APPLICATION OF FLUOROUS METHODOLOGIES FOR THE TOTAL SYNTHESIS OF EIGHT DIASTEREOMERS OF PASSIFLORICIN A AND 6-EPI-DICTYOSTATIN

by

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Submitted to the Graduate Faculty of

Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2008

UNIVERSITY OF PITTSBURGH

SCHOOL OF ARTS AND SCIENCES

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It was defended on

November 19, 2007

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APPLICATION OF FLUOROUS METHODOLOGIES FOR THE TOTAL SYNTHESIS OF EIGHT DIASTEREOMERS OF PASSIFLORICIN A AND 6-EPI-DICTYOSTATIN

Gustavo Moura-Letts, PhD

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A soluble fluorous palladacycle complex that promotes the Heck coupling and can be recovered and reused is reported herein. This complex promoted the Heck coupling of acrylates and haloarenes in high yields and with high turnover numbers.

Passifloricin A, a natural product isolated from the tree *Passiflora foetida* is a polyol δ-lactone containing four stereocenters. The fluorous mixture synthesis (FMS) of all eight diastereomers of passifloricin A is reported herein. Utilizing a multiple-tag FMS strategy we successfully obtained the eight quasiisomers from the natural product. The spectroscopic data for synthetic passifloricin A matched the spectroscopic data for natural passifloricin A.

The ene-diene cross-metathesis reaction was succesfully applied to a wide variety of enes and dienes in high yields and streoselectivities. This reaction was applied for the synthesis of 10 grams of the bottom fragment of dictyostatin.

Dictyostatin, a marine sponge-derived macrolactone has been extensively studied in the Curran group because of its high potency as a microtubule-stabilizing agent. Based on SAR studies it was synthesized the 6-epimer (four times more potent). We successfully coupled the fragments *via* dimethylsilaketal formation and ring closing metathesis reaction of the silaketal intermediate. The final steps led to the synthesis of 30 mg of 6-*epi*-dictyostatin for the testing of its antiploriferative activity *in vivo*.

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PREFACE

I would like to thank Professor Dennis P. Curran for his guidance, patience and motivation. I would also like to thank Professors Peter Wipf, Paul Floreancig and Billy Day for serving on my thesis committee.

I would like to thank all the Curran group members, past and present, for providing a sociable and stimulating work environment. Special thanks to Dr. Mathias Pholman for his contributions in the passifloricin A project, and to Mr. Won-Huyk Jung for his contributions in the 6-*epi*-dictyostatin project.

I would also like to thank Dr. Fu Tyan Lin, Dr. Kasi Somayajula, Dr. Steven Geib, Mr. John Williams and Dr. Damoderan Krishnan for their support with NMR spectroscopy, mass spectroscopy and X-ray crystallography.

I would like finally to thank my parents and my friends for their patience and sacrifice in dealing with me throughout this experience.

LIST OF ABREVIATIONS

Ac	acetyl
APCI	atmospheric pressure chemical ionization mass spectrometry
Bu	butyl
9-BBN	9-borabicyclo[3.3.1]nonane
COSY	correlation spectroscopy
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
DIPEA	diisopropylethylamine
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
equiv	equivalent
Et	ethyl
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
HPLC	high performance liquid chormatography
HRMS	high resolution mass spectropmetry
IR	infrared spectropmetry
J	coupling constant (Hz)

KHMDS   potassium hexamethyldisilazine

M   molar

Me   methyl

NMR   nuclear magnetic resonance

Ph   phenyl

PMB   *p*-methoxybenzyl

PPTS   pyridinium *p*-toluensulfonate

RT   room temperature

T$_R$ retention time

TBAF   tetrabutylamonium fluoride

TBS   t-butyldimethyl

THF   tetrahydrofuran

TLC   thin layer chromatography

TfO   triflate

UV   ultraviolet

1.0 A SOLUBLE PALLADIUM COMPLEX THAT PROMOTES HECK REACTIONS AND CAN BE RECOVERED AND REUSED

1.1 INTRODUCTION

Palladium-catalyzed C-C bond formation reactions have emerged as powerful tools in organic synthesis due to their mild reaction conditions and high yields.[1,2] Among these, the Heck reaction,[3] coupling of readily available olefins with aryl or alkenyl halides or triflates, offers enticing possibilities for obtaining a wide range of vinylic products used as intermediates in pharmaceutical and fine chemical synthesis.[4]

The development of efficient methods to assist the recovery and recycling of palladium complexes remains an important goal.[5] Thus, several reports in the literature have described new recycling techniques involving the binding of the catalyst to an insoluble support, facilitating catalyst separation after reaction completion.[6] Moreover, the development of soluble polymer supported catalysts to achieve high levels of recycling have increased palladacycles applicability.[7]

The concept of catalyst recycling was extended by the introduction of fluorous biphasic catalysis.[8] This well established technique exploits the temperature dependent miscibility of organic and fluorous phases.[9] The reaction of organic substrates promoted by a heavy fluorous catalyst can be conducted under homogeneous conditions at high temperature. The resulting

mixture at RT will separate into a fluorous phase (containing the heavy fluorous catalyst) and an organic phase (containing the organic product). This technique has great applicability in large scale process chemistry but lacks the generality that is so important in small scale discovery chemistry.[10] This is because introducing large numbers of fluorines to ligands, or catalysts, as "ponytails" conveys unusual physical and chemical properties (lack of solubility in organic solvents, high molecular weight, little reactivity under standard organic reaction conditions).[11]

1.1.1 Light fluorous chemistry

Fluorous reagents, reactants, catalysts and protecting groups are primed to move from a relatively small community into standard organic synthesis.[12] Light fluorous compounds (less than 21 fluorines) are usually soluble in standard organic reaction solvents, though they still can be separated from organic products by fluorous silica gel solid phase extraction (FSPE).[13] The Curran group pioneered light fluorous catalysis[14] by using fluorous phosphines as ligands for platinum- and palladium-catalyzed reactions. In those experiments, the fluorous residue was collected by FSPE, but the intact catalyst was not recovered because it was unstable to the reaction conditions. As a consequence, the development of a light fluorous palladium catalyst that can be recovered and reused would be of great advantage for the continuously growing field of light fluorous chemistry.

1.1.2 Palladacycles

Palladacycles have been known for over 20 years, although they have not been used as catalysts until recently.[15] Nitrogen-, phosphorus-, and sulfur-containing palladacycles are

emerging as a new family of palladium complexes, and they have become the most simple and efficient complexes to promote palladium coupling reactions.[16] The robustness, recycling, and air stability of palladacycles[17] makes them good candidates for catalysis.

The general structure of palladacycles complexes is represented in Figure 1. The class of compounds in the palladacycles family that is commonly used as promoters for palladium coupling reactions is the so-called "pincer" complex (3).

L = donor, Y = linker group
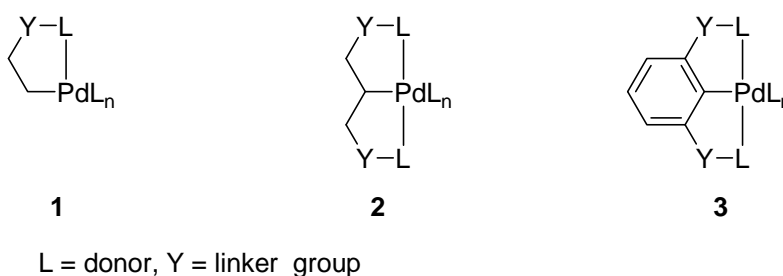
Figure 1. Classes of palladacycles

There are many examples of different types of pincer-palladacycles that promote the Heck reaction; nitrogen-[18], oxygen-,[19] and sulfur-contaning[20] pincer-palladacycles (**4**, **5** and **6**, respectively) are among the most important examples of this type of complexes. Sulfur-containing palladacycles like **6a** and **6b** are known to promote Heck couplings with high yields and high catalyst turnover.

Most textbooks describe the mechanism for the Heck reaction as a Pd(0)/Pd(II) based mechanism.[21] However, it has been proposed that a Pd(II)/Pd(IV) mechanism may be operative in the case of pincer PCP complexes **3**.[22] The issue of having Pd(IV) intermediacy is surprising due to the high reactivity of the Pd-C bond in palladacycles towards electrophiles and nucleophiles.[23] In turn, sulfur-containing palladacycles have one of the most stable Pd-C bonds

in this class of organopalladium complexes, supporting a possible Pd(II)/Pd(IV) mechanism (Figure 3).[24] The postulated mechanism starts with the oxidative addition of the olefin to Pd(II) complex **7** to obtain Pd(IV) complex, followed by reductive elimination to Pd(II), oxidative addition of the aryl halide, and final reductive elimination to provide the Heck product and Pd(II) complex **7**. Although this mechanism is valid for standard Pd(IV) species, there is no experimental evidence that proves or disproves this mechanism for cross coupling reactions mediated by palladium pincer-type of complexes.[25]

	R
4a	Me
4b	PEG

	X	R
5a	C,C	iPr
5b	O,O	iPr
5c	O,C	tBu

	R^1	R^2
6a	NHAc	Ph
6b	OPEG	Ph
6c	H	tBu
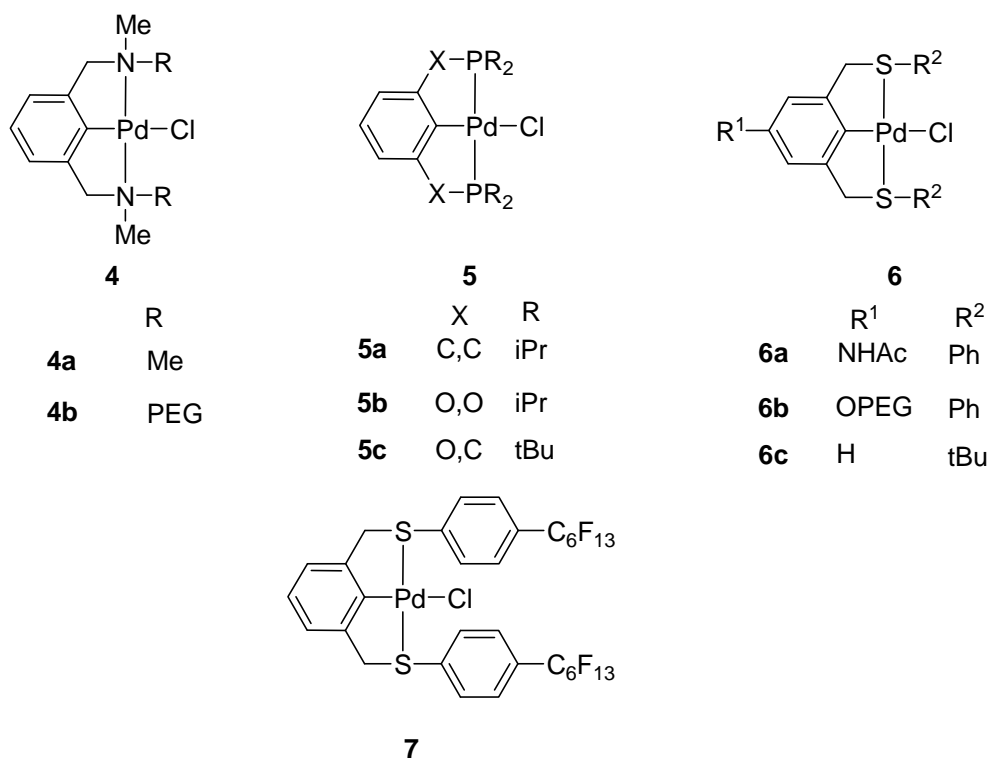
Figure 2. Palladium pincer complexes

More recently, it has been suggested that these palladacycles are not catalysts but instead reservoirs of highly catalytic palladium nanoparticules.[23b] Literature reported measured formation of palladium nanoparticules during palladacycle-promoted Heck coupling reactions by

transmission electron microscopy (TEM).[26] However, there is no record of complete characterization of these palladium nanoparticules. Therefore, it is still not clear if this is the general mechanism for palladacycle-promoted Heck couplings.[27]
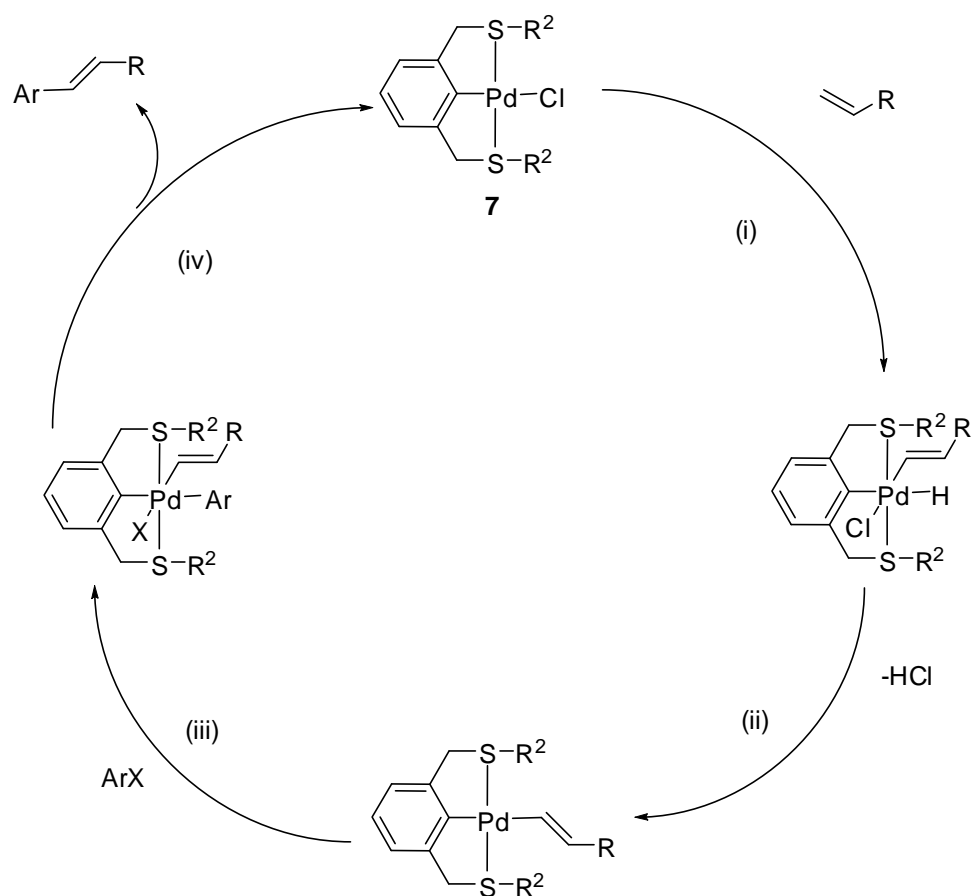
(i) Oxidative addition of a vinylic C-H bond, (ii) rate-determining HX reductive elimination, (iii) aryl chloride oxidative addition, (iv) reductive elimination.

Figure 3. Mechanism for the palladacycle promoted Heck reaction

1.1.3   Synthesis of fluorous palladacycle complex 7

The synthesis of fluorous palladacycle **7** started with the lithium-halogen exchange of commercially available bromide **8**, followed by thionation and then treatment with acetyl chloride to furnish crystalline compound **9** in 52% yield after silica gel flash chromatography. Deacylation with MeLi followed by reaction of the thiolate with α,α-dibromo-*m*-xylene provided light fluorous ligand **10** in 58% yield. An equimolar mixture of light fluorous ligand **10** and *bis*-acetonitrile palladium dichloride (Cl$_2$Pd(CH$_3$CN)$_2$) was heated for 48 h in a mixture of ACN/BTF.[28] Cooling of the reaction mixture and the filtration of precipitate furnished the first batch of **7** (between 65-75% of mass before recrystalization). The mother liquor was concentrated and allowed to cool for 1 h and the precipitate was filtrated to furnish a second batch of complex **7** (30% of mass before recrystalization). Both batches were mixed and then recrystalized in a mixture of ACN/hexanes to obtain pure complex **7** in 71% yield, as fine yellow crystals, with a mp of 224 °C (Scheme 1).
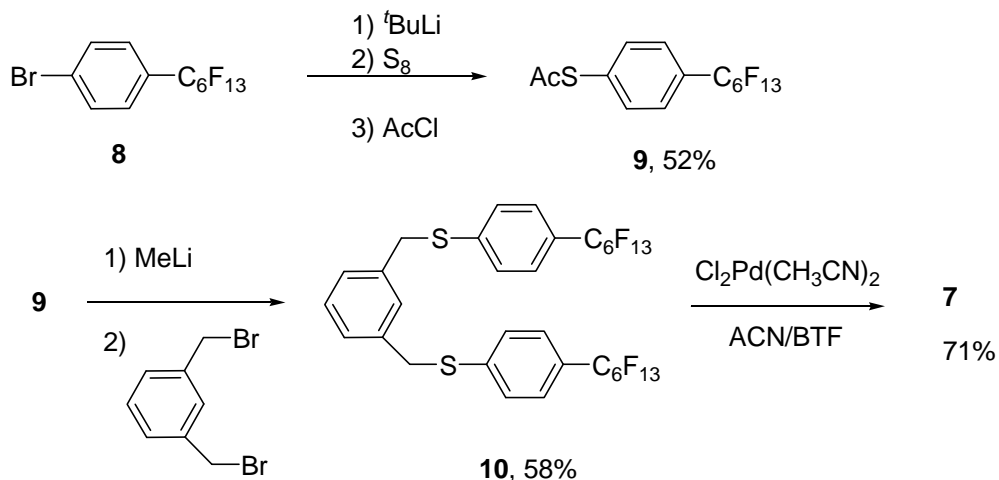
Scheme 1. Synthesis of fluorous palladacycle complex 7

1.2   RESULTS AND DISCUSSION

1.2.1   Characterization of a light fluorous palladacycle complex

The first task in this project was to complete the characterization of complex **7**. We obtained ^{1}H, ^{13}C, and ^{19}F NMR spectra for complex **7** along with crystals suitable for X-ray analysis (The crystals were grown from recrystalization in hexanes and X-ray analysis was done by Dr. Steven Geib).

Fluorous palladacycle
complex **7**

Bergbreiter SCS-Pd
Complex **6a**
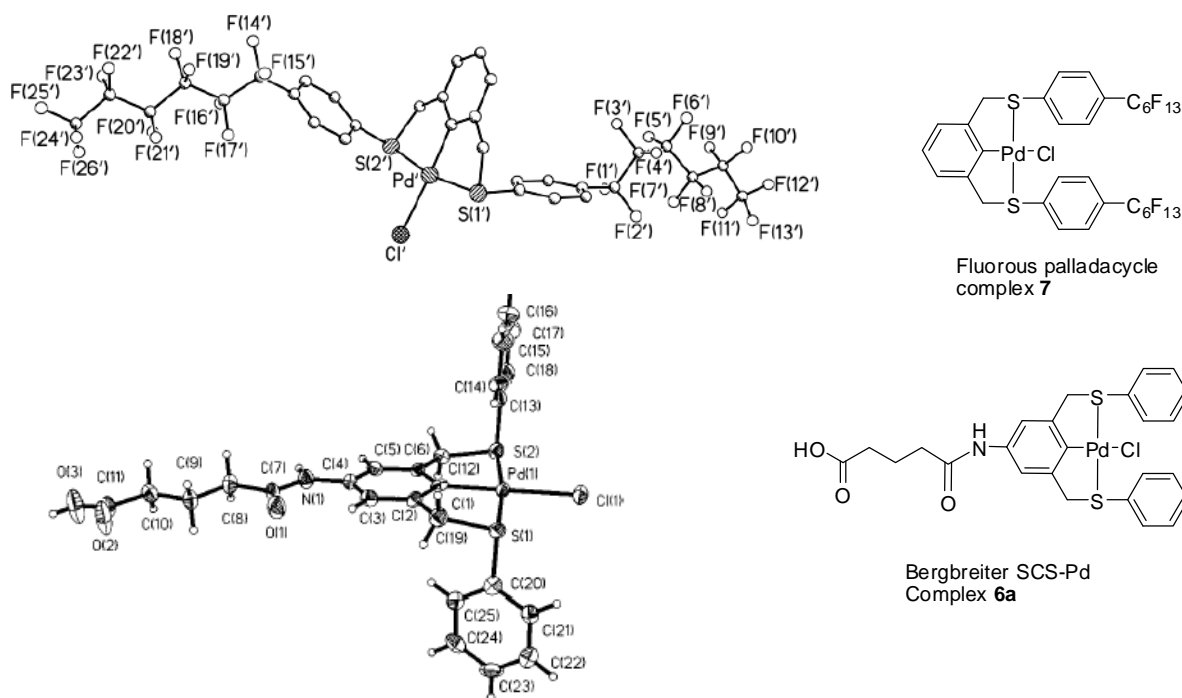
Bond lenghts	SCS-Pd complex **7**	Fluorous Palladacycle complex **6a**
Pd-C(Å)	1.97	1.98
Pd-Cl(Å)	2.41	2.39
Pd-S(Å)	2.30	2.30

Figure 4. ORTEP diagrams for fluorous palladacycle complex 7 and Bergbreiter SCS-Pd complex 6a

Complex **7** crystallizes in the space group P2₁/n with three crystallographically independent but chemically similar molecules per asymmetric unit. The symmetry suggests an orthorombic arrangement of the asymmetric unit and the environment around the palladium center is slightly distorted square-planar. The Bergbreiter SCS-Pd complex **6a** showed a similar symmetry pattern.[29] Figure 4 shows both ORTEP diagrams and selected bond lengths for complexes **6a** and **7**. Palladacycle **7** showed a retention time (T$_R$) of 8.4 min in a Fluofix^{TM} HPLC column under 80/20 ACN/H$_2$O to 100% ACN gradient elution, and a melting point of 224 ^{o}C with immediate an decomposition.

