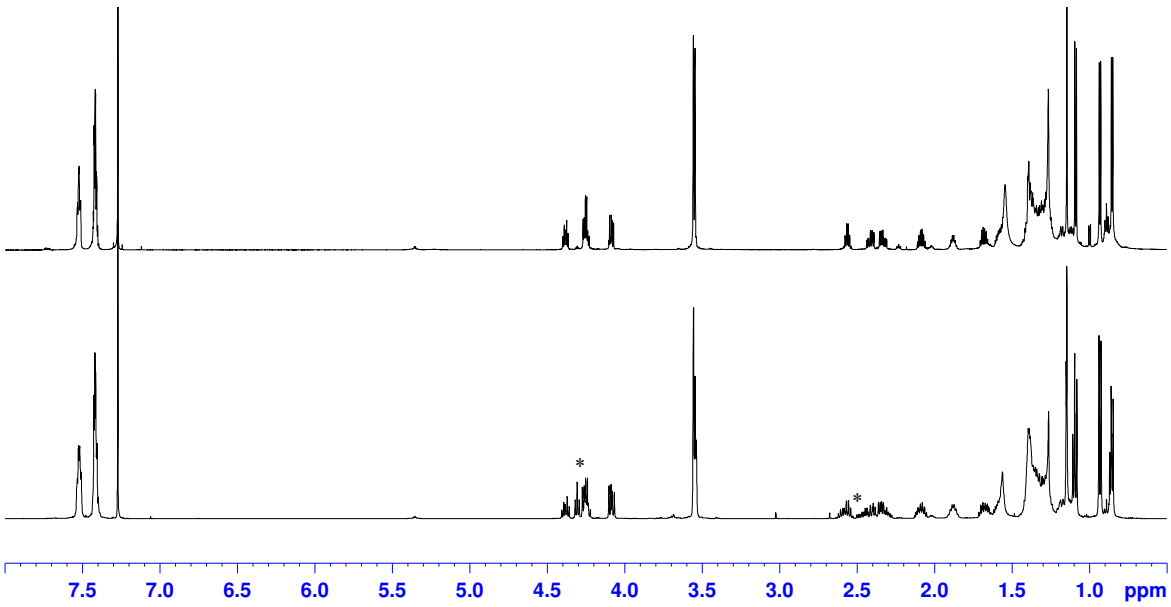


Figure 21. ^{1}H NMR (700 MHz) spectra of **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10** before (bottom) and after (top) HPLC purification. The peaks corresponding to the minor C3 epimer are indicated by an asterisk.

Inspired by the successful purification of bis-*S*-MTPA ester **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10**, we also subjected the remaining 15 bis-MTPA esters to HPLC purification under identical conditions and the ^{1}H NMR (700 MHz) spectra of the purified samples were recorded. We found that 12 out of these 15 esters were essentially pure after HPLC purification and the peaks of the minor isomer (C3 epimer) were no longer seen in their ^{1}H NMR spectra. The remaining three bis-MTPA esters **(*S*,3*S*,7*R*,11*R*,15*R*,*S*)-10**, **(*S*,3*R*,7*R*,11*R*,15*R*,*S*)-10** and **(*R*,3*R*,7*S*,11*R*,15*S*,*R*)-10** were still contaminated with 28% (28% before HPLC), 17% (16% before HPLC) and 11% (26% before HPLC) of the corresponding C3 epimer, respectively. Because there was considerable overlap of peaks of the major and minor isomers in the HPLC chromatogram, peak shaving was needed to obtain pure fractions. It is possible that these three bis-MTPA esters could have been purified by resubmission to chiral HPLC. However, because we could assign all the

minor peaks we did not make any further attempts to purify these sample. The Table 7 summarizes the results of the HPLC purification of the 16 bis MTPA esters.

Table 7. Results of HPLC purification of the 16 bis-MTPA esters, along with their configuration at C3, C7, C11, C15 and MTPA ester configurations.

bis-MTPA ester	MTPA ester configuration	C3	C7	C11	C15	amount (mg) after HPLC	% C3 epimer after HPLC
(*R*,3*S*,7*S*,11*R*,15*R*,*R*)-10	*R*	*S*	*S*	*R*	*R*	1.6	n.d.
(*S*,3*S*,7*S*,11*R*,15*R*,*S*)-10	*S*	*S*	*S*	*R*	*R*	1.4	n.d.
(*R*,3*S*,7*S*,11*R*,15*S*,*R*)-10	*R*	*S*	*S*	*R*	*S*	0.7	n.d.
(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10	*S*	*S*	*S*	*R*	*S*	1.2	n.d.
(*R*,3*R*,7*S*,11*R*,15*R*,*R*)-10	*R*	*R*	*S*	*R*	*R*	0.8	n.d.
(*S*,3*R*,7*S*,11*R*,15*R*,*S*)-10	*S*	*R*	*S*	*R*	*R*	1.3	n.d.
(*R*,3*R*,7*S*,11*R*,15*S*,*R*)-10	*R*	*R*	*S*	*R*	*S*	0.5	11%
(*S*,3*R*,7*S*,11*R*,15*S*,*S*)-10	*S*	*R*	*S*	*R*	*S*	1.0	n.d.
(*R*,3*S*,7*R*,11*R*,15*R*,*R*)-10	*R*	*S*	*R*	*R*	*R*	1.5	n.d.
(*S*,3*S*,7*R*,11*R*,15*R*,*S*)-10	*S*	*S*	*R*	*R*	*R*	1.6	28%
(*R*,3*S*,7*R*,11*R*,15*S*,*R*)-10	*R*	*S*	*R*	*R*	*S*	0.4	n.d.
(*S*,3*S*,7*R*,11*R*,15*S*,*S*)-10	*S*	*S*	*R*	*R*	*S*	1.5	n.d.
(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10	*R*	*R*	*R*	*R*	*R*	0.5	n.d.
(*S*,3*R*,7*R*,11*R*,15*R*,*S*)-10	*S*	*R*	*R*	*R*	*R*	1.2	17%
(*R*,3*R*,7*R*,11*R*,15*S*,*R*)-10	*R*	*R*	*R*	*R*	*S*	1.1	n.d.
(*S*,3*R*,7*R*,11*R*,15*S*,*S*)-10	*S*	*R*	*R*	*R*	*S*	0.8	n.d.

n.d. = not determined by ^{1}H NMR spectroscopy

1.4.2 Spectroscopic analysis of the 16 bis-MTPA esters

The ^{19}F NMR spectra of the 16 bis-MTPA esters were obtained at 282 MHz and are shown in Figure 22. In the ^{19}F NMR spectra of eight bis-MTPA esters, the peaks due to the two CF_3 groups overlap and these spectra show a single peak at about δ −72.53. The ^{19}F NMR spectra of the remaining eight bis-MTPA esters show two well-resolved peaks at about δ −72.53 and −72.47.

We suggest that the CF_3 group of the C16 MTPA ester has a chemical shift value of about δ −72.53 in all the 16 bis-MTPA esters, independent of the ester configuration and of the C15 configuration. The CF_3 group in the C1 MTPA ester also appears at δ −72.53 for bis-*R*-MTPA esters of C3 *R* isomers and for bis-*S*-MTPA esters of C3 *S* isomers. In these eight bis-MTPA esters, the peaks of the two CF_3 groups overlap and only one peak is seen in their ^{19}F NMR spectra. The CF_3 group in the C1 MTPA ester group appears at about δ −72.47 for bis-*R*-MTPA esters of C3 *S* isomers and for bis-*S*-MTPA esters of C3 *R* isomers. The ^{19}F NMR spectra of these eight isomers show two separate peaks, one for each CF_3 group.

Taken together, the ^{19}F NMR spectra give information only about the C3 configuration. In bis-MTPA esters that show one peak in the ^{19}F NMR spectrum, the C3 configuration is same as the MTPA ester configuration. In the bis-MTPA esters that show two peaks in the ^{19}F NMR spectrum, the C3 configuration is opposite to the MTPA ester configuration.

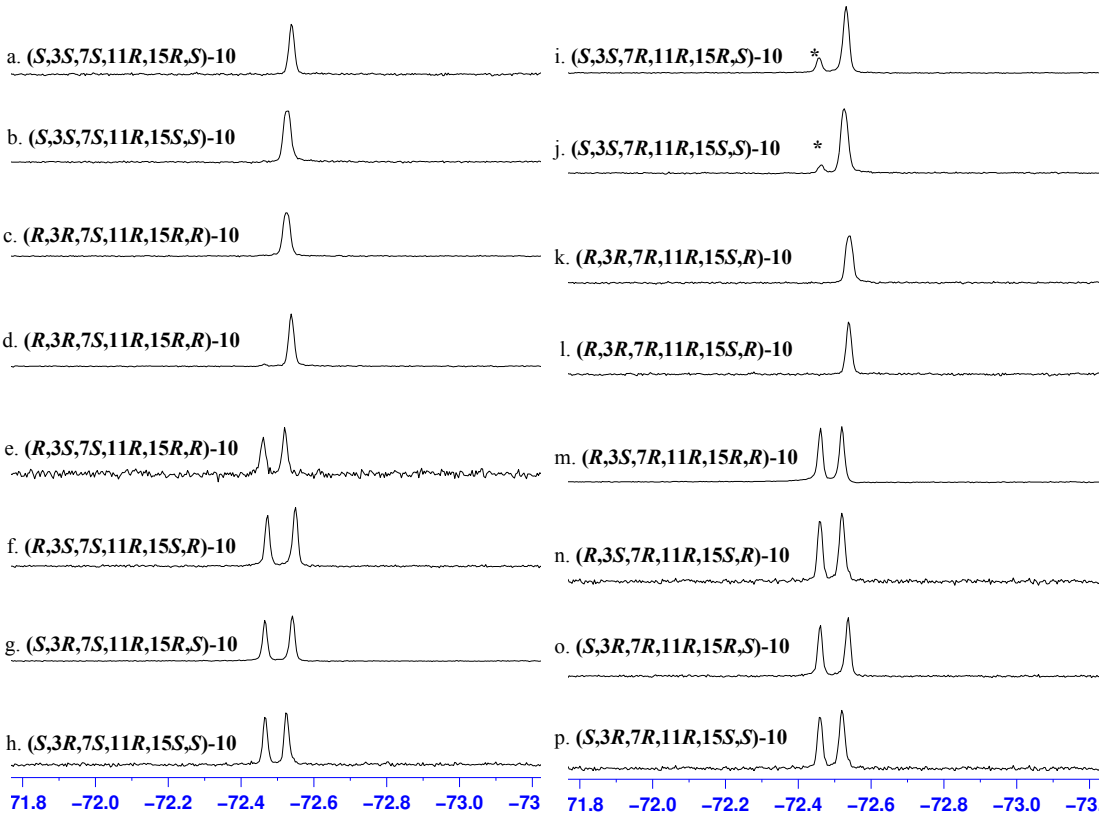


Figure 22. ^{19}F NMR spectra of the 16 bis-MTPA esters, the peaks marked with an asterisk correspond to the minor C3 epimer impurity. In the ^{19}F NMR spectrum of the bis-MTPA ester **(*R*,3*R*,7*S*,11*R*,15*S*,*R*)-10** (spectra d) a minor isomer must be present but the peak due to the minor product is very small.

We also obtained the 700 MHz ^{1}H NMR spectra of the 16 bis-MTPA esters and assigned all the non-overlapping peaks by a combination of ^{1}H NMR and ^{1}H-^{1}H COSY data. ^{1}H NMR spectra of the 16 bis-MTPA esters were then carefully compared with each other. Because we could see differences in the ^{1}H NMR spectra of C3,C7-syn and anti compounds in the PMB^{F} ethers **127** and in the eight isomers of **1**, we first looked for such differences in the ^{1}H NMR spectra of the 16 bis-MTPA esters.

Indeed it is possible to determine the relative configuration of C3 and C7 stereocenters by the ^{1}H NMR analysis of the bis-MTPA esters. The Figure 23 shows the expansion of the C5

methylene protons in the ^{1}H NMR spectra of the bis-MTPA esters **(*S*,3*S*,7*R*,11*R*,15*S*,*S*)-10** and **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10**. These two bis-MTPA esters differ only in their configuration at the C7 stereocenter. In **(*S*,3*S*,7*R*,11*R*,15*S*,*S*)-10** the C3 and C7 methylene groups are syn while in **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10** C3 and C7 methyl groups are anti. In the C3,C7-syn compound **(*S*,3*S*,7*R*,11*R*,15*S*,*S*)-10**, the two C5 methylene protons appear as two doublets of doublets of doublets centered at δ 2.45 and δ 2.29 (Δδ = 0.16 ppm). In the C3,C7-anti compound **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10** these two doublets of doublets of doublets come closer together at δ 2.43 and δ 2.35 (Δδ = 0.08 ppm). Table 8 summarizes the chemical shift values of the two C5 methylene protons in the 16 bis-MTPA esters, and the difference in the chemical shift values of the two C5 methylene protons (Δδ), and the relative configuration of the C3 and C7 stereocenters (syn or anti).

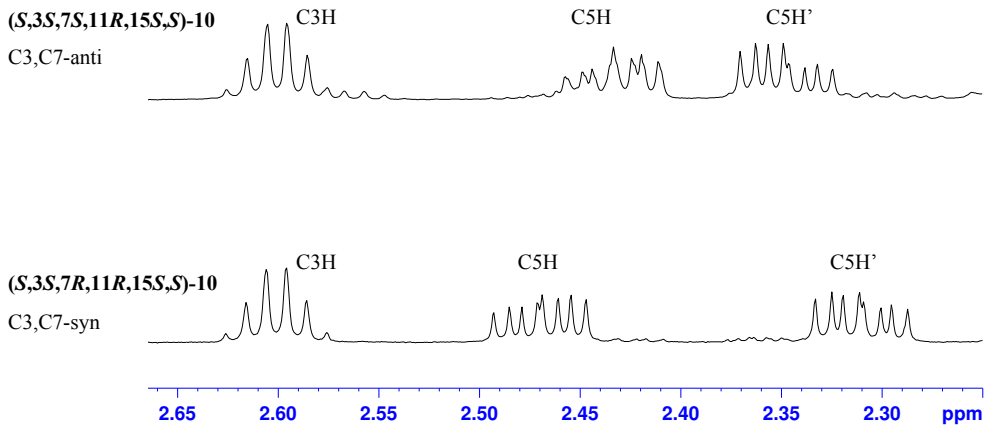


Figure 23. An expansion of the C5 methylene protons in the ^{1}H NMR (700 MHz) spectra of **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10** (top, C3,C7-anti) and **(*S*,3*S*,7*R*,11*R*,15*S*,*S*)-10** (bottom, C3,C7-syn).

Table 8. Chemical shift values of the C5 methylene protons in the 16 bis-MTPA esters (δ H5 and δ H5′) and the difference δ H5 – δ H5′ (ppm) in relation to the C3 and C7 relative configuration.

bis-MTPA ester	δ H5	δ H5′	δ H5 – δ H5′ (ppm)	C3 and C7
(*R*,3*S*,7*S*,11*R*,15*R*,*R*)-10	2.43	2.35	0.08	anti
(*S*,3*S*,7*S*,11*R*,15*R*,*S*)-10	2.42	2.33	0.09	anti
(*R*,3*S*,7*S*,11*R*,15*S*,*R*)-10	2.43	2.35	0.08	anti
(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10	2.42	2.34	0.08	anti
(*R*,3*R*,7*S*,11*R*,15*R*,*R*)-10	2.45	2.29	0.16	syn
(*S*,3*R*,7*S*,11*R*,15*R*,*S*)-10	2.47	2.31	0.16	syn
(*R*,3*R*,7*S*,11*R*,15*S*,*R*)-10	2.45	2.30	0.15	syn
(*S*,3*R*,7*S*,11*R*,15*S*,*S*)-10	2.47	2.31	0.16	syn
(*R*,3*S*,7*R*,11*R*,15*R*,*R*)-10	2.47	2.31	0.16	syn
(*S*,3*S*,7*R*,11*R*,15*R*,*S*)-10	2.45	2.30	0.15	syn
(*R*,3*S*,7*R*,11*R*,15*S*,*R*)-10	2.47	2.31	0.16	syn
(*S*,3*S*,7*R*,11*R*,15*S*,*S*)-10	2.45	2.29	0.16	syn
(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10	2.41	2.33	0.08	anti
(*S*,3*R*,7*R*,11*R*,15*R*,*S*)-10	2.43	2.35	0.08	anti
(*R*,3*R*,7*R*,11*R*,15*S*,*R*)-10	2.42	2.33	0.09	anti
(*S*,3*R*,7*R*,11*R*,15*S*,*S*)-10	2.43	2.35	0.08	anti

There were also significant differences in the signals for C1 and C16 methylene protons in the ^{1}H NMR spectra of the 16 bis-MTPA esters as depicted in Figure 24. In the ^{1}H NMR spectra of the eight bis-MTPA esters with C3 *S* configuration, the two C1 methylene protons

appear as a triplet at δ 4.31 in the bis-*R*-MTPA esters (spectra b, c, e and g) and as two separate signals (a triplet of doublet centered at δ 4.38 and a doublet of doublets of doublets at δ 4.25) in bis-*S*-MTPA esters (spectra j, k, m and o). In the ^{1}H NMR spectra of the eight isomers with C3 *R* configuration, this pattern is reversed and the C1 methylene protons appear as separate signals (a td at δ 4.38 and a ddd at δ 4.25) in bis-*R*-MTPA esters (spectra i, l, n and p) and as a triplet at δ 4.31 in bis-*S*-MTPA esters (spectra a, d, f and h).

When the C15 configuration is *R*, the C16 methylene protons appear as two doublets of doublets centered at δ 4.19 and 4.16 (Δδ = 0.03 ppm) in the ^{1}H NMR spectra of the bis-*S*-MTPA esters (spectra a, d, m and o) and at δ 4.26 and 4.09 ppm (Δδ = 0.17 ppm) in the ^{1}H NMR spectra of bis-*R*-MTPA esters (spectra e, g, i and l). In the isomers with C15 *S* configuration the C16 methylene protons appear at δ 4.26 and 4.09 (Δδ = 0.17 ppm) in the ^{1}H NMR spectra of bis-*S*-MTPA esters (spectra f, h, j and k) and at δ 4.19 and 4.16 ppm (Δδ = 0.03 ppm) in the ^{1}H NMR spectrum of bis-*R*-MTPA esters (spectra b, c, n and p).

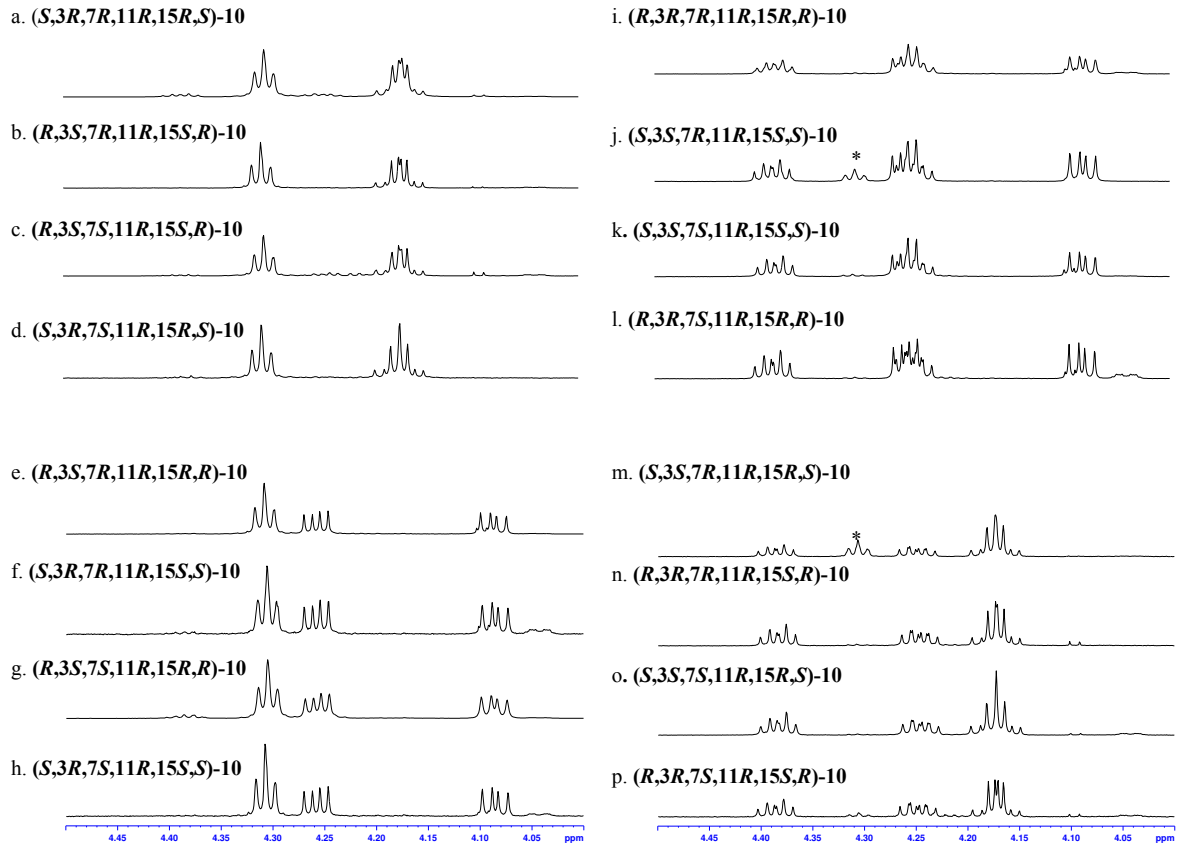


Figure 24. Expansions of the C1 and C16 methylene protons in the ^{1}H NMR (700 MHz) spectra of the 16 bis-MTPA esters. The peaks marked with an asterisk are due to the minor C3 epimer

On careful comparison of the ^{1}H NMR spectra of the 16 bis-MTPA esters, we found that the ^{1}H NMR spectra of the pairs bis-MTPA esters that have different configuration at all stereocenters except at the tertiary C11 stereocenter (the C11 configuration was *R* in all our 16 bis-MTPA esters) are substantially identical. For example ^{1}H NMR spectrum of **(*R*,3*R*,7*R*,11*R*, 15*R*,*R*)-10** was substantially identical to the ^{1}H NMR spectrum of **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10**. An overlap of these two ^{1}H NMR spectra is shown in Figure 25.

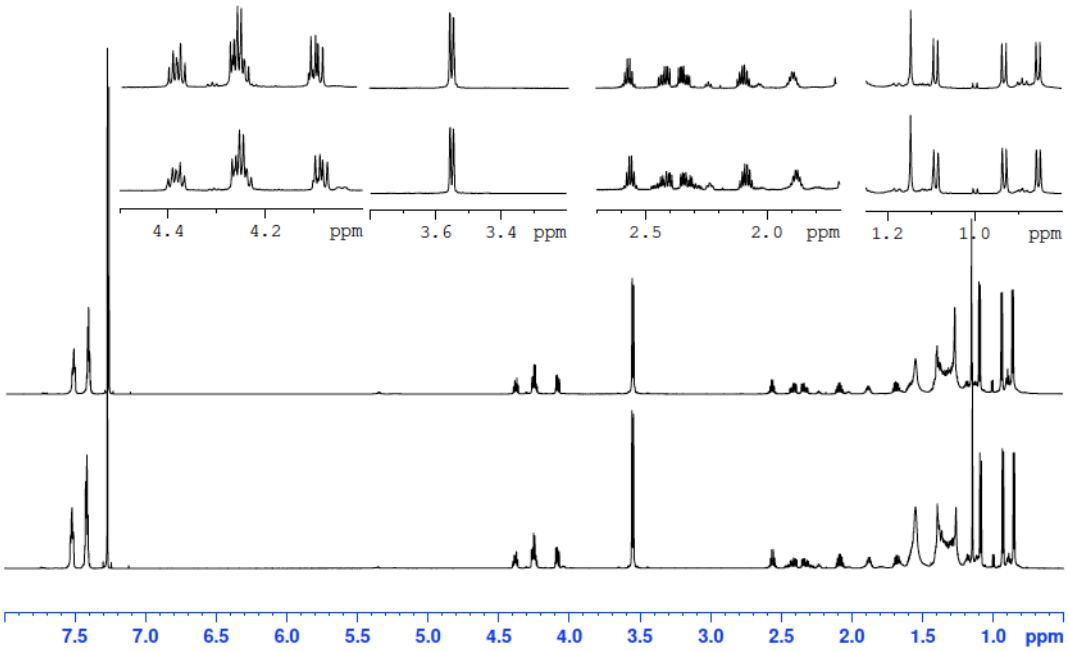


Figure 25. ^{1}H NMR (700 MHz) spectra of **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10** (top) and **(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10** (bottom).

To learn if there were any meaningful differences in the ^{13}C NMR spectra of these two bis-MTPA esters, we also compared the 2D ^{1}H-^{13}C HMQC spectra of **(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10** and **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10** with each other. These spectra were obtained at the 700 MHz NMR instrument and are shown on page 224 and 225 of the Appendix. The two HMQC spectra were also substantially identical and no differences were seen in the non-overlapping cross-peaks. Thus it is not currently possible to differentiate **(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10** and **(*S*,3*S*,7*S*,11*R*,15*S*, *S*)-10** by NMR analysis.

Since **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10** will also have the same ^{1}H and ^{13}C NMR spectra as its enantiomer **(*R*,3*R*,7*R*,11*S*,15*R*,*R*)-10** (C11 *S* configuration, not synthesized in this work) we can conclude that the ^{1}H and ^{1}H-^{13}C HMQC (and hence ^{13}C) NMR spectra of **(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10** will be substantially identical to that of **(*R*,3*R*,7*R*,11*S*,15*R*,*R*)-10**. These results suggest that it

is not be possible to differentiate the pairs of the bis-MTPA esters that differ only in their C11 configuration by NMR spectroscopy under current conditions.

1.4.3 Comparison of spectroscopic data of the 16 bis-MTPA esters with previous bis-MTPA esters of 1

We first compared the ^{1}H NMR spectrum of the bis-*R*-MTPA ester of the natural hormone α1 with the ^{1}H NMR spectra of our 16 bis-MTPA esters. The FID of the ^{1}H NMR spectrum of the natural hormone α1 was kindly provided by Dr. Ojika.[26]

The peaks of the major isomer in the ^{1}H NMR spectrum of bis-*R*-MTPA ester of the natural product match with the ^{1}H NMR spectrum of bis-*R*-MTPA ester **(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10** and the peaks of the minor isomer in the ^{1}H NMR spectrum of the natural bis-*R*-MTPA ester match the ^{1}H NMR spectrum of **(*R*,3*S*,7*R*,11*R*,15*R*,*R*)-10**. An overlap of the partial ^{1}H NMR spectra of the bis-*R*-MTPA of the natural product, **(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10** and **(*R*,3*S*,7*R*,11*R*, 15*R*,*R*)-10** are shown in Figure 26.

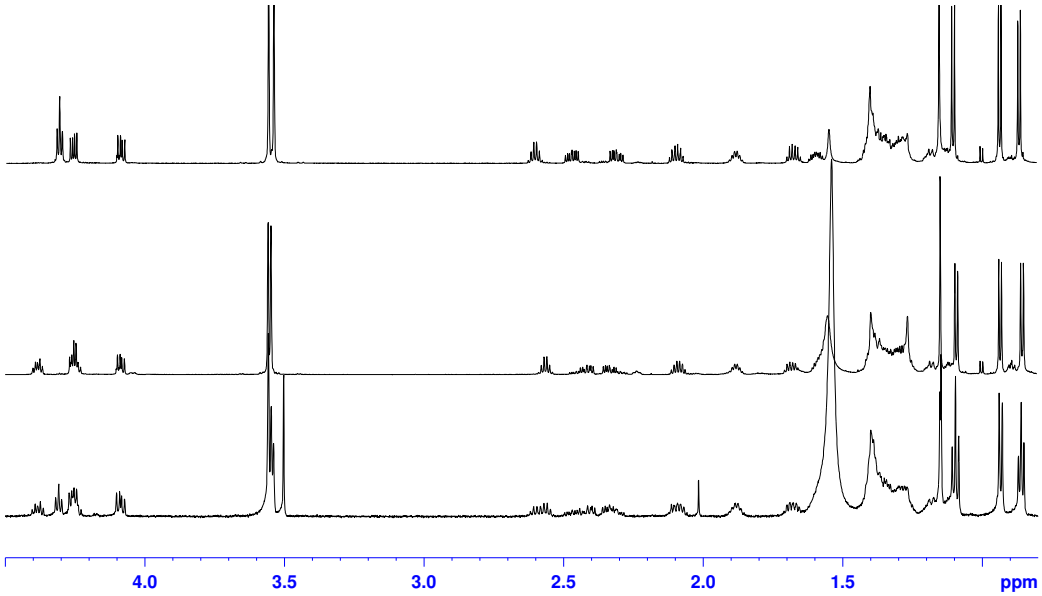


Figure 26. Partial ^{1}H NMR spectra of the bis-*R*-MTPA ester from the natural hormone α1 (bottom), **(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10** (middle) and **(*R*,3*S*,7*R*,11*R*,15*R*,*R*)-10** (top).

This confirms the assignment of the C3, C7 and C15 stereocenters in natural hormone α1 as *R* by Yajima and coworkers.[28] However, the assignment of the C11 configuration as *R* cannot be confirmed by this analysis because according to our results the ^{1}H NMR spectrum of **(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10** will be substantially identical to the ^{1}H NMR spectrum of **(*R*,3*R*,7*R*,11*S*,15*R*,*R*)-10**, which differs only at its C11 configuration.

Yajima and coworkers have previously converted their four synthetic isomers of **1** to the corresponding bis-*R*-MTPA esters.[28] The structures of the four bis-*R*-MTPA esters synthesized by them are shown in Figure 27. They provided the copies of the ^{1}H NMR (400 MHz) spectra of the four bis-*R*-MTPA esters as a part of the supporting information to their publication[28] but did not report the tabulated ^{1}H NMR data for their bis-*R*-MTPA esters.

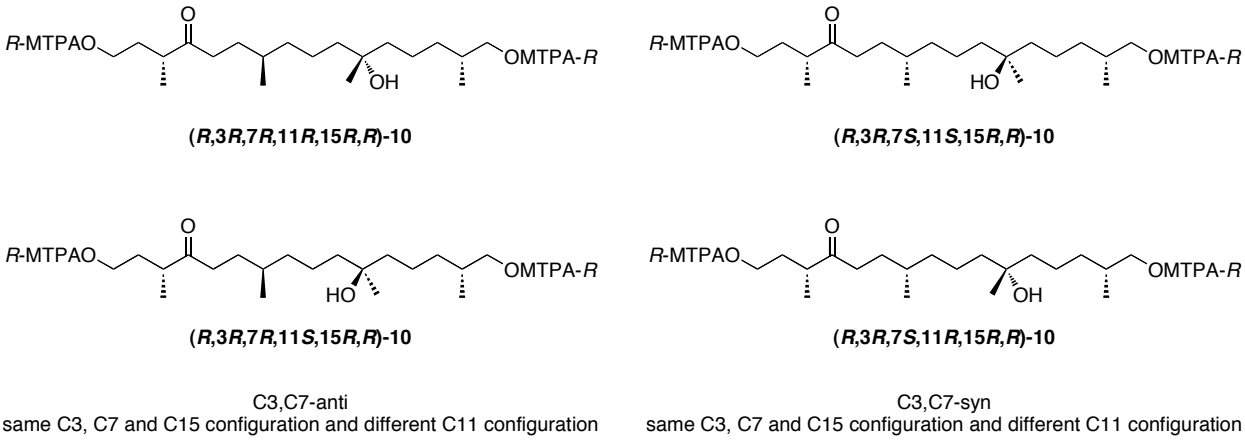


Figure 27. The four bis-*R*-MTPA esters synthesized by Yajima and coworkers.

Because, all the four bis-MTPA esters synthesized by Yajima and coworkers have (3*R*,15*R*) configuration, their ^{1}H NMR spectra are expected to show similar resonances for the C1 and C16 methylene protons. Out of these four bis-MTPA esters, **(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10** and **(*R*,3*R*,7*R*,11*S*,15*R*,*R*)-10** are C3,C7-anti while **(*R*,3*R*,7*S*,11*S*,15*R*,*R*)-10** and **(*R*,3*R*,7*S*,11*R*, 15*R*,*R*)-10** are C3,C7-syn. According to our results these two sets of bis-MTPA esters should have different chemical shift for the two C5 methylene protons. However, because their ^{1}H NMR spectra were recorded at 400 MHz it is possible that the two C5 methylene protons were not well resolved.

The bis-MTPA esters **(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10** and **(*R*,3*R*,7*R*,11*S*,15*R*,*R*)-10** only differ in their C11 configuration so they should have substantially identical ^{1}H NMR spectra. Similarly the bis-*R*-MTPA esters **(*R*,3*R*,7*S*,11*R*,15*R*,*R*)-10** and **(*R*,3*R*,7*S*,11*S*,15*R*,*R*)-10** also differ only in their C11 configuration and will have identical ^{1}H NMR spectra**.** Thus the four bis-MTPA esters synthesized by Yajima and coworkers should give two pairs of ^{1}H NMR spectra at 700 MHz. Even though they did report a through analysis of the ^{1}H NMR spectra of the four bis-MTPA esters, their spectra look pure and their synthetic isomers of **1** must be isomerically pure.

Feringa and coworkers have also reported the synthesis of two isomers of **1**,[30] but they did not do the Mosher ester analysis of their final products. However, they report identical ^{1}H NMR spectra for their two synthetic isomers of **1** (one of then is C3,C7-syn and the other is C3,C7-anti). If this is true then it is likely that their final products were epimerized at the C3 stereocenter during the synthesis.

1.5 CONCLUSIONS

Eight stereoisomers of the hormone α1 were synthesized by FMS. Based on the ^{1}H NMR spectra of these eight isomers it is only possible to assign the relative configuration of the C3 and C7 stereocenters. The ^{13}C NMR spectra of these eight isomers show very small differences. These eight stereoisomers were subsequently converted to the corresponding *R* and *S* bis-MTPA esters.

The analysis of the ^{1}H NMR spectra of these 16 Mosher esters suggested about 16-34% epimerization at the C3 stereocenter of the eight stereoisomers of **1**. All the sixteen bis-MTPA esters were purified by chiral HPLC over (*S*,*S*)-Whelk-O column to get rid of the minor C3 epimer impurity. The 700 MHz ^{1}H NMR and 282 MHz ^{19}F NMR spectra of the 16 bis-Mosher esters were obtained and compared with each other. While the ^{19}F NMR spectra provide information only about the C3 stereochemistry, the configurations of the C3, C7 and C15 stereocenters can be successfully assigned by ^{1}H NMR analysis of the bis-MTPA esters. However, assignment of the C11 configuration by ^{1}H and ^{19}F NMR analysis of the 16 bis-MTPA esters is not possible.

By comparison of the ^{1}H NMR spectrum of the bis-*R*-MTPA ester of the natural hormone α1 with the ^{1}H NMR spectra of the 16 synthetic bis-MTPA esters, we confirmed the assignment of the C3, C7 and C15 stereocenters in natural product as *R*. The assignment of the C11 stereocenter in the natural product as *R* could not be confirmed by this analysis.

1.6 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 a column of activated alumina. THF was freshly distilled from Na/benzophenone. Methylene chloride, diethyl ether and toluene were dried by activated alumina according to literature.[86] All 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, ^{19}F NMR, FT-IR, low and high resolution mass spectroscopy, and HPLC. NMR spectra were taken on a Bruker WH-300, IBM AF-300, a Bruker Avance™ 500 NMR, 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 $CDCl_3$ (7.27 ppm) or central $CDCl_3$ carbon peak (77.00 ppm) as the internal standard. In reporting spectral data, the following

abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, sxt = sextet, m = multiplet, dd = doublet doublet, td = triplet doublet, ddd = doublet doublet doublet. Infrared spectra were taken on a Mattson Genesis Series FTIR using thin film on NaCl plate. Peaks are reported in wave numbers (cm^{-1}). Low resolution mass spectra was obtained on a V/G 70/70 double focusing machine and were reported in units of *m/z*. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at a 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. Compound names have been obtained from ChemDraw Ultra 12.0 (Cambridge Soft Corp.).

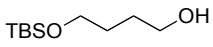
General conditions for analytical fluorous HPLC experiments:

A solution of the fluorous sample in THF was injected into the Waters HPLC system (Waters 600 Controller and Waters 2487 dual λ Absorbance Detector) with a Fluoro*Flash*TM PF-C8 column (5 μm, 10 A°, 4.6 × 150 mm). The flow rate was 1.0 mL/min. The UV wave-lengths for detection were 230 nm and 254 nm. The three frequently used elution conditions were:

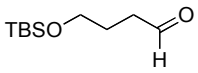
Conditions 1: The gradient elution started at 80:20 CH_3CN:H_2O, and changed to 100% CH_3CN in 30 min.

Conditions 2: The gradient elution started at 70:30 CH_3CN:H_2O, and changed to 100% CH_3CN in 30 min.

Conditions 3: The gradient elution started at 60:40% CH_3CN:H_2O, and changed to 100% CH_3CN in 30 min.

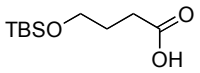


4-(*tert*-Butyldimethylsilyloxy)butan-1-ol (64):[42] Sodium hydride (60% suspension in mineral oil, 2.2 g, 55.6 mmol) was washed with hexanes and suspended in dry THF (110 mL). 1,4-Butanediol **63** (5.0 g, 55.6 mmol) was added to this suspension and the reaction mixture was stirred at room temperature for 45 min during which time a large amount of opaque white precipitate formed. *tert*-Butyldimethylsilyl chloride (8.4 g, 55.6 mmol) was then added and the mixture was stirred at room temperature for 45 min. The reaction mixture was diluted with Et_2O and washed with 10% aqueous solution of potassium carbonate. The layers were separated and the aqueous layer was further extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 30% ethyl acetate/hexanes) gave 9.6 g (85%) of the desired alcohol **64** as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70–3.63 (m, 4H), 2.54 (br s, 1H), 1.71–1.60 (m, 4H), 0.91 (s, 9H), 0.08 (s, 6H).

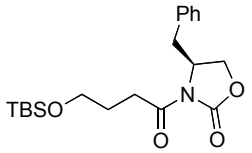


4-(*tert*-Butyldimethylsilanyloxy)butanal (65):[87] A solution of DMSO (4.9 mL, 68.2 mmol) in DCM (100 mL) was added dropwise to a solution of oxalyl chloride (6.5 mL, 74.4 mmol) in DCM (90 mL) at −78 °C. After 5 min, a solution of starting alcohol **64** (12.7 g, 62.0 mmol) in DCM (80 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 15 min, then triethylamine (43.7 mL, 310.2 mmol) was added in one portion. The mixture was stirred at −78 °C for 10 min and at room temperature for 2 h. The reaction mixture was diluted with DCM, water was added and the layers were separated. The aqueous layer was further extracted with DCM. The combined organic extracts were washed with saturated NH_4Cl solution and brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. Purification by flash column

chromatography (SiO_2, 10% ethyl acetate/hexanes) gave 11.3 g (90%) of pure aldehyde **65** as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (t, J = 1.8 Hz, 1H), 3.66 (t, J = 6.0 Hz, 2H), 2.51 (td, J = 7.2, 1.8 Hz, 2H), 1.91–1.82 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H).

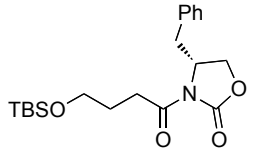


4-(*tert*-Butyldimethylsilyloxy)butanoic acid (66):[88] NaH_2PO_4•H_2O (1.80 g, 12.9 mmol), 2-methyl-2-butene (2 M in THF, 19.0 mL, 38.0 mmol) and $NaClO_2$ (1.3 g, 11.5 mmol) were added to a solution of the starting aldehyde **65** (0.77 g, 3.8 mmol) in 3:1 *t*-BuOH:H_2O (96 mL) at room temperature. The resulting yellowish green mixture was stirred vigorously at room temperature for 15 h. Most of the reaction solvent was then removed under vacuum. The remaining aqueous portion was diluted with EtOAc and the layers were separated. The aqueous layer was further extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash chromatography (SiO_2, 20% ethyl acetate/hexanes) afforded 0.71 mg (86%) of the desired carboxylic acid **66** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.84 (br s, 1H), 3.68 (t, J = 6.0 Hz, 2H), 2.47 (t, J = 7.2 Hz, 2H), 1.90–1.82 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H).



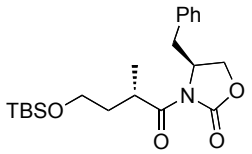
(*S*)-4-Benzyl-3-(4-(*tert*-butyldimethylsilyloxy)butanoyl)oxazolidin-2-one ((*S*)-67):[41]
Triethylamine (6.3 mL, 44.8 mmol) was added dropwise to a solution of the starting carboxylic acid **66** (8.5 g, 38.9 mmol) in diethyl ether (370 mL) and the resulting mixture was stirred at

room temperature for 15 min. The reaction mixture was cooled to 0 °C and ethyl chloroformate (3.8 mL, 38.9 mmol) was added. The mixture was warmed to room temperature and stirred for 1 h. In a separate flask *n*-BuLi (1.6 M in hexanes, 28.0 mL, 44.8 mmol) was added dropwise to a solution (4*S*)-benzyloxazolidinone (6.9 g, 38.9 mmol) in THF (55 mL) at −78 °C. The oxazolidinone anion solution was then transferred dropwise via cannula to the reaction mixture containing the carboxylic acid. The mixture was stirred at − 78 °C for 30 min and at room temperature for 3 h. The reaction was quenched by addition of saturated NH_4Cl solution, water was added and the layers were separated. The aqueous layer was further extracted with Et_2O. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography (SiO_2, 10% ethyl acetate/hexanes) gave 8.4 g (57%) of pure (***S*)-67** as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.28 (m, 3H), 7.24–7.20 (m, 2H), 4.72–4.64 (m, 1H), 4.23–4.14 (m, 2H), 3.71 (t, *J* = 6.2 Hz, 2H), 3.32 (dd, *J* = 3.3, 13.4 Hz, 1H), 3.03 (dd, *J* = 6.8, 7.7 Hz, 2H), 2.77 (dd, *J* = 9.7, 13.3 Hz, 1H), 1.97–1.88 (m, 2H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 153.4, 135.3, 129.4, 128.9, 127.3, 66.1, 62.0, 55.2, 37.9, 32.1, 27.2, 25.9, 18.3, − 5.4; IR (neat) 2954, 2928, 1786, 1701, 1388, 1257, 1100, 837 cm^{-1}; EIMS *m/z* 377 $(M)^+$; HRMS (EI) $(M)^+$ calcd for $C_{20}H_{31}NO_4Si$, 377.2022; found, 377.2010; $[\alpha]_D^{25}$ +32.32 (*c* 0.95, $CHCl_3$).

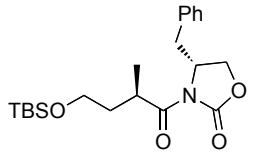


(*R*)-4-Benzyl-3-(4-(*tert*-butyldimethylsilyloxy)butanoyl)oxazolidin-2-one ((*R*)-67):[41]

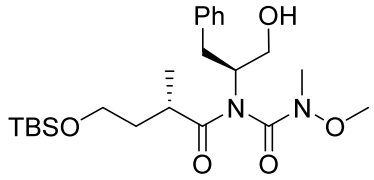
This compound was prepared by reaction of the carboxylic acid **66** with (4*R*)-benzyloxazolidinone according to the procedure described for preparation of **(*S*)-67**. The spectral data was in good accordance to that reported for (***S*)-67**: $[\alpha]_D^{25}$ −32.84 (*c* 0.81, $CHCl_3$).



(*S*)-4-Benzyl-3-((*S*)-4-(*tert*-butyldimethylsilyloxy)-2-methylbutanoyl)oxazolidin-2-one ((*S*,*S*)-68):[45] A solution of oxazolidinone derivative **(*S*)-67** (8.4 g, 22.2 mmol) in THF (30 mL) was added dropwise to a solution of NaHMDS (1.0 M in THF, 31.0 mL, 31.0 mmol) in THF (30 mL) at −78 °C. After 1 h MeI (7.0 mL, 110.8 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 3 h. The reaction was quenched by addition of acetic acid (1.5 mL) and the mixture was warmed to room temperature. The reaction mixture was diluted with EtOAc, water was added and the layers were separated. The aqueous layer was further extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 10% ethyl acetate/hexanes) afforded 7.5 g (87%) of **(*S*,*S*)-68** as white solid (mp 51–52 °C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.28 (m, 3H), 7.26–7.20 (m, 2H), 4.71–4.63 (m, 1H), 4.19–4.14 (m, 2H), 3.93–3.81 (m, 1H), 3.72–3.60 (m, 2H), 3.27 (dd, *J* = 3.3, 13.3 Hz, 1H), 2.77 (dd, *J* = 9.6, 13.3 Hz, 1H), 2.11–1.99 (m, 1H), 1.70–1.60 (m, 1H), 1.26 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 152.9, 135.4, 129.4, 128.9, 127.3, 65.9, 61.0, 55.3, 37.9, 36.0, 34.7, 25.9, 18.3, 17.9, −5.5; IR (thin film) 2953, 2929, 2882, 2856, 1766, 1696, 1462, 1101 cm^{-1}; EIMS *m/z* 391 $(M)^+$; HRMS (EI) $(M)^+$ calcd for $C_{21}H_{33}NO_4Si$, 391.2179; found 391.2160; $[\alpha]_D^{25}$ +59.83 (*c* 0.43, $CHCl_3$).

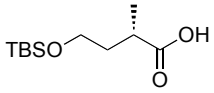


(*R*)-4-Benzyl-3-((*R*)-4-(*tert*-butyldimethylsilyloxy)-2-methylbutanoyl)oxazolidin-2-one ((*R*,*R*)-68):[45] This compound was prepared from **(*R*)-67** in 85% yield according to the procedure described above for preparation of **(*S*,*S*)-68**: mp 51–52 °C; $[\alpha]_D^{25}$ −60.37 (*c* 0.46, $CHCl_3$); other spectroscopic data were in good accordance to that reported for **(*S*,*S*)-68**.

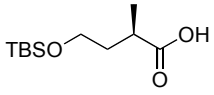


1-((*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-methylbutanoyl)-1-((*S*)-1-hydroxy-3-phenylpropan-2-yl)-3-methoxy-3-methylurea ((*S*,*S*)-69):[46] A solution of $AlMe_3$ (2 M in toluene, 1.0 mL, 2.0 mmol) was added dropwise to a solution of *N*,*O*-hydroxylamine hydrochloride (200.2 mg, 2.0 mmol) in dry DCM (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then cooled to −50 °C. A solution of **(*S*,*S*)-68** (387.5 mg, 0.10 mmol) in dry DCM (1 mL) was added and the mixture was stirred at room temperature overnight. The reaction mixture was cooled to 0 °C, quenched with 1 M aqueous tartaric acid, and stirred vigorously for 1 h. Water was added and the layers were separated. The aqueous layer was further extracted twice with DCM. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 20% ethyl acetate/hexanes) gave 280 mg (63%) of the urea **(*S*,*S*)-69** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 6.00 (d, J = 8.4 Hz, 1H), 4.40–4.24 (m, 1H), 4.14 (d, J = 5.1 Hz,

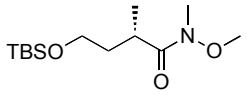
2H), 3.70 (t, J = 6.0 Hz, 2H,), 3.61 (s, 3H), 3.10 (s, 3H), 3.03–2.86 (m, 2H), 2.74 (sextet, J = 6.9 Hz, 1H), 2.01 (dtd, J = 6.3, 6.6, 13.5 Hz, 1H), 1.65 (dtd, J = 6.3, 6.5, 13.8 Hz, 1H), 1.25 (d, J = 6.9 Hz, 3H), 0.94 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 159.4, 137.0, 129.1, 128.3, 126.5, 64.5, 61.0, 60.4, 50.1, 37.7, 36.1, 35.8, 35.1, 25.7, 18.1, 16.8, −5.6; IR (neat) 3338, 2931, 2857, 1733, 1683, 1456, 1099, 835 cm^{-1}; EIMS *m/z* 453 $(M + H)^+$; HRMS (EI) $(M)^+$ calcd for $C_{23}H_{40}N_2O_5Si$, 452.2707; found, 452.2704.



(*S*)-4-(*tert*-Butyldimethylsilyloxy)-2-methylbutanoic acid ((*S*)-70):[48] Hydrogen peroxide (30% aqueous solution, 7.1 mL, 62.9 mmol) and LiOH•H_2O (1.3 g, 31.5 mmol) were added to a solution of **(*S*,*S*)-68** (6.2 g, 15.7 mmol) in THF (37 mL) and water (37 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. Most of the THF was then evaporated under vacuum and the remaining aqueous portion was extracted with DCM. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 20–50% ethyl acetate/hexanes) gave 3.5 g (95%) of the pure carboxylic acid **(*S*)-70** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.94 (br s, 1H), 3.77–3.65 (m, 2H), 2.71–2.60 (m, 1H), 2.03–1.91 (m, 1H), 1.70–1.60 (m, 1H), 1.22 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7, 60.8, 36.2, 36.0, 25.9, 18.3, 17.0, −5.5; IR (neat) 2930, 2858, 2663, 1713, 1416, 1105, 1006, 882 cm^{-1}; EIMS *m/z* 217 $(M - CH_3)^+$; HRMS (EI) $(M - CH_3)^+$ calcd for $C_{10}H_{21}O_3Si$, 217.1260; found, 217.1258; $[\alpha]_D^{25}$ −14.06 (*c* 1.8, $CHCl_3$).

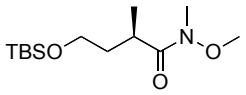


(*R*)-4-(*tert*-Butyldimethylsilyloxy)-2-methylbutanoic acid ((*R*)-70):[48] This compound was prepared from **(*R*,*R*)-68** in 95% yield, according to the procedure described above for preparation of **(*S*)-70**: $[\alpha]_D^{25}$ +13.51 (*c* 1.8, $CHCl_3$); other spectroscopic data was in good accordance to that reported above for **(*S*)-70**.



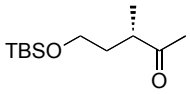
(*S*)-4-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*,2-dimethylbutanamide ((*S*)-71):[49]

1,1′-Carbonyldiimidazole (3.9 g, 23.7 mmol) was added in equal portions over a period of 15 min to a solution of carboxylic acid **(*S*)-70** (3.5 g, 14.9 mmol) in DCM (80 mL) at room temperature. After final addition the reaction mixture was stirred at room temperature for 1 h. *N,O*-dimethylhydroxylamine hydrochloride (3.7 g, 37.1 mmol) was added in one portion and the resulting mixture was stirred overnight. The reaction mixture was diluted with ether and filtered. The filtrate was diluted with diethyl ether and was washed with 5% aq. citric acid and brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography (SiO_2, 20% ethyl acetate/hexanes) gave 3.9 g (95%) of Weinreb amide **(*S*)-71** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.69–3.55 (m, 2H), 3.20 (s, 3H), 3.18–3.06 (m, 1H), 1.99–1.88 (m, 1H), 1.60–1.50 (m, 1H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.89(s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 61.4, 60.7, 36.5, 32.2, 31.4, 25.9, 18.3, 17.2, −5.40; IR (neat) 2956, 2931, 2857, 1667, 1463, 1255, 1101, 836 cm^{-1}; EIMS *m/z* 260 (M − CH_3)$^+$; HRMS (EI) (M − CH_3)$^+$ calcd for $C_{12}H_{26}O_3NSi$, 260.1682; found, 260.1693; $[\alpha]_D^{25}$ +20.60 (*c* 0.03, $CHCl_3$).

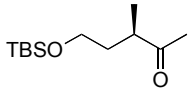


(*R*)-4-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*,2-dimethylbutanamide ((*R*)-71):[49]

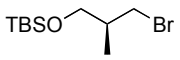
This compound was prepared in 95% yield from **(*R*)-70** according to the procedure described above for preparation of **(*S*)-71**: $[\alpha]_D^{25}$ −21.48 (*c* 2.0, $CHCl_3$); other spectroscopic data was in good accordance to that reported for **(*S*)-71**.



