FLUOROUS SYNTHESIS OF A TRI-β-PEPTIDE LIBRARY AND EIGHT STEREOISOMERS OF MACROLACTONE SCH725674

by

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Chapter 1 of this dissertation describes a new strategy to make β-peptide libraries. A 27-membered tri-β-peptide library was prepared. β-Azido acids as building blocks were tagged with fluorous PMB group. Two reduction-amide coupling cycles were done. Intermediates were separated by Fluorous Solid Phase Extraction (FSPE). The reductive deprotection gave the final 27 tri-β-peptide, which were purified by reverse phase HPLC. Purity of the library was checked by LC-MS. Mass spectroscopy data of 25 products matched with calculation.

Chapter 2 describes the Fluorous Mixture Synthesis (FMS) of eight stereoisomers of 14-membered macrolactone Sch725674. The configurations of Sch725674 were completely unknown when discovered. A single diastereomer of Sch725674 was prepared first by traditional solution phase synthesis. In the FMS, stereoisomeric starting materials were tagged with different fluorous TIPS groups. The tagged quasidiastereomers were mixed and the mixture underwent a series of steps to make the fluorous tagged macrolactones, which were separated by fluorous HPLC followed by individual deprotections to provide the eight final products. The NMR data of the eight synthetic macrolactones were compared with those of Sch725674. The absolute configuration of Sch725674 was confirmed as (4*R*,5*S*,7*R*,13*R*).

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LIST OF ABBREVIATIONS

Bn	benzyl
^{i}Bu	isobutyl
^{t}Bu	*tert*-butyl
COSY	correlation spectroscopy
DBU	diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
dr	diastereomeric ratio
DIC	diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMP	Dess-Martin periodinane
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
equiv	equivalent
Et	ethyl
EtOAc	ethyl acetate
FSPE	fluorous solid-phase extraction
FMS	fluorous mixture synthesis
^{F}*t*-BuOH	2-methyl-4-perfluorodecyl-2-butanol (fluorous *t*-butanol)
^{F}PMBOH	4-[3-(perfluorooctyl)propyl-1-oxy]benzyl alcohol (fluorous PMB alcohol)
GC	gas chromatography
HMBC	heteronuclear multiple bond coherence
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Ipc	isopinocamphenyl
IR	infrared spectroscopy
LC-MS	liquid chromatography-mass spectrometry
Me	methyl
MeCN	acetonitrile
MIC	minimum inhibitory concentration
MS	mass spectrometry
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
Ph	phenyl
PPTS	pyridinium *p*-toluensulfonate
PPY	4-(pyrrolidin-1-yl)pyridine

*i*Pr	isopropyl
RCM	ring-closing metathesis
R_F	retention factor
SPS	solid-phase synthesis
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TEA	triethylamine
TFA	trifluoroacetic acid
TfO	triflate
THF	tetrahydrofuran
TIC	total ion count
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSQ	9-trimethylsilylquinidine
TMSq	9-trimethylsilylquinine
t_R	retention time
UV	ultraviolet

PREFACE

I would like to thank Professor Dennis P. Curran for bringing me to this stage of education. I am grateful for his continuous encouragement. His guidance, patience and inspiration made this work possible. I would like to thank Professors Scott G. Nelson, Paul E. Floreancig and Billy W. Day for serving on my thesis committee.

I would like to thank all the Curran group members, past and present, for their friendship and help, and for providing a sociable and stimulating working environment.

I would also like to thank NMR and MS facilities at the University of Pittsburgh. Special thanks to Professor Day for his help with mass spectroscopy.

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

CHAPTER 1. THE PARALLEL SYNTHESIS OF A TRI-β-PEPTIDE LIBRARY BY FLUOROUS TAGGING

1.1 INTRODUCTION

1.1.1 β-Amino acids and β-peptides.

Peptides constructed from α-amino acids play an important role in numerous biological and physiological processes in living organisms. Since the first synthesis of a dipeptide by Emil Fischer in 1901, tremendous progress has been made in peptide science, and large proteins can be synthesized nowadays.[1] α-Amino acids are carboxylic acids that bear amino groups at the α carbons. The 20 naturally occurring α-amino acids serve as the basic structural units of natural proteins. β-Amino acids have their amino groups bonded to β-carbons.[1] Peptides that consist of β-amino acids are called β-peptides. Several typical structures of β-amino acids and β-peptides are shown in Figure 1.1.

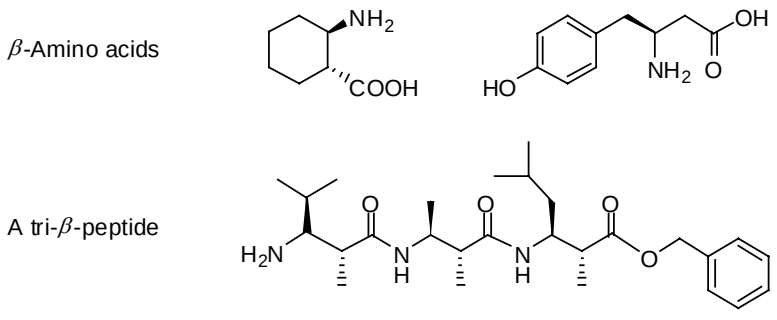
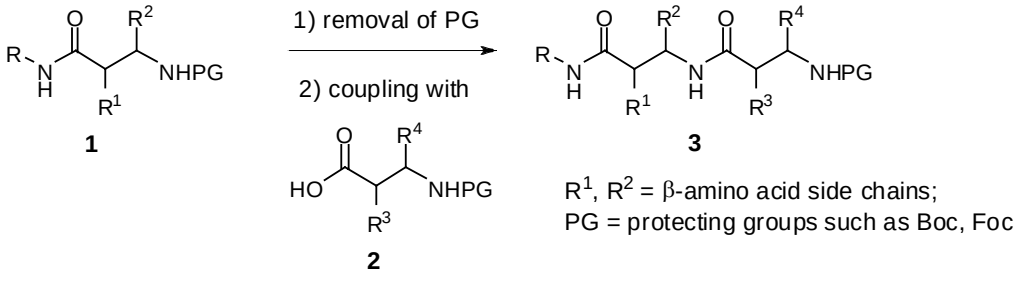


Figure 1.1. Typical structures of β-amino acids (top) and β-peptides (bottom)

Because β-peptides do not appear in nature, they are often evaluated as a potential source of drugs to evade antibiotic resistance.[2] They are also interesting scaffolds for building catalysts. From a structural viewpoint, β-peptides have predictable folding patterns and exhibit many kinds of secondary structures. These features have promoted the intensive study of the structures of β-peptide foldamers to better understand protein structures.[3]

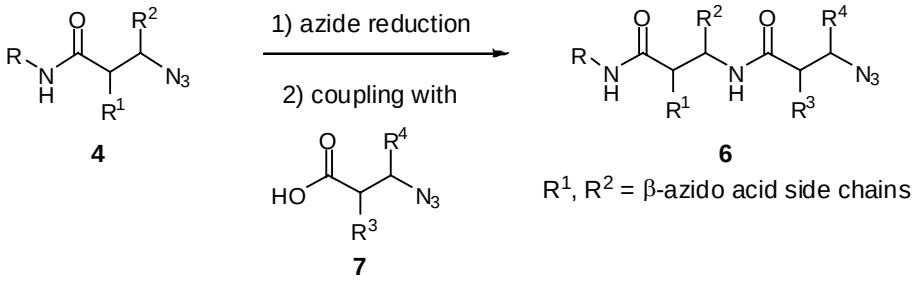
1.1.2 β-Peptides synthesis.

Most syntheses of β-peptides are patterned after the traditional approach to make α-peptides.[4] The key building blocks are N-protected β-amino acids **2**, which are joined with **1** to form β-peptides **3** by an iterative sequence of N-deprotection and amide coupling (Scheme 1.1). Some of the most important ways[5] to synthesize β-amino acids are the homologation of α-amino acids,[6] preparation from aspartic acid and asparagines, Michael addition of amines to acrylates,[7,8] and the nucleophilic addition to imine equivalents.[9]



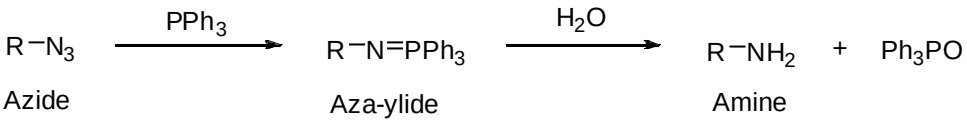
Scheme 1.1. The protected amino acid approach to β-peptides

α-Peptides have also been made from α-azido acids.[11] But the azide approach is not used very often because: 1) α-amino acids are much more readily available than α-azido acids; 2) α-azido acids are prone to epimerization. The azido acid approach is much more useful for β-peptide synthesis because: 1) the small size makes the azido group more atom economic compared to protected amines; 2) β-azido acids do not have the epimerization problem. Nelson and coworkers recently developed the β-azido acid approach to make β-peptides. It involves an iterative sequence of reduction of the azide (**4** or **6**) to the amine followed by coupling of the amine with the next β-azido acid (**7**) (Scheme 1.2).[10]



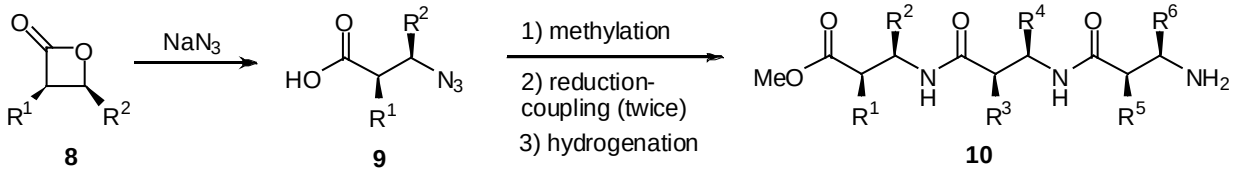
Scheme 1.2. The azido acid approach to β-peptides

The azido group of a β-azido acid can be readily reduced by the well-known Staudinger reaction.[12] The azide reacts with triphenylphosphine to give an aza-ylide, which is subsequently hydrolyzed to give the primary amine (Scheme 1.3). Heat sometimes is required for conducting the Staudinger reaction, especially in the hydrolysis step.



Scheme 1.3. The Staudinger reaction

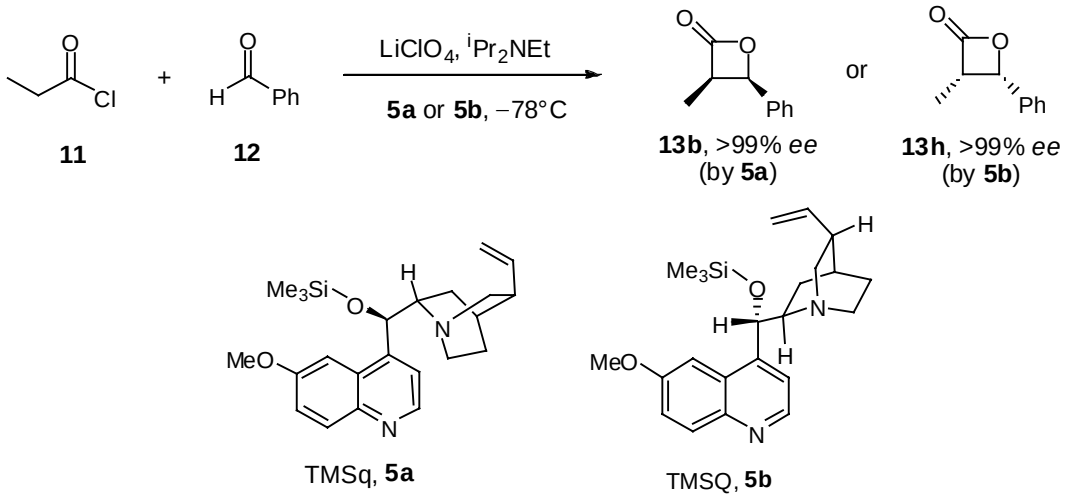
In Nelson's β-peptide synthesis, β-azido acids are prepared from β-lactones via a ring-opening process (Scheme 1.4).[10,13] β-Lactone **8** reacts with NaN_3 to give β-azido acid **9**. The regioselectivity of the nucleophilic attack of β-lactones can be explained by the Hard-Soft Acid-Base theory.[14,15] Soft nuleophiles (such as azides) prefer to attack the soft, sp^3-hybridized β-carbon, while hard nucleophiles (such as amines) prefer to attack the hard, sp^2-hybridized carbonyl carbon. β-Azido acid **9** then undergoes methylation, two reduction-coupling cycles and hydrogenation to give tri-β-peptide **10**.[10]



Scheme 1.4. The Nelson's approach to tri-β-peptide

β-Lactones can be synthesized by the cycloaddition reactions of aldehydes and acid chlorides such as the Wynberg reaction.[16,17] In 2004, Nelson and coworkers developed an asymmetric cinchona alkaloid-catalyzed acid chloride-aldehyde cyclocondensation (AAC) reaction.[18] An example of the Nelson reaction is described in Scheme 1.5. Acid chloride **11** reacts with aldehyde **12** in the presence of the Lewis acid ($LiClO_4$) and the protected cinchona alkaloid

9-trimethylsilylquinine ("TMSq", **5a**) or 9-trimethylsilylquinidine ("TMSQ", **5b**) to give β-lactone **13b** or **13h**, respectively. Unlike the Wynberg reaction, which is limited to electron-deficient aldehydes, the Nelson reaction can be used for many other aldehydes.



Scheme 1.5. An example of Nelson's cinchona alkaloid-catalyzed AAC reaction

The combination of the Nelson's AAC reaction and the azide ring-opening of the resulting β-lactones provides a powerful way to make β-azido acids for the β-peptide synthesis.

1.1.3 Light fluorous tagging strategy for peptide synthesis.

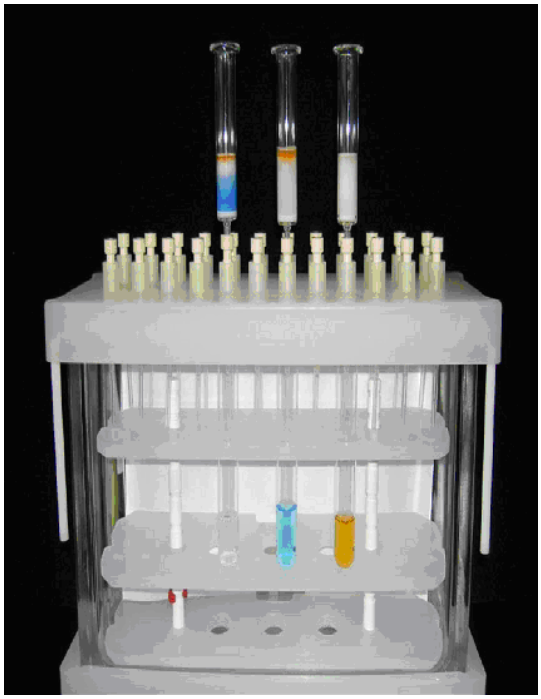
Solid-phase synthesis (SPS) is the most frequently used method to make peptides, and it is highlighted by the simple purification by filtration.[23] Substrates are bonded to a solid phase and reactions can be done by adding reactants in the liquid phase in large excess. However, there are several advantages of the solution-phase synthesis. First, compared to SPS, much less reagents in

the liquid phase are needed. Second, compared to SPS, the yields of solution-phase reactions are generally higher because of the reaction homogeneity. And monitoring the reaction process and characterizing the product by NMR, LC and MS are much easier for solution-phase synthesis than for SPS.

Recently, small libraries have been made by solution-phase synthesis with light fluorous technologies.[24,25] Light fluorous molecules are organic molecules that bear small perfluoroalkyl tags such as C_6F_{13} and C_8F_{17}.[19-21] Light fluorous tags are chemically inert and the tagged compounds can react with other organic substrates under the same conditions as their nonfluorous relatives. The fluorous tags can be removed under the similar deprotection conditions to their nonfluorous relatives. The advantage of the fluorous approach is that fluorous compounds can be easily and rapidly separated from organic reaction products by fluorous solid-phase extraction (FSPE). The fluorous silica gel is used as sorbent in FSPE, and it is synthesized by functionalizing normal phase silica gel with a silane containing a perfluorocarbon chain. The fluorous affinity interaction between the fluorous silica gel and fluorous-tagged compounds separates them from nonfluorous compounds.[21]

FSPE is easy to conduct. A washed and pre-conditioned FSPE cartridge is loaded with the reaction mixture of the fluorous-tagged compound and other nonfluorous compounds. The cartridge is washed with a fluorophobic solvent like MeCN, MeOH, DMF and DCM, usually in combination with water, to obtain a fraction containing nonfluorous compounds. The cartridge is subsequently washed with a fluorophilic solvent like THF, MeCN or MeOH to obtain the

fraction containing the fluorous compounds.[21] A picture of FSPE is shown in Figure 1.2.

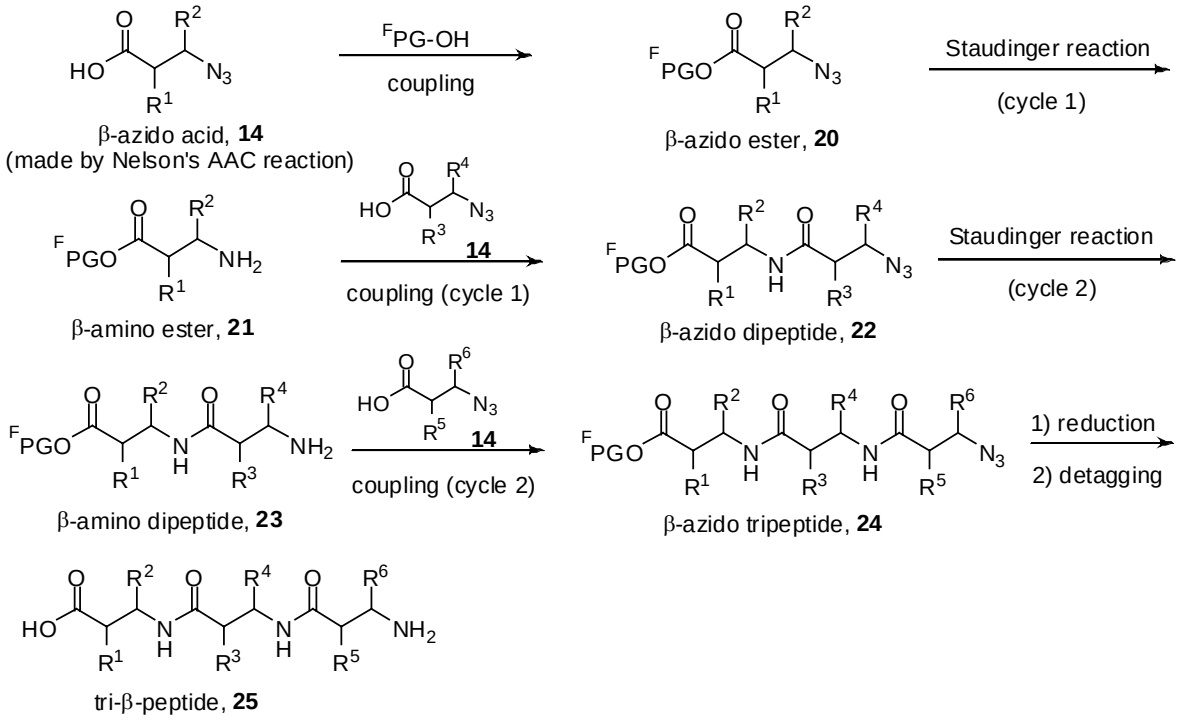


Left tube: beginning of fluorophobic wash with 80:20 MeOH:H_2O
Center tube: end of fluorophobic wash (blue: organic dye)
Right tube: end of fluorophilic wash with 100% MeOH (orange: fluorous-tagged dye)
(Picture from www.fluorous.com)

Figure 1.2. An illustration of FSPE

Reactions of fluorous tagged α-amino acids with separation by FSPE were previously reported by our group.[22] We set out to develop a route for the synthesis of β-peptides by combining Nelson's azido acid approach with separation of intermediates and products by FSPE. The proposed synthesis is shown in Scheme 1.6. After the tagging of β-azido acid **14** with a fluorous protecting group (^{F}PG), the resulting β-azido ester **20** undergoes the reduction by the Staudinger reaction to give amine **21**, which is coupled with a same or different β-azido acid **14** to give azido dipeptide **22**. Peptide **22** is subjected to the second reduction-coupling cycle to give

azido tripeptide **24**. At last, the reduction of the azido group to the amino group and the removal of the fluorous tag furnish tri-β-peptide **25**. A small tri-β-peptide library can be synthesized by performing these reactions in parallel. By using three different β-azido acids as building blocks in each stage, a 27-membered library of tri-β-peptides can be made.



Scheme 1.6. The proposed synthesis of a tri-β-peptide library

1.2. RESULTS AND DISCUSSION

1.2.1 The synthesis of β-lactones.

To make the 27-membered tri-β-peptide library, three β-azido acids derived from β-lactones are required as the building blocks. The choice of building blocks was primarily based on: 1) the yield and the enantiopurity of the β-lactone from the AAC reaction; 2) the feasibility of the azide-mediated ring-opening reaction of the β-lactone. The structures of the seven β-lactones (**13a**-**13g**) that were synthesized and evaluated are shown in Figure 1.3.

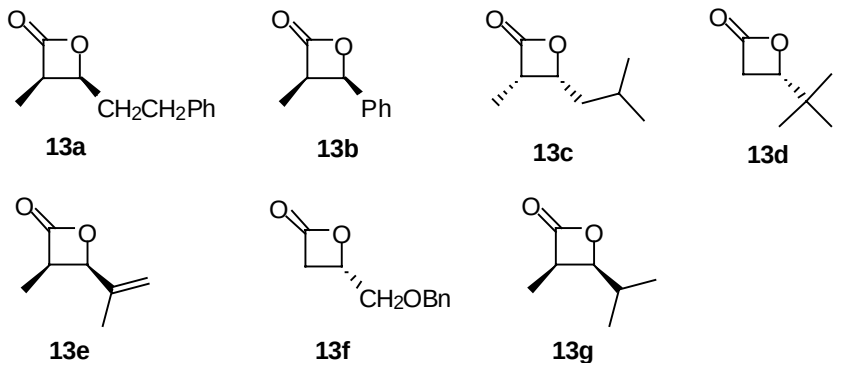
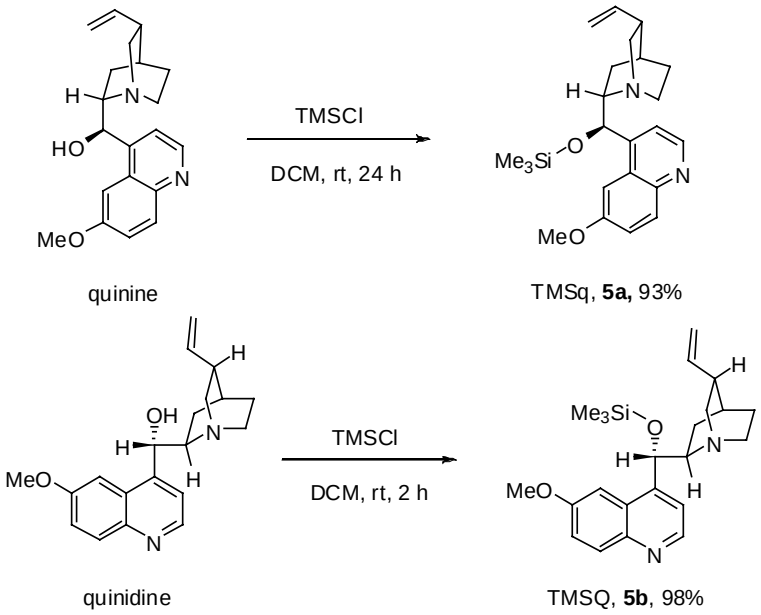


Figure 1.3. The β-lactones prepared by Nelson's AAC reactions

The needed organocatalysts 9-trimethylsilylquinine ("TMSq", **5a**) and 9-trimethylsilylquinidine ("TMSQ", **5b**) were synthesized by the addition of chlorotrimethylsilane to quinine and quinidine at ambient temperature.[29] The HCl produced in the reaction was neutralized by the alkaloid, so no extra base was added. The crude products were purified by flash chromatography to give **5a** and **5b** in 93% and 98% yields, respectively

(Scheme 1.7).



Scheme 1.7. The synthesis of the cinchona alkaloid catalysts **5a** and **5b**

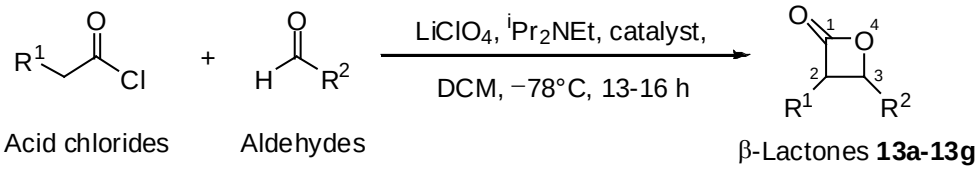
β-Lactones **13a-13d** and **13f** were previously synthesized by Nelson and coworkers,[18] while **13e** and **13g** had not been prepared by the AAC reaction. In a typical reaction, propionyl chloride (2.0 equiv) reacted with hydrocinnamaldehyde (1.0 equiv) in the presence of *N,N*-diisopropylethylamine (2.5 equiv), $LiClO_4$ (0.75 equiv) and TMSq (**5a**, 0.1 equiv) in DCM at –78 °C in 16 h to afford β-lactone **13a** in 54% yield as a single *cis* isomer and 94% *ee* after flash chromatography (Scheme 1.8; Table 1.1, entry 1).[18] The *ee* was determined by chiral HPLC analysis.

propionyl chloride hydrocinnamaldehyde **13a**, 54% yield, 94% *ee*

Scheme 1.8. The synthesis of β-lactone **13a**

Six other β-lactones were similarly synthesized and purified by flash chromatography (Table 1.1).[18] The AAC reaction of propionyl chloride and benzaldehyde gave **13b** in 97% yield (>99% *ee*) (entry 2). The volatile **13c** was made from the reaction of propionyl chloride and isovaleraldehyde (entry 3), and it was directly subjected to the azide ring-opening reaction without the complete removal of solvent. For this reason, the yield of **13c** is not reported in Table 1. Acetyl chloride readily reacted with pivalaldehyde to give **13d** in 91% yield and 96% *ee* (entry 4). β-Lactone **13e** was made from propionyl chloride and methacrolein in 32% yield (entry 5). β-Lactone **13f** was prepared in only 30% yield and 84% *ee* (entry 6). The reaction of propionyl chloride and isobutyraldehyde was expected to give **13g**, but no product formation was observed, and the aldehyde never disappeared on TLC analysis (entry 7). When describing configurations of the β-lactones, we used the numbering system for carboxylic acids rather than that for lactones, because the β-lactones would be converted to β-azido acids.

Table 1.1. The synthesis of β-lactones **13a-13g**



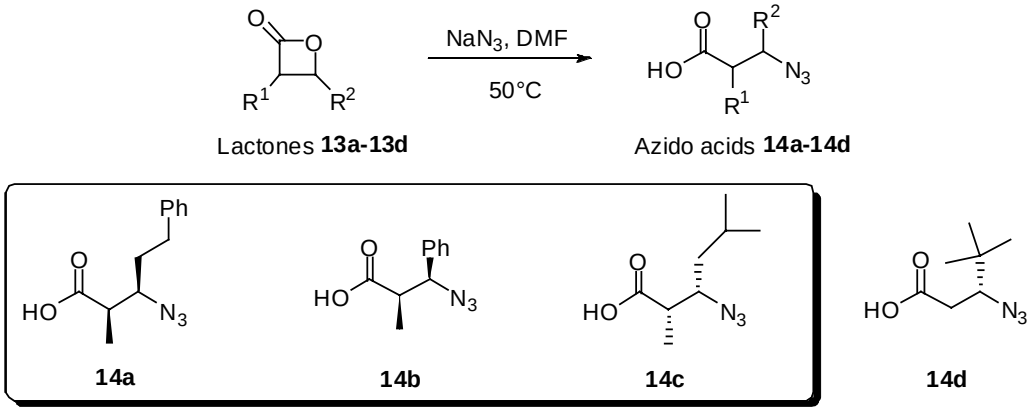
Entry	Product	Configuration	R^1	R^2	Catalyst	Equiv of $LiClO_4$	Yield %	*ee* %
1	**13a**	(2*R*,3*S*)	Me	CH_2CH_2Ph	TMSq	0.75	54	94 [a]
2	**13b**	(2*R*,3*S*)	Me	Ph	TMSq	2.0	97	>99 [a]
3	**13c**	(2*S*,3*R*)	Me	^{i}Bu	TMSQ	2.0	— [c]	99 [b]
4	**13d**	(2*S*,3*R*)	H	^{t}Bu	TMSQ	3.0	91	96 [b]
5	**13e**	(2*R*,3*S*)	Me	$C(CH_3)=CH_2$	TMSq	2.0	32	— [d]
6	**13f**	(2*S*,3*R*)	H	CH_2OBn	TMSQ	0.30	30	84 [a]
7	**13g**	(2*R*,3*S*)	Me	^{i}Pr	TMSq	2.0	— [e]	— [e]

a. Determined by chiral HPLC analysis; *b*. Determined by chiral GLC analysis;
c. Not measured due to volatility; *d*. Not measured; *e.* No product was detected.

Since β-lactones **13a-13d** were obtained with good *ee*, they were selected for the azide ring-opening reactions. The yields of **13e** and **13f** were low, and the attack of sodium azide to **13e** might proceed through the S_N2' fashion, thus they were not advanced. In a representative experiment, sodium azide reacted with lactone **13a** in DMF at 50 °C in 5 h to give β-azido acid **14a** in quantitative yield after purification by flash chromatography (Table 1.2, entry 1). Likewise, the reaction of **13b** with sodium azide gave **14b** in 100% yield (entry 2), while azido acid **14c** was prepared from crude lactone **13c** in a two-step yield of 65% calculated from the AAC reaction (entry 3). In contrast to these successful reactions, no product was formed for the reaction of **13d** over 96 h (entry 4). It was possible that the bulky β-*tert*-Bu group of **13d** retarded the S_N2 ring-opening process. Based on these results, we decided to use β-azido acids

14a-14c as the three building blocks for the library synthesis.

Table 1.2. The azide ring-opening reactions



Entry	β-Lactone	β-Azido Acid	Configuration	R^1	R^2	Reaction Time (h)	Yield %
1	**13a**	**14a**	(2*R*,3*R*)	Me	CH_2CH_2Ph	5	100
2	**13b**	**14b**	(2*R*,3*R*)	Me	Ph	4	100
3	**13c**	**14c**	(2*S*,3*S*)	Me	^{i}Bu	5	65 [a]
4	**13d**	**14d**	(3*S*)	H	^{t}Bu	96	— [b]

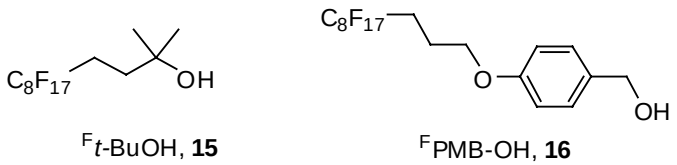
a. 2-step yield from isovaleraldehyde; *b.* SM recovered.

In summary, β-lactones **13a-13f** were synthesized by the alkaloid-catalyzed ketene-aldehyde cycloadditions. Lactones **13a-13c** were successfully converted to β-azido acids **14a-14c** as the building blocks for the parallel synthesis. In the next step, the carboxylate groups of **14a-14c** would be protected with a fluorous tag.

1.2.2 The synthesis of single fluorous β-azido esters.

We evaluated protection of the carboxy group of β-azido acids as either the fluorous Boc or

the fluorous Cbz group. Accordingly, two commercially available fluorous tagging reagents were selected: 2-methyl-4-perfluorodecyl-2-butanol (^{F}t-BuOH, **15**)[30a] and 4-[3-(perfluorooctyl)propyl-1-oxy]benzyl alcohol (^{F}PMBOH, **16**)[30b] (Figure 1.4).

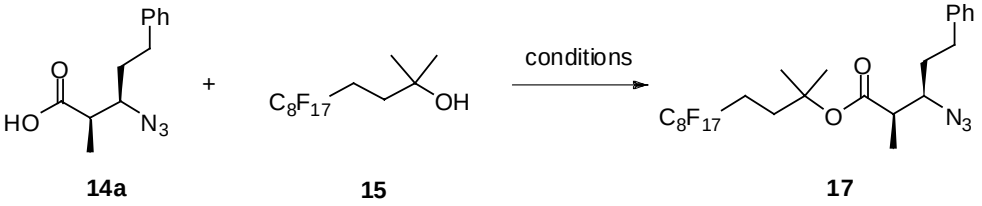


^{F}t-BuOH, **15** ^{F}PMB-OH, **16**

Figure 1.4. The structures of ^{F}t-BuOH and ^{F}PMBOH

We first tried the tagging reactions of β-azido acid **14a** with alcohol **15**. Direct coupling of acid **14a** and **15** in the presence of EDCI and DMAP in DCM did not provide the desired β-azido ester **17** (Table 1.3, entry 1). The coupling reaction of **14a** and **15** with DCC at 40 ºC in trifluorotoluene gave no product (entry 2).[30a] And no reaction occurred when 4-(pyrrolidin-1-yl)pyridine (PPY), a more reactive catalyst than DMAP, was used (entry 3).[28,31] The low reactivity of **15** was probably due to the steric hindrance at its tertiary carbon. Next, treating **14a** with $(COCl)_2$ and DMF gave the corresponding acid chloride **18**. Addition of alcohol **15** to the DCM solution of **18** in the presence of pyridine and DMAP did not give any product (entry 4). And no product was formed when the lithium salt of **15** was mixed with **18** in THF (entry 5).

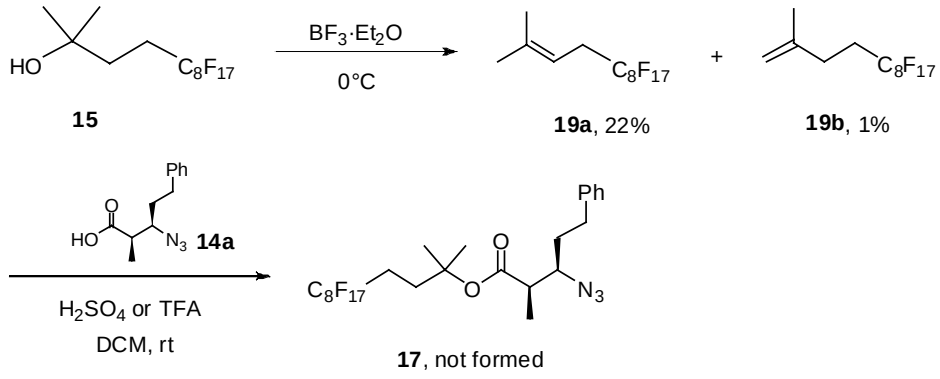
Table 1.3. Conditions of coupling reactions of β-azido acid **14a** with **15**



14a **15** **17**

Entry	Conditions	Yield%
1	EDCI, DMAP, DCM, rt, 48 h	0
2	DCC, DMAP, trifluorotoluene, 40 ºC**,** 22 h	0
3	EDCI, PPY, DCM, 120 ºC (μW), 0.5 h	0
4	1) **14a**, $(COCl)_2$, DCM, DMF (to give **18**) 2) **15**, pyridine, DMAP, DCM, rt, 24 h	0
5	1) ^{n}BuLi, **15**, THF, 0 °C 2) **14a**, THF, 0 °C, 12 h	0

To esterify **14a** by the alkene method, alcohol **15** was dehydrated with $BF_3 \cdot Et_2O$ to give a mixture of two alkenes **19a** and **19b** in 22% and 1% yield after flash chromatography (Scheme 1.9). However, no reaction took place when **19a/b** was treated with β-azido acid **14a** in the presence of a catalytic amount of trifluoroacetic acid (TFA) or sulfuric acid.



15 **19a**, 22% **19b**, 1%

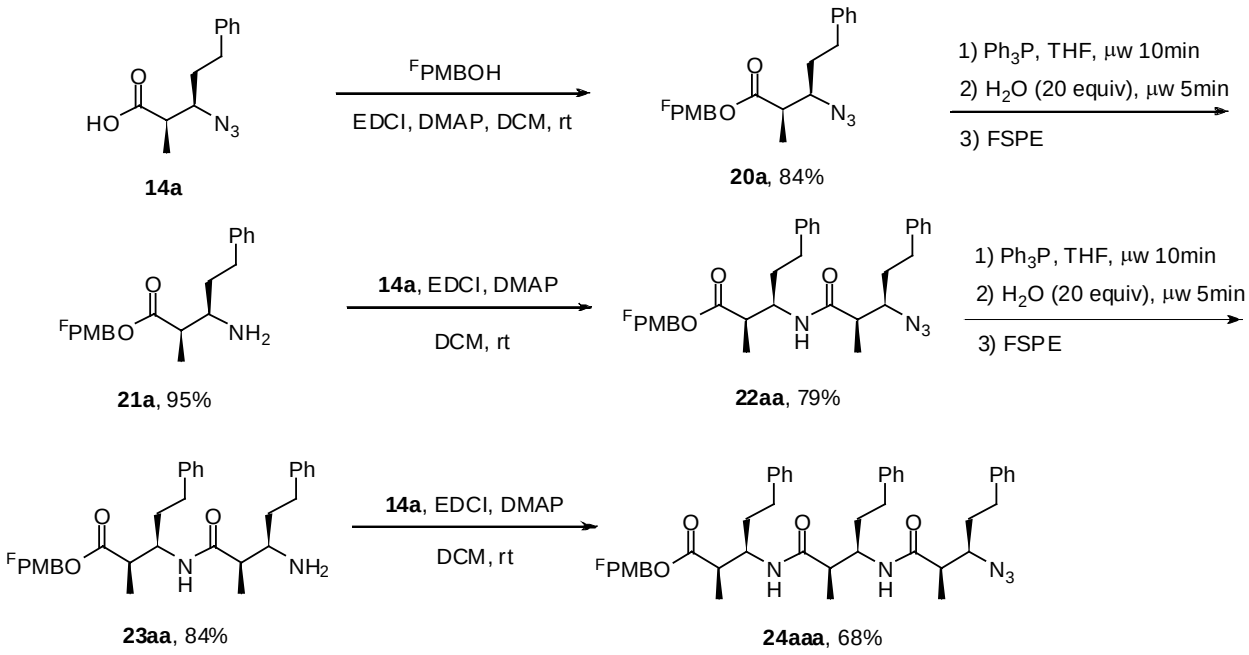
17, not formed

Scheme 1.9. Esterification of β-azido acid **14a** with alkenes **19a/b**

In contrast to the problems with installing the ^{F}tBu group to **14a**, the tagging reaction of **14a** with ^{F}PMBOH **16** was straightforward. ^{F}PMBOH (**16,** 1.2 equiv) was coupled with β-azido acid **14a** (1.0 equiv) in the presence of EDCI and DMAP in DCM to give azido ester **20a** in 84% yield after extractive workup to remove the reagents and purification by flash chromatography (Scheme 1.10). EDCI was chosen because both EDCI and its derived urea are relatively polar and eluted very quickly under the first pass conditions of FSPE.[27]

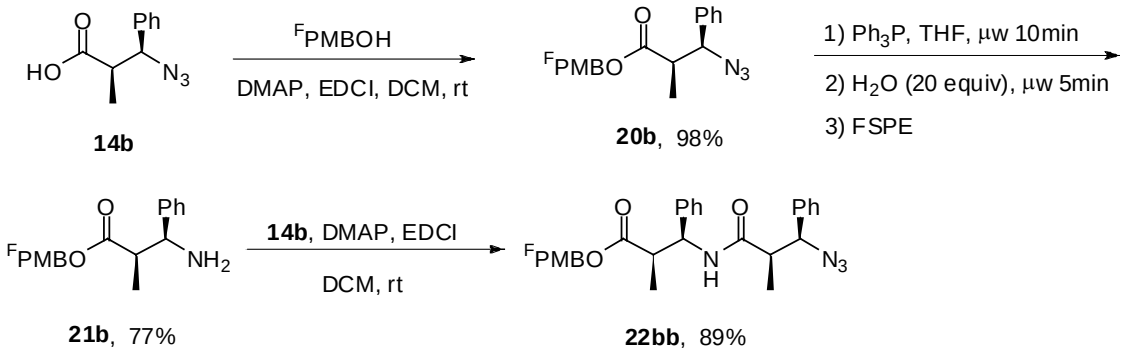
To reduce its azido group, **20a** was microwaved at 120 ºC, 250 W in the presence of Ph_3P (1.2 equiv) in THF, then H_2O (20 equiv) was added and the mixture was microwaved again for 5 min. Subjection of the cooled reaction mixture to FSPE provided amine **21a** in 95% yield.

Similarly, the amide coupling reaction of amine **21a** (1.0 equiv) and β-azido acid **14a** (1.2 equiv) in the presence of EDCI and DMAP followed by FSPE provided azido-dipeptide **22aa** in 79% yield. The code "**22aa**" designates the azido-β-dipeptide (starts with number "**22**") that consists β-azido acid **14a** as building blocks. The second reduction-coupling cycle was initiated by reducing azido-dipeptide **22aa** to amine **23aa** (84% yield after FSPE). Amine **23aa** was then coupled with **14a** to give azido-tripeptide **24aaa** in 68% yield after FSPE and flash chromatography. The structures of azido-dipeptide **22aa** and azido-tripeptide **24aaa** were confirmed by ^{1}H, ^{13}C, COSY and HMQC NMR experiments. These reactions indicated that β-azido acid **14a** was a qualified building block for the synthesis of the tri-β-peptide library.



Scheme 1.10. Synthesis of azido-tripeptide **24aaa**

β-Azido acid **14b** was also esterified with ^{F}PMBOH **16** in the presence of EDCI and DMAP in DCM to give azido-ester **20b** in 98% yield after flash chromatography (Scheme 1.11). Azido-ester **20b** was subjected to Staudinger reaction to give amine **21b** in 77% yield after FSPE. Amide coupling reaction of **21b** and **14b** in the presence of EDCI and DMAP gave azido-dipeptide **22bb** in 79% yield after flash chromatography. These reactions qualified β-azido acid **2b** as a building block, so the corresponding azido-tripeptide was not synthesized. We expected **14c** to have similar reactivity to **14a/14b**, thus no tagging-reduction-coupling reactions were done for **14c**.



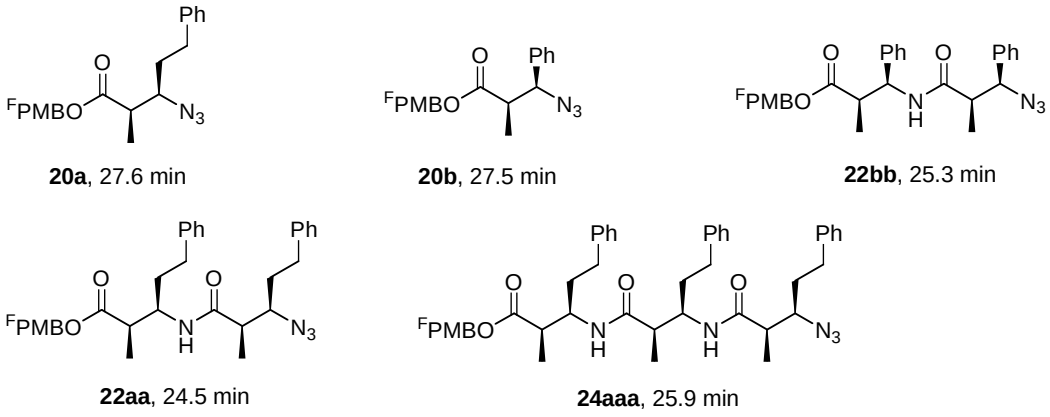
Scheme 1.11. Synthesis of azido-dipeptide **22bb**

All Staudinger reactions described above were followed by ^{31}P NMR analysis (δ (THF-*d*8) for Ph_3P: –5 ppm; for Ph_3P=NR: 2 ppm; for Ph_3PO: 27 ppm). The formation of the resonance of Ph_3PO and the disappearance of the resonance of Ph_3P=NR indicated the completion of the reaction. Comparing ^{31}P NMR spectra and TLC results, we found that TLC was also convenient to follow the transformation of the azide to the amines. After the addition of water and the microwave irradiation, a very polar new spot on TLC indicated the formation of the amine, while the concomitant Ph_3PO could always be detected by ^{31}P NMR analysis.

1.2.3 Fluorous HPLC analysis of the azido-peptides.

Before starting the library synthesis, we needed more data to know how well FSPE can separate the fluorous tagged peptides from organic impurities. Since the fluorous HPLC column is packed with fluorous silica gel, which is also used in the FSPE cartridge, we measured the retention times of the already made azido-peptides **20a**, **20b**, **22aa**, **22bb** and **24aaa** on the fluorous HPLC column (Figure 1.5). Under the conditions described in Figure 5, **20a**, **20b**, **22aa**,

22bb and **24aaa** were all strongly retained on the fluorous HPLC column with retention times around 25 min. Because non-fluorous compounds elute at the solvent front under these conditions, the results suggested that FSPE would be an efficient and rapid separation technique for separating ^{F}PMB tagged compounds from any non-fluorous impurities in a library setting.



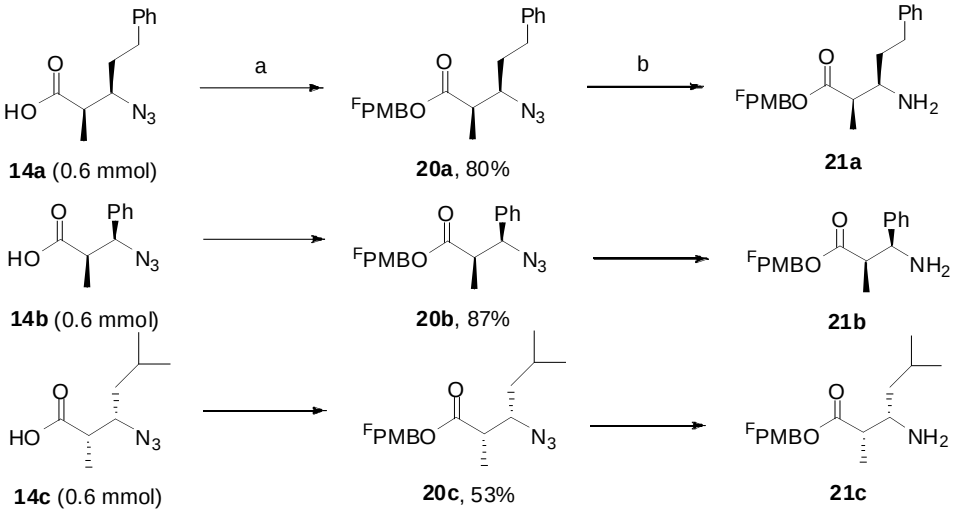
Conditions: Fluoro*Flash*^{TM} PF-C8 HPLC column (4.6 × 150 mm), 1 mL/min, gradient elution, 80:20 to 100:0 MeCN:H_2O in 30 min

Figure 1.5. Retention times of azido-peptides on the fluorous HPLC column

In spadework for the parallel synthesis, the ^{F}PMB group was used successfully to tag the C-terminus of several β-peptides. Several amide coupling reactions and Staudinger reactions were accomplished with good yields. The retention times of several β-azido peptides on the fluorous HPLC column were measured to confirm the feasibility of FSPE separation. With this knowledge gained, we commenced the library synthesis.

1.2.4 Parallel synthesis: the first reduction-coupling cycle.

The synthesis of the library started with the fluorous tagging reactions of **14a-14c**. β-Azido acids **14a**, **14b** and **14c** (0.6 mmol of each) were esterified with **16** in the presence of EDCI and DMAP to give azido-esters **20a**, **20b** and **20c** in 80%, 87% and 53% yields, respectively (Scheme 1.12). The reactions were monitored by TLC and the products were purified by standard flash chromatography. With all six precursors: azido acids **14a-14c** and ^{F}PMB esters **20a-20c** in hand, we started the parallel synthesis. The three azido-esters **20a**-**20c** were treated with Ph_3P (1.2 equiv) in THF under microwave (120 ºC, 250 W) for 5 min, followed by the addition of H_2O (20 equiv) and irradiation by microwave again for 10 min (Scheme 1.12). At this time, each Staudinger reaction was complete by regular TLC analysis. Amines **21a**-**21c** were isolated by FSPE and carried on directly to the coupling reactions without characterization.

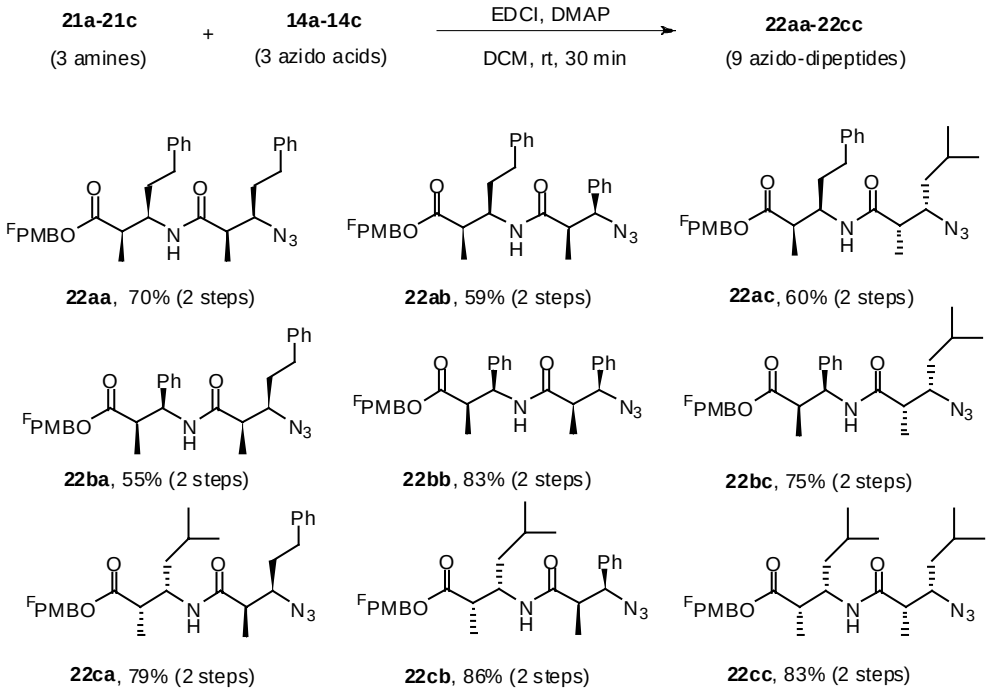


a. ^{F}PMBOH, EDCI, DMAP, DCM, rt, 30 min

b. 1) PPh_3, THF, μw 5 min; 2) H_2O (20 equiv), μw 10 min; 3) FSPE

Scheme 1.12. Synthesis of amines **21a-21c**

Each one of amines **21a-21c** (approximately 0.5 mmol) was split into three equal portions and each portion was coupled with three β-azido acids **14a-14c** in the presence of EDCI and DMAP in DCM. These nine reactions were done in parallel and all were complete in 30 min according to TLC analysis. Purification of the crude products by FSPE gave the nine azido-dipeptides **22aa-22cc** in two-step yields of 55-86% (Scheme 1.13). The structures and purities of the products were confirmed by ^{1}H, ^{13}C NMR and LC-MS analysis.[34b]

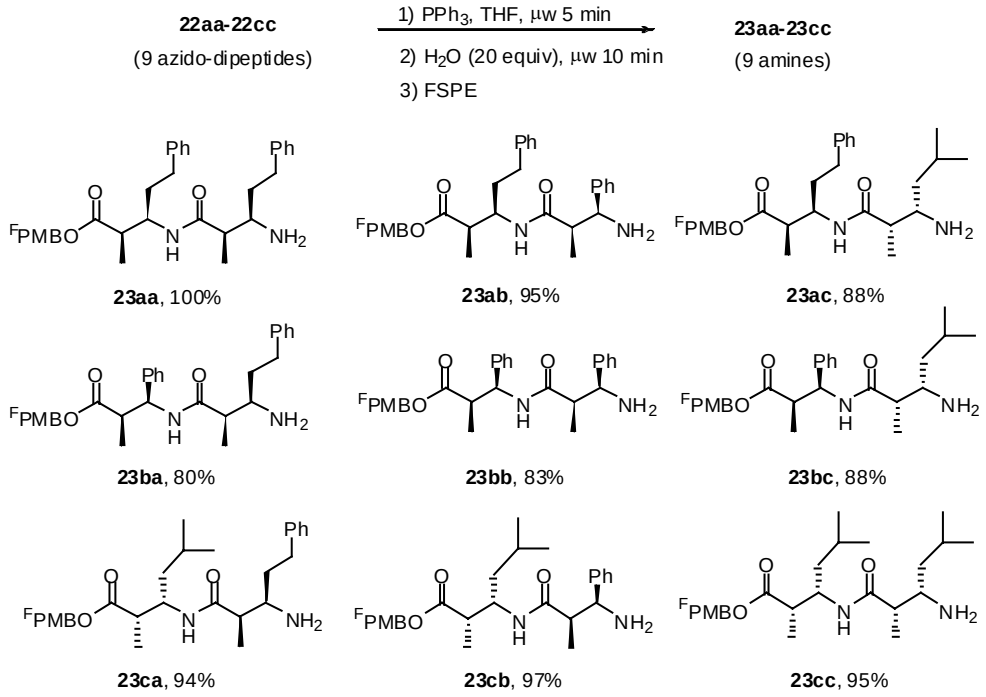


Scheme 1.13. Synthesis and structures of azido-dipeptides **22aa-22cc**

1.2.5 The second reduction-coupling cycle.

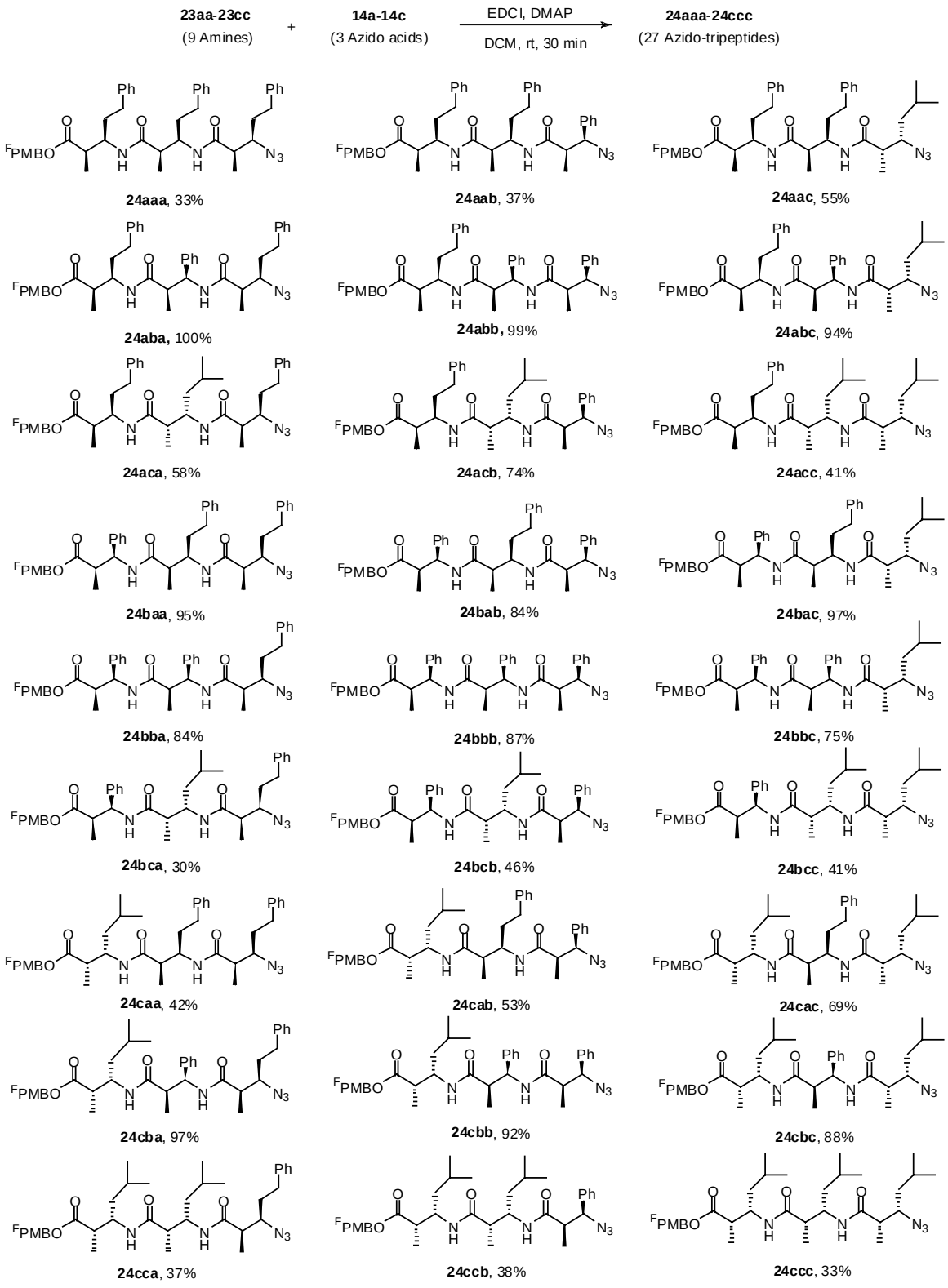
To begin the second reduction-coupling cycle, the nine azido-dipeptides **22aa-22cc** (approximately 0.15 mmol for each one) were treated in parallel with Ph_3P (1.2 equiv) in THF

under microwave (120 ºC, 250 W) for 5 min, followed by the addition of H_2O (20 equiv) and irradiation by microwave again for 10 min (Scheme 1.14). All nine reactions were complete according to TLC analysis. The nine amines **23aa-23cc** were isolated by FSPE with 80-100% yields.



Scheme 1.14. The reductions of azido-esters **22aa-22cc**

Each of the nine amines **23aa-22cc** was divided into three equal portions and each portion was coupled with the three β-azido acids **14a-14c** in the presence of EDCI and DMAP to give 27 azido-tripeptides **24aaa-24ccc** in 33-100% yields after FSPE (Scheme 1.15). Reactions were done in parallel and all were complete in 30 min according to TLC analysis.



Scheme 1.15. Synthesis of the 27 azido-tripeptides **24aaa-24ccc**

The azido-tripeptides **24aaa**-**24ccc** were characterized by LC-MS analysis on the Fluoro*Flash*^{TM} PF-C8 HPLC column under the conditions described in Table 1.4. Since we had many samples to test, a more rapid condition starting with 90:10 MeCN:H_2O was used thus the retention times of the 27 products (all about 10 min) were much shorter than that of **24aaa** from the single peptide synthesis (25.9 min, see Figure 1.5). The LC chromatograms of **24aaa**-**24ccc** showed that the average purity of the samples is greater than 90%, and the MS data (with APCI detector) of the products matched well with the calculated molecular weights (Table 1.4).[34a,b]

Table 1.4. LC-MS data of the 27 azido-tripeptides

Peptide	Calculated Mass	Measured Mass	Peptide	Calculated Mass	Measured Mass
24aaa	1177.4 $[M^+]$	1178.2 $[M + H]^+$	**24bbc**	1073.3 $[M^+]$	1074.2 $[M + H]^+$
24aab	1149.4 $[M^+]$	1150.0 $[M + H]^+$	**24bca**	1101.4 $[M^+]$	1102.2 $[M + H]^+$
24aac	1129.4 $[M^+]$	1130.2 $[M + H]^+$	**24bcb**	1073.3 $[M^+]$	1074.2 $[M + H]^+$
24aba	1149.4 $[M^+]$	1150.2 $[M + H]^+$	**24bcc**	1053.4 $[M^+]$	1054.2 $[M + H]^+$
24abb	1121.3 $[M^+]$	1122.0 $[M + H]^+$	**24caa**	1129.4 $[M^+]$	1130.2 $[M + H]^+$
24abc	1101.4 $[M^+]$	1102.2 $[M + H]^+$	**24cab**	1101.4 $[M^+]$	1102.2 $[M + H]^+$
24aca	1129.4 $[M^+]$	1130.2 $[M + H]^+$	**24cac**	1081.4 $[M^+]$	1082.2 $[M + H]^+$
24acb	1101.4 $[M^+]$	1102.2 $[M + H]^+$	**24cba**	1101.4 $[M^+]$	1102.2 $[M + H]^+$
24acc	1081.4 $[M^+]$	1082.2 $[M + H]^+$	**24cbb**	1073.3 $[M^+]$	1074.2 $[M + H]^+$
24baa	1149.4 $[M^+]$	1150.0 $[M + H]^+$	**24cbc**	1053.4 $[M^+]$	1054.2 $[M + H]^+$
24bab	1121.3 $[M^+]$	1122.2 $[M + H]^+$	**24cca**	1081.4 $[M^+]$	1082.2 $[M + H]^+$
24bac	1101.4 $[M^+]$	1102.2 $[M + H]^+$	**24ccb**	1053.4 $[M^+]$	1054.2 $[M + H]^+$
24bba	1121.3 $[M^+]$	1122.2 $[M + H]^+$	**24ccc**	1033.4 $[M^+]$	1034.2 $[M + H]^+$
24bbb	1093.3 $[M^+]$	1094.2 $[M + H]^+$			

Conditions: Fluoro*Flash*^{TM} PF-C8 HPLC column (4.6 × 150 mm), 1 mL/min, gradient elution, 90:10 to 100:0 MeCN:H_2O in 15 min, APCI detector

Five of the azido-tripeptides (**24aaa**, **24bbb**, **24cba**, **24ccb** and **24ccc**) were selected by molecular weight (including highest, median, and lowest) for ^{1}H and ^{13}C NMR analysis to provide additional support for structure and purity. The fluorous HPLC trace, MS and ^{1}H NMR spectra of a typical azido-tripeptide **24cba** are shown in Figure 1.6.[34a,b] The first three HPLC chromatograms show the UV absorbances at 254, 210 and 230 nm, while the last one shows the total ion count (TIC). Azido-tripeptide **24cba** had a retention time of 9.6 min, and was visible at 210 and 230 nm, but not 254 nm. The MS spectrum of the major peak at 9.6 min showed a strong signal of 1102.2 $[M + H]^{+}$, which matched with the calculated mass of **24cba** (1101.4 $[M^{+}]$) within 0.2 mass units. In the ^{1}H NMR spectrum of **24cba**, two amide proton resonances were found (δ 8.24, 5.85 ppm), indicating the formation of the azido-tripeptide.

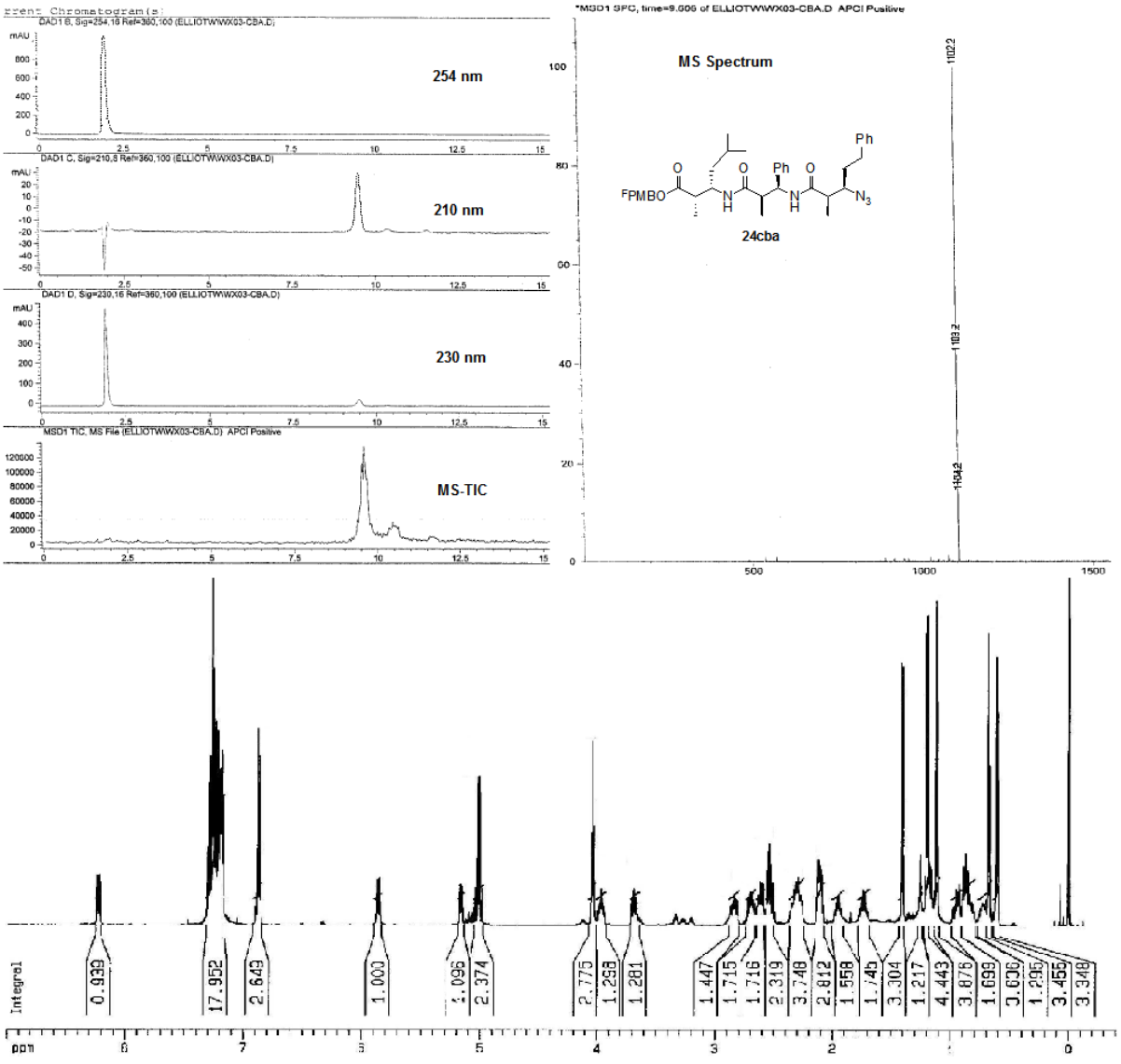


Figure 1.6. The fluorous HPLC traces (top left), MS spectrum (peak at 9.6 min, top right) and ^{1}H NMR spectrum (bottom, 500MHz, $CDCl_3$) of azido-tripeptide **24cba**

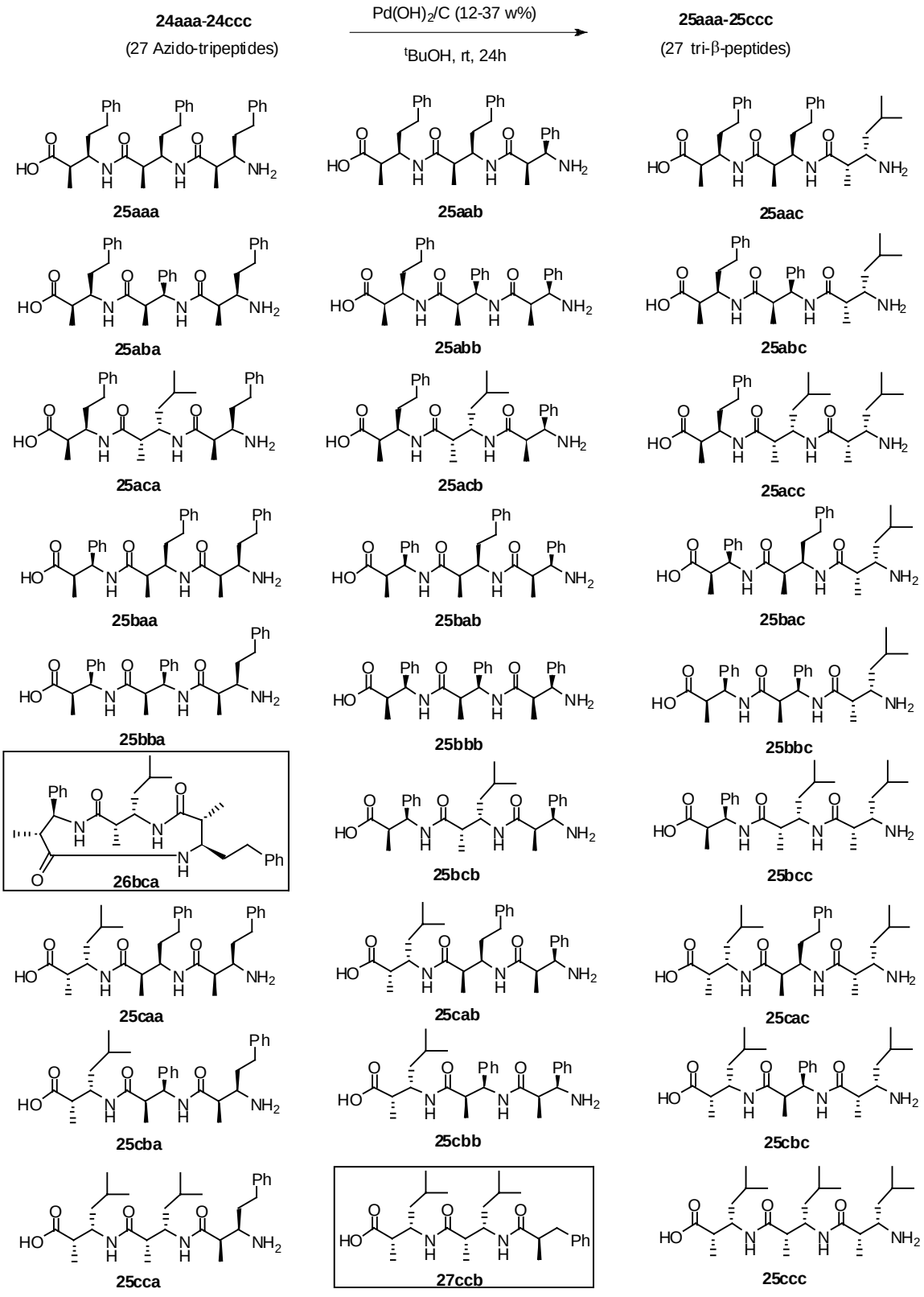
1.2.6 The detagging reactions.