1.2.2   Application of the fluorous palladacycle complex to Heck coupling reactions

The application of complex **7** was investigated by studying Heck couplings under thermal conditions, as is summarized in Table 1. In a typical reaction, iodobenzene was mixed with methyl acrylate, triethylamine, and 3 mol% of complex **7** in DMA under ambient atmosphere. The reaction was heated at 140 ^{o}C in an oil bath for 48 h, and then an aliquot of the crude mixture was injected in the GC using iodotoluene as an internal standard. The ratio of the integrated peaks in the chromatogram indicated that we obtained methyl cinnamate in 45% yield (Entry 1).

A similar reaction using styrene and iodobenzene provided stilbene in 60% yield by GC integration (Entry 2). The reaction using DMF as a solvent with methyl acrylate and iodobenzene for 52 h provided methylcinnamate in 35% yield (Entry 2). Styrene and iodobenze under the same reaction conditions reacted for 54 h to provide stilbene in 30% yield (Entry 3). The thermal

reaction conditions along with the long reaction times did not provide the product in good yields when 3 mol% of catalyst **7** was used.

Table 1. Preliminary results in Heck couplings with fluorous palladacycle complex
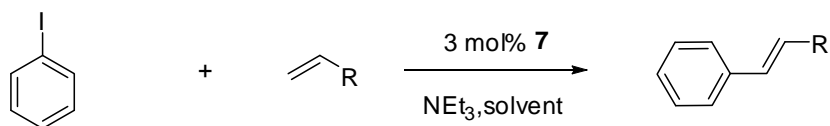
Entry	R	Solvent	Temp. (^{o}C)	Yield(%)[a]	Rx time (h)
1	COOMe	DMA	140	45	48
2	Ph	DMA	140	60	46
3	COOMe	DMF	120	35	52
4	Ph	DMF	120	30	54

a) Yields were calculated from the integration of peaks in GC chromatogram using iodotoluene as internal standard

Because of the low yields under thermal conditions, and the reported advantage of using microwave irradiation for Pd-mediated coupling reactions.[30] Next, we investigated the cross-coupling reaction mediated by microwave irradiation. These results are summarized in Table 2.

In a typical reaction, iodobenzene was mixed with styrene, tributylamine and complex **7** in DMA under ambient atmosphere and in a sealed microwave reaction tube. The reaction mixture was heated at 110 ^{o}C for 15 min, and then an aliquot of the crude mixture was injected in the GC using iodotoluene as an internal standard. The ratio of the integrated peaks in the chromatogram indicated that we obtained stilbene in 8% yield (Entry 1).

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Moreover, the reaction in DMF at 110 °C and for 10 min provided stilbene in 40% yield by GC integration (Entry 2). The reaction using DMA at 150 °C for 10 min provided stilbene in 74% yield and, when the reaction was run for 15 min provided stilbene in 80% yield (Entries 3 and 4). Finally, the same reaction but at 140 °C was run for 30 min and the crude mixture product was purified by silica gel flash chromatography to provide stilbene in 82% isolated yield (Entry 5).

Table 2. Optimization results for the microwave mediated Heck coupling with complex 7
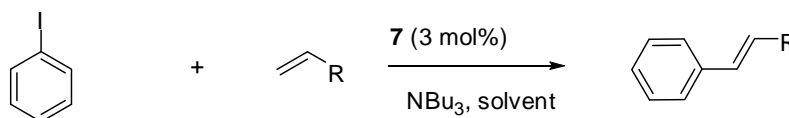
Entry	R	Solvent	Temp. (^{o}C)	Yield(%)^a	Rx time (min)
1	Ph	DMA	110	8	15
2	Ph	DMF	120	40	10
3	Ph	DMA	150	74	10
4	Ph	DMA	150	80	15
5	Ph	DMA	140	82^b	30

a) Yields were calculated from the integration of peaks in GC chromatogram using iodotoluene as internal standard
b) Isolated yield.

We also tested different coupling substrates to expand the scope and applicability of fluorous palladacycle complex **7**, as summarized in Table 3. The reactions were set up the same way as the reactions reported in Table 2, and the organic product was isolated initially by fluorous solid phase extraction (FSPE), followed by silica gel flash chromatography. The scale

of the reaction (0.3 mmol) did not allow complex **7** to be recovered by FSPE in measurable

amounts. The reaction of 4-iodo-anisole and methyl acrylate under the optimized conditions

provided (*E*)-methyl-3-(4-methoxyphenyl) acrylate in 89% isolated yield (Entry 1). Similarly, 4-

bromo-benzonitrile and methyl acrylate provided (*E*)-methyl 3-(4-cyanophenyl) acrylate in 84%

yield (Entry 2).

Table 3. Heck reactions with fluorous palladacycle complex 7
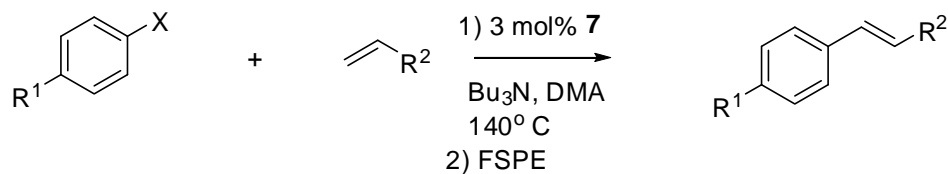
Entry	R^1	X	R^2	Time (min)	Yield (%)
1	MeO	I	CO_2Me	45	89
2	CN	Br	CO_2Me	45	84
3	COMe	I	CO_2Me	30	90
4	COMe	Br	CO_2Me	30	94
5	COMe	OTf	CO_2Me	30	87
6	NO_2	I	CO_2Me	30	79
7	H	I	Ph	30	82
8	MeO	I	Ph	45	76
9	CN	Br	Ph	45	78
10	MeCO	I	Ph	45	89
11	MeCO	Br	Ph	45	92
12	MeO	I	CO_2Me	45	89

a) Isolated yields.

The reactions with 4-iodo, 4-bromo and 4-trifluoromethanosulfonate acetophenones and methyl acrylate provided (*E*)-methyl 3-(4-acetylphenyl) acrylate in 90, 94 and 87% yield respectively (Entries 3-5). The reaction of electron-deficient 4-iodo-nitrobenzene and methyl acrylate provided (*E*)-methyl 3-(4-nitrophenyl) acrylate in 79% isolated yield (Entry 6). Next, the reaction of iodobenzene and styrene was found to provide stilbene in a very good 82% yield (Entry 7). Similarly, 4-iodo-anisole, 4-bromo-benzonitrile, 4-iodo-acetophenone and 4-bromo-acetophenone provided the respective Heck products in very high yields (76, 78, 89 and 92% isolated yield, Entries 8-11).

1.2.3   Recycling experiments with fluorous palladacycle complex 7

The next step was to evaluate the recycling of complex **7**. Previous work done in the Curran laboratory showed that FSPE is an excellent method for separating organic compounds from fluorous compounds.[31] When using FSPE, the first elution with 80-90% MeOH/H_2O gives the organic product and the second elution with ethyl ether, or THF, provides the fluorous compound. Based on the reliability of FSPE, a larger scale experiment was designed to obtain an accurate recovery percentage of complex **7** through several cycles. The reaction of bromoacetophenone (1.25 mmol) and methyl acrylate was promoted by complex **7** (41.5 mg, 3 mol%) in DMA (4 mL) at 140°C for 30 min. After cooling, the reaction mixture was loaded on a 20 g FSPE cartridge and compound **12** was isolated in 94% yield from the fractions eluted with 90% MeOH/H_2O. The fractions eluted with diethyl ether were concentrated and the residue was recrystalized from a 1/1 mixture of ACN/hexanes, providing complex **7** in 76% yield (31.4 mg). The recrystalized complex was reused for another 1.25 mmol scale coupling reaction. Three cycles of recovery and reuse of complex **7**, were performed with very good results (Table 4). The

^{1}H NMR spectrum of recovered **7** showed the expected peaks with no trace of free ligand after recrystalization. The ^{1}H NMR spectra of all three recovered samples were identical to the spectrum of the original sample of complex **7**, and to each other, proving that in each cycle the same complex was recovered and reused as new.

Table 4. Recovery experiments with fluorous palladacycle complex 7

11, 1.25 mmol/cycle

3 mol% **7**

Bu$_3$N, DMA
140° C, 30 min

12
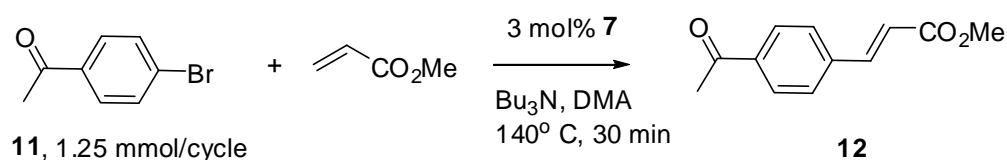
Cycle	Amount **7** used	mol% **7**	Yield (%)	Amount recov. **7**[a]
1	41.5 mg	3	94	31.4 mg
2	31.4 mg	2	97	26.0 mg
3	26.0 mg	1	98	19.6 mg

a) Mass of complex **7** recovered after recrystalization in 1/1 mixture of ACN/hexanes.

The recovery experiments showed clearly that most of fluorous palladacycle **7** survived the reaction conditions. These results indicated that either **7** catalyzes the Heck coupling reaction or functions as a source of small amounts of highly active palladium nanoparticules that are the true catalyst of the reaction. It was noted that the reaction mixture changes from a clear yellow to a dark red color, which is evidence for palladium nanoparticles in polar solvents.[32]

Finally, a large scale experiment was performed wherein 1 g of bromoacetophenone was coupled with methyl acrylate in 3 mol% of complex **7** (167 mg). Product **12** was obtained in high

yield (951 mg), and was tested for traces of palladium (by elemental analysis with resolution as low as parts per billion).[33] Only 74 ppm of palladium was found in the organic product, corresponding to 0.45% of the original amount of palladium that was added. If it is assumed that all of the palladium nanoparticules eluted together with the organic product during purification and that indeed those nanoparticules are the true catalyst, then the Heck reaction was promoted by 0.01 mol% of **7**.

1.3   CONCLUSIONS

The air stable light fluorous palladacycle complex **7** was synthesized and used to promote the Heck reaction with a variety of substrates in very high yields and in short reaction times. The highly convenient microwave irradiation technology was used to facilitate the reaction.[34]

High levels of recycling (75% recovered each cycle) of the light fluorous palladacycle complex was uncovered. The complex showed high stability to the reaction conditions allowing us to recover, recrystalize and reuse it "as good as new", reproducing the yields cycle by cycle.

The reaction was successfully scaled-up to 1 g of bromoacetophenone without any loss in yield of the product or of the recovered catalyst. Regardless whether complex **7** is a precursor of highly catalytic palladium nanoparticules or a true catalyst, it is an attractive new kind of palladacycle that is soluble under standard palladium coupling reaction conditions, can be recovered very easily by FSPE, and can be reused for future small or big scale experiments.

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1.4   EXPERIMENTAL

General

All reactions were performed under an atmosphere of argon unless otherwise specified or the reaction solvent contained water. The reaction times reported are dictated by TLC analysis of the reaction mixture in comparison to the starting material. Reaction solvents were freshly dried either by distillation or passing through an activated alumina column. Methylene chloride (CH_2Cl_2) was distilled from CaH_2 and toluene, benzene, diethyl ether, and tetrahydrofuran (THF) were distilled from Na/benzophenone. All other commercially available solvents and reagents were used without further purification.

Products were analyzed by ^1H NMR, ^{13}C NMR, ^{19}F NMR, LC-MS, FT-IR, high and low resolution mass spectrometry, and HPLC. NMR spectra were recorded on a Bruker WH-300, an IBM AF-300, an AM-500, or a Bruker Avance^{TM} 600 NMR spectrometer. Spectra were recorded at room temperature in the indicated deuterated solvents and chemical shifts were reported in parts per million (ppm) from the residual solvent signal of the deuterated solvent. In the case of ^{19}F NMR spectroscopy no internal standard was used or any special care was taken to measure it. IR spectra were recorded on an IBM IR/32 spectrometer and ran as chloroform solutions. Low resolution mass spectra were obtained on a Hewlett Packard-9000 GC-MS, and high resolution spectra were recorded on a Varian MATCH-5DF instrument. HPLC analysis was performed on a Waters 600E system with UV detector. LC-MS spectra were obtained on a Hewlett Packard-1100 LC-MS using APCI positive mode. All MS peaks were reported in units of m/z. Melting points were measured on a MEL-TEMP II apparatus and were not corrected.
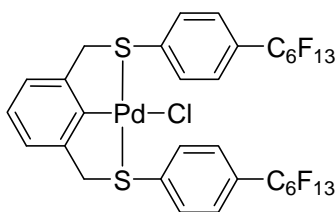
Fluorous palladacycle complex (7): In a 10 mL dry round bottom flask $Cl_2Pd(ACN)_2$ (65 mg, 0.25mmol) was dissolved in acetonitrile (3 mL). Then 1,3-bis((4-(perfluorohexyl) phenylthio) methyl)benzene (235 mg, 0.25 mmol) was added followed by the addition of BTF (3 mL). The reaction mixture was refluxed and stirred for 2 days, cooled to 0° C and then the yellow precipitate was filtrated with cold acetonitrile. The crude product was recrystalized from a 1:1 mixture of acetonitrile/hexanes to give pure 7 (178 mg, 71% yield) as fine light yellow crystals (Mp: 224° C): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 4H), 7.59 (d, J = 8.3 Hz, 4H), 7.08 (m, 4H), 4.68 (s, 3H); ^{19}F NMR (282.4 MHz, $CDCl_3$) δ -79.57 (3F), -109.86 (2F), -120.32 (4F), -121.59 (2F), -124.96 (2F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 149.0, 136.8, 130.7, 130.2, 128.3, 125.6, 122.8, 50.3; LCMS (APCI, positive mode): m/z = 1063 (M − Cl); EIMS: m/e = 1100 (M$^+$), 1063 (M − Cl), 958 (M − PdCl).

General procedure for the Microwave-Mediated Heck Reaction: The haloarene (0.3 mmol) was mixed with catalyst 7 (10 mg, 3 mol%) in a microwave tube with a stirring bar. To this was added DMA (1 mL), tributylamine (39 mg, 0.3 mmol) and methyl acrylate or styrene (0.38 mmol). The reaction tube was sealed and reacted in a CEM Discover Microwave reactor for 30 to 45 min at 140°C with continuous stirring. After 5 min of cooling, the reaction mixture was loaded on a 10 g FluoroFlash^{TM} cartridge that had been preconditioned with 9:1 MeOH-H_2O. The cartridge was eluted with 60 mL of the solvent mixture to give the non-fluorous compounds, followed by elution with 30 mL of Et_2O to give fluorous complex 7. The non-fluorous

compounds were purified by a quick column chromatography to afford the Heck product in high yields. The products are known compounds that were analyzed by ^{1}H NMR spectroscopy and GC.

Gram-scale reaction and complex recovery experiments: Bromoacetophenone (1.0 g, 5.05 mmol) was mixed with palladacycle **7** (167 mg, 3 mol%). To the resulting mixture was added DMA (8 mL), tributylamine (652 mg, 5.05 mmol), and methyl acrylate (6.3 mmol). The reaction tube was sealed and reacted in a CEM Discover Microwave reactor for 30 min at 140°C with continuous stirring. After 5 min of cooling, the reaction mixture was loaded on a 50 g FluoroFlash^{TM} cartridge that had been preconditioned with 9:1 MeOH-H$_2$O. The cartridge was eluted with 100 mL of the mentioned solvent mixture to give the non-fluorous compound, followed by elution with 80 mL of Et$_2$O, to give fluorous complex **7** (160 mg). The ethereal solution was concentrated and recrystalized from hexanes, giving light yellow crystals (116 mg, 60%).

Stability experiments with fluorous palladacycle complex: In a round bottom flask fluorous palladacycle **7** (20 mg, 0.018mmol) was dissolved in THF (5 mL). TBABr or TBAI (0.036 mmol) was then added. The reaction mixture was stirred or refluxed for 24h and the solvent was removed and the crude was analyzed by ^{1}H NMR, HPLC, LCMS, and melting point. The results indicated the lack of formation of any halogen-exchanged complex (no standard compound was prepared to measure the formation of exchanged complex).

1.5   REFERENCES

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2.0 APPLICATION OF FLUOROUS MIXTURE SYNTHESIS (FMS) FOR THE SYNTHESIS OF NATURAL PRODUCT STEREOISOMER LIBRARIES: TOTAL SYNTHESIS OF EIGHT DIASTEREOMERS OF PASSIFLORICIN A.

2.1 INTRODUCTION

A natural product stereoisomer library is a family or a group of stereoisomers from a natural product that may present a similar biological profile. The synthesis and biological activity of natural product stereoisomer libraries have become progressively more important because of the fundamental relationship between different stereostructures and the specific active site for the respective natural product. Furthermore, their synthesis is relevant because it allows the unequivocal structural assignments of natural products whose stereoisomers may have similar spectra.[1] However, literature on stereoisomers library synthesis has been for the most part limited to compounds with a core structure that is available from nature or compounds with only a single functional group or stereocenter that is modified.[2] This shortage surely is not because there is a lack of interest. Stereostructure is an important target for variation in any structure-activity study.[3] Moreover, stereoselective methods in synthesis are available for most transformations; therefore, it is clear that stereoisomer libraries represent a difficult challenge for current solution phase synthesis.[4]

To streamline the synthesis of multiple stereoisomers, the technique of fluorous mixture synthesis (FMS) was developed.[5] FMS has emerged as a general and powerful alternative to traditional solution-phase synthesis and to solid-phase synthesis because it fuses many of the most attractive features of both types of approaches.[6] This technique exploits the simplicity and velocity of working with mixtures of compounds, yet still permits a systematic separation of the mixtures to provide individual pure stereoisomers or analogs.[7]

FMS has three main stages: 1) premix, 2) mixture synthesis, and 3) postmix. The premix stage involves tagging of individually synthesized substrates with homologous fluorous protecting groups (e.g., fluorous silanes, PMBs, or MOMs),[8] followed by the mixing of the tagged substrates. The mixture synthesis stage involves the stepwise construction of the molecules through standard synthetic reactions. This stage ends with the demixing, where each mixture is separated over fluorous silica gel into its individual fluorous-tagged components based on their fluorous content (i.e., the number of fluorine atoms in a single compound). In the final postmix stage, the fluorous tags are removed in parallel providing the target compounds.[9]

Early FMS work used only a single fluorous tag per component of the mixture. A recent project in the Curran group demonstrated that components with *fluorinated* scaffolds and *fluorous* tags showed longer retention times on fluorous HPLC than the components without the *fluorinated* scaffold. This redundant tagging, based on the accumulated fluorine content of each component of a mixture, gave birth to the idea of multiple-tag FMS.[10] This technique permits the systematic fluorous tagging of *N* stereocenters in each component of a single mixture. The steps are in the following sequence: 1) split the substrate into two batches, 2) diastereoselective reaction with the reagent of opposite chirality for each batch, and 3) individual tag and mix of the components. This sequence of steps is repeated as many times as stereocenters to be tagged

(Figure 5). Multiple-tag FMS becomes doubly attractive because it saves steps over linear, or parallel, approaches and it allows the use of fewer fluorous tags than the number of stereoisomers in the library.[11]

The number of components in a fluorous mixture is limited by the number of tags; in turn, multiple-tag FMS for a library of n components is distinctively encoded with $n/2 + 1$ tags. For example: encoding a mixture of four components where two stereocenters are tagged requires three fluorous tags (P^1, P^2 and P^3, in order of increasing fluorine content). This strategy provides a mixture of four fluorous compounds in the following order of accumulated fluorous content: $P^1P^1 < P^1P^2 < P^1P^3 < P^2P^3$. This rationale can be extended to larger libraries if we assume that the minimal requirement to achieve fluorous demixing is one fluorine atom between each component of a mixture.