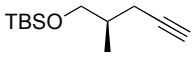
(*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-methylpentan-2-one ((*S*)-40):[50] MeMgBr (3 M in ether, 7.0 mL, 20.9 mmol) was added dropwise to a solution of starting Weinreb amide **(*S*)-71** (3.8 g, 13.9 mmol) in dry THF (60 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h and then gradually warmed to 0 °C and stirred for 3.5 h. The reaction was quenched by slow addition of saturated NH_4Cl solution. Water was added and the layers were separated. The aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 5% ethyl acetate/hexanes) gave 2.9 g (91%) of pure ketone **(*S*)-40** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.62 (t, *J* = 6.2 Hz, 2H), 2.71 (sxt, *J* = 6.9 Hz, 1H), 2.16 (d, *J* = 0.19 Hz, 3H), 1.97–1.87 (m, 1H), 1.60–1.47 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.5, 60.7, 43.7, 35.7, 28.3, 25.9, 18.8, 16.2, −5.45; IR (neat) 2956, 2930, 2857, 1716, 1472, 1256, 1100, 836 cm^{-1}; EIMS *m/z* 215 $(M - CH_3)^+$; HRMS (EI) $(M - H)^+$ calcd for $C_{12}H_{25}O_2Si$, 229.1624; found, 229.1622; $[\alpha]_D^{25}$ +13.21 (*c* 1.20, $CHCl_3$).



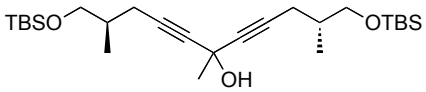
(*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-methylpentan-2-one ((*R*)-40):[89] This compound was prepared in 73% yield from Weinreb amide **(*S*)-71** according to the procedure described for preparation of **(*S*)-40**: $[\alpha]_D^{25}$ −12.97 (*c* 0.61, $CHCl_3$); other spectroscopic data was in good accordance to that reported for **(*S*)-40**.



(*S*)-(3-Bromo-2-methylpropoxy)(*tert*-butyl)dimethylsilane ((*S*)-56):[90] TBSCl (9.0 g, 59.7 mmol) was added to a stirred mixture of (*S*)-3-bromo-2-methylpropan-1-ol **(*S*)-55** (7.3 g, 47.7 mmol) and imidazole (8.2 g, 119.4 mmol) in DMF (180 mL). The resulting mixture was stirred at room temperature for 5 h. The reaction was quenched by addition of saturated NH_4Cl solution. The reaction mixture was diluted with pentanes, water was added and the layers were separated. The aqueous layer was further extracted with pentanes. The combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 2% ethyl acetate/hexanes) gave 11.9 g (94%) of pure bromide **(*S*)-56** as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.58 (dd, *J* = 5.0, 10.0 Hz, 1H), 3.50 (dd, *J* = 5.3, 9.6 Hz, 1H), 3.49 (dd, *J* = 6.8, 9.9 Hz, 1H), 3.45 (dd, *J* = 5.5, 9.7 Hz, 1H), 2.05–1.93 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).

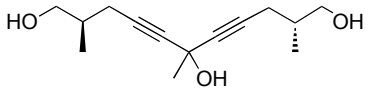


(*R*)-*tert*-Butyldimethyl(2-methylpent-4-ynyloxy)silane ((*R*)-54):[90] A solution of the above bromide **(*S*)-56** (11.5 g, 43.0 mmol) in DMPU (115 mL) was added dropwise to a suspension of lithium acetylide ethylene diamine complex (8.8 g, 86.1 mmol) in THF (230 mL) at 0 °C. The cooling bath was removed and the reaction mixture was stirred at room temperature for 2 h (the reaction was monitored by GC). The reaction was quenched by addition of saturated NH_4Cl solution. The resulting mixture was diluted with pentanes, water was added, and the layers were separated. The aqueous layer was further extracted with pentanes. The combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 2% ethyl acetate/hexanes) gave 5.3 g of alkyne **(*R*)-54** as an inseparable mixture with the elimination product **57** (ratio 9:1 based on ^{1}H NMR spectroscopic analysis): ^{1}H NMR (major product) (300 MHz, $CDCl_3$) δ 3.52 (dd, *J* = 5.5, 9.9 Hz, 1H), 3.47 (dd, *J* = 6.7, 9.9 Hz, 1H), 2.30 (ddd, *J* = 2.7, 5.7, 16.7 Hz, 1H), 2.13 (ddd, *J* = 2.7, 6.9, 16.7 Hz, 1H), 1.95 (dd, *J* = 2.7, 2.7 Hz, 1H), 1.90–1.79 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).



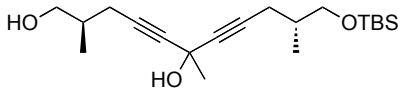
(2*R*,10*R*)-1,11-Bis(*tert*-butyldimethylsilyloxy)-2,6,10-trimethylundeca-4,7-diyn-6-ol ((*R*,*R*)-53): A solution of alkyne **(*R*)-54** (1.2 g, 4.6 mmol) in Et_2O (2.5 mL) was added dropwise to a solution of ethylmagnesium bromide (3 M in ether, 1.3 mL, 3.9 mmol) in Et_2O (2.5 mL) and the resulting mixture was stirred at reflux temperature for 2 h. The reaction mixture was cooled to 0 °C and acetyl chloride (0.1 mL, 1.5 mmol) in THF (0.8 mL) was added dropwise. The resulting mixture was stirred at 0 °C for 1 h and at 45 °C overnight. The reaction mixture was cooled to room temperature and was quenched by addition of saturated NH_4Cl solution. Water was added

and the layers were separated. The aqueous layer was further extracted Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography (SiO_2, 8% ethyl acetate/hexanes) gave 650 mg (90%) of pure **(*R*,*R*)-53** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.50 (dd, *J* = 5.6, 9.8 Hz, 2H), 3.46 (dd, *J* = 6.6, 9.8 Hz, 2H), 2.36 (br s, 1H), 2.32 (dd, *J* = 5.8, 16.7 Hz, 2H), 2.14 (dd, *J* = 6.8, 16.6 Hz, 2H), 1.89–1.78 (m, 2H), 1.72 (s, 3H), 0.96 (d, *J* = 6.8 Hz, 6H), 0.90 (s, 18H), 0.5 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.3, 81.4, 66.8, 60.2, 35.3, 32.5, 25.9, 22.2, 18.3, 16.0, −5.4; IR (neat) 3431, 2956, 2929, 2857, 2244, 1471, 1256, 1096, 837 cm^{-1}; EIMS *m/z* 451 $(M - CH_3)^+$; HRMS (EI) $(M - CH_3)^+$ calcd for $C_{25}H_{47}O_3Si_2$, 451.3064; found, 451.3066.



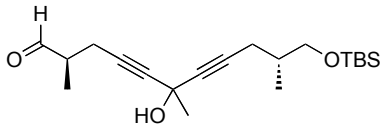
(2*R*,10*R*)-2,6,10-Trimethylundeca-4,7-diyne-1,6,11-triol ((*R*,*R*)-58): TBAF (1 M in THF, 2.4 mL, 2.4 mmol) was added dropwise to a solution of the disilylether **(*R*,*R*)-53** (183.0 mg, 0.4 mmol) in THF (2.2 mL) at 0 °C. The reaction mixture was stirred at this temperature for 30 min and at room temperature for 5 h. The reaction was quenched by addition of saturated aqueous NH_4Cl solution, diluted with EtOAc and the layers were separated. The aqueous layer was further extracted with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 100% ethyl acetate) gave 91.4 mg (96%) of the desired triol **(*R*,*R*)-58** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (br s, 1H), 3.57 (d, *J* = 6.0 Hz, 4H), 2.87 (br s, 2H), 2.30 (dd, *J* = 6.3, 16.8 Hz, 2H), 2.23 (dd, *J* = 6.3, 16.8 Hz, 2H), 1.97–1.82 (m, 2H), 1.71 (s, 3H), 0.98 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.8, 80.9, 66.7, 59.8, 34.8, 32.2, 22.5, 16.3; IR (neat)

3421, 2961, 2274, 1458 cm^{-1}; EIMS *m/z* 223 $(M - CH_3)^+$; HRMS (EI) $(M - CH_3)^+$ calcd for $C_{13}H_{19}O_3$, 223.1334; found 223.1328.

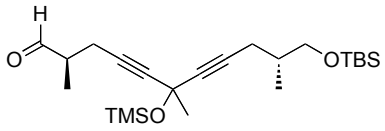


(2*R*,6*RS*,10*R*)-11-(*tert*-Butyldimethylsilyloxy)-2,6,10-trimethylundeca-4,7-diyne-1,6-diol ((*R*,*RS*,*R*)-59):[39] Triethylamine (0.20 mL, 1.50 mmol) and DMAP (4.0 mg, 0.03 mmol) were added to a solution of the starting triol **(*R*,*R*)-58** (332.0 mg, 1.40 mmol) in DCM (4 mL). The mixture was stirred for 5 min and *tert*-butyldimethylsilyl chloride (236.3 mg, 1.50 mmol) was added. The resulting mixture was stirred at room temperature for 15 h during which some white precipitate was formed. The reaction was quenched by the addition of saturated aqueous NH_4Cl solution, diluted with Et_2O, water was added and the layers were separated. The aqueous layer was further extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by gradient flash column chromatography. First elution with (8% ethyl acetate/hexanes) gave 172.1 mg (26%) of the bisprotected product **(*R*,*R*)-53**, second elution with (50% ethyl acetate/hexanes) gave 240.4 mg (49%) of the desired monoprotected mixture **(*R*,*RS*,*R*)-59** and third elution with (100% ethyl acetates) gave 76.2 mg (23%) of the recovered triol **(*R*,*R*)-58**. Spectroscopic data for **(*R*,*RS*,*R*)-59**: ^1H NMR (500 MHz, $CDCl_3$) δ 3.58 (t, *J* = 5.0 Hz, 2H), 3.51 (dd, *J* = 5.5, 10.0 Hz, 1H), 3.47 (dd, *J* = 7.0, 10.0 Hz, 1H), 2.37 (br s, 1H), 2.32 (dd, *J* = 5.5, 16.5 Hz, 1H), 2.31 (dd, *J* = 6.5, 17.0 Hz, 1H), 2.25 (dd, *J* = 6.5, 16.5 Hz, 1H), 2.15 (dd, *J* = 7.0, 17.0 Hz, 1H), 1.95–1.87 (m, 1H), 1.87–1.81 (m, 1H), 1.73 (s, 3H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 83.7, 83.0, 81.6, 80.8, 67.0, 66.8, 60.1, 35.2, 35.1, 32.5, 25.9, 22.5, 22.2, 18.3, 16.2, 16.0, −5.4; IR(neat) 3369, 2956, 2929, 2857, 2247,

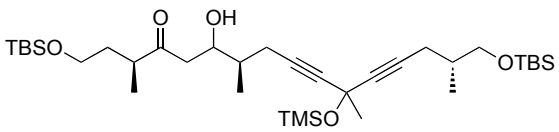
1471, 1456, 1092 cm^{-1}; EIMS *m/z* 337 $(M - CH_3)^+$; HRMS (EI) $(M - CH_3)^+$ calcd for $C_{19}H_{33}O_3Si$, 337.2199; found 337.2204.



(2*R*,6*RS*,10*R*)-10-((*tert*-Butyldimethylsilyloxy)methyl)-6-hydroxy-2,6 dimethylundeca-4,7-di ynal ((*R*,*RS*,*R*)-60):[40] Dess-Martin periodinane (315.0 mg, 0.74 mmol) was added to a solution of the starting alcohol mixture **(*R*,*RS*,*R*)-59** (238.0 mg, 0.68 mmol) and pyridine (0.55 mL, 6.80 mmol) in DCM (108 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. If the TLC indicated incomplete completion an additional 1 equiv of DMP was added at 0 °C and the reaction was stirred for 1 h. The reaction was then quenched by the addition of a 1:1 mixture of saturated aqueous $NaHCO_3$ solution and saturated aqueous Na_2SO_3 solution (70 mL) and the mixture was stirred until two layers could be seen. The layers were separated and the aqueous layer was further extracted twice with DCM. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. Flash column chromatography (SiO_2, 20% ethyl acetate/hexanes) gave 193.3 mg (82%) of the desired aldehyde **(*R*,*RS*,*R*)-60** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H), 3.51 (dd, *J* = 5.5, 9.9 Hz, 1H), 3.45 (dd, *J* = 6.7, 9.9 Hz, 1H), 2.60-2.50 (m, 2H), 2.39 (dd, *J* = 9.0, 18.3 Hz, 1H), 2.30 (dd, *J* = 5.7, 16.5 Hz, 1H), 2.13 (dd, *J* = 6.9, 16.8 Hz, 1H), 1.88–1.77 (m, 1H), 1.71 (s, 3H), 1.22 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 84.3, 82.8, 81.7, 79.1, 66.7, 60.0, 45.0, 35.1, 32.4, 25.9, 22.1, 19.9, 18.3, 16.0, 13.1, −5.4 ; IR (neat) 3435, 2930, 2857, 2246, 1728, 1462, 1256, 1095 cm^{-1}; EIMS *m/z* 335 $(M - CH_3)^+$; HRMS (EI) $(M - CH_3)^+$ calcd for $C_{19}H_{31}O_3Si$, 335.2036; found, 335.2043.

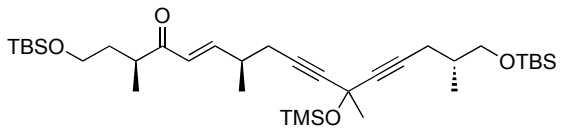


(2*R*,6*RS*,10*R*)-11-(*tert*-Butyldimethylsilyloxy)-2,6,10-trimethyl-6-(trimethylsilyloxy) undeca-4,7-diynal ((*R*,*RS*,*R*)-61): Chlorotrimethylsilane (0.24 mL, 1.63 mmol) was added to a stirred mixture of the tertiary alcohol **(*R*,*RS*,*R*)-60** (190.0 mg, 0.54 mmol), triethylamine (0.30 mL, 2.17 mmol) and DMAP (6.0 mg, 0.05 mmol) in DCM (5.60 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by addition of saturated $NaHCO_3$ solution. The mixture was diluted with DCM, water was added and the layers were separated. The aqueous layer was further extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 5% ethyl acetate/hexanes) gave 200.1 mg (88%) of the pure aldehyde **(*R*,*RS*,*R*)-61** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (s, 1H), 3.51 (dd, *J* = 6.0, 9.9 Hz, 1H), 3.47 (dd, *J* = 6.6, 9.9 Hz, 1H), 2.65–2.50 (m, 2H), 2.43–2.28 (overlapping dd, 2H), 2.13 (dd, *J* = 6.9 Hz, 16.8 Hz, 1H), 1.93–1.78 (m, 1H), 1.71 (s, 3H), 1.24 (d, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.23 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 85.2, 83.5, 81.7, 78.8, 66.8, 61.0, 45.1, 35.2, 35.0, 25.9, 22.3, 20.1, 18.3, 16.1, 13.2, 1.6, −5.4; IR (neat) 2958, 2930, 2857, 2241, 1733, 1472, 1463, 843 cm^{-1}; EIMS *m/z* 407 $(M - CH_3)^+$; HRMS (EI) $(M - CH_3)^+$ calcd for $C_{22}H_{39}O_3Si_2$, 407.2438; found, 407.2422.



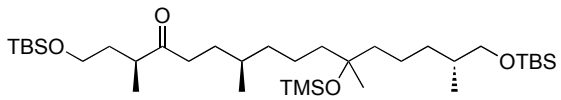
(3*S*,6*RS*,7*R*,11*RS*,15*R*)-1,16-Bis(*tert*-butyldimethylsilyloxy)-6-hydroxy-3,7,11,15-tetramethyl-11-(trimethylsilyloxy)hexadeca-9,12-diyn-4-one (*S*,*RS*,*R*,*RS*,*R*)-72):[51] *n*-BuLi (1.6 M in hexanes, 0.30 mL, 0.48 mmol) was added dropwise to a stirring solution of diisopropylamine (0.07 mL, 0.50 mmol) in THF (0.4 mL) at 0 °C. The reaction mixture was stirred at this temperature for 5 min and then cooled to −78 °C. A solution of starting ketone **(*S*)-40** (103.5 mg, 0.45 mmol) in THF (0.4 mL) was added dropwise and the mixture was stirred at −78 °C for 30 min. A solution of aldehyde **(*R*,*RS*,*R*)-61** (127.0 mg, 0.30 mmol) in THF (0.4 mL) was added dropwise and the resulting mixture was stirred at −78 °C for 3.5 h. The reaction was quenched by addition of saturated NH_4Cl solution and warmed to room temperature. The mixture was diluted with Et_2O, water was added and the layers were separated. The aqueous layer was further extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, polarity was gradually increased from 5% ethyl acetate/hexanes to 10% ethyl acetate/hexanes) gave 157.0 mg (80%) of the desired aldol product **(*S*,*RS*,*R*,*RS*,*R*)-72** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.12–4.00 (m, 0.5H), 3.93–3.80 (m, 0.5H), 3.61 (t, *J* = 6.0 Hz, 2H), 3.47 (d, *J* = 6 Hz, 2H), 3.31–3.14 (m, 1H), 2.81–2.65 (m, 1H), 2.65–2.36 (m, 2H), 2.36–2.05 (m, 3H), 2.00–1.73 (overlapping multiplets, 3H), 1.70 (s, 3H), 1.60–1.45 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 1.5 H), 1.00 (d, *J* = 6.9 Hz, 1.5H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.21 (s, 9H), 0.04 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.0, 215.8, 84.23, 84.20, 83.8, 83.7, 81.32, 81.28, 81.2, 81.1, 81.02, 80.99, 70.7, 70.6, 69.8, 69.7, 66.8, 61.1, 60.7, 60.6, 44.9, 44.8, 44.6, 43.64, 43.56, 43.42, 43.40, 37.7, 37.6, 37.5, 35.44, 35.41, 35.4, 35.3, 35.1, 25.9, 22.72, 22.68, 22.3, 21.9, 18.3, 16.3, 16.2, 16.1, 15.8, 15.7, 14.01,

13.97, 1.6, −5.4, IR (neat) 3503, 2955, 2929, 2856, 2240, 1700, 1458 cm^{-1}; EIMS *m/z* 637 $(M - CH_3)^+$; HRMS (EI) $(M)^+$ calcd for $C_{35}H_{68}O_5Si_3$, 652.4375; found, 652.4363.

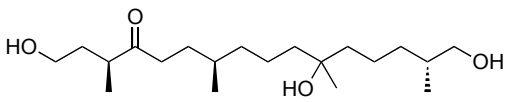


(3*S*,7*R*,11*RS*,15*R*,*E*)-1,16-Bis(*tert*-butyldimethylsilyloxy)-3,7,11,15-tetramethyl-11-(trimethylsilyl-oxy)hexadeca-5-en-9,12-diyn-4-one ((*S*,*R*,*RS*,*R*)-73): Methanesulfonyl chloride (0.03 mL, 0.42 mmol) was added dropwise to a stirring mixture of aldol adduct **((*S*,*RS*,*R*,*RS*,*R*)-72** (139.0 mg, 0.21 mmol) and triethylamine (0.12 mL, 0.84 mmol) in DCM (0.65 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and at room temperature for 12 h. The reaction was quenched by addition of saturated NH_4Cl solution. DCM was added and the layers were separated. The aqueous layer was further extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 10% ethyl acetate/hexanes) gave 110.2 mg (83%) of the desired enone **(*S*,*R*,*RS*,*R*)-73** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 6.83 (dd, *J* = 6.6, 15.6 Hz, 0.5H), 6.82 (dd, *J* = 7.2, 15.9 Hz, 0.5H), 6.16 (d, *J* = 15.6 Hz, 1H), 3.70–3.55 (m, 2H), 3.49 (d, *J* = 6H, 2H), 3.05–2.90 (m, 1H), 2.63–2.48 (m, 1H), 2.40–2.20 (overlapping dd, 3H), 2.13 (dd, *J* = 6.9, 16.5 Hz, 1H), 2.02–1.88 (m, 1H), 1.88–1.75 (m, 1H), 1.71 (s, 3H), 1.60–1.43 (m, 1H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.23 (s, 9H), 0.05 (s, 6H), 0.04 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.6, 203.5, 149.8, 149.7, 127.92, 127.85, 84.9, 83.6, 81.5, 79.7, 66.8, 61.0, 60.6, 40.1, 40.0, 35.9, 35.8. 35.3, 35.1, 25.9, 25.4, 22.3, 18.8, 18.7, 18.3, 16.64, 16.55, 16.1,

1.6, −5.4; IR (neat) 2957, 2926, 2855, 2240, 1699, 1674, 1630, 1463 cm^{-1}; EIMS *m/z* 619 $(M - CH_3)^+$; HRMS (EI) $(M - CH_3)^+$ calcd for $C_{34}H_{63}O_4Si_3$, 619.4034; found, 619.4024.

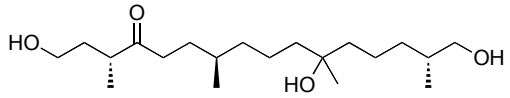


(3*S*,7*R*,11*RS*,15*R*)-1,16-Bis(*tert*-butyldimethylsilyloxy)-3,7,11,15-tetramethyl-11-(trimethylsilyl-oxy)hexadecan-4-one ((*S*,*R*,*RS*,*R*)-74):[52] To a solution of enone **(*S*,*R*,*RS*,*R*)-73** (65.0 mg, 0.10 mmol) in methanol (0.5 mL) was added Pd/C (10% by wt., 5.2 mg) and the mixture was stirred under hydrogen from balloon for 3 h. The reaction mixture was filtered though a small pad of celite and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 5% ethyl acetate/hexanes) gave 60.1 mg (91%) of the pure product **(*S*,*R*,*RS*,*R*)-74** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) 3.64–3.56 (m, 2H), 3.454 (dd, *J* = 6, 10 Hz, 0.5H), 3.450 (dd, *J* = 6.0, 10 Hz, 0.5H), 3.369 (dd, *J* = 6.5, 10 Hz, 0.5H), 3.367 (dd, J = 6.5, 9.5 Hz, 0.5H), 2.75 (sxt, 2H), 2.54–2.39 (m, 2H), 1.94–1.88 (m, 1H), 1.64–1.55 (m, 2H), 1.55–1.46 (m, 1H), 1.45–1.31 (m, 9H), 1.30–1.20 (m, 4H), 1.17 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.89-0.87 (overlapping doublets, 6H), 0.09 (s, 9H), 0.04 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.9, 76.2, 68.4, 60.8, 42.8, 42.73, 42.71, 42.69, 42.6, 39.1, 37.4, 35.78, 35.76, 33.7, 32.5, 30.8, 27.44, 27.42, 27.0, 26.0, 21.51, 21.46, 21.4, 19.4, 18.4, 18.3, 16.8, 16.5, 2.7, −5.3 , −5.39 , −5.4 1, EIMS *m/z* 629 $(M - CH_3)^+$; HRMS (EI) $(M - CH_3)^+$ calcd for $C_{34}H_{73}O_4Si_3$, 629.4817; found, 629.4827.



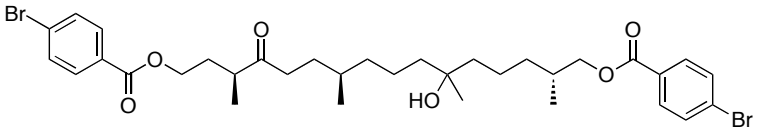
(3*S*,7*R*,11*RS*,15*R*)-1,11,16-Trihydroxy-3,7,11,15-tetramethylhexadecan-4-one (*S*,*R*,*RS*,*R*)-1: TBAF (1 M in THF, 0.64 mL, 0.64 mmol) was added dropwise to a solution of the compound **(*S*,*R*,*RS*,*R*)-74** (60.5 mg, 0.09 mmol) in THF (10 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at room temperature for 15 h. The reaction was then quenched by the addition of saturated NH_4Cl solution. The reaction mixture was diluted with Et_2O and the layers were separated. The aqueous layer was further extracted with Et_2O. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. Purification by flash column chromatography (SiO_2, polarity was gradually increased from 70% ethyl acetate/hexanes–100% EtOAc) gave 20.4 mg (65%) of the desired compound **(*S*,*R*,*RS*,*R*)-1** as a colorless oil: ^{1}H NMR (500 MHz, CD_3OD) δ 3.52 (t, *J* = 7.0 Hz, 2H), 3.41 (dd, *J* = 6.0, 10.5 Hz, 1H), 3.33 (dd, *J* = 7.0, 11.0 Hz, 1H), 2.77 (sxt, *J* = 6.9 Hz, 1H), 2.60–2.46 (m, 2H), 1.89 (sxt, *J* = 7.0, 1H), 1.62–1.55 (m, 2H), 1.52–1.46 (m, 1H), 1.46–1.28 (m, 12H), 1.15–1.05 (m, 2H), 1.12 (s, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 217.5, 73.4, 68.5, 60.6, 44.0, 43.0*, 42.9*, 40.0, 38.6, 36.9, 36.8*, 35.0, 33.6, 31.7, 26.9*, 22.4*, 19.9, 17.1, 16.9; EIMS *m/z* 326 $(M - H_2O)^+$; HRMS (EI) $(M - H_2O)^+$ calcd for $C_{20}H_{38}O_3$, 326.2821; found, 326.2824.

* doublets or multiplets, see tabulated data in Table 1, page 32.

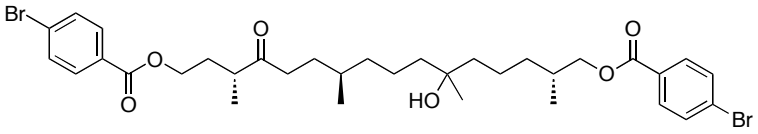


(3*R*,7*R*,11*RS*,15*R*)-1,11,16-Trihydroxy-3,7,11,15-tetramethylhexadecan-4-one ((*R*,*R*,*RS*,*R*)-1):[18] This compound was prepared by aldol coupling of the ketone **(*R*)-40** with the aldehyde mixture **(*R*,*RS*,*R*)-61** followed by elimination, hydrogenation and global deprotection as

described for the synthesis of **(*S*,*R*,*RS*,*R*)-1**. The NMR data was in good accordance to that reported for **(*S*,*R*,*RS*,*R*)-1**. See Table 1, page 32 for detailed data.

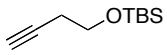


Bis-4-bromobenzoate derivative (*S*,*R*,*RS*,*R*)-2:[18] 4-bromobenzoyl chloride (36.1 mg, 0.16 mmol) was added to a solution of the alcohol **(*S*,*R*,*RS*,*R*)-1** (6.5 mg, 0.02 mmol) in pyridine (2 mL). The resulting mixture was stirred at room temperature for 4 h. The reaction was quenched by the addition of sat NH_4Cl solution. DCM and water were added and the layers were separated. The aqueous layer was extracted with DCM. The combined organic layers were washed with 10% aqueous $CuSO_4$ solution, dried over saturated $MgSO_4$ solution, filtered and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 20% ethyl acetate/hexanes) gave 9.5 mg (77%) of the desired bis-4-bromobenzoate as colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 4H), 4.30 (t, *J* = 6.6 Hz, 2H), 4.20 (dd, *J* = 6.0, 10.8 Hz, 1H), 4.10 (dd, *J* = 6.6, 10.2 Hz, 1H), 2.72 (m, 1H), 2.58–2.34 (m, 2H), 2.23–2.14 (m, 1H), 2.00–1.90 (m, 1H), 1.81–1.71 (m, 1H), 1.63–1.54 (m, 1H), 1.53–1.20 (m, 14H), 1.16 (d, *J* = 8.4 Hz, 3H), 1.15 (s, 3H), 1.13–1.05 (m, 1H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 6 Hz, 1.5 H), 0.82 (d, *J* = 6.0 Hz, 1.5H)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.75, 213.72, 165.91, 165.75, 131.73, 131,68, 131.08, 131.05, 129.35, 129.00, 128.12, 127.93, 72.62, 70.04, 63.36, 63.35, 43.16, 43.12, 42.26, 42.23, 42.17, 42.14, 42.12, 42.10, 42.01, 39.10, 37.37, 37.31, 33.98, 32.70, 32.38, 32.33, 31.48, 31.46, 30.54, 30.48, 26.94, 26.86, 26.80, 21.21, 21.18, 21.16, 21.14, 19.34, 19.30, 16.97.

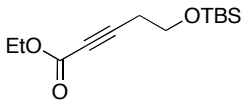


Bis-4-bromobenzoate derivative (*R*,*R*,*RS*,*R*)-2: This compound was prepared from **(*R*,*R*,*RS*,*R*)-1** by the procedure described for the synthesis of **(*S*,*R*,*RS*,*R*)-2**. The NMR data was in good accordance to that reported for **(*S*,*R*,*RS*,*R*)-2**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz,

2H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 4H), 4.30 (t, *J* = 6.6 Hz, 2H), 4.20 (dd, *J* = 6.0, 10.8 Hz, 1H), 4.10 (dd, *J* = 6.6, 10.2 Hz, 1H), 2.72 (m, 1H), 2.58–2.34 (m, 2H), 2.23–2.14 (m, 1H), 2.00–1.90 (m, 1H), 1.81–1.71 (m, 1H), 1.63–1.54 (m, 1H), 1.53–1.20 (m, 14H), 1.16 (d, *J* = 8.4 Hz, 3H), 1.15 (s, 3H), 1.13–1.05 (m, 1H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.83 (d, *J* = 6 Hz, 1.5 H), 0.82 (d, *J* = 6.0 Hz, 1.5H)); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.76, 213.73, 213.71, 165.90, 165.75, 131.72, 131,68, 131.07, 131.05, 129.34, 129.00, 128.11, 127.92, 72.62, 70.03, 63.36, 43.16, 43.12, 42.25, 42.22, 42.16, 42.14, 42.11, 42.10, 42.00, 39.10, 37.36, 37.31, 33.98, 32.69, 32.38, 32.33, 31.48, 31.46, 30.54, 30.48, 26.93, 26.85, 26.79, 21.21, 21.18, 21.16, 21.14 19.34, 19.30, 16.97.

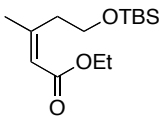


(But-3-ynyloxy)(*tert*-butyl)dimethylsilane (99):[91] Imidazole (10.3 g, 150.0 mmol), TBSCl (21.1 g, 140.0 mmol) and DMAP (1.0 g, 7.9 mmol) were added to a solution of but-3-ynol **89** (3.0 g, 42.4 mmol) in THF (150 mL) and the resulting reaction mixture was stirred at room temperature for 4 h. The reaction was quenched by the addition of saturated NH_4Cl solution, water and ether were added, and the layers were separated. The aqueous layer was further extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 5% EtOAc in hexanes) gave the desired alkyne **99** (7.8 mg, 99%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.35 (t, *J* = 7.2 Hz, 2H), 2.41 (dt, *J* = 2.4, 7.2 Hz, 2H), 1.97 (t, *J* = 2.4, 1H), 0.91 (s, 9H), 0.09 (s, 6H).



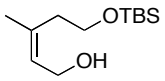
Ethyl 5-(*tert*-butyldimethylsilyloxy)pent-2-ynoate (88):[92] *n*-BuLi (1.6 M in hexanes, 33.4 mL, 53.4 mmol) was added dropwise to a solution of diisopropylamine (8.1 mL, 57.2 mmol) in THF

(108 mL) at −78 °C. The resulting solution was stirred at this temperature for 5 min and at room temperature for 2 min. The reaction mixture was cooled to −78 °C and a solution of the starting alkyne **99** (7.8 g, 42.4 mmol) in THF (40 mL) was added dropwise. The resulting mixture was stirred at −78 °C for 15 min followed by dropwise addition of ethylchloroformate (12.4 mL, 127.1 mmol). The reaction mixture was stirred at this temperature for 10 min and at room temperature for 3 h. The reaction was quenched by the addition of saturated NH_4Cl solution. Water and ether were added and the layers were separated. The aqueous layer was further extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 5% EtOAc in hexanes) gave the desired ester **88** (7.3 g, 86%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (q, *J* = 6.9 Hz, 2H), 3.79 (t, *J* = 6.9 Hz, 2H), 2.55 (t, *J* = 6.9, 2H), 1.31 (t, *J* = 6.9, 3H), 0.90 (s, 9H), 0.09 (s, 6H).

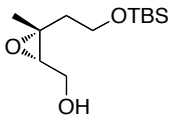


(*Z*)-Ethyl 5-(*tert*-butyldimethylsilyloxy)-3-methylpent-2-enoate (100):[68] MeLi (1.6 M in Et_2O, 43.9 mL, 70.3 mmol) was added dropwise to a suspension of CuI (6.9 g, 35.3 mmol) in dry THF (270 mL) at 0 °C. The reaction mixture was stirred at this temperature for 5 min and cooled to −78 °C. A solution of the starting alkyne **88** (9.0 g, 35.1 mmol) in THF (90 mL) was added dropwise and the reaction mixture was stirred at this temperature for 1 h. The reaction was quenched by addition of water, stirred for 5 min, and allowed to warm to room temperature. The reaction mixture was filtered through celite and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 3% EtOAc in hexanes) gave the desired *Z*-alkene **100** (6.2 g,

64%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (d, *J* = 0.6 Hz, 1H), 4.14 (q, *J* = 7.2 Hz, 2H), 3.80 (t, *J* = 6.6 Hz, 2H), 2.85 (t, *J* = 6.6 Hz, 2H), 1.96 (d, *J* = 1.2 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

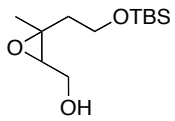


(*Z*)-5-(*tert*-Butyldimethylsilyloxy)-3-methylpent-2-en-1-ol (87):[68] $LiAlH_4$ (1 M in diethylether, 18.0 mL, 18.0 mmol) was added dropwise to a solution of the starting ester **100** (6.2 g, 22.6 mmol) in ether (27 mL). The reaction mixture was stirred at this temperature for 1 h. The reaction was quenched by slow and careful addition of saturated NH_4Cl solution, water and ether were added, and the layers were separated. The aqueous layer was further extracted with ether. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 30% EtOAc in hexanes) gave the desired allylic alcohol **87** (4.6 mg, 88%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (t, *J* = 6.9 Hz, 1H), 4.05 (d, *J* = 6.0 Hz, 1H), 4.02 (s, 1H), 3.71 (t, *J* = 6.0 Hz, 2H), 2.36 (t, *J* = 6 Hz, 2H), 2.12 (bs, 1H), 1.76 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H).

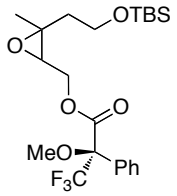


((2*S*,3*R*)-3-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-3-methyloxiran-2-yl)methanol (2*S*,3*R*)-101):[70] *t*-BuOOH (~ 5–6 M in toluene, 2.2 mL, 10.9 mmol) stored over 4 A° molecular sieves was added dropwise to a solution of diisopropyl-*L*-tartrate (0.1 mL, 0.5 mmol) and $Ti(O^iPr)_4$ (123.4 mg, 0.4 mmol) over 4 A° molecular sieves in DCM (1.4 mL) at –20 °C. After 30 min this solution was added via cannula to a solution of allylic alcohol **87** (1.0 g, 4.3 mmol) in

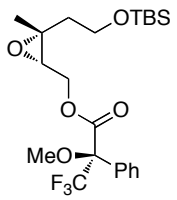
DCM (1.9 mL) over 4 °A molecular sieves. The resulting mixture was stirred at −20 °C for 18 h. A 10% aqueous solution of tartaric acid (11 mL) was added and the mixture was stirred at −20 °C for 30 min and at room temperature for 1 h. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 60% EtOAc in hexanes) gave the desired epoxide **(2*S*,3*R*)-101** (0.98 g, 92%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (dd, *J* = 3.9, 12.0 Hz, 1H), 3.74 (dd, *J* = 5.4, 6.9 Hz, 2H), 3.69 (dd, *J* = 6.9, 12.0 Hz, 1H), 3.07 (dd, *J* = 4.2, 6.9 Hz, 1H), 1.91 (td, *J* = 5.4, 14.1 Hz, 1H), 1.67 (td, *J* = 6.9, 14.1 Hz 1H), 1.35 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H).



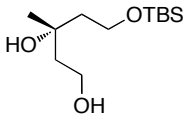
(3-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-3-methyloxiran-2-yl)methanol (rac-101): MCPBA (56.5 mg, 0.2 mmol) was added to a solution of allylic alcohol **87** (48.0 mg, 0.2 mmol) in DCM (1.8 mL) and the reaction mixture was stirred at room temperature for 16 h, The reaction was quenched by addition of saturated $NaHCO_3$ solution, water and DCM were added, and the layers were separated. The aqueous layer was further extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 60% EtOAc in hexanes) gave the desired epoxide **rac-101** (49.0 mg, 99%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (dd, *J* = 3.9, 12.0 Hz, 1H), 3.74 (dd, *J* = 5.4, 6.9 Hz, 2H), 3.69 (dd, *J* = 6.9, 12.0 Hz, 1H), 3.07 (dd, *J* = 4.2, 6.9 Hz, 1H), 1.91 (td, *J* = 5.4, 14.1 Hz, 1H), 1.67 (td, *J* = 6.9, 14.1 Hz 1H), 1.35 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H).



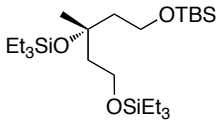
(2*R*)-(3-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-3-methyloxiran-2-yl)methyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((*R*,rac)-102):[32e] Triethylamine (0.06 mL, 0.41 mmol), *S*-MTPA chloride (0.04 mL, 0.20 mmol) and DMAP (5.0 mg, 0.04 mmol) were added to a solution of the starting epoxyalcohol **rac-101** (10.0 mg, 0.04 mmol) in DCM (1.3 mL). The reaction mixture was stirred at room temp for 30 min. The reaction was quenched by the addition of water, DCM was added and the layers were separated. The aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 10% EtOAc in hexanes) gave the desired ester **(*R*,rac)-102** (17.5 mg, 94%) as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.54 (m, 2H), 7.44–7.40 (m, 3H), 4.66 (dd, *J* = 3.5, 12.0 Hz, 0.5H), 4.59 (dd, *J* = 3.5, 12.0 Hz, 0.5H), 4.34 (dd, *J* = 8.0, 12.0 Hz, 0.5H), 4.28 (dd, *J* = 8.0, 12.0 Hz, 0.5H), 3.77–3.73 (m, 2H), 3.59 (s, 3H), 3.06 (dd, *J* = 3.5, 7.5 Hz, 0.5H), 3.04 (dd, *J* = 3.5, 7.5 Hz, 0.5H), 1.90–1.84 (m, 1H), 1.77–1.69 (m, 1H), 1.37 (s, 1.5H), 1.36 (s, 1.5H), 0.91 (s, 9H), 0.08 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.71, −71.83.



(*R*)-((2*S*,3*R*)-3-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-3-methyloxiran-2-yl)methyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((*R*,2*S*,3*R*)-102):[32e] This compound was prepared from the epoxide **(2*S*,3*R*)-101** using the same procedure as described above for **(*R*,rac)-102**. The ^{1}H and ^{19}F NMR of the crude product were recorded to calculate the diastereomeric ratio (observed dr = 92:8): ^{1}H NMR of the major isomer (300 MHz, $CDCl_3$) δ 7.56–7.54 (m, 2H), 7.44–7.40 (m, 3H), 4.59 (dd, *J* = 3.3, 12.3 Hz, 1H), 4.34 (dd, *J* = 7.8, 12.3 Hz, 1H), 3.77–3.78 (dd, *J* = 5.7, 10.5 Hz, 2H), 3.59 (s, 3H), 3.04 (dd, *J* = 3.0, 7.8 Hz, 1H), 1.90–1.82 (m, 1H), 1.78–1.67 (m, 1H), 1.37 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.71.

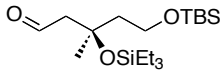


(*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-methylpentane-1,3-diol ((*S*)-86):[70] A solution of starting epoxide **(2*S*,3*R*)-101** (970.0 mg, 3.94 mmol) in THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (299.0 mg, 7.88 mmol) in THF (10 mL) at −40 °C. The reaction mixture was stirred at this temperature for 30 min and then allowed to warm to 0 °C over a period of 3 h. The reaction mixture was stirred at 0 °C for 30 min and quenched by slow and careful addition of sat NH_4Cl solution. Water and ether were added and the layers were separated. The aqueous layer was further extracted with ether. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (60% EtOAc in hexanes) gave the desired diol **(*S*)-86** (635.4 mg, 65%) as colorless oil along with recovered epoxide **(2*S*,3*R*)-101** (87.7 mg, 9%): ^{1}H NMR of diol (300 MHz, $CDCl_3$) δ 4.25 (bs, 1H), 3.75 (bs, 1H), 4.10–3.60 (m, 4H), 2.10–1.50 (m, 4H), 1.29 (s, 3H), 0.91 (s, 9H), 0.10 (s, 6H).



(*S*)-1-(*tert*-Butyldimethylsilyloxy)-3-methyl-3,5-bis(triethylsilyloxy)pentane ((*S*)-103):

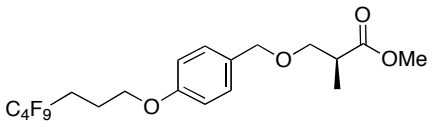
2,6-Lutidine (8.9 mL, 75.7 mmol) and TESOTf (13.0 mL, 56.8 mmol) were added dropwise to the solution of the starting diol **(*S*)-86** (4.7 g, 18.9 mmol) in DCM (375 mL) at 0 °C. The resulting solution was stirred at this temperature for 30 min and at room temperature for 2 h. The reaction was quenched by the addition of water and the layers were separated. The aqueous layer was extracted with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 4% EtOAc in hexanes) gave the pure product **(*S*)-103** (7.3 g, 90%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72 (t, *J* = 7.8 Hz, 4H), 1.77–1.70 (m, 4H), 1.24 (s, 3H), 0.97 (t, *J* = 7.8 Hz, 9H), 0.95 (t, *J* = 7.8 Hz, 9H), 0.90 (s, 9H), 0.60 (q, *J* = 7.8 Hz, 6H), 0.58 (q, *J* = 7.8 Hz, 6H) 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.8, 59.8, 59.4, 45.5 (2C), 28.6, 26.0, 18.3, 7.1, 6.83, 6.80, 4.4, −5.3; EIMS *m*/*z* 447 $(M - C_2H_5)^+$; HRMS (EI) $(M - C_2H_5)^+$ calcd for $C_{22}H_{51}O_3Si_3$, 447.3146; found 447.3126; IR (neat) 2955, 2878, 1462, 1414, 1252, 1090, 1009 cm^{-1}; $[\alpha]_D^{25}$ –0.91 (*c* 0.72, $CHCl_3$).



(*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-methyl-3-(triethylsilyloxy)pentanal ((*R*)-82):[71]

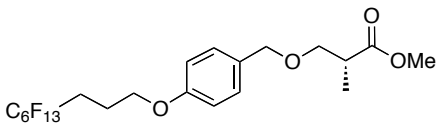
A solution of oxalyl chloride (0.4 mL, 4.4 mmol) in DCM (2.2 mL) was added dropwise to a solution of DMSO (0.6 mL, 8.8 mmol) in DCM (4 mL) at –78 °C. The resulting solution was stirred at this temperature for 20 min and then a solution was starting bis-triethylsilyl ether **(*S*)-**

103 (476.7 mg, 1.0 mmol) in DCM (4.0 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 20 min and at −40 °C for 20 min. The reaction mixture was cooled back to −78 °C and triethylamine (1.8 mL, 13.0 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 20 min followed by warming to room temperature over a period of 2 h. The reaction was quenched by the addition of water, the layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification with flash column chromatography (SiO_2, 5% EtOAc in hexanes) gave the pure aldehyde **(*R*)-82** (279.0 mg, 77%) as yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (t, *J* = 3.0 Hz, 1H), 3.77 (td, *J* = 6.5, 17.0 Hz, 1H), 3.74 (td, *J* = 6.5, 17.0 Hz, 1H), 2.55 (dd, *J* = 3.0, 5.5 Hz, 2H), 1.86 (t, *J* = 6.5 Hz, 2H), 1.37 (s, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.89 (s, 9H), 0.06 (q, *J* = 8.0 Hz, 6H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.6, 73.7, 59.1, 55.3, 45.6, 29.0, 25.7, 18.0, 6.9, 6.6, −5.6; EIMS *m*/*z* 333 $(M - C_2H_5)^+$; HRMS (EI) $(M - CH_3)^+$ calcd for $C_{17}H_{37}O_3Si_2$, 345.2281; found 345.2290; IR (neat) 2955, 2878, 1724, 1463, 1254 cm^{-1}; $[\alpha]_D^{25}$ −2.14 (*c* 0.73, $CHCl_3$).



(*S*)-Methyl-3-(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzyloxy)-2-methylpropanoate ((*S*)-97a):[65] A solution of $PMB^{F9}OH$ **95a** (1000.0 mg, 2.60 mmol) in ether (1.4 mL) was added to a suspension of NaH (60% in mineral oil, 10.4 mg, 0.26 mmol) in ether (1.7 mL). The reaction mixture was stirred at room temperature for 1 h and cooled to 0 °C. CCl_3CN (375.4 mg, 2.60 mmol) was added dropwise and resulting mixture was stirred at 0 °C for 5 min and at room temperature for 1 h. The reaction mixture was washed with saturated $NaHCO_3$ solution and

brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum to afford the trichloroacetimidate **96a**, which was used without further purification. The trichloroacetimidate **96a** was dissolved in DCM (3.5 mL) and (*S*)-methyl 3-hydroxy-2-methylpropanoate **(*S*)-85** (204.8 mg, 1.73 mmol) and PPTS (20 mg, 0.08 mmol) were added. The reaction mixture was stirred at room temperature for 24 h followed by addition of water. The layers were separated and the aqueous layer was further extracted with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 4% EtOAc in hexanes) gave the pure product **(*S*)-97a** (805.4 mg, 96%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.47 (s, 2H), 4.05 (t, J = 6.0 Hz, 2H), 3.71 (s, 3H), 3.66 (dd, J = 7.2, 9.0 Hz, 1H), 3.48 (dd, J = 6.0, 9.3 Hz, 1H), 2.84–2.73 (m, 1H), 2.42–2.24 (m, 2H), 2.16–2.06 (m, 2H), 1.19 (d, J = 7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.8 (m, 3F), −114.6 (m, 2F), −124.4 (m, 2F), −126.0 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 158.2, 130.8, 129.2, 114.3, 72.7, 71.7, 66.3, 51.6, 40.2, 27.9 (t, $^2J_{CF}$ = 22.5 Hz), 20.6, 14.0; EIMS m/z 507 $(M + Na)^+$; HRMS (ESI) $(M + Na)^+$ calcd for $C_{19}H_{21}O_4F_9Na$, 507.1194; found 507.1153; IR (neat) 2953, 2869, 1739, 1613, 1513, 1358, 1243 cm^{-1}; $[\alpha]_D^{25}$ +5.2 (*c* 0.35, $CHCl_3$).

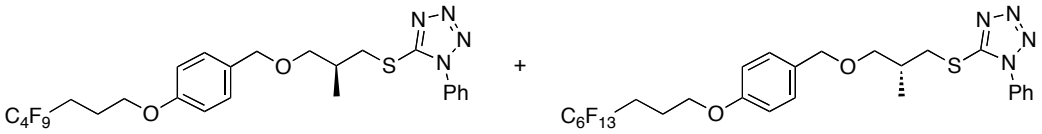


(*R*)-Methyl-3-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzyloxy)-2-methylpropanoate ((*R*)-97b):[65] This compound was prepared in 95% yield starting from (*R*)-methyl 3-hydroxy-2-methylpropanoate **(*R*)-85** (1.2 g, 10.4 mmol) and $PMB^{F13}OH$ **95b** (7.6 g, 15.6 mmol) following the procedure described above for preparation of compound **(*S*)-97a**: ^{1}H NMR (300

MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.46 (s, 2H), 4.05 (t, *J* = 6.0 Hz, 2H), 3.70 (s, 3H), 3.65 (dd, *J* = 7.5, 9.3 Hz, 1H), 3.47 (dd, *J* = 6.0, 9.3 Hz, 1H), 2.84–2.72 (m, 1H), 2.42–2.23 (m, 2H), 2.15–2.06 (m, 2H), 1.18 (d, *J* = 7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.9 (m, 3F), −114.3 (m, 2F), −121.9 (m, 2F), −122.9 (m, 2F), −123.5 (m, 2F), −126.1 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 158.2, 130.8, 129.2, 114.4, 72.7, 71.7, 66.4, 51.7, 40.2, 28.0 (t, $^2J_{CF}$ = 22.5 Hz), 20.6, 14.0; EIMS *m*/*z* 584 $(M)^+$; HRMS (EI) $(M)^+$ calcd for $C_{21}H_{21}O_4F_{13}$, 584.1232; found 584.1225; IR (neat) 2953, 2868, 1740, 1613, 1513, 1364, 1250 cm^{-1}; $[\alpha]_D^{25}$ −3.61 (*c* 0.71, $CHCl_3$).

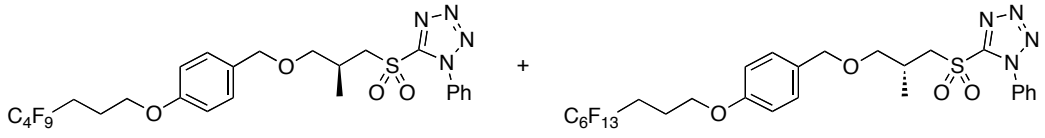
(*R*)-3-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-2-methylpropan-1-ol and (*S*)-3-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononyloxy)benzyloxy)-2-methylpropan-1-ol (M84):[55a] Esters **(*S*)-97a** (3.5 g, 7.3 mmol) and **(*R*)-97b** (4.3 g, 7.3 mmol) were combined to obtain the mixture **M97**. DIBALH (1 M in hexanes, 32.2 mL, 32.2 mmol) was added dropwise to a solution of **M97** (7.8 g, 14.6 mmol) in DCM (101 mL) at −78 °C. The reaction mixture was allowed to gradually warm to room temperature in 3 h and stirred at this temperature for 1 h. The reaction was quenched by the addition of saturated sodium potassium tartrate and the mixture was stirred at room temperature for 1 h. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by column chromatography (SiO_2, 30% EtOAc in hexanes) gave the desired alcohol mixture **M84** (7.2 g, 98%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 7.2 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.46 (s, 2H), 4.05 (t, *J* = 5.9 Hz, 2H), 3.68–3.52 (m, 3H), 3.40 (dd, *J* = 8.3, 8.9 Hz, 1H), 2.56 (dd, *J* = 4.4, 7.1 Hz, 1H), 2.41–

2.23 (m, 2H), 2.16–2.04 (m, 3H), 0.89 (d, J = 7.0 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.9 (m, 3F), −81.1 (m, 3F), −114.5 (m, 2F), −114.7 (m, 2F), −122.0 (m, 2F), −123.0 (m, 2F), −123.5 (m, 2F), −124.5 (m, 2F), −126.2 (m, 4F); EIMS **(*R*)-84a** *m/z* 456 M^+; **(*S*)-84b** *m/z* 556 M^+; HRMS (ESI) **(*R*)-84a** $(M + Na)^+$ calcd for $C_{18}H_{21}O_3F_9Na$ 479.1245, found 479.1238; **(*S*)-84b** $(M + Na)^+$ calcd for $C_{20}H_{21}N_4O_3F_{13}Na$ 579.1181, found 579.1176; analytical fluorous HPLC (conditions 2) t_R = 4.3 min (**(*R*)-84a**), 9.9 min (**(*S*)-84b**).