The final step of the library synthesis involves the deprotection of the ^{F}PMB group and the simultaneous reduction of the azido group. The hydrogenations of **24aaa-24ccc** with $Pd(OH)_2/C$ (12–37 w%) in ^{t}BuOH in a parallel synthesizer went smoothly to give tri-β-peptides **25aaa-25ccc** (Scheme 1.16). Other frequently used solvents for hydrogenation such as MeOH or EtOH led to partial esterification by the solvent at the C-terminus. Peptides **25aaa-25ccc** were separated from the ^{F}PMB residue by plate-to-plate FSPE to give crude final products in yields listed in Table 6.[33]

We further purified 22 of the 27 peptides (since 5 of them were pure) individually by preparative reverse phase HPLC with gradient conditions (see Experimental section), then all purified peptides were analyzed by LCMS (Table 1.5). Almost all peptides had retention times at about 2.5 min (near the solvent front) since they were probably zwitterionic. Under the conditions described under Table 1.5, 25 peptides ionized well and showed the expected masses, and no impurities were detected in their LCMS spectra. Five peptides among these 25 (**25aba**, **25bab**, **25bba**, **25bbb** and **25cba**) were selected arbitrarily to conduct ^{1}H NMR experiments (D_2O/CD_3CN) to confirm structure and purity. The NMR spectrum of **25cba** is typical and is shown is Figure 1.7.

Two expected products, **25bca** and **25ccb** were not found according to LCMS analysis. However, the two isolated products were pure and their proposed structures are shown in Scheme 1.16. Product **26bca** exhibited the peak for $[M - H_2O + 2Na]^{+}$, so we tentatively

assigned the structure as a dehydrated cyclic peptide. Product **27ccb** exhibited the peak for [M – 15 + Na]$^+$, suggesting that this product resulted from reductive deamination (hydrogenolysis) of the terminal benzylic amino group. A much longer retention time (5 min) also supported the proposed structure of **25ccb** since the polarity of the deaminated product is less than the desired zwitterionic product. These side reactions seemed to be sequence specific, since they were not observed for any other members of the library.



Scheme 1.16. Synthesis of the 27 tri-*β*-peptides **25aaa-25ccc**

Table 1.5. LC-MS data of the 27 tri-β-peptides

Peptide	Yield (%) [a]	Recovery (%) [b]	Retention Time (min)	Calculated Mass	Measured Mass
25aaa	92	— [c]	2.4	585.4 [M^+]	586.3 [M + H]$^+$
25aab	89	— [c]	2.5	557.3 [M^+]	558.3 [M + H]$^+$
25aac	80	76	2.3	537.4 [M^+]	538.3 [M + H]$^+$
25aba	84	94	2.2	557.3 [M^+]	558.3 [M + H]$^+$
25abb	71	— [c]	2.6	529.3 [M^+]	530.2 [M + H]$^+$
25abc	64	45	2.3	509.3 [M^+]	510.3 [M + H]$^+$
25aca	61	80	2.3	537.4 [M^+]	538.3 [M + H]$^+$
25acb	72	67	2.2	509.3 [M^+]	510.2 [M + H]$^+$
25acc	68	— [c]	2.3	489.4 [M^+]	490.4 [M + H]$^+$
25baa	80	84	2.4	557.3 [M^+]	558.3 [M + H]$^+$
25bab	70	94	2.4	529.3 [M^+]	530.2 [M + H]$^+$
25bac	97	93	2.1	509.3 [M^+]	510.2 [M + H]$^+$
25bba	51	99	2.2	529.3 [M^+]	530.2 [M + H]$^+$
25bbb	60	— [c]	2.7	501.3 [M^+]	502.2 [M + H]$^+$
25bbc	88	86	2.1	481.3 [M^+]	482.2 [M + H]$^+$
26bca	82	64	— [d]	509.3 [M^+]	537.3 [M – H_2O + 2Na]$^+$ [e]
25bcb	76	53	1.9	481.3 [M^+]	482.3 [M + H]$^+$
25bcc	79	87	2.0	461.3 [M^+]	462.3 [M + H]$^+$
25caa	87	91	2.0	537.4 [M^+]	538.3 [M + H]$^+$
25cab	71	75	2.3	509.3 [M^+]	510.4 [M + H]$^+$
25cac	55	78	2.2	489.4 [M^+]	490.3 [M + H]$^+$
25cba	69	71	2.3	509.3 [M^+]	510.2 [M + H]$^+$
25cbb	88	90	2.2	481.3 [M^+]	482.2 [M + H]$^+$
25cbc	88	57	2.2	461.3 [M^+]	462.3 [M + H]$^+$
25cca	82	40	2.1	489.4 [M^+]	490.4 [M + H]$^+$
27ccb	97	83	5.0	461.3 [M^+]	469.2 [M – 15 + Na]$^+$ [e]
25ccc	78	88	2.1	441.4 [M^+]	442.4 [M + H]$^+$

Conditions: XTerra® MS-C18 HPLC column (4.6 × 100 mm), 0.4 mL/min, gradient elution, 70:30 to 100:0 MeCN:H_2O (w/ 0.1% TFA) in 15 min, ESI detector.

a. After FSPE; *b.* After HPLC purification; *c.* The product after FSPE was pure by HPLC analysis and was not further purified; *d.* Only MS analysis was done due to low solubility of the sample; *e*. Undesired product ("M" is the molecular weight of the desired product).

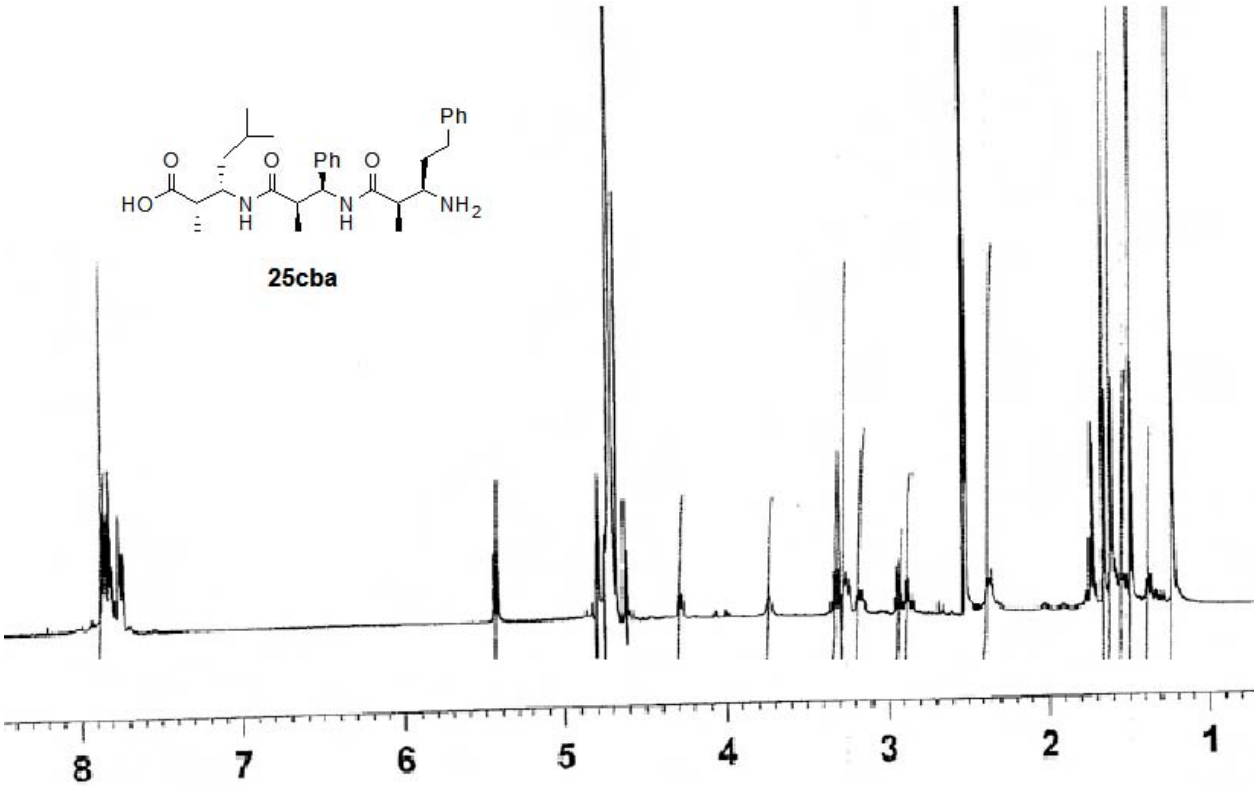


Figure 1.7. The ^{1}H NMR spectrum of tri-β-peptide **25cba** (500MHz, $CDCl_3$)

1.3 CONCLUSIONS

In conclusion, we developed a convenient way to make β-peptide libraries. Starting from light fluorous tagged β-azido acids, followed by two reduction-amide coupling cycle and the reductive deprotection, we did the solution phase parallel synthesis of a 27-membered tri-β-peptide library with rapid separation by FSPE. Peptides were tested for purities by fluorous or reverse phase HPLC. Mass spectroscopy data of the products matched with calculation. The results suggest that the azido acid approach to make β-peptides deserves serious consideration as

an alternative to the traditional amino acid approach. The results further show the usefulness of fluorous solid phase extraction as a rapid and effective purification method of light fluorous molecules. By applying the same methodology, we expect that larger and more complex libraries of β-peptide can be made.

1.4 EXPERIMENTAL

1.4.1 General Information.

All reaction solvents were freshly purified either by distillation or by passing through an activated alumina column. THF, CH_2Cl_2, Et_2O were dried by activated alumina according to Pangborn, A.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmer, F.; *J. Organometallics*, **1996**, 15, 1518.

All reactions were followed by TLC. The Staudinger reactions were also followed by fluorous TLC. All Fluorous Solid Phase Extractions (FSPE) were done in a standard SPE manifold with Fluoro*Flash*™ SPE Cartridges (5 g, 10 cc tube). The Staudinger reactions of **20a-20c** were done in a CEM Discover® LabMate™ microwave reactor one at a time. The Staudinger reactions of azido di-β-peptides **22aa-22cc** were done in an Emrys™ Optimizer microwave reactor. Solvent from FSPE was removed in a ThermoSavant SC210A SpeedVac®

Plus. All hydrogenation reactions were done in a GreenHouse Classic Parallel Synthesizer.

^{1}H and ^{13}C NMR spectra were taken on a Bruker models Advance DPX 300 (300 MHz), Advance 300 (300 MHz) NMR spectrometer. Chemical shifts were reported in parts per million (ppm) downfield relative to TMS using the residue solvent proton resonance of $CDCl_3$ (7.27 ppm) or central $CDCl_3$ carbon peak (77.0 ppm) as internal standard. In reporting spectral data, the following abbreviations were used: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintuplet, m = multiplet, dd = doublet doublet, td = doublet triplet, qd = doublet quartet, ddd = doublet doublet doublet.

Azido di-β-peptides **22aa-22cc** and azido tri-β-peptides **24aaa-24ccc** were characterized by LC-MS in an Agilent HP 1100 series LC-MSD system with the Fluoro*Flash*™ PF-C8 HPLC column (5 μm, 10 Å, 4.6 × 150 mm) and APCI detector, 1.0 mL/min, gradient elution (90:10 MeCN:H_2O to 100:0 in 15 min). Tri-β-peptides **25aaa-25ccc** were characterized by LC-MS in an Agilent HP 1100 series LC-MSD with a XTerra® MS C_{18} (3.5 μm, 4.6 × 100 mm) HPLC column and ESI detector, 0.4 mL/min, gradient elution (70:30 MeCN:H_2O (with 0.1% TFA) to 100:0 in 15 min). Tri-β-peptides **25aaa-25ccc** were purified in a HPLC instrument (Waters 600 Controller and Waters 2487 dual λ Absorbance Detector) with Waters SymmetryPrep™ C_{18} (7 μm, 7.8 × 150 mm) preparative HPLC column, 1.6 mL/min, gradient elution (MeCN:H_2O = 20:80 (0-5 min), 20:80 to 100:0 (5-25 min), 100:0 (25-35 min), 100:0 to 20:80 (35-40 min)).

1.4.2 General Experimental Procedures:

General procedure 1: synthesis of β-lactones.[18]

CH_2Cl_2 (2.0 mL) was added to a solution of 9-trimethylsilylquinine **5a** or 9-trimethylsilylquinidine **5b** (0.10 mmol) and $LiClO_4$ (0.3-3.0 mmol) in diethyl ether (1.0 mL). The reaction mixture was cooled to –78 °C. *N,N*-Diisopropylethylamine (0.44 mL, 2.5 mmol) was added to the resulting mixture followed by the addition of the aldehyde (1.0 mmol). A solution of acid chloride (2.0 mmol) in CH_2Cl_2 (0.5 mL) was then added over 1 h via syringe pump. The mixture was stirred for 13-16 h and the reaction was quenched with Et_2O (10 mL). The resulting mixture was partitioned between Et_2O (30 mL) and saturated NH_4Cl (15 mL). The organic layer was separated and washed with brine (10 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography.

General procedure 2: S_N2 addition of NaN_3 to β-lactones.[10]

β-Lactone **13** (6.0 mmol) was added to a solution of NaN_3 (12.0 mmol) in anhydrous DMF (35 mL, 0.3 M for lactone) via syringe at 50 °C. The resulting homogeneous solution was stirred for 4-5 h. The reaction mixture was cooled to ambient temperature, and saturated aqueous $NaHCO_3$ (30 mL) was added. The resulting heterogeneous mixture was triturated with water until all the precipitated salts dissolved. The resulting mixture was washed with ethyl acetate (2 × 50 mL) and the aqueous layer was acidified with 1 M aqueous HCl to pH ≈ 1. The acidic

aqueous layer was extracted with ethyl acetate (3 × 50 mL) and the combined organic portions were washed with water (2 × 50 mL) and brine (2 × 50 mL). The organic portion was dried with Na_2SO_4 and evaporated *in vacuo* to afford the β-azido acid **14**.

General procedure 3: ^{F}PMB tagging reaction.[30b]

To a solution of β-azido acid **14** (0.2 mmol) in CH_2Cl_2 (10 mL) was added DMAP (12 mg, 0.10 mmol). ^{F}PMBOH (**16**, 140 mg, 0.240 mmol) was added to the solution followed by the addition of EDCI (46 mg, 0.24 mmol). After 30 min, the mixture was partitioned between Et_2O (30 mL) and 1M aqueous HCl (15 mL). The organic layer was separated and washed with H_2O (10 mL) and brine (10 mL), then dried with Na_2SO_4 and evaporated *in vacuo* to afford the crude ^{F}PMB ester **20**, which was purified by flash chromatography (4:1 Hex:EtOAc).

General procedure 4: Staudinger reaction.[12,26]

In a microwave tube, the azido-ester **20** or **22** (0.2 mmol) was dissolved in dry THF (0.5 mL). A solution of triphenylphosphine (63 mg, 0.24 mmol) in dry THF (1 mL) was added to the microwave tube by syringe. The mixture was heated in the microwave reactor under stirring at 120 ºC, 250 W, for 5 min. H_2O (72 mg, 4.0 mmol) was added to the microwave tube via syringe. The resulting mixture was microwaved for 10 min, at 120 ºC, 250 W. The reaction progress can be monitored either by regular TLC or ^{31}P NMR analysis (δ (THF-*d*8) for Ph_3P: –5 ppm; for Ph_3P=NR: 2 ppm; for Ph_3PO: 27 ppm). A very polar new spot on TLC indicates the formation of

the amine. In the ^{31}P NMR spectrum of the reaction mixture, the formation of Ph_3PO and the disappearance of Ph_3P=NR indicate the completion of the reaction. The solvent was removed *in vacuo* when the reaction is complete. A new FSPE cartridge (5 g) was washed with THF (20 mL) under vacuum on a SPE manifold, and was preconditioned by passing through 70:30 MeCN:H_2O (30 mL). The concentrated reaction mixture was dissolved in MeCN (1 mL) and loaded onto the cartridge by vacuum to ensure that the sample was completely adsorbed to the silica gel. The cartridge was washed with 70:30 MeCN:H_2O (50 mL) to obtain the fraction containing organic compounds (Ph_3PO and Ph_3P), and washed with MeCN (30 mL) to obtain the fraction containing fluorous compounds (the amine). The fluorous fraction was dried with Na_2SO_4 and the solvent was evaporated *in vacuo* to afford amine **21** or **23**.

General procedure 5: amide coupling.

DMAP (12 mg, 0.10 mmol) was added to a solution of amine **21** or **23** (0.2 mmol) in CH_2Cl_2 (2 mL). β-Azido acid **14** (0.24 mmol) was added to the solution, followed by the addition of EDCI (46 mg, 0.24 mmol) and CH_2Cl_2 (1 mL). The mixture was stirred for 30 min before the solvent was removed *in vacuo*. A new FSPE cartridge (5 g) was washed with THF (20 mL) under vacuum on a SPE manifold, and was preconditioned by passing through 70:30 MeCN:H_2O (30 mL). The concentrated reaction mixture was dissolved in MeCN (1 mL) and loaded onto the cartridge by vacuum to ensure that the sample was completely adsorbed to the silica gel. The cartridge was washed with 70:30 MeCN:H_2O (50 mL) to obtain the fraction containing organic

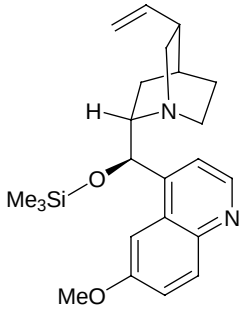
compounds, and washed with MeCN (30 mL) to obtain the fraction containing the fluorous compound. The fluorous fraction was dried with Na_2SO_4 and the solvent was evaporated *in vacuo* to afford azido-peptide **22** or **24**.

General procedure 6: hydrogenation.

In a GreenHouse Classic Parallel Synthesizer, the solution of each azido-tripeptide **24** (8 mg) in *tert*-butanol (2 mL) was loaded to each reaction tube. $Pd(OH)_2/C$ (2 mg, 25 w%) was added to each solution. The reactor was first vacuumed and then filled with hydrogen gas in a balloon, which was attached to the reactor during the reaction. With stirring on, all reactions were complete in 24 h according to TLC analysis. The solvent was removed *in vacuo* by the speed-vac. The reaction mixtures were directly loaded onto a preconditioned SPE cartridge plate, with each cartridge packed with Fluoro*Flash*^{TM} silica gel (3 g).[33] The cartridges were eluted with 70:30 MeCN:H_2O (2 × 5 mL). The solvent was removed *in vacuo* by speed-vac to afford *β*-tripeptides **25**. The cartridges were washed with THF (3 × 5 mL) to remove the ^{F}PMB residue before they were ready for reuse.

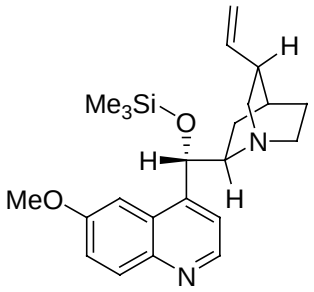
1.4.3 Specific Experimental Procedures and Compound Data:

(All NMR/MS spectra and HPLC traces can be found in the published paper. [34])



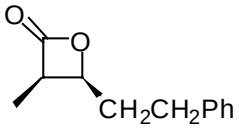
9-Trimethylsilylquinine ("TMSq", 5a): [29]

Trimethylsilyl chloride (1.56 mL, 12.3 mmol) was added to a solution of quinine (4.00 g, 12.3 mmol) in CH_2Cl_2 (40 mL). The reaction mixture was stirred at room temperature for 24 h and then partitioned between CH_2Cl_2 (40 mL) and saturated aqueous $NaHCO_3$ (80 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 16 mL). The combined organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (93:7 CH_2Cl_2:MeOH) afforded 9-trimethylsilylquinine (4.49 g, 93%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.15 (br, s, 1H), 8.71 (d, *J* = 4.5 Hz, 1H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.72 (d, *J* = 1.9 Hz, 1H), 7.46 (d, *J* = 4.5, 1H), 7.38 (dd, *J* = 9.2, 2.4 Hz, 1H), 6.74 (s, 1H), 5.56 (ddd, *J* = 16.7, 10.3, 6.8 Hz, 1H), 5.03 (d, *J* = 15.1 Hz, 1H), 5.02 (d, *J* = 11.4 Hz, 1H), 4.15 (s, 3H), 4.03 (m, 1H), 3.44 (t, *J* = 12.0 Hz, 2H), 3.27 (t, *J* = 9.0 Hz, 1H), 3.10 (m, 2H), 2.69 (br, s, 1H), 2.22 (dd, *J* = 13.2, 7.7 Hz, 1H), 2.09 (m, 2H), 1.88 (m, 1H), 1.44 (td, *J* = 10.2, 1.8 Hz, 1H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 147.8, 147.5, 144.7, 142.2, 131.9, 126.5, 121.4, 119.2 (br), 114.1, 101.2 (br), 61.2, 57.5, 55.7, 43.2 (br), 40.2, 28.1, 0.2.



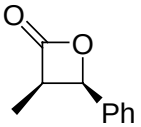
9-Trimethylsilylquinidine ("TMSQ", 5b):[29]

Trimethylsilyl chloride (0.79 mL, 6.16 mmol) was added to a solution of quinidine (2.00 g, 6.16 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at room temperature for 2 h and then partitioned between CH_2Cl_2 (20 mL) and saturated aqueous $NaHCO_3$ (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 8 mL). The combined organic layer was dried with Na_2SO_4 and the solvent was removed *in vacuo*. Purification of the crude product by flash chromatography (93:7 CH_2Cl_2:MeOH) afforded 9-trimethylsilylquinidine (2.39 g, 98%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.10 (br, s, 1H), 8.71 (d, *J* = 4.4 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.70 (d, *J* = 2.9 Hz, 1H), 7.46 (d, *J* = 4.4, 1H), 7.37 (dd, *J* = 9.2, 2.9 Hz, 1H), 6.91 (s, 1H), 5.98 (ddd, *J* = 17.1, 9.7, 7.1 Hz, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 5.22 (d, *J* = 17.6 Hz, 1H), 4.12 (s, 3H), 3.95 (m, 1H), 3.38 (t, *J* = 11.5 Hz, 2H), 3.25 (t, *J* = 9.5 Hz, 1H), 3.13 (m, 1H), 2.59 (q, *J* = 8.0 Hz, 1H), 2.49 (t, *J* = 11.3 Hz, 1H), 2.02 (br, s, 1H), 1.92 (m, 1H), 1.72 (m, 1H), 1.14 (m, 1H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 147.2, 145.0, 144.4, 136.8, 132.1, 126.2, 123.7, 119.1, 118.2, 101.2, 68.6, 60.7, 58.23, 49.5, 48.0, 37.8, 28.0, 23.9, 18.3, 0.8.



(3*R*,4*S*)-3-Methyl-4-phenethyloxetan-2-one (13a):[18]

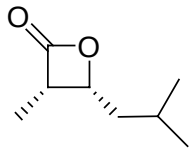
General procedure 1 was followed by employing TMSq (**5a**, 4.80 g, 12.1 mmol), $^{i}Pr_2NEt$ (52.8 mL, 300 mmol), $LiClO_4$ (9.54 g, 89.7 mmol) and hydrocinnamaldehyde (15.9 mL, 120 mmol). Addition of a solution of propionyl chloride (21.0 mL, 240 mmol) in CH_2Cl_2 (30 mL) via syringe pump was done over 1 h. The reaction mixture was stirred for 16 h. Purification of the crude product by flash chromatography (9:1 Hex:EtOAc) gave the title compound (12.60 g, 54%) as a colorless oil: Analysis by chiral HPLC [Daicel Chiracel™ OD column, flow rate 1.0 mL/min, 5% ^{i}PrOH, 95% hexane, t_R: 8.8 min (3*S*,4*R*), 11.5 min (3*R*,4*S*)] showed an enantiomeric ratio of 96.8/3.2 (3*R*,4*R*)/(3*S*,4*S*) (93.6% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.20 (m, 5H), 4.56 (ddd, *J* = 9.6, 6.2, 4.1 Hz, 1H), 3.78 (quin, *J* = 7.7 Hz, 1H), 2.88 (ddd, *J* = 12.4, 9.2, 5.2 Hz, 1H), 2.73 (m, 1H), 2.08 (m, 1H), 1.97 (m, 1H), 1.28 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 140.3, 128.5, 128.4, 126.3, 74.5, 47.1, 31.8, 31.4, 8.0.



(3*R*,4*R*)-3-Methyl-4-phenyloxetan-2-one (13b):[18]

General procedure 1 was followed by employing TMSq (**5a**, 0.48 g, 1.21 mmol), $^{i}Pr_2NEt$ (5.30 mL, 30.0 mmol), $LiClO_4$ (2.55 g, 24.0 mmol) and benzaldehyde (1.23 mL, 12.0 mmol).

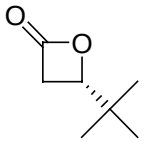
Addition of a solution of propionyl chloride (2.10 mL, 24.0 mmol) in CH_2Cl_2 (3 mL) via syringe pump was done over 1 h. The reaction mixture was stirred for 16 h. Purification of the crude product by flash chromatography (8:1 Hex:EtOAc) gave the title compound (1.89 g, 97%) as a colorless oil: Analysis by chiral HPLC [Daicel Chiracel™ OD column, flow rate 1.0 mL/min, 3% ^{i}PrOH, 97% hexane, t_R: 9.4 min (3*R*,4*R*)] showed only one enantiomer (3*R*,4*R*) (>99% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.27 (m, 5H), 5.64 (d, *J* = 6.5 Hz, 1H), 4.05 (quin, *J* = 7.7 Hz, 1H), 0.90 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 135.0, 129.0, 128.9, 126.1, 75.6, 50.5, 9.8.



(3*S*,4*R*)-4-Isobutyl-3-methyloxetan-2-one (13c): [18]

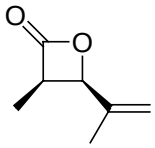
General procedure 1 was followed by employing TMSQ (**5b**, 0.48 g, 1.21 mmol), $^{i}Pr_2NEt$ (5.30 mL, 30.0 mmol), $LiClO_4$ (2.55 g, 24.0 mmol) and isovaleraldehyde (1.31 mL, 12.0 mmol). Addition of a solution of propionyl chloride (2.10 mL, 24.0 mmol) in CH_2Cl_2 (3 mL) via syringe pump was done over 1 h. The reaction mixture was stirred for 16 h. Purification of the crude product by flash chromatography (4:1 Hex:EtOAc) gave the title compound. A small amount of solvent remained in the sample and was not further removed because of the volatility of the title compound: Analysis by chiral GLC [Chiraldex™ G-TA column 20m × 0.25 mm, flow rate 0.6 mL/min, method: 80 °C for 5.0 min, ramp @ 5.0 °C/min to 100 °C for 10.0 min, ramp @ 5.0

°C/min to 130 °C for 5.0 min, t_R: 23.9 min (3*R*,4*S*) and 25.0 min (3*S*,4*R*)] showed an enantiomeric ratio of 99.7/0.3 (3*S*,4*R*)/(3*R*,4*S*) (99.4% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.63 (m, 1H), 3.72 (quin, *J* = 7.2 Hz, 1H), 1.77 (m, 1H), 1.63 (m, 1H), 1.47 (m, 1H), 1.23 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 74.2, 47.3, 38.5, 25.3, 22.8, 22.0, 8.0.



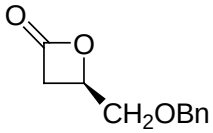
(*S*)-4-*tert*-Butyloxetan-2-one (13d):[18]

General procedure 1 was followed by employing TMSQ (**5b**, 0.48 g, 1.20 mmol), ^{i}Pr$_2$NEt (5.30 mL, 30.0 mmol), $LiClO_4$ (3.83 g, 36.0 mmol) and pivalaldehyde (1.31 mL, 12.0 mmol). Addition of the solution of acetyl chloride (1.71 mL, 24.0 mmol) in CH_2Cl_2 (3 mL) via syringe pump was done over 1 h. The reaction mixture was stirred for 16 h. Purification of the crude product by flash chromatography (8:1 Hex:EtOAc) gave the title compound (1.40 g, 91%) as a colorless oil: Analysis by chiral GLC [Chiraldex™ G-TA column 20 m × 0.25 mm, flow rate 0.6 mL/min, method: 80 °C for 5.0 min, ramp @ 5.0 °C/min to 100 °C for 10.0 min, ramp @ 5.0 °C/min to 130 °C for 5.0 min, ramp @ 15.0 °C/min to 150 °C for 5.0 min, t_R: 17.8 min (4*R*) and 19.0 min (4*S*)] showed an enantiomeric ratio of 98/2 (4*S*)/(4*R*) (96% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (dd, *J* = 5.8, 4.8 Hz, 1H), 3.24 (dd, *J* = 6.0 Hz, 16.5 Hz, 1H), 3.09 (dd, *J* = 4.5 Hz, 16.5 Hz, 1H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 78.1, 38.4, 33.0, 24.2.



(3*R*,4*R*)-3-Methyl-4-(prop-1-en-2-yl)oxetan-2-one (13e):

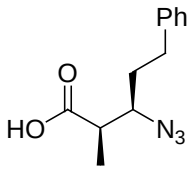
General procedure 1 was followed by employing TMSq (**5a**, 0.20 g, 0.50 mmol), $^{i}Pr_2NEt$ (2.30 mL, 12.6 mmol), $LiClO_4$ (1.07 g, 10.1 mmol) and methacrolein (0.42 mL, 5.0 mmol). Addition of the solution of propionyl chloride (0.89 mL, 10.1 mmol) in CH_2Cl_2 (2 mL) via syringe pump was done over 1 h. The reaction mixture was stirred for 13 h. Purification of the crude product by flash chromatography (7:1 Hex:EtOAc) gave the title compound (198 mg, 32%) as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (m, 2H), 4.89 (d, *J* = 6.5 Hz, 1H), 3.81 (quin, *J* = 7.4 Hz, 1H), 1.70 (s, 3H), 1.18 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 138.2, 113.3, 75.9, 47.0, 18.9, 8.5.



(*R*)-4-(Benzyloxymethyl)oxetan-2-one (13f):[18]

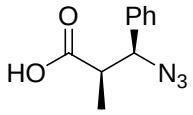
General procedure 1 was followed by employing TMSq (**5a**, 0.24 g, 0.60 mmol), $^{i}Pr_2NEt$ (2.70 mL, 15.0 mmol), $LiClO_4$ (0.19 mg, 1.8 mmol) and benzyloxyacetaldehyde (0.84 mL, 6.0 mmol). Addition of the solution of acetyl chloride (0.86 mL, 12.0 mmol) in CH_2Cl_2 (3 mL) via syringe pump was done over 1 h. The reaction mixture was stirred for 16 h. Purification of the

crude product by flash chromatography (4:1 Hex:EtOAc) gave the title compound (351 mg, 30%) as a colorless oil: Analysis by chiral HPLC [Daicel Chiracel™ OD column, flow rate 0.9 mL/min, 15% ^{i}PrOH, 85% hexane, t_R 13.9 min (*R*) and 24.8 min (*S*)] showed an enantiomeric ratio of 92/8 (*R*)/(*S*) (84% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.40 (m, 5H), 4.68 (m ,1H), 4.66 (d, *J* = 1.9 Hz, 2H), 3.86 (dd, *J* = 11.7, 2.8 Hz, 1H), 3.73 (dd, *J* = 11.7, 4.5 Hz, 1H), 3.46 (d, *J* = 3.9 Hz, 1H), 3.44 (d, *J* = 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 137.8, 128.6, 128.0, 127.8, 73.7, 69.7, 69.4, 39.7.



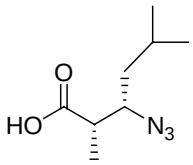
(2*R*,3*R*)-3-Azido-2-methyl-5-phenylpentanoic acid (14a):

General procedure 2 was followed by employing β-lactone **13a** (0.54 g, 2.8 mmol), NaN_3 (0.37 g, 5.7 mmol) and DMF (19 mL). The reaction mixture was stirred for 5 h. β-Azido acid **14a** (0.66 g, 100%) was isolated as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.48 (br, s, 1H), 7.36–7.22 (m, 5H), 3.60 (td, *J* = 7.0, 3.3 Hz, 1H), 2.87 (ddd, *J* = 14.1, 9.5, 5.0 Hz, 1H), 2.72 (m, 1H), 2.70 (quin, *J* = 7.2 Hz, 1H), 1.96 (m, 1H), 1.85 (m, 1H), 1.25 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.9, 141.2, 129.3, 129.0, 126.7, 64.1, 44.5, 33.5, 32.8, 13.9.



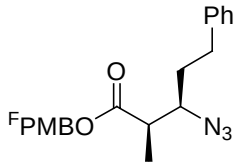
(2*R*,3*S*)-3-Azido-2-methyl-3-phenylpropanoic acid (14b):

General procedure 2 was followed by employing β-lactone **13b** (1.00 g, 6.17 mmol), NaN_3 (0.80 g, 12 mmol) and DMF (35 mL). The reaction mixture was stirred for 4 h. β-Azido acid **14b** (1.27 g, 100%) was isolated as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.54 (br, s, 1H), 7.44–7.27 (m, 5H), 4.67 (d, *J* = 10.4 Hz, 1H), 2.81 (td, *J* = 10.4, 7.1 Hz, 1H), 0.98 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.8, 151.5, 136.4, 129.0, 127.7, 68.1, 45.7, 14.6.



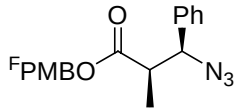
(2*S*,3*S*)-3-Azido-2,5-dimethylhexanoic acid (14c):

General procedure 2 was followed by employing β-lactone **13c** (from the AAC reaction), NaN_3 (1.56 g, 24.0 mmol) and DMF (50 mL). The reaction mixture was stirred for 5 h. β-Azido acid **14c** (1.44 g, 65% in two steps) was isolated as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.94 (br, s, 1H), 3.63 (ddd, *J* = 10.4, 7.1, 3.2 Hz, 1H), 2.65 (quin, *J* = 7.1 Hz, 1H), 1.82 (m, 1H), 1.51 (td, *J* = 10.4, 3.9 Hz, 1H), 1.28 (td, *J* = 9.7, 3.2 Hz, 1H), 1.23 (d, *J* = 7.1 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 62.3, 44.5, 40.0, 25.0, 23.4, 21.3, 13.3.



(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl-3-azido-2-methyl-5-phenylpentanoate (20a):

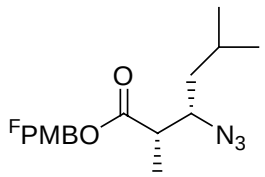
General procedure 3 was followed by employing β-azido acid **14a** (140 mg, 0.600 mmol), DMAP (37 mg, 0.30 mmol), ^{F}PMBOH (**16**, 421 mg, 0.720 mmol) and EDCI (115 mg, 0.600 mmol). Purification of the crude product by flash chromatography (4:1 Hex:EtOAc) gave the title compound (385 mg, 80%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.22 (m, 5H), 7.17 (d, *J* = 6.8 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.10 (d, *J* = 4.8 Hz, 2H), 4.05 (t, *J* = 5.9 Hz, 2H), 3.60 (ddd, *J* = 9.7, 6.3, 3.9 Hz, 1H), 2.83 (ddd, *J* = 14.5, 8.7, 5.8 Hz, 1H), 2.69 (quin, *J* = 7.1 Hz, 1H), 2.68 (m, 1H), 2.30 (m, 2H), 2.12 (m, 2H), 1.86 (m, 1H), 1.78 (m, 1H), 1.19 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 159.2, 141.3, 130.7, 129.0, 128.9, 128.7, 126.7, 115.0, 66.9, 66.8, 64.3, 44.7, 33.5, 32.7, 28.7, 28.4, 28.1, 21.0, 13.9.



(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl-3-azido-2-methyl-3-phenylpropanoate (20b):

General procedure 3 was followed by employing β-azido acid **14b** (123 mg, 0.600 mmol), DMAP (37 mg, 0.30 mmol), ^{F}PMBOH (**16**, 421 mg, 0.720 mmol) and EDCI (115 mg, 0.600

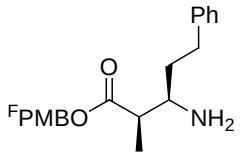
mmol). Purification of the crude product by flash chromatography (4:1 Hex:EtOAc) gave the title compound (405 mg, 87%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43–7.34 (m, 5H), 7.29 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.18 (s, 2H), 4.66 (d, *J* = 10.4 Hz, 1H), 4.06 (t, *J* = 5.8 Hz, 2H), 2.82 (qd, *J* = 10.4, 7.1 Hz, 1H), 2.31 (m, 2H), 2.13 (m, 2H), 0.94 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 158.7, 136.7, 130.1, 128.9, 128.8, 128.4, 127.7, 114.6, 68.5, 66.5, 66.4, 45.8, 28.3, 28.0, 27.7, 20.6, 14.6.



(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-azido-2,5-dimethylhexanoate (20c):

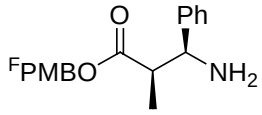
General procedure 3 was followed by employing β-azido acid **14c** (111 mg, 0.600 mmol), DMAP (37 mg, 0.30 mmol), ^{F}PMBOH (**16**, 421 mg, 0.720 mmol) and EDCI (115 mg, 0.600 mmol). Purification of the crude product by flash chromatography (4:1 Hex:EtOAc) gave the title compound (241 mg, 53%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J =7.0 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.09 (q, *J* = 12.1 Hz, 2H), 4.05 (t, *J* = 5.8 Hz, 2H), 3.61 (ddd, *J* = 10.5, 7.2, 3.1 Hz, 1H), 2.65 (quin, *J* = 7.1 Hz, 1H), 2.31 (m, 2H), 2.12 (m, 2H), 1.79 (m, 1H), 1.43 (m, 1H), 1.27 (m, 1H), 1.18 (d, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 158.8, 130.2, 128.5, 114.6, 66.5, 66.3, 62.6, 44.6,

40.1, 28.3, 28.0, 27.7, 25.0, 23.4, 21.3, 20.7, 13.3.



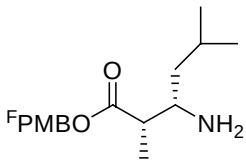
(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl-3-amino-2-methyl-5-phenyl-pentanoate (21a):

General procedure 4 was followed by employing β-azido ester **20a** (385 mg, 0.482 mmol), triphenylphosphine (179 mg, 0.682 mmol) and H_2O (189 mg, 10.5 mmol). Purification by FSPE gave the title compound as a yellow oil.



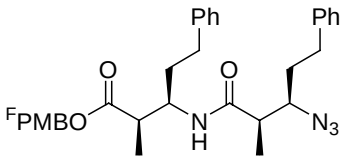
(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl-3-amino-2-methyl-3-phenylpropanoate (21b):

General procedure 4 was followed by employing β-azido ester **20b** (405 mg, 0.524 mmol), triphenylphosphine (179 mg, 0.682 mmol) and H_2O (189 mg, 10.5 mmol). Purification by FSPE gave the title compound as a yellow oil.



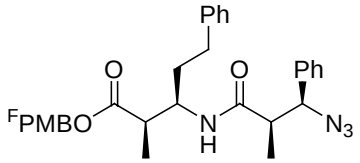
(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-amino-2,5-dimethylhexanoate (21c):

General procedure 4 was followed by employing β-azido ester **20c** (241 mg, 0.320 mmol), triphenylphosphine (179 mg, 0.682 mmol) and H_2O (189 mg, 10.5 mmol). Purification by FSPE gave the title compound as a yellow oil.



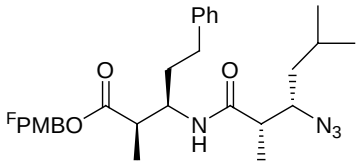
(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*R*)-3-azido-2-methyl-5-phenyl-pentanamido)-2-methyl-5-phenylpentanoate (22aa):

General procedure 5 was followed by employing amine **21a** (1/3 of its total weight, and the yield of amine was assumed to be 100%), DMAP (11 mg, 0.087 mmol), β-azido acid **14a** (49 mg, 0.21 mmol) and EDCI (40 mg, 0.21 mmol). Purification by FSPE gave the title compound (111 mg, 70% in two steps) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.09 (m, 10H), 6.95 (d, *J* = 7.4 Hz, 2H), 6.78 (d, *J* = 8.2 Hz, 2H), 6.45 (d, *J* = 9.6 Hz, 1H), 5.02 (d, *J* = 11.9 Hz, 1H), 4.96 (d, *J* = 11.9 Hz, 1H), 4.10 (m, 1H), 3.91 (t, *J* = 5.8 Hz, 2H), 3.51 (td, *J* = 8.7, 3.5 Hz, 1H), 2.75 (ddd, *J* = 13.3, 9.6, 4.6 Hz, 1H), 2.69–2.64 (m, 2H), 2.51 (t, *J* = 8.1 Hz, 2H), 2.26 (quin, *J* = 7.1 Hz, 1H), 2.24 (m, 2H), 2.00 (m, 2H), 1.86 (m, 1H), 1.66 (m, 3H), 1.16 (d, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 172.4, 157.8, 140.5, 140.0, 129.2, 127.6, 127.4, 125.2, 124.9, 117.5, 113.6, 65.4, 65.2, 63.6, 49.9, 45.4, 41.5, 35.1, 32.7, 31.7, 31.2, 28.7, 27.4, 27.0, 26.7, 19.6, 14.0, 13.9; LC-MS (APCI) *m/z* $[M + H]^+$ 989.2, t_R = 8.4 min.



(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*S*)-3-azido-2-methyl-3-phenylpropanamido)-2-methyl-5-phenylpentanoate (22ab):

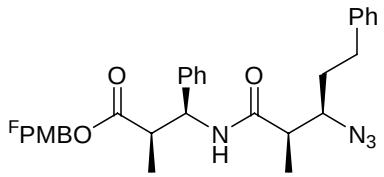
General procedure 5 was followed by employing amine **21a** (1/3 of its total weight, and the yield of amine was assumed to be 100%), DMAP (11 mg, 0.087 mmol), β-azido acid **14b** (43 mg, 0.21 mmol) and EDCI (40 mg, 0.21 mmol). Purification by FSPE gave the title compound (91 mg, 59% in two steps) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.07 (m, 10H), 7.01 (d, *J* = 6.9 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 6.52 (d, *J* = 9.6 Hz, 1H), 5.03 (d, *J* = 12.0 Hz, 1H), 4.98 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 10.3 Hz, 1H), 4.15 (m, 1H), 3.92 (t, *J* = 5.8 Hz, 2H), 2.71 (qd, *J* = 7.2, 3.5 Hz, 1H), 2.52 (t, *J* = 8.0 Hz, 2H), 2.38 (qd, *J* = 10.3, 6.9 Hz, 1H), 2.22 (m, 2H), 2.01 (m, 2H), 1.66 (m, 2H), 1.23 (d, *J* = 7.2 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 173.8, 157.5, 141.5, 137.3, 130.1, 128.7, 128.4, 127.8, 118.5, 114.6, 68.7, 66.4, 66.2, 51.0, 47.8, 42.5, 36.1, 32.6, 29.7, 28.3, 28.0, 27.7, 20.6, 19.6, 15.5, 15.0; LC-MS (APCI) *m/z* $[M + H]^+$ 961.2, t_R = 8.4 min.



(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl-3-((2*S*,3*S*)-3-azido-2,5-dimethylhexan-

amido)-2-methyl-5-phenylpentanoate (22ac):

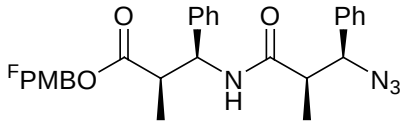
General procedure 5 was followed by employing amine **21a** (1/3 of its total weight, and the yield of amine was assumed to be 100%), DMAP (11 mg, 0.087 mmol), β-azido acid **14c** (39 mg, 0.21 mmol) and EDCI (40 mg, 0.21 mmol). Purification by FSPE gave the title compound (91 mg, 60% in two steps) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21–7.06 (m, 5H), 7.03 (d, *J* = 6.9 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 6.35 (d, *J* = 9.6 Hz, 1H), 5.02 (d, *J* = 11.9 Hz, 1H), 4.96 (d, *J* = 12.0 Hz, 1H), 4.11 (m, 1H), 3.94 (t, *J* = 5.8 Hz, 2H), 3.56 (td, *J* = 8.6, 4.7 Hz, 1H), 2.65 (qd, *J* = 7.1, 3.8 Hz, 1H), 2.56 (m, 2H), 2.22 (quin, *J* = 7.1 Hz, 1H), 2.21 (m, 2H), 2.03 (m, 2H), 1.76 (m, 1H), 1.74 (m, 1H), 1.66 (m, 2H), 1.33 (td, *J* = 9.6, 5.1 Hz, 1H), 1.12 (d, *J* = 4.6 Hz, 3H), 1.10 (d, *J* = 4.4 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 173.6, 158.8, 141.5, 130.1, 128.3, 125.8, 118.5, 114.6, 66.4, 66.2, 63.4, 50.8, 46.8, 42.7, 40.9, 36.0, 32.6, 32.4, 28.3, 28.0, 27.7, 25.1, 23.4, 22.4, 21.4, 20.6, 15.1, 15.0; LC-MS (APCI) *m/z* $[M + H]^+$ 941.2, t_R = 9.7 min.



(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*R*)-3-azido-2-methyl-5-phenyl-pentanamido)-2-methyl-3-phenylpropanoate (22ba):

General procedure 5 was followed by employing amine **21b** (1/3 of its total weight, and the

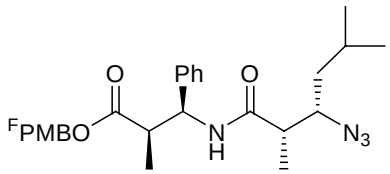
yield of amine was assumed to be 100%), DMAP (11 mg, 0.087 mmol), β-azido acid **14a** (49 mg, 0.21 mmol) and EDCI (40 mg, 0.21 mmol). Purification by FSPE gave the title compound (92 mg, 55% in two steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.19 (m, 11H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 5.25 (dd, *J* = 8.9, 4.9 Hz, 1H), 4.97 (br, s, 2H), 4.04 (t, *J* = 5.8 Hz, 2H), 3.64 (td, *J* = 7.8, 3.4 Hz, 1H), 3.06 (qd, *J* = 6.9, 5.2 Hz, 1H), 2.83 (ddd, *J* = 14.0, 9.6, 4.7 Hz, 1H), 2.73 (ddd, *J* = 15.3, 13.0, 6.1 Hz, 1H), 2.48 (quin, *J* = 7.1 Hz, 1H), 2.33 (m, 2H), 2.12 (m, 2H), 1.93 (m, 1H), 1.79 (m, 1H), 1.33 (d, *J* = 7.1 Hz, 3H), 1.20 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 173.0, 158.7, 140.9, 140.5, 129.9, 128.5, 128.0, 127.3, 126.2, 118.5, 114.5, 66.4, 66.2, 64.7, 54.8, 46.2, 44.7, 33.6, 32.2, 29.7, 29.3, 28.3, 28.0, 27.7, 20.6, 15.4, 14.8; LC-MS (APCI) *m/z* $[M + H]^+$ 961.2, t_R = 8.5 min.



(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*S*)-3-azido-2-methyl-3-phenyl-propanamido)-2-methyl-3-phenylpropanoate (22bb):

General procedure 5 was followed by employing amine **21b** (1/3 of its total weight, and the yield of amine was assumed to be 100%), DMAP (11 mg, 0.087 mmol), β-azido acid **14b** (43 mg, 0.21 mmol) and EDCI (40 mg, 0.21 mmol). Purification by FSPE gave the title compound (135 mg, 83% in two steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.13 (m, 11H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 8.4 Hz, 2H), 5.21 (dd, *J* = 8.9, 4.7 Hz, 1H), 4.88 (br, s, 2H),

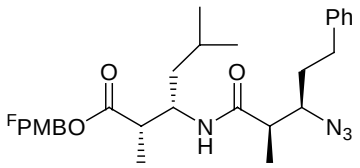
4.60 (d, J = 10.0 Hz, 1H), 3.92 (t, J = 5.8 Hz, 2H), 2.99 (qd, J = 6.8, 5.1 Hz, 1H), 2.50 (qd, J = 9.6, 6.8 Hz, 1H), 2.19 (m, 2H), 2.01 (m, 2H), 1.29 (d, J = 7.1 Hz, 3H), 0.80 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 173.4, 158.7, 140.5, 137.3, 129.9, 128.9, 128.6, 128.1, 127.7, 127.3, 126.2, 118.5, 114.5, 68.6, 66.4, 66.2, 54.8, 47.5, 44.6, 29.2, 28.2, 28.0, 27.7, 20.6, 15.5, 15.1, 14.1; LC-MS (APCI) *m/z* $[M + H]^+$ 933.2, t_R = 8.3 min.



(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl-3-((2*S*,3*S*)-3-azido-2,5-dimethylhexan-amido)-2-methyl-3-phenylpropanoate (22bc):

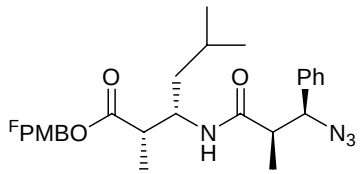
General procedure 5 was followed by employing amine **21b** (1/3 of its total weight, and the yield of amine was assumed to be 100%), DMAP (11 mg, 0.087 mmol), β-azido acid **14c** (39 mg, 0.21 mmol) and EDCI (40 mg, 0.21 mmol). Purification by FSPE gave the title compound (120 mg, 75% in two steps) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.11 (m, 6H), 6.99 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 8.6 Hz, 2H), 5.12 (dd, J = 8.9, 5.2 Hz, 1H), 4.89 (d, J = 12.1 Hz, 1H), 4.84 (d, J = 12.0 Hz, 1H), 3.94 (t, J = 5.8 Hz, 2H), 3.52 (td, J = 8.5, 4.0 Hz, 1H), 2.96 (qd, J = 7.0, 5.4 Hz, 1H), 2.30 (quin, J = 7.0 Hz, 1H), 2.23 (m, 2H), 2.02 (m, 2H), 1.79 (m, 1H), 1.74 (m, 1H), 1.31 (td, J = 10.4, 4.5 Hz, 1H), 1.19 (d, J = 7.1 Hz, 3H), 1.12 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 7.2 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 173.2, 158.7,

140.3, 129.9, 128.5, 128.0, 127.3, 126.2, 118.4, 114.5, 66.3, 66.2, 63.4, 54.9, 46.6, 44.6, 40.9, 28.4, 28.2, 27.9, 25.0, 23.4, 22.4, 21.4, 20.6, 15.6, 14.8; LC-MS (APCI) *m/z* $[M + H]^+$ 913.2, t_R = 9.8 min.



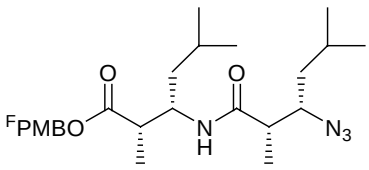
(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl-3-((2*R*,3*R*)-3-azido-2-methyl-5-phenyl-pentanamido)-2,5-dimethylhexanoate (22ca):

General procedure 5 was followed by employing amine **21c** (1/3 of its total weight, and the yield of amine was assumed to be 100%), DMAP (11 mg, 0.087 mmol), β-azido acid **14a** (49 mg, 0.21 mmol) and EDCI (40 mg, 0.21 mmol). Purification by FSPE gave the title compound (79 mg, 79% in two steps) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.13 (m, 5H), 7.11 (d, *J* = 7.4 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 6.16 (d, *J* = 9.6 Hz, 1H), 5.02 (d, *J* = 11.9 Hz, 1H), 4.96 (d, *J* = 12.0 Hz, 1H), 4.20 (m, 1H), 3.95 (t, 2H), 3.51 (td, *J* = 8.5, 3.3 Hz, 1H), 2.75 (ddd, *J* = 13.7, 9.7, 5.1 Hz, 1H), 2.68–2.56 (m, 2H), 2.24 (quin, *J* = 7.3 Hz, 1H), 2.22 (m, 2H), 2.01 (m, 2H), 1.91 (m, 1H), 1.68 (m, 1H), 1.52 (m, 1H), 1.28 (m, 1H), 1.18 (m, 1H), 1.10 (d, *J* = 7.4 Hz, 2H), 1.07 (d, *J* = 7.3 Hz, 2H), 0.81 (d, *J* = 6.3 Hz, 3H), 0.80 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 173.2, 158.8, 141.0, 130.1, 128.6, 128.4, 126.1, 118.5, 114.6, 66.4, 66.1, 64.6, 49.1, 46.2, 43.2, 43.0, 33.6, 32.2, 28.3, 28.0, 27.7, 25.0, 23.0, 22.0, 20.6, 15.0; LC-MS (APCI) *m/z* $[M + H]^+$ 941.2, t_R = 9.4 min.



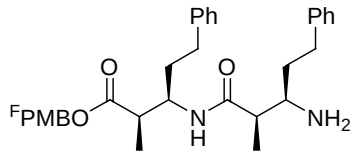
(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl-3-((2*R*,3*S*)-3-azido-2-methyl-3-phenylpropanamido)-2,5-dimethylhexanoate (22cb):

General procedure 5 was followed by employing amine **21c** (1/3 of its total weight, and the yield of amine was assumed to be 100%), DMAP (11 mg, 0.087 mmol), β-azido acid **14b** (43 mg, 0.21 mmol) and EDCI (40 mg, 0.21 mmol). Purification by FSPE gave the title compound (84 mg, 86% in two steps) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.20 (m, 7H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.18 (d, *J* = 9.6 Hz, 1H), 5.03 (d, *J* = 12.0 Hz, 1H), 4.97 (d, *J* = 12.0 Hz, 1H), 4.58 (d, *J* = 10.2 Hz, 1H), 4.19 (m, 1H), 3.95 (t, *J* = 5.8 Hz, 2H), 2.61 (qd, *J* = 7.1, 3.7 Hz, 1H), 2.35 (qd, *J* = 10.1, 7.0 Hz, 1H), 2.22 (m, 2H), 2.01 (m, 2H), 1.63 (m, 1H), 1.34 (m, 1H), 1.18 (m, 1H), 1.07 (d, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 6.2 Hz, 3H), 0.83 (d, *J* = 6.0 Hz, 3H), 0.81 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 173.5, 158.8, 137.5, 130.1, 128.8, 128.6, 128.4, 127.7, 118.0, 114.6, 68.7, 66.4, 66.1, 49.3, 47.6, 43.3, 43.0, 29.3, 28.3, 28.0, 27.7, 24.9, 23.0, 22.0, 20.6, 15.4, 14.9; LC-MS (APCI) *m/z* $[M + H]^+$ 913.2, t_R = 9.3 min.



(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl-3-((2*S*,3*S*)-3-azido-2,5-dimethylhexan-amido)-2,5-dimethylhexanoate (22cc):

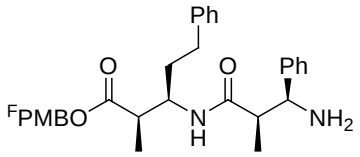
General procedure 5 was followed by employing amine **21c** (1/3 of its total weight, and the yield of amine was assumed to be 100%), DMAP (11 mg, 0.087 mmol), β-azido acid **14c** (39 mg, 0.21 mmol) and EDCI (40 mg, 0.21 mmol). Purification by FSPE gave the title compound (79 mg, 83% in two steps) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 6.25 (d, *J* = 9.5 Hz, 1H), 5.02 (d, *J* = 11.8 Hz, 1H), 4.98 (d, *J* = 12.0 Hz, 1H), 4.15 (m, 1H), 3.96 (t, *J* = 5.8 Hz, 2H), 3.54 (td, *J* = 8.1, 4.5 Hz, 1H), 2.63 (qd, *J* = 6.9, 3.6 Hz, 1H), 2.23 (m, 2H), 2,20 (quin, *J* = 7.3 Hz, 1H), 2.03 (m, 2H), 1.85 (m, 1H), 1.75 (m, 1H), 1.46 (m, 1H), 1.30 (m, 2H), 1.18 (m, 1H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.80 (d, *J* = 6.3 Hz, 3H), 0.79 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 173.4, 158.8, 130.1, 128.4, 118.5, 114.7, 66.5, 66.1, 63.5, 49.1, 46.9, 43.2, 42.9, 40.9, 29.7, 28.3, 28.0, 27.7, 25.1, 23.4, 23.0, 22.0, 21.4, 20.6, 14.9, 14.6; LC-MS (APCI) *m/z* $[M + H]^+$ 893.2, t_R = 11.5 min.



(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*R*)-3-amino-2-methyl-5-phenyl-pentanamido)-2-methyl-5-phenylpentanoate (23aa):

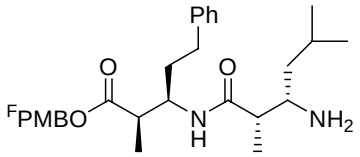
General procedure 4 was followed by employing azido-dipeptide **22aa** (102 mg, 0.103

mmol), triphenylphosphine (45 mg, 0.17 mmol) and H_2O (52 mg, 2.9 mmol). Purification by FSPE gave the title compound (99 mg, 100%) as a white solid.



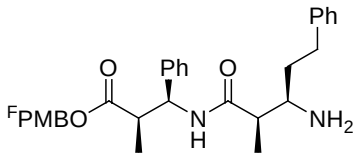
(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*S*)-3-amino-2-methyl-3-phenyl-propanamido)-2-methyl-5-phenylpentanoate (23ab):

General procedure 4 was followed by employing azido-dipeptide **22ab** (83 mg, 0.086 mmol), triphenylphosphine (45 mg, 0.17 mmol) and H_2O (52 mg, 2.9 mmol). Purification by FSPE gave the title compound (77 mg, 95%) as a white solid.



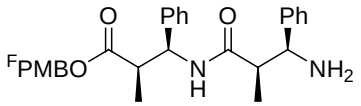
(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl-3-((2*S*,3*S*)-3-amino-2,5-dimethylhexan-amido)-2-methyl-5-phenylpentanoate (23ac):

General procedure 4 was followed by employing azido-dipeptide **22ac** (83 mg, 0.088 mmol), triphenylphosphine (45 mg, 0.17 mmol) and H_2O (52 mg, 2.9 mmol). Purification by FSPE gave the title compound (71 mg, 88%) as a white solid.



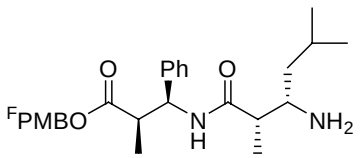
(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*R*)-3-amino-2-methyl-5-phenyl-pentanamido)-2-methyl-3-phenylpropanoate (23ba):

General procedure 4 was followed by employing azido-dipeptide **22ba** (84 mg, 0.087 mmol), triphenylphosphine (45 mg, 0.17 mmol) and H_2O (52 mg, 2.9 mmol). Purification by FSPE gave the title compound (65 mg, 80%) as a white solid.



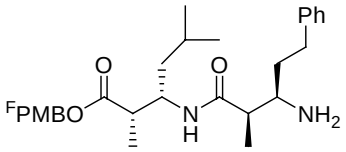
(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*S*)-3-amino-2-methyl-3-phenyl-propanamido)-2-methyl-3-phenylpropanoate (23bb):

General procedure 4 was followed by employing azido-dipeptide **22bb** (123 mg, 0.132 mmol), triphenylphosphine (45 mg, 0.17 mmol) and H_2O (52 mg, 2.9 mmol). Purification by FSPE gave the title compound (99 mg, 83%) as a white solid.



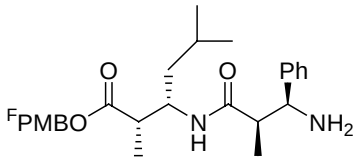
(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl-3-((2*S*,3*S*)-3-amino-2,5-dimethylhexan-amido)-2-methyl-3-phenylpropanoate (23bc):

General procedure 4 was followed by employing azido-dipeptide **22bc** (108 mg, 0.118 mmol), triphenylphosphine (45 mg, 0.17 mmol) and H_2O (52 mg, 2.9 mmol). Purification by FSPE gave the title compound (82 mg, 78%) as a white solid.



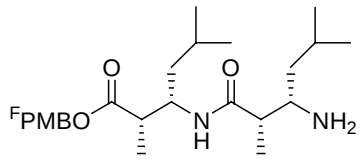
(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl-3-((2*R*,3*R*)-3-amino-2-methyl-5-phenylpentanamido)-2,5-dimethylhexanoate (23ca):

General procedure 4 was followed by employing azido-dipeptide **22ca** (71 mg, 0.075 mmol), triphenylphosphine (45 mg, 0.17 mmol) and H_2O (52 mg, 2.9 mmol). Purification by FSPE gave the title compound (65 mg, 94%) as a white solid.



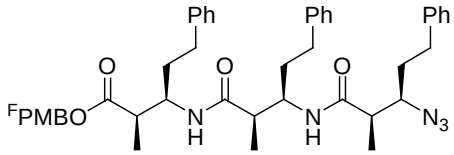
(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl-3-((2*R*,3*S*)-3-amino-2-methyl-3-phenylpropanamido)-2,5-dimethylhexanoate (23cb):

General procedure 4 was followed by employing azido-dipeptide **22cb** (76 mg, 0.083 mmol), triphenylphosphine (45 mg, 0.17 mmol) and H_2O (52 mg, 2.9 mmol). Purification by FSPE gave the title compound (72 mg, 97%) as a white solid.



(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl-3-((2*S*,3*S*)-3-amino-2,5-dimethylhexan-amido)-2,5-dimethylhexanoate (23cc):

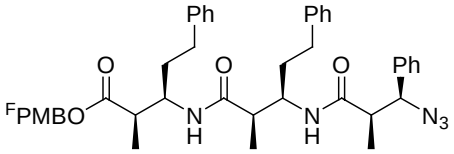
General procedure 4 was followed by employing azido-dipeptide **22cc** (71 mg, 0.080 mmol), triphenylphosphine (45 mg, 0.17 mmol) and H_2O (52 mg, 2.9 mmol). Purification by FSPE gave the title compound (66 mg, 95%) as a white solid.



(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*R*)-3-((2*R*,3*R*)-3-azido-2-methyl-5-phenylpentanamido)-2-methyl-5-phenylpentanamido)-2-methyl-5-phenylpentanoate (24aaa):

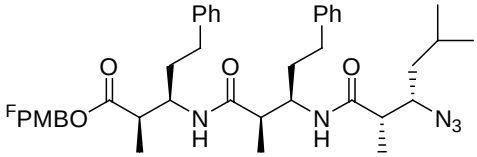
General procedure 5 was followed by employing amine **23aa** (33 mg, 0.034 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14a** (13 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (13 mg, 33%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 9.2 Hz, 1H), 7.29–7.14 (m, 15H), 7.08 (d, *J* = 7.3 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.49 (d, *J* = 9.7 Hz, 1H), 5.06 (d, *J* = 11.9 Hz, 1H), 5.01 (d, *J* = 11.9 Hz, 1H), 4.12 (m, 2H), 4.00 (t, *J* = 5.9 Hz, 2H), 3.67 (td, *J* = 9.4, 3.0 Hz, 1H), 2.85 (ddd, *J* = 14.3, 10.5, 4.9 Hz, 1H), 2.76–2.68 (m, 2H), 2.66 (dd, *J* = 10.5, 5.9 Hz, 2H), 2.58 (t, *J* = 8.2 Hz, 2H), 2.39

(quin, J = 7.4 Hz, 1H), 2.39 (qd, J = 10.7, 3.8 Hz, 1H), 2.31 (m, 2H), 2.10 (dtd, J = 9.8, 5.8, 5.8 Hz, 2H), 1.98 (dddd, J = 17.3, 10.2, 6.8, 3.0 Hz, 1H), 1.85 (m, 1H), 1.78–1.66 (m, 4H), 1.28 (d, J = 7.0 Hz, 3H), 1.19 (d, J = 7.0 Hz, 3H), 1.16 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 175.5, 173.6, 158.8, 141.6, 141.1, 130.1, 128.5, 128.4, 128.3, 128.0, 126.1, 125.9, 114.6, 110.8, 66.3, 64.5, 51.3, 50.9, 46.4, 43.5, 42.0, 36.6, 36.2, 33.5, 32.8, 32.6, 32.2, 27.9, 20.6, 16.3, 15.4, 15.0; LC-MS (APCI) m/z $[M + H]^+$ 1178.2, t_R = 8.7 min.



(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*R*)-3-((2*R*,3*S*)-3-azido-2-methyl-3-phenylpropanamido)-2-methyl-5-phenylpentanamido)-2-methyl-5-phenylpentanoate (24aab):

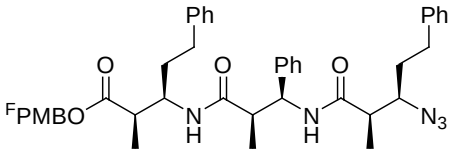
General procedure 5 was followed by employing amine **23aa** (33 mg, 0.034 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14b** (12 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (13 mg, 37%) as a white solid: LC-MS (APCI) m/z $[M + H]^+$ 1150.0, t_R = 8.6 min.



(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*R*)-3-((2*S*,3*S*)-3-azido-2,5-

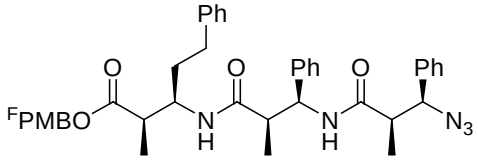
dimethylhexanamido)-2-methyl-5-phenyl-pentanamido)-2-methyl-5-phenylpentanoate (24aac):

General procedure 5 was followed by employing amine **23aa** (33 mg, 0.034 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14c** (11 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (21 mg, 55%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1130.2, t_R = 9.8 min.



(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*S*)-3-((2*R*,3*R*)-3-azido-2-methyl-5-phenylpentanamido)-2-methyl-3-phenylpropanamido)-2-methyl-5-phenylpentanoate (24aba):

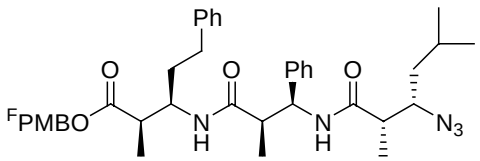
General procedure 5 was followed by employing amine **23ab** (26 mg, 0.027 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14a** (13 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (31 mg, 100%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1150.2, t_R = 8.6 min.



(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*S*)-3-((2*R*,3*S*)-3-azido-2-methyl-3-

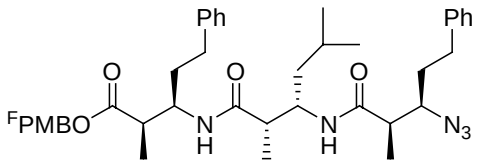
phenylpropanamido)-2-methyl-3-phenylpropanamido)-2-methyl-5-phenylpentanoate (24abb):

General procedure 5 was followed by employing amine **23ab** (26 mg, 0.027 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14b** (12 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (30 mg, 99%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1122.0, t_R = 8.5 min.



(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*S*)-3-((2*S*,3*S*)-3-azido-2,5-dimethylhexanamido)-2-methyl-3-phenylpropanamido)-2-methyl-5-phenylpentanoate (24abc):

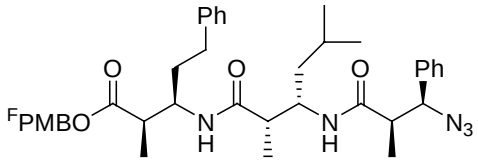
General procedure 5 was followed by employing amine **23ab** (26 mg, 0.027 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14c** (11 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (28 mg, 94%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1102.2, t_R = 10.0 min.



(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*S*,3*S*)-3-((2*R*,3*R*)-3-azido-2-methyl-

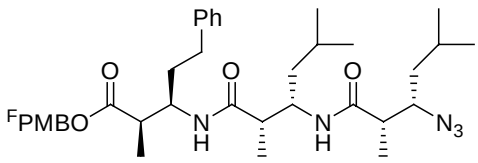
5-phenylpentanamido)-2,5-dimethylhexanamido)-2-methyl-5-phenylpentanoate (24aca):

General procedure 5 was followed by employing amine **23ac** (24 mg, 0.026 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14a** (13 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (17 mg, 58%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1130.2, t_R = 9.4 min.



(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*S*,3*S*)-3-((2*R*,3*S*)-3-azido-2-methyl-3-phenylpropanamido)-2,5-dimethylhexanamido)-2-methyl-5-phenylpentanoate (24acb):

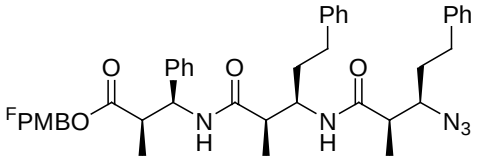
General procedure 5 was followed by employing amine **23ac** (24 mg, 0.026 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14b** (12 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (21 mg, 74%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1102.2, t_R = 9.3 min.



(2*R*,3*R*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*S*,3*S*)-3-((2*S*,3*S*)-3-azido-2,5-dimethylhexanamido)-2,5-dimethylhexanamido)-2-methyl-5-phenylpentanoate (24acc):

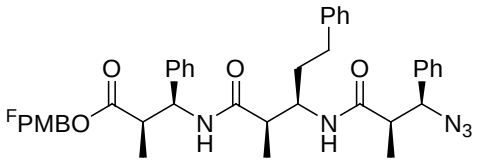
General procedure 5 was followed by employing amine **23ac** (24 mg, 0.026 mmol), DMAP

(3 mg, 0.02 mmol), β-azido acid **14c** (11 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (12 mg, 41%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1082.2, t_R = 11.0 min.



(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*R*)-3-((2*R*,3*R*)-3-azido-2-methyl-5-phenylpentanamido)-2-methyl-5-phenylpentanamido)-2-methyl-3-phenylpropanoate (24baa):

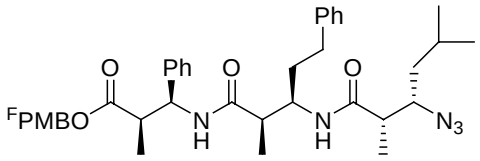
General procedure 5 was followed by employing amine **23ba** (22 mg, 0.023 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14a** (13 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (25 mg, 95%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1150.0, t_R = 8.6 min.



