FLUOROUS MIXTURE SYNTHESIS OF SCH725674 AND ITS FIFTEEN STEREOISOMERS

by

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Sch725674 is a 14-membered macrolactone isolated from the culture of an *Aspergillus* sp. by a group at Schering-Plough in 2005. A two-dimensional structure with four stereocenters was proposed for Sch725674, leaving sixteen candidate stereostructures for the natural product. Herein, we report the fluorous mixture synthesis (FMS) of all sixteen candidate stereoisomers of Sch725674 to determine its relative and absolute configuration. Initially, the synthesis of a single stereoisomer of Sch725674 was executed to secure a route to the natural product and to confirm the 2D connectivity of Sch725674. The synthesis established in the single isomer pilot study was then applied to the FMS of the 4,5-*trans*-dihydroxy isomer family of Sch725674, in which all eight members bear a *trans* relationship between the C4 and C5 stereocenters. An eight-member library of ring-open Sch725674 analogs was also prepared by demixing and detagging two intermediate mixtures from the FMS of the 4,5-*trans*-dihydroxy isomer family. We then executed a second, parallel FMS of the 4,5-*cis*-dihydroxy family of Sch725674, in which each member has a *cis* relationship between the C4 and C5 stereocenters. All three of these libraries employed a new minimalist tagging strategy which used two sorting tags in an FMS, only one of which was fluorous. By comparing spectra of the macrocycle library members with each other and the natural product, we confidently assigned the absolute configuration of natural Sch725674 as (4*R*,5*S*,7*R*,13*R*).

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$_t$Bu	*tert*-butyl
COSY	correlation spectroscopy
DBU	1,8-diazabicyclo-[5.4.0]-undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutyl aluminum hydride
DIPT	diisopropyl tartrate
DH	Duthaler-Hafner
DMAP	4-dimethylamino pyridine
DMF	*N*,*N*′-dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EI	electron ionization
equiv	equivalents
ESI	electrospray ionization
Et	ethyl
FMS	fluorous mixture synthesis
HKR	hydrolytic kinetic resolution
HMBC	heteronuclear multiple bond coherence
HMQC	heteronuclear multiple quantum coherence
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
IR	infrared spectrometry
LRMS	low resolution mass spectrometry
Me	methyl
MS	mass spectrometry
MTPA	α-methoxytrifluorophenylacetic acid
NMR	nuclear magnetic resonance
Ph	phenyl
PMB	*p*-methoxybenzyl
$_i$Pr	isopropyl
PTSA	*p*-toluenesulfonic acid
Py	pyridine
rt	room temperature

SAD	Sharpless asymmetric dihydroxylation
SAE	Sharpless asymmetric epoxidation
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TOCSY	total correlation spectroscopy
TLC	thin layer chromatography
TfO	triflate
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TPA	trimethylphosphonoacetate

PREFACE

I would like to thank my research advisor, Professor Dennis P. Curran, for his patience and guidance during the last four years. The warm atmosphere in his research group has been a hospitable environment for all of us to mature as free-thinking scientists. During the past years in the Curran group, I've had the privilege of learning among some truly talented people from every corner of the world. I'd like to thank all members of the Curran group both past and present for their friendship, help, and moral support – there are too many wonderful people in the group to name them all here! Special thanks go to Professor Seth Horne for serving as my proposal mentor. Also, special thanks are due to Professors Doemling, Floreancig, and Wilcox for serving on my thesis committee and for their valuable comments. I would also like to thank my undergraduate advisor from the Lehigh University, Professor Robert Flowers, for being one of the first ones to excite me about scientific research. Thank you ***everyone***.

This dissertation is dedicated to my wife Melissa – my constant companion. Without her love and encouragement over the years, I would never have survived the rigors of a higher education. In addition, I credit my parents Andrew and Denise Moretti for all of the wonderful years of life that I've enjoyed. My older brother Adam and younger sister Carolyn have also been sorely missed during my extended stay in school. Lastly, I'd like to include my late grandfathers, Mario and Michael, in the dedication of this thesis – for whom my title of "Dr. Moretti" would have meant so much.

1.0 INTRODUCTION

A natural product stereoisomer library is a partial or full set of possible enantiomers and diastereomers for a given natural product. The synthesis and biological evaluation of such libraries is valuable due to the intrinsic relationship between the three-dimensional structure of a natural product and the binding site of its biological target, usually the active site of a protein. Stereochemistry is therefore a relevant parameter for variation in any structure-activity relationship study.[1-3] In addition, a stereoisomer library is a useful tool for rigorously assigning the absolute configuration of non-crystalline natural products whose stereoisomers may have similar, or even indistinguishable, spectral or optical properties. Natural product stereoisomer libraries are rare, however, because they are relatively inaccessibile by typical "one-at-a-time" reaction sequences.[4-6] The main problem with the traditional serial or parallel synthesis of stereoisomer libraries lies in the exponential doubling of work during the course of the synthesis. The reaction products must be divided into two portions prior to the installation of each new stereocenter and then carried along separately.[7]

1.1 FLUOROUS MIXTURE SYNTHESIS

The problem of synthesizing natural product stereoisomers one at a time began to fade in the 1990s with the emergence of combinatorial synthetic methods, particularly solid-phase mixture

synthesis,[8,9] in which reactions are conducted on mixtures of compounds to reduce the number of individual reactions executed. For instance, Takahashi and coworkers reported the combinatorial synthesis of a macrosphelide library on solid support.[10] Waldmann and coworkers later synthesized all stereoisomers of cryptocarya diacetate on polymer support.[11] Compared to conventional solution-phase methods, however, the solid-phase mixture synthesis approach for small molecules is limited by unfavorable heterogenous reaction kinetics, longer development times, and difficulties during analysis of resin-bound intermediates.[12] To date, the breadth of mixture synthesis reactions developed for solid-phase synthesis remains limited.

By the turn of the millennium, techniques of solution-phase mixture synthesis had emerged which complemented solid-phase methods.[13,14] While such mixture synthesis reactions are straightforward, the analysis, identification, and ultimate separation of individual, pure target molecules by solution-phase methods were longstanding problems. The new technique of "fluorous mixture synthesis" (FMS) solves these problems with the use of perfluoroalkyl sorting tags.[15-17] Precursors are labeled with "fluorous tags" differing in fluorine content, and the resulting tagged substrates are mixed and carried through a sequence of reactions.[18] Throughout the FMS, intermediate mixtures can be separated at any point based on the fluorous tags ("demixed") to isolate pure, single compounds. The demixing stage of FMS is performed over a fluorous stationary phase by using high-performance liquid chromatography (HPLC) and relies on elution of tagged substrates in order of increasing fluorine content.[19,20] The combination of fluorous tags as "molecular labels" with this systematic HPLC separation method makes FMS the first solution-phase mixture synthesis technique that allows for isolation of pure, individual compounds.

1.1.1 Tagging Strategies in FMS

In recent years, two main tagging methods have emerged for the incorporation of fluorous tags into organic substrates for the purpose of natural product stereoisomer library synthesis – single-tagging and double-tagging. In single-tagging, the encoded stereocenters are premade and pretagged with one tag. The common approach was illustrated by the synthesis of all sixteen stereoisomers of the pinesaw fly sex pheromone.[21] The problem with single-tagging is that one tag is needed for each isomer. This problem can be mitigated by splitting, though extra reactions are needed. The single-tagging strategy successfully encoded the configurations of all library members, requiring only 44 individual reactions and four fluorous tags to synthesize the full library. Compared to a traditional "one at a time" approach, FMS saved a total of 132 steps, thereby providing more compounds per unit work.

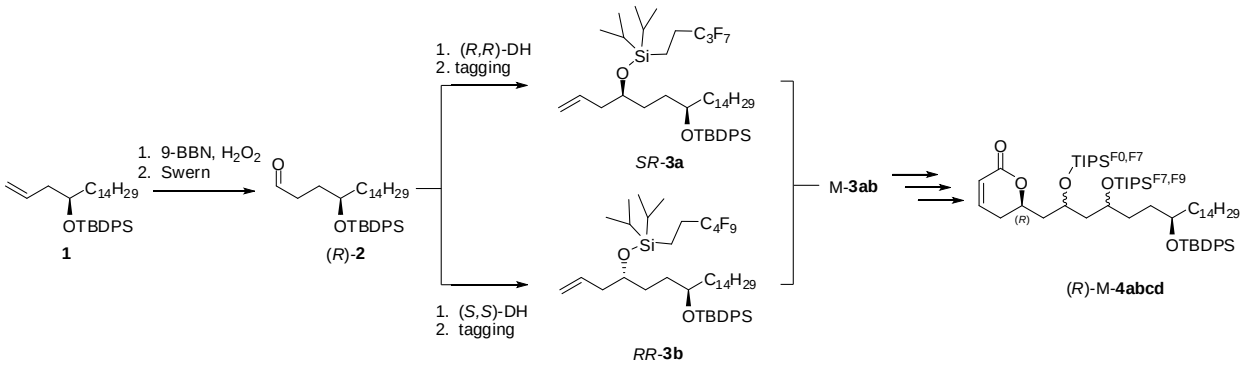
The efficiency and throughput of FMS were extended when the double-tagging method was introduced in a synthesis of sixteen stereoisomers of the acetogenin murisolin.[22] Fluorous tags were used in conjunction with orthogonal oligo-ethylene glycol (OEG) tags and isolation of the final products synthesis was achieved by "double demixing" with two separate demixing processes that target each class of sorting tag. Double tagging in the murisolin synthesis economized the available fluorous tags and OEG tags by using eight tags to encode sixteen compounds.

The double-tagging strategy was further expanded by only using fluorous tags with *en route* tagging used in a library synthesis of passifloricin A.[7] Pairwise combinations of three different fluorous tags were used *en route* after introduction of each new stereocenter in both possible configurations. The aggregate fluorine content of the tagged molecules was determined by two fluorous tags, whereas a single fluorous tag had been used in all previous work. Only

three tags were needed to encode four compounds in a mixture. The *en route* double tagging approach economizes steps because the route diverges during stereocenter introduction and tagging, but then immediately reconverges.

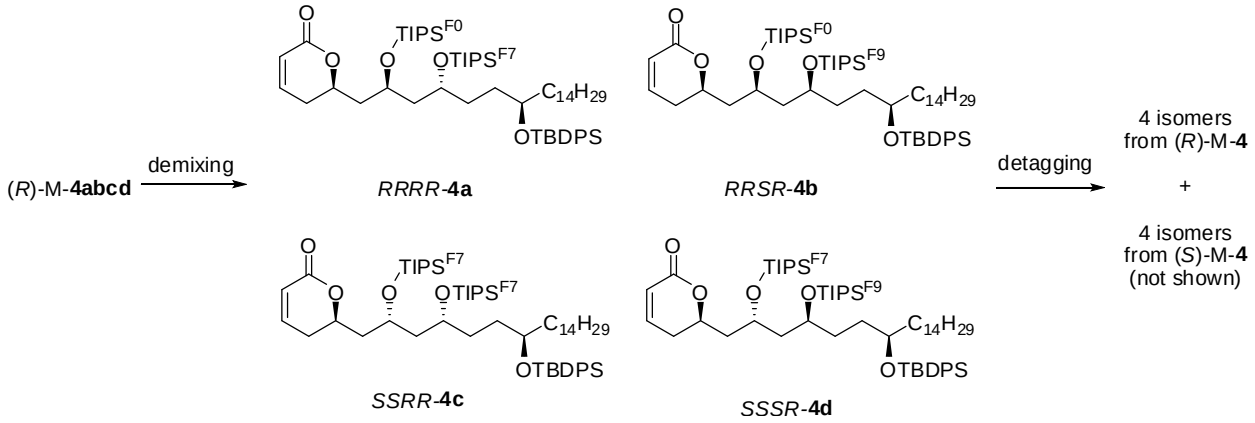
To illustrate the different stages of FMS in the context of a natural product stereoisomer library with double-tagging, Scheme 1.1 shows an abridged sequence from the Curran group's synthesis of the passifloricin A stereoisomer library. During the premixing stage alkene **1** was subjected to a hydroboration-oxidation sequence to afford aldehyde **2**. The next phase involved the splitting of **2** into two nearly equal portions, then treatment of one portion with the (*S,S*)-Duthaler-Hafner (DH) allytitanocene,[23] and the other with the (*R,R*)-DH-reagent. The resulting homoallylic alcohols were separately tagged by perfluoroalkyl silyl triflates to afford the quasiisomers[24] ("quasi" because the compounds are not true isomers due to the fluorous tags) *SR*-**3** and *RR*-**3**. The fluorous tags used in the passifloricin synthesis were the perfluoroalkyl analogs of the triisopropylsilyl (TIPS) ether (hereafter referred to as $TIPS^{Fn}$, where *n* is the number of fluorine atoms in the perfluoroalkyl chain). As shown in Scheme 1.1, the tags on *SR*-**3** and *RR*-**3** differ by only two fluorine atoms. The uniquely tagged compounds *SR*-**3** and *RR*-**3** were then mixed in nearly equal batches to form the first mixture M-**3ab,** thus initiating the mixture synthesis stage. The mixture M-**3ab** was taken through several additional steps (not shown) during which a second stereocenter was introduced in both possible configurations and tagged, to conclude the mixture synthesis stage with the four-compound mixture (*R*)-M-**4abcd**. Here, two- and four-compound mixtures are denoted with the prefix "M" and the letters of the respective quasiisomers. The contents of any mixture can thus be traced to the original quasiisomers by letters.

Scheme 1.1. Premixing and mixture synthesis stages during passifloricin FMS



The pairwise combination of tags employed in the *en route* tagging strategy provided four products, each having different numbers of fluorine atoms. The unambiguous demixing of (*R*)-M-**4abcd** was accomplished in accordance with the principle of fluorine additivity during fluorous chromatography. The four products in (*R*)-M-**4abcd** were demixed with the quasiisomer *RRRR*-**4a** (bearing seven fluorine atoms) eluting first, followed by those bearing 9 (*RRSR*-**4b**), 14 (*SSRR*-**4c**), and 16 (*SSSR*-**4d**) fluorine atoms. These final, demixed compounds were next subjected to four parallel detagging reactions in the post-mix stage to afford four individual isomers of the natural product. Likewise, four additional stereoisomers of passifloricin A were isolated from the demixing and detagging of (*S*)-M-**4abcd** (steps not shown).

Scheme 1.2. Post-mix stage of passifloricin FMS



Thanks to these kinds of "proof-of-principle" studies, it is now possible to make stereoisomer libraries of natural products for structural assignment and/or biological testing. Our group has recently applied the single or double FMS tagging strategies to the synthesis of four diastereomers each of lagunapyrone,[25] cytostatin,[26] (–)-dictyostatin,[27] and petrocortyne A.[28] To move the field forward, it is important to expand the scope of FMS by targeting stereoisomer libraries of more structurally diverse natural products. New minimalist tagging strategies in FMS to economize the available perfluoroalkyl sorting tags would also be beneficial.

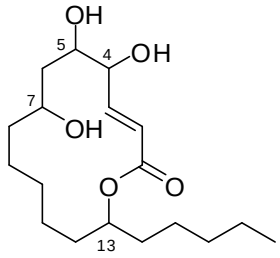
1.2 MACROLACTONE NATURAL PRODUCTS

A common structural motif present in many natural products is a macrocyclic ester.[29] Such "macrolactones" are believed to balance conformational preorganization with flexibility to achieve optimal binding properties to their biological targets.[30] Macrolactones are attractive synthetic targets because of their interesting structures, and because many macrolactones harbor potent biological activity often unrivaled by smaller-ring compounds.[31]

1.2.1 Sch725674

Sch725674 is a novel macrolactone recently isolated from a culture of an *Aspergillus* sp. by a group at Schering-Plough and assigned the 2D structure shown as **5** (Scheme 1.3).[32] Sch725674 displayed antifungal activity against *Saccharomyces cerevisiae* and *Candida albicans* with MICs 8 and 32 μg/mL, respectively. The connectivity of **5** was established by extensive 2D NMR spectroscropic analysis, including HMBC, HSQC-TOCSY, and HSQC experiments. The structure of **5** consists of a 14-membered α,β-unsaturated lactone, containing a 4,5,7-hydroxyl stereotriad as well as a pentyl sidechain at C13. The *E*-geometry of the double bond was assigned based on the coupling constant between the olefinic protons (15.8 Hz). Due to the small quantity of the isolated sample (~1 mg), the configurations of the four oxygenated methine stereocenters could not be established. This leaves sixteen candidate stereostructures for natural Sch725674.

Scheme 1.3. Proposed 2D structure of Sch725674



5, Sch725674

Most macrolactones feature both hydroxyl and methyl groups along their carbon skeleton (Scheme 1.4).[33,34] Macrocycles with 14-membered mono-lactone skeletons lacking extensive methyl substitution on the ring are very rare in nature, with gloeosporone being the only other

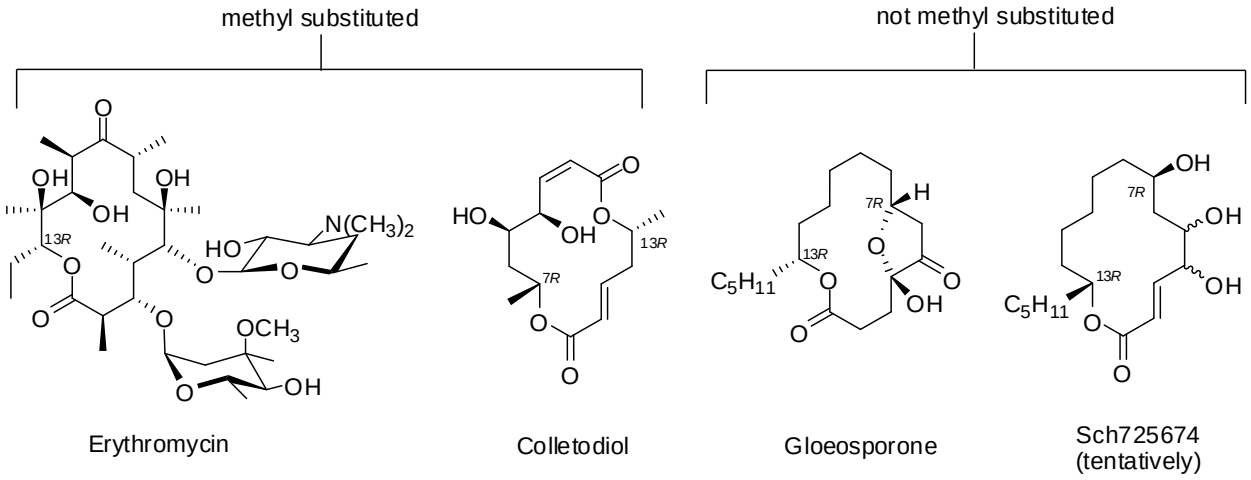
well-known member of this class.[35-38] Once we isolate all sixteen stereoisomers of Sch625674, we can assign the absolute configuration of the natural product and evaluate the biological activity of the full library. Synthesis of the Sch725674 stereoisomer library will also provide insight on how stereochemistry affects the overall optical, spectroscopic, and biological properties of this natural product.

1.2.2 Macrolactone Stereochemistry

While the library should provide a firm assignment, the assignment of absolute configuration to Sch725674 is complicated by a lack of an optical rotation measurement and by a lack of a pure sample of the natural product. Interestingly however, the structural assignment of many macrolides can be predicted by a striking stereochemical regularity that exists within this class of molecules.[39] Celmer's rule, as anunciated by Seebach,[36] states that all 14-membered macrolactones for which absolute configurations have been determined bear the 13*R* configuration. In addition, all 14- to 18-membered macrolactones which contain the 4,7- or 4,5,7-oxygenation pattern have the 7*R* configuration. Applying the Celmer rule to Sch725674, therefore, the (7*R*,13*R*) configuration of **5** is more probable than that of its enantiomer. A few 14-membered macrolactones obeying Celmer's rule are shown in Scheme 1.4.

Since there are no known exceptions to Celmer's rule, we propose that Sch725674 has the *R* configuration at C13. This proposition cannot be tested. However, Celmer's rule also provides the relative configuration of C7 and C13 (both *R*), and this proposition can be tested by the stereoisomer library synthesis. Thus, if Celmer's rule provides the correct relative configuration, then it should also provide the correct absolute configuration.

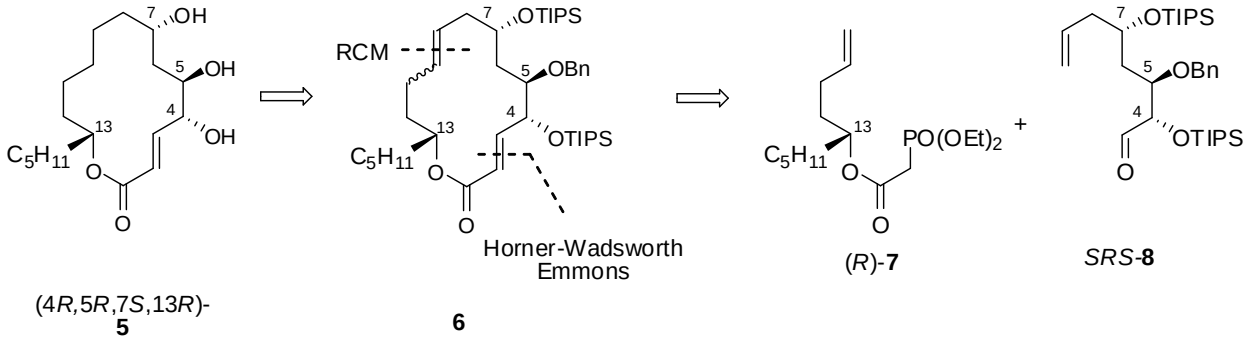
Scheme 1.4. Representative 14-membered macrolactones obeying Celmer's rule



1.3 INITIAL STUDIES BY DR. XIAO WANG

The first objective of a stereoisomer library synthesis is often to conduct a pilot synthesis of a single stereoisomer to develop a concise and selective route toward the natural product. In addition, an effective tagging strategy of the precursors must be identified for the analysis and demixing of mixtures. The (4*R*,5*R*,7*S*,13*R*)-**5** stereoisomer of Sch725674 was made by Dr. Xiao Wang[40] by a ring-closing metathesis (RCM)[41-46] approach for closing the 14-membered ring, as shown by the retrosynthesis in Scheme 1.5. The triol **5** could be produced by a partial hydrogenation and global deprotection of the ring-closed macrolactone **6**. The key intermediate **6** in turn could be produced by RCM of the Horner-Wadsworth-Emmons (HWE) olefination[47-49] product of phosphonate ester (*R*)-**7** and α-chiral aldehyde *SRS*-**8**.

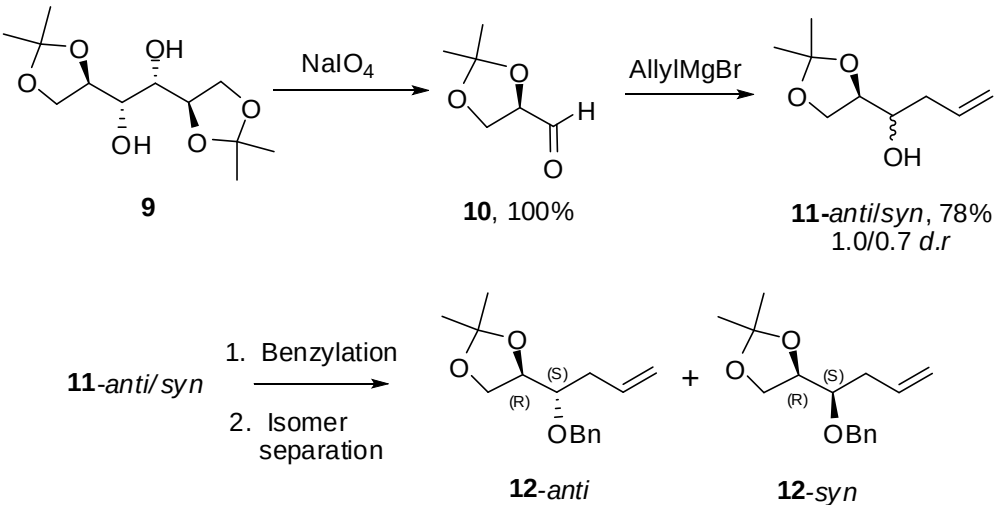
Scheme 1.5. Retrosynthetic analysis of (4*R*,5*R*,7*S*,13*R*)-5



1.3.1 Preparation of Aldehyde *SRS*-8

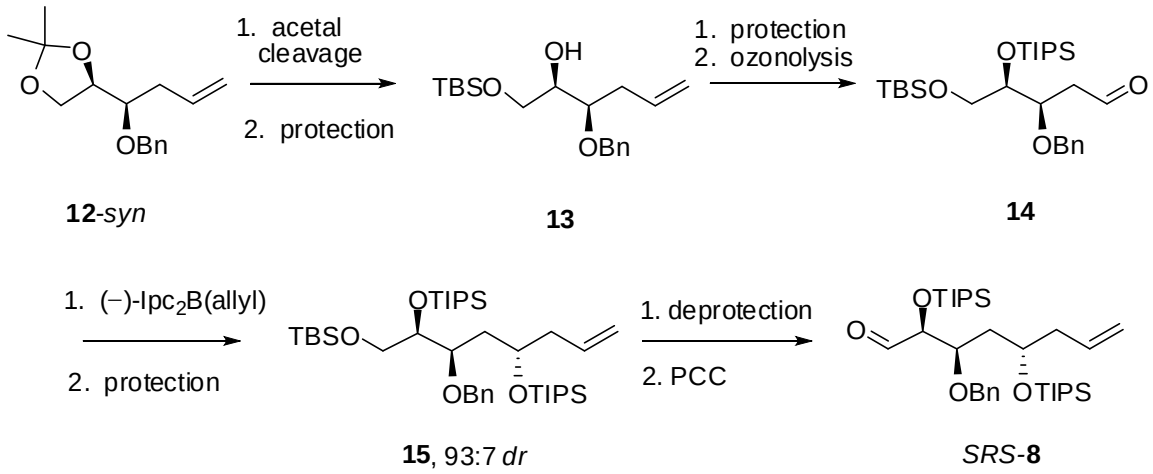
Wang's synthesis started with the cleavage of commercially available diol **9** with sodium metaperiodate to deliver D-glyceraldehyde acetonide **10** (Scheme 1.6).[50] Addition of allyl magnesium bromide to **10** provided a 0.7/1.0 mixture of diastereomeric alcohols, **11**-*syn* and **11**-*anti*. The mixture was directly benzylated and the resulting known isomers[51] **12**-*syn* and **12**-*anti* were separated by flash chromatography.

Scheme 1.6. Synthesis of key intermediates 12-*anti* and 12-*syn*



The acetal of the **12**-*syn* isomer was then cleaved with $FeCl_3 \cdot 6H_2O$, and the primary alcohol was subsequently protected as the *t*-butyldimethylsilyl (TBS) ether **13** (Scheme 1.7). The free alcohol **13** was protected as the secondary TIPS ether, which was subjected to an ozonolysis of the terminal olefin to yield the aldehyde **14**. Asymmetric allylboration of **14** with the commercially available (–)-Ipc_2B(allyl) reagent followed by protection of the homoallylic alcohol with TIPSOTf gave silyl ether **15**. The TBS ether was selectively desilylated, and the free alcohol was oxidized by PCC to afford the key intermediate *SRS*-**8**.

Scheme 1.7. Completion of fragment *SRS*-8

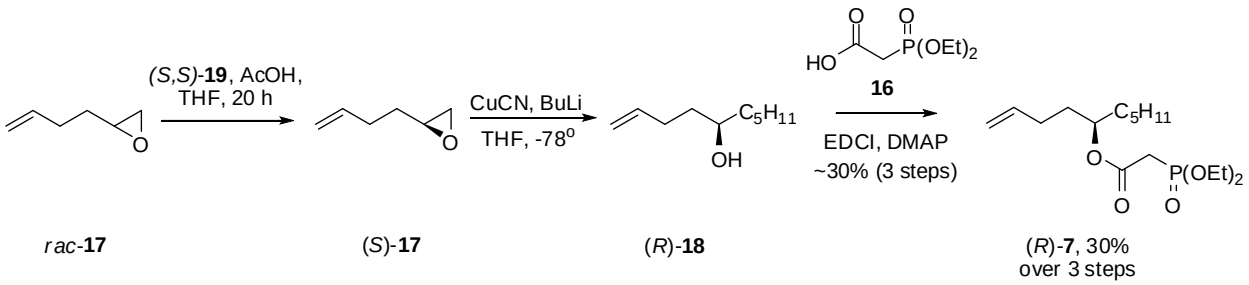


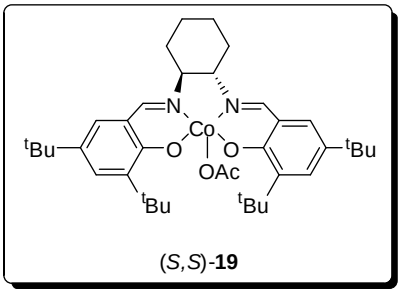
1.3.2 Completion of the Pilot Synthesis of a Single Stereoisomer

Fragment (*R*)-**7** was synthesized by Mr. Claude Ogoe in three steps starting from racemic 1,2-epoxy-5-hexene, *rac*-**17** (Scheme 1.8). The racemate was resolved by a hydrolytic kinetic resolution (HKR)[52] by reaction of (*S*,*S*)-**19** with *rac*-**17** to afford (*S*)-**17**. The epoxide was then opened upon exposure to dibutyllithium cyanocuprate[53] to furnish alcohol (*R*)-**18**, which was esterified with phosphonic acid **16** to deliver fragment (*R*)-**7** in about 30% yield over three steps.

The enantiomer (*S*)-**7** (not shown) was prepared analogously by using the (*R*,*R*)-**19** catalyst in this three step sequence.

Scheme 1.8. Preparation of fragment (*R*)-7

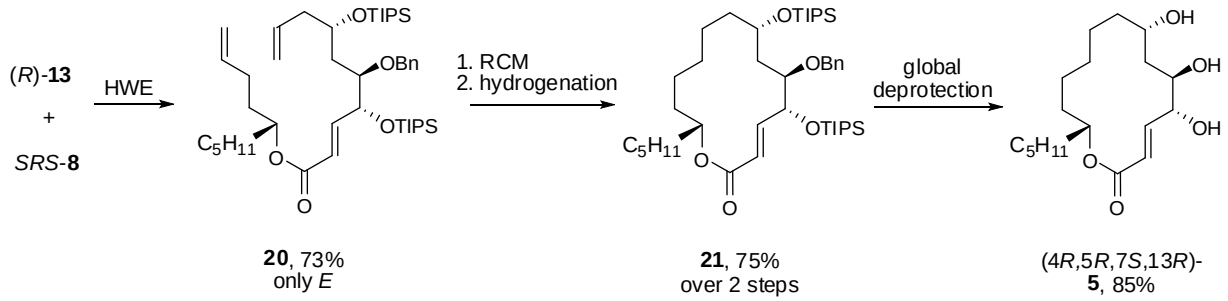




(*S*,*S*)-**19**

Fragments (*R*)-**7** and *SRS*-**8** were subjected to an HWE olefination under the Masamune-Roush[54] conditions to afford ester **20** as a single *E*-isomer (Scheme 1.9). The ester was cyclized by RCM upon reaction with a stoichiometric amount of the 1st generation Grubbs catalyst (Grubbs I, 1 equiv) in CH_2Cl_2 at reflux for 14 h. The resulting macrolactone was partially hydrogenated[55] using the Rosenmund catalyst under an atmosphere of hydrogen gas to afford **27**. The pilot synthesis was completed by a global deprotection with BF_3•Et_2O and ethanethiol[56] to afford the final triol (4*R*,5*R*,7*S*,13*R*)-**5** in 85% yield. The 2D connectivity prescribed in the isolation of **5** was supported, but the NMR spectra of synthetic (4*R*,5*R*,7*S*,13*R*)-**5** did not match the natural product. Therefore, the (4*R*,5*R*,7*S*,13*R*) configuration is not correct for Sch725674.

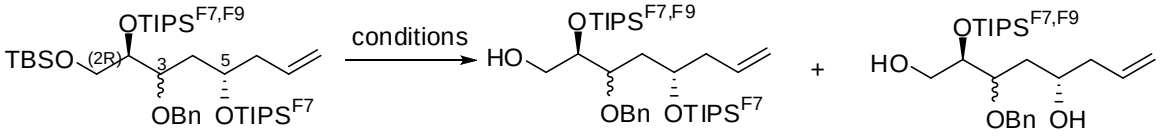
Scheme 1.9. Completion of the single isomer synthesis



1.3.3 FMS of the 4*R* Series of Sch725674

Dr. Wang then applied the pilot synthesis to an FMS of eight stereoisomers of Sch725674, all containing the 4*R* configuration. However, a major problem was encountered at a late stage of the FMS - the selective cleavage of the TBS ether in the two-compound mixture M-**22** (Table 1-1). As shown in entries 1-3, all attempts to selectively cleave the primary TBS ether of M-**22** resulted in concomitant desilylation of the C5 fluorous tag, providing low yields of the desired alcohol M-**23** and the diol M-**24**. Ultimately, the low yield of mixture M-**23** upon reaction of mixture M-**22** with H_2SiF_6 in buffered acetonitrile (entry 1) was accepted and the FMS resumed.

Table 1-1: Chemoselective cleavage conditions for the TBS ether in M-22

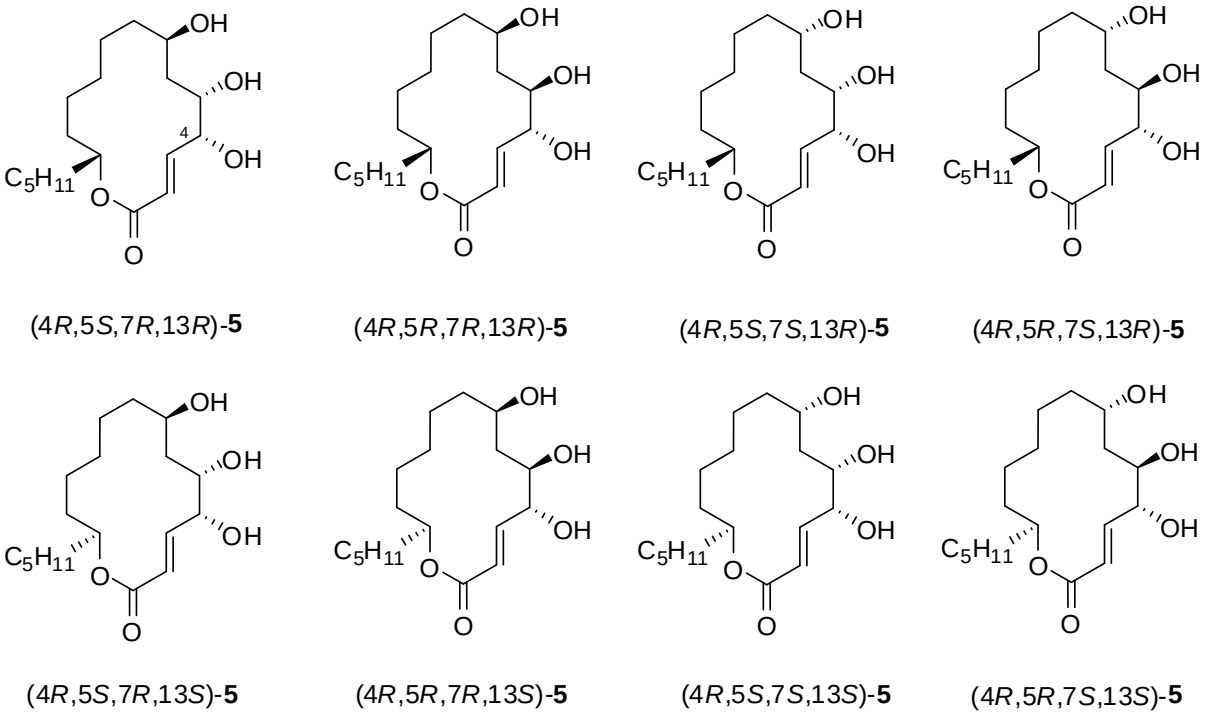


M-**22** M-**23** M-**24**

entry	conditions	yield
1	H_2SiF_6, Et_3N, MeCN, 0°C-rt, 1h	M-**23**, 29%; M-**24**, 27%
2	$BF_3{\cdot}Et_2O$, $CHCl_3$, 0°C-rt, 1h	M-**24**, 75%
3	K_2CO_3, MeOH, rt, 24 h	no reaction

Later, reproducibility problems were encountered with both the RCM and partial hydrogenation steps. Despite the problems, eight stereoisomers of **5** were isolated (Scheme 1.10) in very low quantities (<1 mg for each isomer). Based on Celmer's rule and comparison of the ^{1}H NMR spectra of the four triols to the literature, Dr. Wang tentatively assigned the absolute configuration of the natural product as (4*R*,5*S*,7*R*,13*R*)-**5**. Although the 4*R* enantioseries of Sch725674 was successfully prepared by Dr. Wang, the low isolated quantities posed a problem for full spectroscopic characterization and biological evaluation.

Scheme 1.10. Isolation of eight 4*R* diastereomers of Sch725674 by FMS



1.3.4 New Directions for the FMS of the Sch725674 Stereoisomer Library

My objective was to prepare more of the 4*R*-Sch725674 enantiomeric series for biological evaluation and adequate spectroscopic characterization. In addition, the 4*S* enantioseries was to

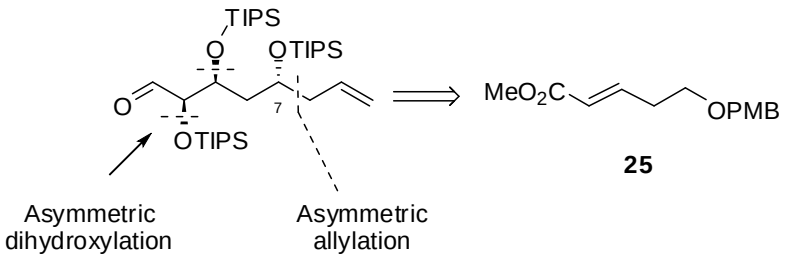
be prepared along with a library of ring-open Sch725674 analogs. To meet these objectives, a better-yielding synthesis needed to be developed. Also, a better fluorous tagging strategy that leverages the available fluorous tags was to be realized.

2.0 2ND GENERATION PILOT SYNTHESIS OF A SINGLE STEREOISOMER OF SCH725674

2.1 REVISED RETROSYNTHESIS OF ALDEHYDE 8

To avoid the late-stage desilylation problem with Dr. Wang's FMS plan, a new synthetic route was devised and a fresh pilot synthesis of a single stereoisomer of **5** was executed. A retrosynthesis of key fragment *RSR*-**8** is shown in Scheme 2.1. We hypothesized that the vicinal diol of *RSR*-**8** could be installed by the Sharpless asymmetric dihydroxylation (SAD)[57,58] of ester **25**. The homoallylic stereocenter at C7 could then be set and encoded by a reagent-controlled asymmetric allylation followed by protection of the homoallylic alcohol. Finally, a partial reduction of the ester will deliver the key aldehyde *RSR*-**8** and avoid the chemoselectivity issues that Dr. Wang encountered. In addition, the use of only silyl protective groups was expected to simplify the global deprotection step.

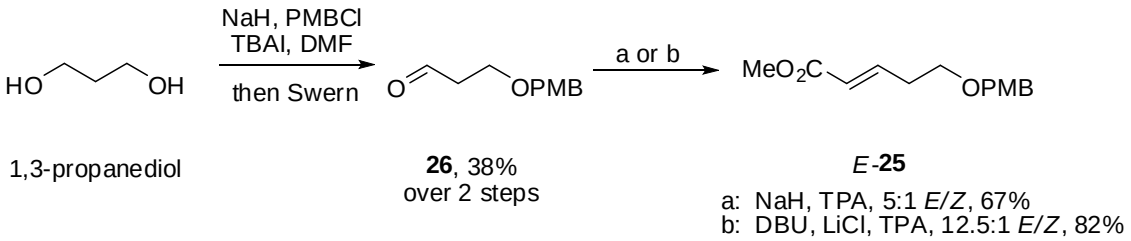
Scheme 2.1. Retrosynthesis of fragment *RSR*-8



RSR-**8**

The initial task in the synthesis of *RSR*-**8** was to develop a concise method for preparing the unsaturated methyl ester **25** (Scheme 2.2). Treatment of commercially available 1,3-propanediol with NaH, *p*-methoxybenzyl chloride (PMB-Cl), and tetrabutylammonium iodide (TBAI) afforded a primary alcohol, which upon Swern oxidation[59] gave the known aldehyde[60] **26** in 38% yield over two steps. Treatment of **26** with trimethylphosphonoacetate (TPA) and NaH as base with no additive[49] (*a* in Scheme 2.2) afforded **25** as a 5:1 *E/Z* mixture as determined by ^{1}H NMR analysis of the crude product. Flash chromatography afforded the desired ester *E*-**25** in 62% yield. Treatment of **26** with TPA in the presence of 1,8-diazabicyclo-[5.4.0]-undec-7-ene (DBU) and LiCl[54] under the Masamune-Roush conditions afforded a 12.5:1 mixture of *E/Z* isomers as determined by ^{1}H NMR analysis of the crude product. Flash chromatography afforded pure *E*-**25** in 82% yield. This three step sequence was scaled up to provide >13 g of pure *E*-**25**.

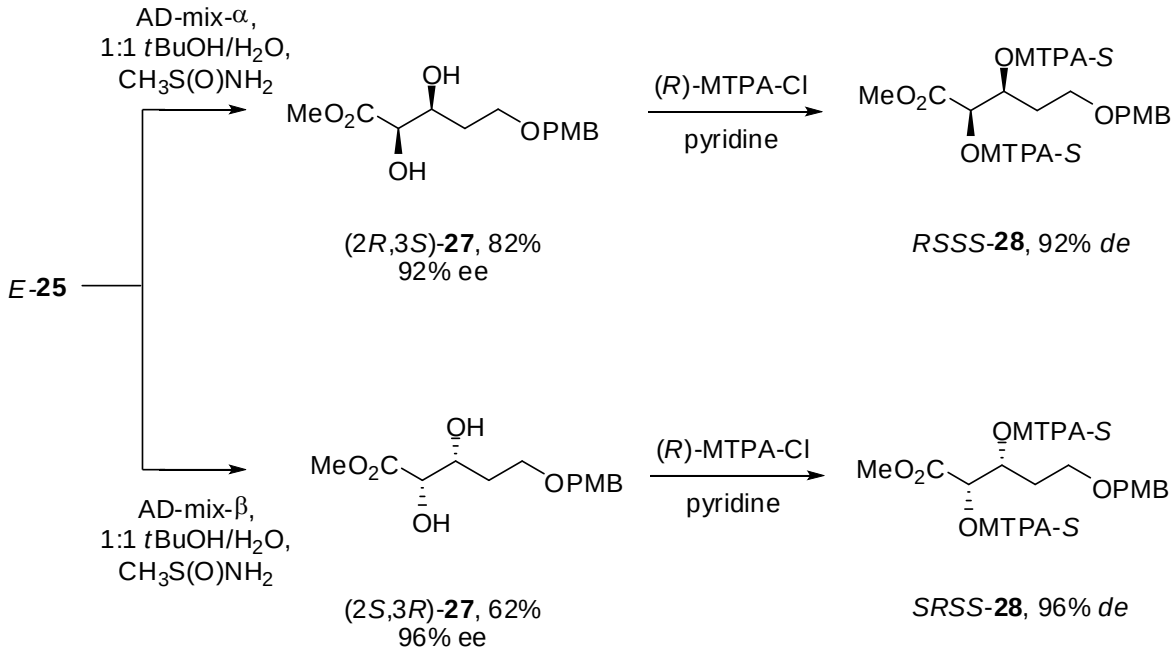
Scheme 2.2. Preparation of methyl ester *E*-25



The ester *E*-**25** was then subjected to the typical SAD conditions as shown in Scheme 2.3. Treatment of *E*-**25** with AD-mix-α in the presence of methanesulfonamide (2 equiv) in 1:1 tBuOH/H_2O afforded diol (2*R*,3*S*)-**27** in 82% yield. Likewise, reaction of *E*-**25** with AD-mix-β afforded (2*S*,3*R*)-**27** in 62% yield. The configurations of the products **27** were assigned by the mnemonic device developed by Sharpless and coworkers.[57,58] To assess enantiomeric excess

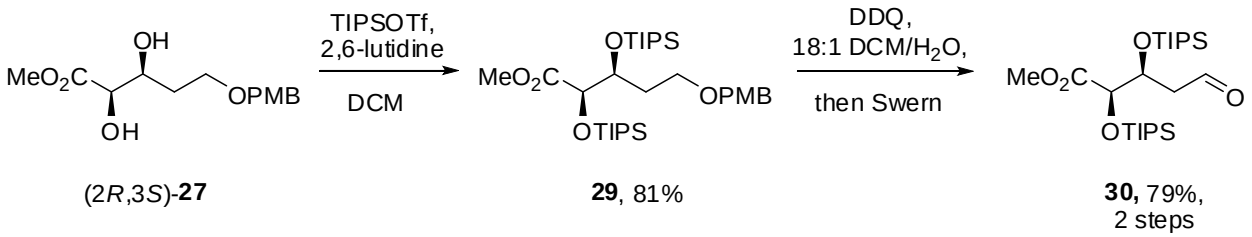
(ee), each enantiomer of **27** was treated with excess (*R*)-α-methoxy-α-trifluouromethyl-α-phenylacetyl chloride (MTPA-Cl, or Mosher chloride) in pyridine to furnish the *bis*-Mosher esters *RSSS*-**28** and *SRSS*-**28**.[61-63] Integration of the major and minor singlets in the ^{19}F NMR spectra of the two crude Mosher ester samples indicated enantiomeric excesses of 92% and 96% for the AD-mix products (2*R*,3*S*)-**27** and (2*S*,3*R*)-**27**, respectively.

Scheme 2.3. Synthesis and enantiomer analysis of SAD diols 27



The next several steps of the pilot synthesis set the stage for the asymmetric allylation to install the homoallylic stereocenter (Scheme 2.4). *Bis*-silylation of diol (2*R*,3*S*)-**27** with triisopropylsilyl triflate (TIPSOTf, 2.5 equiv) and 2,6-lutidine provided **29** in 81% yield. Oxidative cleavage of the PMB group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[64] was followed by Swern oxidation[59] to provide the key aldehyde **30** in 79% yield over two steps.

Scheme 2.4. Preparation of aldehyde 30

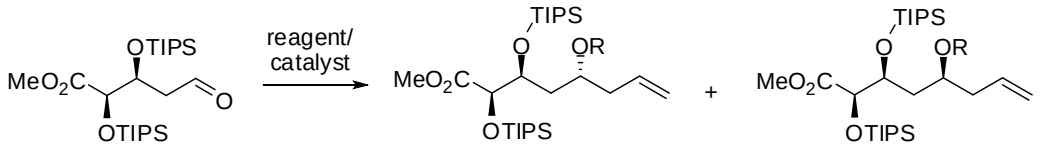


(2*R*,3*S*)-**27** **29**, 81% **30,** 79%, 2 steps

The optimized conditions of the diastereselective allylation reaction for aldehyde **30** are shown in Figure 1. Reaction of **30** with the commercially available Brown allylborane[65,66] (+)-**32** at −78 °C in Et_2O was followed by silylation of the crude product with TIPSOTf to afford a 4:1 mixture of diastereomers **31c** (major) and **31d** (minor) in 60% yield (Figure 1, entry 1a). The crude product from the allylboration was taken directly to the next silylation step because the silylated homoallylic alcohol was very easily separable from silylated 3-pinanol (resulting from oxidative workup of **32**). Similarly, reaction of **30** with antipodal (−)-**32** followed by silylation of the crude product with TIPSOTf afforded a 4:1 mixture of diastereomers **31d** (major) and **31c** (minor) in 55% yield (Figure 1, entry 1b). The configuration of each newly formed stereocenter in **31c** and **31d** was assigned by the transition state model described by Brown.[65]

Seeking to improve the diastereoselectivity of the allylation, we treated **30** with the Duthaler-Hafner allyltitanocene,[23] (*R*,*R*)-**33** (Figure 1, entry 2a). Reaction of (*R*,*R*)-**33** with **30** at −78 °C in Et_2O afforded the homoallylic alcohol **31b** in 44% yield. ^{1}H NMR analysis of the crude product indicated a 10:1 *dr* (**31a**:**31b**). Accordingly, treatment of **30** with antipodal (*S*,*S*)-**33** provided **37a** in 77% yield as a single diastereomer, with no minor isomer detected by crude ^{1}H NMR spectroscopy.

Ultimately, the Brown allylboration was the method of choice for the pilot synthesis because of the convenience of an inexpensive commercially available reagent. Despite the higher levels of stereoselectivity and ease of product purification, the Duthaler-Hafner allylation was not selected due to the expense and sensitivity of the reagents. The Keck allylation is also attractive due to its catalytic nature and commonly robust levels of stereoselectivity,[67] but neither enantiomer of the Keck catalyst **34** provided any desired product upon reaction with **30**.



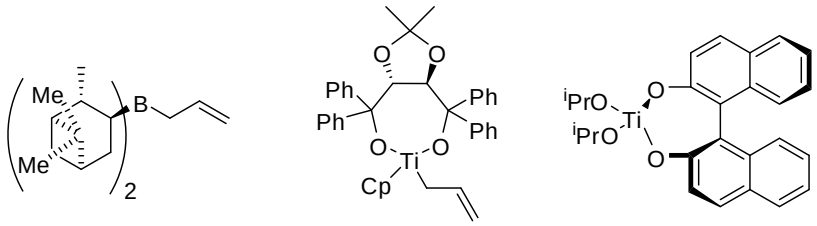
30

31a: R = H
31c: R = TIPS

31b: R = H
31d: R = TIPS

entry	reagent/catalyst	conditions	time	Yield (%)[a]	*dr* (**31a**:**31b**)[b]	*dr* (**31c**:**31d**)
1a	(+)-**32**	Et_2O/−78 °C	4 h	60%	--------	4:1
1b	(−)-**32**	Et_2O/−78 °C	4 h	55%	--------	1:4
2a	(*R*,*R*)-**33**	Et_2O/−78 °C	3 h	44%	1:10	--------
2b	(*S*,*S*)-**33**	Et_2O/−78 °C	3 h	77%	>20:1	--------

[a] Isolated yields
[b] Determined by crude ^{1}H NMR analysis



(+)-**32**

(*R*,*R*)-**33**

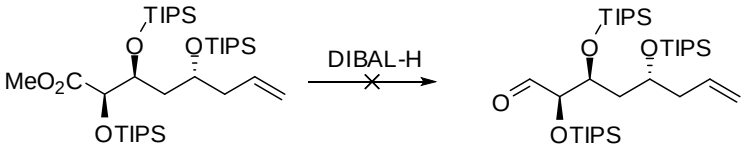
(*R*,*R*)-**34**

Figure 1: Diastereoselective allylations of aldehyde 30 with 32 and 33

Scheme 2.5 shows attempts to complete the synthesis of fragment *RSR*-**8**. Reduction of **31c** with diisobutylaluminum hydride (DIBAL-H, Scheme 2.5)[68] did not produce the

corresponding aldehyde or alcohol even after the addition of excess reagent. Likewise, attempts to produce the alcohol with lithium borohydride,[69] lithium triethylborohydride,[70] lithium aluminum hydride,[71] and alane,[71] were equally unsuccessful. A contingency plan to hydrolyze the ester to the free acid was thwarted when ester **31c** proved unreactive toward excess LiOH in 4:1 THF/H_2O,[72] as well as methanolic KOH under reflux for 3 h.[73]

Scheme 2.5. Attempted completion of fragment *RSR*-8

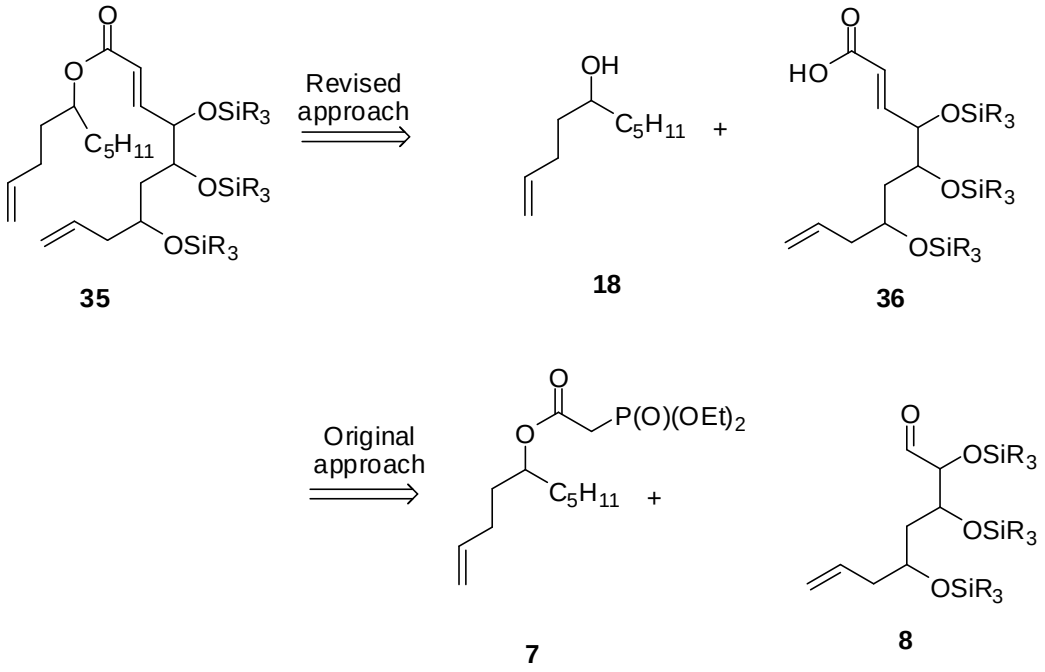


31c *RSR*-**8**

2.2 REVISED RETROSYNTHESIS OF KEY INTERMEDIATE 35

Due to the difficulty in finding a concise route to fragment *RSR*-**8**, a revised retrosynthetic analysis of the RCM substrate **35** was devised as shown in Scheme 2.6. Ester **35** can be prepared by an esterification of the acid **36** with the chiral alcohol **18**. Compared to the original approach, the revised route installs the *trans*-alkene of the natural product by HWE olefination early in the synthesis. Changing the fragment coupling strategy to an esterification saves steps and bypasses the unreactive ester **31c**.

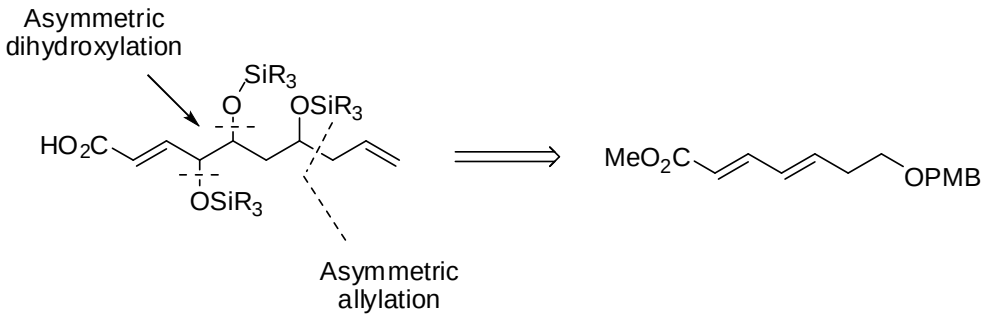
Scheme 2.6. Comparison of retrosynthetic analyses of 35



35 **18** **36** **7** **8**

The acid **36** can be prepared from a similar sequence of reactions as *RSR*-**8**, relying on the Sharpless asymmetric dihydroxylation (SAD) and an asymmetric allylation (Scheme 2.7). Prospects of a chemoselective SAD on the (2*E*,3*E*)-dienoate **37** are good because Sharpless and coworkers showed that osmylation of unsymmetrical, conjugated dienes occurred at the γ,δ-double bond, leaving the other olefin as a spectator.[74]

Scheme 2.7. Retrosynthesis of fragment 36



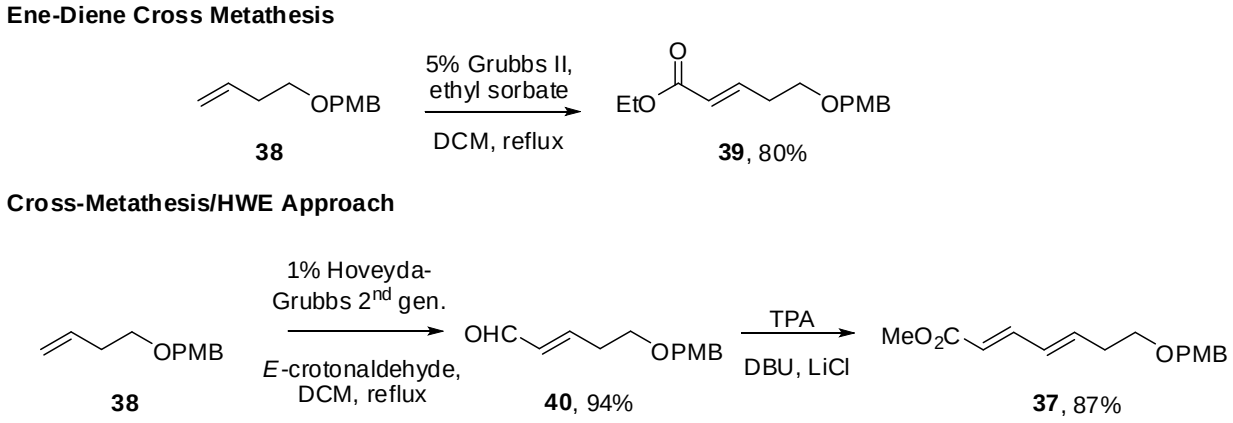
36 **37**

2.2.1 Pilot Synthesis of (4*R*,5*R*,7*R*,13*R*)-Sch725674

To implement the new retrosynthetic strategy, the first task was to develop a convenient synthesis of diene **37**. Scheme 2.8 summarizes two approaches that feature a cross-metathesis (CM) reaction.[75,76] In a one-step approach patterned after ene-diene CM reactions of Grubbs,[77,78] alkene **38**, ethyl sorbate and the second-generation Grubbs catalyst (Grubbs II, 5 mol %) were refluxed in DCM for 16 h. Smooth conversion occurred but the expected product **44** was not produced. Instead, the truncated product **46** was isolated in 80% yield. Apparently, the metathesis of the diene component of ethyl sorbate occurred at C2 rather than C4.