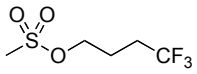
(*S*)-5-(3-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-2-methylpropylthio)-1-phenyl-1*H*-tetrazole and (*R*)-5-(3-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononyloxy) benzyloxy)-2-methylpropylthio)-1-phenyl-1*H*-tetrazole (M98):[59] Triphenylphosphine (5.7 g, 14.2 mmol) was added to a solution of mixture **M84** (7.2 g, 21.4 mmol) in THF (36 mL) and the resulting reaction mixture was cooled to 0 °C. A solution of DIAD (4.2 mL, 21.4 mmol) and PTSH (3.9 g, 21.4 mmol) in THF (36 mL) was then added dropwise. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 1 h. The reaction was quenched by the addition of saturated NH_4Cl solution, water and ether were added, and the layers were separated. The aqueous layer was further extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 18% EtOAc in hexanes) gave 8.6 g (91%) of pure product **M98** as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (m, 5H), 7.25 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.45 (dd, J = 13.5, 12.0 Hz, 2H), 4.02 (t, J = 11.7 Hz, 2H), 3.57 (dd, J = 6.0, 12.6 Hz, 1H), 3.47 (dd, J = 5.1,

9.3 Hz, 1H), 3.41 (dd, J = 6.0, 9.3 Hz, 1H), 3.39 (dd, J = 6.6, 12.9 Hz, 1H), 2.40–2.22 (m, 3H), 2.14–2.05 (m, 2H), 1.09 (d, J = 6.6 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.8 (t, J = 8.2 Hz, 3F), −81.0 (m, 3F), −114.4 (m, 2F), −114.6 (m, 2F), −121.9 (m, 2F), −122.9 (m, 2F), −123.5 (m, 2F), −124.4 (m, 2F), −126.1 (m, 4F); EIMS **(*S*)-98a** *m*/*z* 616 M^+; **(*R*)-98b** *m*/*z* 716 M^+; HRMS (ESI) **(*S*)-98a** M^+ calcd for $C_{25}H_{25}N_4O_2F_9S$ 616.1554, found 616.1542; **(*R*)-98b** M^+ calcd for $C_{27}H_{25}N_4O_2F_{13}S$ 716.1491, found 716.1458; analytical fluorous HPLC (conditions 2) t_R = 12.1 min (**(*S*)-98a**), 20.2 min (**(*R*)-98b**).

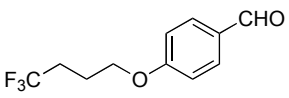


(*S*)-5-(3-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-2-methylpropylsulfonyl)-1-phenyl-1*H*-tetrazole and (*R*)-5-(3-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononyloxy) benzyl oxy)-2-methylpropylsulfonyl)-1-phenyl-1*H*-tetrazole (M83):[59] A solution of $(NH_4)_6Mo_7O_{24}$•$4H_2O$ (3.2 g, 2.6 mmol) in H_2O_2 (30% aqueous solution, 29.0 mL, 255.2 mmol) was added dropwise to a solution of starting sulfide **M98** (8.5 g, 12.8 mmol) in ethanol (80.8 mL) at 0 °C. The reaction mixture was stirred at this temperature for 30 min and at room temperature overnight. The mixture was diluted with DCM and quenched with saturated $NaHCO_3$ solution. Water and ether were added and the layers were separated. The aqueous layer was extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 20% EtOAc in hexanes) gave the desired sulfone mixture **M83** (8.0 g, 90%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65–7.56 (m, 5H), 7.24 (d, J = 11.0 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.41 (q, J = 11.5 Hz, 2H), 4.05

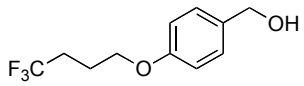
(t, J = 6.0 Hz, 2H), 4.05 (dd, J = 5.0, 15.0 Hz, 1H), 3.57 (dd, J = 7.5, 14.5 Hz, 1H), 3.52 (dd, J = 4.5, 9.5 Hz, 1H), 3.36 (dd, J = 6.5, 9.5 Hz, 1H), 2.65–2.56 (m, 1H), 2.38–2.27 (m, 2H), 2.14–2.08 (m, 2H), 1.19 (d, J = 7.0 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.9 (m, 3F), −81.1 (m, 3F), −114.5 (m, 2F), −114.7 (m, 2F), −122.0 (m, 2F), −123.0 (m, 2F), −123.5 (m, 2F), −124.5 (m, 2F), −126.2 (m, 4F); EIMS **(*S*)-83a** *m*/*z* 671 M^+; **(*R*)-83b** *m*/*z* 771 M^+; HRMS (ESI) **(*S*)-83a** M^+ calcd for $C_{25}H_{25}N_4O_4F_9SNa$ 671.1351, found 671.1290; **(*R*)-83b** M^+ calcd for $C_{27}H_{25}N_4O_4F_9SNa$ 771.1287, found 771.1215; analytical fluorous HPLC (conditions 2) t_R = 10.3 min (**(*S*)-83a**), 18.6 min (**(*R*)-83b**).



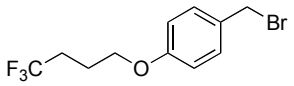
4,4,4-Trifluorobutyl methanesulfonate (109):[93] Triethylamine (11.04 mL, 78.07 mmol) and trifluoromethanesulfonyl chloride (4.60 mL, 58.55 mL) were added to the solution of the starting 4,4,4-trifluorobutanol **108** (5.00 g, 39.04 mmol) in DCM (210 mL) at 0 °C. The reaction mixture was stirred at this temperature for 1 h. The reaction was quenched with water, the layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum to obtain 8.05 g of the desired mesolate **109** as yellow oil, which was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.23 (t, J = 6.0 Hz, 2H), 3.04 (s, 3H), 2.35–2.19 (m, 2H), 2.08–1.99 (m, 2H).



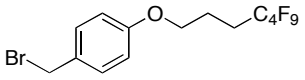
4-(4,4,4-Trifluorobutoxy)benzaldehyde (111):[94] 4-Hydroxybenzaldehye **110** (5.72 g, 46.84 mmol) and K_2CO_3 (6.47 g, 46.84 mmol) were added to a solution of the starting mesolate **109** (39.03 mmol) in DMF (115 mL). The resulting mixture was stirred at 70 °C for 12 h. The reaction was quenched by the addition of water, pentanes were added, and the layers were separated. The aqueous layer was further extracted with pentanes. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 10% EtOAc in hexanes) gave the aldehyde **111** (9.01 g, 99%) as yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 4.11 (t, J = 6.0 Hz, 2H), 2,41–2.25 (m, 2H), 2.14–2.04 (m, 2H).



(4-(4,4,4-Trifluorobutoxy)phenyl)methanol (95c): $NaBH_4$ (2.21 g, 58.14 mmol) was added to a solution of the starting aldehyde **111** (9.01 g, 38.76 mmol) in MeOH (345 mL) at 0 °C and the reaction mixture was stirred at this temperature for 1 h. The reaction was quenched by addition water and most of the MeOH was evaporated under vacuum. The remaining reaction mixture was extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 30% EtOAc in hexanes) gave the alcohol **95c** (9.00 g, 99%) as a viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 4.62 (s, 2H), 4.03 (t, J = 6.0 Hz, 2H), 2,41–2.25 (m, 2H), 2.11–2.00 (m, 2H), 1.73 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 133.4, 128.7, 114.5, 66.0, 65.0, 30.7 (q, $^2J_{CF}$ = 29.3 Hz), 22.1 (q, $^3J_{CF}$ = 3.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (t, J = 11.3 Hz, 3F).



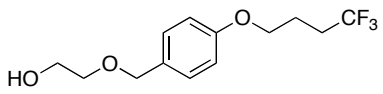
1-(Bromomethyl)-4-(4,4,4-trifluorobutoxy)benzene (105c): PBr_3 (0.94 mL, 9.70 mmol) was added dropwise to a solution of the starting alcohol **95c** (4.55 g, 19.41 mmol) in DCM (39 mL) and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was then cooled to 0 °C and carefully quenched by addition of water. The layers were separated and aqueous layer extracted with DCM. The combined organic layers were washed with brine and $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum to obtain the target bromide **105c** (5.52 g, 96%) as a white solid. The crude product was used in the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.51 (s, 2H), 4.03 (t, J = 6.0 Hz, 2H), 2,41–2.25 (m, 2H), 2.11–2.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 130.5, 130.3, 114.7, 66.0, 33.8, 30.7 (q, $^2J_{CF}$ = 29.3 Hz), 22.1 (q, $^3J_{CF}$ = 3.0 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ –66.3 (t, J = 11.3 Hz, 3F).



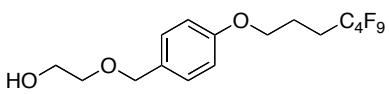
1-(Bromomethyl)-4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzene (105a):[56a,95]

This compound was prepared in quantitative yield starting from PMB^{F9}OH **95a** (5.0 g, 13.0 mmol) following the procedure described above for preparation of compound **105c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.51 (s, 2H), 4.05 (t, J = 6.0 Hz, 2H), 2.42–2.24 (m, 2H), 2.16–2.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 158.6, 130.5,

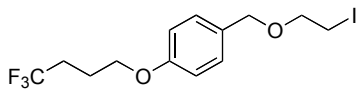
130.4, 114.7, 66.3, 33.8, 27.8 (m), 20.5 (m); ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.2 (m, 3F), −114.7 (m, 2F), −124.5 (m, 2F), −126.1 (m, 2F).



2-(4-(4,4,4-Trifluorobutoxy)benzyloxy)ethanol (107c):[73] Ethylene glycol **106** (14.6 g, 235.50 mmol) was added dropwise to a suspension of NaH (60% in mineral oil, 0.47 g, 11.78 mmol) in THF (20 mL). The reaction mixture was stirred at room temperature for 30 min followed by addition of a solution of the PMB^{F3} bromide **105c** (3.50 g, 11.78 mmol) and TBAI (0.44 g, 1.18 mmol) in THF (20 mL). The reaction mixture was stirred at reflux temperature for 12 h and quenched by the addition of water. The mixture was allowed to cool to room temperature, ether was added, and the layers were separated. The aqueous layer was further extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 30% EtOAc in hexanes) gave the desired alcohol **107c** (3.21 g, 98%) as viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.51 (s, 2H), 4.03 (t, J = 6.0 Hz, 2H), 3.76 (t, J = 4.8 Hz, 2H), 3.60–3.57 (m, 2H), 2.42–2.26 (m, 2H), 2.11–2.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 130.4, 129.4, 114.3, 72.8, 71.1, 66.0, 61.8, 30.6 (q, $^2J_{CF}$ = 28.5 Hz), 22.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (t, 3F); EIMS m/z 287 M^+; HRMS (EI) M^+ calcd for $C_{13}H_{17}O_3F_3$, 278.1129; found 278.1126; IR (neat) 3418, 2867, 1613, 1514, 1299 cm^{-1}.

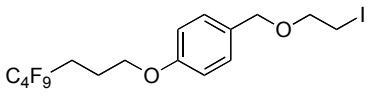


2-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)ethanol (107a):[73] This compound was prepared in 95% yield starting from PMB^{F9} bromide **105a** (3.36 g, 7.50 mmol) and ethylene glycol **106** (9.32 g, 150.3 mmol) following the procedure described above for preparation of compound **107c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 8.1 Hz, 2H), 6.89 (d, J = 8.1 Hz, 2H), 4.51 (s, 2H), 4.05 (t, J = 5.7 Hz, 2H), 3.76 (dd, J = 4.8, 9.0 Hz, 2H), 3.59 (t, J = 4.5 Hz, 2H), 2.42–2.24 (m, 2H), 2.16–2.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 130.5, 129.5, 114.4, 72.9, 71.1, 66.3, 61.8, 27.8 (t, $^2J_{CF}$ = 22.5 Hz), 20.5 (m); ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.2 (m, 3F), −114.7 (m, 2F), −124.5 (m, 2F), −126.1 (m, 2F); EIMS m/z 451 $(M + Na)^+$; HRMS (ESI) $(M + Na)^+$ calcd for $C_{16}H_{17}O_3F_9Na$, 451.0932; found 451.0945; IR (neat) 3419, 2927, 2870, 1613, 1514, 1242 cm^{-1}.

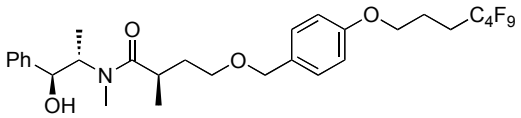


1-((2-Iodoethoxy)methyl)-4-(4,4,4-trifluorobutoxy)benzene (94c):[74] Imidazole (2.41 g, 35.35 mmol) and iodine (4.49 g, 35.35 mmol) were added to a solution of PPh_3 (4.68 g, 17.68 mmol) in DCM (46 mL) at room temperature. The resulting solution was cooled to 0 °C and a solution of the starting alcohol **107c** (3.50 g, 12.59 mmol) in DCM (4.4 mL) was added dropwise. The reaction mixture was allowed to gradually warm to room temperature and stirred for 12 h. The reaction was quenched by the addition of saturated NH_4Cl solution, water was added, and the layers were separated. The aqueous layer was further extracted with DCM. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 5% EtOAc in hexanes) gave the desired iodide **94c** (4.45 g, 91%) as a viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 4.52 (s, 2H), 4.02 (t, J = 6 Hz, 2H), 3.72 (t, J = 6.9 Hz, 2H), 3.28

(t, J = 6.9 Hz, 2H), 2.41–2.52 (m, 2H), 2.11–2.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 130.2, 129.4, 114.3, 72.4, 70.4, 65.9, 30.6 (q, $^{2}J_{CF}$ = 28.5 Hz), 22.1 (m), 3.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.4 (t, 3F); EIMS m/z 388 $(M)^+$; HRMS (EI) $(M)^+$ calcd for $C_{13}H_{16}O_2F_3I$, 388.0147; found 388.0140; IR (neat) 2953, 2867, 1612, 1513, 1387, 1256 cm^{-1}.

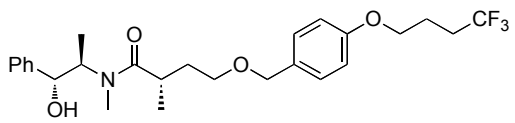


1-((2-Iodoethoxy)methyl)-4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzene (94a):[74] This compound was prepared in 92% yield starting from alcohol **107a** (3.36 g, 7.50 mmol) according to the procedure described above for preparation of iodide **94c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 4.53 (s, 2H), 4.50 (t, J = 6.0 Hz, 2H), 3.72 (t, J = 6.6 Hz, 2H), 3.28 (t, J = 6.6 Hz, 2H), 2.42–2.24 (m, 2H), 2.16–2.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 130.3, 129.4, 114.4, 72.4, 70.4, 66.3, 27.8 (t, $^{2}J_{CF}$ = 22.5 Hz), 20.5 (t, $^{3}J_{CF}$ = 3.8 Hz), 3.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.1 (m, 3F), −114.7 (m, 2F), −124.5 (m, 2F), −126.1 (m, 2F); EIMS m/z 561 $(M + Na)^+$; HRMS (ESI) $(M + Na)^+$ calcd for $C_{16}H_{16}O_2F_9INa$, 560.9949; found 560.9955; IR (neat) 2952, 2868, 1612, 1513, 1299, 1237 cm^{-1}.

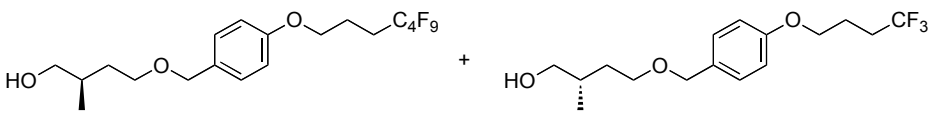


(*R*)-4-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-*N*-((1*S*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylbutanamide ((3*R*,*S*,*S*)-93a):[75] Anhydrous LiCl (3.0 g, 71.3 mmol) was suspended in THF (8 mL) and the suspension was cooled to −78 °C. Diisopropylamine (3.8 mL, 26.8 mmol) was slowly added to this suspension followed by the dropwise

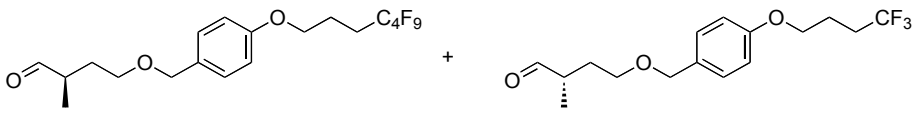
addition of *n*-BuLi (1.6 M in hexanes, 15.6 mL, 25.0 mmol). The reaction mixture was stirred at 0 °C for 10 min and cooled back to −78 °C. A solution of (*S*,*S*)-pseudoephiderine propionamide **(*S*,*S*)-112** (2.6 g, 11.9 mmol) in THF (29 mL) was added and the reaction mixture was stirred at −78 °C for 1.25 h, 0 °C for 15 min, and at room temperature for 5 min. The reaction mixture was cooled back to 0 °C and a solution of iodide **94a** (3.2 g, 5.7 mmol) in THF (3 mL) was added dropwise. The reaction mixture was stirred at this temperature for 12 h after which it was poured into a 0 °C mixture of saturated NH_4Cl solution (40 mL), MeOH (20 mL), and ether (20 mL) and stirred for 15 min. The mixture was allowed to warm to room temperature and the layers were separated. The aqueous layer was further extracted with ether. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 50% EtOAc in hexanes) gave the desired amide **(3*R*,*S*,*S*)-93a** (3.6 g, 95%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ7.40–7.22 (m, 7H), 6.89–6.85 (m, 2H), 4.65 (bt, *J* = 6.9 Hz, 1H), 4.51–4.31 (m, 3H), 4.22–4.11 (m, 0.3H), 4.06–4.02 (m, 2H), 3.62–3.54 (m, 0.7H), 3.54–3.40 (m, 1H), 3.33–3.18 (m, 1H), 2.97–2.84 (m, 4H), 2.39–2.21 (m, 2H), 2.21–2.06 (m, 2H), 2.06–1.89 (m, 1H), 1.80–1.58 (m, 1H), 1.16–1.04 (three overlapping doublets, *J* = 6.6, 6.9 and 6.9 Hz, 5H), 0.97 (d, J = 6.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.1 (m, 3F), −114. 7 (m, 2F), −124. 5 (m, 2F), −126.1 (m, 2F); ^{13}C NMR (75 MHz, $CDCl_3$) major rotamer δ 178.51, 158.11, 142.62, 130.94, 129.22, 128.23, 127.44, 126.27, 114.29, 76.22, 72.45, 67.63, 66.28, 58.26, 34.01, 33.11, 27.78 (t, $^2J_{CF}$ = 22.5 Hz), 26.65, 20.51 (m), 17.28, 14.27; minor rotamer δ 177.08, 141.44, 130.74, 129.49, 128.49, 127.99, 126.93, 75.31, 72.25, 68.21, 33.95, 32.62, 18.39, 15.66; EIMS *m*/*z* 631 $(M)^+$; HRMS (EI) $(M)^+$ calcd for $C_{29}H_{34}O_4NF_9$, 631.2344; found 631.2330; IR (neat) 3341, 2967, 2870, 2240, 1953, 1885, 1611, 1232 cm^{-1}; $[\alpha]_D^{25}$ +2.7 (*c* 2.4, $CHCl_3$).



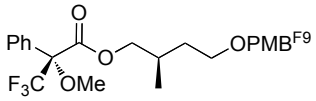
(*S*)-4-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-*N*-((1*R*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)-*N*,2-dimethylbutanamide ((3*S*,*R*,*R*)-93c):[75] This compound was prepared in 95% yield starting from iodide **94c** (4.2 g, 10.8 mmol) and (*R*,*R*)-pseudoephiderine propionamide **(*R*,*R*)-112** (4.9 g, 21.6 mmol) following the procedure described above for preparation of compound **(3*R*,*S*,*S*)-93a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ7.40–7.22 (m, 7H), 6.89–6.85 (m, 2H), 4.65 (bt, J = 6.9 Hz, 1H), 4.51–4.31 (m, 3H), 4.22–4.11 (m, 0.3H), 4.06–4.02 (m, 2H), 3.62–3.54 (m, 0.7H), 3.54–3.40 (m, 1H), 3.33–3.18 (m, 1H), 2.97–2.84 (m, 4H), 2.39–2.21 (m, 2H), 2.21–2.06 (m, 2H), 2.06–1.89 (m, 1H), 1.80–1.58 (m, 1H), 1.16–1.04 (three overlapping doublets, J = 6.6, 6.9 and 6.9 Hz, 5H), 0.97 (d, J = 6.6 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.31 (t, J = 11.3 Hz, 3F); ^{13}C NMR (75 MHz, $CDCl_3$) major rotamer δ 178.28, 157.99, 142.52, 130.69, 129.15, 128.10, 127.29, 126.16, 114.12, 75.97, 72.33, 67.49, 65.81, 58.08, 33.88, 32.91, 30.48 (q, $^{2}J_{CF}$ = 28.5 Hz), 26.61, 21.98 (q, $^{3}J_{CF}$ = 3.0 Hz), 17.20, 14.16; minor rotamer δ 176.97, 141.44, 130.56, 129.38, 128.36, 127.84, 126.82, 114.08, 75.12, 72.12, 68.09, 57.90, 33.76, 32.46, 18.27, 15.57; ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.4 (t, 3F); EIMS m/z 481 $(M)^+$; HRMS (EI) $(M)^+$ calcd for $C_{26}H_{34}O_4NF_3$, 481.2439; found 481.2452; IR (neat) 3399, 2966, 2214, 1956, 1886, 1619, 1247 cm^{-1}; $[\alpha]_D^{25}$ +3.8 (c 2.0, $CHCl_3$).



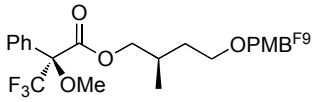
(*S*)-4-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-2-methylbutan-1-ol and (*R*)-4-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-2-methylbutan-1-ol (M113):[78] The amides **(3*R*,*S*,*S*)-93a** (2.21 g, 3.50 mmol) and **(3*S*,*R*,*R*)-93c** (1.68 g, 3.50 mmol) were combined to obtain the mixture (3.89 g, 7.0 mmol) **M93**. *n*-BuLi (1.6 M in hexanes, 16.95 mL, 27.12 mmol) was added dropwise to a solution of diisoproplyamine (4.11 mL, 29.21 mmol) in THF (29 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 10 min and then at 0 °C for 10 min. BH_3•NH_3 (0.96 g, 27.87 mmol) was added and the reaction mixture was stirred at 0 °C for 15 min, at room temperature for 15 min, and cooled back to 0 °C. A solution of amide mixture **M93** (3.88 g, 6.96 mmol) in THF (19 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 5 min and at room temperature for 4 h. The reaction was quenched by the addition of 3 N HCl (70 mL), water and ether were added, and the layers were separated. The aqueous layer was further extracted with ether. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 35% EtOAc in hexanes) gave the desired alcohol **M113** (2.39 g, 87%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 7.8 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 4.46 (s, 2H), 4.03 (dd, *J* = 6.0, 12.6 Hz, 2H), 3.62–3.38 (m, 4H), 2.69 (bt, *J* = 5.7 Hz, 1H), 2.39–2.21(m, 2H), 2.20–2.00 (m, 2H), 1.90–1.73 (m, 1H), 1.73–1.52 (m, 2H), 0.93 (d, *J* = 6.6 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.4 (t, *J* = 11.3 Hz, 3F), −81.2 (m, 3F), −114.7 (m, 2F), −124.45 (m, 2F), −126.1 (m, 2F); EIMS **(*S*)-113c** *m*/*z* 320 M^+; **(*R*)-113a** *m*/*z* 470 M^+; HRMS (EI) **(*S*)-113c** M^+ calcd for $C_{16}H_{23}O_3F_3$ 320.1599, found 320.1589; **(*R*)-113a** M^+ calcd for $C_{19}H_{23}O_3F_9$ 470.1504, found 470.1498; analytical fluorous HPLC (conditions 3) t_R = 4.3 min (**(*S*)-113c**), 9.9 min (**(*R*)-113a**).



(*S*)-4-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-2-methylbutanal and (*R*)-4-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-2-methylbutanal (M92):[43] Oxalyl chloride (6.3 mL, 71.7 mmol) was added dropwise to a solution of DMSO (11.4 mL, 160.1 mmol) in DCM (230 mL) at −78 °C. The resulting solution was stirred at this temperature for 15 min. A solution of starting alcohol **M113** (9.45 g, 23.9 mmol) in DCM (120 mL) was then added dropwise and the mixture was stirred at −78 °C for 30 min. Diisopropylamine (41.8 mL, 239.0) was added dropwise and the mixture stirred at −78 °C for 30 min and then allowed to warm to room temperature over a period of 2 h. The reaction was quenched by the addition of saturated sodium bisulfate solution. Water was added and the layers were separated. The aqueous layer was extracted with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 5% EtOAc in hexanes) gave the desired aldehyde mixture **M92** (6.79 g, 72%) as yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (d, *J* = 1.8 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 4.42 (s, 2H), 4.03 (dd, *J* = 6.0, 12.6 Hz, 2H), 3.58–3.45 (m, 2H), 2.57–2.50 (m, 1H), 2.40–2.24 (m, 2H), 2.15–1.99 (m, 3H), 1.75–1.64 (m, 1H), 1.11 (d, *J* = 7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.37 (m, 3F), −81.08 (m, 3F), −114.63 (m, 2F), −124.45 (m, 2F), −126.08 (m, 2F); EIMS **(*S*)-92c** *m*/*z* 318 M^+; **(*R*)-92a** *m*/*z* 468 M^+; HRMS (ESI) **(*S*)-92c** $(M + Na)^+$ calcd for $C_{16}H_{21}O_3F_3Na$ 341.1340, found 341.1340; **(*R*)-92a** $(M + Na)^+$ calcd for $C_{19}H_{21}O_3F_9Na$ 491.1245, found 491.1282; analytical fluorous HPLC (conditions 3) t_R = 6.2 min (**(*S*)-92c**), 16.8 min (**(*R*)-92a**).

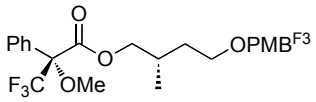


(*R*)-((*R*)-2-Methyl-4-(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)phenoxy)butyl)3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((*R*,3*R*)-114a):[32e] Triethylamine (23.7 μL, 0.17 mmol), *S*-MTPA chloride (16.0 μL, 0.09 mmol) and DMAP (1.0 mg, 0.01 mmol) were added to a solution of alcohol **(*R*)-113a** (4.0 mg, 0.01 mmol) in DCM (0.5 mL). The resulting mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of water, DCM was added and the layers were separated. The aqueous layer was further extracted with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to obtain the crude MTPA ester **(*R*,3*R*)-114a**: ^{1}H NMR major diastereomer (500 MHz, $CDCl_3$) δ 7.53–7.51 (m, 2H), 7.43–7.38 (m, 3H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.41 (dd, *J* = 11.5, 12.5 Hz, 2H), 4.28 (dd, *J* = 5.5, 11.0 Hz, 1H), 4.12 (dd, *J* = 6.5, 11.0 Hz, 1H), 4.04 (t, *J* = 6.0 Hz, 2H), 3.55 (s, 3H), 3.51–3.46 (m, 2H), 2.38–2.26 (m, 2H), 2.14–2.03 (m, 3H), 1.70 (sxt, *J* = 6.5 Hz, 1H), 1.51–1.44 (m, 1H), 0.94 (d, *J* = 6.5 Hz, 3H).

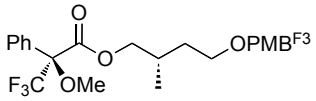


(*S*)-((*R*)-2-Methyl-4-(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)phenoxy)butyl)3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((*S*,3*R*)-114a): This compound was prepared from alcohol **(*R*)-113a** (4.0 mg, 0.01 mmol) by reaction with *R*-MTPA chloride, triethylamine and DMAP following the procedure described above for the preparation of the MTPA ester **(*R*,3*R*)-114a**. The ^{1}H NMR spectrum of the crude product was obtained and compared with the ^{1}H NMR spectrum of **(*R*,3*R*)-114a**. Based on these spectra the enantiomeric ratio of the alcohol **(*R*)-113a** was found to be 94:6. ^{1}H NMR major diastereomer (500 MHz, $CDCl_3$) δ 7.53–7.51 (m, 2H),

7.42–7.39 (m, 3H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 9.5 Hz, 2H), 4.06 (s, 2H), 4.21 (dd, *J* = 0.5 Hz, 5.5 Hz, 1H), 4.18 (dd, *J* = 1.5, 6.0 Hz, 1H), 4.04 (t, *J* = 6.0 Hz, 2H), 3.55 (s, 3H), 3.49–3.44 (m, 2H), 2.38–2.25 (m, 2H), 2.14–2.02 (m, 3H), 1.66 (sxt, *J* = 7.0 Hz, 1H), 1.50–1.44 (m, 1H), 0.95 (d, *J* = 7.0 Hz, 3H).

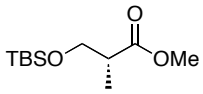


(*R*)-((*S*)-2-Methyl-4-(4-(4,4,4-trifluorobutoxy)phenoxy)butyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((*R*,3*S*)-114c): This compound was prepared from alcohol **(*S*)-113c** (5.0 mg, 0.16 mmol) by reaction with *S*-MTPA chloride, triethylamine and DMAP following the procedure described above for the preparation of the MTPA ester **(*R*,3*R*)-114a**. The ^{1}H NMR spectrum of the crude product was obtained. ^{1}H NMR major diastereomer (500 MHz, $CDCl_3$) δ 7.53–7.51 (m, 2H), 7.42–7.39 (m, 3H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 9.5 Hz, 2H), 4.41 (s, 2H), 4.21 (dd, *J* = 0.5 Hz, 5.5 Hz, 1H), 4.18 (dd, *J* = 1.5, 6.0 Hz, 1H), 4.04 (t, *J* = 6.0 Hz, 2H), 3.55 (s, 3H), 3.49–3.44 (m, 2H), 2.38–2.25 (m, 2H), 2.14–2.02 (m, 3H), 1.66 (sxt, *J* = 7.0 Hz, 1H), 1.50–1.44 (m, 1H), 0.95 (d, *J* = 6.0 Hz, 3H).

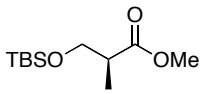


(*S*)-((*S*)-2-Methyl-4-(4-(4,4,4-trifluorobutoxy)phenoxy)butyl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((*S*,3*S*)-114c): This compound was prepared from alcohol **(*S*)-113c** (5.0 mg, 0.16 mmol) by reaction with *R*-MTPA chloride, triethylamine and DMAP following the procedure described above for the preparation of the MTPA ester **(*R*,3*R*)-114a**. The ^{1}H NMR spectrum of the crude product was obtained and compared with the ^{1}H NMR spectrum of major

diastereomer (500 MHz, $CDCl_3$) δ 7.53–7.51 (m, 2H), 7.43–7.38 (m, 3H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 4.41 (s, 2H), 4.28 (dd, *J* = 5.5, 11.0 Hz, 1H), 4.12 (dd, *J* = 6.5, 11.0 Hz, 1H), 4.04 (t, *J* = 6.0 Hz, 2H), 3.55 (s, 3H), 3.51–3.46 (m, 2H), 2.38–2.26 (m, 2H), 2.14–2.03 (m, 3H), 1.72–1.65 (m, 1H), 1.51–1.44 (m, 1H), 0.94 (d, *J* = 7.0 Hz, 3H). Based on these spectra the enantiomeric ratio of the alcohol **(*S*)-113c** was found to be 93:7.

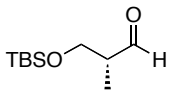


***R*-Methyl 3-(*tert*-butyldimethylsilyloxy)-2-methylpropanoate ((*R*)-115)**:[96] Imidazole (4.3 g, 63.5 mmol), TBSCl (8.9 g, 59.3 mmol) and DMAP (0.4 g, 3.4 mmol) were added to solution of (*R*)-methyl 3-hydroxy-2-methylpropanoate **(*R*)-85** (5.0 g, 42.3 mmol) in THF (150 mL). The resulting mixture was stirred at room temperature for 4 h. The reaction was quenched by addition of water, ether was added, and the layers were separated. The aqueous layer was further extracted and with ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 5% EtOAc in hexanes) gave 9.6 g (97%) of pure compound **(*R*)-115** as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (dd, *J* = 6.9, 9.6 Hz, 1H), 3.67 (s, 3H), 3.65 (dd, *J* = 6.0, 9.9 Hz, 1H), 2.65 (sxt, *J* = 6.9 Hz, 1H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.33 (s, 6H).

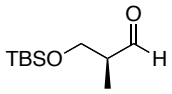


***S*-Methyl 3-(*tert*-butyldimethylsilyloxy)-2-methylpropanoate ((*S*)-115)**:[62] This compound was prepared in 95% yield starting from (*S*)-methyl 3-hydroxy-2-methylpropanoate **(*S*)-85** (5.0 g,

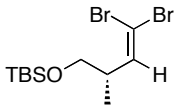
42.3 mmol) following the procedure described above for preparation of compound **(*R*)-115**. The ^{1}H NMR data of this compound was identical to that reported above for compound **(*R*)-115**.



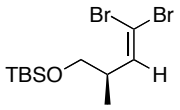
***R*-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropanal ((*R*)-116)**:[97] DIBAL (1 M in hexanes, 43.4 mL, 43.4 mmol) was added dropwise to a solution of the ester **(*R*)-115** (9.6 g, 41.3 mmol) in DCM (293 mL) at −78 °C. The resulting mixture was stirred at this temperature for 1.5 h. The reaction was quenched by addition of saturated sodium potassium tartrate solution (300 mL) and the mixture was allowed to stir at room temperature till the layers became clear. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated under vacuum to afford 8.2 g of the aldehyde **(*R*)-116** as a yellow oil which was carried to the next step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (d, J = 1.8 Hz, 1H), 3.87 (dd, J = 5.1, 10.2 Hz, 1H), 3.81 (dd, J = 6.3, 10.2 Hz, 1H), 2.57–2.48 (m, 1H), 1.10 (d, J = 6.9 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H).



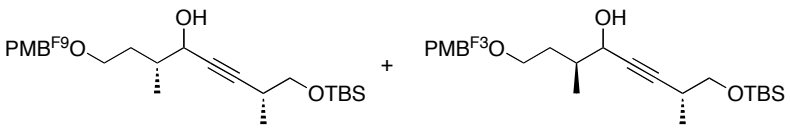
***S*-3-(*tert*-Butyldimethylsilyloxy)-2-methylpropanal ((*S*)-116)**:[62] This compound was prepared from **(*S*)-115** following the procedure described above for preparation of compound **(*R*)-116**. The NMR data of this compound was in accordance to that mentioned above for compound **(*R*)-116**.



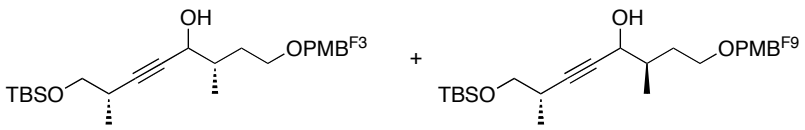
***S-tert*-Butyl(4,4-dibromo-2-methylbut-3-enyloxy)dimethylsilane ((*S*)-91)**:[64] Carbon tetrabromide (27.67 g, 82.59 mmol) was dissolved in DCM (300 mL) and the solution was cooled to 0 °C. Triphenylphosphine (43.76 g, 165.18 mmol) was added and the resulting dark red solution was stirred at this temperature for 1 h followed by cooling to −78 °C. A solution of the aldehyde **(*R*)-116** (8.36 g, 41.30 mmol) and 2,6-Lutidine (4.84 mL, 41.30 mmol) in DCM (20 mL) was added dropwise. After stirring at −78 °C for 1h the mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched by the addition of hexanes. The reaction mixture was filtered and the filtrate was concentrated under vacuum. Purification by flash column chromatography (SiO_2, 2% EtOAC in hexanes) gave the dibromoolefin **(*S*)-91** (8.88 g, 60% over two steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (d, J = 9.3 Hz, 1H), 3.52 (d, J = 5.7, 2H), 2.71–2.57 (m, 1H), 1.03 (d, J = 6.9 Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H).



***R-tert*-Butyl(4,4-dibromo-2-methylbut-3-enyloxy)dimethylsilane ((*R*)-91)**:[62] This compound was prepared in yield from aldehyde **(*S*)-116** according to the procedure described above for preparation of compound **(*S*)-91**. The NMR data of this compound was in accordance to that mentioned for compound **(*S*)-91**.



(3*R*,7*R*)-1-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-8-(*tert*-butyldimethylsilyl oxy)-3,7-dimethyloct-5-yn-4-ol and (3*S*,7*R*)-1-(4-(4,4,4-Trifluorobutoxy) benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-3,7-dimethyloct-5-yn-4-ol ((7*R*)-M117):[98] *n*-BuLi (1.6 M in hexanes, 11.21 mL, 17.94 mmol) was added dropwise to a solution of the dibromoolefin **(*R*)-91** (3.18 g, 8.54 mmol) in THF (70 mL) at −78 °C. The reaction mixture was stirred at this temperature for 1 h and a solution of the aldehyde **M92** (2.80 g, 7.12 mmol) in THF (35 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h followed by warming to room temperature over a period of 4 h. The reaction was quenched by the addition of saturated NH_4Cl solution, water and ether were added and the layers were separated. The aqueous layer was further extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 15% EtOAc in hexanes) gave the desired alcohol **(7*R*)-M117** (4.21 g, 100%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 4.53–4.41 (m, 2H), 4.33–4.19 (m, 1H), 4.03 (dd, *J* = 6.0, 12.3 Hz, 2H), 3.73–3.64 (m, 1H), 3.64–3.47 (m, 2H), 3.43 (dd, *J* = 8.1, 9.3 Hz, 1H), 3.27 (d, *J* = 7.2 Hz, 0.5H), 2.68 (d, *J* = 5.7 Hz, 0.5H), 2.68–2.54 (m, 1H), 2.43–2.20 (m, 2H), 2.20–1.99 (m, 2H), 1.99–1.83 (m, 1H), 1.83–1.60 (m, 1H), 1.60–1.14 (m, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 1.5H), 0.99 (d, *J* = 6.6 Hz, 1.5 H), 0.90 (s, 9H), 0.06 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (m, 3F), −81.0 (m, 3F), −114.6 (m, 2F), −124.4 (m, 2F), −126.0 (m, 2F); EIMS **(3*S*,7*R*)-117c** *m*/*z* 516 M^+; **(3*R*,7*R*)-117a** *m*/*z* 666 M^+; HRMS (ESI) **(3*S*,7*R*)-117c** $(M + Na)^+$ calcd for $C_{27}H_{43}O_4F_3SiNa$ 539.2780, found 539.2766; **(3*R*,7*R*)-117a** $(M + Na)^+$ calcd for $C_{30}H_{43}O_4F_9SiNa$ 689.2685, found 689.2676; analytical fluorous HPLC (conditions 3) t_R = 15.3 min (**(3*S*,7*R*)-117c**), 26.4 min (**(3*R*,7*R*)-117a**).



(3*R*,7*S*)-1-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-8-(*tert*-butyldimethylsilyl oxy)-3,7-dimethyloct-5-yn-4-ol and (3*S*,7*S*)-1-(4-(4,4,4-Trifluorobutoxy) benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-3,7-dimethyloct-5-yn-4-ol ((7*S*)-M117):[98] This compound was prepared in 80% yield starting from dibromide **(*S*)-91** (3.65 g, 10.2 mmol) and aldehyde **M92** (3.34 g, 8.5 mmol) following the procedure described above for preparation of compound **(7*R*)-M117**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 4.71 (q, *J* = 11.4 Hz, 1H), 4.45 (s, 1H), 4.31–4.20 (m, 1H), 4.03 (q, *J* = 6.0 Hz, 2H), 3.71–3.64 (m, 1H), 3.63–3.47 (m, 2H), 3.43 (dd, *J* = 8.1, 9.3 Hz, 1H), 3.25 (d, *J* = 7.2 Hz, 0.5H), 2.67 (d, *J* = 6.0 Hz, 0.5H), 2.68–2.55 (m, 1H), 2.42–2.23 (m, 2H), 2.17–2.02 (m, 2H), 2.02–1.84 (m, 1H), 1.84–1.44 (m, 2H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 1.5H), 0.99 (d, *J* = 6.6 Hz, 1.5 H), 0.90 (s, 9H), 0.06 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (m, 3F), −81.0 (m, 3F), −114.6 (m, 2F), −124.4 (m, 2F), −126.0 (m, 2F); EIMS **(3*S*,7*S*)-117c** *m*/*z* 516 M^+; **(3*R*,7*S*)-117a** *m*/*z* 666 M^+; HRMS (ESI) **(3*S*,7*S*)-117c** $(M + Na)^+$ calcd for $C_{27}H_{43}O_4F_3SiNa$ 539.2780, found 539.2775; **(3*R*,7*S*)-117a** $(M + Na)^+$ calcd for $C_{30}H_{43}O_4F_9SiNa$ 689.2685, found 689.2634; analytical fluorous HPLC (conditions 3) t_R = 14.2 min (**(3*S*,7*S*)-117c**), 24.3 min (**(3*R*,7*S*)-117a**).

(2*R*,6*S*)-8-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-2,6-dimethyloct-3-yne-1,5-diol and (2*R*,6*R*)-8-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-2,6-dimethyloct-3-yne-1,5-diol

((7*R*)-M90):[99] A mixture of TBAF (35 mL, 35 mmol) and CH_3COOH (2 mL, 35 mmol) was added to a solution of the silyl ether **(7*R*)-M117** (4.1 g, 7.0 mmol) in THF (50 mL) at 0 °C. The resulting solution was stirred at this temperature for 10 min and at room temperature for 24 h. The reaction was quenched by the addition of saturated NH_4Cl solution, water and ether were added and the layers were separated. The aqueous layer was further extracted with ether. The combined organic layer were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 40%–60% EtOAc in hexanes) gave the diol **(7*R*)-M90** (2.1 g, 91%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.26 (m, 2H), 6.89–6.86 (m, 2H), 4.53–4.42 (m, 2H), 4.29–4.23 (m, 1H), 4.03 (q, *J* = 6.3 Hz, 2H), 3.65–3.40 (m, 4H), 2.80–2.60 (m, 1H), 2.43–2.20 (m, 2H), 2.18–1.98 (m, 2H), 1.98–1.80 (m, 1H), 1.80–1.60 (m, 1H), 1.60–1.44 (m, 1H), 1.17–1.14 (m, 3H), 1.02 (d, *J* = 7.2 Hz, 1.5 H), 0.99 (d, *J* = 6.9 Hz, 1.5H); ^{19}F NMR (282 MHz, $CDCl_3$) −66.3 (3F), −81.0 (3F), −114.2 (2F), −124.4 (2F), −126.0 (2F); EIMS **(3*S*,7*R*)-90c** *m*/*z* 425 M^+; **(3*R*,7*R*)-90a** *m*/*z* 575 M^+; HRMS (ESI) **(3*S*,7*R*)-90c** $(M + Na)^+$ calcd for $C_{21}H_{29}O_4F_3Na$ 425.1916, found 425.1911; **(3*R*,7*R*)-90a** $(M + Na)^+$ calcd for $C_{24}H_{29}O_4F_9Na$ 575.1820, found 575.1815; analytical fluorous HPLC (conditions 3) t_R = 3.8 min (**(3*S*,7*R*)-90c**), 11.8 min (**(3*R*,7*R*)-90a**).

(2*S*,6*S*)-8-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-2,6-dimethyloct-3-yne-1,5-diol and (2*S*,6*R*)-8-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-2,6-dimethyloct-3-yne-1,5-diol ((7*S*)-M90):[99] This compound was prepared in 91% yield starting from protected alcohol **(7*S*)-M117** (6.70 g, 1.13 mmol) following the procedure described above for preparation of compound **(7*R*)-**

M90: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.25 (m, 2H), 6.87(d, *J* = 8.4 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 4.47 (q, *J* = 11.4 Hz, 1H), 4.45 (s, 1H), 4.30–4.20 (m, 1H), 4.03 (q, *J* = 6.0 Hz, 2H), 3.64–3.42 (m, 4H), 2.72–2.65 (m, 1H), 2.42–2.22 (m, 2H), 2.14–1.98 (m, 2H), 1.98–1.85 (m, 1H), 1.85–1.46 (m, 2H), 1.16–1.13 (four overlapping doublets, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 1.5 H), 0.99 (d, *J* = 6.9 Hz, 1.5H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (3F), −81.0 (3F), −114.2 (2F), −124.4 (2F), −126.0 (2F); EIMS **(3*S*,7*S*)-90c** *m/z* 425 $(M + Na)^+$; **(3*R*,7*S*)-90a** *m/z* 575 $(M + Na)^+$; HRMS (ESI) **(3*S*,7*S*)-90c** $(M + Na)^+$ calcd for $C_{21}H_{29}O_4F_3Na$ 425.1916, found 425.1908; **(3*R*,7*S*)-90a** $(M + Na)^+$ calcd for $C_{24}H_{29}O_4F_9Na$, 575.1820; found 575.1865; analytical fluorous HPLC (conditions 3) t_R = 3.9 min (**(3*S*,7*S*)-90c**), 11.8 min (**(3*R*,7*S*)-90a**).

(3*S*,7*R*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-3,7-dimethyl-8-(1-phenyl-1*H*-tetrazol-5-yl-thio)oct-5-yn-4-ol and (3*R*,7*R*)-1-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-3,7-dimethyl-8-(1-phenyl-1*H*-tetrazol-5-ylthio)oct-5-yn-4-ol ((7*R*)-M118):[81] PPh_3 (549.4 mg, 2.1 mmol) and PTSH (377.1 mg, 2.1 mmol) were added to a solution of stating alcohol **(7*R*)-M90** (900.0 mg, 1.9 mmol) in THF (22.6 mL) at 0 °C and the mixture was stirred to allow the reagents to dissolve. DIAD (0.4 mL, 2.1 mmol) was then added dropwise and the reaction mixture was stirred for 30 min at 0 °C. The reaction was quenched by the addition of sat NH_4Cl solution, water and ether were added and the layers were separated. The aqueous layer was further extracted with ether. The combined organic layers were dried over saturated $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 25% EtOAc in hexanes) gave the desired sulfide **(7*R*)-M118** (776.4 mg, 65%) contaminated with

about 10% of the hydrazine byproduct (^{1}H NMR analysis). This product was used in next step without any further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.53 (m, 5H), 7.24 (d, J = 8.5 Hz, 2H), 6.86–6.84 (m, 2H), 4.44 (q, J = 11.5 Hz, 1H), 4.43 (s, 1H), 4.30–4.25 (m, 0.5H), 4.21 (tt, J = 1.5, 5.5 Hz, 0.5 H), 4.04–3.99 (m, 2H), 3.57–3.39 (m, 4 H), 3.13–3.05 (m, 1H), 2.36–2.26 (m, 2H), 2.12–2.01 (m, 2H), 1.98–1.85 (m, 1H), 1.76–1.40 (m, 2H), 1.33 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 7.0 Hz, 1.5H), 0.95 (d, J = 6.5 Hz, 1.5); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (m, 3F), −81.0 (m, 3F), −114.6 (m, 2F), −124.4 (m, 2F), −126.0 (m, 2F); EIMS **(3*S*,7*R*)-118c** *m*/*z* 585 $(M + Na)^+$; **(3*R*,7*R*)-118a** 735 $(M + Na)^+$; HRMS (ESI) **(3*S*,7*R*)-118c** $(M + Na)^+$ calcd for $C_{28}H_{33}N_4O_3F_3SNa$ 585.2123, found 585.2075; **(3*R*,7*R*)-M118a** $(M + Na)^+$ calcd for $C_{31}H_{33}N_4O_3F_9SNa$ 735.2027, found 735.2050; analytical fluorous HPLC (conditions 3) t_R = 6.6 min (**(3*S*,7*R*)-118c**), 15.7 min (**(3*R*,7*R*)-118a**).

(3*S*,7*S*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-3,7-dimethyl-8-(1-phenyl-1*H*-tetrazol-5-ylthio)oct-5-yn-4-ol and (3*R*,7*S*)-1-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-3,7-dimethyl-8-(1-phenyl-1*H*-tetrazol-5-ylthio)oct-5-yn-4-ol ((7*S*)-M118):[81] This compound was prepared in 54% yield starting from diol **(7*S*)-M90** (650.0 mg, 1.4 mmol) according to the procedure described above for preparation of compound **(7*R*)-M118**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.53 (m, 5H), 7.24 (d, J = 8.4 Hz, 2H), 6.87–6.83 (m, 2H), 4.44 (q, J = 11.4 Hz, 1H), 4.43 (s, 1H), 4.31–4.25 (m, 0.5H), 4.21 (tt, J = 6.0, 1.8 Hz, 0.5 H), 4.02 (q, J = 6.3 Hz, 2H), 3.61–3.38 (m, 4.5 H), 3.15–3.05 (m, 1H), 2.85 (bd, J = 5.7 Hz, 0.5H), 2.40–2.23 (m, 2H), 2.14–1.97 (m, 2H), 1.97–1.80 (m, 1H), 1.80–1.40 (m, 2H), 1.34 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 6.9

Hz, 1.5H), 0.95 (d, J = 6.9 Hz, 1.5); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (m, 3F), −81.0 (m, 3F), −114.6 (m, 2F), −124.4 (m, 2F), −126.1 (m, 2F); EIMS **(3*S*,7*S*)-118c** *m/z* 585 $(M + Na)^+$; **(3*R*,7*S*)-118a** *m/z* 735 $(M + Na)^+$; HRMS (ESI) **(3*S*,7*S*)-118c** $(M + Na)^+$ calcd for $C_{28}H_{33}N_4O_3F_3NaS$ 585.2123, found 585.2083; **(3*R*,7*S*)-118a** $(M + Na)^+$ calcd for $C_{31}H_{33}N_4O_3F_9NaS$ 735.2027, found 735.2065; analytical fluorous HPLC (conditions 3) t_R = 6.6 min (**(3*S*,7*S*)-118c**), 15.8 min (**(3*R*,7*S*)-118a**).

(3*S*,7*R*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-3,7-dimethyl-8-(1-phenyl-1*H*-tetrazol-5-yl-sulfonyl)oct-5-yn-4-ol and (3*R*,7*R*)-1-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-3,7-dimethyl-8-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)oct-5-yn-4-ol ((7*R*)-M80):[59] A solution of $(NH_4)_6Mo_7O_{24}•4H_2O$ (100.2 mg, 0.08 mmol) in H_2O_2 (30% in water, 0.45 mL, 4.00 mmol) was added dropwise to a solution of the sulfide **(7*R*)-M118** (130.0 mg, 0.20 mmol) in EtOH (1.3 mL) at 0 °C. The resulting yellow mixture was stirred at 0 °C for 30 min and at room temperature for 24 h. The reaction was quenched by the addition of saturated $NaHCO_3$ solution, water and DCM were added, and the layers were separated. The aqueous layer was further extracted with DCM. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 5% EtOAc in DCM) gave the desired sulfone **(7*R*)-M80** (121.7 mg, 90%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.57 (m, 5H), 7.26 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 4.52–4.40 (m, 2H), 4.23–3.90 (m, 4H), 3.78–3.62 (m, 1H), 3.62–3.40 (m, 2.5H), 3.38–3.20 (m, 1H), 2.93 (d, J = 6.0 Hz, 0.5H), 2.36–2.23 (m, 2H), 2.14–1.97 (m, 2H), 1.97–1.80 (m, 1H), 1.80–

1.40 (m, 2H), 1.39 (d, J = 7.2 Hz, 3H), 0.95 (d, J = 6.6 Hz, 1.5H), 0.94 (d, J = 6.6 Hz, 1.5); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (m, 3F), −81.0 (m, 3F), −114.6 (m, 2F), −124.4 (m, 2F), −126.0 (m, 2F); EIMS **(3*S*,7*R*)-80c** *m/z* 617 $(M + Na)^+$; **(3*R*,7*R*)-80a** *m/z* 767 $(M + Na)^+$; HRMS (ESI) **(3*S*,7*R*)-80c** $(M + Na)^+$ calcd for $C_{28}H_{33}N_4O_5F_3SNa$ 617.2021, found 617.2016; **(3*R*,7*R*)-80a** $(M + Na)^+$ calcd for $C_{31}H_{33}N_4O_5F_9SNa$ 767.1926, found 767.1976; analytical fluorous HPLC (conditions 3) t_R = 6.6 min (**(3*S*,7*R*)-80c**), 15.7 min (**(3*R*,7*R*)-80a**).