P^1, P^2, P^3, P^4 are fluorous tags with different fluorine content

$P^1 = C_3F_7$, $P^2 = C_4F_9$, $P^3 = C_6F_{13}$, $P^4 = C_8F_{17}$

R and S are a stereoselective reagent that gives the opposite stereochemical outcome under reagent control

X, Y = stereocenters of opposite chirality.

A = chiral or achiral substrate.
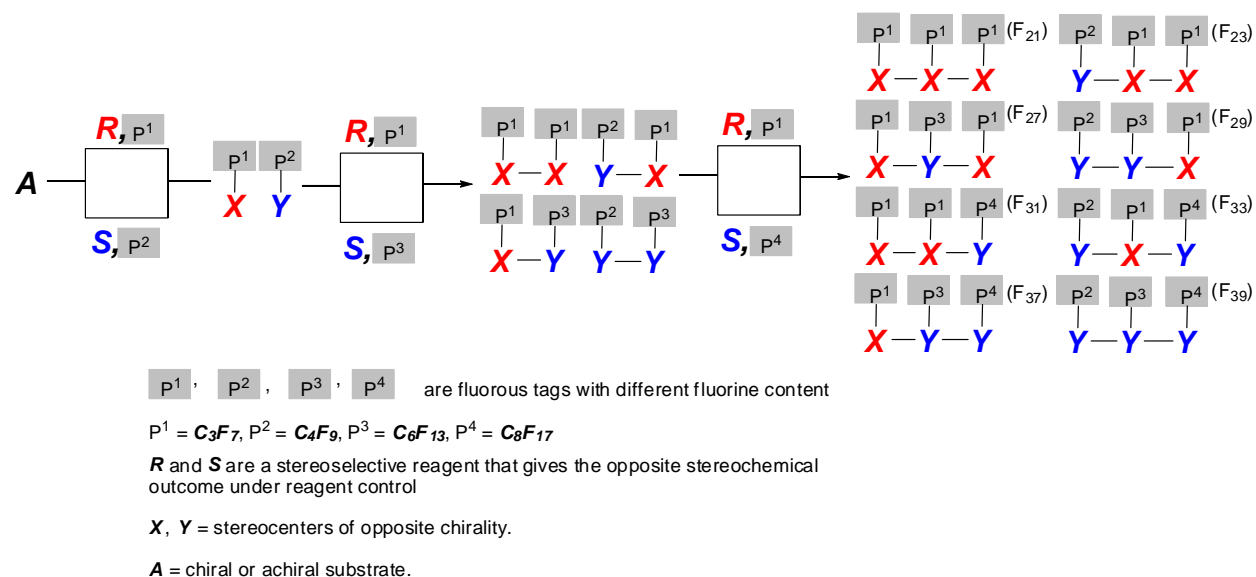
Figure 5. Schematic representation of a multiple-tag FMS for stereoisomer library synthesis

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FMS has been applied successfully to the synthesis of natural products, their isomers, and libraries. The Curran group pioneered the field with the synthesis of a 560-compound library of mappicine analogs.[10a] Next, the Curran group developed the first stereoisomer library FMS with the synthesis of all sixteen isomers of the pinesaw fly pheromone;[10b] followed by the development of an orthogonal tagging strategy using fluorous tags and OEG (olygoethylene glycol) tags with the synthesis of the acetogenin murisolin.[10c] More recently, the Curran group completed the synthesis of four diastereomers of lagunapyrone, four diastereomers of cytostatin, and four diastereomers of (−)-dictyostatin, all by fluorous mixture synthesis (Figure 6).[10d-f]

560 analogs of mappicine

16 isomers of the pinesaw fly pheromone

16 isomers of of murisolin

4 diastereomers of cytostatin

4 diastereomers of lagunapyrone

4 diastereomers of dictyostatin
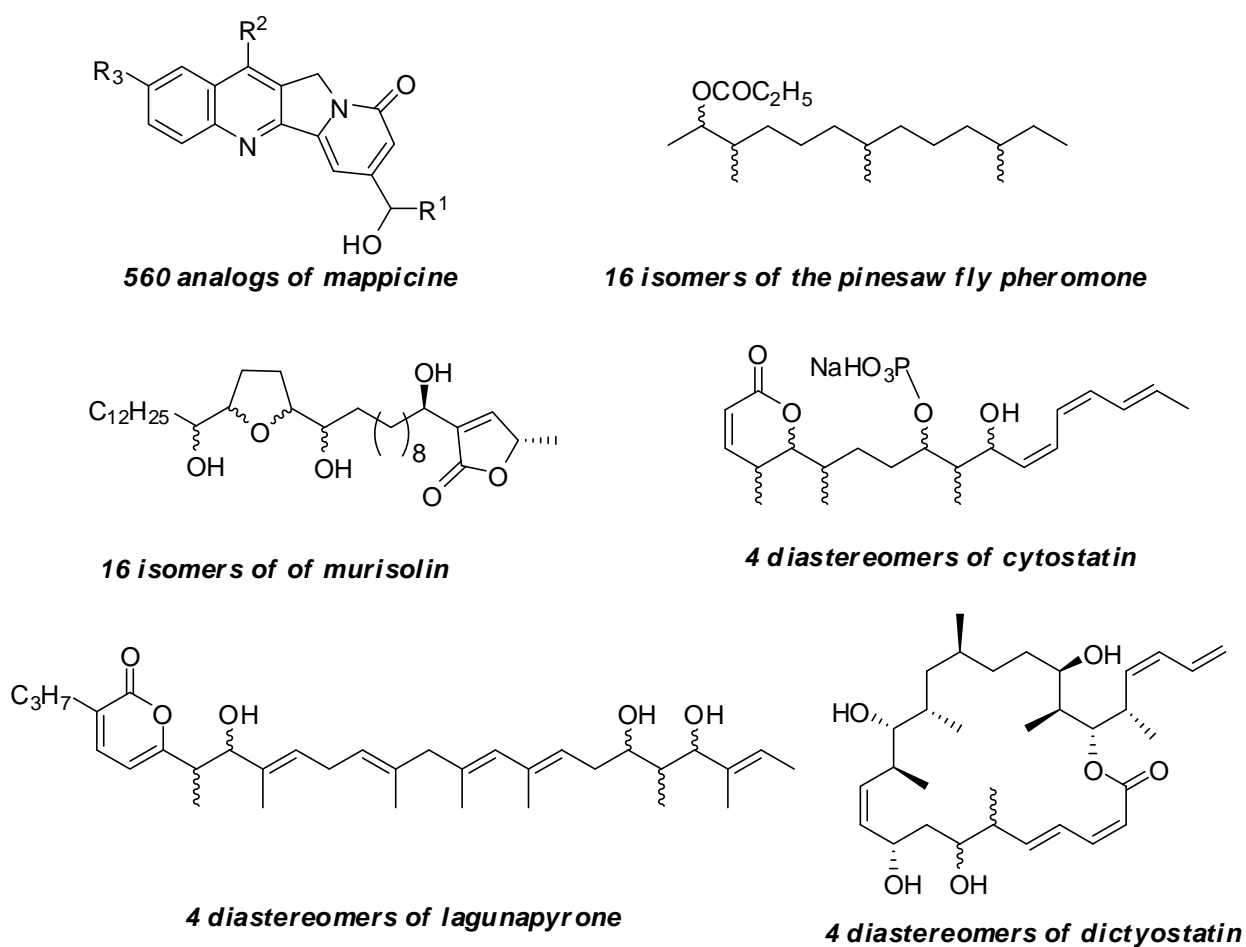
Figure 6. Recently completed FMS projects

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2.1.1   Passifloricin A and its isomers

Passifloricin A was isolated from the tree *Passiflora foetida* (a member of the passion flower family) in the tropical regions of Colombia.[14] Passifloricin A has moderate to good levels of cytotoxicity (LC_{50} = 2.3 μg/mL) and antifungal activity (LC_{50} = 5.61 μg/mL);[17] and a recent paper shows that this natural product also displays activity against parasites (EC_{50} = 0.36 μg/mL).[13] Pasifloricin A was characterized as either structure **1** or **2** by the Echeverri group (Scheme 2). Triols **1** and **2** were synthesized by Marco[15] and later by Cossy.[16] However, the spectroscopic data from synthetic samples **1** and **2** did not match that of the natural product. These results indicated that the initial structure assigned for the natural product was not correct.
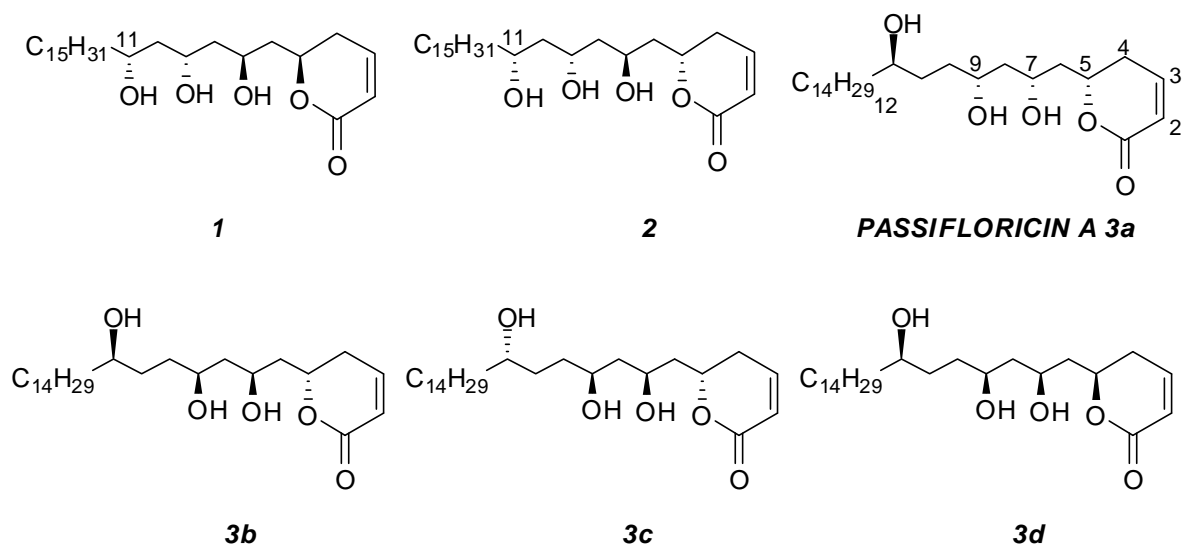
Scheme 2. Proposed structures for passifloricin A

Comparison of the mass spectra of natural passifloricin A and synthetic **1** and **2** exposed differences in the mass fragmentation pattern. Based on the observed fragmentation, Marco postulated that passifloricin A was the constitutional isomer **3a** with the left most hydroxyl group in the C12 instead of the C11.
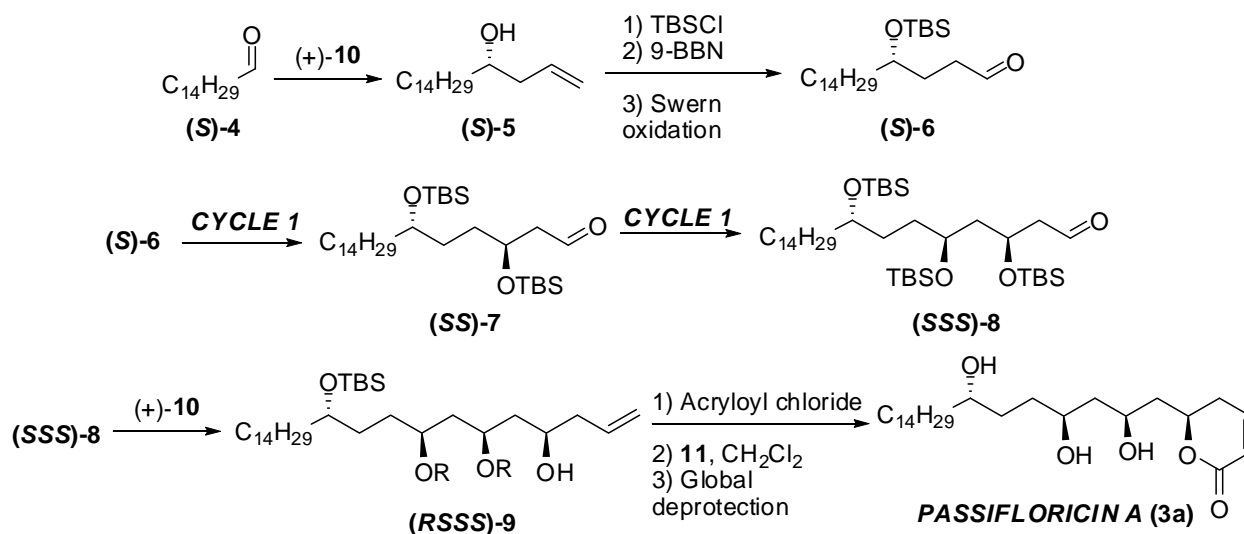
CYCLE = allylation with (+)-**10**, protection as a TBS ether, ozonolysis.

(+)-allyldiisopinocampheyl borane

(+)-**10**

(-)-allyldiisopinocampheyl borane

(-)-**10**

Grubbs second generation catalyst

11
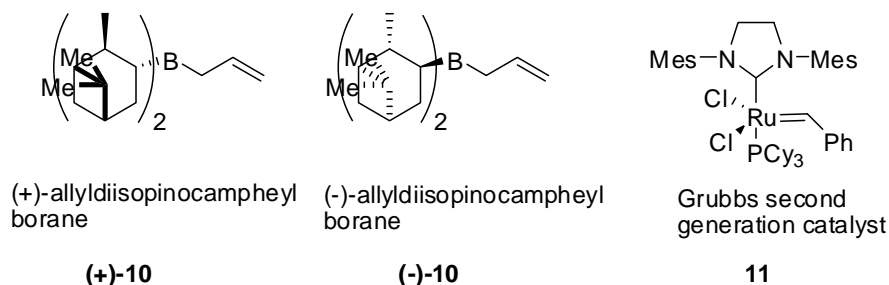
Scheme 3. Marco's synthesis of passifloricin A

In a second synthetic effort, Marco's group made **3a** and found that its ^1H NMR, ^{13}C NMR, and mass spectra matched the spectroscopic data for natural passifloricin A. Along with

constitutional isomer **3a**, they synthesized three other diastereomers (**3b**, **3c** and **3d**).[17] Marco's synthetic approach to **3a** relied on iterative diastereoselective allylation reactions to set the stereocenters. The construction of each stereocenter was obtained by a "cycle" of diastereoselective allylation, protection, and oxidative cleavage reactions, as summarized in Scheme 3.

Each stereocenter was obtained by using Brown's diastereoselective allylation reaction with the commercially available allyldi*iso*pinimcampheylborane (+)-**10**. The synthesis began with the allylation of **4** with (+)-**10** to obtain homoallylic alcohol (**S**)-**5** in 80% yield and 92% *ee*. Homoallylic alcohol (**S**)-**5** was protected as a TBS ether, followed by the hydroboration of the olefin with 9-BBN, and the final oxidation to obtain aldehyde (**S**)-**6** in 66% overall yield. Aldehyde (**S**)-**6** was subjected to cycle 1 (allylation with (+)-**10**, protection as a TBS ether, and ozonolysis) to provide aldehyde (**SS**)-**7** in 42% overall yield and 90% *de*. Moreover, aldehyde (**S,S**)-**7** after cycle 2 provided aldehyde (**SSS**)-**8** in 55% overall yield and 90% *de*. Final diastereoselective allylation of (**SSS**)-**8** provided homoallylic alcohol (**RSSS**)-**9** in 68% yield and 90% *de*. The construction of the δ-lactone was achieved by reacting (**RSSS**)-**9** with acryloyl chloride, followed by ring closing metathesis (RCM) of the resulting ester with Grubbs second generation catalyst **11**, and final global deprotection with HCl 1M in MeOH; to obtain passifloricin A (**3a**) in 64% yield from (**RSSS**)-**9**. The same synthetic pathway was used to prepare diastereomers **3b**, **3c** and **3d**.

2.1.2   Multiple-tag FMS strategy

It was envisioned for this project that the application of a multiple-tag FMS for the synthesis of all eight diastereomers of passifloricin A would be achievable. This synthesis is important for the complete stereochemical assignment due to the potential similarity of the diastereomers spectroscopic data. It is even more important as a proof of principle for the proposed multiple-tag FMS strategy. Because of the mixture nature of this technique, purification of diastereomeric impurities during the mixture synthesis stage becomes cumbersome. Therefore, this technique requires that each stereocenter is built with complete reagent control and no influence of the inherited chirality of the substrate (substrate control). To fulfill this requirement, diastereoselective allylation reactions were chosen to establish the stereocenters.

The synthetic approach chosen has three similar iterative sequences of reactions or cycles (Figure 7). The first cycle is done on a single compound and starts with: 1) allylation of aldehyde **4** with (*R*)-chiral reagent, 2) protection as a silyl ether, 3) hydroboration, and 4) oxidation to obtain aldehyde (***R***)-**12**. The second cycle is done on a single compound but produces a fluorous mixture and starts with: 1) the split of (***R***)-**12**, followed by the allylation of one half of (***R***)-**12** with (*R*)-chiral reagent and the allylation of the other half of (***R***)-**12** with (*S*)-chiral reagent, 2) the protection of each allylated product with a different fluorous tag, followed by mixing of both fluorous tagged compounds and 3) the oxidative cleavage of the resulting mixture to obtain aldehyde **M13**. The final cycle will provide, in the same fashion as the second cycle, aldehyde **M14** now as a mixture of 4 quasiisomers. The final steps involve the split of **M14**, followed by the allylation of one half of **M14** with (*R*)-chiral reagent and the allylation of the other half of

M14 with (*S*)-chiral reagent, and the acylation of each mixture to provide (***R***)-**M15** and (***S***)-**M15**. Lastly, the RCM reaction of each mixture will provide (***R***)-**M16** and (***S***)-**M16**, followed by the demixing and the individual global deprotection of each quasiisomer to provide the eight diastereomers of passifloricin A.
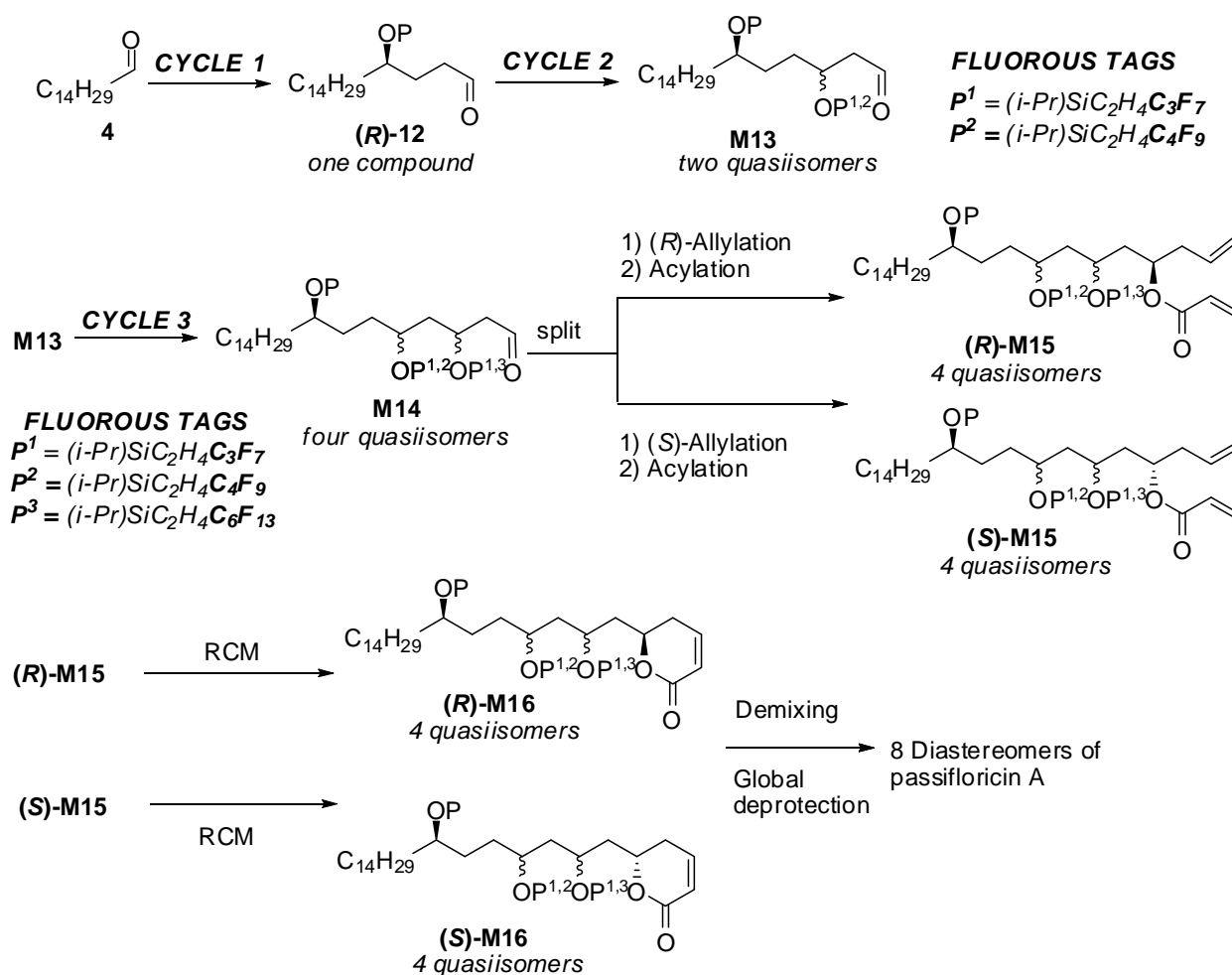
CYCLE 1 = a) allylation with (*R*)-chiral reagent, b) protection, c) hydroboration, d) oxidation
CYCLE 2 = a) split, one half of (***R***)-**12** reacts with (*R*)-chiral reagent and other half of (***R***)-**12** reacts with (*S*)-chiral reagent, b) protection of each allylated product with a different fluorous tag and then mixing, c) oxidative cleavage.
CYCLE 3 = a) split, one half of **M13** reacts with (*R*)-chiral reagent and other half of **M13** reacts with (*S*)-chiral reagent, b) protection of each allylated product with a different fluorous tag and then mixing, c) oxidative cleavage.