(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*R*)-3-((2*R*,3*S*)-3-azido-2-methyl-3-phenylpropanamido)-2-methyl-5-phenylpentanamido)-2-methyl-3-phenylpropanoate (24bab):

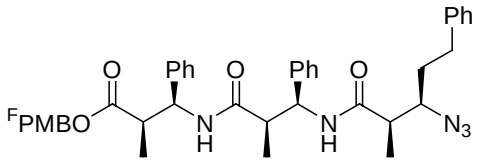
General procedure 5 was followed by employing amine **23ba** (22 mg, 0.023 mmol), DMAP

(3 mg, 0.02 mmol), β-azido acid **14b** (12 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (22 mg, 84%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1122.2, t_R = 8.6 min.



(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*R*)-3-((2*S*,3*S*)-3-azido-2,5-dimethylhexanamido)-2-methyl-5-phenylpentanamido)-2-methyl-3-phenylpropanoate (24bac):

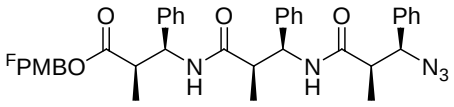
General procedure 5 was followed by employing amine **23ba** (22 mg, 0.023 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14c** (11 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (25 mg, 97%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1102.2, t_R = 9.9 min.



(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*S*)-3-((2*R*,3*R*)-3-azido-2-methyl-5-phenylpentanamido)-2-methyl-3-phenylpropanamido)-2-methyl-3-phenylpropanoate (24bba):

General procedure 5 was followed by employing amine **23bb** (33 mg, 0.036 mmol), DMAP

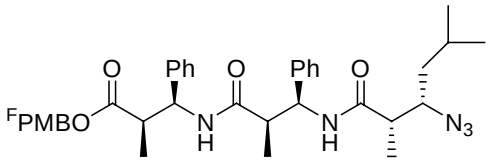
(3 mg, 0.02 mmol), β-azido acid **14a** (13 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (34 mg, 84%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1122.2, t_R = 8.5 min.



(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*S*)-3-((2*R*,3*S*)-3-azido-2-methyl-3-phenylpropanamido)-2-methyl-3-phenylpropanamido)-2-methyl-3-phenylpropanoate (24bbb):

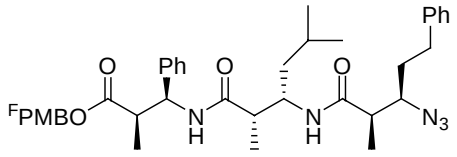
General procedure 5 was followed by employing amine **23bb** (33 mg, 0.036 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14b** (12 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (34 mg, 87%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.5 Hz, 1H), 7.39–7.08 (m, 15H), 7.05 (d, *J* = 8.6 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 5.27 (dd, *J* = 8.5, 3.4 Hz, 1H), 4.91 (dd, *J* = 8.5, 4.1 Hz, 1H), 4.82 (d, *J* = 12.1 Hz, 1H), 4.79 (d, *J* = 12.1 Hz, 1H), 4.71 (d, *J* = 10.3 Hz, 1H), 4.02 (t, *J* = 5.9 Hz, 2H), 2.83 (qd, *J* = 7.1, 3.6 Hz, 1H), 2.81 (qd, *J* = 7.4, 4.1 Hz, 1H), 2.62 (dq, *J* = 10.3, 6.9 Hz, 1H), 2.31 (m, 2H), 2.11 (dtd, *J* = 9.8, 5.8, 5.8 Hz, 2H), 1.48 (d, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.68 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 175.0, 173.6, 158.7, 141.2, 140.0, 137.4, 129.8, 128.8, 128.7, 128.6, 127.8, 127.5, 127.2, 126.0, 125.7, 114.4,

109.5, 68.5, 66.4, 66.2, 55.4, 54.8, 47.6, 46.3, 44.0, 27.9, 20.6, 16.5, 15.2, 15.1; LC-MS (APCI) *m/z* $[M + H]^+$ 1094.2, t_R = 8.4 min.



(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*S*)-3-((2*S*,3*S*)-3-azido-2,5-dimethylhexanamido)-2-methyl-3-phenylpropanamido)-2-methyl-3-phenylpropanoate (24bbc):

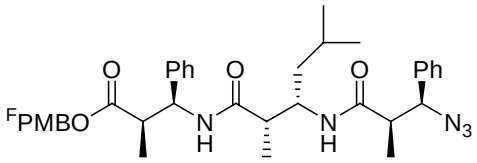
General procedure 5 was followed by employing amine **23bb** (33 mg, 0.036 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14c** (11 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (29 mg, 75%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1074.2, t_R = 9.7 min.



(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*S*,3*S*)-3-((2*R*,3*S*)-3-azido-2-methyl-5-phenylpentanamido)-2,5-dimethylhexanamido)-2-methyl-3-phenylpropanoate (24bca):

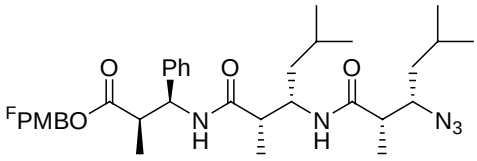
General procedure 5 was followed by employing amine **23bc** (27 mg, 0.031 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14a** (13 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (10 mg, 30%) as a white solid: LC-MS (APCI)

m/z $[M + H]^+$ 1102.2, t_R = 9.1 min.



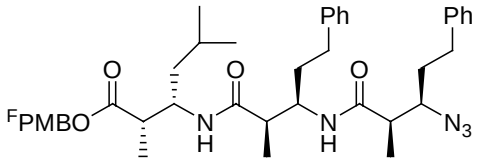
(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*S*,3*S*)-3-((2*R*,3*S*)-3-azido-2-methyl-3-phenylpropanamido)-2,5-dimethylhexanamido)-2-methyl-3-phenylpropanoate (24bcb):

General procedure 5 was followed by employing amine **23bc** (27 mg, 0.031 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14b** (12 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (15 mg, 46%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1074.2, t_R = 9.0 min.



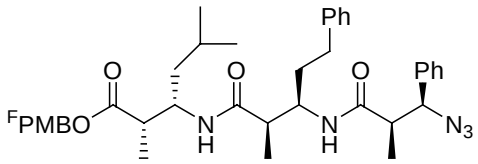
(2*R*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*S*,3*S*)-3-((2*S*,3*S*)-3-azido-2,5-dimethylhexanamido)-2,5-dimethylhexanamido)-2-methyl-3-phenylpropanoate (24bcc):

General procedure 5 was followed by employing amine **23bc** (27 mg, 0.031 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14c** (11 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (13 mg, 41%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1054.2, t_R = 10.7 min.



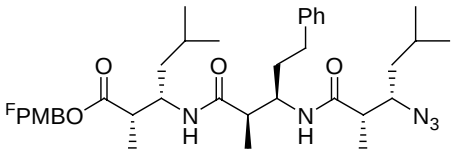
(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*R*)-3-((2*R*,3*R*)-3-azido-2-methyl-5-phenylpentanamido)-2-methyl-5-phenylpentanamido)-2,5-dimethylhexanoate (24caa):

General procedure 5 was followed by employing amine **23ca** (22 mg, 0.024 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14a** (13 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (11 mg, 42%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1130.2, t_R = 9.6 min.



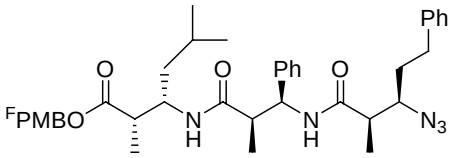
(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*R*)-3-((2*R*,3*S*)-3-azido-2-methyl-3-phenylpropanamido)-2-methyl-5-phenylpentanamido)-2,5-dimethylhexanoate (24cab):

General procedure 5 was followed by employing amine **23ca** (22 mg, 0.024 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14b** (12 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (14 mg, 53%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1102.2, t_R = 9.4 min.



(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*R*)-3-((2*S*,3*S*)-3-azido-2,5-dimethylhexanamido)-2-methyl-5-phenylpentanamido)-2,5-dimethylhexanoate (24cac):

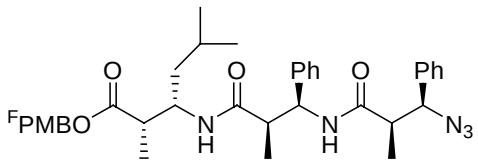
General procedure 5 was followed by employing amine **23ca** (22 mg, 0.024 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14c** (11 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (18 mg, 69%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1082.2, t_R = 11.0 min.



(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*S*)-3-((2*R*,3*R*)-3-azido-2-methyl-5-phenylpentanamido)-2-methyl-3-phenylpropanamido)-2,5-dimethylhexanoate (24cba):

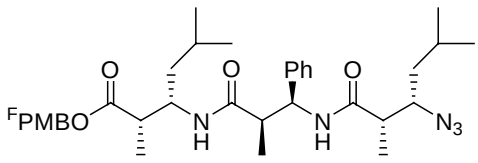
General procedure 5 was followed by employing amine **23cb** (24 mg, 0.027 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14a** (13 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (29 mg, 97%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.5 Hz, 1H), 7.30–7.17 (m, 12H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.86 (d, *J* = 9.9 Hz, 1H), 5.16 (dd, *J* = 8.5, 3.3 Hz, 1H), 5.03 (d, *J* = 12.0 Hz, 1H), 4.99 (d, *J* = 12.0 Hz, 1H), 4.04 (t, *J* = 5.9 Hz, 2H), 3.96 (m, 1H), 3.69 (td, *J* = 9.4, 3.2 Hz, 1H), 2.84 (ddd, *J* = 14.8, 10.3, 4.9 Hz, 1H), 2.69 (ddd, *J* = 13.9, 10.2, 6.6 Hz, 1H), 2.60 (qd, *J* = 7.0, 3.5 Hz, 1H), 2.55 (qd,

J = 7.2, 3.6 Hz, 1H), 2.52 (quin, J = 7.9 Hz, 1H), 2.31 (m, 2H), 2.11 (dtd, J = 9.8, 5.8, 5.8 Hz, 2H), 1.95 (dddd, J = 16.0, 8.8, 5.0, 2.5 Hz, 1H), 1.75 (m, 1H), 1.41 (d, J = 7.0 Hz, 3H), 1.20 (d, J = 7.0 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H), 0.94 (m, 1H), 0.87 (m, 2H), 0.68 (d, J = 5.9 Hz, 3H), 0.61 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 175.0, 173.2, 159.0, 130.0, 128.6, 128.4, 127.1, 126.2, 114.9, 66.7, 66.1, 64.7, 55.7, 49.0, 46.5, 46.2, 43.2, 42.8, 33.5, 32.4, 28.2, 24.3, 23.0, 21.8, 20.8, 16.9, 14.8, 14.6; LC-MS (APCI) m/z $[M + H]^+$ 1102.2, t_R = 9.6 min.



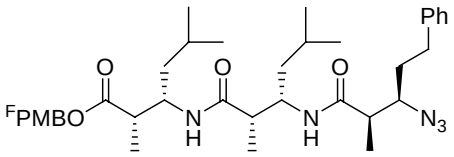
(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*S*)-3-((2*R*,3*S*)-3-azido-2-methyl-3-phenylpropanamido)-2-methyl-3-phenylpropanamido)-2,5-dimethylhexanoate (24cbb):

General procedure 5 was followed by employing amine **23cb** (24 mg, 0.027 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14b** (12 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (27 mg, 92%) as a white solid: LC-MS (APCI) m/z $[M + H]^+$ 1074.2, t_R = 9.5 min.



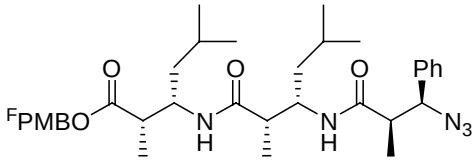
(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*R*,3*S*)-3-((2*S*,3*S*)-3-azido-2,5-dimethylhexanamido)-2-methyl-3-phenylpropanamido)-2,5-dimethylhexanoate (24cbc):

General procedure 5 was followed by employing amine **23cb** (24 mg, 0.027 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14c** (11 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (25 mg, 88%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1054.2, t_R = 11.1 min.



(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*S*,3*S*)-3-((2*R*,3*R*)-3-azido-2-methyl-5-phenylpentanamido)-2,5-dimethylhexanamido)-2,5-dimethylhexanoate (24cca):

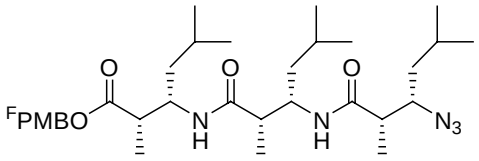
General procedure 5 was followed by employing amine **23cc** (22 mg, 0.025 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14a** (13 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (10 mg, 37%) as a white solid: LC-MS (APCI) *m/z* $[M + H]^+$ 1082.2, t_R = 10.5 min.



(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*S*,3*S*)-3-((2*R*,3*S*)-3-azido-2-methyl-3-phenylpropanamido)-2,5-dimethylhexanamido)-2,5-dimethylhexanoate (24ccb):

General procedure 5 was followed by employing amine **23cc** (22 mg, 0.025 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14b** (12 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol).

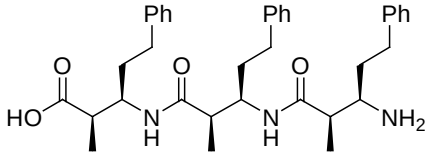
Purification by FSPE gave the title compound (10 mg, 38%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.28 (m, 7H), 7.20 (d, *J* = 9.4 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.36 (d, *J* = 9.8 Hz, 1H), 5.12 (d, *J* = 11.9 Hz, 1H), 5.06 (d, *J* = 11.9 Hz, 1H), 4.68 (d, *J* = 10.5 Hz, 1H), 4.21–4.10 (m, 2H), 4.05 (t, *J* = 5.9 Hz, 2H), 2.72 (qd, *J* = 7.2, 3.4 Hz, 1H), 2.51 (dq, *J* = 10.5, 6.9 Hz, 1H), 2.37–2.25 (m, 3H), 2.11 (dtd, *J* = 10.0, 5.9, 5.9 Hz, 2H), 1.74 (m, 1H), 1.52 (m, 2H), 1.33 (m, 2H), 1.26 (m, 1H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 175.4, 173.5, 158.8, 137.7, 130.1, 128.8, 128.5, 128.4, 127.8, 114.7, 68.8, 66.6, 66.3, 49.8, 49.3, 47.6, 44.2, 44.1, 43.3, 42.5, 29.7, 28.1, 25.1, 22.9, 22.8, 22.4, 22.2, 20.7, 16.2, 15.6, 15.2; LC-MS (APCI) *m/z* $[M + H]^+$ 1054.2, t_R = 10.4 min.



(2*S*,3*S*)-4-[3-(Perfluorooctyl)propyl-1-oxy]benzyl 3-((2*S*,3*S*)-3-((2*S*,3*S*)-3-azido-2,5-dimethylhexanamido)-2,5-dimethylhexanamido)-2,5-dimethylhexanoate (24ccc):

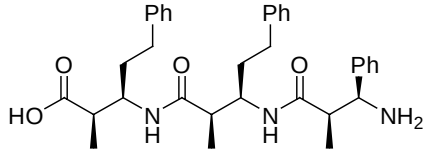
General procedure 5 was followed by employing amine **23cc** (22 mg, 0.025 mmol), DMAP (3 mg, 0.02 mmol), β-azido acid **14c** (11 mg, 0.058 mmol) and EDCI (11 mg, 0.058 mmol). Purification by FSPE gave the title compound (9 mg, 33%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H), 7.21 (d, *J* = 9.3 Hz, 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.30 (d, *J* = 9.8 Hz, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 5.05 (d, *J* = 11.9 Hz, 1H), 4.17–4.10 (m, 2H), 4.04 (t, *J*

= 5.9 Hz, 2H), 3.66 (td, *J* = 9.2, 3.5 Hz, 1H), 2.69 (qd, *J* = 7.2, 3.4 Hz, 1H), 2.30 (m, 4H), 2.11 (dtd, *J* = 9.6, 5.8, 5.8 Hz, 2H), 1.84 (m, 1H), 1.61–1.51 (m, 3H), 1.44 (ddd, *J* = 14.1, 9.0, 6.4 Hz, 1H), 1.38–1.31 (m, 4H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 7.2 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.1 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 175.6, 173.6, 158.8, 130.1, 128.2, 114.6, 109.6, 66.4, 66.2, 63.3, 49.5, 49.0, 46.9, 43.9, 43.7, 43.2, 42.3, 40.6, 27.9, 25.1, 25.0, 23.7, 22.8, 22.4, 22.2, 21.3, 20.6, 16.0, 15.2, 15.0; LC-MS (APCI) *m/z* $[M + H]^+$ 1034.2, t_R = 12.2 min.



(2*R*,3*R*)-3-((2*R*,3*R*)-3-((2*R*,3*R*)-3-Amino-2-methyl-5-phenylpentanamido)-2-methyl-5-phenylpentanamido)-2-methyl-5-phenylpentanoic acid (25aaa):

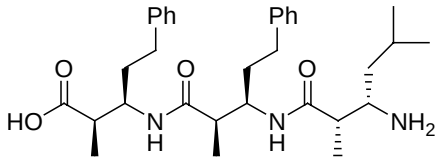
General procedure 6 was followed by employing **24aaa** (6.8 mg, 0.0058 mmol). Purification by FSPE gave the title compound (3.1 mg, 92%) as a white solid: LC-MS (ESI) *m/z* $[M + H]^+$ 586.3, t_R = 2.4 min.



(2*R*,3*R*)-3-((2*R*,3*R*)-3-((2*R*,3*S*)-3-Amino-2-methyl-3-phenylpropanamido)-2-methyl-5-

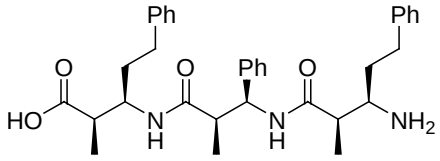
phenylpentanamido)-2-methyl-5-phenylpentanoic acid (25aab):

General procedure 6 was followed by employing **24aab** (7.4 mg, 0.0064 mmol). Purification by FSPE gave the title compound (3.2 mg, 89%) as a white solid: LC-MS (ESI) *m/z* $[M + H]^+$ 558.3, t_R = 2.5 min.



(2*R*,3*R*)-3-((2*R*,3*R*)-3-((2*S*,3*S*)-3-Amino-2,5-dimethylhexanamido)-2-methyl-5-phenyl-pentanamido)-2-methyl-5-phenylpentanoic acid (25aac):

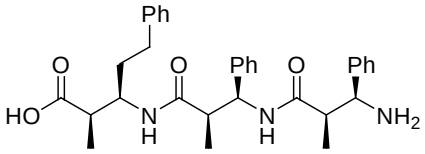
General procedure 6 was followed by employing **24aac** (13.4 mg, 0.0119 mmol). Purification by FSPE gave the title compound (5.1 mg, 80%) as a white solid. A part of it (1.7 mg) was further purified by preparative reverse phase HPLC to afford pure product (1.3 mg, 76% recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 538.3, t_R = 2.3 min.



(2*R*,3*R*)-3-((2*R*,3*S*)-3-((2*R*,3*R*)-3-Amino-2-methyl-5-phenylpentanamido)-2-methyl-3-phenylpropanamido)-2-methyl-5-phenylpentanoic acid (25aba):

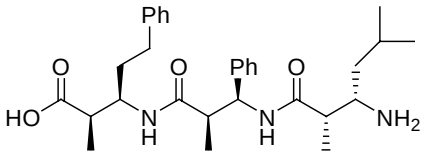
General procedure 6 was followed by employing **24aba** (11.5 mg, 0.0100 mmol). Purification by FSPE gave the title compound (4.7 mg, 84%) as a white solid. A part of it (1.7

mg) was further purified by preparative reverse phase HPLC to afford pure product (1.6 mg, 94% recovery): ^{1}H NMR (500 MHz, 1:1 D_2O:CD_3CN, δ (CHD_2CN) = 1.92 ppm) δ 7.37–7.09 (m, 15H), 4.80 (d, *J* = 10.3 Hz, 1H), 3.87 (td, *J* = 10.1, 3.7 Hz, 1H), 3.08 (br, m, 1H), 2.79–2.65 (m, 3H), 2.57 (m, 1H), 2.51 (m, 2H), 2.26 (quin, *J* = 7.2 Hz, 1H), 1.82 (m, 2H), 1.74 (m, 1H), 1.55 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H); LC-MS (ESI) *m/z* $[M + H]^+$ 558.3, t_R = 2.2 min.



(2*R*,3*R*)-3-((2*R*,3*S*)-3-((2*R*,3*S*)-3-Amino-2-methyl-3-phenylpropanamido)-2-methyl-3-phenylpropanamido)-2-methyl-5-phenylpentanoic acid (25abb):

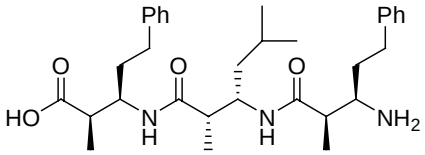
General procedure 6 was followed by employing **24abb** (9.6 mg, 0.0086 mmol). Purification by FSPE gave the title compound (3.2 mg, 71%) as a white solid: LC-MS (ESI) *m/z* $[M + H]^+$ 530.2, t_R = 2.6 min.



(2*R*,3*R*)-3-((2*R*,3*S*)-3-((2*S*,3*S*)-3-Amino-2,5-dimethylhexanamido)-2-methyl-3-phenylpropanamido)-2-methyl-5-phenylpentanoic acid (25abc):

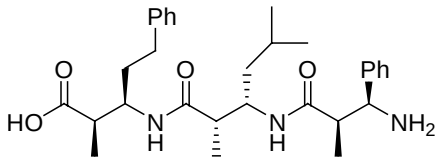
General procedure 6 was followed by employing **24abc** (10.2 mg, 0.00926 mmol).

Purification by FSPE gave the title compound (3.0 mg, 64%) as a white solid. A part of it (1.1 mg) was further purified by preparative reverse phase HPLC to afford pure product (0.5 mg, 45% recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 510.3, t_R = 2.3 min.



(2*R*,3*R*)-3-((2*S*,3*S*)-3-((2*R*,3*R*)-3-Amino-2-methyl-5-phenylpentanamido)-2,5-dimethyl-hexanamido)-2-methyl-5-phenylpentanoic acid (25aca):

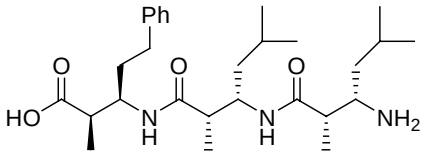
General procedure 6 was followed by employing **24aca** (9.6 mg, 0.0085 mmol). Purification by FSPE gave the title compound (2.8 mg, 61%) as a white solid. A part of it (1.0 mg) was further purified by preparative reverse phase HPLC to afford pure product (0.8 mg, 80% recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 538.3, t_R = 2.3 min.



(2*R*,3*R*)-3-((2*S*,3*S*)-3-((2*R*,3*S*)-3-Amino-2-methyl-3-phenylpropanamido)-2,5-dimethyl-hexanamido)-2-methyl-5-phenylpentanoic acid (25acb):

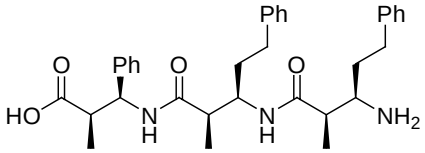
General procedure 6 was followed by employing **24acb** (9.3 mg, 0.0084 mmol). Purification by FSPE gave the title compound (3.1 mg, 72%) as a white solid. A part of it (0.9 mg) was further purified by preparative reverse phase HPLC to afford pure product (0.6 mg,

67% recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 510.2, t_R = 2.2 min.



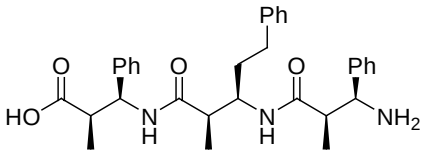
(2*R*,3*R*)-3-((2*S*,3*S*)-3-((2*S*,3*S*)-3-Amino-2,5-dimethylhexanamido)-2,5-dimethylhexanamido)-2-methyl-5-phenylpentanoic acid (25acc):

General procedure 6 was followed by employing **24acc** (6.5 mg, 0.0060 mmol). Purification by FSPE gave the title compound (2.0 mg, 68%) as a white solid: LC-MS (ESI) *m/z* $[M + H]^+$ 490.4, t_R = 2.3 min.



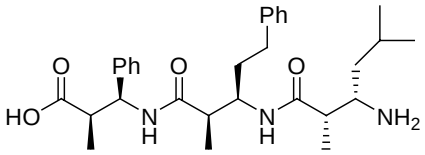
(2*R*,3*S*)-3-((2*R*,3*R*)-3-((2*R*,3*R*)-3-Amino-2-methyl-5-phenylpentanamido)-2-methyl-5-phenylpentanamido)-2-methyl-3-phenylpropanoic acid (25baa):

General procedure 5 was followed by employing **24baa** (10.0 mg, 0.00870 mmol). Purification by FSPE gave the title compound (3.9 mg, 80%) as a white solid. A part of it (1.9 mg) was further purified by preparative reverse phase HPLC to afford pure product (1.6 mg, 84% recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 558.3, t_R = 2.4 min.



(2*R*,3*S*)-3-((2*R*,3*R*)-3-((2*R*,3*S*)-3-Amino-2-methyl-3-phenylpropanamido)-2-methyl-5-phenylpentanamido)-2-methyl-3-phenylpropanoic acid (25bab):

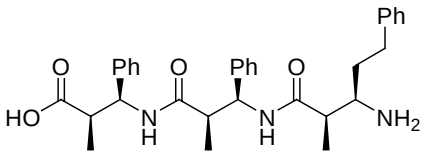
General procedure 6 was followed by employing **24bab** (8.8 mg, 0.0078 mmol). Purification by FSPE gave the title compound (2.9 mg, 70%) as a white solid. A part of it (1.7 mg) was further purified by preparative reverse phase HPLC to afford pure product (1.6 mg, 94% recovery): ^{1}H NMR (500 MHz, 1:1 D_2O:CD_3CN, δ (CHD_2CN) = 1.92 ppm) δ 7.44–7.10 (m, 15H), 4.68 (d, *J* = 8.0 Hz, 1H), 3.99 (ddd, *J* = 10.5, 7.5, 3.5 Hz, 1H), 3.92 (br, d, *J* = 9.3 Hz, 1H), 2.56–2.51 (m, 3H), 2.47 (ddd, *J* = 16.7, 10.4, 6.0 Hz, 1H), 2.34 (m, 1H), 1.75 (m, 1H), 1.63 (m, 1H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H); LC-MS (ESI) *m/z* $[M + H]^+$ 530.2, t_R = 2.4 min.



(2*R*,3*S*)-3-((2*R*,3*R*)-3-((2*S*,3*S*)-3-Amino-2,5-dimethylhexanamido)-2-methyl-5-phenyl-pentanamido)-2-methyl-3-phenylpropanoic acid (25bac):

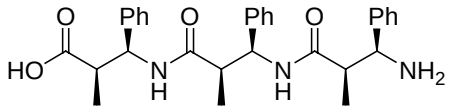
General procedure 6 was followed by employing **24bac** (9.8 mg, 0.0089 mmol). Purification by FSPE gave the title compound (4.4 mg, 97%) as a white solid. A part of it (1.5 mg) was further purified by preparative reverse phase HPLC to afford pure product (1.4 mg,

93% recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 510.2, t_R = 2.1 min.



(2*R*,3*S*)-3-((2*R*,3*S*)-3-((2*R*,3*R*)-3-Amino-2-methyl-5-phenylpentanamido)-2-methyl-3-phenylpropanamido)-2-methyl-3-phenylpropanoic acid (25bba):

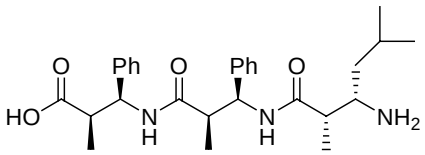
General procedure 6 was followed by employing **24bba** (11.7 mg, 0.0104 mmol). Purification by FSPE gave the title compound (2.8 mg, 51%) as a white solid. A part of it (1.2 mg) was further purified by preparative reverse phase HPLC to afford pure product (1.2 mg, >99% recovery): ^{1}H NMR (500 MHz, 1:1 D_2O:CD_3CN, δ (CHD_2CN) = 1.92 ppm) δ 7.56–7.15 (m, 15H), 4.77 (d, *J* = 10.7 Hz, 3H), 4.75 (d, *J* = 9.0 Hz, 1H), 3.17 (m, 1H), 2.85–2.72 (m, 2H), 2.66 (m, 2H), 2.55 (dq, *J* = 10.2, 7.0 Hz, 1H), 1.81 (m, 1H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.76 (d, *J* = 6.9 Hz, 3H), 0.63 (d, *J* = 6.9 Hz, 3H); LC-MS (ESI) *m/z* $[M + H]^+$ 530.2, t_R = 2.2 min.



(2*R*,3*S*)-3-((2*R*,3*S*)-3-((2*R*,3*S*)-3-Amino-2-methyl-3-phenylpropanamido)-2-methyl-3-phenylpropanamido)-2-methyl-3-phenylpropanoic acid (25bbb):

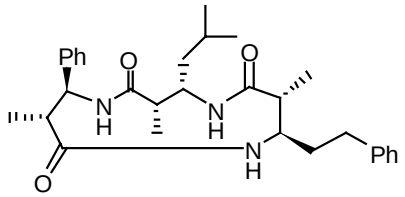
General procedure 6 was followed by employing **24bbb** (8.7 mg, 0.0080 mmol). Purification by FSPE gave the title compound (2.4 mg, 60%) as a white solid: ^{1}H NMR (500

MHz, 1:1 D_2O:CD_3CN, δ (HOD) = 4.67 ppm) δ 7.95–7.48 (m, 15H), 5.24 (d, *J* = 10.9 Hz, 1H), 5.20 (d, *J* = 10.9 Hz, 1H), 3.66 (dq, *J* = 10.1, 6.7 Hz, 1H), 3.07 (dq, *J* = 11.5, 7.4 Hz, 1H), 3.04 (dq, *J* = 11.1, 7.3 Hz, 1H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 7.1 Hz, 3H); LC-MS (ESI) *m/z* $[M + H]^+$ 502.2, t_R = 2.7 min.



(2*R*,3*S*)-3-((2*R*,3*S*)-3-((2*S*,3*S*)-3-Amino-2,5-dimethylhexanamido)-2-methyl-3-phenyl-propanamido)-2-methyl-3-phenylpropanoic acid (25bbc):

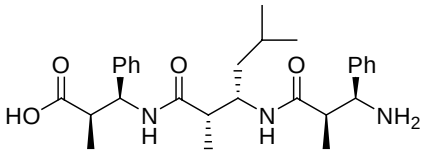
General procedure 6 was followed by employing **24bbc** (12.1 mg, 0.0113 mmol). Purification by FSPE gave the title compound (4.8 mg, 88%) as a white solid. A part of it (2.1 mg) was further purified by preparative reverse phase HPLC to afford pure product (1.8 mg, 86% recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 482.2, t_R = 2.1 min.



(3*S*,4*S*,7*R*,8*R*,11*R*,12*S*)-4-Isobutyl-3,7,11-trimethyl-8-phenethyl-12-phenyl-1,5,9-triazacyclo-dodecane-2,6,10-trione (26bca):

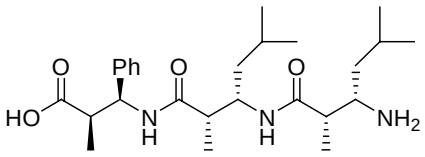
General procedure 6 was followed by employing **24bca** (7.1 mg, 0.0064 mmol).

Purification by FSPE gave the title compound (2.7 mg, 82%) as a white solid. A part of it (1.4 mg) was further purified by preparative reverse phase HPLC to afford pure product (0.9 mg, 64% recovery): MS (ESI) *m/z* $[M - H_2O + 2Na]^+$ 537.3 ("M" is the mass of the desired product).



(2*R*,3*S*)-3-((2*S*,3*S*)-3-((2*R*,3*S*)-3-Amino-2-methyl-3-phenylpropanamido)-2,5-dimethyl-hexanamido)-2-methyl-3-phenylpropanoic acid (25bcb):

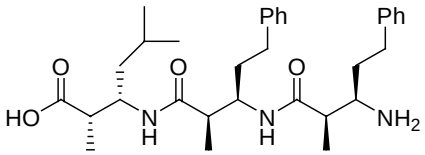
General procedure 6 was followed by employing **24bcb** (10.6 mg, 0.00987 mmol). Purification by FSPE gave the title compound (3.6 mg, 76%) as a white solid. A part of it (1.9 mg) was further purified by preparative reverse phase HPLC to afford pure product (1.0 mg, 53% recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 482.3, t_R = 1.9 min.



(2*R*,3*S*)-3-((2*S*,3*S*)-3-((2*S*,3*S*)-3-Amino-2,5-dimethylhexanamido)-2,5-dimethylhexan-amido)-2-methyl-3-phenylpropanoic acid (25bcc):

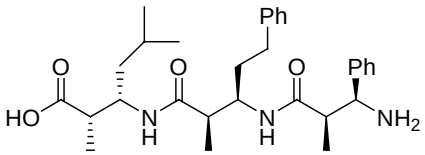
General procedure 6 was followed by employing **24bcc** (9.2 mg, 0.0087 mmol). Purification by FSPE gave the title compound (3.2 mg, 79%) as a white solid. A part of it (1.5 mg) was further purified by preparative reverse phase HPLC to afford pure product (1.3 mg, 87%

recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 462.3, t_R = 2.0 min.



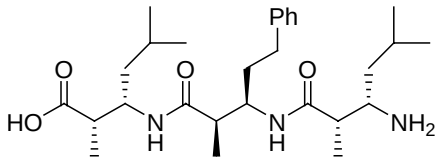
(2*S*,3*S*)-3-((2*R*,3*R*)-3-((2*R*,3*R*)-3-Amino-2-methyl-5-phenylpentanamido)-2-methyl-5-phenylpentanamido)-2,5-dimethylhexanoic acid (25caa):

General procedure 6 was followed by employing **24caa** (6.5 mg, 0.0058 mmol). Purification by FSPE gave the title compound (2.7 mg, 87%) as a white solid. A part of it (1.1 mg) was further purified by preparative reverse phase HPLC to afford pure product (1.0 mg, 91% recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 538.3, t_R = 2.0 min.



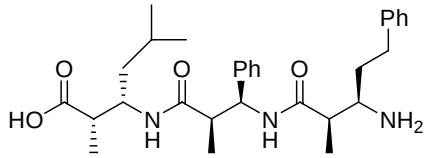
(2*S*,3*S*)-3-((2*R*,3*R*)-3-((2*R*,3*S*)-3-Amino-2-methyl-3-phenylpropanamido)-2-methyl-5-phenylpentanamido)-2,5-dimethylhexanoic acid (25cab):

General procedure 6 was followed by employing **24cab** (7.0 mg, 0.0064 mmol). Purification by FSPE gave the title compound (2.3 mg, 71%) as a white solid. A part of it (0.8 mg) was further purified by preparative reverse phase HPLC to afford pure product (0.6 mg, 75% recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 510.4, t_R = 2.3 min.



(2*S*,3*S*)-3-((2*R*,3*R*)-3-((2*S*,3*S*)-3-Amino-2,5-dimethylhexanamido)-2-methyl-5-phenyl-pentanamido)-2,5-dimethylhexanoic acid (25cac):

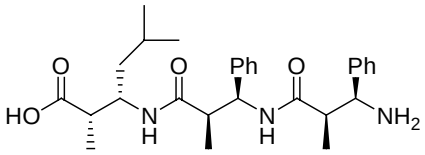
General procedure 6 was followed by employing **24cac** (12.8 mg, 0.0118 mmol). Purification by FSPE gave the title compound (3.2 mg, 55%) as a white solid. A part of it (0.9 mg) was further purified by preparative reverse phase HPLC to afford pure product (0.7 mg, 78% recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 490.3, t_R = 2.2 min.



(2*S*,3*S*)-3-((2*R*,3*S*)-3-((2*R*,3*R*)-3-Amino-2-methyl-5-phenylpentanamido)-2-methyl-3-phenylpropanamido)-2,5-dimethylhexanoic acid (25cba):

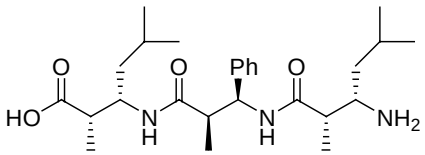
General procedure 6 was followed by employing **24cba** (16.7 mg, 0.0152 mmol). Purification by FSPE gave the title compound (5.3 mg, 69%) as a white solid. A part of it (2.4 mg) was further purified by preparative reverse phase HPLC to afford pure product (1.7 mg, 71% recovery): ^{1}H NMR (500 MHz, 1:1 D_2O:CD_3CN, δ (HOD) = 4.67 ppm) δ 7.86–7.69 (m, 10H), 5.40 (d, *J* = 7.0 Hz, 1H), 4.25 (ddd, *J* = 9.6, 4.1, 4.1 Hz, 1H), 3.69 (br, m, 1H), 3.30 (quin, *J* = 7.1 Hz, 1H), 3.28–3.17 (m, 2H), 3.14 (ddd, *J* = 16.9, 9.6, 6.8 Hz, 1H), 2.84 (qd, *J* = 7.0, 5.5 Hz, 1H), 2.33 (m, 2H), 1.62 (d, *J* = 7.5 Hz, 3H), 1.57 (d, *J* = 7.0 Hz, 3H), 1.45 (d, *J* = 7.0 Hz,

3H), 1.21 (d, J = 4.6 Hz, 3H), 1.20 (d, J = 4.7 Hz, 3H); LC-MS (ESI) *m/z* $[M + H]^+$ 510.2, t_R = 2.3 min.



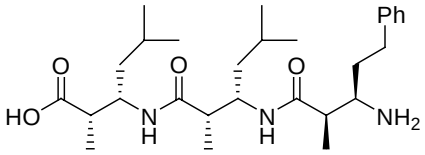
(2*S*,3*S*)-3-((2*R*,3*S*)-3-((2*R*,3*S*)-3-Amino-2-methyl-3-phenylpropanamido)-2-methyl-3-phenylpropanamido)-2,5-dimethylhexanoic acid (25cbb):

General procedure 6 was followed by employing **24cbb** (10.6 mg, 0.00987 mmol). Purification by FSPE gave the title compound (4.2 mg, 88%) as a white solid. A part of it (2.0 mg) was further purified by preparative reverse phase HPLC to afford pure product (1.8 mg, 90% recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 482.2, t_R = 2.2 min.



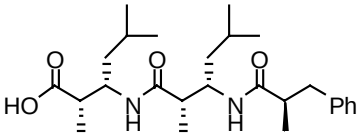
(2*S*,3*S*)-3-((2*R*,3*S*)-3-((2*S*,3*S*)-3-Amino-2,5-dimethylhexanamido)-2-methyl-3-phenylpropanamido)-2,5-dimethylhexanoic acid (25cbc):

General procedure 6 was followed by employing **24cbc** (9.6 mg, 0.0091 mmol). Purification by FSPE gave the title compound (3.7 mg, 88%) as a white solid. A part of it (1.4 mg) was further purified by preparative reverse phase HPLC to afford pure product (0.8 mg, 57% recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 462.3, t_R = 2.2 min.



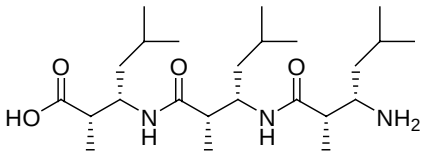
(2*S*,3*S*)-3-((2*S*,3*S*)-3-((2*R*,3*R*)-3-Amino-2-methyl-5-phenylpentanamido)-2,5-dimethyl-hexanamido)-2,5-dimethylhexanoic acid (25cca):

General procedure 6 was followed by employing **24cca** (6.7 mg, 0.0062 mmol). Purification by FSPE gave the title compound (2.5 mg, 82%) as a white solid. A part of it (1.0 mg) was further purified by preparative reverse phase HPLC to afford pure product (0.4 mg, 40% recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 490.4, t_R = 2.1 min.



(2*S*,3*S*)-3-((2*S*,3*S*)-2,5-Dimethyl-3-((*R*)-2-methyl-3-phenylpropanamido)hexanamido)-2,5-dimethylhexanoic acid (27ccb):

General procedure 6 was followed by employing **24ccb** (7.3 mg, 0.0069 mmol). Purification by FSPE gave the title compound (3.1 mg, 97%) as a white solid. A part of it (1.2 mg) was further purified by preparative reverse phase HPLC to afford pure product (1.0 mg, 83% recovery): LC-MS (ESI) *m/z* $[M - 15 + Na]^+$ 469.2 ("M" is the mass of the desired product), t_R = 5.0 min.



(2*S*,3*S*)-3-((2*S*,3*S*)-3-((2*S*,3*S*)-3-Amino-2,5-dimethylhexanamido)-2,5-dimethylhexanamido)-2,5-dimethylhexanoic acid (25ccc):

General procedure 6 was followed by employing **24ccc** (5.4 mg, 0.0052 mmol). Purification by FSPE gave the title compound (1.8 mg, 78%) as a white solid. A part of it (0.8 mg) was further purified by preparative reverse phase HPLC to afford pure product (0.7 mg, 88% recovery): LC-MS (ESI) *m/z* $[M + H]^+$ 442.4, t_R = 2.1 min.

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CHAPTER 2. FLUOROUS MIXTURE SYNTHESIS OF EIGHT STEREOISOMERS OF MACROLACTONE SCH725674

2.1 INTRODUCTION

2.1.1 Fluorous Mixture Synthesis.

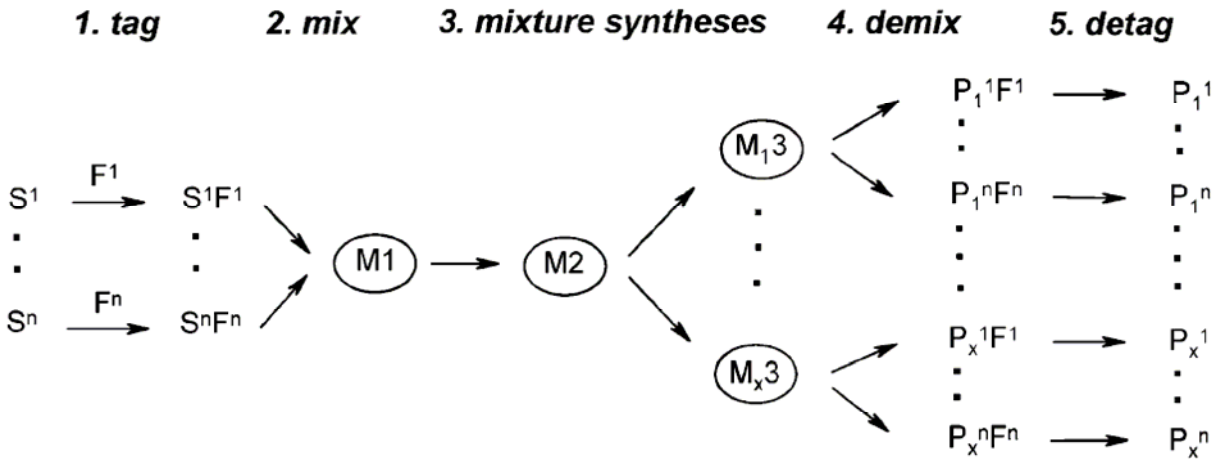
In the traditional total synthesis of a natural product, the ultimate goal is to obtain the target molecule in enantiomerically pure form. The synthesis of stereoisomers is only necessary when: 1) the isomer is also a natural product (such as epoxyquinol A and B[1]); 2) the configurations of the natural product are not fully assigned (such as aurilol[2]); 3) the original structure assignment is not correct (such as homononactinic acid and azaspiracid-1[3]). To solve problems 2 and 3, people usually synthesize the stereoisomer one at a time. If the first is not proved be the natural product, then another one will be prepared, and so on. This is adventurous since it is not adequate to prove the proposed structure simply because the spectroscopic data match with those of the natural product. The disproval of other stereoisomers has to be demonstrated at the same time. Thus, systematic synthesis of the stereoisomers of the natural product becomes necessary.

Compared to the traditional total synthesis, modern combinatorial techniques can generate a large number of isomers in a short time. Among these techniques, solution-phase parallel synthesis deals with individual pure compounds and most reactions are carried out separately for

different isomers.[4] However, parallel synthesis involves a large amount of work and may not be suitable to generate a large library of isomers. Solution-phase mixture synthesis is more attractive with regard to reduced number of steps.[5-7] However, it has several drawbacks: 1) it usually does not target the isolation of the individual target molecules but uses deconvolution methods to identify only the most active compounds;[8] 2) the time saved during the mixture synthesis is often spent in finding the hit structure. The separation of final products in the mixture synthesis can be accomplished by a strategy based on separation tags. Thus, the technique of fluorous mixture synthesis (FMS) was developed. [9-16]

FMS is a solution-phase synthetic technique to prepare multiple isomers in a single series of reactions. While single intermediates and final product are obtained in a traditional organic synthesis, FMS allows us to conduct reactions on mixtures of quasiisomers (isomeric compounds with different tags). FMS has five stages: tagging, mixing, mixture syntheses, demixing and detagging (Scheme 2.1). To start, the required isomeric subtrates (S^1-S^n) are prepared, and the configuration of each isomer is encoded by a unique, highly fluorinated tag (fluorous tag, F^1-F^n) which has a unique number of florines. Fluorous tags have been used to encode enantiomers (to give quasienantiomers), diastereomers (to give quasidiastereomers), and analogues. During the mixture synthesis stage, the quasiisomers (S^1F^1-S^nF^n) are mixed to get the starting mixture (M1). The bulk of the synthesis is then carried out on the mixture, so only one synthesis is performed. When an additional stereocenter is introduced, the splitting of the mixture is required for the stereoselective reaction and adding different new tags. When this is done, remixing occurs (not

shown in Scheme 2.1). At the end of the synthesis, demixing of the end mixture (M3) by chromatography over fluorous silica gel separates the quasiisomers (P^1F^1-P^nF^n) in the order of increasing fluorine content. In the detagging stage, removal of the fluorous tags from each individual pure compound furnishes the final stereoisomeric products (P^1-P^n).



S = Substrate; F = Fluorous tag; M1 = Starting mixture; M2 = Intermediate mixture; M3 = End mixture; P = Product

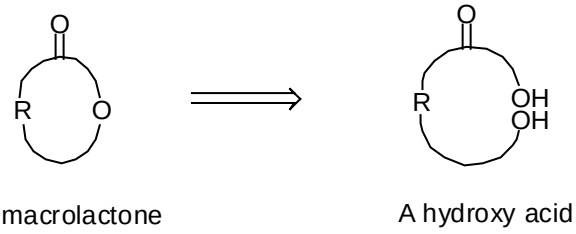
Scheme 2.1. The conceptual basis of Fluorous Mixture Synthesis

FMS has the advantages of both the solution-phase parallel synthesis (homogeneous reactions) and the solid-phase mixture synthesis (reduced amount of work). The early work validated the principles and features of FMS, such as the synthesis of the stereoisomer libraries of murisolin,[11] passifloricin[12] and dictyostatin,[13] and the analogs of mappicine.[14] After that, we started to use FMS to solve structure problems. For the natural products whose three-dimensional structure is not fully assigned, a set of stereoisomers is synthesized unambiguously and the spectroscopic data of the synthetic samples are compared with those of the natural sample to

determine the configurations. With this purpose, we successfully performed the stereoisomer synthesis and the structure elucidation of (+)-cytostatin[15] and lagunapyrone B,[16] whose relative configurations were only partially assigned. We now seek to solve even more challenging problems with natural products for which no configurations were assigned.

2.1.2 Macrolactones.

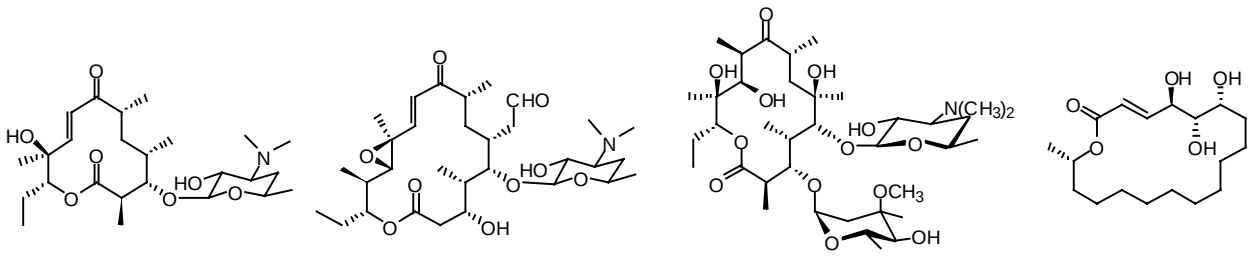
Many natural products are macrolactones, such as erythromycins,[17] epothilone[18] and spongistatins.[19] The definition of a macrolactone is sometimes expanded to a macrocyclic lactone with the ring size often greater than 12-membered and with many substituents asymmetrically placed on the periphery of the ring.[20,21] From a chemical viewpoint, a macrolactone can be viewed as the intramolecular esterification product of a hydroxy acid (Scheme 2.2). A macrolactone can also have more than one ester linkage.



Scheme 2.2. The general structure of a macrolactone

Macrolactones are often of immense pharmacological importance. Since the discovery of the first clinically useful macrolactone erythromycin (also can be classified as "macrolactone" since it is a macrolactone glycoside antibiotics) in the 1950's, macrolactone antibiotics have been

used as therapeutic agents to treat infections in humans and animals for over 50 years. Four biologically active macrolactones with ring sizes of 12 (methymycin,[22] **1a**), 14 (rosamicin,[23] **1b**), 16 (erythromycin A,[17] **1c**) and 18 ((+)-aspicilin,[24] **1d**) are shown in Figure 2.1.



1a, methymycin, anti-Gram-negative

1b, rosamicin, anti-Gram-positive

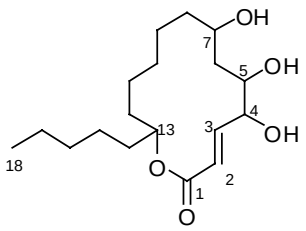
1c, erythromycin A, anti-Gram-positive

1d, (+)-aspicilin

Figure 2.1. Representative biologically active macrolactones with different ring sizes

2.1.3 Sch725674.

Sch725674 (**2**) is a natural product isolated by Schering-Plough Research Institute from *Aspergillus* sp. culture in 2005.[25] Approximately 1.5 mg of the pure compound was isolated. Sch725674 displays antifungal activity against *Saccharomyces* (PM503) and *Candida albicans* (C43) with MICs (Minimum Inhibitory Concentration) 8 and 32 mg/mL. Sch725674 was identified as a 14-membered macrolactone based on the analysis of its MS, 1D and 2D NMR spectra (Figure 2.2).



Sch725674, **2**

Figure 2.2. The 2D structure of Sch725674

The molecular formula of Sch725674 was established as $C_{18}H_{32}O_5$, which was consistent with a positive ESI-MS measurement (*m*/*z* 329, $[M + H]^+$). In the ^1H and ^{13}C NMR spectra, 29 proton and 18 carbon signals were found. Based on the APT, HSQC and TOCSY experiments, multiplicity and the proton-attached carbon resonances were assigned and a cyclic structure through an ester linkage was proposed. The 18 carbon signals were assigned as one methyl (C18), one carbonyl (C1), two olefinic methine ($\Delta^{2,3}$), four oxygenated-methine (C4, C5, C7, and C13), ten aliphatic methylene carbons. The resonance of H2 (δ 6.07, dd, *J* = 15.8, 1.6 Hz) indicated that C2 was adjacent to the carbonyl. The coupling constant (*J* = 15.8 Hz) between H2 and H3 established the *trans* configuration of the $\Delta^{2,3}$ olefin.

No configuration of any stereogenic center of Sch725674 was assigned, and no synthesis of any isomer has been reported to date. The ultimate goal of this project is to synthesize a set of stereoisomers of Sch725674 by FMS to confirm the constitution (2D structure) and to determine the configuration (3D structure) of the natural product. The relative configurations will be assigned by comparing the spectra of a set of diastereomers with those of Sch725674.

We can tentatively and partially assign the most likely absolute configuration for **2** based on

literature guidelines. The structures of several known 14-membered macrolactones are shown in Figure 2.3. All such 14-membered macrolactones for which the absolute configurations have been determined have the (13*R*) configuration (such as **1c**, **1e-h**).[26] Also, all known 14-membered macrolactones that have the 4,7 or 4,5,7 polyoxygenation pattern have the (7*R*) configuration (such as **1e-f**, **1h**). Based on these guidelines, we postulate that both C13 and C7 of Sch725674 are very likely to have (*R*) configurations.

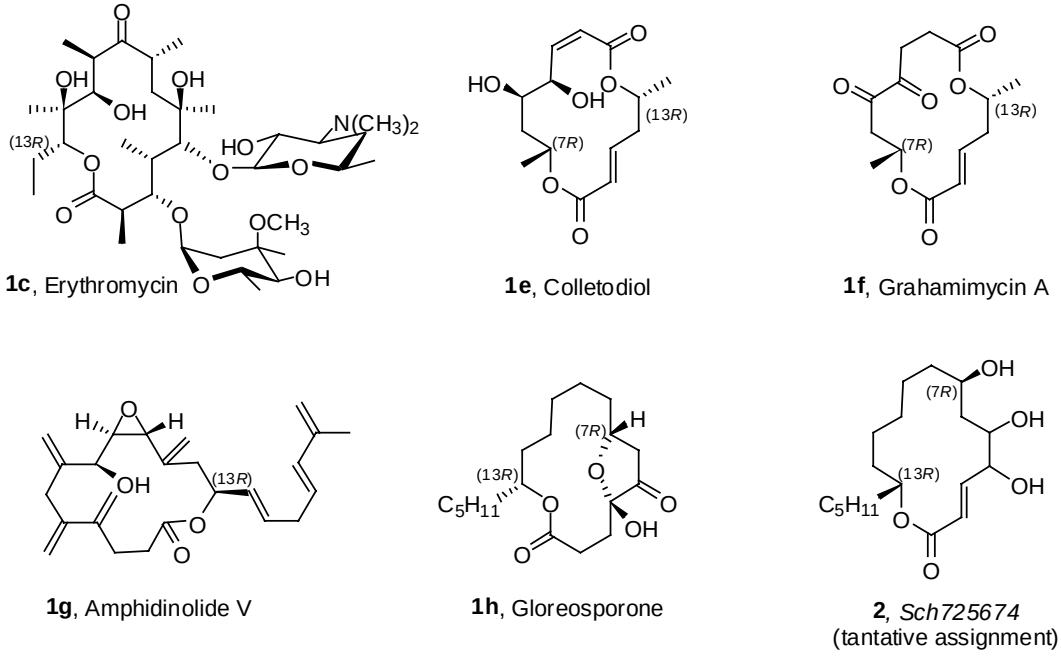
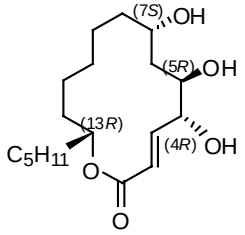


Figure 2.3. Some known 14-membered macrolactones

2.2 RESULTS AND DISCUSSION

2.2.1 The retrosynthesis of a single isomer of Sch725674.

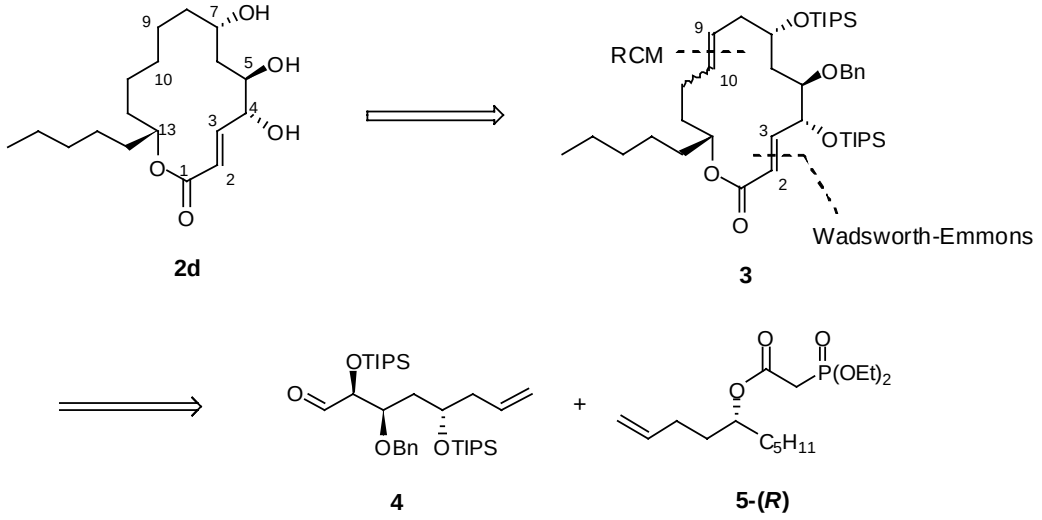
Prior to the FMS of eight isomers of Sch725674, a total synthesis of one isomer was performed. The first aim for this synthesis was to make sure that every step could work for FMS. The second aim was to know if the 2D structure of Sch725674 had been assigned correctly in the original paper. The structure of the selected isomer **2d** (numbered as "**d**" because it is the fourth isomer made in the later FMS) is shown in Figure 2.4. The C13 configuration of the isomer was set as (*R*) based on the "13*R* rule", while other configurations were selected on the fly as the synthesis progressed.



2d

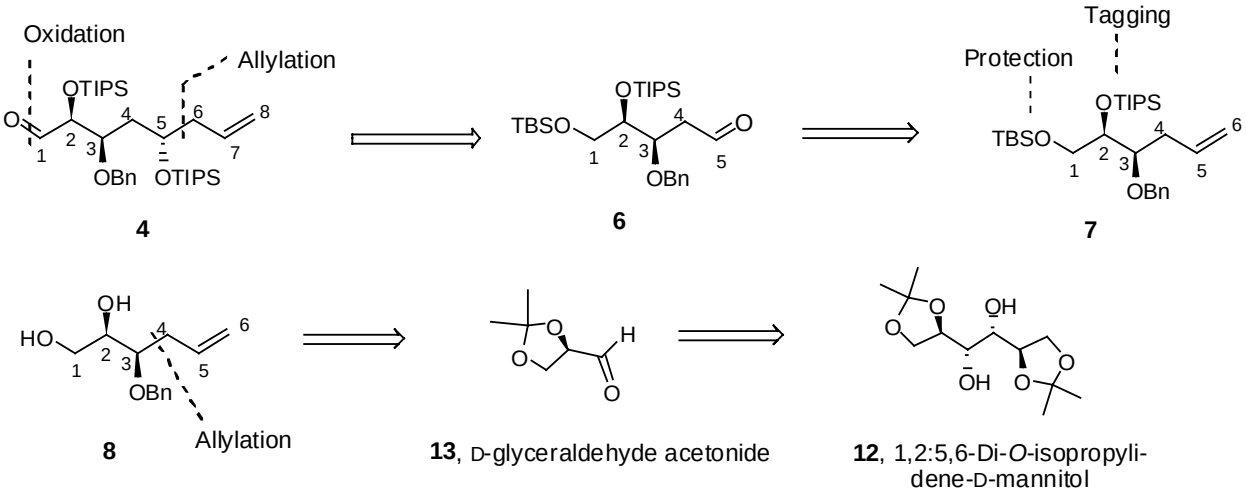
Figure 2.4. The structure of the selected isomer

The retrosynthesis of the single isomer **2d** is shown in Scheme 2.3. Macrolactone **2d** can be prepared from protected lactone triol **3** by the reduction of $\Delta^{9,10}$ alkene followed by debenzylation and desilylation. Breaking of the C9-C10 bond by a RCM transform followed by the cleavage of the $\Delta^{2,3}$ alkene by a Wadsworth-Emmons transformation provides aldehyde **4** and phosphonate ester **5-(*R*)**.



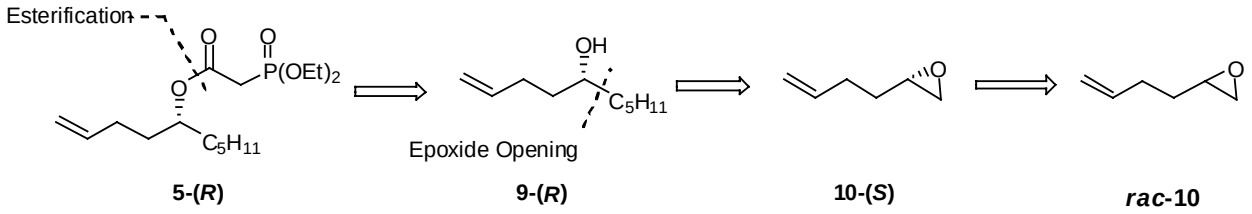
Scheme 2.3. The retrosynthetic analysis of macrolactone **2d**

As shown in Scheme 2.4, aldehyde **4** can be prepared from aldehyde **6** by allylation reaction, TIPS protection, TBS desilylation and oxidation. Further retrosynthesis of aldehyde **6** leads to olefin **7**, which can be prepared by TBS and TIPS protection reactions of **8**. Diol **8** can be constructed from D-glyceraldehyde acetonide **13** by allylation, benzylation and removal of the ketal. Aldehyde **13** can be made from the oxidative cleavage of diol **12**.[27-28]



Scheme 2.4. Retrosynthesis of aldehyde **4**

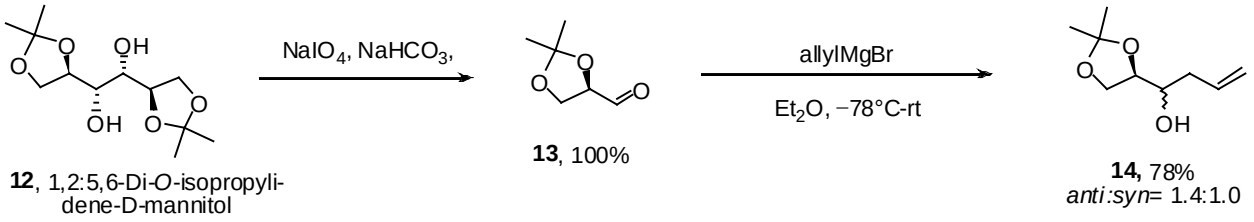
As shown in Scheme 2.5, ester **5-(*R*)** can be prepared from alcohol **9-(*R*)** by the esterification with phosphorylacetic acid, while alcohol **9-(*R*)** can derive from epoxide **10-(*S*)** by the ring opening reaction. Enantiopure **10-(*S*)** can be resolved from the racemic epoxide ***rac*-10** by Jacobsen HKR resolution.[29]



Scheme 2.5. Retrosynthesis of ester **5-(*R*)**

2.2.2 The synthesis of single isomer 2d.

The synthesis of the single isomer **2d** commenced with the construction of aldehyde **4**. Diol **12** was oxidatively cleaved with $NaIO_4$ in the presence of $NaHCO_3$ in DCM to afford D-glyceraldehyde acetonide **13** in quantitative yield (Scheme 2.6).[27,28] The reason for choosing the D-isomer is that the starting material to make L-isomer is not readily available. Aldehyde **13** was then treated with allylMgBr in diethyl ether to afford homoallylic alcohol **14** in 78% yield as a mixture of unseparable *anti*/*syn* isomers with a diastereomeric ratio of 1.4/1.0 based on ^1H NMR analysis.[30] We did the non-selective allylation of **13** at this point because both **14-anti** and **14-syn** were ultimately needed in FMS.



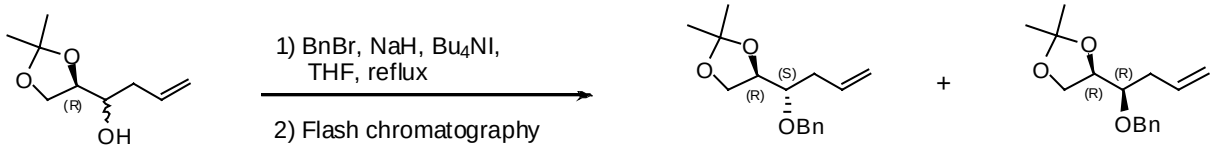
12, 1,2:5,6-Di-*O*-isopropylidene-D-mannitol

13, 100%

14, 78%
anti:syn= 1.4:1.0

Scheme 2.6. Preparation of homoallylic alcohol **14**

The benzylation products of **14-anti** and **14-syn** are separable on silica gel according to a literature report.[30] Therefore, alcohol **14** was benzylated with BnBr in the presence of NaH and a catalytic amount of $^{n}Bu_4NI$ in refluxing THF to afford **15-anti** (the (2*R*,3*S*) isomer) and **15-syn** (the (2*R*,3*R*) isomer) with a diastereomeric ratio of 1.6/1.0 based on ^{1}H NMR analysis of the crude product (Scheme 2.7).[30-32] This matched well with the reported *anti/syn* ratio of 1.5/1.0.[30] Separation of the reaction mixture by flash chromatography provided 50% **15-anti** and 33% **15-syn** (83% total yield). The configurations of **15-anti** and **15-syn** were assigned by comparing their ^{1}H NMR spectra with literature data.[30]



14

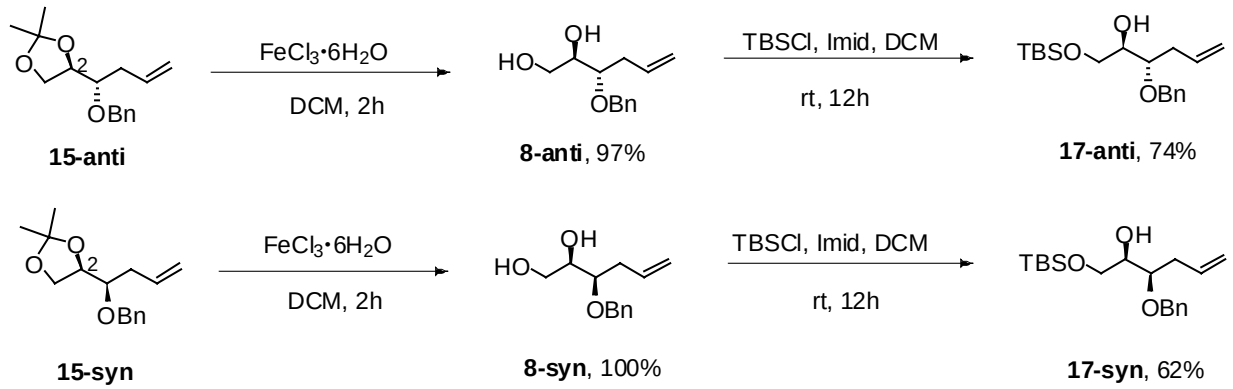
15-anti, 50%

15-syn, 33%

Scheme 2.7. Benzylation of homoallylic alcohol **14**

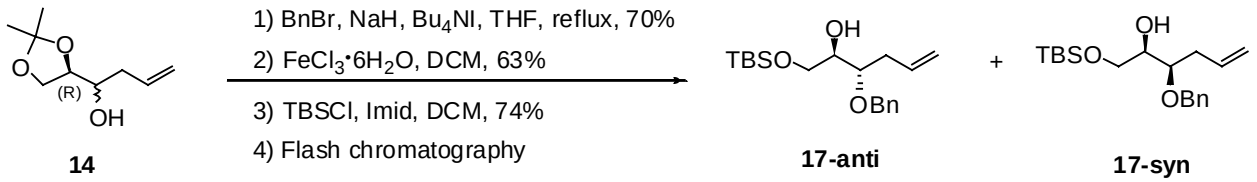
The acetonides of **15-anti** and **15-syn** were removed with 3.5 equiv of $FeCl_3 \cdot 6H_2O$ in DCM to give the two diols **8-anti** and **8-syn** in 97% and 100% yields.[33] The primary hydroxy groups of

8-anti and **8-syn** were selectively protected with TBSCl in the presence imidazole in DCM to give **17-anti** and **17-syn** in 74% and 62% yields (Scheme 2.8).



Scheme 2.8. Synthesis of alcohols **17-anti** and **17-syn**

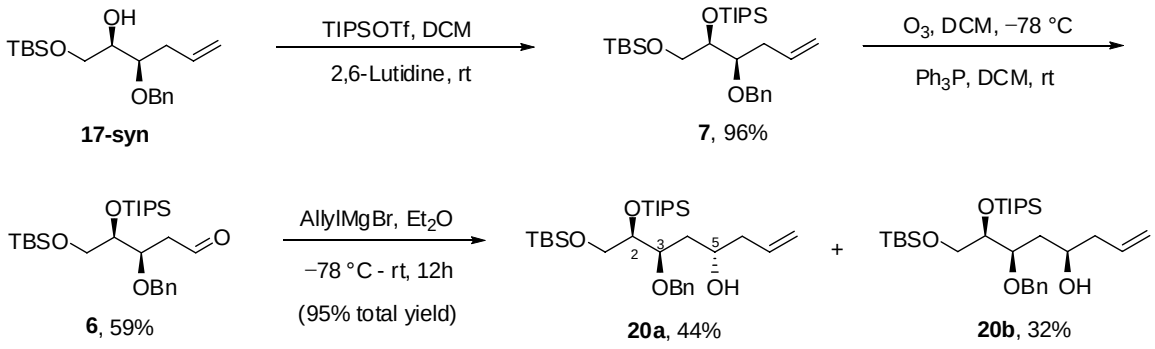
Comparison of the TLC data of **17-anti** and **17-syn** showed that these two diastereomers could also be separated by silica gel flash chromatography. Accordingly, on scale up, we decided to save two steps by synthesizing **17-anti** and **17-syn** together in only one reaction sequence. Starting from homoallylic alcohol **14**, benzylation followed by acetonide deprotection and TBS protection gave alcohol **17** as a mixture of two diastereomers (1.6/1.0 mixture of *anti* and *syn* isomers based on ^{1}H NMR analysis) in 33% yield over 3 steps. Approximately 23 g of alcohol **17** was prepared. Separating 10.6 g of **17** by flash chromatography gave 2.5 g of pure **17-anti** and 3.4 g of pure **17-syn** (Scheme 2.9). The mixture fractions (4.8 g) were also saved for future separation.