(3*S*,7*S*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-3,7-dimethyl-8-(1-phenyl-1*H*-tetrazol-5-yl-sulfonyl)oct-5-yn-4-ol and (3*R*,7*S*)-1-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-3,7-dimethyl-8-(1-phenyl-1*H*-tetrazol-5-ylsulfonyl)oct-5-yn-4-ol ((7*S*)-M80):[59]

This compound was prepared in 87% yield from sulfide **(7*S*)-M118** (466.9 mg, 0.7 mmol) according to the procedure described above for preparation of compound **(7*R*)-M80**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.54 (m, 5H), 7.26 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.51–4.40 (m, 2H), 4.31–4.25 (m, 0.5H), 4.21 (tt, J = 6.0, 1.8 Hz, 0.5 H), 4.02 (q, J = 6.3 Hz, 2H), 3.61–3.38 (m, 4.5 H), 3.15–3.05 (m, 1H), 2.85 (bd, J = 5.7 Hz, 0.5H), 2.40–2.23 (m, 2H), 2.14–1.97 (m, 2H), 1.97–1.80 (m, 1H), 1.80–1.40 (m, 2H), 1.34 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 6.9 Hz, 1.5H), 0.95 (d, J = 6.9 Hz, 1.5); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (m, 3F), −81.0 (m, 3F), −114.6 (m, 2F), −124.4 (m, 2F), −126.0 (m, 2F); EIMS **(3*S*,7*S*)-80c** *m/z* 617 $(M + Na)^+$; **(3*R*,7*S*)-80a** *m/z* 767 $(M + Na)^+$; HRMS (ESI) **(3*S*,7*S*)-80c** $(M + Na)^+$ calcd for $C_{28}H_{33}N_4O_5F_3SNa$ 617.2021, found 617.2028; **(3*R*,7*S*)-80a** $(M + Na)^+$ calcd for

$C_{31}H_{33}N_4O_5F_9SNa$ 767.1926, found 767.1976; analytical fluorous HPLC (conditions 3) t_R = 6.6 min (**(3*S*,7*S*)-80c**), 15.7 min (**(3*R*,7*S*)-80a**).

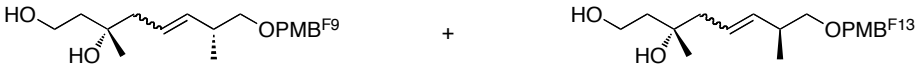
5-((2*R*,6*S*)-8-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-2,6-dimethyl-5-(triethylsilyloxy)oct-3-ynylsulfonyl)-1-phenyl-1*H*-tetrazole and 5-((2*R*,6*R*)-8-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-2,6-dimethyl-5-(triethylsilyloxy)oct-3-ynylsulfonyl)-1-phenyl-1*H*-tetrazole ((7*R*)-M123): 2,6-Lutidine (1.20 mL, 10.30 mmol) and TESOTf (1.60 mL, 7.70 mmol) were added dropwise to the solution of the starting alcohol **(7*R*)-M80** (1.15 g, 1.71 mmol) in DCM (36 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min, allowed to warm to room temperature, and stirred for 30 min. The reaction was quenched by the addition of water and the layers were separated. The aqueous layer was further extracted with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 15% EtOAc in hexanes) gave the sulfone **(7*R*)-M123** (1.13 g, 84%) as colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.66 (m, 2H), 7.65–7.58 (m, 3H), 7.28 (d, *J* = 7.0 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 4.48–4.42 (m, 2H), 4.25–4.22 (m, 1H), 4.06–3.97 (m, 3H), 3.82–3.76 (m, 1H), 3.54–3.46 (m, 2H), 3.37–3.31 (m, 1H), 2.36–2.27 (m, 2H), 2.14–2.00 (m, 2H), 1.98–1.75 (m, 2H), 1.50–1.40 (m, 1H), 1.42 (d, *J* = 7.0 Hz, 3H), 1.02–0.93 (m, 12H), 0.71–0.60 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (m, 3F), −81.0 (m, 3F), −114.6 (m, 2F), −124.4 (m, 2F), −126.1 (m, 2F); EIMS **(3*S*,7*R*)-123c** *m/z* 731 $(M + Na)^+$; **(3*R*,7*R*)-123a** *m/z* 881 $(M + Na)^+$; HRMS (ESI) **(3*S*,7*R*)-123c** $(M + Na)^+$ calcd for $C_{34}H_{47}N_4O_5F_3SSiNa$ 731.2886, found 731.2908; **(3*R*,7*R*)-**

123a $(M + Na)^+$ calcd for $C_{37}H_{47}N_4O_5F_9SSiNa$ 881.2790, found 881.2762; analytical fluorous HPLC (conditions 3) t_R = 16.1 min (**(3*S*,7*R*)-123c**), 24.8 min (**(3*R*,7*R*)-123a**).

5-((2*S*,6*S*)-8-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-2,6-dimethyl-5-(triethylsilyloxy)oct-3-ynylsulfonyl)-1-phenyl-1*H*-tetrazole and 5-((2*S*,6*R*)-8-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-2,6-dimethyl-5-(triethylsilyloxy)oct-3-ynylsulfonyl)-1-phenyl-1*H*-tetrazole ((7*S*)-M123): This compound was prepared in 78% yield from alcohol **(7*S*)-M80** (419.1 mg, 0.6 mmol) according to the procedure described above for preparation of compound **(7*R*)-M123**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.57 (m, 5H), 7.28–7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 4.43 (dd, *J* = 11.7, 15.0 Hz, 2H), 4.23–4.17 (m, 1H), 4.06–3.95 (m, 3H), 3.83–3.74 (m, 1H), 3.52–3.45 (m, 2H), 3.35–3.29 (m, 1H), 2.41–2.25 (m, 2H), 2.14–2.00 (m, 2H), 1.97–1.76 (m, 2H), 1.70–1.40 (m, 1H), 1.41 (d, *J* = 6.9 Hz, 3H), 0.99–0.89 (m, 12H), 0.66–0.57 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (m, 3F), −81.0 (m, 3F), −114.6 (m, 2F), −124.4 (m, 2F), −126.1 (m, 2F); EIMS **(3*S*,7*S*)-123c** *m/z* 731 $(M + Na)^+$; **(3*R*,7*S*)-123a** *m/z* 881 $(M + Na)^+$; HRMS (ESI) **(3*S*,7*S*)-123c** $(M + Na)^+$ calcd for $C_{34}H_{47}N_4O_5F_3SiSNa$ 731.2886, found 731.2941; **(3*R*,7*S*)-123a** $(M + Na)^+$ calcd for $C_{37}H_{47}N_4O_5F_9SiSNa$ 881.2790, found 881.2712; analytical fluorous HPLC (conditions 3) t_R = 16.1 min (**(3*S*,7*S*)-123c**), 24.9 min (**(3*R*,7*S*)-123a**).

1-(((2*R*,6*S*)-8-(*tert*-Butyldimethylsilyloxy)-2,6-dimethyl-6-(triethylsilyloxy)oct-3-enyloxy)-methyl)-4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzene and 1-(((2*S*,6*S*)-8-(*tert*-Butyldimethylsilyloxy)-2,6-dimethyl-6-(triethylsilyloxy)oct-3-enyloxy)methyl)-4-(4,4,5,5, 6,6,7,7,8,8, 9,9,9-tridecafluorononyloxy)benzene ((3*S*)-M119):[59] *n*-BuLi (1.6 M in hexanes, 0.37 mL, 0.60 mmol) was added dropwise to a solution of diisopropylamine (0.09 mL, 0.63 mmol) in THF (0.6 mL) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 10 min and then at room temperature for 2 min. This solution of LDA was then transferred dropwise to a solution of the sulfone **M83** (387.2 mg, 0.55 mmol) in THF (2.8 mL) at −78 °C. The resulting yellow reaction mixture was stirred at this temperature for 30 min after which a solution of aldehyde **(*R*)-82** (142.80 mg, 0.40 mmol) in THF (0.6 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 3 h and quenched by the addition of saturated NH_4Cl solution. Water and ether were added and the layers were separated. The aqueous layer was further extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 2% EtOAc in hexanes) gave (274.5 mg, 83%) of the desired product **(3*S*)-M119** as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.55–5.46 (m, 1H), 5.43–5.29 (m, 1H), 4.45 (s, 2H), 4.05 (t, *J* = 11.7 Hz, 2H), 3.74 (t, *J* = 7.5 Hz, 2H), 3.36 (dd, *J* = 6.3, 9.0 Hz, 1H), 3.24 (dd, *J* = 7.2, 9.0 Hz, 1H), 2.51–2.42 (m, 1H), 2.39–2.22 (m, 3H), 2.20–2.06 (m, 3H), 1.77–1.62 (m, 2H), 1.18 (s, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.96 (t, *J* = 8.1 Hz, 9H), 0.90 (s, 9H), 0.58 (q, *J* = 8.1 Hz, 6H), 0.06 (s, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.7 (m, 3F), −81.0 (m, 3F), −114.5 (m, 2F), −114.7 (m, 2F), −121.9 (m, 2F), −122.9 (m, 2F), −123.5 (m, 2F), −124.4 (m, 2F), −126.1 (m, 4F); EIMS **(3*S*,7*R*)-119a** *m*/*z* 805 $(M + Na)^+$; **(3*S*,7*S*)-119b** *m*/*z* 905 $(M + Na)^+$; HRMS (ESI) **(3*S*,7*R*)-119a** $(M + Na)^+$ calcd for $C_{36}H_{59}O_4F_9Si_2Na$ 805.3706, found 805.3740;

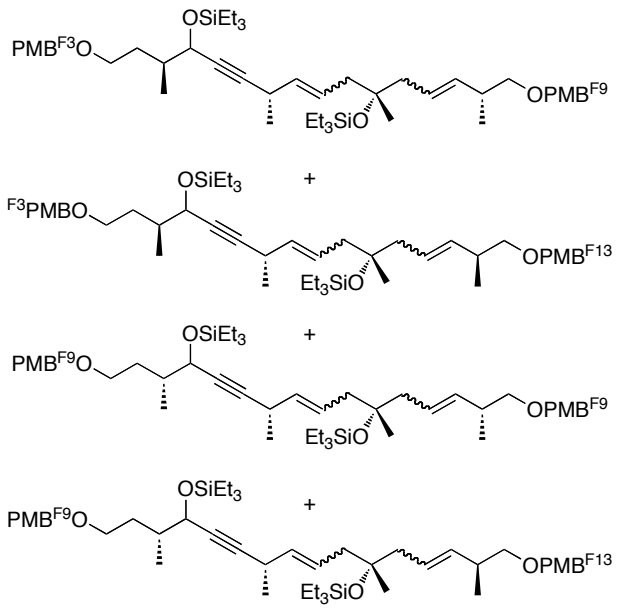
(3*S*,7*S*)-119b $(M + Na)^+$ calcd for $C_{38}H_{59}O_4F_{13}Si_2Na$ 905.3642, found 905.3732; analytical fluorous HPLC (conditions 2) t_R = 32.4 min (**(3*S*,7*R*)-119a**), 36.9 min (**(3*S*,7*S*)-119b**).



(3*S*,7*R*)-8-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-3,7-dimethyloct-5-ene-1,3-diol and (3*S*,7*S*)-8-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononyloxy)benzyloxy)-3,7-dimethyloct-5-ene-1,3-diol ((3*S*)-M120):[99] A mixture of TBAF (1 M in THF, 28.8 mL, 28.8 mmol) and CH_3COOH (1.7 mL, 28.8 mmol) was added dropwise to the solution of the starting bis-silyl ether **(3*S*)-M119** (2.4 g, 2.9 mmol) in THF (16.5 mL) at 0 °C. The resulting mixture was stirred at this temperature 30 min and at room temperature for 24 h. The reaction was quenched by the addition of saturated NH_4Cl solution. Water and ether were added and the layers were separated. The aqueous layer was further extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by column chromatography (SiO_2, 40% EtOAc in hexanes–60% EtOAc in hexanes) gave the pure diol **(3*S*)-M120** (1.7 g, 100%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 9.9 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 5.53–5.46 (m, 2H), 4.44 (s, 2H), 4.05 (t, J = 5.7 Hz, 2H), 3.98–3.75 (m, 2H), 3.39–3.14 (m, 2H), 2.60–2.41 (m, 1H), 2.41–2.19 (m, 4H), 2.19–2.02 (m, 3H), 1.88–1.50 (m, 3H), 1.23 (s, 1.5 H), 1.20 (s, 1.5 H), 1.03 (d, J = 6.9 Hz, 1.5H), 1.01 (d, J = 6.6 Hz, 1.5H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.7 (m, 3F), −81.0 (m, 3F), −114.5 (m, 2F), −114.7 (m, 2F), −121.9 (m, 2F), 122.9 (m, 2F), 123.5 (m, 2F), 124.4 (m, 2F), 126.1 (m, 4F); analytical fluorous HPLC (conditions 2) t_R = 7.3 min (**(3*S*,7*R*)-120a**), 15.7 min (**(3*S*,7*S*)-120b**).

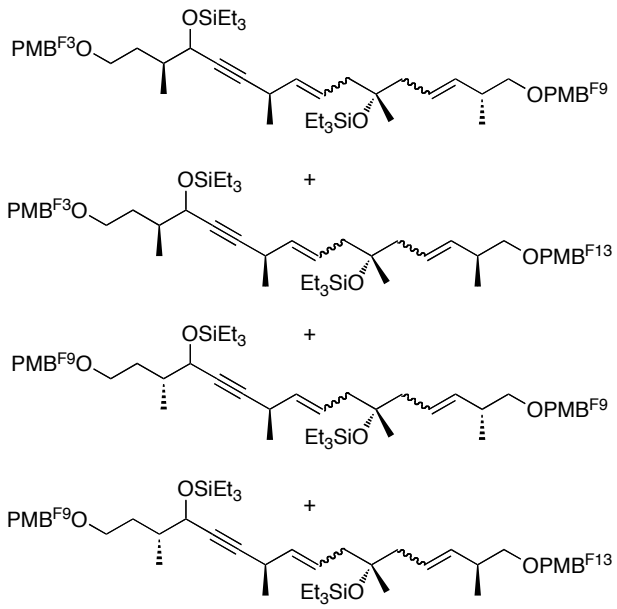
1-(((2*R*,6*S*)-2,6-Dimethyl-6,8-bis(triethylsilyloxy)oct-3-enyloxy)methyl)-4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzene and 1-(((2*S*,6*S*)-2,6-Dimethyl-6,8-bis(triethylsilyloxy)oct-3-enyloxy)methyl)-4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzene ((3*S*)-M121): 2,6-Lutidine (1.28 mL, 10.90 mmol) and TESOTf (1.86 mL, 8.15 mmol) were sequentially added dropwise to a solution of the starting diol **(3*S*)-M120** (1.64 g, 2.72 mmol) in DCM (58 mL) at −30 °C. The resulting solution was stirred at this temperature for 2 h. The reaction was quenched by the addition of water. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by column chromatography (SiO_2, 2% EtOAc in hexanes) gave the desired product **(3*S*)-M121** (1.76 g, 78%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.54–5.23 (m, 2H), 4.45 (s, 2H), 4.04 (t, *J* = 6.0 Hz, 2H), 3.74 (t, *J* = 7.5 Hz, 2H), 3.35 (dd, *J* = 6.3, 9.3 Hz, 1H), 3.23 (dd, *J* = 7.2, 9.0 Hz, 1H), 2.53–2.06 (m, 7H), 1.79–1.63 (m, 2H), 1.73 (s, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 7.8 Hz, 9H), 0.96 (t, *J* = 7.5 Hz, 9H), 0.64–0.53 (m, 12H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.7 (m, 3F), −81.0 (m, 3F), −114.5 (m, 2F), −114.7 (m, 2F), −121.9 (m, 2F), −122.9 (m, 2F), −123.5 (m, 2F), −124.4 (m, 2F), −126.1 (m, 4F); EIMS **(3*S*,7*R*)-121a** *m*/*z* 805 (M + Na)$^+$; **(3*S*,7*S*)-121b** *m*/*z* 905 (M + Na)$^+$; HRMS (ESI) **(3*S*,7*R*)-121a** (M + Na)$^+$ calcd for $C_{36}H_{59}O_4F_9Si_2Na$ 805.3706, found 805.3688; **(3*S*,7*S*)-121b** (M + Na)$^+$ calcd for $C_{38}H_{59}O_4F_{13}Si_2Na$ 905.3642, found 905.3641; analytical fluorous HPLC (conditions 2) t_R = 30.9 min (**(3*S*,7*R*)-121a**), 35.9 min (**(3*S*,7*S*)-121b**).

(3*S*,7*R*)-8-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-3,7-dimethyl-3-(triethylsilyl oxy)oct-5-enal and (3*S*,7*S*)-8-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononyloxy)benzyloxy)-3,7-dimethyl-3-(triethylsilyloxy)oct-5-enal ((3*S*)-M81):[71] A solution of oxalyl chloride (0.19 mL, 2.11 mmol) in DCM (2.4 mL) was added dropwise to a solution of DMSO (0.30 mL, 4.23 mmol) in DCM (4.8 mL) at −78 °C. The resulting solution was stirred at this temperature for 20 min after which a solution of the starting bis triethylsilyl ether **(3*S*)-M121** (400.0 mg, 0.48 mmol) in DCM (4.8 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 20 min, at −40 °C for 20 min and cooled back to −78 °C. Triethylamine (0.88 mL, 6.24 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 30 min followed by warming to room temperature over a period of 2 h. The reaction was quenched by the addition of water, the layers were separated, and the aqueous layer was further extracted with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by column chromatography (SiO_2, 4% EtOAc in hexanes) gave the pure aldehyde **(3*S*)-M81** (265.1 mg, 77%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.86 (q, J = 2.4 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.53–5.29 (m, 2H), 4.44 (s, 2H), 4.04 (q, J = 6.0 Hz, 2H), 3.37–3.24 (m, 2H), 2.54–2.45 (m, 2H), 2.45–2.24 (m, 5H), 2.16–2.05 (m, 2H), 1.32 (s, 3H), 1.02–0.93 (m, 12H), 0.66–0.56 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.7 (m, 3F), −81.0 (m, 3F), −114.5 (m, 2F), −114.7 (m, 2F), −121.9 (m, 2F), −122.9 (m, 2F), −123.5 (m, 2F), −124.4 (m, 2F), −126.1 (m, 4F); EIMS **(3*S*,7*R*)-81a** *m/z* 689 $(M + Na)^+$; **(3*S*,7*S*)-81b** *m/z* 789 $(M + Na)^+$; HRMS (ESI) **(3*S*,7*R*)-81a** $(M + Na)^+$ calcd for $C_{30}H_{43}O_4F_9SiNa$ 689.2685, found 689.2651; **(3*S*,7*S*)-81b** $(M + Na)^+$ calcd for $C_{32}H_{43}O_4F_{13}SiNa$ 789.2621, found 789.2628; analytical fluorous HPLC (conditions 2) t_R = 21.1 min (**(3*S*,7*R*)-81a**), 28.7 min (**(3*S*,7*S*)-81b**).



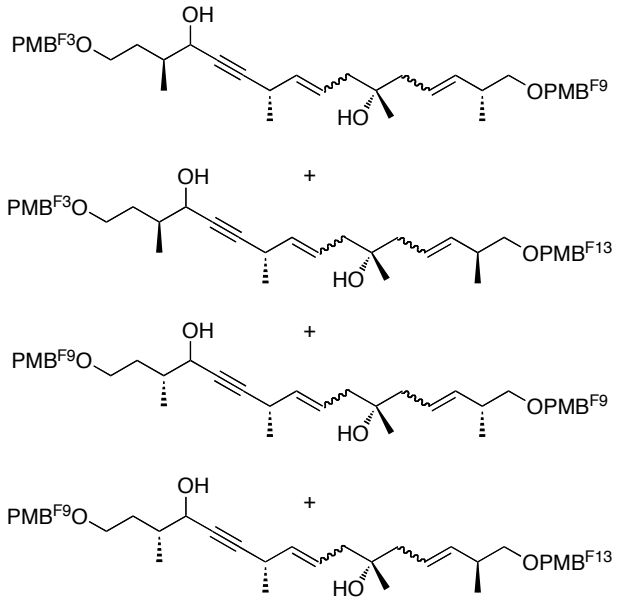
1-(((3*S*,7*S*,11*R*,15*R*)-16-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-3,7,11,15-tetramethyl-4,11-bis(triethylsilyloxy)hexadeca-8,13-dien-5-ynyloxy)methyl)-4-(4,4,4-trifluorobutoxy)benzene, 1-(((3*S*,7*S*,11*R*,15*S*)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononyloxy)benzyloxy)-3,7,11,15-tetramethyl-4,11-bis(triethylsilyloxy)hexadeca -8,13-dien-5-ynyloxy)methyl)-4-(4,4,4-trifluorobutoxy)benzene, 1-(((3*R*,7*S*,11*R*,15*R*)-16-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-3,7,11,15-tetramethyl-4,11-bis(triethylsilyloxy)hexadeca-8,13-dien-5-ynyloxy)methyl)-4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzene, and 1-(((3*R*,7*S*,11*R*,15*S*)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononyloxy)benzyloxy)-3,7,11,15-tetramethyl-4,11-bis(triethylsilyloxy)hexadeca-8,13-dien-5-ynyloxy)methyl)-4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzene ((7*S*,11*R*)-M124): NaHMDS (1.0 M in THF, 0.88 mL, 0.88 mmol) was added dropwise to a solution of the starting sulfone **(7*R*)-M123** (659.6 mg, 0.84 mmol) in THF (15 mL) at −78 °C. The resulting yellow solution was stirred at this temperature for 30 min followed by the addition of a solution of aldehyde **(3*S*)-M81** (500.0 mg, 0.70 mmol) in THF (11 mL). The reaction mixture was stirred at −78 °C for 2 h and quenched by the addition of saturated NH_4Cl solution. The mixture was allowed to warm to room temperature and the

layers were separated. The aqueous layer was further extracted with ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography (SiO_2, 5% EtOAc in hexanes) afforded the desired product **(7*S*,11*R*)-M124** (485.1 mg, 55%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 4H), 6.87 (d, *J* = 8.7 Hz, 4H), 5.69–5.23 (m, 4H), 4.49–4.39 (m, 4H), 4.31–4.22 (m, 1H), 4.04 (t, *J* = 6.0 Hz, 4H), 3.56–3.44 (m, 2H), 3.36 (dd, *J* = 6.6, 9.3 Hz, 1H), 3.31–3.20 (m, 1H), 3.20–3.05 (m, 1H), 2.54–2.43 (m, 1H), 2.43–2.20 (m, 4H), 2.20–1.99 (m, 8H), 1.99–1.75 (m, 2H), 1.53–1.38 (m, 1H), 1.24–1.14 (m, 6H), 1.04–0.93 (m, 24H), 0.68–0.54 (m, 12H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.4 (3F), −80.8 (3F), −81.1 (6F), −114.4 (2F), −114.7 (4F), −121.9 (2F), −122.9 (2F), −123.5 (2F), −124.4 (4F), −126.11 (6F); EIMS **(3*S*,7*S*,11*R*,15*R*)-124ca** *m/z* 1172 $(M + Na + H)^+$; **(3*S*,7*S*,11*R*,15*S*)-124cb** *m/z* 1272 $(M + Na + H)^+$; **(3*R*,7*S*,11*R*,15*R*)-124aa** *m/z* 1322 $(M + Na + H)^+$; **(3*R*,7*S*,11*R*,15*S*)-124ab** *m/z* 1422 $(M + Na + H)^+$; HRMS (ESI) **(3*S*,7*S*,11*R*,15*R*)-124ca** $(M + Na)^+$ calcd for $C_{57}H_{84}O_6F_{12}Si_2Na$ 1171.5513, found 1171.5521; **(3*S*,7*S*,11*R*,15*S*)-124cb** $(M + Na)^+$ calcd for $C_{59}H_{84}O_6F_{16}Si_2Na$ 1271.5449, found 1271.5408; **(3*R*,7*S*,11*R*,15*R*)-124aa** $(M + Na)^+$ calcd for $C_{60}H_{84}O_6F_{18}Si_2Na$ 1321.5417, found 1321.5359; **(3*R*,7*S*,11*R*,15*S*)-124ab** $(M + Na)^+$ calcd for $C_{62}H_{84}O_6F_{22}Si_2Na$ 1421.5353, found 1421.5298; analytical fluorous HPLC (conditions 2) t_R = 29.2 min (**(3*S*,7*S*,11*R*,15*R*)-M124ca**), 34.4 min (**(3*S*,7*S*,11*R*,15*S*)-M124cb**), 36.2 min (**(3*R*,7*S*,11*R*,15*R*)-M124aa**), 41.9 min (**(3*R*,7*S*,11*R*,15*S*)-M124ab**).



(1-(((3*S*,7*R*,11*R*,15*R*)-16-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-3,7,11,15-tetramethyl-4,11-bis(triethylsilyloxy)hexadeca-8,13-dien-5-ynyloxy)methyl)-4-(4,4,4-trifluorobutoxy)benzene, 1-(((3*S*,7*R*,11*R*,15*S*)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononyloxy)benzyloxy)-3,7,11,15-tetramethyl-4,11-bis(triethylsilyloxy)hexadeca -8,13-dien-5-ynyloxy)methyl)-4-(4,4,4-trifluorobutoxy)benzene, 1-(((3*R*,7*R*,11*R*,15*R*)-16-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-3,7,11,15-tetramethyl-4,11-bis(triethylsilyloxy)hexadeca-8,13-dien-5-ynyloxy)methyl)-4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzene, and 1-(((3*R*,7*R*,11*R*,15*S*)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-Tridecafluorononyloxy)benzyloxy)-3,7,11,15-tetramethyl-4,11-bis(triethylsilyloxy)hexadeca-8,13-dien-5-ynyloxy)methyl)-4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzene ((7*R*,11*R*)-M124): This compound was prepared in 89% yield starting from sulfone **(7*S*)-M123** (170.1 mg, 0.22 mmol) and aldehyde **(3*S*)-M81** (130.0 mg, 0.18 mmol) according to the procedure described above for preparation of compound **(7*S*,11*R*)-M124**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 4H), 6.89–6.88 (d, *J* = 8.7 Hz, 4H), 5.79–5.24 (m, 4H), 4.50–4.39 (m, 4H), 4.32–4.23 (m, 1H), 4.04 (t, *J* = 6.0 Hz, 4H), 3.57–3.45 (m, 2H), 3.55–3.45 (m, 3H), 2.52–2.22 (m, 5H), 2.22–1.78 (m, 10H), 1.55–1.39 (m, 1H), 1.27–

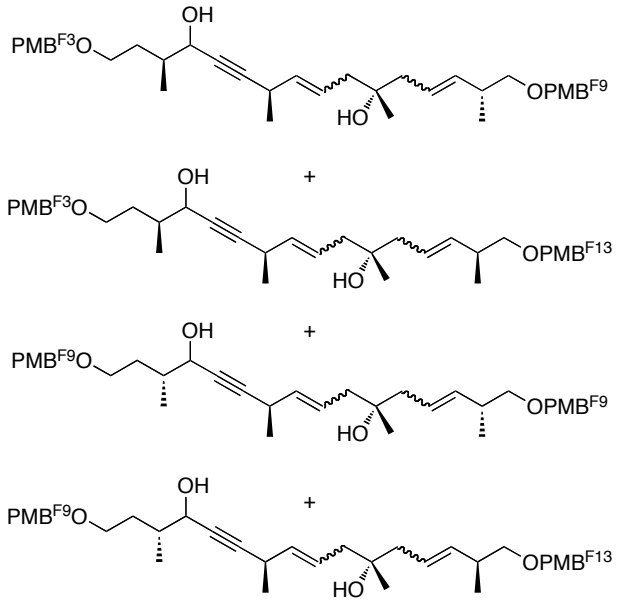
1.14 (m, 6H), 1.05–0.94 (m, 24H), 0.71–0.55 (m, 12H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.4 (m, 3F), −80.8 (m, 3F), −81.1 (m, 6F), −114.4 (m, 2F), −114.7 (m, 4F), −121.9 (m, 2F), −122.9 (m, 2F), −123.5 (m, 2F), −124.5 (m, 4F), −126.1 (m, 6F); EIMS **(3*S*,7*R*,11*R*,15*R*)-M124ca** *m/z* 1172 $(M + Na + H)^+$; **(3*S*,7*R*,11*R*,15*S*)-M124cb** *m/z* 1272 $(M + Na + H)^+$; **(3*R*,7*R*,11*R*,15*R*)-M124aa** *m/z* 1322 $(M + Na + H)^+$; **(3*R*,7*R*,11*R*,15*S*)-M124ab** *m/z* 1422 $(M + Na + H)^+$; HRMS (ESI) **(3*S*,7*R*,11*R*,15*R*)-M124ca** $(M + Na)^+$ calcd for $C_{57}H_{84}O_6F_{12}Si_2Na$ 1171.5513, found 1171.5459; **(3*S*,7*R*,11*R*,15*S*)-M124cb** $(M + Na)^+$ calcd for $C_{59}H_{84}O_6F_{16}Si_2Na$ 1271.5449, found 1271.5374; **(3*R*,7*R*,11*R*,15*R*)-M124aa** $(M + Na)^+$ calcd for $C_{60}H_{84}O_6F_{18}Si_2Na$ 1321.5417, found 1321.5513; **(3*R*,7*R*,11*R*,15*S*)-M124ab** $(M + Na)^+$ calcd for $C_{62}H_{84}O_6F_{22}Si_2Na$ 1421.5353, found 1421.5436; analytical fluorous HPLC (conditions 2) t_R = 29.6 min (**(3*S*,7*R*,11*R*,15*R*)-M124ca**), 34.8 min (**(3*S*,7*R*,11*R*,15*S*)-M124cb**), 36.5 min (**(3*R*,7*R*,11*R*,15*R*)-M124aa**), 42.2 min (**(3*R*,7*R*,11*R*,15*S*)-M124ab**).



(3*S*,7*S*,11*R*,15*R*)-3,7,11,15-Tetramethyl-16-(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)-

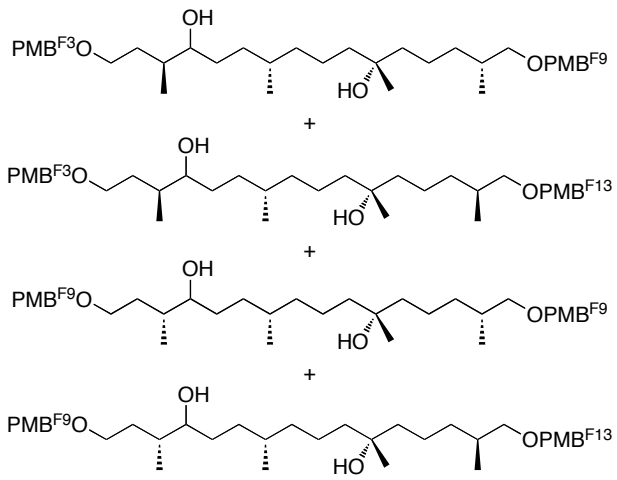
benzyloxy)-1-(4-(4,4,4-trifluorobutoxy)benzyloxy)hexadeca-8,13-dien-5-yne-4,11-diol, (3*S*,7*S*,11*R*,15*S*)-3,7,11,15-Tetramethyl-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzyloxy)-1-(4-(4,4,4-trifluorobutoxy)benzyloxy)hexadeca-8,13-dien-5-yne-4,11-diol, (3*R*,7*S*,11*R*,15*R*)-3,7,11,15-Tetramethyl-1,16-bis(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)-benzyloxy)hexadeca-8,13-dien-5-yne-4,11-diol and (3*R*,7*S*,11*R*,15*S*)-3,7,11,15-Tetramethyl-1-(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzyloxy)hexadeca-8,13-dien-5-yne-4,11-diol ((7*S*,11*R*)-M125):[83] 2N HCl (32.3 mL, 64.6 mmol) was added dropwise to a solution of the starting bis-silyl ether **(7*S*,11*R*)-M124** (450.2 mg, 0.35 mmol) in THF (111 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 10 min and at room temperature for 4 h. The reaction was quenched by addition of water. Ether was added and the layers were separated. The aqueous layer was further extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (SiO_2, 40% EtOAc in hexanes) gave the product **(7*S*,11*R*)-M125** (360.0 mg, 98%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.24 (overlapping doublets, J = 8.4 Hz, 4H), 6.87 (d, J = 8.7 Hz, 4H), 5.78–5.30 (m, 4H), 4.44 (s, 4H), 4.38–4.18 (m, 1H), 4.03 (t, J = 6.0 Hz, 4H), 3.64–3.40 (m, 2H), 3.40–3.25 (m, 2H), 3.25–3.10 (m, 1H), 2.95–2.60 (m, 1H), 2.60–2.43 (m, 1H), 2.43–2.22 (m, 5H), 2.22–2.00 (m, 7H), 2.00–1.83 (m, 1H), 1.83–1.58 (m, 2H), 1.58–1.43 (m, 1H), 1.26–1.22 (m, 3H), 1.17–1.13 (m, 3H), 1.02 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.4 (m, 3F), −80.9 (m, 3F), −81.1 (m, 6F), −114.4 (m, 2F), −114.7 (m, 4F), −121.9 (m, 2F), −122.9 (m, 2F), −123.5 (m, 2F), −124.5 (m, 4F), −126.1 (m, 6F); EIMS **(3*S*,7*S*,11*R*,15*R*)-M125ca** *m/z* 943 $(M + Na)^+$; **(3*S*,7*S*,11*R*,15*S*)-M125cb** *m/z* 1043 $(M + Na)^+$; **(3*R*,7*S*,11*R*,15*R*)-M125aa** *m/z* 1093 $(M + Na)^+$; **(3*R*,7*S*,11*R*,15*S*)-M125ab** *m/z* 1193 $(M + Na)^+$;

HRMS (ESI) **(3*S*,7*S*,11*R*,15*R*)-M125ca** $(M + Na)^+$ calcd for $C_{45}H_{56}O_6F_{12}Na$ 943.3783, found 943.3704; **(3*S*,7*S*,11*R*,15*S*)-M125cb** $(M + Na)^+$ calcd for $C_{47}H_{56}O_6F_{16}Na$ 1043.3719, found 1043.3619; **(3*R*,7*S*,11*R*,15*R*)-M125aa** $(M + Na)^+$ calcd for $C_{48}H_{56}O_6F_{18}Na$ 1093.3687, found 1093.3583; **(3*R*,7*S*,11*R*,15*S*)-M125ab** $(M + Na)^+$ calcd for $C_{50}H_{56}O_6F_{22}Na$ 1193.3623, found 1193.3634; analytical fluorous HPLC (conditions 2) t_R = 7.9 min (**(3*S*,7*S*,11*R*,15*R*)-M125ca**), 14.6 min (**(3*S*,7*S*,11*R*,15*S*)-M125cb**), 17.5 min (**(3*R*,7*S*,11*R*,15*R*)-M125aa**), 25.6 min (**(3*R*,7*S*,11*R*,15*S*)-M125ab**).



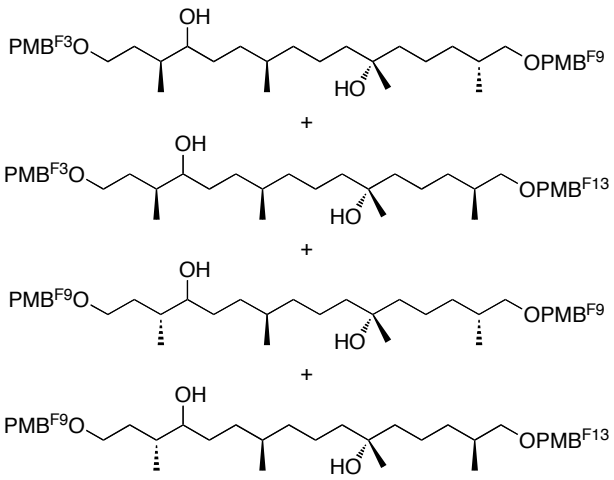
(3*S*,7*R*,11*R*,15*R*)-3,7,11,15-Tetramethyl-16-(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzyloxy)-1-(4-(4,4,4-trifluorobutoxy)benzyloxy)hexadeca-8,13-dien-5-yne-4,11-diol, (3*S*,7*R*,11*R*,15*S*)-3,7,11,15-Tetramethyl-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzyloxy)-1-(4-(4,4,4-trifluorobutoxy)benzyloxy)hexadeca-8,13-dien-5-yne-4,11-diol, (3*R*,7*R*,11*R*,15*R*)-3,7,11,15-Tetramethyl-1,16-bis(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzyloxy)hexadeca-8,13-dien-5-yne-4,11-diol and (3*R*,7*R*,11*R*,15*S*)-3,7,11,15-Tetramethyl-1-(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluoronon-

yloxy)benzyloxy)hexadeca-8,13-dien-5-yne-4,11-diol ((7*R*,11*R*)-M125): This compound was prepared in 95% yield starting from bis-silyl ether **(7*R*,11*R*)-M124** (196.0 mg, 0.16 mmol) according to the procedure described above for preparation of compound **(7*S*,11*R*)-M125**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.24 (overlapping doublets, J = 8.4 Hz, 4H), 6.87 (d, J = 8.7 Hz, 4H), 5.76–5.31 (m, 4H), 4.46 (q, J = 11.7 Hz, 2H), 4.44 (s, 2H), 4.37–4.20 (m, 1H), 4.03 (t, J = 6.0 Hz, 4H), 3.61–3.43 (m, 2H), 3.38–3.17 (m, 3H), 2.95–2.60 (m, 1H), 2.60–2.42 (m, 1H), 2.42–2.00 (m, 12H), 2.00–1.83 (m, 1H), 1.83–1.44 (m, 3H), 1.27–1.22 (m, 3H), 1.18–1.25 (m, 3H), 1.03–0.92 (m, 6H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.4 (m, 3F), −80.9 (m, 3F), −81.1 (m, 6F), −114.4 (m, 2F), −114.7 (m, 4F), −121.9 (m, 2F), −122.9 (m, 2F), −123.5 (m, 2F), −124.5 (m, 4F), −126.1 (m, 6F); EIMS **(3*S*,7*R*,11*R*,15*R*)-M125ca** *m/z* 943 $(M + Na)^+$; **(3*S*,7*R*,11*R*,15*S*)-M125cb** *m/z* 1043 $(M + Na)^+$; **(3*R*,7*R*,11*R*,15*R*)-M125aa** *m/z* 1093 $(M + Na)^+$; **(3*R*,7*R*,11*R*,15*S*)-M125ab** *m/z* 1193 $(M + Na)^+$; HRMS (ESI) **(3*S*,7*R*,11*R*,15*R*)-M125ca** $(M + Na)^+$ calcd for $C_{45}H_{56}O_6F_{12}Na$ 943.3783, found 943.3789; **(3*S*,7*R*,11*R*,15*S*)-M125cb** $(M + Na)^+$ calcd for $C_{47}H_6O_6F_{16}Na$ 1043.3719, found 1043.3619; **(3*R*,7*R*,11*R*,15*R*)-M125aa** $(M + Na)^+$ calcd for $C_{48}H_{56}O_6F_{18}Na$ 1093.3687, found 1093.3726; **(3*R*,7*R*,11*R*,15*S*)-M125ab** $(M + Na)^+$ calcd for $C_{50}H_{56}O_6F_{22}Na$ 1193.3623, found 1193.3723; analytical fluorous HPLC (conditions 2) t_R = 8.0 min (**(3*S*,7*R*,11*R*,15*R*)-M125ca**), 14.9 min (**(3*S*,7*R*,11*R*,15*S*)-M125cb**), 17.8 min (**(3*R*,7*R*,11*R*,15*R*)-M125aa**), 26.1 min (**(3*R*,7*R*,11*R*,15*S*)-M125ab**).



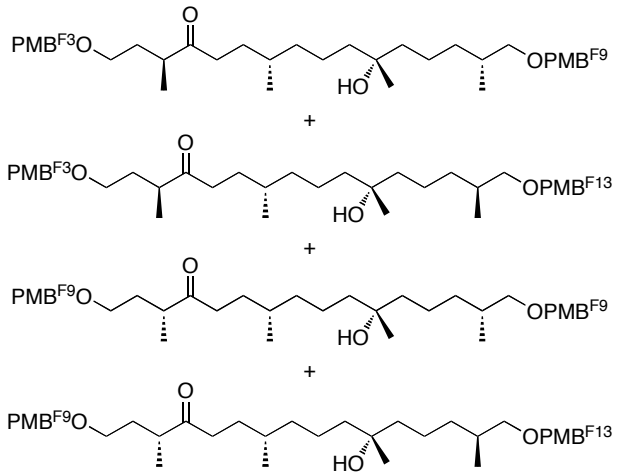
(3*S*,7*S*,11*R*,15*R*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzyloxy)-3,7,11,15-tetramethylhexadecane-4,11-diol, (3*S*,7*S*,11*R*,15*S*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzyloxy)-3,7,11,15-tetramethylhexadecane-4,11-diol, (3*R*,7*S*,11*R*,15*R*)-1,16-Bis(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzyloxy)-3,7,11,15-tetramethylhexadecane-4,11-diol, and (3*R*,7*S*,11*R*,15*S*)-1-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzyloxy)-3,7,11,15-tetramethylhexadecane-4,11-diol ((7*S*,11*R*)-M126):[13,55a] $CuSO_4$•$5H_2O$ (3.32 g, 13.31 mmol) was added to solution of the starting diene **(7*S*,11*R*)-M125** (0.35 g, 0.34 mmol) in THF/EtOH (1:1, 9.2 mL) followed by careful dropwise addition (exothermic reaction) of anhydrous hydrazine (4.2 mL, 135.0 mmol). The resulting mixture was stirred at room temperature for 15 min and at 65 °C for 24 h. The reaction mixture was cooled to room temperature, filtered over celite, water and Et_2O were added, and the layers were separated. The aqueous layer was extracted with ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. If the reaction was found to be incomplete by crude ^{1}H NMR spectroscopy, it was restarted under similar conditions and allowed to stir at 65 °C for 24 h. Purification by flash column chromatography (SiO_2, 40%

EtOAc in hexanes) gave the desired product **(7*S*,11*R*)-M126** (0.31 g, 89%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.25 (m, 4H), 6.90–6.85 (m, 4H), 4.45 (s, 2H), 4.44 (s, 2H), 4.04 (t, *J* = 6.0 Hz, 4H), 3.61–3.42 (m, 2H), 3.45–3.30 (m, 1H), 3.30 (dd, *J* = 6.3, 9.0 Hz, 1H), 3.23 (dd, *J* = 6.6, 9.0 Hz, 1H), 2.41–2.20 (m, 4H), 2.20–2.00 (m, 4H), 1.84–1.48 (m, 6H), 1.48–1.20 (m, 14H), 1.20–1.02 (m, 3H), 1.15 (s, 3H), 0.94–0.86 (m, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (m, 3F), −80.8 (m, 3F), −81.0 (m, 6F), −114.4 (m, 2F), −114.7 (m, 4F), −121.9 (m, 2F), −122.9 (m, 2F), −123.5 (m, 2F), −124.4 (m, 4F), −126.1 (m, 6F); EIMS **(3*S*,7*S*,11*R*,15*R*)-126ca** *m/z* 951 $(M + Na)^+$; **(3*S*,7*S*,11*R*,15*S*)-126cb** *m/z* 1051 $(M + Na)^+$; **(3*R*,7*S*,11*R*,15*R*)-126aa** *m/z* 1101 $(M + Na)^+$; **(3*R*,7*S*,11*R*,15*S*)-126ab** *m/z* 1201 $(M + Na)^+$; HRMS (ESI) **(3*S*,7*S*,11*R*,15*R*)-126ca** $(M + Na)^+$ calcd for $C_{45}H_{64}O_6F_{12}Na$ 951.4409, found 951.4335; **(3*S*,7*S*,11*R*,15*S*)-126cb** $(M + Na)^+$ calcd for $C_{47}H_{64}O_6F_{16}Na$ 1051.4345, found 1051.4413; **(3*R*,7*S*,11*R*,15*R*)-126aa** $(M + Na)^+$ calcd for $C_{48}H_{64}O_6F_{18}Na$ 1101.4313, found 1101.4382; **(3*R*,7*S*,11*R*,15*S*)-126ab** $(M + Na)^+$ calcd for $C_{50}H_{64}O_6F_{22}Na$ 1201.4249, found 1201.4335; analytical fluorous HPLC (conditions 2) t_R = 9.5 min (**(3*S*,7*S*,11*R*,15*R*)-126ca**), 17.0 min (**(3*S*,7*S*,11*R*,15*S*)-126cb**), 19.9 min (**(3*R*,7*S*,11*R*,15*R*)-126aa**), 28.0 min (**(3*R*,7*S*,11*R*,15*S*)-126ab**).



(3*S*,7*R*,11*R*,15*R*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzyloxy)-3,7,11,15-tetramethylhexadecane-4,11-diol, (3*S*,7*R*,11*R*,15*S*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzyloxy)-3,7,11,15-tetramethylhexadecane-4,11-diol, (3*R*,7*R*,11*R*,15*R*)-1,16-Bis(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzyloxy)-3,7,11,15-tetramethylhexadecane-4,11-diol, and (3*R*,7*R*,11*R*,15*S*)-1-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzyloxy)-3,7,11,15-tetramethylhexadecane-4,11-diol ((7*R*,11*R*)-M126):[13,55a] This compound was prepared in 40% yield starting from diol **(7*R*,11*R*)-M125** (150.0 mg, 0.14 mmol) according to the procedure described above for preparation of compound **(7*S*,11*R*)-M126**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.25 (m, 4H), 6.90–6.85 (m, 4H), 4.45 (s, 2H), 4.44 (s, 2H), 4.04 (t, *J* = 6.0 Hz, 4H), 3.61–3.42 (m, 2H), 3.45–3.35 (m, 1H), 3.32 (dd, *J* = 6.3, 9.0 Hz, 1H), 3.22 (dd, *J* = 6.6, 9.0 Hz, 1H), 2.44–2.20 (m, 4H), 2.20–2.00 (m, 4H), 1.84–1.48 (m, 6H), 1.48–1.20 (m, 14H), 1.20–1.02 (m, 3H), 1.15 (s, 3H), 0.94–0.86 (m, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (m, 3F), −80.8 (m, 3F), −81.0 (m, 6F), −114.4 (m, 2F), −114.7 (m, 4F), −121.9 (m, 2F), −122.9 (m, 2F), −123.5 (m, 2F), −124.4 (m, 4F), −126.1 (m, 6F); EIMS **(3*S*,7*R*,11*R*,15*R*)-126ca** *m/z* 951 $(M + Na)^+$; **(3*S*,7*R*,11*R*,15*S*)-126cb** *m/z* 1051 $(M + Na)^+$; **(3*R*,7*R*,11*R*,15*R*)-126aa** *m/z* 1101 $(M + Na)^+$; **(3*R*,7*R*,11*R*,15*S*)-126ab** *m/z* 1201 $(M + Na)^+$; HRMS (ESI) **(3*S*,7*R*,11*R*,15*R*)-126ca** $(M + Na)^+$ calcd for $C_{45}H_{64}O_6F_{12}Na$ 951.4409, found 951.4334; **(3*S*,7*R*,11*R*,15*S*)-126cb** $(M + Na)^+$ calcd for $C_{47}H_{64}O_6F_{16}Na$ 1051.4345, found 1051.4338; **(3*R*,7*R*,11*R*,15*R*)-126aa** $(M + Na)^+$ calcd for $C_{48}H_{64}O_6F_{18}Na$ 1101.4313, found 1101.4351; **(3*R*,7*R*,11*R*,15*S*)-126ab** $(M + Na)^+$ calcd for $C_{50}H_{64}O_6F_{22}Na$ 1201.4249, found 1201.4144; analytical fluorous HPLC (conditions 2) t_R = 9.6 min (**(3*S*,7*R*,11*R*,15*R*)-126ca**), 16.8

min (**(3*S*,7*R*,11*R*,15*S*)-126cb**), 19.8 min (**(3*R*,7*R*,11*R*,15*R*)-126aa**), 27.9 min (**(3*R*,7*R*,11*R*,15*S*)-126ab**).

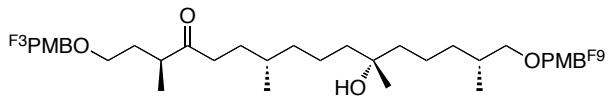


(3*S*,7*S*,11*R*,15*R*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one, (3*S*,7*S*,11*R*,15*S*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one, (3*R*,7*S*,11*R*,15*R*)-1,16-Bis(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one, and (3*R*,7*S*,11*R*,15*S*)-1-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one ((7*S*,11*R*)-M127): $NaHCO_3$ (87.2 mg, 1.04 mmol) and DMP (193.4 mg, 0.44 mmol) were added to a solution of the starting diol **(7*S*,11*R*)-M126** (202.0 mg, 0.19 mmol) in DCM (3 mL). The resulting solution was stirred at 0 °C for 2 h and at room temperature for 1 h. The reaction was quenched by the addition of saturated $Na_2S_2O_3$ solution and the mixture was stirred until the organic layer became clear. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification by flash column chromatography

(SiO_2, 30% EtOAc in hexanes) gave the ketone **(7*S*,11*R*)-M127** (185.0 mg, 92%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.23 (m, 4H), 6.89–6.85 (m, 4H), 4.44 (s, 2H), 4.39 (s, 2H), 4.03 (t, *J* = 6.0 Hz, 4H), 3.48–3.36 (m, 2H), 3.30 (dd, *J* = 6.3, 9.0 Hz, 1H), 3.23 (dd, *J* = 6.6, 8.9 Hz, 1H), 2.75 (sxt, *J* = 7.0 Hz, 1H), 2.55–2.23 (m, 6H), 2.14–1.95 (m, 5H), 1.82–1.71 (m, 1H), 1.65–1.54 (m, 2H), 1.46–1.24 (m, 12H), 1.20–1.15 (m, 1H), 1.15 (s, 3H), 1.15–1.09 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 5.9 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.4 (t, *J* = 11.0 Hz, 3F), −80.8 (m, 3F), −81.1 (m, 6F), −114.4 (m, 2F), −114.7 (m, 4F), −122.0 (m, 2F), −122.9 (m, 2F), −123.5 (m, 2F), −124.4 (m, 4F), −126.1 (m, 6F).

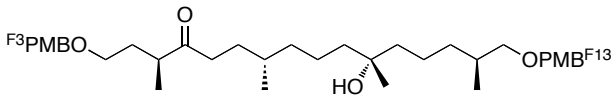
Demixing of mixture (7*S*,11*R*)-M127.