Figure 7. Multiple-tag FMS strategy for the synthesis of eight diastereomers of passifloricin A

The next goal was to design the tagging strategy for this multiple-tag FMS. Previous FMS developed in the Curran lab has shown that components of a mixture with redundant tagging have an order of elution directly proportional to the accumulated fluorine content.[10] Based on those results, it was decided to use diisopropyl fluoroalkyl silanes as the tags for our multiple-tag FMS.[18] It was proposed that to unambiguously separate two mixtures of four quasiisomers each, three different fluorous groups would be needed to tag two stereocenters. Therefore, binary combinations of P^1 (seven fluorine atoms), P^2 (nine fluorine atoms) and P^3 (thirteen fluorine atoms) diisopropyl fluoroalkyl silanes were used (Figure 7).

2.1.3   Diastereoselective allylation reactions

Addition of chiral allyl-metal reagents to aldehydes is one of the most important approaches for the construction of stereocenters in open-chain systems. [19] Enantioselecive allylations can be catalytic or stoichiometric in terms of the amount of chiral reagent and also can be classified as type I (closed transition state) or type II (open transition state) depending on the metal that bears the allyl group.[20] Most common reagents and catalysts for diastereoselective allylation reactions use one or more of the following metals to transfer allyl groups to aldehyde electrophiles: boron, titanium, silicon, silver, zirconium, and chromium.[21]

Allyl-boron reagents are classified as type I and are among the most efficient diastereoselective allylation reagents.[22] H. C. Brown discovered that the allylation of achiral aldehydes with allyl-boranes, like allyldi*iso*pinocampheylborane **(+)-10,** yields homoallylic alcohols with very good enantioselectivities. In a typical Brown allylation reaction, **(+)-10** at

−100 °C in diethyl ether was reacted with benzaldehyde for 6 h at the same temperature. The reaction was quenched with basic H_2O_2 and the crude product was purified to provide homoallylic alcohol **17** in 81% yield and 96% *ee* (Scheme 4). Similarly, Brown found that **(+)-10** reacted with *n*-butyraldehyde under the same conditions to provide homoallylic alcohol **18** in 72% yield and 93% *ee*.[23] Similarly, the allylation of α-chiral aldehydes was found to provide homoallylic alcohols with poor levels of reagent control stereoselectivity. The reaction of **19** with **(+)-10** provided homoallylic alcohol **20** in 68% yield and 96% *de*; and the allylation of **19** with **(−)-10** provided **21** in 71% yield and 34% *de*.[24]

R	product	yield(%)	ee(%)
C_6H_5	**17**	81	96
n-C_3H_7	**18**	72	93

(+)-10 68% yield 96% *de* for **20**

(−)-10 71% yield 34% *de* for **21**

R	product	yield(%)	ee(%)
C_6H_5	**17**	78	72
n-C_3H_7	**18**	97	87

Allylbisamidoboronate **(S,S)-22**
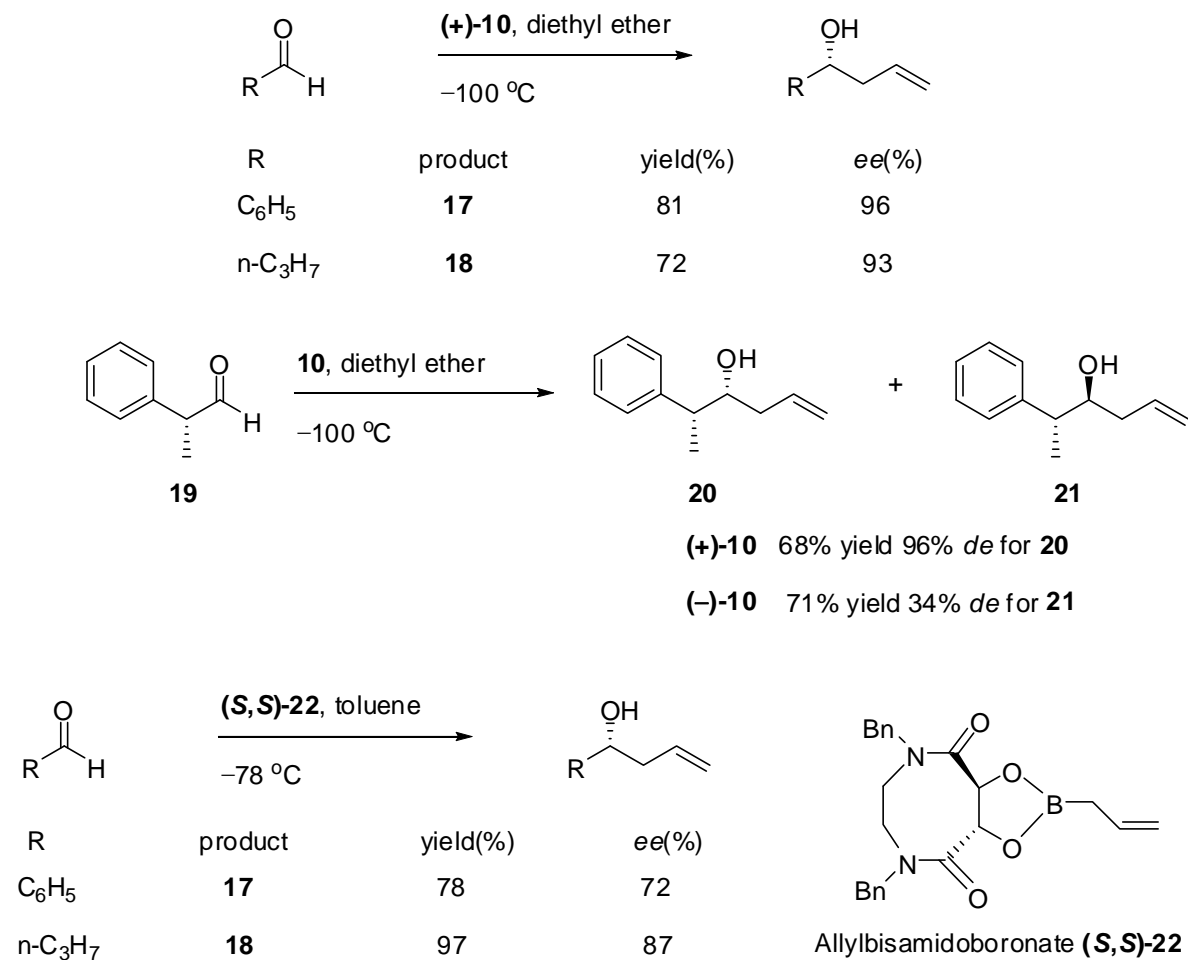
Scheme 4. Allyl-boron reagents for stereoselective allylations

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Roush found that the reaction of allyl-boronates like **(S,S)-22** and aldehydes provides homoallylic alcohols in high yields and moderate stereoselectivities.[25a] The reaction of **(S,S)-22** with benzaldehyde at −78 °C in toluene provided **17** in 78% yield and 72% *ee*, and the reaction with *n*-butyraldehyde provided **18** in 97% yield and 87% *ee* (Scheme 4).[25b] However, the synthesis of **(S,S)-22** requires six steps from commercially available (*S,S*)-diethyl tartrate; in turn, reagent (+)-**10** is commercially available.

Duthaler and Hafner found that strained allyl-titanium type I allylation reagents react with aldehydes to provide homoallylic alcohols with high levels of stereoselectivity. In a typical reaction, a solution of allyltitanocene **(S,S)-23** in diethyl ether was cooled to −78 °C, and benzaldehyde was added. After 3 h, the reaction was quenched with a 45% NH$_4$F aqueous solution and then the crude mixture was purified to provide **17** in 93% yield and 95% *ee*. Correspondingly, the reaction with *n*-butyraldehyde provided **18** in 94% yield and 94% *ee* (Scheme 5).[26] Moreover, the allylation of α-chiral aldehyde **19** with **(R,R)-23** provided homoallylic alcohol **20** in 91% yield and 90% *de*; and the reaction with **(S,S)-23** provided homoallylic alcohol **21** in 94% yield and 98% *de*. The allylation of chiral aldehyde **19** with allyltitanocenes **23** was shown to provide good levels of reagent control diastereoselectivity.[27] Allyltitanocene **(S,S)-23** was obtained by the reaction of (*S,S*)-Taddol and CpTiCl$_3$, followed by the addition of allylMgCl.

The Keck reaction, using titanium-based Lewis acids as type II allylation reagent, promotes the reaction of allylstannanes and aldehydes with good levels of stereocontrol (Scheme 5). In a typical Keck allylation reaction, Ti(i-OPr)$_4$ and (*R,R*)-BINOL were dissolved in CH$_2$Cl$_2$ to form catalyst **(R,R)-24**. The resulting solution containing 10 mol% of catalyst was added at RT to benzaldehyde and after 30 min to allyltributyltin. The reaction was stirred for 20 h and

quenched by adding water, then the crude mixture was purified to provide **17** in 98% yield and 92% *ee*. The reaction using *n*-butyraldehyde provided **18** in 95% yield and 92% *ee*.[28] Keck's catalyst promoted the allylation of chiral aldehydes with low levels of reagent control stereoselectivity. Thus the reaction of β-chiral aldehyde **25**, allyltributyltin, and **(S,S)-24** provided homoallylic alcohol **26** in 79% yield and 88% *de* and the reaction with **(R,R)-24** provided **27** in 65% yield and 50% *de*.[29]

Maruoka further improved the allylation reaction of aldehydes with allyltributyltin and titanium-based chiral Lewis acids by developing more enantioselective μ-oxo-type chiral Lewis acid **(R,R)-28**.[30] In a typical reaction, $Ti(i\text{-}OPr)Cl_3$ was dissolved in CH_2Cl_2 and at RT was added Ag_2O followed by (R,R)-BINOL to provide catalyst **(R,R)-28**. A solution containing 10 mol% of **(R,R)-28** at 0 °C was treated with benzaldehyde then allyltributyltin, and after 48 h the reaction was quenched with water and the crude mixture was purified to provide **17** in 90% yield and 96% *ee*. The reaction with *n*-butyraldehyde provided **18** in 85% yield and 99% *ee* (Scheme 5).[31]

Chiral allylsilanes, as type I allylation reagents, were initially developed by Kira.[32] He found that a tartrate-derived allylsilane added to aldehydes with high levels of conversion and stereoselectivity. Leighton found that strained chiral allylsilacycles reacted with aldehydes to provide homoallylic alcohols in excellent *ee* and yields (Scheme 6).[33] In a typical reaction, a solution of allylcyclohexylbisaminosilacycle **(S,S)-29** in CH_2Cl_2 was cooled to −10 °C and benzaldehyde was added. After stirring for 20 h, the reaction was quenched with aqueous 1 M HCl, and then the crude mixture was purified to provide **17** in 69% yield and 98% *ee*. The reaction with *n*-butyraldehyde provided **18** in 80% yield and 96% *ee*.[34a]

R-CHO reaction with (S,S)-23, diethyl ether, −78 °C → allylic alcohol

R	product	yield(%)	ee(%)
C$_6$H$_5$	**17**	93	95
n-C$_3$H$_7$	**18**	94	94

allyltitanocene (**S,S**)-23

Compound **19** reaction with **23**, diethyl ether, −78 °C → **20** + **21**

(**S,S**)-23   94% yield 98% *de* for **20**

(**R,R**)-23   91% yield 90% *de* for **21**

R-CHO reaction with reagent, CH$_2$Cl$_2$, temperature → allylic alcohol

R	reagent	temp (°C)	product	yield(%)	ee(%)
C$_6$H$_5$	(**R,R**)-24	RT	**17**	98	92
n-C$_3$H$_7$	(**R,R**)-24	RT	**18**	95	92
C$_6$H$_5$	(**R,R**)-28	0	**17**	90	96
n-C$_3$H$_7$	(**R,R**)-28	0	**18**	85	99

catalyst (**R,R**)-24

catalyst (**R,R**)-28

Compound **25** reaction with **24**, CH$_2$Cl$_2$, −20 °C → **26** + **27**

(**R,R**)-24   65% yield 50% *de* for **26**

(**S,S**)-24   79% yield 88% *de* for **27**

Scheme 5. Allyl-titanium reagents for stereoselective allylations

Leighton proved that allylsilacycles reacted with aldehydes with high levels of reagent control stereoselectivity. For example; β-chiral aldehyde **30** reacted with **(R,R)-29** to provide homoallylic alcohol **31** in 86% yield and 90% *de*, and the reaction with **(S,S)-29** provided **32** in 86% yield and 96% *de*.[34b] Reagent **(S,S)-29** was obtained by reacting (S,S)-N,N′-di-*p*-bromobenzylcyclohexane-1,2-diamine with allyltrichlorosilane and DBU in CH₂Cl₂.

R	product	yield(%)	ee(%)
C₆H₅	**17**	69	98
n-C₃H₇	**18**	80	96

allylcyclohexylbisaminosilacycle **(S,S)-29**

(S,S)-29   86% yield 90% *de* for **31**

(R,R)-29   86% yield 96% *de* for **32**
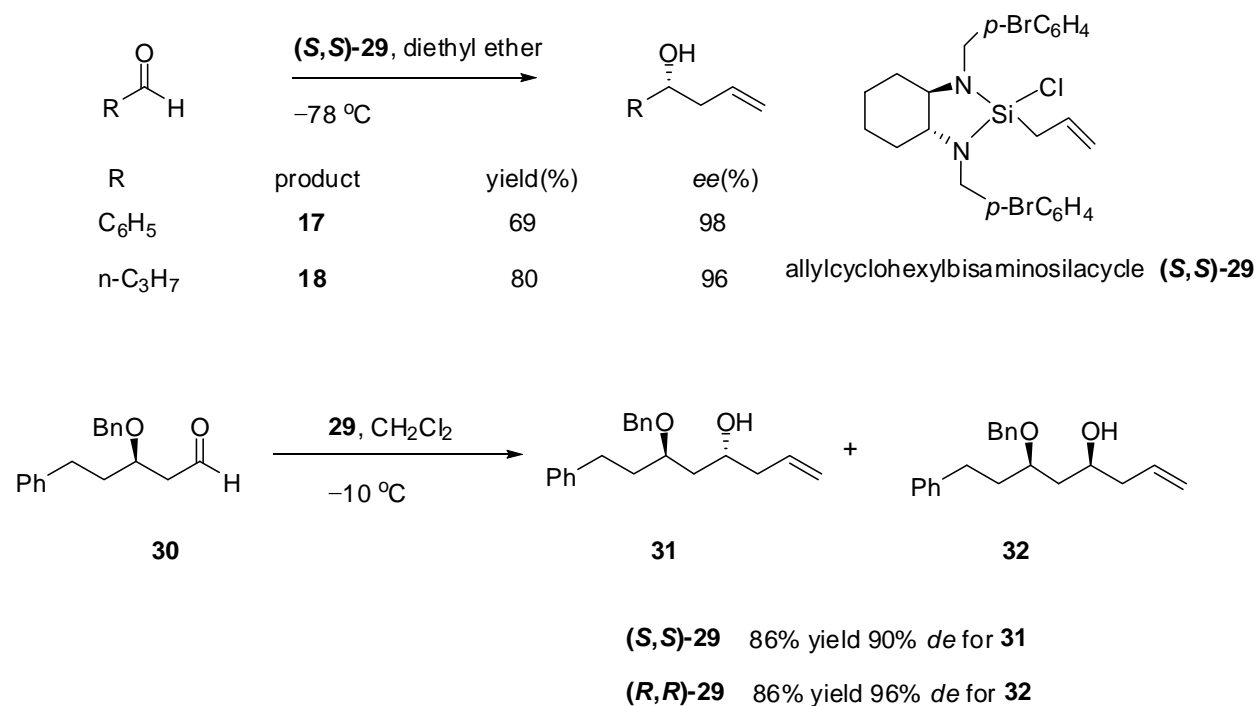
Scheme 6. Allyl-silicon reagents for stereoselective allylations

2.2   RESULTS AND DISCUSSION

As shown in the multiple-tag FMS strategy, allylations are the key reactions for the planned synthesis of passiflorcins. Three different types of allylations must be executed; a first allylation on an achiral substrate (aldehyde **4**), a second allylation on a substrate with a stereocenter at the γ-position (aldehyde **(R)-13**) and a third allylation and fourth allylation on a substrate with a stereocenter at the β-position (aldehyde **M13** and **M14**). FMS requires reactions with very high levels of reagent-controlled stereoselectivity. To evaluate this crucial aspect, the following range of commonly used asymmetric allylation reagents and catalysts were selected for the different substrates: Brown's allyldi*iso*pinocampheylborane **10**, Keck's catalyst **24**, Duthaler-Hafner's allyltitanocene **23**, Leighton's allylcyclohexylbisaminosilacycle **29**, and Maruoka's catalyst **28**.

2.2.1   First allylation

The initial task was to develop an efficient and reliable analytical tool to determine the enantioselectivity of each reagent and catalyst tested for the allylation reaction of aldehyde **4** to create the C12 stereocenter. Initially, pentadecanal (**4**) was reacted with allylMgBr to provide alcohol **rac-5** in 100% yield. Direct analysis of **rac-5** by chiral HPLC or GC did not show evidence of a mixture of enantiomers. Therefore, the derivatization of **rac-5** with (*S*)-*O*-methyl-mandelic acid was attempted. Mandelate mixture **33** was obtained in 95% yield by DCC-mediated coupling of **rac-5** and (*S*)-O-methylmandelic acid in CH_2Cl_2 and DMAP.[35] The spectroscopic analysis of **33** clearly showed a 1:1 mixture of diastereomers and the HPLC analysis of **33** (normal phase Silicapak column, eluted with 99:1 Hex:EtAc) also showed two

peaks in a 1:1 ratio of mandelates **33** (Scheme 7). HPLC analysis of the mandelate derivatives became the analytical tool of choice to measure the enantioselectivities of the different allylation reagents and catalysts for the allylation of aldehyde **4**.