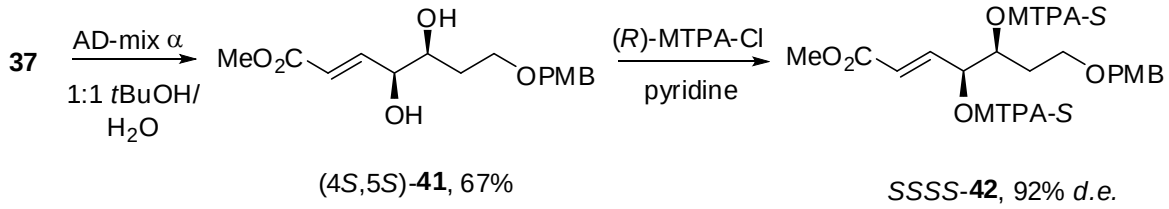
The successful two-step approach also started with a cross-metathesis reaction. Grubbs ene-ene CM[75,76] of **38** and *E*-crotonaldehyde (5 equiv) mediated by the second generation Hoveyda-Grubbs catalyst (1 mol %) provided **40** in 94% yield as a single *E*-isomer. HWE olefination of **40** under the Masamune-Roush conditions with TPA, DBU, and LiCl in MeCN solvent gave the target *E*,*E*-**37**, again as a single stereoisomer. The two-step sequence was conveniently scaled up to make about 10 g of **37**.

Scheme 2.8. Alternative cross-metathesis routes to the ester 37



The results of the SAD of **37** are shown in Scheme 2.9. Treatment of **37** with AD-mix-α in 1:1 *t*BuOH/H_2O gave *syn*-diol (4*S*,5*S*)-**41** in 67% yield. Diol (4*S*,5*S*)-**41** was esterified with excess (*R*)- and (*S*)-MTPA-Cl in pyridine to form the *bis*-MTPA esters *SSSS*-**42** and *SSRR*-**42** (not shown), respectively.[63] Comparative integration of the major and minor singlets in the ^{19}F NMR spectra of *SSSS*-**42** and *SSRR*-**42** indicated a diastereomeric excess of 92% in each case, reflecting an enantiopurity of 92% ee for (4*S*,5*S*)-**41**. The (4*R*,5*R*)-**41** enantiomer (not shown) was likewise obtained by reaction of diene **37** with AD-mix-β in 61% yield.

Scheme 2.9. Synthesis and Mosher ester analysis of (4*S*,5*S*)-41

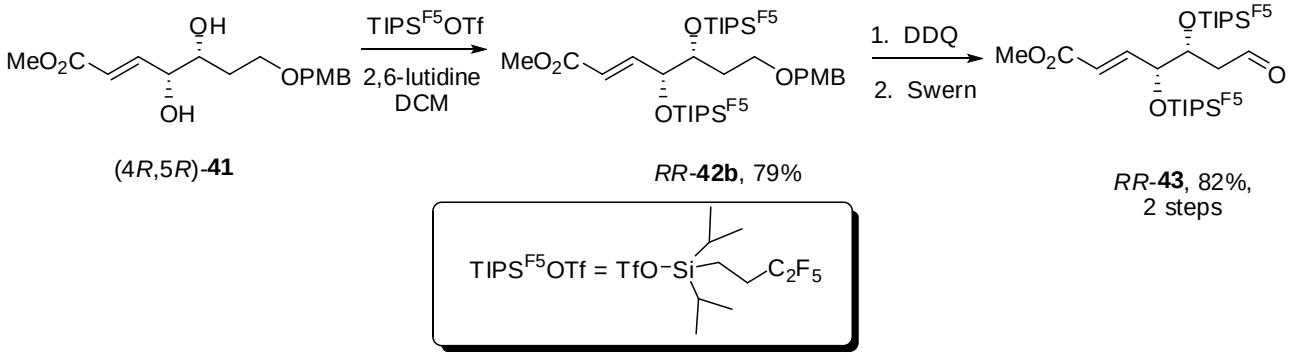


(4*S*,5*S*)-**41**, 67%

SSSS-**42**, 92% *d.e.*

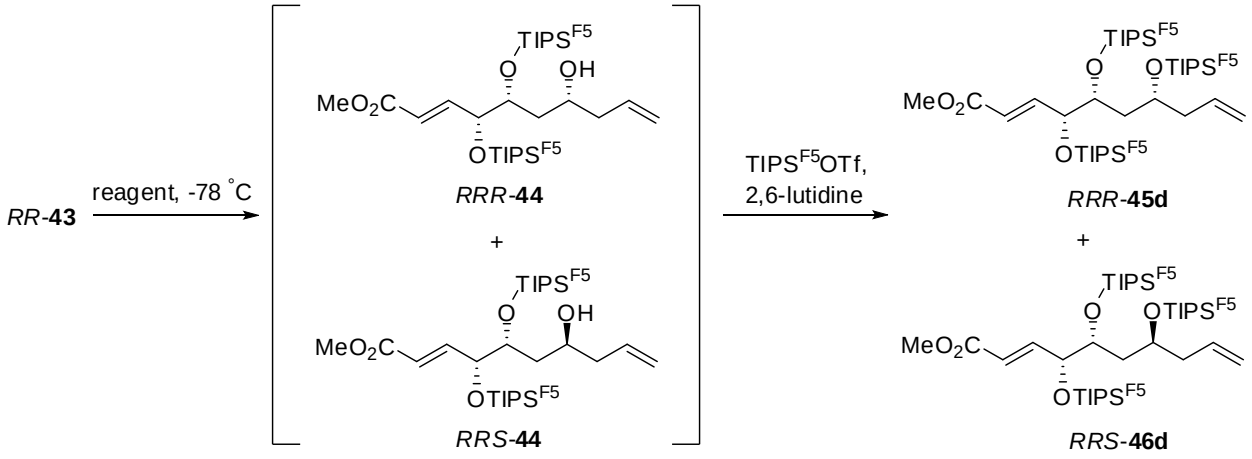
Because of the desilylation problem encountered by Dr. Wang during his FMS (see Section 1.1.3), we used fluorous tags for protection of all hydroxyl stereocenters in the single isomer pilot study to ensure that the tags survive all reaction conditions. Treatment of (4*R*,5*R*)-**41** with $TIPS^{F5}OTf$ (2.5 equiv) and 2,6-lutidine in CH_2Cl_2 furnished the PMB ether **42b** in 79% yield (Scheme 2.10). The *bis*-silylation was followed by oxidative cleavage of the PMB ether in *RR*-**42b** with DDQ[64] and Swern oxidation[59] to afford aldehyde *RR*-**43** in 82% yield over two steps.

Scheme 2.10. Preparation of aldehyde *RR*-43



We next tested the reaction of *RR*-**43** with the allylboranes (+)- and (–)-**32** (Scheme 2.11). The (+)-allylboration was conducted as described in Section 2.1.1 for **31c**, while the (–)-allylboration was carried out by generating (–)-**32** *in situ* with (–)-DIP-Cl and allylmagnesium bromide.[79] The reaction of *RR*-**43** with (+)-**32** followed by silylation of the crude product with TIPS^{F5}OTf provided a 4:1 mixture of diastereomers *RRR*-**45d** (major) and *RRS*-**46d** (minor) in 49% yield. Likewise, reaction of *RR*-**43** with (–)-**32** followed by silylation of the crude product with TIPS^{F5}OTf showed the same two products only now in a reversed 1:4 ratio and 70% yield. The Maruoka[80,81] and Duthaler-Hafner[23] asymmetric allylation reactions were also attempted with *RR*-**43**, but formed no useful product. For the purpose of the single isomer pilot synthesis, emphasis was placed on obtaining an isomerically pure sample of *RRR*-**44** prior to the silylation step. About 1 g each of the free homoallylic alcohols *RRR*-**44** and *RRS*-**44** was isolable by careful flash chromatography of the crude product. These were obtained as essentially single diastereomers in 73% and 77% yields, respectively.

Scheme 2.11. Diastereoselective allylations of *RR*-43 with (+)- and (–)-32

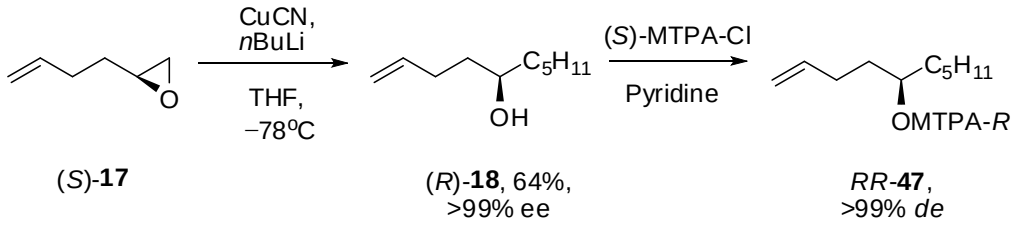


reagent	yield[a]	*dr* (*RRR*-**45d**:*RRS*-**46d**)
(+)-**32**	49%	4:1
(–)-**32**	70%	1:4

[a]Two-step yield of the mixture of diastereomers after silylation

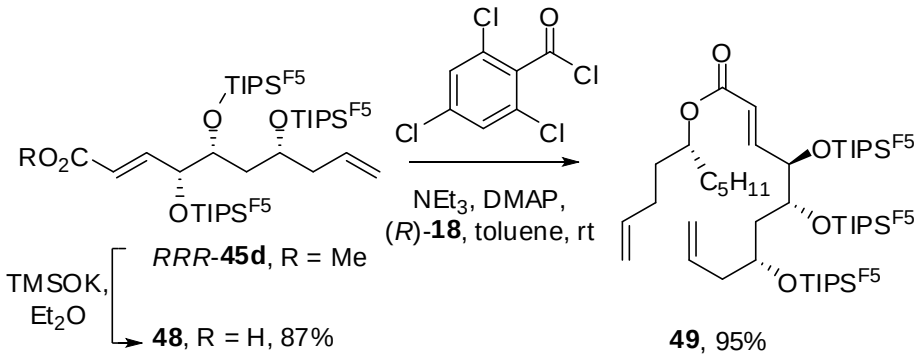
Each enantiomer of fragment **18** was next prepared by Ogoe's two-step sequence (see Section 1.4.2). The epoxide (*S*)-**17** was obtained by the Jacobsen hydrolytic kinetic resolution,[52] and then opened to form the free alcohol (*R*)-**18** upon treatment with dibutyllithium cyanocuprate[53] (Scheme 2.12). Enantiomeric alcohol (*S*)-**18** (not shown) was obtained in the same manner. The enantiopurity of each enantiomer of **18** was established by Mosher ester analysis as shown in Scheme 2.12. Alcohols (*R*)- and (*S*)-**18** were derivatized with excess (*S*)-MTPA-Cl in pyridine as described for diol **41**. Analysis of the resulting (*R*)-MTPA esters *RR*-**47** and *SR*-**47** (not shown) by ^{19}F NMR spectroscopy indicated only a single diastereomer present in each crude sample.[63]

Scheme 2.12. Preparation and Mosher ester analysis of (*R*)-18



The conversion of isomerically pure methyl ester *RRR*-**45d** to the key intermediate **49** is shown in Scheme 2.13. Although conventional methods of saponification led to decomposition, reaction of *RRR*-**45d** with a large excess of potassium trimethylsilanolate[82] (TMSOK, 15 equiv) in Et_2O gave the free acid **48** in 87% yield. Yamaguchi esterification[83,84] of the untagged alcohol (*R*)-**18** and fluorous-tagged acid **48** was then carried out with 2,4,6-trichlorobenzoyl chloride, *N*,*N*′-dimethylaminopyridine (DMAP, 2.2 equiv), and triethylamine (NEt_3, 2.0 equiv) in toluene to deliver the RCM precursor **49** in 95% yield.

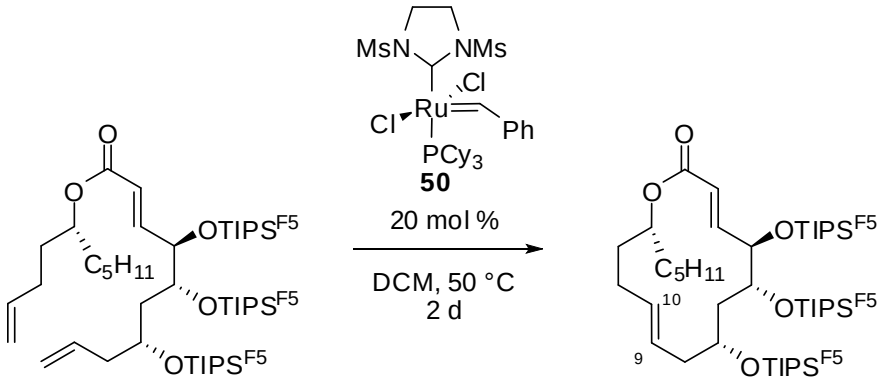
Scheme 2.13. Key esterification to form ester 49



The 14-membered ring was next closed by means of RCM under highly dilute conditions (3 mM) as shown in Scheme 2.14. Preliminary attempts to close **49** under Dr. Wang's conditions with Grubbs 1st generation catalyst (Grubbs I) were not encouraging. Low

conversions were observed even with large catalyst loadings (1.0 equiv). However, reaction of **49** with Grubbs 2nd generation catalyst **50** (Grubbs II, 20 mol%) over two days at 50 °C in freshly distilled CH_2Cl_2 resulted in clean cyclization to the target macrolactone **51** in 76% yield.[85,86] Integration of the distinct proton resonances of the newly-formed C9-C10 double bond in the ^{1}H NMR spectrum of **51** indicated about 5:1 *E/Z*-selectivity.

Scheme 2.14. RCM of 49 to form macrolactone 51

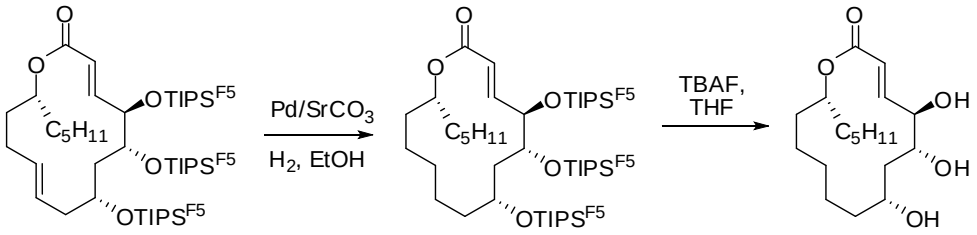


49 **51**, 76%, 5:1 *E:Z*

The completion of the single isomer pilot synthesis of (4*R*,5*R*,7*R*.13*R*)-**5** is shown in Scheme 2.15. A partial hydrogenation of **51** was conducted under an atmosphere of hydrogen gas with Pd/$SrCO_3$ (1.0 equiv) in ethanol (20 mM) to afford the reduced product **52** in 75% yield. A ^{1}H NMR spectrum of **52** recorded after flash chromatography showed that the C9-C10 olefin of **51** was fully reduced, while the vinyl protons from the C2-C3 olefin remained in full proportion. The hydrogenated compound **52** was treated with tetrabutylammonium fluoride (TBAF, 6.0 equiv)[87] to afford 24.8 mg of the final triol (4*R*,5*R*,7*R*,13*R*)-**5** as an amorphous white solid in 79% yield after flash chromatography. As expected, the ^{1}H and ^{13}C NMR spectra of

(4*R*,5*R*,7*R*,13*R*)-**5** did not match those of the natural product. Copies of the ^{1}H and ^{13}C NMR spectra for (4*R*,5*R*,7*R*,13*R*)-**5** are included in the Appendix.

Scheme 2.15. Completion of the single isomer pilot synthesis of (4*R*,5*R*,7*R*,13*R*)-5



51 **52**, 75% (4*R*,5*R*,7*R*,13*R*)-**5**, 79%, 24.8 mg

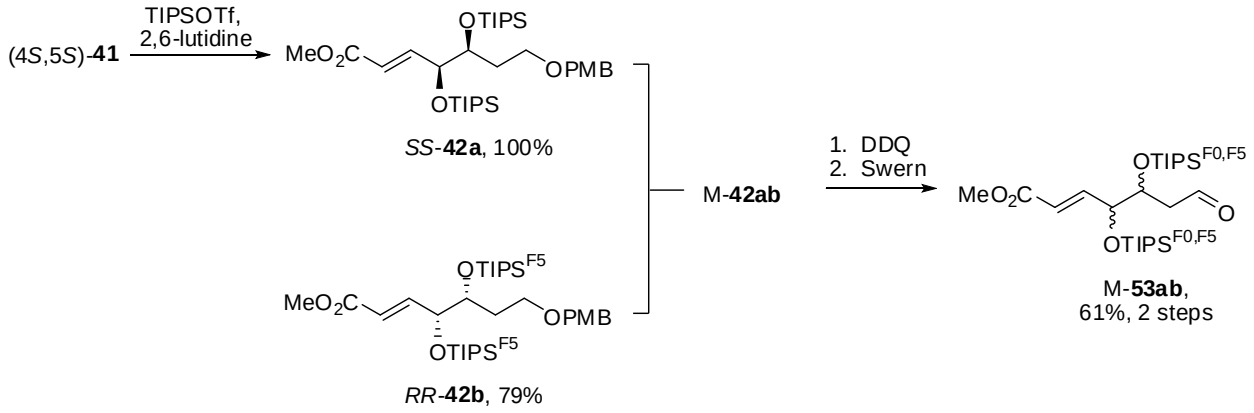
In summation, the single stereoisomer (4*R*,5*R*,7*R*,13*R*)-**5** was synthesized by a revised route in only 16 individual reactions in an overall 6.8% yield. Starting from 3-buten-1-ol, the longest linear sequence contained only 10 steps and each of the reactions was reliable on multi-milligram scale. We projected that multiple stereoisomers of Sch725674 could be made by this synthetic route provided that a convenient tagging strategy could be identified.

3.0 FMS OF THE 4,5-*TRANS*-DIHYDROXY FAMILY OF SCH725674

3.1 INITIAL MULTI-TAG FMS STRATEGY

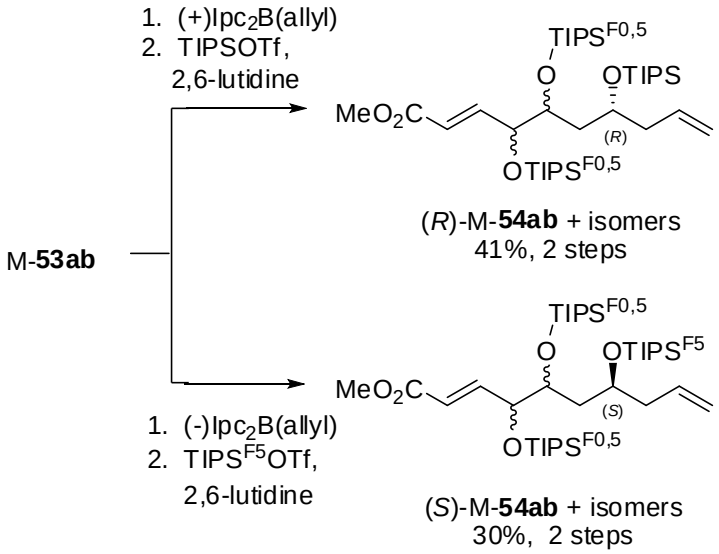
With the single isomer synthesis complete, we set out to synthesize eight stereoisomers of Sch725674 by FMS. Scheme 3.1 shows the initial mixture synthesis stages in the FMS of the 4,5-*trans*-dihydroxy series of Sch725674. The diol (4*S*,5*S*)-**41** was *bis*-silylated using TIPSOTf to form the *bis*-triisopropyl ether *SS*-**42a** in 100% yield. The quasienantiomers *RR*-**42b** (see Section 2.2.1) and *SS*-**42a** were mixed in approximately equimolar ratio to form the first mixture of two compounds M-**42ab**. The PMB ether of M-**42ab** was cleaved with DDQ[64] and the crude alcohol product was directly subjected to a Swern oxidation[59] to yield aldehyde M-**53ab** in 61% yield over two steps. The yields of these and other reactions executed on fluorous mixtures were calculated based on the average molecular weight of the components in the mixture, assuming equimolar ratio of the constituent components.

Scheme 3.1. Early mixture synthesis stages



The aldehyde mixture M-**53ab** was subjected to the critical diastereoselective allylboration step as shown in Scheme 3.2. The sample of M-**53ab** was split and each half treated with commercially available solutions of (+)- and (–)-**32**. After flash chromatography of the crude product, the (*R*)-alcohol from the allylboration with (+)-**32** was silylated with TIPSOTf to yield (*R*)-M-**54ab** in 41% yield over two steps. Likewise, the (*S*)-alcohol product after flash chromatography from the allylboration with (–)-**32** was silylated with $TIPS^{F5}OTf$ to form (*S*)-M-**54ab** in 30% yield over two steps. Based on the 4:1 diastereoselectivity that we observed for the allylboration during the single isomer pilot synthesis (see Section 2.2.1), each two-compound mixture (*R*)- and (*S*)-M-**54ab** was expected to contain a maximum of four possible products (two major and two minor). Indeed, ^{1}H NMR and fluorous HPLC analysis of each of these mixtures indicated a complex isomeric composition. Because isomer separation of (*R*)- and (*S*)-M-**54ab** was not successful, we decided to change our FMS strategy to avoid performing the allylboration on fluorous mixtures.

Scheme 3.2. Diastereoselective allylations of aldehyde M-53ab

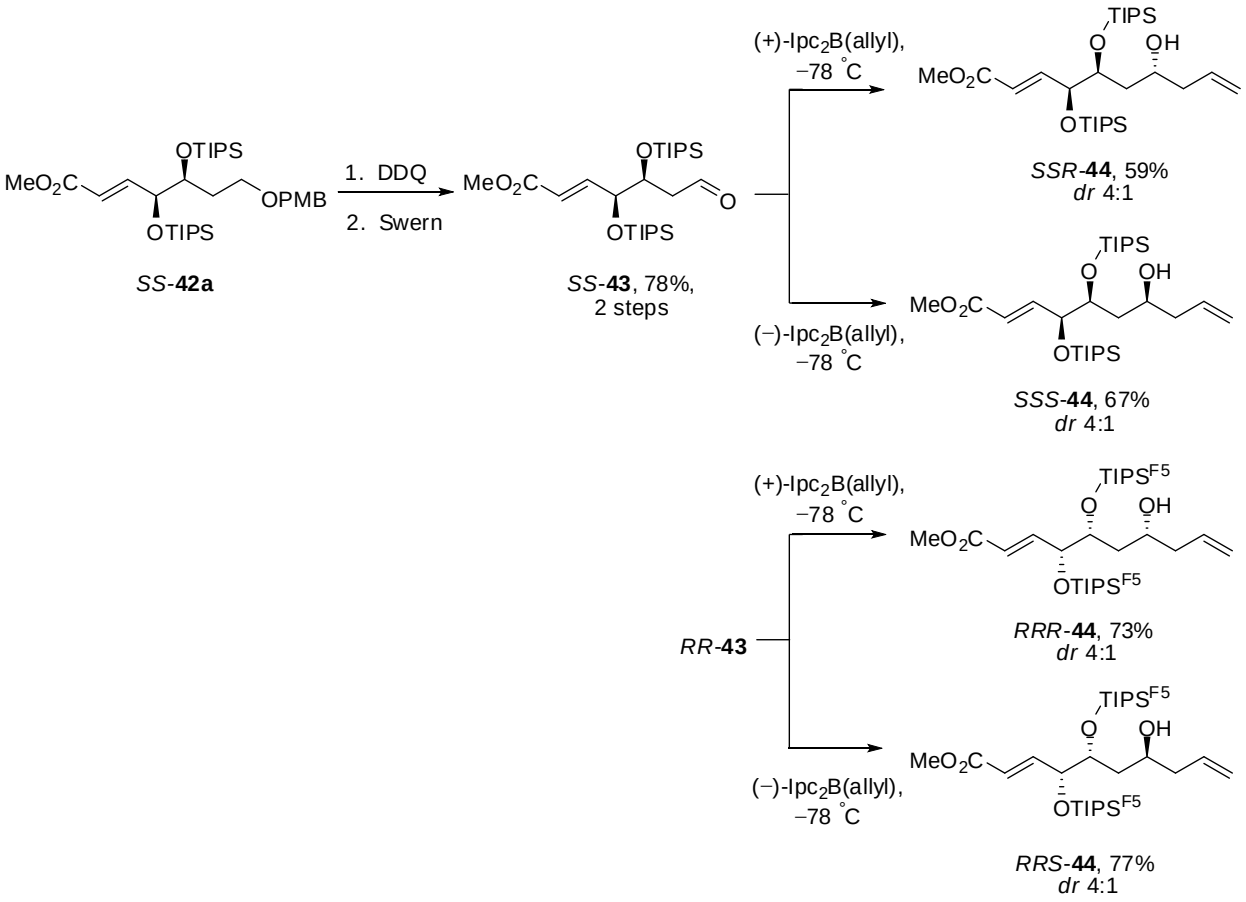


3.2 REVISED MULTI-TAG FMS STRATEGY

To avoid the isomer purification problem with the FMS plan in Section 3.1, we shifted the mixture synthesis stage of the FMS to after the critical asymmetric allylation reaction. Scheme 3.3 shows the synthesis of isomerically pure homoallylic alcohols **44**. Diastereomers *RRR*-**44** and *RRS*-**44** were already available as single isomer samples from allylboration of *RR*-**43** with the allylboranes **32** during the single isomer synthesis (see Section 2.2.1). Compound *SS*-**42a** (see Section 3.1) was subjected to a two-step sequence of PMB ether cleavage with DDQ,[64] followed by Swern oxidation[59] to produce the aldehyde *SS*-**43** in 78% yield over two steps. The sample of quasienantiomer *SS*-**43** was split and each half was treated with commercially available solutions of (+) and (–)-**32** at –78 °C as reported for **31c** (Section 2.1.1). Consistent with prior results, the diastereoselectivities of these two asymmetric allylborations were estimated as 4:1 *dr* by ^{1}H NMR spectroscopy of the crude products. Careful flash

chromatography of the crude product from both allylations furnished multigram quantities of the homoallylic alcohols *SSR*-**44** and *SSS*-**44** as essentially single diastereomers in 59% and 67% yields, respectively.

Scheme 3.3. Synthesis of the new premixing precursors

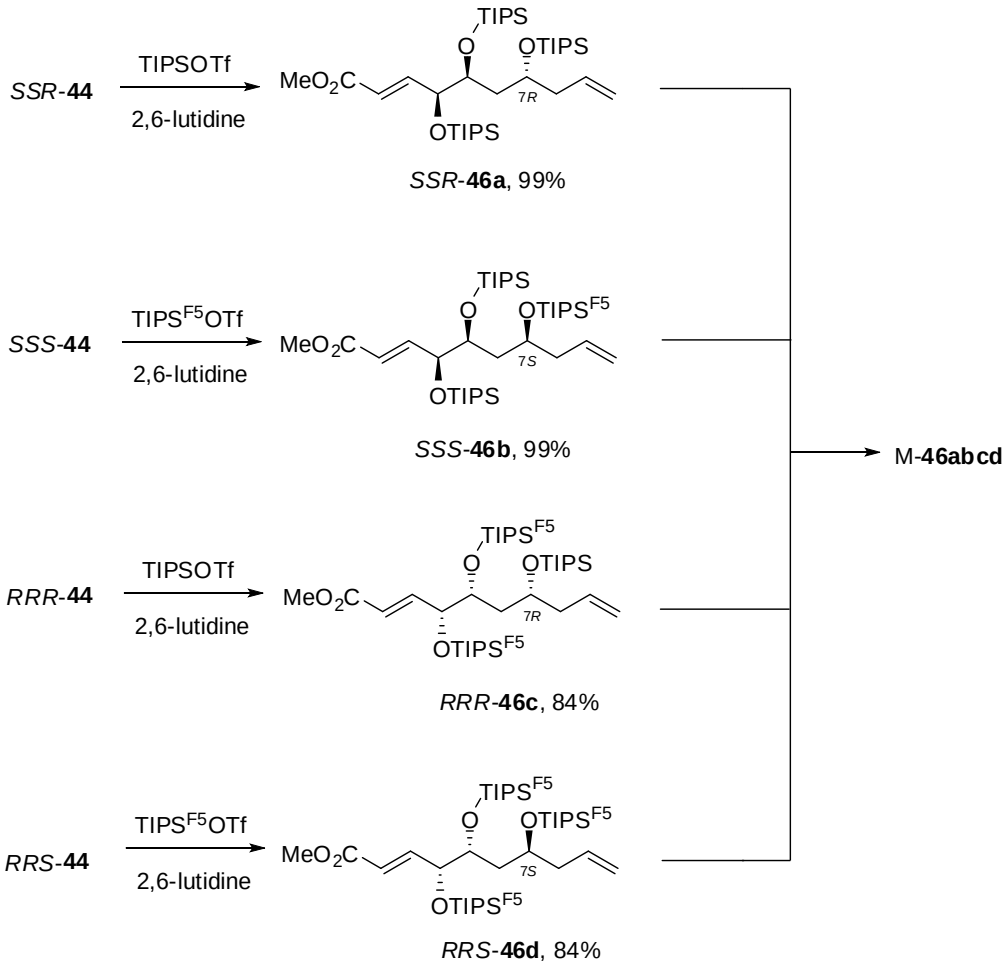


3.2.1 New Minimalist Tagging Strategy

With four isomerically pure alcohols **44** in hand, we were ready to initiate the mixture synthesis stage of FMS. Scheme 3.4 shows the tagging reactions that were executed to encode the C7 stereocenters of alcohols **44**. To be consistent, we encoded the 7*R* configuration using the non-

fluorous TIPS tag, while the 7*S* configuration was encoded by the TIPS^{F5} tag. Accordingly, reaction of *SSR* and *RRR*-**44** with TIPSOTf and 2,6-lutidine provided the quasiisomers *SSR*-**46a** and *RRR*-**46c** in 99% and 84% yields, respectively. Likewise, reaction of *SSS*-**44** and *RRS*-**44** with TIPS^{F5}OTf and 2,6-lutidine provided the quasiisomers *SSS*-**46b** and *RRS*-**46d** (from Section 2.1.3) in 99% and 84% yields, respectively. Each of the four quasiisomers **46** was fully characterized by by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, IR, HRMS, and optical rotation. The four quasiisomers **46** were mixed in approximately equimolar ratio to form the first fluorous mixture M-**46abcd**.

Scheme 3.4. Tagging schedule of the quasiisomers 46



Mixture M-**46abcd** was analyzed by a fluorous analytical HPLC column (PF-C8) under gradient elution (90:10 MeCN/H_2O for 10 min, then 100% MeCN for 60 min). Figure 2 shows the analytical HPLC trace of M-**46abcd**. Pleasingly, M-**46abcd** exhibited four well-spaced peaks eluting at 14.4, 21.5, 27.4, and 35.0 min. The four quasiisomers comprising M-**46abcd** were encoded using two tags (TIPS, and $TIPS^{F5}$), only one of which is fluorous. This is noteworthy because in all previous FMS work, three or four tags were needed to encode a four-quasiisomer mixture. This new minimalist tagging strategy arises from double usage of two tags – once from *bis*-silylation of enantiomeric diols **41** and once again after introducing the C7 stereoecenter in both possible configurations. The tagging schedule developed herein allows us to maintain the throughput and efficiency of FMS, while economizing the available fluorous tags.

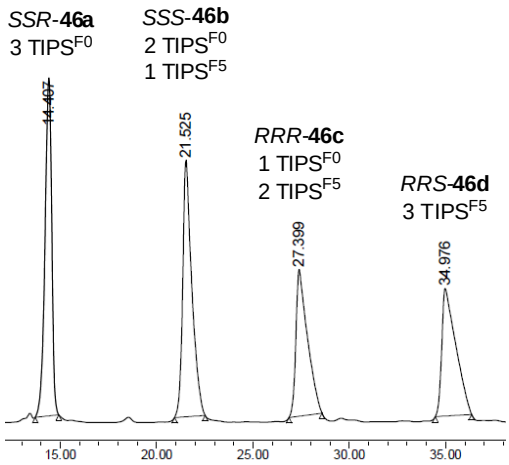
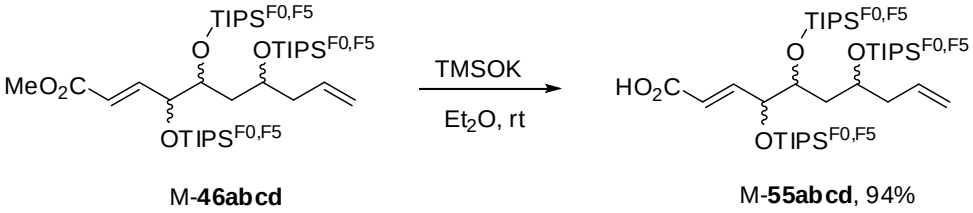


Figure 2: Fluorous analytical HPLC trace of M-46abcd

3.2.2 Mixture synthesis stage

With a convenient tagging strategy secured, we proceeded with the FMS of the 4,5-*trans*-dihydroxy family of Sch725674. The steps of the mixture synthesis were executed in the same manner as during the single isomer pilot synthesis (see Section 2.2.1). Scheme 3.5 shows the cleavage of methyl ester M-**46abcd**. Treatment of M-**46abcd** with TMSOK furnished M-**55abcd** in 94% yield. The product mixtures after this and all other FMS reaction steps were carefully monitored by ^{1}H and ^{19}F NMR spectroscopy, MS, and fluorous analytical HPLC.

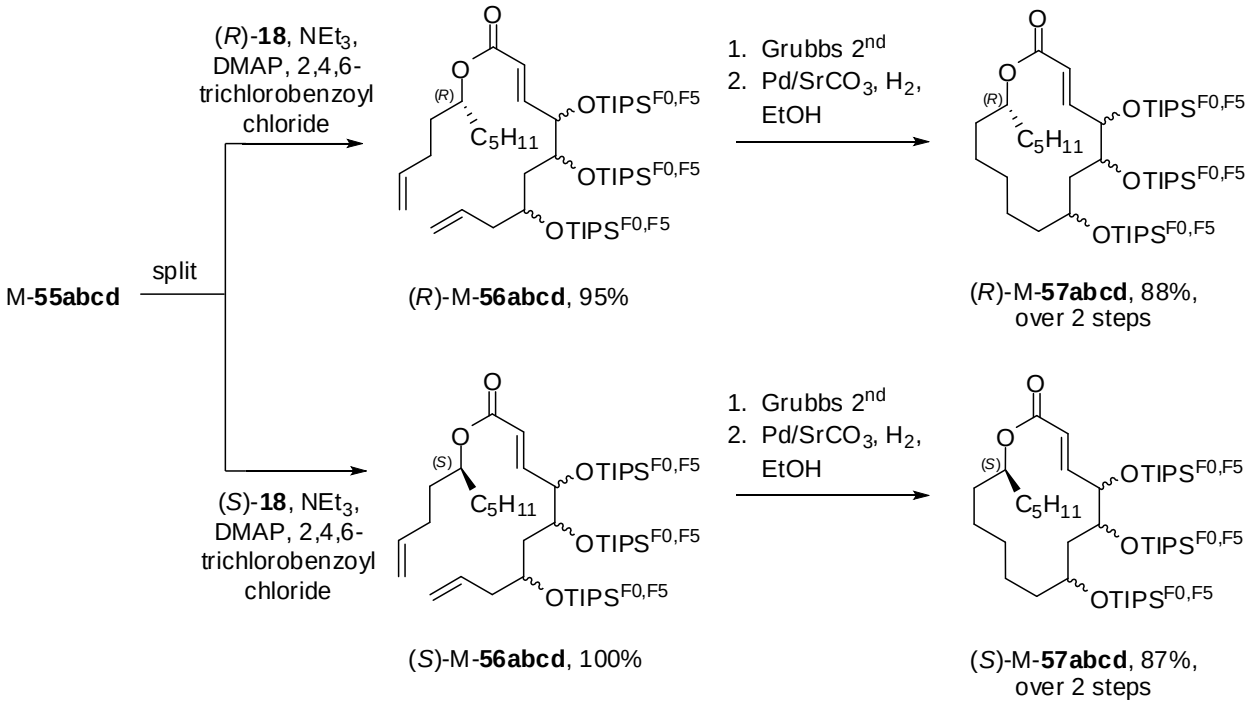
Scheme 3.5. Cleavage of methyl ester M-46abcd



M-**46abcd** M-**55abcd**, 94%

The rest of the mixture synthesis stage is shown in Scheme 3.6. The sample of free acid M-**55abcd** was split and each half was esterified under the Yamaguchi conditions with both enantiomers of the chiral alcohol **18** to afford (*R*)- and (*S*)-M-**56abcd** in 95% and 100% yields, respectively. Parallel treatment of (*R*)- and (*S*)-M-**56abcd** with the optimized conditions for the ring-closing metathesis followed by partial hydrogenation with Pd/$SrCO_3$ provided the final mixtures (*R*)- and (*S*)-M-**57abcd** in 88% and 87% yields, respectively.

Scheme 3.6. Completion of the mixture synthesis phase of the 4,5-trans isomer family



3.2.3 Post-Mix Stage

After careful analysis of the final mixtures (*R*)- and (*S*)-M-**57abcd** (^{1}H and ^{19}F NMR spectroscopy, MS, and fluorous HPLC), each mixture was demixed using gradient elution with a fluorous semi-preparative PF-C8 HPLC column (90:10 MeCN/H_2O to 100% MeCN in 15 min, then 100% MeCN for 90 min) with a constant flow rate of 10 mL/min. Interestingly, the two final mixtures M-**57abcd** did not show identical separation with the semipreparative fluorous HPLC column (Figure 3). The four components in (*R*)-M-**57abcd** (left trace) resolved into four well-separated peaks, while the four components of (*S*)-M-**57abcd** (right trace) showed significant overlap between the second and third-eluting compounds at 70-100 min.

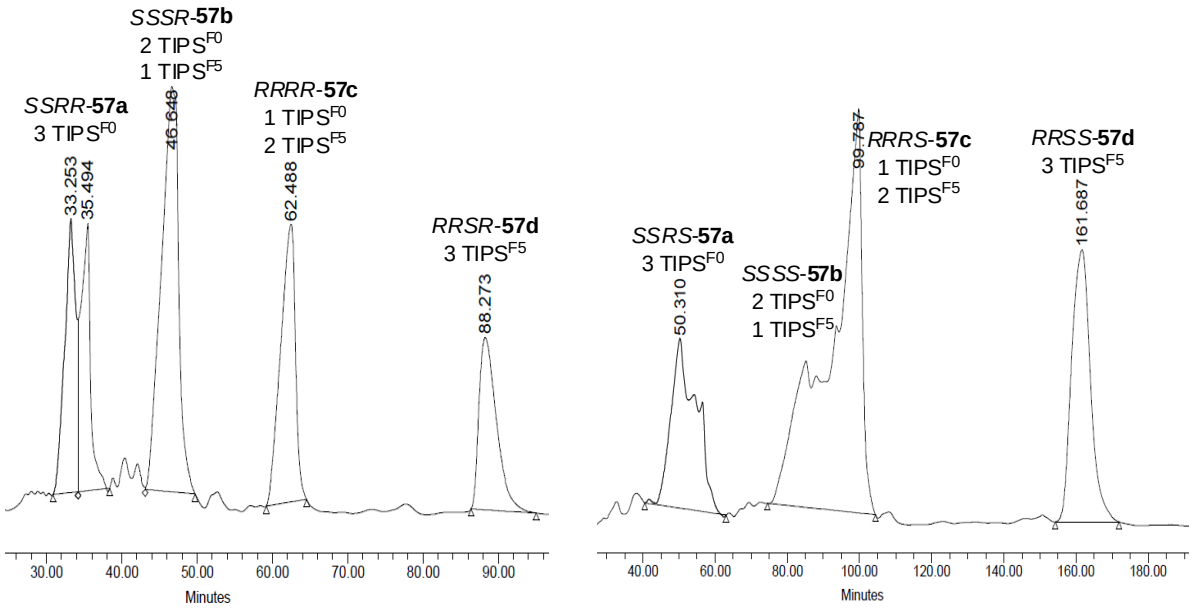
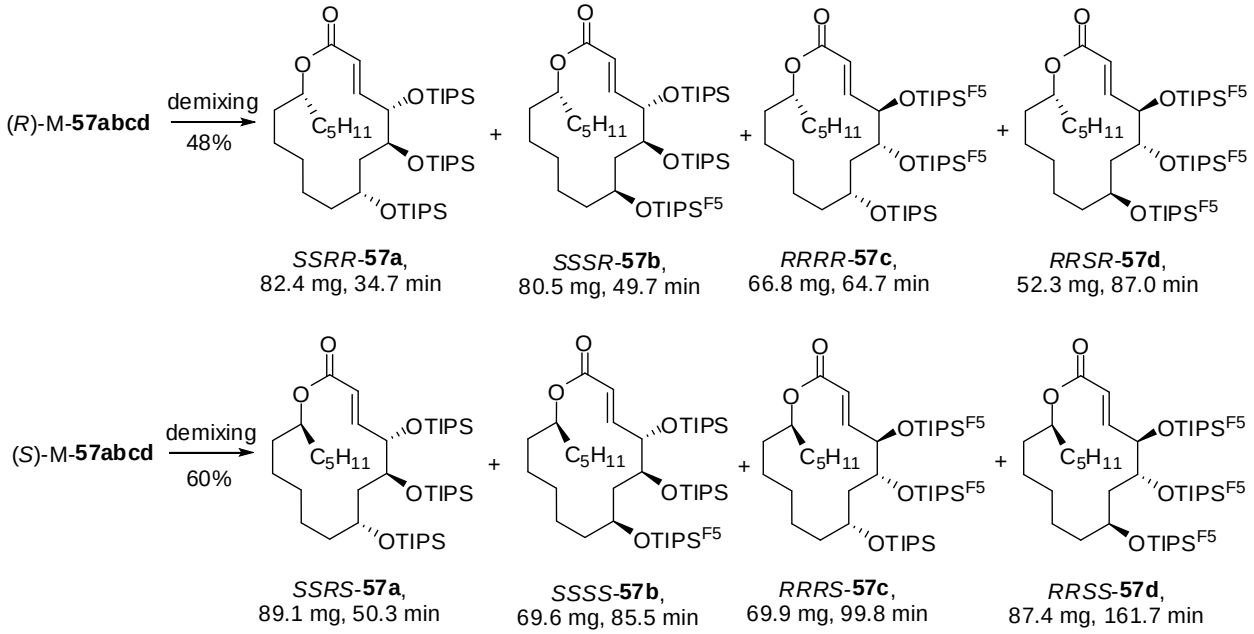


Figure 3: Fluorous HPLC demix traces of (*R*)- M-57abcd (left) and (*S*)-M-57abcd (right)

Scheme 3.6 shows the quasiisomers resulting from the demixing of (*R*)- and (*S*)-M-**57abcd**. The sample comprising (*R*)-M-**57abcd** (584 mg) was demixed in ~90 mg/mL aliquots to obtain, eluting in order of increasing fluorine content, the following quasiisomers: *SSRR*-**57a** (82.4 mg), *SSSR*-**57b** (80.5 mg), *RRRR*-**57c** (66.8 mg), and *RRSR*-**57d** (52.3 mg). Likewise, the sample comprising (*S*)-M-**57abcd** (524 mg) was also demixed in ~90 mg/mL aliquots to obtain, eluting in order of increasing fluorine content, the following quasiisomers: *SSRS*-**57a** (89.1 mg), *SSSS*-**57b** (69.6 mg), *RRRS*-**57c** (69.9 mg), and *RRSS*-**57d** (87.4 mg). Careful cutting of fractions in the demixing of (*S*)-M-**57abcd** furnished *SSSS*-**57b** as a single quasiisomer, but *RRRS*-**57c** was isolated as a cross-contamined mixture of quasiisomers (~3:1 *RRRS*-**57c**/*SSSS*-**57b**) as determined by ^{1}H NMR spectroscopy. Collection of the cross-contaminated mixture and resubmission to the fluorous semipreparative HPLC column did not improve the purity of quasiisomer *RRRS*-**57c**, so this impure product was taken to the detagging step. The overall mass recoveries for the demixing of (*R*)- and (*S*)-M-**57abcd** were 48% and 60%, respectively.

Each of the demixed products **57** were fully characterized by ^{1}H, ^{13}C and ^{19}F NMR, IR, HRMS, and optical rotation measurement.

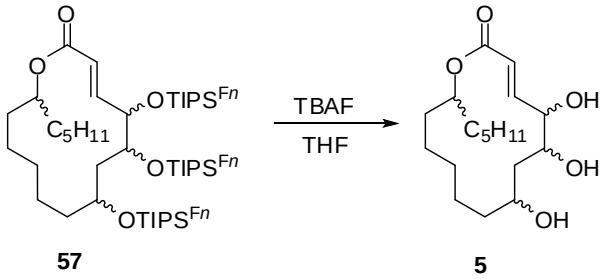
Scheme 3.7. Demixing of two final mixtures M-57abcd into individual quasiisomers



The remaining task in the synthesis of the first eight-compound Sch725674 isomer family was the global detagging. The typical reaction conditions with TBAF (6 equiv) in THF optimized during the single isomer pilot synthesis (see Section 2.2.1) were used for the eight quasiisomers **57** to afford final triols **5** (Figure 4). Five of the eight triols were sufficiently pure after standard flash chromatography of the crude products. To eliminate non-isomeric impurities, triols (4*S*,5*S*,7*R*,13*R*)-**5** and (4*S*,5*S*,7*R*,13*S*)-**5** were purified by injection onto the (*S,S*)-Whelk-*O*-1 column with gradient elution (90:10 hexanes/isopropanol for 15 min, then 80:20 hexanes/isopropanol for 30 min, at 10.0 mL/min) and obtained in 19 and 15% isolated yields, respectively.

Only one of the final triols in this series (4*R*,5*R*,7*R*,13*S*)-**5** required additional isomer purification due to cross-contamination from demixing of (*S*)-M-**57abcd**. Analysis of the cross-contaminated sample of (4*R*,5*R*,7*R*,13*S*)-**5** by HPLC with the Chiralcel OD column and isocratic elution (92:8 hexanes/isopropanol for 75 min) showed two peaks in approximately 4:1 ratio (see HPLC trace in Figure 4). The identity of the minor peak in Figure 4 as the (4*S*,5*S*,7*S*,13*S*)-**5** triol was confirmed by HPLC analysis of the isomerically pure sample of (4*S*,5*S*,7*S*,13*S*)-**5** isolated by FMS. Final purification of pure (4*R*,5*R*,7*R*,13*S*)-**5** was achieved by semipreparative HPLC with the Chiralcel OD column and isocratic elution (92:8 hexanes/isopropanol for 75 min) at 4.5 mL/min. The overall yield of this isomer is low (3.2 mg, 14%) due to conservative fraction cutting during semipreparative HPLC. This was necessary since emphasis was placed on obtaining an isomerically pure sample of (4*R*,5*R*,7*R*,13*S*)-**5**.

Each enantiomeric pair in the 4,5-*trans*-dihydroxy family of Sch725674 was fully characterized by ^{1}H, ^{13}C NMR and IR spectroscopy, HRMS, and optical rotation. Copies of ^{1}H and ^{13}C NMR spectra for all (4,5-*trans*-dihydroxy-13*R*)-**5** triols are included in the Appendix. Assignment of the ^{1}H and ^{13}C NMR signals was assisted by 2D NMR experiments, including ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMQC, and ^{1}H-^{13}C HMBC. In accordance with the results obtained by Dr. Wang's FMS, no compound in the 4,5-*trans*-dihydoxy family of Sch725674 matched the NMR spectra of the natural isomer. As expected, the NMR spectra for the sample of (4*R*,5*R*,7*R*,13*R*)-**5** isolated by FMS matched those obtained from the single isomer pilot synthesis (see Section 2.2.1). This lends proof to the principle of stereocenter encoding with fluorous tags in FMS. Also noteworthy is the ample quantity of final triols that can be isolated along this FMS route (3-17 mg).



57 **5**

Isomer	tags, TIPS^{Fn}	amount (mg)	yield (%)[a]
(4*S*,5*S*,7*R*,13*R*)-**5**	3TIPS	6.4	19[b]
(4*S*,5*S*,7*S*,13*R*)-**5**	2TIPS + TIPS^{F5}	14.6	51
(4*R*,5*R*,7*R*,13*R*)-**5**	TIPS + 2TIPS^{F5}	13.1	60
(4*R*,5*R*,7*S*,13*R*)-**5**	3TIPS^{F5}	7.6	51
(4*S*,5*S*,7*R*,13*S*)-**5**	3TIPS	5.4	15[b]
(4*S*,5*S*,7*S*,13*S*)-**5**	2TIPS + TIPS^{F5}	16.5	67
(4*R*,5*R*,7*R*,13*S*)-**5**	TIPS + 2TIPS^{F5}	3.2	14[c]
(4R,5R,7S,13S)-**5**	3TIPS^{F5}	11.0	29

[a] Unless otherwise noted, isolated yields after flash chromatography
[b] Isolated yield after purification by Whelk-*O*-1 column
[c] Isolated yield after purification by Chiralcel OD column

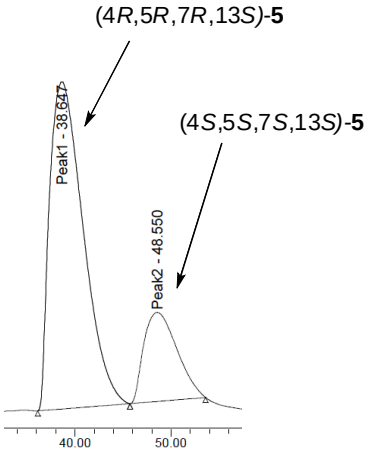


Figure 4: Global detagging results for 4,5-*trans*-dihydroxy isomer family and HPLC trace for (4*R*,5*R*,7*R*,13*S*)-5

3.2.4 Synthesis of 4,5-*syn* Ring-Open Sch725674 Analogs

We next synthesized an eight-membered family of ring-open Sch725674 analogs. The purpose of this exercise was to compare the properties of the macrocyclic Sch725674 stereoisomer library to those of a ring-open stereoisomer library. Accordingly, the RCM-precursor mixtures (*R*)- and (*S*)-M-**56abcd** were demixed using the same HPLC method as for the macrocyclic mixtures M-**57abcd** (see Section 3.2.3). Unlike what we observed upon demixing of mixtures M-**57abcd**, the ring-open mixtures (*R*)- and (*S*)-M-**56abcd** exhibited adequate separation on the fluorous semi-preparative HPLC column (Figure 5). No isomer cross-contamination occurred during demixing of either mixture M-**56abcd** as shown by the presence of four well-separated peaks in each demix trace.

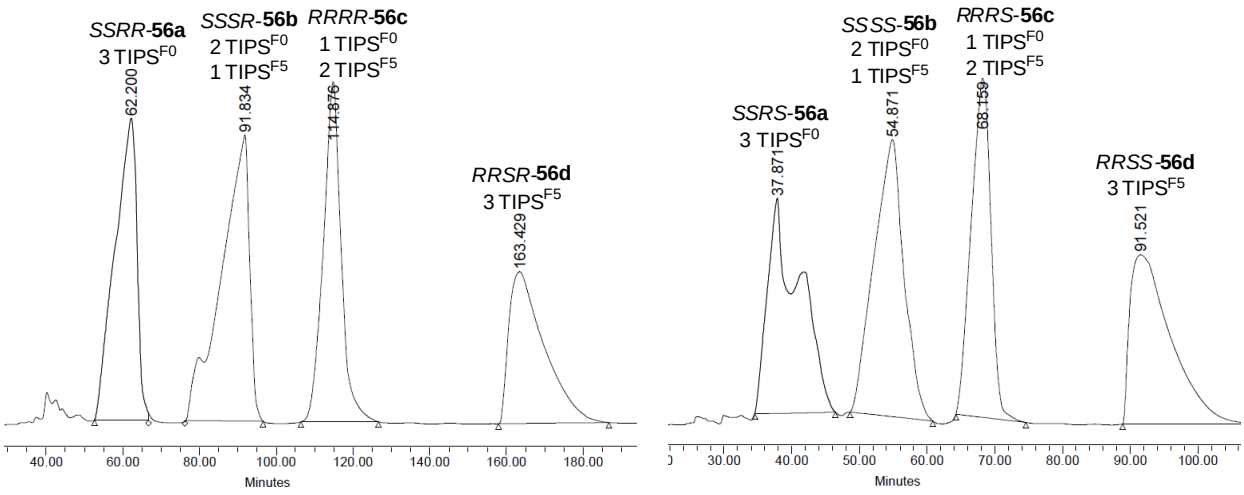


Figure 5: Fluorous HPLC demix traces of (*R*)-56abcd (left) and (*S*)-56abcd (right)

Scheme 3.8 shows the amounts of each quasiisomer demixed from mixtures (*R*)- and (*S*)-M-**56abcd**. Aliquots of the sample comprising (*R*)-M-**56abcd** (50 mg/mL) were injected to obtain, in order of increasing fluorine content, the following acyclic quasiisomers: *SSRR*-**56a** (58.8 mg), *SSSR*-**56b** (68.2 mg), *RRRR*-**56c** (111.6 mg), and *RRSR*-**56d** (60.0 mg). Likewise, aliquots of the sample comprising (*S*)-M-**56abcd** (50 mg/mL) were injected to obtain, in order of increasing fluorine content, the following acyclic quasiisomers: *SSRS*-**56a** (83.0 mg), *SSSS*-**56b** (92.4 mg), *RRRS*-**56c** (90.4 mg), and *RRSS*-**56d** (105.7 mg). The mass recoveries for the demixing of mixtures (*R*)- and (*S*)-**56abcd** were 93% and 80%, respectively. All eight quasiisomers **56** were fully characterized by ^{1}H, ^{13}C, ^{19}F and IR spectroscopy, HRMS, and optical rotation.

Scheme 3.8. Demixing of mixtures (*R*)-M-56abcd and (*S*)-M-56abcd

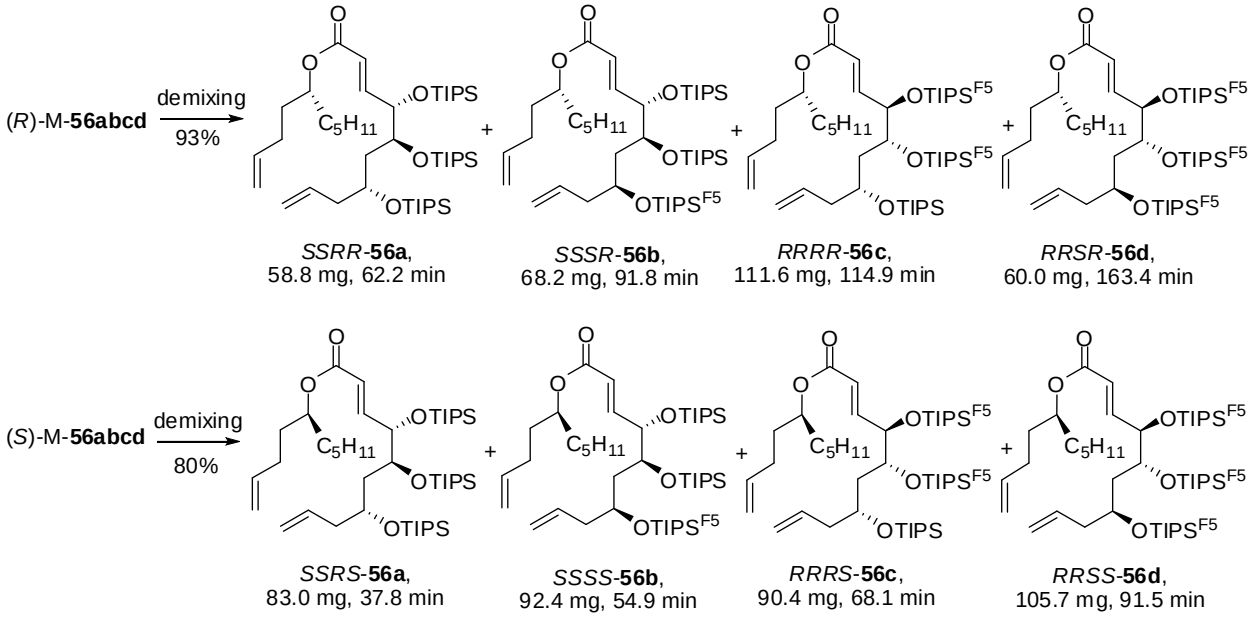


Figure 6 shows expansions of the CF_2 region of the ^{19}F NMR spectra for macrocyclic epimers *RRSR*-**57** (top left) and *RRSS*-**57** (bottom left) alongside ring-open epimers *RRSR*-**56** (top right) and *RRSS*-**56** (bottom right). All four spectra were recorded at 282 MHz using chloroform as solvent. The CF_2 resonances from the $TIPS^{F5}$ tags (see Scheme 2.10 in Section 2.2.1 for the structure of the $TIPS^{F5}$ tag) are triplets due to coupling with the adjacent CH_2 groups and each spectrum shows three more-or-less overlapping triplets. Figure 6 shows that the CF_2 resonances are clearly different for the macrocyclic epimers **57**, but are substantially identical for the ring-open epimers **56**. We propose that the different configurations of the remote C13 stereocenter in epimers **57** change the general conformation of the macrocycle. Consequently, the CF_2 substituent from the fluorous tag is placed in different environments, as evidenced by the distinct CF_2 resonances in epimers **57**. The detection of this interaction by ^{19}F

NMR spectroscopy therefore provides an added benefit to the use of fluorous tags in mixture synthesis.