Scheme 2.9. A more expedient synthesis of **17-anti** and **17-syn**

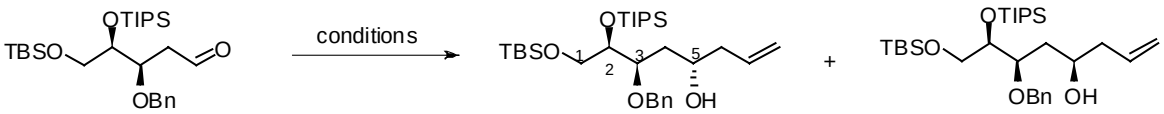
On the surface, **17-syn** and **17-anti** are equally suitable for the single isomer synthesis because the relative configuration of **2** is unknown. Although **17-anti** was the major product according to ^{1}H NMR analysis of the crude product, **17-syn** was selected for the single isomer synthesis because it was obtained in larger quantity in pure form after chromatography. Alcohol **17-syn** was treated with TIPSOTf and 2,6-lutidine in DCM to give **7** in 96% yield (Scheme 2.10). The ozonolysis of olefin **7** with Ph_3P as the reducing agent afforded aldehyde **6** in 59% yield.[34] We also tried small-scale ozonolysis with Me_2S as the reductant, but the spot suspected as the intermediate ozonide never disappeared on TLC.

The construction of the C7 stereocenter in the target molecule requires a diastereoselective allylation of aldehyde **6**. To generate both possible diastereomers, we first carried out a non-selective allylation of **6** with allylMgBr in Et_2O. Separation of the reaction mixture by flash chromatography provided pure homoallylic alcohols **20a**, **20b** and the overlapped fractions in 44%, 32% and 21% yields, respectively. The total yield of the allylation was 95%. The configurations of **20a** and **20b** were confirmed by the later asymmetric allylations as discussed below.



Scheme 2.10. Preparation of homoallylic alcohols **20a** and **20b**

Several asymmetric allylations of aldehyde **6** were attempted. The Duthaler-Hafner allylation[35] and the Soderquist allylation[36] of **6** only gave the recovered starting material. The Brown allylation with (−)-Ipc_2Ballyl in Et_2O at –78 ºC afforded a mixture of **20a/b** in 83% yield with a diastereomeric ratio of 93/7 (Scheme 2.11, entry 1).[37] The C5 configuration of **20a** was assigned as (*S*) based on Brown's model, and the diastereoselectvity was determined by comparing the ^{1}H NMR spectrum of **20a/b** mixture with those of pure **20a** and **20b** from the non-selective reaction in Scheme 10. The allylation of **6** with (+)-Ipc_2Ballyl gave **20a/b** mixture in 65% yield with a diastereomeric ratio of 16/84 (entry 2). Needing only one pure homoallylic alcohol to complete the single isomer synthesis, we selected alcohol **20a** (major product in entry 1) since the yield and diastereoselectivity was higher than those of **20b** (major product in entry 2).

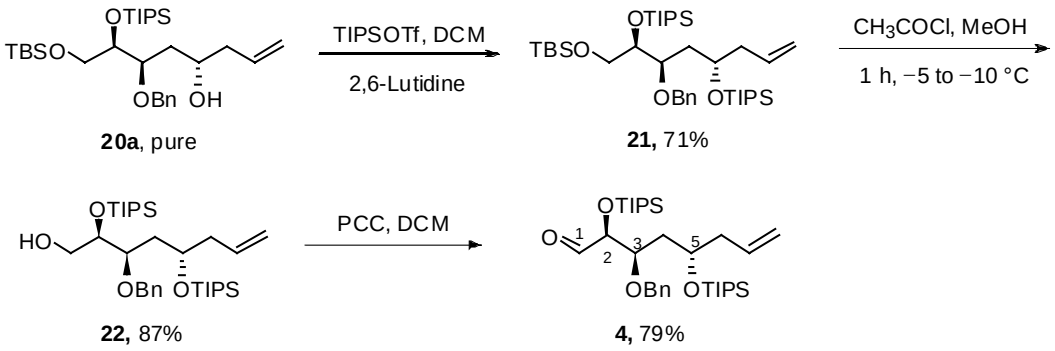


6 **20a** **20b**

Entry	Condition	Yield	Ratio (20a:20b)
1	(⁻)-IpcB$_2$allyl, Et$_2$O, –78 °C	83%	93:7
2	(+)-Ipc$_2$BAllyl, Et$_2$O, –78 °C	65%	16:84

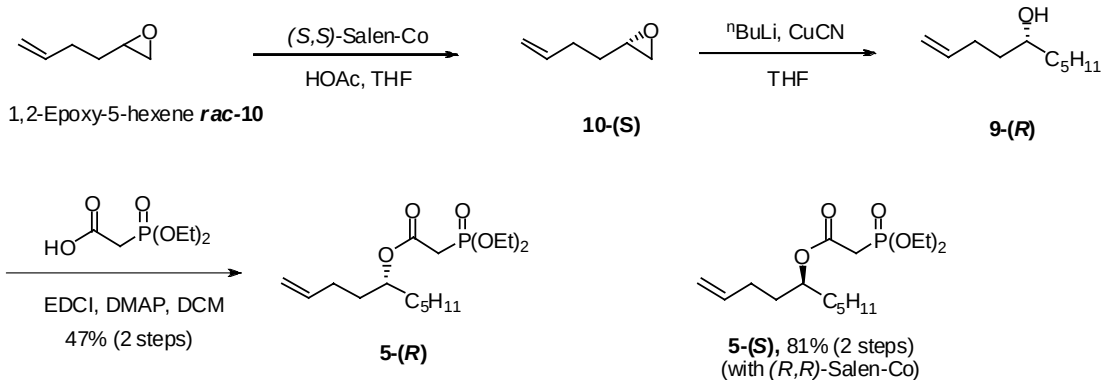
Scheme 2.11. Brown allylations of aldehyde **6**

To continue the synthesis, alcohol **20a (**with 93/7 *dr*) was purified by flash chromatography to remove **20b**. Pure **20a** was silylated with TIPSOTf in the presence of 2,6-lutidine to give **21** in 71% yield (Scheme 2.12). The TBS group of **21** was selectively removed with CH_3COCl at –10 °C in MeOH to give primary alcohol **22** in 87% yield.[38] The reaction temperature was crucial to the yield and the selectivity. We found that no desilylation of **21** occurred below –10 °C according to TLC analysis, while the desired product **22** was formed at between –10 and –5 °C. However, when the temperature was raised above –5 °C, a new and more polar spot showed on TLC analysis. We suspected that this spot was a diol from the concomitant desilylation of the TIPS group at O5. Alcohol **22** was then subjected to PCC oxidation to afford aldehyde **4** in 79% yield. Although PCC is known to be acidic, aldehyde **4** was a single isomer confirmed by ^{1}H NMR analysis, suggesting there was no epimerization at C2.



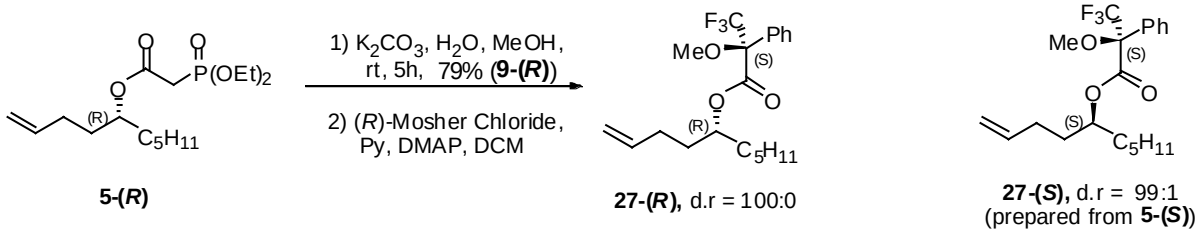
Scheme 2.12. Preparation of aldehyde **4**

The synthesis of HWE reaction fragments **5-(*S*)** and **5-(*R*)** is shown in Scheme 2.13. This work was done by Mr. Claude A. Ogoe. Jacobsen HKR resolution of 1,2-epoxy-5-hexene ***rac*-10** with (*S,S*)-Salen-Co complexes afforded epoxide **10-(*S*)**, which was treated with *n*-butyllithium in the presence of CuCN to afford the secondary alcohol **9-(*R*)**.[29] Esterification of alcohol **9-(*R*)** with 2-(diethoxyphosphoryl)acetic acid in the presence of EDCI and DMAP provided ester **5-(*R*)** in a two-step yield of 47%. Ester **5-(*S*)** was prepared with the same route from ***rac*-10** with (*R,R*)-Salen-Co complexes in a two-step yield of 81%. Approximately 5 g of each ester was made.



Scheme 2.13. Synthesis of esters **5-(*S*)** and **5-(*R*)**

To determine the enantiopurities of **5-(*R*)** and **5-(*S*)** provided by Mr. Ogoe, the esters were hydrolyzed with K_2CO_3 in the water-methanol mixed solvent to afford alcohols **9-(*R*)** and **9-(*S*)** in 79% and 94% yields, respectively (Scheme 2.14). Alcohols **9-(*R*)** and **9-(*S*)** were esterified with (*R*)-3,3,3-trifluoro-2-methoxy-2-phenyl-propanoyl chloride (Mosher chloride) in the presence of pyridine and a catalytic amount of DMAP.[39] When **9-(*R*)** and **9-(*S*)** were totally consumed according to TLC analysis, both reactions were worked up and analyzed by ^{19}F NMR experiment. The diastereomeric ratios of Mosher esters **27-(*R*)** and **27-(*S*)** were 100/0 (major peak at –71.92 ppm) and 99/1 (major peak at –71.97 ppm) respectively. This means the presusors **5-(*R*)** and **5-(*S*)** are enantiopure as needed for the Wadsworth-Emmons reactions with aldehyde **4**. As previously stated, the 13*R* configuration had been seen in many 14-membered macrolactones. Accordingly, ester **5-(*R*)** was selected for the single isomer synthesis.



5-(*R*)

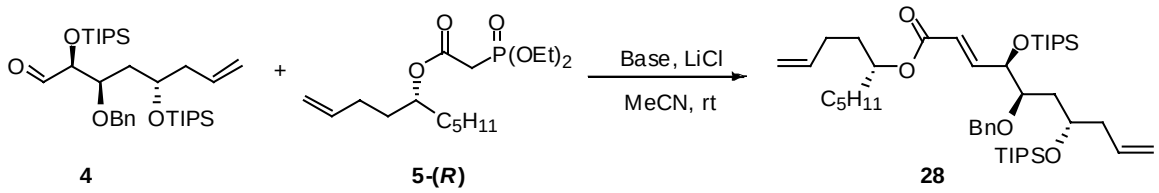
27-(*R*), d.r = 100:0

27-(*S*), d.r = 99:1
(prepared from **5-(*S*)**)

Scheme 2.14. Determine the enantiopurities of **5-(*S*)** and **5-(*R*)**

To prevent the possible base-induced epimerization of aldehyde **4** and the decomposition of ester **5-(*R*)** in the Wadsworth-Emmons reaction, we used the mild Masamune-Roush conditions.[40,41] Aldehyde **4** was coupled with ester **5-(*R*)** in the presence of LiCl and DBU to

afford α,β-unsaturated ester **28** (152 mg) in 73% yield (Scheme 2.15, entry 1). DIPEA was also used in place of DBU but the yield of **28** was only 34% (entry 2).

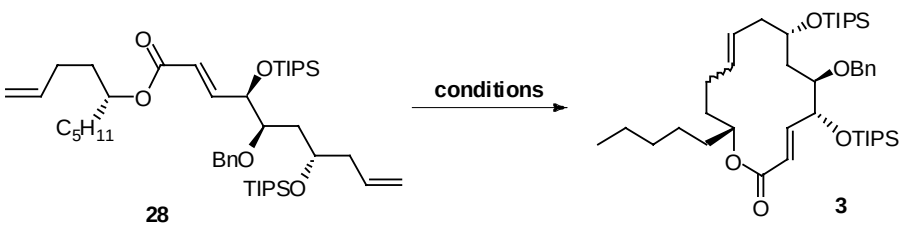


4 **5-(*R*)** **28**

Entry	Base	Yield
1	DBU	73%
2	DIPEA	34%

Scheme 2.15. Masamune-Roush coupling of **4** and **5-(*R*)**

The ring-closing metathesis of **28** is the key reaction to construct the backbone of the 14-membered macrolactone,[42] and we surveyed different conditions on small-scale as summarized in Scheme 2.16. Treating **28** with Grubbs 2nd generation catalyst in DCM at both 23 °C and 50 °C gave only 20% yields of the desired cyclized product **3** (entry 1 and 2).[43] However, the reaction of **28** with Grubbs 1st generation catalyst in DCM at 23 °C gave **3** in 75% yield (entry 3).[44,45] No competing reaction such as the formation of the 7-membered rings via involvement of the conjugated alkene was observed. We also tried the Hoveyda-Grubbs catalyst but no reaction occurred.[46] Repeating the RCM reaction of **28** in entry 3 on large scale afforded **3** (112 mg) in 73% yield.

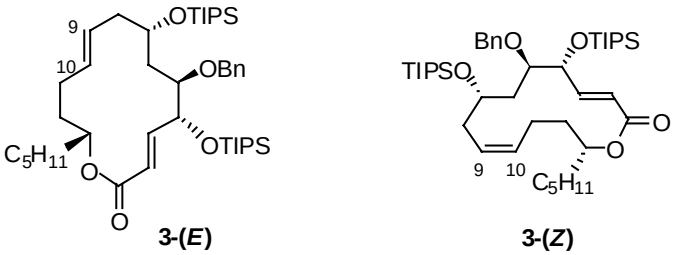


Entry	Catalyst	Concentration (mM)	T (°C)	t (h)	Yield
1	Grubbs 2nd (20%)	0.7 in DCM	23	96	20%
2	Grubbs 2nd (20%)	0.7 in DCM	50	24	20%
3	Grubbs 1st (100%)	0.7 in DCM	23	18	75%

Scheme 2.16. Ring-closing metathesis of ester **28**

The *E*/*Z* rario of the newly formed double bond of **3** (from entry 3) was 6/1 according to ^{1}H NMR analysis of product **28**. The chemical shifts and coupling constants of H9 and H10 of **3-(*E*)/(*Z*)** are listed in Table 2.1. The *E* and *Z* isomers could not be separated by silica gel flash chromatography, but this was not a problem since the next step was the reduction of $\Delta^{9,10}$ alkene.

Table 2.1. Comparison of ^{1}H NMR resonances for H9 and H10 of **3-(*E*)/(*Z*)** [a]

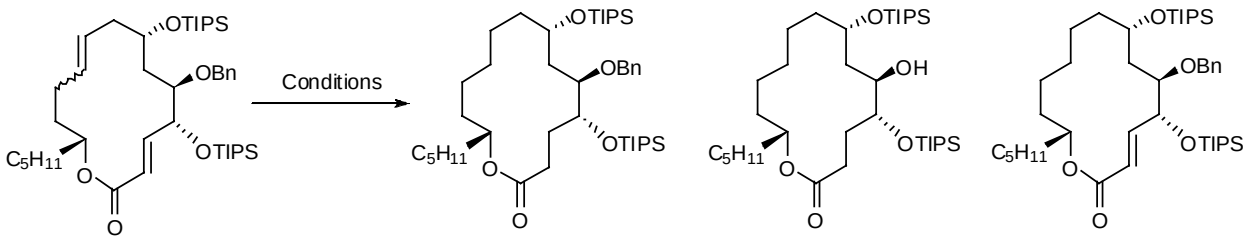


Prodcut	δ (H9, ppm)	*J* (H9, Hz)	δ (H10, ppm)	*J* (H10, Hz)
3-(*E*)	5.43 (ddd)	14.8, 7.9, 4.7	5.27 (ddd)	14.6, 8.3, 4.5
3-(*Z*)	5.50 (ddd)	9.7, 6.5, 2.8	5.36 (m)[b]	—

a. NMR spectra were taken on a 500 MHz spectrometer with samples dissolved in $CDCl_3$;

b. Overlapped with other peaks.

Different conditions for reducing the $\Delta^{9,10}$ alkene of **3** were tried as summarized in Scheme 2.17. Diimide reduction of **3** with hydrazine and $CuSO_4$ led to the overly hydrogenated product **30** in quantitative yield (entry 1).[10c] The hydrogenation of **3** with Pd/C (0.1 equiv) gave the over-reduced product **31** in which both double bonds were reduced and the benzyl group was hydrogenolyzed in 76% yield (entry 2). The hydrogenation of **3** with 1.05 equiv of $Pd/BaSO_4$ (Rosenmund catalyst) in EtOH gave the desired product **32** in 100% yield (entry 3).[44]



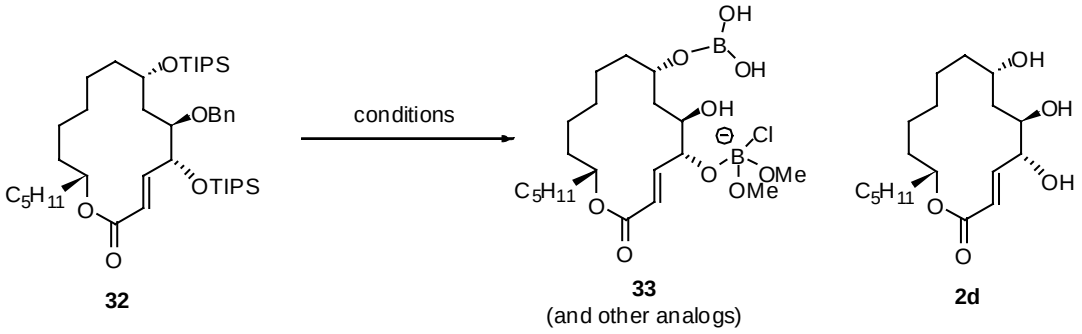
3-(*E*/*Z*) **30** **31** **32**

Entry	Conditions	Yield
1	Hydrazine, $CuSO_4$, EtOH, 70 °C, 12h	**30**, 100%
2	H_2, Pd/C (0.1 equiv), EtOH, rt, 20h	**31**, 76%
3	H_2, $Pd/BaSO_4$ (1.05 equiv), EtOH, rt, 48h	**32**, 100%

Scheme 2.17. Reductions of lactone **3-(*E*)/(*Z*)**

Several conditions for the benzyl deprotection of **32** were tried as shown in Scheme 2.18. The debenzylation of **32** with BCl_3 in DCM at −78 °C led to product mixture in which six different mass signals (ESI, M^-) were detected: 437.1, 451.2, 465.3, 479.3, 493.3, 507.3 (entry 1).[44] This result indicated that the product was a mixture of triols bearing different boron residues. One proposed structure of **33** with a mass of 479.3 is shown in Scheme 18. Other analogs of **33**

in the product mixture were different in the numbers of OH and OMe groups. We tried to remove the boron residues and free the OH groups by treating **33** with MeOH or $NH_3 \cdot H_2O$, but **2d** was not detected. The oxidative debenzylation of **32** with DDQ in a mixed solvent of DCM and buffer (pH = 7) gave decomposition (entry 2).[47] Finally, treating **32** with $BF_3 \cdot Et_2O$ and EtSH in DCM at 32 °C removed the benzyl group and both TIPS groups to give target triol **2d** (1.9 mg) in 85% yield (entry 3).[48] Triol **2d** was purified by preparative reverse phase HPLC with gradient conditions eluting with CH_3CN and H_2O to give 1.3 mg (68%) of pure sample as a white solid.



Entry	Condition	Yield
1	BCl_3, DCM, −78 - 0 °C, 18h	**33**, products with boron residues
2	DDQ (10 equiv), DCE/Buffer (9/1), rt - reflux	decomposition
3	$BF_3 \cdot Et_2O$, EtSH, DCM, 32 °C	**2d**, 85%

Scheme 2.18. Deprotections of lactone **32**

Triol **2d** was characterized by ^1H NMR, ^{13}C NMR, COSY and HMQC experiments. The NMR resonances (δ and *J*) of **2d** were similar to those of the natural product but had slight differences (see Table 2.3 in section 2.2.4). However, all ^1H-^1H and ^1H-^{13}C correlations of Sch725674 could be found in the 2D NMR spectra of **2d**. Thus we concluded that: 1) the 2D

structure of Sch725674 was assigned correctly; 2) **2d** is a diastereomer of Sch725674.

2.2.3 The tagging strategy for the FMS.

With all the steps of the single isomer synthesis validated, we targeted the FMS of stereoisomers of Sch725674. We made a complete set of eight diastereomers **2a-2h** (all with C4 being (*R*)) and one of them (**2a**) proved to have the same relative configurations as the natural product (Figure 2.5).

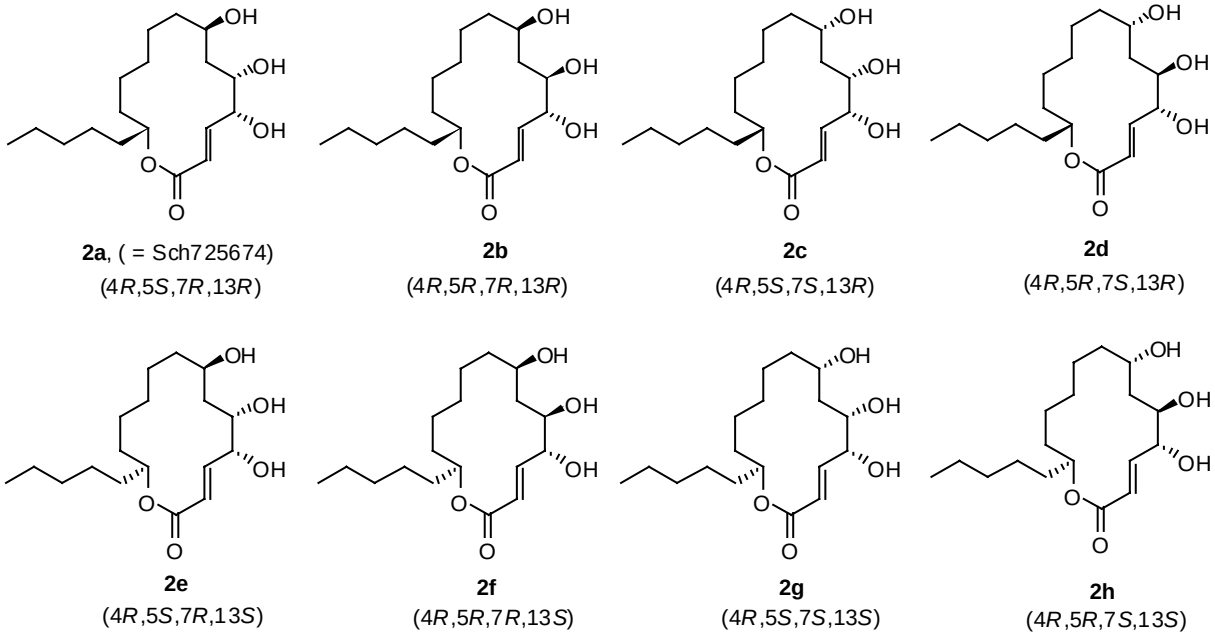
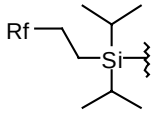


Figure 2.5. The eight stereoisomers of Sch725674 prepared by FMS

In the FMS, diisopropyl(perfluoroalkylethyl)silyl groups (^{F}TIPS) are used as tags because they are stable under most reaction conditions and easily deprotected.[12,16] The structures of two frequently used ^{F}TIPS groups are shown in Figure 2.6. In the numbering of the following text,

"**M**" is used to denote a mixture of fluorous tagged quasiisomers. The letter "**F**" followed by a number (0, 7 or 9) is an abbreviation of the ^{F}TIPS group with a certain fluorine content (when used in a coding scheme, the regular TIPS group is displayed as ^{F0}TIPS). A single component in the mixture is designated as the combination of a number and abbreviations of flourous tags. For example, "**35[F9F7]**" represents a quasiisomer in mixture **M-35** that bears ^{F9}TIPS and ^{F7}TIPS groups. The total fluorine content of **35[F9F7]** is 16, the sum of 9 and 7.

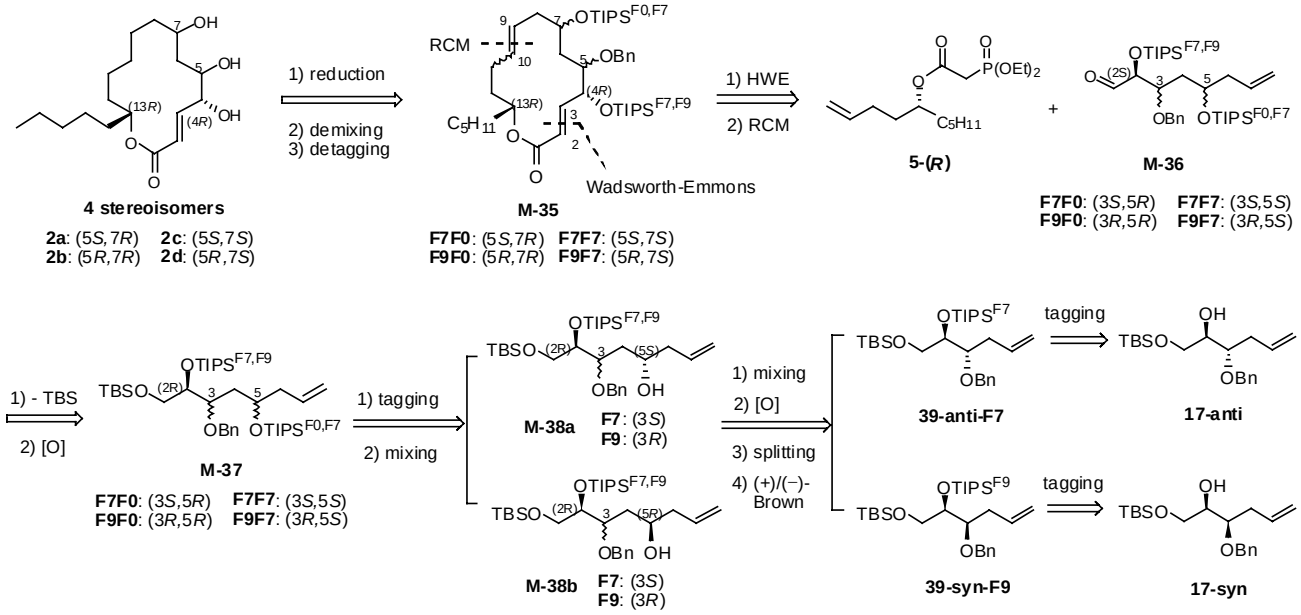


TIPS^{F7} (Rf = C_3F_7): diisopropyl(3,3,4,4,5,5,5-heptafluoropentyl)silyl
TIPS^{F9} (Rf = C_4F_9): diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyl

Figure 2.6. The structures of ^{F}TIPS groups

The retrosynthesis and the tagging strategy of FMS are shown in Scheme 2.19. Take the synthesis of the four (13*R*) isomers **2a-2d** as example. Instead of making the single lactone **3** (see Scheme 2.16 in section 2.2.1), we will prepare a mixture of four tagged quasidiastereomers **M-35**. The OH groups in **M-35** provide convenient locations for fluorous tags. The configurations of C4 and C13 are fixed as (*R*) so that four quasidiastereomers will be prepared. Different combinations of tags are used to encode different configurations of C5 and C7. We used ^{F7}TIPS (O4) and ^{F0}TIPS (O7) to encode (5*S*,7*R*), ^{F9}TIPS (O4) and ^{F0}TIPS (O7) to encode (5*R*,7*R*), ^{F7}TIPS (O4) and ^{F7}TIPS (O7) to encode (5*S*,7*S*), ^{F9}TIPS (O4) and ^{F7}TIPS (O7) to encode (5*R*,7*S*). Thus the total fluorine contents of the four quasidiastereomers of **M-35** are 7, 9, 14 and 16. The OH at C3

is protected with Bn group. The choosing of the tags is based on: 1) the easiness of separating the four quasiisomers by fluorous HPLC; 2) the minimum fluorine contents of quasiisomers to avoid long retention times on the fluorous HPLC column; 3) the similar polarities of quasiisomers to make sure that they do not separate on regular silica gel. Lactone **M-35** will be converted to the four final products **2a-2d** by the reduction of the $\Delta^{9,10}$ alkene followed by demixing and detagging. **M-35** can be assembled by the HWE reaction of ester **5-(*R*)** and aldehyde **M-36** followed by the RCM reaction. Aldehyde **M-36** can be prepared from silyl ether **M-37** by TBS desilylation and oxidation. **M-37** can be formed by the tagging and mixing of the two homoallylic alcohols **M-38a** and **M-38b**, which can be synthesized from **39-anti-F7** and **39-syn-F9** by mixing, ozonolysis, splitting and (+)/(–)-Brown allylations. Silyl ethers **39-anti-F7** and **39-syn-F9** can be made by the tagging reactions of **17-anti** and **17-syn**, which were already prepared in the single isomer synthesis. The synthesis of the four (13*S*) isomers **2e-2h** followed the same route.

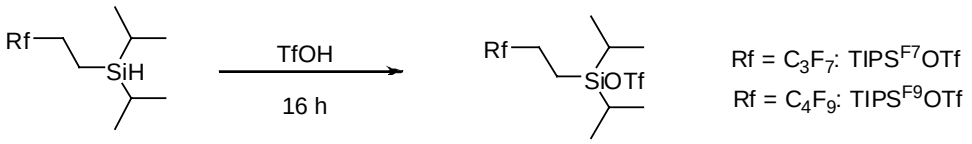


Scheme 2.19. Retrosynthesis and tagging strategy for FMS

2.2.4 The FMS of eight stereoisomers of Sch725674.

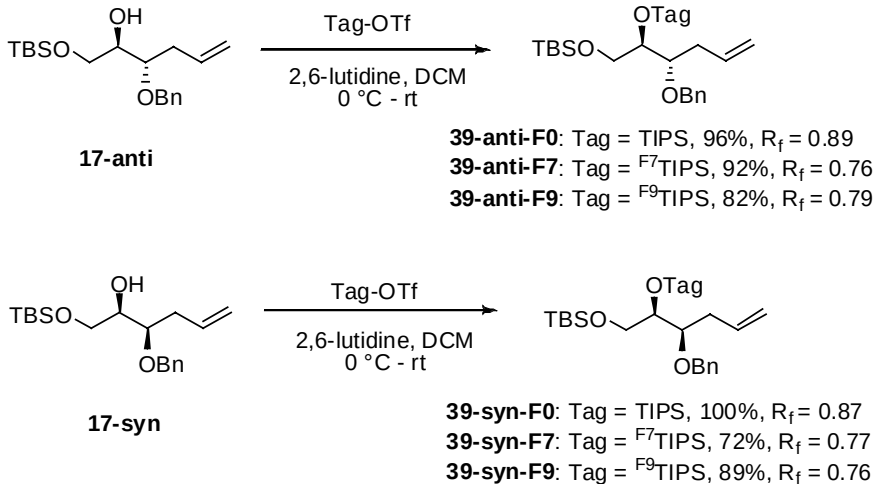
The FMS of the eight isomers of Sch725674 commenced with the tagging reactions of alcohols **17-anti** (4.50 g) and **17-syn** (4.50 g), which were already made in the single isomer synthesis. In the mixture synthesis stage, the product (fluorous mixture of quasidiastereomers) is usually purified by regular flash chromatography. During purification, it is helpful that the mixture components have similar polarities so they do not separate on the silica gel. To make sure that the tagging products of **17-syn** and **17-anti** have similar polarities, we did six small-scale silylations of **17-anti** and **17-syn** with three different silyl groups: TIPS, ^{F7}TIPS (diisopropyl(3,3,4,4,5,5,5-heptafluoropentyl)silyl), ^{F9}TIPS (diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyl). Tagging reagents ^{F7}TIPSOTf and ^{F9}TIPSOTf were made *in situ* by adding triflic

acid to diisopropyl(perfluoroalkylethyl)silane and stirring the mixture for 16 h (Scheme 2.20).[12,16]



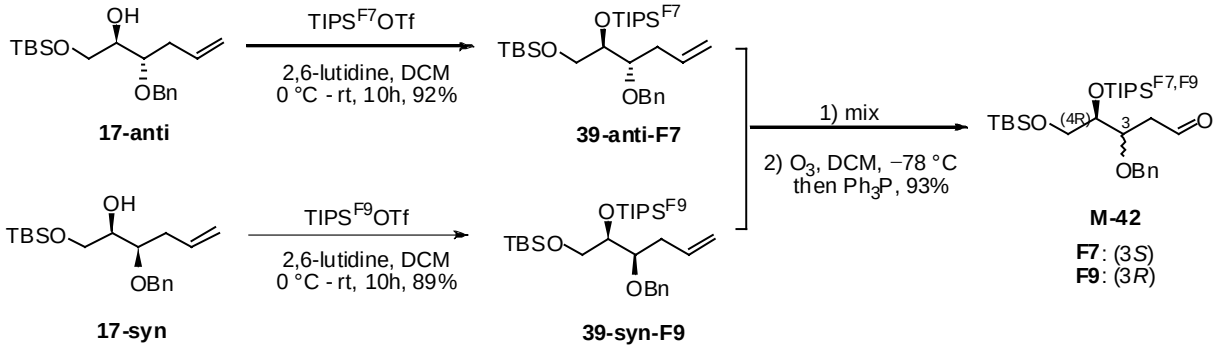
Scheme 2.20. Preparation of the tagging reagents ^{F}TIPSOTf

Alcohol **17-anti** was tagged with ^{F0}TIPSOTf, ^{F7}TIPSOTf and ^{F9}TIPSOTf in the presence of 2,6-lutidine in DCM to give products **39-anti-F0**, **39-anti-F7** and **39-anti-F9** in 96%, 92% and 82% yields, respectively. Under the same conditions, **17-syn** was tagged to give **39-syn-F0**, **39-syn-F7** and **39-syn-F9** in 100%, 72% and 89% yields, respectively. The TLC data of the six products were compared. Products **39-anti-F0** and **39-syn-F0**, which bore the null tag (TIPS), had higher R_f than the other four (Scheme 2.21). The four fluorous silyl ethers did not have much difference on TLC. However, co-spot experiments showed that **39-anti-F7** and **39-syn-F9** had the closest R_f, thus they were selected to continue the synthesis.



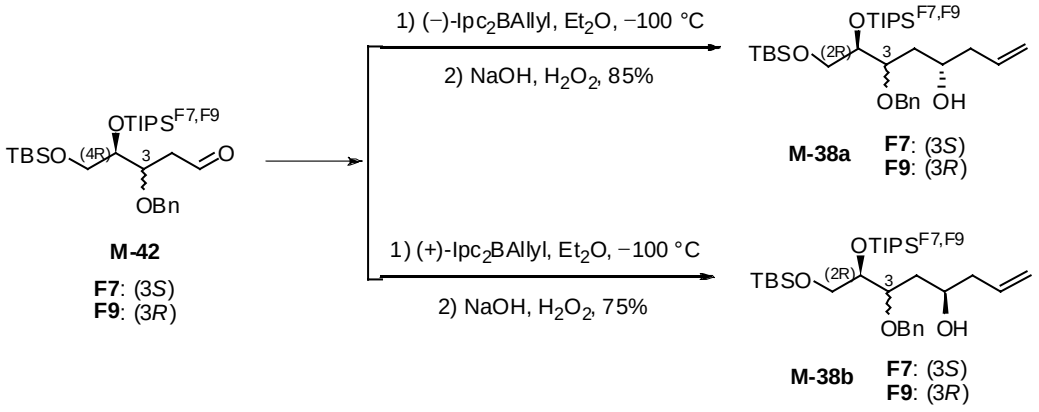
Scheme 2.21. Small-scale tagging reactions of **17-anti** and **17-syn** and R_f on silica gel (20:1 Hex:EtOAc)

Large-scale tagging reactions of **17-anti** and **17-syn** with ^{F7}TIPSOTf and ^{F9}TIPSOTf gave **39-anti-F7** (8.50 g) and **39-syn-F9** (8.90 g) in 92% and 89% yields, respectively (Scheme 2.22). Equimolar amounts of **39-anti-F7** (3.00 g) and **39-syn-F9** (3.20 g) were mixed, and the mixture was subjected to ozonolysis followed by the reduction by Ph_3P to afford aldehyde **M-42** (5.80 g) in 93% yield after silica gel flash chromatography. Aldehyde **M-42** showed only one spot on TLC (20:1 Hex:EtOAc).



Scheme 2.22. Preparation of aldehyde **M-42**

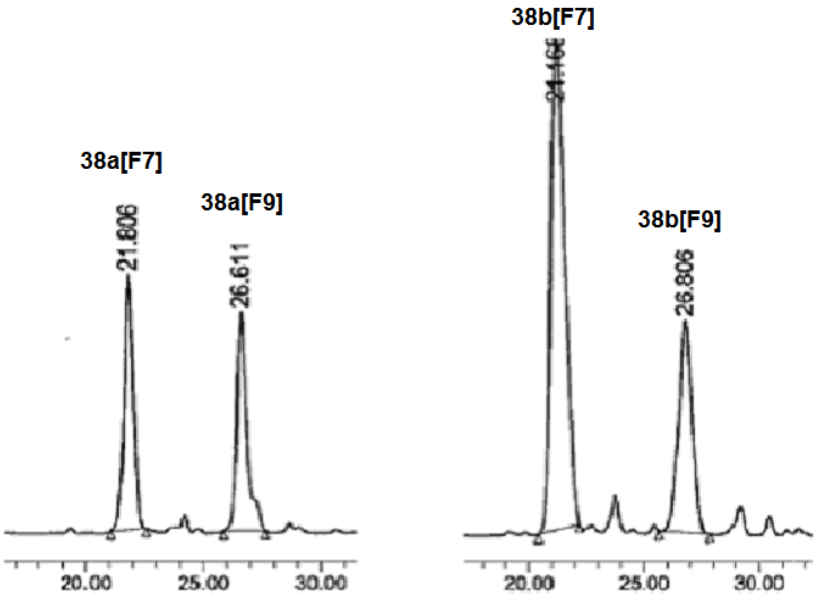
Aldehyde **M-42** was split in half and subjected to Brown allylations. It was reported by Brown and coworkers that when a salt-free solution of $Ipc_2Ballyl$ was used, the allylation reactions of aldehydes gave more than 95% *de*.[37] Addition of commercially available, salt-free (–)-$Ipc_2Ballyl$ solution (1 M in pentane) to the Et_2O solution of **M-42** at –100 °C provided (4*S*)-homoallylic alcohol **M-38a** in 85% yield after flash chromatography, as a mixture of two compounds (Scheme 2.23). (4*R*)-Homoallylic alcohol **M-38b** was prepared from the other half of **M-42** with (+)-$Ipc_2Ballyl$ under the same conditions in 75% yield. Both **M-38a** and **M-38b** showed only one spot on TLC.



Scheme 2.23. Brown allylations of aldehyde **M-42**

To determine the diastereoselectivities of the Brown allylations, we analyzed alcohols **M-38a** and **M-38b** by fluorous HPLC. Two major peaks were observed in both HPLC traces of **M-38a** and **M-38b** (Figure 2.7). The co-injection of **M-38a** and **M-38b** also gave only two peaks. After the analytical HPLC experiments, 5.0 mg of each alcohol was demixed by preparative fluorous HPLC to produce four quasidiastereomers **38a[F7]** (1.8 mg), **38a[F9]** (2.3 mg), **38b[F7]**

(2.0 mg) and **38b[F9]** (1.9 mg), which were characterized by ^{1}H NMR analysis. The NMR spectra of the four quasidiastereomers were different (Figure 2.8). No minor products were detected in any sample. For example, in the spectrum of **38a[F7]**, we did not observe any resonances of **38b[F7]**, which was the expected minor product. The small impurity peaks in the spectrum was from **38a[F9]**, which was the other quasidiastereomer in **M-38a**. This contamination was probably caused by incomplete demixing. These results suggested that: 1) both Brown allylations worked with excellent diastereoselectivities for both components of the starting mixture; 2) the two quasidiastereomers with a difference of one CF_2 group could be well separated on the fluorous HPLC column.



Conditions: PF-C8 column, 1 mL/min, 80:20 MeCN:H_2O to 100% MeCN in 30 min, then isocratic MeCN for 30 min

Figure 2.7. The analytical fluorous HPLC traces of **M-38a** (left) and **M-38b** (right)

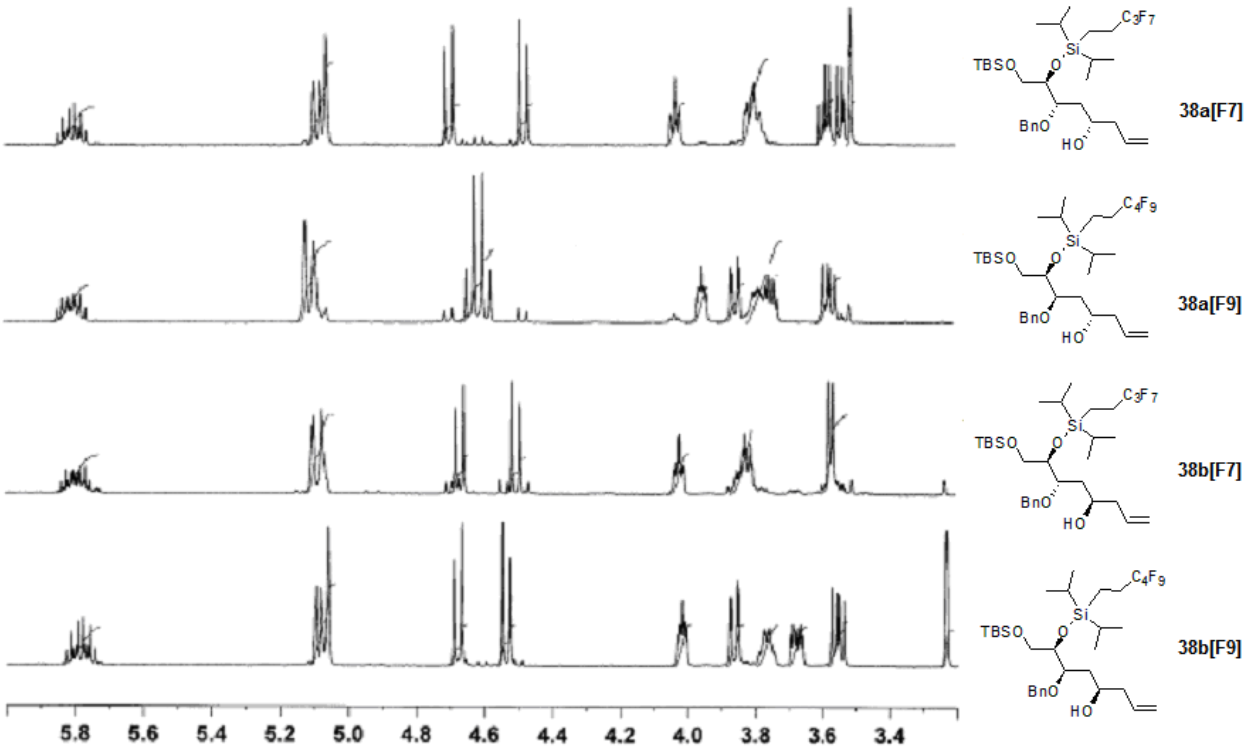
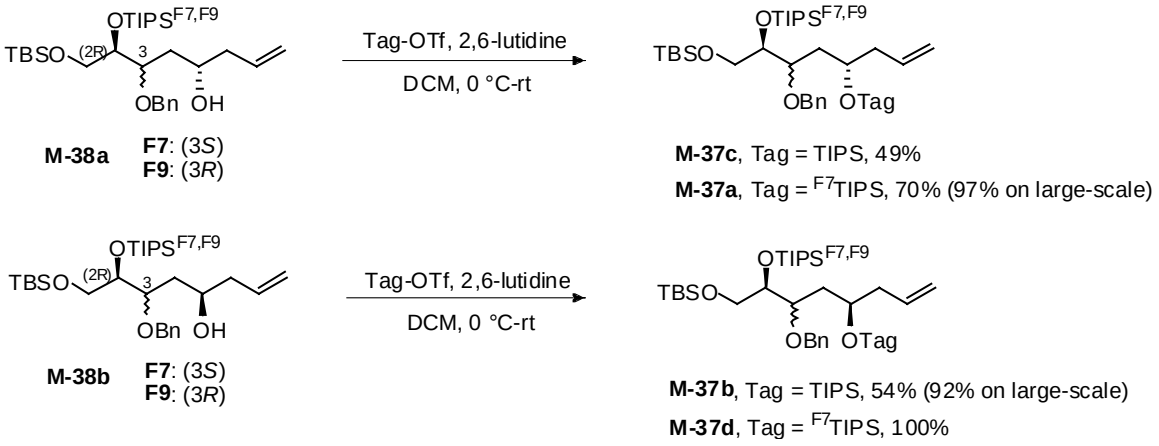


Figure 2.8. ^{1}H NMR spectra (δ 6.0–3.2 ppm, 500MHz, $CDCl_3$) of quasidiastereomers of **M-38a** and **M-38b** after demixing

The C5 configurations of allylation products **M-38a** and **M-38b** were next encoded by tagging with silyl groups. We used the null tag (TIPS) to protect **M-38b** and ^{F7}TIPS to protect **M-38a**. The use of TIPS minimizes the fluorine content of the tagged compounds. High fluorine content often causes a problem because compounds are too strongly retained in the fluorous HPLC column. Again, the tagged quasidiastereomers should have similar polarities. To find the best combination of tags and substrates, **M-38a** and **M-38b** were silylated with TIPS and ^{F7}TIPS on multi-milligram scale to give four products **M-37c**, **M-37a**, **M-37b** and **M-37d** in 49%, 70%, 54% and 100% yields, respectively (Scheme 2.24). TLC data showed that **M-37a** and **M-37b** had smaller difference in R_f than **M-37c** and **M-37d**. Therefore, **M-38a** (1.80 g) and **M-38b** (1.60 g)

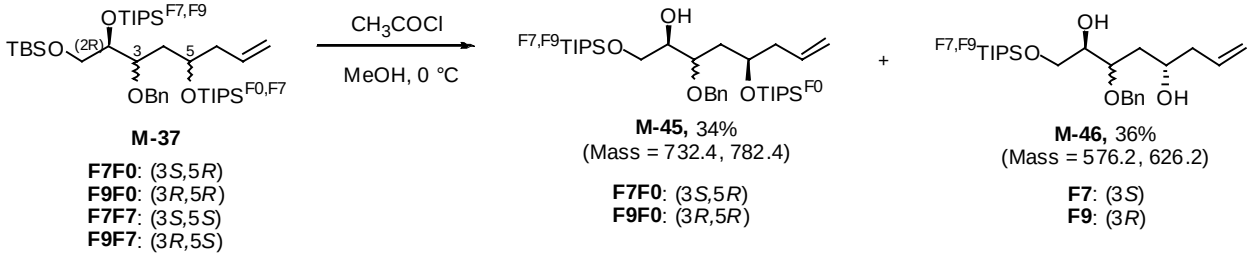
were treated with ^{F7}TIPSOTf and TIPSOTf in the presence of 2,6-lutidine to produce silyl ethers **M-37a** (2.50 g) and **M-37b** (1.80 g) in 97% and 92% yields after flash chromatography.



Scheme 2.24. Tagging reactions of **M-38a** and **M-38b**

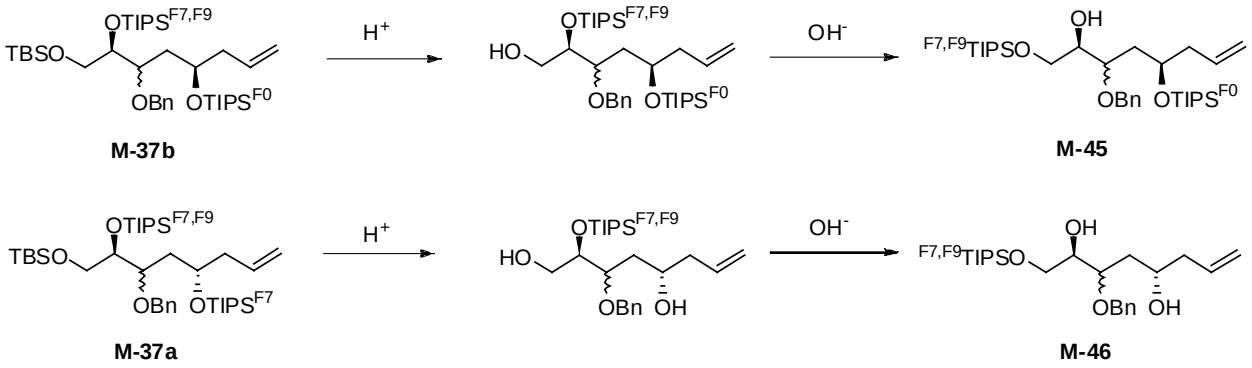
Fluorous mixtures **M-37a** (0.66 g) and **M-37b** (0.60 g) were next mixed in equimolar ratio to give **M-37** as a mixture of four quasidiastereomers (Scheme 2.25). Mixture **M-37** was treated with CH_3COCl in MeOH to remove the TBS group.[38] No reaction occurred at –10 °C, the same temperature used to desilylate the non-fluorous analog **21** in the single isomer synthesis (see Scheme 2.12). When the temperature was raised to 0 °C, two products were formed and isolated by flash chromatography: the less polar **M-45** (34%) and the more polar **M-46** (36%). The MS data of **M-45** showed two components (**45**[**F7F0**] and **45**[**F9F0**]) with masses of 732.4 and 782.4, indicating that **M-45** was the TBS desilylation product from **M-37b**. The MS data of **M-46** also showed two components (**46**[**F7**] and **46**[**F9**]) with masses of 576.2 and 626.2, indicating that **M-46** was the bis-desilylation product from **M-37a** with both TBS and ^{F7}TIPS (O5) groups fallen

off.



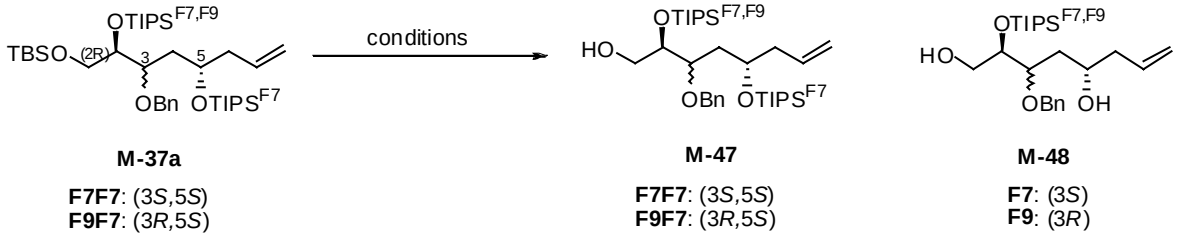
Scheme 2.25. Desilylation of **M-37** by CH_3COCl in MeOH

In addition to desilylation, the ^{F7}TIPS/ ^{F9}TIPS groups that should be at O2 of **M-45** and **M-46** were suspected to transfer to O1. The desilylation reaction of **M-37** was quenched with saturated aqueous $NaHCO_3$, which might act as the base to initiate the silyl transfer (Scheme 2.26). Three experiments were done to confirm the silyl transfer. First, treating alcohol **M-45** with Dess-Martin periodinane gave a ketone instead of an aldehyde, based on NMR analysis. Then, diol **M-46** was treated with TBSCl in the presence of imidazole to protect the primary alcohol; however, no reaction occurred. At last, a small amount of **M-45** was demixed by fluorous HPLC to give two alcohols **45[F7F0]** and **45[F9F0]**. Their ^{1}H NMR spectra showed that the OH proton resonances were doublets instead of doublets of doublet, indicating that **45[F7F0]** and **45[F9F0]** were secondary alcohols.



Scheme 2.26. The base-induced silyl transfer

Due to the reactivity difference of the TIPS and ^{F7}TIPS groups at O5, we decided to desilylate **M-37a** and **M-37b** separately. Several desilylations of **M-37a** were tried as summarized in Scheme 2.27. The desilylation of **M-37a** with H_2SiF_6 and Et_3N gave the desired primary alcohol **M-47** and the undesired diol **M-48** in 29% and 27% yields, respectively (entry 1).[49] The reaction of **M-37a** with BF_3•Et_2O in $CHCl_3$ gave diol **M-48** in 75% yield (entry 2).[50] No reaction took place when **M-37a** was treated with K_2CO_3 in MeOH (entry 3).[51]



M-37a

F7F7: (3*S*,5*S*)
F9F7: (3*R*,5*S*)

M-47

F7F7: (3*S*,5*S*)
F9F7: (3*R*,5*S*)

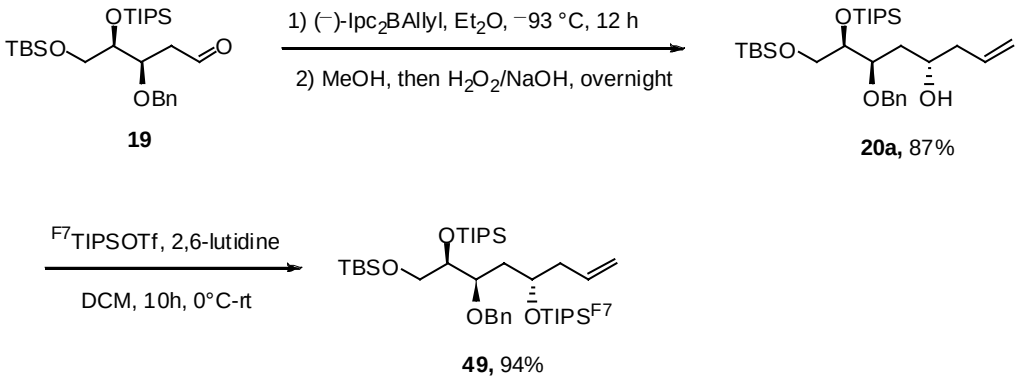
M-48

F7: (3*S*)
F9: (3*R*)

Entry	Condition	Yield
1	H_2SiF_6, Et_3N, MeCN, 0°C-rt, 1h	**M-47**, 29%; **M-48**, 27%
2	BF_3·Et_2O, $CHCl_3$, 0°C-rt, 1h	**M-48**, 75%
3	K_2CO_3, MeOH, rt, 24 h	no reaction

Scheme 2.27. Desilylations of **M-37a**

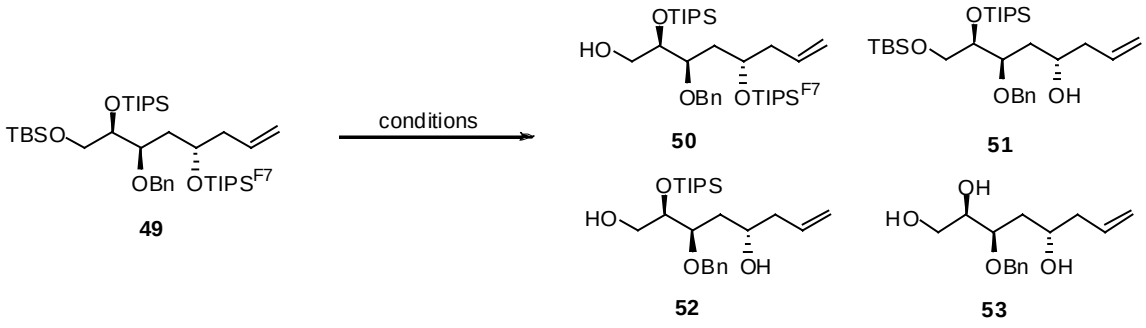
To conserve **M-37a** and **M-37b**, we decided to try other TBS deprotection conditions on a single TBS ether. The needed compound **49** (560 mg) was prepared from aldehyde **19** by Brown allylation and the subsequent tagging reaction with ^{F7}TIPS group (Scheme 2.28).



Scheme 2.28. Preparation of the single silyl ether **49**

Several desilylation reactions of **49** were tried as shown in Scheme 2.29. The desilylation of **49** under acidic conditions such as HCl/EtOH,[52] PPTS/MeOH[53] or THF/H_2O/HOAc[54] afforded **50** in only 20-30% yields (entry 1-3). The concomitant formation of diol **52** forced us to quench the reaction before the starting material **49** was completely consumed. The reaction of **49** with Lewis acid $ZrCl_4$ gave fully desilylated product **53** in 46% yield in only 15 min (entry 4).[55] The reaction of **49** with $Zn(OTf)_2$ led to the decomposition of the starting material according to TLC analysis (entry 5). No reaction occurred when **49** was treated with $CeCl_3 \cdot 7H_2O$ and NaI in MeCN (entry 6). An interesting observation was that the desilylation of **49** with 1.0 equiv of TBAF in THF at –30 °C gave homoallylic alcohol **51** in 52% yield (entry 7).[56,57] And when the mixture of **49** and TBAF (1.0 equiv) was stirred at 10 °C for 12 h, all three silyl groups were

removed to give triol **53** in 59% yield (entry 8). Since only 1.0 equiv of TBAF was added, the global desilylation was probably done by the base. None of these desilylations selectively gave the desired primary alcohol **50** in good yield.



Entry	Condition	Yield
1	HCl (1.0 equiv), EtOH, 4 h	**50**, 25%
2	PPTS, MeOH, rt, 15 h	**50**, 30%
3	THF/H_2O/HOAc (8:1:8), 50 °C, 24 h	**50**, 23%
4	$ZrCl_4$, MeCN, rt, 15 min	**53**, 46%
5	$Zn(OTf)_2$, MeCN, rt, 5 h	decomposition
6	$CeCl_3 \cdot 7H_2O$, NaI, MeCN, 24 h	no reaction
7	TBAF (1.0 equiv), THF, -30 °C, 3 h	**51**, 52%
8	TBAF (1.0 equiv), THF, 10 °C, 12 h	**53**, 59%

Scheme 2.29. TBS desilylations of the single silyl ether **49**

The difference of desilylation products of entry 1-3 and entry 7 in Scheme 2.29 can be explained by the substituent effect of the silyl groups as a function of the reaction conditions. The desilylation under acidic conditions is accelerated by electron-donating substituents on the O atom of the silyloxy group. While under basic conditions, electron-withdrawing substituents on the Si atom accelerate the reaction (Figure 2.9). The ^{F7}TIPS group is supposed to be electron-poor because of its C_3F_7 group.[58,59]

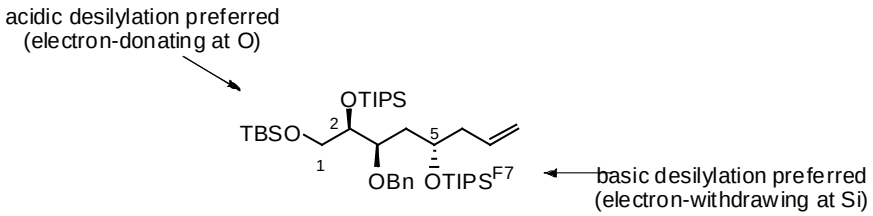
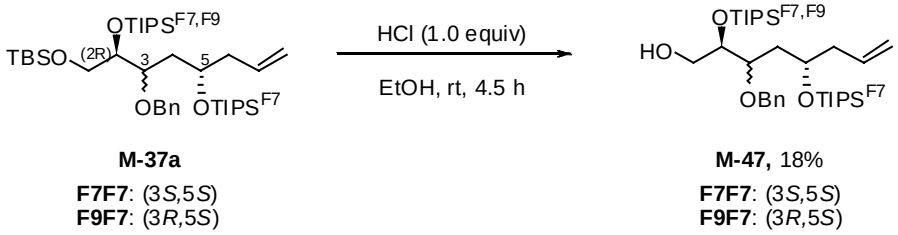


Figure 2.9. The reactivity difference of silyl groups under acidic/basic conditions

Comparing the desilylation results in Scheme 2.29, we decided to use HCl/EtOH for the TBS deprotection of **M-37a** and **M-37b** since the reaction was fast and easy to perform. The desilylation of **M-37a** with 1.0 equiv of HCl in EtOH gave primary alcohol **M-47** in 18% yield after flash chromatography (Scheme 2.30). The reaction was quenched with the buffer solution (pH = 7) to prevent the intramolecular silyl transfer. The low yield was due to the early quenching of the reaction before the formation of the diol. Approximately 58% of **M-37a** was recovered.



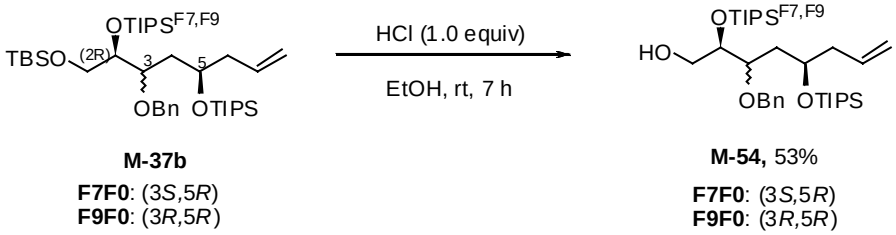
M-37a
F7F7: (3*S*,5*S*)
F9F7: (3*R*,5*S*)

M-47, 18%
F7F7: (3*S*,5*S*)
F9F7: (3*R*,5*S*)

Scheme 2.30. Preparation of primary alcohol **M-47**

Under the same conditions as desilylating **M-37a**, TBS ether **M-37b** was converted to the corresponding primary alcohol **M-54** in 53% yield after flash chromatography (Scheme 2.31). Because the TIPS group (O5) of **M-37b** was not as labile as the ^{F7}TIPS group (O5) of **M-37a**, the diol was formed much more slowly. Thus we were able to run the reaction for a longer period of

time (7 h) to obtain **M-54** in a higher yield than that of **M-47**. Approximately 30% of **M-37b** was recovered.

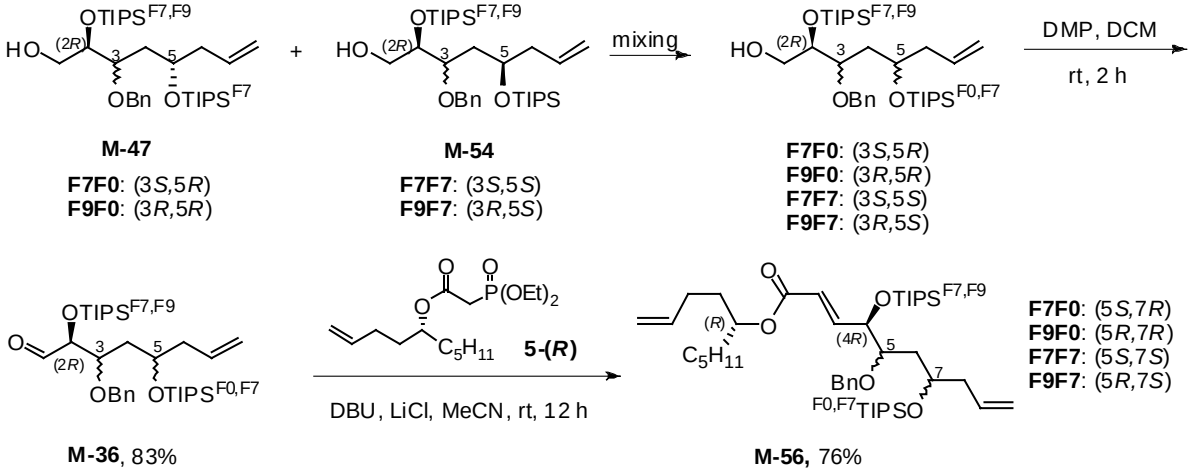


M-37b
F7F0: (3*S*,5*R*)
F9F0: (3*R*,5*R*)

M-54, 53%
F7F0: (3*S*,5*R*)
F9F0: (3*R*,5*R*)

Scheme 2.31. Preparation of primary alcohol **M-54**

The primary alcohols **M-47** (106 mg) and **M-54** (87 mg) were mixed in a ratio of 1/1 and subjected to Dess-Martin oxidation to afford aldehyde **M-36** (160 mg) in 83% yield.[60] To make the four triols with C13 being (*R*), **M-36** was coupled with ester **5-(*R*)** in the presence of LiCl and DBU in MeCN to afford α,β-unsaturated ester **M-56** in 76% yield after flash chromatography (Scheme 2.32).



M-47
F7F0: (3*S*,5*R*)
F9F0: (3*R*,5*R*)

M-54
F7F7: (3*S*,5*S*)
F9F7: (3*R*,5*S*)

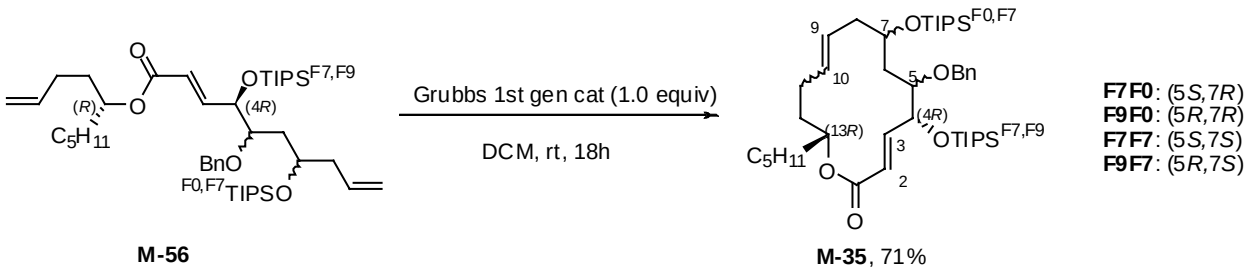
F7F0: (3*S*,5*R*)
F9F0: (3*R*,5*R*)
F7F7: (3*S*,5*S*)
F9F7: (3*R*,5*S*)

M-36, 83%

M-56, 76%
F7F0: (5*S*,7*R*)
F9F0: (5*R*,7*R*)
F7F7: (5*S*,7*S*)
F9F7: (5*R*,7*S*)

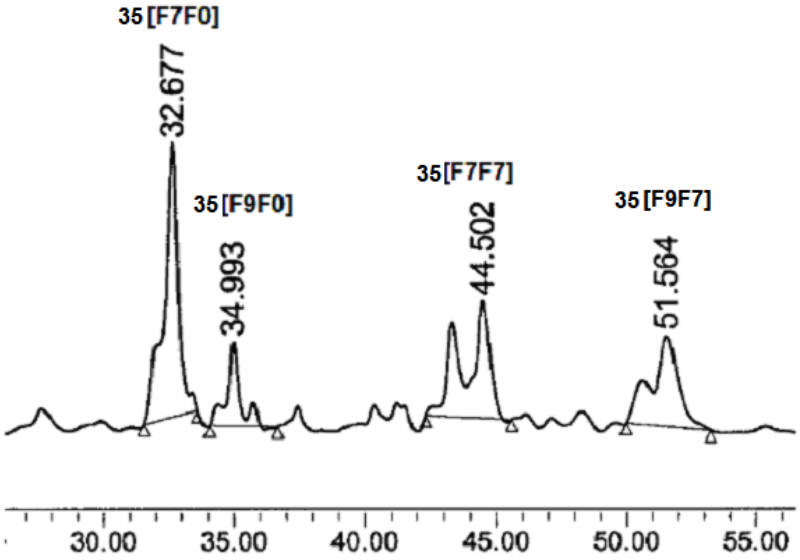
Scheme 2.32. Preparation of α,β-unsaturated ester **M-56**

The RCM reaction of ester **M-56** with Grubbs 1st generation catalyst gave the cyclized product **M-35** (93 mg) in 71% yield after flash chromatography (Scheme 2.33). The formation of the $\Delta^{9,10}$ double bond was confirmed by ^{1}H NMR and MS analysis. However, unlike prior mixtures, lactone **M-35** showed multiple spots on TLC.



Scheme 2.33. The RCM reaction of ester **M-56**

Analysis of **M-35** by fluorous HPLC gave four groups of peaks (Figure 2.10). It was suspected that each group of peaks represented a quasidiastereomer consisting of *E*/*Z* isomers ($\Delta^{9,10}$) and ring conformers. Since **M-35** bears two double bonds, the rigid cyclic structure could possibly develop multiple conformers. However, after the reduction of $\Delta^{9,10}$ alkene of **M-35**, the ring tension would be relieved, thus less conformers of each quasidiastereomer would be formed. We expected that the reduction product of **M-35** would have a less complicated HPLC trace.

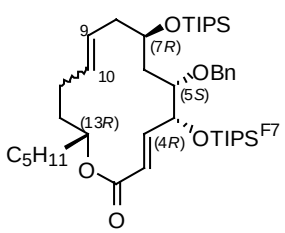


Conditions: PF-C8 column, 1 mL/min, 80:20 MeCN:H_2O to 100% MeCN in 30 min, then isocratic MeCN for 30 min

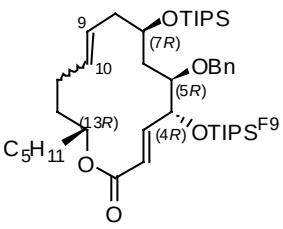
Figure 2.10. The fluorous HPLC trace of lactone **M-35**

A sample of lactone **M-35** (5.0 mg) was demixed by preparative fluorous HPLC to give four quasidiastereomers **35[F7F0]** (1.5 mg), **35[F9F0]** (1.0 mg), **35[F7F7]** (0.7 mg) and **35[F9F7]** (1.0 mg). The ^{1}H NMR resonances of H9 and H10 of the quasidiastereomers are listed in Table 2.2. Although nearby minor products were also collected and combined with each of the four major product, the NMR spectra of the four saved fractions showed they were single compounds. This indicated that the minor products were probably conformers.