The mixture **(7*S*,11*R*)-M127** (200.0 mg, 0.19 mmol) was dissolved in THF (2.5 mL) and demixed by semi-preparative fluorous HPLC (FluoroFlashTM PFC8 column, CH_3CN:H_2O = 80:20 to 100:0 in 30 min, then 100:0 for further 50 min). The following four compounds were obtained:



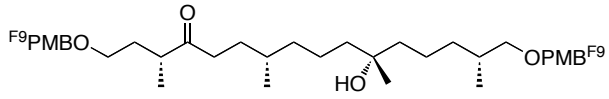
(3*S*,7*S*,11*R*,15*R*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,7-nonafluoro-heptyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one ((3*S*,7*S*,11*R*,15*R*)-127ca): 35.0 mg, t_R = 30.8 min: ^{1}H NMR (500 Hz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.44 (dd, *J* = 11.5, 13.5 Hz, 2H), 4.39 (s, 2H), 4.04 (t, *J* = 6.0 Hz, 2H), 4.01 (t, *J* = 6.0 Hz, 2H), 3.47–3.39 (m, 2H), 3.32 (dd, *J* = 6.5, 9.0 Hz, 1H), 3.23 (dd, *J* = 7.0, 9.0 Hz, 1H), 2.74 (sxt, *J* = 7.0 Hz, 1H), 2.44 (t, *J* = 7.5 Hz, 2H), 2.37–2.27 (m, 4H), 2.13–1.96 (m, 5H), 1.81–1.72 (m, 1H), 1.62–1.56 (m, 2H), 1.50–1.24 (m, 12H), 1.20–1.15 (m, 1H), 1.15 (s, 3H), 1.15–1.09 (m, 1H), 1.08 (d, *J* = 7.0 Hz, 3H),

0.93 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 158.2, 158.0, 131.3, 130.9, 129.3, 129.2, 114.3, 114.3, 75.8, 72.7, 72.6, 72.5, 67.7, 66.3, 66.0, 43.1, 42.2, 39.1, 37.4, 34.2, 33.5, 32.8, 32.4, 30.7 (q, $^2J_{CF}$ = 27.1 Hz), 30.6, 27.7 (t, $^2J_{CF}$ = 22.5 Hz), 26.8, 22.2 (m), 21.2, 20.6 (m), 19.4, 17.1, 16.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (t, J = 11.3 Hz, 3F), −81.0 (m, 3F), −114.6 (m, 2F), −124.4 (m, 2F), −126.1 (m, 2F); IR (neat) 2933, 1711, 1613, 1513, 1242, 1135 cm^{-1}; EIMS *m/z* 949 $(M + Na)^+$; HRMS (ESI) $(M + Na)^+$ calcd for $C_{45}H_{62}O_6F_{12}Na$ 949.4252, found 949.4304; $[\alpha]_D^{25}$ +5.19 (*c* 2.8, $CHCl_3$).

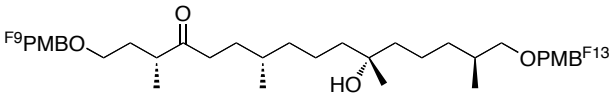


(3*S*,7*S*,11*R*,15*S*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tri-decafluorononyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one ((3*S*,7*S*, 11*R*,15*S*)-127cb): 39.7 mg, t_R = 40.7 min: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 4.44 (dd, J = 12.0, 13.5 Hz, 2H), 4.39 (s, 2H), 4.04 (t, J = 6.0 Hz, 2H), 4.01 (t, J = 6 Hz, 2H), 3.47–3.38 (m, 2H), 3.30 (dd, J = 6.0, 9.0 Hz, 1H), 3.23 (dd, J = 7.0, 9.0 Hz, 1H), 2.75 (sxt, J = 7.0 Hz, 1H), 2.44 (t, J = 7.5 Hz, 2H), 2.40–2.27 (m, 4H), 2.16–1.97 (m, 5H), 1.83–1.74 (m, 1H), 1.62–1.56 (m, 2H), 1.46–1.27 (m, 12H), 1.20–1.15 (m, 1H), 1.15 (s, 3H), 1.15–1.10 (m, 1H), 1.07 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 214.8, 158.1, 158.0, 131.3, 130.8, 129.3, 129.2, 114.3, 114.3, 75.7, 72.7, 72.6, 72.5, 67.7, 66.3, 66.0, 43.1, 42.2, 42.1, 39.1, 37.4, 34.2, 33.4, 32.8, 32.4, 30.7 (q, $^2J_{CF}$ = 28.8 Hz), 30.5, 27.9 (q, $^2J_{CF}$ = 21.3 Hz), 26.8, 22.2 (m), 21.2, 21.2, 20.6 (m), 19.4, 17.1, 16.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.4 (t, J = 11.3 Hz, 3F), −80.8 (m, 3F), −114.3 (m, 2F), −121.9 (m, 2F), −122.8 (m,

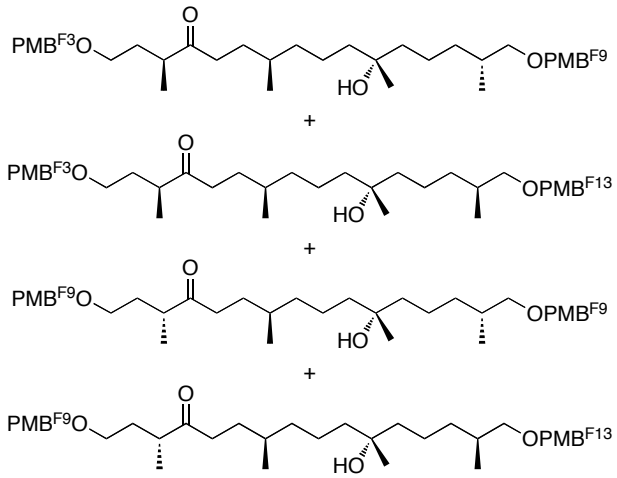
2F), −123.4 (m, 2F), −126.1 (m, 2F); IR (neat) 2933, 1711, 1613, 1513, 1242, 1135 cm^{-1}; EIMS *m/z* 1049 $(M + Na)^+$; HRMS (ESI) $(M + Na)^+$ calcd $C_{47}H_{62}O_6F_{16}Na$, 1049.4189; found 1049.4155; $[\alpha]_D^{25}$ +3.27 (*c* 1.4, $CHCl_3$).



(3*R*,7*S*,11*R*,15*R*)-1,16-Bis(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one ((3*R*,7*S*,11*R*,15*R*)-127aa). 42.1 mg, t_R = 44.3 min: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.43 (dd, *J* = 12.6, 15.0 Hz, 2H), 4.39 (dd, *J* = 12.0, 13.8 Hz, 2H), 4.04 (t, *J* = 6.0 Hz, 2H), 4.04 (t, *J* = 6.0 Hz, 2H), 3.47–3.39 (m, 2H), 3.30 (dd, *J* = 6.0, 9.0 Hz, 1H), 3.23 (dd, *J* = 6.6, 9.0 Hz, 1H), 2.75 (sxt, *J* = 7.2 Hz, 1H), 2.51–2.45 (m, 1H), 2.42–2.37 (m, 1H), 2.37–2.27 (m, 4H), 2.13–2.08 (m, 4H), 2.00 (sxt, *J* = 7.2 Hz, 1H), 1.80–1.73 (m, 1H), 1.63–1.55 (m, 2H), 1.46–1.25 (m, 12H), 1.25–1.18 (m, 1H), 1.14 (s, 3H), 1.15–1.10 (m, 1H), 1.07 (d, *J* = 7.2 Hz, 3H), 0.93(d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 214.8, 158.1, 131.3, 130.9, 129.3, 129.2, 114.30, 114.25, 75.7, 72.7, 72.6, 72.5, 67.7, 66.3, 43.1, 42.3, 42.2, 39.0, 37.4, 34.2, 33.4, 32.8, 32.4, 30.6, 27.8 (t, $^2J_{CF}$ = 22.5 Hz), 26.8, 21.2, 20.5, 19.4, 17.1, 16.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.1 (m, 6F), −114.5 (m, 4F), −124.4 (m, 4F), −126.0 (m, 4F); IR (neat) 2933, 1711, 1613, 1513, 1242, 1135 cm^{-1}; EIMS *m/z* 1099 (M + Na)+; HRMS (ESI) (M + Na)+ calcd $C_{48}H_{62}O_6F_{18}Na$, 1099.4157; found 1099.4122; $[\alpha]_D^{25}$ −3.83 (*c* 0.36, $CHCl_3$).



(3*R*,7*S*,11*R*,15*S*)-1-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one ((3*R*,7*S*,11*R*,15*S*)-127ab): 45.3 mg, t_R = 61.2 min: ^{1}H NMR (600 Hz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.43 (dd, *J* = 12.0, 15.0 Hz, 2H), 4.39 (dd, *J* = 12.0, 13.8 Hz, 2H), 4.04 (t, *J* = 6.0 Hz, 2H), 4.04 (t, *J* = 6.0 Hz, 2H), 3.47–3.39 (m, 2H), 3.30 (d, *J* = 6.0, 9.0 Hz, 1H), 3.23 (dd, *J* = 6.6, 9.0 Hz, 1H), 2.75 (sxt, *J* = 7.2 Hz, 1H), 2.51–2.45 (m, 1H), 2.44–2.37 (m, 1H), 2.37–2.27 (m, 4H), 2.13–2.07 (m, 4H), 2.03–1.98 (m, 1H), 1.80–1.73 (m, 1H), 1.63–1.55 (m, 2H), 1.44–1.25 (m, 12H), 1.20–1.17 (m, 1H), 1.15 (s, 3H), 1.15–1.10 (m, 1H), 1.08 (d, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 214.8, 158.1, 158.2, 131.3, 130.9, 129.3, 129.1, 114.3, 114.3, 75.7, 72.7, 72.6, 72.5, 67.7, 66.3, 43.1, 42.3, 42.1, 39.0, 37.8, 34.2, 33.4, 32.8, 32.4, 30.6, 27.9 (q, J_{CF} = 22.5 Hz), 26.9, 21.2, 21.2, 20.6 (m), 19.4, 17.1, 16.6; ^{19}F NMR (282 MHz, $CDCl_3$) –80.0 (m, 3F), –81.0 (m, 3F), –114.4 (m, 2H), –114.7 (m, 2F), –121.9 (m, 2F),–122.9 (m, 2F), –123.5 (m, 2F), –124.4 (m, 2F), –126.1 (m, 4F); IR (neat) 2933, 2867, 1710, 1613, 1513, 1239 cm^{-1}; EIMS *m/z* 1199 $(M + Na)^+$; HRMS (ESI) $(M + Na)^+$ calcd for $C_{50}H_{62}O_6F_{22}Na$ 1199.4093, found 1199.4063; $[\alpha]_D^{25}$ +3.35 (*c* 1.2, $CHCl_3$).

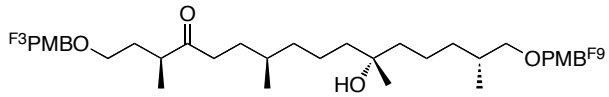


(3*S*,7*R*,11*R*,15*R*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one, (3*S*,7*R*,11*R*,15*S*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one, (3*R*,7*R*,11*R*,15*R*)-1,16-Bis(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one, and (3*R*,7*R*,11*R*,15*S*)-1-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)-benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one ((7*R*,11*R*)-M127): This mixture was prepared in 82% yield starting from alcohol **(7*R*,11*R*)-M126** (80.0 mg, 0.76 mmol) according to the procedure described above for preparation of compound **(7*S*,11*R*)-M127**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.23 (m, 4H), 6.89–6.85 (m, 4H), 4.44 (s, 2H), 4.39 (s, 2H), 4.03 (t, *J* = 6.0 Hz, 4H), 3.48–3.36 (m, 2H), 3.30 (dd, *J* = 6.3, 9.0 Hz, 1H), 3.23 (dd, *J* = 6.6, 8.9 Hz, 1H), 2.75 (sxt, *J* = 7.0 Hz, 1H), 2.55–2.23 (m, 6H), 2.14–1.95 (m, 5H), 1.82–1.71 (m, 1H), 1.65–1.54 (m, 2H), 1.46–1.24 (m, 12H), 1.20–1.15 (m, 1H), 1.15 (s, 3H), 1.15–1.09 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 5.9 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.4 (t, *J* = 11.0 Hz,

3F), −80.8 (m, 3F), −81.1 (m, 6F), −114.4 (m, 2F), −114.7 (m, 4F), −122.0 (m, 2F), −122.9 (m, 2F), −123.5 (m, 2F), −124.4 (m, 4F), −126.1 (m, 6F).

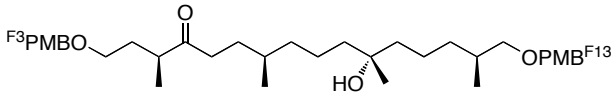
Demixing of mixture (7*R*,11*R*)-M127.

The mixture **(7*R*,11*R*)-M127** (165.2 mg, 0.16 mmol) was dissolved in THF (2.0 mL) and demixed by semi-preparative fluorous HPLC under same conditions as used for demixing of mixture **(7*S*,11*R*)-M127**. The following four compounds were obtained.

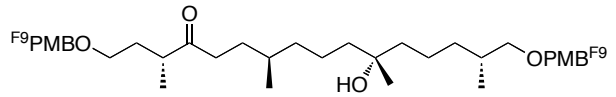


(3*S*,7*R*,11*R*,15*R*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,7-nonafluoro-heptyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one ((3*S*,7*R*,11*R*,15*R*)-127ca): 32.3 mg, t_R = 30.8 min: ^{1}H NMR (500 Hz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.43 (dd, *J* = 11.8, 14.0 Hz, 2H), 4.39 (s, 2H), 4.04 (t, *J* = 5.9 Hz, 2H), 4.01 (t, *J* = 6.0 Hz, 2H), 3.47–3.39 (m, 2H), 3.30 (d, *J* = 6.2, 9.0 Hz, 1H), 3.23 (dd, *J* = 6.7, 9.0 Hz, 1H), 2.75 (sxt, *J* = 7.0 Hz, 1H), 2.52–2.45 (m, 1H), 2.42–2.38 (m, 1H), 2.37–2.27 (m, 4H), 2.13–1.97 (m, 5H), 1.82–1.71 (m, 1H), 1.62–1.55 (m, 2H), 1.47–1.23 (m, 12H), 1.20–1.15 (m, 1H), 1.15 (s, 3H), 1.15–1.10 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 158.1, 158.0, 131.3, 130.8, 129.3, 129.2, 114.29, 114.26, 75.7, 72.7, 72.6, 72.5, 67.7, 66.3, 66.0, 43.1, 42.3, 42.1, 39.0, 37.4, 34.2, 33.4, 32.8, 32.4, 30.7 (q, $^2J_{CF}$ = 28.5 Hz), 30.6, 27.8 (t, $^2J_{CF}$ = 22.5 Hz), 26.8, 22.2 (m), 21.23, 21.21, 20.5 (m), 19.4, 17.1, 16.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (t, *J* = 11.3 Hz, 3F), −81.0 (m, 3F), −114.6 (m, 2F), −124.4 (m, 2F), −126.1 (m,

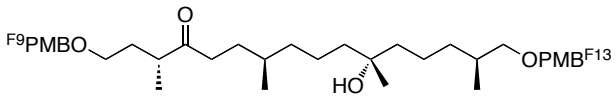
2F); IR (neat) 2934, 1711, 1613, 1513, 1242 cm^{-1}; EIMS *m/z* 949 $(M + Na)^+$; HRMS (ESI) $(M + Na)^+$ calcd $C_{45}H_{62}O_6F_{12}Na$ 949.4252, found 949.4288; $[\alpha]_D^{25}$ +3.66 (*c* 0.92, $CHCl_3$).



(3*S*,7*R*,11*R*,15*S*)-1-(4-(4,4,4-Trifluorobutoxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tri-decafluorononyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one ((3*S*,7*R*,11*R*,15*S*)-127cb): 35.7 mg, t_R = 40.8 min: ^{1}H NMR (500 Hz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 4.43 (dd, *J* = 11.8, 14.0 Hz, 2H), 4.39 (s, 2H), 4.04 (t, *J* = 5.9 Hz, 2H), 4.01 (t, *J* = 6.0 Hz, 2H), 3.47–3.39 (m, 2H), 3.30 (d, *J* = 6.2, 9.0 Hz, 1H), 3.23 (dd, *J* = 6.7, 9.0 Hz, 1H), 2.75 (sxt, *J* = 7.0 Hz, 1H), 2.52–2.45 (m, 1H), 2.42–2.38 (m, 1H), 2.37–2.27 (m, 4H), 2.13–1.97 (m, 5H), 1.82–1.71 (m, 1H), 1.62–1.55 (m, 2H), 1.47–1.23 (m, 12H), 1.20–1.15 (m, 1H), 1.15 (s, 3H), 1.15–1.10 (m, 1H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.8, 158.1, 158.0, 131.3, 130.8, 129.3, 129.1, 114.3, 114.2, 75.8, 72.7, 72.6, 72.5, 67.7, 66.3, 66.0, 43.1, 42.1, 39.0, 37.4, 34.2, 33.4, 32.8, 32.4, 30.7 (q, $^2J_{CF}$ = 28.5 Hz), 30.6, 27.9 (t, $^2J_{CF}$ = 22.5 Hz), 26.9, 22.2 (q, $^3J_{CF}$ = 3.0 Hz), 21.2, 20.6 (t, $^3J_{CF}$ = 3.0 Hz), 19.4, 17.1, 16.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −66.3 (t, *J* = 11.3 Hz, 3F), −80.8 (m, 3F), −114.4 (m, 2F), −121.9 (m, 2F), −122.9 (m, 2F), −123.5 (m, 2F), −126.2 (m, 2F); IR (neat) 2933, 1712, 1614, 1514, 1245 cm^{-1}; EIMS *m/z* 1049 $(M + Na)^+$; HRMS (ESI) $(M + Na)^+$ calcd $C_{47}H_{62}O_6F_{16}Na$ 1049.4189, found 1049.4155; $[\alpha]_D^{25}$ +4.59 (*c* 0.97, $CHCl_3$).



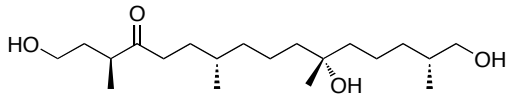
(3*R*,7*R*,11*R*,15*R*)-1,16-Bis(4-(4,4,5,5,6,6,7,7,7-nonafluoroheptyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one ((3*R*,7*R*,11*R*,15*R*)-127aa): 37.4 mg, t_R = 44.4 min: ^{1}H NMR (500 Hz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 4.44 (dd, *J* = 12.0, 13.5 Hz, 2H), 4.39 (s, 2H), 4.04 (t, *J* = 6.0 Hz, 4H), 3.47-3.39 (m, 2H), 3.30 (d, *J* = 6.0, 8.5 Hz, 1H), 3.23 (dd, *J* = 6.5, 9.0 Hz, 1H), 2.75 (sxt, *J* = 7.0 Hz, 1H), 2.44 (t, *J* = 7.5 Hz, 2H), 2.37–2.26 (m, 4H), 2.13–2.08 (m, 4H), 2.01 (sxt, *J* = 7.0 Hz, 1H), 1.82–1.73 (m, 1H), 1.62–1.56 (m, 2H), 1.44–1.22 (m, 12H), 1.20–1.05 (m, 2H), 1.15 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 214.8, 158.1, 158.0, 131.3, 130.9, 129.3, 129.1, 114.3, 114.2, 75.71, 72.69, 72.6, 72.5, 67.7, 66.3, 43.1, 42.2, 42.1, 39.1, 37.4, 34.2, 33.4, 32.8, 32.4, 30.5, 27.8 (t, $^2J_{CF}$ = 22.5 Hz), 26.8, 21.2, 21.2, 25.5 (m), 19.4, 17.1, 16.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −82.1 (m, 6F), −115.6 (m, 4F), −125.4 (m, 4F), −127.1 (m, 4F); IR (neat) 2928, 1711, 1613, 1514, 1242 cm^{-1}; EIMS *m/z* 1099 (M + Na)$^+$; HRMS (ESI) (M + Na)$^+$ calcd $C_{48}H_{62}O_6F_{18}Na$ 1099.4157, found 1099.4167; $[\alpha]_D^{25}$ = −5.98 (*c* 0.8, $CHCl_3$).



(3*R*,7*R*,11*R*,15*S*)-1-(4-(4,4,5,5,6,6,7,7,7-Nonafluoroheptyloxy)benzyloxy)-16-(4-(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyloxy)benzyloxy)-11-hydroxy-3,7,11,15-tetramethylhexadecan-4-one ((3*R*,7*R*,11*R*,15*S*)-127ab): 40.8 mg, t_R = 61.3 min: ^{1}H NMR (500 Hz, $CDCl_3$) δ 7.26 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.43 (dd, *J* = 12.0, 15.0 Hz, 2H), 4.39 (dd, *J* = 12.0, 13.8 Hz, 2H), 4.04 (t, *J* = 6.0 Hz, 2H), 4.04 (t, *J* = 6.0 Hz, 2H), 3.47–3.39 (m, 2H), 3.30 (d, *J* = 6.0, 9.0 Hz, 1H), 3.23 (dd, *J* = 6.6, 9.0 Hz, 1H),

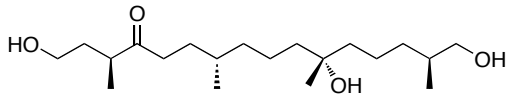
2.75 (sxt, J = 7.2 Hz, 1H), 2.51–2.45 (m, 1H), 2.44–2.37 (m, 1H), 2.37–2.27 (m, 4H), 2.13–2.07 (m, 4H), 2.03–1.98 (m, 1H), 1.80–1.73 (m, 1H), 1.63–1.55 (m, 2H), 1.44–1.25 (m, 12H), 1.20–1.17 (m, 1H), 1.15 (s, 3H), 1.15–1.10 (m, 1H), 1.08 (d, J = 7.2 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 214.8, 158.1, 158.0, 131.3, 130.9, 129.3, 129.1, 114.3, 114.2, 75.7, 72.7, 72.6, 72.5, 67.7, 66.3, 43.1, 42.1, 39.1, 37.4, 34.2, 33.4, 32.8, 32.4, 30.5, 27.9 (t, $^2J_{CF}$ = 22.5 Hz), 27.8 (t, $^2J_{CF}$ = 22.5 Hz), 26.9, 21.2, 20.5 (m), 19.4, 17.1, 16.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −80.8 (m, 3F), −81.1 (m, 3F), −114.4 (m, 2F), 114.5 (m, 2F), −122.0 (m, 2F), −122.9 (m, 2F), −123.5 (m, 2F), −124.4 (m, 2F), −126.2 (m, 4F); IR (neat) 2928, 1711, 1613, 1514, 1242 cm^{-1}; EIMS m/z 1199 $(M + Na)^+$; HRMS (ESI) $(M + Na)^+$ calcd $C_{50}H_{62}O_6F_{22}Na$ 1199.4093, found 1199.4080; $[\alpha]_D^{25}$ −4.68 (c 0.86, $CHCl_3$).

General procedure for hydrogenolysis of PMB^F ether 127: The starting fluorous PMB ether **(3*S*,7*S*,11*R*,15*R*)-127ca** (35.0 mg, 0.04 mmol) was dissolved in ethyl acetate (2.7 mL) and Pd/C (10% w/v, 4.4 mg) was added. The resulting black mixture was stirred under hydrogen from balloon for 48 h. The reaction mixture was filtered through celite and the filtrate was concentrated under vacuum. Purification by flash column chromatography (SiO_2, 70–100% EtOAc in hexanes) gave desired triol **(3*S*,7*S*,11*R*,15*R*)-1** (8.0 mg, 62%) as colorless oil.



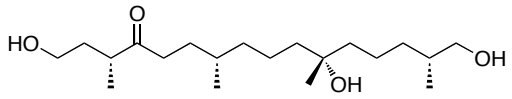
(3*S*,7*S*,11*R*,15*R*)-1,11,16-Trihydroxy-3,7,11,15-tetramethylhexadecan-4-one ((3*S*,7*S*,11*R*,15*R*)-1)). ^{1}H NMR (700 MHz, CD_3OD) δ 3.52 (m, 2H), 3.41 (dd, J = 6.3, 10.5 Hz, 1H), 3.32 (dd, J = 10.5, 7.0 Hz, 1H), 2.76 (sxt, J = 7.0 Hz, 1H), 2.53 (t, J = 7.0 Hz, 2H), 1.89

(sxt, *J* = 7.0 Hz, 1H), 1.62–1.56 (m, 2H), 1.51–1.46 (m, 1H), 1.46–1.28 (m, 12H), 1.15–1.05 (m, 2H), 1.12 (s, 3H), 1.07 (s, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.3 Hz, 3H), 0.89 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (175 MHz, CD_3OD) δ 217.48, 73.37, 68.45, 60.62, 43.97, 43.00, 42.96, 39.97, 38.62, 36.88, 36.71, 35.03, 33.57, 31.74, 26.88, 22.36, 22.29, 19.86, 17.08, 16.90; EIMS *m/z* 367 $(M + Na)^+$; HRMS (ESI) $(M + Na)^+$ calcd for $C_{20}H_{40}O_4Na$, 367.2824; found 367.2802.



(3*S*,7*S*,11*R*,15*S*)-1,11,16-Trihydroxy-3,7,11,15-tetramethylhexadecan-4-one

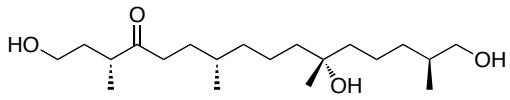
((3*S*,7*S*,11*R*,15*S*)-1)): 9.2 mg, 69%: ^{1}H NMR (700 MHz, CD_3OD) δ 3.52 (m, 2H), 3.41 (dd, *J* = 5.6, 10.6 Hz, 1H), 3.32 (dd, *J* = 6.7, 10.6 Hz, 1H), 2.77 (sxt, *J* = 6.9 Hz, 1H), 2.54 (t, *J* = 7.1 Hz, 2H), 1.89 (sxt, *J* = 6.9 Hz, 1H), 1.62–1.55 (m, 2H), 1.51–1.46 (m, 1H), 1.45–1.28 (m, 12H), 1.15–1.05 (m, 2H), 1.12 (s, 3H), 1.07 (s, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (175 MHz, CD_3OD) δ 217.48, 73.37, 68.42, 60.61, 43.95, 43.00, 42.87, 39.98, 38.62, 36.88, 36.70, 35.02, 33.56, 31.71, 26.93, 22.34, 22.32, 19.87, 17.10, 16.91; EIMS *m/z* 367 $(M + Na)^+$; HRMS (ESI) $(M + Na)^+$ calcd for $C_{20}H_{40}O_4Na$, 367.2824; found 367.2820.



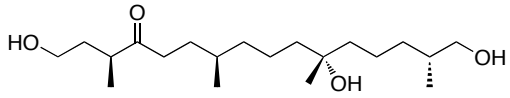
(3*R*,7*S*,11*R*,15*R*)-1,11,16-Trihydroxy-3,7,11,15-tetramethylhexadecan-4-one

((3*R*,7*S*,11*R*,15*R*)-1)): 6.2 mg, 69%: ^{1}H NMR (700 MHz, CD_3OD) δ 3.52 (m, 2H), 3.41 (dd, *J* = 5.9, 10.6 Hz, 1H), 3.32 (dd, *J* = 6.6, 10.6 Hz, 1H), 2.77 (sxt, *J* = 6.8 Hz, 1H), 2.59–2.48 (m, 2H), 1.88 (sxt, *J* = 6.9 Hz, 1H), 1.62–1.55 (m, 2H), 1.51–1.47 (m, 1H), 1.45–1.28 (m, 12H), 1.15–1.05 (m, 2H), 1.12 (s, 3H), 1.07 (s, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H);

^{13}C NMR (150 MHz, CD_3OD) δ 217.50, 73.37, 68.44, 60.61, 43.95, 42.99, 42.94, 39.99, 38.60, 36.88, 36.74, 35.02, 33.58, 31.73, 26.88, 22.36, 22.30, 19.88, 17.08, 16.91; EIMS *m/z* 367 (M + Na)$^+$; HRMS (ESI) (M + Na)$^+$ calcd for $C_{20}H_{40}O_4Na$, 367.2824; found 367.2816.

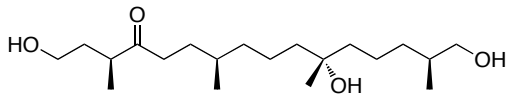


(3*R*,7*S*,11*R*,15*S*)-1,11,16-Trihydroxy-3,7,11,15-tetramethylhexadecan-4-one ((3*R*,7*S*,11*R*,15*S*)-1)). 5.3 mg, 86%: ^{1}H NMR (700 MHz, CH_3OD) δ 3.52 (m, 2H), 3.41 (dd, *J* = 5.6, 10.5 Hz, 1H), 3.32 (dd, *J* = 7.0, 11.2 Hz, 1H), 2.77 (sxt, *J* = 7.0 Hz, 1H), 2.59–2.48 (m, 2H), 1.89 (sxt, *J* = 7.0 Hz, 1H), 1.62–1.55 (m, 2H), 1.50–1.46 (m, 1H), 1.45–1.28 (m, 12H), 1.16–1.05 (m, 2H), 1.12 (s, 3H), 1.07 (s, *J* = 6.3 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 217.50, 73.37, 68.42, 60.61, 43.95, 43.00, 42.88, 39.98, 38.60, 36.87, 36.74, 35.02, 33.57, 31.72, 26.94, 22.33, 22.33, 19.89, 17.01, 16.91; EIMS *m/z* 367 (M + Na)$^+$; HRMS (ESI) (M + Na)$^+$ calcd for $C_{20}H_{40}O_4Na$, 367.2824; found 367.2812.

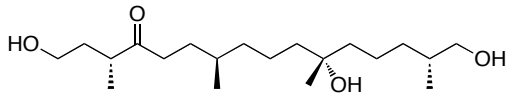


(3*S*,7*R*,11*R*,15*R*)-1,11,16-Trihydroxy-3,7,11,15-tetramethylhexadecan-4-one ((3*S*,7*R*,11*R*,15*R*)-1)). 4.3 mg, 64%: ^{1}H NMR (700 MHz, CD_3OD) δ 3.52 (m, 2H), 3.41 (dd, *J* = 5.9, 10.6 Hz, 1H), 3.32 (dd, *J* = 6.5, 10.8 Hz, 1H), 2.77 (sxt, *J* = 6.9 Hz, 1H), 2.59–2.48 (m, 2H), 1.89 (sxt, *J* = 6.7 Hz, 1H), 1.62–1.56 (m, 2H), 1.50–1.47 (m, 1H), 1.46–1.28 (m, 12H), 1.16–1.05 (m, 2H), 1.12 (s, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (175 MHz, CD_3OD) δ 217.51, 73.38, 68.44, 60.62, 43.96, 42.96, 42.90, 39.98, 38.61,

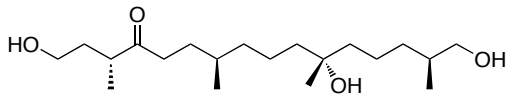
36.88, 36.74, 35.03, 33.59, 31.72, 26.91, 22.37, 22.30, 19.88, 17.09, 16.90; EIMS *m/z* 367 (M + Na)$^+$; HRMS (ESI) (M + Na)$^+$ calcd for $C_{20}H_{40}O_4Na$, 367.2824; found 367.2816.



(3*S*,7*R*,11*R*,15*S*)-1,11,16-Trihydroxy-3,7,11,15-tetramethylhexadecan-4-one ((3*S*,7*R*,11*R*,15*S*)-1)). 6.3 mg, 66%: ^{1}H NMR (700 MHz, CD_3OD) δ 3.52 (m, 2H), 3.41 (dd, *J* = 5.6, 10.5 Hz, 1H), 3.32 (dd, *J* = 7.0, 11.2 Hz, 1H), 2.77 (sxt, *J* = 7.0 Hz, 1H), 2.59–2.48 (m, 2H), 1.89 (sxt, *J* = 7.0 Hz, 1H), 1.62–1.55 (m, 2H), 1.51–1.46 (m, 1H), 1.46–1.28 (m, 12H), 1.16–1.05 (m, 2H), 1.12 (s, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 217.52, 73.38, 68.45, 60.63, 43.97, 42.97, 42.90, 39.99, 38.61, 36.89, 36.75, 35.04, 33.59, 31.74, 26.97, 22.37, 22.33, 19.89, 17.10, 16.91; EIMS *m/z* 367 (M + Na)$^+$; HRMS (ESI) (M + Na)$^+$ calcd for $C_{20}H_{40}O_4Na$, 367.2824; found 367.2796.

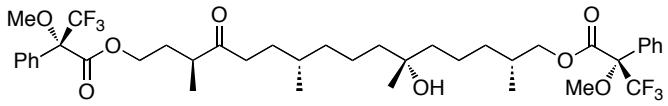


(3*R*,7*R*,11*R*,15*R*)-1,11,16-Trihydroxy-3,7,11,15-tetramethylhexadecan-4-one ((3*R*,7*R*,11*R*,15*R*)-1)): 9.0 mg, 85%; ^{1}H NMR (700 MHz, CD_3OD) δ 3.52 (m, 2H), 3.41 (dd, *J* = 6.0, 10.6 Hz, 1H), 3.32 (dd, *J* = 6.7, 11.0 Hz, 1H), 2.77 (sxt, *J* = 7.0 Hz, 1H), 2.55 (t, *J* = 6.7 Hz, 2H), 1.89 (sxt, *J* = 6.9 Hz, 1H), 1.63–1.55 (m, 2H), 1.51–1.47 (m, 1H), 1.46–1.28 (m, 12H), 1.16–1.05 (m, 2H), 1.12 (s, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 217.47, 73.36, 68.43, 60.61, 43.95, 42.95, 42.95, 39.97, 38.62, 36.88, 36.70, 35.02, 33.57, 31.71, 26.91, 22.36, 22.30, 19.88, 17.09, 16.91; EIMS *m/z* 367 (M + Na)$^+$; HRMS (ESI) (M + Na)$^+$ calcd for $C_{20}H_{40}O_4Na$ 367.2824, found 367.2812.

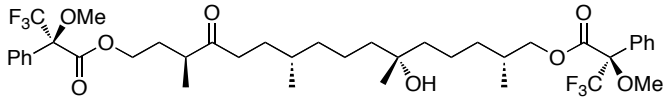


((3*R*,7*R*,11*R*,15*S*)-1)): 4.8 mg, 63%; ^{1}H NMR (700 MHz, CD_3OD) δ 3.53 (m, 2H), 3.41 (dd, *J* = 6.0, 10.5 Hz, 1H), 3.32 (dd, *J* = 7.0, 11.2 Hz, 1H), 2.77 (sxt, *J* = 7.0 Hz, 1H), 2.53 (t, *J* = 6.5 Hz, 2H), 1.89 (sxt, *J* = 7.0 Hz, 1H), 1.62–1.52 (m, 2H), 1.51–1.46 (m, 1H), 1.45–1.28 (m, 12H), 1.16–1.05 (m, 2H), 1.12 (s, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 217.48, 73.37, 68.45, 60.61, 43.97, 43.00, 42.96, 39.97, 38.62, 36.82, 36.71, 35.03, 33.57, 31.74, 26.88, 22.36, 22.30, 19.86, 17.09, 16.90; EIMS *m/z* 367 $(M + Na)^+$; HRMS (ESI) $(M + Na)^+$ calcd for $C_{20}H_{40}O_4Na$ 367.2824, found 367.2802.

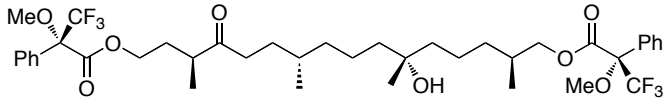
General procedure for synthesis of bis-MTPA esters 10:[32e] The starting triol **(3*S*,7*S*,11*R*, 15*R*)-1** (1.5 mg, 0.04 mmol, 1 equiv) was dissolved in DCM (0.33 mL) and treated with DCC (27 mg, 0.13 mmol) and *S*-MTPA acid (31 mg, 0.13 mmol). The resulting reaction mixture with thick white precipitate was stirred at room temperature for 24 h. The reaction mixture was filtered through a plug of cotton and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography (SiO_2, 30% EtOAc in hexanes) to obtain the bis-*S*-MTPA ester **(*S*,3*S*,7*S*,11*R*,15*R*,*S*)-10** contaminated with 19% of the corresponding C3 epimer. This mixture of epimers was subjected to HPLC purification with a chiral (*S*,*S*) whelk column (25 cm X 10.0 mm ID) to obtain the major isomer as a colorless oil. The column was eluted under isocratic condition with 97:3 hexanes/2-propanol for 70 min. The flow rate was maintained at 3 mL/min.



(*S*,3*S*,7*S*,11*R*,15*R*,*S*)-10: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.44–7.39 (m, 6H), 4.38 (td, *J* = 6.3, 10.5 Hz, 1H), 4.25 (ddd, *J* = 5.6, 7.0 Hz, 1H), 4.19 (dd, *J* = 6.3, 10.5 Hz, 1H), 4.16 (dd, *J* = 6.3, 11.2 Hz, 1H), 3.56 (s, 3H), 3.55 (s, 3H), 2.56 (sxt, *J* = 7.0 Hz, 1H), 2.42 (ddd, *J* = 5.6, 9.1, 16.8 Hz, 1H), 2.33 (ddd, *J* = 4.9, 9.1, 16.8 Hz, 1H), 2.12–2.06 (m, 1H), 1.90–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.14 (s, 3H), 1.09 (d, *J* = 7.7 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.54.

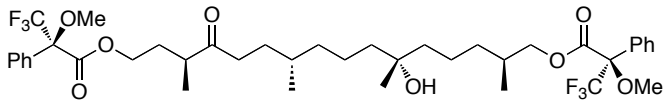


(*R*,3*S*,7*S*,11*R*,15*R*,*R*)-10: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.43–7.40 (m, 6H), 4.31 (t, *J* = 7.0 Hz, 2H), 4.26 (dd, *J* = 5.6, 11.2 Hz, 1H), 4.09 (dd, *J* = 7.0, 10.5 Hz, 1H), 3.56 (s, 3H), 3.54 (s, 3H), 2.60 (sxt, *J* = 7.0 Hz, 1H), 2.43 (ddd, *J* = 6.3, 9.8, 16.8 Hz, 1H), 2.35 (ddd, *J* = 5.6, 9.8, 16.8 Hz, 1H), 2.12–2.07 (m, 1H), 1.90–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.15 (s, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.46, −72.54.

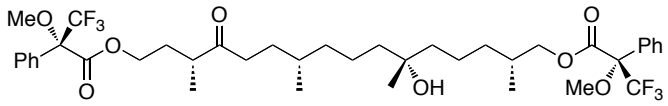


(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.43–7.40 (m, 6H), 4.38 (td, *J* = 6.3, 11.2 Hz, 1H), 4.26 (dd, *J* = 5.6, 10.5 Hz, 1H), 4.25 (ddd, *J* = 6.3, 7.0, 11.2 Hz, 1H), 4.09 (dd, *J* = 6.3, 10.5 Hz, 1H), 3.56 (s, 3H), 3.55 (s, 3H), 2.56 (sxt, *J* = 7.0 Hz, 1H), 2.42

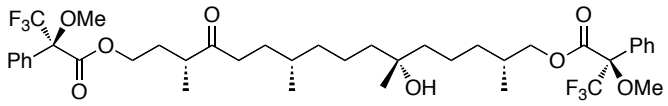
(ddd, J = 6.3, 9.5, 16.5 Hz, 1H), 2.34 (ddd, J = 5.6, 9.5, 16.5 Hz, 1H), 2.11–2.07 (m, 1H), 1.90–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.15 (s, 3H), 1.09 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 6.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.53.



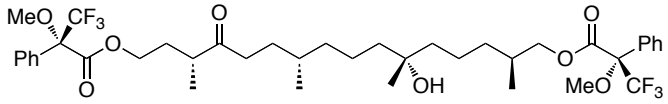
(*R*,3*S*,7*S*,11*R*,15*S*,*R*)-10: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.43–7.40 (m, 6H), 4.31 (t, J = 5.6 Hz, 2H), 4.18 (dd, J = 6.3, 10.5 Hz, 1H), 4.16 (dd, J = 5.6, 10.5 Hz, 1H), 3.56 (s, 3H), 3.54 (s, 3H), 2.60 (sxt, J = 7.0 Hz, 1H), 2.43 (ddd, J = 5.6, 9.1, 16.8 Hz, 1H), 2.35 (ddd, J = 4.9, 9.1, 16.8 Hz, 1H), 2.11–2.07 (m, 1H), 1.90–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.15 (s, 3H), 1.10 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.46, −72.54.



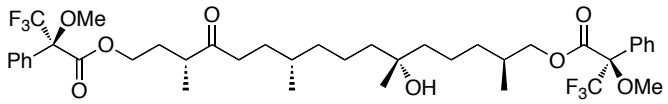
(*S*,3*R*,7*S*,11*R*,15*R*,*S*)-10: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.43–7.40 (m, 6H), 4.31 (t, J = 5.6 Hz, 2H), 4.19 (dd, J = 7.0, 11.2 Hz, 1H), 4.16 (dd, J = 5.6, 10.5 Hz, 1H), 3.56 (s, 3H), 3.54 (s, 3H), 2.60 (sxt, J = 7.0 Hz, 1H), 2.47 (ddd, J = 5.6, 9.8, 15.4 Hz, 1H), 2.31 (ddd, J = 5.6, 9.8, 15.4 Hz, 1H), 2.11–2.07 (m, 1H), 1.90–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.15 (s, 3H), 1.10 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.3 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.47, −72.54.



(*R*,3*R*,7*S*,11*R*,15*R*,*R*)-10: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.43–7.40 (m, 6H), 4.38 (td, *J* = 6.3, 11.2 Hz, 1H), 4.26 (dd, *J* = 5.6, 10.5 Hz, 1H), 4.25 (ddd, *J* = 6.3, 7.0, 11.2 Hz, 1H), 4.09 (dd, *J* = 6.3, 10.5 Hz, 1H), 3.56 (s, 3H), 3.55 (s, 3H), 2.57 (sxt, *J* = 7.0 Hz, 1H), 2.45 (ddd, *J* = 5.6, 9.8, 15.4 Hz, 1H), 2.29 (ddd, *J* = 6.3, 9.8, 15.4 Hz, 1H), 2.11–2.07 (m, 1H), 1.90–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.15 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.53.

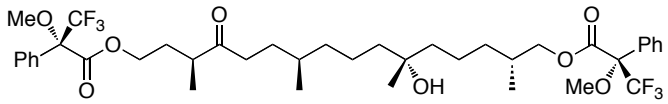


(*S*,3*R*,7*S*,11*R*,15*S*,*S*)-10: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.43–7.40 (m, 6H), 4.39 (td, *J* = 6.3, 11.2 Hz, 1H), 4.25 (ddd, *J* = 6.3, 7.0, 11.2 Hz, 1H), 4.18 (dd, *J* = 6.3, 10.5 Hz, 1H), 4.16 (dd, *J* = 6.3, 10.5 Hz, 1H), 3.56 (s, 3H), 3.55 (s, 3H), 2.56 (sxt, *J* = 7.0 Hz, 1H), 2.45 (ddd, *J* = 5.6, 9.8, 16.8 Hz, 1H), 2.30 (ddd, *J* = 5.6, 9.1, 16.1 Hz, 1H), 2.11–2.06 (m, 1H), 1.91–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.15 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H);^{19}F NMR (282 MHz, $CDCl_3$) δ −72.47, −72.52.

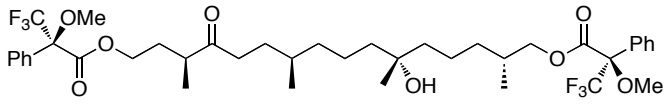


(*R*,3*R*,7*S*,11*R*,15*S*,*R*)-10: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.43–7.40 (m, 6H), 4.39 (td, *J* = 6.3, 11.2 Hz, 1H), 4.25 (ddd, *J* = 6.3, 7.0, 11.2 Hz, 1H), 4.18 (dd, *J* = 6.3, 10.5 Hz,

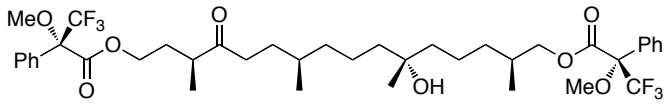
1H), 4.16 (dd, *J* = 6.3, 10.5 Hz, 1H), 3.56 (s, 3H), 3.55 (s, 3H), 2.56 (sxt, *J* = 7.0 Hz, 1H), 2.45 (ddd, *J* = 5.6, 9.8, 16.8 Hz, 1H), 2.30 (ddd, *J* = 5.6, 9.1, 16.1 Hz, 1H), 2.11–2.06 (m, 1H), 1.91–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.15 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.54.



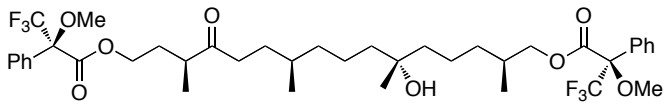
(*S*,3*S*,7*R*,11*R*,15*R*,*S*)-10: ^{1}H NMR major isomer (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.43–7.40 (m, 6H), 4.39 (td, *J* = 6.3, 11.2 Hz, 1H), 4.25 (ddd, *J* = 6.3, 7.0, 11.2 Hz, 1H), 4.19 (dd, *J* = 6.3, 11.2 Hz, 1H), 4.16 (dd, *J* = 6.3, 11.2 Hz, 1H), 3.56 (s, 3H), 3.55 (s, 3H), 2.56 (sxt, *J* = 7.0 Hz, 1H), 2.45 (ddd, *J* = 5.6, 9.8, 16.8 Hz, 1H), 2.30 (ddd, *J* = 5.6, 9.1, 16.1 Hz, 1H), 2.11–2.06 (m, 1H), 1.91–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.15 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.54.



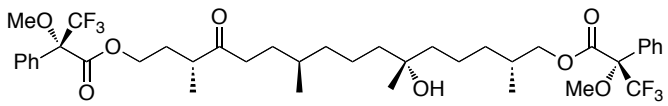
(*R*,3*S*,7*R*,11*R*,15*R*,*R*)-10: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.43–7.40 (m, 6H), 4.31 (t, *J* = 7.0, 2H), 4.26 (dd, *J* = 5.6, 10.5 Hz, 1H), 4.09 (dd, *J* = 7.0, 11.2 Hz, 1H), 3.56 (s, 3H), 3.54 (s, 3H), 2.60 (sxt, *J* = 7.0 Hz, 1H), 2.47 (ddd, *J* = 4.9, 9.8, 16.8 Hz, 1H), 2.31 (ddd, *J* = 5.6, 9.8, 16.8 Hz, 1H), 2.12–2.07 (m, 1H), 1.91–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.15 (s, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.46, −72.52.



(*S*,3*S*,7*R*,11*R*,15*S*,*S*)-10: ^{1}H NMR major isomer (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.43–7.40 (m, 6H), 4.39 (td, *J* = 6.3, 11.2 Hz, 1H), 4.26 (dd, *J* = 5.6, 10.5 Hz, 1H), 4.25 (ddd, *J* = 6.3, 7.0, 11.2 Hz, 1H), 4.09 (dd, *J* = 6.3, 10.5 Hz, 1H), 3.56 (s, 3H), 3.55 (s, 3H), 2.56 (sxt, *J* = 7.0 Hz, 1H), 2.45 (ddd, *J* = 5.6, 9.8, 16.8 Hz, 1H), 2.29 (ddd, *J* = 5.6, 9.8, 16.8 Hz, 1H), 2.11–2.07 (m, 1H), 1.90–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.15 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.53.

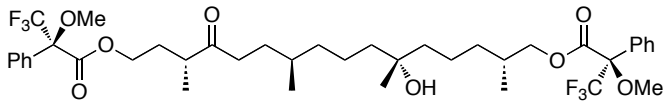


(*R*,3*S*,7*R*,11*R*,15*S*,*R*)-10: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.43–7.40 (m, 6H), 4.31 (t, *J* = 6.3 Hz, 2H), 4.19 (dd, *J* = 6.3, 11.2 Hz, 1H), 4.16 (dd, *J* = 5.6, 11.2 Hz, 1H), 3.56 (s, 3H), 3.54 (s, 3H), 2.60 (sxt, *J* = 7.0 Hz, 1H), 2.47 (ddd, *J* = 5.6, 9.8, 16.8 Hz, 1H), 2.31 (ddd, *J* = 5.6, 9.8, 16.8 Hz, 1H), 2.11–2.07 (m, 1H), 1.90–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.15 (s, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.47, −72.54.

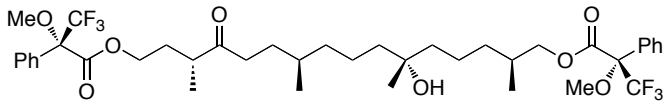


(*S*,3*R*,7*R*,11*R*,15*R*,*S*)-10: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.43–7.40 (m, 6H), 4.31 (t, *J* = 6.3 Hz, 2H), 4.18 (dd, *J* = 7.0, 11.2 Hz, 1H), 4.16 (dd, *J* = 5.6, 10.5 Hz, 1H), 3.56 (s,

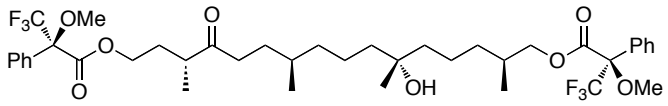
3H), 3.54 (s, 3H), 2.60 (sxt, *J* = 7.0 Hz, 1H), 2.43 (ddd, *J* = 6.3, 9.8, 16.8 Hz, 1H), 2.35 (ddd, *J* = 5.6, 9.8, 16.8 Hz, 1H), 2.11–2.07 (m, 1H), 1.90–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.15 (s, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.46, −72.54.



(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.43–7.40 (m, 6H), 4.38 (td, *J* = 6.3, 11.2 Hz, 1H), 4.26 (dd, *J* = 5.6, 10.5 Hz, 1H), 4.25 (ddd, *J* = 6.3, 7.0, 11.2 Hz, 1H), 4.09 (dd, *J* = 6.3, 10.5 Hz, 1H), 3.56 (s, 3H), 3.55 (s, 3H), 2.56 (sxt, *J* = 7.0 Hz, 1H), 2.42 (ddd, *J* = 5.6, 9.1, 16.8 Hz, 1H), 2.34 (ddd, *J* = 5.6, 9.8, 16.8 Hz, 1H), 2.11–2.07 (m, 1H), 1.90–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.15 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.53.



(*S*,3*R*,7*R*,11*R*,15*S*,*S*)-10: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.43–7.40 (m, 6H), 4.31 (t, *J* = 6.3 Hz, 2H), 4.26 (dd, *J* = 5.6, 11.2 Hz, 1H), 4.09 (dd, *J* = 7.0, 10.5 Hz, 1H), 3.56 (s, 3H), 3.54 (s, 3H), 2.60 (sxt, *J* = 7.0 Hz, 1H), 2.43 (ddd, *J* = 6.3, 9.8, 16.8 Hz, 1H), 2.35 (ddd, *J* = 5.6, 9.8, 16.8 Hz, 1H), 2.12–2.07 (m, 1H), 1.90–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.15 (s, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.46, −72.54.



(*R*,3*R*,7*R*,11*R*,15*S*,*R*)-10: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53–7.51 (m, 4H), 7.44–7.39 (m, 6H), 4.38 (td, *J* = 6.3, 11.2 Hz, 1H), 4.25 (ddd, *J* = 5.6, 7.0, 11.2 Hz, 1H), 4.18 (dd, *J* = 6.3, 10.5 Hz, 1H), 4.16 (dd, *J* = 5.6, 10.5 Hz, 1H), 3.56 (s, 3H), 3.55 (s, 3H), 2.56 (sxt, *J* = 7.0 Hz, 1H), 2.42 (ddd, *J* = 6.3, 9.8, 16.8 Hz, 1H), 2.33 (ddd, *J* = 4.9, 9.8, 16.8 Hz, 1H), 2.12–2.06 (m, 1H), 1.90–1.86 (m, 1H), 1.70–1.65 (m, 1H), 1.61–1.54 (m, 1H), 1.42–1.22 (m, 13H), 1.18–1.10 (m, 2H), 1.14 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.54.

1.7 BIBLIOGRAPHY

1. (a) Paterson, I.; Anderson, E. A. *Science* **2005,** *310*, 451. (b) Butler, M. S. *Nat. Prod. Rep.* **2005,** *22*, 162. (c) Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003,** *66*, 1022.

2. (a) Nicolaou, K. C.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2005,** *44*, 1012. (b) Nadja, B. W.; Kuehn, T.; Moskau, D.; Zerbe, O. *Chem. BiodiVersity* **2005,** *2*, 147. (c) Wipf, P.; Kerekes, A. D. *J. Nat. Prod.* **2003,** *66*, 716.