The synthesis of diastereopure mandelate **(SR)-33** from enantiopure **(R)-5** (obtained from the allylation reaction of **4** with **(R,R)-23**, Table 5) and further HPLC analysis of the diastereopure sample proved that the peak at 7.5 min corresponded to **(SR)-33** and the peak at 8.5 min corresponded to **(SS)-33**. The optical rotation measured in $CHCl_3$ for **(R)-5** matched the literature values for this compound in $CHCl_3$.[36] Therefore, it was confirmed that **5** had the desired (**R**) configuration. Based on these results, it was decided to use the allylation reagents and catalysts which predict the *R* configuration in the allylation of aldehydes. The HPLC traces for pure **(SR)-33** and mixture **33** are in Appendix A.
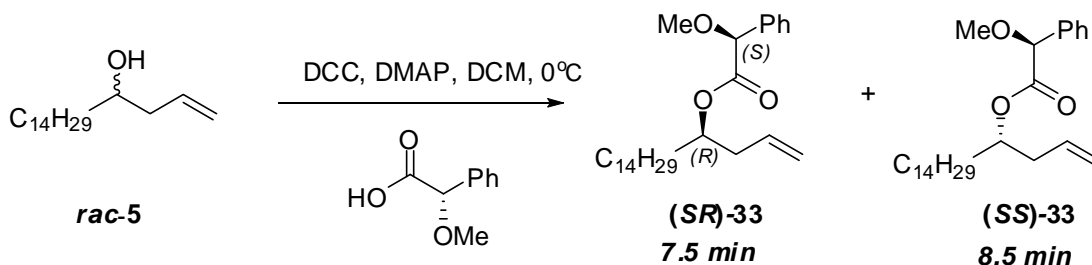
Scheme 7. *O*-**Methyl mandelates for the determination of the stereoselectivities**

With a quick analytical tool to measure stereoselectivities, the reaction of aldehyde **4** with the allylation reagents and catalysts was tested. The reagents and catalystswere available using the procedures described in the introduction. The results of these experiments are summarized in Table 5. Brown's allyldi*iso*pinocampheylborane (−)-**10** reacted with **4** to give **(R)-5** in 97.5:2.5 *er* and 82% yield (Entry 1). Catalyst **(S,S)-24** promoted the reaction of **4** and allyltributyltin to provide **(R)-5** in 53% yield and 98:2 *er* (Entry 2). Commercially available allyltitanocene **(R,R)-**

23 reacted with aldehyde **4** to provide (**R**)-**5** in a very encouraging 99:1 *er* and 86% yield. This result was reproducible with freshly prepared (**R,R**)-**23** (Entry 3). The reaction of allylcyclohexylbisaminosilacycle (**R,R**)-**29** with aldehyde **4** provided (**R**)-**5** in a similar 99:1 *er* but a disappointing 52% isolated yield (Entry 4). Similarly, Maruoka's catalyst (**S,S**)-**28** promoted the reaction of **4** and allyltributyltin to obtain (**R**)-**5** in 91% yield and 99.5:0.5 *er* (Entry 5). Maruoka's catalyst gave the best results in terms of yield and enantioselectivity for the synthesis of (**R**)-**5**.

Table 5. Enantioselective allylation of achiral aldehyde 4

C14H29 (aldehyde, **4**) — reagent → C14H29 with OH (**R**)-**5**
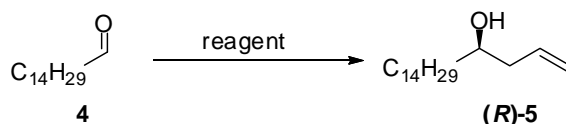
Entry	reagent/catalyst	conditions	Time	Yield of (**R**)-**5** (%)[a]	*er* of (**R**)-**5**[b]
1	(−)-**10**	diethylether/−100 °C	6h	82	97.5:2.5
2	(**S,S**)-**24** (20mol%)	allyltributyltin/toluene/RT	20h	53	98:2
3	(**R,R**)-**23**	diethylether/−78 °C	3h	86	99:1
4	(**R,R**)-**29**	CH$_2$Cl$_2$/−10 °C	20h	51	99:1
5	(**S,S**)-**28** (20 mol%)	allyltributyltin/CH$_2$Cl$_2$/RT	48h	91	>99.5:5

a) Isolated yields.
b) Measured by HPLC analysis of *O*-methyl mandelates.

2.2.2 Second allylation

The construction of the C9 stereocenter requires a diastereoselective allylation on a chiral substrate with a γ-stereocenter (aldehyde (**R**)-**12**). There is little background on substrate

induction due to γ-stereocenters. However, to minimize the chance of substrate control, it was decided to protect the hydroxyl group in C12 with a well known non-chelating group (TBDPS).[37] The reaction of (*R*)-4-(*tert*-butyldiphenylsilyloxy)octadecanal (**(R)-12**) with allylMgBr provided alcohol **34** in 100% yield. Although we expected a 1:1 mixture of diastereomers, direct analysis of **34** by ^{1}H NMR spectroscopy, chiral HPLC, or chiral GC did not show any evidence for a mixture. However, derivatization of alcohol **34** with (*S*)-*O*-methyl-mandelic acid provided separable mandelates **35**. ^{1}H NMR analysis of **35**, prior to separation, showed a 1:1 mixture of diastereomers and HPLC analysis of **35** (normal phase Silicapak column, eluted with 99:1 Hex:EtOAc) showed also a 1:1 ratio of mandelates **35** (Scheme 8). This initial result indicated that allylMgBr adds to aldehyde **(R)-12** without any substrate control. Mandelate mixture **35** was obtained in 93% yield using the same conditions as for mandelate's **33** (Scheme 8).

The synthesis of diastereopure mandelate **(SSR)-35** from enantiopure **(SR)-34** (obtained from the allylation of **(R)-12** with reagent **(S,S)-23**, Table 6) and further HPLC analysis of the diastereopure sample proved that the peak at 10.2 min corresponded to **(SSR)-35** and the peak at 12.6 min corresponded to **(SRR)-35**. The individual synthesis and HPLC analysis of diastereopure **(SRR)-35** confirmed the assignment by providing the isomer with a retention time (T_R) = 12.6 min. HPLC analysis of mandelate derivatives became the analytical tool of choice to measure the diastereoselectivity of different allylation reagents and catalysts for the allylation of aldehyde **(R)-12**. The HPLC traces for pure **(SSR)-35** and **(SRR)-35** and mixture **35** are in Appendix A.
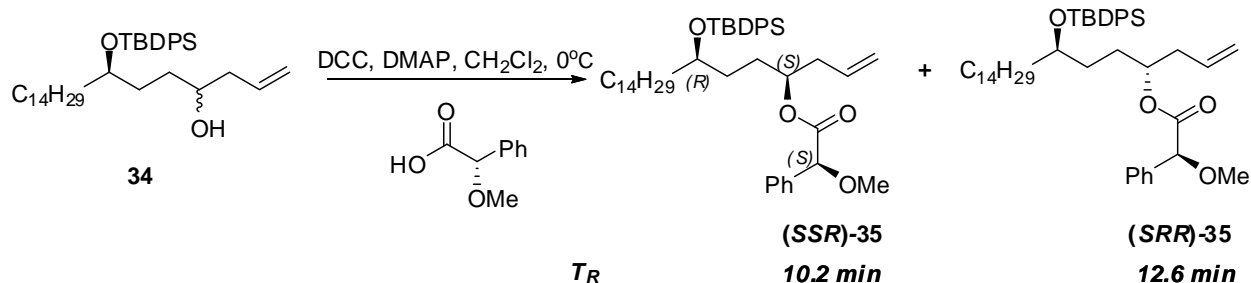
Scheme 8. *O*-Methyl mandelates for the determination of the diastereoselectivities

The results for the reaction of aldehyde **(R)-12** with allylation reagents and catalysts to provide homoallylic alcohol **(SR)-34** and **(RR)-34** are summarized in Table 6. The diastereomeric ratios are shown as the ratio of **(SR)-34**:**(RR)-34**, which are determined by conversion of the product to the mandelate **35** and HPLC analysis. Reagent (−)-**10** reacted with **(R)-12** to give **(RR)-34** in 78% yield and 5:95 *dr*. However, the reaction with (+)-**10** produced **(SR)-34** in 72% yield and 99:1 *dr* (entries 1a and 1b). This difference in the diastereoselectivity indicated a small influence of chiral aldehyde **(R)-12** on the stereochemical outcome of the reaction.

Keck's catalyst **(S,S)-24** promoted the reaction of allyltributyltin with aldehyde **(R)-12** in 35% yield and 88:12 *dr*. Catalyst **(R,R)-24** promoted the reaction in a similar 30% yield and 12:88 *dr* (entries 2a and 2b). The reactions of allyltitanocene **(S,S)-23** and **(R,R)-23** with **(R)-12** provided **(SR)-34** and **(RR)-34** in good yields (75 and 73% yield) and nearly complete reagent control diastereoselectivity (99:1 *dr* and 1:99 *dr*, entries 3a and 3b). Leighton's silacycles **(S,S)-29** and **(R,R)-29** reacted with **(R)-12** to provide **(SR)-34** and **(RR)-34** in low yields but high *dr* (50/31% and 98:2/1:99, Entries 4a and 4b respectively). Unexpectedly, the reaction of Maruoka's catalysts **(R,R)-28** and **(S,S)-28** with **(R)-12** provided **(SR)-34** and **(RR)-34** in low yields but high *dr* (48%, 99:1 and 55%, 1:99; entries 5a and 5b). Optimization of the reaction by

increasing the catalyst load to 40% led to similar yields for homoallylic alcohols (**SR**)-**34** and (**RR**)-**34** (42 and 49% yield, entries 6a and 6b). In summary, Duthaler-Hafner allyltitanocenes **23** gave the best results in terms of yield and diastereoselectivity for the synthesis of (**SR**)-**34** and (**RR**)-**34**.
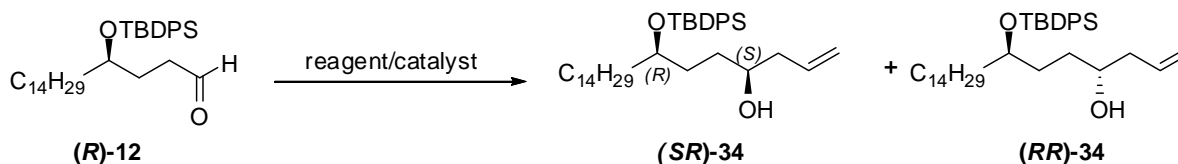
| Entry	reagent/catalyst	conditions	Time	Yield of **34**(%)[a]	dr((**SR**)-**34**:(**RR**)-**34**)[b]
1a	(−)-**10**	diethylether/−100 °C	4h	78	5:95
1b	(+)-**10**	diethylether/−100 °C	4h	72	99:1
2a	(**S,S**)-**24** (20mol%)	allyltributyltin/toluene/RT	20h	30	12:88
2b	(**R,R**)-**24** (20 mol%)	allyltributyltin/toluene/RT	20h	35	88:12
3a	(**R,R**)-**23**	diethylether/−78 °C	3h	73	1:99
3b	(**S,S**)-**23**	diethylether/−78 °C	3h	75	99:1
4a	(**R,R**)-**29**	CH_2Cl_2/−78 °C	20h	31	1:99
4b	(**S,S**)-**29**	CH_2Cl_2/−78 °C	20h	50	98:2
5a	(**S,S**)-**28** (20 mol%)	allyltributyltin/CH_2Cl_2/RT	48h	48	99:1
5b	(**R,R**)-**28** (20 mol%)	allyltributyltin/CH_2Cl_2/RT	48h	55	1:99
6a	(**S,S**)-**28** (40 mol%)	allyltributyltin/CH_2Cl_2/RT	48h	42	——
6b	(**R,R**)-**28** (40 mol%)	allyltributyltin/CH_2Cl_2/RT	48h	49	——

a) Isolated yields.
b) Measured by HPLC analysis of O-methyl mandelates.

Table 6. Diastereoselective allylation of chiral aldehyde (R)-12

2.2.3   Third allylation

The construction of the C7 stereocenter requires a diastereoselective allylation using a chiral substrate with a β-stereocenter (aldehyde **M13**). There are two issues to consider for this reaction: first, the influence of the substrate chirality on the stereochemical outcome and second, the effect that the fluorous tags may have on reactivity and selectivity.[38] The model aldehyde substrate (**M13**, mixture of two quasiisomers) that has fluorous TIPS ethers in the β position was designed. Aldehyde **M13** reacted with allylMgBr in THF and provided **M36** in 100% yield. Since **M13** was a mixture of two quasiisomers and little to no selectivity was expected in the allylation, **M36** should have been a mixture of four isomers. Fluorous HPLC analysis and further demixing of a small sample provided a 1:1 mixture of alcohols **36A** and **36B** in 88% yield. Analysis of **36A** or **36B** by ^{1}H NMR spectroscopy and HPLC did not show evidence of a mixture of two diastereomers.

However, the deprotection reaction of alcohols **36A** and **36B** with 0.5N HCl in ethanol provided diols **37A** and **37B** that were shown to be equimolar mixtures of diastereomers by HPLC analysis (normal phase Silicapak column, eluted wit 9:1 Hex:EtOAc). The retention times for diol mixtures **37A** and **37B** were the following: 11.7 min for (*SRR*)-**37A**, 14.8 min for (*RRR*)-**37A**, 11.8 min for (*RSR*)-**37B**, and 14.9 min for (*SSR*)-**37B** (Scheme 7). The HPLC analysis of diols **37A** and **37B** was a very efficient analytical tool to determine the stereoselectivities for the allylation reaction of aldehyde **M13**. The determination of which diol was *syn* or *anti* was achieved by obtaining the acetonides derivatives of diastereopure diols (*SRR*)-**37A** and (*SSR*)-**37B** (Scheme 10). The HPLC traces for (*SRR*)-**36A** and (*SSR*)-**36B** and mixtures **36A** and **36B** are in Appendix A.
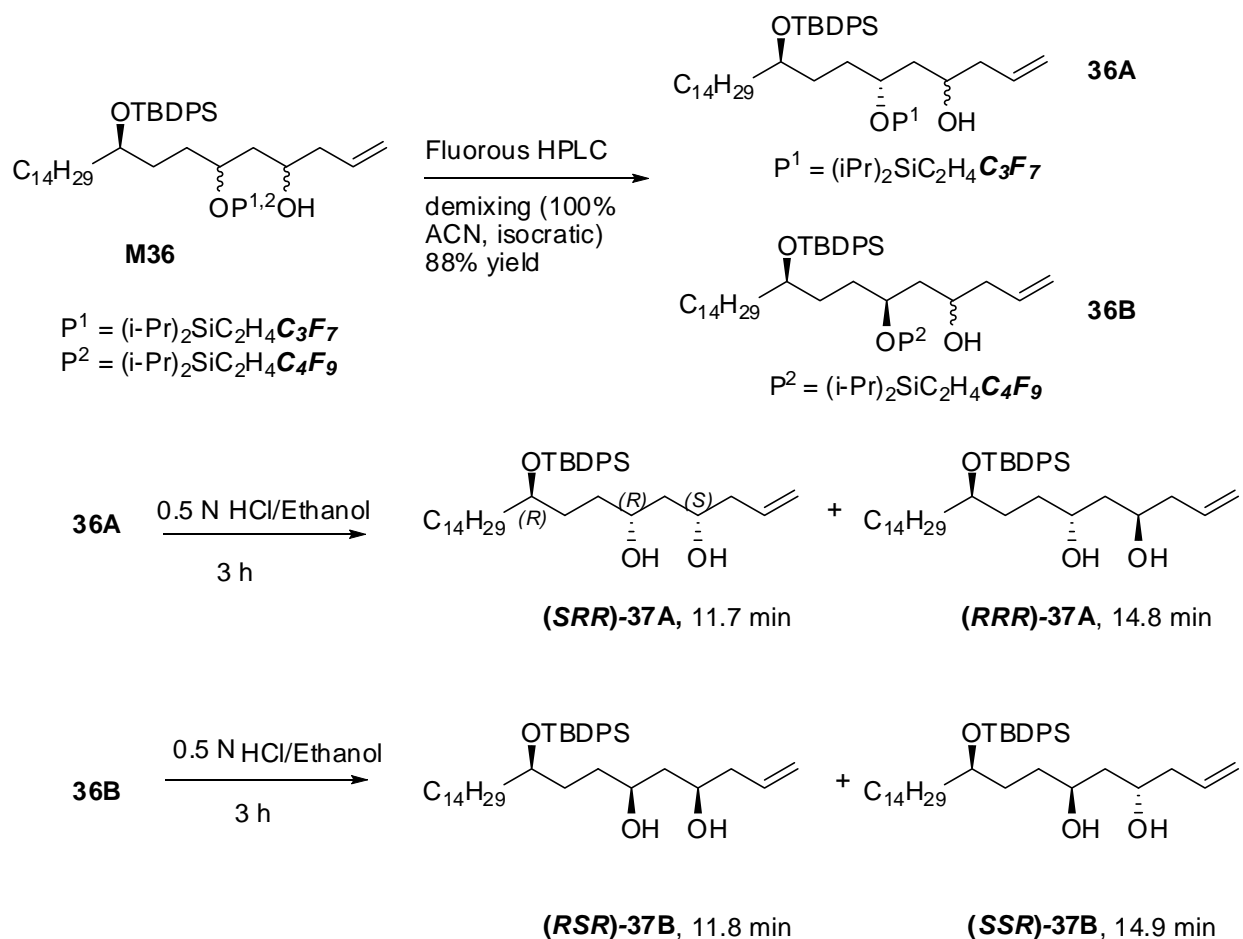
Scheme 9. Analysis of diastereoselectivities for the allylation of aldehyde M13

The results for the reaction of aldehyde **M13** with the allylation reagents and catalysts provided homoallylic alcohols **M36**; the results are summarized in Table 7. Diastereomer ratios are shown as the ratio of homoallylic alcohols after demixing and HPLC analysis as follows: (**SRR**)-**36A**:(**RRR**)-**36A** and (**RSR**)-**36B**:(**SSR**)-**36B**. Because of the unknown influence of the fluorous tags on reactivity, it was decided to use Walsh's conditions using tetraallyltin instead of allyltributyltin for the allylation reaction with catalyst (**R,R**)-**24**.[39] The reaction with catalyst (**R,R**)-**24**, aldehyde **M13**, and tetraallyltin provided alcohol **M36** in 83% yield but only fair diastereomeric ratios: 45:55 for **36A** and 55:45 for **36B** (Entry 1). The reaction was next tested

using FC-72 as a cosolvent and **M36** was obtained in 86% yield and 40:60 *dr* for **36A** and 55:45

dr for **36B** (Entry 2). It was hypothesized that the background reaction might be faster than the

asymmetric reaction at RT, so the reaction was tried at −78 ^{o}C and alcohol **M36** was isolated in

25% yield with no improvement in the *dr* (45:55 *dr* for **36A** and 55:45 *dr* for **36B**, Entry 3). The

reaction of allyltitanocene **(S,S)-23** and aldehyde **M13** provided **M36** in 65% yield with almost

complete reagent control diastereoselectivities: 5:95 *dr* for **36A** and 97:3 *dr* for **36B** (Entry 4).

The reaction with Maruoka's catalyst **(R,R)-28**, aldehyde **M13**, and allyltributyltin provided

M36 in trace amounts (Entry 5). However, replacing allyltributyltin with tetraallyltin provided

M36 in 91% yield and low *dr* (45:55 *dr* for **36A** and 70:30 *dr* for **36B**, entry 6). Attempts were

made to optimize the selectivity for the reaction with catalyst **(R,R)-28** by decreasing the

reaction temperature (0 ^{o}C and −15 ^{o}C, entries 7 and 8), but the results did not improve (91%

yield and 45:55 *dr* for **36A** and 75:25 *dr* for **36B,** 69% yield and 45:55 *dr* for **36A** and 75:25 *dr*

for **36B**). Allyldi*iso*pinocampheylborane (−)-**10** reacted with aldehyde **M13** to provide **M36** in

74% yield with good levels of reagent control diastereoselectivity: 87:13 *dr* for **36A** and 14:86 *dr*

for **36B** (Entry 9).

Next, the reaction with FC-72 as a cosolvent was tried. **M36** was obtained in 86% yield

and 96:4 *dr* for **36A** and 25:75 *dr* for **36B** (Entry 10). The reaction with

allylcyclohexylbisaminosilacycle **(R,R)-29** and aldehyde **M13** provided **M36** in less than 10%

yield (Entry 11). The reaction with 5 equiv of **(S,S)-29** gave **M36** in 55% yield and 10:90 *dr* for

36A and 90:10 *dr* for **36B** (Entry 12). Moreover, the reaction at RT provided **M36** in a similar

58% yield and 10:90 *dr* for **36A** and 74:26 *dr* for **36B** (Entry 13). The reaction with

allyltitanocene **(S,S)-23** gave the best results in terms of yield and reagent control

diastereoselectivity for the synthesis of **M36**. As a consequence, **23** became the reagent of choice

for the allylation of aldehydes **M13** and **M14**. The fourth allylation (aldehyde **M14**) is very similar to the third, so no further studies were needed.