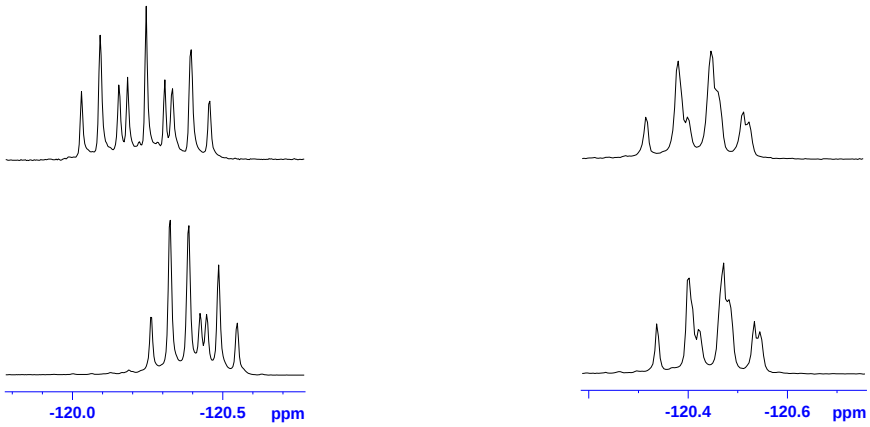
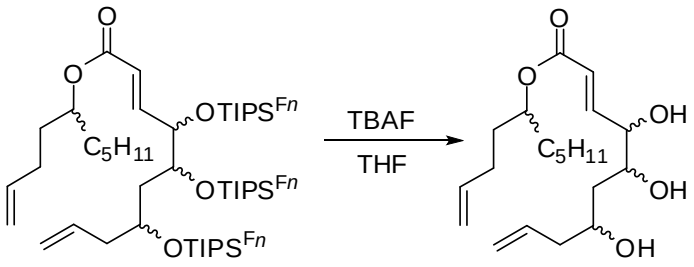


Figure 6: Comparison of the CF_2 resonances of *SSSR*-57 and *SSSS*-57 (left) to *SSSR*-56 and *SSSS*-56 (right)

The final task in the synthesis of the ring-open analog library was the global detagging. The typical reaction conditions with TBAF in THF optimized during the single isomer pilot synthesis in Section 2.2.1 were used for the eight ring-open quasiisomers **56** to afford the final triols **58** (Table 3-1). All eight ring-open triols **58** in this library had sufficient purity after conventional flash chromatography of the crude product. The detagging reactions provided ample amounts of the triols **58** (15-30 mg) in 60-88% yield. Copies of ^{1}H and ^{13}C NMR spectra for (4,5-*trans*-dihydroxy,15*S*)-**58** series are included in the Appendix.

Table 3-1: Detagging of the ring-open Sch725674 analogs



56 **58**

Isomer	tag, $TIPS^{Fn}$	amount (mg)	yield (%)[a]
(4*S*,5*S*,7*R*,15*R*)-**58**	3TIPS	16.5	65
(4*S*,5*S*,7*S*,15*R*)-**58**	2TIPS + $TIPS^{F5}$	15.6	60
(4*R*,5*R*,7*R*,15*R*)-**58**	TIPS + 2$TIPS^{F5}$	26.4	69
(4*R*,5*R*,7*S*,15*R*)-**58**	3$TIPS^{F5}$	11.0	63
(4*S*,5S,7*R*,15*S*)-**58**	3TIPS	23.9	67
(4*S*,5*S*,7*S*,15*S*)-**58**	2TIPS + $TIPS^{F5}$	30.1	85
(4*R*,5*R*,7*R*,15*S*)-**58**	TIPS + 2$TIPS^{F5}$	23.8	77
(4*R*,5*R*,7*S*,15*S*)-**58**	3$TIPS^{F5}$	29.0	88

[a] Isolated yields after flash chromatography

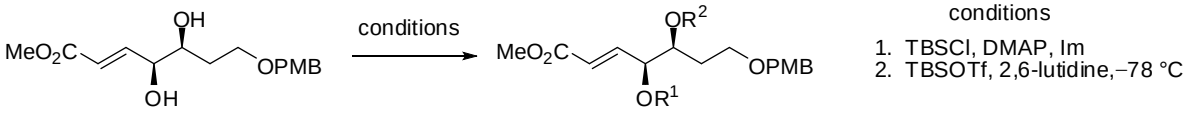
4.0 FMS OF THE 4,5-*CIS*-DIHYDROXY FAMILY OF SCH725674

We next sought to prepare the eight stereoisomers comprising the 4,5-*cis*-dihydroxy Sch725674 isomer family. Once all sixteen stereoisomers of Sch725674 were characterized, the absolute configuration of Sch725674 could be positively identified upon comparison to the literature NMR data. To prepare the new isomer family, we needed to develop a concise route to enantiomeric 1,2-*anti*-diols as the key starting material.

4.1 MITSUNOBU APPROACH

The initial approach to prepare the requisite enantiomeric (*R*,*S*)- and (*S*,*R*)-diols was inspired by a Mitsunobu inversion strategy employed in the Smith-Omura[88] synthesis of macrosphelides A and B. Monosilylation of (4*S*,5*S*)-**41** followed by Mitsunobu inversion of the free allylic alcohol **59a** would deliver the key *anti*-diol building block (Scheme 4.1). Initially, (4*S*,5*S*)-**41** was treated with TBSCl, DMAP, and imidazole at room temperature. An alternate set of procedures to produce **59a** was tried with syringe-pump addition of TBSOTf to a solution of (4*S*,5*S*)-**41** and 2,6-lutidine at −78 °C.[89] Each set of conditions, however, resulted in an inseparable mixture of C4 (**59b**) and C5 (**59a**) *O*-monosilylated isomers as the predominant products. As a result, the Mitsunobu strategy was not pursued further.

Scheme 4.1. Attempted monosilylation of diol 41



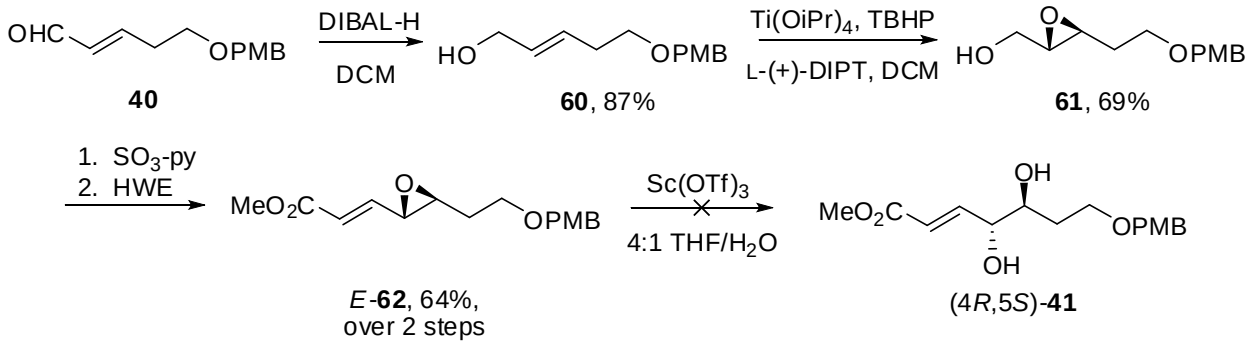
(4*S*,5*S*)-**41**

59a: R^1 = H, R^2 = TBS
59b: R^1 = TBS, R^2 = H

4.2 EPOXIDE-OPENING APPROACH

We next adapted an epoxide-opening strategy from a synthesis of aigialomycin D by Winssinger and coworkers.[90] Reduction of the aldehyde **40** to the known allylic alcohol **60** set the stage for a Sharpless asymmetric epoxidation (SAE)[91,92] with L-(+)-diisopropyl tartrate (DIPT) to form the known epoxy alcohol[93] **61** in 69% yield (Scheme 4.2). Upon Parikh-Doering oxidation[94] of the primary alcohol, the crude aldehyde product was directly subjected to an HWE olefination under the Masamune-Roush conditions.[54] The vinyl epoxide *E*-**62** was formed in 64% yield over two steps and no *Z*-isomer was detected. Treatment of **62** with $HClO_4$[95] or $Sc(OTf)_3$,[96] however, did not provide the target diol **41**. The electron-withdrawing ester subsitutent on the double bond in **62** presumably deactivated the epoxide for S_N2 opening.

Scheme 4.2. Attempted epoxide-opening sequence

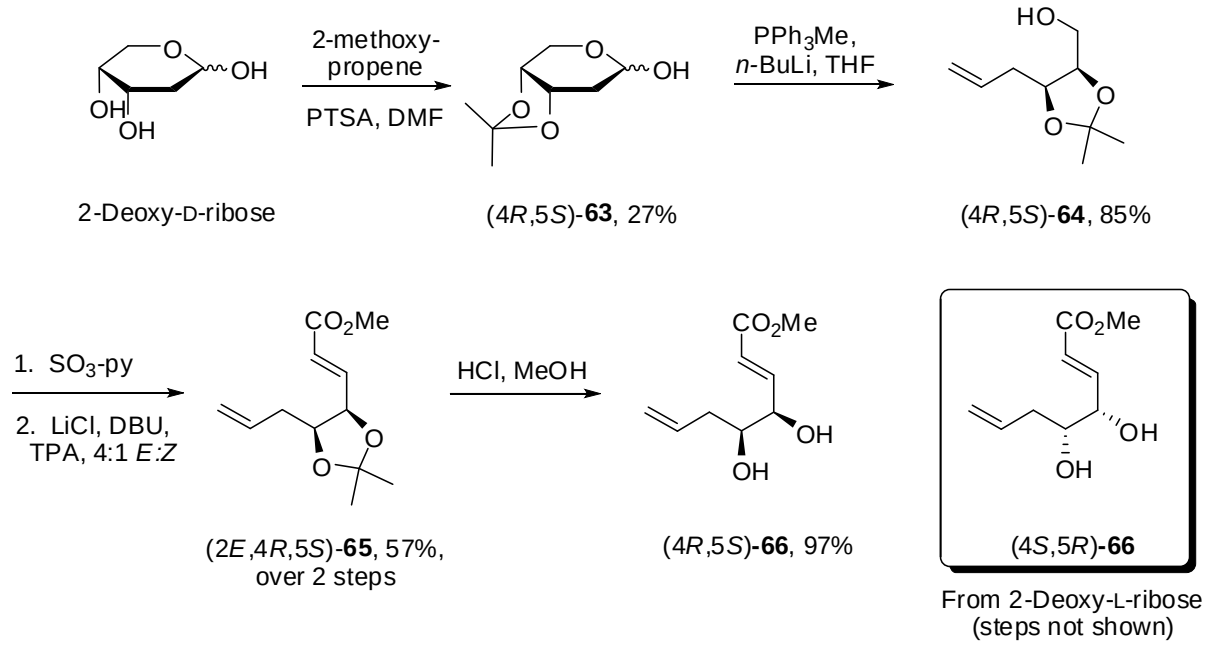


4.3 CHIRAL POOL APPROACH FROM 2-DEOXYRIBOSE

We then accessed the chiral pool in a strategy adapted from a recent synthesis of aigialomycin D by Danishefsky and coworkers.[97] Protection of the 1,2-diol unit in 2-deoxy-D-ribose using 2-methoxypropene (2.0 equiv), *p*-toluenesulfonic acid (PTSA) (20 mol %) in *N*,*N*′-dimethylformamide (DMF) led to the acetonide (4*R*,5*S*)-**63**, in 27% yield (Scheme 4.3).[98] Many conditions were tried to improve the yield for this transformation, including acid[99]- and iodine[100]-catalyzed solvolysis with acetone. However, these reactions either failed or gave **63** in even lower yield. The masked aldehyde character of the sugar lactol (4*R*,5*S*)-**63** was exploited by a Wittig chain extension with butyllithium (2.8 equiv) and methyltriphenylphosphonium iodide[97] (3 equiv) in THF to form the primary alcohol (4*R*,5*S*)-**64** in 85% yield. After oxidation of (4*R*,5*S*)-**64** under the Parikh-Doering conditions,[94] the crude aldehyde product was directly subjected to HWE olefination with the Masamune-Roush conditions[54] to form a separable 4:1 *E/Z* mixture of **65** (estimated by ^{1}H NMR analysis of crude product). The isolated yield of pure (2*E*,4*R*,5*S*)-**65** was 57% over two steps. Acid-catalyzed cleavage of the acetonide[101] furnished the requisite *anti*-diol (4*R*,5*S*)-**66** in 97% yield and excellent purity. The enantiomer (4*S*,5*R*)-**66**

was also prepared using 2-deoxy-L-ribose as the starting material by this five step sequence (steps not shown). This sequence was scaled up to provide >2 g of each enantiomer of **66**.

Scheme 4.3. Sugar-based syntheses of diols 66

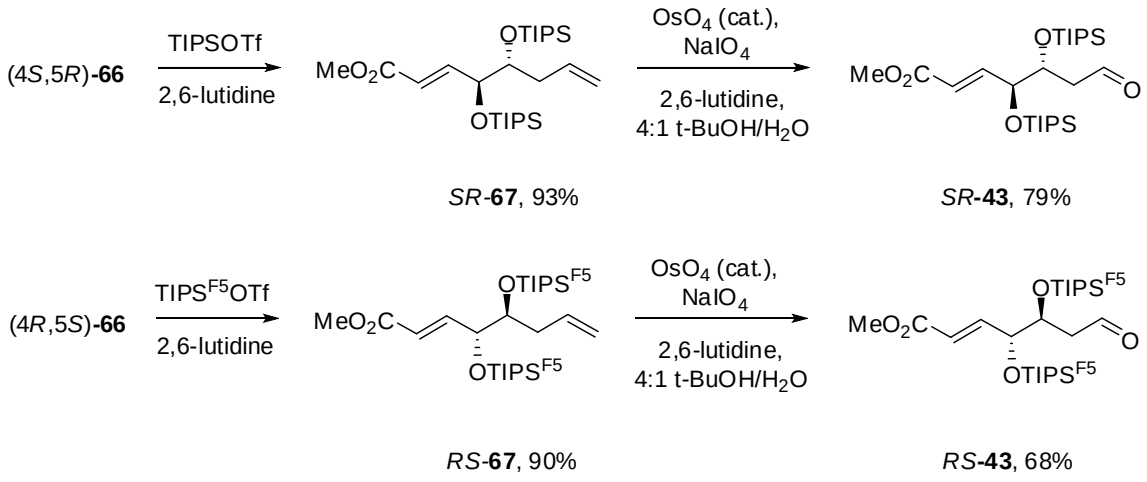


4.3.1 Pre-mix Stage

We next adopted the same minimalist tagging strategy (see Section 3.2.1) used in the FMS of the 4,5-*trans*-dihydroxy Sch725674 isomer family (Scheme 4.4). Accordingly, (4*S*,4*R*)-**66** was *bis*-silylated using TIPSOTf (2.5 equiv) and 2,6-lutidine to form *SR*-**67** in 93% yield (Scheme 4.4). Likewise, (4*R*,5*S*)-**66** was *bis*-silylated with TIPS^{F5}OTf (2.5 equiv) to form *RS*-**67** in 90% yield. Oxidative cleavage of the terminal olefins present in *SR*-**67** and *RS*-**67** was achieved with catalytic OsO_4 (2 mol %), $NaIO_4$ (4 equiv), and 2,6-lutidine[102] (2 equiv) at room temperature to furnish the quasienantiomers, *SR*-**43** and *RS*-**43** in 79% and 68% yields, respectively.

Conveniently, this FMS route to the 4,5-*cis*-dihydroxy family directly intersects that of the 4,5-*trans*-dihydroxy family with the preparation of quasienantiomers **43**.

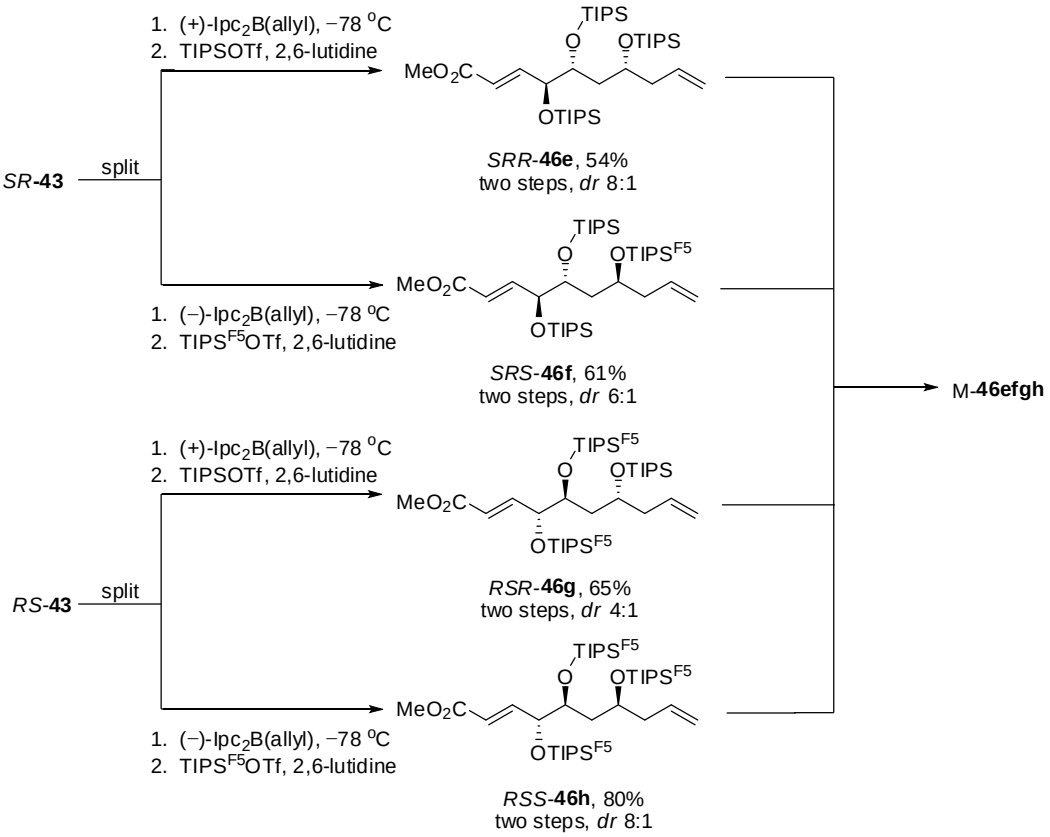
Scheme 4.4. Synthesis of quasienantiomers 43



The asymmetric allylboration was the next critical step in the premixing stage. As shown in Scheme 4.5, the sample of aldehyde *SR*-**43** was split and one half was initially treated with (+)-**32** (prepared *in situ*, see Section 2.2.1). ^{1}H NMR analysis of the crude product indicated a 6:1 mixture of diastereomers. In contrast to the FMS of the 4,5-*trans* series, these diastereomers were not as easily separable by conventional flash chromatography or HPLC. The diastereomeric mixture after flash chromatography was advanced to the next silylation step with TIPSOTf to afford quasiisomer *SRR*-**46e** in 54% yield and approximately 8:1 *dr* over two steps. Likewise, the allylboration of *SR*-**43** with (–)-**32** (prepared *in situ*) produced an inseparable 6:1 mixture of diastereomers as determined by ^{1}H NMR analysis of the crude product. Silylation of this mixture with TIPS^{F5}OTf gave quasiisomer *SRS*-**46f** in 61% yield and approximately 6:1 *dr* over two steps.

Similarly, the allylboration reactions of *RS*-**43** with (+) and (–)-**32** gave comparable diastereoselectivities (~6:1 in each case) and the resulting diastereomeric mixtures were difficult to separate. Flash chromatography followed by protection of the (*R*)-alcohol product from the (+)-allylboration with TIPSOTf gave quasiisomer *RSR*-**46g** in 65% yield and 4:1 *dr* over two steps. Likewise, flash chromatography and tagging of the (*S*)-alcohol from the (–)-allylboration with $TIPS^{F5}OTf$ gave quasiisomer *RSS*-**46h** in 80% yield and 8:1 dr over two steps. Unlike the FMS of the 4,5-*trans*-dihydroxy-**5** series, quasiisomers *SRR*-**46e**, *SRS*-**46f**, *RSR*-**46g**, and *RSS*-**46h** were advanced to the mixture synthesis stage as diastereomeric mixtures and combined in approximately equimolar fashion to form mixture M-**46efgh**. Ultimately, we would have to find an HPLC method for purifying the final triols after the detagging stage.

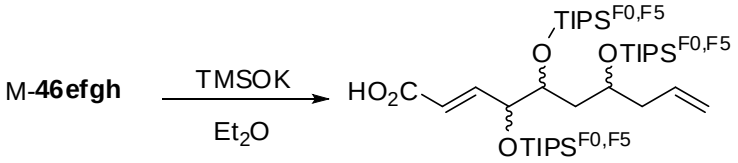
Scheme 4.5. Synthesis of the tagged FMS precursors



4.3.2 Mixture synthesis stage

The mixture synthesis sequence was executed in the same manner as for the FMS of the 4,5-*trans*-dihydroxy-**5** series (see Section 3.2.2) and the first step is shown in Scheme 4.6. Treatment of methyl ester M-**46efgh** with TMSOK furnished the acid M-**55efgh** in 90% yield. The product mixtures after every reaction step were analyzed by ^{1}H and ^{19}F NMR spectroscopy, LRMS, and fluorous HPLC.

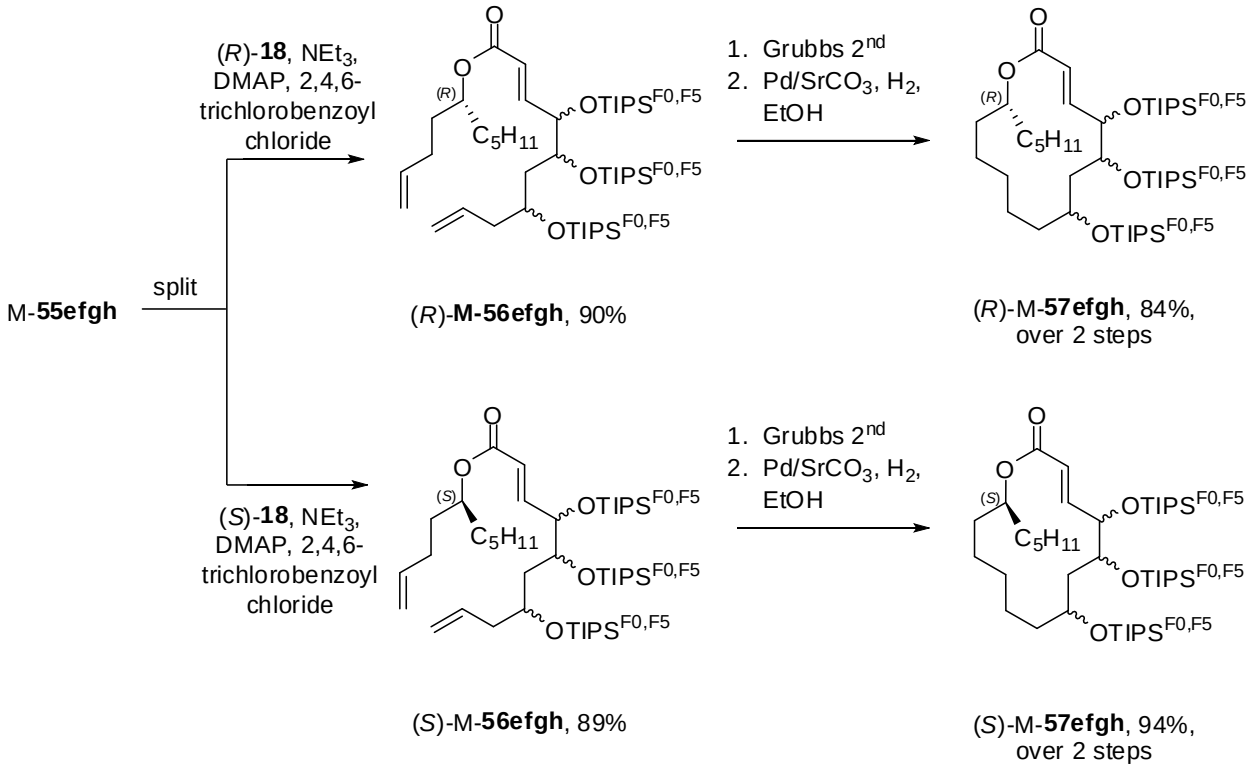
Scheme 4.6. Cleavage of methyl ester M-46efgh with TMSOK



M-**55efgh**, 80%

The rest of the mixture synthesis stage is shown in Scheme 4.7. Splitting the sample of M-**55efgh** and coupling each half with both enantiomers of the chiral alcohol **18** gave mixtures (*R*)- and (*S*)-M-**56efgh** in 90% and 89% yields, respectively. Macrocyclization of (*R*)- and (*S*)-M-**56efgh** with Grubbs II catalyst (20 mol %), followed by partial hydrogenation with Pd/$SrCO_3$ (1 equiv) provided the final mixtures *(R)*- and (*S*)-M-**57efgh** in 84% and 94% two step yields, respectively.

Scheme 4.7. Mixture synthesis stage



4.3.3 Post-Mix Stage

After careful analysis of the final mixtures *(R)*- and (*S*)-M-**57efgh**, each mixture was demixed using the same HPLC method as for M-**57abcd** (see Section 3.2.3). Similar to what was observed during the demixing of *(R)*- and (*S*)-M-**57abcd**, the final mixtures *(R)*- and (*S*)-M-**57efgh** did not show identical separation with the semipreparative fluorous HPLC column (Figure 7). The demix trace of *(R)*-M-**57efgh** (left trace) exhibits four well-separated peaks. The demix trace of (*S*)-M-**57efgh** (right trace) exhibits tighter separation between the second and third-eluting components (35-50 min), but still better separation than (*S*)-M-**57abcd** (see Section 3.2.4) which overlapped.

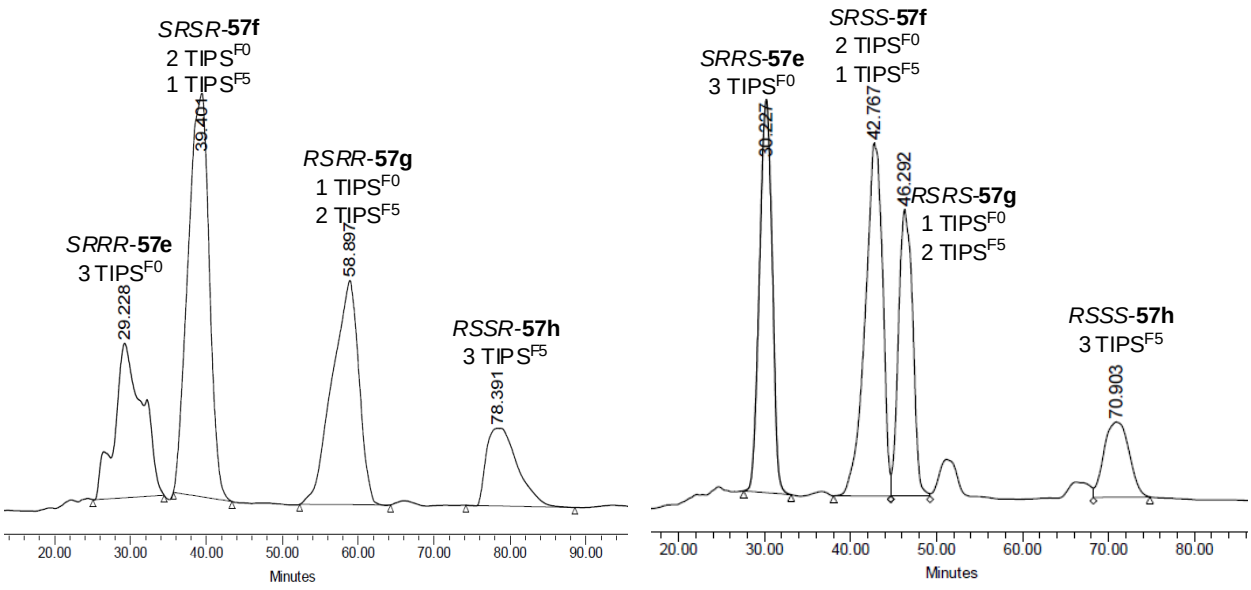


Figure 7: Fluorous HPLC demix traces of *(R)*-M-57efgh (left) and (*S*)-M-57efgh (right)

Scheme 4.8 shows the quasiisomers resulting from the demixing of *(R)*- and (*S*)-M-**57efgh**. The sample comprising *(R)*-M-**57efgh** (463 mg) was demixed in ~90 mg/mL aliquots to obtain, eluting in order of increasing fluorine content, the following quasiisomers: *SRRR*-**57e** (59.2 mg), *SRSR*-**57f** (94.1 mg), *RSRR*-**57g** (114 mg), and *RSSR*-**57h** (41.5 mg). Likewise, the sample comprising (*S*)-M-**57efgh** (547 mg) was demixed in ~50 mg/mL aliquots to obtain, eluting in order of increasing fluorine content, the following quasiisomers: *SRRS*-**57e** (73.4 mg), *SRSS*-**57f** (52.0 mg), *RSRS*-**57g** (60.3 mg), and *RSSS*-**57h** (65.8 mg). The tight separation in (*S*)-M-**57efgh** resulted in cross-contamination in some fractions between the second and third-eluting compounds at 35-50 min. Combination of the cross-contaminated fractions and re-subjecting this mixture, however, furnished *SRSS*-**57f** and *RSRS*-**57g** as individually pure quasiisomers. The overall mass recoveries for the demixing of *(R)*- and (*S*)-M-**57efgh** were 69% and 56%, respectively.

Once the eight quasiisomers **57** were obtained in good purity based on the tags, each one was subjected to a full battery of characterization including: ^{1}H, ^{13}C, ^{19}F NMR and IR spectroscopy, HRMS, and optical rotation measurement. As expected from the allylboration stage (see Section 4.3.1), each demixed quasiisomer **57** was isolated with its residual C7 diastereomer as an inseparable mixture. The isomer content of each quasiisomer **57** is listed in Scheme 4.7 and ranges from 3:1 to 10:1 *dr* as evaluated by ^{1}H NMR spectroscopy. Each quasiisomer was submitted to the detagging stage as a mixture of diastereomers and a method for isomer purification of the final triols **5** was developed.

Scheme 4.8. Demixing of the final mixtures M-57efgh into quasiisomers

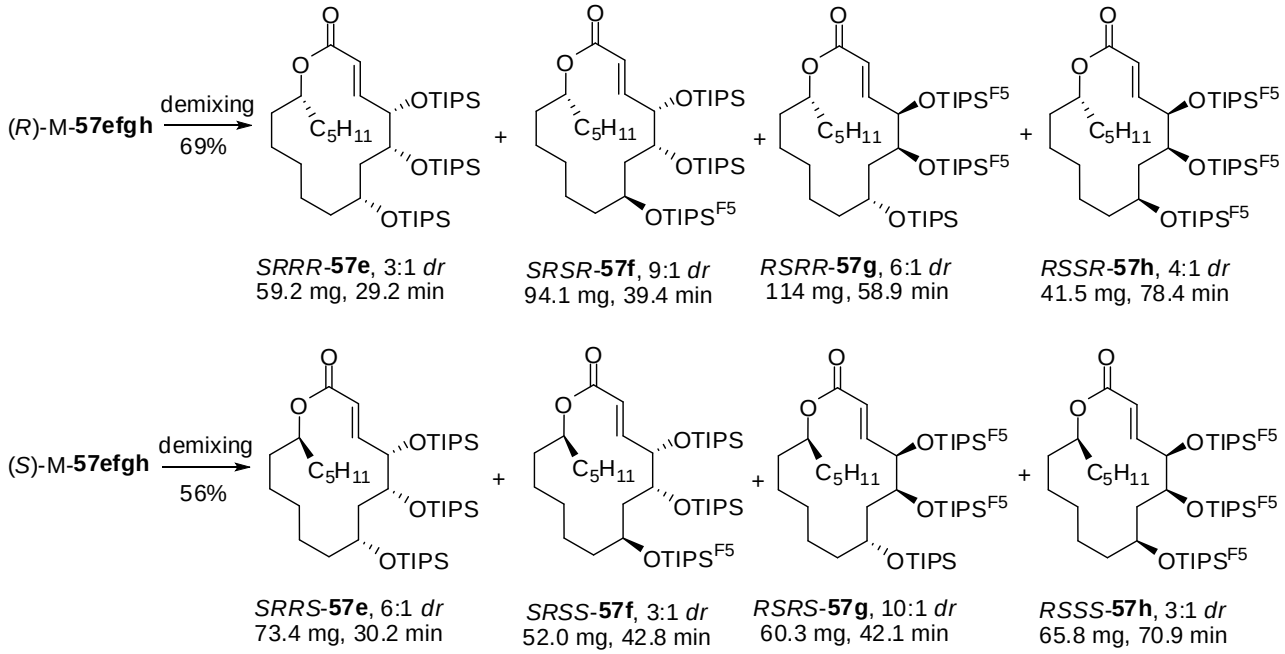
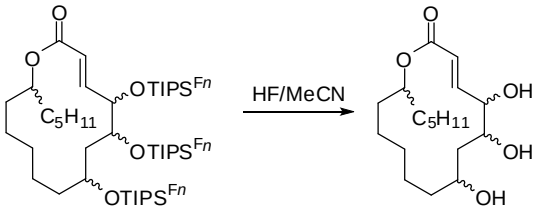


Figure 8 shows the results from the global detagging of quasiisomers **57** to triols **5**. Detagging of *SRSR*-**57f** with the usual conditions (TBAF, 6 equiv) proved sluggish and incomplete by TLC. Alternatively, treatment of the remaining seven quasiisomers **57** in this

series with HF/MeCN[103] over 16 h improved the conversion of the detagging reactions as analyzed by TLC. The crude mixture of each global detagging reaction was initially purified by conventional flash chromatography to afford the eight final triols **5**, each isolated as a mixture of diastereomers in various ratios (not shown).

The two true C7 diastereomers comprising the sample of (4*R*,5*S*,7*R*,13*R*)-**5** after flash chromatography were separated by HPLC with the (*S*,*S*)-Whelk-*O*-1 column and gradient elution (90:10 hexanes/isopropanol for 15 min, then 80:20 hexanes/isopropanol for 30 min). Figure 8 shows an analytical HPLC trace with excellent separation between (4*R*,5*S*,7*R*,13*R*)-**5** (t_R = 18.2 min) and its C7 epimer, (4*R*,5*S*,7*S*,13*R*)-**5** (t_R = 12.0 min). The retention times of each of these isomers match the retention times of the corresponding minor/major isomers in two other products, as expected. Application of this HPLC method to all eight 4,5-*cis*-dihydroxy-**5** triols in this series allowed for the enhancement of diastereomeric mixtures to single isomer samples, with the only exception being (4*S*,5*R*,7*S*,13*R*)-**5** which was isolated as a 14:1 isomeric composition. As we observed in the preparation of the 4,5-*trans*-dihydroxy isomer family, the quantity of final 4,5-*cis*-dihydroxy triols that was isolated along this FMS route (4-14 mg) was plentiful for full characterization by ^{1}H, ^{13}C NMR and IR spectroscopy, HRMS, and optical rotation. Copies of ^{1}H and ^{13}C NMR spectra for all (4,5-*cis*-dihydroxy-13*R*)-**5** triols are included in the Appendix.



57 **5**

Isomer	tags, $TIPS^{Fn}$	amount (mg)	yield (%)[a]
(4*S*,5*R*,7*R*,13*R*)-**5**	3TIPS	11.0	29
(4*S*,5*R*,7*S*,13*R*)-**5**[b]	2TIPS + $TIPS^{F5}$	12.4	37
(4*R*,5*S*,7*R*,13*R*)-**5**	TIPS + $2TIPS^{F5}$	11.4	32
(4*R*,5*S*,7*S*,13*R*)-**5**	$3TIPS^{F5}$	4.7	40
(4*S*,5*R*,7*R*,13*S*)-**5**	3TIPS	13.4	45
(4*S*,5*R*,7*S*,13*S*)-**5**	2TIPS + $TIPS^{F5}$	5.5	17
(4*R*,5*S*,7*R*,13*S*)-**5**	TIPS + $2TIPS^{F5}$	14.0	73
(4*R*,5*S*,7*S*,13*S*)-**5**	$3TIPS^{F5}$	6.9	36

[a] Isolated yield after HPLC purification by Whelk-*O*-1 column
[b] TBAF/THF for detagging this isomer

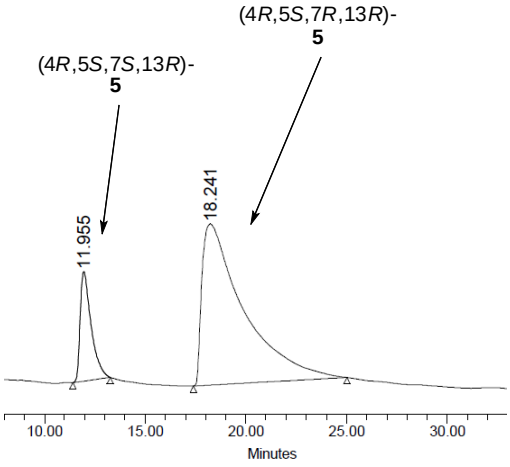


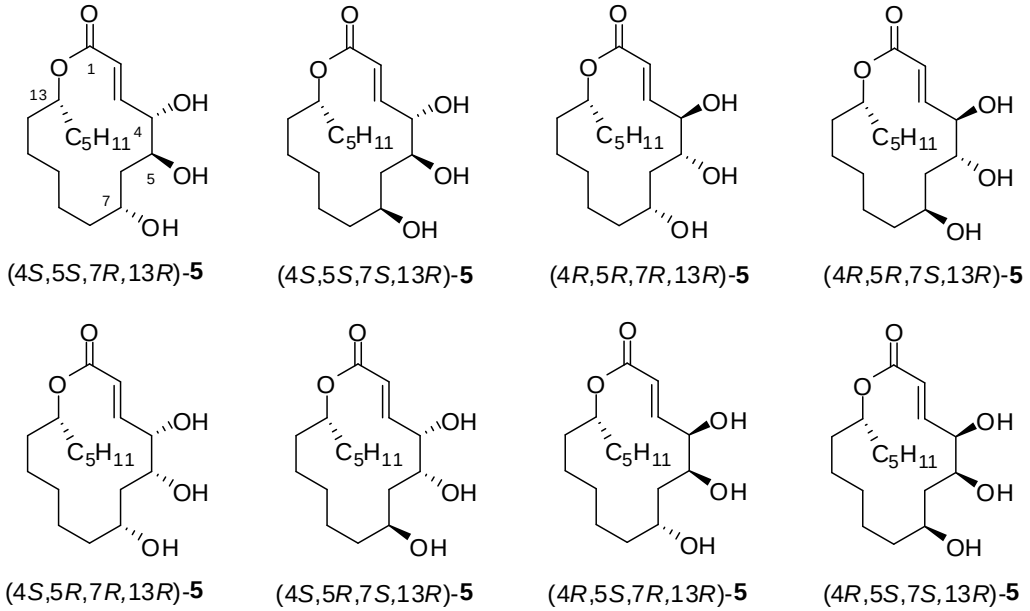
Figure 8: Global detagging results for 4,5-*cis*-dihydroxy isomer family and HPLC trace for (4*R*,5*S*,7*R*,13*R*)-5

5.0 CHARACTERIZATION OF THE SCH725674 STEREOISOMER LIBRARY MEMBERS

5.1.1 Ring-Closed Sch725674 Stereoisomer Library, Macrocyles 5

Once all sixteen macrocycles **5** comprising the full ring-closed stereoisomer library of Sch725674 were purified, the eight 13*R* enantiomers (Scheme 5.1) were carefully characterized by ^{1}H and ^{13}C NMR, IR, HRMS, and optical rotation measurement. The members of the 13*S* series were characterized only by ^{1}H NMR and optical rotation. The assignment of ^{1}H and ^{13}C signals was assisted by 2D NMR spectroscopy, particularly the ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMQC, and ^{1}H-^{13}C HMBC experiments. As expected, the ^{1}H NMR spectra of corresponding enantiomeric pairs **5** were identical. This shows that stereocenter encoding by fluorous tags and the demixing both succeeded.

Scheme 5.1. 3D structures of the ring-closed 13*R*-5 enantioseries



The ^{1}H NMR spectral data of the 4,5-*trans*-dihydroxy-13*R*-**5** series and 4,5-*cis*-dihydroxy-13*R*-**5** series are listed in Tables 5-1 and 5-2, respectively. All eight ^{1}H NMR spectra were recorded in d_4-MeOD at 700 MHz. Due to overlap in the aliphatic region, the ^{1}H signals of C9-C11 could not be assigned for the ring-closed compounds, even with the aid of 2D NMR experiments. Throughout all eight sets of data, the ^{1}H NMR resonances of the C15-C18 sidechain remain unchanged regardless of absolute configuration. Also, the vinyl protons at C2 and C3 show only slight differences in chemical shift based on absolute configuration. The most notable differences between the eight ^{1}H NMR spectra, however, exist at the C4, C5, and C7 carbinol proton resonances.

Table 5-1: ^{1}H NMR data (700 MHz) of the ring-closed (4,5-*trans*-dihydroxy-13*R*)-5 series in d_4-MeOD

C no.	(4*S*,5*S*,7*R*,13*R*)-**5**	(4*S*,5*S*,7*S*,13*R*)-**5**	(4*R*,5*R*,7*R*,13*R*)-**5**	(4*R*,5*R*,7*S*,13*R*)-**5**
2	6.11 (dd, 15.8, 1.5, 1H)	6.10 (dd, 15.8, 1.3, 1H)	6.11 (d, 15.8, 1H)	6.12 (dd, 15.8, 1.5, 1H)
3	7.04 (dd, 15.8, 5.3, 1H)	6.96 (dd, 15.8, 5.9, 1H)	6.91 (dd, 15.8, 6.4, 1H)	7.07 (dd, 15.8, 5.4, 1H)
4	4.95 (dddd, 12.5, 7.6, 5.0, 2.3, 1H)	4.03 (ddd, 7.6, 6.0, 1.5, 1H)	4.16 (t, 6.0, 1H)	4.26 (td, 6.5, 1.5, 1H)
5	3.77 (dt, 7.4, 4.5, 1H)	3.54 (td, 8.5, 1.5, 1H)	3.82 (ddd, 9.2, 6.0, 3.8, 1H)	3.90 (td, 6.5, 2.8, 1H)
6	1.70 (dd, 5.4, 4.5, 2H)	1.76 (ddd, 14.6, 8.5, 2.7, 1H) 1.67 (m, 1H)	1.63 (m, 1H) 1.45 (m, 1H)	1.70 (m, 2H)
7	3.92 (m, 1H)	3.47 (m, 1H)	3.79 (m, 1H)	3.78 (sept, 4.20, 1H)
8	1.43 (m, 1H) 1.33 (m, 1H)	1.55 (m, 1H) 1.34 (m, 1H)	1.45 (m, 2H)	1.31 (m, 2H)
9	1.19 (m, 2H)	nd*	nd	nd
10	nd	nd	nd	nd
11	nd	nd	nd	nd
12	1.62 (m, 1H) 1.54 (m, 1H)	1.67 (m, 2H)	1.78 (m, 1H) 1.56 (m, 1H)	1.70 (m, 2H)
13	4.95 (dddd, 12.5, 7.6, 5.0, 2.3, 1H)	4.93 (m, 1H)	5.03 (m, 1H)	4.97 (m, 1H)
14	1.62 (m, 1H) 1.54 (m, 1H)	1.67 (m, 1H) 1.64 (m, 1H)	1.56 (m, 1H) 1.45 (m, 1H)	1.63 (m, 2H)
15	1.33 (m, 2H)	1.34 (m, 2H)	1.33 (m, 2H)	1.31 (m, 2H)
16	1.33 (m, 2H)	1.34 (m, 2H)	1.33 (m, 2H)	1.31 (m, 2H)
17	1.33 (m, 2H)	1.34 (m, 2H)	1.33 (m, 2H)	1.31 (m, 2H)
18	0.91 (t, 6.9, 3H)	0.91 (t, 6.9, 3H)	0.90 (t, 6.9, 3H)	0.91 (t, 6.9, 3H)

* nd = not determined

Table 5-2: ^{1}H NMR data (700 MHz) of the ring-closed (4,5-*cis*-dihydroxy-13*R*)-5 series in d_4-MeOD

C no.	(4*S*,5*R*,7*R*,13*R*)-**5**	(4*S*,5*R*,7*S*,13*R*)-**5**	(4*R*,5*S*,7*R*,13*R*)-**5**	(4*R*,5*S*,7*S*,13*R*)-**5**
2	6.09 (dd, 15.8, 1.8, 1H)	6.06 (dd, 15.8, 2.2, 1H)	6.08 (dd, 15.8, 1.5, 1H)	6.14 (dd, 15.8, 1.4, 1H)
3	6.94 (dd, 15.8, 4.7, 1H)	7.00 (dd, 15.8, 3.6, 1H)	6.87 (dd, 15.8, 6.1, 1H)	6.95 (dd, 15.8, 4.2, 1H)
4	4.47 (ddd, 4.7, 3.0, 1.8, 1H)	4.46 (m, 1H)	4.49 (ddd, 5.8, 2.7, 1.5, 1H)	4.54 (m, 1H)
5	3.89 (ddd, 7.2, 4.7, 3.0, 1H)	3.95 (ddd, 7.6, 4.5, 2.2, 1H)	3.85 (m, 1H)	3.89 (dt, 8.8, 2.1, 1H)
6	1.71 (ddd, 14.6, 7.2, 4.7, 1H) 1.33 (m, 1H)	2.02 (ddd, 14.1, 8.1, 4.5, 1H) 1.54 (m, 1H)	1.83 (dt, 14.7, 6.1, 1H) 1.65 (dt, 14.7, 5.0,1H)	1.32 (m, 2H)
7	3.71 (m, 1H)	3.68 (sept, 4.5, 1H)	3.99 (quint, 6.2, 1H)	3.38 (m, 1H)
8	1.45 (m, 2H)	1.28 (m, 2H)	1.34 (m, 2H)	1.32 (m, 2H)
9	nd*	nd	nd	nd
10	nd	nd	nd	nd
11	nd	nd	nd	nd
12	1.76 (m, 1H) 1.63 (m, 1H)	1.69 (m, 2H)	1.65 (m, 2H) 1.71 (dddd, 14.2, 6.7, 4.6, 2.0, 1H)	
13	5.01 (m, 1H)	4.95 (m, 1H)	4.95 (dddd, 10.4, 7.9, 5.4, 2.9, 1H)	4.93 (m, 1H)
14	1.56 (m, 1H) 1.45 (m, 1H)	1.61 (m, 2H)	1.55 (m, 1H) 1.61 (m, 1H)	1.65 (m, 1H) 1.54 (m, 1H)
15	1.33 (m, 2H)	1.34 (m, 2H)	1.34 (m, 2H)	1.32 (m, 2H)
16	1.33 (m, 2H)	1.34 (m, 2H)	1.34 (m, 2H)	1.32 (m, 2H)
17	1.33 (m, 2H)	1.34 (m, 2H)	1.34 (m, 2H)	1.32 (m, 2H)
18	0.90 (t, 6.9, 3H)	0.90 (t, 6.9, 3H)	0.90 (t, 6.9, 3H)	0.90 (t, 6.9, 3H)

* nd = not determined

Figure 9 shows ^{1}H NMR expansions of the sensitive carbinol region (4.80 - 3.30 ppm) for the 13*R*-**5** series. The carbinol protons at C4, C5, and C7 are labeled directly on the expansions and follow the general left-to-right order H4-H5-H7, as confirmed by the 2D ^{1}H-^{1}H COSY experiment. For (4*S*,5*S*,7*R*,13*R*)-**5** (top spectrum) and (4*R*,5*S*,7*R*,13*R*)-**5** (second spectrum from bottom), however, the H5 and H7 carbinol proton resonances are reversed and follow the left-to-

right order H4-H7-H5. The H5 and H7 resonances for (4*R*,5*R*,7*R*,13*R*)-**5** (third spectrum from top) partially overlap, but still follow the left-to-right H4-H5-H7 order.

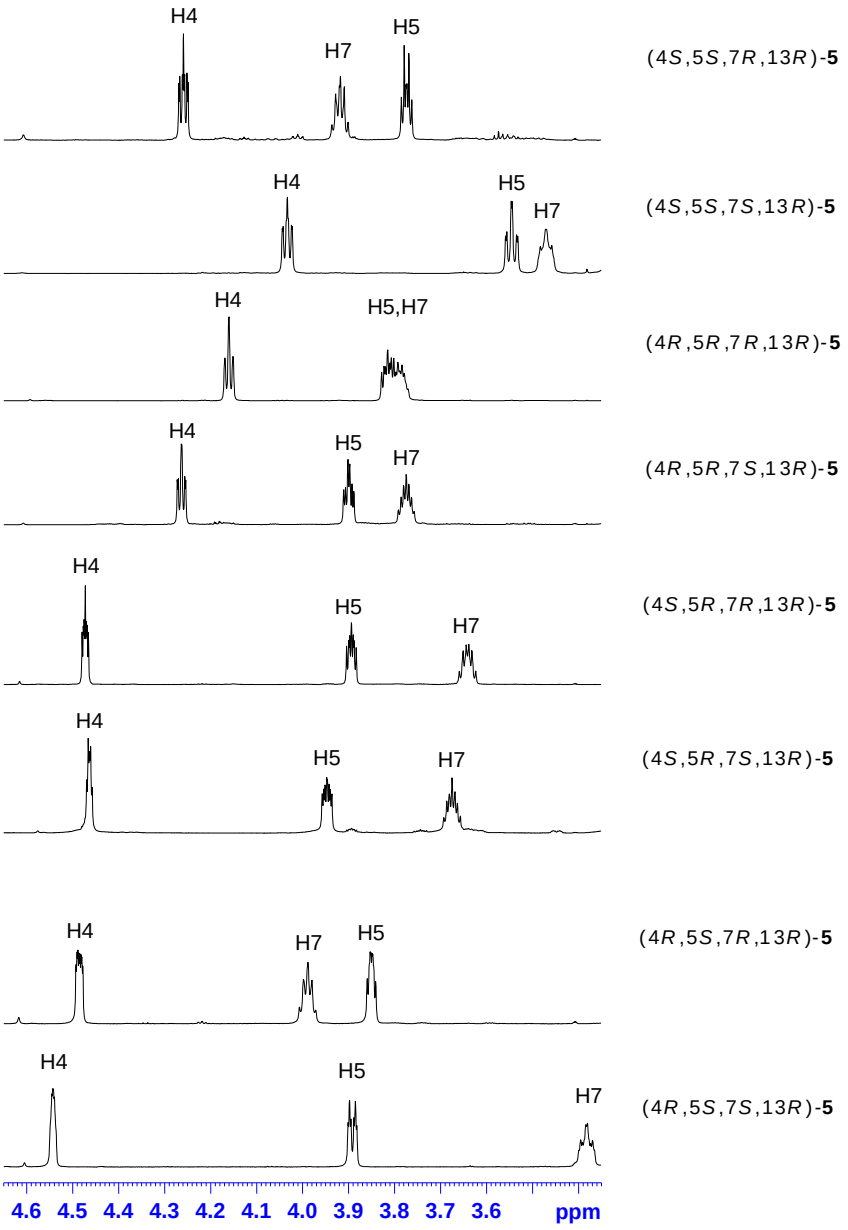


Figure 9: ^{1}H NMR expansion (700 MHz) of the carbinol region for the 13*R*-5 enantioseries in d_4-MeOD

The ^{13}C NMR spectral data of the full 13*R*-**5** enantioseries are listed in Table 5-3. As observed with the ^{1}H NMR spectra, the carbon signals pertaining to the C15-C18 sidechain were

substantially identical for all eight recorded ^{13}C NMR spectra. The vinyl carbon resonances at C2 and C3 show only modest differences based on absolute configuration. As expected, the carbinol region (78-74 ppm) was most sensitive to absolute configuration. In conclusion, all eight members of the 13*R*-**5** series have unique ^{1}H and ^{13}C NMR spectra and only one member should match the spectral data of the natural product.

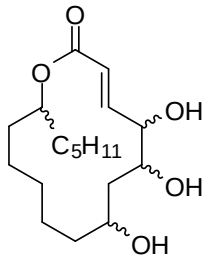
Table 5-3: ^{13}C NMR data (175 MHz) for the 13*R*-5 enantioseries in d_4-MeOD

C no.	(4*S*,5*S*,7*R*,13*R*)-**5**	(4*S*,5*S*,7*S*,13*R*)-**5**[a]	(4*R*,5*R*,7*R*,13,*R*)-**5**[a]	(4*R*,5*R*,7*S*,13*R*)-**5**	(4*S*,5*R*,7*R*,13*R*)-**5**	(4*S*,5*R*,7*S*,13*R*)-**5**	(4*R*,5*S*,7*R*,13*R*)-**5**	(4*R*,5*S*,7*S*,13*R*)-**5**
1	168.0	168.1	168.2	168.9	168.0	168.0	168.4	169.0
2	123.5	123.1	124.3	123.3	123.4	122.3	123.1	121.8
3	148.7	149.4	148.4	149.8	148.6	150.2	149.3	150.0
4	75.8	77.8	77.5	75.3	74.6	75.7	76.0	75.0
5	74.4	74.6	73.4	73.9	72.3	72.1	72.9	72.1
6	37.9	43.8	42.0	nd[b]	39.1	39.5	38.3	40.5
7	69.2	68.3	67.6	69.9	68.8	68.8	69.5	68.8
8	nd	nd	nd	nd	36.4	39.5	nd	nd
9	nd	nd	nd	nd	nd	nd	nd	nd
10	nd	nd	nd	nd	nd	nd	nd	nd
11	nd	nd	nd	nd	nd	nd	nd	nd
12	36.4	35.8	34.5	nd	34.4	34.9	34.1	33.9
13	77.6	75.9	77.6	75.8	77.4	76.1	77.6	75.5
14	36.8	33.3	36.0	nd	35.7	32.8	36.5	36.2
15	26.4	26.4	26.6	26.5	26.6	26.6	26.4	23.8
16	33.0	33.0	32.9	33.0	33.0	33.0	33.0	33.0
17	23.8	23.8	23.8	23.8	23.8	23.8	23.8	23.8
18	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5

[a] Measured at 125 MHz
[b] nd = not determined

The optical rotation measurements of the sixteen macrocycles **5** are listed pairwise in Table 5-4. All measurements were made in absolute MeOH at room temperature. Corresponding enantiomers have optical rotation measurements that are about equal in magnitude but opposite in sign. Interestingly, the magnitude of the optical rotation values for macrocycles **5** varies widely from 2 to almost 40. Also, each isomer has a unique optical rotation value except for (4*S*,5*R*,7*S*,13*R*)-**5**, (4*R*,5*S*,7*R*,13*S*)-**5**, (4*R*,5*S*,7*R*,13*R*)-**5**, and (4*S*,5*R*,7*S*,13*S*)-**5**, all four of which are close to zero in magnitude.

Table 5-4: Optical rotation measurements of macrocyclic triols 5



5

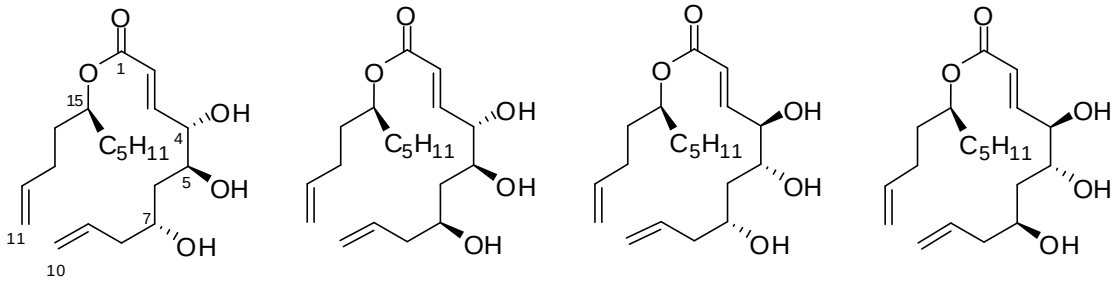
Isomer	*c* (g/100 mL)	$[\alpha]_D^a$
(4*S*,5*S*,7*R*,13*R*)-**5**	0.54	−9.43
(4*R*,5*R*,7*S*,13*S*)-**5**	0.89	+11.3
(4*S*,5*S*,7*S*,13*R*)-**5**	0.77	−18.8
(4*R*,5*R*,7*R*,13*S*)-**5**	0.32	+16.5
(4*R*,5*R*,7*R*,13*R*)-**5**	1.25	+24.8
(4*S*,5*S*,7*S*,13*S*)-**5**	0.83	−25.9
(4*R*,5*R*,7*S*,13*R*)-**5**	0.38	+7.66
(4*S*,5*S*,7*R*,13*S*)-**5**	0.27	−4.04
(4*S*,5*R*,7*R*,13*R*)-**5**	0.55	+15.5
(4*R*,5*S*,7*S*,13*S*)-**5**	0.35	−13.8
(4*S*,5*R*,7*S*,13*R*)-**5**	0.54	+1.66
(4*R*,5*S*,7*R*,13*S*)-**5**	0.70	−2.14
(4*R*,5*S*,7*R*,13*R*)-**5**	0.27	+5.15
(4*S*,5*R*,7*S*,13*S*)-**5**	0.21	−2.93
(4*S*,5*R*,7*S*,13*R*)-**5**	0.24	−38.6
(4*S*,5*R*,7*R*,13*S*)-**5**	0.67	+38.7

[a] Measured at room temperature in absolute MeOH

5.1.2 Ring-Open Stereoisomer Library, Esters 58

Once the eight ring-open triols **58** were isolated, the 15*S*-**58** enantioseries (Scheme 5.2) was carefully characterized by ^{1}H and ^{13}C NMR, IR, HRMS, and optical rotation measurement. The 15*R*-**58** enantiomers were characterized by only ^{1}H NMR and optical rotation. In addition, the assignment of all 1D ^{1}H and ^{13}C signals in this enantioseries was assisted by 2D NMR spectroscopy, particularly the ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMQC, and ^{1}H-^{13}C HMBC experiments. Lastly, the matching spectra of all four enantiomeric pairs **58** were further proof to the principle of stereocenter encoding by multiple tags in FMS.