3. Curran, D. P.; Zhang, Q. S.; Lu, H. J.; Gudipati, V. *J. Am. Chem. Soc.* **2006,** *128*, 9943.

4. Jung, W.-H.; Guyenne, S.; Riesco-Fagundo, C.; Mancuso, J.; Nakamura, S.; Curran, D. P. *Angew. Chem. Int. Ed.* **2008,** *47*, 1130.

5. Sui, B.; Curran, D. P. *J. Am. Chem. Soc.* **2009,** *131*, 5411.

6. (a) Wakabayashi, T.; Mori, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2001,** *123*, 1372. (b) Nakamura, M.; Mori, Y.; Okuyama, K.; Tanikawa, K.; Yasuda, S.; Hanada, K.; Kabayashi, S. *Org. Biomol. Chem.* **2003,** *1*, 3362.

7. Garcia, A. B.; Leβmann, T.; Umarye, J. D.; Mamane, V.; Sommer, S.; Waldman, H. *Chem. Commun.* **2006**, 38668.

8. Takahashi, T.; Kusaka, S.-i.; Doi, T.; Sunazuka, T.; Ō mura, S. *Angew. Chem. Int. Ed.* **2003,** *42*, 5230.

9. (a) Gladysz, J. A.; Curran, D. P.; Horvath, I. T., The Handbook of Fluorous Chemistry, Wiley-VCH, Weinheim, **2004,** pp. 101-156. (b) Luo, Z.; Zhang, Q.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001,** *291*, 1766.

10. (a) Curran, D. P. *Synlett* **2001**, 1488. (b) Curran, D. P.; Oderaotoshi, Y. *Tetrahedron* **2001,** *57*, 5243.

11. Zhang, Q.; Curran, D. P. *Chem. Eur. J.* **2005,** *11*, 4866.

12. Zhang, Q. S.; Rivkin, A.; Curran, D. P. *J. Am. Chem. Soc.* **2002,** *124*, 5774.

13. Dandapani, S.; Jeske, M.; Curran, D. P. *Proc. Nat. Acad. Sci.* **2004,** *101*, 12008.

14. Curran, D. P.; Moura-Letts, G.; Pohlman, M. *Angew. Chem. Int. Ed.* **2006,** *45*, 2423.

15. (a) Zhang, Q. L., H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.* **2004,** *126*, 36. (b) Wilcox, C. S.; Gudipati, V.; Lu, H.; Turkyilmaz, S.; Curran, D. P. *Angew. Chem. Int. Ed.* **2005,** *44*, 6938.

16. Yang, F. L.; Newsome, J. J.; Curran, D. P. *J. Am. Chem. Soc.* **2006,** *128*, 14200.

17. Zhang, W.; Luo, Z.; Chen, C. H.-T.; Curran, D. P. *J. Am. Chem. Soc.* **2002,** *124*, 10443.

18. Qi, J.; Asano, T.; Jinno, M.; Matsui, K.; Atsumi, K.; Sakagami, Y.; Ojika, M. *Science* **2005,** *309*, 1828.

19. Ko, W. H. *Ann. Rev. Phytopathol.* **1988,** *26*, 57.

20. (a) Fry, W. E.; Goodwin, S. B. *Bioscience* **1997,** *47*, 363. (b) Savage, E. J. *Phytopathology* **1968,** *58*, 1004.

21. Fabritius, A. L.; Cvitanich, C.; Judelson, H. S. *Mol. Microbiol.* **2002,** *45*, 1057.

22. Ashby, S. F. *Trans. Br. Mycol. Soc.* **1929,** *14*, 18.

23. (a) Galloway, L. D. *Sci. Rep. Agr. Res. inst. Pusa* **1936,** *1934-1935*, 120. (b) Kouyeas, V. *Ann. Inst. Phytopathol. Benaki* **1953,** *7*, 40.

24. (a) Stamps, D. J. *Trans. Br. Mycol. Soc.* **1953,** *36*, 255. (b) Apple, J. L. *Phytopathology* **1959,** *49*, 37. (c) Haasis, F. A.; Nelson, R. R. *Plant Dis. Rep.* **1963,** *48*, 705. (d) Marx, D. H.; Haasis, F. A.; Nelson, R. R. *J. Elisha Metchell Sci. Soc.* **1965,** *81*, 75. (e) Brasier, C. M. *Trans. Br. Mycol. Soc.* **1972,** *58*, 237. (f) Chang, S. T.; Shepherd, C. J.; Pratt, B. H. *Aust. J. Bot* **1974,** *22*, 669. (g) Ko, W. H. *J. Gen. Microbiol.* **1978,** *107*, 15. (h) Ko, W. H. *J. Gen. Microbiol.* **1983,** *129*, 1397. (i) Chern, L. L.; Tang, S. S.; Ko, W. H. *Bot. Bull. Acad. Sin.* **1999,** *40*, 79.

25. Yajima, A.; Kawanishi, N.; Qi, J.; Asano, T.; Sakagami, Y.; Nukada, T.; Yabuta, G. *Tetrahedron Lett.* **2007,** *48*, 4601.

26. Ojika, M.; Qi, J.; Kito, Y.; Sakagami, Y. *Tetrahedron Asymmetry* **2007,** *18*, 1763.

27. (a) Yajima, A.; Akasaka, K.; Nakai, T.; Maehara, H.; Nukada, T.; Ohrui, H.; Yabuta, G. *Tetrahedron* **2006,** *62*, 4590. (b) Yajima, A.; Akasaka, K.; Yamamoto, M.; Ohmori, S.; Nukada, T.; Yabuta, G. *J. Chem. Ecol.* **2007,** *33*, 1328.

28. Yajima, A.; Qin, Y.; Zhou, X.; Kawanishi, N.; Xiao, X.; Wang, J.; Zhang, D.; Wu, Y.; Nukada, T.; Yabuta, G.; Qi, J.; Asano, T.; Sakagami, Y. *Nat. Chem. Biol.* **2008,** *4*, 235.

29. Nakai, T. Y., A.; Akasaka, K.; Kaihoku, T.; Ohtaki, M.; Nukada, T.; Ohrui, H.; Yabuta, G. *Biosci. Biotechnol. Biochem.* **2005,** *69*, 2401.

30. Harutyunyan, S. R.; Zhao, Z.; Hartog, T. D.; Bouwmesster, K.; Minnaard, A. J.; Feringa, B. L.; Govers, F. *Proc. Nat. Acad. Sci.* **2008,** *105*, 8507.

31. Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004,** *104*, 17.

32. (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973,** *95*, 512. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968,** *90*, 3732. (c) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969,** *34*, 2453. (d) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. **1973,** *38*, 2143. (e) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nature Protocols* **2007,** *2*.

33. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991,** *113*, 4092.

34. (a) Latypov, S. K.; Ferreiro, M. J.; E., Q.; Riguera, R. *J. Am. Chem. Soc.* **1998,** *120*, 4771. (b) Yasuhara, F.; Yamaguchi, S.; Kasai, R.; Tanaka, O. *Tetrahedron Lett.* **1986,** *27*, 4033.

35. (a) Seco, J. M.; Quinoa, E. *Tetrahedron Asymmetry* **2000,** *11*, 2781. (b) Kusumi, T.; Ooi, T.; Ohkubo, Y.; Yabuuchi, T.; 2006, 965–980. *Bull. Chem. Soc. Jpn.* **2006,** *79*, 965.

36. (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1996,** *118*, 9422. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981,** *22*, 3815.

37. Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994,** *27*, 9.

38. Reed, S. F. *J. Org. Chem.* **1962,** *27*, 4116.

39. Posner, G. H.; Johnson, N. *J. Org. Chem.* **1994,** *59*, 7855.

40. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983,** *48*, 4155.

41. Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981,** *53*, 1109.

42. McDougal, P. G.; Rico, J. G.; Oh, I. Y.; Condon, B. D. *J. Org. Chem.* **1986,** *51*, 3388.

43. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

44. Bal, B. S.; Childers, W. E.; Jr. Pinnick, H. W. *Tetrahedron* **1981,** *37*, 2091.

45. Ghosh, A. K.; Gong, G. J. *J. Am. Chem. Soc.* **2004,** *126*, 3704.

46. Poigny, S.; Nouri, S.; Chiaroni, A.; Guyot, M.; Samadi, M. *J. Org. Chem.* **2001,** *66*, 7263.

47. Chen, B.; Ko, R. Y. Y.; Yuen, M. S. M.; Cheng, K.-F.; Chiu, P. *J. Org. Chem.* **2003,** *68*, 4195.

48. Wattanasereekul, S.; Maier, M. E. *Adv. Synth. Catal.* **2004,** *346*, 855.

49. Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004,** *126*, 9552.

50. Denmark, S. E.; Fujimori, S. *Synlett* **2001**, 1024.

51. Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987,** *109*, 3353.

52. Fleming, I.; Ramarao, C. *Org. Biomol. Chem.* **2004,** *2*, 1504.

53. Cavicchioli, S.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1984,** *49*, 1246.

54. Fukui, Y.; Brückner, A. M.; Shin, Y.; Balachandran, R.; Day, B. W.; Curran, D. P. *Org. Lett.* **2006,** *8*, 301.

55. (a) Dandapani, S.; Jeske, M.; Curran, D. P. *J. Org. Chem.* **2005,** *70*, 9447. (b) Gudipati, V.; Curran, D. P.; Wilcox, C. S. *J. Org. Chem.* **2006,** *71*, 3599.

56. (a) Zhang, Q.; Lu, H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.* **2004,** *126*, 36. (b) Green, T. W.; -Wuts, P. G. M., Protective Groups in Organic Synthesis., Wiley, **1991,** pp.

57. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.

58. Mitsunobu, O. *Synthesis* **1981**, 1.

59. Jasper, C.; Wittenberg, R.; Quitschalle, M.; Jakupovic, J.; Kirschning, A. *Org. Lett.* **2005,** *7*, 479.

60. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980,** *102*, 5974.

61. N., K.; Lagrange, J.-M.; Ohmi, M.; Uenishi, J. *J. Org. Chem.* **2006,** *71*, 4530.

62. Kalesse, M.; Chary, K. P.; Quitschalle, M.; Burzlaff, A.; Kasper, C.; Scheper, T. *Chem. Eur. J.* **2003,** *9*, 1129.

63. (a) Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994,** *116*, 9361. (b) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997,** *119*, 6496.

64. Zeng, F.; Negishi, E. *Org. Lett.* **2002,** *4*, 703.

65. Organ, M. G.; Wang, J. *J. Org. Chem.* **2003,** *68*, 5568.

66. Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963,** *28*, 1140.

67. Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952,** *17*, 1630.

68. Sanchez, C. C.; Keck, G. E. *Org. Lett.* **2005,** *7*, 3053.

69. (a) Siddall, J. B.; Biskup, M.; Fried, J. H. *J. Am. Chem. Soc.* **1969,** *91*, 1853. (b) Schneider, J. A.; Yoshihar, K. *J. Org. Chem.* **1986,** *51*, 1077.

70. Bonadies, F.; Giovanni, R.; Carlo, B. *Tetrahedron Lett.* **1984,** *25*, 5431.

71. Rodrígueza, A.; M. Nomena, M.; Spura, B. W.; Godfroidb, J. J. *Tetrahedron Lett.* **1999,** *40*, 5161.

72. Curran, D. P.; Zhang, Q.; Richard, C.; Lu, H.; VGudipati, V.; Wilcox, C. S. *J. Am. Chem. Soc.* **2006,** *128*, 9561.

73. Marshall, J. A.; Trometer, J. D.; Blough, B. E.; Crute, T. D. *J. Org. Chem.* **1988,** *53*, 4274.

74. Schomaker, J. M.; Bhattacharjee, S.; Yan, J.; Borhan, B. *J. Am. Chem. Soc.* **2007,** *129*, 1996.

75. Paterson, I.; Tudge, M. *Tetrahedron* **2003,** *59*, 6833.

76. Chain, W. J.; Myers, A. G. *Org. Lett.* **2007,** *9*, 355.

77. (a) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996,** *37*, 3623. (b) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Synlett* **1997,** *5*, 457.

78. Smith, A. B. I.; Mesaros, E. F.; Meyer, E. A. *J. Am. Chem. Soc.* **2006,** *128*, 5292.

79. Romo, D.; Johnson, D. D.; Plamondon, L.; Miwa, T.; Schreiber, S. L. *J. Org. Chem.* **1992,** *57*, 5060.

80. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972,** *13*, 3769.

81. Hanessian, S.; Yang, Y.; Giroux, S.; Mascitti, V.; Ma, J.; Raeppel, F. *J. Am. Chem. Soc.* **2003,** *125*, 13784.

82. (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993,** *130*, 856. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991,** *32*, 1175.

83. Dudley, G. B.; Engel, D. A.; Ghiviriga, I.; Lam, H.; Poon, K. W. C.; Singletary, J. A. *Org. Lett.* **2007,** *9*, 2839.

84. (a) K.-K., C.; Cohen, N.; De Noble, J. P.; Specian, A. C., Jr.; Saucy, G. *J. Org. Chem.* **1976,** *41*, 3497. (b) Schwartz, B. D.; Hayes, P. Y.; Kitching, W.; De Voss, J. J. *J. Org. Chem.* **2005,** *70*, 3054.

85. (a) Miller, C. E. *J. Chem. Ed.* **1965,** *42*, 254. (b) Pasto, D. T.; Taylor, R. T. *Org. React.* **1991,** *40*, 91.

86. Pangborn, A.; Giardello, M. A.; Grubbs, R., H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996,** *15*, 1518.

87. Taillier, C.; Gille, B.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2005,** *70*, 2097.

88. Gugiu, B. G.; Salomon, R. G. *Org. Lett.* **2003,** *5*, 2797.

89. Myers, A. G.; McKinstry, L. *J. Org. Chem.* **1996,** *61*, 2428.

90. Berg, T. C.; Gundersen, L.-L.; Eriksen, A. B.; Malterud, K. E. *Eur. J. Org. Chem.* **2005**, 4988.

91. Sneddon, H. F.; Gaunt, M. J.; Ley, S. V. *Org. Lett.* **2003,** *5*, 1147.

92. Krafft, M. E.; Cheung, Y. Y.; Abboud, K. A. *J. Org. Chem.* **2001,** *66*, 7443.

93. Koenig, J.-J.; Jegham, S.; Puech, F.; Burnier, P. Eur. Pat. Appl. 655445, 31 May, **1995**.

94. Kelly, S. M.; Skelton, G. W. *PCT Int. Appl. WO 2000039062 A1 20000706* **2000**, 33.

95. Curran, D. P.; Takashi, F. *Org. Lett.* **2002,** *4*, 2233.

96. Mulzer, J.; Mantoulidis, A.; Ohler, E. *J. Org. Chem.* **2000,** *65*, 7456.

97. Woush, W. R.; Palkowitz, A. D.; Palmer, M. A. *J. Org. Chem.* **1987,** *52*.

98. Mulzer, J.; Berger, M. *J. Org. Chem.* **2004,** *69*, 891.

99. Pelchat, N.; Caron, D.; Chenevert, R. *J. Org. Chem.* **2007,** *72*, 8484.

1.8 APPENDIX

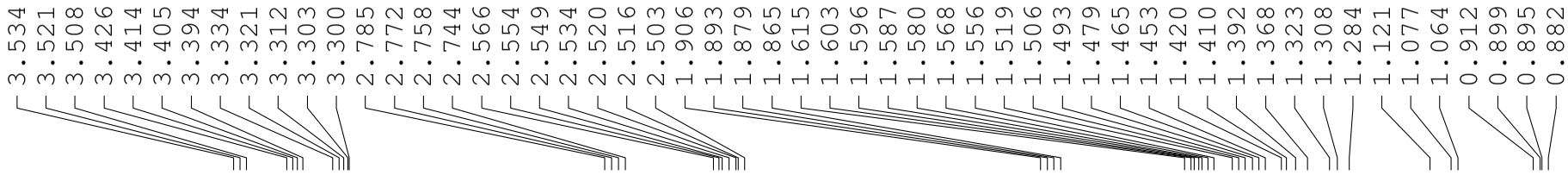
1. ^{1}H and ^{13}C NMR spectra of **(*S*,*R*,*RS*,*R*)-1** and **(*R*,*R*,*RS*,*R*)-1**.

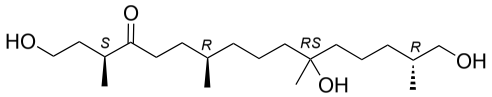
2. ^{1}H and ^{13}C NMR spectra of **(*S*,*R*,*RS*,*R*)-2** and **(*R*,*R*,*RS*,*R*)-2**.

3. ^{1}H and ^{13}C NMR spectra of eight isomers of **1** synthesized by FMS.

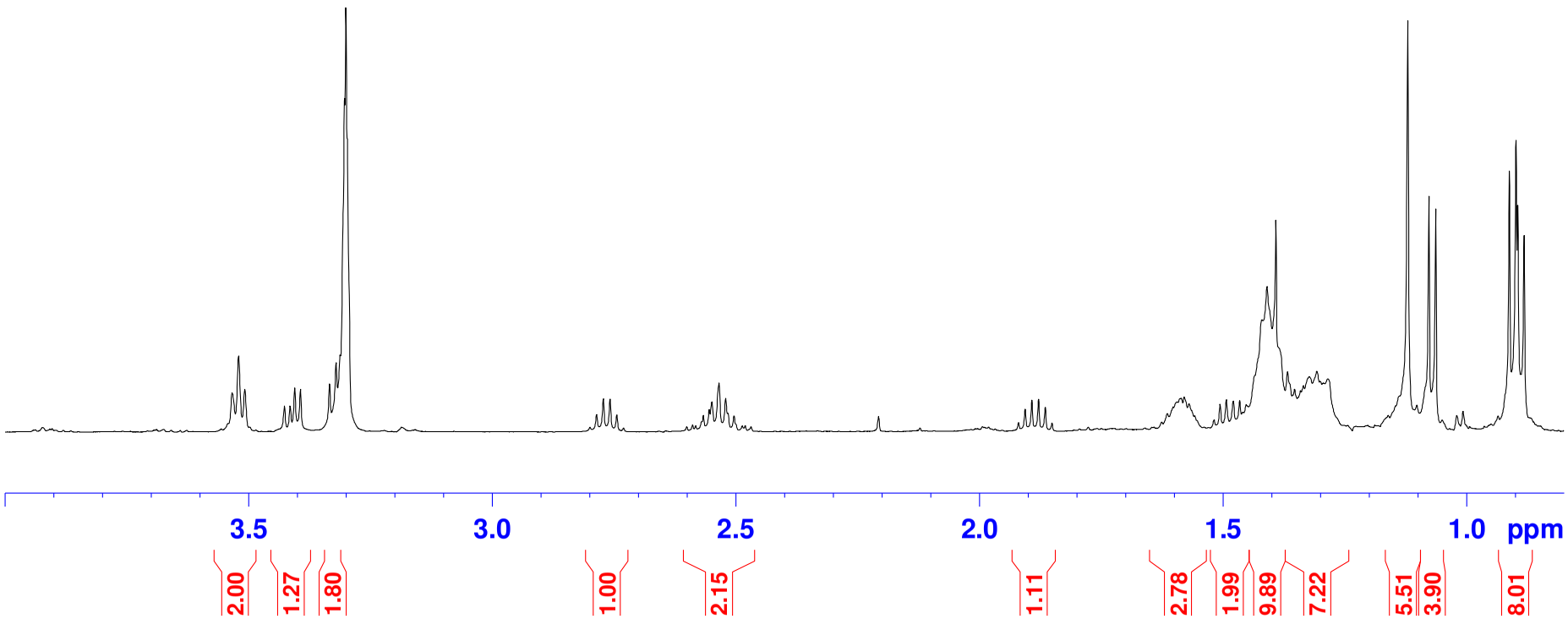
4. ^{1}H NMR of the 16-bis MTPA esters.

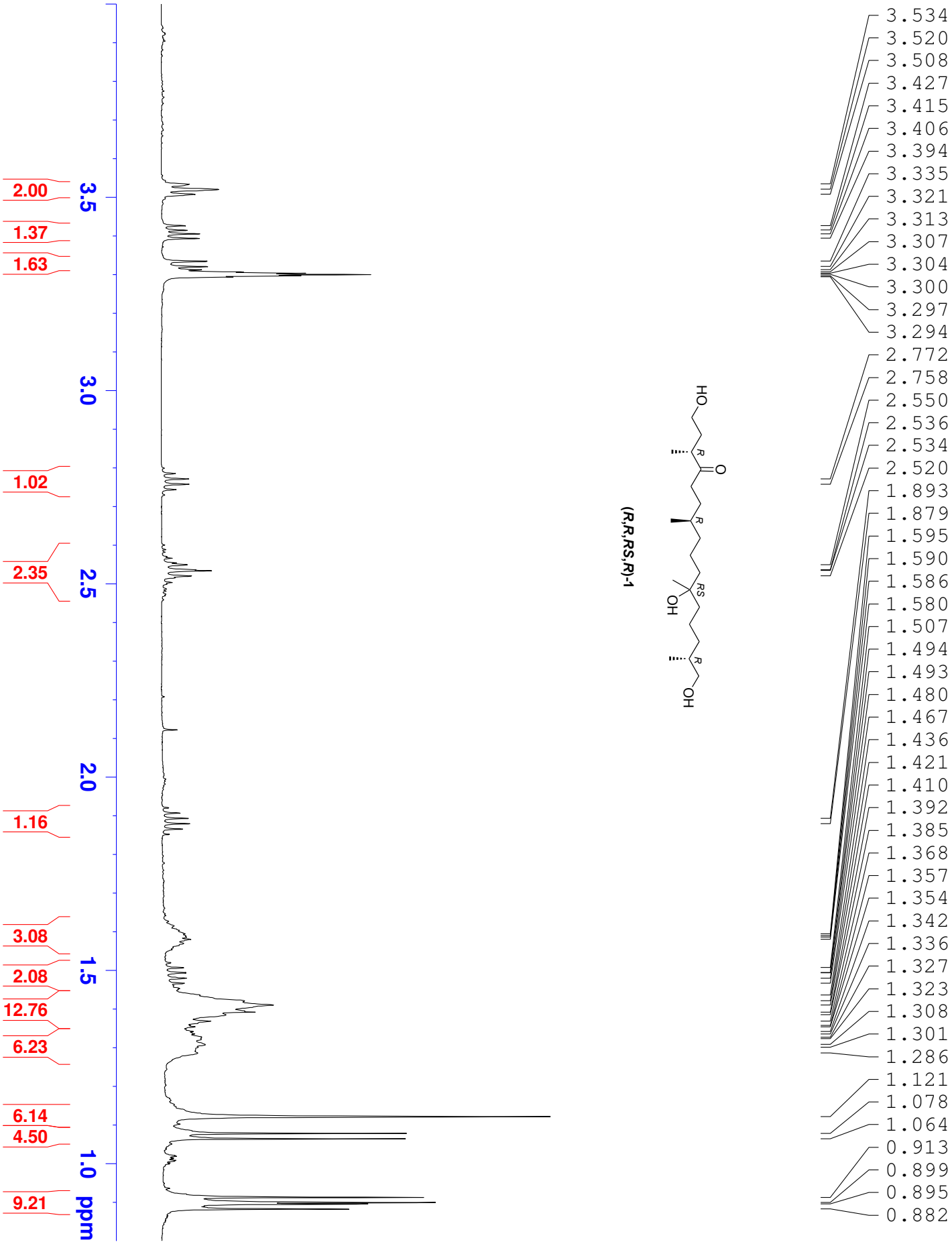
5. ^{1}H-^{13}C HMQC spectra of **(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10** and **(*S*,3*S*,7*S*,11*R*,15*S*,*S*)-10**.

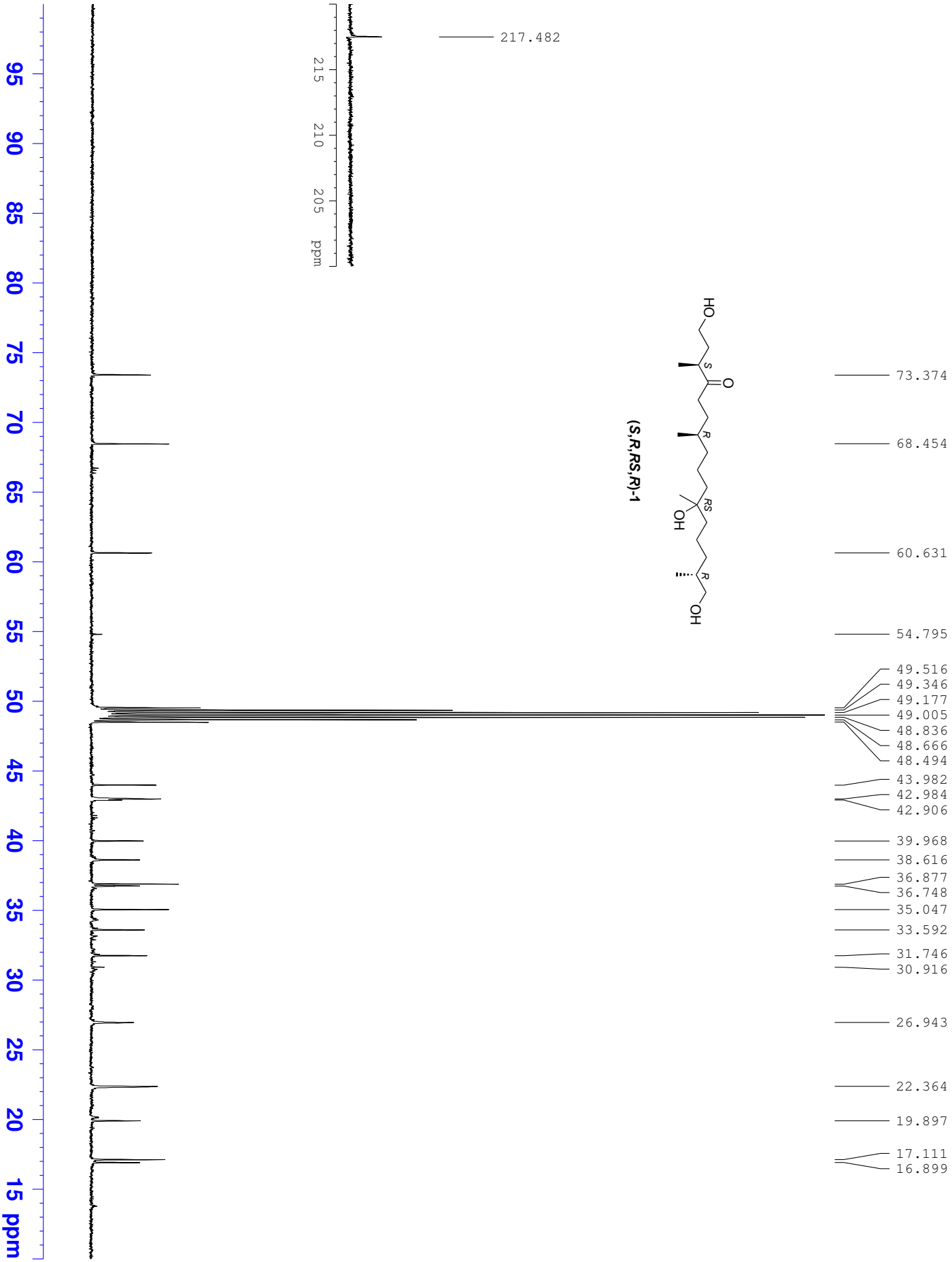

3.534
3.521
3.508
3.426
3.414
3.405
3.394
3.334
3.321
3.312
3.303
3.300
2.785
2.772
2.758
2.744
2.566
2.554
2.549
2.534
2.520
2.516
2.503
1.906
1.893
1.879
1.865
1.615
1.603
1.596
1.587
1.580
1.568
1.556
1.519
1.506
1.493
1.479
1.465
1.453
1.420
1.410
1.392
1.368
1.323
1.308
1.284
1.121
1.077
1.064
0.912
0.899
0.895
0.882

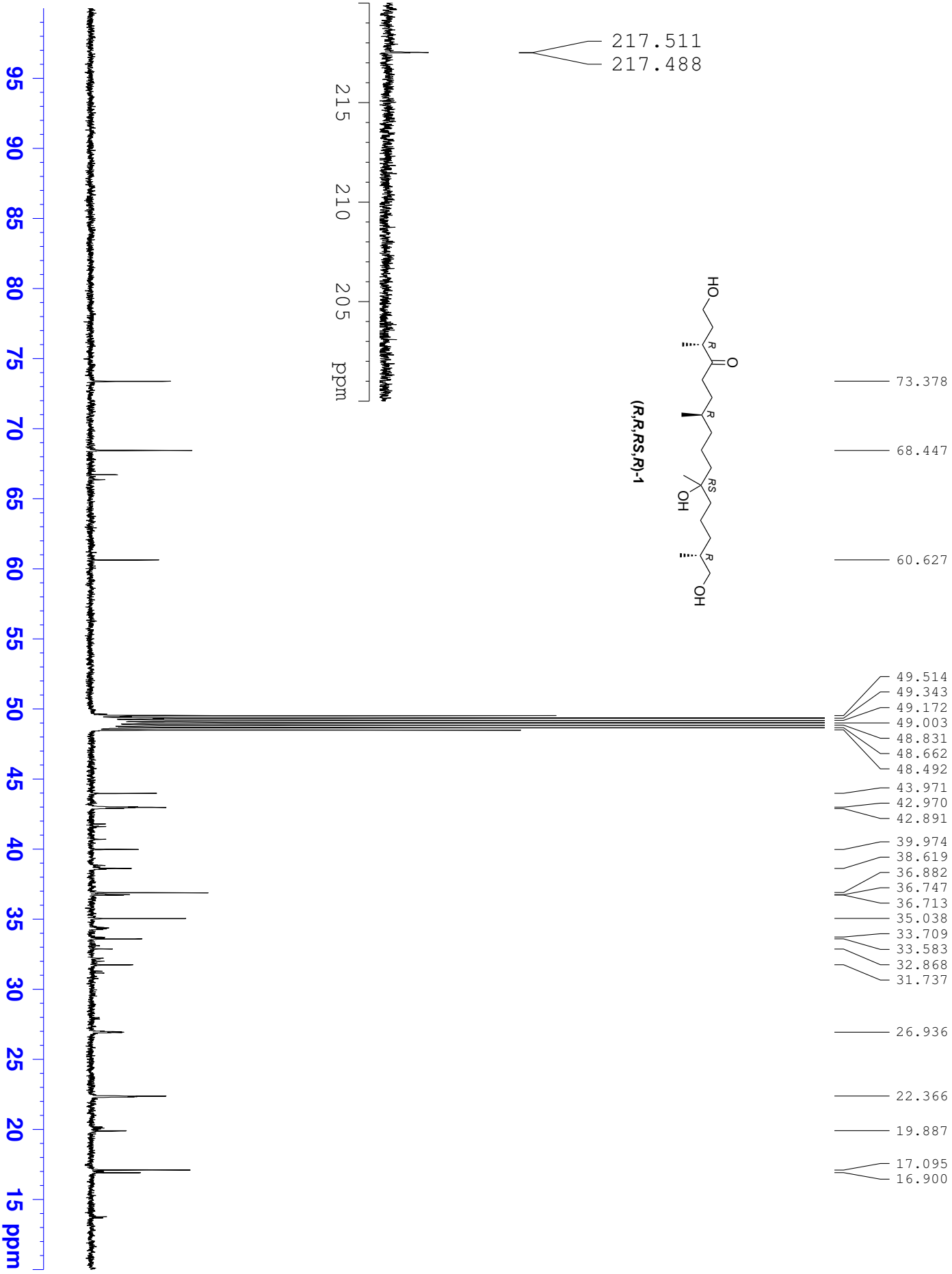

HO
O
S
R
RS
R
OH
OH

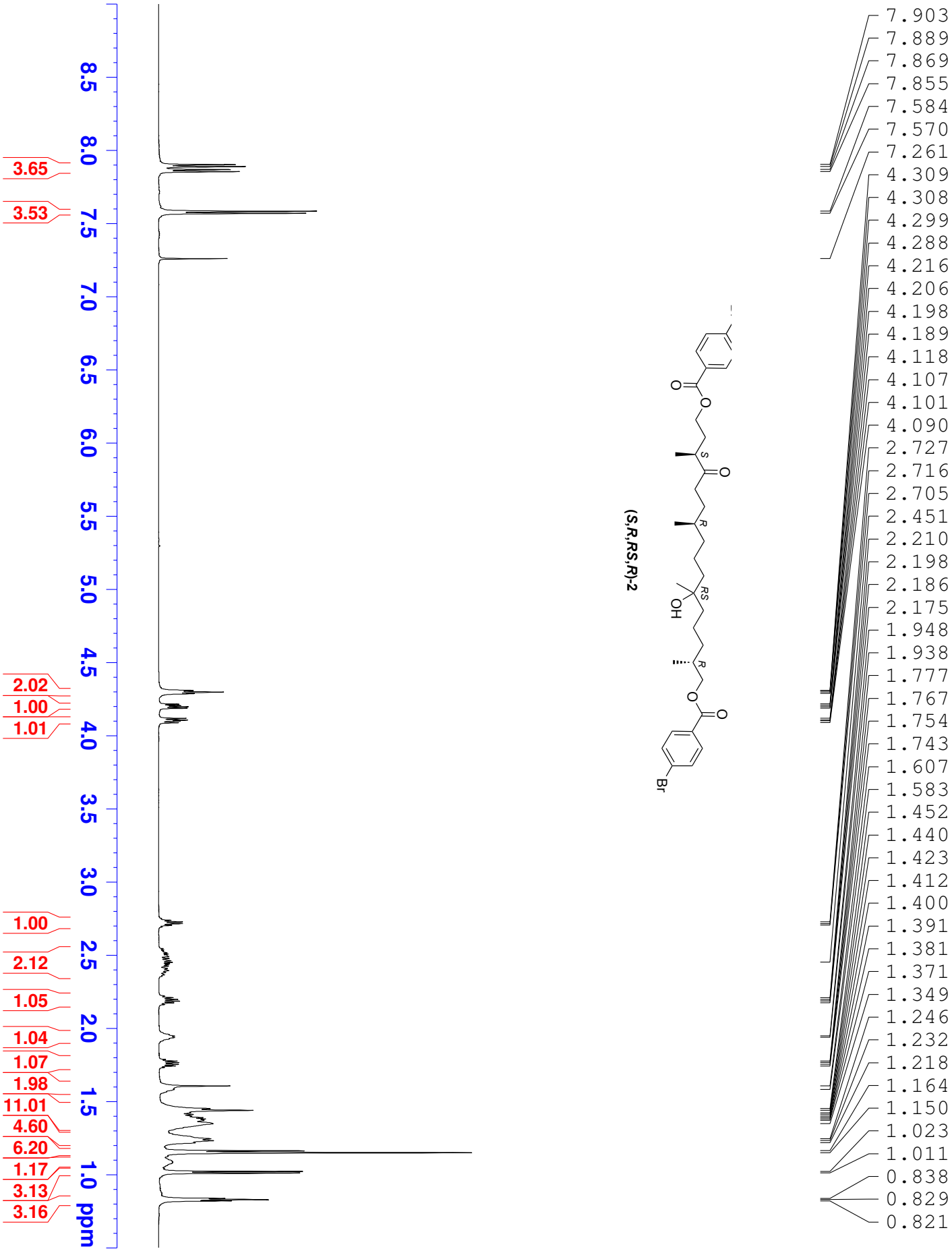
(*S*,*R*,*RS*,*R*)-1


3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.00
1.27
1.80
1.00
2.15
1.11
2.78
1.99
9.89
7.22
5.51
3.90
8.01

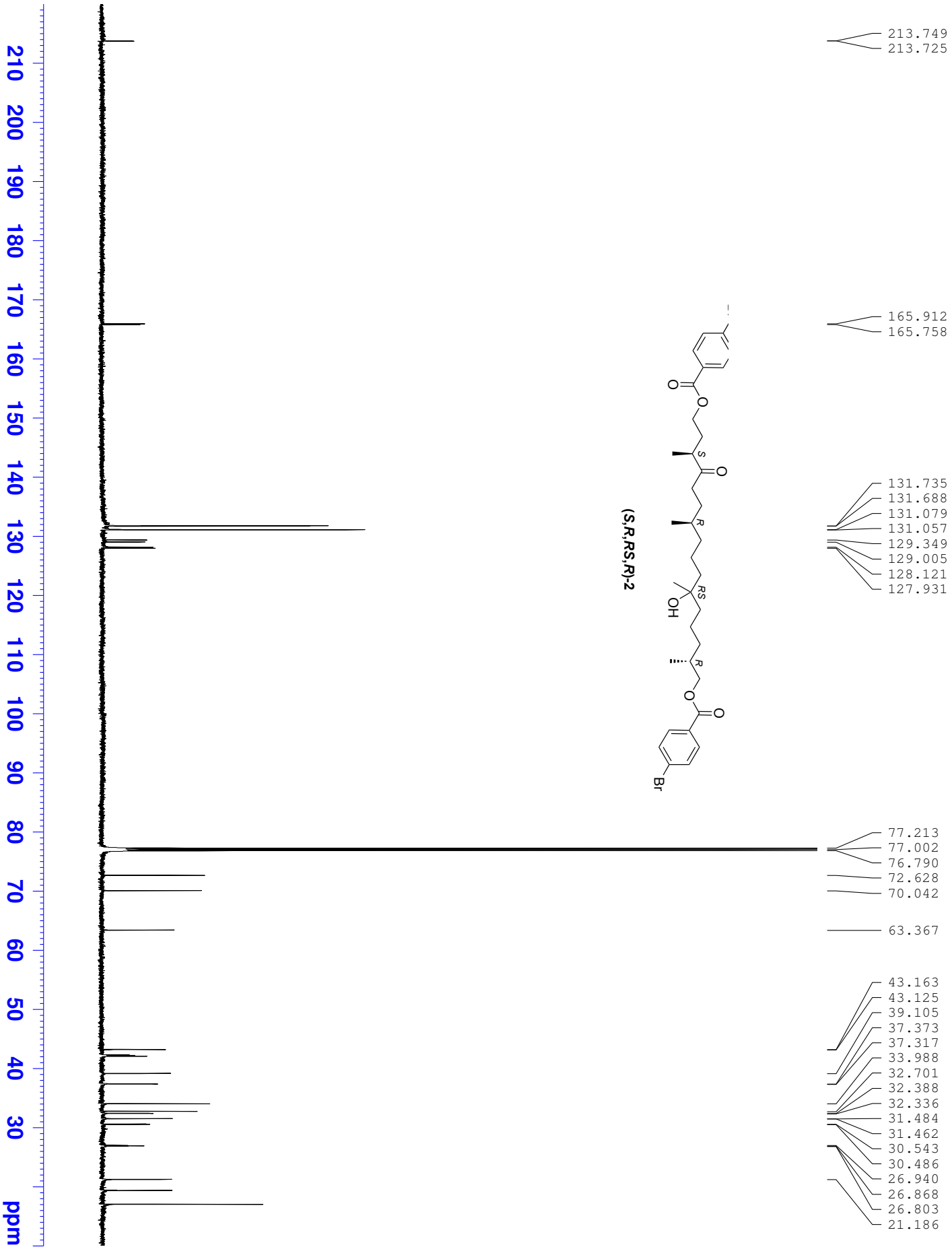

3.534
3.520
3.508
3.427
3.415
3.406
3.394
3.335
3.321
3.313
3.307
3.304
3.300
3.297
3.294
2.772
2.758
2.550
2.536
2.534
2.520
1.893
1.879
1.595
1.590
1.586
1.580
1.507
1.494
1.493
1.480
1.467
1.436
1.421
1.410
1.392
1.385
1.368
1.357
1.354
1.342
1.336
1.327
1.323
1.308
1.301
1.286
1.121
1.078
1.064
0.913
0.899
0.895
0.882
HO
O
OH
OH
R
R
RS
R
(R,R,RS,R)-1
2.00
1.37
1.63
1.02
2.35
1.16
3.08
2.08
12.76
6.23
6.14
4.50
9.21
3.5
3.0
2.5
2.0
1.5
1.0
ppm

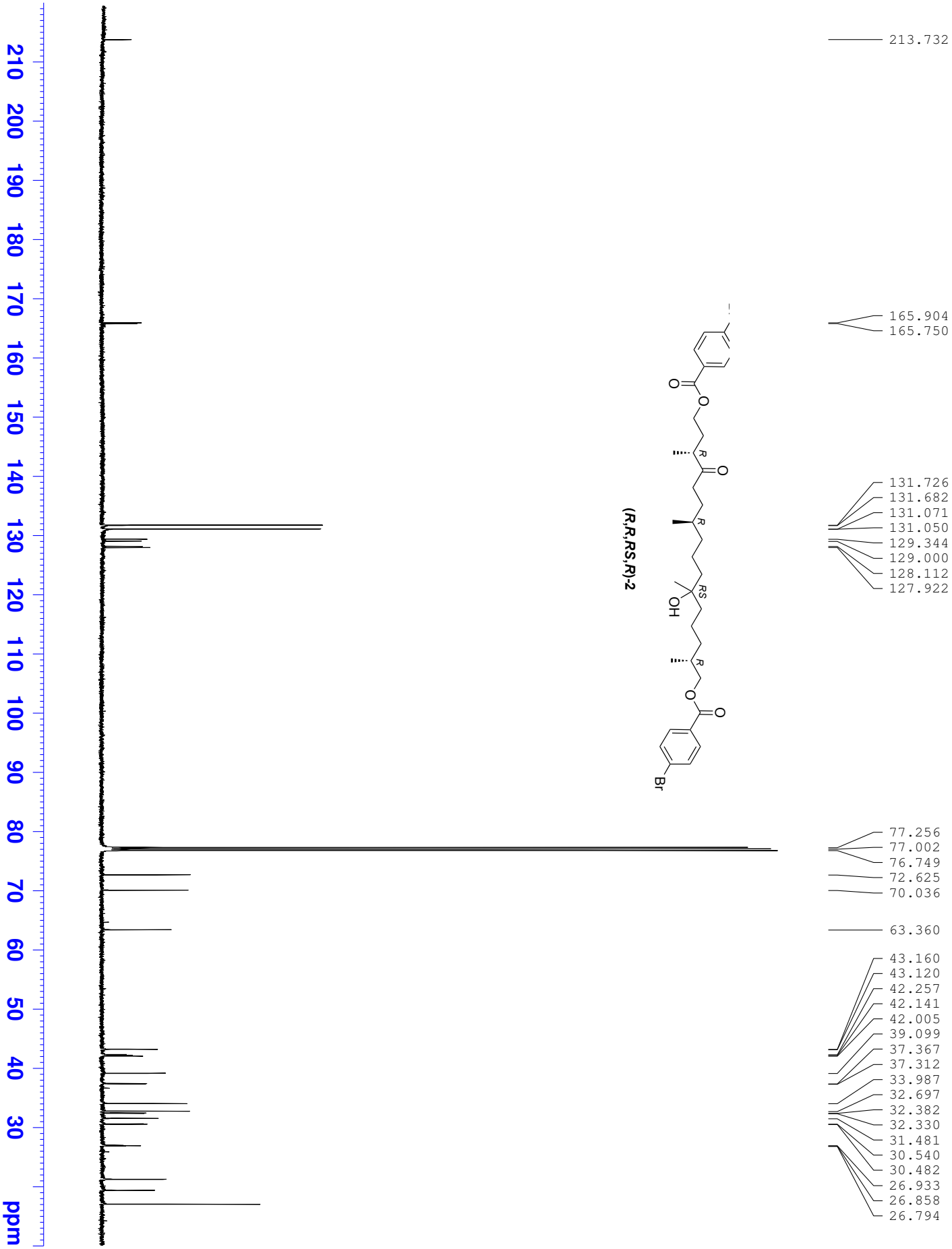

217.482
215
210
205
ppm
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15 ppm
HO
S
O
R
RS
OH
R
OH
(S,R,RS,R)-1
73.374
68.454
60.631
54.795
49.516
49.346
49.177
49.005
48.836
48.666
48.494
43.982
42.984
42.906
39.968
38.616
36.877
36.748
35.047
33.592
31.746
30.916
26.943
22.364
19.897
17.111
16.899

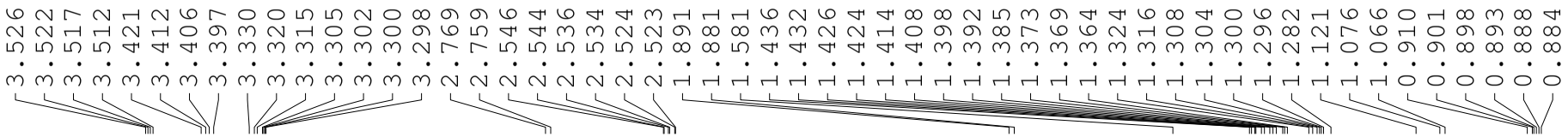

217.511
217.488
215
210
205
ppm
HO
O
OH
OH
(R,R,RS,R)-1
73.378
68.447
60.627
49.514
49.343
49.172
49.003
48.831
48.662
48.492
43.971
42.970
42.891
39.974
38.619
36.882
36.747
36.713
35.038
33.709
33.583
32.868
31.737
26.936
22.366
19.887
17.095
16.900
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
ppm

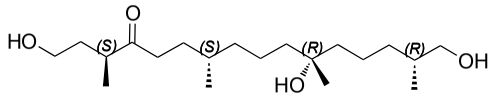

3.65
3.53
2.02
1.00
1.01
1.00
2.12
1.05
1.04
1.07
1.98
11.01
4.60
6.20
1.17
3.13
3.16
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
7.903
7.889
7.869
7.855
7.584
7.570
7.261
4.309
4.308
4.299
4.288
4.216
4.206
4.198
4.189
4.118
4.107
4.101
4.090
2.727
2.716
2.705
2.451
2.210
2.198
2.186
2.175
1.948
1.938
1.777
1.767
1.754
1.743
1.607
1.583
1.452
1.440
1.423
1.412
1.400
1.391
1.381
1.371
1.349
1.246
1.232
1.218
1.164
1.150
1.023
1.011
0.838
0.829
0.821
(S,R,RS,R)-2

7.900
7.886
7.866
7.864
7.852
7.580
7.566
7.261
5.294
4.307
4.296
4.286
4.213
4.204
4.196
4.186
4.116
4.105
4.098
4.087
2.725
2.714
2.196
2.184
2.172
1.935
1.775
1.765
1.751
1.741
1.594
1.580
1.451
1.439
1.421
1.411
1.399
1.388
1.380
1.372
1.347
1.245
1.231
1.220
1.206
1.161
1.148
1.132
1.020
1.009
0.836
0.829
0.826
0.819
3.88
3.73
1.99
0.92
0.90
0.98
2.03
1.06
0.04
0.20
1.12
1.23
1.52
11.76
4.75
6.46
1.25
3.20
3.23
8.5
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
ppm
(R,R,RS,R)-2
O
O
R
O
R
RS
OH
R
O
O
Br

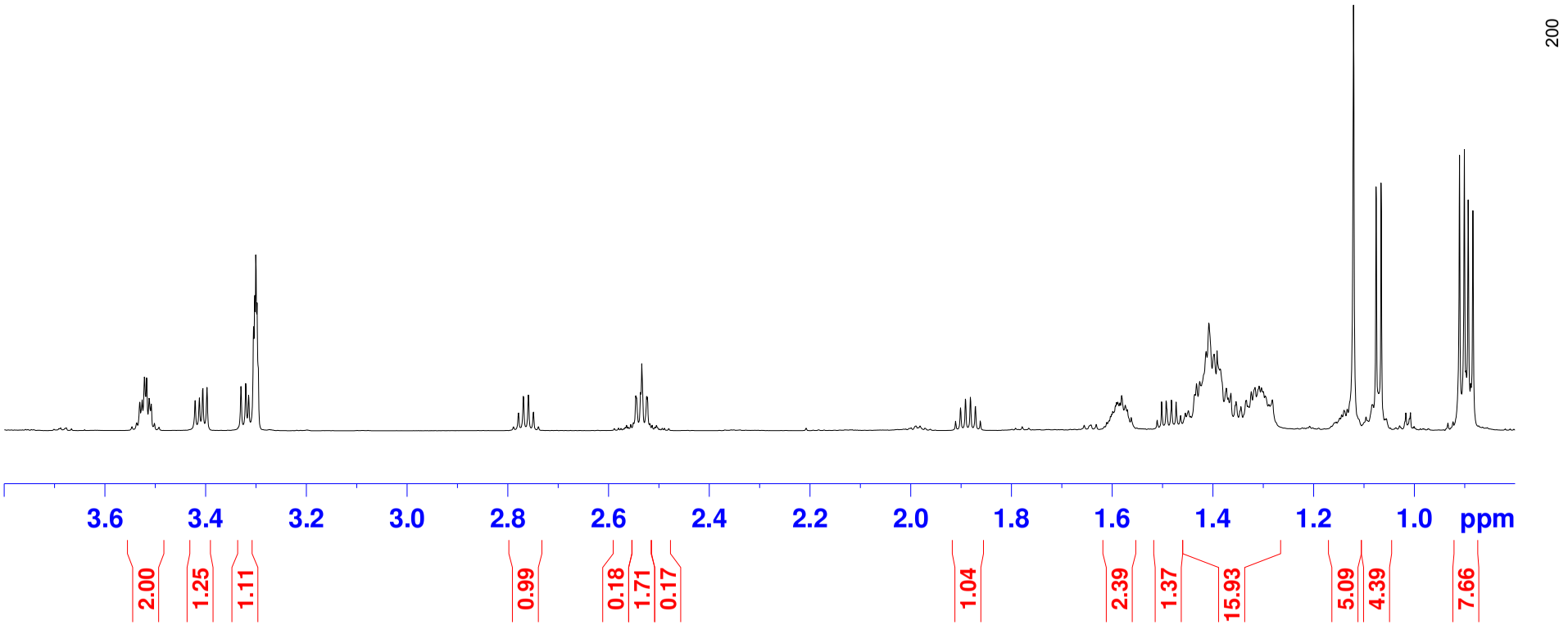

213.749
213.725
165.912
165.758
131.735
131.688
131.079
131.057
129.349
129.005
128.121
127.931
77.213
77.002
76.790
72.628
70.042
63.367
43.163
43.125
39.105
37.373
37.317
33.988
32.701
32.388
32.336
31.484
31.462
30.543
30.486
26.940
26.868
26.803
21.186
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm
(S,R,RS,R)-2
OH
Br


213.732
165.904
165.750
131.726
131.682
131.071
131.050
129.344
129.000
128.112
127.922
77.256
77.002
76.749
72.625
70.036
63.360
43.160
43.120
42.257
42.141
42.005
39.099
37.367
37.312
33.987
32.697
32.382
32.330
31.481
30.540
30.482
26.933
26.858
26.794
(R,R,RS,R)-2
OH
Br
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

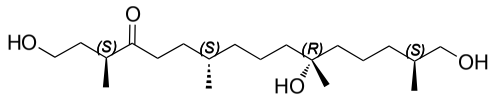




(3*S*,7*S*,11*R*,15*R*)-1



3.5296
3.5244
3.5203
3.5179
3.5156
3.5109
3.4204
3.4120
3.4052
3.3969
3.3285
3.3190
3.3133
3.3020
3.2999
3.2978
2.7701
2.7602
2.5471
2.5361
2.5259
1.8903
1.8805
1.5880
1.5836
1.5799
1.5736
1.4324
1.4173
1.4135
1.4071
1.3970
1.3884
1.3827
1.3712
1.3682
1.3607
1.3503
1.3293
1.3198
1.3154
1.3081
1.3041
1.2959
1.2807
1.1207
1.0808
1.0748
1.0648
0.9101
0.9005
0.8930
0.8886
0.8836