Table 7. Yields and diastereoselectivities for the third allylation

$P^1 = (i\text{-}Pr)_2SiC_2H_4\textbf{\textit{C}}_3\textbf{\textit{F}}_7$
$P^2 = (i\text{-}Pr)_2SiC_2H_4\textbf{\textit{C}}_4\textbf{\textit{F}}_9$

| Entry	Reagent[a]	yield%[b]	conditions	RT	T (°C)	(*SRR*)-36A:(*RRR*)-36A[c]	(*RSR*)-36B:(*SSR*)-36B
1	(*R,R*)-24	83	(allyl)$_4$Sn	10 h	rt	45:55	55:45
2	(*R,R*)-24	86	(allyl)$_4$Sn/FC-72	10h	rt	40:60	55:45
3	(*R,R*)-24	25	(allyl)$_4$Sn	12h	−78	45:55	55:45
4	(*S,S*)-23	65	1.2 equiv/Ether	6h	−78	95:5	3:97
5	(*R,R*)-28	traces	allyl(Bu)$_3$Sn	48 h	rt	-	-
6	(*R,R*)-28	91	(allyl)$_4$Sn	16 h	rt	45:55	70:30
7	(*R,R*)-28	91	(allyl)$_4$Sn	16 h	0	45:55	75:25
8	(*R,R*)-28	84	(allyl)$_4$Sn	16 h	−15	45:55	75:25
9	(-)-10	74	1.2 equiv/Ether	8 h	−100	87:13	14:86
10[d]	(-)-10	86	1.2 equiv/Ether/FC-72	8 h	−100	96:4	24:76
11	(*R,R*)-29	<10	2 equiv/CH$_2$Cl$_2$	20 h	−10	96:4	6:94
12[d]	(*S,S*)-29	55	5 equiv/CH$_2$Cl$_2$	20 h	−10	10:90	90:10
13[d]	(*S,S*)-29	58	5 equiv/CH$_2$Cl$_2$	20 h	rt	10:90	74:26

a) Reaction conditions and reagents are the same as previous allylations unless specified.
b) Isolated yields for homoallylic alcohols **36** before demixing.
c) Measured by HPLC analysis of desilylated products of (*SRR*)-36A:(*RRR*)-36A and (*RSR*)-36B:(*SSR*)-36B.
d) Entries were done by Dr. Mathias Pholman.

The reaction in entry 4 produced the set of homoallylic alcohols **(SRR)-36A** and **(SSR)-36B** with the best selectivity. To confirm the configuration in the stereocenter formed during this allylation, the individual alcohols **(SRR)-36A** and **(SSR)-36B** were deprotected with 0.5 N HCl in ethanol to provide diastereopure diols **(SRR)-37A** and **(SSR)-37B** in 82 and 78% yield, respectively.
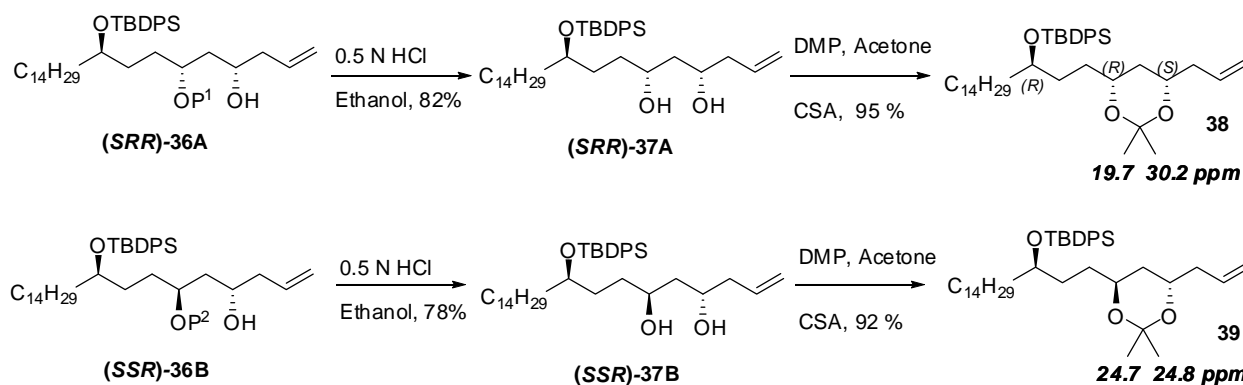
Scheme 10. Formation of the acetonide derivatives for 37A and 37B

The crude diols reacted individually with excess 2,2-dimethoxypropane and catalytic CSA to provide their respective dimethyl acetonides (**38** in 95% yield for 2 steps and **39** in 92% yield for 2 steps, Scheme 10).[40] *syn*-Acetonide **38**, made from **(SRR)-37A**, displayed the ^{13}C NMR resonances of the acetal methyls at 19.7 and 30.2 ppm and the acetal quaternary carbon resonance at 98.3 ppm. Moreover, *anti*-acetonide **39**, made from **(SSR)-37B**, displayed the acetal methyls' ^{13}C NMR resonances at 24.7 and 24.8 ppm and the acetal quaternary carbon resonance at 100.1 ppm. These results corroborated that the relative configuration for alcohol **(SRR)-36A** is *syn* and for alcohol **(SSR)-36B** is *anti*.[40]

2.2.4   Model studies on the acylation and ring closing metathesis (RCM) reactions

Ring closing metathesis reactions (RCM) to form six membered ring carbocycles are a common approach in natural product synthesis.[41] Cossy and Marco used the RCM reaction to form the δ-lactone moiety in their synthetic approaches to passifloricin A.[15,16]

Based on those results, it was decided to investigate the RCM reaction of (**R**)-**40** and (**R**)-**41** using Grubbs I **11B** and Grubbs II **11A** ruthenium catalysts. The reaction of (**R**)-**5** with acryloyl chloride and DIPEA in CH_2Cl_2 at 0 °C provided model acryloyl ester (**R**)-**40** in 78% yield. Moreover, the reaction of (**R**)-**5** with cinnamoyl chloride and DMAP in CH_2Cl_2 at 0 °C provided model cinnamoyl ester (**R**)-**41** in 89% yield (Scheme 11). The RCM reaction of (**R**)-**40** and 10 mol% of **11A**, in refluxing toluene, provided (**R**)-**42** in 79% yield (Entry 1, Scheme 11). When the reaction was done with refluxing CH_2Cl_2, (**R**)-**42** was isolated in 82% yield (Entry 2). When the RCM reaction of (**R**)-**40** was promoted by 10 mol% of **11B** in refluxing CH_2Cl_2, (**R**)-**42** was isolated in 35% yield; and when the RCM reaction was done at RT, (**R**)-**42** was isolated only in 15% yield (Entries 3 and 4).

The RCM reaction of cinnamoyl ester (**R**)-**41** and 10 mol% of **11A** in refluxing toluene or CH_2Cl_2 provided (**R**)-**42** in high yields (89 and 87% yield respectively, entries 5 and 6). Similar results were obtained when the RCM reaction of (**R**)-**41** was done with 10 mol% of **11B** catalyst in refluxing toluene or CH_2Cl_2 (81 and 75% yield respectively, entries 7 and 8). However, when the RCM reaction of (**R**)-**41** was promoted by 10 mol% of **11B** at RT, (**R**)-**42** was isolated in only 36% yield (Entry 9).

Scheme 11. RCM and acylation reactions
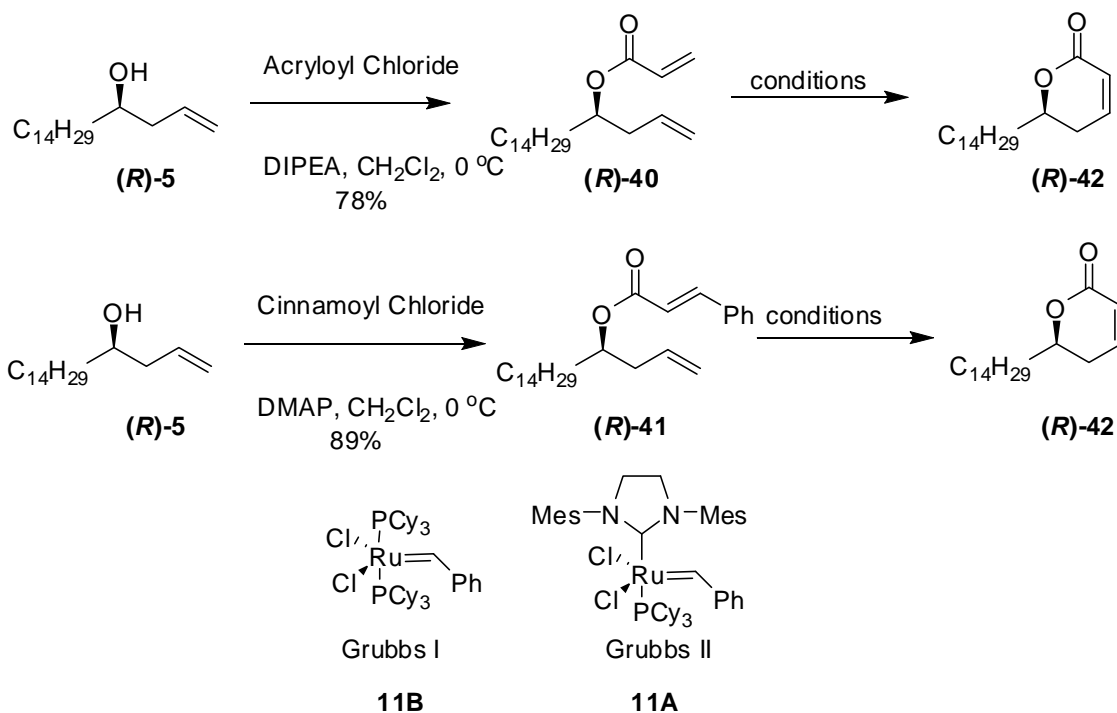
entry	substrate	Catalyst	yield of (R)-42(%)^a	solvent	Temperature (^{o}C)
1	(R)-40	Grubbs II	79	toluene	120
2	(R)-40	Grubbs II	82	CH_2Cl_2	40
3	(R)-40	Grubbs I	35	CH_2Cl_2	40
4	(R)-40	Grubbs I	15	CH_2Cl_2	RT
5	(R)-41	Grubbs II	89	Toluene	120
6	(R)-41	Grubbs II	87	CH_2Cl_2	40
7	(R)-41	Grubbs I	81	Toluene	120
8	(R)-41	Grubbs I	75	CH_2Cl_2	40
9	(R)-41	Grubbs I	36	CH_2Cl_2	RT

a) Isolated yields. Reaction concentration = 0.01M.

Although both catalysts promoted the reaction in similar yields, purification of (R)-42 was easier when the reaction was promoted with catalyst 11A. The yield was higher when using

cinnamoyl ester (*R*)-41 as the RCM substrate. Therefore, acylation with cinnamoyl chloride and RCM reaction with catalyst 11A are the best reactions to achieve the final steps of this FMS.

2.2.5   Fluorous mixture synthesis of passifloricin A diastereomers

2.2.5.1 Pre-mix stage

The synthesis began with the enantioselective allylation of aldehyde 4 using Maruoka catalyst (*S,S*)-28 to furnish homoallylic alcohol (*R*)-5 in 91% yield and *er* >99.5:0.5. Alcohol (*R*)-5 was protected with TBDPS chloride in 92% yield to furnish silyl ether (*R*)-43. The resulting silylether (*R*)-43 was hydroborated with 9-BBN and the resulting borane was oxidized with H_2O_2 to furnish alcohol (*R*)-44 in 79% yield.[42] Primary alcohol (*R*)-44 was then oxidized in the presence of catalytic TEMPO and 2 equiv of commercial bleach[43] to provide aldehyde (*R*)-12 in 91% yield. Other oxidations provided (*R*)-12 in similar yields but were not easy to scale-up.[44]

Aldehyde (*R*)-12 was split in half. The first batch was reacted with allyltitanocene (*S,S*)-23 to produce (*SR*)-34 in 83% yield and 98.5:1.5 *dr*. The second batch was reacted with allyltitanocene (*R,R*)-23 to produce (*RR*)-34 in 82% yield and 1.5:98.5 *dr* (Scheme 12). The yields and diastereoselectivities for the scale-up reactions with allyltitanocenes (*S,S*)-23 and (*R,R*)-23 were similar to the small-scale test reactions. Homoallylic alcohol (*SR*)-34 was protected using $TfOSi(iPr)_2C_2H_4C_4F_9$ (P^2) and 2,6-lutidine in CH_2Cl_2 to provide (*SR*)-45 in 81% yield. Accordingly, homoallylic alcohol (*RR*)-34 was also protected using $TfOSi(iPr)_2C_2H_4C_3F_9$ (P^1) and 2,6-lutidine in CH_2Cl_2 to provide (*RR*)-46 in 95% yield. The two single tagged compounds were mixed in an equimolar ratio to produce M47.
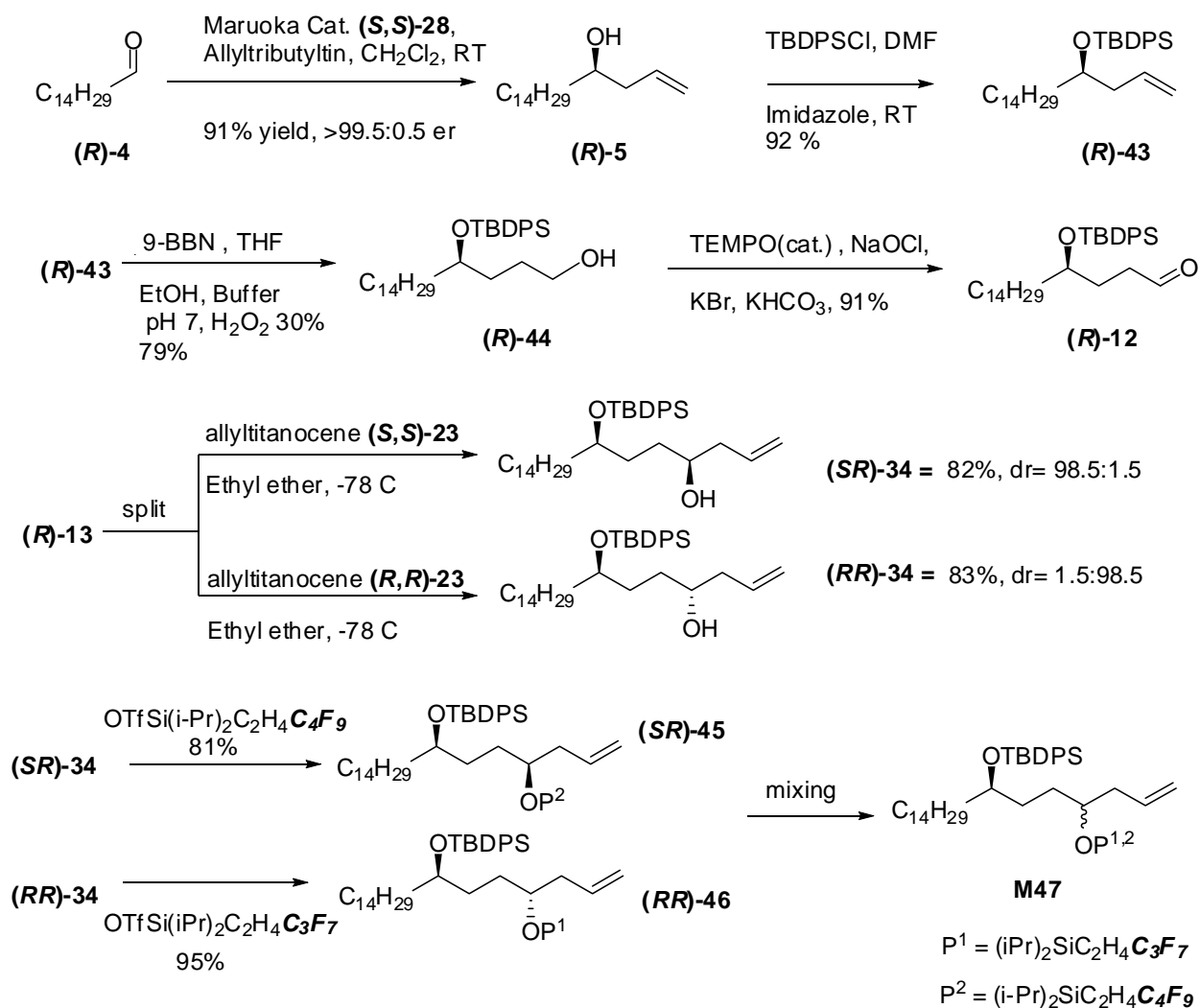
Scheme 12. Pre-mix stage of the FMS

2.2.5.2 Mixture synthesis stage

The mixture synthesis stage started with the oxidative cleavage of **M47** to obtain aldehyde **M13**. The reaction of **M47** and catalytic amounts of OsO_4 with 2 equiv of $NaIO_4$, as a cooxidant, produced aldehyde **M13** in 50% yield together with 45% of recovered olefin **M47**. This result prompted a stepwise oxidation/diol cleavage sequence. Oxidation of **M47** with 5 mol% of OsO_4 and 1 equiv of NMO provided a crude diol. The resulting crude mixture was dissolved in THF/H_2O and reacted with 3 equiv of $NaIO_4$ to give aldehyde **M13** in 73% isolated

yield. **M13** was carefully analyzed by ^{1}H NMR, ^{19}F NMR, fluorous HPLC, and fluorous LCMS

before the next step.[45]

M47

1) OsO_4 (cat.), NMO

2) $NaIO_4$, 73 %

OTBDPS

$C_{14}H_{29}$ ... O

OP^{1,2}

M13

P^2 = (i-Pr)$_2$SiC$_2$H$_4$**C$_4$F$_9$**

P^1 = (i-Pr)$_2$SiC$_2$H$_4$**C$_3$F$_7$**

split

(S,S)-23

OTBDPS

$C_{14}H_{29}$

OP^{1,2}OH

(RMR)-36, 91%

5:95 for **(RRR)-36A**[a]

4.5:95.5 for **(RSR)-36B**

(R,R)-23

OTBDPS

$C_{14}H_{29}$

OP^{1,2}OH

(SMR)-36, 88%

97.5:3.5 for **(SRR)-36A**

95.5:4.5 for **(SSR)-36B**

TIPSOTf,
2,6-Lutidine,
CH$_2$Cl$_2$, 90%

(RMR)-36

OTBDPS

$C_{14}H_{29}$

OP^{1,2}OP^0

(RMR)-51

(SMR)-36

OTfSi(iPr)$_2$C$_5$H$_4$F$_7$,
2,6-Lutidine, CH$_2$Cl$_2$, 94%

OTBDPS

$C_{14}H_{29}$

OP^{1,2}OP^1

(SMR)-49

(RMR)-51

Mixing

(SMR)-49

OTBDPS

$C_{14}H_{29}$

OP^{1,2}OP^{0,1}

M50B

P^2 = (i-Pr)$_2$SiC$_2$H$_4$**C$_4$F$_9$**

P^1 = (i-Pr)$_2$SiC$_2$H$_4$**C$_3$F$_7$**

P^0 = (i-Pr)$_3$Si

1) OsO_4 (cat.),
2eq. NMO

2) $NaIO_4$, 73%
over 2 steps

OTBDPS

$C_{14}H_{29}$ ... O

OP^{1,2}OP^{0,1}

M14

P^2 = (i-Pr)$_2$SiC$_2$H$_4$**C$_4$F$_9$**

P^1 = (i-Pr)$_2$SiC$_2$H$_4$**C$_3$F$_7$**

P^0 = (i-Pr)$_3$Si

a) Ratios are for HPLC traces of diols after removal of fluorous tag. Ratios = **(SRR)-37**:**(RRR)-37** and **(SSR)-37**:**(RSR)-37**.
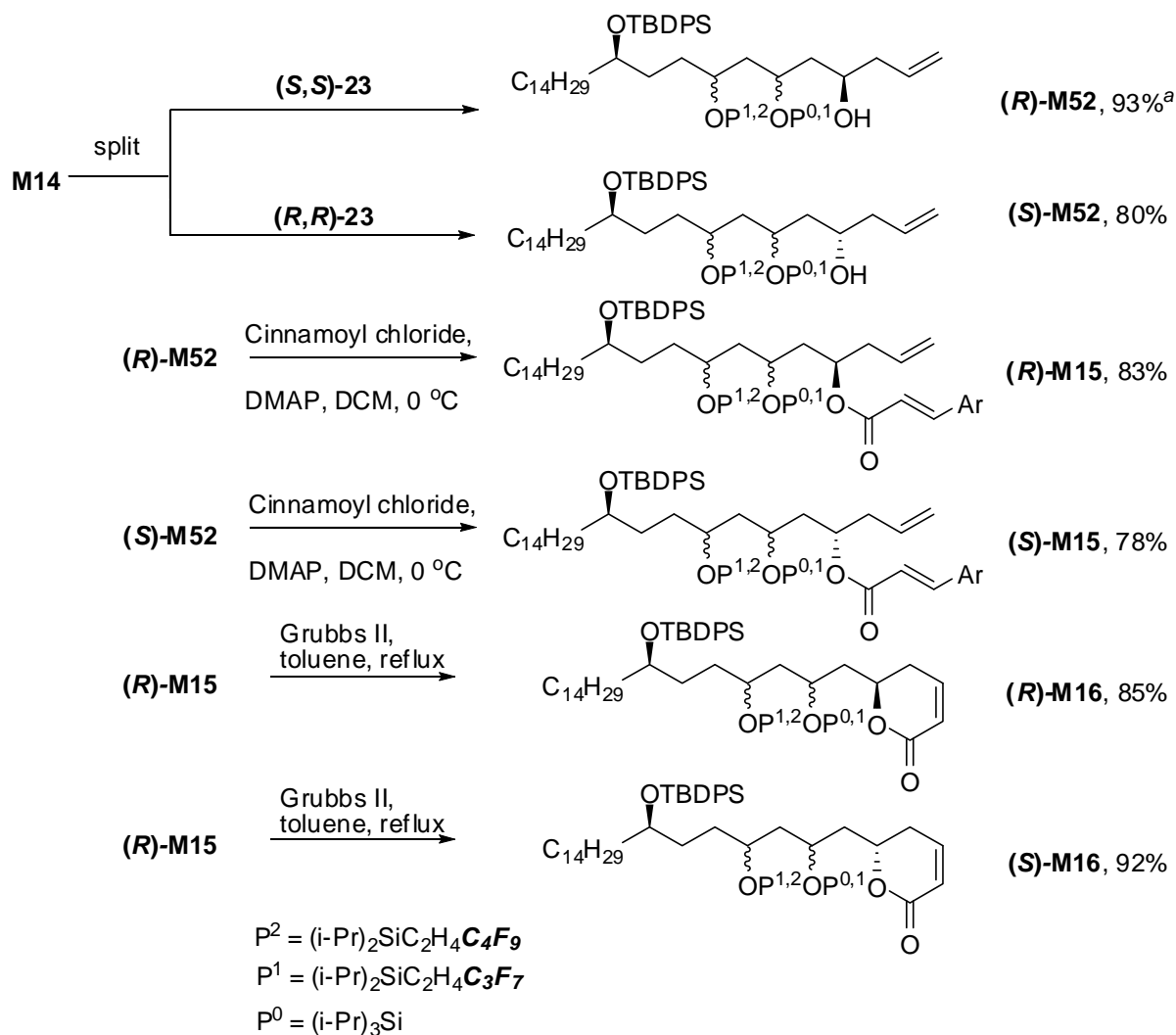
Scheme 13. Mixture synthesis stage