Scheme 5.2. 3D structures of the ring-open 15*S*-58 triols



(4*S*,5*S*,7*R*,15*S*)-**58** (4*S*,5*S*,7*S*,15*S*)-**58** (4*R*,5*R*,7*R*,15*S*)-**58** (4*R*,5*R*,7*S*,15*S*)-**58**

Interestingly, all four triols in the ring-open 15*S*-**58** series exhibited very similar ^{1}H NMR spectra. The ^{1}H NMR spectral data of the 15*S*-**58** series are tabulated in Table 5-6. All four ^{1}H NMR spectra were recorded in d_4-MeOD at 600 MHz. As expected, the ^{1}H NMR signals of the C17-C19 sidechain remain unchanged regardless of absolute configuration. The vinyl protons at C2 and C3 likewise show only slight differences based on absolute configuration. The most notable differences between the four ^{1}H NMR spectra, however, exist at the more sensitive C4, C5, and C7 carbinol stereogenic atoms.

Table 5-5: ^{1}H NMR data (600 MHz) for the full ring-open 15*S*-58 enantioseries in *d*4-MeOD

C no.	(4*S*,5*S*,7*R*,15*S*)-**58**	(4*S*,5*S*,7*S*,15*S*)-**58**	(4*R*,5*R*,7*R*,15*S*)-**58**	(4*R*,5*R*,7*S*,15*S*)-**58**
2	6.10 (dd, 15.7, 1.7, 1H)	6.11 (dd, 15.7, 1.8, 1H)	6.11 (dd, 15.7, 1.7, 1H)	6.11 (dd, 15.7, 1.7, 1H)
3	7.05 (dd, 15.7, 4.7, 1H)	7.05 (dd, 15.7, 4.6, 1H)	7.05 (dd, 15.7, 4.6, 1H)	7.05 (dd, 15.7, 4.7, 1H)
4	4.19 (td, 4.7, 1.7, 1H)	4.22 (td, 4.5, 1.8, 1H)	4.22 (td, 4.4, 1.8, 1H)	4.19 (td, 4.7, 1.7, 1H)
5	3.87 (m, 2H)	3.82 (quint, 4.3, 1H)	3.82 (quint, 4.4 Hz, 1H)	3.88 (m, 2H)
6	1.54 (m, 2H)	1.74 (dt, 14.2, 4.4, 1H) 1.55 (dt, 17.2, 8.7, 1H)	1.74 (dt, 14.1, 4.4, 1H) 1.54 (dt, 14.1, 8.7, 1H)	1.55 (m, 2H)
7	3.87 (m, 2H)	3.87 (m, 1H)	3.87 (m, 1H)	3.88 (m, 2H)
8	2.24 (m, 2H)	2.25 (m, 2H)	2.25 (m, 2H)	2.24 (m, 2H)
9	5.87 (ddt,17.2,10.2,7.0,1H)	5.87 (ddt,17.2,10.2,7.0,1H)	5.87 (ddt,17.2,10.2,7.0,1H)	5.87 (ddt,17.2,10.2,7.0,1H)
10	5.02 (m, 2H)	5.00 (m, 2H)	5.01 (m, 2H)	5.00 (m, 2H)
11	5.02 (m, 2H)	5.00 (m, 2H)	5.01 (m, 2H)	5.00 (m, 2H)
12	5.82 (ddt,16.9,10.2,6.7,1H)	5.82 (ddt,16.9,10.2,6.7,1H)	5.82 (ddt,16.9,10.2,6.7,1H)	5.82 (ddt,16.9,10.2,6.7,1H)
13	2.07 (m, 2H)	2.08 (m, 2H)	2.08 (m, 2H)	2.08 (m, 2H)
14	1.68 (m, 2H)	1.67 (m, 2H)	1.68 (m, 2H)	1.68 (m, 2H)
15	5.02 (m, 1H)	5.00 (m, 1H)	5.01 (m, 1H)	5.00 (m, 1H)
16	1.58 (m, 2H)	1.59 (m, 2H)	1.59 (m, 2H)	1.58 (m, 2H)
17	1.32 (m, 2H)	1.32 (m, 2H)	1.32 (m, 2H)	1.32 (m, 2H)
18	1.32 (m, 2H)	1.32 (m, 2H)	1.32 (m, 2H)	1.32 (m, 2H)
19	1.32 (m, 2H)	1.32 (m, 2H)	1.32 (m, 2H)	1.32 (m, 2H)
20	0.90 (t, 6.9, 3H)	0.90 (t, 6.9, 3H)	0.90 (t, 6.9, 3H)	0.90 (t, 6.9, 3H)

Figure 10 shows expansions of the sensitive carbinol region of the ^{1}H NMR spectra for the 13*S*-**58** triols. The proton resonances of the stereogenic C4, C5, and C7 atoms were assigned by the 2D ^{1}H-^{1}H COSY experiment and are labeled directly on each spectrum. The carbinol proton resonances at C5 and C7 overlap in (4*S*,5*S*,7*R*,15*S*)-**58** and (4*R*,5*R*,7*S*,15*S*)-**58** (top two spectra, respectively). The carbinol proton resonances of (4*S*,5*S*,7*S*,15*S*)-**58** and (4*R*,5*R*,7*R*,15*S*)-**58** (bottom two spectra, respectively), however, follow the left-to-right order H4-H7-H5.

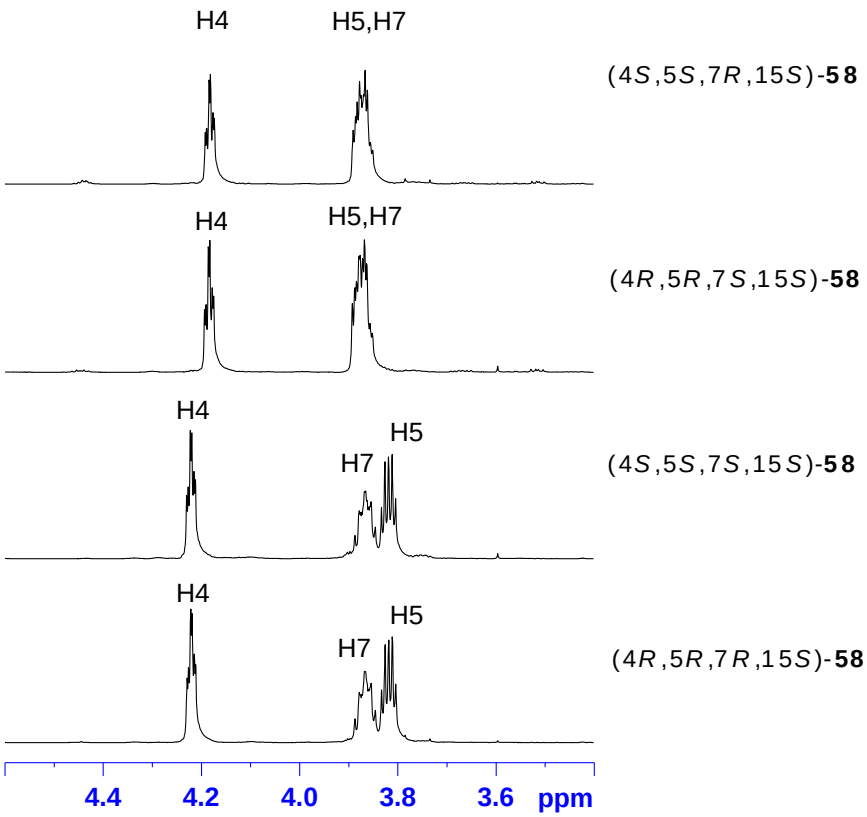


Figure 10: ^{1}H NMR expansions (600 MHz) of the carbinol region for the ring-open 15*S*-58 triols in d_4-MeOD

The ^{13}C NMR spectral data of the 15*S*-**58** series are tabulated in Table 5-6. The chemical shifts of C17-C19 sidechain and vinyl C2-C3 carbon atoms indicate no dependence on absolute configuration. As expected, the chemical shifts of carbon signals pertaining to the carbinol (C4, C5, and C7) atoms are most sensitive to absolute configuration. Overall, the appearance of the NMR spectra for the ring-open series **58** show little dependence on absolute stereochemistry.

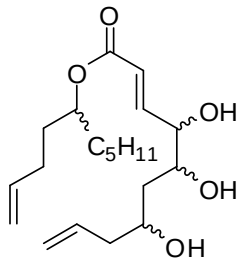
Table 5-6: ^{13}C NMR data (125 MHz) for the full ring-open 15*S*-58 enantioseries in *d*4-MeOD

C no.	(4*S*,5*S*,7*R*,15*S*)-**58**	(4*S*,5*S*,7*S*,15*S*)-**58**	(4*R*,5*R*,7*R*,15*S*)-**58**	(4*R*,5*R*,7*S*,15*S*)-**58**
1	168.1	168.1	168.1	168.1
2	122.8	122.8	122.8	122.8
3	149.8	149.9	149.9	149.8
4	75.5	74.7	74.7	75.5
5	71.8	70.9	70.9	71.8
6	40.6	39.8	39.8	40.6
7	68.8	73.8	73.8	68.8
8	43.9	43.1	43.1	44.0
9	136.5	136.2	136.2	136.5
10	117.5	117.7	117.7	117.5
11	115.6	115.6	115.6	115.6
12	139.2	139.2	139.2	139.2
13	30.9	30.9	31.0	31.0
14	34.8	34.8	34.8	34.8
15	75.2	75.2	75.2	75.2
16	35.4	35.4	35.4	35.4
17	26.2	26.2	26.2	26.2
18	32.9	32.9	32.9	32.9
19	23.8	23.7	23.8	23.8
20	14.5	14.5	14.5	14.5

The optical rotation measurements of all eight ring-open triols **58** are listed pairwise in Table 5-7. Corresponding enantiomers have optical rotation measurements that are about equal in magnitiude but opposite in sign. Because of the amount of isolated material of the ring-open triols (up to ~30 mg), the mass of each triol **58** was measured with greater accuracy than macrocyles **5**. All measurements were made in absolute MeOH at room temperature. Interestingly, (4*S*,5*S*,7*S*,15*R*)-**58** and (4*R*,5*R*,7*R*,15*S*)-**58** are indistinguishable by ^{1}H NMR

spectroscopy but can be easily identified by their unique optical rotation values of −13.3 and +15.2, respectively.

Table 5-7: Optical rotation measurements of the ring-open triols 58



58

Isomer	*c* (g/100 mL)	$[\alpha]_D$[a]
(4*S*,5*S*,7*R*,15*R*)-**58**	1.08	−30.7
(4*R*,5*R*,7*S*,15*S*)-**58**	1.45	+33.2
(4*S*,5*S*,7*S*,15*R*)-**58**	0.83	−15.1
(4*R*,5*R*,7*R*,15*S*)-**58**	1.19	+15.2
(4*R*,5*R*,7*R*,15*R*)-**58**	1.02	+17.9
(4*S*,5*S*,7*S*,15*S*)-**58**	1.51	−13.3
(4*R*,5*R*,7*S*,15*R*)-**58**	1.02	+34.6
(4*S*,5*S*,7*R*,15*S*)-**58**	1.20	−23.0

[a] Measured at room temperature in absolute MeOH

5.1.3 Spectral Comparison of the Ring-Open and Ring-Closed Libraries

The NMR spectroscopic data of the ring-open and macrocyclic triols were compared. Figure 10 shows ^{1}H NMR expansions (4.60–3.35 ppm) of the carbinol region for the macrocyclic C13-epimers (4*R*,5*R*,7*R*,13*R*)-**5** and (4*R*,5*R*,7*R*,13*S*)-**5** (top two spectra, respectively), and ring-open C15-epimers (4*R*,5*R*,7*R*,15*R*)-**58** and (4*R*,5*R*,7*R*,15*S*)-**58** (bottom two spectra, respectively). All four compounds have the (4*R*,5*R*,7*R*) configuration and were recorded in d_4-MeOH with high-field NMR instruments (500-700 MHz). There is substantial similarity between the three ^{1}H NMR carbinol resonances of the 15*R* and 15*S* ring-open triols **58**. The drastically different

spectra of the 13*R* and 13*S* ring-closed macrocycles **5**, however, indicate communication between the remote C13 stereocenter and the carbinol stereogenic atoms along the carbon skeleton of **5**. Indeed, the different ^{1}H NMR spectra of epimers (4*R*,5*R*,7*R*,13*R*)-**5** and (4*R*,5*R*,7*R*,13*S*)-**5** suggest that the configuration at the remote C13 stereocenter has a clear effect on the ring conformation of the natural product.

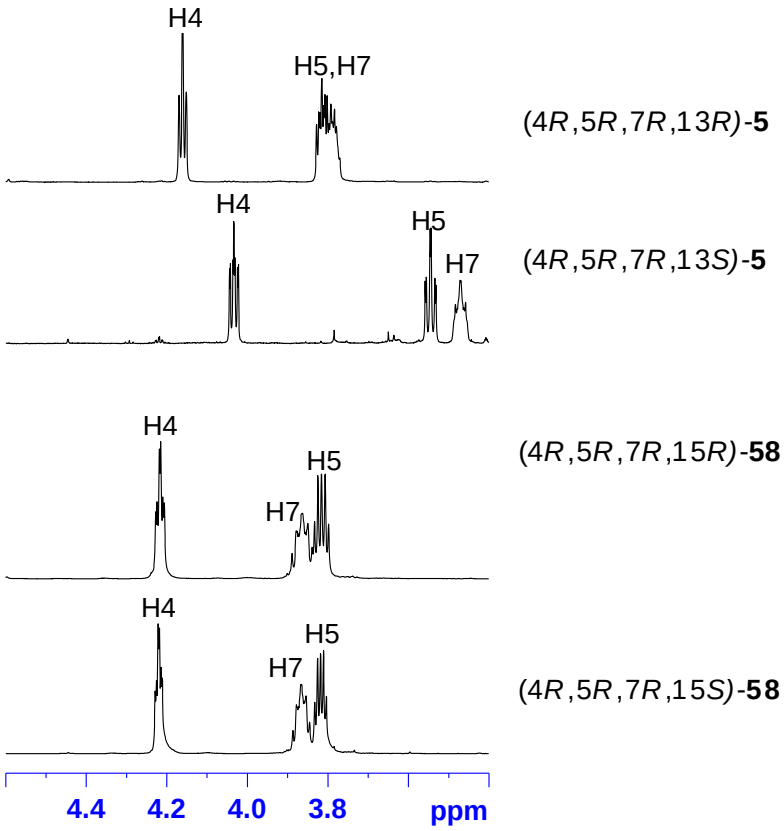


Figure 11: Spectral comparison of the carbinol protons in ring-open vs. ring-closed triols

5.1.4 Assignment of Absolute Configuration to Sch725674

The spectral data from the 13*R*-**5** enantioseries was compared to the NMR spectral data reported for the natural product. As shown in Table 5-8, the synthetic sample (4*R*,5*S*,7*R*,13*R*)-**5** matched

the ^{1}H and ^{13}C NMR spectra of the natural product. Supported by the Celmer guideline of macrolide stereochemistry (see Section 1.2.2), we can confidently assign (4*R*,5*S*,7*R*,13*R*)-**5** as the natural configuration of Sch725674.

Table 5-8: Comparison of ^{1}H and ^{13}C NMR data between natural Sch725674 and (4*R*,5*S*,7*R*,13*R*)-5

C/H no.	^{1}H (δ)		^{13}C (δ)	
	Sch725674[a]	(4*R*,5*S*,7*R*,13*R*)-**5**[b]	Sch725674[c]	(4*R*,5*S*,7*R*,13*R*)-**5**[d]
1			168.4	168.4
2	6.07 (dd, 15.8, 1.6, 1H)	6.08 (dd, 15.8, 1.5, 1H)	123.1	123.1
3	6.86 (dd, 15.8, 6.0, 1H)	6.87 (dd, 15.8, 6.1, 1H)	149.3	149.3
4	4.48 (ddd, 6.0, 3.0, 1.6, 1H)	4.49 (ddd, 5.8, 2.7, 1.5, 1H)	76.0	76.0
5	3.84 (ddd, 6.0, 4.7, 3.0, 1H)	3.85 (m, 1H)	72.9	72.9
6	1.82 (ddd, 14.7, 6.5, 6.0, 1H) 1.65 (m, 1H)	1.83 (dt, 14.7, 6.1, 1H) 1.65 (dt, 14.7, 5.0, 1H)	38.3	38.3
7	3.98 (quart, 6.5, 1H)	3.99 (quint, 6.2, 1H)	69.5	69.5
8	1.36 (m, 2H)	1.34 (m, 2H)	36.8	nd
9	1.19 (m, 1H) 1.37 (m, 1H)	nd[e]	25.8	nd
10	1.15 (m, 1H) 1.40 (m, 1H)	nd	29.5	nd
11	1.19 (m, 1H)	nd	27.0	nd
12	1.54 (m, 1H) 1.70 (m, 1H)	1.55 (m, 1H) 1.71 (dddd, 14.2, 6.7, 4.6, 2.0, 1H)	34.1	34.1
13	4.94 (dddd, 9.8, 7.5, 5.0, 2.2, 1H)	4.95 (dddd, 10.4, 7.9, 5.4, 2.9, 1H)	77.6	77.6
14	1.57 (m, 1H) 1.61 (m, 1H)	1.55 (m, 1H) 1.61 (m, 1H)	36.5	36.5
15	1.32 (m, 2H)	1.34 (m, 2H)	26.4	26.4
16	1.30 (m, 2H)	1.34 (m, 2H)	32.9	33.0
17	1.30 (m, 2H)	1.34 (m, 2H)	23.8	23.8
18	0.89 (t, 6.8, 3H)	0.90 (t, 6.9, 3H)	14.5	14.5

[a] Measured at 500 MHz
[b] Measured at 700 MHz
[c] Measured at 125 MHz
[d] Measured at 175 MHz
[e] nd = not determined

5.2 CONCLUSION

The technique of fluorous mixture synthesis was applied to obtain all sixteen candidate stereoisomers of the macrolactone natural product Sch725674. Initially, the synthesis of a single stereoisomer of Sch725674 was performed as a pilot study to secure a stereoselective route to the natural product stereoisomer library and to confirm the 2D connectivity of Sch725674. The synthetic sequence established in the pilot study was then applied to an eight-member isomer family of Sch725674, with each member of the family having a *trans* relationship between the C4 and C5 stereocenters. An eight-member library of ring-open Sch725674 analogs was also synthesized by FMS. A second eight-member family of macrocycles was then synthesized, with each member of this family having a *cis* relationship between the C4 and C5 stereocenters. All three of these libraries employed a novel tagging strategy which used two sorting tags, only one of which is fluorous. Finally, we confidently assigned the configuration of natural Sch725674 as (4*R*,5*S*,7*R*,13*R*) by comparing the NMR spectral data of our synthetic samples to those of the natural isomer.

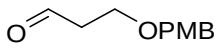
6.0 EXPERIMENTAL

General: Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker WH-300 MHz, IBM AF-300, Bruker Avance™ 500 NMR, Bruker Avance™ 600 NMR, or a Bruker Avance™ 700 NMR spectrometer using deuterated chloroform as solvent, unless otherwise indicated. Signal positions are given as part per million (δ) and were determined relative to the residual proton resonance of $CDCl_3$ (7.27 ppm) or central $CDCl_3$ carbon peak carbon peak (77.03 ppm) as the internal standards. Coupling constants (*J* values) are in Hz. Spectral content is listed in the following order: chemical shift (δ), multiplicity, coupling constants (Hz), number of nuclei. All spectra were acquired at room temperature. In the case of ^{19}F NMR spectral data, an internal standard (α,α,α-trifluorotoluene) was used only for Mosher ester analyses.

Infrared (IR) spectra were recorded on a Mattson Genesis series FTIR spectrometer as thin films on NaCl plates and peaks are reported in wave numbers (cm^{-1}). Optical rotations were measured on a Perkin-Elmer 241 polarimeter at a Na D-line (λ = 589 nm) using a 1 dm cell. Low-resolution mass spectra were obtained on a V/G 70/70 double focusing machine and were reported in units of *m/z*. HPLC analyses and separations were performed on a Waters 600E system with a Waters 2487 dual λ absorption detector. Compound names were obtained from ChemDraw Ultra 12.0 (Cambridge Soft Corp.).

All reactions were monitored by either thin layer chromatography or ^{1}H NMR spectroscopy. Visualization of the thin layer chromatography plates was achieved with ultraviolet light (254 nm), followed by development in a staining solution of anisaldehyde in ethanol, or 5% aqueous potassium permanganate. Conventional flash chromatography was performed with 230-400 mesh silica gel (E. Merck, Silica gel 60). All dry solvents were obtained by passing over activated alumina. Unless water was a cosolvent or reagent, all reactions were carried out under inert an atmosphere of dry argon. Deionized water was used for all workup operations. Standard syringe/septa techniques were employed throughout all reactions.

6.1 EXPERIMENTAL DATA FOR THE 2ND GENERATION PILOT SYNTHESIS



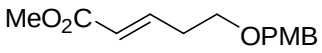
3-(4-Methoxybenzyloxy)propanal (26).[60] CAS registry number: [128461-65-4]. Solid NaH (60% in mineral oil, 5.78 g, 144.55 mmol) was added to anhydrous dimethylformamide (200 mL). The resultant suspension was quickly cooled to 0 °C and a catalytic amount of tetrabutylammonium iodide (4.85 g, 13.14 mmol) was added. Then, 1,3-propanediol (9.50 mL, 131.41 mmol) was slowly added dropwise by syringe. After 30 min at 0 °C, 4-methoxybenzyl chloride (18.63 mL, 137.98 mmol) was added dropwise by syringe. The suspension was stirred for 30 min at 0 °C, then at room temperature for 16 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (100 mL). The resultant bilayer was transferred to a separatory funnel and Et_2O (250 mL) was added. The layers were separated and the aqueous layer was extracted

with Et_2O (3 x 200 mL). The combined organic extracts were washed with water (150 mL) and brine (150 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. Flash chromatography of the crude product (1:1 hexanes/EtOAc) gave the PMB ether as a pale yellow oil (12.48 g, 48%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.44 (s, 2H), 3.79 (s, 3H), 3.74 (t, J = 5.7 Hz, 2H), 3.62 (t, J = 5.8 Hz, 2H), 2.56 (broad s, 1H), 1.84 (quintet, J = 5.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 130.1, 129.2, 113.8, 72.8, 68.8, 61.6, 55.2, 32.1.

General Procedure for Swern oxidations.[59]

Swern Oxidation of 3-(4-methoxybenzyloxy)-1-propanol:

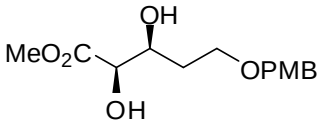
A solution of DMSO (18.2 mL, 255.6 mmol) in CH_2Cl_2 (100 mL) was slowly added by syringe to a solution of oxalyl chloride (1.65 mL, 19.18 mmol) in CH_2Cl_2 (600 mL) at −78 °C. After 15 min, the above alcohol (12.48 g, 63.3 mmol) in CH_2Cl_2 (125 mL) was added dropwise by cannula transfer. The flask containing the alcohol was rinsed with CH_2Cl_2 (25 mL) and the rinse was also transferred by cannula. The resulting mixture was stirred at −78 °C for 15 min, then Et_3N (6.68 mL, 47.95 mmol) was added slowly dropwise by syringe. The reaction mixture was maintained at −78 °C for 15 min then warmed to 0 °C, and the stirring continued for 30 min. Water was then added and the mixture was diluted with Et_2O. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with Et_2O. The organic layers were combined, dried over $MgSO_4$, filtered, and then concentrated by rotary evaporation. The crude product was then purified by flash chromatography (3:1 hexanes:EtOAc) to afford the title compound as a pale yellow oil (13.03 g, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, J = 1.8 Hz, 1H), 7.26 (d, J = 8.3 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 3.79 (t, J = 6.1 Hz, 2H), 4.47 (s, 2H), 3.81 (s, 3H), 2.69 (td, J_1 = 1.8 Hz, J_2 = 6.1 Hz, 2H).



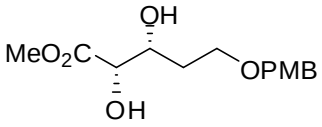
(2*E*)-Methyl-5-(4-methoxybenzyloxy)pent-2-enoate (*E*-25). CAS registry number: [201667-72-3].

General Procedure for the HWE (Masamune-Roush) olefination:[54]

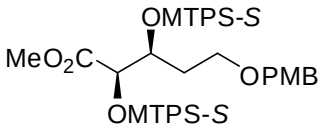
Trimethylphosphonoacetate (11.64 mL, 80.51 mmol) was added dropwise by syringe to a stirring slurry of LiCl (3.41 g, 80.51 mmol) in anhydrous MeCN (650 mL). 1,8-Diazabicyclo-[5.4.0]-undec-7-ene (11.03 mL, 73.80 mmol) was added dropwise by syringe at room temperature. The resultant suspension was cooled to 0 °C, and a solution of the propanal **26** in acetonitrile (125 mL) was added dropwise by cannula transfer. The flask containing the propanal was rinsed with acetonitrile (25 mL) and the rinse was transferred to the reaction mixture by cannula. The resultant suspension was stirred at 0 °C for 5 min, then at room temperature for 45 min. Deionized water (300 mL) was then added to the suspension to dissolve the phosphonic acid byproduct, and the mixture was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 500 mL). The combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. ^{1}H NMR analysis of the crude product revealed a 12.5:1 ratio of *E*/*Z* isomers. Flash chromatography of the crude product gave the title compound as a pale yellow oil (13.8 g, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.6 Hz, 2H), 6.99 (dt, J_1 = 15.7 Hz, J_2 = 6.9 Hz, 1H), 6.91 (d, J = 8.7 Hz, 2H), 5.90 (dt, J_1 = 15.6 Hz, J_2 = 1.6 Hz, 1H), 4.46 (s, 2H), 3.81 (s, 3H), 3.74 (s, 3H), 3.56 (t, J = 6.4 Hz, 2H), 2.51 (qd, J_1 = 6.6 Hz, J_2 = 1.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 159.3, 146.0, 130.2, 129.3, 122.5, 113.8, 72.7, 68.0, 55.3, 51.4, 32.7.



(2*R*,3*S*)-Methyl 2,3-dihydroxy-5-(4-methoxybenzyloxy)pentanoate ((2*R*,3*S*)-27). AD-mix-α[58] (22.37 g) and methanesulfonamide (3.04 g, 31.96 mmol) were added to 1:1 *t*BuOH/H_2O (145 mL) at room temperature. The orange suspension was stirred at room temperature for 30 min, then cooled to 0 °C by Cryocooler. A solution of the ester **25** (4.00 g, 15.98 mmol) in 1:1 *t*BuOH/H_2O (15 mL) was added to the cooled suspension dropwise by syringe. The reaction mixture was stirred at 0 °C for 24 h. The reaction was quenched by addition of saturated aqueous sodium thiosulfate (75 mL) and the mixture was stirred for 1 h at room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 150 mL). The combined organic extracts were washed with brine (80 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. Flash chromatography of the crude product (1:2 hexanes/EtOAc) gave the title compound as a highly viscous solid that solidified upon freezing (3.71 g, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 9.0 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.47 (s, 2H), 4.18 (dtd, J_1 = 11.2 Hz, J_2 = 3.7 Hz, J_3 = 2.0 Hz, 1H), 4.10 (dd, J_1 = 6.9 Hz, J_2 = 2.0 Hz,1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.70 (m, 2H), 3.12 (d, J = 7.0 Hz, 1H), 2.99 (d, J = 5.5 Hz, 1H), 2.04 (m, 1H), 1.83 (ddt, J_1 = 16.3 Hz, J_2 = 8.7 Hz, J_3 = 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 159.4, 129.9, 129.4, 113.9, 73.7, 73.1, 71.7, 67.9, 55.3, 52.7, 33.2; FTIR (thin film) ν_{max} 3315, 2946, 1463, 1227, 1180, 1118 cm^{-1}; HRMS calcd (ESI) for $C_{14}H_{20}O_6Na$ [M + Na]$^+$: 307.1158, found 307.1141; $[\alpha]_D^{25} - 2.78$ (*c* 0.87, $CHCl_3$).

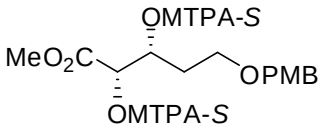


(2*S*,3*R*)-Methyl-2,3-di-hydroxy-5-(4-methoxy-benzy-loxy)-pentanoate ((2*S*,3*R*)-27). The procedure[58] used for the preparation of (2*R*,3*S*)-**27** was repeated using AD-mix-β (2.29 g), methanesulfonamide (312 mg, 3.28 mmol), and the ester **25** (410 mg, 1.64 mmol) in 1:1 *t*BuOH/H_2O (16 mL). Flash chromatography of the crude product (1:2 hexanes/EtOAc) gave the title compound as a white amorphous solid that solidified upon freezing (299 mg, 62%). The ^1H and ^{13}C NMR spectra matched those of (2*R*,3*S*)-**27** (see above); HRMS calcd (ESI) for $C_{14}H_{20}O_6Na$ $[M + Na]^+$: 307.1158, found 307.1152; $[\alpha]_D^{25} + 4.3$ (*c* 1.04, $CHCl_3$).

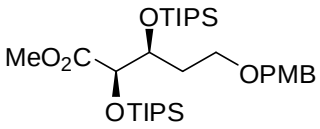


***RSSS*-28**. **General procedure for Mosher ester derivatization:**[63] Commercially available (*R*)-MTPA-Cl (120 µl, 0.633 mmol) was added in portion to a solution of the diol (2*S*,3*R*)-**27** (60.0 mg, 0.211 mmol) in pyridine (2.00 mL) at 0 °C. The reaction mixture was stirred at this temperature for 15 min, then at room temperature for 3 h. The reaction was quenched by addition of water (3 mL) and transferred to a separatory funnel by pipette. The contents were then diluted with Et_2O (10 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with 20% aqueous $CuSO_4$ (3 x 5 mL), water (5 mL), and brine (5 mL). The organic solution was dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The crude product was analyzed without

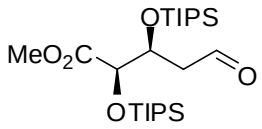
purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.9 Hz, 2H), 7.48 (d, *J* = 7.1 Hz, 2H), 7.37 (m, 6H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 5.80 (td, J_1 = 8.2 Hz, J_2 = 1.7 Hz, 1H), 5.40 (d, *J* = 1.8 Hz, 1H), 4.35 (d, *J* = 11.5 Hz, 1H), 4.28 (d, *J* = 11.5 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.48 (s, 3H), 3.38 (m, 1H), 3.34 (s, 3H), 3.25 (m, 1H), 1.96 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.2, −72.8. The minor peaks in the ^{19}F NMR spectrum of (*RSSS*)-**28** match the major peaks of (*SRSS*)-**28** (see below).



***SRSS*-28**. The general procedure for Mosher ester derivatization[63] was followed using the diol (2*R*,3*S*)-**27** (47.0 mg, 0.165 mmol) and (*R*)-MTPA-Cl (100 μl, .496 mmol) in pyridine (2 mL). The crude product was analyzed without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 6.9 Hz, 2H), 7.47 (d, *J* = 6.4 Hz, 2H), 7.35 (m, 6H), 7.22 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.72 (td, J_1 = 7.9 Hz, J_2 = 1.6 Hz, 1H), 5.44 (d, *J* = 1.8 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 4.31 (d, *J* = 11.6 Hz, 1H), 3.79 (s, 3H), 3.63 (s, 3H), 3.54 (s, 3H), 3.39 (s, 3H), 3.34 (m, 2H), 1.93 (m, 1H), 1.78 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −72.3, −72.5. The minor peaks in the ^{19}F NMR spectrum of *SRSS*-**28** match the major peaks of *RSSS*-**28** (see above).

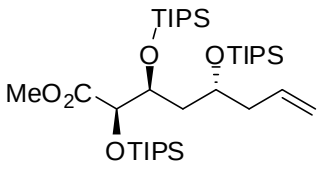


(2*R*,3*S*)-Methyl-5-(4-methoxy-benzyloxy)-2,3-bis-(tri-isopropyl-silyl-oxy)-pentanoate (29). Triisopropyl trifluoromethanesulfonate (7.30 mL, 27.08 mmol) was added dropwise to a solution of the diol (2*R*,3*S*)-**27** (3.50 g, 12.31 mmol) and 2,6-lutidine (3.14 mL, 27.08 mmol) in CH_2Cl_2 (80 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, then at room temperature for 4 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (30 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 75 mL). The combined organic extracts were washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. Flash chromatography of the crude product (10:1 hexanes/EtOAc) gave the title compound as a colorless oil (5.96 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, 8.6 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.42 (m, 3H), 4.23 (td, J_1 = 6.2 Hz, J = 4.3 Hz, 1H), 3.81 (s 3H), 3.69 (s, 3H), 3.55 (m, 2H), 2.28 (sextet, J = 7.1 Hz, 1H), 1.74 (J = 6.5 Hz, 1H) 1.05 (broad s, 42H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 159.0, 130.8, 129.1, 113.6, 75.1, 72.3, 72.0, 66.7, 55.2, 51.2, 33.1, 18.0, 17.9, 17.9, 12.8, 12.4; FTIR (thin film) ν_{max} 2944, 2866, 1754, 1513, 1464, 1248 cm^{-1}; HRMS calcd (ESI) for $C_{32}H_{60}O_6Si_2Na$ $[M + Na]^+$: 619.3826, found 617.3799; $[\alpha]_D^{25} -15.6$ (*c* 1.09, $CHCl_3$).

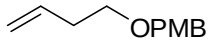


(2*R*,3*S*)-Methyl 5-oxo-2,3-bis(triisopropylsilyloxy)pentanoate (30). The PMB ether **29** (2.77 g, 4.65 mmol) was dissolved in 18:1 CH_2Cl_2/H_2O (38 mL). The mixture was cooled to 0 °C and DDQ[64] (1.16 g, 5.12 mmol) was added in one portion. The green suspension was stirred at 0 °C for 5 min, then at room temperature for 2 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (15 mL). The resulting emulsion was broken in the separatory funnel by addition of chloroform (20 mL). The layers were separated and the aqueous layer was extracted with chloroform (3 x 50 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude product was taken to the next step as an inseparable mixture of the free alcohol and anisaldehyde.

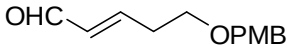
The general procedure for Swern oxidation[59] was followed with DMSO (0.86 mL, 12.12 mmol), oxalyl chloride (0.70 mL, 8.08 mmol), and NEt_3 (2.82 mL, 20.20 mmol). Flash chromatography gave the title compound as a pale yellow oil (1.62 g, 79% over two steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.85 (t, J = 2.0 Hz, 1H), 4.62 (q, J = 5.5 Hz, 1H), 4.52 (d, J = 5.3 Hz, 1H), 3.72 (s, 3H), 3.19 (ddd, J_1 = 16.6 Hz, J_2 = 6.1 Hz, J_3 = 1.6 Hz, 1H), 2.61 (ddd, J_1 = 16.4 Hz, J_2 = 5.5 Hz, J_3 = 2.1 Hz, 1H), 1.04 (broad s, 42H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 171.6, 76.4, 73.9, 69.6, 51.2, 46.6, 17.7, 17.6, 17.5, 12.1, 11.9; FTIR (thin film) ν_{max} 2945, 2867, 1751, 1130 cm^{-1}; HRMS calcd (ESI) for $C_{24}H_{50}O_5Si_2Na$ $[M + Na]^+$: 497.3095, found 497.3119; $[\alpha]_D^{25} -15.4$ (c 1.02, $CHCl_3$).



(2*R*,3*S*,5*R*)-Methyl-5-hydroxy-2,3-bis(triisopropylsilyloxy)oct-7-enoate (31c). Commercially available (+)-Ipc_2B(allyl) (1.0 M solution in pentane, 3.82 mL, 3.82 mmol) was added to a solution of aldehyde **30** (1.30 g, 2.73 mmol) in Et_2O (20 mL) at −78 °C. The reaction mixture was stirred at this temperature for 3 h, and warmed to room temperature. The reaction was quenched by the addition of 1:2:1 30% aq. H_2O_2/MeOH/pH 7 buffer (60 mL), and the resulting suspension was stirred for 16 h. The layers were separated and the aqueous layer extracted with ether (3 x 80 mL). The combined organic extracts were washed with water (50 mL), sat. aq. $NaHCO_3$ (50 mL), more water (50 mL), brine (50 mL), then dried over $MgSO_4$. Flash chromatography of the crude product (10:1 hexanes/EtOAc) gave a mixture of the major and minor alcohol epimers along with 3-pinanol byproduct. The mixture was dissolved in CH_2Cl_2 (30 mL) then silylated as reported for compound **29** using 2,6-lutidine (1.20 mL, 10.04 mmol) and TIPSOTf (2.71 mL, 10.04 mmol). Flash chromatography of the crude product (40:1 hexanes/EtOAc) afforded the title compound as a colorless oil (1.10 g, 60% over two steps, 4:1 mixture of diastereomers): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (m, 1H), 5.06 (dd, J_1 = 15.9 Hz, J_2 = 11.6 Hz, 2H), 4.47 (d, J = 3.9 Hz, 1H), 4.28 (m, 1H), 4.17 (ddd, J_1 = 7.7 Hz, J_2 = 5.6 Hz, J_3 = 1.9 Hz, 1H), 2.39 (m, 2H), 1.97 (ddd, J_1 = 13.9 Hz, J_2 = 7.7 Hz, J_3 = 6.1 Hz, 1H), 1.71 (ddd, J_1 = 14.2 Hz, J_2 = 7.9 Hz, J_3 = 5.7 Hz, 1H), 1.08 (broad s, 63 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 172.2, 135.0, 134.5, 117.2, 116.2, 72.5, 72.1, 69.2, 68.9, 42.0, 41.7, 18.1, 13.1; FTIR (thin film) ν_{max} 2944, 2893, 2866, 1752, 1463 cm^{-1}; $[\alpha]_D^{25}$ −11.6 (*c* 1.02, $CHCl_3$).

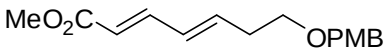


1-((But-3-enyloxy)methyl)-4-methoxybenzene (38).[104] CAS registry number: [142860-83-1]. The general procedure for 4-methoxy-benzyl protection for compound **26** was followed using buten-1-ol (5.00 mL, 58.45 mmol), NaH (95%, 1.92 g, 75.99 mmol), and 4-methoxybenzyl chloride (9.52 mL, 70.14 mmol) in dimethylformamide (200 mL). Flash chromatography of the crude product (1:1 hexanes/EtOAc) gave the title compound as a yellow oil (9.52 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 5.84 (ddt, J_1 = 17.0 Hz, J_2 = 10.2 Hz, J_3 = 6.7 Hz, 1H), 5.10 (ddd, J_1 = 17.5 Hz, J_2 = 10.2 Hz, J_3= 1.7 Hz, 2H), 4.46 (s, 2H), 3.82 (s, 3H), 3.53 (t, J = 6.8 Hz, 2H), 2.38 (ddd, J_1 = 14.8 Hz, J_2 = 6.7 Hz, J_3 = 1.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 135.5, 130.5, 129.1, 115.7, 113.2, 72.4, 69.2, 55.1, 34.2.

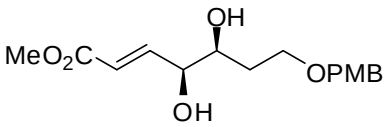


(*E*)-5-(4-Methoxybenzyloxy)pent-2-enal (40).[85] CAS registry number: [671232-57-8]. Alkene **38** (10.25 g, 53.1 mmol) was dissolved in anhydrous, degassed CH_2Cl_2 (100 mL). Crotonaldehyde (22.0 mL, 266 mmol) was then added by syringe at room temperature. The Grubbs-Hoveyda 2nd generation catalyst (333 mg, 0.53 mmol) was then added at room temperature in one portion. The flask was then fitted with a reflux condenser and the reaction mixture was stirred at reflux for 16 h (~50 °C, bath temperature). The reaction mixture was then cooled to room temperature and concentrated by rotary evaporation. Flash chromatography of the crude product (3:1 hexanes/EtOAc) gave the title compound as a pale brown oil (11.21 g,

95%, *E*/*Z*>20:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 6.8 Hz, 2H), 6.88 (dt, J_1 = 15.7 Hz, J_2 = 6.7 Hz, 1H), 6.18 (ddt, J_1 = 15.8 Hz, J_2 = 7.9 Hz, J_3 = 1.4 Hz, 1H), 4.47 (s, 2H), 3.82 (s, 3H), 3.62 (t, J = 6.2 Hz, 2H), 2.63 (qd, J_1 = 6.5 Hz, J_2 = 1.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 159.2, 133.9, 129.8, 129.1, 113.7, 72.6, 67.4, 55.1, 32.9.

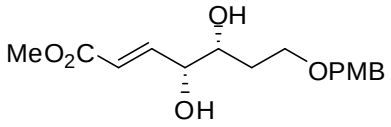


(2*E*,4*E*)-Methyl-7-(4-methoxybenzyloxy)hepta-2,4-dienoate (37). The general procedures for the Masamune-Roush conditions[54] were employed with aldehyde **40** (11.21 g, 50.66 mmol), trimethylphosphonoacetate (8.79 mL, 60.79 mmol), LiCl (2.58 g, 60.79), and 1,8-diazabicyclo-[5.4.0]-undec-7-ene (8.33 mL, 55.73 mmol). Filtration of the crude product over a silica plug afforded the title compound as a pale yellow oil (12.49 g, 89%, *E*/*Z*>20:1): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (dd, J_1= 15.4 Hz, J_2 = 10.2 Hz, 1H), 7.26 (d, J = 8.2 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.19 (m, 2H), 8.81 (d, J = 15.4 Hz, 1H), 4.46 (s, 2H), 3.82 (s, 3H), 3.75 (s, 3H), 3.53 (t, J = 6.5 Hz, 2H), 2.48 (q, J = 6.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 159.3, 150.0, 140.7, 129.9, 129.3, 119.4, 113.8, 72.7, 67.8, 55.3, 51.5, 33.4.

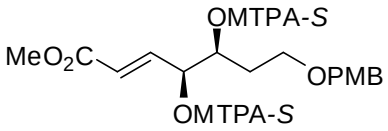


(4*S*,5*S*,2*E*)-Methyl-4,5-dihydroxy-7-(4-methoxybenzyloxy)hept-2-enoate ((4*S*,5*S*)-41): The same procedure[58] used for the preparation of (2*R*,3*S*)-**27** was followed with $K_2Os(OH)_2$ (84.5 mg, 0.230 mmol), $(DHQ)_2PHAL$ (376 mg, 0.459 mmol), $K_3Fe(CN)_6$ (22.7 g, 68.82 mmol),

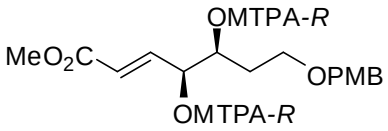
K_2CO_3 (9.51 g, 68.82 mmol), methanesulfonamide (4.36 g, 45.88 mmol), and dienoate **37** (6.34 g, 22.94 mmol). Flash chromatography of the crude product (1:2 hexanes/EtOAc) afforded the title compound as a highly viscous, pale yellow syrup (4.89 g, 67%, 92% *ee*): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.6 Hz, 2H), 6.96 (dd, J_1 = 15.3 Hz, J_2 = 4.7 Hz, 1H), 6.89 (d, J = 8.6 Hz, 2H), 6.15 (dd, J_1 = 15.7 Hz, J_2 = 1.8 Hz, 1H), 4.46 (s, 2H), 4.17 (qd, J_1= 4.9 Hz, J_2 = 1.8 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.68 (m, 2H), 3.39 (d, J = 3.4 Hz, 1H), 2.97 (d, J = 5.3 Hz, 1H), 1.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 159.1, 147.4, 129.6, 129.2, 121.4, 113.7, 73.6, 72.7, 72.5, 67.4, 55.0, 51.5, 32.5; FTIR (thin film) ν_{max} 3455, 2915, 1723, 1586, 1249 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O_6Na$ [M + Na]$^+$: 333.1314, found 333.1287; $[\alpha]_D^{25} - 4.2$ (*c* 1.08, $CHCl_3$).



(4*R*,5*R*,2*E*)-Methyl-4,5-dihydroxy-7-(4-methoxy-benzyloxy)-heptenoate ((4*R*,5*R*-41)). The same procedure used for the preparation of (2*R*,3*S*)-**27** was followed with commercially available AD-mix-β[58] (93.0 g), $(DHQD)_2PHAL$ (55 mg, 0.67 mmol), methanesulfonamide (4.23 g, 44.5 mmol), and dienoate **37** (6.15 g, 22.26 mmol) in 1:1 *t*BuOH/H_2O (225 mL). Flash chromatography of the crude product (1:2 hexanes/EtOAc) afforded the title compound as a highly viscous, pale yellow syrup (4.33 g, 61%). The ^{1}H and ^{13}C NMR spectra matched those of (4*S*,5*S*)-**41** (above); HRMS calcd (EI) for $C_{16}H_{22}O_6$ [M + H]$^+$: 310.1416, found 310.1421; $[\alpha]_D^{25} + 5.50$ (*c* 1.01, $CHCl_3$).

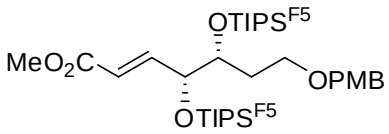


***SSSS*-42**. The general procedure for Mosher ester derivatization[63] was followed using the diol (2*S*,3*S*)-**41** (12.8 mg, 0.040 mmol) and (*R*)-MTPA (31 μl, 0.162 mmol) in pyridine (1 mL). The crude product was then analyzed without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (m, 10H), 7.24 (d, J = 6.7 Hz, 2H), 6.89 (d, J_1 = 6.7 Hz, 2H), 6.74 (dd, J_2 = 15.8 Hz, J = 5.0 Hz, 1H), 5.81 (ddd, J_1 = 4.8 Hz, J_2 = 3.0 Hz, J_3 = 1.6 Hz, 1H), 5.77 (dd, J_1 = 15.9 Hz, J_2 = 1.6 Hz, 1H), 5.55 (ddd, J_1 = 8.0 Hz, J_2 = 5.2 Hz, J_3 = 3.1 Hz, 1H), 4.34 (d, J = 3.4 Hz, 2H), 3.81 (s, 3H), 3.72 (s, 3H), 3.49 (s, 3H), 3.44 (s, 3H), 3.38 (m, 1H), 3.25 (m, 1H), 1.84 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –71.7 (s, 3F), –71.9 (s, 3F). The minor peaks in the ^{19}F NMR spectrum of *SSSS*-**42** matched the major peaks of *SSRR*-**42** (below).



***SSRR*-42**. The general procedure for Mosher ester derivatization[63] was followed using the diol (2*S*,3*S*)-**41** (21.6 mg, 0.068 mmol) and (*S*)-MTPA (51 μl, 0.273 mmol) in pyridine (2 mL). The crude product was then analyzed without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 10H), 7.23 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.67 (dd, J_1 = 15.8 Hz, J_2 = 5.6 Hz, 1H), 5.80 (dd, J_1 = 15.8 Hz, J_2 = 1.5 Hz, 1H), 5.74 (ddd, J_1 = 7.1 Hz, J_2 = 2.6 Hz, J_3 = 1.6 Hz, 1H), 5.49 (td, J_1 = 6.6 Hz, J_2 = 2.7 Hz, 1H), 4.36 (s, 2H), 3.81 (s, 3H), 3.72 (s 3H), 3.47 (s, 3H), 3.40 (s, 3H), 3.35 (m, 2H), 1.82 (m, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ –71.8 (s, 3F), –72.0 (s, 3F).

The minor peaks in the ^{19}F NMR spectrum of *SSRR*-**49** matched the major peaks of *SSSS*-**49** (above).

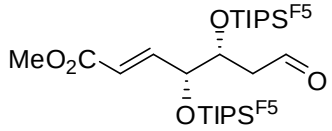


(4*R*,5*R*,2*E*)-Methyl-4,5-bis(diisopropyl(3,3,4,4,4-pentafluorobutyl)silyloxy)-7-(4-methoxy-benzyloxy)-hept-2-enoate (*RR*-42b).

General Procedure for Fluorous tagging[105]:

Freshly distilled CF_3SO_3H (2.34 mL, 26.36 mmol) was added dropwise by syringe to neat, stirring (3,3,4,4,4-pentafluorobutyl)diisopropylsilane (7.41 g, 28.24 mmol) at 0 °C. The turbid, orange reaction mixture was allowed to stir at 0 °C for 15 min, and then at room temperature for 45 min. The reaction mixture was then diluted with CH_2Cl_2 (25 mL) and the resulting solution was transferred by cannula into a separate flask (cooled to 0 °C) containing a solution of the (4*R*,5*R*)-**41** (3.97 g, 12.55 mmol) and 2,6-lutidine (4.37 mL, 37.65 mmol) in CH_2Cl_2 (100 mL). The reaction mixture was stirred at 0 °C for 15 min, then warmed to room temperature. After 1 h, the reaction was quenched at 0 °C with saturated aqueous NH_4Cl (50 mL). The mixture was stirred at 0 °C for 15 min, after which the contents of the flask were transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 75 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. Flash chromatography of the crude product (10:1 hexanes/EtOAc) afforded the title compound as a pale yellow oil (8.37 g, 86%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.42 Hz, 2H), 7.07

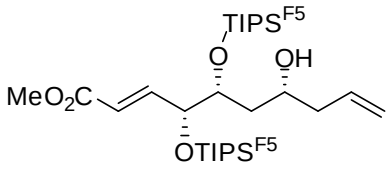
(dd, J_1 = 15.8 Hz, J_2 = 4.0 Hz, 1H), 6.86 (d, J = 8.3 Hz, 2H), 6.05 (dd, J_1 = 15.7 Hz, J_2 = 1.1 Hz, 1H), 4.44 (m, 1H), 4.38 (d, J = 2.4 Hz, 2H), 4.03 (quintet, J = 3.9 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.46 (m, 2H), 2.02 (m, 5H), 1.45 (m, 1H), 1.03 (broad s, 28H), 0.86 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 159.2, 146.8, 130.5, 129.2, 121.9, 113.7, 74.7, 72.6, 72.5, 65.9, 55.1, 51.5, 32.3, 27.6, 25.3, 17.5, 17.4, 17.4, 18.5, 17.1, 12.9, 12.8, 12.7, 12.6, 1.1, 0.8; FTIR (thin film) ν_{max} 3389, 2949, 1729, 1199 cm^{-1}; HRMS calcd (EI) for $C_{36}H_{56}O_6F_{10}Si_2Na$ $[M + Na]^+$: 853.3353, found 853.3400; $[\alpha]_D^{25} + 27.1$(*c* 1.08, $CHCl_3$).



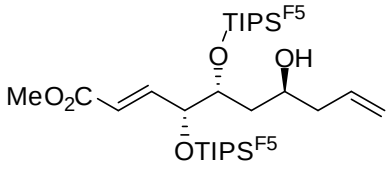
(4*R*,5*R*,2*E*)-Methyl-4,5-bis(diisopropyl(3,3,4,4,4-pentafluorobutyl)silyloxy)-7-oxohept-2-enoate (*RR*-43)). The same deprotection conditions used in the preparation of aldehyde **30** were used with *RR*-**42b** (7.43 g, 9.59 mmol), DDQ[64] (2.83 g, 12.5 mmol), and 18:1 CH_2Cl_2/H_2O (100 mL). The crude product was taken to the next step without further purification as a mixture of the free alcohol and anisaldehyde byproduct.

This mixture was then subjected to the general procedure for Swern oxidation[59] was followed with DMSO (2.04 mL, 28.77 mmol), oxalyl chloride (1.65 mL, 19.18 mmol), NEt_3 (6.68 mL, 47.95 mmol). Flash chromatography of the crude product gave the title compound as a pale yellow oil (5.56 g, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.06 (dd, J_1 = 15.6 Hz, J_2 = 3.5 Hz, 1H), 6.09 (d, J = 15.8 Hz, 1H), 4.49 (m, 2H), 3.78 (s, 3H), 2.72 (dd, J_1 = 16.8 Hz, J_2 = 2.9 Hz, 1H), 2.45 (dd, J_1 = 17.1 Hz, J_2 = 6.4 Hz, 1H), 2.02 (m, 4H), 1.04 (broad s, 28H), 0.86 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 166.1, 145.6, 122.8, 74.0, 70.3, 51.5, 46.4;

FTIR (thin film) ν_{max} 3376, 2359, 2339, 1728, 1199 cm^{-1}; HRMS calcd (ESI) for $C_{28}H_{46}O_5Si_2F_{10}Na$ $[M + Na]^+$: 731.2622, found 731.2675; $[\alpha]_D^{25} + 47.5$ (*c* 1.16, $CHCl_3$).

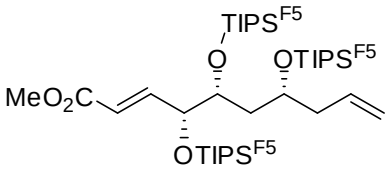


(4*R*,5*R*,7*R*,2*E*)-Methyl-4,5-bis(diisopropyl(3,3,4,4,4-pentafluorobutyl)silyloxy)-7-hydroxy-deca-2,9-dienoate (*RRR*-44). The same procedure employed in the preparation of **31c** was followed using commercially available (+)-Ipc_2B(allyl) (4.35 mL, 4.35 mmol, 1.0 M in pentane) and aldehyde *RR*-**43** (2.57 g, 3.63 mmol) in Et_2O (45 mL). ^1H NMR analysis of the crude product indicated an approximately 4:1 mixture of diastereomers. Flash chromatography of the crude product (10:1 hexanes/EtOAc) afforded the title compound as a single diastereomer (colorless oil), with minor impurities (1.91 g, 73%). The compound was taken to the next step for fuller characterization. Selected ^1H NMR data (300 MHz, $CDCl_3$) δ 7.08 (dd, J_1 = 15.8 Hz, J_2 = 4.3 Hz, 1H), 6.07 (dd, J_1 = 15.8 Hz, J_2 = 1.7 Hz, 1H), 5.76 (m, 1H), 5.12 (dd, J_1 = 18.3 Hz, J_2 = 10.7 Hz, 4.50 (td, J_1 = 4.4 Hz, J_2 = 1.8 Hz, 1H), 4.13 (m, 1H), 3.77 (s, 3H).



(4*R*,5*R*,7*S*,2*E*)-Methyl-4,5-bis(diisopropyl(3,3,4,4,4-pentafluorobutyl)silyloxy)-7-hydroxy-deca-2,9-dienoate (*RRS*-44). The *in situ* preparation of the Brown reagent was followed

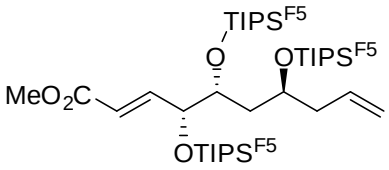
according to the literature precedent.[79] A solution of commercially available (–)-DIP-Cl (2.15 g, 6.71 mmol) in Et_2O (20 mL) was treated with allyl magnesium bromide (5.50 mL, 5.50 mmol, 1.0 M in Et_2O) at –78 °C. The reaction was warmed to 0 °C and stirred at this temperature for 1 h. The stirring was turned off to allow the magnesium mixed halide salt to settle to the bottom of the flask. The supernatant fluid was transferred dropwise by cannula to a solution of the aldehyde *RR*-**43** (2.93 g, 4.14 mmol) in Et_2O (40 mL) at –78 °C. The reaction was stirred at this temperature for 3 h and quenched by addition of 1:2:1 pH 7 buffer/methanol/30% aq. H_2O_2 (160 mL). The mixture was stirred for 20 h at room temperature, diluted with Et_2O (150 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 125 mL). The combined organic extracts were washed with water (75 mL), saturated aqueous $NaHCO_3$ (75 mL), then again with water (75 mL), and brine (75 mL). The organic solution was then dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. ^{1}H NMR analysis of the crude product indicated an approximately 4:1 mixture of diastereomers. Flash chromatography of the crude product (10:1 hexanes/EtOAc) afforded the title compound as a single diastereomer (colorless oil), with minor impurities (2.23 g, 77%). The compound was taken to the next step for fuller characterization. Selected ^{1}H NMR data (300 MHz, $CDCl_3$) δ 7.11 (dd, J_1 = 15.7 Hz, J_2 = 3.8 Hz, 1H), 6.09 (dd, J_1 =15.8 Hz, J_2 = 1.8 Hz, 1H), 5.77 (m, 1H), 5.14 (dd, J_1 = 18.4 Hz, J_2 = 10.0 Hz, 2H), 4.50 (m, 1H), 4.16 (m, 1H), 3.77 (s, 3H), 3.73 (m, 1H), 1.07 (broad s, 28H).



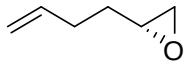
(4*R*,5*R*,7*R*,2*E*)-Methyl-4,5,7-tris(diisopropyl(3,3,4,4,4-pentafluorobutyl)silyloxy)deca-2,9-dienoate (*RRR*-45d). The same procedure employed in the preparation of **31c** was followed using commercially available (+)-Ipc_2B(allyl) (1.0 M solution in pentane, 6.83 mL, 6.83 mmol) and aldehyde *RR*-**43** (3.87 g, 5.46 mmol) in Et_2O (55 mL) at −78 °C. ^{1}H NMR of the crude product indicated a 4:1 mixture of diastereomers, along with 3-pinanol byproduct. Flash chromatography of the crude product (10:1 hexanes/EtOAc) gave a mixture of the major alcohol along with 3-pinanol, which was then taken to the next protection step without further purification.

The general procedure for fluorous tagging[105] was then followed using diisopropyl(3,3,4,4,4-pentafluorobutyl)silane (3.29 g, 12.56 mmol), CF_3SO_3H (1.02 mL, 11.47 mmol), and 2,6-lutidine (1.90 mL, 16.38 mmol) in CH_2Cl_2 (50 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) afforded the title compound as a colorless oil (2.69 g, 49% over two steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (dd, J_1 = 15.8 Hz, J_2 = 4.4 Hz, 1H), 6.04 (dd, J_1 = 15.8 Hz, J_2 = 1.6 Hz, 1H), 5.83 (ddt, J_1 = 17.1 Hz, J_2 = 10.6 Hz, J_3 = 7.3 Hz, 1H), 5.06 (dd, J_1 = 17.7 Hz, J_2 = 10.2 Hz, 2H), 4.44 (ddd, J_1 = 5.9 Hz, J_2 = 4.4 Hz, J_3 = 1.7 Hz, 1H), 3.99 (ddt, J_1 = 10.1 Hz, J_2 = 5.8 Hz, J_3 = 4.2 Hz, 1H), 3.90 (J = 9.4 Hz, J = 3.2 Hz, 1H), 3.75 (s, 3H), 2.34 (m, 1H), 2.07 (m, 6H), 1.84 (ddd, J_1 = 13.7 Hz, J_2 = 9.6 Hz, J_3 = 3.0 Hz, 1H), 1.47 (ddd, J_1 = 13.9 Hz, J_2 = 9.1 Hz, J_3 = 4.2 Hz, 1H), 1.05 (broad s, 42H), 0.85 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 146.3, 134.0, 120.8, 117.0, 74.3, 73.1, 69.1, 51.6, 40.9, 39.3, 25.3,

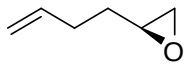
17.5, 13.0, 12.9, 12.9, 12.8, 12.6, 1.5, 0.9, 0.8; FTIR (thin film) ν_{max} 3343, 2949, 2870, 1731, 1197 cm^{-1}; $[\alpha]_D^{25} + 30.2$ (*c* 1.12, $CHCl_3$).