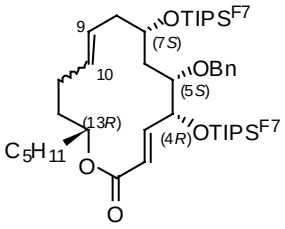
Table 2.2. Comparison of ^{1}H NMR resonances for H9 and H10 of quasiisomers of **M-35** [a]



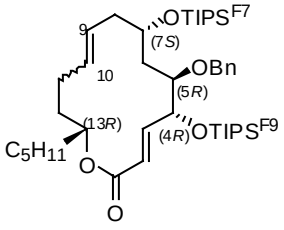
35[F7F0]



35[F9F0]



35[F7F7]

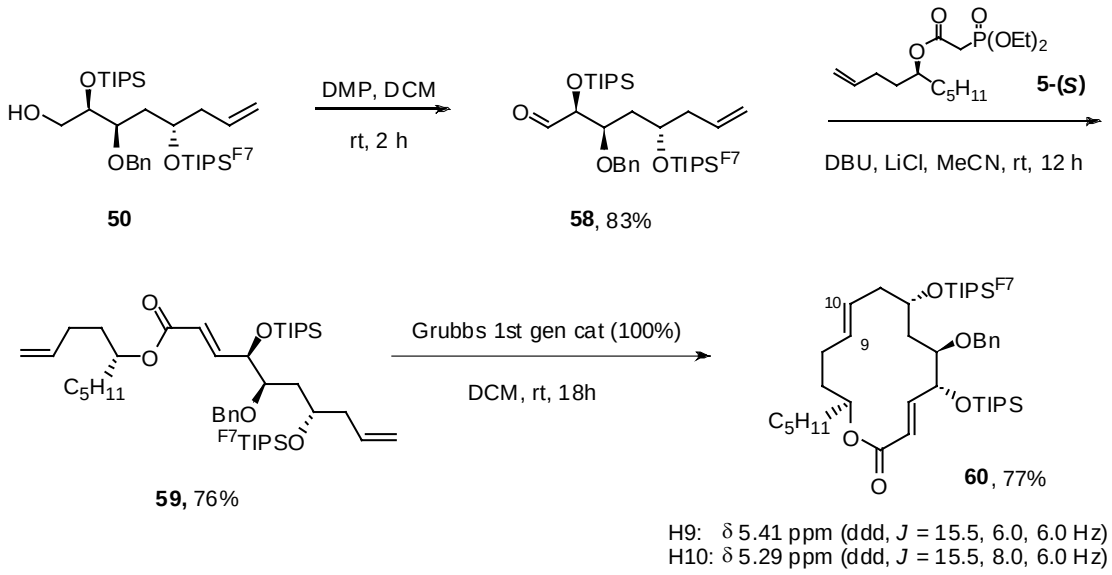


35[F9F7]

Quasiisomer	Configuration	δ (H9, ppm)	*J* (H9, Hz)	δ (H10, ppm)	*J* (H10, Hz)
35[F7F0]	(4*R*,5*S*,7*R*,13*R*)	5.39 (ddd)	15.5, 9.0, 4.0	5.20 (ddd)	15.0, 9.5, 4.5
35[F9F0]	(4*R*,5*R*,7*R*,13*R*)	5.57 (m)	—	5.35 (m)	—
35[F7F7]	(4*R*,5*S*,7*S*,13*R*)	5.36 (m)	—	5.05 (ddd)	14.0, 9.0, 3.5
35[F9F7]	(4*R*,5*R*,7*S*,13*R*)	5.40 (ddd)	15.5, 8.0, 5.0	5.18 (ddd)	14.5, 8.5, 3.5

a. NMR spectra were taken on a 500 MHz spectrometer with samples dissolved in $CDCl_3$.

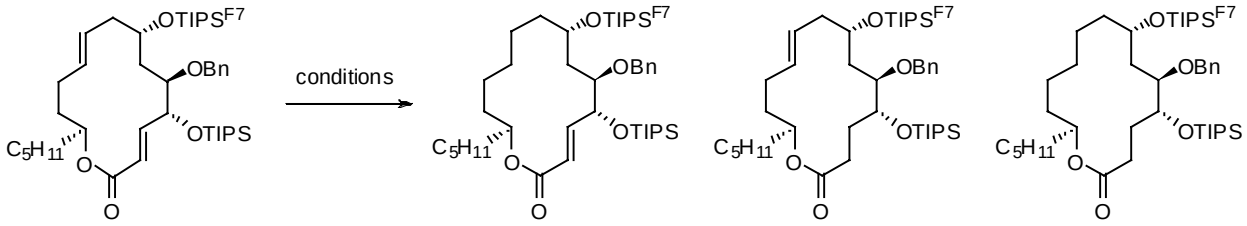
The hydrogenation of **M-35** with $Pd/BaSO_4$ (1.0 equiv) in EtOH gave no product over 24 h according to MS analysis. To find the best conditions of this reaction, we decided to explore the reduction of a single lactone first.[61] The single lactone **60** was prepared from primary alcohol **50**, which was already made (Scheme 2.34). Dess-Martin oxidation of **50** afforded aldehyde **58** in 83% yield. Masamune-Roush coupling of aldehyde **58** with ester **5-(*S*)** in the presence of DBU and LiCl gave ester **59** in 76% yield. The RCM reaction of **59** with Grubbs 1st generation catalyst gave lactone **60** (72 mg) in 77% yield after flash chromatography. The $\Delta^{9,10}$ alkene of **60** had only (*E*) configuration according to ^{1}H NMR analysis. It was possible that the minor (*Z*) product was removed during purification by chromatography. The resonances of H9 and H10 of **60** are listed in Scheme 2.34.



Scheme 2.34. Preparation of the single lactone **60**

Reductions of **60** by diimide and hydrogenations with palladium catalysts are summarized in Scheme 2.35. The diimide reduction of **60** with $CuSO_4$ and NH_2NH_2 in EtOH gave **62** in 42% yield, in which the electron-poor $\Delta^{2,3}$ alkene was reduced (entry 1).[10c] The other diimide reduction of **60** with $TsNHNH_2$ and NaOAc gave many new spots on TLC, indicating the possible decomposition of the starting material (entry 2).[62] We next performed the Pd/$BaSO_4$-catalyzed hydrogenation of **60** in MeOD-*d*4. ^{1}H NMR analysis of the reaction mixture showed that no reaction occurred in 3 h (entry 3). This result further confirmed that the Rosenmond catalyst (Pd/$BaSO_4$) did not work for this reduction. The hydrogenation of **60** with 1.0 equiv of Pd/$SrCO_3$, a similar catalyst to Pd/$BaSO_4$, gave the desired product **61** in a yield of 55% in only 1.5 h.[63] No side product was formed, and approximately 30% of the starting material was recovered (entry 4). To confirm the chemoselectivity of Pd/$SrCO_3$, we repeated the

reaction in entry 4 by running it for 20 h. The starting material **60** was completely consumed to give **61** and the over-reduced product **63** in yields of 23% and 40%, respectively (entry 5). Even though **63** was the major product after 20 h, $Pd/SrCO_3$ still seemed to be selective to the $\Delta^{9,10}$ alkene and could be used for the reduction of **M-35**.



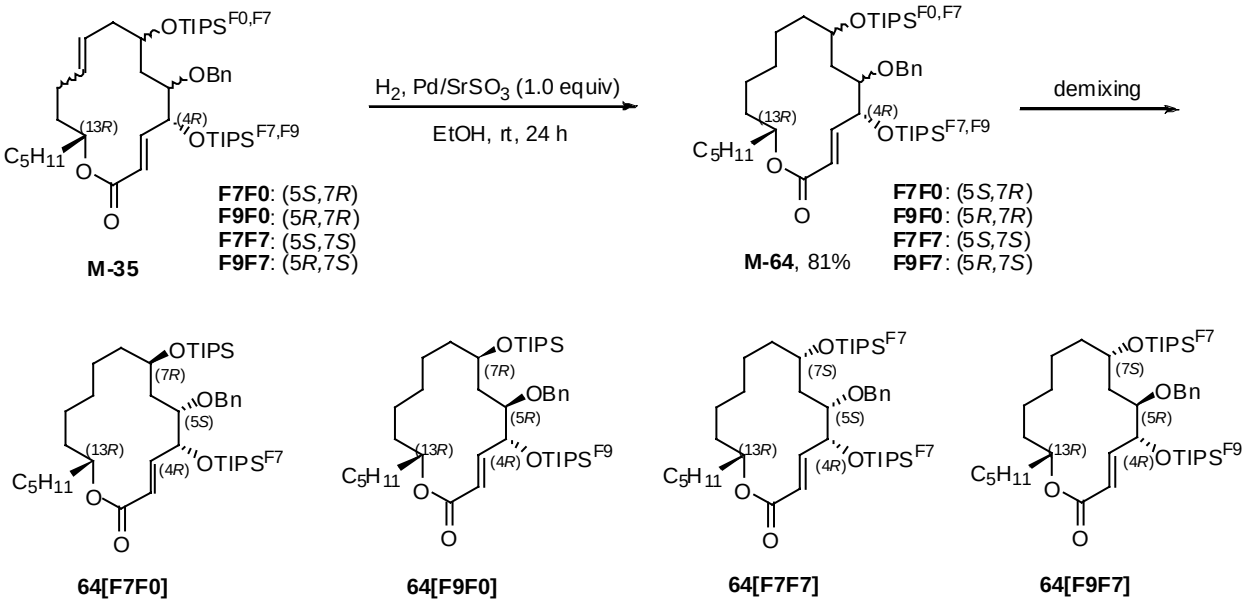
60 **61** **62** **63**

Entry	Condition	Yield
1	$CuSO_4$, NH_2NH_2, EtOH, rt-70 °C, 20 h	**62**, 42%
2	$TsNHNH_2$, NaOAc, DME, H_2O, reflux, 4 h	decomposition
3	$Pd/BaSO_4$ (5 wt%, 1 equiv), H_2, MeOD-*d*4, 3 h	no reaction
4	$Pd/SrCO_3$ (2 wt%, 1 equiv), H_2, EtOH, 1.5 h	**61**, 55%
5	$Pd/SrCO_3$ (2 wt%, 1 equiv), H_2, EtOH, 20 h	**61**, 23%; **63**, 40%

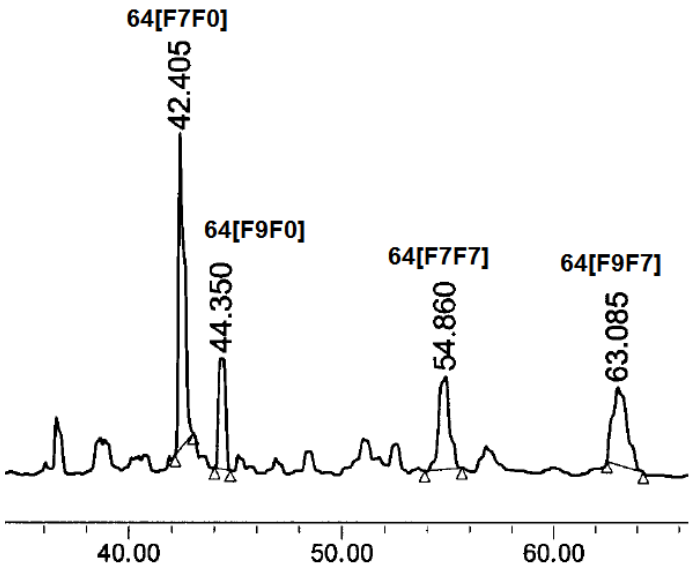
Scheme 2.35. Reductions of the single lactone **60**

The hydrogenation of **M-35** (15.0 mg) with $Pd/SrCO_3$ (1.0 equiv) in EtOH was conducted with monitoring by fluorous HPLC (Scheme 2.36). Approximately 24 h after the reaction started, the several peaks of **M-35** were completely converted to only four new peaks, indicating the formation of the products. The crude product **M-64** (16.0 mg) was demixed by preparative fluorous HPLC to afford four quasidiastereomers **64[F7F0]** (3.3 mg), **64[F9F0]** (2.4 mg), **64[F7F7]** (2.9 mg) and **64[F9F7]** (3.5 mg). The total yield of the reaction was 81% and the recovery of the demixing was 76%. As we expected, the HPLC trace of the reduction reaction

mixture (24 h) looked much simpler than that of **M-35** (Figure 2.11). This result suggested that **M-35** was indeed a mixture of isomers and conformers.



Scheme 2.36. The hydrogenation of **M-35** and the demixing of **M-64**

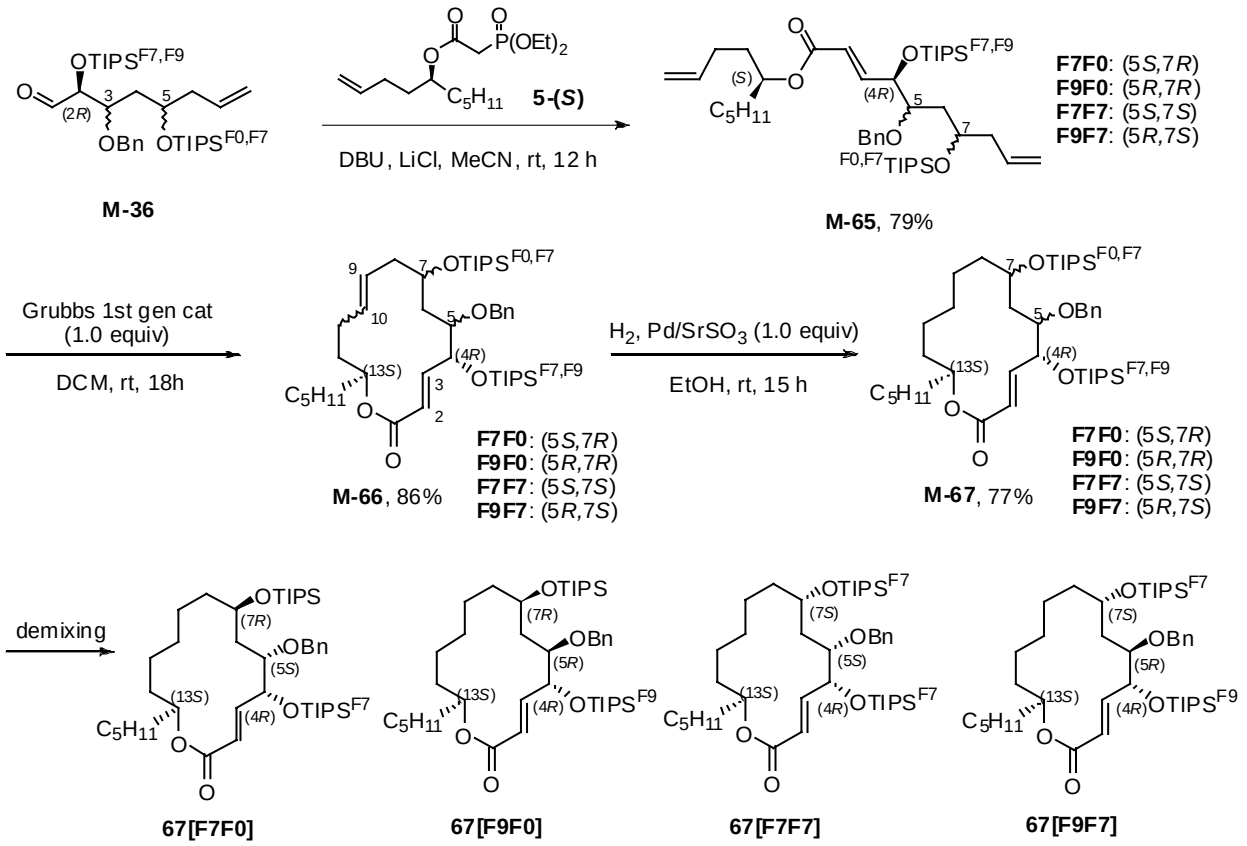


Conditions: PF-C8 column, 1 mL/min, 80:20 MeCN:H_2O to 100% MeCN in 30 min, then isocratic MeCN for 30 min

Figure 2.11. The fluorous HPLC trace of **M-64**

The four quasidiastereomers **64[F7F0]**, **64[F9F0]**, **64[F7F7]** and **64[F9F7]** were then individually deprotected with $BF_3 \cdot Et_2O$ and EtSH in DCM at 35 ºC to give four final products **2a** (0.9 mg), **2b** (0.5 mg), **2c** (0.7 mg) and **2d** (1.0 mg) in 74%, 53%, 59% and 94% yields, respectively (Table 2.3). Product **2d** is the same compound as the single isomer which was already made (see Section 2.2.2). Macrolactones **2a-2d** were first purified by silica gel flash chromatography then by preparative HPLC with a Symmetry C-18 column (7.8 × 150 mm) under gradient conditions. The HPLC purification was done to remove nonpolar impurities such as grease.

To make the other four triols with C13 being (*S*), aldehyde **M-36** was then coupled with ester **5-(*S*)** in the presence of LiCl and DBU in MeCN to afford α,β-unsaturated ester **M-65** in 79% yield after flash chromatography (Scheme 2.37). The RCM reaction of ester **M-65** with Grubbs 1st generation catalyst gave the cyclized product **M-66** in 86% yield after flash chromatography. The hydrogenation of **M-66** (25.0 mg) with $Pd/SrCO_3$ (1.0 equiv) in EtOH gave four quasidiastereomers **67[F7F0]** (5.4 mg), **67[F9F0]** (4.5 mg), **67[F7F7]** (5.0 mg) and **67[F9F7]** (4.4 mg) after demixing by preparative fluorous HPLC. The total yield of the hydrogenation was 77%.



Scheme 2.37. The preparation and demixing of **M-67**

The four quasidiastereomers **67[F7F0]**, **67[F9F0]**, **67[F7F7]** and **67[F9F7]** were individually deprotected with $BF_3 \cdot Et_2O$ and EtSH in DCM at 35 ºC followed by purification by preparative HPLC with a Symmetry C-18 column (7.8 × 150 mm) under gradient conditions to give four products **2e** (1.4 mg), **2f** (0.6 mg), **2g** (0.9 mg) and **2h** (1.1 mg) in 70%, 38%, 57% and 83% yields, respectively (Table 2.3).

The structures of the eight triols **2a-2h** were confirmed by ^{1}H NMR, ^{13}C NMR, COSY and HMQC experiments. The ^{1}H and ^{13}C NMR spectra of **2a-2h** are all different. The resonances were assigned also based on 2D NMR experiments (COSY and HMQC). The comparison of

resonances of the eight synthetic isomers with those of Sch725674 are shown in Table 2.3. The ^{1}H NMR data of the synthetic samples show that the olefin protons (H2 and H3), the methine protons (H4, H5, H7 and H13) and one methylene proton (H6) have all different chemical shifts. Large differences of δ are observed at H4 (4.48, 4.16, 4.55, 4.27, 4.46, 4.03, 4.47 and 4.26 ppm; $\Delta\delta_{max}$ = 0.39 ppm), H7 (3.99, 3.78, 3.38, 3.78, 3.67, 3.47, 3.64 and 3.92 ppm; $\Delta\delta_{max}$ = 0.61 ppm) and one H6 (1.83, 1.63, 2.02, 1.73, 2.02, 1.77, 1.71 and 1.70 ppm; $\Delta\delta_{max}$ = 0.39 ppm). The upfield proton resonances are not distinctive because of overlapping. In the ^{13}C NMR spectra, the differences of δ are normally less than 3 ppm (for example, δ (C4) are 76.0, 77.6, 75.0, 75.4, 75.7, 77.8, 74.7, 75.8 ppm, $\Delta\delta_{max}$ = 3.1 ppm), except that a large difference of δ (C6) of **2b** (42.0 ppm) and **2f** (35.9 ppm) was observed (Δδ = 6.1 ppm).

Table 2.3. Comparison of the NMR data of the natural product and **2a-2h**

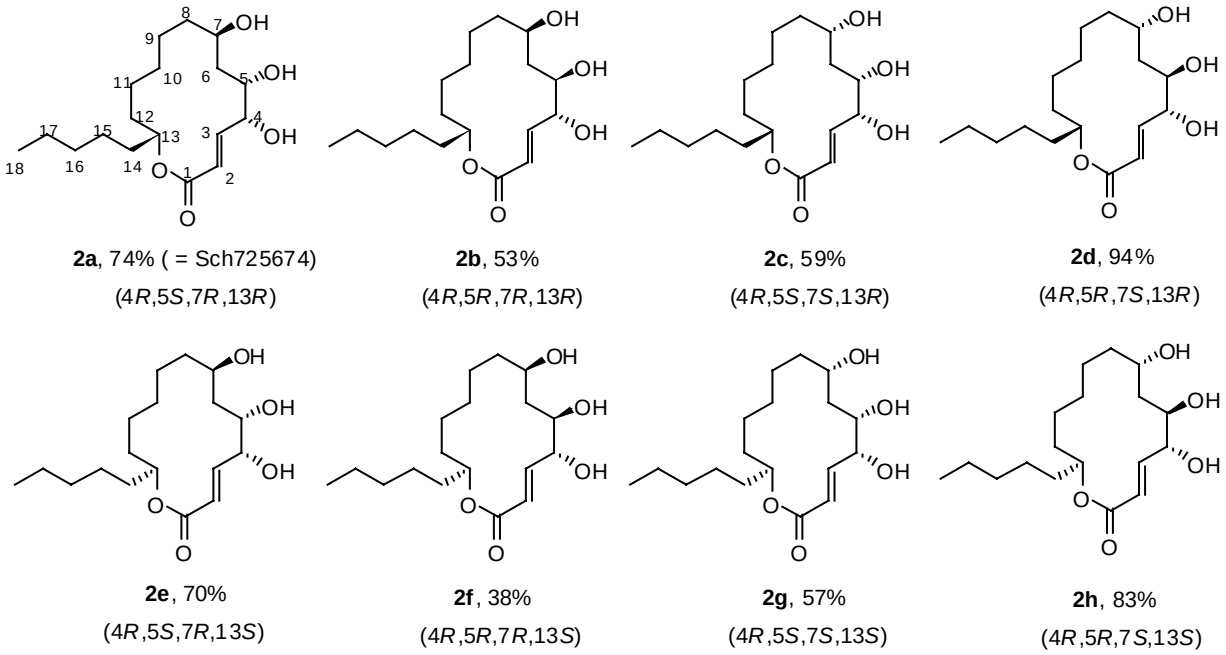


Table 2.3. Comparison of the NMR data of the natural product and **2a-2h** (continued)

δ ppm (multiplicity, *J* Hz)

H [a]	Sch725674	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**
2	6.07 (dd, 15.8, 1.6)	6.08 (dd, 15.5, 1.5)	6.11(dd, 15.5, 1.0)	6.14 (dd, 15.5, 1.5)	6.12 (dd, 16.0, 1.5)	6.06 (dd, 15.6, 2.1)	6.09 (dd, 16.2, 1.8)	6.09 (dd, 15.6, 1.8)	6.11 (dd, 15.6, 1.2)
3	6.86 (dd, 15.8, 6.0)	6.87 (dd, 16.0, 6.0)	6.91 (dd, 16.0, 6.5)	6.95 (dd, 16.0, 4.5)	7.07 (dd, 16.0, 5.5)	7.01 (dd, 16.2, 3.6)	6.96 (dd, 15.6, 6.0)	6.93 (dd, 15.6, 4.2)	7.04 (dd, 15.6, 5.4)
4	4.48 (ddd, 6.0, 3.0, 1.6)	4.48 (ddd, 6.0, 3.0, 1.5)	4.16 (td, 6.5, 1.0)	4.55 (dddd, 4.3, 2.6, 1.8, 0.9)	4.27 (td, 5.0, 1.0)	4.46 (dt, 3.6, 2.1)	4.03 (ddd, 7.8, 6.0, 1.8)	4.47 (ddd, 4.8, 3.0, 1.8)	4.26 (ddd, 6.6, 5.4, 1.2)
5	3.84 (ddd, 6.0, 4.7, 3.0)	3.85 (ddd, 6.0, 4.5, 3.5)	3.82 (ddd, 8.7, 5.7, 3.7)	3.89 (dt, 9.0, 2.5)	3.90 (td, 6.0, 3.0)	3.95 (ddd, 8.4, 4.2, 2.4)	3.55 (td, 8.4, 2.4)	3.89 (ddd, 7.2, 4.2, 3.0)	3.77 (dt, 7.2, 4.2)
6	1.82 (ddd, 14.7, 6.5, 6.0), 1.65 (m)	1.83 (ddd, 14.6, 6.2, 6.2), 1.65 (m)	1.63 (ddd, 14.0, 9.0, 3.5), 1.43 (m)	2.02 (ddd, 14.5, 9.0, 2.0), 1.29 (m)	1.73 (m), 1.68 (m)	2.02 (ddd, 13.8, 7.8, 4.2), 1.53 (ddd, 13.8, 7.8, 4.8)	1.77 (ddd, 15.0, 9.0, 3.0), 1.56 (ddd, 14.4, 9.6, 1.8)	1.71 (ddd, 14.4, 6.6, 4.2), 1.36 (ddd, 14.4, 9.0, 4.8)	1.70 (t, 5.1)
7	3.98 (quint, 6.5)	3.99 (quint, 6.5)	3.78 (m)	3.38 (ddt, 11.6, 7.7, 2.8)	3.78 (tt, 8.0, 3.5)	3.67 (tt, 7.8, 4.2)	3.47 (ddt, 9.0, 7.2, 3.0)	3.64 (dq, 10.2, 5.4)	3.92 (quint, 6.0)
13	4.94 (dddd, 9.8, 7.5, 5.0, 2.2)	4.95 (dddd, 9.5, 7.5, 4.5, 2.0)	5.02 (m)	4.94 (tt, 8.4, 5.6)	4.97 (dddd, 16.5, 9.0, 5.5, 3.5)	4.95 (ddt, 13.2, 5.4, 2.4)	4.92 (m)	5.00 (ddt, 13.8, 4.8, 3.0)	4.95 (ddt, 12.6, 7.2, 2.4)

Table 2.3. Comparison of the NMR data of the natural product and **2a-2h** (continued)

C [a]	Sch725674	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**
1	168.4	168.5	168.3	169.1	167.8	168.1	168.1	168.1	168.1
2	123.1	123.1	124.3	121.8	123.3	122.4	123.1	123.4	123.5
3	149.3	149.3	148.4	150.0	149.8	150.1	149.3	148.7	148.7
4	76.0	76.0	77.6	75.0	75.4	75.7	77.8	74.7	75.8
5	72.9	72.9	73.4	72.1	73.9	72.1	74.7	72.4	74.4
6	38.3	38.3	42.0	40.5	38.3	39.5	35.9	39.2	37.9
7	69.5	69.5	67.7	68.8	69.0	68.8	68.5	68.9	69.2
8	36.8	36.8	37.0	35.9	35.8	35.0	35.1	36.4	36.9
9	25.8	25.8	25.4	24.6	24.6	23.8	24.3	24.3	25.4
10	29.5	29.5	30.1	27.3	27.9	28.7	30.5	30.3	29.7
11	27.0	27.0	26.4	26.5	26.6	26.6	27.7	26.0	26.6
12	34.1	34.1	34.5	33.9	33.7	33.0	33.4	34.4	34.2
13	77.6	77.6	77.5	75.6	75.9	76.1	75.9	77.4	77.6
14	36.5	36.5	36.0	36.2	35.6	34.7	35.6	35.7	36.3
15	26.4	26.4	26.5	24.8	25.2	24.9	26.5	26.6	26.4
16	32.9	33.0	32.9	33.1	33.1	32.8	33.1	32.9	33.0
17	23.8	23.8	23.8	23.8	23.8	23.5	23.9	23.8	23.8
18	14.5	14.5	14.6	14.1	14.5	14.5	14.5	14.5	14.5

a. NMR spectra were taken on a 500 or 600 MHz spectrometer with samples dissolved in MeOD-*d*4.

The ^{1}H and ^{13}C resonances of **2a** are identical to those of Sch725674 in terms of δ and *J* values, thus we expect **2a** to be either Sch725674 itself or its enantiomer. The confirmation of the absolute configurations of Sch725674 requires other data such as the optical rotation of the natural sample, for which we do not have. However, based on the "13*R* law" for 14-membered

macrolactones, **2a** is very likely to be the natural product since the configuration of C13 is (*R*).

2.3 CONCLUSIONS

Fluorous mixture synthesis (FMS) was applied to the synthesis of eight isomers of 14-membered macrolactone Sch725674. A single diastereomer of Sch725674 was prepared first by traditional solution phase synthesis. In the FMS, stereoisomeric starting materials were tagged with different fluorous TIPS groups. The tagged quasidiastereomers were mixed and the mixture underwent a series of steps to make the fluorous tagged macrolactones, which were separated by fluorous HPLC followed by individual deprotections to provide the eight final products. The single isomer synthesis took 18 steps and the FMS of eight compounds only took 32 steps, with the longest linear sequence of 15 steps. The NMR data of the eight synthetic macrolactones were compared with those of Sch725674. Together with the 13*R* rule, the data show that the absolute configuration of Sch725674 is (4*R*,5*S*,7*R*,13*R*).

2.4 EXPERIMENTAL

2.4.1 General Information.

All reactions were performed under an atmosphere of argon unless the reaction solvent

contained water. Reaction solvents were freshly dried either by distillation or by passing through an activated alumina column. DCM, THF, Et_2O, toluene were dried by activated alumina according to Pangborn, A.; Giardello, M. A.; Grubbs, R, H.; Rosen, R. K.; Timmers, F.; *J. Organometallics*, **1996**, *15*, 1518. Products were analyzed by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, FT-IR, high and low resolution mass spectroscopy, HPLC and TLC.

^{1}H and ^{13}C NMR spectra were taken on Bruker models Avance DPX 300 (300 MHz), Avance 300 (300 MHz), Avance DRX 500 (500 MHz) or Avance 600 (600 MHz) NMR spectrometers. Chemical shifts are reported in parts per million (ppm) downfield relative to TMS using the residue solvent proton resonance of $CDCl_3$ (7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR) or MeOD-*d*4 (3.31 ppm for ^{1}H NMR and 49.2 ppm for ^{13}C NMR) as internal standards. In reporting spectral data the format (δ) chemical shift (multiplicity, *J* values in Hz, integration) was used with the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet. Infrared spectra were taken on a Mattson Genesis Series FTIR using thin film on NaCl plate. Peaks are reported in wavenumbers (cm^{-1}). High resolution mass spectra were reported in units of *m/z,* and were obtained on a V/G 70/70 double focusing machine, an Applied Biosystems 4700 instrument, or a Bruker Daltonics 12 Tesla FT-MS. HPLC analysis was performed on a Waters 600E Controller system with a Waters 2487 dual λ absorbance detector using a Fluoro*Flash*^{TM} PF-C8 HPLC column (5 μm, 10 Å, 4.6 × 150 mm). LC-MS spectra were obtained on an Agilent HP 1100 series LC-MSD using ESI mode. Solvent from the demixing was removed by the ThermoSavant SC210A SpeedVac Plus.

All chemical names (except fluorous mixtures) were generated by ChemDraw Ultra 10.0. In the numbering of the following text, "**M**" is used to denote a mixture of fluorous tagged quasiisomers. The letter "**F**" followed by a number (0, 7 or 9) is an abbreviation of the ^{F}TIPS group with a certain fluorine content (the regular TIPS group is often displayed as ^{F0}TIPS). A single component in the mixture is designated as the combination of a number and abbreviations of flourous tags. For example, "**35[F9F7]**" represents a quasiisomer in mixture **M-35** that bears ^{F9}TIPS and ^{F7}TIPS groups.

2.4.2 General Experimental Procedures.

General conditions for analytical fluorous HPLC:

A solution of the fluorous sample in 80:20 CH_3CN:H_2O 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 Å, 4.6 × 150 mm). The flow rate was 1.0 mL/min. The UV wavelengths for detection were 220 nm and 254 nm. The two frequently used elution conditions were:

Condition 1: The gradient elution started at 80% CH_3CN-20% H_2O, and changed to 100% CH_3CN in 30 min. The elution lasted for another 60 min with 100% CH_3CN.

Condition 2: The isocratic elution stays at 100% CH_3CN (for a quick test).

General conditions for preparative fluorous HPLC (demixing):

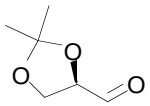
A solution of the fluorous mixture in 80:20 $CH_3CN:H_2O$ was injected into the Waters HPLC system (Waters 600 controller and Waters 2487 dual λ absorbance detector) with a Fluoro*Flash*^{TM} PF-C8 column (20 × 250 mm). The gradient elution started at 80% CH_3CN-20% H_2O, and changed to 100% CH_3CN in 30 min. The elution lasted for another 60 min with 100% CH_3CN. The flow rate was 10.0 mL/min. The UV wavelengths for detection were 220 nm and 254 nm. Fractions containing fluorous compounds were collected in culture tubes (16 × 150 mm) and the solvent was removed by a ThermoSavant SC210A SpeedVac Plus.

General conditions for preparative reverse phase HPLC:

A solution of the crude final triol **2** (purified by flash column first) in 20:80 $CH_3CN:H_2O$ was injected to the Waters HPLC system (Waters 600 Controller and Waters 2487 dual λ Absorbance Detector) with the Waters SymmetryPrep^{TM} C_{18} column (7 μm, 7.8 × 150 mm). The gradient elution started at 20% CH_3CN-80% H_2O, and changed to 100% CH_3CN in 30 min. The elution lasted for another 30 min with 100% CH_3CN. The flow rate was 4.0 mL/min. The UV wavelengths for detection were 220 nm and 254 nm. The fractions containing the product were collected in culture tubes (16 × 150 mm) and the solvent was removed by a ThermoSavant SC210A SpeedVac Plus.

2.4.3 Specific Experimental Procedures and Compound Data:

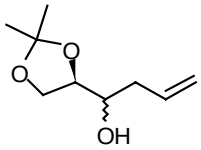
(Compounds **30**, **31**, **49**, **50**, **53**, **58-63** were model compounds or side products. Compounds **39-anti-F0**, **39-syn-F0**, **39-syn-F7** and **39-syn-F9** were prepared for TLC experiment only. These compounds were only characterized by ^{1}H NMR. Compounds **38a[F7]**, **38a[F9]**, **38b[F7]** and **38b[F9]** were quasidiastereomers after demixing, and they were only characterized by ^{1}H NMR and HRMS.)



(*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde (13):[27,28]

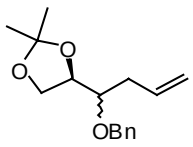
A 1 L three-necked flask equipped with a mechanical stirrer was filled with dry DCM (250 mL) followed by addition of 1,2:5,6-di-*O*-isopropylidene-D-mannitol **12** (25.0 g, 194 mmol) and saturated aqueous $NaHCO_3$ (10.4 mL). $NaIO_4$ (40.8 g, 191 mmol) was added portionwise to make sure that the temperature of the suspension did not exceed 35 °C. The mixture was stirred at 23 °C for 2 h and then quenched with $MgSO_4$ (12.5 g, 104 mmol). The mixture was stirred for another 20 min. The slurry was vacuum-filtered, and the filter cake was removed, and transferred back into the three-necked flask. DCM (100 mL) was added, and the resulting slurry was stirred for 10 min. The slurry was vacuum-filtered again and the filtrate was combined with the previous one. The solution was concentrated to yield aldehyde **13** (25.3 g, approximately 100%, containing very little DCM) as a colorless oil. The product polymerized on storage so it was subjected to allylation immediately: MS (EI) *m/z* [$M^{+\cdot}$] 115; HRMS (EI) *m/z* [$M^{+\cdot}$] calcd for

$C_5H_7O_3$: 115.0395, found 115.0394.



(*R*/*S*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (14):[30]

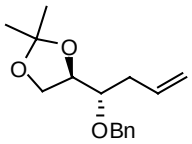
A 1 L round bottom flask was filled with dry diethyl ether (200 mL) followed by addition of aldehyde **13** (25.3 g, 194 mmol). At –78 °C, allylMgBr (1M in Et_2O, 253 mL, 253 mmol) was added dropwise. The reaction was slowly warmed to 23 °C and stirred for 4 h. The reaction was quenched by addition of a saturated NH_4Cl aqueous solution. The layers were separated and the aqueous layer was extracted with diethyl ether (2x). The combined organic fractions were dried over $MgSO_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexane/EtOAc (4:1) to yield a mixture of two unseparable diastereomers **14** (23.2 g, 70 %, with a diastereomeric ratio of 1.4/1.0 *anti/syn* based on ^{1}H NMR) as a yellow oil: ^{1}H NMR (see appendix); MS (EI) *m/z* [$M^{+\cdot}$] 157; HRMS (EI) *m/z* [$M^{+\cdot}$] calcd for $C_8H_{13}O_3$: 157.0865, found 157.0862.



(*R*)-4-((*R*/*S*)-1-(Benzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane (15): [31,32]

A 1 L round bottom flask was filled with dry THF (300 mL) followed by addition of

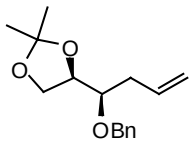
homoallylic alcohol **14** (23.0 g, 134 mmol, 1.0:0.70 mixture of diastereomers). At room temperature benzyl bromide (75.1 g, 307 mmol), tetrabutylammonium iodide (1.06 g, 2.00 mmol) and NaH (60 w% in mineral oil, 17.5 g, 174 mmol) were added. The mixture was refluxed for 12 h. The reaction was quenched by addition of EtOAc (100 mL) and was extracted with diethyl ether (2x). The combined organic fractions were dried over $MgSO_4$. The solution was concentrated and the crude mixture was purified by silica gel flash chromatography eluting with hexane/EtOAc (15:1) to yield **15** (35.0 g, 76 %, 1.0:0.61 mixture of (2*R*,3*S*) and (2*R,*3*R*) isomers based on ^{1}H NMR) as a colorless oil: ^{1}H NMR (see appendix). Separation of a small sample of **15** (70.0 mg) by silica gel flash chromatography with hexane/EtOAc (20:1) afforded **15-anti** (40.0 mg, less polar) and **15-syn** (26.0 mg, more polar) as two diastereomers.



(*R*)-4-((*S*)-1-(Benzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane (15-anti):

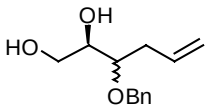
$[\alpha]_D^{25}$ +26.6 (c 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 5.90 (ddt, *J* = 17.4, 10.2, 7.2 Hz, 1H), 5.15 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.10 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.66 (d, *J* = 11.4, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.11 (q, *J* = 6.3 Hz, 1H), 4.04 (dd, *J* = 7.8, 6.3 Hz, 1H), 3.90 (dd, *J* = 7.8, 6.0 Hz, 1H), 3.57 (q, *J* = 5.7 Hz, 1H), 2.50–2.30 (m, 2H), 1.42 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 134.2, 128.3, 127.8, 127.7, 117.5, 109.1, 78.9, 77.2, 72.5, 66.4, 35.6, 26.6, 25.4; IR (thin film) 3055, 2987, 1641, 1496, 1373, 1265, 1073 cm^{-1}; MS

(EI) *m/z* [$M^{+\cdot}$] 262; HRMS (EI) *m/z* [$M^{+\cdot}$] calcd for $C_{16}H_{22}O_3$: 262.1569, found 262.1578.



(*R*)-4-((*R*)-1-(Benzyloxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolane (15-syn):

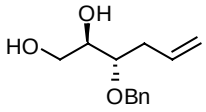
$[\alpha]_D^{25}$ +13.0 (c 0.39, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H), 5.88 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.11 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.07 (dd, *J* = 9.3, 1.2 Hz, 1H), 4.73 (d, *J* = 11.7, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.22 (q, *J* = 6.6 Hz, 1H), 3.99 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.71 (dd, *J* = 8.1, 7.5 Hz, 1H), 3.51 (td, *J* = 6.9, 4.5 Hz, 1H), 2.38–2.19 (m, 2H), 1.44 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 134.6, 128.3, 127.8, 127.6, 117.2, 109.3, 79.3, 77.9, 72.5, 65.8, 35.3, 26.5, 25.4; IR (thin film) 3031, 2934, 1641, 1496, 1373, 1265, 1212, 1071 cm^{-1}; MS (EI) *m/z* [$M^{+\cdot}$] 262; HRMS (EI) *m/z* [$M^{+\cdot}$] calcd for $C_{16}H_{22}O_3$: 262.1569, found 262.1568.



(2*R*,3*R/S*)-3-(Benzyloxy)hex-5-ene-1,2-diol (8):[33]

To a solution of **15** (34.0 g, 130 mmol, 1.0:0.61 mixture of (2*R*,3*S*) and (2*R*,3*R*) isomers) in DCM (400 mL) at 23 °C was added $FeCl_3 \cdot 6H_2O$ (123 mg, 454 mmol). The resulting yellow-to-amber suspension was stirred for 2 h and the reaction was quenched by the addition of

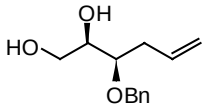
saturated aqueous $NaHCO_3$ (150 mL). The aqueous layer was extracted three times with DCM, and the combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting oil was redissolved in a minimum amount of DCM and passed through a short silica gel plug to remove any remaining iron species. The solution was concentrated and the crude mixture was purified by silica gel flash chromatography eluting with hexane/EtOAc (2:1) to yield a mixture of two unseparable diastereomers **8** (18.0 g, 63%, 1.0:0.44 mixture of (2*R*,3*S*) and (2*R*,3*R*) isomers based on ^{1}H NMR) as a colorless oil: ^{1}H NMR (see appendix).



(2*R*,3*S*)-3-(Benzyloxy)hex-5-ene-1,2-diol (8-anti):

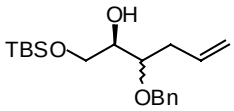
The same procedure as **8** was followed by employing **15-anti** (40.0 mg, 0.152 mmol), $FeCl_3{\cdot}6H_2O$ (144 mg, 0.534 mmol). The title compound **8-anti** was prepared as a colorless oil (33.0 mg, 97%): $[\alpha]_D^{25}$ +20.4 (c 0.22, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.28 (m, 5H), 5.88 (ddt, *J* = 17.1, 10.2, 7.2 Hz, 1H), 5.16 (dd, *J* = 17.7, 1.5 Hz, 1H), 5.12 (dd, *J* = 9.3, 0.9 Hz, 1H), 4.68 (d, *J* = 11.4, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 3.83–3.69 (m, 3H), 3.65 (q, *J* = 5.5 Hz, 1H), 2.53–2.32 (m, 2H), 2.47 (d, *J* = 6.0 Hz, 1H), 2.15 (br, dd, *J* = 7.2, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 134.1, 128.5, 128.0, 127.9, 117.8, 80.6, 72.5, 72.3, 63.2, 35.1; IR (thin film) 3579, 3054, 2986, 1422, 1265, 1076, 896 cm^{-1}; MS (EI) *m/z* [$M^{+\cdot}$] 222; HRMS (EI) *m/z*

[$M^{+\cdot}$] calcd for $C_{13}H_{18}O_3$: 222.1256, found 222.1261.



(2*R*,3*R*)-3-(Benzyloxy)hex-5-ene-1,2-diol (8-syn):

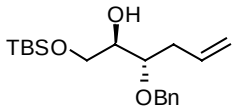
The same procedure as **8** was followed by employing **15-syn** (26.0 mg, 0.0991 mmol), $FeCl_3{\cdot}6H_2O$ (93.7 mg, 0.347 mmol). The title compound **8-syn** was prepared as a colorless oil (22.0 mg, 100%): $[\alpha]_D^{25}$ –40.0 (c 0.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 5.87 (ddt, *J* = 17.1, 10.2, 7.2 Hz, 1H), 5.17 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.12 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.73 (d, *J* = 11.4, 1H), 4.47 (d, *J* = 11.4 Hz, 1H), 3.87–3.60 (m, 3H), 3.56 (q, *J* = 5.4 Hz, 1H), 2.58 (br, s, 1H), 2.57–2.35 (m, 2H), 2.11 (br, s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 133.8, 128.6, 128.0, 128.0, 118.0, 79.0, 72.5, 72.1, 63.8, 34.6; IR (thin film) 3426, 3054, 2986, 1641, 1422, 1265, 1071, 896 cm^{-1}; MS (ESI) *m/z* $[M + Na]^+$ 245; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{13}H_{18}NaO_3$: 245.1154, found 245.1158.



(2*R*,3*R/S*)-3-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)hex-5-en-2-ol (17):

To a solution of **8** (17.0 g, 76.5 mmol, 1.0:0.44 mixture of (2*R*,3*S*) and (2*R*,3*R*) isomers) in DCM (400 mL) at 23 °C was added imidazole (10.4 g, 153 mmol). The suspension was stirred until the imidazole was completely dissolved. The solution was cooled to 0 °C and TBSCl (12.7

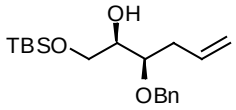
g, 84.1 mmol) was added. The solution was slowly warmed to 23 °C and was stirred for 30 min. The reaction was quenched by addition of H_2O (100 mL) and was extracted with DCM (2x). The combined organic fractions were dried over $MgSO_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexane/EtOAc (10:1) to yield **17** (23.0 g, 89%, 1.0:0.84 mixture of (2*R*,3*S*) and (2*R*,3*R*) isomers based on ^{1}H NMR) as a colorless oil: ^{1}H NMR (see appendix). The first separation of **17** (10.6 g) by silica gel flash chromatography with pentane/Et_2O (10:1) afforded diastereomers **17-anti** (2.48 g, less polar) and **17-syn** (3.35 g, more polar), and unseparated mixture (4.77 g, combined with the rest of **17**). The second separation of **17** (17.1 g) afforded **17-anti** (4.50 g), **17-syn** (4.50 g), and unseparated mixture (8.10 g). The characterizations of the two diastereomers of **17** are shown below.



(2*R*,3*S*)-3-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)hex-5-en-2-ol (17-anti):

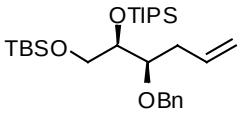
$[\alpha]_D^{25}$ +34.2 (c 0.42, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.19 (m, 5H), 5.92 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.17 (dd, *J* = 17.1, 2.0 Hz, 1H), 5.11 (dd, *J* = 10.2, 2.0 Hz, 1H), 4.65 (d, *J* = 11.4, 1H), 4.53 (d, *J* = 11.4 Hz, 1H), 3.77 (quint, *J* = 6.6 Hz, 1H), 3.68 (m, 2H), 3.53 (q, *J* = 6.1 Hz, 1H), 2.56–2.38 (m, 3H), 0.83 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 128.4, 127.8, 127.6, 117.2, 78.8, 72.5, 72.2, 63.7, 34.7, 25.9, –5.4; IR (thin film) 3564, 3471, 3068, 3032, 2953, 2858, 1641, 1496, 1256, 1096, 838 cm^{-1}; MS (ESI) *m/z* $[M + Na]^+$ 359;

HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{19}H_{32}NaO_3Si$: 359.2018, found 359.2041.



(2*R*,3*R*)-3-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)hex-5-en-2-ol (17-syn):

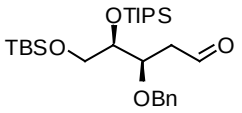
$[\alpha]_D^{25}$ –31.0 (c 0.19, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 5.87 (ddt, *J* = 17.2, 10.1, 7.0 Hz, 1H), 5.15 (dd, *J* = 17.1, 2.0 Hz, 1H), 5.10 (dd, *J* = 10.3, 1.7 Hz, 1H), 4.69 (d, *J* = 11.4, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 3.75–3.60 (m, 5H), 2.55–2.40 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.7, 128.4, 127.9, 127.7, 117.3, 78.1, 72.7, 72.5, 63.8, 35.0, 25.9, –5.4; IR (thin film) 3447, 3054, 2954, 2931, 2858, 1641, 1468, 1265, 1110, 839 cm^{-1}; MS (ESI) *m/z* $[M + Na]^+$ 359; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{19}H_{32}NaO_3Si$: 359.2018, found 359.2044.



(*R*)-6-((*R*)-1-(Benzyloxy)but-3-enyl)-8,8-diisopropyl-2,2,3,3,9-pentamethyl-4,7-dioxa-3,8-di-siladecane (7):

A 500 mL round bottom flask was filled with DCM (200 mL), followed by **17-syn** (3.20 g, 9.51 mmol). The solution was cooled to 0 °C and 2,6-lutidine (5.17 mL, 44.6 mmol) was added. TIPSOTf (7.99 mL, 29.7 mmol) was added, and stirring was continued for 3 hours. The reaction was quenched with H_2O (100 mL). The layers were separated and the aqueous layer was

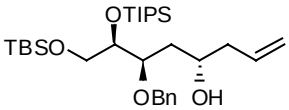
extracted with DCM (2x). The combined organic layers were dried over $MgSO_4$, the resulting solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/EtOAc (30:1) to yield **7** (4.54 g, 96%) as a colorless oil: $[\alpha]_D^{25}$ +18.2 (c 0.33, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.24 (m, 5H), 5.88 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.09 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.03 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.60 (s, 2H), 4.00 (ddd, *J* = 7.2, 4.2, 3.3 Hz, 1H), 3.87 (dd, *J* = 10.5, 3.3 Hz, 1H), 3.59 (dd, *J* = 10.2, 6.6 Hz, 1H), 3.53 (ddd, *J* = 9.1, 4.0, 3.4 Hz, 1H), 2.52 (dddt, *J* = 14.4, 6.9, 3.0, 1.5, 1H), 2.17 (dddt, *J* = 16.2, 9.0, 7.2, 0.9, 1H), 1.11–1.02 (m, 3H), 1.06 (s, 18H), 0.90 (s, 9H), 0.050 (s, 3H), 0.047 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 136.5, 128.2, 127.7, 127.5, 116.3, 81.0, 74.5, 72.5, 64.6, 34.1, 26.0, 18.4, 18.2, 12.6, –5.38, –5.41; IR (thin film) 3053, 2945, 2865, 1641, 1496, 1465, 1264, 1095, 838 cm^{-1}; MS (ESI) *m/z* $[M + Na]^+$ 515; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{28}H_{52}NaO_3Si_2$: 515.3353, found 515.3330.



(3*R*,4*R*)-3-(Benzyloxy)-5-(*tert*-butyldimethylsilyloxy)-4-(triisopropylsilyloxy)pentanal (6): [34]

Ozone was bubbled through a solution of the alkene **7** (4.00 g, 8.12 mmol) in DCM (150 mL) at –78 °C. After the solution turned blue (about 20 min), the vessel was removed from the ozone atmosphere and the mixture was bubbled with argon for 20 min. Ph_3P (2.77 g, 10.6 mmol) was added. The reaction mixture was slowly warmed up to 23 °C and stirred for 12 h. The

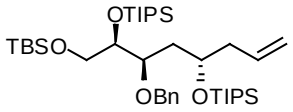
solvent was removed under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with hexanes/EtOAc (20:1) to yield aldehyde **6** (2.2 g, 55%) as a colorless oil: $[\alpha]_D^{25}$ +33.0 (c 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (br, dd, *J* = 2.4, 1.2 Hz, 1H), 7.50–7.26 (m, 5H), 4.62 (s, 2H), 4.11 (ddd, *J* = 8.1, 4.2, 4.2 Hz, 1H), 4.04 (dt, *J* = 5.4, 3.3 Hz, 1H), 3.87 (dd, *J* = 10.5, 3.3 Hz, 1H), 3.63 (dd, *J* = 10.5, 6.0 Hz, 1H), 2.82 (ddd, *J* = 16.8, 3.3, 1.2 Hz, 1H), 2.63 (ddd, *J* = 16.8, 8.7, 2.1 Hz, 1H), 1.14–0.98 (m, 3H), 1.05 (s, 18H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 138.1, 128.3, 127.8, 127.7, 75.5, 73.5, 72.4, 64.2, 44.5, 25.9, 18.3, 18.1, 12.5, –5.5; IR (thin film) 3054, 2944, 2866, 1723, 1641, 1464, 1265, 1095, 838 cm^{-1}; MS (ESI) *m/z* $[M + Na]^+$ 517.3; HRMS (ESI) *m/z* $[M + K]^+$ calcd for $C_{27}H_{50}KO_4Si_2$: 533.2885, found 533.2843.



(4*S*,6*R*,7*R*)-6-(Benzyloxy)-8-(*tert*-butyldimethylsilyloxy)-7-(triisopropylsilyloxy)oct-1-en-4-ol (20a): [37]

(–)-Methoxydiisopinocampheylborane (10.0 g, 31.6 mmol) was dissolved in dry diethyl ether (30 mL) in a 2-neck 100 mL flask previously heated under vacuum and flushed with argon. The solution was cooled to 0 °C before allylMgBr (1M in Et_2O, 26.7 mL, 26.7 mmol) was added slowly via syringe. After 10 min, the cooling bath was removed and stirring of the mixture was continued for 3 h at 23 °C. Aldehyde **6** (1.90 g, 3.84 mmol) in Et_2O (40 mL) was added slowly

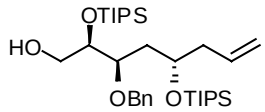
via syringe. After 12 h at −78 °C, the reaction was quenched by addition of methanol (1 mL). The solution was warmed to 23 °C overnight before 3 N NaOH (4 mL) and 30% wt. H_2O_2 (8 mL) were added at 0 °C. After 10 min at 0 °C, the mixture was refluxed for 3 h. After cooling to 0 °C, a saturated Na_2SO_3 aqueous solution was added and the aqueous layer was extracted with diethyl ether (2x). The combined organic fractions were dried over $MgSO_4$. The solution was concentrated and the crude mixture was purified by silica gel flash chromatography eluting with hexanes/EtOAc (30:1) to yield homoallylic alcohol **20a** (1.18 g, 57 %) as a colorless oil: $[\alpha]_D^{25}$ +24.8 (c 0.65, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5H), 5.82 (m, 1H), 5.10 (d, *J* = 15.9 Hz, 1H), 5.09 (d, *J* = 11.1 Hz, 1H), 4.65 (d, *J* = 11.7 Hz, 1H), 4.58 (d, *J* = 11.4 Hz, 1H), 4.06 (ddd, *J* = 6.9, 4.2, 3.0 Hz, 1H), 3.87 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.84–3.72 (m, 2H), 3.63 (dd, *J* = 10.5, 6.6 Hz, 1H), 2.49 (d, *J* = 4.5 Hz, 1H), 2.22 (t, *J* = 6.9 Hz, 2H), 1.67 (m, 2H), 1.15–1.06 (m, 6H), 1.11 (s, 18H), 1.09 (s, 18H), 0.91 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 135.1, 128.4, 127.9, 127.7, 117.5, 78.4, 74.6, 72.4, 68.1, 64.8, 42.3, 36.5, 26.0, 18.4, 18.2, 18.1, 12.6, –5.38, –5.43; IR (thin film) 3427, 3054, 2946, 2866, 1641, 1465, 1265, 1091, 838 cm^{-1}; MS (ESI) *m/z* $[M + Na]^+$ 559; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{30}H_{56}NaO_4Si_2$: 559.3615, found 559.3617.



(6*R*,7*R*,9*S*)-9-Allyl-7-(benzyloxy)-11,11-diisopropyl-2,2,3,3,12-pentamethyl-6-(triisopropyl-

silyloxy)-4,10-dioxa-3,11-disilatridecane (21):

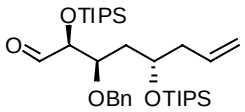
The same procedure as **7** was followed by employing **20a** (1.18 g, 2.20 mmol), 2,6-lutidine (0.764 mL, 6.59 mmol), TIPSOTf (1.18 mL, 4.40 mmol) and DCM (60 mL). The title compound **21** was prepared as a colorless oil (1.10 g, 71%): $[\alpha]_D^{25}$ +46.2 (c 0.26, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5H), 5.86 (m, 1H), 5.05 (d, *J* = 13.8 Hz, 1H), 5.04 (d, *J* = 12.3 Hz, 1H), 4.67 (d, *J* = 11.7 Hz, 1H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.17–4.06 (m, 2H), 3.89 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.84 (dt, *J* = 10.2, 3.3 Hz, 1H), 3.59 (dd, *J* = 9.9, 6.6 Hz, 1H), 2.41–2.30 (m, 2H), 1.78 (ddd, *J* = 14.4, 7.8, 3.0 Hz, 1H), 1.67 (ddd, *J* = 14.4, 9.9, 4.5 Hz, 1H), 1.25–0.97 (m, 6H), 1.11 (s, 18H), 1.09 (s, 18H), 0.91 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 134.9, 128.2, 127.5, 127.3, 117.0, 77.8, 74.8, 71.5, 69.6, 64.8, 42.9, 36.7, 26.0, 18.4, 18.3, 18.3, 18.2, 13.0, 12.9, –5.40, –5.43; IR (thin film) 3071, 3031, 2943, 2866, 1640, 1464, 1254, 1093, 1000, 838 cm^{-1}; MS (ESI) *m/z* $[M + Na]^+$ 715.5; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{39}H_{76}NaO_4Si_3$: 715.4949, found 715.5006.



(2*R*,3*R*,5*S*)-3-(Benzyloxy)-2,5-bis(triisopropylsilyloxy)oct-7-en-1-ol (22): [38]

A 250 mL round bottom flask was filled with MeOH (100 mL) and **21** (1.10 g, 1.59 mmol). The solution was cooled to –10 °C and acetyl chloride (1.11 g, 14.1 mmol) was added. The reaction was stirred for 1 h. The reaction was quenched by slowly adding saturated aqueous

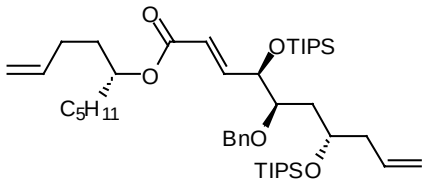
$NaHCO_3$ until pH was 7. The layers were separated and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over $MgSO_4$. The resulting solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/EtOAc (30:1) to yield **22** (0.80 g, 87%) as a yellow oil: $[\alpha]_D^{25}$ +46.6 (c 0.09, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 5.83 (ddt, *J* = 17.7, 9.6, 7.2 Hz, 1H), 5.10–4.99 (m, 2H), 4.67 (d, *J* = 11.1 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.21 (dt, *J* = 6.9, 4.5 Hz, 1H), 4.12 (tt, *J* = 7.2, 4.5 Hz, 1H), 3.92 (dt, *J* = 9.3, 3.9 Hz, 1H), 3.78 (ddd, *J* = 11.1, 7.2, 3.3 Hz, 1H), 3.66 (ddd, *J* = 10.8, 8.4, 4.5 Hz, 1H), 2.56 (dd, *J* = 8.4, 3.3 Hz, 1H), 2.45–2.26 (m, 2H), 1.80 (ddd, *J* = 14.4, 7.2, 3.0 Hz, 1H), 1.78 (ddd, *J* = 14.4, 9.0, 4.5 Hz, 1H), 1.12–1.04 (s, 36H), 1.04–0.82 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.1, 134.7, 128.4, 127.7, 127.7, 117.1, 79.4, 72.1, 69.9, 69.4, 63.8, 42.8, 35.9, 18.4, 18.3, 18.1, 18.1, 13.0, 12.5; IR (thin film) 3454, 3054, 2945, 2867, 1640, 1464, 1265, 1111, 1066, 884 cm^{-1}; MS (ESI) *m/z* $[M + Na]^+$ 601.3; HRMS (ESI) *m/z* $[M + K]^+$ calcd for $C_{33}H_{60}KO_4Si_2$: 615.3667, found 615.3690.



(2*S*,3*R*,5*S*)-3-(Benzyloxy)-2,5-bis(triisopropylsilyloxy)oct-7-enal (4):

Alcohol **22** (750 mg, 1.30 mmol) was dissolved in dry DCM (100 mL) in a 250 mL round bottom flask. PCC (838 mg, 3.89 mmol) was added to the solution. The mixture was stirred for 12 h. The solution was concentrated and the crude product was purified by silica gel flash

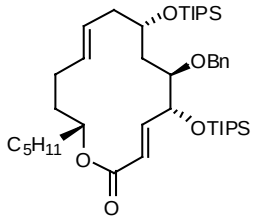
chromatography eluting with hexanes/EtOAc (30:1) to yield aldehyde **4** (590 mg, 79%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (d, *J* = 1.8 Hz, 1H), 7.37–7.23 (m, 5H), 5.78 (ddt, *J* = 17.7, 9.3, 7.2 Hz, 1H), 5.03 (dd, *J* = 12.3, 0.6 Hz, 1H), 5.02 (dd, *J* = 15.3, 0.6 Hz, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.35 (dd, *J* = 4.5, 1.5 Hz, 1H), 4.09 (tt, *J* = 7.8, 3.9 Hz, 1H), 4.01 (ddd, *J* = 10.2, 4.5, 2.4 Hz, 1H), 2.42–2.23 (m, 2H), 1.84 (ddd, *J* = 14.4, 8.4, 2.7 Hz, 1H), 1.68 (ddd, *J* = 14.1, 10.5, 3.9 Hz, 1H), 1.17–0.92 (m, 6H), 1.05 (s, 36H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1, 138.3, 134.4, 128.3, 127.6, 127.6, 117.3, 78.5, 77.7, 72.1, 69.0, 42.8, 37.7, 18.3, 18.3, 18.0, 17.9, 12.9, 12.2; IR (thin film) 3054, 2926, 2865, 1731, 1423, 1265, 1107, 896 cm^{-1}.



(4*R*,5*R*,7*S*,*E*)-((*R*)-Dec-1-en-5-yl)-5-(benzyloxy)-4,7-bis(triisopropylsilyloxy)deca-2,9-dieno-ate (28): [40,41]

DBU (42.2 mg, 0.277 mmol) was added to a stirred suspension of LiCl **(**14.1 mg, 0.333 mmol) and phosphonate **5-(*R*)** (102 mg, 0.333 mmol) in anhydrous acetonitrile (8 mL). After the solution became clear, aldehyde **4** (160 mg, 0.277 mmol) was added. The reaction mixture was allowed to stir for 24 h, and then it was concentrated under reduced pressure. Purification of the residue by silica gel flash chromatography eluting with hexanes/EtOAc (30:1) gave **28** (152 mg,

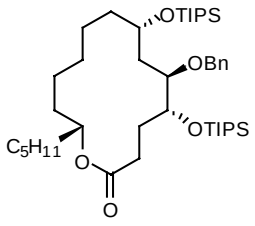
73%) as a colorless oil: $[\alpha]_D^{25}$ +40.5 (c 0.19, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 7.02 (dd, *J* = 15.6, 4.5 Hz, 1H), 6.01 (dd, *J* = 15.6, 1.5 Hz, 1H), 5.87–5.70 (m, 2H), 5.07–4.90 (m, 4H), 4.99 (m, 1H), 4.67 (td, *J* = 4.5, 1.5 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.07 (tt, *J* = 6.9, 4.8 Hz, 1H), 3.81 (ddd, *J* = 9.6, 4.5, 2.7 Hz, 1H), 2.35–2.28 (m, 2H), 2.11–2.00 (m, 2H), 1.78–1.60 (m, 3H), 1.60–1.45 (3H), 1.37–1.18 (m, 6H), 1.12–0.95 (m, 6H), 1.05 (s, 36H), 0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 147.5, 138.5, 138.0, 134.7, 128.3, 127.6, 127.6, 122.3, 117.0, 114.8, 79.5, 73.7, 72.1, 71.7, 69.3, 42.6, 36.8, 34.1, 33.4, 31.7, 29.6, 24.9, 22.5, 18.3, 18.3, 18.1, 18.0, 14.0, 12.9, 12.3; IR (thin film) 3054, 2944, 2867, 1711, 1641, 1463, 1265, 1098, 884 cm^{-1}; MS (ESI) *m/z* $[M + Na]^+$ 779.3; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{45}H_{81}O_5Si_2$: 757.5623, found 757.5640.



(3*E*,5*R*,6*R*,8*S*,10*E*,14*R*)-6-(Benzyloxy)-14-pentyl-5,8-bis(triisopropylsilyloxy)oxacyclotetra-deca-3,10-dien-2-one (3): [44,45]

Ester **28** (150 mg, 0.198 mmol) was dissolved in dry and degassed DCM (250 mL) in a 500 mL round bottom flask. Under vigorous stirring, a solution of Grubbs 1st generation catalyst $[(PCy_3)_2Cl_2Ru{=}CHPh]$ (160 mg, 0.198 mmol) in dichloromethane (15 mL) was added dropwise via syringe over 25 min. After being stirred for 12 h at 23 °C under an atmosphere of argon, the

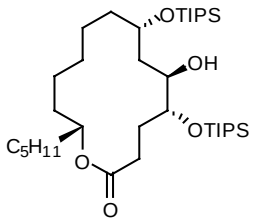
reaction mixture was concentrated under reduced pressure to afford a brown oil, which was subjected to silica gel flash chromatography eluting with hexanes/EtOAc (30:1) to yield an inseparable 6:1 mixture of the *E/Z* isomers (as judged by ^{1}H NMR) **3** (112 mg, 75%) as a yellow/brown oil: $[\alpha]_D^{25}$ +15.3 (c 0.78, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) (the *E*-isomer) δ 7.37–7.27 (m, 5H), 6.80 (dd, *J* = 16.0, 5.0 Hz, 1H), 6.00 (dd, *J* = 16.0, 1.5 Hz, 1H), 5.43 (ddd, *J* = 14.8, 7.9, 4.7 Hz, 1H), 5.27 (ddd, *J* = 14.6, 8.3, 4.5 Hz, 1H), (for the *Z*-isomer: 5.50 (ddd, *J* = 9.7, 6.5, 2.8 Hz, 1H), 5.36 (m, 1H)), 4.94 (m, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.60 (m, 1H), 3.95 (m, 1H), 3.77 (quint, *J* = 4.5 Hz, 1H), 2.38–2.25 (m, 2H), 2.12 (m, 1H), 2.04 (m, 1H), 1.87 (ddd, *J* = 19.0, 10.0, 4.2 Hz, 1H), 1.80 (m, 1H), 1.72–1.62 (m, 2H), 1.55 (m, 1H), 1.49 (ddd, *J* = 15.3, 7.9, 4.2 Hz, 1H), 1.39–1.21 (m, 6H), 1.10–0.95 (m, 42H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0, 147.3, 138.7, 134.5, 128.3, 127.6, 127.5, 125.9, 123.4, 79.0, 75.4, 72.4, 71.6, 68.2, 42.5, 36.3, 34.1, 32.8, 31.7, 28.7, 25.1, 22.5, 18.3, 18.0, 14.0, 12.7, 12.2; IR (thin film) 3054, 2944, 2867, 1712, 1423, 1265, 1108, 895 cm^{-1}; MS (ESI) *m/z* $[M + Na]^+$ 751.3; HRMS (MALDI) *m/z* $[M + Na]^+$ calcd for $C_{43}H_{76}NaO_5Si_2$: 751.5129, found 751.5131.



(5*R*,6*R*,8*S*,14*R*)-6-(Benzyloxy)-14-pentyl-5,8-bis(triisopropylsilyloxy)oxacyclotetradecan-2-

one (30): [10c]

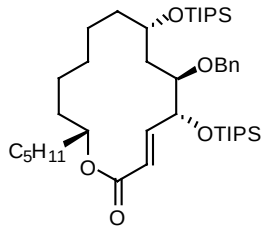
$NH_2NH_2 \cdot H_2O$ (50.0 μL, 1.00 mol) was added to a suspension of **3** (3.0 mg, 0.00412 mmol) and $CuSO_4$ (34.0 mg, 0.213 mmol) in ethanol (2 mL). After being stirred at room temperature for 15 min, the reaction mixture was warmed to 70 °C. After being stirred at 70 °C for 20 h, the reaction was cooled to room temperature. H_2O (1.5 mL) was added, and the reaction mixture was extracted with ether (3x). The organic layers were combined, washed with brine. The combined organic layers were dried over $MgSO_4$. The resulting solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/EtOAc (30:1) to yield **30** (3.4 mg, 100%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H), 4.90 (m, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 3.95 (dt, *J* = 8.7, 3.0 Hz, 1H), 3.88 (t, *J* = 6.0 Hz, 1H), 3.59 (ddd, *J* = 8.1, 5.1, 3.0 Hz, 1H), 2.28 (m, 1H), 2.05 (m, 1H), 1.95 (dt, *J* = 13.5, 5.7 Hz, 1H), 1.79 (dt, *J* = 13.2, 6.6 Hz, 1H), 1.61–1.39 (m, 7H), 1.39–1.17 (m, 13H), 1.13–0.97 (m, 42H), 0.87 (t, *J* = 6.6 Hz, 3H).



(5*R*,6*R*,8*S*,14*R*)-6-Hydroxy-14-pentyl-5,8-bis(triisopropylsilyloxy)oxacyclotetradecan-2-one (31):

Following the same procedure as **32**, lactone **3** (3.0 mg, 0.00411 mmol), Pd/C (5 wt.%) (1.0

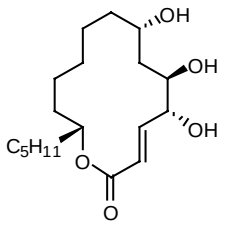
mg catalyst, 0.000470 mmol Pd), ethanol (3 mL) were mixed and the mixture was stirred at 23 °C for 20 h. The title compound **31** was prepared as a colorless oil (2.0 mg, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (m, 1H), 4.09 (m, 1H), 3.89 (d, *J* = 9.9 Hz, 1H), 3.78 (dd, *J* = 9.6, 4.5 Hz, 1H), 2.58 (ddd, *J* = 16.8, 12.6, 4.2 Hz, 1H), 2.44 (dt, *J* = 16.8, 3.9 Hz, 1H), 2.13 (m, 2H), 1.93 (m, 1H), 1.80 (m, 1H), 1.70–1.21 (m, 18H), 1.21–0.95 (m, 42H), 0.87 (t, *J* = 6.6 Hz, 3H).



(5*R*,6*R*,8*S*,14*R*,*E*)-6-(Benzyloxy)-14-pentyl-5,8-bis(triisopropylsilyloxy)oxacyclotetradec-3-en-2-one (32): [44]

A mixture of **3** (10.5 mg, 0.0144 mmol), ethanol (40 mL), and $Pd/BaSO_4$ (5 wt.%) (22.0 mg catalyst, 0.0104 mmol Pd) was placed under a hydrogen atmosphere and stirred at 23 °C for 48 h. The reaction mixture was then filtered and the filtrate was concentrated under reduced pressure to afford a light yellow oil, which was subjected to silica gel flash chromatography eluting with hexanes/EtOAc (30:1) to yield **32** (8.2 mg, 78%) as a colorless oil: $[\alpha]_D^{25}$ +13.3 (c 0.08, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.26 (m, 5H), 6.86 (dd, *J* = 16.0, 5.5 Hz, 1H), 6.08 (dd, *J* = 16.0, 1.5 Hz, 1H), 5.01 (m, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.63 (d, *J* = 11.0 Hz, 1H), 4.62 (t, *J* = 6.0 Hz, 1H), 3.89 (m, 1H), 3.80 (quint, *J* = 4.5 Hz, 1H), 1.73 (m, 2H), 1.71–1.61 (m, 3H), 1.57 (m, 1H), 1.52–1.45 (m, 2H), 1.42 (m, 2H), 1.38–1.15 (m, 10H), 1.10–0.98 (m, 42H), 0.88 (t, *J* =

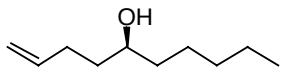
7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 147.5, 138.8, 128.2, 127.5, 127.4, 123.6, 79.2, 75.7, 72.5, 72.3, 69.6, 37.5, 37.4, 34.2, 32.4, 31.7, 30.6, 25.2, 25.0, 24.2, 22.5, 18.3, 18.3, 18.0, 18.0, 14.0, 12.8, 12.2; IR (thin film) 3055, 2986, 2930, 2866, 1712, 1643, 1422, 1265, 896 cm^{-1}; MS (ESI) *m/z* $[M + Na]^+$ 753.5.