The batch of aldehyde **M13** was split in half. The first batch was subjected to another

diastereoselective allylation with **(S,S)-23** to produce **(RMR)-36** in 88% yield after silica gel

flash chromatography. Homoallylic alcohol **(RMR)-36** was demixed and fractions **(RRR)-36A**

and (**RSR**)**-36B** were selectively desilylated to discover that diastereoselective ratios were 97.5:3.5 and 95.5:4.5, respectively. The second batch of aldehyde **M13** reacted with allyltitanocene (***R,R***)**-23** to produce (***SMR***)**-36** in 91% yield and 5:95/4.5:95.5 *dr* for compounds (***SRR***)**-36A**/(***SSR***)**-36B** respectively (Scheme 13). Homoallylic alcohol (***RMR***)**-36** was protected using TfOSi(iPr)$_2$C$_2$H$_4$***C$_3$F$_9$*** (P^1) and 2,6-lutidine in CH$_2$Cl$_2$ to provide **48** in 94% yield. Furthermore, homoallylic alcohol (***SMR***)**-36** was protected using TfOSi(iPr)$_2$C$_2$H$_4$***C$_6$F$_{13}$*** (P^3) and 2,6-lutidine in CH$_2$Cl$_2$ to provide **49** in 97% yield.

Both double tagged mixtures **48** and **49** were mixed to obtain a mixture of four quasiisomers **M50A** (P^{1}P^1, P^{2}P^1, P^{1}P^3, P^{2}P^3). HPLC analysis of **M50A** only showed two peaks (compounds with P^{1}P^1 and P^{2}P^1 fluorous tags combinations) when eluting with 100% ACN. The other two compounds (P^{1}P^3 and P^{2}P^3) only came off the column when they were eluted with a 1:1 mixture of THF/ACN. Because of the high retention time showed by compounds with P^{1}P^3 and P^{2}P^3 fluorous tags in **M50A**, it was hypothesized that the introduction of a tag with no fluorines P^0 (Si(iPr)$_3$) in replacement of P^3 (Si(iPr)$_2$C$_2$H$_4$***C$_6$F$_{13}$***) will decrease the retention time of the compounds on the fluorous HPLC column enough so they will be demixed under standard conditions. Homoallylic alcohol (***RMR***)**-36** was then protected using TfOTIPS (P^0) and 2,6-lutidine in CH$_2$Cl$_2$ to provide **51** in 90% yield. Olefins **49** and **51** were mixed to form **M50B**. HPLC analysis of this four compound mixture showed four peaks using 100% ACN as solvent. The synthesis was continued using **M50B**. The oxidative cleavage reaction, under the conditions for **M13**, provided the mixture of four aldehydes **M14** in 73% isolated yield (Scheme 13).

The construction of the last stereocenter started when the batch of aldehyde **M14** was split in half. The first half was reacted with allyltitanocene (***R,R***)**-23** to produce (***S***)**-M52** in 80% yield. The second half of **M14** reacted with allyltitanocene (***S,S***)**-23** to produce (***R***)**-M52** in 93%

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yield (Scheme 14). The diastereoselectivities for homoallylic alcohols **52** were assumed to be the same as for homoallylic alcohols **36**. The HPLC traces for **M14** and alcohols **M52** are in Appendix A.


a) HPLC traces for samples **52**, **15** and **16** are in appendix A.

Scheme 14. Mixture synthesis stage for final mixtures

Homoallylic alcohols **(R)-M52** and **(S)-M52** were individually reacted with cinnamoyl chloride at 0 °C and DMAP in CH_2Cl_2 to provide mixtures **(R)-M15** and **(S)-M15** in 83 and 78%

yield, respectively. Finally, RCM reaction of mixtures **(R)-M15** and **(S)-M15** under conditions developed for model system (10 mol% of Grubbs II in refluxing toluene) provided final mixtures **(R)-M16** and **(S)-M16** in 85 and 92% isolated yield respectively.
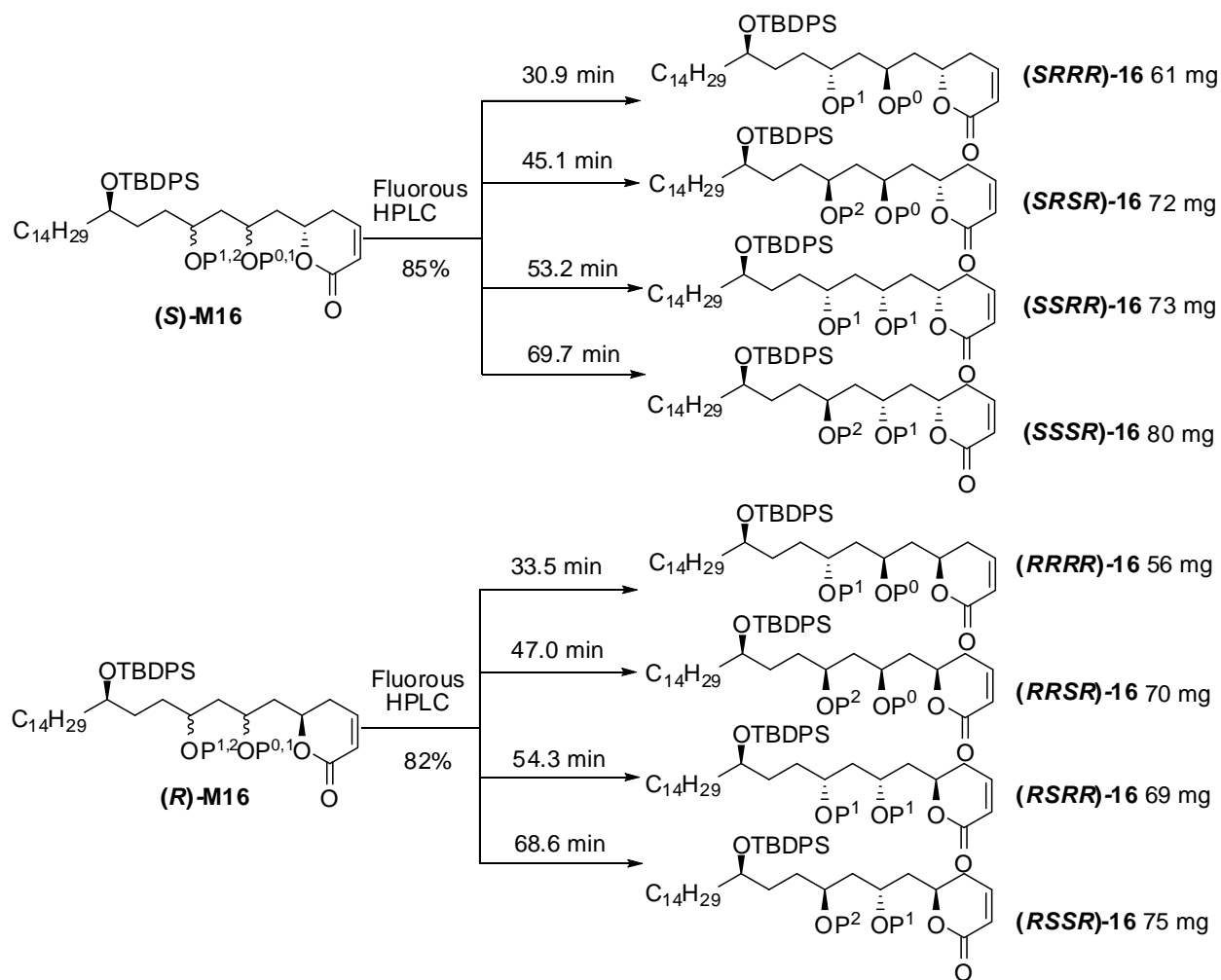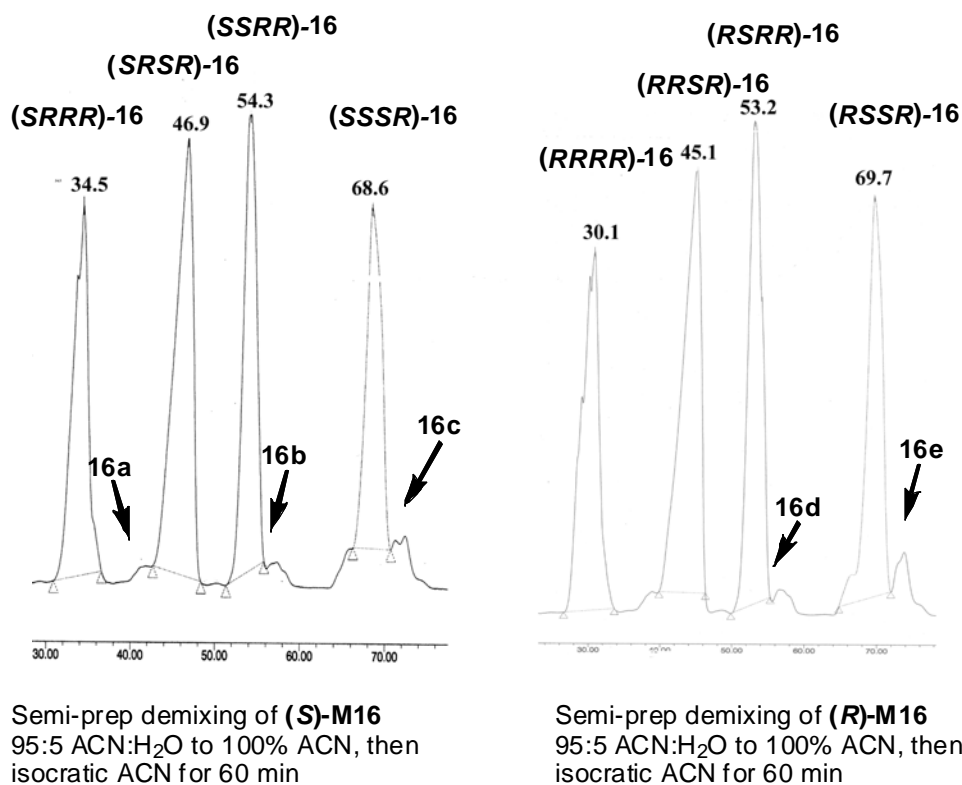

Scheme 15. Demixing of final mixtures 16

Analytical HPLC analysis of mixtures **(R)-M16** and **(S)-M16** showed 4 peaks for each mixture with the following retention times 30.9, 45.1, 53.2, and 69.7 min for **(S)-M16** and 33.5,

47.0, 54.3, and 68.6 min for **(R)-M16** (Scheme 15). The HPLC traces for mixtures **M15** and **M16** are in Appendix A.

2.2.5.3 Post-mix stage

After a careful analysis of mixtures **(S)-M16** and **(R)-M16** (^{19}F NMR, ^{1}H NMR, fluorous HPLC and fluorous LCMS), each mixture was demixed using a gradient elution on the fluorous semi-preparative HPLC (95:5 ACN:H$_2$O to 100% ACN in 30 min plus another 30 min of 100 % ACN), as is shown in Scheme 15. The 384 mg of **(S)-M16** was demixed in 39 mg/mL aliquots, to obtain, eluting in order of increasing fluorine content, the following quasidiastereomers: 61 mg of **(SRRR)-16**, 72 mg of **(SRSR)-16**, 73 mg of **(SSRR)-16**, and 80 mg of **(SSSR)-16**. The overall yield for the demixing was 85%.

The 378 mg of **(R)-M16** was demixed in 38 mg/mL aliquots, to obtain, eluting in order of increasing fluorine content, the remaining quasidiastereomers: 56 mg of **(RRRR)-16**, 70 mg of **(RRSR)-16**, 69 mg of **(RSRR)-16,** and 75 mg of **(RSSR)-16**. The overall yield for the demixing was 82%. Each quasiisomer was carefully characterized by ^{19}F NMR, ^{1}H NMR, ^{13}C NMR, HPLC and HRMS, showing a unique spectrum for each isomer. The demixing also allowed collection of some small impurities (shoulders in the HPLC trace) from each mixture: **(S)-M16** produced three impurities and **(R)-M16** produced two.

Semi-prep demixing of **(S)-M16**
95:5 ACN:H$_2$O to 100% ACN, then
isocratic ACN for 60 min

Semi-prep demixing of **(R)-M16**
95:5 ACN:H$_2$O to 100% ACN, then
isocratic ACN for 60 min

Entry	Impurity[a]	^{1}H NMR match **16**[b]	^{19}F NMR match **16**	amount (mg)	allylation[c]
1	**16a**	(**RRSR**)-16	(**SRSR**)-16	7	4th
2	**16b**	(**SRRR**)-16	(**SSRR**)-16	5	3th
3	**16c**	(**RSSR**)-16	(**SSSR**)-16	8	4th
4	**16d**	(**RRRR**)-16	(**RSRR**)-16	6	3th
5	**16e**	(**SSSR**)-16	(**SRRR**)-16	5	4th

a Isolated from semi prep demixing experiments on mixtures **(S)-M16** and **(R)-M16**.
b Matching done by comparing ^{1}H NMR spectra of impurities with isolated quasidiasteromers **16**
c Corresponds to diastereoselective allylation reaction that gave this impurity.

Figure 8. Fluorous HPLC traces of mixtures (R)-M16 and (S)-M16

Figure 8 shows a representative preparative HPLC trace for each mixture of quasidiastereomers **(S)-M16** and **(R)-M16**. These HPLC traces also show the shoulder impurities isolated from the demixing of each mixture. Five diastereomeric impurities (**16a** (5 mg), **16b** (7 mg), **16c** (8 mg), **16d** (6 mg), and **16e** (6 mg)) were isolated. Each impurity's ^{1}H NMR spectrum

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matched a ^{1}H NMR spectrum of quasiisomer **16**. However, each ^{19}F NMR spectrum matched a different quasiisomer spectrum, allowing determination of which diastereoselective allylation the impurity was formed (Figure 8). The spectroscopic data from impurities **16a**, **16c**, and **16e** matched the ^{1}H NMR and ^{19}F NMR of the following quasiisomer (**(*RRSR*)-16**, **(*RSSR*)-16**, and **(*SSSR*)-16** respectively), but were isolated from the opposite mixture. For example: **16e** matched spectroscopic data for **(*SSSR*)-16** but was isolated from **(*R*)-M16**, not from **(*S*)-M16**. These results indicated that these compounds were the diastereomeric impurities formed in the allylation of aldehyde **M14** (4th allylation). Accordingly, **19b** and **19d** spectroscopic data matched the ^{1}H NMR of quasiisomer (**(*SRRR*)-16**, **(*RRRR*)-16**) but the ^{19}F NMR of quasiisomer (**(*SSRR*)-16**, **(*RSRR*)-16**). These results clearly indicated that these compounds were the diastereomeric impurities formed in the allylation of aldehyde **M13** (3rd allylation).

Each quasiisomer **16** showed a unique ^{1}H NMR spectrum. Figure 9 shows an expansion of the carbinol region (5-3.5 ppm) of each quasiisomer **16** ^{1}H NMR resonance. Analysis of the carbinol region from the ^{1}H NMR spectrum also showed a pairing pattern among the quasiisomers. For example: quasiisomer **(*SRRR*)-16** stereocenters C5, C7, and C9 are of the opposite configuration to those of **(*RSSR*)-16** and, by comparing the carbinol region, the peaks have similar chemical shifts. This relationship is seen clearly in the carbinol region from the ^{1}H NMR spectrum shown in Figure 9. The same pattern is seen for pairs **(*SRSR*)-16:(*RSRR*)-16**, **(*SSRR*)-16:(*RRSR*)-16**, and **(*SSSR*)-16:(*RRRR*)-16**.
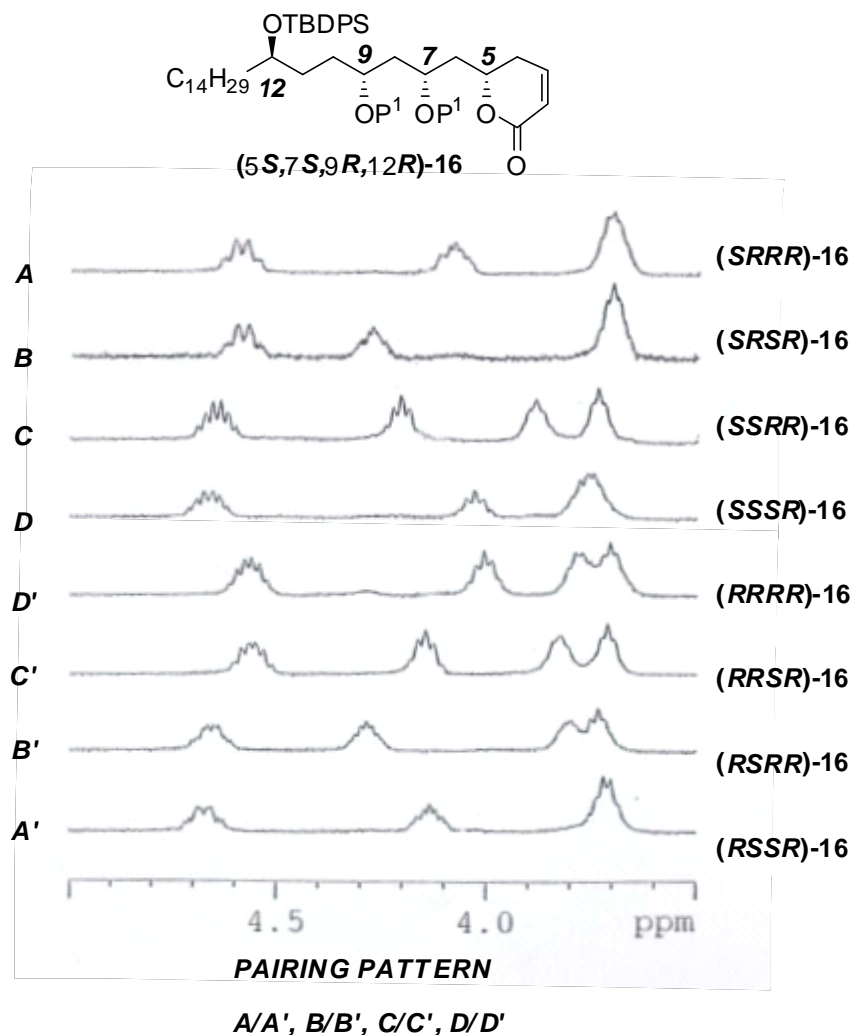
Figure 9. ^{1}H NMR carbinol region for compounds 16

The next step was the global deprotection of the individual quasiisomers **16**. Deprotection conditions were tested with the impurities collected from the demixing (**16a-e**) and the results are listed in Table 8. The reaction of **16a** with TBAF in THF gave a messy TLC with no trace of lactone by ^{1}H NMR spectroscopy (Entry 1).[46] The reaction was next tried with PPTS in MeOH at RT, but only starting material was recovered. However, when the reaction was heated to 80 °C, the crude ^{1}H NMR spectrum showed decomposition (Entry 2). Similar results were obtained when **16b** reacted with HF·Py in THF and HCl 0.5M in MeOH (Entries 3 and 4). However, when

16b was reacted with HCl 2M in THF/H_2O, traces of the product were observed in the crude ^1H

NMR spectrum (Entry 5).