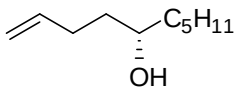
(4*R*,5*R*,7*S*)-Methyl-4,5,7-tris-(diiso-propyl-(3,3,4,4,4-penta-fluoro-butyl)-silyloxy)-deca-2,9-dienoate (*RRS*-46d). The general procedure for fluorous tagging[105] was employed using the alcohol *RRS*-**44** (2.38 g, 3.170 mmol), (3,3,4,4,4-pentafluorobutyl)diisopropylsilane (1.83 g, 6.980 mmol), trifluoromethanesulfonic acid (0.46 mL, 5.160 mmol), 2,6-lutidine (1.10 mL, 9.520 mmol) in CH_2Cl_2 (32.0 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) afforded the title compound as a colorless oil (2.68 g, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (dd, J_1 = 15.8 Hz, J_2 = 4.3 Hz, 1H), 6.07 (dd, J_1 = 15.8 Hz, J_2 = 1.7 Hz, 1H), 5.82 (m, 1H), 5.07 (ddd, J_1 = 17.1 Hz, J_2 = 10.2 Hz J_3 = 3.5 Hz, 2H), 4.46 (td, J_1 = 4.2 Hz, J_2 = 1.6 Hz, 1H), 4.06 (m, 1H), 4.00 (m, 1H), 3.78 (s, 3H), 2.32 (m, 2H), 2.05 (m, 6H), 1.73 (m, 1H), 1.59 (m, 1H), 1.04 (broad s, 42H), 0.89 (m, 4H), 0.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 146.5, 133.9, 122.3, 117.8, 76.1, 72.7, 68.9, 51.6, 41.5, 41.2, 25.7, 25.6, 25.4, 25.3, 25.2, 25.1, 25.0, 24.9, 17.7, 17.6, 17.5, 13.0, 12.9, 12.8, 12.6, 12.5, 1.1, 0.8; ^{19}F NMR (282 MHz, $CDCl_3$) –85.12 (s, 3F), –85.15 (s, 3F), –85.17 (s, 3F), –120.48 (t, $^3J_{HF}$ = 17.7 Hz, 2F), –120.58 (t, $^3J_{HF}$ = 17.5 Hz, 4F); FTIR (thin film) ν_{max} 2949, 2870, 1731, 1464, 1440, 1196, 885 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{41}H_{69}O_5F_{15}Si_3Na$ $[M + Na]^+$: 1,033.4111, found 1,033.4192; $[\alpha]_D^{25} + 10.8$ (*c* 1.09, $CHCl_3$).



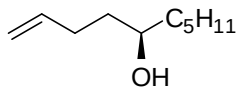
(*R*)-2-(But-3-enyl)oxirane ((*R*)-17).[52] CAS registry number: [137688-20-1]. A 100-mL round bottom flask was charged with (*R,R*)-(−)-*N,N′*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) catalyst (289 mg, 0.479 mmol), followed by racemic 1,2-epoxy-5-hexene (10.8 mL, 95.73 mmol) and acetic acid (110 μL). The resultant red suspension was then cooled to 0 °C and deionized water (0.95 mL) was slowly added over 5 min. The reaction mixture was stirred at 0 °C for 3 h, then at room temperature for 20 h. The mixture was concentrated by rotary evaporation and the crude product was purified by Kügelrohr distillation (60 °C, 40 torr) to afford the title compound as a colorless liquid (4.68 g, 49%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86 (ddt, J_1 = 16.9 Hz, J_2 = 10.2 Hz, J_3 = 6.7 Hz, 1H), 5.05 (ddd, J_1 = 17.1 Hz, J_2 = 10.2 Hz, J_3 = 1.6 Hz, 2H), 2.95 (m, 1H), 2.77 (dd, J_1 = 4.9 Hz, J_2 = 4.2 Hz, 1H), 2.50 (dd, J_1 = 5.0 Hz, J_2 = 2.7 Hz, 1H), 2.24 (m, 2H).



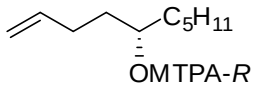
(*S*)-2-(But-3-enyl)oxirane ((*S*)-17).[52] CAS registry number: [137688-21-2]. The literature procedure for (*R*)-**17** was followed using 1,2-epoxy-5-hexene (11.00 mL, 97.50 mmol), acetic acid (120 μL, 2.10 mmol), THF (1.00 mL), and (*S,S*)-(+)-*N,N′*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (319 mg, 0.528 mmol). Kügelrohr distillation of the crude product (60 °C, 25 torr) gave the title compound as a colorless liquid (2.01 g, 21%). The ^{1}H NMR spectrum matched that of (*R*)-**17**.



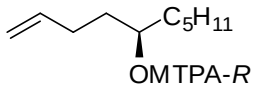
(5*S*)-Dec-1-en-5-ol ((*S*)-18).[53] A solution of butyllithium (1.6 M in hexanes, 34.2 mL, 54.7 mmol) was added dropwise to a stirred suspension of CuCN (269 g, 30.0 mmol) in THF (80 mL) at −78 °C. The reaction mixture was warmed to −20 °C and the epoxide (*R*)-**17** (3.57 g, 36.4 mmol) in THF (35 mL) was slowly added by cannula. The original flask containing the epoxide was then washed with THF (10 mL) and the rinse was also added to the reaction mixture by cannula at −20 °C. The resultant yellow suspension was stirred for 3 h at room temperature. The reaction was quenched by addition of 90:10 saturated aqueous NH_4Cl/ NH_4OH at 0°C and the mixture was stirred for 1 h at room temperature. The quenched mixture was then filtered through a Büchner funnel and the filtrate was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with water (75 mL) and brine (75 mL), dried with $MgSO_4$, filtered, and concentrated by rotary evaporation. Flash chromatography of the crude product (1:1 pentanes/ Et_2O) gave the title compound as a colorless liquid (5.12 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (ddt, J_1 = 17.0 Hz, J_2 = 10.2 Hz, J_3 = 6.7 Hz, 1H), 5.02 (dd, J_1 = 17.0 Hz, J_2 = 10.2 Hz, 2H), 3.63 (m, 1H), 2.18 (m, 2H), 1.57 (m, 2H), 1.42 (m, 4H), 1.32 (broad s, 4H), 0.90 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 114.7, 71.6, 37.5, 36.5, 31.9, 30.1, 25.3, 22.7, 14.1; FTIR (thin film) ν_{max} 3350, 2929, 2858 cm^{-1}; HRMS calcd (EI) for $C_{10}H_{20}O$ $[M]^+$: 156.1514, found 156.1510; $[\alpha]_D^{25}$ −16.0 (*c* 1.01, $CHCl_3$).



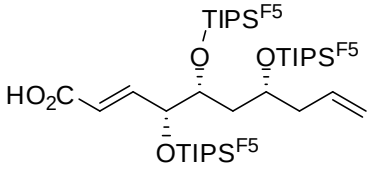
(5*R*)-Dec-1-en-5-ol ((*R*)-18). The literature precedent[53] for (*S*)-**18** (above) was followed using the epoxide (*S*)-**17** (1.73 g, 17.63 mmol), CuCN (2.32 g, 25.92 mmol), and a solution of butyllithium (1.6 M in pentane, 29.42 mL, 47.07 mmol) in THF (75 mL). Flash chromatography (1:1 pentane/ Et_2O) of the crude product gave the title compound as a colorless liquid (1.76 g, 64%). The ^1H and ^{13}C NMR match those of (*S*)-**18** (see above); HRMS calcd (EI) for $C_{10}H_{20}O$ $[M]^+$: 156.1514, found 156.1512; $[\alpha]_D^{25}$ +17.6 (*c* 1.17, $CHCl_3$).



***SR*-47**. The general procedure for Mosher ester derivatization[63] was followed using the alcohol (*S*)-**18** (12.8 mg, 0.078 mmol) and (*S*)-MTPA-Cl (29 μl, 0.155 mmol) in pyridine (3 mL). The crude product was then analyzed without purification: ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (m, 2H), 7.41 (m, 3H), 5.74 (ddt, J_1 = 16.4 Hz, J_2 = 9.7 Hz, J_3 = 6.6 Hz, 1H), 5.12 (m, 1H), 4.96 (m, 2H), 3.57 (s, 3H), 1.95 (m, 2H), 1.66 (m, 4H), 1.31 (m, 6H), 0.89 (t, J = 6.6 Hz, 3H); ^{19}F NMR (300 MHz, $CDCl_3$) δ −71.8 (s, 3F). No minor peaks were observed in the ^{19}F NMR spectrum of *SR*-**47**.

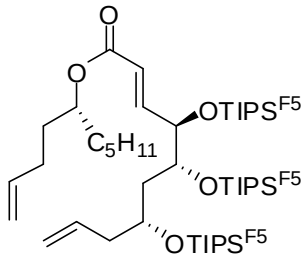


***RR*-47**. The general procedure for Mosher ester derivatization[63] was followed using the diol (*R*)-**18** (11.6 mg, 0.074 mmol) and (*S*)-MTPA-Cl (28 μl, 0.149 mmol) in pyridine (2 mL). The crude product was then analyzed without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (m, 2H), 7.41 (m, 3H), 5.81 (ddt, J_1 = 16.9 Hz, J_2 = 10.2 Hz, J_3 = 6.6 Hz, 1H), 5.12 (m, 1H), 5.02 (m, 2H), 3.57 (s, 3H), 2.09 (m, 2H), 1.75 (m, 2H), 1.59 (m, 2H), 1.22 (m, 6H), 0.85 (t, J = 6.8 Hz, 3H); ^{19}F NMR (300 MHz, $CDCl_3$) δ –71.6 (s, 3F). No minor peaks were observed in the ^{19}F NMR spectrum of *RR*-**47**.



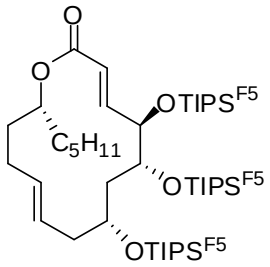
(4*R*,5*R*,7*R*)-4,5,7-Tris-(di-isopropyl-(3,3,4,4,4-penta-fluoro-butyl)-silyloxy)-deca-2,9-dienoic acid (48). Potassium trimethylsilanolate[82] (90%, 3.67 g, 25.8 mmol) was added in one portion to a solution of the methyl ester *RRR*-**45d** (2.61 g, 2.58 mmol) in Et_2O (26 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min then at room temperature for 16 h. The reaction was quenched by addition of 0.5 M citric acid (25 mL) at 0 °C. After 10 minutes, the quenched mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic extracts were washed with water (30 mL and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. Flash chromatography of the crude product (10:1 hexanes/EtOAc) gave the title compound as a

colorless, viscous oil (2.23 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, J_1 = 15.7 Hz, J_2 = 4.3 Hz, 1H), 6.05 (dd, J_1 = 15.8 Hz, J_2 = 1.4 Hz, 1H), 5.83 (ddt, J_1 = 17.0 Hz, J_2 = 10.0 Hz, J_3 = 6.8 Hz, 1H), 5.07 (dd, J_1 = 10.1 Hz, J_2 = 17.7 Hz, 2H), 4.48 (td, J_1 = 4.3 Hz, J_2 = 1.6 Hz, 1H), 4.01 (m, 1H), 3.93 (m, 1H), 2.35 (m, 1H), 2.08 (m, 7H), 1.86 (ddd, J_1 = 13.6 Hz, J_2 = 9.6 Hz, J_3 = 2.9 Hz, 1H), 1.48 (ddd, J_1 = 13.8 Hz, J_2 = 9.7 Hz, J_3 = 4.2 Hz, 1H), 1.06 (broad s, 42H), 1.02 (broad s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 149.0, 134.0, 121.9, 117.7, 74.3, 73.1, 69.1, 40.9, 39.4, 25.3, 17.5, 13.0, 12.9, 12.9, 12.8, 12.6, 1.5, 0.8; FTIR (thin film) ν_{max} 29.48, 2870, 1702, 1198, 759 cm^{-1}; HRMS calcd (ESI) for $C_{40}H_{67}O_5F_{15}Si_3Na$ $[M + Na]^+$: 1019.3955, found 1019.3895; $[\alpha]_D^{25} + 33.8$ (*c* 0.93, $CHCl_3$).



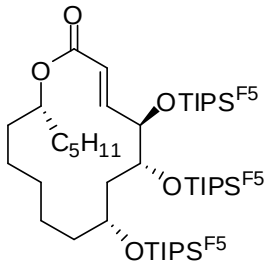
(4*R*,5*R*,7*R*,2*E*)-((*R*)-Dec-1-en-5-yl)-4,5,7-tris-(di-isopropyl-(3,3,4,4,4-pentafluorobutyl)-silyl-oxy)-deca-2,9-dienoate (49).[82] Triethylamine (0.59 mL, 4.26 mmol) was added to a solution of the acid **48** (2.13 g, 2.13 mmol) in toluene (21.0 mL) at room temperature. 2,4,6-trichlorobenzoyl chloride (0.35 mL, 2.24 mmol) was then added by syringe and the resulting white slurry was stirred at room temperature for 1 h. A solution of the alcohol (*R*)-**18** (401 mg, 2.56 mmol) and DMAP (678 mg, 5.55 mmol) in toluene (3 mL) was then slowly added to the reaction mixture by cannula transfer. The milky emulsion was stirred at room temperature for 3 h. Toluene (50 mL) and saturated aqueous $NaHCO_3$ (50 mL) were added and the emulsion

became a clear bilayer. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 75 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. Flash chromatography of the crude product (40:1 hexanes/EtOAc) gave the title compound as a pale yellow oil (2.31 g, 95%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (dd, J_1 = 15.7 Hz, J_2 = 4.7 Hz, 1H), 6.01 (dd, J_1 = 15.8 Hz, J_2 = 1.6 Hz, 1H), 5.83 (m, 2H), 5.00 (m, 5H), 4.43 (td, J_1 = 4.6 Hz, J_2 = 1.6 Hz, 1H), 3.99 (sextet, J = 4.5 Hz, 1H), 3.92 (dt, J_1 = 3.6 Hz, J_2 = 7.7 Hz, 1H), 2.34 (m, 1H), 2.16 (quintet, J = 6.8 Hz, 1H), 2.05 (m, 6H), 1.87 (ddd, J_1 = 12.7 Hz, J_2 = 9.3 Hz, J_3 = 3.3 Hz, 1H), 1.67 (m, 2H), 1.50 (ddd, J_1 = 13.9 Hz, J_2 = 9.4 Hz, J_3 = 4.4 Hz, 1H), 1.29 (broad s, 6H), 1.09 (broad s, 46H), 0.87 (broad s, 7H), 0.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 145.8, 137.9, 133.9, 123.1, 117.7, 114.8, 74.3, 74.0, 73.2, 69.2, 41.0, 39.3, 34.1, 33.3, 31.7, 29.6, 25.3, 24.9, 25.3, 22.5, 17.6, 17.5, 13.9, 12.9, 12.9, 12.7, 1.6, 0.8; HRMS calcd (ESI) for $C_{50}H_{85}O_5Si_3F_{15}Na$ $[M + Na]^+$: 1157.5363, found 1157.5317; $[\alpha]_D^{25} + 25.8$ (*c* 1.17, $CHCl_3$).



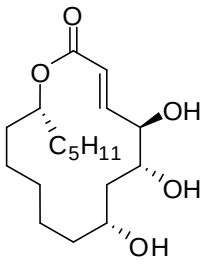
(2*E*,4*R*,5*R*,7*R*,10*E*,13*R*,)-4,5,7-Tris-(di-isopropyl-(3,3,4,4,4-penta-fluoro-butyl)-silyloxy)-14-pentyl-oxacyclotetradeca-3,10-dien-2-one (51).[85] Grubbs 2nd generation catalyst (41 mg, 48.3 μmol) was added in portion to a stirring solution of the ester **49** (550 mg, 0.484 mmol) in CH_2Cl_2 (240 mL, degassed). The reaction flask was fitted with a reflux condenser, heated to a steady

reflux (50 °C, external bath temperature), and stirred for 1 day. The reaction mixture was cooled to room temperature and an additional loading of the catalyst (42 mg, 49.8 μmol) was added in one portion. The reaction mixture was heated again to reflux (50 °C, external bath temperature) and stirred for an additional 24 h. The reaction mixture was again cooled to room temperature and concentrated by rotary evaporation. Flash chromatography of the crude product gave the title compound as a highly viscous, colorless oil (410 mg, 5:1 *E:Z*, 76%). The compound was taken to the next step for fuller characterization. Selected ^{1}H NMR spectral data (500 MHz, $CDCl_3$) δ 6.88 (dd, J_1 = 16.0 Hz, J_2 = 5.0 Hz, 1H), 5.91 (dd, J_1 = 16.0 Hz, J_2 = 3.5 Hz, 1H), 5.38 (dt, J_1 = 15.0 Hz, J_2 = 6.5 Hz, 1H), 5.29 (dt, J_1 = 15.0 Hz, J_2 = 7.0 Hz, 1H).



(5*R*,6*R*,8*R*,14*R*,*E*)-5,6,8-Tris-(di-isopropyl-(3,3,4,4,4-pentafluoro-butyl)-silyloxy)-14-pentyl-oxacyclotetradec-3-en-2-one (52).[55] A 25-mL flask was charged with the diene **51** (193 mg, 0.174 mmol) in ethanol (8.72 mL), treated with $Pd/SrCO_3$ (927 mg, 0.172 mmol). The flask was fitted with a three-junction vacuum adaptor, connected to a vacuum line and a balloon full of hydrogen gas. The flask was purged of air through the vacuum line and the flask was entrained with hydrogen gas. This "vac-fill" cycle was repeated three times to completely purge the flask with dihydrogen. The reaction mixture was stirred for exactly 80 min, at which point the vacuum adaptor/balloon assembly was removed and the catalyst was filtered. The supernatant

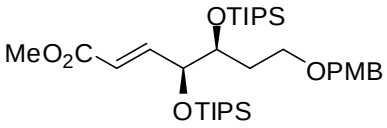
liquid was concentrated by rotary evaporation. Flash chromatography of the crude product (40:1 hexanes/EtOAc) gave the title compound as a viscous, colorless oil (140 mg, 75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (dd, J_1 = 15.9 Hz, J_2 = 6.4 Hz, 1H), 5.96 (dd, J_1 = 15.9 Hz, J_2 = 1.2 Hz, 1H), 5.00 (m, 1H), 4.45 (dt, J_1 = 5.9 Hz, J_2 = 1.1 Hz, 1H), 4.13 (q, J = 5.3 Hz, 1H), 4.04 (quintet, J = 6.2 Hz, 1H), 2.05 (m, 8H), 1.78 (t, J = 6.0 Hz, 2H), 1.70 (m, 1H), 1.64 (m, 1H), 1.55 (m, 4H), 1.42 (m, 2H), 1.30 (broad s, 6H), 1.23 (m, 2H), 1.05 (broad s, 42H), 0.89 (m, 7H), 0.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 146.4, 123.9, 76.7, 73.4, 70.5, 41.9, 37.3, 34.1, 31.7, 31.2, 28.2, 25.3, 25.1, 24.5, 24.2, 22.5, 17.9, 17.8, 17.8, 17.7, 17.6, 17.5, 17.5, 17.4, 14.1, 13.3, 13.1, 12.7, 12.6, 12.5, 12.4, 1.5, 0.8, 0.7; FTIR (thin film) ν_{max} (thin film, cm^{-1}) 2943, 2868, 1721, 1198 cm^{-1}; $[\alpha]_D^{25} + 48.5$ (*c* 0.79, $CHCl_3$).



(4*R*,5*R*,7*R*,13*R*)-4,5,7-Tri-hydroxy-13-pentyl-oxa-cyclotetradecenone ((4*R*,5*R*,7*R*,13*R*)-5).[87] Tetrabutylammonium fluoride (0.60 mL, 0.60 mmol, 6 equiv) was added dropwise to a solution of the macrolactone **52** (111 mg, 0.10 mmol) in THF (2.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min, and then warmed to room temperature. After stirring at room temperature for 4 h, the reaction was quenched by addition of sat. aq. NH_4Cl (3.0 mL) at 0 °C. After stirring at 0 °C for 15 minutes, the white suspension was diluted with water (1.0 mL) and ether (3.0 mL) and transferred to a separatory funnel. The aqueous layer was separated and

extracted with ether (3 x 10 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (3:1 hexanes/EtOAc, then 100% EtOAc) of the crude product gave the title compound as an amorphous white solid (24.8 mg, 79%): ^{1}H NMR (700 MHz, CD_3OD) δ 6.91 (dd, J_1 = 15.8 Hz, J_2 = 6.4 Hz, 1H), 6.11 (d, J = 15.8 Hz, 1H), 5.03 (m, 1H), 4.16 (t, J = 6.0 Hz, 1H), 3.82 (ddd, J_1 = 9.2 Hz, J_2 = 6.0 Hz, J_3 = 3.8 Hz, 1H), 3.79 (m, 1H), 1.78 (m, 1H), 1.63 (m, 2H), 1.56 (m, 1H), 1.45 (m, 4H) 1.39 (m, 2H), 1.33 (m, 7H), 1.18 (m, 2H), 1.11 (m, 1H) 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 168.2, 148.4, 124.3, 77.6, 77.5, 73.4, 67.6, 42.0, 37.0, 36.0, 34.5, 32.9, 30.1, 26.6, 26.5, 25.2, 23.8, 14.5; FTIR (thin film) ν_{max} 3384, 2927, 2858, 1716, 1650, 1267 cm^{-1}; HRMS calcd (EI) for $C_{18}H_{33}O_5$ $[M + H]^+$: 329.2338, found 329.2328; $[\alpha]_D^{25} + 24.8$ (*c* 1.25, MeOH).

6.2 EXPERIMENTAL DATA FOR THE FMS OF THE 4,5-*TRANS*-DIHYDROXY FAMILY OF SCH725674



(4*S*,5*S*,*E*)-Methyl-7-(4-methoxy-benzyloxy)-4,5-bis(triisopropyl-silyloxy)hept-2-enoate (*SS*-42a). TIPSOTf (10.2 mL, 37.71 mmol) was added dropwise to a solution of the diol (4*S*,5*S*)-**41** (4.77 g, 15.08 mmol) and 2,6-lutidine (5.25 mL, 45.25 mmol) in CH_2Cl_2 (150 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, then at room temperature for 4 h. The reaction

was quenched by addition of saturated aqueous NH_4Cl (60 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 175 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. Flash chromatography of the crude product (10:1 hexanes/EtOAc) gave the title compound as a colorless oil (9.68 g, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 8.8 Hz, 2H), 7.19 (dd, J_1 = 15.6 Hz, J_2 = 3.4 Hz, 1H), 6.86 (d, J = 8.7 Hz, 2H), 6.14 (dd, J_1 = 15.7 Hz, J_2 = 1.9 Hz, 1H), 4.59 (ddd, J_1 = 5.1 Hz, J_2 = 3.4 Hz, J_3 = 2.0 Hz, 1H), 4.391 (s, 2H), 4.12 (dt, J_1 = 8.1 Hz, J_2 = 4.4 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.53 (m, 2H), 2.00 (tdd, J_1 = 11.8 Hz, J_2 = 8.0 Hz, J_3 = 3.9 Hz, 1H), 1.50 (m, 1H), 1.06 (broad s, 42H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 159.0, 148.2, 130.7, 129.0, 121.1, 113.5, 74.7, 72.3, 66.6, 55.1, 51.3, 32.4, 18.1, 18.0, 12.6, 12.3; FTIR (thin film) ν_{max} 3398, 2944, 2867, 1464, 1110 cm^{-1}; HRMS calcd (ESI) for $C_{34}H_{62}O_6Si_2Na$ $[M + Na]^+$: 645.3983, found 645.4012; $[\alpha]_D^{25} - 37.1$ (c 0.98, $CHCl_3$).

(4*S*,5*S*,*E*)-Methyl-7-oxo-4,5-bis(triisopropylsilyloxy)hept-2-enoate, (4*R*,5*R*,*E*)-Methyl-7-oxo-4,5-bis(1,1,1,2,2-pentafluorobutyldiisopropylsilyloxy)hept-2-enoate (**M-53ab**). DDQ[64] (857 mg, 3.776 mmol) was added in portion to a solution of M-**42ab** (2.03 g, 2.904 mmol) in 19:1 CH_2Cl_2/H_2O (29 mL) at 0 °C. The green reaction mixture was then stirred at room temperature for 3 h, at which time a brown suspension had formed. The reaction was quenched by addition saturated aqueous $NaHCO_3$ (20 mL) which caused a thick dark emulsion to form. The contents of the reaction flask were transferred to a separatory funnel where the emulsion was broken by

the addition of chloroform (15 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were washed with water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude product was taken to the next oxidation step and used without further purification.

The general procedure for Swern oxidation[59] was then employed using the crude alcohol, DMSO (0.62 mL, 8.712 mmol), oxalyl chloride (0.50 mL, 5.808 mmol), NEt_3 (2.02 mL, 14.52 mmol) in CH_2Cl_2 (30 mL). Flash chromatography of the crude product (10:1 hexanes/EtOAc) afforded the title compound as a pale yellow oil (1.06 g, 61% based on average molecular weight).

(4*S*,5*S*,7*R*,*E*)-Methyl-4,5,7-tris(triisopropylsilyloxy)deca-2,9-dienoate, (4*R*,5*R*,7*R*,*E*)-Methyl 4,5-(bis-(1,1,1,2,2,-penta-fluoro-butyldi-isopropyl-silyoxy)-7-tri-isopropyl-silyloxy-deca-2,9-dienoate ((*R*)-M-54ab). A solution of (+)-Ipc_2B(allyl) (1.15 ml, 1.15 mmol, 1.0 M in pentane) was added dropwise by syringe to a solution of the aldehyde mixture M-**53ab** (532 mg, 0.880 mmol) in Et_2O (9 mL) at −78 °C. The reaction was stirred at this temperature for 3 h and was quenched by addition of 1:2:1 pH 7 buffer/methanol/30% aq. H_2O_2 (32 mL). The reaction was quenched for 20 h at room temperature, diluted with Et_2O (25 mL) and was then transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with water (25 mL), saturated aqueous $NaHCO_3$ (25 mL), then again with water (25 mL), and brine (25 mL). The organic solution was

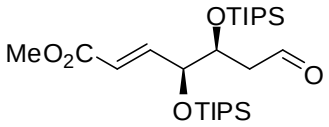
then dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. Flash chromatography of the crude product (10:1 hexanes/EtOAc) afforded an enriched mixture of quasiisomers as a colorless oil. This mixture was then taken to the next silylation step and used without further purification.

TIPSOTf (0.83 mL, 3.08 mmol) was added dropwise by syringe to a solution of the purified homoallyl alcohol mixture and 2,6-lutidine (0.33 mL, 2.86 mmol) in CH_2Cl_2 (7 mL) at 0 °C. The reaction mixture was then stirred for 2 h at room temperature, then quenched by addition of saturated aqueous NH_4Cl (4 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were then washed with water (5 mL), brine (5 ml), dried over $MgSO_4$, filtered, and then concentrated by rotary evaporation. Flash chromatography of the crude product (40:1 hexanes/EtOAc) afforded the title mixture as a colorless oil (240 mg, 41% based on average molecular weight).

(4*S*,5*S*,7*S*,*E*)-Methyl-4,5,7-tris(triisopropylsilyloxy)deca-2,9-dienoate, (4*R*,5*R*,7*S*,*E*)-Methyl 4,5-(tris(1,1,1,2,2,-pentafluorobutyldiisopropylsilyoxy)-deca-2,9-dienoate ((*S*)-M-54ab). A solution of (–)-Ipc_2B(allyl) (1.15 ml, 1.15 mmol, 1.0 M in pentane) was added dropwise by syringe to a solution of the aldehyde mixture M-**53ab** (532 mg, 0.880 mmol) in Et_2O (9 mL) at –78 °C. The reaction was stirred at this temperature for 3 h and was quenched by addition of 1:2:1 pH 7 buffer/methanol/30% aq. H_2O_2 (32 mL). The reaction was quenched for 20 h at room temperature, diluted with Et_2O (25 mL) and was then transferred to a separatory funnel. The

layers were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with water (25 mL), saturated aqueous $NaHCO_3$ (25 mL), then again with water (25 mL), and brine (25 mL). The organic solution was then dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. After flash chromatography of the crude product (10:1 hexanes/EtOAc) the mixture of quasiisomers was taken to the next silylation step and used without further purification.

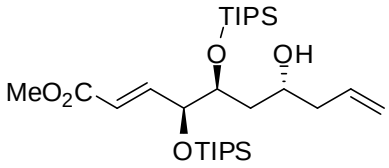
The general procedure for fluorous tagging was followed[105] with (3,3,4,4,4-pentafluorobutyl)diisopropylsilane (807 mg, 3.08 mmol), CF_3SO_3H (0.25 mL, 2.77 mmol), 2,6-lutidine (0.34 mL, 2.86 mmol) and the purified homoallyl alcohol mixture and in CH_2Cl_2 (5 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) afforded the title mixture as a colorless oil (120 mg, 30% based on average molecular weight).



(4*S*,5*S*,2*E*)-Methyl-7-oxo-4,5-bis(triisopropylsilyloxy)hept-2-enoate (*SS*-43). The ester *SS*-**42a** (5.83 g, 9.35 mmol) was dissolved in 19:1 CH_2Cl_2/H_2O (100 mL). The mixture was cooled to 0 °C and DDQ[64] (2.76 g, 12.16 mmol) was added in one portion. The green suspension was stirred at 0 °C for 5 min, then at room temperature for 2 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ (40 mL). The emulsion was broken in the separatory funnel by addition of chloroform (50 mL). The layers were then separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extracts were washed with

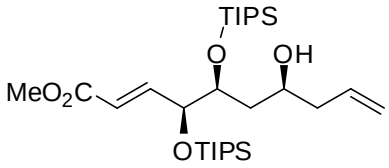
brine (60 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude product was taken to the next step as a mixture of the free alcohol and anisaldehyde.

The general procedure for Swern oxidation[59] was followed using DMSO (2.00 mL, 28.06 mmol), oxalyl chloride (1.61 mL, 18.71 mmol), NEt_3 (6.52 mL, 46.77 mmol). Flash chromatography of the crude product gave the title compound as a pale yellow oil (3.67 g, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, J = 1.2 Hz, 1H), 7.18 (dd, J_1 = 15.8 Hz, J_2 = 3.6 Hz, 1H), 6.16 (dd, J_1 = 15.6 Hz, J_2 = 1.8 Hz, 1H), 4.67 (m, 1H), 6.90 (dd, J_1 = 11.4 Hz, J_2 = 5.5 Hz), 3.77 (s, 3H), 2.68 (ddd, J_1 = 16.0 Hz, J_2 = 5.6 Hz, J_3 = 2.2 Hz, 1H), 2.45 (ddd, J_1 = 16.1 Hz, J_2 = 6.0 Hz, J_3 = 2.2 Hz, 1H), 1.07 (broad s, 42H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.2, 166.6, 147.1, 122.2, 74.1, 70.8, 51.6, 46.7, 18.0, 12.3; FTIR (thin film) ν_{max} 3889, 2946, 2866, 1730, 1464, 1113 cm^{-1}; HRMS calcd (ESI) for $C_{26}H_{52}O_5Si_2Na$ $[M + Na]^+$: 523.3251, found 523.3234; $[\alpha]_D^{25} -56.9$ (*c* 1.01, $CHCl_3$).

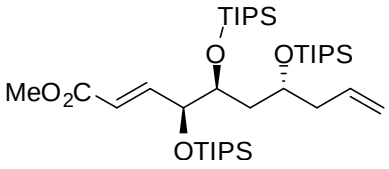


(4*S*,5*S*,7*R*,2*E*)-Methyl-7-hydroxy-4,5-bis(tri-isopropyl-silyl-oxy)deca-2,9-dienoate (*SSR*-44). The same procedure employed in the preparation of **31c** was followed using commercially available (+)-Ipc_2B(allyl) (5.00 mL, 5.00 mmol, 1.0 M in pentane) and the aldehyde *SS*-**43** (2.26 g, 4.51 mmol) in Et_2O (45 mL) at –78 °C. ^{1}H NMR analysis of the crude product indicated an approximately 4:1 mixture of diastereomers. Flash chromatography of the crude product (10:1 hexanes/EtOAc) afforded the title compound as a single diastereomer (colorless oil), contaminated with 3-pinanol (1.45 g, 59%). The compound was taken to the next step for fuller

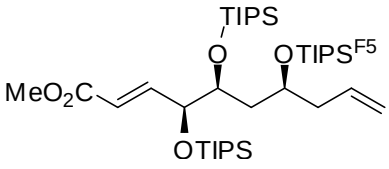
characterization. Selected ^{1}H NMR data (300 MHz, $CDCl_3$) δ 7.20 (dd, J_1 = 15.8 Hz, J_2 = 3.7 Hz, 1H), 6.14 (dd, J_1 = 15.8 Hz, J_2 = 1.9 Hz, 1H), 5.78 (m, 1H), 5.11 (dd, J_1 = 16.0 Hz, J_2 = 11.2 Hz, 2H), 4.64 (m, 1H), 4.21 (m, 1H).



(4*S*,5*S*,7*S*,2*E*)-Methyl-7-hydroxy-4,5-bis(triisopropylsilyloxy)deca-2,9-dienoate (*SSS*-44). The same procedure employed in the preparation of **31c** was followed using commercially available (–)-Ipc_2B(allyl) (4.72 mL, 4.72 mmol, 1.0 M in pentane) and aldehyde *SS*-**43** (2.15 g, 4.29 mmol) in Et_2O (45 mL). ^{1}H NMR analysis of the crude product indicated an approximately 4:1 mixture of diastereomers. Flash chromatography of the crude product (10:1 hexanes/EtOAc) afforded the title compound as a single diastereomer (colorless oil), with minor impurities (1.51 g, 67%). The compound was taken to the next step for fuller characterization. Selected ^{1}H NMR data (300 MHz, $CDCl_3$) δ7.18 (dd, J_1 = 15.9 Hz, J_2 = 3.6 Hz, 1H), 6.14 (dd, J_1 = 15.9 Hz, J_2 = 1.8 Hz, 1H), 5.80 (ddt, J_1 = 17.4 Hz, J_2 = 10.5 Hz, J_3 = 6.9 Hz, 1H), 5.10 (dd, J_1 = 16.8 Hz, J_2 = 10.8 Hz, 2H), 4.63 (td, J_1 = 4.8 Hz, J_2 = 2.1 Hz, 1H), 4.25 (m, 1H), 3.91 (m, 1H), 3.77 (s, 3H).

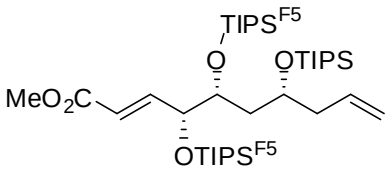


(4*S*,5*S*,7*R*,2*E*)-Methyl-4,5,7-tris-(tri-isopropyl-silyloxy)-deca-2,9-dienoate (*SSR*-46a): The same silylation procedure used in the preparation of *SS*-**42a** was followed using the homoallylic alcohol *SSR*-**44** (1.22 g, 2.250 mmol), TIPSOTf (64 μL, 0.235 mmol), and 2,6-lutidine (0.55 mL, 0.282 mmol) in CH_2Cl_2 (25 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) afforded the title compound as a colorless oil (1.56 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (dd, J_1 = 15.8 Hz, J_2 = 3.8 Hz, 1H), 6.15 (dd, J_1 = 15.8 Hz, J_2 = 1.8 Hz, 1H), 5.95 (m, 1H), 5.06 (d, J = 13.1 Hz, 2H), 2.30 (m, 1H), 4.17 (m, 1H), 4.08 (m, 1H), 1.082 (broad s, 42H), 1.05 (broad s, 21H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 148.5, 135.0, 121.4, 116.9, 72.6, 67.8, 51.5, 42.0, 40.9, 18.3, 18.2, 18.1, 12.7, 12.6, 12.4; FTIR (thin film) ν_{max} 2945, 2893, 2867, 1731, 1463, 1267, 1109, 1062, 883 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{38}H_{78}O_5Si_3Na$ $[M + Na]^+$: 721.5055, found 721.5074; $[\alpha]_D^{25} - 26.8$ (*c* 1.26, $CHCl_3$).



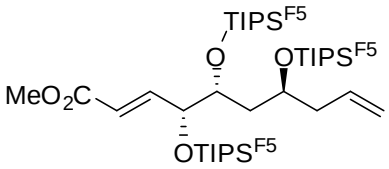
(4*S*,5*S*,7*S*,)-Methyl-7-(diisopropyl(3,3,4,4,4-pentafluorobutyl)silyloxy)-4,5-bis(triisopropyl-silyloxy)deca-2,9-dienoate (*SSS*-46b). The general procedure for fluorous tagging was employed[105] with alcohol *SSS*-**44** (1.40 g, 2.580 mmol), (3,3,4,4,4-pentafluorobutyl)diisopropylsilane (1.49 g, 5.680 mmol), trifluoromethanesulfonic acid (0.46

mL, 5.160 mmol), 2,6-lutidine (0.90 mL, 7.740 mmol) in CH_2Cl_2 (2.0 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) afforded the title compound as a colorless oil (1.38 g, 67%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (dd, J_1 = 15.8 Hz, J_2 = 3.4 Hz, 1H), 6.14 (dd, J_1 = 15.8 Hz, J_2 = 1.8 Hz, 1H), 5.87 (ddt, J_1 = 16.7 Hz, J_2 = 9.5 Hz, J_3 = 7.1 Hz, 1H), 5.06 (d, J = 14.1 Hz, 2H), 2.31 (m, 1H), 4.01 (m, 2H), 3.75 (s, 3H), 2.39 (m, 1H), 2.06 (m, 3H), 1.84 (ddd, J_1 = 13.4 Hz, J_2 = 10.6 Hz, J_3 = 2.0 Hz, 1H), 1.51 (m, 1H), 1.10 (broad s, 21H), 1.07 (broad s, 21H), 1.01 (broad s, 14H), 0.79 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 148.0, 134.8, 121.6, 117.3, 74.2, 73.0, 69.5, 51.4, 40.8, 39.8, 25.7, 25.4, 25.1, 18.2, 18.1, 17.7, 17.6, 17.5, 13.1, 12.9, 12.5, 0.83; ^{19}F NMR (282 MHz, $CDCl_3$) –85.03 (s, 3F), –120.45 (t, $^3J_{HF}$ = 18.0 Hz, 2F); FTIR (thin film) ν_{max} 1069, 2924, 2361, 2340, 1069 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{39}H_{75}O_5F_5Si_3Na$ $[M + Na]^+$: 825.4740, found 825.4769; $[\alpha]_D^{25} + 5.78$ (*c* 1.05, $CHCl_3$).



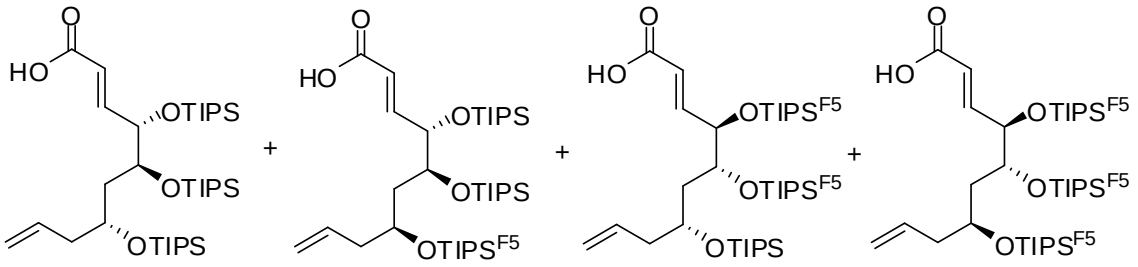
(4*R*,5*R*,7*S*)-Methyl-4,5-bis-(di-iso-propyl-(3,3,4,4,4-penta-fluoro-butyl)-silyloxy)-7-(tri-iso-propyl-silyloxy)deca-2,9-dienoate (*RRR*-46c). The same silylation procedure used in the preparation of *SS*-**42a** was followed using the homoallylic alcohol *RRR*)-**44** (1.85 g, 2.46 mmol), TIPSOTf (1.00 mL, 3.690 mmol), and 2,6-lutidine (0.60 mL, 5.166 mmol) in CH_2Cl_2 (25 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) afforded the title compound as a colorless oil (1.88 g, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (dd, J_1 = 15.8 Hz, J_2 = 4.7 Hz,

1H), 6.03 (dd, J_1 = 15.8 Hz, J_2 = 1.4 Hz, 1H), 5.90 (ddt, J_1 = 16.6 Hz, J_2 = 11.2 Hz, J_3 = 6.9 Hz, 1H), 5.05 (dd, J_1 = 16.8 Hz, J_2 = 10.2 Hz, 2H), 4.45 (m, 1H), 4.04 (sextet, J = 4.6 Hz, 1H), 3.94 (m, 1H), 3.76 (s, 3H), 2.40 (m, 1H), 2.38 (m, 1H), 2.19 (m, 1H), 2.05 (m, 4H), 1.86 (ddd, J_1 = 13.1 Hz, J_2 = 9.0 Hz, J_3 = 3.6 Hz, 1H), 1.51 (ddd, J_1 = 13.9 Hz, J_2 = 9.3 Hz, J_3 = 4.7 Hz, 1H), 1.04 (broad s, 49H), 0.87 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 146.9, 134.3, 122.1, 117.2, 74.3, 73.3, 68.6, 51.6, 41.0, 39.1, 25.3 (m), 18.1, 17.6, 17.5, 17.5, 13.0, 12.7, 12.6, 1.5, 0.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ –85.03 (s, 3F), –85.08 (s, 3F), –120.52 ($^3J_{HF}$ = 17.4 Hz, 4F); FTIR (thin film) ν_{max} 2947, 2869, 1732, 1464, 1439, 1333, 1270, 1198 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{40}H_{72}O_5F_{10}Si_3Na$ $[M + Na]^+$: 929.4426, found 929.4509; $[\alpha]_D^{25} + 24.1$(*c* 1.32, $CHCl_3$).



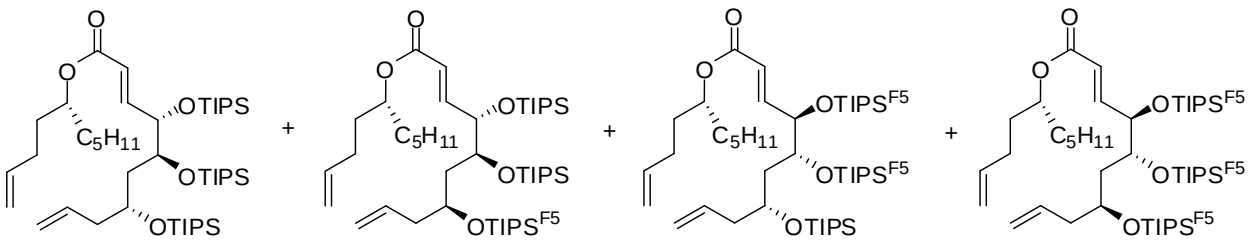
(4*R*,5*R*,7*S*,*E*)-Methyl-4,5,7-tris-(di-isopropyl-(3,3,4,4,4-penta-fluorobutyl)-silyloxy)deca-2,9-dienoate (*RRS*-46d). The general procedure for fluorous tagging[105] was employed using the alcohol *RRS*-**44** (2.38 g, 3.170 mmol), (3,3,4,4,4-pentafluorobutyl)diisopropylsilane (1.83 g, 6.980 mmol), CF_3SO_3H (0.46 mL, 5.160 mmol), and 2,6-lutidine (1.10 mL, 9.520 mmol) in CH_2Cl_2 (32.0 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) afforded the title compound as a colorless oil (2.68 g, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (dd, J_1 = 15.8 Hz, J_2 = 4.3 Hz, 1H), 6.07 (dd, J_1 = 15.8 Hz, J_2 = 1.7 Hz, 1H), 5.82 (m, 1H), 5.07 (ddd, J_1 = 17.1 Hz, J_2 = 10.2 Hz J_3 = 3.5 Hz, 2H), 4.46 (td, J_1 = 4.2 Hz, J_2 = 1.6 Hz, 1H), 4.06 (m, 1H), 4.00 (m, 1H), 3.78 (s, 3H), 2.32 (m, 2H), 2.05 (m, 6H), 1.73 (m, 1H), 1.59 (m, 1H), 1.04 (broad

s, 42H), 0.89 (m, 4H), 0.81 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 146.5, 133.9, 122.3, 117.8, 76.1, 72.7, 68.9, 51.6, 41.5, 41.2, 25.7, 25.6, 25.4, 25.3, 25.2, 25.1, 25.0, 24.9, 17.7, 17.6, 17.5, 13.0, 12.9, 12.8, 12.6, 12.5, 1.1, 0.8; ^{19}F NMR (282 MHz, $CDCl_3$) –85.12 (s, 3F), –85.15 (s, 3F), –85.17 (s, 3F), –120.48 (t, $^3J_{HF}$ = 17.7 Hz, 2F), –120.58 (t, $^3J_{HF}$ = 17.5 Hz, 4F); FTIR (thin film) ν_{max} 2949, 2870, 1731, 1464, 1440, 1196, 885 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{41}H_{69}O_5F_{15}Si_3Na$ $[M + Na]^+$: 1,033.4111, found 1,033.4192; $[\alpha]_D^{25} +10.8$, (*c* 1.09, $CHCl_3$).



(4*S*,5*S*,7*R*,*E*)-4,5,7-Tris(triisopropylsilyloxy)deca-2,9-dienoic acid, (4*S*,5*S*,7*S*,*E*)-4,5-Bis(tri-iso-propyl-silyloxy)-7-((1,1,1,2,2)-penta-fluoro-butyl-di-isopropyl-silyloxy)-deca-2,9-dienoic acid, (4*R*,5*R*,7*R*,*E*)-4,5-Bis((1,1,1,2,2)-penta-fluorobutyl(diisopropylsilyloxy))-7-(triiso-propyl-silyloxy)-deca-2,9-dienoic acid, (4*R*,5*R*,7*S*,*E*)-4,5,7-Tris((1,1,1,2,2)-pentafluorobutyl-(diisopropylsilyloxy))deca-2,9-dienoic acid (M-55abcd). The same procedure employed for compound **48** was repeated using *SSR*-**46a** (250 mg, 0.36 mmol), *SSS*-**46b** (287 mg, 0.36 mmol), *RRR*-**46c** (324 mg, 0.36 mmol), *RRS*-**46d** (362 mg, 0.36 mmol), and TMSOK (3.05 g, 21.41 mmol) in Et_2O (13.0 mL). Flash chromatography of the crude product (3:1 hexanes/EtOAc) gave the title compound as a colorless oil (1.01 g, 84% based on average molecular weight): LRMS (ESI, positive mode) (*SSR*-**55a**) *m/z* 709 $(M + Na)^+$; (*SSS*-**55b**) *m/z* 813 $(M + Na)^+$; (*RRR*-

55c) *m/z* 915 $(M + Na)^+$; **(***RRS*-**55d**) *m/z* 1019 $(M + Na)^+$; fluorous analytical HPLC (90:10 MeCN/H_2O for 10 min, then 100% MeCN for 60 min, 1.0 mL/min): t_R = 9.0 min (*SSR*-**55a**), 14.9 min (*SSS*-**55b**), 20.3 min (*RRR*-**55c**), 28.6 min **(***RRS*-**55d**).

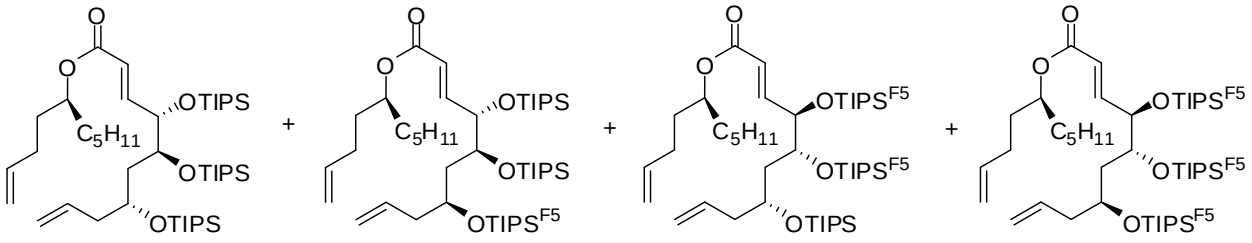


(4*S*,5*S*,7*R*)-((*R*)-Dec-1-en-5-yl)-4,5,7-tris(triisopropylsilyloxy)-deca-2,9-dienoate, (4*S*,5*S*,7*S*)-((*R*)-Dec-1-en-5-yl)-4,5-bis-(triisopropyl-silyloxy)-7-diisopropyl-(1,1,1,2,2-pentafluorobutyl-silyl-oxy)deca-2,9-dienoate, (4*R*,5*R*,7*R*)-((*R*)-Dec-1-en-5-yl)-4,5-bis-(di-iso-propyl-(1,1,1,2,2-pentafluorobutylsilyloxy))-7-triisopropylsilyloxy-deca-2,9-dienoate, (4*R*,5*R*,7*S*,*E*)-((*R*)-Dec-1-en-5-yl)-4,5,7-tris(diisopropyl(1,1,1,2,2-pentafluorobutylsilyloxy)) deca-2,9-dienoate ((*R*)-M-56abcd): The same method employed in the preparation of **49** was repeated using mixture M-**55abcd** (1.16 g, 1.38 mmol based on average molecular weight), alcohol (*R*)-**18** (237 mg, 1.52 mmol), NEt_3 (385 μL), DMAP (338 mg, 2.76 mmol), and 2,4,6-trichlorobenzoyl chloride (227 μL, 1.45 mmol) in toluene (28.0 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) gave the title compound as a colorless oil (1.29 g, 95% based on average molecular weight). HRMS (ESI, positive mode): calcd for $C_{47}H_{94}0_5Si_3Na$ $[M + Na]^+$ 845.6307, found 845.6340 for *SSRR*-**56a**; calcd for $C_{48}H_{91}O_5F_5Si_3Na$ $[M + Na]^+$ 949.5992, found 949.6046 for *SSSR*-**56b**; calcd for $C_{49}H_{88}O_5F_{10}Si_3Na$ $[M + Na]^+$ 1,053.5678, found 1,053.5725 for *RRRR*-**56c**; calcd for $C_{50}H_{85}O_5F_{15}Si_3Na$ $[M+ Na]^+$ 1,157.5363, found 1,157.5360 for *RRSR*-**56d**; fluorous analytical HPLC (90:10 MeCN/H_2O for 10 min, then 100% MeCN for 60 min, 1.0

mL/min): t_R = 22.9 min (*SSRR*-**56a**), 29.5 min (*SSSR*-**56b**), 33.9 min (*RRRR*-**56c**), 40.5 min (*RRSR*-**56d**).

Demixing of Mixture (*R*)-M-**56abcd**:

Semi-preparative separation of (*R*)-M-**56abcd** was carried out on a Waters 600E HPLC system. The mixture (*R*)-M-**56abcd** of four compounds was dissolved in THF (4.5 mL) and filtered through a Whatman syringe filter (0.45 μm pore size) prior to injection. The separation was carried out on a FluoroFlash PF-C8 HPLC column (20 mm x 250 mm). The separation was achieved by gradient elution with 90:10 acetonitrile/water up to 100% acetonitrile in 15 minutes, followed by isocratic elution with 100% acetonitrile for 180 minutes with a constant flow rate of 10.0 mL/min. A UV detector (230 nm) was used to manually identify the peaks. Aliquots of (*R*)-M-**56abcd** (50 mg/mL) were injected per chromatographic run. The yield of the demixing over six injections was 93% and the following four compounds were isolated: *SSRR*-**56a**: 58.8 mg, t_R = 62.2 min; *SSRR*-**56b**: 68.2 mg, t_R = 91.8 min; *SSRR*-**56c** 111.6 mg, t_R = 114.9 min; *SSRR*-**56d**: 60.0 mg, t_R = 163.4 min.

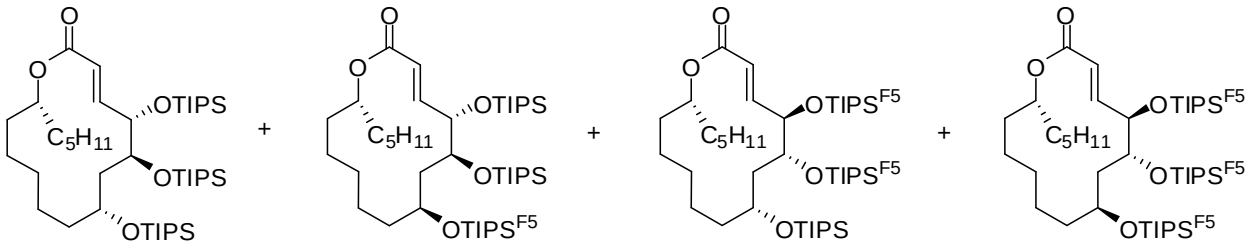


(4*S*,5*S*,7*R*)-((*S*)-Dec-1-en-5-yl)-4,5,7-tris(triisopropylsilyloxy)deca-2,9-dienoate, (4*S*,5*S*,7*S*)-((*S*)-Dec-1-en-5-yl)-4,5-bis(triisopropyl-silyl-oxy)-7-diisopropyl-(1,1,1,2,2-pentafluorobutyl-silyl-oxy)deca-2,9-dienoate, (4*R*,5*R*,7*R*)-((*S*)-Dec-1-en-5-yl)-4,5-bis-(diisopropyl-(1,1,1,2,2-pentafluorobutylsilyloxy))-7-triisopropylsilyloxy-deca-2,9-dienoate, (4*R*,5*R*,7*S*)-((*S*)-Dec-1-

en-5-yl)-4,5,7-tris-(diisopropyl(1,1,1,2,2-pentafluorobutylsilyloxy))-deca-2,9-dienoate ((*S*)-M-56abcd): The same method employed in the preparation of **49** was repeated using mixture M-**55abcd** (977 mg, 1.16 mmol based on average molecular weight), alcohol (*S*)-**18** (236 mg, 1.51 mmol), NEt_3 (1.78 mL), DMAP (369 mg, 3.02 mmol), and 2,4,6-trichlorobenzoyl chloride (360 μL, 2.32 mmol) in toluene (25.0 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) gave the title compound as a colorless oil (1.16 g, 100% based on average molecular weight): HRMS (ESI, positive mode): calcd for $C_{47}H_{94}0_5Si_3Na$ $[M + Na]^+$ 845.6307, found 845.6323 for *SSRS*-**56a**; calcd for $C_{48}H_{91}O_5F_5Si_3Na$ $[M + Na]^+$ 949.5992, found 949.6074 for *SSSS*-**56b**; calcd for $C_{49}H_{88}O_5F_{10}Si_3Na$ $[M + Na]^+$ 1,053.5678, found 1,053.5664 for *RRRS*-**56c**; calcd for $C_{50}H_{85}O_5F_{15}Si_3Na$ $[M + Na]^+$ 1,157.5363, found 1,157.5306 for *RRRS*-**56d**; fluorous analytical HPLC (90:10 MeCN/H_2O for 10 min, then 100% MeCN for 60 min, 1.0 mL/min): t_R = 5.1 min (*SSRS*-**56a**), 7.3 min (*SSSS*-**56b**), 9.9 min (*RRRS*-**56c**), 15.8 min (*RRRS*-**56d**).

Demixing of (*S*)-M-**56abcd**:

The semi-preparative separation of the four-compound mixture (*S*)-M-**56abcd** was carried out in the same manner as (*R*)-M-**56abcd**. Aliquots of (*S*)-M-**56abcd** (50 mg/mL) were injected per chromatographic run. The yield of the demixing over six injections was 80% and the following four compounds were isolated: *SSRS*-**56a**: 83.0 mg, t_R = 37.8 min; *SSSS*-**56b**: 92.4 mg, t_R = 54.9 min; *RRRS*-**56c**: 90.4 mg, t_R = 68.1 min; *RRSS*-**56d**: 105.7 mg, t_R = 91.5 min.