(5*R*,6*R*,8*S*,14*R*,*E*)-5,6,8-Trihydroxy-14-pentyloxacyclotetradec-3-en-2-one (2d): [48]

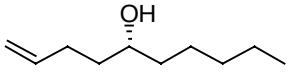
Lactone **32** (5.0 mg, 0.00685 mmol) was dissolved in dry DCM (3 mL) in a 50 mL round bottom flask. Ethane thiol (18.0 μL, 0.234 mmol) was added, and mixture was cooled to –78 °C. Under an atmosphere of argon, BF_3•Et_2O (6.0 μL, 0.0465 mmol) was added via syringe. The reaction mixture was stirred for 20 min and then slowly warmed to 23 °C. A condenser was set up on the top of the flask and the mixture was heated to 32 °C. After 24 h, the reaction was quenched by adding saturated aqueous $NaHCO_3$ (0.5 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over $MgSO_4$. The resulting solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with DCM/MeOH (20:1) to yield **2d** (1.9 mg, 85%), which was further purified by preparative reverse phase HPLC to afford a white solid (1.3 mg, 68% recovery): $[\alpha]_D^{25}$ +12.4 (c 0.056, MeOH); ^{1}H NMR (500 MHz, MeOD-*d*4) δ 7.07 (dd, *J* = 16.0,

5.5 Hz, 1H), 6.12 (dd, *J* = 16.0, 1.5 Hz, 1H), 4.97 (dddd, *J* = 16.5, 9.0, 5.5, 3.5 Hz, 1H), 4.27 (td, *J* = 5.0, 1.0 Hz, 1H), 3.90 (td, *J* = 6.0, 3.0 Hz, 1H), 3.78 (tt, *J* = 8.0, 3.5 Hz, 1H), 1.75–1.71 (m, 2H), 1.71–1.60 (m, 2H), 1.59–1.51 (m, 2H), 1.48–1.18 (m, 14H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, MeOD-*d*4) δ 167.6, 149.6, 123.1, 75.7, 75.2, 73.7, 68.8, 38.1, 35.6, 35.4, 33.5, 32.9, 27.7, 26.4, 25.0, 24.4, 23.6, 14.3; IR (thin film) 3583, 3385, 3020, 2925, 1712, 1431, 1215, 1020 cm^{-1}; MS (ESI) *m/z* [M + Na]$^+$ 351.2; HRMS (MALDI) *m/z* [M + Na]$^+$ calcd for $C_{18}H_{32}NaO_5$: 351.2147, found 351.2143.



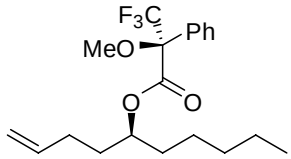
(*S*)-Dec-1-en-5-ol (9-(*S*)):

A solution of **5-(*S*)** (32.0 mg, 0.0958 mmol) in MeOH (1 mL) was added K_2CO_3 (26.5 mg, 0.192 mmol). The mixture was stirred at 23 °C for 5 h before it was concentrated under reduced pressure. Purification of the residue by silica gel flash chromatography eluting with hexanes/EtOAc (4:1) gave **9-(*S*)** (14.0 mg, 94%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.06 (dd, *J* = 17.4, 1.8 Hz, 1H), 4.97 (d, *J* = 10.2 Hz, 1H), 3.62 (m, 1H), 2.19 (m, 2H), 1.65–1.54 (m, 2H), 1.54–1.39 (m, 2H), 1.39–1.20 (m, 6H), 0.89 (t, *J* = 6.6 Hz, 3H).



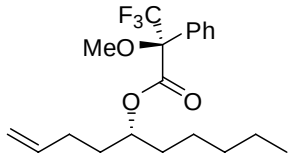
(*R*)-Dec-1-en-5-ol (9-(*R*)):

The same procedure as **9-(*S*)** was followed by employing **5-(*R*)** (30.0 mg, 0.0898 mmol), K_2CO_3 (24.8 mg, 0.180 mmol) and MeOH (1 mL). The title compound **9-(*R*)** was prepared as a colorless oil (11.0 mg, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.05 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.97 (d, *J* = 9.9 Hz, 1H), 3.62 (m, 1H), 2.19 (m, 2H), 1.66–1.52 (m, 2H), 1.52–1.39 (m, 2H), 1.39–1.20 (m, 6H), 0.89 (t, *J* = 6.6 Hz, 3H).



(*S*)-((*S*)-Dec-1-en-5-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (27-(*S*)): [39]

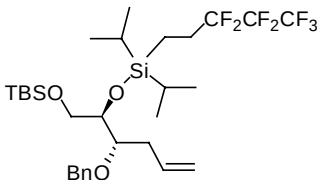
Alcohol **9-(*S*)** (5.0 mg, 0.03201 mmol) was dissolved in DCM (10 mL) in a 50 mL round bottom flask. Pyridine (25.3 mg, 0.320 mmol), (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (81.0 mg, 0.320 mmol) and DMAP (2.0 mg, 0.0160 mmol) were added to the solution. The mixture was stirred for 12 h and ^{19}F NMR was done to determine the *ee*: ^{19}F NMR δ –71.97 (major diastereomer), –71.92 (minor diastereomer), major:minor = 1.00:0.01 (98% *ee*).



(*S*)-((*R*)-dec-1-en-5-yl) 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (27-(*R*)):

Following the same procedure as **27-(*S*)**, alcohol **9-(*R*)** (5.0 mg, 0.03201 mmol) and the same amount of all other reagents were stirred for 12 h and ^{19}F NMR of the mixture was done:

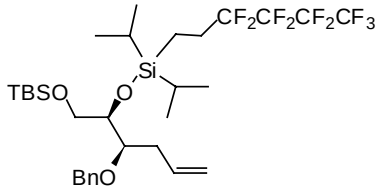
^{19}F NMR δ –71.92 (major diastereomer), –71.97 (minor diastereomer), major:minor = 1.00:0.00 (> 99% *ee*).



(*R*)-6-((*S*)-1-(Benzyloxy)but-3-enyl)-11,11,12,12,13,13,13-heptafluoro-8,8-diisopropyl-2,2,3,3-tetramethyl-4,7-dioxa-3,8-disilatridecane (39-anti-F7): [12,16]

Trifluoromethanesulfonic acid (neat, 1.54 mL, 17.4 mmol) was added to (3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilane (neat, 7.52 g, 24.1 mmol) at 0 °C quickly via syringe. The reaction mixture was slowly warmed to 23 °C and stirred for 16 h. Alcohol **17-anti** (4.50 g, 13.4 mmol) and 2,6-lutidine (3.90 mL, 33.5 mmol) in DCM (150 mL) were added at 0 °C via syringe. The solution was slowly warmed to room temperature and stirred for 24 h before the reaction was quenched with H_2O (100 mL). The reaction mixture was extracted with DCM (3x) and the combined organic extracts were washed with brine, and dried over $MgSO_4$. The crude product was purified by column chromgatography (hexane/EtOAc = 30:1) to afford the title compound **39-anti-F7** (8.50 g, 98%) as a colorless oil: $[\alpha]_D^{25}$ –9.6 (c 0.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.26 (m, 5H), 5.86 (ddt, *J* = 16.8, 9.5, 6.1 Hz, 1H), 5.10 (d, *J* = 16.9 Hz, 1H), 5.04 (d, *J* = 11.6 Hz, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 3.94 (td, *J* = 5.7, 2.4 Hz, 1H), 3.74–3.51 (m, 3H), 2.35 (m, 2H), 2.13 (m, 2H), 1.16–0.93 (m, 14H), 0.88 (s,

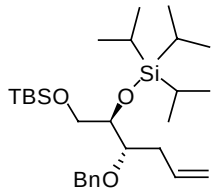
9H), 0.83 (m, 2H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 135.7, 128.2, 127.8, 127.5, 116.7, 80.3, 75.6, 72.3, 64.8, 34.6, 25.9, 18.8, 17.7–17.6 (m), 12.8, 12.6, 0.7, –5.5, –5.6; IR (thin film) 3054, 2950, 2866, 1465, 1353, 1265, 1229, 1181, 1111, 838 cm^{-1}; MS (ESI): *m/z* [M + Na]$^+$ 669.2; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{30}H_{49}F_7NaO_3Si_2$: 669.3006, found 669.2941.



(*R*)-6-((*R*)-1-(Benzyloxy)but-3-enyl)-11,11,12,12,13,13,14,14,14-nonafluoro-8,8-diisopropyl-2,2,3,3-tetramethyl-4,7-dioxa-3,8-disilatetradecane (39-syn-F9):

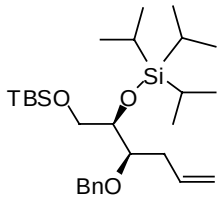
Trifluoromethanesulfonic acid (neat, 1.54 mL, 17.4 mmol) was added to diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silane (neat, 8.73 g, 24.1 mmol) at 0 °C quickly via syringe. The reaction mixture was slowly warmed to room temperature and stirred for 16 h. Alcohol **17-syn** (4.50 g, 13.4 mmol) and 2,6-lutidine (3.90 mL, 33.5 mmol) in DCM (150 mL) were added at 0 °C via syringe. The solution was slowly warmed to room temperature and stirred for 24 h before the reaction was quenched with H_2O (100 mL). The reaction mixture was extracted with DCM (3x) and the combined organic extracts were washed with brine, and dried over $MgSO_4$. The crude product was purified by column chromgatography (hexane/EtOAc = 30:1) to afford the title compound **39-syn-F9** (8.90 g, 95%) as a colorless oil: $[\alpha]_D^{25}$ +8.8 (c 0.16, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.26 (m, 5H), 5.85 (ddt, *J* = 17.1, 9.9, 6.9 Hz, 1H),

5.10 (d, J = 17.1 Hz, 1H), 5.04 (d, J = 10.2 Hz, 1H), 4.60 (d, J = 11.7 Hz, 1H), 4.54 (d, J = 11.7 Hz, 1H), 3.87 (m, 1H), 3.82 (dd, J = 10.2, 3.0 Hz, 1H), 3.55 (dd, J = 10.2, 6.6 Hz, 1H), 3.47 (dt, J = 8.7, 4.2 Hz, 1H), 2.45 (m, 1H), 2.25–2.00 (m, 3H), 1.09–0.98 (m, 14H), 0.88 (s, 9H), 0.85 (m, 2H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 135.7, 128.2, 127.7, 127.5, 116.5, 80.4, 75.0, 72.5, 64.5, 34.1, 25.9, 18.7, 17.6–17.5 (m), 12.9, 12.7, 0.6, –5.6; IR (thin film) 3054, 2951, 2866, 1464, 1423, 1265, 1235, 1132, 1085, 886, 840 cm^{-1}; HRMS (MALDI) *m/z* [M + Na]$^+$ calcd for $C_{31}H_{49}F_9NaO_3Si_2$: 719.2974, found 719.3015.



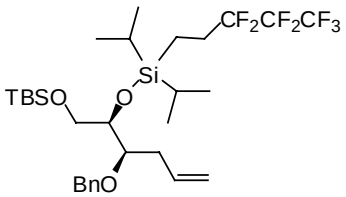
(*R*)-6-((*S*)-1-(Benzyloxy)but-3-enyl)-8,8-diisopropyl-2,2,3,3,9-pentamethyl-4,7-dioxa-3,8-di-siladecane (39-anti-F0):

The same procedure as **7** was followed by employing **17-anti** (10.0 mg, 0.0298 mmol), 2,6-lutidine (10.3 μL, 0.0891 mmol), TIPSOTf (15.9 μL, 0.0595 mmol) and DCM (0.8 mL). The title compound **39-anti-F0** was prepared as a colorless oil (14.0 mg, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 5.91 (ddt, J = 17.1, 10.2, 6.9 Hz, 1H), 5.09 (dd, J = 17.1, 1.8 Hz, 1H), 5.02 (d, J = 10.2 Hz, 1H), 4.67 (d, J = 11.7 Hz, 1H), 4.53 (d, J = 11.7 Hz, 1H), 4.01 (td, J = 5.7, 2.4 Hz, 1H), 3.71–3.60 (m, 3H), 2.38 (m, 2H), 1.18–1.00 (m, 21H), 0.88 (s, 9H), 0.03 (s, 6H).



(*R*)-6-((*R*)-1-(Benzyloxy)but-3-enyl)-8,8-diisopropyl-2,2,3,3,9-pentamethyl-4,7-dioxa-3,8-disiladecane (39-syn-F0):

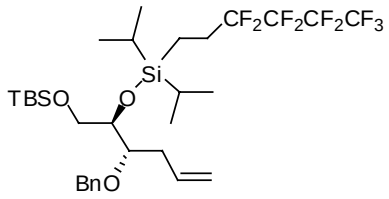
The same procedure as **7** was followed by employing **17-syn** (10.0 mg, 0.0298 mmol), 2,6-lutidine (10.3 μL, 0.0891 mmol), TIPSOTf (15.9 μL, 0.0595 mmol) and DCM (0.8 mL). The title compound **39-syn-F0** was prepared as a colorless oil (15.0 mg, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H), 5.87 (ddt, *J* = 17.1, 10.2, 7.1 Hz, 1H), 5.08 (dd, *J* = 17.1, 1.8 Hz, 1H), 5.02 (d, *J* = 10.2 Hz, 1H), 4.59 (s, 2H), 4.00 (m, 1H), 3.86 (dd, *J* = 10.5, 3.3 Hz, 1H), 3.69 －3.50 (m, 1H), 3.59 (dd, *J* = 10.2, 6.6 Hz, 1H), 2.50 (m, 1H), 2.19 (m, 1H), 1.17–1.02 (m, 21H), 0.89 (s, 9H), 0.04 (s, 6H).



(*R*)-6-((*R*)-1-(Benzyloxy)but-3-enyl)-11,11,12,12,13,13,13-heptafluoro-8,8-diisopropyl-2,2,3,3-tetramethyl-4,7-dioxa-3,8-disilatridecane (39-syn-F7):

The same procedure as **39-anti-F7** was followed by employing **17-syn** (5.0 mg, 0.0149 mmol), 2,6-lutidine (4.3 μL, 0.0372 mmol), trifluoromethanesulfonic acid (1.7 μL, 0.0193

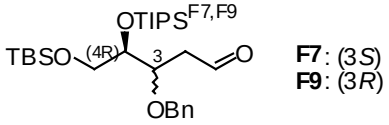
mmol), (3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilane (8.4 mg, 0.0268 mmol) and DCM (0.2 mL). The title compound **39-syn-F7** was prepared as a colorless oil (7.0 mg, 72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H), 5.85 (ddt, *J* = 17.1, 10.2, 7.1 Hz, 1H), 5.08 (d, *J* = 17.1 Hz, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 3.87 (m, 1H), 3.82 (dd, *J* = 10.2, 3.0 Hz, 1H), 3.55 (dd, *J* = 10.2, 6.6 Hz, 1H), 3.47 (dt, *J* = 8.4, 4.2 Hz, 1H), 2.45 (m, 1H), 2.25–1.97 (m, 3H), 1.10–0.92 (m, 14H), 0.89 (s, 9H), 0.85 (m, 2H), 0.04 (s, 3H), 0.04 (s, 3H).



(*R*)-6-((*S*)-1-(Benzyloxy)but-3-enyl)-11,11,12,12,13,13,14,14,14-nonafluoro-8,8-diisopropyl-2,2,3,3-tetramethyl-4,7-dioxa-3,8-disilatetradecane (39-anti-F9):

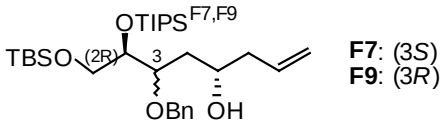
The same procedure as **39-syn-F9** was followed by employing **17-anti** (6.0 mg, 0.0179 mmol), 2,6-lutidine (5.2 μL, 0.0447 mmol), trifluoromethanesulfonic acid (2.1 μL, 0.0232 mmol), diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silane (11.6 mg, 0.0321 mmol) and DCM (0.2 mL). The title compound **39-anti-F9** was prepared as a colorless oil (10.0 mg, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.26 (m, 5H), 5.86 (ddt, *J* = 17.1, 10.2, 7.2 Hz, 1H), 5.10 (d, *J* = 17.4 Hz, 1H), 5.04 (d, *J* = 10.5 Hz, 1H), 4.59 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 11.7 Hz, 1H), 3.93 (td, *J* = 5.7, 3.0 Hz, 1H), 3.67 (dd, *J* = 10.5, 5.7 Hz, 1H), 3.58 (dd, *J* = 10.5, 6.0 Hz, 1H),

3.55 (m, 1H), 2.36 (m, 2H), 2.10 (m, 2H), 1.11–0.92 (m, 14H), 0.88 (s, 9H), 0.83 (m, 2H), 0.03 (s, 6H).



(3*R/S*,4*R*)-3-(Benzyloxy)-4-((perfluoroalkylethyl)diisopropylsilyloxy)-5-(*tert*-butyldimethyl-silyloxy)pentanal (M-42):

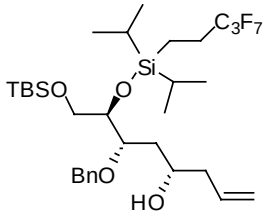
The same procedure as **6** was followed by employing **39-anti-F7** (3.00 g, 4.64 mmol), **39-syn-F9** (3.20 g, 4.59 mmol), DCM (200 mL), and Ph_3P (4.80 g, 18.5 mmol). The title compound **M-42** was prepared as a colorless oil (5.80 g, 93%) with an isomeric ratio of 1.0/0.56 (**42[F7]**/**42[F9]**, based on F-HPLC): ^{1}H NMR (see Appendix); MS (ESI) *m/z* $[M + Na + MeOH]^+$ 703.3 (**42[F7]**), 753.3 (**42[F9]**); HRMS (MALDI) for **42[F7]** *m/z* $[M + K]^+$ calcd for $C_{29}H_{47}F_7KO_4Si_2$: 687.2538, found 687.2567; **42[F9]** *m/z* $[M + K]^+$ calcd for $C_{30}H_{47}F_9KO_4Si_2$: 737.2506, found 737.2501; analytical fluorous HPLC (condition 1) t_R = 18.1 min (**42[F7]**), 23.4 min (**42[F9]**).



(2*R*,3*R/S*,5*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-((perfluoroalkylethyl)diisopropylsilyloxy)-3-(benzyloxy)oct-7-en-5-ol (M-38a):

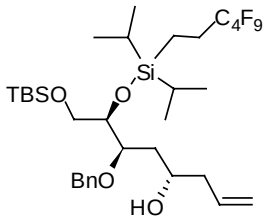
A 500 mL round bottom flask was filled with a mixture of aldehyde **M-42** (2.00 g, 2.97

mmol) followed by dry Et_2O (180 mL). The solution was cooled to –100 °C before (–)-allyldiisopinocampheylborane (1M in pentane, 8.00 mL, 8.00 mmol) was added slowly via syringe. The temperature of the cooling bath was maintained at −100 °C for 15 h, before the reaction was quenched by addition of methanol (2 mL). The solution was warmed to 23 °C overnight before 3 N NaOH (8 mL) and 30% wt. H_2O_2 (16 mL) were added at 0 °C. After 10 min at 0 °C, the mixture was refluxed for 3 h. After cooling to 0 °C, a saturated Na_2SO_3 aqueous solution was added and the aqueous layer was extracted with diethyl ether (2x). The combined organic fractions were dried over $MgSO_4$. The solution was concentrated and the crude mixture was purified by silica gel flash chromatography eluting with pentane/Et_2O (40:1 to 35:1) to yield a mixture of two homoallylic alcohols **M-38a** (1.80 g, 85%) as a colorless oil with an isomeric ratio of 1.0/0.99 (**38a[F7]**/**38a[F9]**, based on F-HPLC): analytical fluorous HPLC (condition 1) t_R = 21.8 min (**38a[F7]**), 26.6 min (**38a[F9]**). A small amount of fluorous mixture **M-38a** (5.0 mg) was subjected to preparative fluorous HPLC with the standard demixing conditions to afford quasidiastereomers **38a[F7]** (1.8 mg) and **38a[F9]** (2.3 mg).



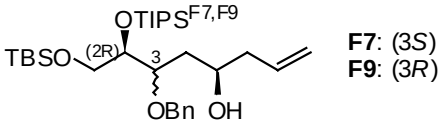
(2*R*,3*S*,5*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-3-(benzyloxy)oct-7-en-5-ol (38a[F7]):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5H), 5.80 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.08 (d, *J* = 17.0 Hz, 1H), 5.06 (d, *J* = 9.5 Hz, 1H), 4.69 (d, *J* = 11.0 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.03 (td, *J* = 13.0, 1.5 Hz, 1H), 3.83—3.77 (m, 2H), 3.58 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.53 (dd, *J* = 10.0, 7.5 Hz, 1H), 3.51 (d, *J* = 1.5 Hz, 1H), 2.24–2.08 (m, 4H), 1.73 (ddd, *J* = 15.0, 9.0, 9.0 Hz, 1H), 1.64 (ddd, *J* = 15.0, 3.0, 3.0 Hz, 1H), 1.05 (s, 12H), 1.04 (m, 2H), 0.89 (m, 2H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); MS (ESI) *m/z* $[M + Na]^+$ 713.3; HRMS (MALDI) *m/z* $[M + Na]^+$ calcd for $C_{32}H_{53}F_7NaO_4Si_2$: 713.3268, found 713.3307.



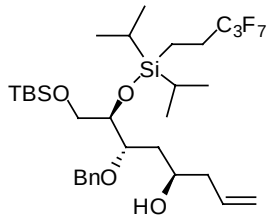
(2*R*,3*R*,5*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)-silyloxy)-3-(benzyloxy)oct-7-en-5-ol (38a[F9]):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 5.80 (ddt, *J* = 17.0, 9.5, 7.0 Hz, 1H), 5.10 (m, 2H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 3.95 (ddd, *J* = 7.0, 4.5, 2.5 Hz, 1H), 3.85 (dd, *J* = 10.5, 2.5 Hz, 1H), 3.78 (m, 1H), 3.75 (ddd, *J* = 17.5, 9.0, 4.0 Hz, 1H), 3.57 (dd, *J* = 9.9, 7.3 Hz, 1H), 2.27–2.08 (m, 4H), 2.15 (d, *J* = 4.0 Hz, 1H), 1.67 (ddd, *J* = 14.0, 9.5, 3.5 Hz, 1H), 1.58 (ddd, *J* = 11.5, 9.0, 2.5 Hz, 1H), 1.07–1.01 (m, 2H), 1.04 (s, 12H), 0.89 (s, 9H), 0.87 (m, 2H), 0.05 (s, 3H), 0.04 (s, 3H); MS (ESI) *m/z* $[M + Na]^+$ 763.3; HRMS (MALDI) *m/z* $[M + Na]^+$ calcd for $C_{33}H_{53}F_9NaO_4Si_2$: 763.3236, found 763.3241.



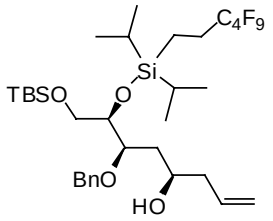
(2*R*,3*R/S*,5*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-((perfluoroalkylethyl)diisopropylsilyloxy)-3-(benzyloxy)oct-7-en-5-ol (M-38b):

A 500 mL round bottom flask was filled with a mixture of aldehyde **M-42** (2.00 g, 2.97 mmol) followed by dry Et_2O (180 mL). The solution was cooled to –100 °C before (+)-allyldiisopinocampheylborane (1M in pentane, 8.00 mL, 8.00 mmol) was added slowly via syringe. The temperature of the cooling bath was maintained at −100 °C for 15 h, before the reaction was quenched by addition of methanol (2 mL). The solution was warmed to 23 °C overnight before 3 N NaOH (8 mL) and 30% wt. H_2O_2 (16 mL) were added at 0 °C. After 10 min at 0 °C, the mixture was refluxed for 3 h. After cooling to 0 °C, a saturated Na_2SO_3 aqueous solution was added and the aqueous layer was extracted with diethyl ether (2x). The combined organic fractions were dried over $MgSO_4$. The solution was concentrated and the crude mixture was purified by silica gel flash chromatography eluting with pentane/Et_2O (40:1 to 35:1) to yield a mixture of two homoallylic alcohols **M-38b** (1.60 g, 75 %) as a colorless oil with an isomeric ratio of 1.0/0.42 (**38b[F7]**/**38b[F9]**, based on F-HPLC): analytical fluorous HPLC (condition 1) t_R = 21.2 min (**38b[F7]**), 26.8 min (**38b[F9]**). A small amount of fluorous mixture **M-38b** (5.0 mg) was subjected to preparative fluorous HPLC with the standard demixing conditions to afford quasidiastereomers **38b[F7]** (2.0 mg) and **38b[F9]** (1.9 mg).



(2*R*,3*S*,5*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-3-(benzyloxy)oct-7-en-5-ol (38b[F7]):

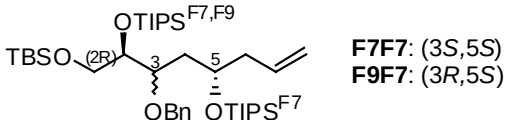
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5H), 5.79 (ddt, *J* = 18.0, 9.5, 7.0 Hz, 1H), 5.09 (m, 2H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.02 (td, *J* = 6.0, 2.5 Hz, 1H), 3.85 (m, 1H), 3.82 (dt, *J* = 9.5, 2.5 Hz, 1H), 3.57 (d, *J* = 6.5 Hz, 2H), 2.21–2.09 (m, 4H), 1.95 (d, *J* = 4.5 Hz, 1H), 1.78 (ddd, *J* = 15.0, 9.5, 2.5 Hz, 1H), 1.49 (ddd, *J* = 14.8, 9.5, 3.0 Hz, 1H), 1.04 (s, 12H), 1.03 (m, 2H), 0.91–0.88 (m, 2H), 0.89 (s, 9H), 0.05 (s, 6H); MS (ESI) *m/z* $[M + Na]^+$ 713.3; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{32}H_{53}F_7NaO_4Si_2$: 713.3268, found 713.3278.



(2*R*,3*R*,5*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-3-(benzyloxy)oct-7-en-5-ol (38b[F9]):

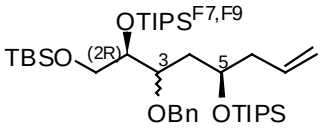
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.24 (m, 5H), 5.77 (ddt, *J* = 17.0, 10.5, 7.0 Hz, 1H), 5.08 (d, *J* = 17.0 Hz, 1H), 5.07 (d, *J* = 9.0 Hz, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.54 (d, *J* = 11.0 Hz, 1H), 4.02 (ddd, *J* = 7.0, 4.5, 2.5 Hz, 1H), 3.86 (dd, *J* = 10.5, 2.5 Hz, 1H), 3.77 (m, 1H), 3.68 (ddd, *J* =

10.0, 4.0, 3.0 Hz, 1H), 3.55 (dd, *J* = 10.5, 7.0 Hz, 1H), 3.32 (d, *J* = 1.5 Hz, 1H), 2.24–2.05 (m, 4H), 1.88 (ddd, *J* = 14.5, 3.0, 3.0 Hz, 1H), 1.48 (ddd, *J* = 15.0, 10.0, 10.0 Hz, 1H), 1.07—1.02 (m, 2H), 1.03 (s, 12H), 0.90 (s, 9H), 0.88 (m, 2H), 0.06 (s, 3H), 0.05 (s, 3H); MS (ESI) *m/z* [M + Na]$^+$ 763.3; HRMS (MALDI) *m/z* [M + Na]$^+$ calcd for $C_{33}H_{53}F_9NaO_4Si_2$: 763.3236, found 763.3183.



(2*R*,3*R*/*S*,5*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-((perfluoroalkylethyl)diisopropylsilyloxy)-3-(benzyloxy)-5-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)oct-7-en (M-37a):

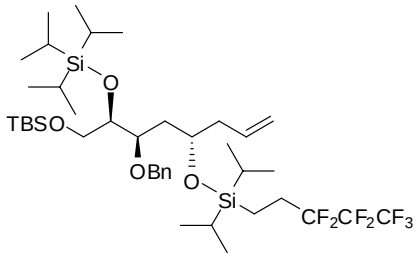
The same procedure as **39-anti-F7** was followed by employing **M-38a** (1.80 g, 2.52 mmol), 2,6-lutidine (0.88 mL, 7.55 mmol), trifluoromethanesulfonic acid (0.33 mL, 3.78 mmol), (3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilane (1.42 g, 4.53 mmol) and DCM (30 mL). The title compound **M-37a** was prepared as a colorless oil (2.50 g, 97%) with an isomeric ratio of 1.0/1.1 (**37a[F7F7]**/**37a[F9F7]**, based on F-HPLC): ^{1}H NMR (see appendix); MS (ESI) *m/z* [M + Na]$^+$ 1023.3 (**37a[F7F7]**), 1073.3 (**37a[F9F7]**); HRMS (MALDI) for **37a[F7F7]** *m/z* [M + Na]$^+$ calcd for $C_{43}H_{70}F_{14}NaO_4Si_3$: 1023.4256, found 1023.4196; **37a[F9F7]** *m/z* [M + Na]$^+$ calcd for $C_{44}H_{70}F_{16}NaO_4Si_3$: 1073.4224, found 1073.4252; analytical fluorous HPLC (condition 1) t_R = 47.7 min (**37a[F7F7]**), 54.1 min (**37a[F7F7]**).



F7F0: (3*S*,5*R*)
F9F0: (3*R*,5*R*)

(2*R*,3*R/S*,5*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-((perfluoroalkylethyl)diisopropylsilyloxy)-3-(benzyloxy)-5-(triisopropylsilyloxy)oct-7-en (M-37b):

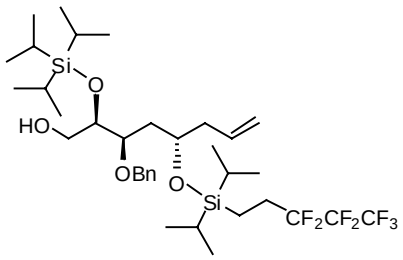
The same procedure as **7** was followed by employing **M-38b** (1.60 g, 2.24 mmol), 2,6-lutidine (0.72 g, 6.71 mmol), TIPSOTf (1.03 g, 3.54 mmol) and DCM (30 mL). The title compound **M-37b** was prepared as a colorless oil (1.80 g, 92%) with an isomeric ratio of 1.0/0.54 (**37b[F7F0]**/**37b[F9F0]**, based on F-HPLC): ^{1}H NMR (see appendix); MS (ESI) *m/z* [M + Na]$^+$ 869.3 (**37b[F7F0]**), 919.3 (**37b[F9F0]**); HRMS (MALDI) for **37b[F7F0]** *m/z* [M + Na]$^+$ calcd for $C_{41}H_{73}F_7NaO_4Si_3$: 869.4603, found 869.4623; **37b[F9F0]** *m/z* [M + Na]$^+$ calcd for $C_{42}H_{73}F_9NaO_4Si_3$: 919.4571, found 919.6423; analytical fluorous HPLC (condition 1) t_R = 39.1 min (**37b[F7F0]**), 42.8 min (**37b[F9F0]**).



(6*R*,7*R*,9*S*)-9-Allyl-7-(benzyloxy)-14,14,15,15,16,16,16-heptafluoro-11,11-diisopropyl-2,2,3,3-tetramethyl-6-(triisopropylsilyloxy)-4,10-dioxa-3,11-disilahexadecane (49):

The same procedure as **39-anti-F7** was followed by employing **20a** (500 mg, 0.931 mmol), 2,6-lutidine (300 mg, 2.79 mmol), trifluoromethanesulfonic acid (210 mg, 1.40 mmol),

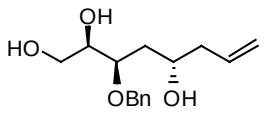
(3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilane (523 mg, 1.68 mmol) and DCM (200 mL). The title compound **49** was prepared as a colorless oil (560 mg, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.24 (m, 5H), 5.78 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.04 (d, *J* = 11.7 Hz, 1H), 5.03 (d, *J* = 15.3 Hz, 1H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.11–4.98 (m, 2H), 3.85 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.74 (dt, *J* = 10.8, 3.6 Hz, 1H), 3.55 (dd, *J* = 10.2, 6.6 Hz, 1H), 2.30 (m, 2H), 2.10 (m, 2H), 1.76 (m, 1H), 1.64 (ddd, *J* = 14.4, 10.2, 4.2 Hz, 1H), 1.20–0.98 (m, 35H), 0.89 (m, 11H), 0.03 (s, 3H), 0.02 (s, 6H).



(2*R*,3*R*,5*S*)-3-(Benzyloxy)-5-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-2-(triiso-propylsilyloxy)oct-7-en-1-ol (50):

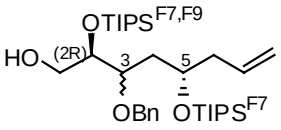
The same procedure as **M-47** was followed by employing **49** (490 mg, 0.578 mmol), hydrochloric acid (1 M in H_2O) (0.58 mL, 0.578 mmol) and EtOH (40 mL). The mixture was stirred for 4 h at 23 °C. The title compound **50** was prepared as a yellow oil (107 mg, 25%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 5.78 (m, 1H), 5.06 (d, *J* = 11.4 Hz, 1H), 5.05 (d, *J* = 15.9 Hz, 1H), 4.67 (d, *J* = 11.1 Hz, 1H), 4.53 (d, *J* = 11.1 Hz, 1H), 4.20 (dt, *J* = 6.6, 4.5 Hz, 1H), 4.08 (m, 1H), 3.85 (ddd, *J* = 9.9, 4.0, 3.0 Hz, 1H), 3.77 (ddd, *J* = 9.6, 6.9, 2.7 Hz, 1H), 3.68 (ddd, *J* = 12.9, 8.1, 4.5 Hz, 1H), 2.46 (dd, *J* = 8.2, 3.0 Hz, 1H), 2.32 (m, 2H), 2.10 (m, 2H), 1.84

(ddd, J = 14.4, 8.1, 3.0 Hz, 1H), 1.74 (ddd, J = 14.4, 10.2, 4.8 Hz, 1H), 1.27–0.95 (m, 35H), 0.86 (m, 2H).



(2*R*,3*R*,5*S*)-3-(Benzyloxy)oct-7-ene-1,2,5-triol (53): [56,57]

Silyl ether **50** (10.2 mg, 0.0120 mmol) was dissolved in THF (2 mL) in a 50 mL round bottom flask. The solution was cooled to –78 °C before TBAF (1 M in THF) (12.0 μL, 0.0120 mmol) was added. The mixture was stirred for 4 h at –78 °C and then warmed to 10 °C over 12 h. The mixture was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/Et_2O (1:1) to yield **53** (1.9 mg, 59%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.25 (m, 5H), 5.80 (m, 1H), 5.15 (d, J = 10.0 Hz, 1H), 5.14 (d, J = 17.5 Hz, 1H), 4.73 (d, J = 11.5 Hz, 1H), 4.59 (d, J = 11.5 Hz, 1H), 3.87 (m, 1H), 3.79 (dt, J = 12.0, 5.0 Hz, 1H), 3.75 (dt, J = 11.0, 5.0 Hz, 1H), 3.70 (m, 1H), 3.64 (dd, J = 11.5, 6.0 Hz, 1H), 2.32–2.19 (m, 2H), 1.79 (ddd, J = 14.5, 7.0, 2.5 Hz, 1H), 1.73 (ddd, J = 15.0, 9.5, 5.0 Hz, 1H).

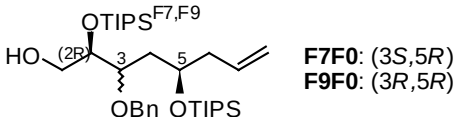


F7F7: (3*S*,5*S*)
F9F7: (3*R*,5*S*)

(2*R*,3*R/S*,5*S*)-2-((Perfluoroalkylethyl)diisopropylsilyloxy)-3-(benzyloxy)-5-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)oct-7-en-1-ol (M-47):[52]

A 250 mL round bottom flask was filled with EtOH (80 mL), followed by **M-37a** (1.05 g,

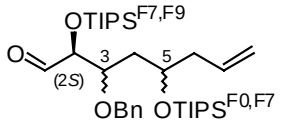
1.02 mmol). Hydrochloric acid (1 M in H_2O) (1.02 mL, 1.02 mmol) was added. The reaction was stirred for 4.5 hours at 23 °C and was carefully monitored by TLC. The reaction was quenched by slowly adding buffer solution (pH = 7, 30 mL). The layers were separated and the aqueous layer was extracted with DCM (3x). The combined organic layers were dried over $MgSO_4$. The resulting solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/EtOAc (20:1) to yield **M-47** (165 mg, 18%) with an isomeric ratio of 1.0/1.2 (**47[F7F7]**/**47[F9F7]**, based on ^{19}F NMR; 1.0/1.2 based on F-HPLC) as a yellow oil: ^1H NMR (see appendix); MS (ESI) *m/z* $[M + Na]^+$ 909.2 (**47[F7F7]**), 959.2 (**47[F9F7]**); HRMS (MALDI) for **47[F7F7]** *m/z* $[M + Na]^+$ calcd for $C_{37}H_{56}F_{14}NaO_4Si_2$: 909.3391, found 909.3353; **47[F9F7]** *m/z* $[M + Na]^+$ calcd for $C_{38}H_{56}F_{16}NaO_4Si_2$: 959.3359, found 959.3391; analytical fluorous HPLC (condition 2) t_R = 3.6 min (**47[F7F7]**), 4.4 min (**47[F9F7]**).



(2*R*,3*R/S*,5*R*)-2-((Perfluoroalkylethyl)diisopropylsilyloxy)-3-(benzyloxy)-5-(triisopropylsily-loxy)oct-7-en-1-ol (M-54):

The same procedure as **M-47** was followed by employing **M-37b** (190 mg, 0.218 mmol), hydrochloric acid (1 M in H_2O) (0.22 mL, 0.218 mmol), and EtOH (15 mL). The mixture was stirred for 7 h at 23 °C. The title compound **M-54** was prepared as a yellow oil (88.0 mg, 53%),

with an isomeric ratio of 1.0/0.74 (**54[F7F0]**/**54[F9F0]**, based on ^{19}F NMR; 1.0/0.79 based on F-HPLC): ^{1}H NMR (see appendix); MS (ESI) *m/z* [M + Na]$^{+}$ 755.3 (**54[F7F0]**), 805.3 (**54[F9F0]**); HRMS (MALDI) for **54[F7F0]** *m/z* [M + Na]$^{+}$ calcd for $C_{35}H_{59}F_7NaO_4Si_2$: 755.3738, found 755.3723; **54[F9F0]** *m/z* [M + Na]$^{+}$ calcd for $C_{36}H_{59}F_9NaO_4Si_2$: 805.3706, found 805.3636; analytical fluorous HPLC (condition 2) t_R = 2.5 min (**54[F7F0]**), 2.8 min (**54[F9F0]**).

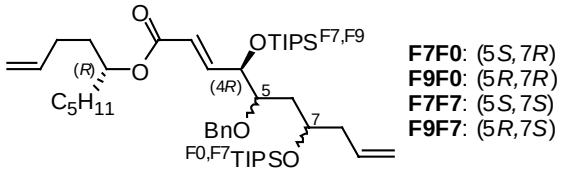


F7F0: (3*S*,5*R*)
F9F0: (3*R*,5*R*)
F7F7: (3*S*,5*S*)
F9F7: (3*R*,5*S*)

(2*S*,3*R*/*S*,5*R*/*S*)-3-(Benzyloxy)-2,5-bis((perfluoroalkylethyl)diisopropylsilyloxy)oct-7-enal (M-36):[60]

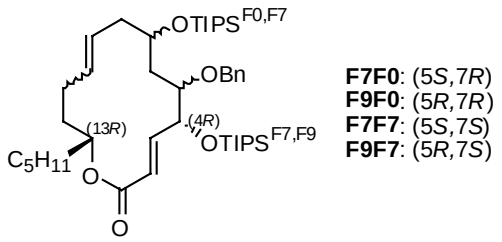
Alcohols **M-47** (106 mg, 0.116 mmol) and **M-54** (87.0 mg, 0.115 mmol) were dissolved in dry DCM (25 mL) in a 50 mL round bottom flask. Dess-Martin periodinane (196 mg, 0.462 mmol) was added to the solution. The reaction was stirred for 2 h. The solution was filtered through a pad of silica gel and then concentrated under reduced pressure to yield **M-36** (160 mg, 83%) with an isomeric ratio of 1.0/0.85/1.3/1.4 (**36[F7F0]**/**36[F9F0]**/**36[F7F7]**/**36[F9F7]**, based on F-HPLC) as a colorless oil: ^{1}H NMR (see appendix); MS (ESI) *m/z* [M + Na]$^{+}$ 753.3 (**36[F7F0]**), 803.2 (**36[F9F0]**), 907.3 (**36[F7F7]**), 957.3 (**36[F9F7]**); HRMS (MALDI) for **36[F7F0]** *m/z* [M + Na]$^{+}$ calcd for $C_{35}H_{57}F_7NaO_4Si_2$: 753.3581, found 753.3495; **36[F9F0]** *m/z* [M + Na]$^{+}$ calcd for $C_{36}H_{57}F_9NaO_4Si_2$: 803.3549, found 803.3471; **36[F7F7]** *m/z* [M + Na]$^{+}$

calcd for $C_{37}H_{54}F_{14}NaO_4Si_2$: 907.3235, found 907.3276; **36[F9F7]** *m/z* $[M + Na]^+$ calcd for $C_{38}H_{54}F_{16}NaO_4Si_2$: 957.3203, found 957.3179; analytical fluorous HPLC (condition 2) t_R = 3.8 min (**36[F7F0]**), 4.6 min (**36[F9F0]**), 7.0 min (**36[F7F7]**), 9.2 min (**36[F9F7]**).



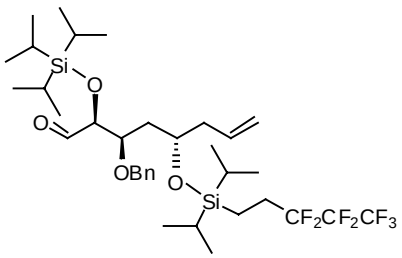
(4*R*,5*R*/*S*,7*R*/*S*,*E*)-((*R*)-Dec-1-en-5-yl)-5-(benzyloxy)-4,7-bis((perfluoroalkylethyl)diisopropylsilyloxy)deca-2,9-dienoate (M-56):

The same procedure as **28** was followed by employing LiCl **(**9.7 mg, 0.229 mmol), phosphonate **5-(*R*)** (76.6 mg, 0.229 mmol), anhydrous acetonitrile (15 mL), DBU (29.1 mg, 0.191 mmol) and aldehyde **M-36** (159 mg, 0.191 mmol). The title compound **M-56** was prepared as a colorless oil (146 mg, 76%), with an isomeric ratio of 1.0/0.46/1.1/0.71 (**56[F7F0]**/**56[F9F0]**/**56[F7F7]**/**56[F9F7]**, based on F-HPLC): ^{1}H NMR (see appendix); HRMS (MALDI) for **56[F7F0]** *m/z* $[M + Na]^+$ calcd for $C_{47}H_{77}F_7NaO_5Si_2$: 933.5095, found 933.5176; **56[F9F0]** *m/z* $[M + Na]^+$ calcd for $C_{48}H_{77}F_9NaO_5Si_2$: 983.5064, found 983.5159; **56[F7F7]** *m/z* $[M + Na]^+$ calcd for $C_{49}H_{74}F_{14}NaO_5Si_2$: 1087.4749, found 1087.4863; **56[F9F7]** *m/z* $[M + Na]^+$ calcd for $C_{50}H_{74}F_{16}NaO_5Si_2$: 1137.4717, found 1137.4756; analytical fluorous HPLC (condition 2) t_R = 3.7 min (**56[F7F0]**), 4.5 min (**56[F9F0]**), 6.5 min (**56[F7F7]**), 9.0 min (**56[F9F7]**).



(2*E*,4*R*,5*R/S*,7*R/S*,9*E/Z*,13*R*)-5-(Benzyloxy)-13-pentyl-4,7-bis((perfluoroalkylethyl)diiso-propylsilyloxy)oxacyclotetradeca-2,9-dien-1-one (M-35):

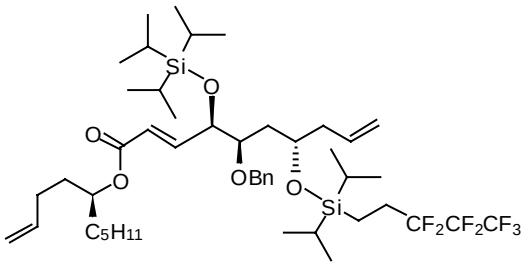
The same procedure as **3** was followed by employing **M-56** (135 mg, 0.133 mmol), Grubbs 1st generation catalyst [$(PCy_3)_2Cl_2Ru$=CHPh] (110 mg, 0.133 mmol) and anhydrous DCM (156 mL, and another 10 mL to dissolve the catalyst). The title compound **M-35** was prepared as a yellow/brown oil (112 mg, 75%) with an isomeric ratio of 1.0/0.32/0.65/0.57 (**35[F7F0]**/**35[F9F0]**/**35[F7F7]**/**35[F9F7]**, based on F-HPLC): ^{1}H NMR (see appendix); MS (ESI) *m/z* [M + Na]$^+$ 905.5 (**35[F7F0]**), 955.5 (**35[F9F0]**), 1059.5 (**35[F7F7]**), 1109.5 (**35[F9F7]**); analytical fluorous HPLC (condition 1, listed as major peaks) t_R = 32.7 min (**35[F7F0]**), 35.0 min (**35[F9F0]**), 44.5 min (**35[F7F7]**), 51.6 min (**35[F9F7]**).



(2*S*,3*R*,5*S*)-3-(Benzyloxy)-5-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-2-(triiso-propylsilyloxy)oct-7-enal (58):

The same procedure as **M-36** was followed by employing **50** (106 mg, 0.145 mmol),

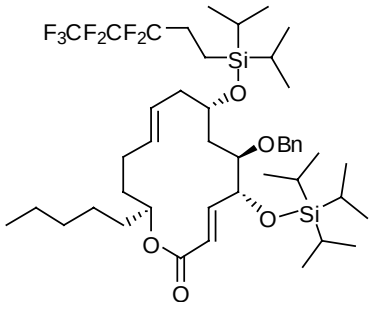
Dess-Martin periodinane (123 mg, 0.289 mmol) and dry DCM (15 mL). The title compound **58** was prepared as a colorless oil (89.0 mg, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (d, *J* = 1.8 Hz, 1H), 7.34–7.26 (m, 5H), 5.78 (ddt, *J* = 16.2, 11.1, 7.2 Hz, 1H), 5.05 (d, *J* = 10.8 Hz, 1H), 5.04 (d, *J* = 16.5 Hz, 1H), 4.70 (d, *J* = 11.4 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.35 (dd, *J* = 4.5, 1.8 Hz, 1H), 4.06 (m, 1H), 3.94 (ddd, *J* = 10.5, 4.5, 2.4 Hz, 1H), 2.28 (m, 2H), 2.11 (m, 2H), 1.85 (ddd, *J* = 14.1, 8.4, 2.4 Hz, 1H), 1.67 (ddd, *J* = 14.1, 10.5, 3.6 Hz, 1H), 1.15–0.92 (m, 35H), 0.86 (m, 2H).



(4*R*,5*R*,7*S*,*E*)-((*S*)-Dec-1-en-5-yl)-5-(benzyloxy)-7-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-4-(triisopropylsilyloxy)deca-2,9-dienoate (59):

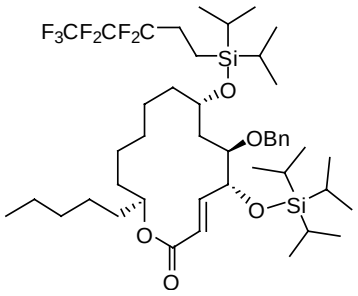
The same procedure as **28** was followed by employing LiCl **(**6.1 mg, 0.145 mmol), phosphonate **5-(*S*)** (48.3 mg, 0.145 mmol), anhydrous acetonitrile (10 mL), DBU (18.3 mg, 0.120 mmol) and aldehyde **58** (88.0 mg, 0.120 mmol). The title compound **59** was prepared as a colorless oil (98.0 mg, 89%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 7.01 (dd, *J* = 15.5, 4.5 Hz, 1H), 6.02 (dd, *J* = 15.5, 1.5 Hz, 1H), 5.78 (m, 2H), 5.00 (m, 4H), 4.69 (dd, *J* = 4.5, 1.5 Hz, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.04 (m, 1H), 3.77 (ddd, *J* =

10.0, 4.0, 2.0 Hz, 1H), 2.28 (t, *J* = 6.0 Hz, 2H), 2.15–2.02 (m, 4H), 1.82 (m, 1H), 1.74 (ddd, *J* = 14.5, 8.0, 2.5 Hz, 1H), 1.66 (m, 2H), 1.50 (m, 1H), 1.33–1.24 (m, 7H), 1.15–0.95 (m, 35H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.83 (m, 2H).



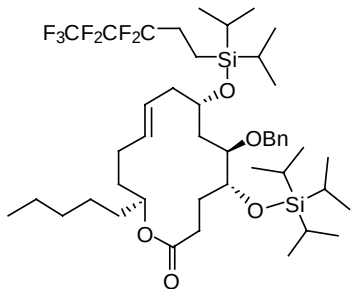
(3*E*,5*R*,6*R*,8*S*,10*E*,14*S*)-6-(Benzyloxy)-8-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-14-pentyl-5-(triisopropylsilyloxy)oxacyclotetradeca-3,10-dien-2-one (60):

The same procedure as **3** was followed by employing **59** (97.0 mg, 0.107 mmol), Grubbs 1st generation catalyst [$(PCy_3)_2Cl_2Ru$=CHPh] (87.6 mg, 0.107 mmol), anhydrous DCM (123 mL, and another 10 mL to dissolve the catalyst). The title compound **60** was prepared as a yellow/brown oil (72 mg, 77%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.26 (m, 5H), 6.96 (dd, *J* = 16.0, 3.0 Hz, 1H), 6.02 (dd, *J* = 16.0, 1.5 Hz, 1H), 5.41 (ddd, *J* = 15.5, 6.0, 6.0 Hz, 1H), 5.29 (ddd, *J* = 15.5, 8.0, 6.0 Hz, 1H), 4.99 (m, 1H), 4.69 (t, *J* = 4.5 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 3.87 (m, 1H), 3.68 (dt, *J* = 10.5, 4.5 Hz, 1H), 2.42 (m, 1H), 2.32 (m, 1H), 2.17–2.01 (m, 4H), 1.97 (ddd, *J* = 14.3, 10.1, 6.9 Hz, 1H), 1.85 (m, 1H), 1.69 (m, 2H), 1.55 (m, 1H), 1.41 (dt, *J* = 13.7, 4.0 Hz, 1H), 1.37–1.25 (m, 6H), 1.10–0.92 (m, 35H), 0.88 (t, *J* = 6.5 Hz, 3H), 0.78 (m, 2H).



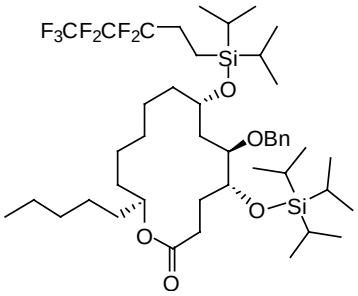
(5*R*,6*R*,8*S*,14*S*,*E*)-6-(Benzyloxy)-8-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-14-pentyl-5-(triisopropylsilyloxy)oxacyclotetradec-3-en-2-one (61):

A magnetically stirred solution of **60** (8.0 mg, 0.00906 mmol) in ethanol (8 mL) containing $Pd/SrCO_3$ (2 wt.%) (48.2 mg catalyst, 0.00906 mmol Pd) was placed under a hydrogen atmosphere at 23 °C for 1.5 h. The reaction was carefully monitored by TLC and was stopped before it was complete. The suspension was then filtered and the filtrate was concentrated under reduced pressure to afford a light yellow oil which was then subjected to silica gel flash chromatography eluting with hexanes/EtOAc (40:1) to yield the title compound **61** (4.4 mg, 55%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 7.10 (dd, *J* = 16.0, 3.0 Hz, 1H), 6.10 (dd, *J* = 16.0, 2.0 Hz, 1H), 4.99 (m, 1H), 4.72 (t, *J* = 2.0 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 3.91 (m, 1H), 3.70 (dt, *J* = 9.5, 5.0 Hz, 1H), 2.06 (m, 2H), 1.84 (ddd, *J* = 14.8, 9.7, 5.0 Hz, 1H), 1.66 (m, 1H), 1.65–1.40 (m, 3H), 1.39–1.15 (m, 15H), 1.15–0.90 (m, 35H), 0.88 (t, *J* = 6.5 Hz, 3H), 0.77 (m, 2H).



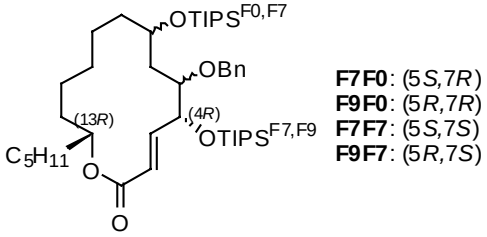
(5*R*,6*R*,8*S*,14*S*,*E*)-6-(Benzyloxy)-8-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-14-pentyl-5-(triisopropylsilyloxy)oxacyclotetradec-10-en-2-one (62): [10c]

Anhydrous hydrazine (18.1 mg, 0.566 mol) was added to a suspension of **60** (5.0 mg, 0.00566 mmol) and $CuSO_4$ (5.1 mg, 0.0566 mmol) in ethanol (0.5 mL). After being stirred at room temperature for 15 min, the reaction mixture was warmed to 70 °C. After being stirred at 70 °C for 20 h, the reaction was cooled to room temperature. H_2O (1.5 mL) was added, and the reaction mixture was extracted with ether (3x). The organic layers were combined, washed with brine. The combined organic layers were dried over $MgSO_4$. The resulting solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/EtOAc (30:1) to yield **62** (2.1 mg, 42%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.26 (m, 5H), 5.45 (ddd, *J* = 15.6, 6.8, 6.8 Hz, 1H), 5.34 (ddd, *J* = 15.3, 7.5, 7.5 Hz, 1H), 4.97 (m, 1H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.16 (dt, *J* = 9.3, 3.1 Hz, 1H), 4.01 (m, 1H), 3.72 (dt, *J* = 12.3, 3.1 Hz, 1H), 2.56–1.95 (m, 10H), 1.75 (m, 1H), 1.61 (m, 1H), 1.50 (m, 2H), 1.35–1.20 (m, 8H), 1.09–0.92 (m, 35H), 0.86 (t, *J* = 6.3 Hz, 3H), 0.82 (m, 2H).



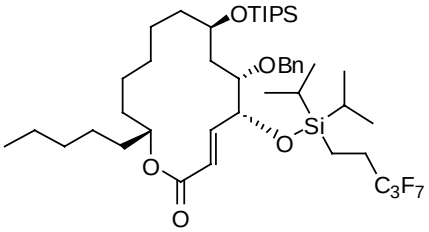
(5*R*,6*R*,8*S*,14*S*)-6-(Benzyloxy)-8-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-14-pentyl-5-(triisopropylsilyloxy)oxacyclotetradecan-2-one (63):

Following the same procedure as **61**, lactone **60** (8.7 mg, 0.00985 mmol), Pd/$SrCO_3$ (2 wt.%) (52.4 mg catalyst, 0.00985 mmol Pd) and ethanol (8 mL) were mixed and the mixture was stirred at 23 °C for 24 h. The filtered and concentrated crude mixture was subjected to the preparative fluorous HPLC with the standard demixing conditions to afford the title compound **63** (3.5 mg, 40%) and **61** (2.0 mg, 23%) as colorless oils: ^{1}H NMR (**63**) (500 MHz, $CDCl_3$) δ 7.35–7.28 (m, 5H), 4.89 (m, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.09 (dt, *J* = 9.5, 3.5 Hz, 1H), 3.98 (quint, *J* = 6.0 Hz, 1H), 3.61 (ddd, *J* = 8.0, 5.0, 3.5 Hz, 1H), 2.55 (dt, *J* = 16.6, 5.9 Hz, 1H), 2.37 (ddd, *J* = 16.0, 9.2, 6.9 Hz, 1H), 2.14–1.97 (m, 4H), 1.87 (ddd, *J* = 15.1, 9.2, 6.5 Hz, 1H), 1.82 (dt, *J* = 14.0, 5.7 Hz, 1H), 1.69 (m, 1H), 1.57 (m, 2H), 1.50–1.39 (m, 5H), 1.39–1.20 (m, 10H), 1.11–0.90 (m, 35H), 0.87 (t, *J* = 6.5 Hz, 3H), 0.82 (m, 2H).



(2*E*,4*R*,5*R/S*,7*R/S*,13*R*)-5-(Benzyloxy)-13-pentyl-4,7-bis((perfluoroalkylethyl)diisopropylsil-yloxy)oxacyclotetradec-2-en-1-one (M-64): [63]

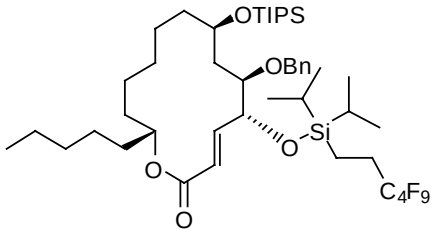
A mixture of **M-35** (15.0 mg, 0.0152 mmol), ethanol (6.5 mL) and Pd/$SrCO_3$ (2 wt.%) (81.0 mg catalyst, 0.0152 mmol Pd) was placed under a hydrogen atmosphere and stirred at 23 °C for 24 h. The reaction was carefully monitored by analytical fluorous HPLC (condition 1): t_R = 42.4 min (**64[F7F0]**), 44.4 min (**64[F9F0]**), 54.9 min (**64[F7F7]**), 63.1 min (**64[F9F7]**). The reaction mixture was then filtered and the filtrate was concentrated under reduced pressure to afford a light yellow oil which was subjected to preparative fluorous HPLC with the standard demixing conditions. Demixing of the crude product (16.0 mg) afforded quasidiastereomers **64[F7F0]** (3.3 mg), **64[F9F0]** (2.4 mg), **64[F7F7]** (2.9 mg), **64[F9F7]** (3.5 mg) as colorless oils. The yield of the reaction was 81% (based on the total weight of four products: 12.1 mg) and the recovery of the demixing was 76%. Characterizations of the four products are shown below.



(4*R*,5*S*,7*R*,13*R*,*E*)-5-(Benzyloxy)-4-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-13-pentyl-7-(triisopropylsilyloxy)oxacyclotetradec-2-en-1-one (64[F7F0]):

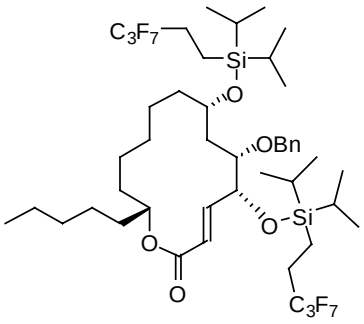
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.20 (m, 5H), 6.67 (dd, *J* = 16.0, 7.5 Hz, 1H), 5.76 (dd, *J* = 16.0, 1.0 Hz, 1H), 4.87 (m, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J*

= 7.5 Hz, 1H), 3.90 (m, 1H), 3.40 (td, *J* = 4.0, 1.0 Hz, 1H), 2.26–2.02 (m, 2H), 1.81 (ddd, *J* = 14.5, 7.0, 5.0 Hz, 1H), 1.65–1.55 (m, 3H), 1.50 (m, 1H), 1.41 (m, 1H), 1.38–1.20 (m, 12H), 1.20–1.09 (m, 2H), 1.09–0.96 (m, 35H), 0.85 (t, *J* = 7.5 Hz, 3H), 0.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 147.8, 137.9, 128.2, 127.7, 127.4, 122.2, 79.4, 75.7, 75.2, 71.5, 70.0, 37.2, 36.4, 35.7, 35.4, 31.7, 27.8, 27.4, 25.2, 24.8, 24.1, 22.5, 18.2 (m), 17.5 (m), 13.9, 12.6 (m), 0.4.



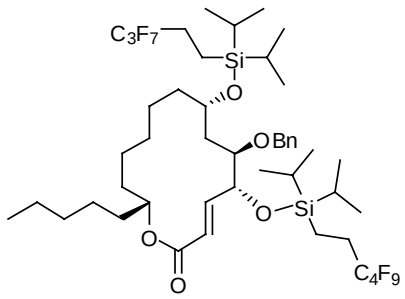
(4*R*,5*R*,7*R*,13*R*,*E*)-5-(Benzyloxy)-4-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-13-pentyl-7-(triisopropylsilyloxy)oxacyclotetradec-2-en-1-one (64[F9F0]):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.22 (m, 5H), 6.76 (dd, *J* = 16.0, 8.0 Hz, 1H), 6.00 (d, *J* = 16.0, 1H), 5.08 (m, 1H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.26 (t, *J* = 8.0 Hz, 1H), 3.78 (tt, *J* = 9.5, 5.0 Hz, 1H), 3.29 (td, *J* = 7.5, 3.0 Hz, 1H), 2.22–2.01 (m, 2H), 1.80–1.60 (m, 2H), 1.50–1.40 (m, 2H), 1.40–1.15 (m, 16H), 1.15–0.94 (m, 35H), 0.85 (t, *J* = 6.0 Hz, 3H), 0.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 146.6, 138.5, 128.2, 127.9, 127.5, 124.8, 81.2, 77.3, 75.9, 74.0, 68.8, 38.0, 34.5, 33.1, 31.6, 31.5, 30.3, 25.3, 25.2, 24.3, 22.5, 21.4, 18.1 (m), 17.5 (m), 13.9, 12.5 (m), 0.5.



(4*R*,5*S*,7*S*,13*R*,*E*)-5-(Benzyloxy)-4,7-bis((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-13-pentyloxacyclotetradec-2-en-1-one (64[F7F7]):

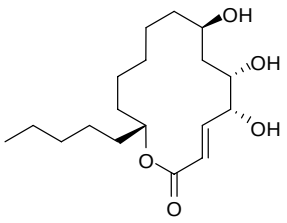
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 6.79 (dd, *J* = 16.0, 7.0 Hz, 1H), 5.87 (dd, *J* = 16.0, 1.0 Hz, 1H), 4.89 (m, 1H), 4.66 (d, *J* = 7.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.36 (d, *J* = 12.0 Hz, 1H), 3.65 (m, 1H), 2.97 (d, *J* = 7.5 Hz, 1H), 2.27–2.00 (m, 4H), 1.95 (dd, *J* = 14.9, 10.3 Hz, 1H), 1.61 (m, 2H), 1.40 (m, 1H), 1.36–1.22 (m, 14H), 1.17 (m, 2H), 1.09–0.91 (m, 28H), 0.87 (t, *J* = 6.5 Hz, 3H), 0.81 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 148.2, 137.6, 128.4, 128.2, 127.9, 122.1, 80.7, 75.8, 72.4, 71.3, 69.4, 37.2, 35.1, 34.1, 32.1, 31.7, 28.2, 25.7, 25.3, 25.0, 24.9, 22.5, 20.0, 17.5 (m), 13.9, 12.6 (m), 0.4, 0.3.



(4*R*,5*R*,7*S*,13*R*,*E*)-5-(Benzyloxy)-4-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-7-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-13-pentyloxacyclotetradec-2-en-1-

one (64[F9F7]):

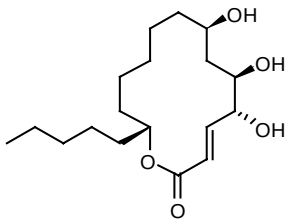
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.25 (m, 5H), 6.81 (dd, *J* = 16.0, 5.5 Hz, 1H), 6.04 (dd, *J* = 16.0, 1.0 Hz, 1H), 5.03 (m, 1H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.47 (t, *J* = 5.5 Hz, 1H), 3.82 (m, 1H), 3.65 (td, *J* = 5.5, 4.5 Hz, 1H), 2.18–1.95 (m, 4H), 1.80–1.60 (m, 2H), 1.41 (m, 2H), 1.39–1.16 (m, 16H), 1.09–0.92 (m, 28H), 0.88 (t, *J* = 6.5 Hz, 3H), 0.82 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 146.2, 138.4, 128.3, 127.6, 127.3, 124.1, 79.2, 75.6, 73.4, 72.8, 69.8, 37.8, 37.0, 33.8, 31.9, 31.7, 31.3, 29.8, 25.3, 25.2, 24.5, 24.3, 22.5, 17.5 (m), 13.9, 12.7 (m), 0.9, 0.2.



(4*R*,5*S*,7*R*,13*R*,*E*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradec-2-en-1-one (2a):

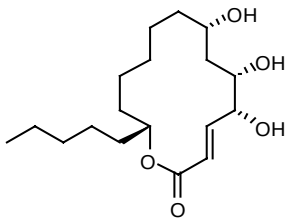
The same procedure as **2d** was followed by employing **64[F7F0]** (3.3 mg, 0.00373 mmol), ethane thiol (15.0 μL, 0.220 mmol), BF_3•Et_2O (5.0 μL, 0.0380 mmol) and dry DCM (3.7 mL). The title compound **2a** was prepared and then purified by preparative reverse phase HPLC to afford a white solid (0.9 mg, 74 %): $[\alpha]_D^{25}$ –22.2 (c 0.081, MeOH); ^{1}H NMR (500 MHz, MeOD-*d*4) δ 6.87 (dd, *J* = 16.0, 6.0 Hz, 1H), 6.08 (dd, *J* = 15.5, 1.5 Hz, 1H), 4.95 (dddd, *J* = 9.5, 7.5, 4.5, 2.0 Hz, 1H), 4.48 (ddd, *J* = 6.0, 3.0, 1.5 Hz, 1H), 3.99 (quint, *J* = 6.5 Hz, 1H), 3.85 (ddd, *J* = 6.0, 4.5, 3.5 Hz, 1H), 1.83 (ddd, *J* = 14.6, 6.2, 6.2 Hz, 1H), 1.71 (m, 1H), 1.68–1.51 (m, 4H),

1.45 (m, 1H), 1.40–1.27 (m, 10H), 1.25–1.12 (m, 3H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, MeOD-*d*4) δ 168.5, 149.3, 123.1, 77.6, 76.0, 72.9, 69.5, 38.3, 36.8, 36.5, 34.1, 33.0, 29.5, 27.0, 26.4, 25.8, 23.8, 14.5; IR (thin film) 3685, 3610, 3020, 2930, 1711, 1521, 1424, 1216, 1035, 929 cm^{-1}; HRMS (MALDI) *m/z* $[M + H]^+$ calcd for $C_{18}H_{33}O_5$: 329.2328, found 329.2356.



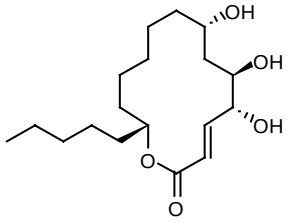
(4*R*,5*R*,7*R*,13*R*,*E*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradec-2-en-1-one (2b):

The same procedure as **2d** was followed by employing **64[F9F0]** (2.4 mg, 0.00257 mmol), ethane thiol (15.0 μL, 0.220 mmol), BF_3•Et_2O (5.0 μL, 0.0380 mmol) and dry DCM (3.7 mL). The title compound **2b** was prepared and then purified by preparative reverse phase HPLC to afford a white solid (0.5 mg, 53 %): $[\alpha]_D^{25}$ +18.7 (c 0.075, MeOH); ^{1}H NMR (500 MHz, MeOD-*d*4) δ 6.91 (dd, J = 16.0, 6.5 Hz, 1H), 6.11 (dd, J = 15.5, 1.0 Hz, 1H), 5.02 (m, 1H), 4.16 (td, J = 6.5, 1.0 Hz, 1H), 3.82 (ddd, J = 8.7, 5.7, 3.7 Hz, 1H), 3.78 (m, 1H), 1.77 (m, 1H), 1.67–1.59 (m, 1H), 1.63 (ddd, J = 14.0, 9.0, 3.5 Hz, 1H), 1.56 (m, 1H), 1.51–1.39 (m, 5H), 1.38–1.26 (m, 6H), 1.26–1.15 (m, 2H), 1.11 (m, 1H), 0.90 (t, J = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, MeOD-*d*4) δ 168.3, 148.4, 124.3, 77.6, 77.5, 73.4, 67.7, 42.0, 37.0, 36.0, 34.5, 32.9, 30.1, 26.5, 26.4, 25.4, 23.8, 14.6; IR (thin film) 3684, 3620, 3020, 2930, 1712, 1525, 1425, 1217, 1029, 929 cm^{-1}; HRMS (MALDI) *m/z* $[M + Na]^+$ calcd for $C_{18}H_{32}NaO_5$: 351.2147, found 351.2143.