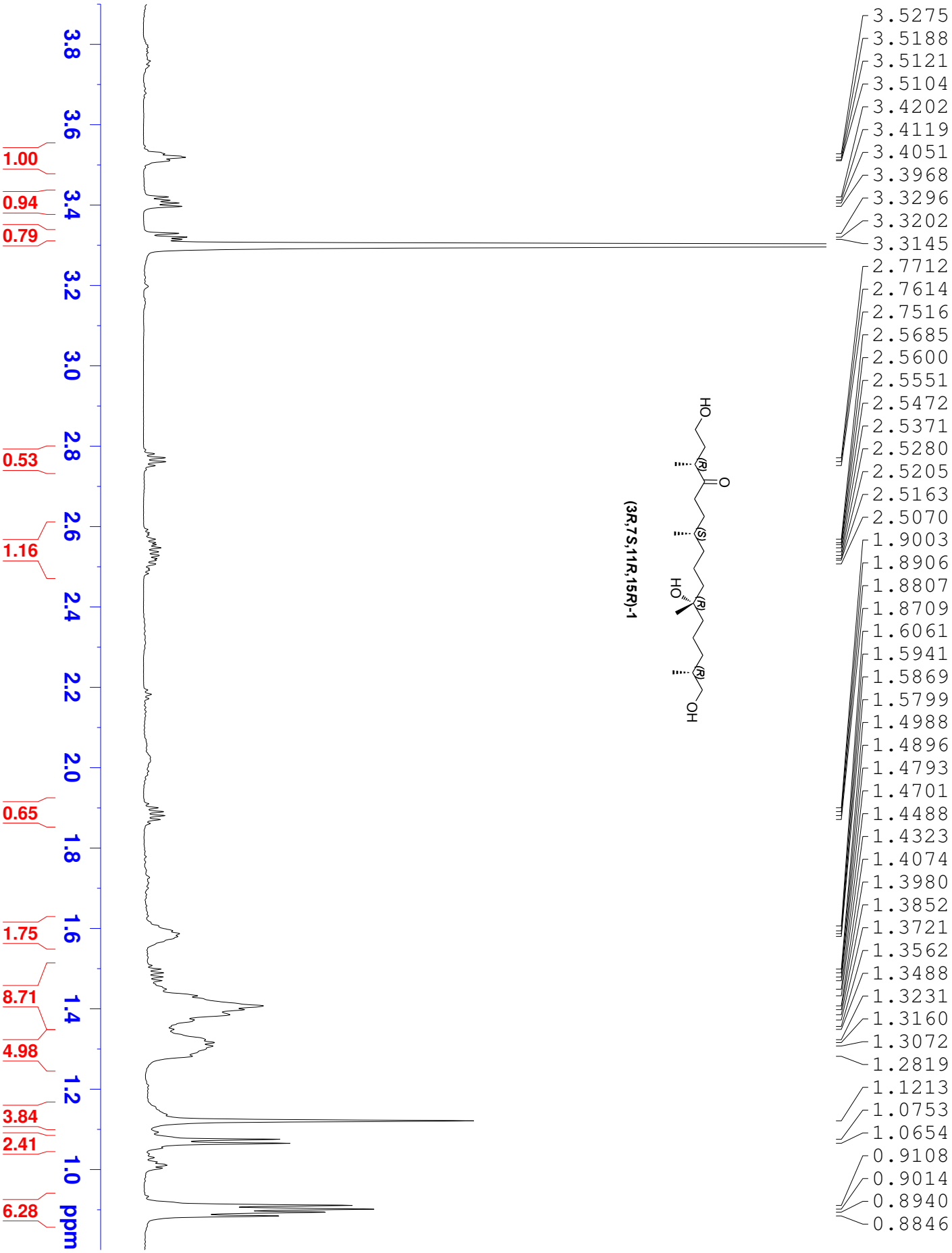


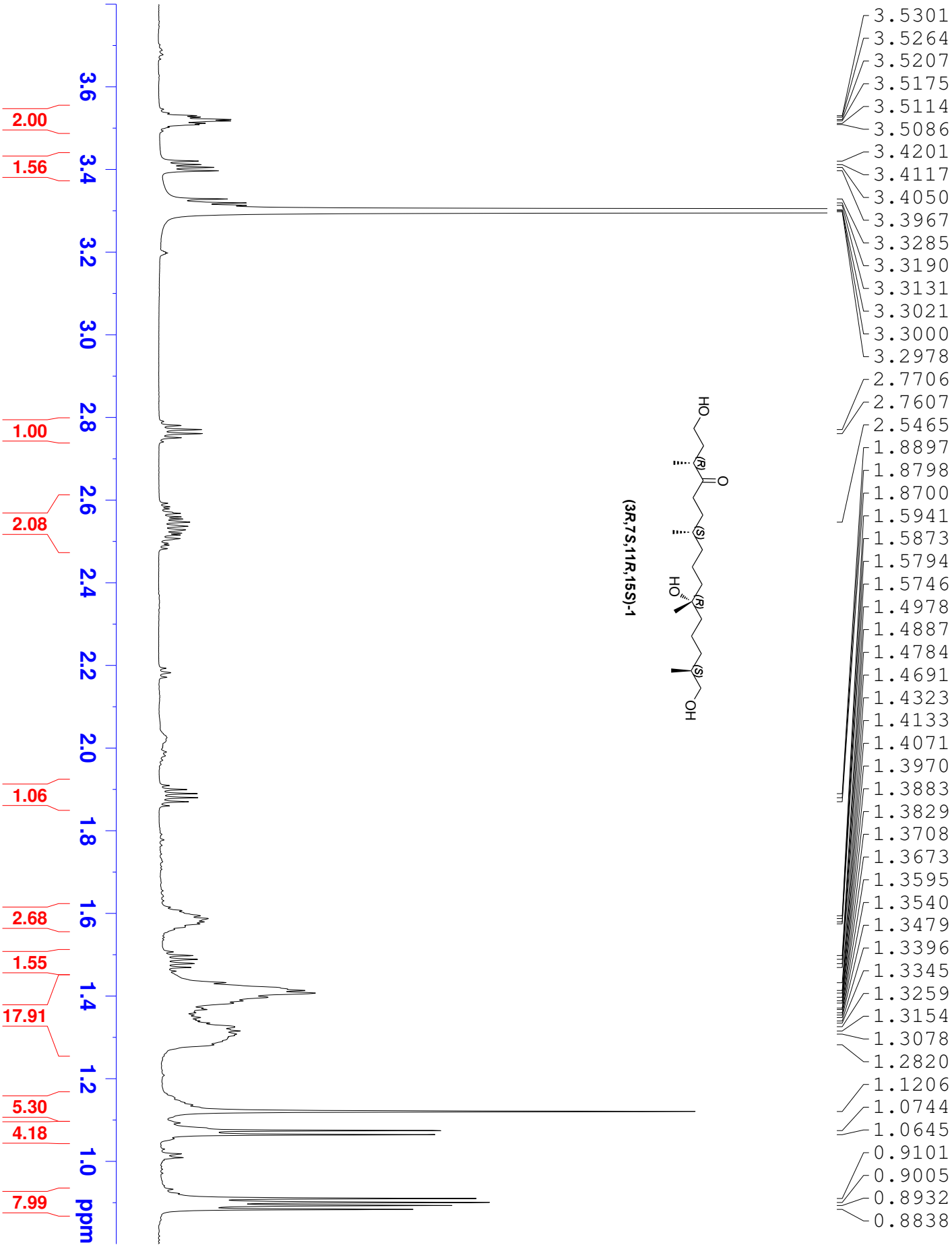
(3*S*,7*S*,11*R*,15*S*)-1

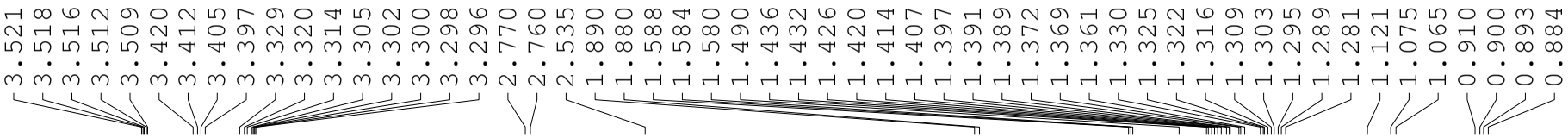
201

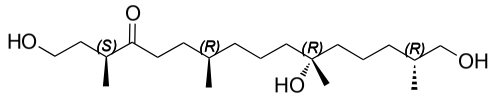
3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 ppm

2.05 1.27 1.09 1.00 0.33 1.42 0.34 1.02 2.51 1.23 11.21 4.69 5.09 4.57 6.85

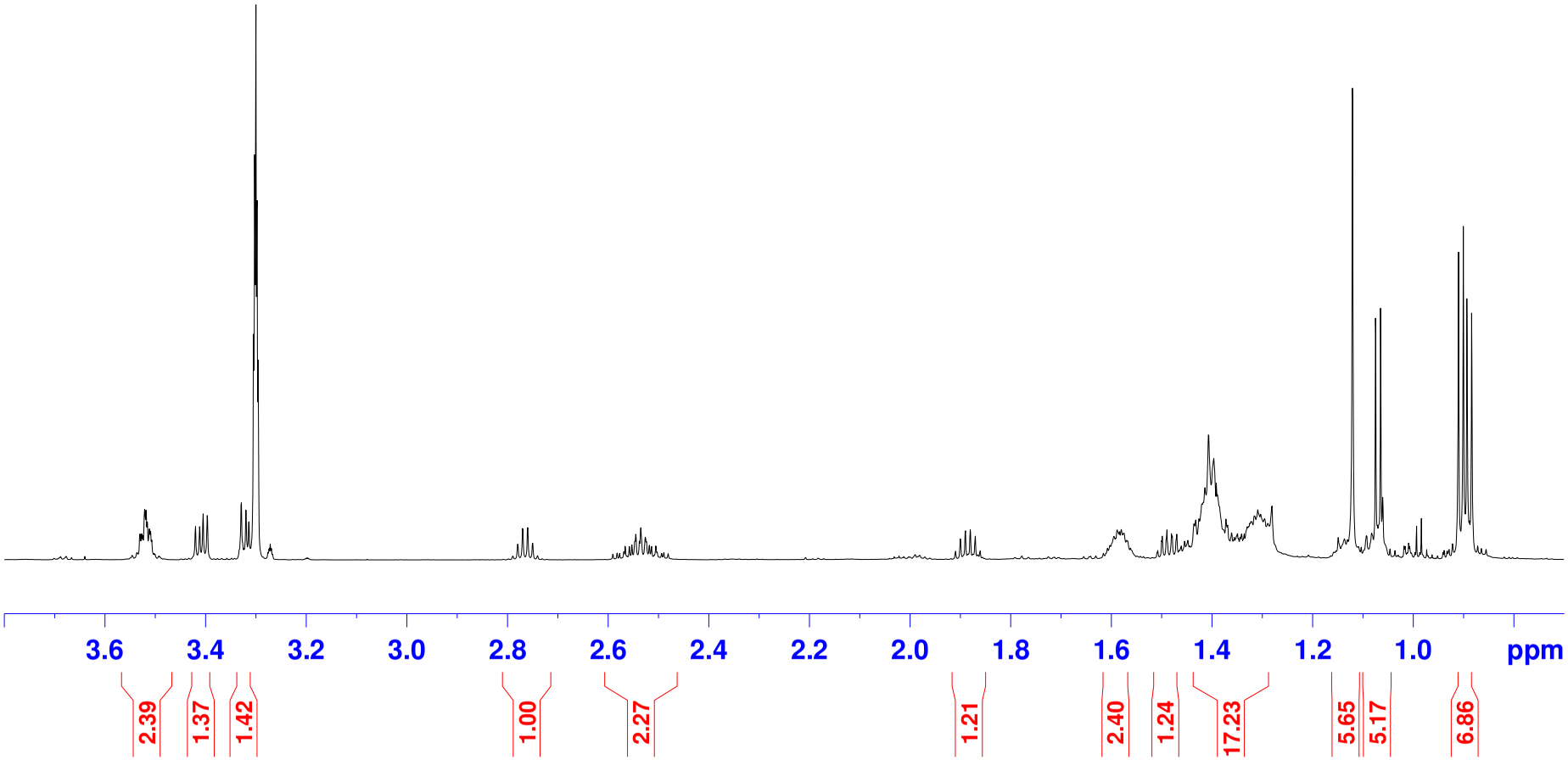

3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
ppm
1.00
0.94
0.79
0.53
1.16
0.65
1.75
8.71
4.98
3.84
2.41
6.28
3.5275
3.5188
3.5121
3.5104
3.4202
3.4119
3.4051
3.3968
3.3296
3.3202
3.3145
2.7712
2.7614
2.7516
2.5685
2.5600
2.5551
2.5472
2.5371
2.5280
2.5205
2.5163
2.5070
1.9003
1.8906
1.8807
1.8709
1.6061
1.5941
1.5869
1.5799
1.4988
1.4896
1.4793
1.4701
1.4488
1.4323
1.4074
1.3980
1.3852
1.3721
1.3562
1.3488
1.3231
1.3160
1.3072
1.2819
1.1213
1.0753
1.0654
0.9108
0.9014
0.8940
0.8846
HO
(R)
O
(S)
HO
(R)
(R)
OH
(3R,7S,11R,15R)-1


3.5301
3.5264
3.5207
3.5175
3.5114
3.5086
3.4201
3.4117
3.4050
3.3967
3.3285
3.3190
3.3131
3.3021
3.3000
3.2978
2.7706
2.7607
2.5465
1.8897
1.8798
1.8700
1.5941
1.5873
1.5794
1.5746
1.4978
1.4887
1.4784
1.4691
1.4323
1.4133
1.4071
1.3970
1.3883
1.3829
1.3708
1.3673
1.3595
1.3540
1.3479
1.3396
1.3345
1.3259
1.3154
1.3078
1.2820
1.1206
1.0744
1.0645
0.9101
0.9005
0.8932
0.8838
(3R,7S,11R,15S)-1
HO
O
OH
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
ppm
2.00
1.56
1.00
2.08
1.06
2.68
1.55
17.91
5.30
4.18
7.99

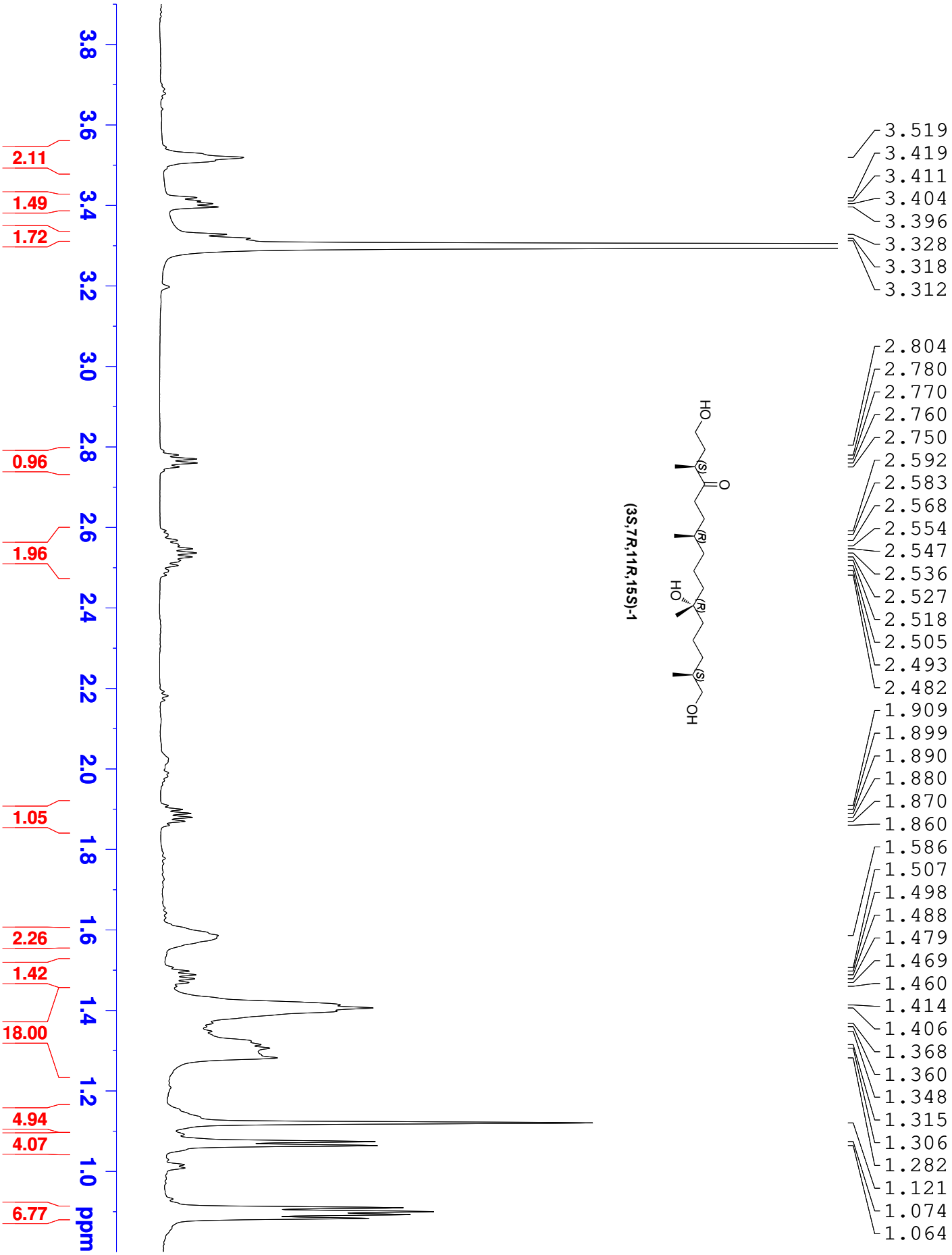


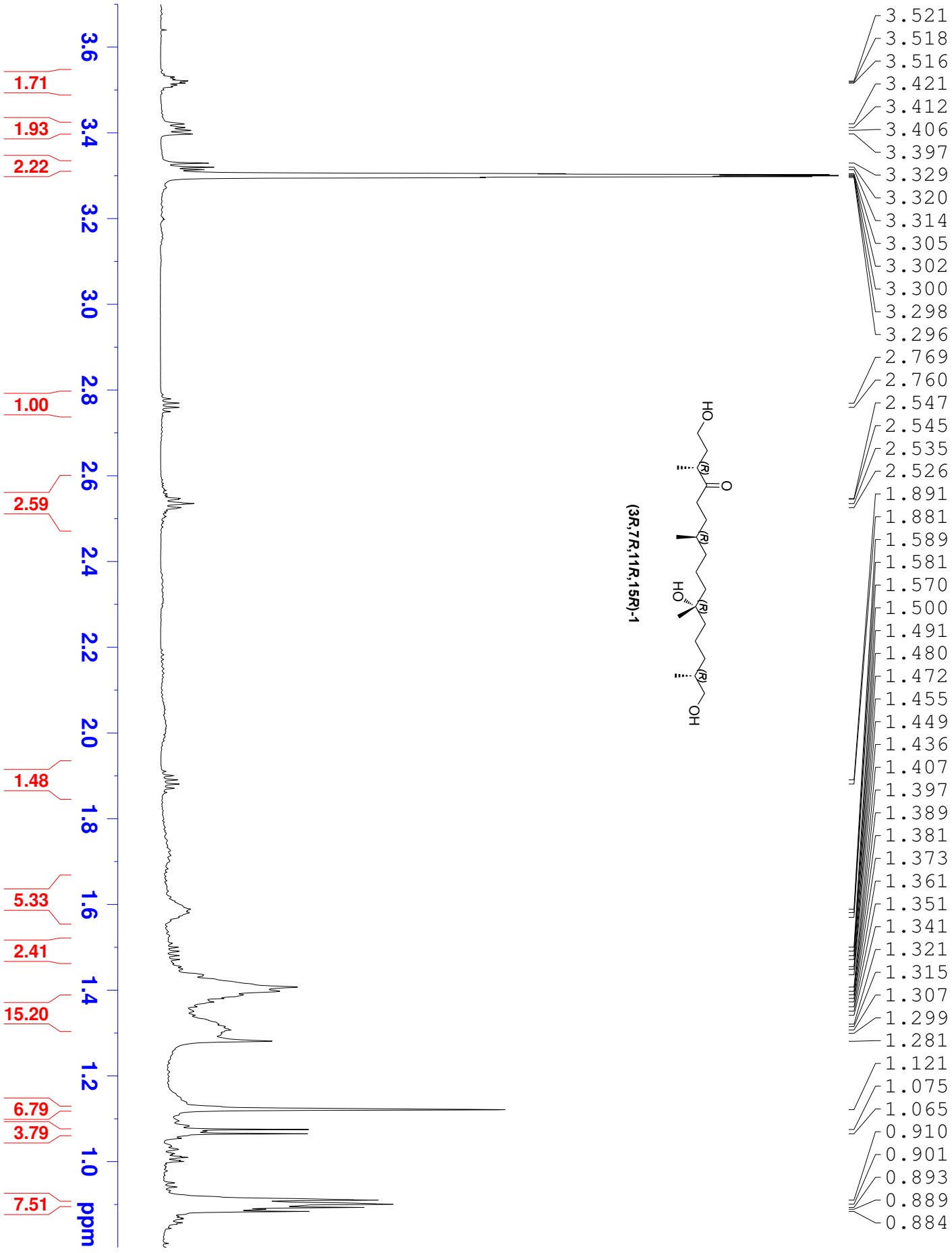


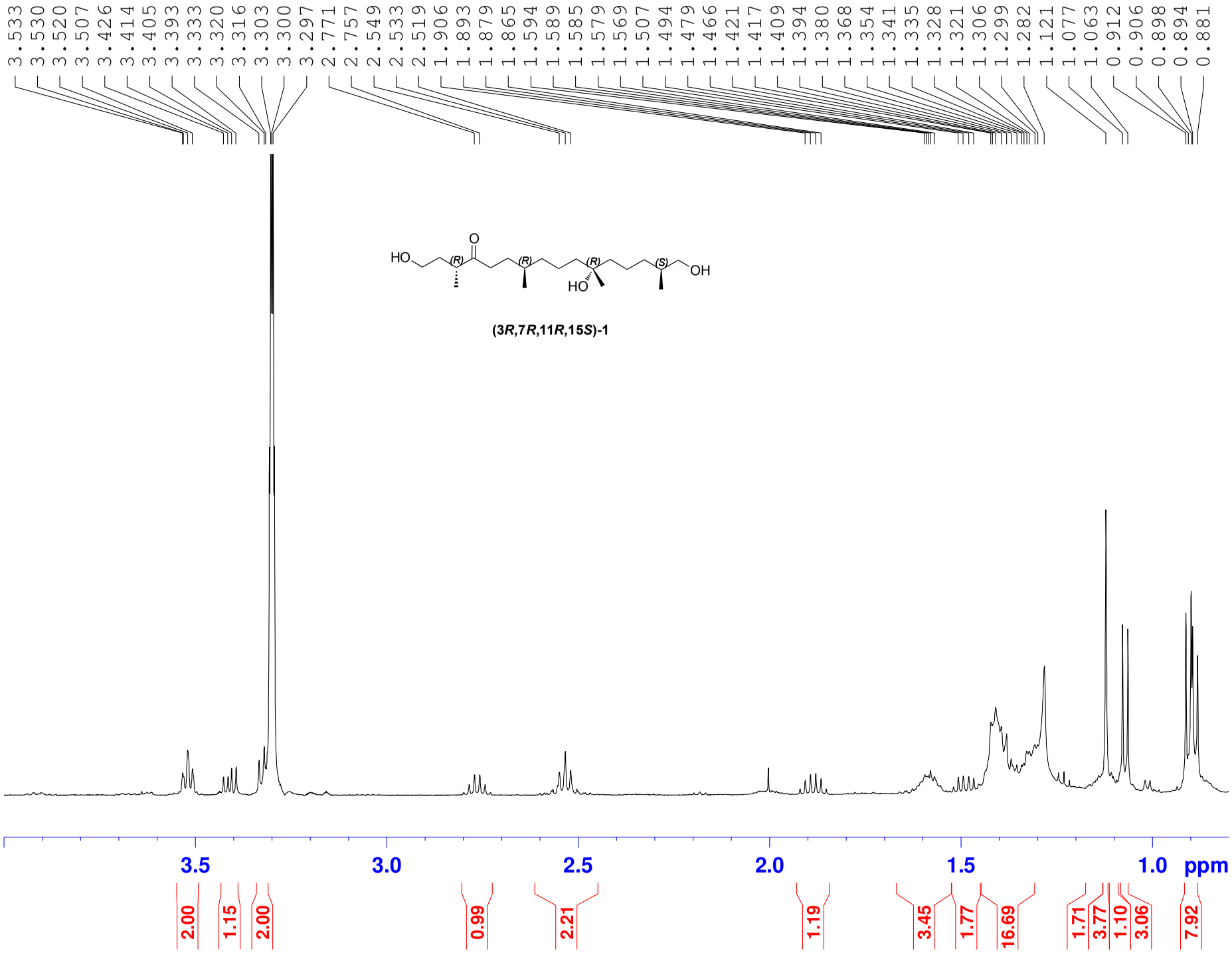
(3*S*,7*R*,11*R*,15*R*)-1

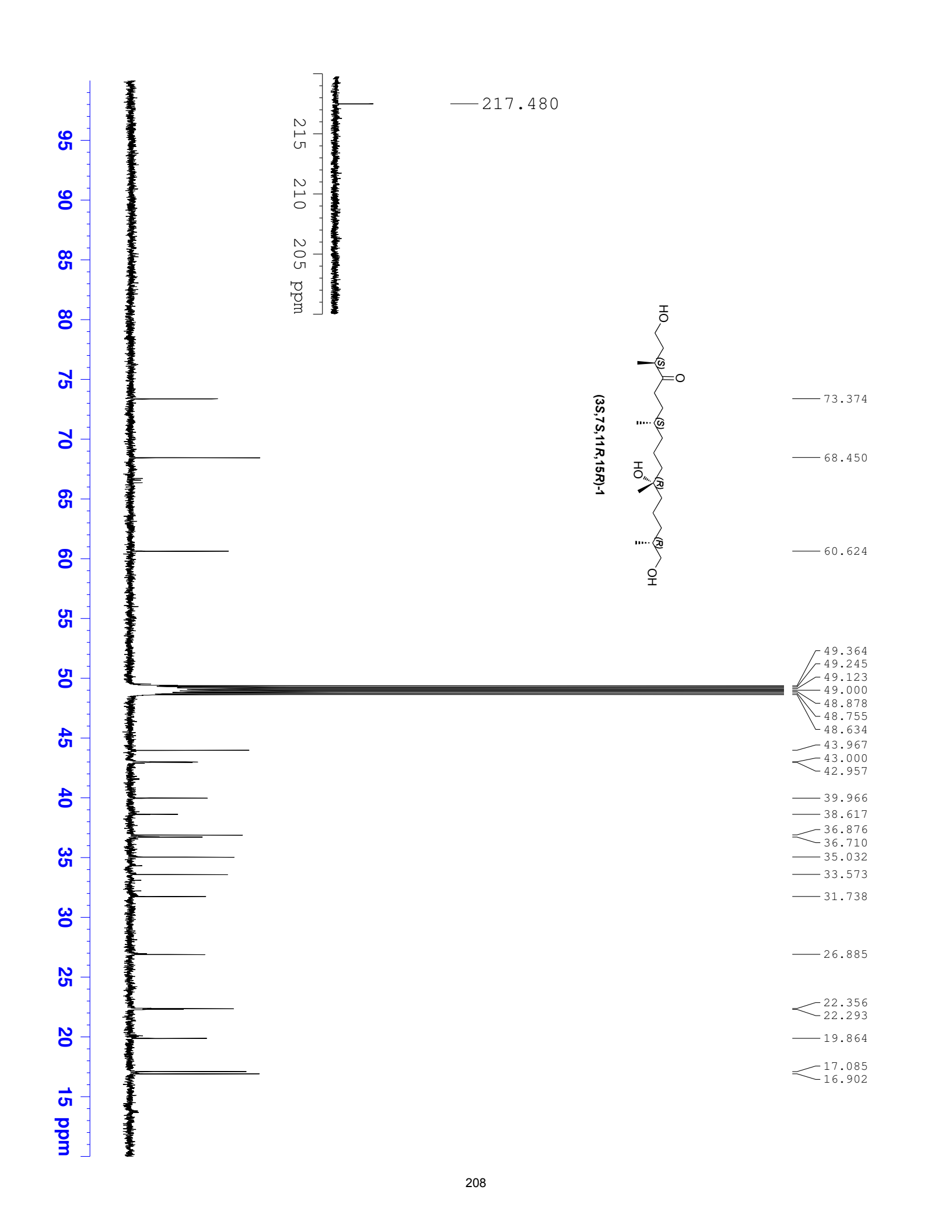


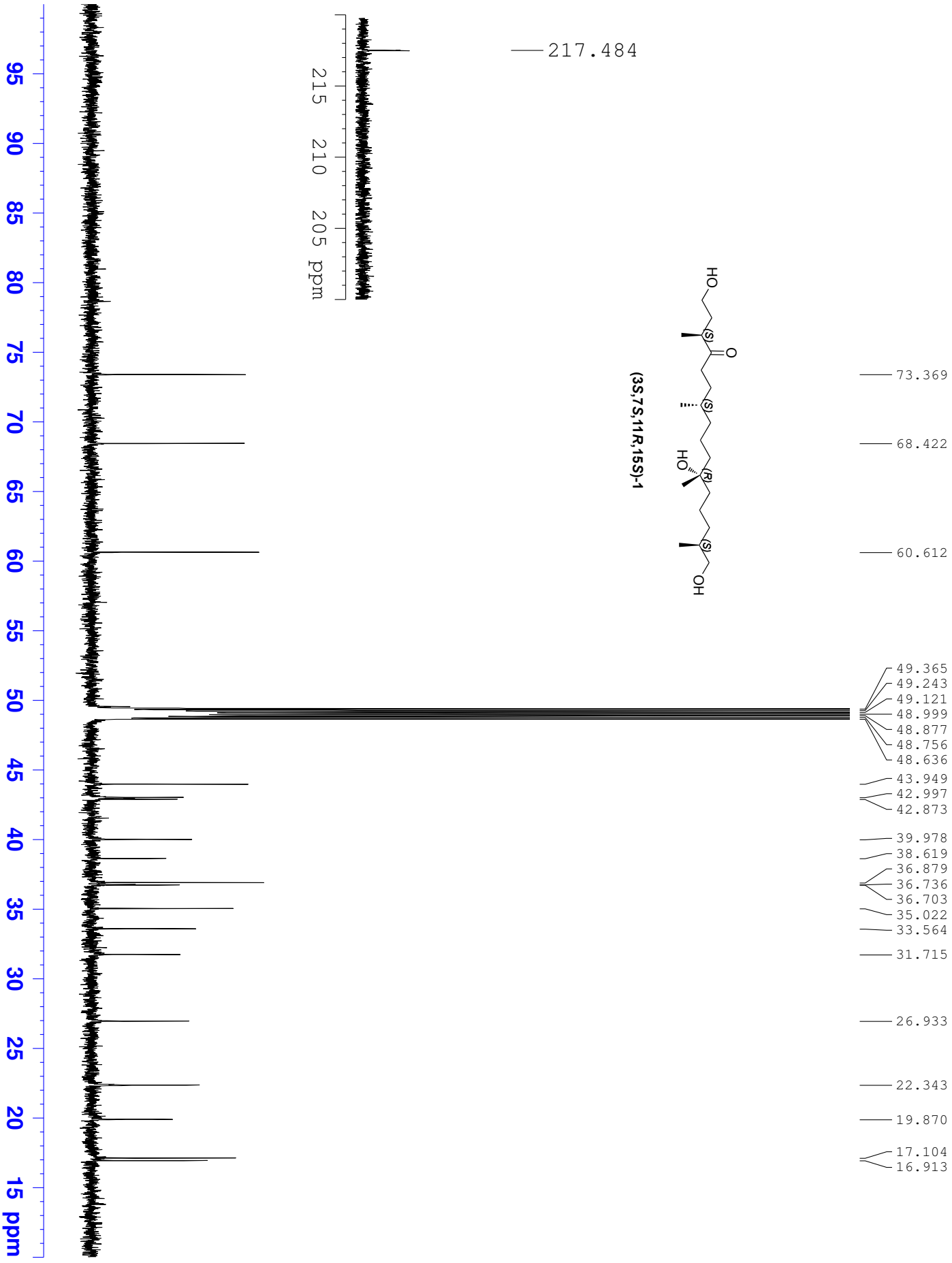
204

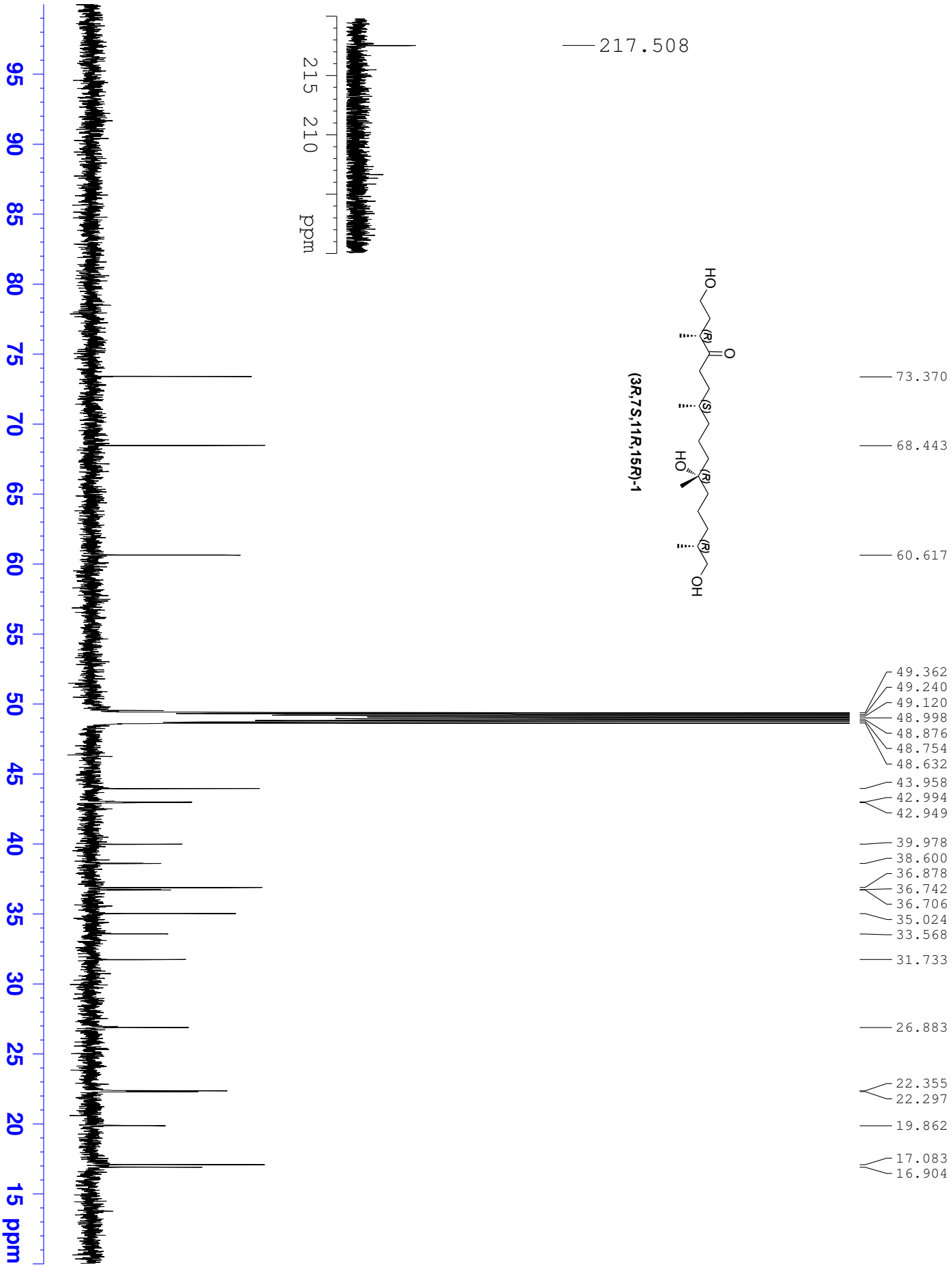

3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
ppm
2.11
1.49
1.72
0.96
1.96
1.05
2.26
1.42
18.00
4.94
4.07
6.77
3.519
3.419
3.411
3.404
3.396
3.328
3.318
3.312
2.804
2.780
2.770
2.760
2.750
2.592
2.583
2.568
2.554
2.547
2.536
2.527
2.518
2.505
2.493
2.482
1.909
1.899
1.890
1.880
1.870
1.860
1.586
1.507
1.498
1.488
1.479
1.469
1.460
1.414
1.406
1.368
1.360
1.348
1.315
1.306
1.282
1.121
1.074
1.064
(3S,7R,11R,15S)-1

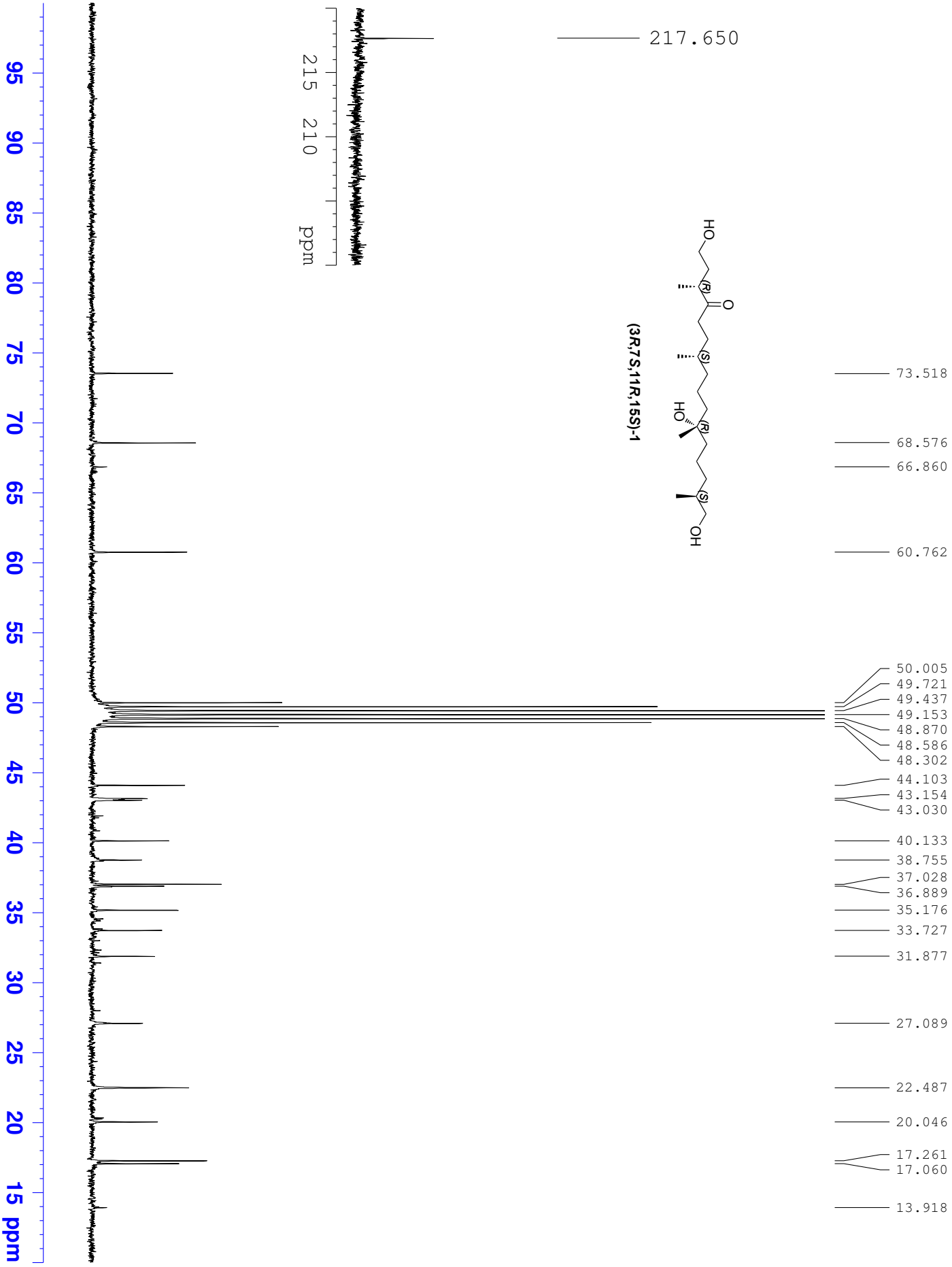

3.521
3.518
3.516
3.421
3.412
3.406
3.397
3.329
3.320
3.314
3.305
3.302
3.300
3.298
3.296
2.769
2.760
2.547
2.545
2.535
2.526
1.891
1.881
1.589
1.581
1.570
1.500
1.491
1.480
1.472
1.455
1.449
1.436
1.407
1.397
1.389
1.381
1.373
1.361
1.351
1.341
1.321
1.315
1.307
1.299
1.281
1.121
1.075
1.065
0.910
0.901
0.893
0.889
0.884
1.71
1.93
2.22
1.00
2.59
1.48
5.33
2.41
15.20
6.79
3.79
7.51
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
ppm
HO
O
HO
OH
(3R,7R,11R,15R)-1

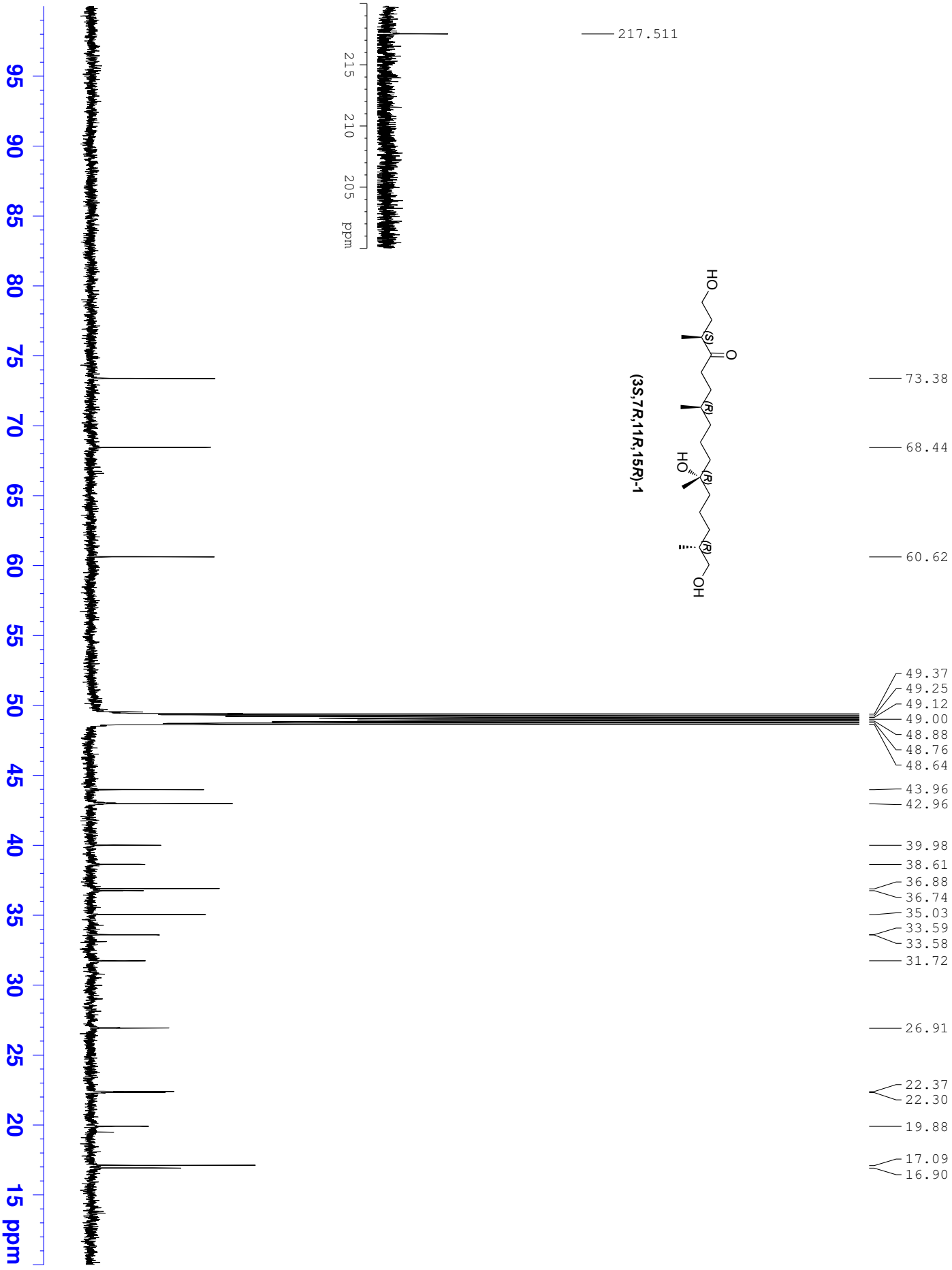

3.533
3.530
3.520
3.507
3.426
3.414
3.405
3.393
3.333
3.320
3.316
3.303
3.300
3.297
2.771
2.757
2.549
2.533
2.519
1.906
1.893
1.879
1.865
1.594
1.589
1.585
1.579
1.569
1.507
1.494
1.479
1.466
1.421
1.417
1.409
1.394
1.380
1.368
1.354
1.341
1.335
1.328
1.321
1.306
1.299
1.282
1.121
1.077
1.063
0.912
0.906
0.898
0.894
0.881
HO
O
(R)
(R)
(R)
(S)
OH
HO
(3R,7R,11R,15S)-1
207
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.00
1.15
2.00
0.99
2.21
1.19
3.45
1.77
16.69
1.71
3.77
1.10
3.06
7.92

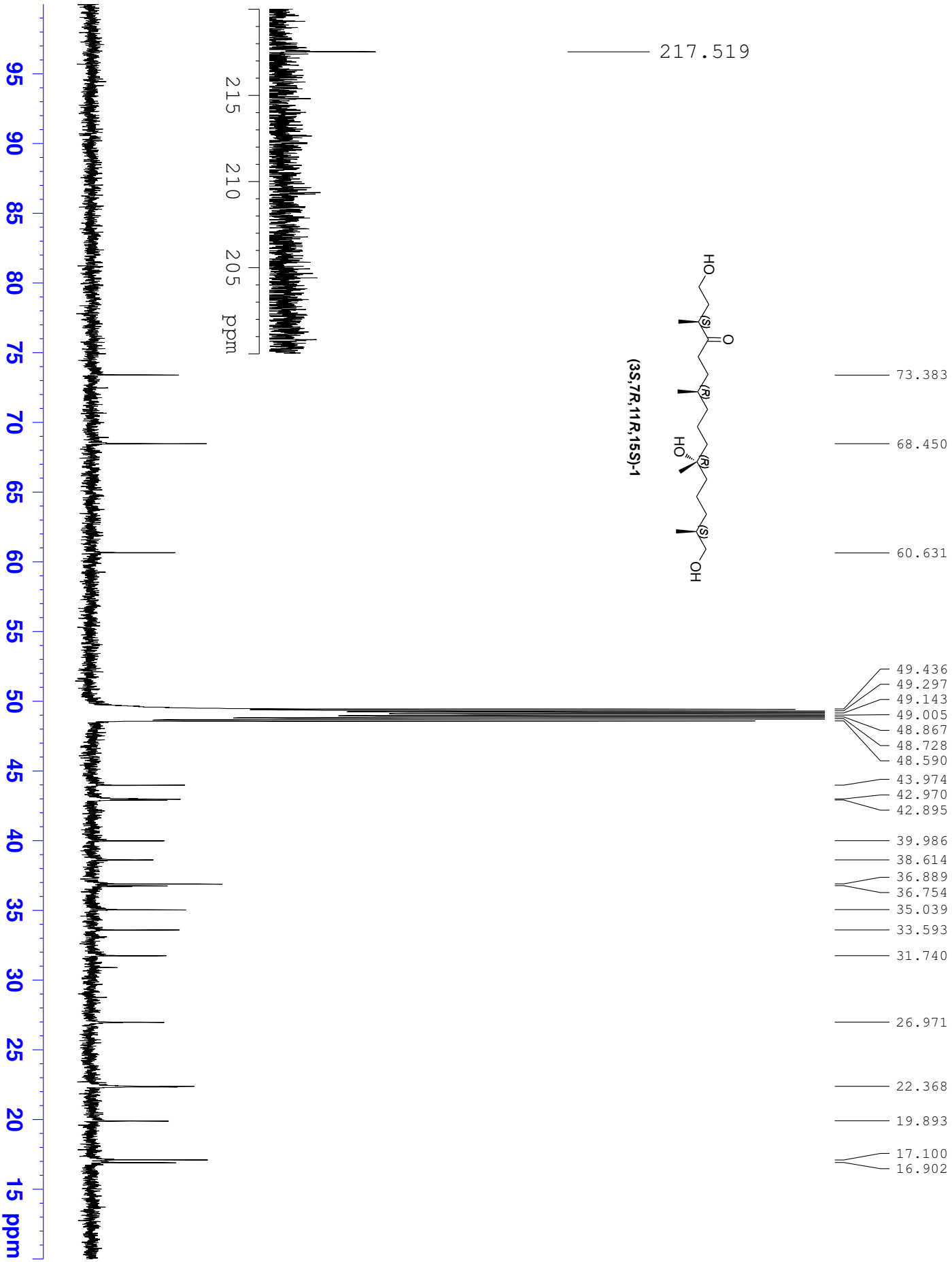

217.480
215
210
205 ppm
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15 ppm
HO
(S)
O
(S)
HO
(R)
(R)
OH
(3S,7S,11R,15R)-1
73.374
68.450
60.624
49.364
49.245
49.123
49.000
48.878
48.755
48.634
43.967
43.000
42.957
39.966
38.617
36.876
36.710
35.032
33.573
31.738
26.885
22.356
22.293
19.864
17.085
16.902

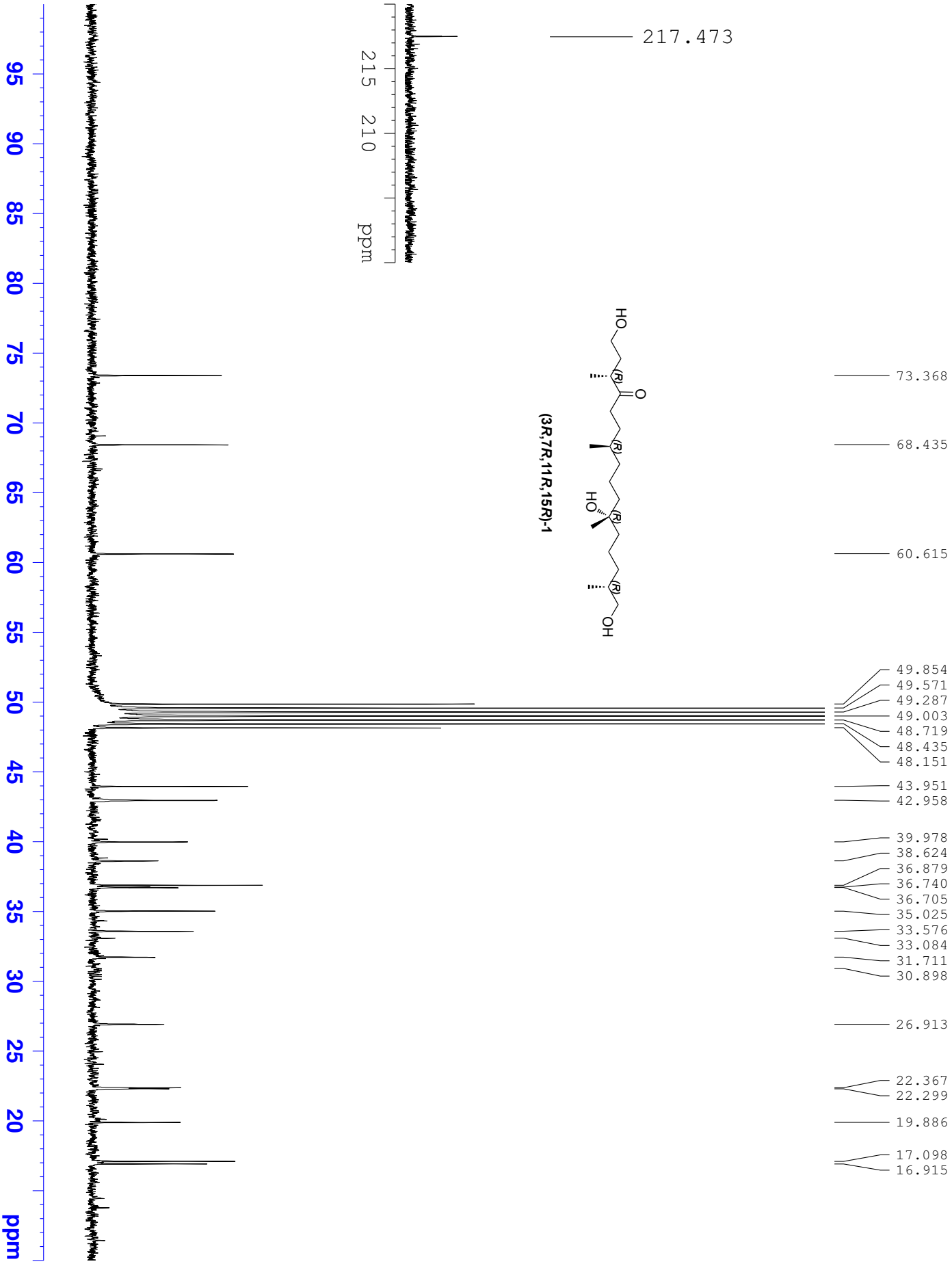

217.484
215
210
205 ppm
HO
(S)
O
(S)
HO
(R)
(S)
OH
(3S,7S,11R,15S)-1
73.369
68.422
60.612
49.365
49.243
49.121
48.999
48.877
48.756
48.636
43.949
42.997
42.873
39.978
38.619
36.879
36.736
36.703
35.022
33.564
31.715
26.933
22.343
19.870
17.104
16.913
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15 ppm