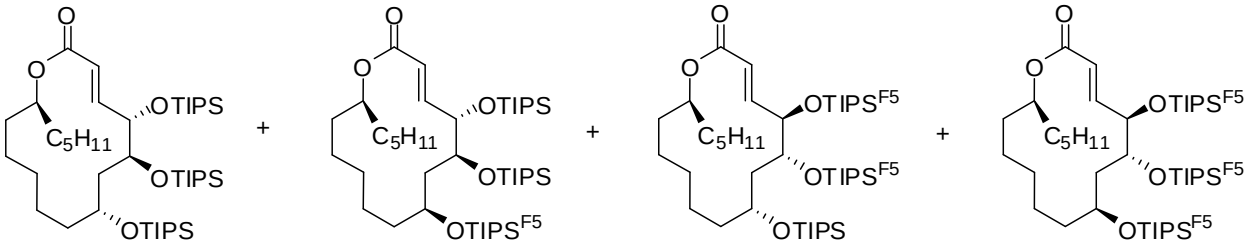


(4*S*,5*S*,7*R*,13*R*,*E*)-14-Pentyl-5,6,8-tris-(triisopropyl-silyl-oxy)-oxacyclo-tetra-dec-3-en-2-one, (4*S*,5*S*,7*S*,13*R*,*E*)-13-Pentyl-4,5-bis-(triisopropyl-silyl-oxy)-7-di-isopropyl-(1,1,1,2,2-penta-fluoro-butyl-silyl-oxy)-oxacyclo-tetra-dec-2-enone, (4*R*,5*R*,7*R*,13*R*,*E*)-13-Pentyl-4,5-bis-(di-isopropyl(1,1,1,2,2-pentafluoro-butyl-silyloxy)-7-triisopropylsilyloxy)-oxacyclotetra-dec-2-enone, (4*R*,5*R*,7*S*,13*R*,*E*)-13-Pentyl-4,5,7-tris-(diisopropyl-(1,1,1,2,2-pentafluoro-butyl-silyloxy)-oxacyclotetra-dec-2-enone ((*R*)-M-57abcd): The procedure for the ring-closing metathesis as executed for compound **51** was repeated for mixture (*R*)-M-**55abcd** (682 mg, 696 μmol based on average molecular weight) using the 2nd generation Grubbs catalyst (118 mg, 139 μmol) in DCM (210 mL). Two successive rounds of flash chromatography (40:1 hexanes/EtOAc) gave the title compound as a pale brown oil (630 mg, 663 μmol). The ring-closed product (630 mg, 663 μmol) was then directly subjected to the partial reduction procedures as reported for preparation of compound **52** using $Pd/SrCO_3$ (3.52 g, 663 μmol) in EtOH (20 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) gave the title compound as a colorless oil (584 mg, 88% over two steps, based on average molecular weight): HRMS (ESI, positive mode): calcd for $C_{45}H_{92}O_5Si_3Na$ $[M + Na]^+$ 819.6145, found 819.6192 for *SSRR*-**57a**; calcd for $C_{46}H_{89}O_5F_5Si_3Na$ $[M + Na]^+$ 923.5836, found 923.5790 for *SSSR*-**57b**; calcd for $C_{47}H_{86}O_5F_{10}Si_3Na$ $[M + Na]^+$ 1,027.5516, found 1,027.5504 for *RRRR*-**57c**; calcd for $C_{48}H_{83}O_5F_{15}Si_3Na$ $[M + Na]^+$ 1,131.5207, found 1,131.5256 for *RRSR*-**57d;** fluorous analytical

HPLC (90:10 MeCN/H_2O for 10 min, then 100% MeCN for 60 min, 1.0 mL/min): t_R = 5.7 min (*SSRR*-**57a**), 8.0 min (*SSSR*-**57b**), 11.1 min (*RRRR*-**57c**), 17.2 min (*RRSR*-**57d)**.

Demixing of (*R*)-M-**57abcd**:

The semi-preparative separation of (*R*)-M-**57abcd** was carried out in the same manner as (*R*)-M-**56abcd**. Aliquots of (*R*)-M-**57abcd** (90 mg/mL) were injected per chromatographic run. The yield of the demixing over six injections was 48% and the following four compounds were isolated: *SSRR*-**57a**: 82.4 mg, t_R = 34.7 min; *SSSR*-**57b**: 80.5 mg, t_R = 49.7 min; *RRRR*-**57c**: 66.8 mg, t_R = 64.7 min; *RRSR*-**57d**: 52.3 mg, t_R = 87.0 min

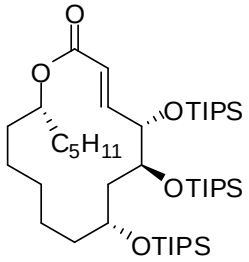


(4*S*,5*S*,7*R*,13*S*,*E*)-14-Pentyl-5,6,8-tris-(tri-isopropyl-silyloxy)-oxacyclo-tetra-dec-3-en-2-one, (4*S*,5*S*,7*S*,13*S*,*E*)-13-Pentyl-4,5-bis-(tri-isopropyl-silyl-oxy)-7-di-iso-propyl-(1,1,1,2,2-penta-fluoro-butyl-silyl-oxy)-oxa-cyclo-tetra-dec-2-enone, (4*R*,5*R*,7*R*,13*S*,*E*)-13-Pentyl-4,5-bis-(di-iso-propyl-(1,1,1,2,2-pentafluorobutylsilyloxy)-7-triisopropylsilyloxy)oxacyclotetradec-2-enone, (4*R*,5*R*,7*S*,13*S*,*E*)-13-Pentyl-4,5,7-tris-(di-isopropyl-(1,1,1,2,2-pentafluoro-butyl-silyloxy)-oxacyclo-tetradec-2-enone ((*S*)-M-57abcd): The procedure for the ring-closing metathesis as executed for compound **51** was repeated for mixture (*S*)-M-**56abcd** (615 mg, 628 μmol based on average molecular weight) using the 2nd generation Grubbs catalyst (107 mg, 126 μmol) in DCM (210 mL). Two successive rounds of flash chromatography (40:1 hexanes/EtOAc) gave the title compound as a pale brown oil (564 mg, 576 μmol). The ring-

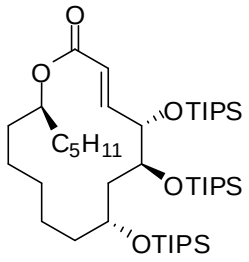
closed product (564 mg, 576 μmol) was then directly subjected to the partial reduction procedures as reported for the preparation of compound **52** using $Pd/SrCO_3$ (3.15 g, 593 μmol) in EtOH (20 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) gave the title compound as a colorless oil (524 mg, 87% over two steps, based on average molecular weight): LRMS (EI) **(***SSRS*-**57a)** *m/z* 797 $(M)^+$; (*SSSS*-**57b**) *m/z* 901 $(M)^+$; (*RRRS*-**57c**) *m/z* 1005 $(M)^+$; (*RRSS*-**57d**) *m/z* 1109 $(M)^+$; HRMS (ESI, positive mode): calcd for $C_{45}H_{92}O_5Si_3Na$ $[M]^+$ 796.6253, found 796.6273 for *SSRS*-**57a**; calcd for $C_{46}H_{89}O_5F_5Si_3Na$ $[M + Na]^+$ 923.5836, found 923.5803 for *SSSS*-**57b**; calcd for $C_{47}H_{86}O_5F_{10}Si_3Na$ $[M + Na]^+$ 1,027.5516, found 1,027.5506 for *RRRS*-**57c**; calcd for $C_{48}H_{83}O_5F_{15}Si_3Na$ $[M+ Na]^+$ 1,131.5207, found 1,131.5254 for *RRSS*-**57d**; fluorous analytical HPLC (90:10 MeCN/H_2O for 10 min, then 100% MeCN for 60 min, 1.0 mL/min): t_R = 5.4 min (*SSRS*-**57a**), 8.5 min (*SSSS*-**57b**), 9.9 min (*RRRS*-**57c**), 17.3 min (*RRSS*-**57d**).

Demixing of (*S*)-M-**57abcd**:

The semi-preparative separation of (*S*)-M-**57abcd** was carried out in the same manner as (*S*)-M-**56abcd**. Aliquots of (*S*)-M-**57abcd** (90 mg/mL) were injected per chromatographic run. The yield of the demixing over six injections was 60% and the following four compounds were isolated: *SSRS*-**57a**: 89.1 mg, t_R = 50.3 min; *SSSS*-**57b**: 69.6 mg, t_R = 85.5 min; *RRRS*-**57c**: 69.9 mg, t_R = 99.8 min; *RRSS*-**57d**: 87.4 mg, t_R = 161.7 min.

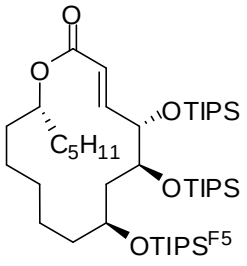


(4*S*,5*S*,7*R*,13*R*,*E*)-14-Pentyl-5,6,8-tris-(tri-isopropyl-silyloxy)-oxa-cyclo-tetra-dec-2-en-one (*SSRR*-57a): From the demixing of **(***S*)-M-**57abcd**, the first peak *SSRR*-**57a** (82.4 mg) at 34.7 minutes was isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (dd, J_1 = 16.0 Hz, J_2 = 2.0 Hz, 1H), 6.11 (dd, J_1 = 16.0 Hz, J_2 = 2.0 Hz, 1H), 5.04 (m, 1H), 4.65 (t, J = 2.5 Hz, 1H), 4.32 (quintet, J = 5.0 Hz, 1H), 4.14 (m, 1H), 2.08 (m, 1H), 1.86 (m, 1H), 1.64 (m, 5H), 1.50 (m, 3H), 1.37 (m, 4H), 1.30 (m, 6H), 1.10 (br s, 63H), 0.89 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 149.0, 122.6, 74.9, 74.5, 73.1, 69.4, 37.0, 35.3, 33.5, 33.1, 31.8, 30.3, 25.3, 23.3, 22.6, 21.1, 18.3, 18.2, 18.1, 14.0, 13.1, 12.5; FTIR (thin film) ν_{max} 2943, 2867, 1718, 1463, 1255, 1200, 1106, 1059, 996, 883 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{45}H_{92}O_5Si_3Na$ $[M + Na]^+$: 819.6145, found 819.6192; $[\alpha]_D^{25} - 34.6$ (*c* 0.76, $CHCl_3$).



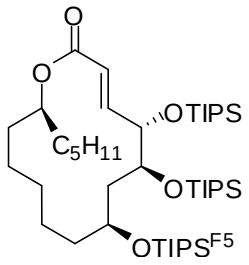
(4*S*,5*S*,7*R*,13*S*,*E*)-14-Pentyl-5,6,8-tris(triisopropylsilyloxy)oxacyclotetradec-2-enone (*SSRS*-57a): From the demixing of (*S*)-M-**57abcd**, the first peak *SSRS*-**57a** (89.1 mg) at 50.3 minutes

was isolated as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.00 (dd, J_1 = 16.0 Hz, J_2 = 4.5 Hz, 1H), 6.10 (d, J = 16.0 Hz, 1H), 5.00 (m, 1H), 4.58 (t, J = 4.5 Hz, 1H), 4.30 (dt, J_1 = 9.0 Hz, J_2 = 4.5 Hz, 1H), 4.02 (m, 1H), 2.07 (m, 1H), 1.81 (m, 1H), 1.65 (m, 3H), 1.56 (m, 2H), 1.44 (m, 1H), 1.32 (m, 6H), 1.26 (m, 6H), 1.07 (br s, 63H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 147.7, 123.5, 75.3, 74.5, 72.7, 69.3, 37.3, 37.2, 34.7, 32.7, 31.8, 29.7, 25.1, 24.9, 22.6, 22.4, 18.3, 18.1, 14.0, 13.0, 12.9, 12.3; FTIR (thin film) ν_{max} 2942, 2866, 1722, 1462, 1261, 1106, 1063, 1016 cm^{-1}; HRMS calcd (EI) for $C_{45}H_{92}O_5Si_3$ $[M]^+$: 796.6253, found 796.6273; $[\alpha]_D^{25} - 30.4$ (*c* 1.12, $CHCl_3$).

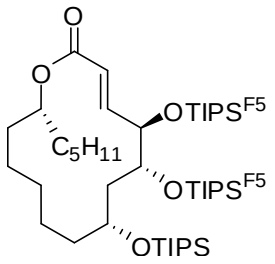


(4*S*,5*S*,7*S*,13*R*)-13-Pentyl-4,5-bis-(triisopropylsilyloxy)-7-diisopropyl(1,1,1,2,2-penta-fluoro-butyl-silyl-oxy)oxa-cyclo-tetra-dec-2-enone (*SSSR*-57b): From the demixing of (*R*)-M-**57abcd**, the second peak *SSSR*-**57b** (80.5 mg) at 49.7 minutes was isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (dd, J_1 = 16.0 Hz, J_2 = 2.0 Hz, 1H), 6.11 (dd, J_1 = 16.0 Hz, J_2 = 2.0 Hz, 1H), 4.99 (m, 1H), 4.62 (m, 1H), 4.25 (quintet, J = 3.0 Hz, 1H), 3.96 (m, 1H), 2.18 (dt, J_1 = 14.5 Hz, J_2 = 3.0 Hz, 1H), 2.05 (m, 3H), 1.69 (m, 3H), 1.51 (m, 5H), 1.31 (br s, 10H), 1.11 (br s, 42H), 1.03 (br s, 14H), 0.89 (t, J = 6.5 Hz, 3H), 0.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 148.7, 120.9, 74.1, 73.9, 73.3, 71.0, 40.7, 35.6, 32.5, 31.8, 30.0, 25.7, 25.4, 23.4, 22.5, 19.8, 18.2, 18.1, 18.0, 17.9, 17.8, 14.0, 12.9, 12.7, 12.5, 12.4, 1.6; ^{19}F NMR (282 MHz, $CDCl_3$)

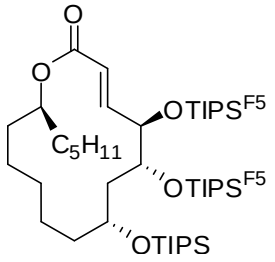
–84.98 (s, 3F), –120.08 (t, $^3J_{HF}$ = 18.0 Hz, 2F); FTIR (thin film) ν_{max} 2944, 2868, 1717, 1463, 1258, 1199, 1106, 1056, 1014, 995, 883 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{46}H_{89}O_5F_5Si_3Na$ $[M + Na]^+$: 923.5836, found 923.5790; $[\alpha]_D^{25} - 21.4$ (*c* 0.89, $CHCl_3$).



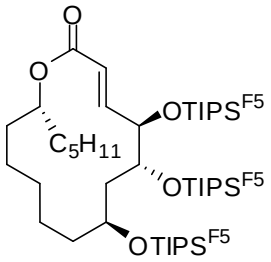
(4*S*,5*S*,7*S*,13*S*)-13-Pentyl-4,5-bis-(triisopropylsilyloxy)-7-diisopropyl(1,1,1,2,2-penta-fluoro-butylsilyloxy)oxacyclotetradec-2-enone (*SSSS*-57b): From the demixing of (*S*)-M-**57abcd**, the second peak *SSSS*-**57b** (69.6 mg) at 85.5 minutes was isolated as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.88 (dd, J_1 = 16.0 Hz, J_2 = 6.5 Hz, 1H), 5.98 (d, *J* = 16.0 Hz, 1H), 4.98 (m, 1H), 4.57 (t, *J* = 6.5 Hz, 1H), 4.22 (m, 1H), 4.08 (t, *J* = 6.5 Hz, 1H), 2.08 (septet, *J* = 9.0 Hz, 2H), 1.94 (m, 1H), 1.79 (quintet, *J* = 7.0 Hz, 3H), 1.65 (m, 4H), 1.53 (m, 4H), 1.40 (m, 2H), 1.30 (br s, 6H), 1.20 (m, 2H), 1.08 (br s, 56H), 0.89 (t, *J* = 6.5 Hz, 3H), 0.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 148.0, 123.3, 76.3, 75.5, 73.3, 71.5, 41.9, 37.1, 34.2, 31.7, 31.0, 29.7, 28.0, 25.0, 24.3, 23.9, 22.6, 18.2, 18.1, 18.0, 17.9, 17.8, 14.0, 13.4, 13.1, 12.4, 12.3, 1.5; ^{19}F NMR (282 MHz, $CDCl_3$) –84.95 (s, 3F), –120.26 (t, $^3J_{HF}$ = 18.0 Hz, 2F); FTIR (thin film) ν_{max} 2943, 2867, 1722, 1463, 1261, 1200, 1103, 1065, 996, 884 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{46}H_{89}O_5F_5Si_3Na$ $[M + Na]^+$: 923.5836, found 923.5803; $[\alpha]_D^{25} - 1.15$ (*c* 1.08, $CHCl_3$).



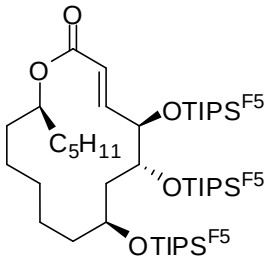
(4*R*,5*R*,7*R*,13*R*)-13-Pentyl-4,5-bis-(diisopropyl(1,1,1,2,2-pentafluorobutylsilyloxy)-7-triiso-propylsilyloxy)oxacyclotetradec-2-enone (*RRRR*-57c): From the demixing of (*R*)-M-**57abcd**, the third peak *RRRR*-**57c** (66.8 mg) at 64.7 minutes was isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (dd, J_1 = 16.0 Hz, J_2 = 6.5 Hz, 1H), 5.95 (d, J = 16.0 Hz, 1H), 5.02 (m, 1H), 4.44 (t, J = 5.3 Hz, 1H), 4.14 (m, 1H), 4.05 (quintet, J = 3.0 Hz, 1H), 2.05 (m, 4H), 1.79 (m, 2H), 1.72 (m, 1H), 1.64 (m, 1H), 1.56 (m, 5H), 1.27 (m, 11H), 1.06 (br s, 49H), 0.88 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 146.7, 123.7, 77.2, 75.9, 73.9, 69.9, 42.1, 37.3, 33.8, 31.7, 31.0, 28.4, 25.4, 25.3, 25.2, 24.1, 22.5, 18.3, 17.7, 17.6, 17.5, 14.0, 13.0, 12.7, 12.6, 12.5, 0.9, 0.8; ^{19}F NMR (282 MHz, $CDCl_3$) –84.91 (s, 3F), –84.93 (s, 3F), –120.19 (t, $^{3}J_{HF}$ = 17.5 Hz, 2F), –120.29 (t, $^{3}J_{HF}$ = 17.5 Hz, 2F); FTIR (thin film) ν_{max} 2944, 2867, 1721, 1199, 1104, 1065 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{47}H_{86}O_5F_{10}Si_3Na$ $[M + Na]^+$: 1,027.5516, found 1,027.5504; $[\alpha]_D^{25} + 2.04$ (*c* 0.90, $CHCl_3$).



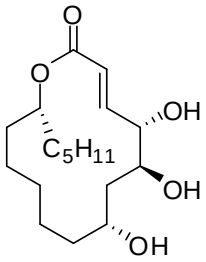
(4*R*,5*R*,7*R*,13*S*)-13-Pentyl-4,5-bis-(diisopropyl-(1,1,1,2,2-pentafluorobutyl-silyloxy)-7-triiso-propyl-silyl-oxy)oxa-cyclo-tetra-dec-2-enone (*RRRS*-57c): From the demixing of (*S*)-M-**57abcd**, the third peak *RRRS*-**57c** (69.9 mg) at 99.8 minutes was isolated as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (dd, J_1 = 16.0 Hz, J_2 = 2.5 Hz, 1H), 6.06 (dd, J_1 = 16.0 Hz, J_2 = 2.5 Hz, 1H), 4.97 (m, 1H), 4.46 (m, 1H), 4.11 (m, 1H), 3.93 (m, 1H), 2.08 (m, 6H), 1.94 (m, 1H), 1.66 (m, 4H), 1.53 (m, 5H), 1.31 (br s, 8H), 1.08 (br s, 28H), 1.04 (br s, 21H), 0.90 (m, 4H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 147.1, 121.6, 74.5, 74.3, 73.7, 70.1, 40.9, 37.1, 34.2, 32.8, 31.8, 31.0, 30.3, 29.7, 28.0, 26.9, 25.4, 25.3, 25.2, 25.0, 24.3, 23.9, 23.6, 22.6, 22.5, 20.6, 18.3, 18.2, 17.5, 14.0, 13.4, 13.1, 12.9, 12.6, 12.4, 12.3, 0.9; ^{19}F NMR (282 MHz, $CDCl_3$) –84.85 (s, 3F), –84.99 (s, 3F), –120.31 (t, $^{3}J_{HF}$ = 17.5 Hz, 2F), –120.48 (t, $^{3}J_{HF}$ = 17.5 Hz, 2F); FTIR (thin film) ν_{max} 2944, 2868, 1719, 1463, 1260, 1199, 1106, 1054, 995, 884 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{47}H_{86}O_5F_{10}Si_3Na$ $[M + Na]^+$: 1,027.5521, found 1,027.5506; $[\alpha]_D^{25} + 2.04$ (*c* 0.90, $CHCl_3$).



(4*R*,5*R*,7*S*,13*R*)-13-Pentyl-4,5,7-tris-(di-isopropyl-(1,1,1,2,2-penta-fluorobutyl-silyloxy)oxa-cyclo-tetradec-2-enone (*RRSR*-57d): From the demixing of (*R*)-M-**57abcd**, the fourth peak *RRSR*-**57d** (52.3 mg) at 87.0 minutes was isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.86 (dd, J_1 = 16.0 Hz, J_2 = 5.5 Hz, 1H), 6.06 (d, J = 16.0 Hz, 1H), 4.99 (m, 1H), 4.41 (t, J = 10.0 Hz, 1H), 4.08 (dt, J_1 = 10.0 Hz, J_2 = 7.5 Hz 1H), 3.85 (m, 1H), 2.05 (m, 6H), 1.71 (m, 2H), 1.61 (m, 3H), 1.54 (m, 3H), 1.46 (m, 1H), 1.33 (m, 11H), 1.20 (m, 2H), 1.05 (br s, 42H), 0.89 (7H), 0.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 145.8, 124.3, 75.6, 74.9, 72.7, 69.7, 38.9, 36.6, 34.6, 32.5, 31.7, 29.4, 25.5, 25.3, 25.1, 25.0, 24.6, 23.1, 22.5, 17.7, 17.6, 17.4, 14.0, 13.2, 13.0, 12.8, 12.6, 1.4, 1.3, 0.8; ^{19}F NMR (282 MHz, $CDCl_3$) –84.93 (s, 3F), –84.95 (s, 3F), –84.98 (s, 3F), –120.09 (t, $^{3}J_{HF}$ = 17.5 Hz, 2F), –120.24 (t, $^{3}J_{HF}$ = 17.5 Hz, 2F), –120.39 (t, $^{3}J_{HF}$ = 17.5 Hz, 2F); FTIR (thin film) ν_{max} 2930, 2360, 2340, 1610, 1465, 1195, 1023 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{48}H_{83}O_5F_{15}Si_3Na$ $[M + Na]^+$: 1,131.5207, found 1,131.5256; $[\alpha]_D^{25}$ +16.1, (*c* 1.30, $CHCl_3$).

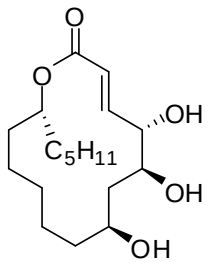


(4*R*,5*R*,7*S*,13*S*)-13-Pentyl-4,5,7-tris-(diisopropyl-(1,1,1,2,2-penta-fluoro-butyl-silyloxy)-oxa-cyclotetradec-2-enone (*RRSS*-57d): From the demixing of (*S*)-M-**57abcd**, the fourth peak *RRSS*-**57d** (87.4 mg) at 161.7 minutes was isolated as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.11 (dd, J_1 = 16.0 Hz, J_2 = 2.5 Hz, 1H), 6.06 (dd, J_1 = 16.0 Hz, J_2 = 2.0 Hz, 1H), 5.04 (m, 1H), 4.50 (t, J = 2.5 Hz, 1H), 4.14 (quintet, J = 5.0 Hz, 1H), 4.00 (m, 1H), 2.05 (m, 6H), 1.85 (m, 1H), 1.68 (m, 1H), 1.62 (m, 1H), 1.57 (m, 2H), 1.50 (m, 4H), 1.31 (m, 5H), 1.26 (br s, 6H), 1.10 (br s, 14H), 1.1.06 (br s, 14H), 1.01 (br s, 14H), 0.89 (7H), 0.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 147.0, 75.3, 74.5, 72.9, 69.8, 37.1, 35.8, 33.7, 32.9, 31.8, 30.4, 30.2, 29.7, 25.7, 25.6, 25.4, 25.2, 25.1, 24.9, 23.6, 22.7, 22.5, 21.7, 17.6, 17.5, 17.4, 14.1, 14.0, 13.0, 12.9, 12.8, 12.7, 12.6, 1.5, 0.8, 0.7; ^{19}F NMR (282 MHz, $CDCl_3$) –84.90 (s, 3F), –84.95 (s, 3F), –84.96 (s, 3F), –120.32 (t, $^{3}J_{HF}$ = 17.5 Hz, 2F), –120.38 (t, $^{3}J_{HF}$ = 17.5 Hz, 2F), –120.48 (t, $^{3}J_{HF}$ = 17.5 Hz, 2F); FTIR (thin film) ν_{max} 2944, 2869, 1719, 1199, 1106, 1051, 996 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{48}H_{83}O_5F_{15}Si_3Na$ $[M + Na]^+$: 1,131.5207, found 1,131.5254; $[\alpha]_D^{25}$ +16.1 (*c* 1.30, $CHCl_3$).

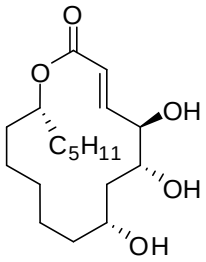


(4*S*,5*S*,7*R*,13*R*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradecenone ((4*S*,5*S*,7*R*,13*R*)-5): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *SSRR*-**57a** (81.1 mg, 102 μmol). The product after flash chromatography (3:1 hexanes/EtOAc, then 100% EtOAc) was dissolved in THF (3.0 mL), filtered using a Whatman syringe filter (0.45 μm pore size), and then further purified using a (*S*,*S*)-Whelk-O-1 column (25 cm x 21.1 mm). The purification was done by isocratic elution first with 90:10 hexanes/isopropanol for the first 15 minutes, then isocratic elution with 80:20 hexanes/isopropanol for 30 minutes. A constant flow rate of 10.0 mL/min was run throughout the separation and a UV detector (230 nm) was used to manually identify the peaks. The reaction after purification on the (*S*,*S*)-Whelk-*O*-1 column after three injections furnished the title compound as an amorphous white solid (6.4 mg, 19%): ^{1}H NMR (700 MHz, CD_3OD) δ 7.04 (dd, J_1 = 15.8 Hz, J_2 = 5.3 Hz, 1H), 6.11 (dd, J_1 = 15.8 Hz, J_2 = 1.5 Hz, 1H), 4.95 (dddd, J_1 = 12.5 Hz, J_2 = 7.6 Hz, J_3 = 5.0 Hz, J_4= 2.3 Hz, 1H), 4.26 (ddd, J_1 = 7.0 Hz, J_2 = 5.3 Hz, J_3 = 1.5 Hz, 1H), 3.92 (m, 1H), 3.77 (dt, J_1 = 7.4 Hz, J_2 = 4.5 Hz, 1H), 1.72 (m, 1H), 1.70 (dd, J_1 = 5.4 Hz, J_2 = 4.5 Hz, 2H), 1.62 (m, 1H), 1.54 (m, 2H), 1.43 (m, 4H), 1.33 (br s, 7H), 1.19 (br s, 3H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR (175 MHz, CD_3OD) δ 168.0, 148.7, 123.5, 77.6, 75.8, 74.4, 69.2, 37.9, 36.8, 36.4, 34.2, 33.0, 29.7, 26.6, 26.4, 25.3, 23.8, 14.5; FTIR (thin film) ν_{max} 2926,

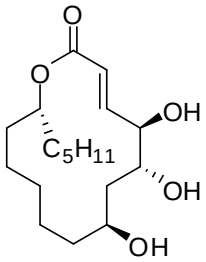
2857, 1705, 1270, 1100 cm^{-1}; HRMS calcd (EI) for $C_{18}H_{32}O_5$ $[M]^+$: 328.2250, found 328.2243; $[\alpha]_D^{25}$ −9.43 (*c* 0.54, MeOH).



(4*S*,5*S*,7*S*,13*R*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradecenone ((4*S*,5*S*,7*S*,13*R*)-5): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *SSSR*-**57b** (79.3 mg, 88.0 μmol). Flash chromatography (3:1 hexanes/EtOAc, then 100% EtOAc) of the crude product gave the title compound as an amorphous white solid (14.6 mg, 51%): ^{1}H NMR (700 MHz, CD_3OD) δ 6.96 (dd, J_1 = 15.8 Hz, J_2 = 5.9 Hz, 1H), 6.10 (dd, J_1 = 15.8 Hz, J_2 = 1.3 Hz, 1H), 4.93 (m, 1H), 4.03 (ddd, J_1 = 7.6 Hz, J_2 = 6.0 Hz, J_3 = 1.5 Hz, 1H), 3.54 (td, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 3.47 (m, 1H), 1.76 (ddd, J_1 = 14.6 Hz, J_2 = 8.5 Hz, J_3 = 2.7 Hz, 1H), 1.67 (m, 2H), 1.64 (m, 1H), 1.55 (m, 2H), 1.52 (m, 2H), 1.34 (br s, 9H), 1.26 (br s, 3H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 168.1, 149.4, 123.1, 77.8, 75.9, 74.6, 68.3, 43.8, 35.8, 35.6, 33.3, 33.0, 27.6, 26.4, 24.2, 23.9, 23.8, 14.5; FTIR (thin film) ν_{max} 3318, 2930, 2854, 1708, 1284 cm^{-1}; HRMS calcd (EI) for $C_{18}H_{32}O_5$ $[M]^+$: 328.2250, found 328.2260; $[\alpha]_D^{25}$ −18.8 (*c* 0.77, MeOH).

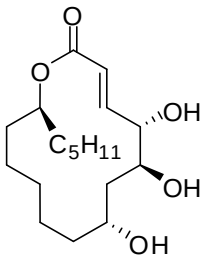


(4*R*,5*R*,7*R*,13*R*)-4,5,7-Tri-hydroxy-13-pentyl-oxacyclo-tetra-decenone ((4*R*,5*R*,7*R*,13*R*)-5): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *RRRR*-**57c** (66.0 mg, 65.8 μmol). Flash chromatography (3:1 hexanes/EtOAc, then 100% EtOAc) of the crude product gave the title compound as an amorphous white solid (13.1 mg, 60%). The ^{1}H NMR spectrum of this sample isolated by detagging *RRRR*-**57c** matched the one recorded during the single isomer pilot synthesis (see Section 6.1).

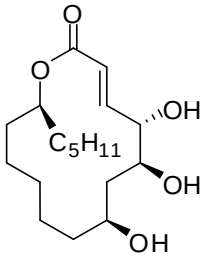


(4*R*,5*R*,7*S*,13*R*)-4,5,7-Trihydroxy-13-pentyl-oxacyclotetra-decenone ((4*R*,5*R*,7*S*,13*R*)-5): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *RRSR*-**57d** (50.0 mg, 45.0 μmol). Flash chromatography of the crude product (3:1 hexanes/EtOAc, then 100% EtOAc) gave the title compound as an amorphous white solid (7.6 mg, 51%): ^{1}H NMR (700 MHz, CD_3OD) δ 7.07

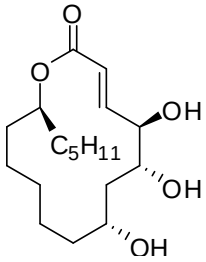
(dd, J_1 = 15.8 Hz, J_2 = 5.4 Hz, 1H), 6.12 (dd, J_1 = 15.8 Hz, J_2 = 1.5 Hz, 1H), 4.97 (m, 1H), 4.26 (td, J_1 = 6.5 Hz, J_2 = 1.5 Hz, 1H), 3.90 (td, J_1 = 6.5 Hz, J_2 = 2.8 Hz, 1H), 3.78 (septet, J = 4.20 Hz, 1H), 1.70 (m, 4H), 1.63 (m, 2H), 1.54 (m, 2H), 1.42 (m, 2H), 1.31 (m, 9H), 1.21 (m, 1H), 0.91 (t, J = 6.9 Hz, 3H); ^{13}C NMR (175 MHz, CD_3OD) δ 168.8, 149.8, 123.2, 75.8, 75.3, 73.8, 68.9, 38.3, 35.8, 35.5, 33.7, 33.0, 27.8, 26.5, 25.1, 24.5, 23.8, 14.5; FTIR (thin film) ν_{max} 3195, 2924, 2854, 1709, 1554, 1272 cm^{-1}; HRMS calcd (EI) for $C_{18}H_{32}O_5$ $[M]^+$: 328.2250, found 328.2242; $[\alpha]_D^{25} + 7.66$ (*c* 0.38, MeOH).



(4*S*,5*S*,7*R*,13*S*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradecenone ((4*S*,5*S*,7*R*,13*S*)-5): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *SSRS*-**57a** (88.1 mg, 111 μmol). The product after flash chromatography (3:1 hexanes/EtOAc, then 100% EtOAc) was further purified using a (*S*,*S*)-Whelk-*O*-1 column as described for compound (4*S*,5*S*,7*R*,13*R*)-**5** (see above) and the title compound was isolated as an amorphous white solid (5.4 mg, 15%). The ^{1}H NMR spectrum matched that of (4*R*,5*R*,7*S*,13*R*)-**11** (see above); $[\alpha]_D^{25} - 4.04$ (*c* 0.27, MeOH).

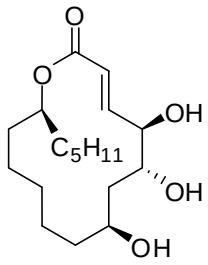


(4*S*,5*S*,7*S*,13*S*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradecenone ((4*S*,5*S*,7*S*,13*S*)-5): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *SSSS*-**57b** (68.0 mg, 75.4 μmol). Flash chromatography of the crude product (3:1 hexanes/EtOAc, then 100% EtOAc) gave the title compound as an amorphous white solid (16.5 mg, 67%). The ^{1}H NMR spectrum matched that of (4*R*,5*R*,7*R*,13*R*)-**5** (see above); $[\alpha]_D^{25} - 25.9$ (*c* 0.83, MeOH).

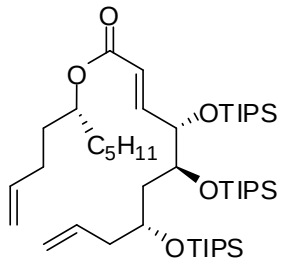


(4*R*,5*R*,7*R*,13*S*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradecenone ((4*R*,5*R*,7*R*,13*S*)-5): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *RRRS*-**57c** (68.8 mg, 68.4 μmol). The product after flash chromatography (3:1 hexanes/EtOAc, then 100% EtOAc) was dissolved in 1:1 hexanes/isopropanol (1.0 mL), filtered through a Whatman syringe filter (0.45 μm pore size), and further purified using a Chiralcel OD semi-preparative HPLC column. The purification was

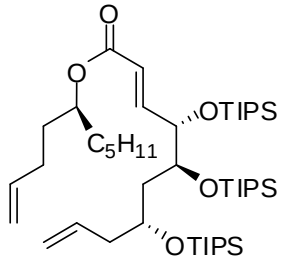
done with isocratic elution (92:8 hexanes/isopropanol, 4.5 mL/min), a UV detector (230 nm) was used to identify the peaks, and the desired compound (4*R*,5*R*,7*R*,13*S*)-**11** was isolated as an amorphous white solid (1 injection, 3.2 mg, 14%) The ^{1}H NMR spectrum matched that of (4*S*,5*S*,7*S*,13*R*)-**5** (see above); $[\alpha]_D^{25}$ +16.5 (*c* 0.32, MeOH).



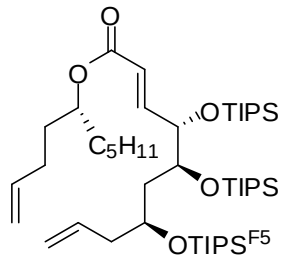
(4*R*,5*R*,7*S*,13*S*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradecenone ((4*R*,5*R*,7*S*,13*S*)-5): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *RRSS*-**57d** (84.9 mg, 76.5 μmol). Flash chromatography of the crude product (3:1 hexanes/EtOAc, then 100% EtOAc) gave the title compound as an amorphous white solid (16.5 mg, 66%). The ^{1}H NMR spectrum matched that of (4*S*,5*S*,7*R*,13*R*)-**5** (see above); $[\alpha]_D^{25}$ +11.3 (*c* 0.89, MeOH).



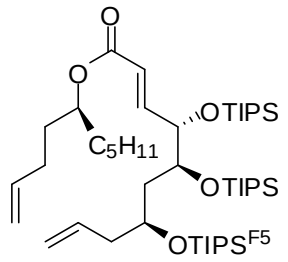
(4*S*,5*S*,7*R*,*E*)-((*R*)-Dec-1-en-5-yl)-4,5,7-tris(triisopropylsilyloxy)deca-2,9-dienoate (*SSRR*-56a): From the demixing of (*R*)-M-**56abcd**, the first peak *SSRR*-**56a** (58.8 mg) at 62.2 minutes was isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, J_1 = 15.8 Hz, J_2 = 4.0 Hz, 1H), 6.08 (dd, J_1 = 15.8 Hz, J_2 = 1.6 Hz, 1H), 5.93 (m, 1H), 5.80 (ddt, J_1 = 16.9 Hz, J_2 = 10.2 Hz, J_3 = 6.6 Hz, 1H), 5.01 (m, 5H), 4.58 (td, J_1 = 4.0 Hz, J_2 = 2.7 Hz, 1H), 4.20 (sextet, J = 4.0 Hz, 1H), 4.10 (m, 1H), 2.43 (m, 1H), 2.33 (ddd, J_1 = 12.9 Hz, J_2 = 8.0 Hz, J_3 = 4.4 Hz, 1H), 2.06 (m, 2H), 1.80 (ddd, J_1 = 13.5 Hz, J_2 = 8.1 Hz, J_3 = 4.9 Hz, 1H), 1.66 (m, 3H), 1.59 (2H), 1.29 (m, 6H), 1.07 (br s, 63 H), 0.88 (t, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 147.6, 138.0, 135.0, 122.5, 116.9, 114.8, 76.4, 73.7, 72.6, 68.3, 41.6, 41.2, 34.2, 33.4, 31.2, 29.7, 29.6, 25.0, 22.6, 18.3, 18.2, 18.1, 14.0, 12.8, 12.7, 12.4; FTIR (thin film) ν_{max} 2943, 2867, 1722, 1463, 1261, 1106, 1063, 994 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{47}H_{94}O_5Si_3$ $[M + Na]^+$: 845.6307, found 845.6340; $[\alpha]_D^{25} - 24.1$ (*c* 1.10, $CHCl_3$).



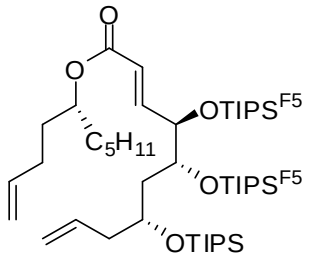
(4*S*,5*S*,7*R*,*E*)-((*S*)-Dec-1-en-5-yl) 4,5,7-tris(triisopropylsilyloxy)deca-2,9-dienoate (*SSRS*-56a): From the demixing of (*S*)-M-**56abcd**, the first peak *SSRS*-**56a** (83.0 mg) at 37.8 minutes was isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (dd, J_1 = 16.0 Hz, J_2 = 4.0 Hz, 1H), 6.08 (dd, J_1 = 16.0 Hz, J_2 = 1.5 Hz, 1H), 5.94 (m, 1H), 5.81 (ddt, J_1 = 17.0 Hz, J_2 = 10.0 Hz, J_3 = 6.5 Hz, 1H), 5.01 (m, 5H), 4.58 (m, 1H), 4.20 (m, 1H), 4.10 (m, 1H), 2.43 (m, 1H), 2.34 (ddd, J_1 = 13.0 Hz, J_2 = 8.5 Hz, J_3 = 4.5 Hz, 1H), 2.09 (m, 2H), 1.80 (ddd, J_1 = 13.5 Hz, J_2 = 8.o Hz, J_3 = 5.0 Hz, 1H), 1.68 (m, 3H), 1.57 (m, 2H), 1.29 (m, 6H), 1.10 (br s, 42 H), 1.05 (br s, 21H), 0.88 (t, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 147.6, 138.0, 135.0, 122.5, 116.9, 114.8, 76.4, 73.7, 72.6, 68.3, 41.6, 41.2, 34.0, 33.4, 31.8, 29.7, 24.9, 22.6, 18.3, 18.2, 18.1, 14.0, 12.8, 12.7, 12.4; FTIR (thin film) ν_{max} 2946, 2868, 1722, 1465, 1262, 1201, 1111, 1064, 995 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{47}H_{94}O_5Si_3$ $[M + Na]^+$: 845.6307, found 845.6323; $[\alpha]_D^{25} - 22.8$ (*c* 1.07, $CHCl_3$).



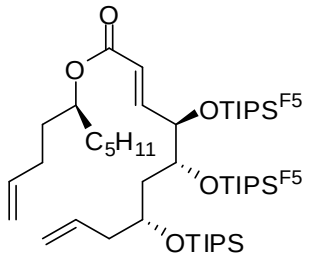
(4*S*,5*S*,7*S*,*E*)-((*R*)-Dec-1-en-5-yl)-4,5-bis(triisopropylsilyloxy)-7-diisopropyl(1,1,1,2,2-penta-fluorobutylsilyloxy)deca-2,9-dienoate (*SSSR*-56b): From the demixing of (*R*)-M-**56abcd**, the second peak *SSSR*-**56b** (68.2 mg) at 91.8 minutes was isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (dd, J_1 = 15.7 Hz, J_2 = 4.0 Hz, 1H), 6.08 (dd, J_1 = 15.7 Hz, J_2 = 1.7 Hz, 1H), 5.86 (m, 1H), 5.81 (ddt, J_1 = 16.9 Hz, J_2 = 10.3 Hz, J_3 = 6.6 Hz, 1H), 5.01 (m, 5H), 4.59 (td, J_1 = 4.5 Hz, J_2 = 1.8 Hz, 1H), 4.07 (m, 1H), 4.02 (ddd, J_1 = 9.8 Hz, J_2 = 4.5 Hz, J_3 = 2.4 Hz, 1H), 2.38 (m, 1H), 2.09 (m, 5H), 1.89 (ddd, J_1 = 13.2 Hz, J_2 = 11.0 Hz, J_3 = 2.2 Hz, 1H), 1.66 (m, 2H), 1.50 (m, 3H), 1.28 (m, 6H), 1.10 (br s, 21H), 1.07 (br s, 21H), 1.02 (br s, 14H), 0.88 (t, J = 6.6 Hz, 3H), 0.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 147.2, 138.0, 134.8, 122.5, 117.3, 114.8, 74.2, 73.7, 73.1, 69.5, 40.9, 39.8, 34.1, 33.4, 31.8, 29.7, 29.6, 25.4, 24.9, 22.6, 18.2, 18.1, 17.7, 17.6, 14.0, 13.1, 12.9, 12.5, 0.8; ^{19}F NMR (282 MHz, $CDCl_3$) –85.02 (s, 3F), –120.42 (t, $^{3}J_{HF}$ = 17.5 Hz, 2F); FTIR (thin film) ν_{max} 2946, 2869, 1721, 1465, 1267, 1107, 994 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{48}H_{91}O_5F_5Si_3$ $[M + Na]^+$: 949.5992, found 949.6046; $[\alpha]_D^{25} - 41.0$ (*c* 1.28, $CHCl_3$).



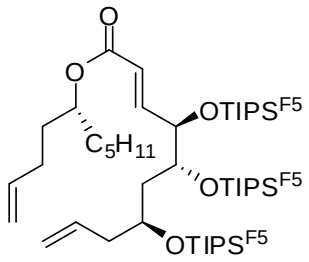
(4*S*,5*S*,7*S*,*E*)-((*S*)-Dec-1-en-5-yl)-4,5-bis(triisopropylsilyloxy)-7-diisopropyl(1,1,1,2,2-pentafluorobutylsilyloxy)deca-2,9-dienoate (*SSSS*-56b): From the demixing of (*S*)-M-**56abcd**, the second peak *SSSS*-**56b** (92.4 mg) at 54.9 minutes was isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (dd, J_1 = 16.0 Hz, J_2 = 4.0 Hz, 1H), 6.08 (dd, J_1 = 16.0 Hz, J_2 = 1.5 Hz, 1H), 5.86 (m, 1H), 5.80 (ddt, J_1 = 17.0 Hz, J_2 = 10.0 Hz, J_3 = 6.5 Hz, 1H), 5.01 (m, 5H), 4.59 (m, 1H), 4.08 (m, 1H), 4.03 (m, 1H), 2.38 (m, 1H), 2.09 (m, 5H), 1.89 (ddd, J_1 = 13.0 Hz, J_2 = 10.5 Hz, J_3 = 2.0 Hz, 1H), 1.67 (m, 2H), 1.52 (m, 3H), 1.29 (m, 6H), 1.10 (br s, 21H), 1.07 (br s, 21H), 1.02 (br s, 14H), 0.88 (t, J = 6.5 Hz, 3H), 0.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 147.2, 138.0, 134.8, 122.5, 117.3, 114.7, 74.3, 73.7, 73.1, 69.5, 40.9, 39.8, 34.1, 33.4, 31.7, 29.7, 25.7, 25.4, 24.9, 22.6, 18.2, 18.1, 17.7, 17.6, 14.0, 13.1, 12.9, 12.5, 0.8; ^{19}F NMR (282 MHz, $CDCl_3$) –85.03 (s, 3F), –120.43 (t, $^{3}J_{HF}$ = 17.5 Hz, 2F); FTIR (thin film) ν_{max} 2946, 2869, 1722, 1465, 1267, 1107, 994 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{48}H_{91}O_5F_5Si_3$ $[M + Na]^+$: 949.5992, found 949.6074; $[\alpha]_D^{25} - 46.4$ (*c* 1.08, $CHCl_3$).



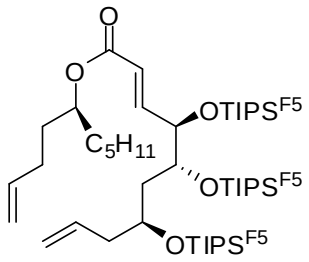
(4*R*,5*R*,7*R*,*E*)-((*R*)-Dec-1-en-5-yl)-4,5-bis(diisopropyl(1,1,1,2,2-pentafluorobutylsilyloxy))-7-triisopropylsilyloxy-deca-2,9-dienoate (*RRRR*-56c): From the demixing of (*R*)-M-**56abcd**, the third peak *RRRR*-**56c** (111.6 mg) at 114.9 minutes was isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (dd, J_1 = 15.8 Hz, J_2 = 4.9 Hz, 1H), 6.00 (dd, J_1 = 15.8 Hz, J_2 = 1.5 Hz, 1H), 5.90 (ddt, J_1 = 17.0 Hz, J_2 = 10.5 Hz, J_3 = 7.2 Hz, 1H), 5.80 (ddt, J_1 = 17.0 Hz, J_2 = 10.5 Hz, J_3 = 6.5 Hz 1H), 5.02 (m, 5H), 4.44 (m, 1H), 4.04 (m, 1H), 3.95 (dt, J_1 = 13.5 Hz, J_2 = 4.0 Hz, 1H), 2.37 (m, 1H), 2.20 (m, 1H), 2.05 (m, 6H), 1.88 (ddd, J_1 = 13.5 Hz, J_2 = 9.0 Hz, J_3 = 4.0 Hz, 1H), 1.67 (m, 2H), 1.54 (m, 3H), 1.28 (br s, 21H), 1.06 (br s, 28H), 0.88 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 146.2, 137.9, 134.3, 122.9, 117.3, 114.8, 74.4, 74.0, 73.3, 68.6, 41.1, 39.1, 34.1, 33.4, 31.7, 29.6, 25.7, 25.6, 25.4, 25.3, 25.1, 22.5, 17.7, 17.6, 17.5, 14.1, 14.0, 13.0, 12.8, 12.7, 12.6, 12.5, 1.6, 0.9; ^{19}F NMR (282 MHz, $CDCl_3$) –84.93 (s, 3F), –85.01 (s, 3F), –120.44 (m, 4F); FTIR (thin film) ν_{max} 2946, 2869, 1723, 1201, 1108 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{49}H_{88}O_5F_{10}Si_3$ $[M + Na]^+$: 1,053.5678, found 1,053.5725; $[\alpha]_D^{25} + 22.4$ (*c* 1.11, $CHCl_3$).



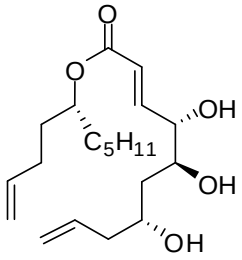
(4*R*,5*R*,7*R*,*E*)-((*R*)-Dec-1-en-5-yl)-4,5-bis(diisopropyl(1,1,1,2,2-pentafluorobutylsilyloxy))-7-triisopropylsilyloxy-deca-2,9-dienoate (*RRRS*-56c): From the demixing of (*S*)-M-**56abcd**, the third peak *RRRS*-**56c** (90.4 mg) at 68.1 minutes was isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (dd, J_1 = 16.0 Hz, J_2 = 5.0 Hz, 1H), 6.00 (dd, J_1 = 16.0 Hz, J_2 = 1.5 Hz, 1H), 5.90 (ddt, J_1 = 17.0 Hz, J_2 = 10.5 Hz, J_3 = 7.0 Hz, 1H), 5.80 (ddt, J_1 = 17.0 Hz, J_2 = 10.5 Hz, J_3 = 6.5 Hz 1H), 5.02 (m, 5H), 4.44 (t, J = 3.5 Hz, 1H), 4.04 (sextet, J = 4.5 Hz, 1H), 3.95 (m, 1H), 2.38 (m, 1H), 2.21 (m, 1H), 2.05 (m, 6H), 1.88 (ddd, J_1 = 13.5 Hz, J_2 = 9.0 Hz, J_3 = 4.0 Hz, 1H), 1.66 (m, 2H), 1.55 (m, 3H), 1.33 (m, 6H), 1.06 (br s, 49H), 0.88 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 146.2, 137.9, 134.3, 122.9, 117.3, 114.8, 74.3, 74.0, 73.3, 68.6, 41.0, 39.1, 34.1, 33.4, 31.7, 29.6, 25.7, 25.6, 25.4, 25.3, 25.1, 24.9, 22.5, 17.6, 17.5, 14.0, 13.0, 12.7, 12.6, 1.6, 0.9; ^{19}F NMR (282 MHz, $CDCl_3$) −84.95 (s, 3F), −85.02 (s, 3F), −120.42 (t, $^{3}J_{HF}$ = 17.0 Hz, 2F), −120.48 (t, $^{3}J_{HF}$ = 17.0 Hz, 2F); FTIR (thin film) ν_{max} 2947, 2870, 1723, 1466, 1266, 1201, 1107, 1065, 994, 885 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{49}H_{88}O_5F_{10}Si_3$ $[M + Na]^+$: 1,053.5678, found 1,053.5664; $[\alpha]_D^{25} + 22.9$ (*c* 1.08, $CHCl_3$).



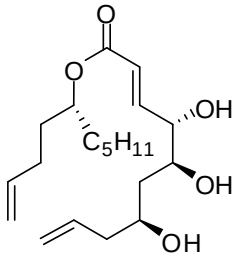
(4*R*,5*R*,7*S*,*E*)-((*R*)-Dec-1-en-5-yl)-4,5,7-tris(diisopropyl(1,1,1,2,2-penta-fluorobutylsilyloxy)) deca-2,9-dienoate (*RRSR*-56d): From the demixing of (*R*)-M-**56abcd**, the fourth peak *RRSR*-**56d** (60.0 mg) at 163.4 minutes was isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (dd, J_1 = 15.8 Hz, J_2 = 4.5 Hz, 1H), 6.03 (dd, J_1 = 15.8 Hz, J_2 = 1.5 Hz, 1H), 5.79 (m, 2H), 5.02 (m, 5H), 4.45 (td, J_1 = 4.5 Hz, J_2 = 1.5 Hz, 1H), 4.05 (m, 1H), 4.01 (m, 1H), 2.32 (m, 2H), 2.04 (m, 8H), 1.70 (m, 3H), 1.57 (m, 3H), 1.28 (m, 6H), 1.04 (br s, 42H), 0.88 (m, 4H), 0.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 145.9, 137.9, 133.9, 123.1, 117.8, 114.8, 75.9, 74.1, 72.7, 69.1, 41.8, 40.8, 34.0, 33.3, 31.7, 29.7, 29.6, 25.6, 25.5, 25.4, 25.3, 25.2, 25.0, 24.9, 22.5, 17.8, 17.7, 17.6, 17.5, 13.9, 13.1, 13.0, 12.9, 12.8, 12.6, 12.5, 1.3, 1.2, 0.8; ^{19}F NMR (282 MHz, $CDCl_3$) –84.99 (s, 3F), –85.03 (s, 3F), –85.05 (s, 3F) –120.42 (m, 6F); FTIR (thin film) ν_{max} 2947, 2871, 1723, 1200, 1107, 1063, 993, 887 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{50}H_{85}O_5F_{15}Si_3$ $[M + Na]^+$: 1,157.5363, found 1,157.5360; $[\alpha]_D^{25}$ +18.6 (*c* 1.11, $CHCl_3$).



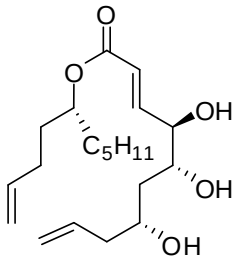
(4*R*,5*R*,7*S*,*E*)-((*S*)-Dec-1-en-5-yl)-4,5,7-tris(diisopropyl(1,1,1,2,2-penta-fluoro-butylsilyloxy)) deca-2,9-dienoate (*RRSS*-79): From the demixing of (*S*)-M-**56abcd**, the fourth peak *RRSS*-**56d** (105.7 mg) at 91.5 minutes was isolated as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (dd, J_1 = 16.0 Hz, J_2 = 4.5 Hz, 1H), 6.03 (dd, J_1 = 16.0 Hz, J_2 = 1.5 Hz, 1H), 5.79 (m, 2H), 5.02 (m, 5H), 4.45 (m, 1H), 4.05 (m, 1H), 4.01 (m, 1H), 2.32 (m, 2H), 2.04 (m, 8H), 1.70 (m, 3H), 1.57 (m, 3H), 1.28 (m, 6H), 1.04 (br s, 42H), 0.88 (m, 4H), 0.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 145.9, 137.9, 133.9, 123.1, 117.8, 114.8, 75.9, 74.1, 72.7, 69.1, 41.8, 40.8, 34.1, 33.3, 31.7, 29.6, 25.7, 25.6, 25.4, 25.3, 25.2, 25.1, 25.0, 24.9, 22.5, 17.8, 17.7, 17.6, 17.5, 14.0, 13.1, 13.0, 12.9, 12.8, 12.6, 12.5, 1.3, 1.2, 0.8; ^{19}F NMR (282 MHz, $CDCl_3$) –84.99 (s, 3F), –85.03 (s, 3F), –85.05 (s, 3F), –120.40 (t, $^{3}J_{HF}$ = 18.0 Hz, 2F), –120.47 (t, $^{3}J_{HF}$ = 18.0 Hz, 2F), –120.48 (t, $^{3}J_{HF}$ = 18.0 Hz, 2F); FTIR (thin film) ν_{max} 2949, 2870, 1723, 1200, 1107, 1065, 993, 886 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{50}H_{85}O_5F_{15}Si_3$ $[M + Na]^+$: 1,157.5363, found 1,157.5306; $[\alpha]_D^{25}$ +18.7 (*c* 1.12, $CHCl_3$).



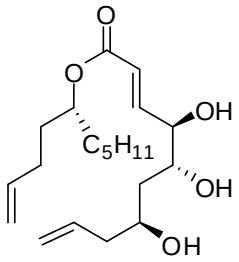
(4*S*,5*S*,7*R*,*E*)-((*R*)-Dec-1-en-5-yl)-4,5,7-trihydroxydeca-2,9-dienoate ((4*S*,5*S*,7*R*,15*R*)-58): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *SSRR*-**56a**. Flash chromatography of the crude product (1:1 hexanes/EtOAc) gave the title compound as a colorless oil (16.5 mg, 65%). The ^{1}H NMR spectrum matched that of (4*R*,5*R*,7*S*,15*S*)-**58** (see below); $[\alpha]_D^{25} -30.7$, (*c* 1.08, MeOH).



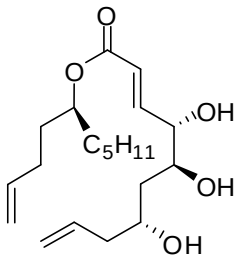
(4*S*,5*S*,7*S*,*E*)-((*R*)-Dec-1-en-5-yl)-4,5,7-Trihydroxydeca-2,9-dienoate ((4*S*,5*S*,7*S*,15*R*)-58): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *SSSR*-**56b** (68.2 mg, 44.1 μmol). Flash chromatography of the crude product (1:1 hexanes/EtOAc) gave the title compound as a colorless oil (15.6 mg, 94%). The ^{1}H NMR spectrum matched that of (4*R*,5*R*,7*R*,15*S*)-**58** (see below); $[\alpha]_D^{25} -15.1$ (*c* 0.83, MeOH).



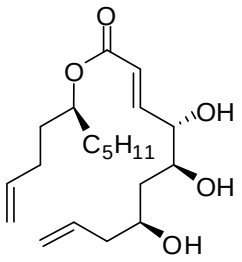
(4*R*,5*R*,7*R*,2*E*)-((*R*)-Dec-1-en-5-yl)-4,5,7-Trihydroxydeca-2,9-dienoate ((4*R*,5*R*,7*R*,15*R*)-58): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *RRRR*-**56c** (112 mg, 108 μmol). Flash chromatography of the crude product (1:1 hexanes/EtOAc) gave the title compound as a colorless oil (26.4 mg, 69%). The ^{1}H NMR spectrum matched that of (4*S*,5*S*,7*S*,15*S*)-**58** (see below); $[\alpha]_D^{25}$ +17.9 (*c* 1.02, MeOH).



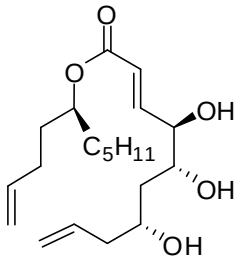
(4*R*,5*R*,7*S*,2*E*)-((*R*)-Dec-1-en-5-yl)-4,5,7-Trihydroxydeca-2,9-dienoate ((4*R*,5*R*,7*S*,15*R*)-58): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *RRSR*-**56d** (137 mg, 120 μmol). Flash chromatography of the crude product (1:1 hexanes/EtOAc) gave the title compound as a colorless oil (11.0 mg, 63%). The ^{1}H NMR spectrum matched that of (4*S*,5*S*,7*R*,15*S*)-**58** (see below); $[\alpha]_D^{25}$ +34.6 (*c* 1.43, MeOH).