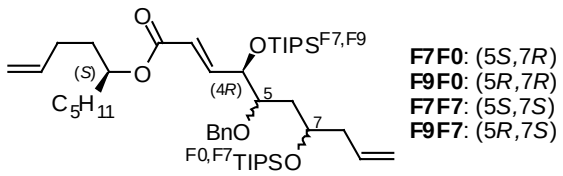
(4*R*,5*S*,7*S*,13*R*,*E*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradec-2-en-1-one (2c):

The same procedure as **2d** was followed by employing **64[F7F7]** (3.9 mg, 0.00375 mmol), ethane thiol (16.0 μL, 0.234 mmol), $BF_3 \cdot Et_2O$ (5.5 μL, 0.0380 mmol) and dry DCM (3.0 mL). The title compound **2c** was prepared and then purified by preparative reverse phase HPLC to afford a white solid (0.7 mg, 59%): $[\alpha]_D^{25}$ –10.7 (c 0.056, MeOH); ^{1}H NMR (700 MHz, MeOD-*d*4) δ 6.95 (dd, *J* = 16.0, 4.5 Hz, 1H), 6.14 (dd, *J* = 15.5, 1.5 Hz, 1H), 4.94 (tt, *J* = 8.4, 5.6 Hz, 1H), 4.55 (dddd, *J* = 4.3, 2.6, 1.8, 0.9 Hz, 1H), 3.89 (dt, *J* = 9.0, 2.5 Hz, 1H), 3.38 (ddt, *J* = 11.6, 7.7, 2.8 Hz, 1H), 2.02 (ddd, *J* = 14.5, 9.0, 2.0 Hz, 1H), 1.68–1.61 (m, 3H), 1.57–1.45 (m, 3H), 1.45–1.25 (m, 10H), 1.24–1.16 (m, 3H), 0.91 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, MeOD-*d*4) δ 169.1, 150.0, 121.8, 75.6, 75.0, 72.1, 68.8, 40.5, 36.2, 35.9, 33.9, 33.0, 27.3, 26.5, 24.8, 24.6, 23.8, 14.5; IR (thin film) 3684, 3381, 3020, 2931, 1708, 1521, 1424, 1216, 1065, 929 cm^{-1}; HRMS (MALDI) *m/z* $[M + Na]^+$ calcd for $C_{18}H_{32}NaO_5$: 351.2147, found 351.2143.



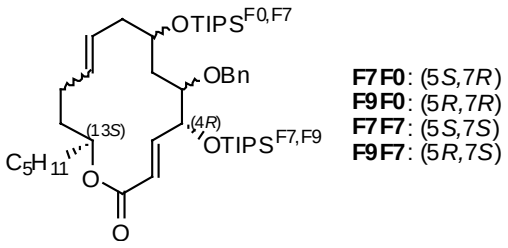
(4*R*,5*R*,7*S*,13*R*,*E*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradec-2-en-1-one (2d):

The same procedure as **2d** in the single isomer synthesis was followed by employing **64[F9F7]** (3.5 mg, 0.00279 mmol), ethane thiol (15.0 μL, 0.220 mmol), BF_3•Et_2O (5.0 μL, 0.0380 mmol) and dry DCM (3.2 mL). The title compound **2d** was prepared and then purified by preparative reverse phase HPLC to afford a white solid (1.0 mg, 94%). Spectroscopy data are identical with **2d** prepared in the single isomer synthesis.



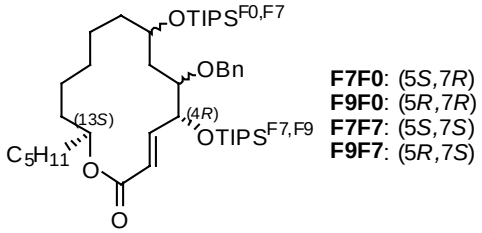
(4*R*,5*R*/*S*,7*R*/*S*,*E*)-((*S*)-Dec-1-en-5-yl)-5-(benzyloxy)-4,7-bis((perfluoroalkylethyl)diisoprop-ylsilyloxy)deca-2,9-dienoate (M-65):

The same procedure as **28** was followed by employing LiCl (12.8 mg, 0.303 mmol), phosphonate **5-(*S*)** (101 mg, 0.303 mmol), anhydrous acetonitrile (20 mL), DBU (38.4 mg, 0.252 mmol) and aldehyde **M-36** (210 mg, 0.252 mmol). The title compound **M-65** was prepared as a colorless oil (202 mg, 79%), with an isomeric ratio of 1.0/0.33/0.80/0.67 (**65[F7F0]**/**65[F9F0]**/**65[F7F7]**/**65[F9F7]**, based on F-HPLC): ^{1}H NMR (see appendix); analytical fluorous HPLC (condition 1) t_R = 32.4 min (**65[F7F0]**), 35.5 min (**65[F9F0]**), 40.5 min (**65[F7F7]**), 45.0 min (**65[F9F7]**).



(2*E*,4*R*,5*R/S*,7*R/S*,9*E/Z*,13*S*)-5-(Benzyloxy)-13-pentyl-4,7-bis((perfluoroalkylethyl)diiso-propylsilyloxy)oxacyclotetradeca-2,9-dien-1-one (M-66):

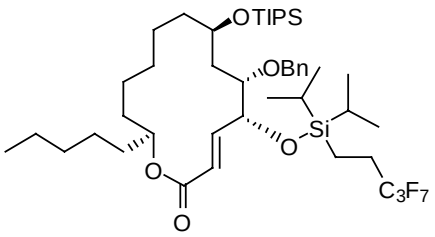
The same procedure as **3** was followed by employing **M-65** (200 mg, 0.197 mmol), Grubbs 1st generation catalyst [$(PCy_3)_2Cl_2Ru$=CHPh] (155 mg, 0.188 mmol) and anhydrous DCM (250 mL, and another 15 mL to dissolve the catalyst). The title compound **M-66** was prepared as a yellow/brown oil (167 mg, 86%) with an isomeric ratio of 1.0/0.34/0.78/0.58 (**66[F7F0]**/**66[F9F0]**/**66[F7F7]**/**66[F9F7]**, based on F-HPLC): ^{1}H NMR (see appendix); analytical fluorous HPLC (condition 1, listed as major peaks) t_R = 28.5 min (**66[F7F0]**), 33.3 min (**66[F9F0]**), 37.2 min (**66[F7F7]**), 41.5 min (**66[F9F7]**).



(2*E*,4*R*,5*R/S*,7*R/S*,13*S*)-5-(Benzyloxy)-13-pentyl-4,7-bis((perfluoroalkylethyl)diisopropylsil-yloxy)oxacyclotetradec-2-en-1-one (M-67): [63]

A mixture of **M-66** (25.0 mg, 0.0253 mmol), ethanol (8.0 mL) and Pd/$SrCO_3$ (2 wt.%) (135 mg catalyst, 0.0253 mmol Pd) was placed under a hydrogen atmosphere and stirred at 23 °C for

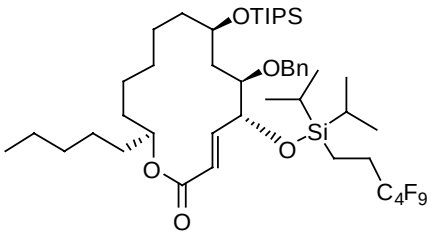
15 h. The reaction was carefully monitored by analytical fluorous HPLC (condition 1): t_R = 29.5 min (**67[F7F0]**), 34.0 min (**67[F9F0]**), 38.6 min (**67[F7F7]**), 43.8 min (**67[F9F7]**). The reaction mixture was then filtered and the filtrate was concentrated under reduced pressure to afford a light yellow oil which was subjected to preparative fluorous HPLC with the standard demixing conditions. Demixing of the crude product afforded quasidiastereomers **67[F7F0]** (5.4 mg), **67[F9F0]** (4.5 mg), **67[F7F7]** (5.0 mg), **67[F9F7]** (4.4 mg) as colorless oils. The yield of the reaction was 77% (based on the total weight of four products: 19.3 mg). Characterizations of the four products are shown below.



(4*R*,5*S*,7*R*,13*S*,*E*)-5-(Benzyloxy)-4-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-13-pentyl-7-(triisopropylsilyloxy)oxacyclotetradec-2-en-1-one (67[F7F0]):

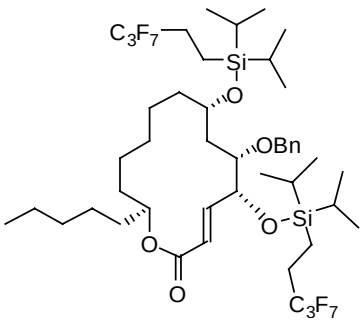
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 6.76 (dd, *J* = 15.5, 3.0 Hz, 1H), 6.03 (dd, *J* = 15.5, 2.0 Hz, 1H), 4.96 (dtd, *J* = 7.5, 6.0, 4.0 Hz, 1H), 4.68 (m, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 3.75 (tt, *J* = 7.0, 3.5 Hz, 1H), 3.53 (ddd, *J* = 7.0, 4.0, 1.5 Hz, 1H), 2.15–1.96 (m, 2H), 1.71–1.60 (m, 2H), 1.67 (ddd, *J* = 13.5, 9.0, 4.0 Hz, 1H), 1.54–1.45 (m, 3H), 1.37–1.15 (m, 14H), 1.09–0.98 (m, 35H), 0.87 (t, *J* = 6.5 Hz, 3H), 0.76 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 147.2, 138.2, 128.3, 127.8, 127.6, 122.0, 78.1, 74.7, 74.5, 71.2, 69.0, 36.8,

34.6, 33.0, 31.7, 30.9, 29.7, 27.5, 25.3, 23.6, 22.5, 21.7, 18.2 (m), 17.6 (m), 14.0, 12.7 (m), 0.8.



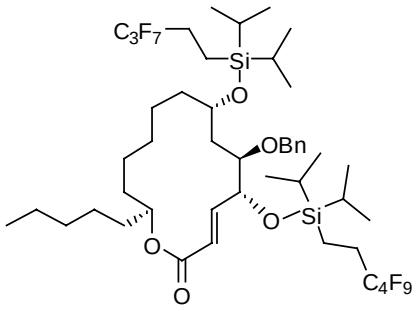
(4*R*,5*R*,7*R*,13*S*,*E*)-5-(Benzyloxy)-4-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-13-pentyl-7-(triisopropylsilyloxy)oxacyclotetradec-2-en-1-one (67[F9F0]):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.22 (m, 5H), 7.12 (dd, *J* = 16.0, 4.5 Hz, 1H), 6.11 (dd, *J* = 16.0, 2.0 Hz, 1H), 4.91 (quint, *J* = 5.5 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.37 (ddd, *J* = 8.0, 4.5, 2.0 Hz, 1H), 3.69 (m, 1H), 3.26 (dt, *J* = 7.0, 3.0 Hz, 1H), 2.20–2.05 (m, 2H), 1.82 (ddd, *J* = 15.0, 8.0, 4.0 Hz, 1H), 1.68–1.59 (m, 3H), 1.58–1.41 (m, 3H), 1.40–1.17 (m, 12H), 1.17–1.10 (m, 1H), 1.09–0.96 (m, 35H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 148.0, 138.4, 128.2, 127.8, 127.5, 122.4, 81.4, 75.6, 75.5, 73.1, 69.2, 38.2, 35.2, 34.8, 31.7, 31.4, 29.7, 28.3, 25.4, 25.0, 22.5, 22.0, 18.4 (m), 17.6 (m), 14.0, 12.6 (m), 0.2.



(4*R*,5*S*,7*S*,13*S*,*E*)-5-(Benzyloxy)-4,7-bis((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-13-pentyloxacyclotetradec-2-en-1-one (67[F7F7]):

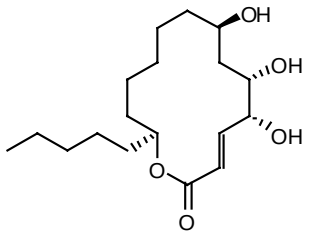
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5H), 6.73 (dd, *J* = 16.0, 3.0 Hz, 1H), 6.05 (dd, *J* = 16.0, 2.0 Hz, 1H), 5.05 (m, 1H), 4.82 (m, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.33 (d, *J* = 12.0 Hz, 1H), 3.73 (m, 1H), 3.14 (d, *J* = 9.5 Hz, 1H), 2.16–1.97 (m, 4H), 1.74–1.58 (m, 4H), 1.53–1.47 (m, 2H), 1.46–1.38 (m, 2H), 1.38–1.23 (m, 8H), 1.22–1.12 (m, 4H), 1.10–0.96 (m, 28H), 0.96–0.90 (m, 2H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 147.9, 137.5, 128.4, 128.3, 128.0, 122.7, 79.1, 75.7, 71.9, 71.5, 68.9, 33.9, 33.6, 33.3, 32.2, 31.7, 30.7, 25.3, 25.3, 25.2, 24.2, 22.5, 20.3, 17.5 (m), 14.0, 12.6 (m), 0.6, 0.2.



(4*R*,5*R*,7*S*,13*S*,*E*)-5-(Benzyloxy)-4-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-7-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-13-pentyloxacyclotetradec-2-en-1-one (67[F9F7]):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.21 (m, 5H), 7.05 (dd, *J* = 16.0, 3.5 Hz, 1H), 6.07 (dd, *J* = 15.5, 2.0 Hz, 1H), 4.96 (qd, *J* = 7.0, 2.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.52 (ddd, *J* = 6.5, 4.5, 3.0 Hz, 1H), 3.89 (m, 1H), 3.55 (td, *J* = 7.0, 4.0 Hz, 1H), 2.14–1.97

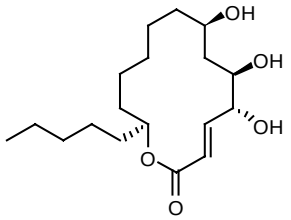
(m, 4H), 1.85 (ddd, *J* = 15.0, 7.5, 5.5 Hz, 1H), 1.70–1.56 (m, 2H), 1.62 (dt, *J* = 15.5, 4.0 Hz, 1H), 1.53–1.39 (m, 4H), 1.38–1.22 (m, 10H), 1.20–1.12 (m, 2H), 1.07–1.02 (m, 4H), 1.02–0.91 (m, 24H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.85–0.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 147.5, 138.4, 128.2, 127.4, 127.1, 122.7, 79.1, 75.8, 73.3, 72.6, 69.9, 37.0, 36.3, 34.7, 32.0, 31.7, 29.7, 29.1, 25.3, 25.2, 25.1, 23.5, 22.5, 17.5 (m), 14.0, 12.7 (m), 0.4, 0.2.



(4*R*,5*S*,7*R*,13*S*,*E*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradec-2-en-1-one (2e):

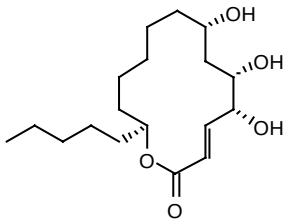
The same procedure as **2d** was followed by employing **67[F7F0]** (5.4 mg, 0.00610 mmol), ethane thiol (50.0 μL, 0.733 mmol), BF_3•Et_2O (7.0 μL, 0.0532 mmol) and dry DCM (1.5 mL). The title compound **2e** was prepared and then purified by preparative reverse phase HPLC to afford a white solid (1.4 mg, 70 %): $[\alpha]_D^{25}$ +4.4 (c 0.14, MeOH); ^{1}H NMR (600 MHz, MeOD-*d*4) δ 7.01 (dd, *J* = 16.2, 3.6 Hz, 1H), 6.06 (dd, *J* = 15.6, 2.1 Hz, 1H), 4.95 (ddt, *J* = 13.2, 5.4, 2.4 Hz, 1H), 4.46 (dt, *J* = 3.6, 2.1 Hz, 1H), 3.95 (ddd, *J* = 8.4, 4.2, 2.4 Hz, 1H), 3.67 (tt, *J* = 7.8, 4.2 Hz, 1H), 2.02 (ddd, *J* = 13.8, 7.8, 4.2 Hz, 1H), 1.72–1.64 (m, 2H), 1.64–1.57 (m, 2H), 1.57–1.50 (m, 2H), 1.53 (ddd, *J* = 13.8, 7.8, 4.8 Hz, 1H), 1.40–1.21 (m, 12H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, MeOD-*d*4) δ 168.1, 150.1, 122.4, 76.1, 75.7, 72.1, 68.8, 39.5, 35.0, 34.7, 33.0, 32.8, 28.7, 26.6, 24.9, 23.8, 23.5, 14.5; IR (thin film) 3684, 3610, 3412, 3020, 2931, 1708, 1521,

1424, 1216, 1044, 929 cm^{-1}; HRMS (MALDI) *m/z* $[M + Na]^+$ calcd for $C_{18}H_{32}NaO_5$: 351.2147, found 351.2143.



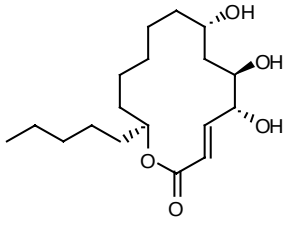
(4*R*,5*R*,7*R*,13*S*,*E*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradec-2-en-1-one (2f):

The same procedure as **2d** was followed by employing **67[F9F0]** (4.5 mg, 0.00481 mmol), ethane thiol (50.0 μL, 0.733 mmol), $BF_3 \cdot Et_2O$ (7.0 μL, 0.0532 mmol) and dry DCM (1.5 mL). The title compound **2f** was prepared and then purified by preparative reverse phase HPLC to afford a white solid (0.6 mg, 38 %): $[\alpha]_D^{25}$ –4.0 (c 0.075, MeOH); ^{1}H NMR (600 MHz, MeOD-*d*4) δ 6.96 (dd, *J* = 15.6, 6.0 Hz, 1H), 6.09 (dd, *J* = 16.2, 1.8 Hz, 1H), 4.92 (m, 1H), 4.03 (ddd, *J* = 7.8, 6.0, 1.8 Hz, 1H), 3.55 (td, *J* = 8.4, 2.4 Hz, 1H), 3.47 (ddt, *J* = 9.0, 7.2, 3.0 Hz, 1H), 1.77 (ddd, *J* = 15.0, 9.0, 3.0 Hz, 1H), 1.72–1.59 (m, 3H), 1.57–1.46 (m, 4H), 1.56 (ddd, *J* = 14.4, 9.6, 1.8 Hz, 1H), 1.39–1.28 (m, 8H), 1.28–1.20 (m, 3H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, MeOD-*d*4) δ 168.1, 149.3, 123.1, 77.8, 75.9, 74.7, 68.5, 35.9, 35.6, 35.1, 33.4, 33.1, 30.5, 27.7, 26.5, 24.3, 23.9, 14.5; IR (thin film) 3684, 3611, 3020, 2927, 1712, 1521, 1425, 1216, 1024, 929 cm^{-1}; HRMS (MALDI) *m/z* $[M + Na]^+$ calcd for $C_{18}H_{32}NaO_5$: 351.2147, found 351.2143.



(4*R*,5*S*,7*S*,13*S*,*E*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradec-2-en-1-one (2g):

The same procedure as **2d** was followed by employing **67[F7F7]** (5.0 mg, 0.00481 mmol), ethane thiol (50.0 μL, 0.733 mmol), $BF_3 \cdot Et_2O$ (7.0 μL, 0.0532 mmol) and dry DCM (1.5 mL). The title compound **2g** was prepared and then purified by preparative reverse phase HPLC to afford a white solid (0.9 mg, 57 %): $[\alpha]_D^{25}$ –7.1 (c 0.11, MeOH); ^{1}H NMR (600 MHz, MeOD-*d*4) δ 6.93 (dd, *J* = 15.6, 4.2 Hz, 1H), 6.09 (dd, *J* = 15.6, 1.8 Hz, 1H), 5.00 (ddt, *J* = 13.8, 4.8, 3.0 Hz, 1H), 4.47 (ddd, *J* = 4.8, 3.0, 1.8 Hz, 1H), 3.89 (ddd, *J* = 7.2, 4.2, 3.0 Hz, 1H), 3.64 (dq, *J* = 10.2, 5.4 Hz, 1H), 1.78–1.74 (m, 1H), 1.71 (ddd, *J* = 14.4, 6.6, 4.2 Hz, 1H), 1.62 (m, 1H), 1.55 (m, 1H), 1.49–1.39 (m, 5H), 1.39–1.27 (m, 7H), 1.36 (ddd, *J* = 14.4, 9.0, 4.8 Hz, 1H), 1.25–1.15 (m, 2H), 1.15–1.06 (m, 1H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, MeOD-*d*4) δ 168.1, 148.7, 123.4, 77.4, 74.7, 72.4, 68.9, 39.2, 36.4, 35.7, 34.4, 32.9, 30.3, 26.6, 26.0, 24.3, 23.8, 14.5; IR (thin film) 3684, 3612, 3412, 3020, 2930, 1709, 1521, 1424, 1216, 1032, 929 cm^{-1}; HRMS (MALDI) *m/z* $[M + Na]^+$ calcd for $C_{18}H_{32}NaO_5$: 351.2147, found 351.2143.



(4*R*,5*R*,7*S*,13*S*,*E*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradec-2-en-1-one (2h):

The same procedure as **2d** was followed by employing **67[F9F7]** (4.4 mg, 0.00404 mmol), ethane thiol (50.0 μL, 0.733 mmol), $BF_3 \cdot Et_2O$ (7.0 μL, 0.0532 mmol) and dry DCM (1.5 mL). The title compound **2h** was prepared and then purified by preparative reverse phase HPLC to afford a white solid (1.1 mg, 83 %): $[\alpha]_D^{25}$ +10.3 (c 0.088, MeOH); ^{1}H NMR (600 MHz, MeOD-*d*4) δ 7.04 (dd, *J* = 15.6, 5.4 Hz, 1H), 6.11 (dd, *J* = 15.6, 1.2 Hz, 1H), 4.95 (ddt, *J* = 12.6, 7.2, 2.4 Hz, 1H), 4.26 (ddd, *J* = 6.6, 5.4, 1.2 Hz, 1H), 3.92 (quint, *J* = 6.0 Hz, 1H), 3.77 (dt, *J* = 7.2, 4.2 Hz, 1H), 1.77–1.67 (m, 1H), 1.70 (t, *J* = 5.1 Hz, 2H), 1.62 (tt, *J* = 14.4, 7.8 Hz, 1H), 1.58–1.49 (m, 2H), 1.49–1.38 (m, 3H), 1.38–1.24 (m, 8H), 1.23–1.13 (m, 3H), 0.90 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, MeOD-*d*4) δ 168.1, 148.7, 123.5, 77.6, 75.8, 74.4, 69.2, 37.9, 36.9, 36.3, 34.2, 33.0, 29.7, 26.6, 26.4, 25.4, 23.8, 14.5; IR (thin film) 3684, 3613, 3412, 3020, 2930, 1712, 1521, 1424, 1216, 1029, 929 cm^{-1}; HRMS (MALDI) *m/z* $[M + Na]^+$ calcd for $C_{18}H_{32}NaO_5$: 351.2147, found 351.2143.

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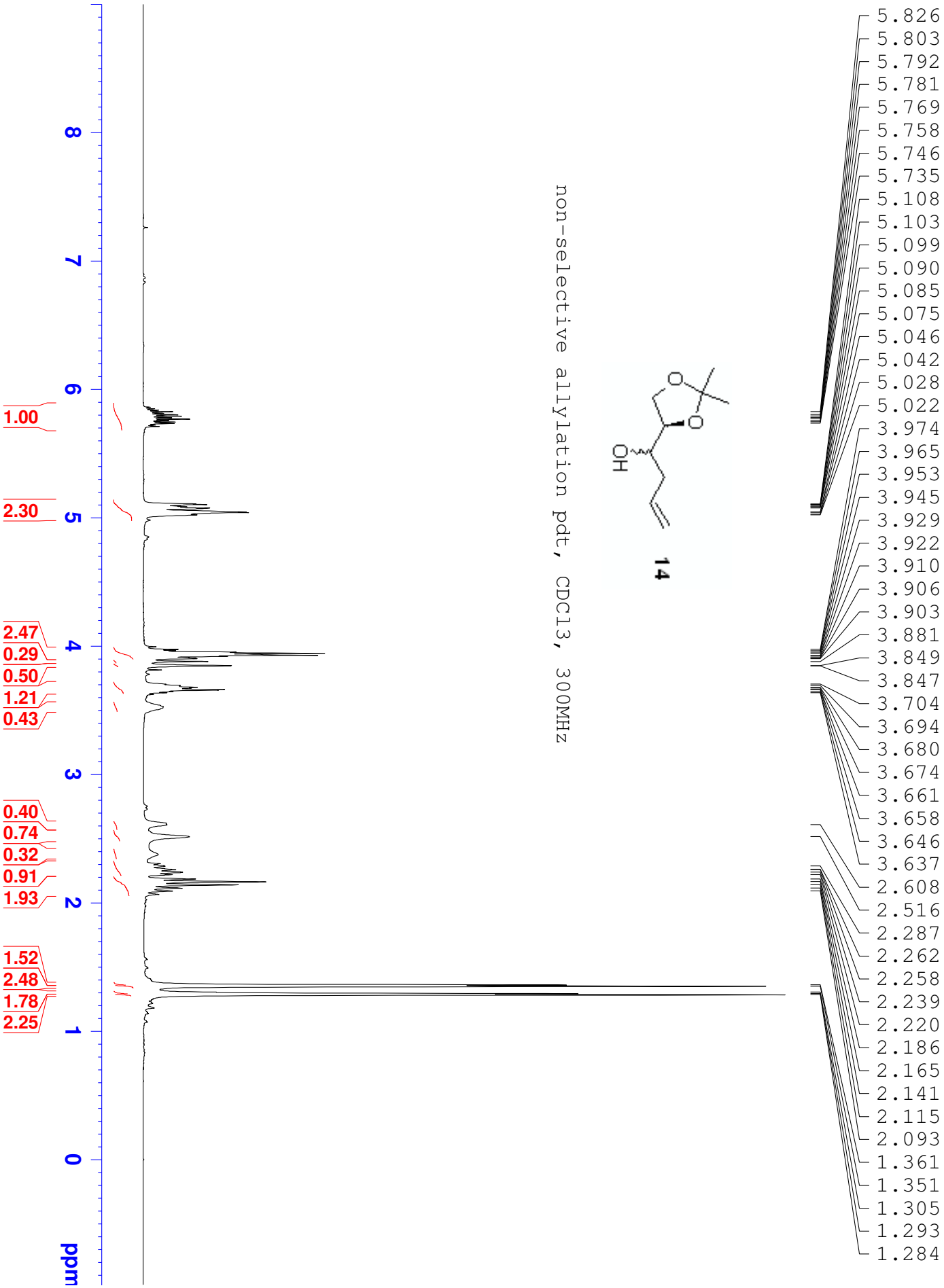
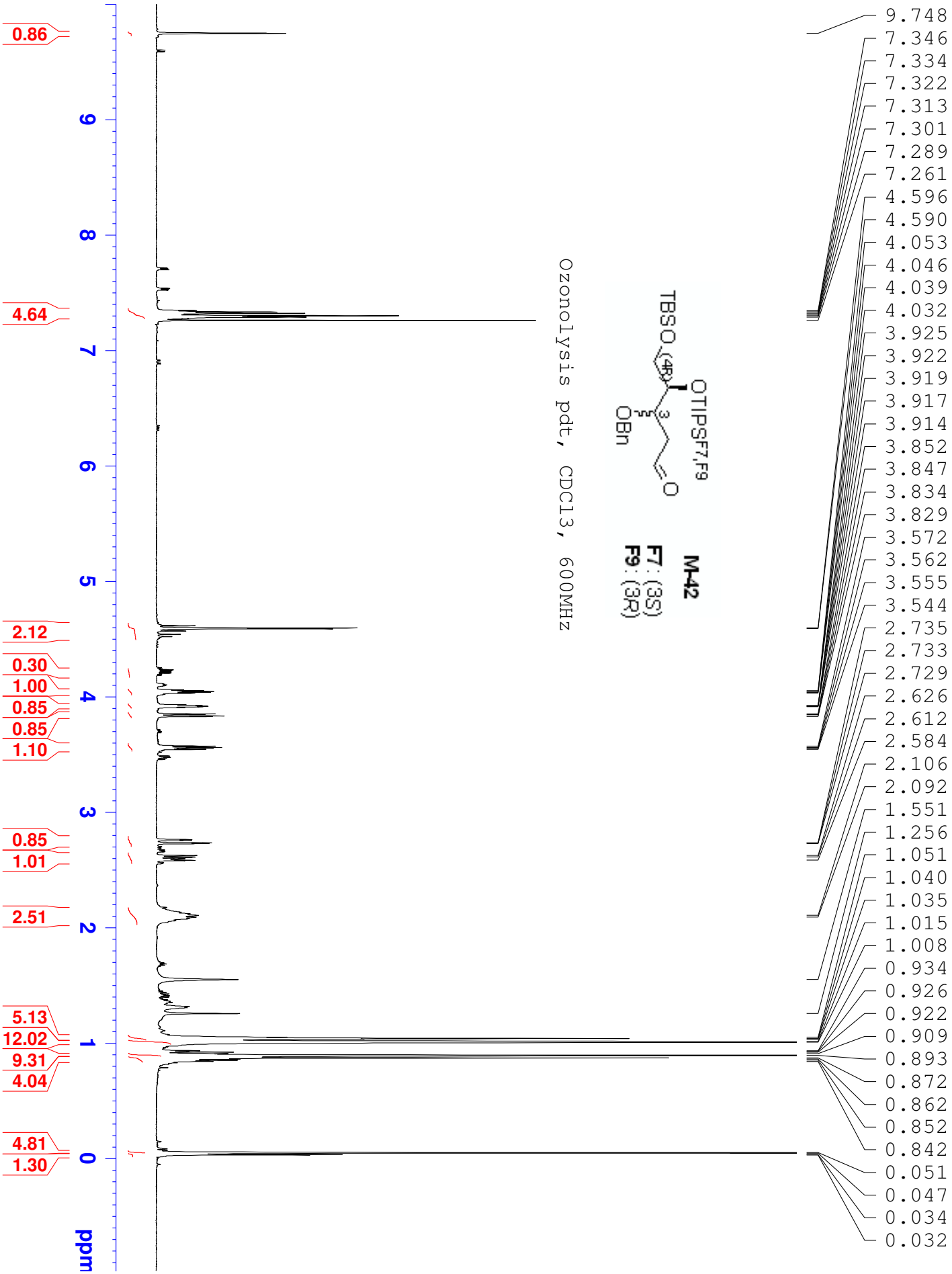
APPENDIX

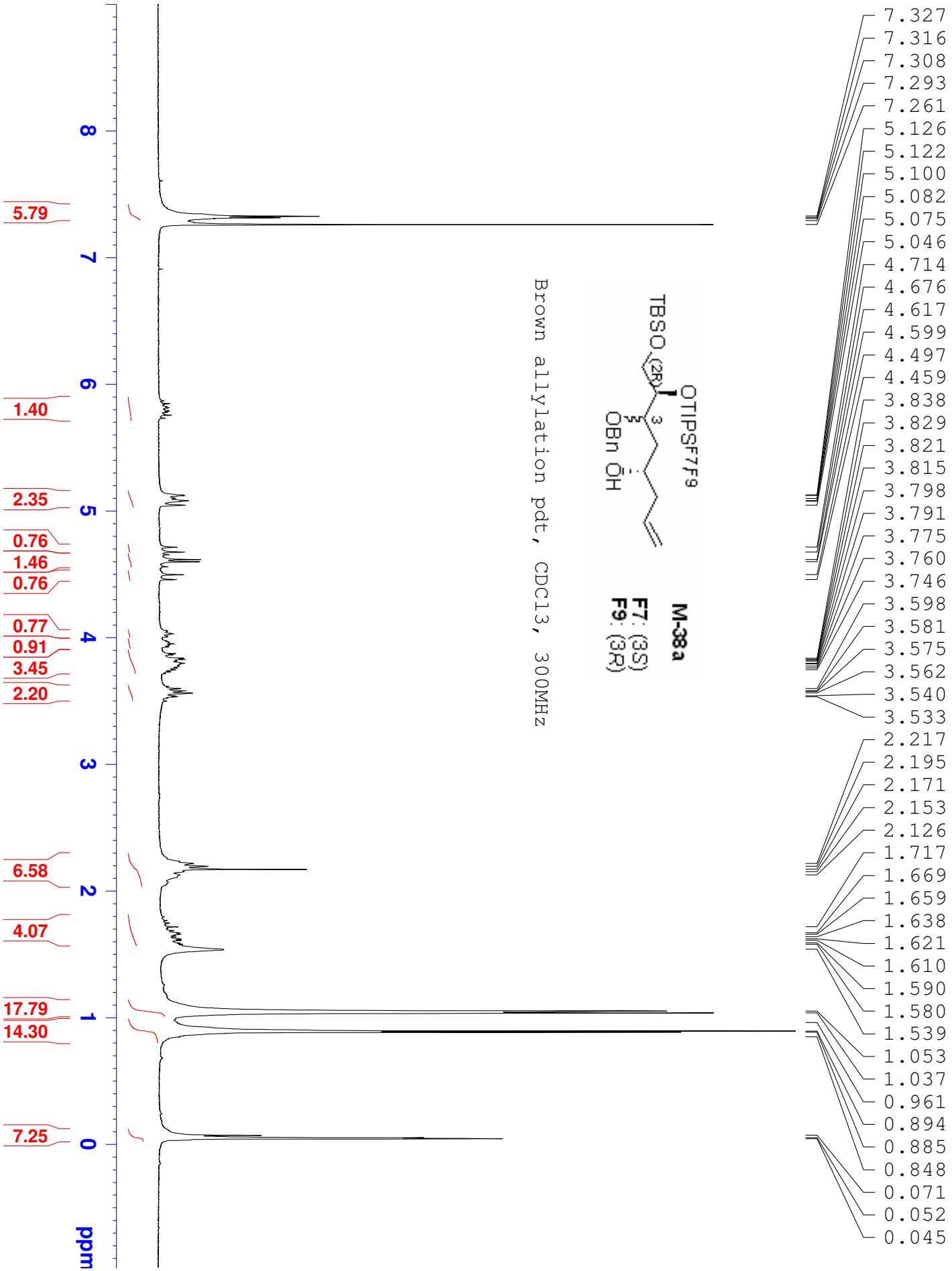
(CHAPTER 2)

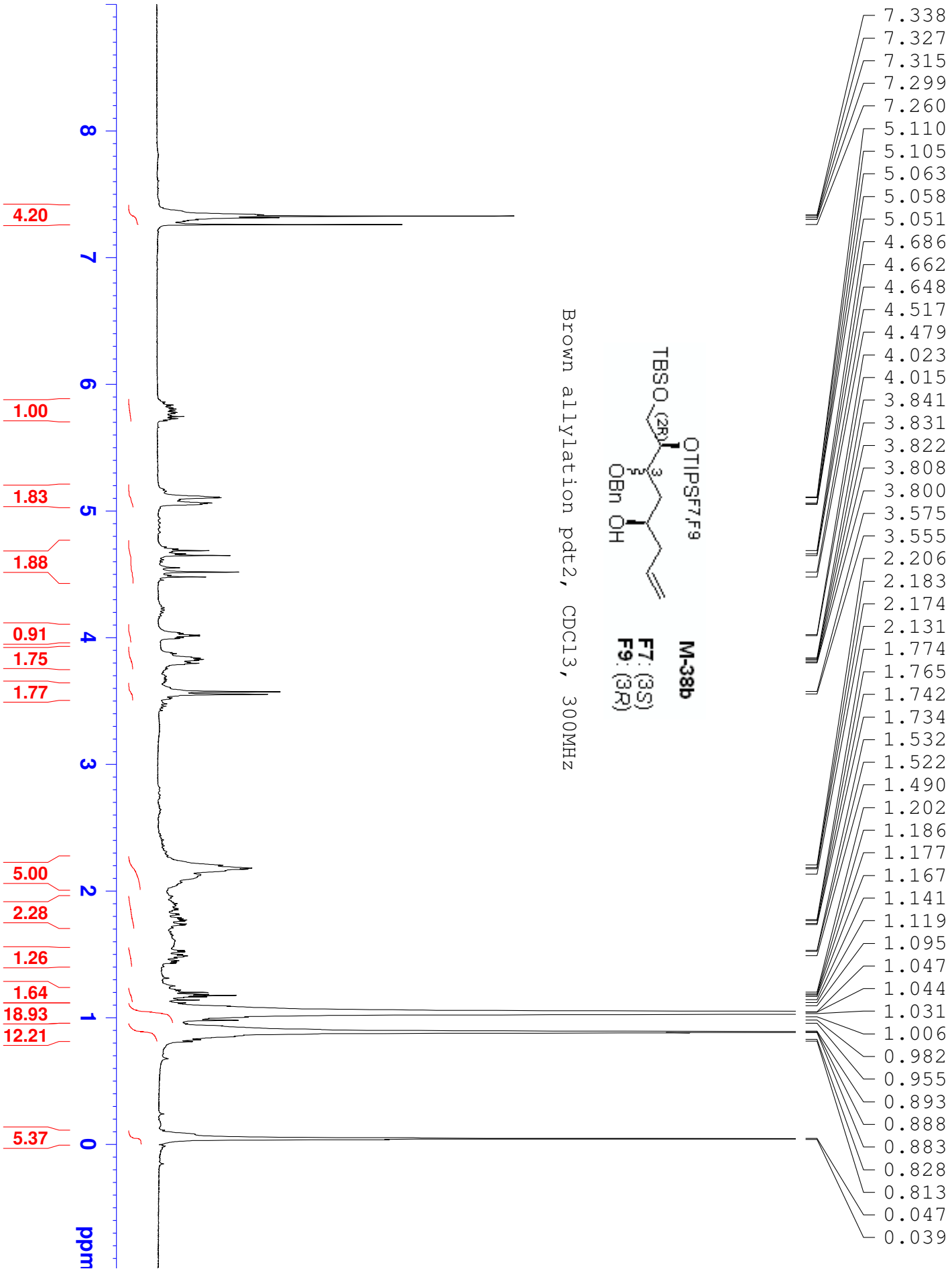
1) ^{1}H NMR spectra of compound **14** and all fluorous mixtures

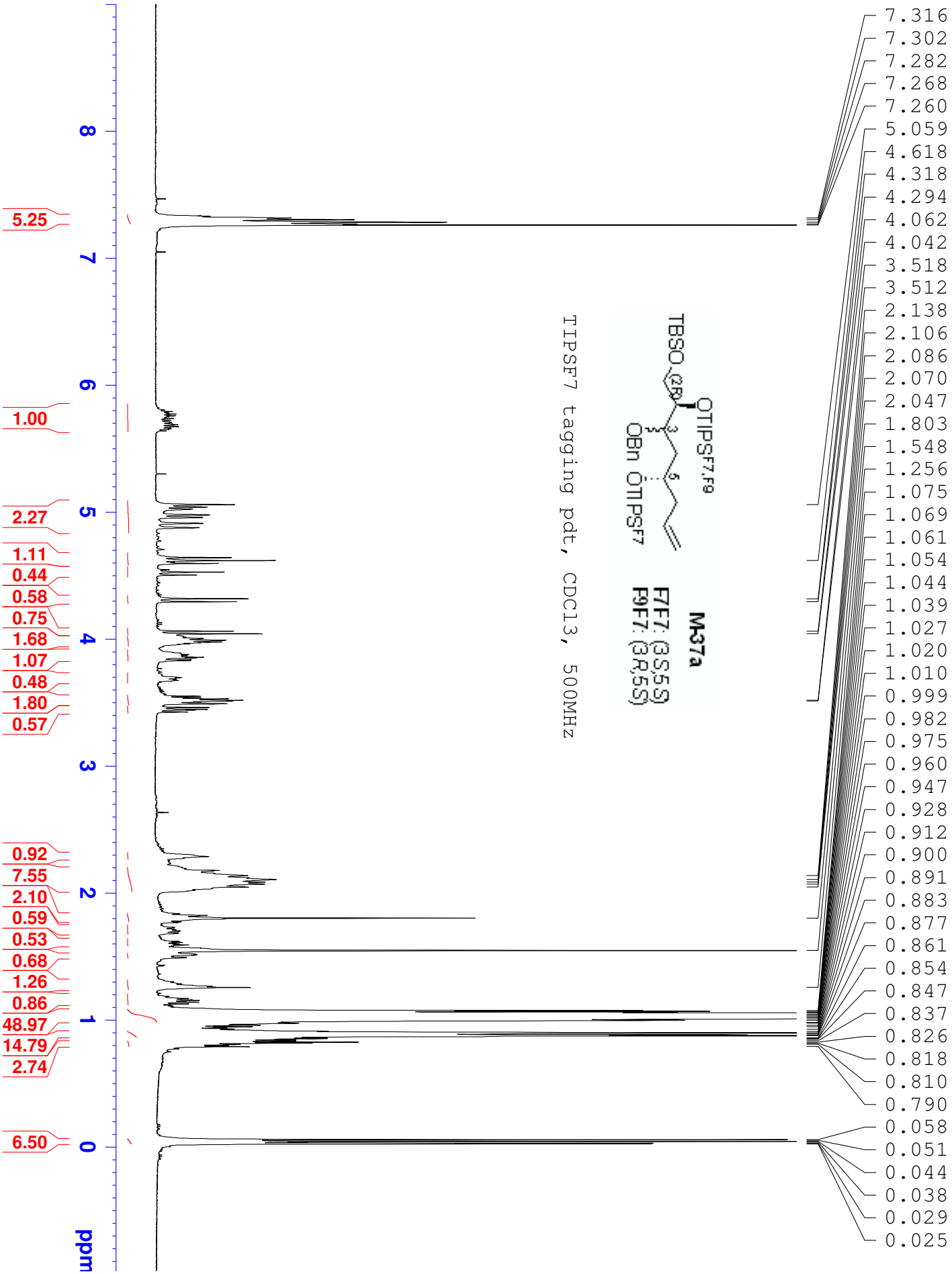
2) ^{1}H, ^{13}C NMR, COSY and HMQC spectra of triols **2a-2h**

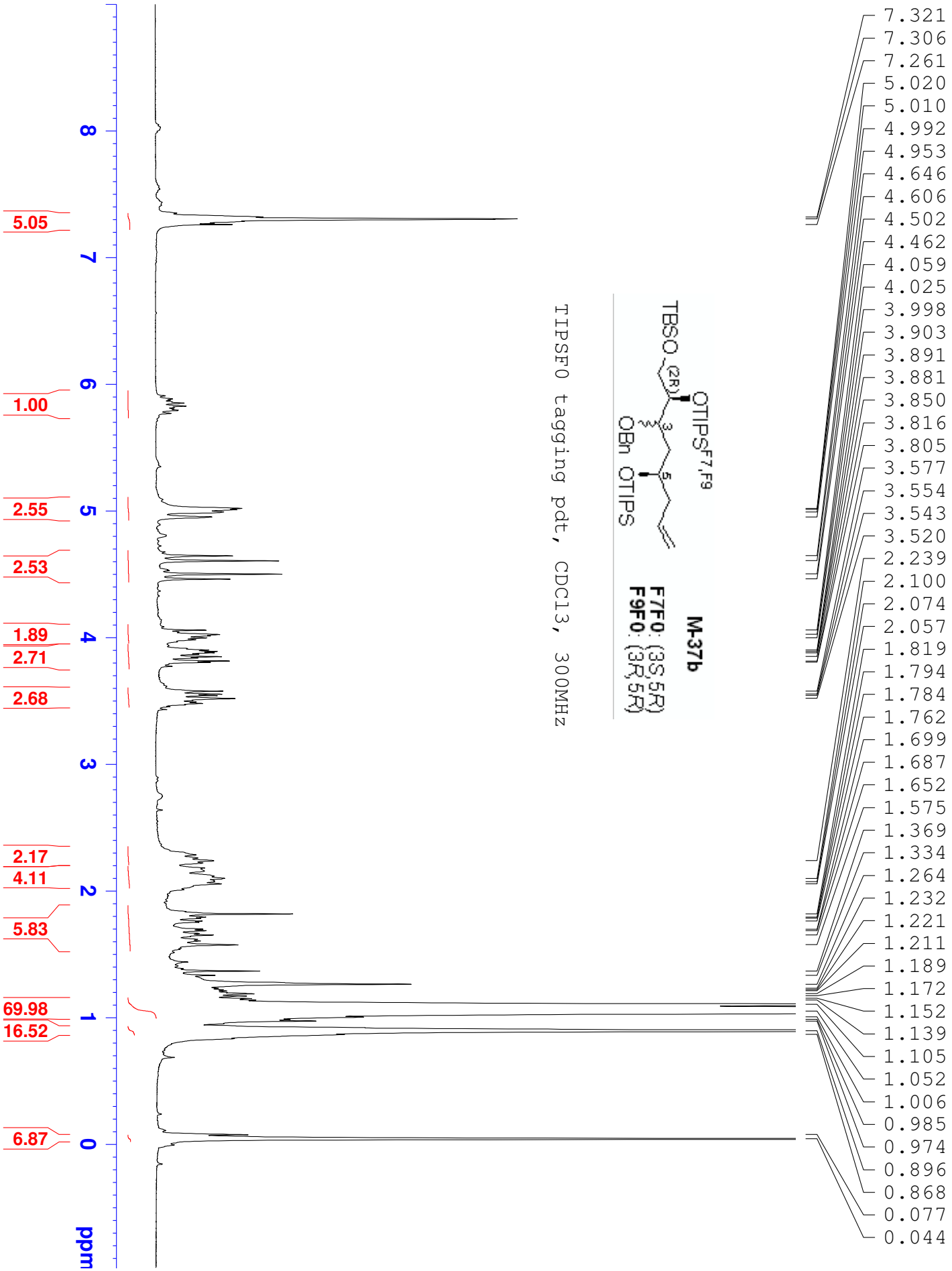

non-selective allylation pdt, CDCl3, 300MHz
14
OH
O
O
5.826
5.803
5.792
5.781
5.769
5.758
5.746
5.735
5.108
5.103
5.099
5.090
5.085
5.075
5.046
5.042
5.028
5.022
3.974
3.965
3.953
3.945
3.929
3.922
3.910
3.906
3.903
3.881
3.849
3.847
3.704
3.694
3.680
3.674
3.661
3.658
3.646
3.637
2.608
2.516
2.287
2.262
2.258
2.239
2.220
2.186
2.165
2.141
2.115
2.093
1.361
1.351
1.305
1.293
1.284
1.00
2.30
2.47
0.29
0.50
1.21
0.43
0.40
0.74
0.32
0.91
1.93
1.52
2.48
1.78
2.25
8
7
6
5
4
3
2
1
0
ppm

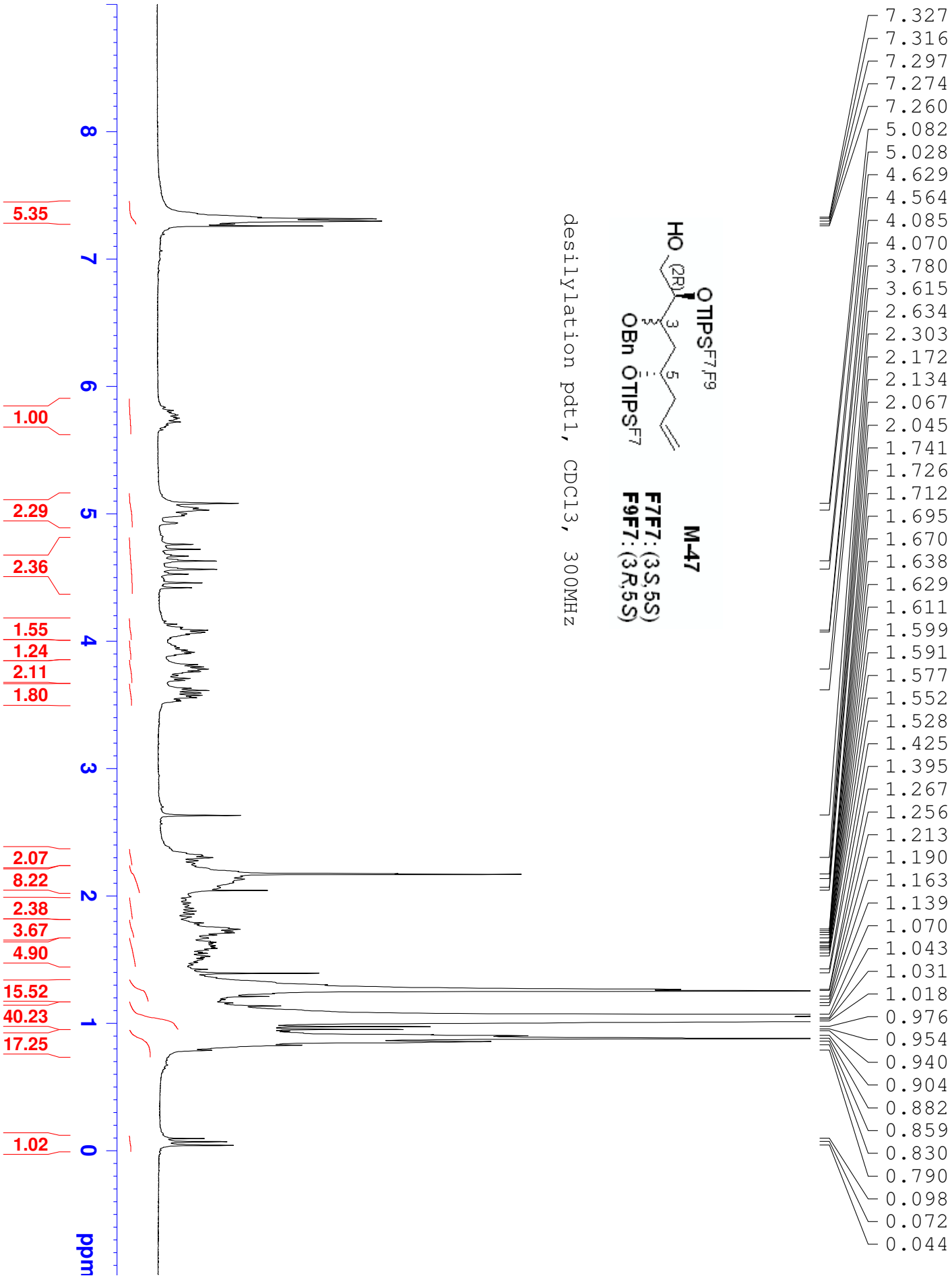

Ozonolysis pdt, CDCl3, 600MHz
M-42
F7: (3S)
F9: (3R)
TBSO
OTIPSF7,F9
OBn
9.748
7.346
7.334
7.322
7.313
7.301
7.289
7.261
4.596
4.590
4.053
4.046
4.039
4.032
3.925
3.922
3.919
3.917
3.914
3.852
3.847
3.834
3.829
3.572
3.562
3.555
3.544
2.735
2.733
2.729
2.626
2.612
2.584
2.106
2.092
1.551
1.256
1.051
1.040
1.035
1.015
1.008
0.934
0.926
0.922
0.909
0.893
0.872
0.862
0.852
0.842
0.051
0.047
0.034
0.032
0.86
4.64
2.12
0.30
1.00
0.85
0.85
1.10
0.85
1.01
2.51
5.13
12.02
9.31
4.04
4.81
1.30
ppm


Brown allylation pdt, CDCl3, 300MHz
M-38a
F7: (3S)
F9: (3R)
OTIPSF7F9
TBSO (2R)
3
OBn OH
5.79
1.40
2.35
0.76
1.46
0.76
0.77
0.91
3.45
2.20
6.58
4.07
17.79
14.30
7.25
ppm
7.327
7.316
7.308
7.293
7.261
5.126
5.122
5.100
5.082
5.075
5.046
4.714
4.676
4.617
4.599
4.497
4.459
3.838
3.829
3.821
3.815
3.798
3.791
3.775
3.760
3.746
3.598
3.581
3.575
3.562
3.540
3.533
2.217
2.195
2.171
2.153
2.126
1.717
1.669
1.659
1.638
1.621
1.610
1.590
1.580
1.539
1.053
1.037
0.961
0.894
0.885
0.848
0.071
0.052
0.045


Brown allylation pdt2, CDCl3, 300MHz
M-38b
F7: (3S)
F9: (3R)
TBSO
OTIPSF7,F9
OBn
OH
7.338
7.327
7.315
7.299
7.260
5.110
5.105
5.063
5.058
5.051
4.686
4.662
4.648
4.517
4.479
4.023
4.015
3.841
3.831
3.822
3.808
3.800
3.575
3.555
2.206
2.183
2.174
2.131
1.774
1.765
1.742
1.734
1.532
1.522
1.490
1.202
1.186
1.177
1.167
1.141
1.119
1.095
1.047
1.044
1.031
1.006
0.982
0.955
0.893
0.888
0.883
0.828
0.813
0.047
0.039
4.20
1.00
1.83
1.88
0.91
1.75
1.77
5.00
2.28
1.26
1.64
18.93
12.21
5.37
ppm


TIPSF7 tagging pdt, CDCl3, 500MHz
M37a
F7F7: (3S,5S)
F9F7: (3R,5S)
TBSO
OBn
OTIPSF7
OTIPSF7,F9
ppm
8
7
6
5
4
3
2
1
0
5.25
1.00
2.27
1.11
0.44
0.58
0.75
1.68
1.07
0.48
1.80
0.57
0.92
7.55
2.10
0.59
0.53
0.68
1.26
0.86
48.97
14.79
2.74
6.50
7.316
7.302
7.282
7.268
7.260
5.059
4.618
4.318
4.294
4.062
4.042
3.518
3.512
2.138
2.106
2.086
2.070
2.047
1.803
1.548
1.256
1.075
1.069
1.061
1.054
1.044
1.039
1.027
1.020
1.010
0.999
0.982
0.975
0.960
0.947
0.928
0.912
0.900
0.891
0.883
0.877
0.861
0.854
0.847
0.837
0.826
0.818
0.810
0.790
0.058
0.051
0.044
0.038
0.029
0.025


TIPSF0 tagging pdt, CDCl3, 300MHz
M-37b
F7F0: (3S,5R)
F9F0: (3R,5R)
TBSO
(2R)
OTIPS F7,F9
OBn OTIPS
7.321
7.306
7.261
5.020
5.010
4.992
4.953
4.646
4.606
4.502
4.462
4.059
4.025
3.998
3.903
3.891
3.881
3.850
3.816
3.805
3.577
3.554
3.543
3.520
2.239
2.100
2.074
2.057
1.819
1.794
1.784
1.762
1.699
1.687
1.652
1.575
1.369
1.334
1.264
1.232
1.221
1.211
1.189
1.172
1.152
1.139
1.105
1.052
1.006
0.985
0.974
0.896
0.868
0.077
0.044
5.05
1.00
2.55
2.53
1.89
2.71
2.68
2.17
4.11
5.83
69.98
16.52
6.87
ppm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7.316
7.297
7.274
7.260
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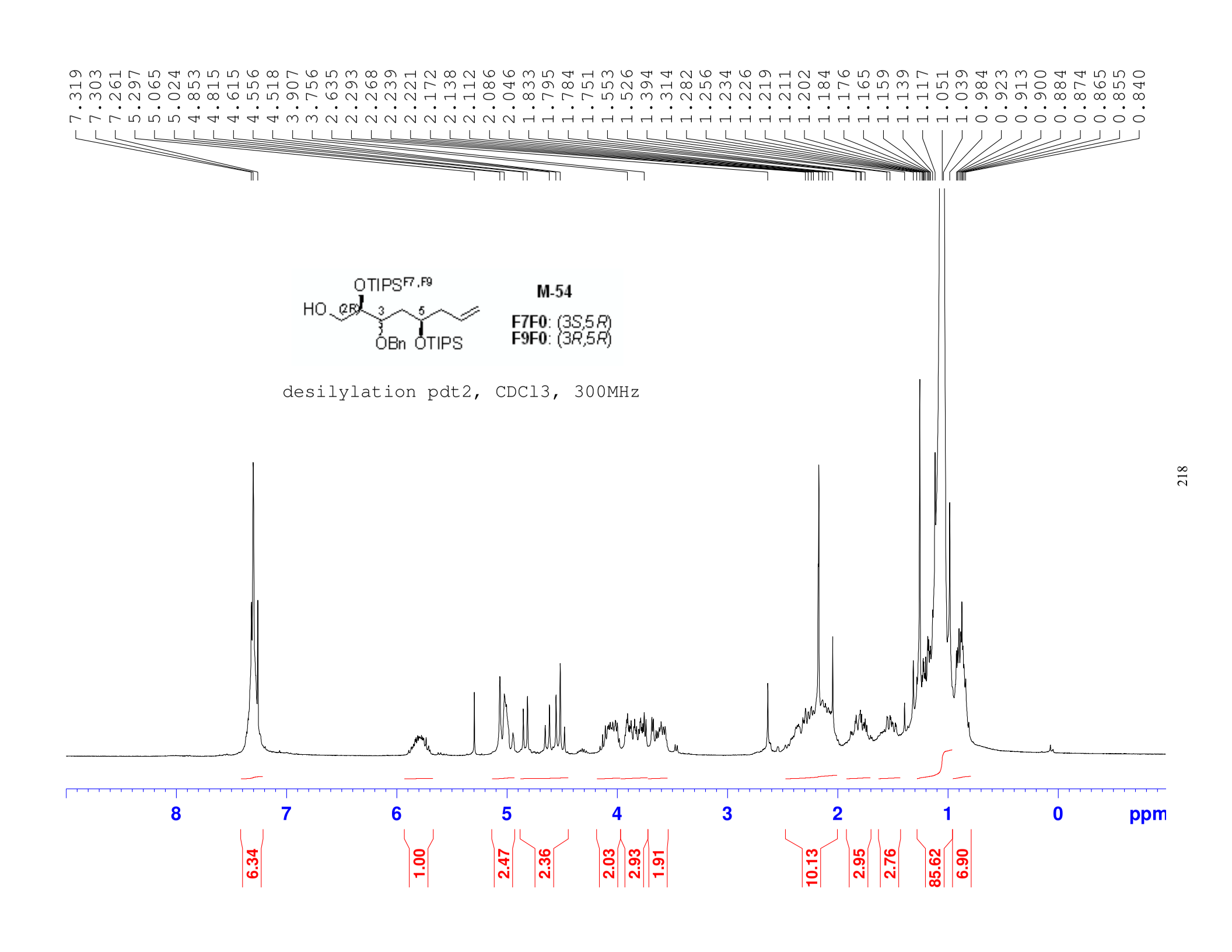
5.028
4.629
4.564
4.085
4.070
3.780
3.615
2.634
2.303
2.172
2.134
2.067
2.045
1.741
1.726
1.712
1.695
1.670
1.638
1.629
1.611
1.599
1.591
1.577
1.552
1.528
1.425
1.395
1.267
1.256
1.213
1.190
1.163
1.139
1.070
1.043
1.031
1.018
0.976
0.954
0.940
0.904
0.882
0.859
0.830
0.790
0.098
0.072
0.044
HO
(2R)
OTIPS F7,F9
3
5
OBn OTIPS F7
M-47
F7F7: (3S,5S)
F9F7: (3R,5S)
desilylation pdt1, CDCl3, 300MHz
5.35
1.00
2.29
2.36
1.55
1.24
2.11
1.80
2.07
8.22
2.38
3.67
4.90
15.52
40.23
17.25
1.02
8
7
6
5
4
3
2
1
0
ppm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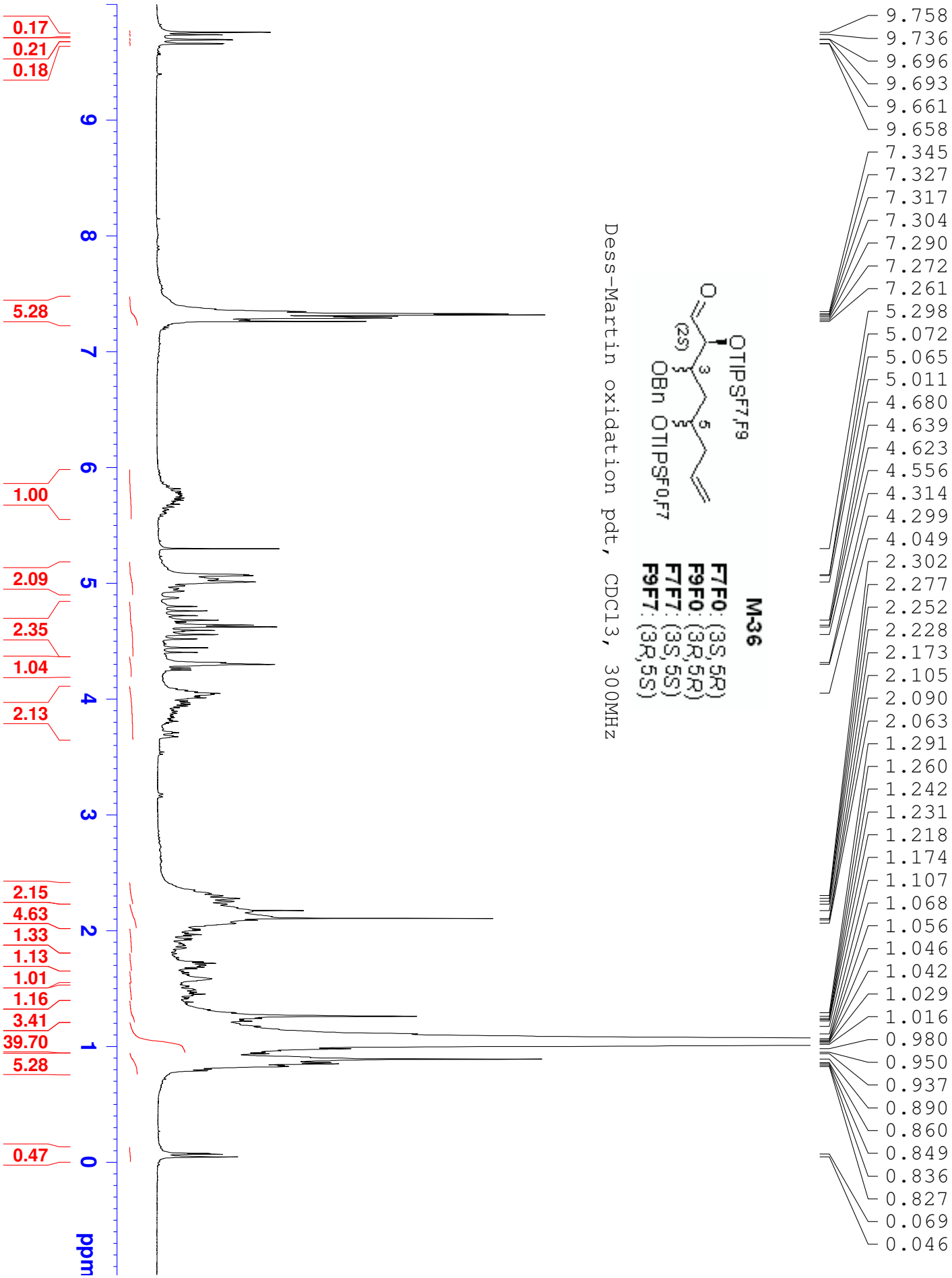
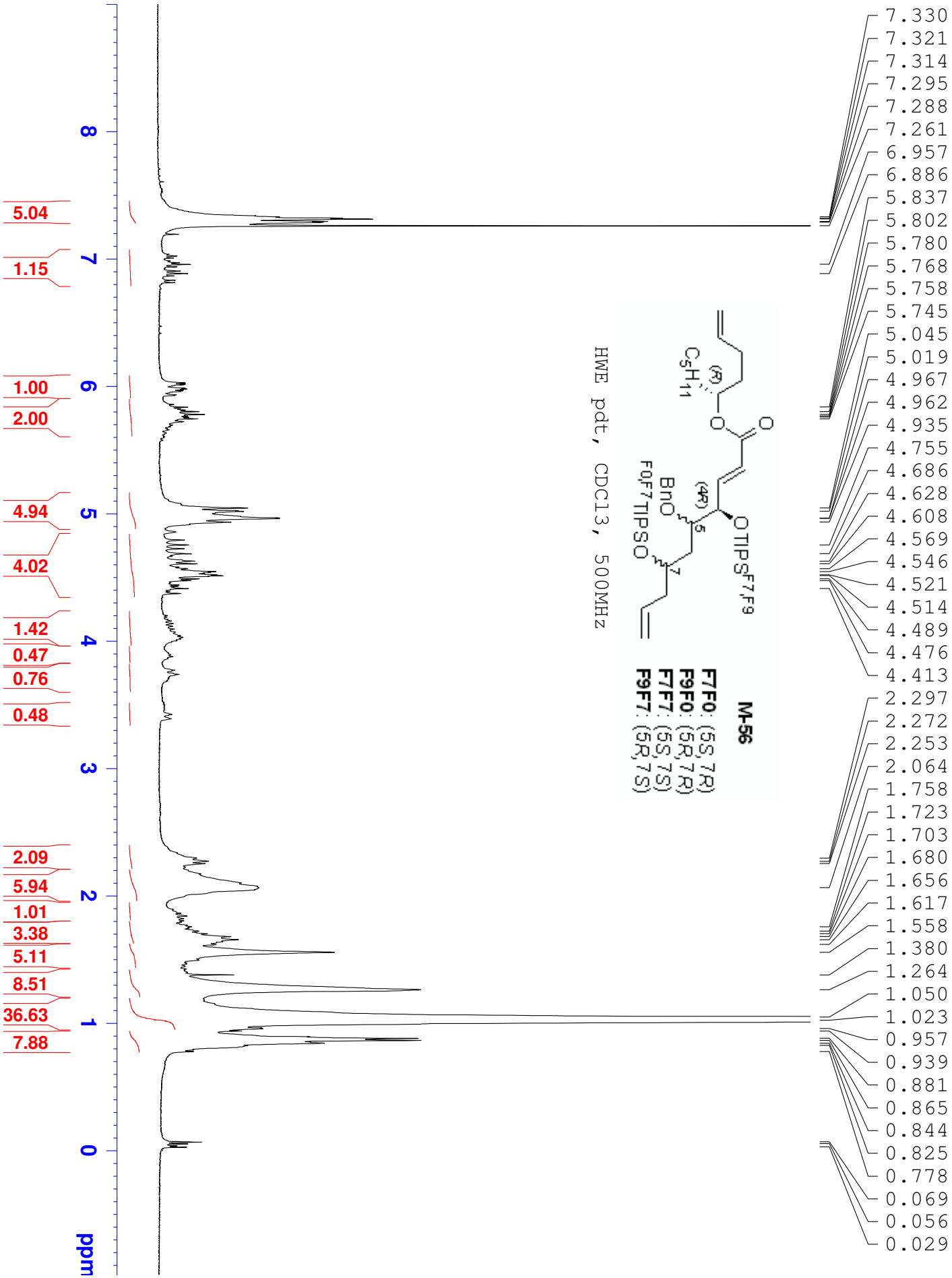
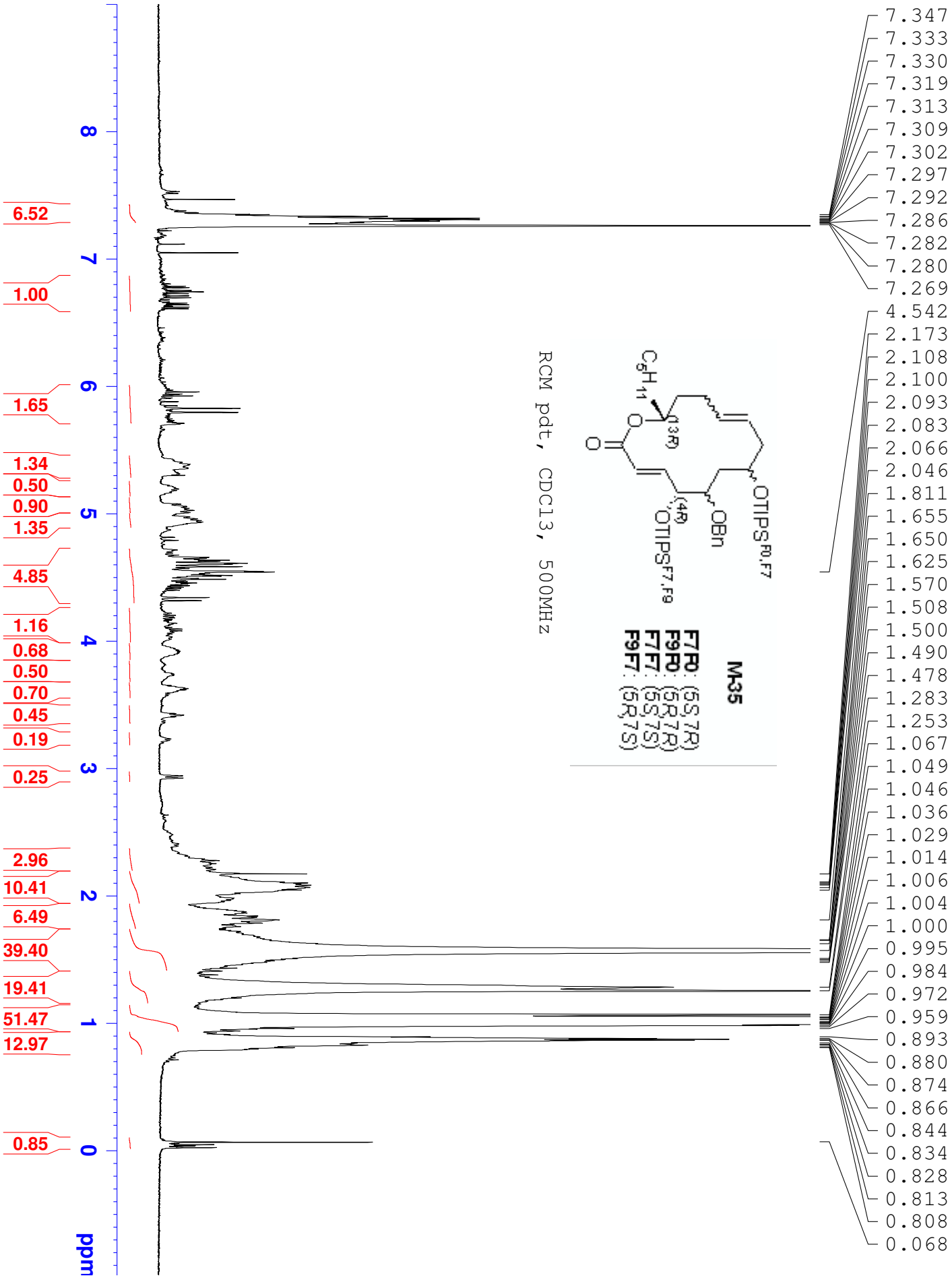
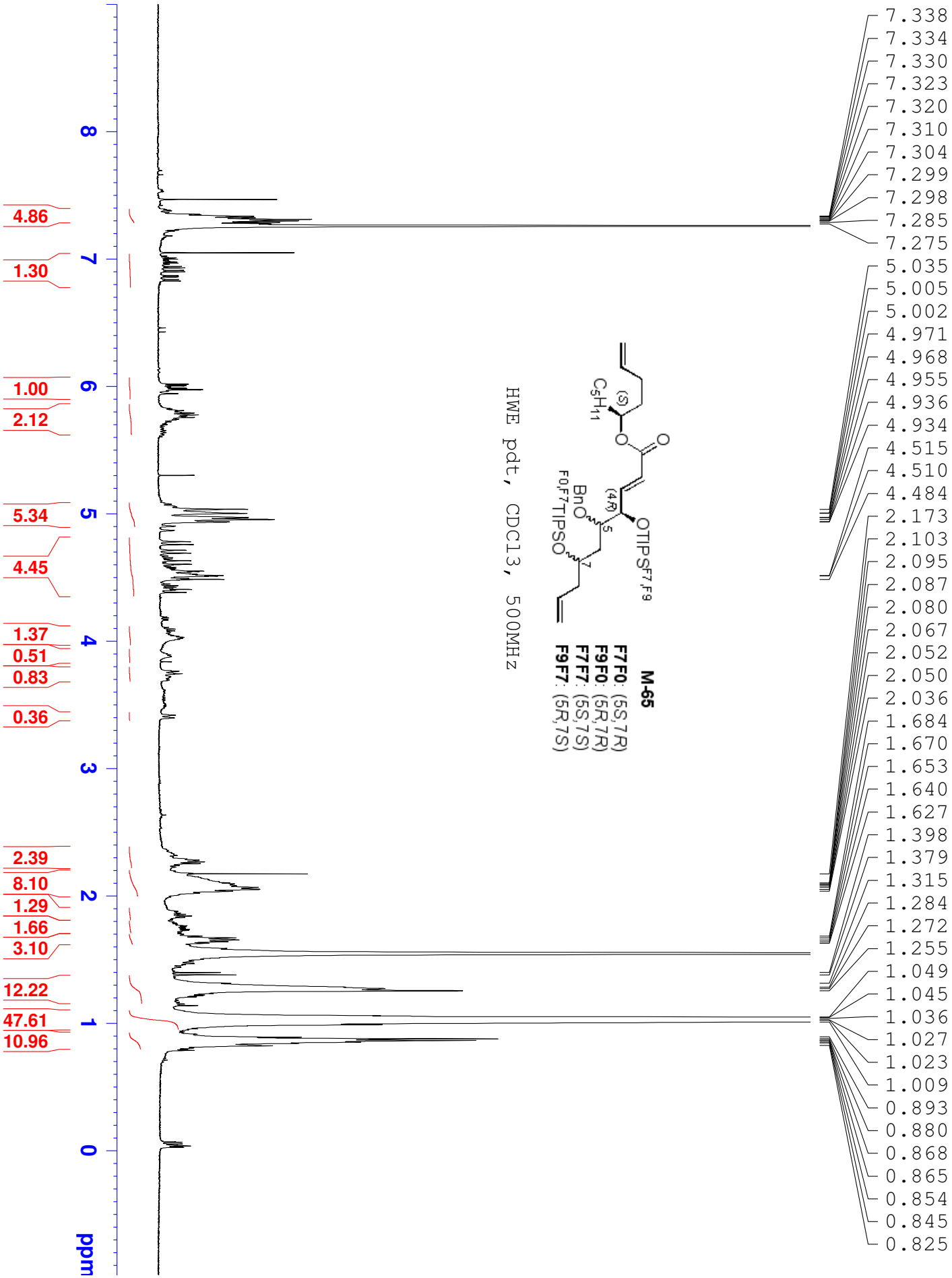
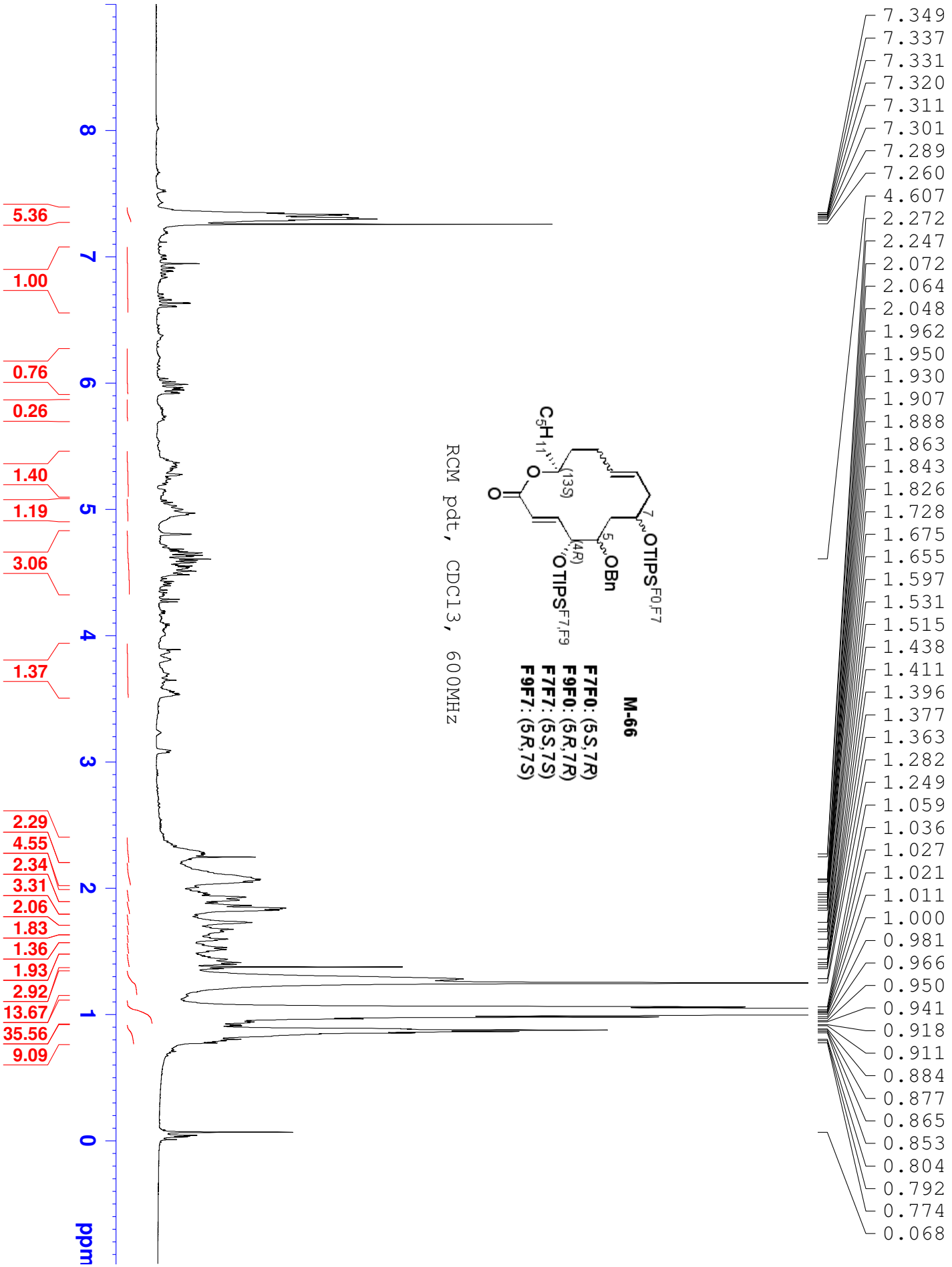
7.303
7.261
5.297
5.065
5.024
4.853
4.815
4.615
4.556
4.518
3.907
3.756
2.635
2.293
2.268
2.239
2.221
2.172
2.138
2.112
2.086
2.046
1.833
1.795
1.784
1.751
1.553
1.526
1.394
1.314
1.282
1.256
1.234
1.226
1.219
1.211
1.202
1.184
1.176
1.165
1.159
1.139
1.117
1.051
1.039
0.984
0.923
0.913
0.900
0.884
0.874
0.865
0.855
0.840
OTIPS F7,F9
HO
OBn OTIPS
M-54
F7F0: (3S,5R)
F9F0: (3R,5R)
desilylation pdt2, CDCl3, 300MHz
8
7
6
5
4
3
2
1
0
ppm
6.34
1.00
2.47
2.36
2.03
2.93
1.91
10.13
2.95
2.76
85.62
6.90