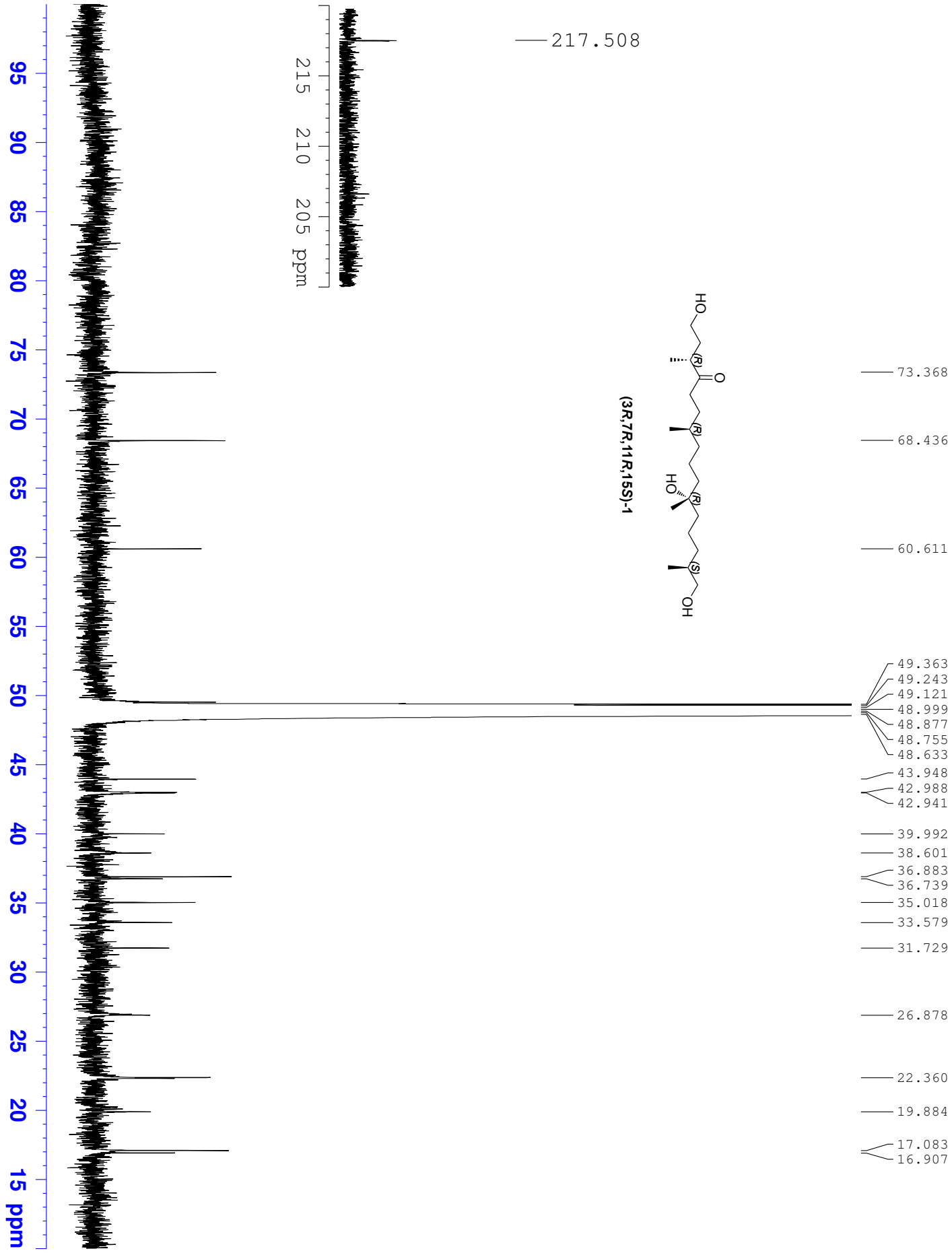

217.508
215
210
ppm
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15 ppm
HO
(R)
O
(S)
HO
(R)
(R)
OH
(3R,7S,11R,15R)-1
73.370
68.443
60.617
49.362
49.240
49.120
48.998
48.876
48.754
48.632
43.958
42.994
42.949
39.978
38.600
36.878
36.742
36.706
35.024
33.568
31.733
26.883
22.355
22.297
19.862
17.083
16.904

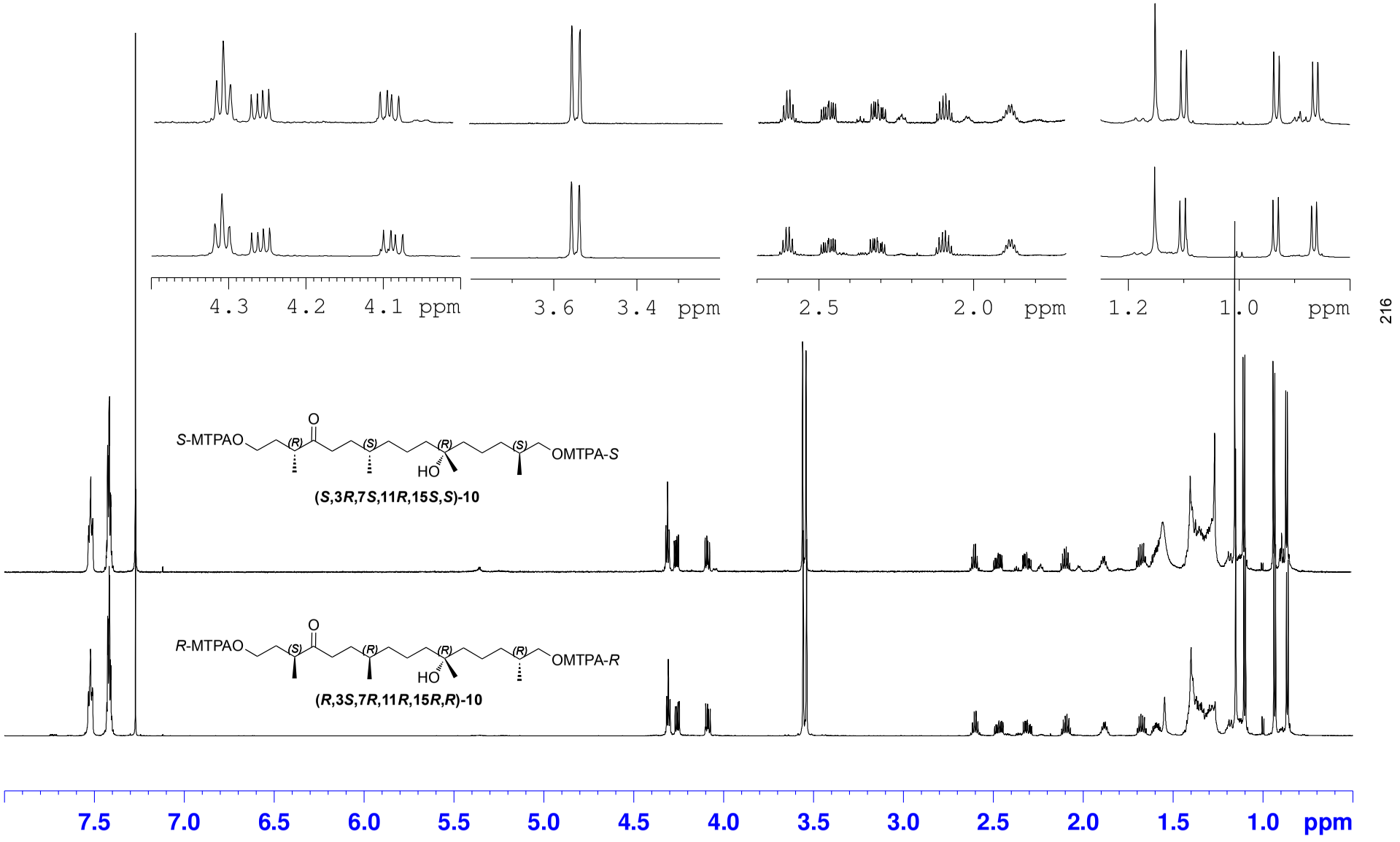

217.650
215
210
ppm
(3R,7S,11R,15S)-1
HO
O
OH
73.518
68.576
66.860
60.762
50.005
49.721
49.437
49.153
48.870
48.586
48.302
44.103
43.154
43.030
40.133
38.755
37.028
36.889
35.176
33.727
31.877
27.089
22.487
20.046
17.261
17.060
13.918
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
ppm

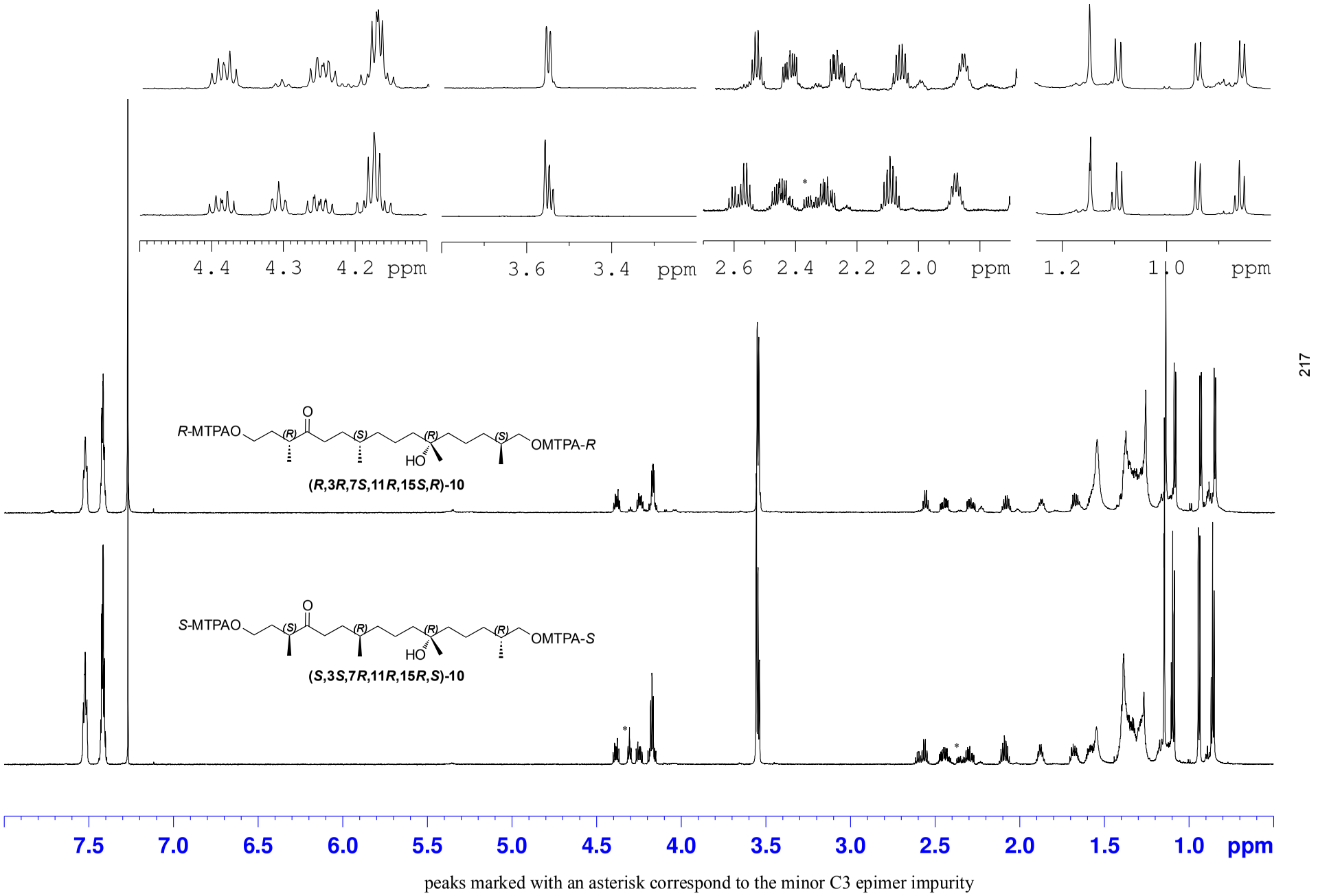

217.511
215
210
205
ppm
HO
(S)
O
(R)
HO
(R)
(R)
OH
(3S,7R,11R,15R)-1
73.38
68.44
60.62
49.37
49.25
49.12
49.00
48.88
48.76
48.64
43.96
42.96
39.98
38.61
36.88
36.74
35.03
33.59
33.58
31.72
26.91
22.37
22.30
19.88
17.09
16.90
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15 ppm


217.519
215
210
205
ppm
(3S,7R,11R,15S)-1
HO
(S)
O
(R)
(R)
HO
(S)
OH
73.383
68.450
60.631
49.436
49.297
49.143
49.005
48.867
48.728
48.590
43.974
42.970
42.895
39.986
38.614
36.889
36.754
35.039
33.593
31.740
26.971
22.368
19.893
17.100
16.902
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
ppm


217.473
215
210
ppm
(3R,7R,11R,15R)-1
73.368
68.435
60.615
49.854
49.571
49.287
49.003
48.719
48.435
48.151
43.951
42.958
39.978
38.624
36.879
36.740
36.705
35.025
33.576
33.084
31.711
30.898
26.913
22.367
22.299
19.886
17.098
16.915
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
ppm

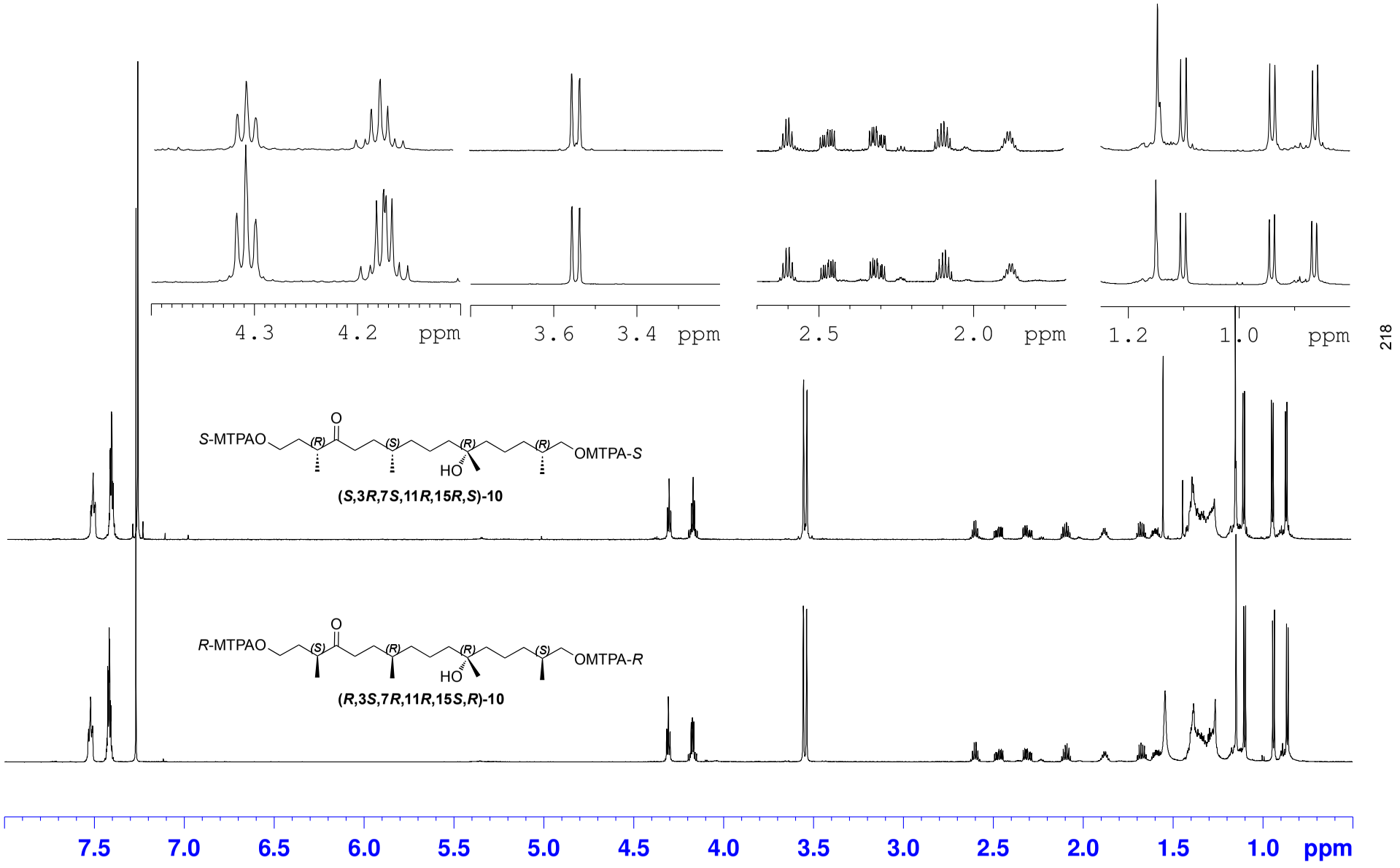

217.508
215 210 205 ppm
95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 ppm
(3R,7R,11R,15S)-1
HO
O
OH
73.368
68.436
60.611
49.363
49.243
49.121
48.999
48.877
48.755
48.633
43.948
42.988
42.941
39.992
38.601
36.883
36.739
35.018
33.579
31.729
26.878
22.360
19.884
17.083
16.907

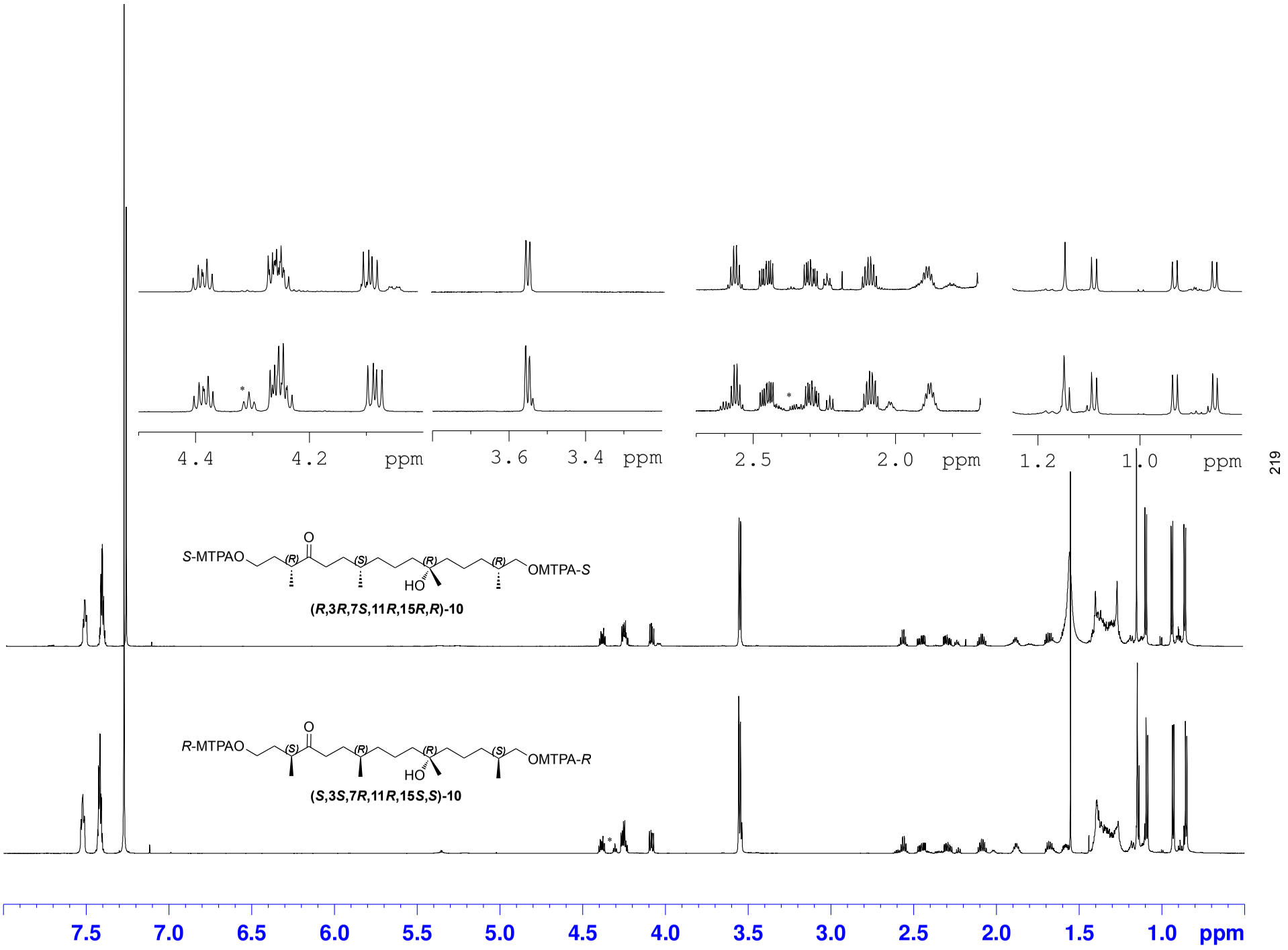

4.3
4.2
4.1 ppm
3.6
3.4 ppm
2.5
2.0 ppm
1.2
1.0 ppm
216
S-MTPAO
O
(R)
(S)
(R)
(S)
HO
OMTPA-S
(S,3R,7S,11R,15S,S)-10
R-MTPAO
O
(S)
(R)
(R)
(R)
HO
OMTPA-R
(R,3S,7R,11R,15R,R)-10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm



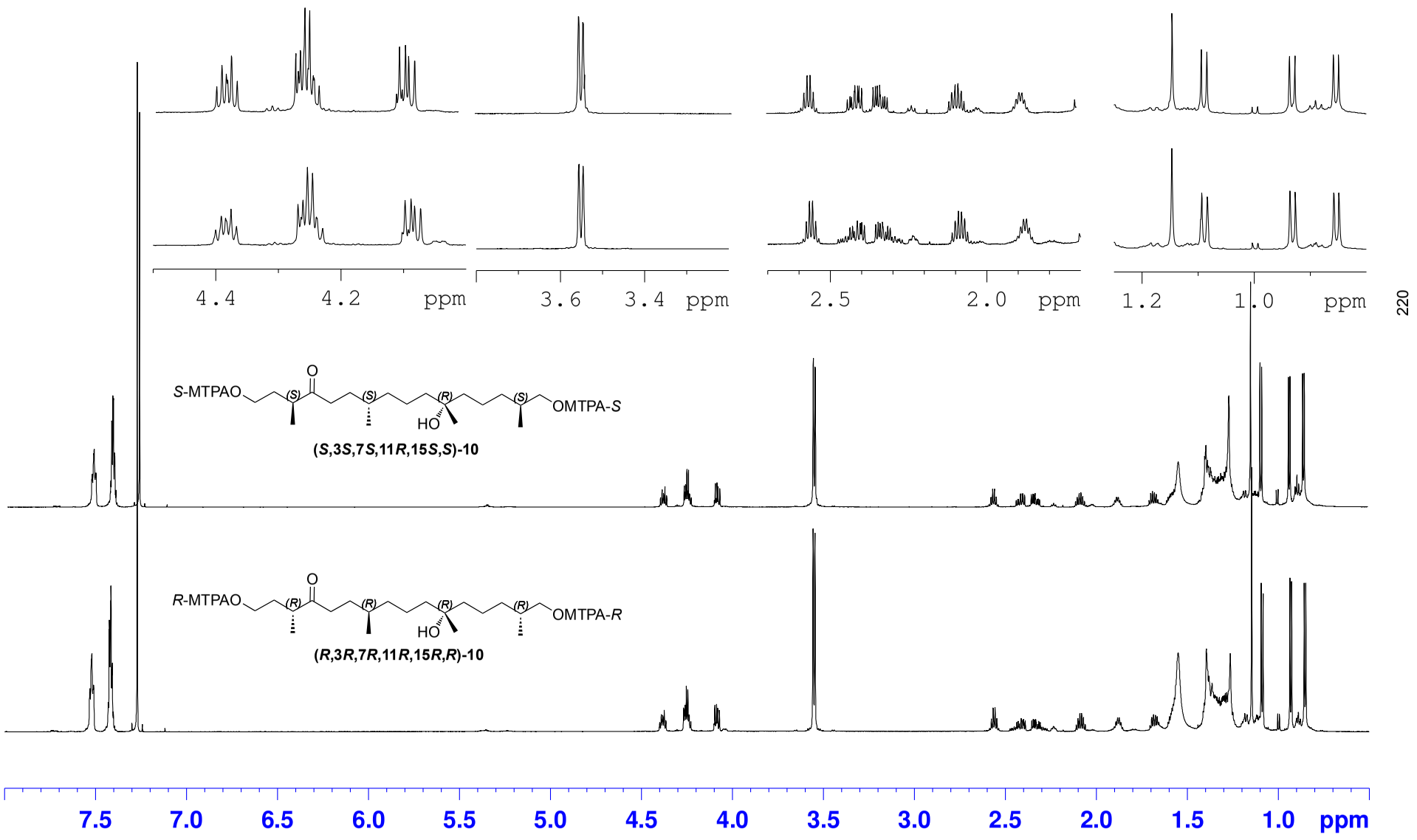
217

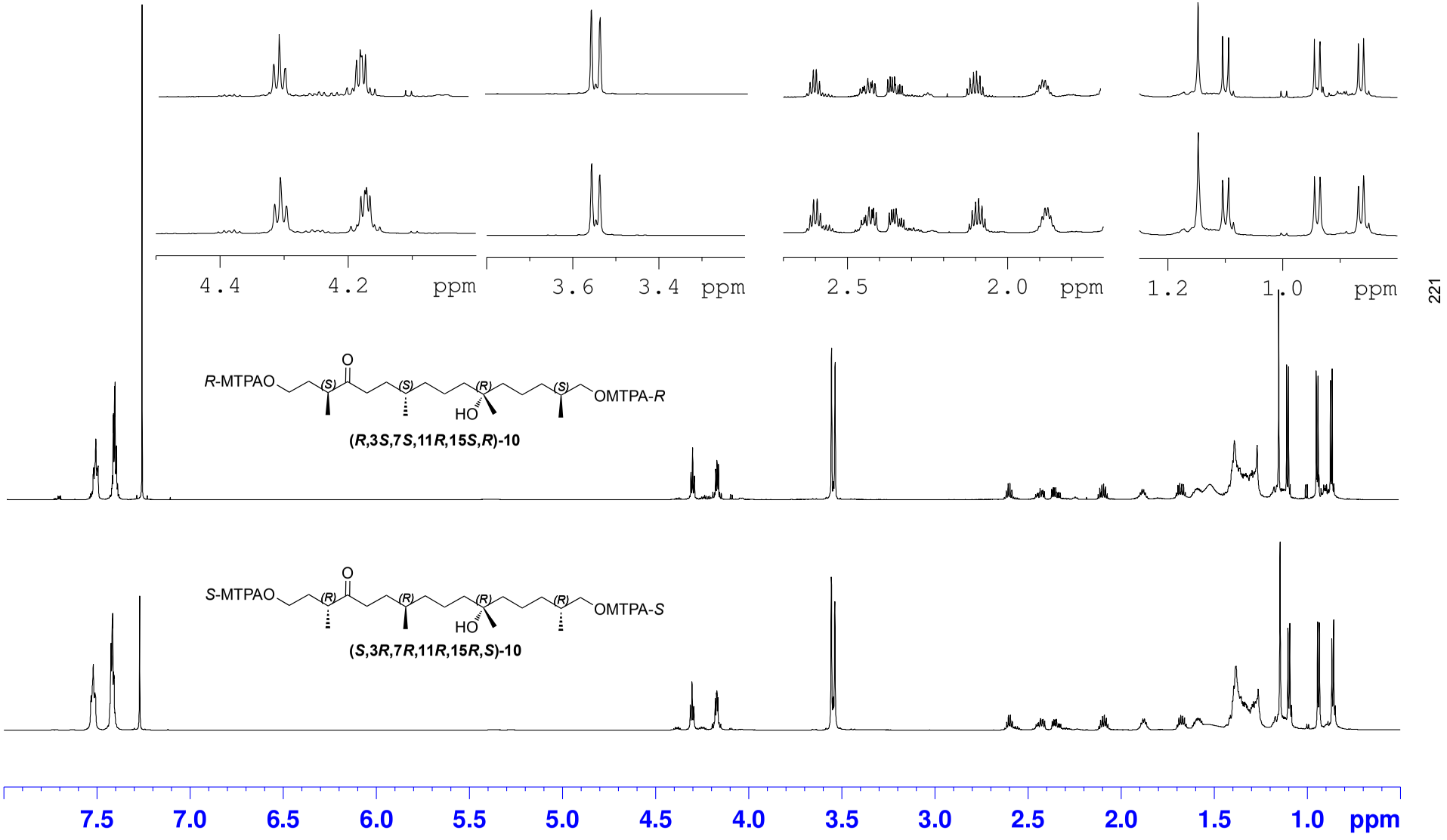
peaks marked with an asterisk correspond to the minor C3 epimer impurity

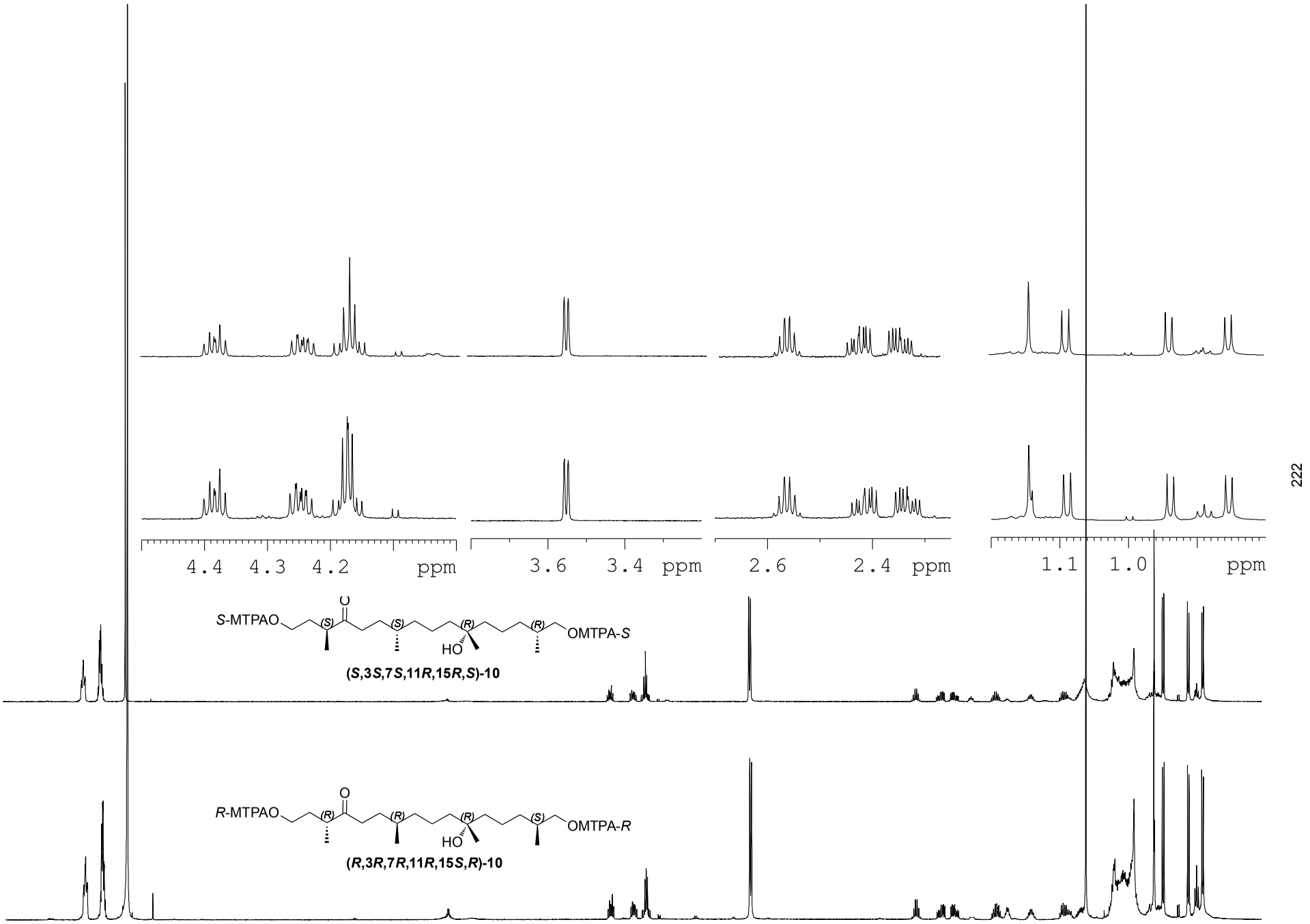

4.3
4.2
ppm
3.6
3.4
ppm
2.5
2.0
ppm
1.2
1.0
ppm
218
S-MTPAO
(R)
O
(S)
(R)
(R)
OMTPA-S
HO
(S,3R,7S,11R,15R,S)-10
R-MTPAO
(S)
O
(R)
(R)
(S)
OMTPA-R
HO
(R,3S,7R,11R,15S,R)-10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

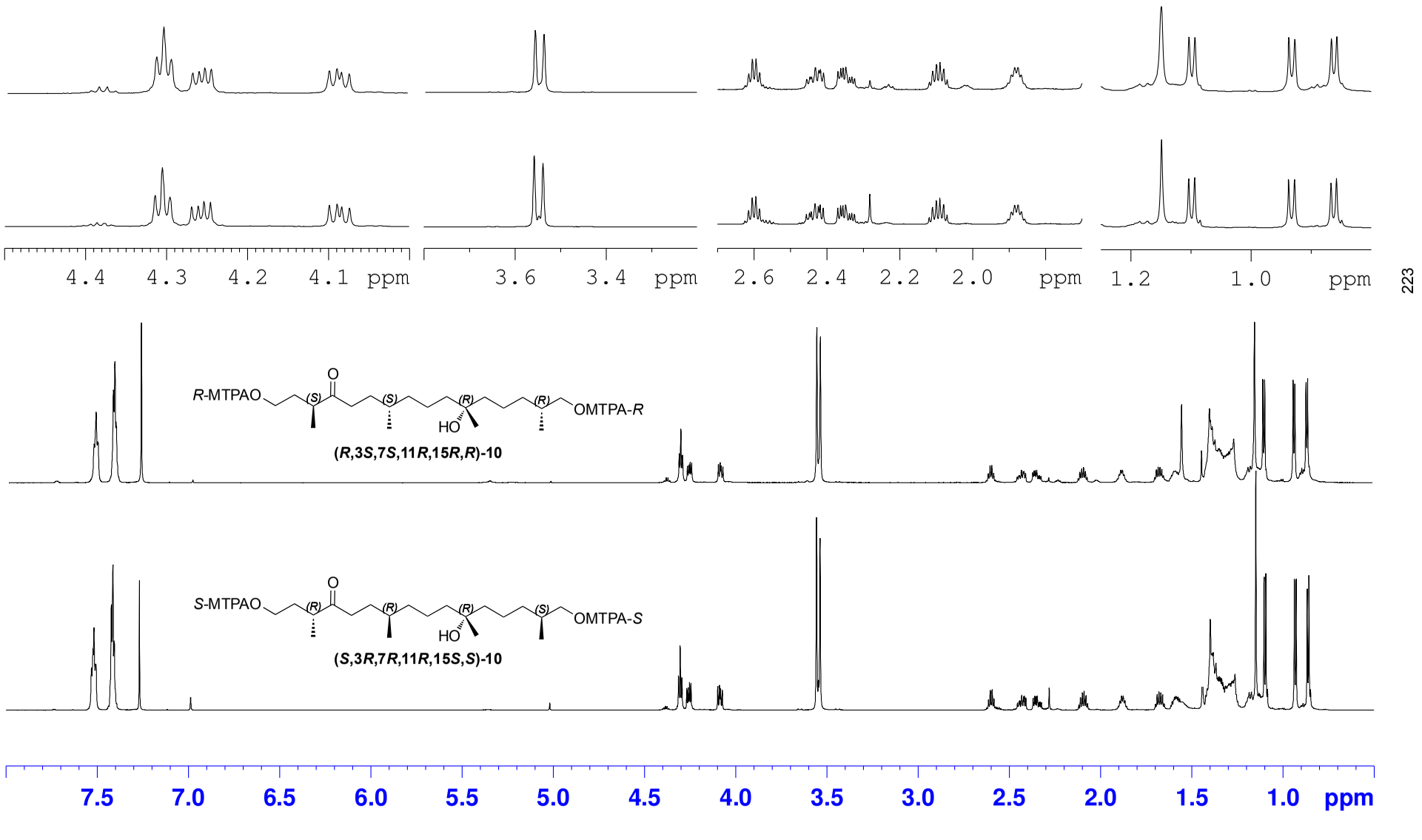


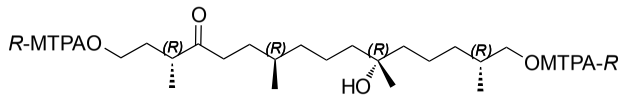
Peaks marked with asterisk correspond to the minor C3 epimer


4.4
4.2
ppm
3.6
3.4
ppm
2.5
2.0
ppm
1.2
1.0
ppm
220
S-MTPAO
O
(S)
(S)
(R)
(S)
HO
OMTPA-S
(S,3S,7S,11R,15S,S)-10
R-MTPAO
O
(R)
(R)
(R)
(R)
HO
OMTPA-R
(R,3R,7R,11R,15R,R)-10
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
ppm

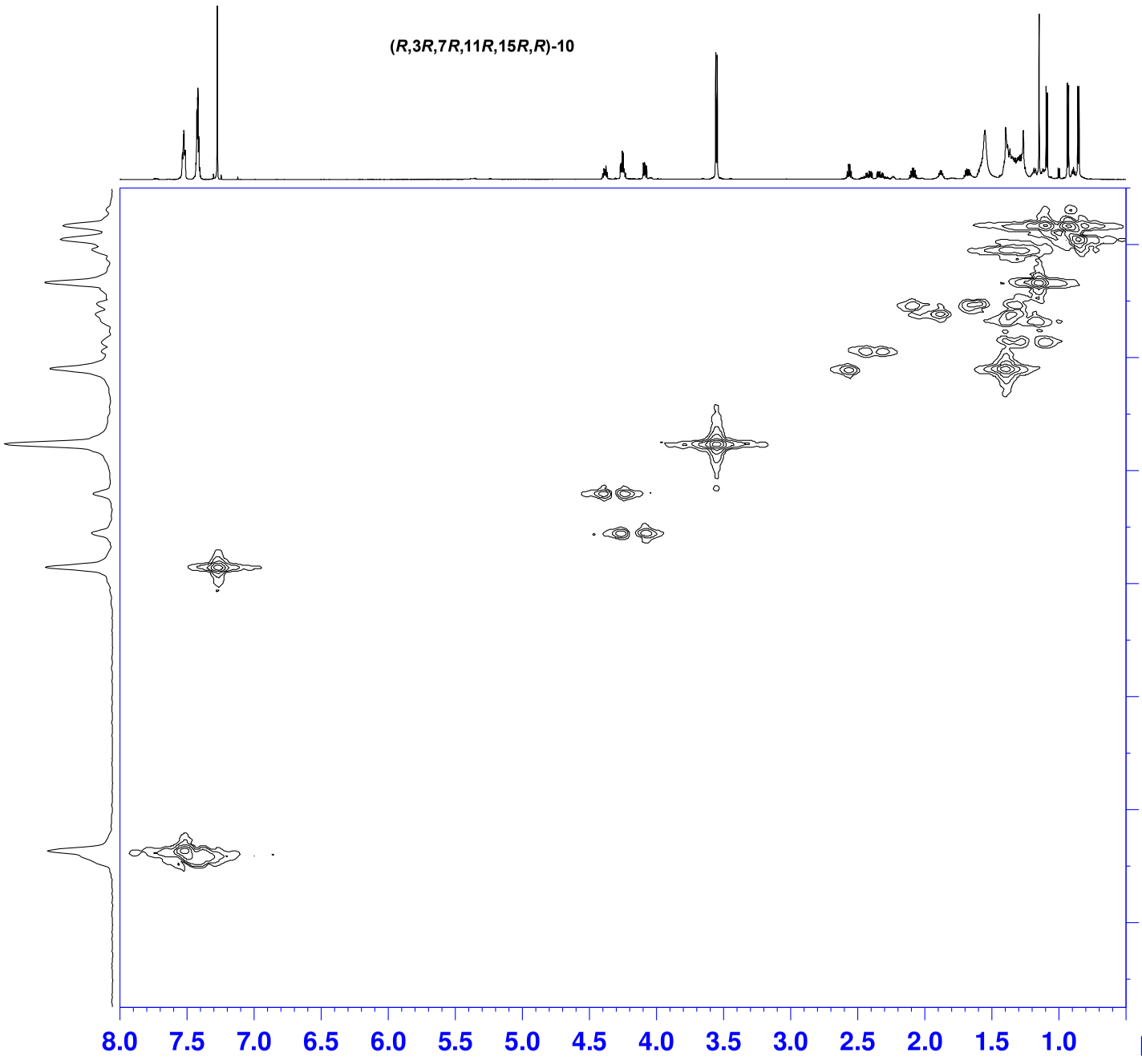

4.4
4.2
ppm
3.6
3.4
ppm
2.5
2.0
ppm
1.2
1.0
ppm
221
R-MTPAO
(S)
(S)
(R)
(S)
HO
OMTPA-R
(R,3S,7S,11R,15S,R)-10
S-MTPAO
(R)
(R)
(R)
(R)
HO
OMTPA-S
(S,3R,7R,11R,15R,S)-10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


4.4 4.3 4.2 ppm
3.6 3.4 ppm
2.6 2.4 ppm
1.1 1.0 ppm
S-MTPAO
OMTPA-S
HO
(S,3S,7S,11R,15R,S)-10
R-MTPAO
OMTPA-R
HO
(R,3R,7R,11R,15S,R)-10
222


4.4
4.3
4.2
4.1
ppm
3.6
3.4
ppm
2.6
2.4
2.2
2.0
ppm
1.2
1.0
ppm
R-MTPAO
OMTPA-R
HO
(R,3S,7S,11R,15R,R)-10
S-MTPAO
OMTPA-S
HO
(S,3R,7R,11R,15S,S)-10
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
ppm



(*R*,3*R*,7*R*,11*R*,15*R*,*R*)-10

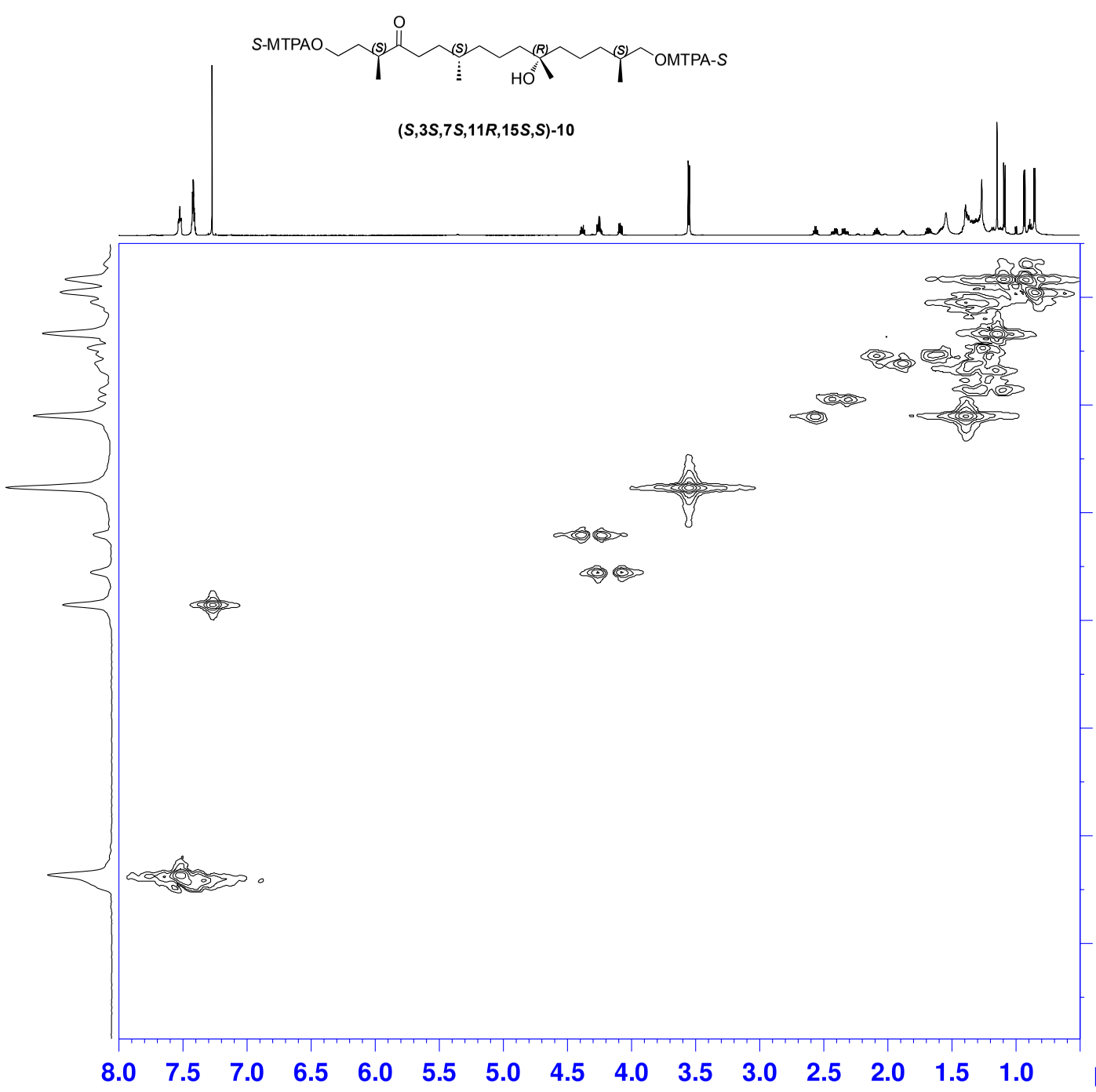



```
NAME            rb00026.092-2
EXPNO                       4
PROCNO                      1
Date_                20100218
Time                    18.59
INSTRUM                 spect
PROBHD    5 mm PATXI 1H-
PULPROG              hmqcgpqf
TD                       1024
SOLVENT                 CDCl3
NS                         80
DS                         16
SWH                 14423.077 Hz
FIDRES                14.085036 Hz
AQ                    0.0355487 sec
RG                         2050
DW                       34.667 usec
DE                         6.50 usec
TE                        295.0 K
CNST2               145.0000000
D0                    0.00000300 sec
D1                    1.50000000 sec
D2                    0.00344828 sec
D12                   0.00002000 sec
D13                   0.00000400 sec
D16                   0.00020000 sec
IN0                   0.00001715 sec

======== CHANNEL f1 ========
NUC1                        1H
P1                        8.36 usec
P2                       16.72 usec
PL1                       2.40 dB
PL1W                13.05232048 W
SFO1                700.1543237 MHz

======== CHANNEL f2 ========
CPDPRG2                  garp
NUC2                       13C
P3                       10.00 usec
PCPD2                   100.00 usec
PL2                      -5.30 dB
PL12                     14.70 dB
PL2W                411.95083618 W
PL12W                 4.11950827 W
SFO2                176.0660602 MHz

===== GRADIENT CHANNEL =====
GPNAM1                SINE.100
GPNAM2                SINE.100
GPNAM3                SINE.100
GPZ1                     50.00 %
GPZ2                     30.00 %
GPZ3                     40.10 %
P16                    1000.00 usec
D0                           2
D                          128
SFO1                176.0661 MHz
FIDRES               227.839355 Hz
SW                      165.639 ppm
FnMODE                      QF
SI                        1024
SF                  700.1500116 MHz
WDW                      QSINE
SSB                          2
LB                        0.00 Hz
GB                           0
PC                        1.40
SI                        1024
MC2                         QF
SF                  176.0528707 MHz
WDW                      QSINE
SSB                          2
LB                        0.00 Hz
GB                           0
```



BRUKER

```
NAME          rb00017.081-2
EXPNO                    12
PROCNO                    1
Date_              20100223
Time                  20.03
INSTRUM               spect
PROBHD    5 mm PATXI 1H-
PULPROG           hmqcgpqf
TD                     1024
SOLVENT               CDCl3
NS                       80
DS                       16
SWH              14423.077 Hz
FIDRES           14.085036 Hz
AQ               0.0355487 sec
RG                    2050
DW                  34.667 usec
DE                    6.50 usec
TE                   295.6 K
CNST2           145.0000000
D0               0.00000300 sec
D1               1.50000000 sec
D2               0.00344828 sec
D12              0.00002000 sec
D13              0.00000400 sec
D16              0.00020000 sec
IN0              0.00001715 sec

======== CHANNEL f1 ========
NUC1                     1H
P1                     8.36 usec
P2                    16.72 usec
PL1                    2.40 dB
PL1W            13.05232048 W
SFO1           700.1543237 MHz

======== CHANNEL f2 ========
CPDPRG2                garp
NUC2                    13C
P3                    10.00 usec
PCPD2                100.00 usec
PL2                   -5.30 dB
PL12                  14.70 dB
PL2W           411.95083618 W
PL12W            4.11950827 W
SFO2           176.0660602 MHz

====== GRADIENT CHANNEL =====
GPNAM1             SINE.100
GPNAM2             SINE.100
GPNAM3             SINE.100
GPZ1                  50.00 %
GPZ2                  30.00 %
GPZ3                  40.10 %
P16                 1000.00 usec
ND0                       2
TD                      128
SFO1           176.0661 MHz
FIDRES         227.839355 Hz
SW               165.639 ppm
FnMODE                  QF
SI                    1024
SF             700.1500116 MHz
WDW                  QSINE
SSB                       2
LB                     0.00 Hz
GB                        0
PC                     1.40
SI                    1024
MC2                     QF
SF             176.0528707 MHz
WDW                  QSINE
SSB                       2
LB                     0.00 Hz
GB                        0
```