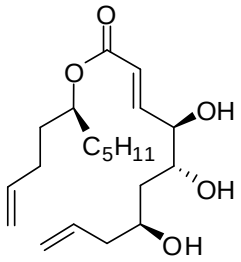
(4*S*,5*S*,7*R*)-((*S*)-Dec-1-en-5-yl)-4,5,7-trihydroxydeca-2,9-dienoate ((4*S*,5*S*,7*R*,15*S*)-58): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *SSRS*-**56a** (83.0 mg, 101 μmol). Flash chromatography of the crude product (1:1 hexanes/EtOAc) gave the title compound as a colorless oil (23.9 mg, 67%): ^{1}H NMR (600 MHz, CD_3OD) δ 7.05 (dd, J_1 = 15.7 Hz, J_2 = 4.7 Hz, 1H), 6.10 (dd, J_1 = 15.7 Hz, J_2 = 1.7 Hz, 1H), 5.87 (ddt, J_1 = 17.2 Hz, J_2 = 10.2 Hz, J_3 = 7.0 Hz, 1H), 5.82 (ddt, J_1 = 16.9 Hz, J_2 = 10.2 Hz, J_3 = 6.7 Hz, 1H), 5.02 (m, 5H), 4.19 (td, J_1 = 4.7 Hz, J_2 = 1.7 Hz, 1H), 3.87 (m, 2H), 2.24 (m, 2H), 2.07 (m, 2H), 1.68 (m, 2H), 1.58 (m, 2H), 1.54 (m, 2H), 1.32 (br s, 6H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 149.8, 139.2, 136.5, 122.8, 117.5, 115.6, 75.5, 75.2, 71.8, 68.8, 43.9, 40.6, 35.4, 34.8, 32.9, 30.9, 26.2, 23.8, 14.5; FTIR (thin film) ν_{max} 3364, 2925, 2857, 1696, 1641, 1271, 1172, 1066, 990 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{20}H_{34}O_5Na$ $[M+Na]^+$: 377.2304, found 377.2276; $[\alpha]_D^{25}$ – 23.0 (*c* 1.20, MeOH).



(4*S*,5*S*,7*S*)-((*S*)-Dec-1-en-5-yl)-4,5,7-trihydroxydeca-2,9-dienoate ((4*S*,5*S*,7*S*,15*S*)-58): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *SSSS*-**56b** (92.4 mg, 99.6 μmol). Flash chromatography of the crude product (1:1 hexanes/EtOAc) gave the title compound as a colorless oil (30.1 mg, 85%): ^{1}H NMR (600 MHz, CD_3OD) δ 7.05 (dd, J_1 = 15.7 Hz, J_2 = 4.6 Hz, 1H), 6.11 (dd, J_1 = 15.7 Hz, J_2 = 1.8 Hz, 1H), 5.87 (ddt, J_1 = 17.2 Hz, J_2 = 10.2 Hz, J_3 = 7.0 Hz 1H), 5.82 (ddt, J_1 = 16.9 Hz, J_2 = 10.2 Hz, J_3 = 6.7 Hz, 1H), 5.00 (m, 5H), 4.22 (td, J_1 = 4.5 Hz, J_2 = 1.8 Hz, 1H), 3.87 (m, 1H), 3.82 (quintet, J = 4.3 Hz, 1H), 2.25 (m, 2H), 2.08 (m, 2H), 1.74 (dt, J_1 = 14.2 Hz, J_2 = 4.4 Hz, 1H), 1.67 (m, 2H), 1.59 (m, 2H), 1.55 (dt, J_1 = 17.2 Hz, J_2 = 8.7 Hz, 1H), 1.32 (br s, 6H), 0.90 (t, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 149.9, 139.2, 136.2, 122.8, 117.7, 115.6, 75.2, 74.7, 73.8, 70.9, 43.1, 39.8, 35.4, 34.8, 32.9, 31.0, 26.2, 23.7, 14.5; FTIR (thin film) ν_{max} 3364, 2925, 2858, 1697, 1274, 1172 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{20}H_{34}O_5Na$ $[M + Na]^+$: 377.2304, found 377.2279; $[\alpha]_D^{25}$ −13.3 (*c* 1.51, MeOH).

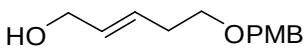


(4*R*,5*R*,7*R*)-((*S*)-Dec-1-en-5-yl)-4,5,7-trihydroxydeca-2,9-dienoate ((4*R*,5*R*,7*R*,15*S*)-58): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *RRRS*-**56c** (90.4 mg, 87.6 μmol). Flash chromatography of the crude product (1:1 hexanes/EtOAc) gave the title compound as a colorless oil (23.8 mg, 77%): ^{1}H NMR (600 MHz, CD_3OD) δ 7.05 (dd, J_1 = 15.7 Hz, J_2 = 4.6 Hz, 1H), 6.11 (dd, J_1 = 15.7 Hz, J_2 = 1.7 Hz, 1H), 5.87 (ddt, J_1 = 17.2 Hz, J_2 = 10.2 Hz, J_3 = 7.1 Hz 1H), 5.82 (ddt, J_1 = 16.9 Hz, J_2 = 10.2 Hz, J_3 = 6.7 Hz, 1H), 5.01 (m, 5H), 4.22 (td, J_1 = 4.4 Hz, J_2 = 1.8 Hz, 1H), 3.87 (m, 1H), 3.82 (quintet, J = 4.4 Hz, 1H), 2.25 (m, 2H), 2.08 (m, 2H), 1.74 (dt, J_1 = 14.1 Hz, J_2 = 4.4 Hz, 1H), 1.68 (m, 2H), 1.59 (m, 2H), 1.54 (dt, J_1 = 14.1 Hz, J_2 = 8.7 Hz, 1H), 1.32 (br s, 6H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 149.9, 139.2, 136.2, 122.8, 117.7, 115.6, 75.2, 74.7, 73.8, 70.9, 43.1, 39.8, 35.4, 34.8, 32.9, 31.0, 26.2, 23.8, 14.5; FTIR (thin film) ν_{max} 3388, 2927, 2859, 1698, 1656, 1270, 1077 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{20}H_{34}O_5Na$ $[M + Na]^+$: 377.2304, found 377.2305; $[\alpha]_D^{25}$ +15.2 (*c* 1.19, MeOH).

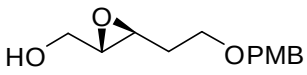


(4*R*,5*R*,7*S*)-((*S*)-Dec-1-en-5-yl)-4,5,7-trihydroxydeca-2,9-dienoate ((4*R*,5*R*,7*S*,15*S*)-58): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *RRSS*-**56d** (106 mg, 93.1 μmol). Flash chromatography of the crude product (1:1 hexanes/EtOAc) gave the title compound as a colorless oil (29.0 mg, 88%): ^{1}H NMR (600 MHz, CD_3OD) δ 7.05 (dd, J_1 = 15.7 Hz, J_2 = 4.7 Hz, 1H), 6.11 (dd, J_1 = 15.7 Hz, J_2 = 1.7 Hz, 1H), 5.87 (ddt, J_1 = 17.2 Hz, J_2 = 10.2 Hz, J_3 = 7.1 Hz 1H), 5.82 (ddt, J_1 = 17.0 Hz, J_2 = 10.2 Hz, J_3 = 6.7 Hz, 1H), 5.00 (m, 5H), 4.19 (td, J_1 = 4.7 Hz, J_2 = 1.7 Hz, 1H), 3.88 (m, 2H), 2.24 (m, 2H), 2.08 (m, 2H), 1.68 (m, 2H), 1.55 (m, 4H), 1.32 (br s, 6H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 149.8, 139.2, 136.5, 122.8, 117.5, 115.6, 75.5, 75.2, 71.8, 68.8, 44.0, 40.6, 35.4, 34.8, 32.9, 31.0, 26.2, 23.8, 14.5; FTIR (thin film) ν_{max} 3344, 2924, 2857, 1695, 1642, 1269, 1172 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{20}H_{34}O_5Na$ $[M + Na]^+$: 377.2304, found 377.2277; $[\alpha]_D^{25} + 33.2$ (*c* 1.45, MeOH).

6.3 EXPERIMENTAL DATA FOR THE FMS OF THE 4,5-*CIS*-DIHYDROXY FAMILY OF SCH725674

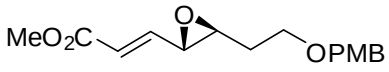


(*E*)-5-(4-Methoxybenzyloxy)pent-2-en-1-ol (60):[93] CAS registry number: [158817-21-1]. DIBAL-H (9.21 mL, 9.21 mmol) was added to a solution of aldehyde **40** in CH_2Cl_2 (40 mL) at −78 °C. The reaction mixture was stirred at this temperature for 4 h and quenched by addition of ethyl acetate (20 mL) at −78 °C. The mixture was then stirred at room temperature for 15 min, and a solution of sat. aq. Rochelle's salt (100 mL) was added at room temperature for 1 h. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic extracts were washed with water (75 mL), brine (75 mL), and then dried over $MgSO_4$. Flash chromatography of the crude product (1:1 hexanes/EtOAc) gave the title compound as a colorless oil (1.49 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 6.8 Hz, 2H), 6.90 (d, *J* = 6.8 Hz, 2H), 5.73 (m, 2H), 4.46 (s, 2H), 4.10 (m, 2H), 3.81 (s, 3H), 3.50 (t, *J* = 6.8 Hz, 1H), 2.37 (m, 2H).



((2*S*,3*S*)-3-(2-(4-Methoxybenzyloxy)ethyl)oxiran-2-yl)methanol (61):[93] CAS registry number: [736140-63-9]. L-(+)-Diisopropyl tartrate (338 μL, 1.60 mmol), Ti(^{i}PrO)$_4$ (403 μL, 1.33 mmol), and *t*-butyl hydroperoxide (3.64 mL, 20.0 mmol) were added to a stirring slurry of molecular sieves (~5 g) in CH_2Cl_2 (35 mL) at -20 °C. The catalyst mixture was allowed to age at this

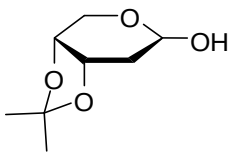
temperature for 30 min prior to the addition of the allylic alcohol **60** (1.48 g, 6.67 mmol) in CH_2Cl_2 (20 mL) by cannula transfer. The resultant reaction mixture was stirred at –20 °C for 20 h and was passed over a pad of Celite. The reaction was quenched by addition to a freshly prepared solution of $FeSO_4$ (~8 g) and citric acid monohydrate (~3.5 g) in 40 mL deionized water. The aqueous solution changed from a bright blue solution to an orange suspension after addition of the reaction mixture. The layers were separated and the aqueous layer extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with water (100 mL), brine (100 mL), and dried over $MgSO_4$. Flash chromatography of the crude product (1:2 hexanes/EtOAc) gave the title compound as a colorless oil (1.10 g, 69%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 6.8 Hz, 2H), 6.89 (d, J = 6.8 Hz, 2H), 4.46 (s, 2H), 3.91 (dq, J_1 = 2.6 Hz, J_2 = 12.5 Hz, 1H), 3.82 (s, 3H), 3.65 (m, 1H), 3.50 (t, J = 6.8 Hz, 1H), 3.11 (ddd, J_1 = 2.3 Hz, J_2 = 4.9 Hz, J_3 = 6.7 Hz, 1H), 2.98 (dt, J_1 = 2.3 Hz, J_2 = 4.3 Hz, 1H), 1.87 (m, 2H), 1.69 (m, 1H), 1.62 (m, 1H).



(*E*)-Methyl-3-((2S,3S)-3-(2-(4-methoxybenzyloxy)ethyl)oxiran-2-yl)acrylate (62): SO_3-pyridine complex (2.63 g, 16.2 mmol) added in one portion to a solution of epoxy alcohol **61** (1.10 g, 4.63 mmol) and NEt_3 (3.23 mL, 23.1 mmol) in 4:1 DCM/DMSO (50 mL) at 0 °C.[94] The reaction mixture was stirred at room temperature for 30 min and then quenched 0 °C by addition of sat. aq. NH_4Cl (40 mL). The suspension was then poured into a separatory funnel. The aqueous layer was then extracted with DCM (3 x 75 mL) and the combined organic extracts were washed with 30% aqueous $CuSO_4$ solution (3 x 100 mL) to remove pyridine. The organic phase was then washed with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, and

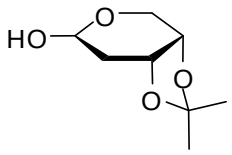
concentrated in vacuo. The crude product was taken to the next step without further purification (1.03 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.03 (d, J = 6.2 Hz, 1H), 7.26 (d, J = 6.8 Hz, 2H), 6.90 (d, J = 6.8 Hz, 2H), 5.84 (m, 1H), 4.47 (s, 2H), 3.82 (s, 3H), 3.61 (m, 2H), 3.41 (m, 1H), 3.22 (dd, J_1 = 1.9 Hz, J_2 = 6.3 Hz, 1H), 1.95 (m, 2H).

The general procedure for the Masamune-Roush olefination[54] was followed with the crude aldhehyde (1.03 g, 4.38 mmol), trimethylphosphonoacetate (773 μL, 5.25 mmol), LiCl (223 mg, 5.25 mmol), and DBU (735 μL, 4.82 mmol) in acetonitrile (42 mL). ^{1}H NMR analysis of the crude product showed a single *E* isomer. Flash chromatogtaphy of the crude product (3:1 hexanes/EtOAc) gave the *E*-isomer as a colorless oil (814 mg, 64% over 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 6.8 Hz, 2H), 6.89 (d, J = 6.8 Hz, 2H), 6.69 (dd, J_1 = 7.1 Hz, J_2 = 15.7 Hz, 1H), 6.13 (d, J = 15.7 Hz, 1H), 4.46 (s, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 3.59 (t, J = 6.2 Hz, 2H), 3.28 (dd, J_1 = 2.0 Hz, J_2 = 7.0 Hz, 1H), 3.04 (m, 1H), 1.91 (m, 2H); HRMS (EI) calcd for $C_{16}H_{20}O_5$ 292.1311, found 292.1298.

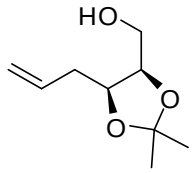


2-Deoxy-3,4-*O*-isopropylidene-D-ribose ((4*R*,5*S*)-63):[98] CAS registry number: [86795-47-3]. *p*-Toluenesulfonic acid (5.61 g, 28.9 mmol) was added to a stirring solution of 2-deoxy-D-ribose (20.0 g, 0.145 mol) and 2-methoxypropene (14.3 mL, 0.145 mol) in *N*,*N*′-dimethylformamide (300 mL) at 0 °C. After stirring at 0 °C for 1 h, another stoichiometric amount of 2-methoxypropene (14.3 mL, 0.145 mmol) was added and the reaction was stirred at 0 °C for another 2 h. The reaction was quenched at 0 °C by addition of saturated aqueous $NaHCO_3$ (~100

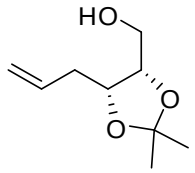
mL) and the resultant suspension was stirred for 1 h at 0 °C. The suspension was then transferred to a separatory funnel and partitioned with diethyl ether (~400 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 300 mL). The combined organic extracts were washed with water (150 mL), brine (150 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography of the crude product (1:1 hexanes/EtOAc) gave the title compound as a colorless oil, isolated as a 4:1 α/β anomeric composition (6.79 g, 27%): ^{1}H NMR (300 MHz, *d*6-DMSO) δ 6.24 (d, J = 5.2 Hz, 1H), 4.94 (dt, J_1 = 7.0 Hz, J_2 = 4.3 Hz, 1H), 4.34 (dt, J_1 = 6.2 Hz, J_2 = 4.4 Hz, 1H), 4.05 (m, 1H), 3.78 (dd, J_1 = 12.6 Hz, J_2 = 3.6 Hz, 1H), 3.46 (dd, J_1 = 12.5 Hz, J_2 = 3.8 Hz, 1H), 1.93 (dt, J_1 = 14.5 Hz, J_2 = 4.2 Hz, 1H), 1.63 (ddd, J_1 = 14.5 Hz, J_2 = 7.1 Hz, J_3 = 4.4 Hz, 1H), 1.36 (s, 3H), 1.24 (s, 3H).



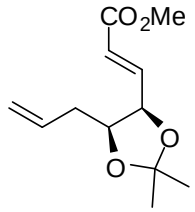
2-Deoxy-3,4-*O*-isopropylidene-L-ribose ((4*S*,5*R*)-63):[98] CAS registry number: [522608-67-9]. The procedure for the preparation of (4*R*,5*S*)-**63** was repeated using 2-deoxy-L-ribose (24.5 g, 0.179 mol), 2-methoxypropene (34.4 mL, 0.350 mol), and *p*-toluenesulfonic acid (6.95 g, 35.8 mmol). Flash chromatography of the crude product (1:1 hexanes/EtOAc) gave the title compound as a colorless oil, isolated as a 4:1 α/β anomeric composition (7.81 g, 25%). The ^{1}H NMR spectrum matched that of (4*R*,5*S*)-**63** (see above); $[\alpha]_D^{25} + 47.3$ (*c* 0.13, water), literature value reported for the D-enantiomer: $[\alpha]_D^{25} - 46.0$ (*c* 0.10, water).



((4*R*,5*S*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)-methanol ((4*R*,5*S*)-64):[97] CAS registry number: [663176-89-4]. Butyllithium (1.6 M in hexanes, 68.2 mL, 0.109 mol) was added dropwise by syringe to a stirred suspension of methyltriphenylphosphonium iodide (48.8 g, 0.117 mol) in THF (450 mL) at −78 °C. The reaction was stirred at −78 °C for 15 min, then warmed to 0 °C and stirred at this temperature for 30 min. A solution of the acetonide (4*R*,5*S*)-**63** (6.79 g, 39.0 mmol) in THF (50 mL) was then transferred to the stirring suspension at −78 °C by cannula (along with a 10 mL THF rinse of the original flask containing the acetonide). The reaction mixture was stirred at −78 °C for 30 min and then warmed to room temperature. After 4 h at room temperature, the reaction was quenched by addition of sat. aq. NH_4Cl (200 mL). The layers were then separated and the aqueous layer was extracted with ether (3 x 300 mL). The combined organic extracts were then washed with water (200 mL), brine (200 mL), dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography of the crude product (2:1 hexanes/EtOAc) gave the title compound as a colorless oil (5.74 g, 85%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddt, J_1 = 17.1 Hz, J_2 = 10.2 Hz, J_3 = 6.7 Hz, 1H), 4.27 (dt, J_1 = 8.2 Hz, J_2 = 6.0 Hz, 1H), 4.19 (quartet, J = 5.8 Hz, 1H), 3.66 (t, J = 5.8 Hz, 1H), 2.42 (m, 1H), 2.30 (m, 1H), 1.89 (t, J = 5.8 Hz, 1H), 1.50 (s, 3H), 1.39 (s, 3H).

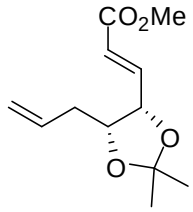


((4*S*,5*R*)-5-Allyl-2,2-dimethyl-1,3-dioxolan-4-yl)methanol ((4*S*,5*R*)-64): The procedure used for the preparation of (4*R*,5*S*)-**64** was employed with acetonide (4*S*,5*R*)-**63** (7.81 g, 44.8 mmol), methyltriphenylphosphonium iodide (59.2 g, 0.144 mol), and butyllithium (1.6 M in hexanes, 81.4 mL, 0.135 mol). Flash chromatography of the crude product gave the title compound as a colorless oil (6.12 g, 79%). The ^{1}H NMR spectrum of (4*S*,5*R*)-**64** matched that of its enantiomer (see above); $[\alpha]_D^{25} -11.6$ (*c* 0.29, $CHCl_3$).



(*E*)-Methyl-3-((4*R*,5*S*)-5-allyl-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate ((4*R*,5*S*)-65): The two-step oxidation-olefination[54, 94] sequence used for **62** was repeated with (4*R*,5*S*)-**64** (5.74 g, 33.3 mmol) using SO_3-pyridine complex (18.9 g, 0.117 mol), NEt_3 (23.9 mL, 0.167 mol) in 4:1 DCM/DMSO (350 mL) at 0 °C. The crude aldehyde product was taken to the next step without further purification (5.29 g, 31.1 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (d, J = 3.5 Hz, 1H), 5.84 (m, 1H), 5.17 (dq, J_1 = 7.1 Hz, J_2 = 1.5 Hz, 1H), 5.13 (t, J = 1.2 Hz, 1H), 4.44 (td, J_1 = 7.5 Hz, J_2 = 5.5 Hz, 1H), 4.32 (dd, J_1 = 7.1 Hz, J_2 = 3.1 Hz, 1H), 2.44-2.25 (m, 2H), 1.61 (s, 3H), 1.43 (s, 3H).

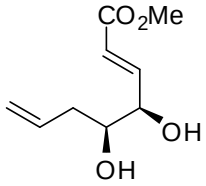
The general procedure for the Masamune-Roush olefination[54] was used with the crude aldhehyde (5.29 g, 31.1 mmol), trimethylphosphonoacetate (5.56 mL, 37.3 mmol), LiCl (1.61 g, 37.3 mmol), and DBU (5.27 mL, 34.2 mmol) in acetonitrile (350 mL). ^{1}H NMR analysis of the crude product showed a 4:1 *E/Z* mixture of geometric isomers. Flash chromatography of the crude product (10:1 hexanes/EtOAc) gave the *E*-isomer as a colorless oil (4.01 g, 57% over 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (dd, J_1 = 15.6 Hz, J_2 = 5.9 Hz, 1H), 6.11 (dd, J_1 = 15.6 Hz, J_2 = 1.4 Hz, 1H), 5.81 (m, 1H), 5.14 (ddd, J_1 = 17.8 Hz, J_2 = 11.0 Hz, J_3 = 6.8 Hz, 2H), 4.71 (td, J_1 = 6.3 Hz, J_2 = 1.3 Hz, 1H), 4.33 (dt, J_1 = 8.2 Hz, J_2 = 6.0 Hz, 1H), 3.77 (s, 3H), 2.24 (m, 2H), 1.54 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 143.7, 133.8, 122.6, 117.7, 109.0, 77.6, 77.1, 51.6, 35.1, 27.9, 25.4; FTIR (thin film) ν_{max} 2987, 2939, 1726, 1380, 1307, 1256, 1217, 1165 cm^{-1}; HRMS calcd (ESI) for $C_{12}H_{18}O_4Na$ $[M + Na]^+$: 249.1103, found 249.1086; $[\alpha]_D^{25}$ −12.8 (*c* 1.26, $CHCl_3$).



(*E*)-Methyl 3-((4*S*,5*R*)-5-allyl-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate ((4*S*,5*R*)-65). The alcohol (4*S*,5*R*)-**64** (6.12 g, 35.5 mmol) was taken through the same two-step oxidation/olefination[54, 94] procedure as reported for (4*R*,5*S*)-**62** using SO_3-pyridine complex (20.2 g, 0.124 mol), NEt_3 (25.0 mL, 0.178 mol) in 4:1 DCM/DMSO (350 mL). The crude aldehyde product was taken to the next olefination step without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (d, *J* = 3.5 Hz, 1H), 5.84 (m, 1H), 5.17 (dq, J_1 = 7.1 Hz, J_2 = 1.5 Hz, 1H), 5.13 (t,

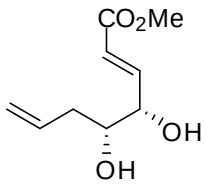
J = 1.2 Hz, 1H), 4.44 (td, J_1 = 7.5 Hz, J_2 = 5.5 Hz, 1H), 4.32 (dd, J_1 = 7.1 Hz, J_2 = 3.1 Hz, 1H), 2.44-2.25 (m, 2H), 1.61 (s, 3H), 1.43 (s, 3H).

The general procedure for the Masamune-Roush olefination[54] was used with the crude aldehyde (4.11 g, 24.1 mmol), trimethylphosphonoacetate (4.27 mL, 29.0 mmol), LiCl (1.25 g, 29.0 mmol), and DBU (4.05 mL, 26.6 mmol) in MeCN (250 mL). ^{1}H NMR analysis of the crude product showed a 4:1 *E/Z* mixture of geometric isomers. Flash chromatogtaphy of the crude product (10:1 hexanes/EtOAc) gave the *E*-isomer (3.40 g, 62% over 2 steps). The ^{1}H NMR spectrum of (4*S*,5*R*)-**65** matched that of its enantiomer (see above); $[\alpha]_D^{25}$ +13.1 (*c* 1.04, $CHCl_3$).

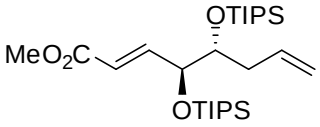


(4*R*,5*S*,*E*)-Methyl-4,5-dihydroxyocta-2,7-dienoate ((4*R*,5*S*)-66): Acetyl chloride (3.82 mL, 52.5 mmol) was added by syringe to a stirring solution of the acetal (4*R*,5*S*)-**65** in MeOH (170 mL) at 0 °C. The reaction was stirred for 15 min at 0 °C, and warmed to room temperature. The reaction was stirred at room temperature for 3 h, and then concentrated *in vacuo*. Flash chromatography of the crude product (1:1 hexanes/EtOAc) gave the title compound as a pale yellow syrup (3.15 g, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (dd, J_1 = 15.8 Hz, J_2 = 4.9 Hz, 1H), 6.16 (dd, J_1 = 15.8 Hz, J_2 = 1.8 Hz, 1H), 5.83 (m, 1H), 5.18 (m, 2H), 4.41 (m, 1H), 3.82 (m, 1H), 3.76 (s, 3H), 2.48 (m, 1H), 2.27 (m, 2H), 2.18 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 145.9, 134.1, 122.0, 118.5, 73.4, 73.0, 51.8, 36.4; FTIR (thin film) ν_{max} 3426, 2953, 1708,

1438, 1281, 1198, 1174 cm^{-1}; HRMS calcd (EI) for $C_9H_{15}O_4$ $[M]^+$: 187.0970, found 187.0964; $[\alpha]_D^{25}$ +16.5 (*c* 1.34, $CHCl_3$).

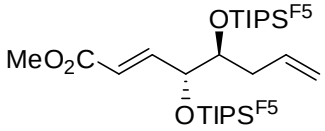


(4*R*,5*S*,*E*)-Methyl-4,5-dihydroxyocta-2,7-dienoate ((4*S*,5*R*)-66): The procedure used for the preparation of (4*R*,5*S*)-**66** was repeated using (4*S*,5*R*)-**65** (3.40 g, 15.0 mmol) with acetyl chloride (3.28 mL, 45.1 mmol) in MeOH (150 mL). Flash chromatography of the crude product (1:1 hexanes/EtOAc) gave the title compound as a pale yellow syrup (2.70 g, 97%). The ^1H NMR spectrum of (4S,5R)-66 matched that of its enantiomer (see above); $[\alpha]_D^{25}$ −16.3 (*c* 1.56, $CHCl_3$).



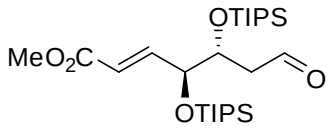
(4*S*,5*R*,*E*)-Methyl 4,5-bis(triisopropylsilyloxy)octa-2,7-dienoate (*SR*-67). The same procedure for the preparation of compound *SS*-**42a** was followed using the diol (4*R*,5*S*)-**66** (2.70 g, 14.5 mmol), TIPSOTf (10.1 mL, 36.2 mmol), and 2,6-lutidine (5.15 mL, 43.5 mL) in DCM (100 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) gave the title compound as a colorless oil (6.74 g, 93%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (dd, J_1 = 15.8 Hz, J_2 = 6.6 Hz, 1H), 5.96 (dd, J_1 = 15.8 Hz, J_2 = 1.2 Hz, 1H), 5.80 (m, 1H), 5.10 (ddd, J_1 = 16.8

Hz, J_2 = 10.7 Hz, J_3 = 7.7 Hz, 2H), 4.39 (dq, J_1 = 6.6 Hz, J_2 = 1.3 Hz, 1H), 4.01 (ddd, J_1 = 7.9 Hz, J_2 = 5.1 Hz, J_3 = 2.5 Hz, 1H), 3.76 (s, 3H), 2.35 (m, 2H), 1.07 (br s, 42H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 148.5, 134.4, 121.5, 117.8, 77.0, 75.5, 51.5, 39.2, 18.2 (br s), 12.7 (br s); FTIR (thin film) ν_{max} 2944, 2893, 2867, 1731, 1464, 1271, 1244, 1166, 1119, 1064 cm^{-1}; HRMS calcd (ESI) for $C_{27}H_{54}O_4Si_2Na$ $[M + Na]^+$: 521.3458, found 521.3481; $[\alpha]_D^{25}$ −12.4 (*c* 1.44, $CHCl_3$).

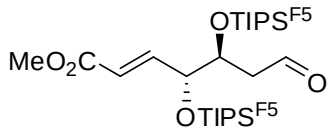


(4*R*,5*S*,*E*)-Methyl-4,5-bis(Diisopropyl-(3,3,4,4,4-pentafluorobutyl)silyloxy)octa-2,7-dienoate (*RS*-67). The general procedure for fluorous tagging[105] was followed using the diol (4*R*,5*S*)-**66** (3.08 g, 16.5 mmol), (3,3,4,4,4-pentafluorobutyl)diisopropylsilane (12.3 g, 45.6 mmol), CF_3SO_3H (3.85 mL, 42.9 mmol), and 2,6-lutidine (5.87 mL, 49.5 mmol) in DCM (100 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) afforded the title compound as a colorless oil (10.5 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (dd, J_1 = 15.8 Hz, J_2 = 6.7 Hz, 1H), 5.96 (dd, J_1 = 15.8 Hz, J_2 = 1.0 Hz, 1H), 5.76 (m, 1H), 5.12 (ddd, J_1 = 16.4 Hz, J_2 = 10.9 Hz, J_3 = 5.4 Hz, 2H), 4.30 (dd, J_1 = 6.7 Hz, J_2 = 1.8 Hz, 1H), 3.89 (m, 1H), 3.76 (s, 3H), 2.29 (m, 2H), 2.05 (m, 4H), 1.04 (br s, 28H), 0.85 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 146.6, 133.7, 122.6, 118.5, 76.8, 75.5, 51.7, 38.7, 25.2 (m), 18.8, 17.6, 17.5 (br s), 17.4, 13.4, 12.9, 12.8, 12.7, 12.6, 10.4, 1.0, 0.9; ^{19}F NMR (282 MHz, $CDCl_3$) −85.01 (s, 3F), −85.06 (s, 3F), −120.46 (m, 4F); FTIR (thin film) ν_{max} 2948, 2870, 1732, 1464, 1440, 1381, 1333, 1276, 1244,

1198, 1107 cm^{-1}; HRMS calcd (ESI) for $C_{29}H_{48}O_4F_{10}Si_2Na$ [M + Na]$^+$: 729.2829, found 729.2823; $[\alpha]_D^{25}$ −1.25 (*c* 1.14, $CHCl_3$).

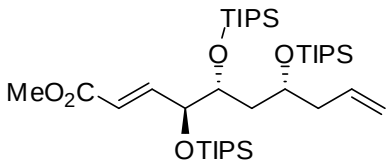


(4*S*,5*R*,*E*)-Methyl-7-oxo-4,5-bis(triisopropylsilyloxy)hept-2-enoate (*SR*-43). The same method employed for the preparation of *RS*-**43** (see below) was followed using 2,6-lutidine (3.17 mL, 26.8 mmol), OsO_4 (2.5 wt. %, 3.36 mL, 0.27 mmol), $NaIO_4$ (11.6 g, 53.6 mmol), and the alkene *SR*-**67** (6.68 g, 13.4 mmol) in 3:1 dioxane/water (120 mL) at room temperature. Flash chromatography of the crude product (10:1 hexanes/EtOAc) gave the title compound as a pale brown oil (5.32 g, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.91 (m, 1H), 6.90 (dd, J_1 = 15.8 Hz, J_2 = 6.4 Hz, 1H), 6.10 (dd, J_1 = 15.8 Hz, J_2 = 1.3 Hz, 1H), 4.56 (dd, J_1 = 6.3 Hz, J_2 = 1.4 Hz, 1H), 4.31 (m, 1H), 3.76 (s, 3H), 2.63 (m, 2H), 1.09 (broad s, 42H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.9, 166.3, 147.9, 122.3, 77.3, 72.5, 51.7, 46.7, 18.1 (br s), 12.5 (br s); FTIR (thin film) ν_{max} 2945, 2892, 2867, 1728, 1463, 1274, 1243, 1166, 1131 cm^{-1}; HRMS calcd (ESI) for $C_{26}H_{52}O_5Si_2Na$ [M + Na]$^+$: 523.3251, found 523.3285; $[\alpha]_D^{25}$ +0.13 (*c* 1.26, $CHCl_3$).



(4*R*,5*S*,2*E*)-Methyl-4,5-bis(diisopropyl(3,3,4,4,4-pentafluorobutyl)silyloxy)-7-oxohept-2-enoate (*RS*-43): 2,6-lutidine (1.60 mL, 13.5 mmol), OsO_4 (2.5 wt. %, 1.70 mL, 0.135 mmol),

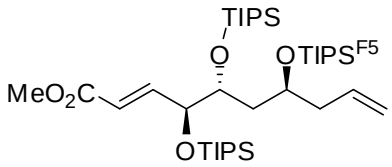
and $NaIO_4$ (5.96 g, 27.1 mmol) were sequentially added to a solution of the alkene *RS*-**67** (4.78 g, 6.76 mmol) in 3:1 dioxane/water (80 mL) at room temperature. The resultant suspension was stirred for 4 h at room temperature, and then water (100 mL) and DCM (200 mL) were added. The bilayer was then transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with DCM (3 x 100 mL) and the combined organic extracts were then washed with water (100 mL), brine (100 mL), dried over $MgSO_4$, and then concentrated in vacuo. Flash chromatography of the crude product (10:1 hexanes/EtOAc) gave the title compound as a pale brown oil (3.27 g, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.82 (m, 1H), 6.85 (dd, J_1 = 15.8 Hz, J_2 = 6.5 Hz, 1H), 5.99 (d, J = 15.8 Hz, 1H), 4.36 (m, 2H), 3.76 (s, 3H), 2.67 (m, 2H), 2.05 (m, 4H), 1.10 (broad s, 28H), 0.85 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.5, 165.9, 146.1, 123.2, 76.8, 71.8, 51.7, 47.3, 25.1 (m), 17.4 (br s), 12.6 (br s), 0.9, 0.8; ^{19}F NMR (282 MHz, $CDCl_3$) –84.96 (s, 3F), –85.00 (s, 3F), –120.29 (t, $^3J_{HF}$ = 17.5 Hz, 2F), –120.39 (t, $^3J_{HF}$ = 17.5 Hz, 2F); FTIR (thin film) ν_{max} 2948, 2870, 1729, 1196, 991 cm^{-1}; HRMS calcd (ESI) for $C_{28}H_{46}O_5Si_2F_{10}K$ $[M + K]^+$: 747.2361, found 747.2334; $[\alpha]_D^{25}$ – 3.00 (*c* 1.06, $CHCl_3$).



(4*S*,5*R*,7*R*,)-Methyl-4,5,7-tris(triisopropylsilyloxy)deca-2,9-dienoate (*SRR*-46e): The *in situ* preparation[79] of the Brown reagent used for preparation of *RRS*-**46d** was repeated with allylmagnesium bromide (9.92 mL, 9.92 mmol), (+)-DIP-Cl (3.55 g, 10.5 mmol), and aldehyde *SR*-**43** (1.51 g, 3.01 mmol) in Et_2O (25 mL) at –78 °C. Flash chromatography of the crude product (10:1 hexanes/EtOAc) gave the untagged homoallylic alcohol as an inseparable mixture

of diastereomers (~6:1 *d.r.*) along with 3-pinanol by-product. This mixture was taken to the next tagging step without further purification.

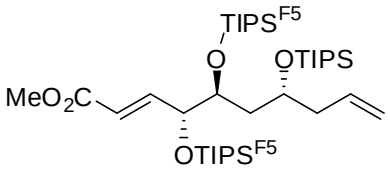
The same silylation procedure used to obtain *SS*-**42a** was used for the inseparable mixture of diastereomers using TIPSOTf (0.90 mL, 3.26 mmol) and 2,6-lutidine (0.52 mL, 4.34 mmol) in DCM (30 mL). Flash chromatography of the crude product gave the title compound as an inseparable mixture of diastereomers (1.04 g, 8:1 *d.r.*, 54% over 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (dd, J_1 = 15.8 Hz, J_2 = 6.3 Hz, 1H), 5.95 (d, J = 15.8 Hz, 1H), 5.82 (m, 1H), 5.04 (dd, J_1 = 17.2 Hz, J_2 = 10.1 Hz, J_2 = 9.6 Hz, 2H), 4.48 (d, J = 6.5 Hz, 1H), 4.10 (t, J = 6.5 Hz, 1H), 4.02 (quintet, J = 4.9 Hz, 1H), 3.75 (s, 3H), 2.30 (m, 2H), 1.75 (m, 2H), 1.07 (broad s, 63H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 148.7, 134.4, 121.4, 117.4, 74.2, 69.2, 51.6, 41.7, 40.8, 18.3 (br s), 12.7 (br s); FTIR (thin film) ν_{max} 2945, 2868, 1733, 1465, 1062, 996 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{38}H_{78}O_5Si_3Na$ $[M + Na]^+$: 721.5055, found 721.5110; $[\alpha]_D^{25} -5.10$ (c 1.93, $CHCl_3$).



(4*S*,5*R*,7*S*,2*E*)-Methyl-7-(di-isopropyl-(3,3,4,4,4-penta-fluoro-butyl)-silyloxy)-4,5-bis(triiso-propyl-silyloxy)deca-2,9-dienoate (*SRS*-46f). The *in situ* preparation[79] of the Brown reagent used for *RRS*-**46d** was repeated with aldehyde *SR*-**43** (1.29 g, 3.01 mmol), (–)-DIP-Cl (3.04 g, 8.99 mmol), and allylmagnesium bromide (8.48 mL, 8.48 mmol) in Et_2O (25 mL). Flash chromatography of the crude product (10:1 hexanes/EtOAc) gave the untagged homoallylic

alcohol as an inseparable mixture of diastereomers (~6:1 *d.r.*) along with 3-pinanol by-product. This mixture was taken to the next tagging step without further purification.

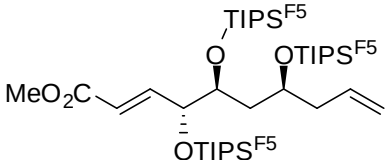
The general procedure for fluorous tagging[105] was used for the inseparable mixture of diastereomers with (3,3,4,4,4-pentafluorobutyl)diisopropylsilane (1.17 g, 4.45 mmol), triflic acid (0.36 mL, 3.92 mmol), and 2,6-lutidine (0.64 mL, 5.34 mmol) in DCM (40 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) gave the title compound as an inseparable mixture of diastereomers (1.27 g, 6:1 *d.r.*, 61% over 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (dd, J_1 = 15.8 Hz, J_2 = 6.4 Hz, 1H), 5.97 (d, J = 15.8 Hz, 1H), 5.80 (m, 1H), 5.07 (ddd, J_1 = 16.7 Hz, J_2 = 10.5 Hz, J_3 = 6.2 Hz, 2H), 4.38 (d, J = 6.5 Hz, 1H), 4.03 (t, J = 6.5 Hz), 3.87 (quintet, J = 5.6 Hz), 3.76 (s, 3H), 2.25 (m, 2H), 2.05 (m, 2H), 1.76 (m, 2H), 1.08 (broad s, 56H), 0.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 148.0, 134.2, 121.7, 117.7, 76.7, 74.3, 69.7, 51.6, 42.4, 41.7, 25.4 (m), 18.1 (br s), 13.2 (br s), 0.9; ^{19}F NMR (282 MHz, $CDCl_3$) –84.97 (s, 3F), –120.35 (t, $^{3}J_{HF}$ = 17.7 Hz, 2F); FTIR (thin film) ν_{max} 2947, 2869, 1733, 1466, 1201, 1168, 1096, 1060, 994 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{39}H_{75}O_5F_5Si_3Na$ [M + Na]$^{+}$: 825.4740, found 825.4711; $[\alpha]_D^{25}$ – 6.41, (*c* 1.57, $CHCl_3$).



(4*R*,5*S*,7*S*)-Methyl-4,5-bis-(di-iso-propyl-(3,3,4,4,4-penta-fluoro-butyl)-silyl-oxy)-7-(tri-iso-propyl-silyl-oxy)deca-2,9-dienoate (*RSR*-46g). The *in situ* preparation[79] of the Brown reagent used for *RRS*-**46d** was repeated with aldehyde *RS*-**43** (1.17 g, 1.65 mmol), (+)-DIP-Cl (1.95 g,

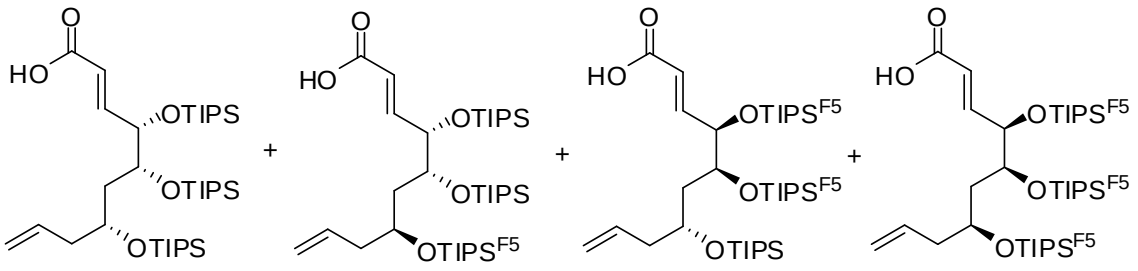
5.77 mmol), and allylmagnesium bromide (5.44 mL, 5.44 mmol) in Et_2O (30 mL). Flash chromatography of the crude product (10:1 hexanes/EtOAc) gave the untagged homoallylic alcohol as an inseparable mixture of diastereomers (~6:1 *d.r.*) along with 3-pinanol by-product.

This mixture was taken to the next tagging step using TIPSOTf (0.813 mL, 2.95 mmol), 2,6-lutidine (0.40 mL) in DCM (15 mL) in the same manner reported for *SS*-**42a**. Flash chromatography of the crude product (40:1 hexanes/EtOAc) gave the title compound as an inseparable mixture of diastereomers (977 mg, 4:1 *d.r.*, 65% over 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (dd, J_1 = 15.8 Hz, J_2 = 6.7 Hz, 1H), 5.97 (dd, J_1 = 15.8 Hz, J_2 = 1.1 Hz, 1H), 5.85 (m, 1H), 5.08 (ddd, J_1 = 17.1 Hz, J_2 = 10.3 Hz, J_3 = 8.7 Hz, 2H), 4.27 (d, J = 6.5 Hz, 1H), 4.01 (td, J_1 = 6.5 Hz, J_2 = 1.9 Hz, 1H), 3.91 (quintet, J = 6.5 Hz, 1H), 3.76 (s, 3H), 2.29 (m, 2H), 2.05 (m, 4H), 1.67 (t, J = 6.7 Hz, 1H), 1.06 (broad s, 49H), 0.86 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 146.2, 134.0, 122.7, 121.3, 117.7, 117.5, 74.4, 68.9, 51.7, 41.9, 25.4 (m), 17.6 (br s), 12.9 (br s), 1.3, 0.9; ^{19}F NMR (282 MHz, $CDCl_3$) δ –85.01 (s, 3F), –85.04 (s, 3F), –120.47 (m, 4F); FTIR (thin film) ν_{max} 2948, 2870, 1734, 1200, 1104, 1061, 993 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{40}H_{72}O_5F_{10}Si_3Na$ $[M + Na]^+$: 929.4426, found 929.4446; $[\alpha]_D^{25} -3.88$ (*c* 1.04, $CHCl_3$).

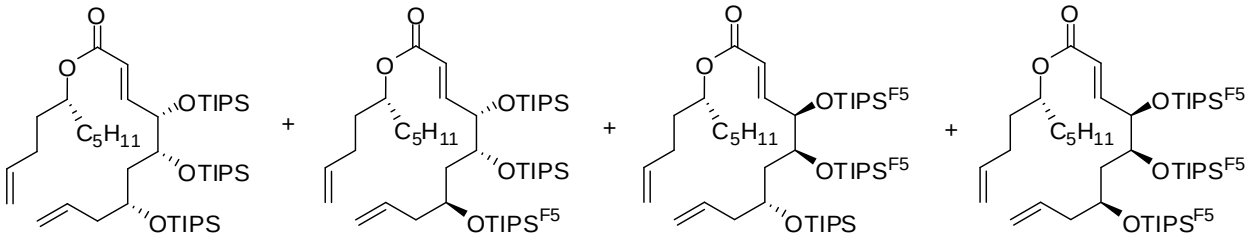


(4*R*,5*S*,7*S*,*E*)-Methyl-4,5,7-tris-(di-isopropyl-(3,3,4,4,4-pentafluorobutyl)-silyloxy)-deca-2,9-dienoate (*RSS*-46g). The *in situ* preparation[79] of the Brown allylborane used for the preparation of *RRS*-**46d** was followed using the aldehyde *RS*-**43** (1.02 g, 1.65 mmol), (–)-DIP-Cl (1.95 g,

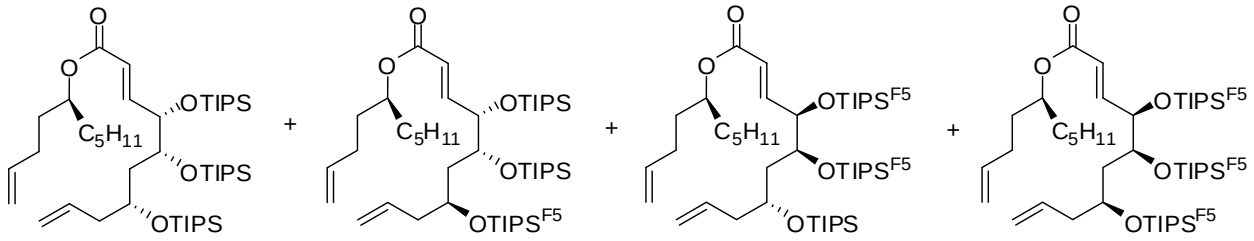
5.77 mmol), and allylmagnesium bromide (5.40 mL, 5.40 mmol) in Et_2O (30 mL). Flash chromatography of the crude product (10:1 hexanes/EtOAc) gave the untagged homoallylic alcohol as an inseparable mixture of diastereomers (~6:1 *d.r.*) along with 3-pinanol by-product. This mixture was taken to the next tagging step using the general procedure for fluorous tagging[105] with (3,3,4,4,4-pentafluorobutyl)diisopropylsilane (0.861 g, 3.28 mmol), CF_3SO_3H (0.27 mL, 3.02 mmol), and 2,6-lutidine (0.47 mL, 3.94 mmol) in DCM (13 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) gave the title compound as an inseparable mixture of diastereomers (1.17 g, 8:1 *d.r.*, 80% over 2 steps): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (dd, J_1 = 15.8 Hz, J_2 = 6.5 Hz, 1H), 5.94 (d, J = 15.8 Hz, 1H), 5.76 (m, 1H), 5.07 (ddd, J_1 = 15.9 Hz, J_2 = 10.8 Hz J_3 = 9.0 Hz, 2H), 4.34 (d, J = 6.6 Hz, 1H), 4.02 (m, 1H), 3.95 (m, 1H), 3.77 (s, 3H), 2.27 (m, 2H), 2.05 (m, 6H), 1.68 (m, 2H), 1.05 (broad s, 42H), 0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 146.4, 133.5, 122.6, 118.1, 76.9, 74.0, 69.4, 51.7, 41.5, 40.9, 25.4 (m), 17.5 (br s), 13.0 (br s), 1.2, 0.9, 0.8; ^{19}F NMR (282 MHz, $CDCl_3$) –84.97 (s, 3F), –84.99 (s, 3F), –85.03 (s, 3F), –120.45 (m, 6F); FTIR (thin film) ν_{max} 2949, 2870, 1733, 1198, 1066, 993, 886 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{41}H_{69}O_5F_{15}Si_3Na$ [M + Na]$^+$: 1,033.4111, found 1,033.4084; $[\alpha]_D^{25} -5.26$ (*c* 1.02, $CHCl_3$).



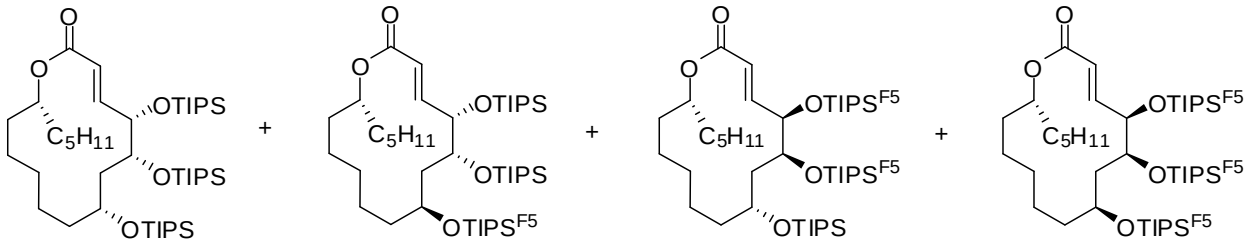
(4*S*,5*R*,7*R*,*E*)-4,5,7-Tris-(tri-iso-propyl-silyl-oxy)deca-2,9-dienoic acid, (4*S*,5*R*,7*S*,*E*)-4,5-Bis-(triiso-propylsilyloxy)-7-((1,1,1,2,2)-penta-fluorobutyldiisopropyl-silyloxy)-deca-2,9-dienoic acid, (4*R*,5*S*,7*R*,*E*)-4,5-Bis((1,1,1,2,2)-penta-fluoro-butyl-(di-isopropyl-silyl-oxy))-7-(triiso-propyl-silyloxy)-deca-2,9-dienoic acid, (4*R*,5*S*,7*S*,*E*)-4,5,7-Tris((1,1,1,2,2)-pentafluorobutyl-(diisopropylsilyloxy))deca-2,9-dienoic acid (M-55efgh). The same procedure employed for compound **43** was repeated using *SRR*-**46e** (300 mg, 0.43 mmol), *SRS*-**46f** (345 mg, 0.43 mmol), *RSR*-**46g** (389 mg, 0.43 mmol), *RSS*-**46h** (434 mg, 0.43 mmol), and TMSOK (3.61 g, 25.36 mmol) in Et_2O (17.0 mL). Flash chromatography of the crude product (3:1 hexanes/EtOAc) gave the title compound as a colorless oil (1.14 g, 80% based on average molecular weight): LRMS (ESI, positive mode) (*SRR*-**55e**) *m/z* 708 $(M + Na)^+$; (*SRS*-**55f**) *m/z* 811 $(M + Na)^+$; (*RSR*-**55g**) *m/z* 915 $(M + Na)^+$; (*RSS*-**55h**) *m/z* 1019 $(M + Na)^+$; fluorous analytical HPLC (90:10 MeCN/H_2O for 10 min, then 100% MeCN for 60 min, 1.0 mL/min): t_R = 15.0 min (*SRR*-**55e**), 18.5 min (*SRS*-**55f**), 20.9 min (*RSR*-**55g**), 24.0 min (*RSS*-**55h**).



(4*S*,5*R*,7*R*)-((*R*)-Dec-1-en-5-yl)-4,5,7-tris(triisopropylsilyloxy)deca-2,9-dienoate, (4*S*,5*R*,7*S*)-((*R*)-Dec-1-en-5-yl)-4,5-bis(triisopropylsilyloxy)-7-diisopropyl-(1,1,1,2,2-penta-fluoro-butyl-silyloxy)deca-2,9-dienoate, (4*R*,5*S*,7*R*)-((*R*)-Dec-1-en-5-yl)-4,5-bis-(di-iso-propyl-(1,1,1,2,2-pentafluorobutylsilyloxy))-7-tri-isopropyl-silyl-oxy-deca-2,9-dienoate, (4*R*,5*S*,7*S*)-((*R*)-Dec-1-en-5-yl)-4,5,7-tris(diisopropyl(1,1,1,2,2-pentafluorobutylsilyloxy))-deca-2,9-dienoate ((*R*)-M-56efgh): The same method employed in the preparation of **49** was repeated using mixture M-**55efgh** (548 mg, 652 μmol based on average molecular weight), alcohol (*R*)-**18** (132 mg, 847 μmol), NEt_3 (186 μL), DMAP (163 mg, 1.30 mmol), and 2,4,6-trichlorobenzoyl chloride (110 μL, 684 μmol) in toluene (13.0 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) gave the title compound as a colorless oil (577 mg, 90% based on average molecular weight): LRMS (ESI, positive mode) (*SRRR*-**56e**) *m/z* 846 $(M + Na)^+$; (*SRSR*-**56f**) *m/z* 950 $(M + Na)^+$; (*RSRR*-**56g**) *m/z* 1054 $(M + Na)^+$; **(***RSSR*-**56h**) *m/z* 1158 $(M + Na)^+$; fluorous analytical HPLC (90:10 MeCN/H_2O for 10 min, then 100% MeCN for 60 min, 1.0 mL/min): t_R = 17.8 min (*SRRR*-**56e**), 21.4 min (*SRSR*-**56f**), 24.7 min (*RSRR*-**56g**), 30.3 min (*RSSR*-**56h**).



(4*S*,5*R*,7*R*)-((*S*)-Dec-1-en-5-yl)-4,5,7-tris(triisopropylsilyloxy)deca-2,9-dienoate, (4*S*,5*R*,7*S*)-((*S*)-Dec-1-en-5-yl)-4,5-bis(triisopropylsilyloxy)-7-di-isopropyl-(1,1,1,2,2-penta-fluorobutyl-silyloxy)deca-2,9-dienoate, (4*R*,5*S*,7*R*)-((*S*)-Dec-1-en-5-yl)-4,5-bis-(di-iso-propyl-(1,1,1,2,2-penta-fluorobutylsilyloxy))-7-triisopropylsilyloxy-deca-2,9-dienoate, (4*R*,5*S*,7*S*)-((*S*)-Dec-1-en-5-yl)-4,5,7-tris(diisopropyl(1,1,1,2,2-pentafluorobutylsilyloxy))-deca-2,9-dienoate ((*S*)-M-56efgh): The same method employed in the preparation of **49** was repeated using mixture M-**55efgh** (584 mg, 694 μmol based on average molecular weight), alcohol (*S*)-**18** (141 mg, 902 μmol), NEt_3 (197 μL), DMAP (173 mg, 1.39 mmol), and 2,4,6-trichlorobenzoyl chloride (117 μL, 729 μmol) in toluene (14.0 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) gave the title compound as a colorless oil (607 mg, 89% based on average molecular weight): LRMS (ESI, positive mode) (*SRRS*-**56e**) *m/z* 846 $(M + Na)^+$; (*SRSS*-**56f**) *m/z* 950 $(M + Na)^+$; (*RSRS*-**56g**) *m/z* 1054 $(M + Na)^+$; (*RSSS*-**56h**) *m/z* 1158 $(M + Na)^+$; fluorous analytical HPLC (90:10 MeCN/H_2O for 10 min, then 100% MeCN for 60 min, 1.0 mL/min): t_R = 17.7 min (*SRRS*-**56e**), 21.4 min (*SRSS*-**56f**), 24.9 min (*RSRS*-**56g**), 30.9 min (*RSSS*-**56h**).

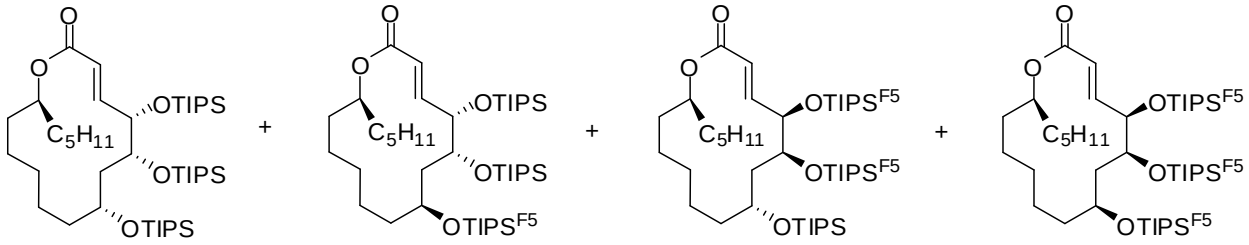


(4*S*,5*R*,7*R*,13*R*)-14-Pentyl-5,6,8-tris-(tri-iso-propyl-silyl-oxy)-oxa-cyclo-tetra-dec-2-enone, (4*S*,5*R*,7*S*,13*R*)-13-Pentyl-4,5-bis(triisopropylsilyloxy)-7-diisopropyl-(1,1,1,2,2-penta-fluoro-butyl-silyl-oxy)oxa-cyclo-tetra-dec-2-enone, (4*R*,5*S*,7*R*,13*R*)-13-Pentyl-4,5-bis-(di-isopropyl-(1,1,1,2,2-pentafluoro-butyl-silyloxy)-7-tri-iso-propyl-silyl-oxy)-oxacyclo-tetra-dec-2-enone, (4*R*,5*S*,7*S*,13*R*)-13-Pentyl-4,5,7-tris-(di-isopropyl-(1,1,1,2,2-pentafluoro-butyl-silyloxy)-oxa-cyclotetradec-2-enone ((*R*)-M-57efgh): The procedure for the ring-closing metathesis as executed for preparation of compound **51** was repeated for mixture (*R*)-M-**56efgh** (577 mg, 589 μmol based on average molecular weight) using the 2nd generation Grubbs catalyst (103 mg, 118 μmol) in DCM (200 mL). Two successive rounds of flash chromatography (40:1 hexanes/EtOAc) gave the title compound as a pale brown oil (541 mg, 569 μmol). The ring-closed product (528 mg, 555 μmol) was then directly subjected to the partial reduction procedures as reported for the preparation of compound **52** using $Pd/SrCO_3$ (2.95 g, 555 μmol) in EtOH (27 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) gave the title compound as a colorless oil (463 mg, 84% over two steps, based on average molecular weight): LRMS (ESI, positive mode) (*SRRR*-**57e**) *m/z* 820 $(M + Na)^+$; (*SRSR*-**57f**) *m/z* 924 $(M + Na)^+$; (*RSRR*-**57g**) *m/z* 1028 $(M + Na)^+$; (*RSSR*-**57h**) *m/z* 1132 $(M + Na)^+$; HRMS (ESI, positive mode): calcd for $C_{45}H_{92}O_5Si_3Na$ $[M + Na]^+$ 819.6150, found 819.6223 for *SRRR*-**57e**; calcd for $C_{46}H_{89}O_5F_5Si_3Na$ $[M + Na]^+$ 923.5836, found 923.5826 for *SRSR*-**57f**; calcd for

$C_{47}H_{86}O_5F_{10}Si_3Na$ $[M + Na]^+$ 1,027.5521, found 1,027.5491 for *RSRR*-**57g**; calcd for $C_{48}H_{83}O_5F_{15}Si_3Na$ $[M + Na]^+$ 1,131.5207, found 1,131.5283 for *RSSR*-**57h**; fluorous analytical HPLC (90:10 MeCN/H_2O for 10 min, then 100% MeCN for 60 min, 1.0 mL/min): t_R = 15.0 min (*SRRR*-**57e**), 18.0 min (*SRSR*-**57f**), 22.8 min (*RSRR*-**57g**), 28.4 min (*RSSR*-**57h**).