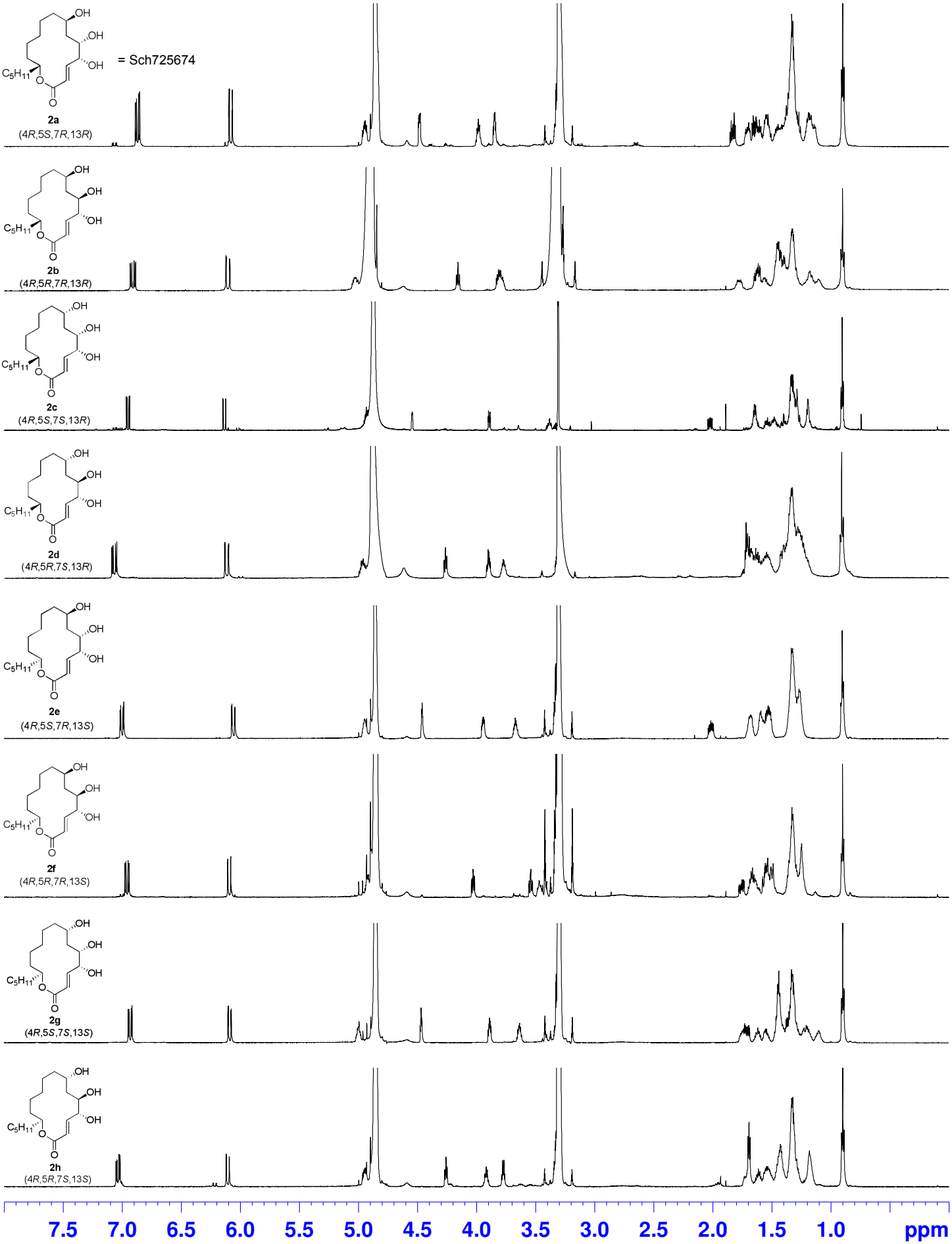

Dess-Martin oxidation pdt, CDCl3, 300MHz
M-36
F7F0: (3S,5R)
F9F0: (3R,5R)
F7F7: (3S,5S)
F9F7: (3R,5S)
OTIPSF7,F9
OBn OTIPSF0,F7
(2S)
9.758
9.736
9.696
9.693
9.661
9.658
7.345
7.327
7.317
7.304
7.290
7.272
7.261
5.298
5.072
5.065
5.011
4.680
4.639
4.623
4.556
4.314
4.299
4.049
2.302
2.277
2.252
2.228
2.173
2.105
2.090
2.063
1.291
1.260
1.242
1.231
1.218
1.174
1.107
1.068
1.056
1.046
1.042
1.029
1.016
0.980
0.950
0.937
0.890
0.860
0.849
0.836
0.827
0.069
0.046
0.17
0.21
0.18
5.28
1.00
2.09
2.35
1.04
2.13
2.15
4.63
1.33
1.13
1.01
1.16
3.41
39.70
5.28
0.47
ppm


HWE pdt, CDCl3, 500MHz
M-56
F7F0: (5S,7R)
F9F0: (5R,7R)
F7F7: (5S,7S)
F9F7: (5R,7S)
7.330
7.321
7.314
7.295
7.288
7.261
6.957
6.886
5.837
5.802
5.780
5.768
5.758
5.745
5.045
5.019
4.967
4.962
4.935
4.755
4.686
4.628
4.608
4.569
4.546
4.521
4.514
4.489
4.476
4.413
2.297
2.272
2.253
2.064
1.758
1.723
1.703
1.680
1.656
1.617
1.558
1.380
1.264
1.050
1.023
0.957
0.939
0.881
0.865
0.844
0.825
0.778
0.069
0.056
0.029
5.04
1.15
1.00
2.00
4.94
4.02
1.42
0.47
0.76
0.48
2.09
5.94
1.01
3.38
5.11
8.51
36.63
7.88
ppm

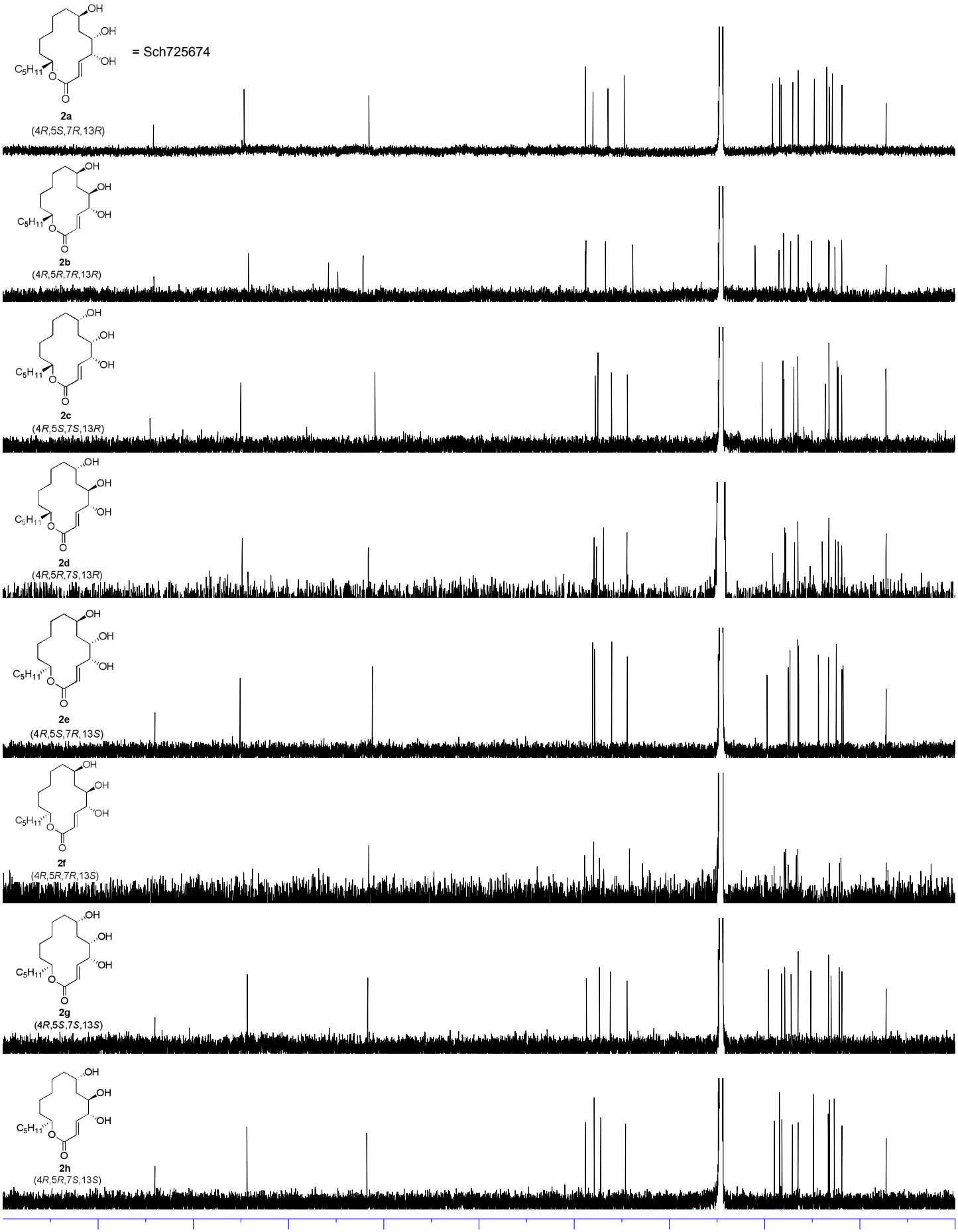

RCM pdt, CDCl3, 500MHz
M-35
F7R: (5S,7R)
F9R: (5R,7R)
F7F: (5S,7S)
F9F: (5R,7S)
OTIPS R0,F7
OBn
OTIPS F7,F9
(4R)
(13R)
C5H11
O
O
7.347
7.333
7.330
7.319
7.313
7.309
7.302
7.297
7.292
7.286
7.282
7.280
7.269
4.542
2.173
2.108
2.100
2.093
2.083
2.066
2.046
1.811
1.655
1.650
1.625
1.570
1.508
1.500
1.490
1.478
1.283
1.253
1.067
1.049
1.046
1.036
1.029
1.014
1.006
1.004
1.000
0.995
0.984
0.972
0.959
0.893
0.880
0.874
0.866
0.844
0.834
0.828
0.813
0.808
0.068
6.52
1.00
1.65
1.34
0.50
0.90
1.35
4.85
1.16
0.68
0.50
0.70
0.45
0.19
0.25
2.96
10.41
6.49
39.40
19.41
51.47
12.97
0.85
8
7
6
5
4
3
2
1
0
ppm


HWE pdt, CDCl3, 500MHz
M-65
F7F0: (5S,7R)
F9F0: (5R,7R)
F7F7: (5S,7S)
F9F7: (5R,7S)
7.338
7.334
7.330
7.323
7.320
7.310
7.304
7.299
7.298
7.285
7.275
5.035
5.005
5.002
4.971
4.968
4.955
4.936
4.934
4.515
4.510
4.484
2.173
2.103
2.095
2.087
2.080
2.067
2.052
2.050
2.036
1.684
1.670
1.653
1.640
1.627
1.398
1.379
1.315
1.284
1.272
1.255
1.049
1.045
1.036
1.027
1.023
1.009
0.893
0.880
0.868
0.865
0.854
0.845
0.825
4.86
1.30
1.00
2.12
5.34
4.45
1.37
0.51
0.83
0.36
2.39
8.10
1.29
1.66
3.10
12.22
47.61
10.96
ppm

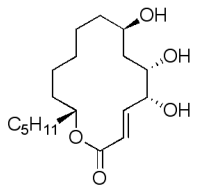

RCM pdt, CDCl3, 600MHz
M-66
F7F0: (5S,7R)
F9F0: (5R,7R)
F7F7: (5S,7S)
F9F7: (5R,7S)
OTIPS F0,F7
OBn
OTIPS F7,F9
(13S)
(4R)
C5H11
O
O
5.36
1.00
0.76
0.26
1.40
1.19
3.06
1.37
2.29
4.55
2.34
3.31
2.06
1.83
1.36
1.93
2.92
13.67
35.56
9.09
ppm
7.349
7.337
7.331
7.320
7.311
7.301
7.289
7.260
4.607
2.272
2.247
2.072
2.064
2.048
1.962
1.950
1.930
1.907
1.888
1.863
1.843
1.826
1.728
1.675
1.655
1.597
1.531
1.515
1.438
1.411
1.396
1.377
1.363
1.282
1.249
1.059
1.036
1.027
1.021
1.011
1.000
0.981
0.966
0.950
0.941
0.918
0.911
0.884
0.877
0.865
0.853
0.804
0.792
0.774
0.068


= Sch725674
2a
(4R,5S,7R,13R)
2b
(4R,5R,7R,13R)
2c
(4R,5S,7S,13R)
2d
(4R,5R,7S,13R)
2e
(4R,5S,7R,13S)
2f
(4R,5R,7R,13S)
2g
(4R,5S,7S,13S)
2h
(4R,5R,7S,13S)
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

The comparison of ^{13}C NMR spectra of triols **2a-2h** (150 MHz, MeOD-*d*4)

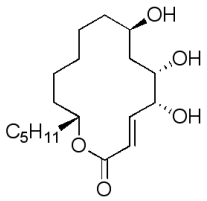


2a, COSY, MeOD, 500MHz

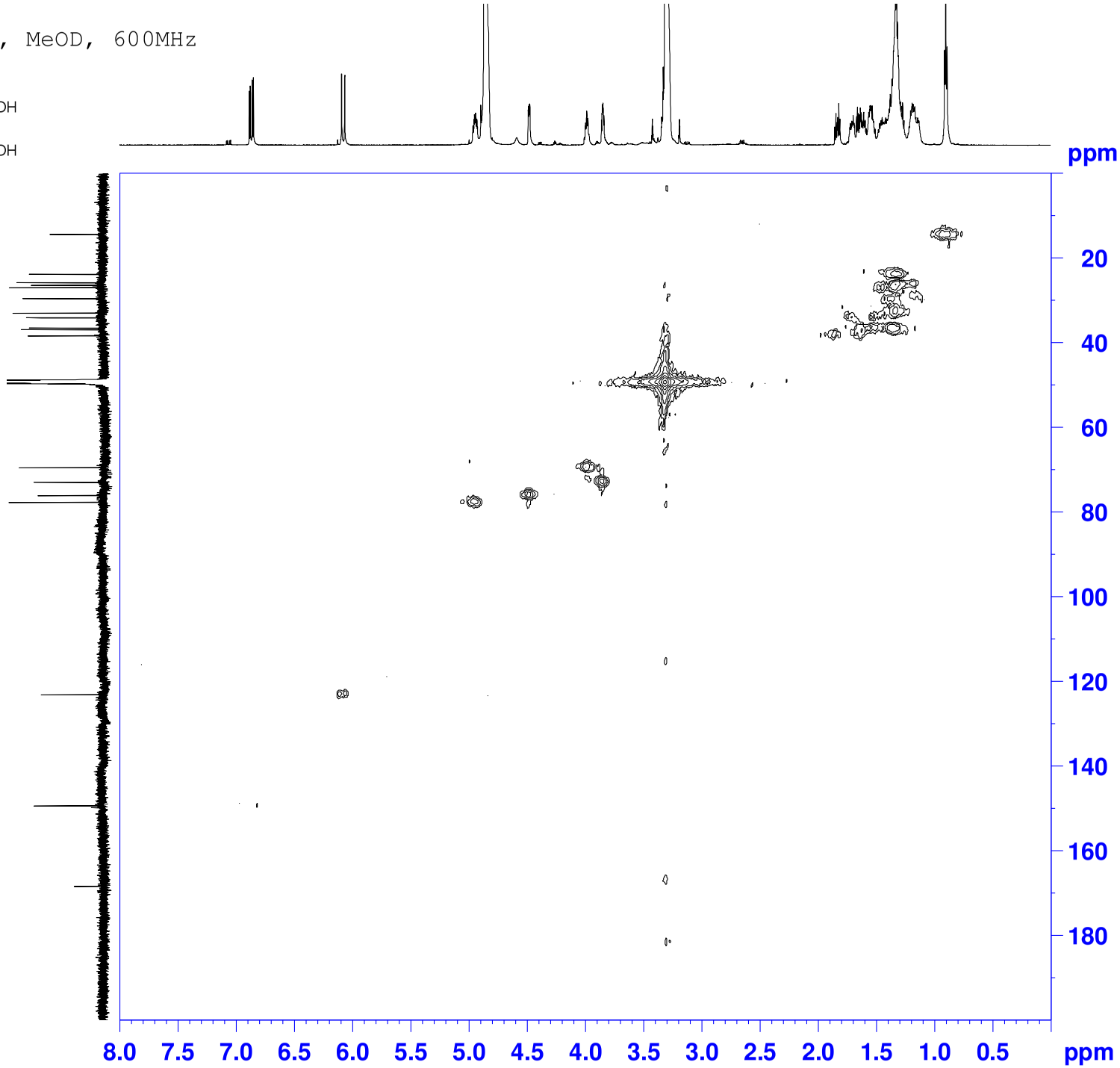


2a
(4*R*,5*S*,7*R*,13*R*)

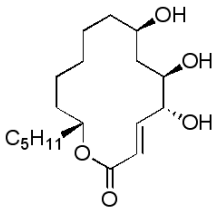
2a, HMQC, MeOD, 600MHz



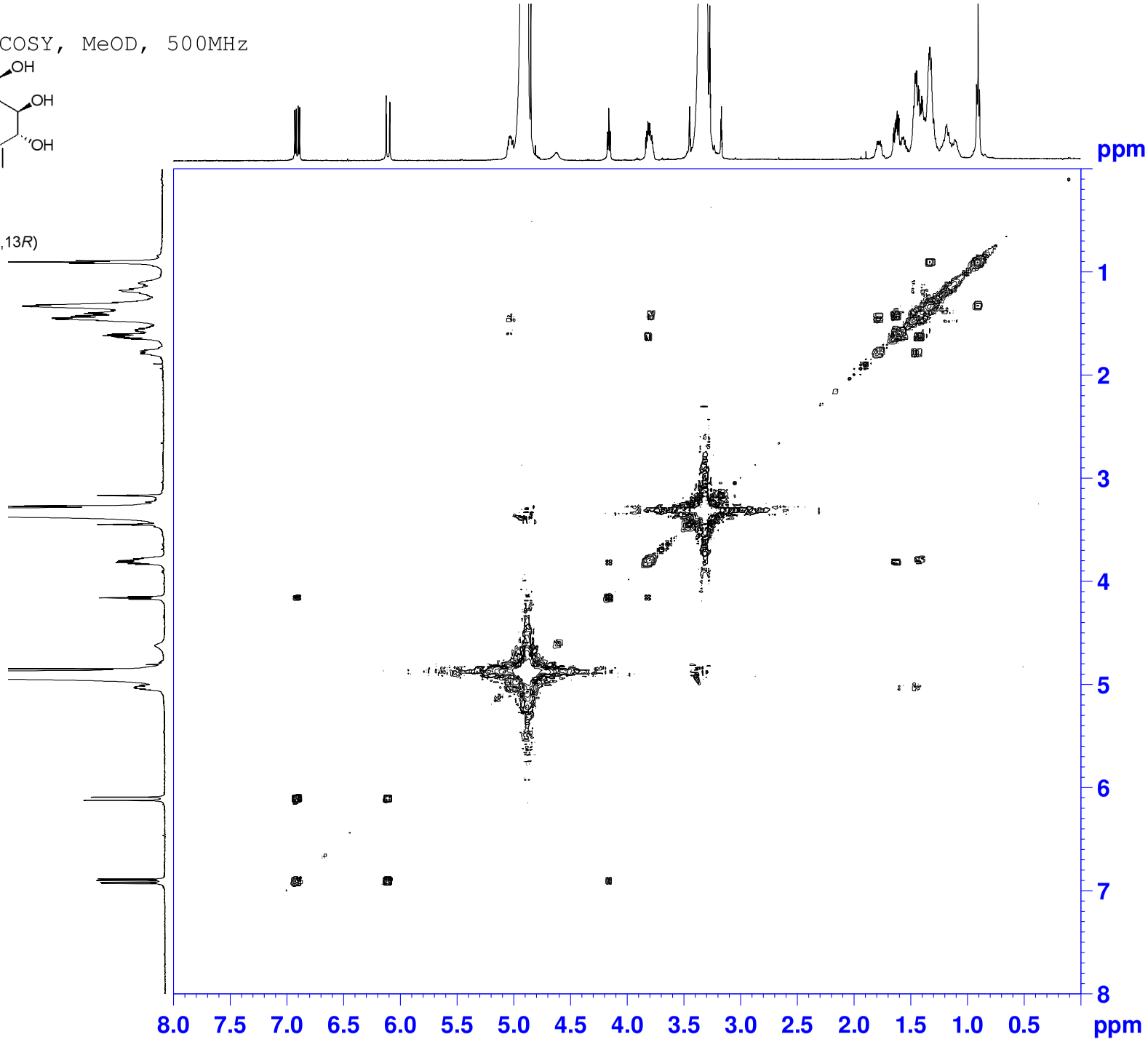
2a
(4*R*,5*S*,7*R*,13*R*)



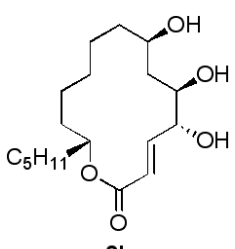
2b, COSY, MeOD, 500MHz



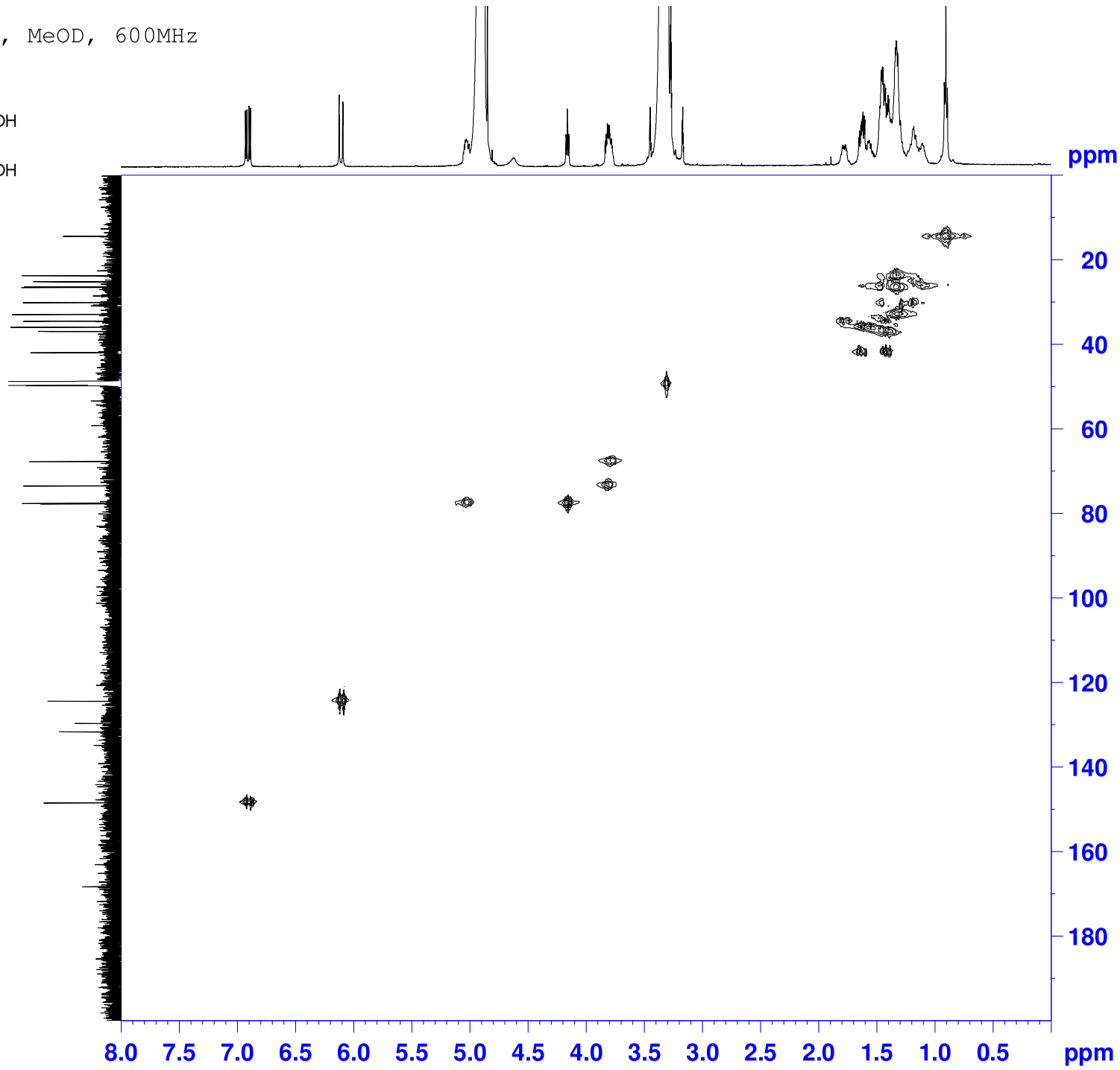
2b
(4*R*,5*R*,7*R*,13*R*)



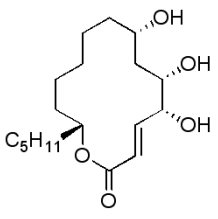
2b, HMQC, MeOD, 600MHz



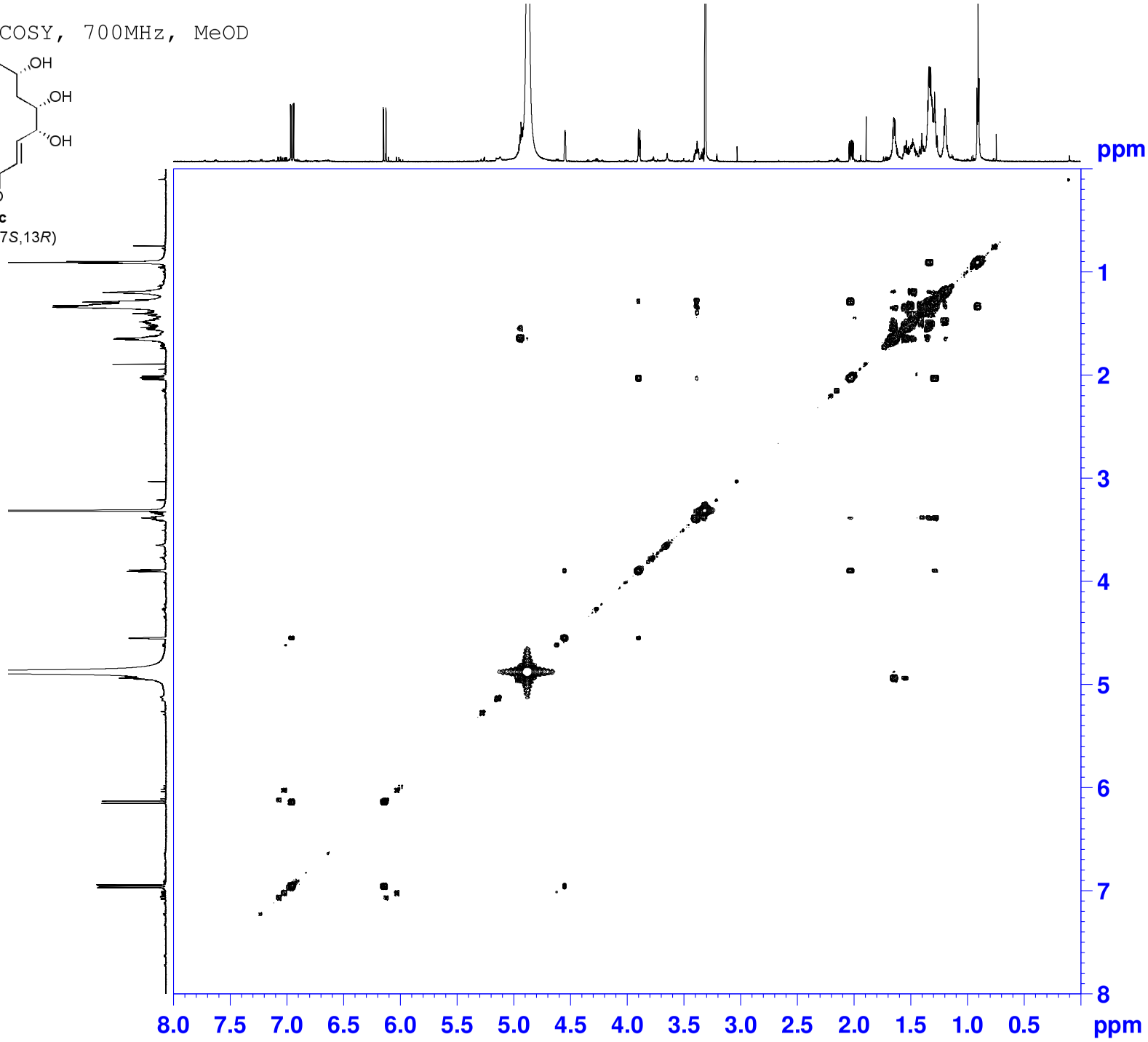
2b
(4*R*,5*R*,7*R*,13*R*)



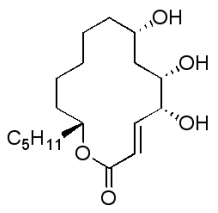
2c, COSY, 700MHz, MeOD



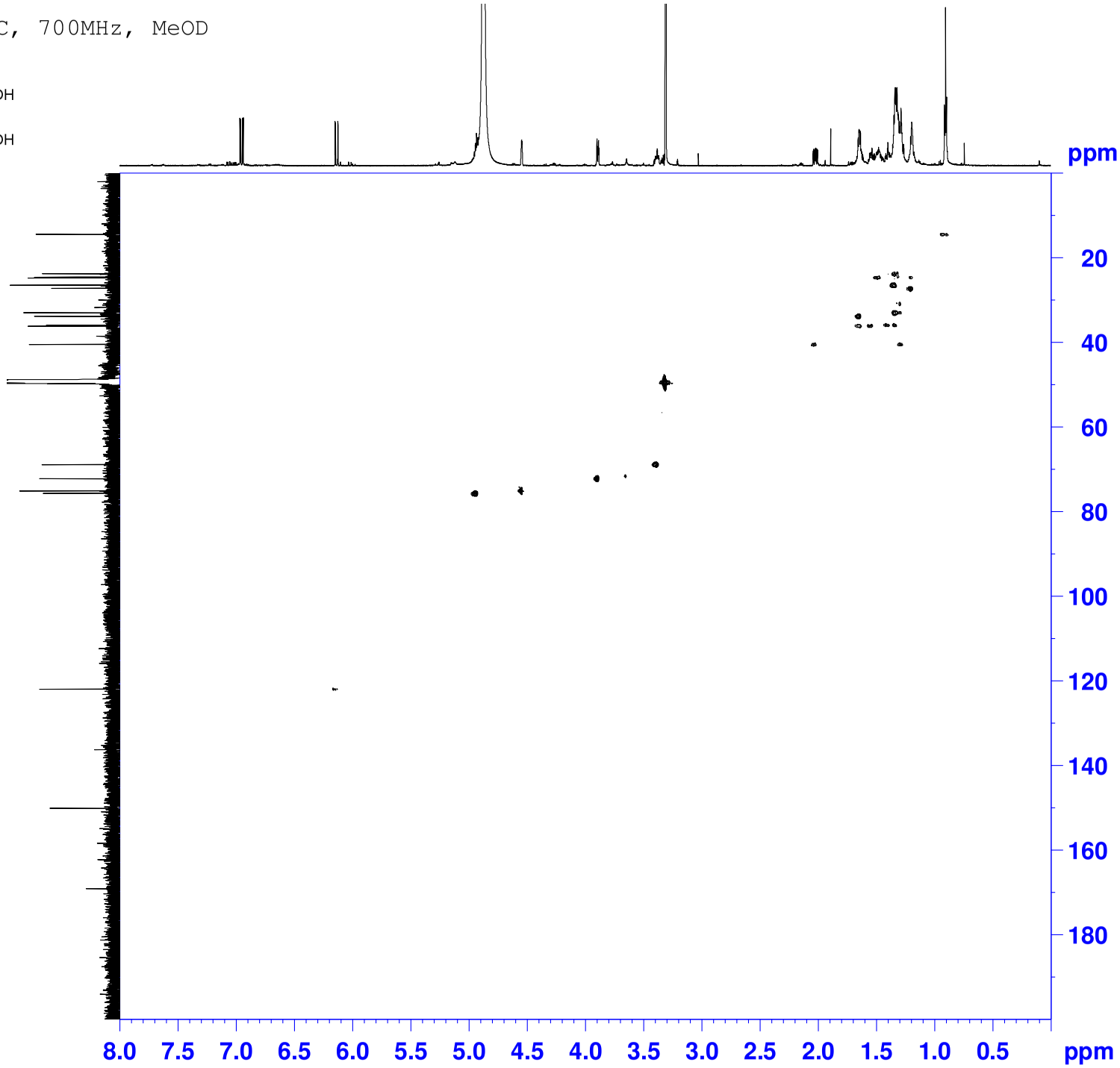
2c
(4*R*,5*S*,7*S*,13*R*)



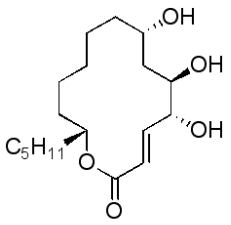
2c, HMQC, 700MHz, MeOD



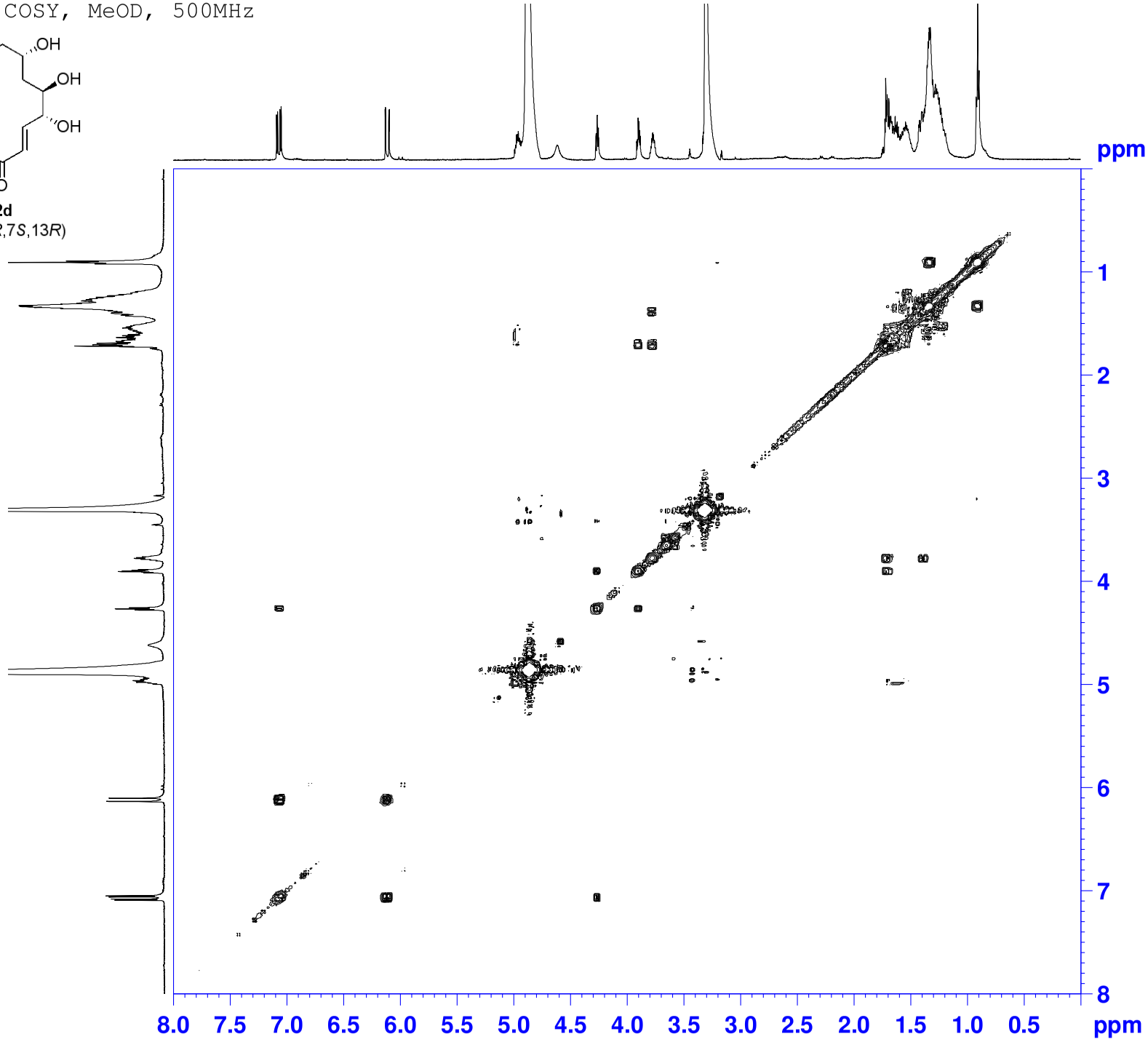
2c
(4*R*,5*S*,7*S*,13*R*)



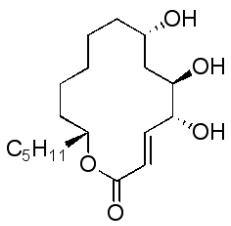
2d, COSY, MeOD, 500MHz



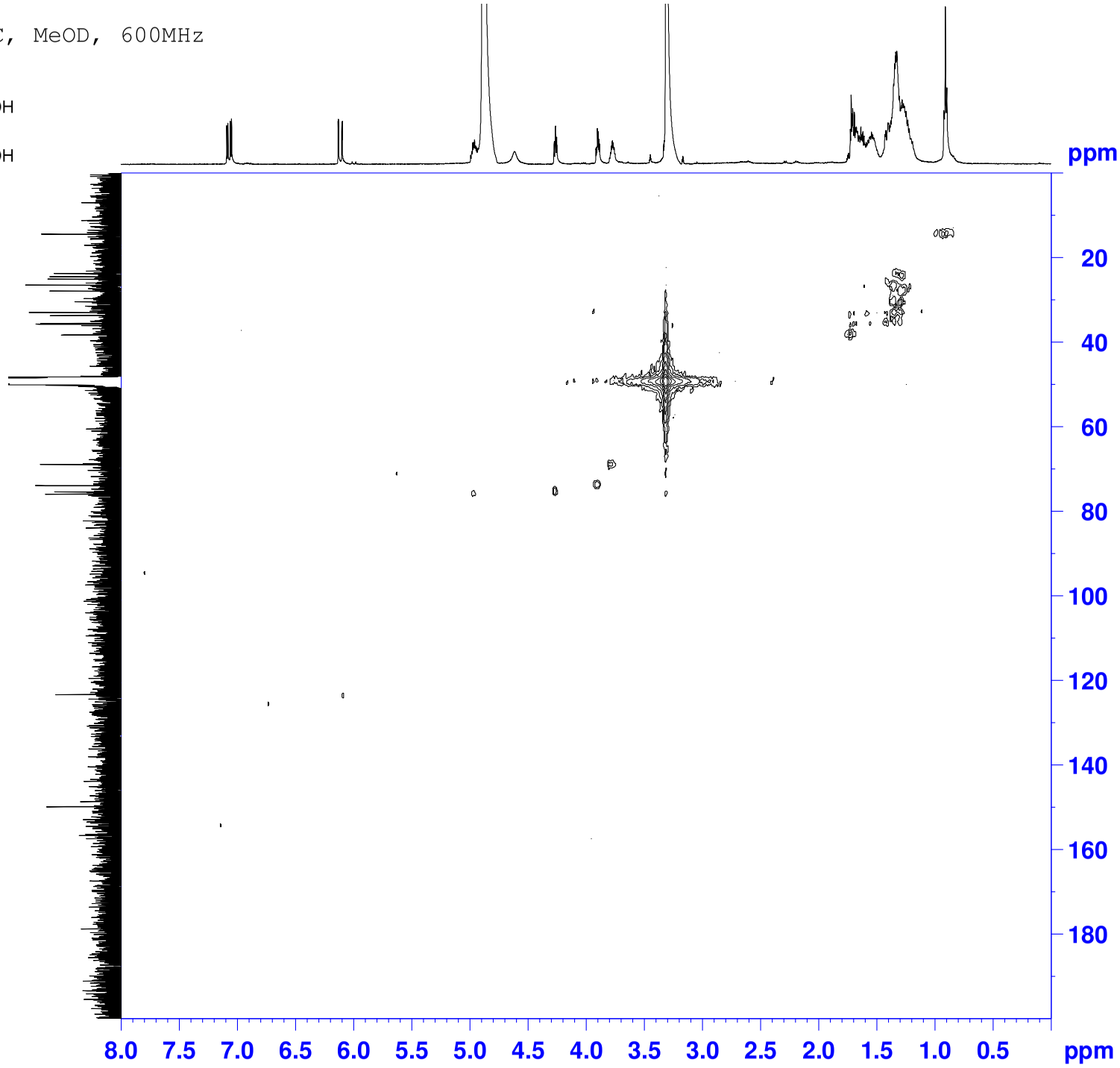
2d
(4*R*,5*R*,7*S*,13*R*)



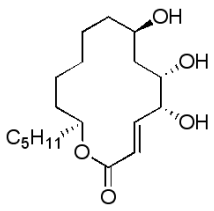
2d, HMQC, MeOD, 600MHz



2d
(4*R*,5*R*,7*S*,13*R*)

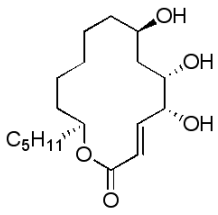


2e, COSY, 600MHz, MeOD



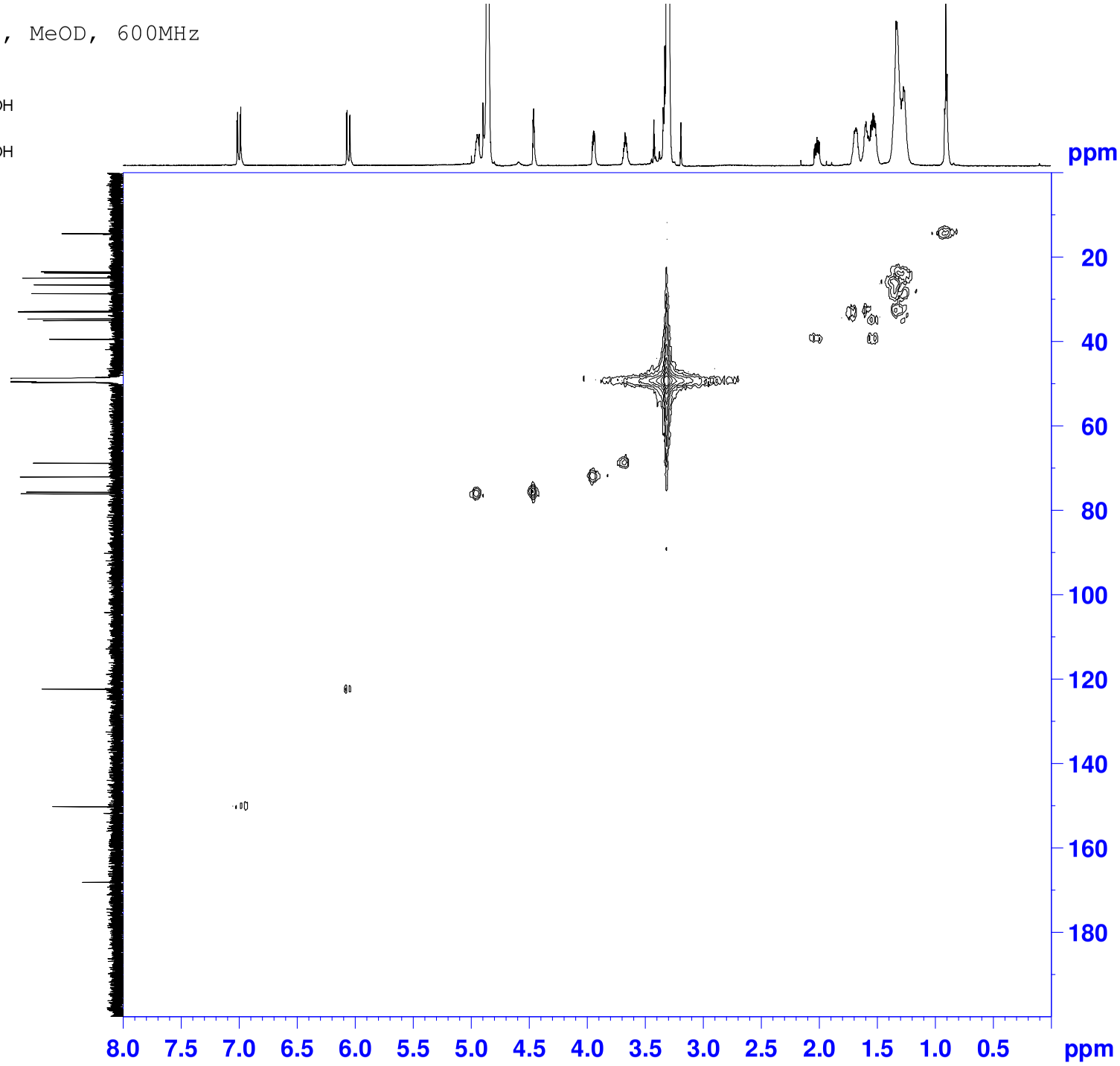
2e
(4*R*,5*S*,7*R*,13*S*)

2e, HMQC, MeOD, 600MHz

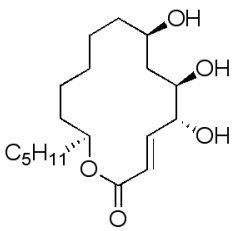


2e

(4*R*,5*S*,7*R*,13*S*)

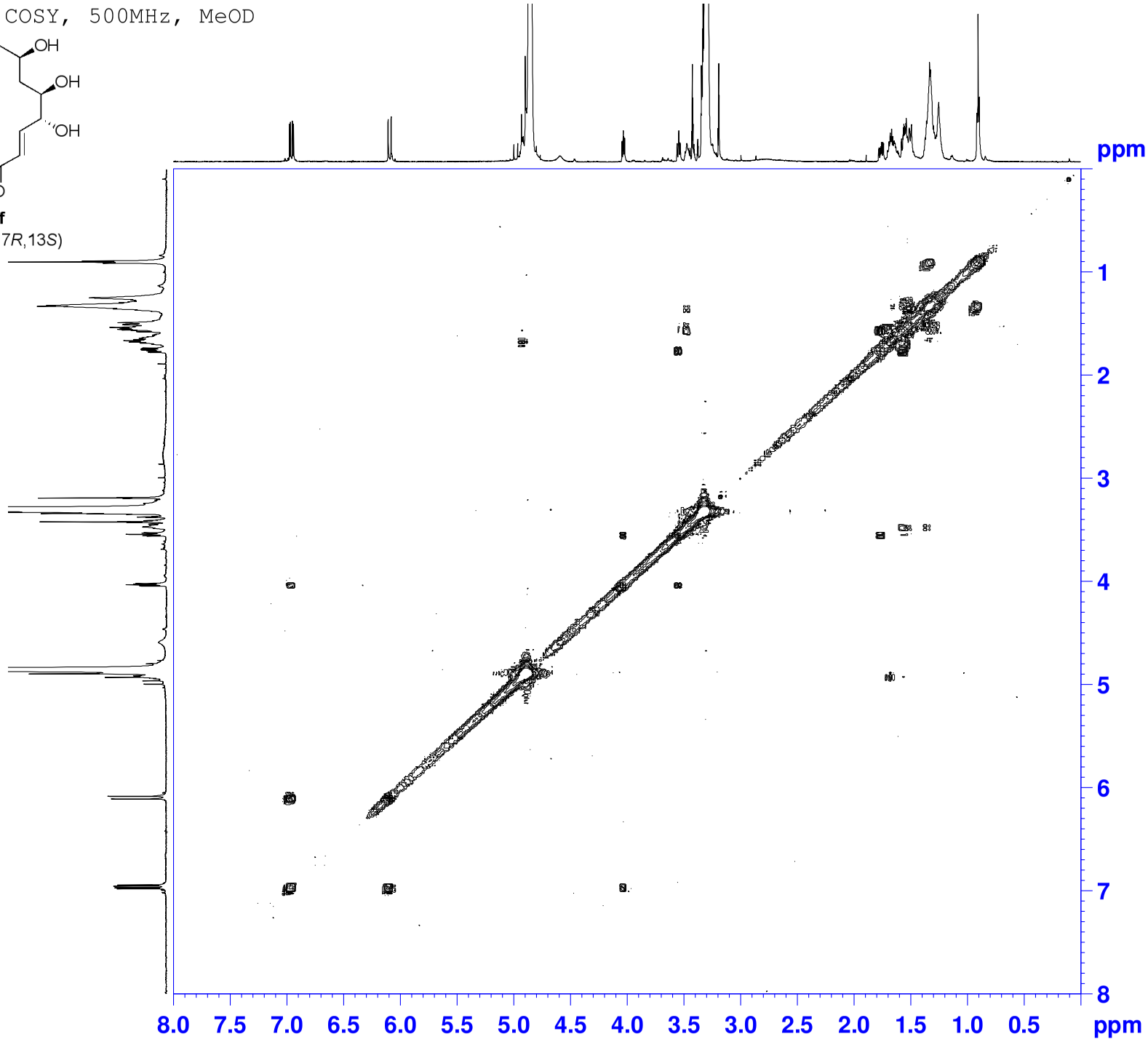


2f, COSY, 500MHz, MeOD

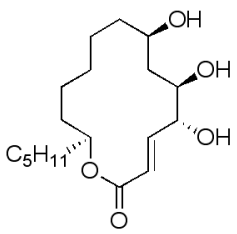


2f

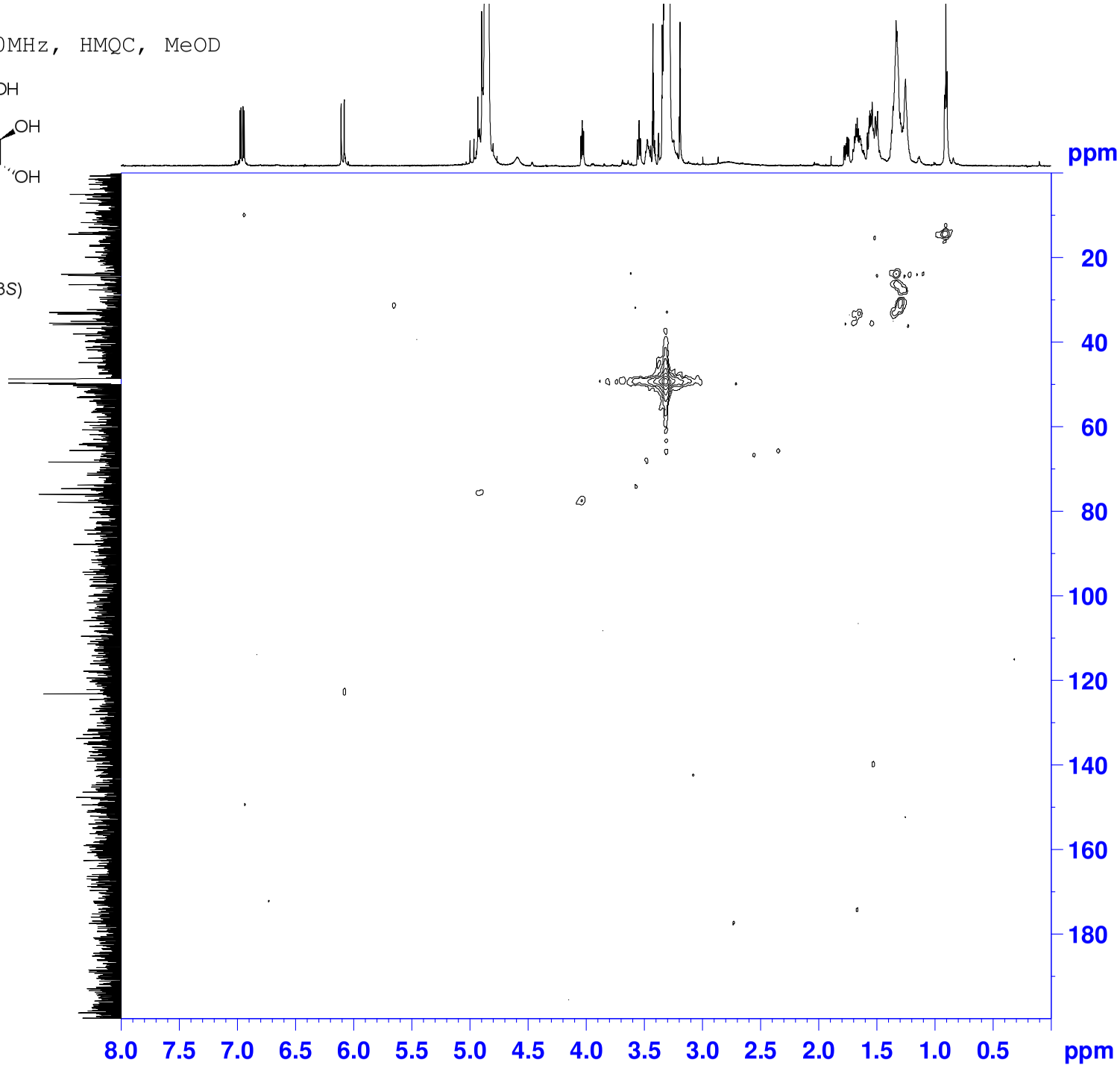
(4*R*,5*R*,7*R*,13*S*)

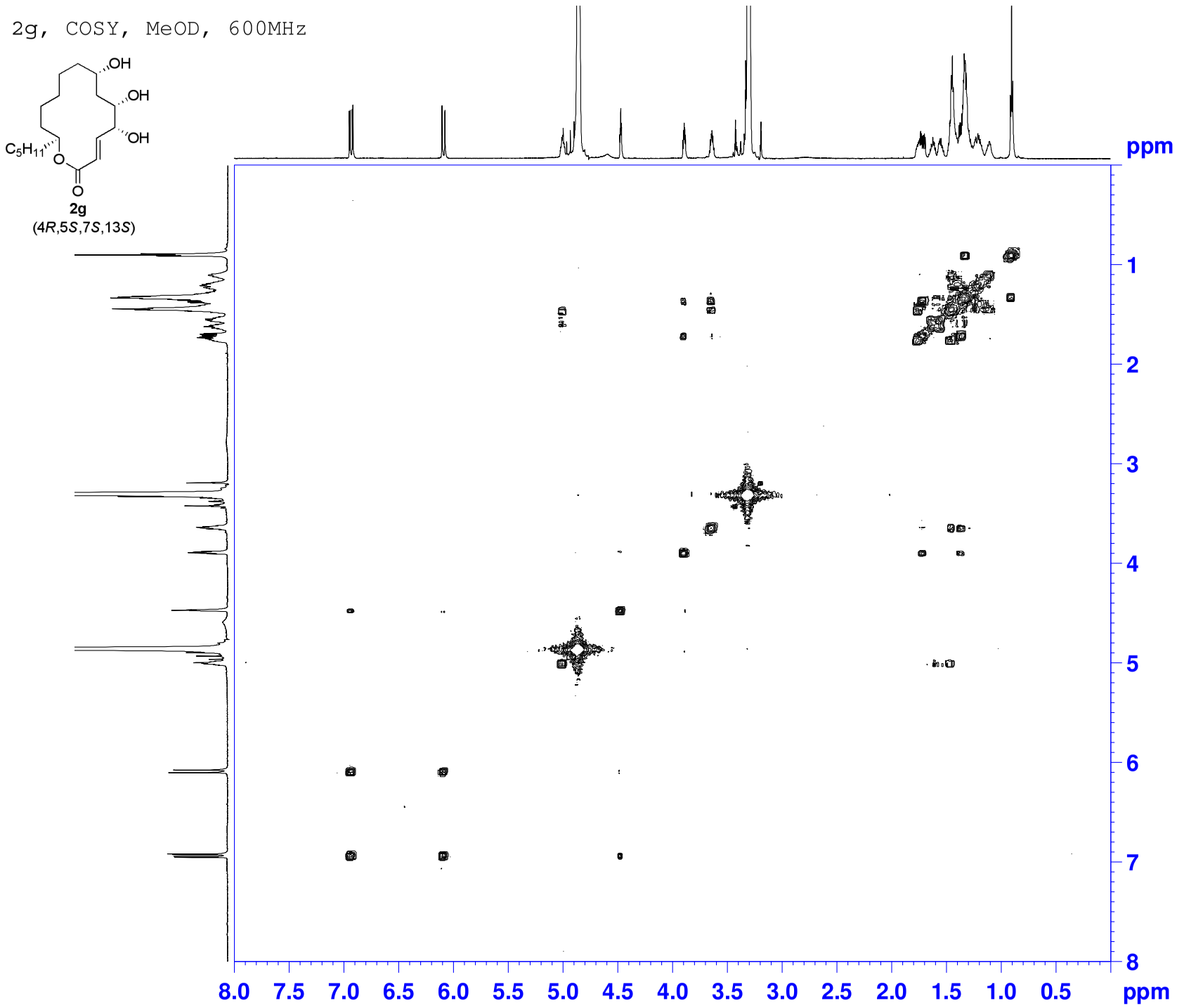


2f, 500MHz, HMQC, MeOD

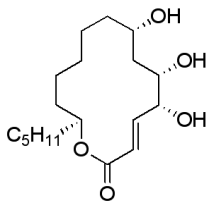


2f
(4*R*,5*R*,7*R*,13*S*)

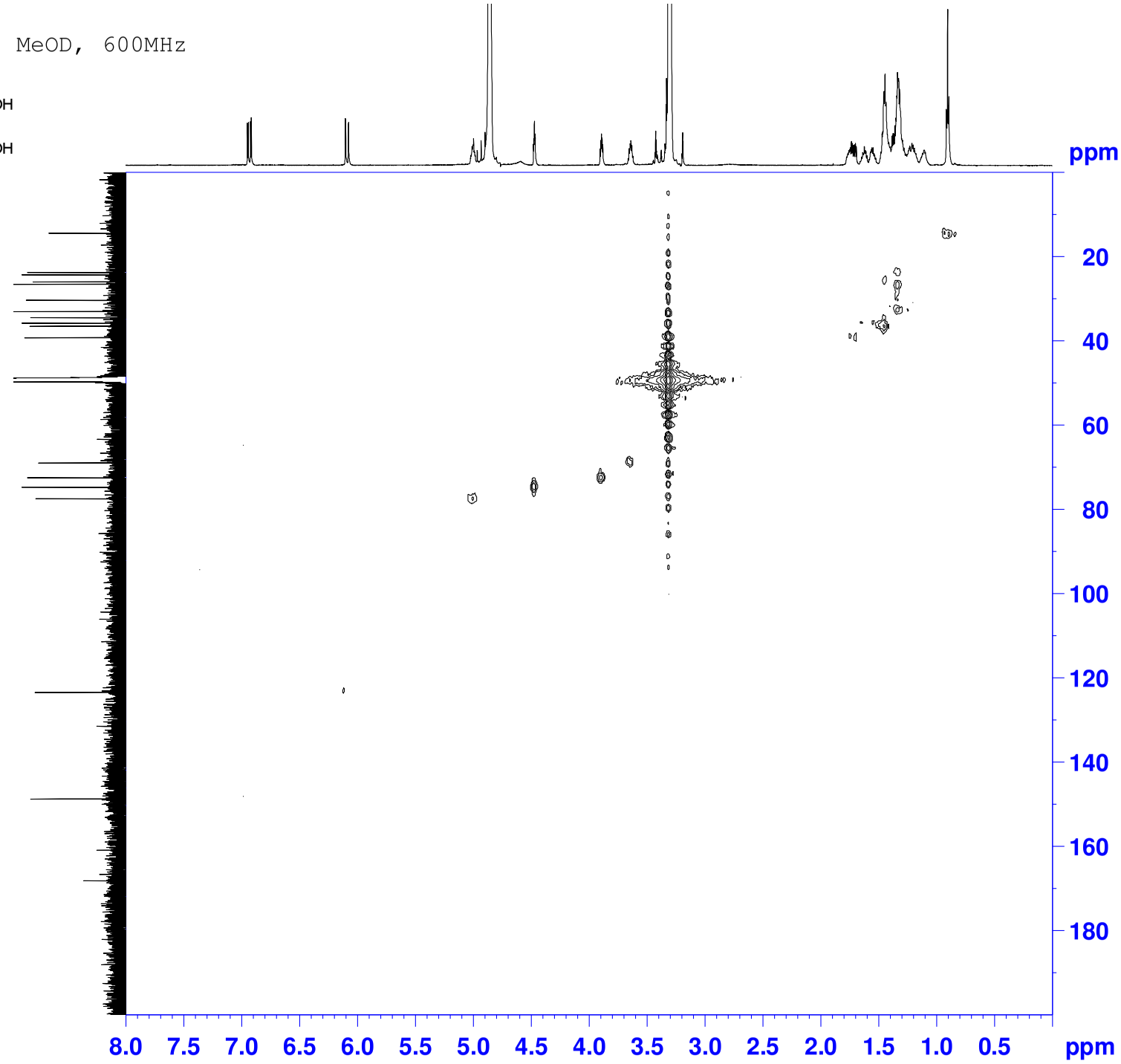



2g, COSY, MeOD, 600MHz
OH
OH
OH
C5H11
O
O
2g
(4R,5S,7S,13S)
ppm
1
2
3
4
5
6
7
8
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

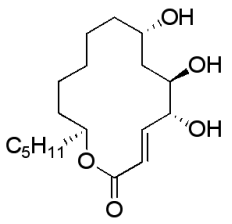
2g, HMQC, MeOD, 600MHz



2g
(4*R*,5*S*,7*S*,13*S*)



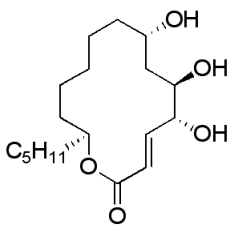
2h, COSY, 600MHz, MeOD



2h

(4*R*,5*R*,7*S*,13*S*)

2h, HMQC, 600MHz, MeOD



2h
(4*R*,5*R*,7*S*,13*S*)