Demixing of (*R*)-M-**57efgh**:

The semi-preparative separation of (*R*)-M-**57efgh** was carried out in the same manner as (*R*)-M-**56abcd** (see Section 6.2). Aliquots of (*R*)-M-**56efgh** (90 mg/mL) were injected per chromatographic run. The yield of the demixing over five injections was 69% and the following four compounds were isolated: *SRRR*-**57e**: 59.2 mg, t_R = 29.2 min; *SRSR*-**57f**: 94.1 mg, t_R = 39.4 min; *RSRR*-**57g**: 114 mg, t_R = 58.9 min; *RSSR*-**57h**: 41.5 mg, t_R = 78.4 min.

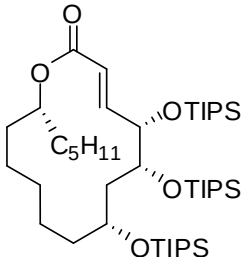


(4*S*,5*R*,7*R*,13*R*,*E*)-14-Pentyl-5,6,8-tris-(tri-isopropyl-silyloxy)oxacyclo-tetra-dec-3-en-2-one, (4*S*,5*R*,7*S*,13*R*,*E*)-13-Pentyl-4,5-bis-(tri-isopropyl-silyloxy)-7-di-iso-propyl-(1,1,1,2,2-penta-fluoro-butyl-silyloxy)-oxacyclo-tetra-dec-2-enone, (4*R*,5*S*,7*R*,13*R*,*E*)-13-Pentyl-4,5-bis-(di-isopropyl(1,1,1,2,2-pentafluoro-butyl-silyloxy)-7-tri-isopropyl-silyloxy)oxacyclo-tetradec-2-enone, (4*R*,5*S*,7*S*,13*R*,*E*)-13-Pentyl-4,5,7-tris-(di-iso-propyl-(1,1,1,2,2-penta-fluoro-butyl-silyloxy)-oxacyclotetradec-2-enone ((*S*)-M-57efgh): The procedure for the ring-closing metathesis as executed for compound **51** was repeated for mixture (*S*)-M-**56efgh** (607 mg, 620 μmol based on average molecular weight) using the 2nd generation Grubbs catalyst (109 mg, 124

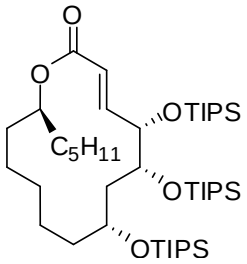
μmol) in DCM (200 mL). Two successive rounds of flash chromatography (40:1 hexanes/EtOAc) gave the title compound as a pale brown oil (584 mg, 614 μmol). The ring-closed product (572 mg, 601 μmol) was then directly subjected to the partial reduction procedures as reported for the preparation of compound **52** using $Pd/SrCO_3$ (3.20 g, 601 μmol) in EtOH (30 mL). Flash chromatography of the crude product (40:1 hexanes/EtOAc) gave the title compound as a colorless oil (547 mg, 94% over two steps, based on average molecular weight): LRMS (ESI, positive mode) (*SRRS*-**57e**) *m/z* 820 $(M + Na)^+$; (*SRSS*-**57f**) *m/z* 924 $(M + Na)^+$; (*RSRS*-**57g**) *m/z* 1028 $(M + Na)^+$; (*RSSS*-**57h**) *m/z* 1132 $(M + Na)^+$; HRMS (ESI, positive mode): calcd for $C_{45}H_{92}O_5Si_3Na$ $[M]^+$ 796.6253, found 796.6250 for *SRRS*-**57e**; calcd for $C_{46}H_{89}O_5F_5Si_3Na$ $[M + Na]^+$ 923.5836, found 923.5859 for *SRSS*-**57f**; calcd for $C_{47}H_{86}O_5F_{10}Si_3Na$ $[M + Na]^+$ 1,027.5521, found 1,027.5510 for *RSRS*-**57g**; calcd for $C_{48}H_{83}O_5F_{15}Si_3Na$ $[M + Na]^+$ 1,131.5207, found 1,131.5223 for *RSSS*-**57h**; fluorous analytical HPLC (90:10 MeCN/H_2O for 10 min, then 100% MeCN for 60 min, 1.0 mL/min): t_R = 15.7 min (*SRRS*-**57e**), 19.8 min (*SRSS*-**57f**), 21.0 min (*RSRS*-**57g**), 27.0 min (*RSSS*-**57h)**.

Demixing of (*S*)-M-**57efgh**:

The semi-preparative separation of (*S*)-M-**57efgh** was carried out in the same manner as (*R*)-M-**56abcd** (see Section 6.2). Aliquots of (*S*)-M-**57efgh** (50 mg/mL) were injected per chromatographic run. The yield of the demixing over ten injections was 56% and the following four compounds were isolated: *SRRS*-**57e**: 73.4 mg, t_R = 30.2 min; *SRSS*-**57f**: 52.0 mg, t_R = 42.8 min; *RSRS*-**57g**: 60.3 mg, t_R = 42.1 min; *RSSS*-**57h**: 65.8 mg, t_R = 70.9 min. Four additional injections were needed for compound *RSRS*-**57g** to improve its quasiisomeric purity.

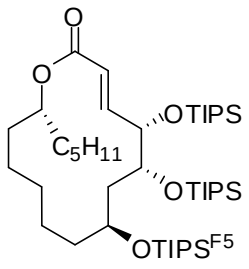


(4*S*,5*R*,7*R*,13*R*,*E*)-14-Pentyl-5,6,8-tris-(tri-iso-propyl-silyl-oxy)oxa-cyclo-tetra-dec-2-en-one (*SRRR*-57e): From the demixing of (*R*)-M-**57efgh**, the first peak *SRRR*-**57e** (59.2 mg) at 29.2 minutes was isolated as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.86 (dd, J_1 = 15.8 Hz, J_2 = 3.0 Hz, 1H), 6.00 (d, J = 15.8 Hz, 1H), 4.98 (m, 1H), 4.24 (m, 1H), 3.91 (d, J = 9.0 Hz, 1H), 3.73 (d, J = 9.0 Hz, 1H), 2.36 (td, J_1 = 12.6 Hz, J_2 = 8.4 Hz, 1H), 2.05 (t, J = 12.1 Hz, 1H), 1.95 (m, 1H), 1.89 (m, 1H), 1.78-1.58 (m, 5H), 1.57-1.43 (m, 5H), 1.40-1.22 (m, 6H), 1.10 (br s, 63H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 148.5, 128.4, 77.3, 74.5, 72.3, 68.7, 36.8, 34.6, 32.5, 32.3, 32.1, 31.8, 31.6, 30.6, 30.3, 22.6 (br s), 18.4 (br s), 14.1; FTIR (thin film) ν_{max} 2944, 2867, 1731, 1464, 1255, 1200, 1106, 1059, 998, 883 cm^{-1}; HRMS calcd (ESI) for $C_{45}H_{92}O_5Si_3Na$ $[M + Na]^+$: 819.6150, found 819.6223; $[\alpha]_D^{25}$ −1.36 (*c* 1.26, $CHCl_3$).



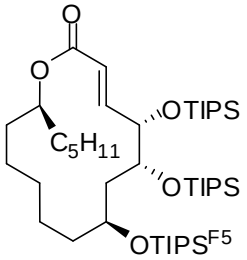
(4*S*,5*R*,7*R*,13*S*,*E*)-14-Pentyl-5,6,8-tris(triisopropylsilyloxy)oxacyclotetradec-2-enone (*SRRS*-57e): From the demixing of (*S*)-M-**57efgh**, the first peak *SRRS*-**57e** (73.4 mg) at 30.2 minutes

was isolated as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.95 (dd, J_1 = 16.0 Hz, J_2 = 8.2 Hz, 1H), 5.84 (dd, J_1 = 16.0 Hz, J_2 = 4.7 Hz, 1H), 4.91 (m, 1H), 4.57 (d, J = 8.2 Hz, 1H), 4.09 (m, 1H), 3.59 (br s, 1H), 2.00 (t, J = 14.3 Hz, 1H), 1.79 (ddd, J_1 = 11.5 Hz, J_2 = 7.0 Hz, J_3 = 3.7 Hz, 1H), 1.70 (m, 2H), 1.63 (m, 3H), 1.55 (m, 2H), 1.48 (m, 1H), 1.42 (m, 1H), 1.30 (br s, 6H), 1.17 (m, 3H), 1.07 (br s, 63 H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 150.1, 121.5, 77.6, 76.3, 75.7, 68.9, 34.7, 34.3, 31.8, 31.6, 29.7, 28.6, 24.7, 22.6, 20.1, 18.3 (br s), 14.0, 13.0 (br s); FTIR (thin film) ν_{max} 2944, 2867, 1723, 1464, 1259, 1058, 1014, 995, 883 cm^{-1}; HRMS calcd (EI) for $C_{45}H_{92}O_5Si_3$ $[M]^+$: 796.6253, found 796.6250; $[\alpha]_D^{25}$ −12.0 (*c* 1.10, $CHCl_3$).

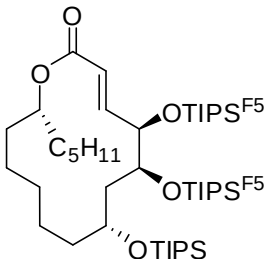


(4*S*,5*R*,7*S*,13*R*)-13-Pentyl-4,5-bis-(tri-isopropylsilyloxy)-7-diisopropyl(1,1,1,2,2-pentafluoro-butylsilyloxy)oxacyclotetradec-2-enone (*SRSR*-57f): From the demixing of (*R*)-M-**57efgh**, the second peak *SRSR*-**57f** (94.1 mg) at 39.4 minutes was isolated as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.85 (dd, J_1 = 15.8 Hz, J_2 = 2.9 Hz, 1H), 6.07 (dd, J_1 = 15.8 Hz, J_2 = 2.2 Hz, 1H), 4.96 (m, 1H), 4.77 (m, 1H), 3.95 (d, J = 9.0 Hz, 1H), 3.64 (td, J_1 = 10.3 Hz, J_2 = 6.6 Hz, 1H), 2.45 (td, J_1 = 12.8 Hz, J_2 = 4.1 Hz, 1H), 2.05 (m, 2H), 1.70 (m, 2H), 1.62-1.45 (m, 8H), 1.40-1.25 (m, 6H), 1.20 (m, 3H), 1.10 (br s, 42H), 1.07 (br s, 14H), 0.89 (t, J = 6.8 Hz, 3H), 0.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 148.4, 121.6, 77.0, 74.3, 73.7, 69.5, 42.4, 34.0,

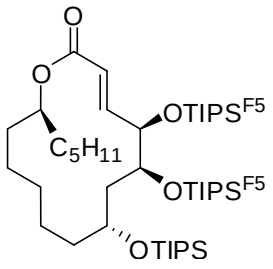
33.4, 32.7, 32.3, 32.2, 31.7, 30.3, 29.9, 25.4, 23.1, 22.6, 20.0, 18.3, 17.8, 1.5; ^{19}F NMR (282 MHz, $CDCl_3$) –84.99 (s, 3F), –120.26 (t, $^3J_{HF}$ = 18.0 Hz, 2F); FTIR (thin film) ν_{max} 2945, 2868, 1720, 1464, 1257, 1120, 1054, 992, 884 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{46}H_{89}O_5F_5Si_3Na$ $[M + Na]^+$: 923.5836, found 923.5826; $[\alpha]_D^{25}$ –12.7 (*c* 1.37, $CHCl_3$).



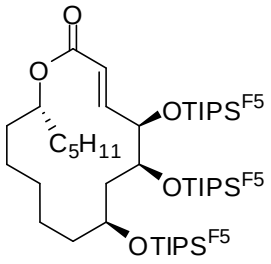
(4*S*,5*R*,7*S*,13*S*)-13-Pentyl-4,5-bis-(triisopropylsilyloxy)-7-diisopropyl-(1,1,1,2,2-pentafluoro-butylsilyloxy)oxacyclotetradec-2-enone (*SRSS*-57f): From the demixing of (*S*)-M-**57efgh**, the second peak *SRSS*-**57f** (52.0 mg) at 42.8 minutes was isolated as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.73 (dd, J_1 = 15.9 Hz, J_2 = 8.6 Hz, 1H), 5.86 (d, J = 15.9 Hz, 1H), 4.91 (m, 1H), 4.66 (d, J = 8.5 Hz, 1H), 3.88 (td, J_1 = 10.5 Hz, J_2 = 6.5 Hz, 1H), 3.78 (dd, J_1 = 10.5 Hz, J_2 = 3.5 Hz, 1H), 2.43 (m, 1H), 2.08 (m, 4H), 1.74-1.45 (m, 9H), 1.44-1.21 (m, 8H), 1.08 (br s, 56H), 0.89 (t, J = 6.8 Hz, 3H), 0.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 149.3, 121.6, 178.9, 75.7, 75.5, 70.3, 42.6, 35.1, 34.3, 31.8, 31.7, 27.1, 25.1, 23.2, 18.2, 14.5, 12.5, 1.5; ^{19}F NMR (282 MHz, $CDCl_3$) –84.98 (s, 3F), –120.34 (t, $^3J_{HF}$ = 18.0 Hz, 2F); FTIR (thin film) ν_{max} 2945, 2868, 1722, 1465, 1261, 1200, 1052, 993, 884 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{46}H_{89}O_5F_5Si_3Na$ $[M + Na]^+$: 923.5836, found 923.5859; $[\alpha]_D^{25}$ – 20.0 (*c* 1.01, $CHCl_3$).



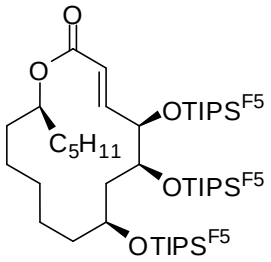
(4*R*,5*S*,7*R*,13*R*)-13-Pentyl-4,5-bis-(di-isopropyl-(1,1,1,2,2-pentafluorobutylsilyloxy)-7-triiso-propylsilyloxy)oxacyclotetradec-2-enone (*RSRR*-57g): From the demixing of (*S*)-M-**57efgh**, the third peak *RSSR*-**57h** (114.0 mg) at 58.9 minutes was isolated as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.68 (dd, J_1 = 15.9 Hz, J_2 = 8.7 Hz, 1H), 5.86 (d, J = 15.9 Hz, 1H), 4.91 (m, 1H), 4.54 (d, J = 8.6 Hz, 1H), 3.92 (td, J_1 = 10.2 Hz, J_2 = 2.0 Hz, 1H), 3.74 (d, J = 8.6 Hz, 1H), 2.05 (m, 4H), 1.72-1.60 (m, 4H), 1.60-1.48 (m, 4H), 1.41 (m, 2H), 1.30 (br s, 6H), 1.08 (br s, 49 H), 0.88 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 147.2, 122.7, 76.2, 75.5, 69.7, 69.5, 42.8, 42.2, 36.1, 35.1, 34.7, 34.5, 33.4, 32.0, 30.3, 27.2, 25.6, 22.5, 18.3, 14.0, 13.4, 13.0, 12.8, 1.5, 0.9; ^{19}F NMR (282 MHz, $CDCl_3$) –85.00 (s, 3F), –85.03 (s, 3F), –120.19 (m, 4F); FTIR (thin film) ν_{max} 2946, 2869, 1723, 1465, 1200, 1106, 1051, 993, 885 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{47}H_{86}O_5F_{10}Si_3Na$ $[M + Na]^+$: 1,027.5521, found 1,027.5491; $[\alpha]_D^{25}$ +15.6 (*c* 1.17, $CHCl_3$).



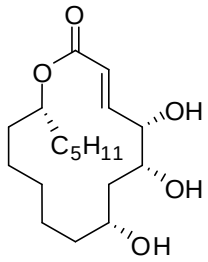
(4*R*,5*S*,7*R*,13*S*)-13-Pentyl-4,5-bis-(diisopropyl-(1,1,1,2,2-pentafluorobutyl-silyloxy)-7-triisopropylsilyloxy)oxacyclotetradec-2-enone (*RSRS*-57g): From the demixing of (*S*)-M-**57efgh**, the third peak *RSRS*-**57g** (60.3 mg) at 42.1 minutes was isolated as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.84 (d, J = 15.6 Hz, 1H), 6.03 (dd, J_1 = 15.6 Hz, J_2 = 2.2 Hz, 1H), 4.97 (m, 1H), 4.64 (m, 1H), 3.91 (d, J = 10.3 Hz, 1H), 3.68 (m, 1H), 2.43 (t, J = 9.7 Hz, 1H), 2.05 (m, 4H), 1.71 (m, 2H), 1.60-1.47 (m, 4H), 1.42 (m, 2H), 1.30 (br s, 9H), 1.21 (m, 2H), 1.08 (br s, 49 H), 0.92 (m, 4H), 0.89 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 146.8, 122.0, 77.2, 74.5, 73.9, 68.8, 42.7, 33.9, 31.8, 30.2, 26.5, 25.7, 25.5, 25.4 (m), 23.3, 22.6, 18.2, 1.0, 0.7; ^{19}F NMR (282 MHz, $CDCl_3$) –85.01 (br s, 6F), –120.38 (m, 4F); FTIR (thin film) ν_{max} 2946, 2869, 1720, 1464, 1260, 1201, 1108, 1054, 992, 885 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{47}H_{86}O_5F_{10}Si_3Na$ $[M + Na]^+$: 1,027.5521, found 1,027.5510; $[\alpha]_D^{25} + 9.27$ (*c* 1.12, $CHCl_3$).



(4*R*,5*S*,7*S*,13*R*)-13-Pentyl-4,5,7-tris-(di-isopropyl(1,1,1,2,2-penta-fluoro-butyl-silyloxy)-oxa-cyclotetradec-2-enone (*RSSR*-57h): From the demixing of (*R*)-M-**57efgh**, the fourth peak *RSSR*-**57h** (41.5 mg) at 78.4 minutes was isolated as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.86 (dd, J_1 = 16.0 Hz, J_2 = 7.9 Hz, 1H), 5.88 (d, J = 16.0 Hz, 1H), 4.92 (m, 1H), 4.47 (d, J = 7.9 Hz, 1H), 3.97 (m, 1H), 3.54 (m, 1H), 2.05 (m, 6H), 1.72-1.58 (m, 8H), 1.58-1.43 (m, 4H), 1.30 (m, 6H), 1.18 (m, 2H), 1.07 (br s, 42H), 0.88 (9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.2, 147.8, 122.7, 76.2, 76.0, 75.7, 69.2, 35.1, 34.8, 34.2, 31.7, 28.2, 24.8 (m), 22.5, 17.7, 13.2, 12.8, 1.5, 0.8, 0.7; ^{19}F NMR (282 MHz, $CDCl_3$) –85.01 (s, 3F), –85.04 (s, 3F), –85.09 (s, 3F), –120.45 (m, 6F); FTIR (thin film) ν_{max} 2947, 2870, 1724, 1465, 1200, 1105, 1052, 993, 886, 750 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{48}H_{83}O_5F_{15}Si_3Na$ $[M + Na]^+$: 1,131.5207, found 1,131.5283; $[\alpha]_D^{25} + 8.88$, (*c* 1.08, $CHCl_3$).

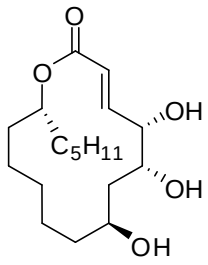


(4*R*,5*S*,7*S*,13*S*)-13-Pentyl-4,5,7-tris-(diisopropyl-(1,1,1,2,2-penta-fluoro-butyl-silyloxy)-oxa-cyclotetradec-2-enone (*RSSS*-57h): From the demixing of (*S*)-M-**57efgh**, the fourth peak *RSSS*-**57h** (65.8 mg) at 70.9 minutes was isolated as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.84 (d, *J* = 15.9 Hz, 1H), 6.00 (d, *J* = 15.9 Hz, 1H), 5.05 (m, 1H), 4.48 (br s, 1H), 3.95 (m, 2H), 2.05 (m, 6H), 1.81 (m, 1H), 1.74 (m, 1H), 1.71-1.60 (m, 3H), 1.59-1.48 (m, 5H), 1.40-1.21 (m, 10H), 1.09 (br s, 42H), 0.89 (t, J = 6.5 Hz, 3H), 0.83 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 146.5, 125.5, 76.0, 73.0, 69.4, 68.7, 40.3, 37.2, 34.3, 32.5, 31.7, 30.3, 29.7, 25.7, 25.3 (m), 22.5 (br s), 17.8, 17.5 (br s), 14.0, 1.5, 0.8, 0.7; ^{19}F NMR (282 MHz, $CDCl_3$) –84.96 (s, 3F), –85.02 (s, 3F), –85.05 (s, 3F), –120.44 (m, 6F); FTIR (thin film) ν_{max} 2948, 2871, 1730, 1466, 1200, 1105, 1062, 995, 886, 750 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{48}H_{83}O_5F_{15}Si_3Na$ $[M + Na]^+$: 1,131.5207, found 1,131.5223; $[\alpha]_D^{25} + 0.19$ (*c* 1.17, $CHCl_3$).

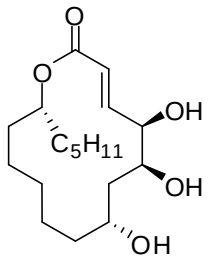


4*S*,5*R*,7*R*,13*R*)-4,5,7-Trihydroxy-13-pentyl-oxa-cyclo-tetradecenone ((4*S*,5*R*,7*R*,13*R*)-5). The macrolactone *SRRR*-**57e** (91.4 mg, 115 μmol) was dissolved in DCM (3.0 mL) and transferred to a polyethylene culture tube. The solution was diluted with acetonitrile (8.0 mL). Aqueous hydrofluoric acid[103] (48 wt. %, 0.60 mL) was then added to the solution at room temperature and the reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (10.0 mL) at 0 °C and the layers were separated. The aqueous layer was extracted with ether (3 x 20 mL). The combined organic extracts were then washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The product after flash chromatography (3:1 hexanes/EtOAc, then 100% EtOAc) was further purified using a (*S*,*S*)-Whelk-*O*-1 column as described for (4*S*,5*S*,7*R*,13*R*)-**5**, and the desired compound was isolated as an amorphous white solid (6 injections, 11.0 mg, 29%): ^{1}H NMR (700 MHz, CD_3OD) δ 6.94 (dd, J_1 = 15.8 Hz, J_2 = 4.7 Hz, 1H), 6.09 (dd, J_1 = 15.8 Hz, J_2 = 1.8 Hz, 1H), 5.01 (m, 1H), 4.47 (ddd, J_1 = 4.7 Hz, J_2 = 3.0 Hz, J_3 = 1.8 Hz, 1H), 3.89 (ddd, J_1 = 7.2 Hz, J_2 = 4.7 Hz, J_3 = 3.0 Hz, 1H), 3.71 (m, 1H), 1.76 (m, 2H), 1.71 (ddd, J_1 = 14.6 Hz, J_2 = 7.2 Hz, J_3 = 4.7 Hz, 1H), 1.63 (m, 1H), 1.56 (m, 1H), 1.45 (m, 5H), 1.33 (m, 8H) 1.21 (m, 2H), 1.11 (m, 1H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (175 MHz, CD_3OD) δ 168.0, 148.6, 123.4, 77.4, 74.6, 72.3, 68.8, 39.1, 36.4, 35.7, 34.4, 33.0, 30.3, 26.6, 26.0, 24.3, 23.8, 14.5; FTIR (thin film) ν_{max} 3288, 2922, 2855,

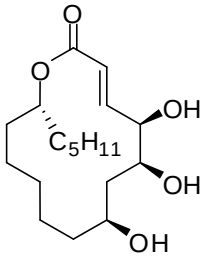
1703, 1265, 1183, 990 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{18}H_{32}O_5Na$ $[M + Na]^+$: 351.2147, found 351.2142; $[\alpha]_D^{25}$ +15.5 (*c* 0.55, MeOH).



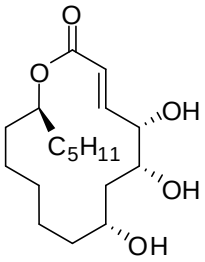
(4*S*,5*R*,7*S*,13*R*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradecenone ((4*S*,5*R*,7*S*,13*R*)-5): The same method employed in the preparation of (4*R*,5*R*,7*R*,15*R*)-**5** during the single isomer pilot synthesis (see Chapter 2.0) was followed using *SRSR*-**57f** (91.1 mg, 101 μmol). The product after flash chromatography (3:1 hexanes/EtOAc, then 100% EtOAc) was further purified using a (*S*,*S*)-Whelk-*O*-1 column as described for (4*S*,5*S*,7*R*,13*R*)-**5**, and the desired compound was isolated as an amorphous white solid (12.4 mg, 37%, 14:1 *d.r.*): ^{1}H NMR (700 MHz, CD_3OD) δ 7.00 (dd, J_1 = 15.8 Hz, J_2 = 3.6 Hz, 1H), 6.06 (dd, J_1 = 15.8 Hz, J_2 = 2.2 Hz, 1H), 4.95 (m, 1H), 4.46 (m, 1H), 3.95 (ddd, J_1 = 7.6 Hz, J_2 = 4.5 Hz, J_3 = 2.2 Hz, 1H), 3.68 (septet, J = 4.5 Hz, 1H), 2.02 (ddd, J_1 = 14.1 Hz, J_2 = 8.1 Hz, J_3 = 4.5 Hz, 1H, 1H), 1.69 (m, 2H), 1.61 (m, 2H), 1.54 (m, 3H), 1.34 (m, 9H), 1.28 (m, 3H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (175 MHz, CD_3OD) δ 168.0, 150.2, 122.3, 76.1, 75.7, 72.1, 68.8, 39.5, 34.9, 34.6, 33.0, 32.8, 28.6, 26.6, 24.9, 23.4, 14.5; FTIR (thin film) ν_{max} 2932, 2360, 2340, 1717, 1270, 1009 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{18}H_{32}O_5Na$ $[M + Na]^+$: 351.2147, found 351.2171; $[\alpha]_D^{25}$ +1.66 (*c* 0.54, MeOH).



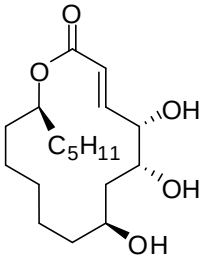
(4*R*,5*S*,7*R*,13*R*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradecenone ((4*R*,5*S*,7*R*,13*R*)-5, (+)-*nat*-Sch725674): The same method employed in the preparation of (4*S*,5*R*,7*R*,13*R*)-**5** was followed using *RSRR*-**57g** (55.1 mg, 54.8 μmol). The product after flash chromatography (3:1 hexanes/EtOAc, then 100% EtOAc) was further purified using a (*S*,*S*)-Whelk-*O*-1 column as described for (4*S*,5*S*,7*R*,13*R*)-**5**, and the desired compound was isolated as an amorphous white solid (6 injections, 5.7 mg); total yield for this isomer (11.4 mg, 32%). The NMR spectroscopic data of (4*R*,5*S*,7*R*,13*R*)-**5** are in complete agreement with those of the natural product[32]: ^{1}H NMR (700 MHz, CD_3OD) δ 6.87 (dd, J_1 = 15.8 Hz, J_2 = 6.1 Hz, 1H), 6.08 (dd, J_1 = 15.8 Hz, J_2 = 1.5 Hz, 1H), 4.95 (dddd, J_1 = 10.4 Hz, J_2 = 7.9 Hz, J_3 = 5.4 Hz, J_4 = 2.9 Hz,1H), 4.49 (ddd, J_1 = 5.8 Hz, J_2 = 2.7 Hz, J_3 = 1.5 Hz, 1H), 3.99 (quintet, J = 6.2 Hz, 1H), 3.85 (m, 1H), 1.83 (dt, J_1 = 14.7 Hz, J_2 = 6.1 Hz, 1H), 1.71 (dddd, J_1 = 14.2 Hz, J_2 = 6.7 Hz, J_3 = 4.6 Hz, J_4 = 2.0 Hz, 1H), 1.65 (dt, J_1 = 14.7 Hz, J_2 = 5.0 Hz,1H), 1.61 (m, 1H), 1.55 (m, 2H), 1.46 (m, 1H), 1.34 (m, 10H) 1.18 (m, 3H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (175 MHz, CD_3OD) δ 168.4, 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; FTIR (thin film) ν_{max} 3436, 2926, 2857, 1703, 1461, 1274, 1077 cm^{-1}; HRMS calcd (EI) for $C_{18}H_{32}O_5$ $[M]^+$: 328.2250, found 328.2248; $[\alpha]_D^{25} + 5.15$ (*c* 0.27, MeOH).



(4*R*,5*S*,7*S*,13*R*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradecenone ((4*R*,5*S*,7*S*,13*R*)-5): The same method employed in the preparation of (4*S*,5*R*,7*R*,13*R*)-**5** was followed using *RSSR*-**57h** (40.1 mg, 36.1 μmol). The product after flash chromatography (3:1 hexanes/EtOAc, then 100% EtOAc) was further purified using a (*S*,*S*)-Whelk-*O*-1 column as described for (4*S*,5*S*,7*R*,13*R*)-**5**, and the desired compound was isolated as an amorphous white solid (3 injections, 4.7 mg, 40%). ^{1}H NMR (700 MHz, CD_3OD) δ 6.95 (dd, J_1 = 15.8 Hz, J_2 = 4.2 Hz, 1H), 6.14 (dd, J_1 = 15.8 Hz, J_2 = 1.4 Hz, 1H), 4.93 (m,1H), 4.54 (m, 1H), 3.89 (dt, J_1 = 8.8 Hz, J_2 = 2.1 Hz, 1H), 3.38 (m, 1H), 2.02 (ddd, J_1 = 14.6 Hz, J_2 = 8.8 Hz, J_3 = 2.4 Hz, 1H), 1.65 (m, 3H), 1.54 (m,1H), 1.48 (m, 2H), 1.40 (m, 1H), 1.32 (m, 10H), 1.20 (m, 3H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (175 MHz, CD_3OD) δ 169.0, 150.0, 121.8, 75.5, 75.0, 72.1, 68.8, 40.5, 36.2, 35.9, 33.9, 33.0, 27.2, 26.5, 24.7, 24.5, 23.8, 14.5; FTIR (thin film) ν_{max} 3360, 2935, 2340, 1715, 1286 cm^{-1}; HRMS calcd (ESI, positive mode) for $C_{18}H_{32}O_5Na$ $[M + Na]^+$: 351.2147, found 351.2174; $[\alpha]_D^{25} -38.6$ (*c* 0.24, MeOH).

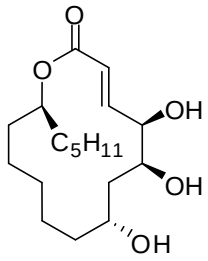


(4*S*,5*R*,7*R*,13*S*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradecenone ((4*S*,5*R*,7*R*,13*S*)-5): The same method employed in the preparation of (4*S*,5*R*,7*R*,13*R*)-**5** was followed using *SRRS*-**57e** (72.7 mg, 91.2 μmol). The product after flash chromatography (3:1 hexanes/EtOAc, then 100% EtOAc) was further purified using a (*S*,*S*)- Whelk-*O*-1 column as described for (4*S*,5*S*,7*R*,13*R*)-**5**, and the desired compound was isolated as an amorphous white solid (5 injections, 13.4 mg, 45%). The ^{1}H NMR spectrum matched that of (4*R*,5*S*,7*S*,13*R*)-**5** (see above); $[\alpha]_D^{25} -38.7$ (*c* 0.67, MeOH).

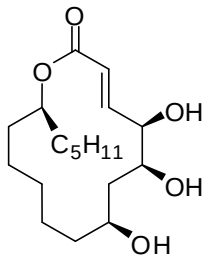


(4*S*,5*R*,7*S*,13*S*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradecenone ((4*S*,5*R*,7*S*,13*S*)-5): The same method employed in the preparation of (4*S*,5*R*,7*R*,13*R*)-**5** was followed using *SRSS*-**57f** (87.0 mg, 96.5 μmol). The product after flash chromatography (3:1 hexanes/EtOAc, then 100% EtOAc) was further purified using a (*S*,*S*)-Whelk-*O*-1 column as described for (4*S*,5*S*,7*R*,13*R*)-**5**, and the desired compound was isolated as an amorphous white solid (3 injections, 5.5 mg, 17%).

The ^{1}H NMR spectrum matched that of (4*R*,5*S*,7*R*,13*R*)-**5** (see above); $[\alpha]_D^{25} - 2.93$, (*c* 0.21, MeOH).



(4*R*,5*S*,7*R*,13*S*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradecenone ((4*R*,5*S*,7*R*,13*S*)-5): The same method employed in the preparation of (4*S*,5*R*,7*R*,13*R*)-**5** was followed using *RSRS*-**57g** (59.1 mg, 58.8 μmol). The product after flash chromatography (3:1 hexanes/EtOAc, then 100% EtOAc) was further purified using a (*S*,*S*)-Whelk-*O*-1 column as described for (4*S*,5*S*,7*R*,13*R*)-**5**, and the desired compound was isolated as an amorphous white solid (4 injections, 14.0 mg, 73%). The ^{1}H NMR spectrum matched that of (4*S*,5*R*,7*S*,13*R*)-**5** (see above); $[\alpha]_D^{25} - 2.14$, (*c* 0.70, MeOH).

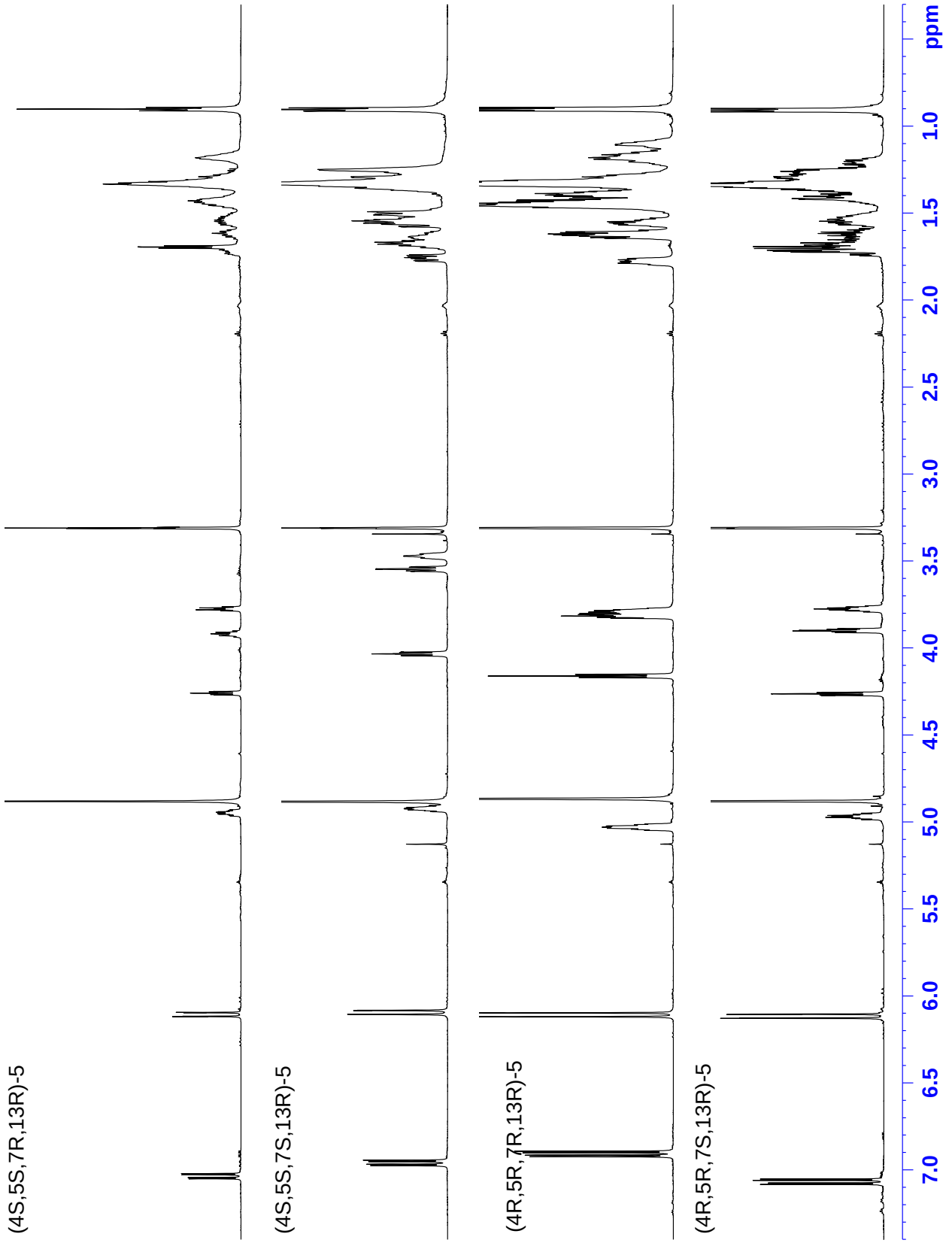


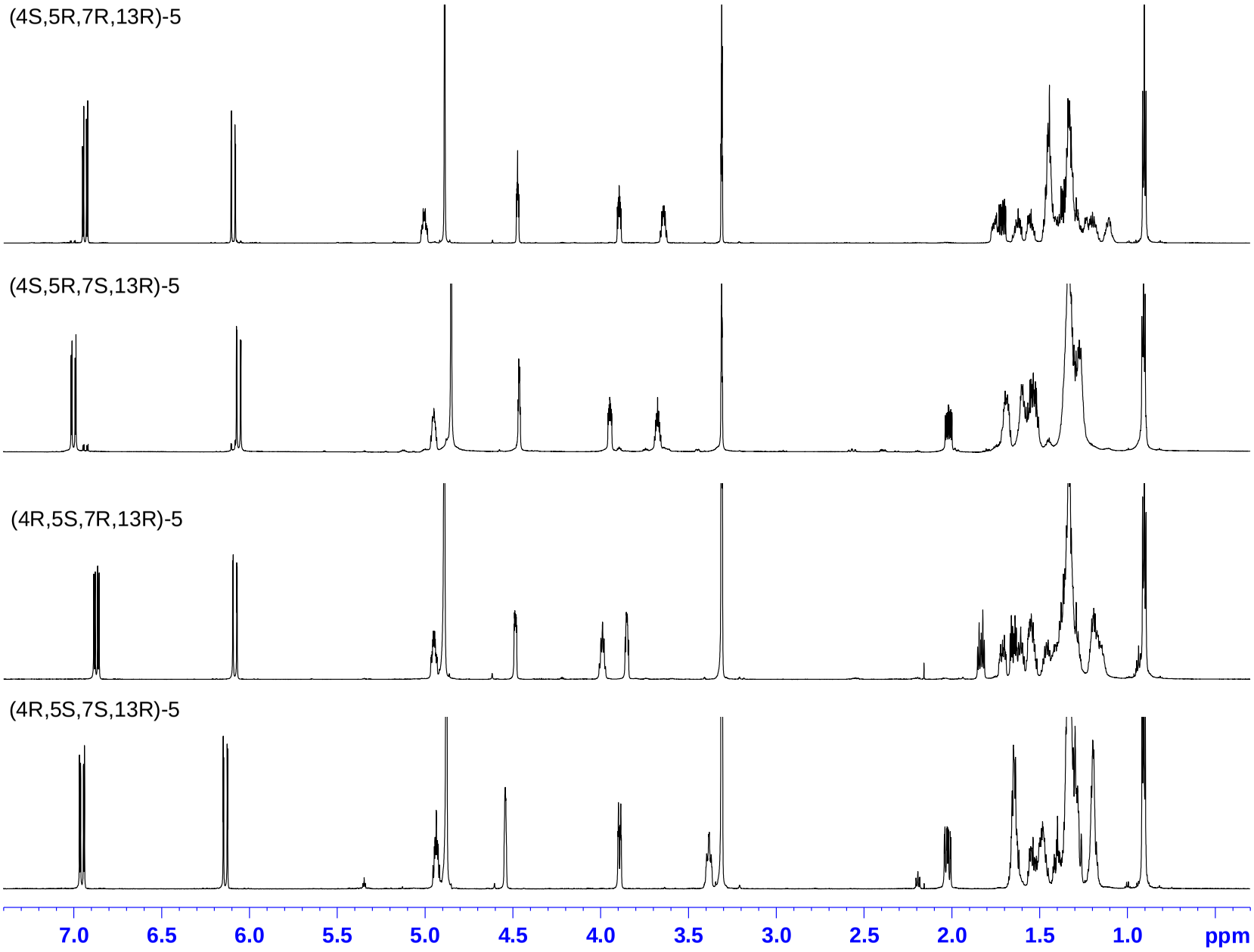
(4*R*,5*S*,7*S*,13*S*)-4,5,7-Trihydroxy-13-pentyloxacyclotetradecenone ((4*R*,5*S*,7*S*,13*S*)-5): The same method employed in the preparation of (4*S*,5*R*,7*R*,13*R*)-**5** was followed using *RSSS*-**57h**

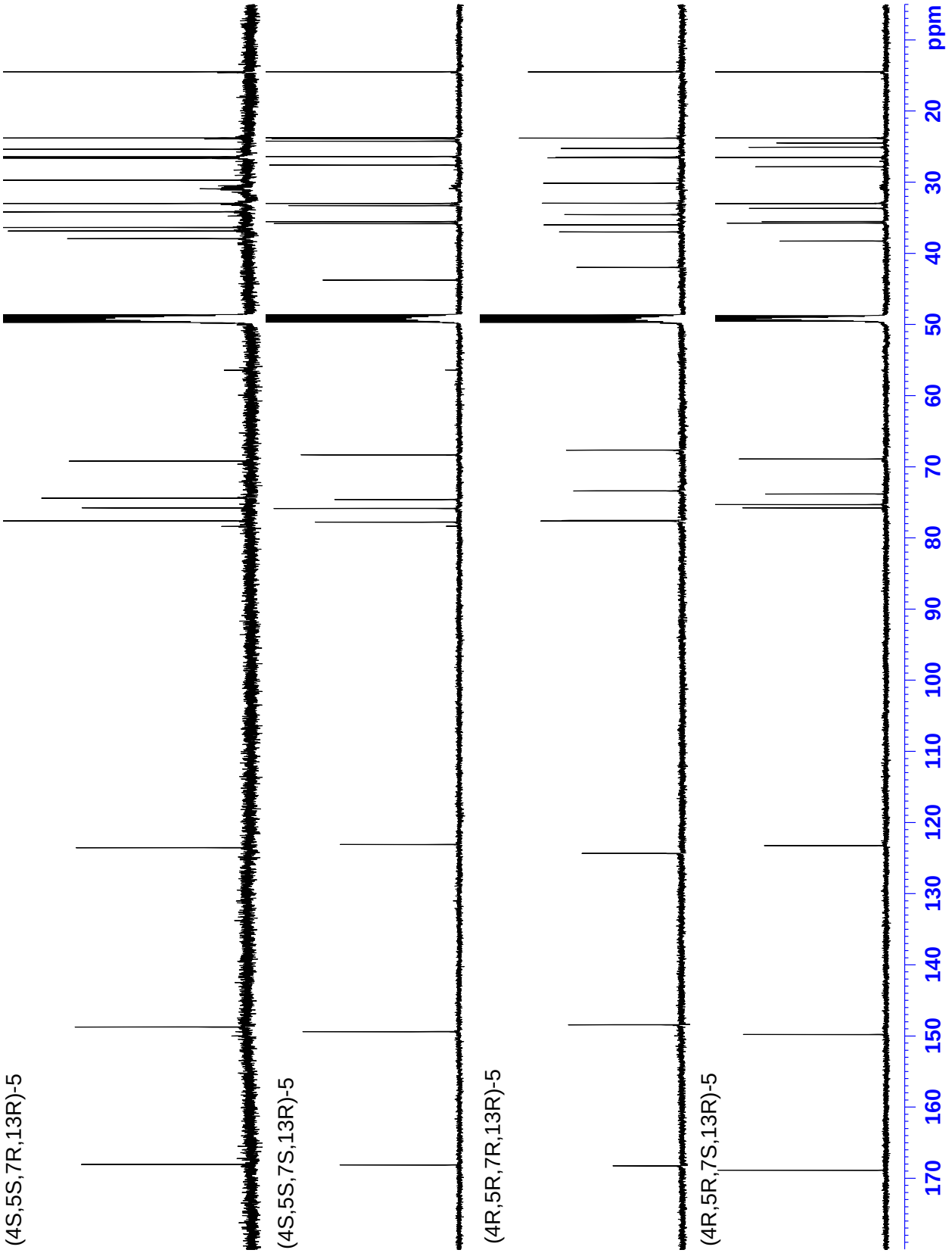
(59.1 mg, 58.8 μmol). The product after flash chromatography (3:1 hexanes/EtOAc, then 100% EtOAc) was further purified using a (*S*,*S*)-Whelk-*O*-1 column as described for (4*S*,5*S*,7*R*,13*R*)-**5**, and the desired compound was isolated as an amorphous white solid (3 injections, 6.9 mg, 36%). The ^{1}H NMR spectrum matched that of (4*S*,5*R*,7*R*,13*R*)-**5** (see above); $[\alpha]_D^{25}$ −13.8 (*c* 0.35, MeOH).

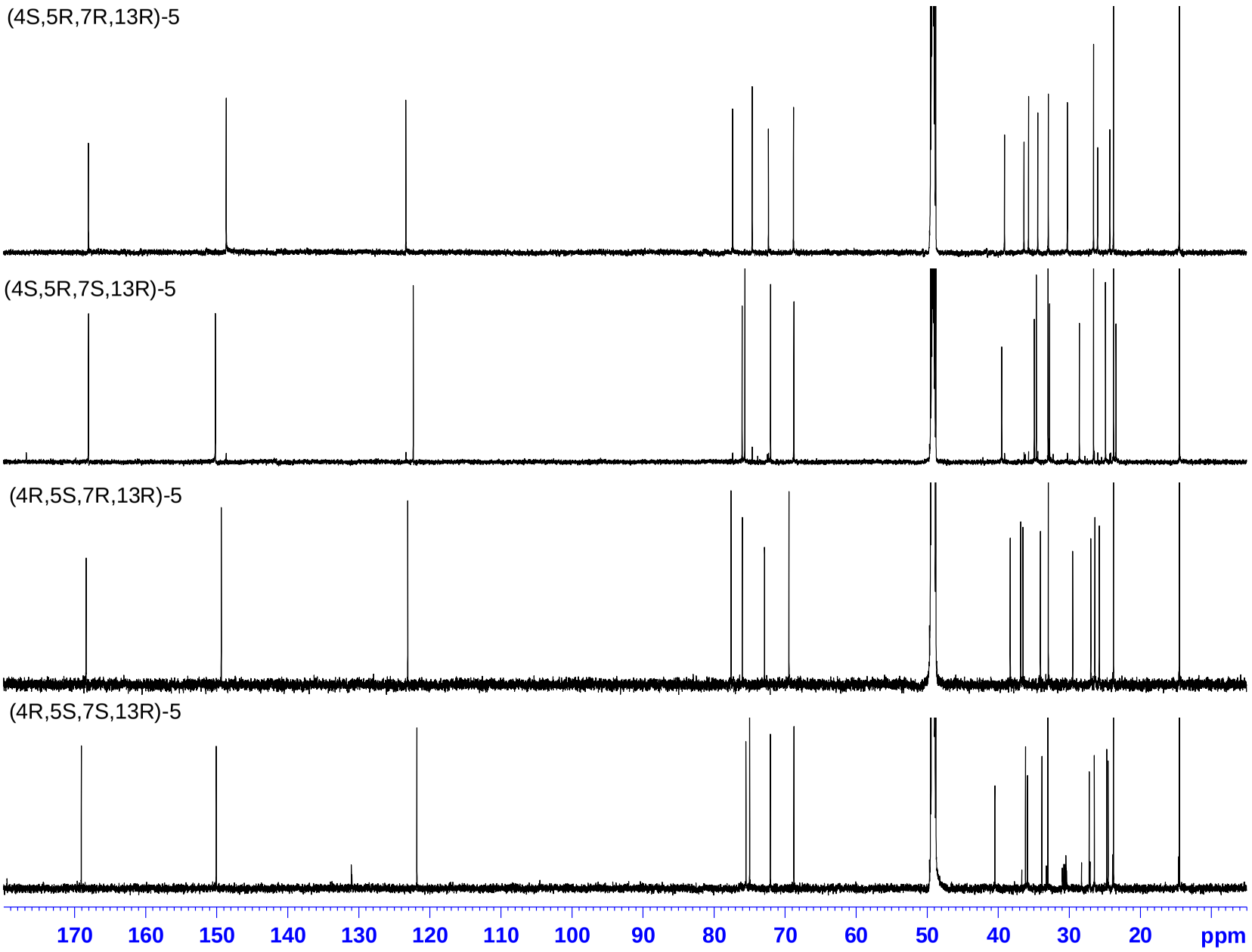
APPENDIX

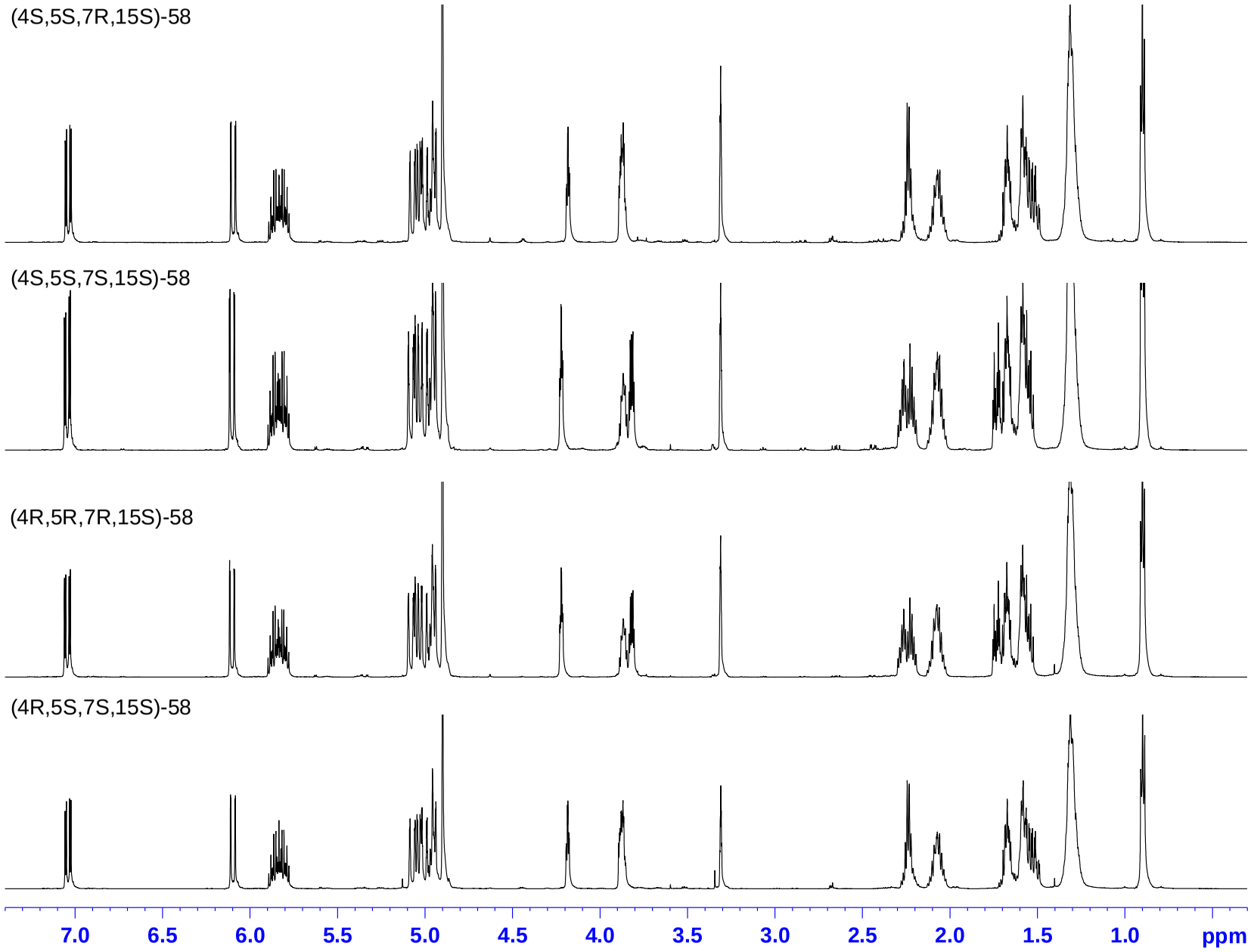
1. ^{1}H and ^{13}C NMR spectra of macrocycles **5**
2. ^{1}H and ^{13}C NMR spectra of ring-open triols **58**

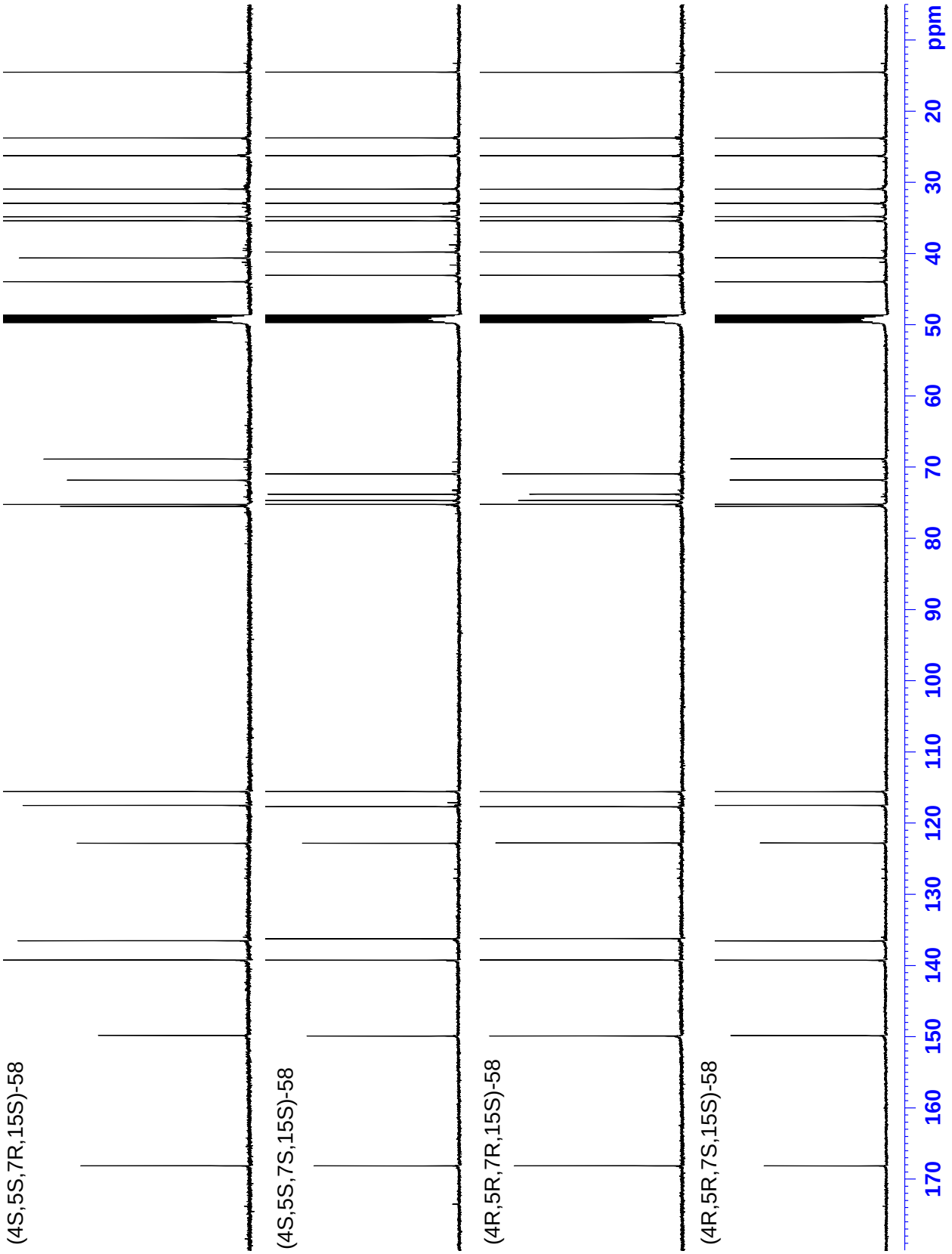

(4S,5S,7R,13R)-5
(4S,5S,7S,13R)-5
(4R,5R,7R,13R)-5
(4R,5R,7S,13R)-5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


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


(4S,5S,7R,13R)-5
(4S,5S,7S,13R)-5
(4R,5R,7R,13R)-5
(4R,5R,7S,13R)-5
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20


(4S,5R,7R,13R)-5
(4S,5R,7S,13R)-5
(4R,5S,7R,13R)-5
(4R,5S,7S,13R)-5
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


(4S,5S,7R,15S)-58
(4S,5S,7S,15S)-58
(4R,5R,7R,15S)-58
(4R,5S,7S,15S)-58
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


(4S,5S,7R,15S)-58
(4S,5S,7S,15S)-58
(4R,5R,7R,15S)-58
(4R,5R,7S,15S)-58
ppm
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

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