Table 8. Optimization of global deprotection reaction

16a-e → **3**
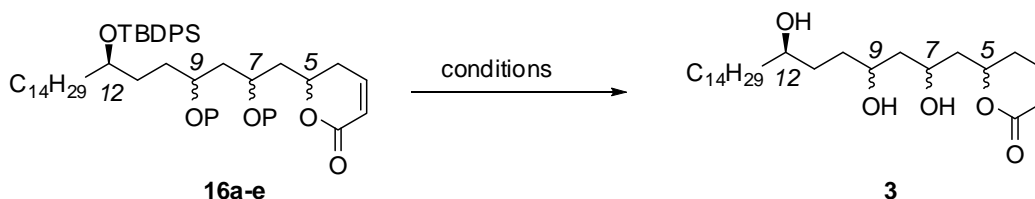
Entry	Conditions	Time (h)	Yield	Entry	Conditions	Time (h)	Yield
1	TBAF/THF (6equiv)	0.5	messy	5	HCl 2M THF/H_2O	12	traces[a]
2	PPTS/MeOH	6	decomposition	6	HCl 0.5M EtOH/THF	20	5[b]
3	HF-Py/THF	12	messy	7	HCl 3M EtOH/THF	20	20[b]
4	HCl/MeOH 0.5N	20	messy	8	HCl 3M EtOH/THF	48	64[b]

a) Traces of lactone olefin resonance on ^1H NMR of crude reaction mixture.
b) Isolated yield.

The global deprotection of **16c** was attempted using HCl 0.5 M in EtOH/THF to provide

triol **3** in 5% yield after silica gel flash chromatography (Entry 6).[47] It was next decided to do the

reaction of **16d** with HCl 3N in EtOH/THF and **3** was isolated in 20% after 20 h of reaction.

Finally, when **16e** was reacted under the same conditions for 48 h, **3** was isolated in 64% yield

(Entries 7 and 8).

These results encouraged us to use the optimized global deprotection conditions on all

eight quasiisomers **16**. Each quasiisomer **16** reacted with HCl 3M in EtOH/THF for 48 h to

provide the respective triols **3**. The crude mixture of each global deprotection reaction for

quasiisomers **16** was purified first by silica gel flash chromatography, then by reverse phase

HPLC (80:20 ACN:H_2O for 20 min, then 100% ACN for 40 min), and finally by chiral HPLC on

a Chiracel OD semi-preparative column (90:10 Hex:iPrOH isocratic for 1 h). The global

deprotection yields and isolated amounts for each diastereomer **3** are listed in Table 9. All the

diastereomers were carefully characterized by NMR spectroscopy, HPLC, and optical rotation.

Table 9. Global deprotection of quasiisomers
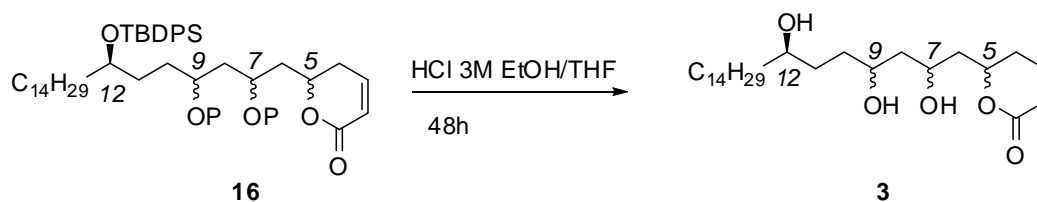
Diasteromer[a]	tag[b]	yield (%)[c]	amount (mg)	T_R (min, OD)[d]	T_R (min, C18)[e]	optical rotation[f]	C (mg/mL)
(**SSRR**)-**3**	P¹+ P⁰	44 (7.8)	8	7.9	9.0	-15.8	0.93
(**SSSR**)-**3**	P²+ P⁰	32 (6.2)	7	8.5	7.3	-21.5	0.7
(**SRRR**)-**3**	P¹+ P¹	27 (3.7)	6	9.1	10.5	-26.8	0.8
(**SRSR**)-**3**	P¹+ P²	28 (3.4)	6	9.4	12.4	+15.3	0.8
(**RSRR**)-**3**	P¹+ P⁰	40 (6.4)	8	8.3	9.1	+3.4	0.31
(**RSSR**)-**3**	P²+ P⁰	22 (4.2)	4	11.9	9.1	+12.2	0.9
(**RRRR**)-**3**	P¹+ P¹	21 (7.8)	4	12.3	11.5	-34.1	0.46
(**RRSR**)-**3**	P¹+ P²	29 (4.0)	5	7.8	14.8	+19.2	0.39

a) The stereochemistry of the four stereocenter reads from right to left.
b) P¹ = (i-Pr)$_2$SiC$_2$H$_4$**C$_3$F$_7$**, P² = (i-Pr)$_2$SiC$_2$H$_4$**C$_4$F$_9$**, P⁰ = (i-Pr)$_3$Si.
c) Yield of the global deprotection after chiral HPLC purification, and the yield in () is the overall yield for that isomer.
d) Chiralcel OD column (isocratic hexanes:isopropanol 86:14).
e) C18 column (isocratic acetonitrile:water 80:20).
f) Measured the same day, all in MeOH.

Once the ¹H NMR, ¹³C NMR, and α_D for diastereomers **3** were obtained, it was possible

to match the natural sample and synthetic passifloricin A to diastereomer (**SRRR**)-**3**. The

matching of passifloricin A as the enantiomer of (**SRRR**)-**3** was a further proof of the

consistency of the tag coding and the efficiency of the multiple-tag FMS route. It was confirmed

that (**SRRR**)-**3** was the enantiomer when its α_D (−26.8, $c = 0.8$, MeOH) was of similar number to

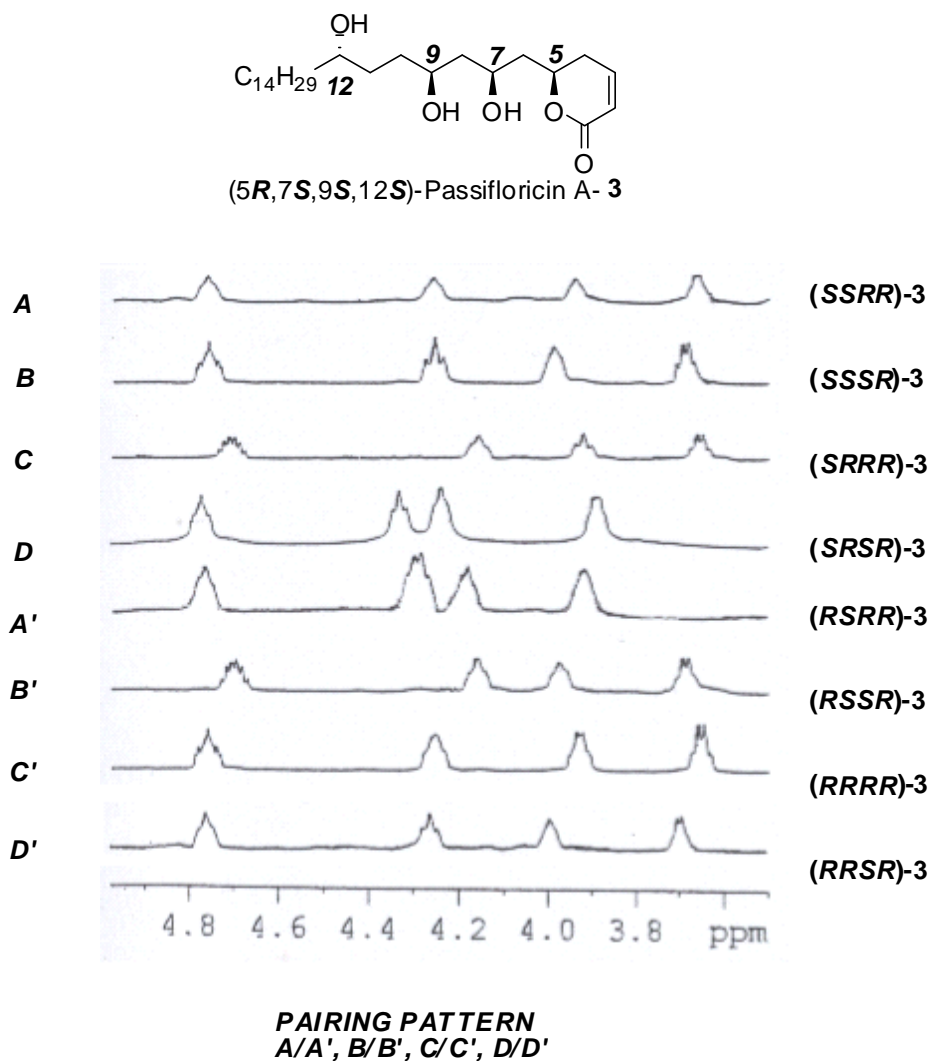passifloricin A (26.8, $c = 0.8$, MeOH) but opposite in sign.

Figure 10. ^{1}H NMR fingerprint region for final diastereomers 3

The other 3 diastereomers made by Marco were also matched with the diastereomers

obtained here. Diastereomer (**RSSR**)-**3** spectroscopic data matched Marco's diastereomer **3d**. In

the same fashion, **(SSSR)-3** matched **3c** and **(RSSR)-3** matched **3b** but their α_D's were of the opposite sign. The other 4 diastereomers had unique ^{1}H and ^{13}C NMR data.

Figure 9 shows an expansion of the carbinol region for ^{1}H NMR resonances (5-3.5 ppm) for all eight diastereomers. Analysis of the carbinol region shows the same pairing pattern seen for the quasiisomers **16** among the final diastereomers. For example: quasiisomer **(SSRR)-3** stereocenter C5, C7, and C9 are of the opposite configuration to those of **(RRSR)-16**, and by comparing the carbinol region the peaks have similar chemical shifts. This relationship is seen clearly in the ^{1}H NMR resonance carbinol region shown in Figure 10. The same pattern is seen for the pairs **(SSSR)-3:(RRRR)-3**, **(SRRR)-3:(RSSR)-3**, and **(SRSR)-3: (RSRR)-3**.

2.3   CONCLUSIONS

All eight diastereomers of passifloricin A have been synthesized by FMS. Spectroscopic data (^{1}H NMR, ^{13}C NMR, ^{1}H^{1}H COSY) have been obtained for the eight diastereomers. The ^{1}H NMR spectrum for **(SRRR)-3** matched the spectrum of the reported natural and synthetic passifloricin A (**(SRRR)-3** is the enantiomer of passifloricin A). Three other diastereomers (**(SSSR)-3**, **(RRRR)-3** and **(RSSR)-3**) matched the corresponding three made by Marco. In addition four new diastereomers (**(SSRR)-3**, **(SRSR)-3**, **(RSRR)-3**, and **(RRSR)-3**) of passifloricin A were synthesized.

This FMS is the first example of multiple tagging fluorous mixture synthesis for the successful synthesis of all diastereomers of a natural product. In addition, this powerful technique demonstrated the accumulative sense of the fluorous tags as expressed by the systematic order of elution during the demixing.

Multiple-tag FMS is very economical in the number of tags. Four diastereomers only required three tags, as eight will need five, and sixteen will need nine tags. We also proved that standard non-fluorous silanes may behave as tags (P^0). This is especially important when too-fluorous compounds get stuck in the fluorous HPLC columns.

Enantioselective allylations are difficult reactions to carry out under complete reagent control with chiral substrates. We proved that Duthaler-Hafner enantioselective allylation is the best reaction for reagent control facial selectivity in acyclic aldehydes with β and δ chiral centers bearing a silyloxy group.

We achieved the FMS of the eight diastereomers of passifloricin A in 18 mixture steps, whereas the synthesis of all the diastereomers in a linear fashion would have required 44 steps. Multiple tagging FMS represents a very useful tool for organic synthesis and combinatorial chemistry. The impact lies on the versatility and efficiency of the method, allowing not only the synthesis of all the diastereomers of a natural product, but also the synthesis of libraries of related compounds.

2.4   EXPERIMENTAL

All reactions were performed under an atmosphere of argon unless otherwise specified or the reaction solvent contained water. The reaction times reported are dictated by TLC analysis of the reaction mixture in comparison to the starting material. Reaction solvents were freshly dried either by distillation or passing through an activated alumina column. Methylene chloride (CH_2Cl_2) was distilled from CaH_2 and toluene, benzene, diethyl ether, and tetrahydrofuran (THF)

were distilled from Na/benzophenone. Acryloyl chloride was freshly distilled before use. All other commercially available solvents and reagents were used without further purification.

Products were analyzed by ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, LC-MS, FT-IR, high and low resolution mass spectrometry, and HPLC. NMR spectra were recorded on a Bruker WH-300, an IBM AF-300, an AM-500, or a Bruker Avance^{TM} 600 NMR spectrometer. Spectra were recorded at room temperature in the indicated deuterated solvents and chemical shifts were reported in parts per million (ppm) from the residual solvent signal of the deuterated solvent. In the case of ^{19}F NMR spectroscopy, no internal standard was used or any special care was taken to measure it. IR spectra were recorded on an IBM IR/32 spectrometer and ran as chloroform solutions. Low resolution mass spectra were obtained on a Hewlett Pakard-9000 GC-MS and high resolution spectra were recorded on a Varian MATCH-5DF instrument. HPLC analysis was performed on a Waters 600E system with UV detector. LC-MS spectra were obtained on a Hewlett Packard-1100 LC-MS using APCI positive mode. All MS peaks are reported in units of *m/z*. Melting points were measured on a MEL-TEMP II apparatus and were not corrected.

General allylation procedures:

(1)-*AllylMgBr allylation of aldehyde 4:* A 50 mL round bottom flask was filled with dry diethyl ether (20 mL) followed by addition of aldehyde **4** (452 mg, 2 mmol). At room temperature allylMgBr 1M (2.5 ml, 2.5 mmol) was added dropwise. The reaction was stirred at RT for 2 h. The reaction was quenched by addition of a saturated NH_4Cl aqueous solution and the aqueous layer was extracted with diethyl ether (2x). The combined organic fractions were dried over $MgSO_4$. The solution was concentrated and the crude mixture was purified by silica gel flash

chromatography eluting with hexanes/ethyl acetate (95:5) to yield homoallylic alcohol **rac-5** (530 mg, 100 %) as a waxy solid.

(2)-Brown stereoselective allylation of aldehydes 4: (−)-methoxydi*iso*pinocampheylborane (3.48 g, 1.1 mmol) was dissolved in dry diethyl ether (10 mL) in a 2-neck 100 ml flask previously heated under vacuum and flushed with argon. The solution was cooled to 0 °C before AllylMgBr 1M (10 mL, 10 mmol) was added slowly *via* syringe. After 10 min, the cooling bath was removed and stirring of the mixture was continued overnight at RT. The solvent was removed to a cooling trap by applying vacuum. Dry petroleum ether (25 ml) was added and the mixture was filtered under argon through a pad of celite in a filter tube to another 100 ml 2-neck flask. The precipitate was washed with dry petroleum ether (5 mL x 2) and the solvent was removed under vacuum. Dry ethyl ether was added to obtain a 0.5 M stock solution of (−)-allyl-di*iso*pinocampheylborane (20 mL, 10 mmol) in dry ether. The stock solution was cooled to −100 °C under Argon and more ethyl ether (10 mL) was added. Aldehyde **4** (1.51 g, 6.67 mmol) was dissolved in a 1:1 mixture of ether:THF (60 mL) and was added slowly (1 h) *via* syringe. The temperature of the cooling bath was maintained at −100 °C for 2 h and another 2 h at −78 °C, before the reaction was quenched by addition of methanol (1 mL). The solution was warmed to RT overnight before 3 N NaOH (4 mL) and 30% wt. H_2O_2 (8 mL) were added at 0 °C. After 10 min at 0 °C, the mixture was refluxed for 3 h. After cooling to 0 °C, a saturated Na_2SO_3 aqueous solution was added and the aqueous layer was extracted with diethyl ether (2x). The combined organic fractions were dried over $MgSO_4$. The solution was concentrated and the crude mixture was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 95:5 to yield homoallylic alcohol **(R)-5** (1.60 g, 91 %) as a waxy solid.

(2)-*Leighton stereoselective allylation of aldehyde 4:* Aldehyde **4** (100 mg, 0.44 mmol) was dissolved in dry dichloromethane (0.5 mL) and added slowly under inert conditions to a solution of silacyle **(R,R)-29** (444 mg, 0.80 mmol) in dry dichloromethane (3.5 mL) at −10 °C. After 4 h at −15 °C, ethyl acetate and 1 M aqueous solution of HCl were added. The mixture was stirred vigorously for 1 h. The aqueous layer was extracted with diethyl ether (2x). The combined organic fractions were dried over $MgSO_4$. The solution was concentrated and the crude mixture was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 92:8 to yield homoallylic alcohol **(R)-5** (54 mg, 51 %) as a waxy solid.

(4)-*Keck stereoselective allylation of aldehyde 4:* (*S*)-BINOL (120 mg, 0.4 mmol) was slurred in dry toluene (4 mL) under an argon atmosphere at RT followed by the addition of Ti(O*i*Pr)₄ (120 μl, 0.40 mmol) over a time period of 5 min. A color change to deep red was observed and stirring at RT was continued for 60 min. Aldehyde **4** (184 mg, 0.81 mmol) was added, followed by allyltributyltin (0.3 ml, 0.9 mmol) After 20 h at RT, the reaction was quenched by the addition of water. The aqueous layer was extracted with diethyl ether (2x). The combined organic fractions were dried over $MgSO_4$. The solution was concentrated and the crude mixture was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 9:1 to yield homoallylic alcohol **(R)-5** (110 mg, 50 %) as a waxy solid.

(5)-*Duthaler-Hafner stereoselective allylation of aldehdye 4:* (R,R)-Duthaler-Hafner reagent (676 mg, 1.1 mmol) was dissolved in dry diethyl ether (12 mL) under an argon atmosphere. The solution was cooled to 0 °C. AllylMgCl 2M (0.4 ml, 0.8 mmol) was added dropwise over a 10 min time period. The reaction was stirred at 0 °C for 1.5 h. Before the solution was cooled to −78 °C, aldehyde **4** (360 mg, 0.4 mmol), dissolved in diethyl ether (1 mL), was added. After 3 h, a 45% aqueous NH_4F solution was added. The mixture was stirred overnight allowing it to warm

up to RT. The mixture was diluted with water. The aqueous layer was extracted with diethyl ether (2x). The combined organic fractions were dried over $MgSO_4$. The solution was concentrated and the crude mixture was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 9:1 to yield homoallylic alcohol (***R***)-**5** (162 mg, 86 %) as a waxy solid.

(6)-*Maruoka stereoselective allylation of aldehyde 4:* A 25 mL round bottom flask was filled with Ti(*i*-PrO)$_4$ (88 μL, 0.3 mmol) followed by 1M $TiCl_4$ (0.1 mL, 0.1 mmol) and dissolved in dichloromethane (2 mL). The solution was cooled to 0 °C then stirred for 1 h. Ag_2O (46 mg, 0.2 mmol) was added. The reaction mixture was protected from light by wrapping the reaction flask with aluminium foil. Stirring at RT continued for 5 h and (*S*)-BINOL (114 mg, 0.4 mmol), dissolved in dichloromethane (1 mL), was added. The resulting solution was stirred for 2 h. Aldehyde **4** (452 mg, 2 mmol) dissolved in dichloromethane (5 mL) was added slowly to the solution. The solution was stirred at RT for 5 min then allylBu$_3$Sn (680 μL, 2.2 mmol) was added. The resulting mixture was stirred for 48 h. The reaction was quenched by addition of water. The aqueous layer was extracted with diethyl ether (2x). The combined organic fractions were dried over $MgSO_4$. The solution was concentrated and the crude mixture was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 9:1 to yield homoallylic alcohol (***R***)-**5** (172 mg, 91 %) as a waxy solid.

(7)-*Walsh stereoselective allylation of aldehyde 4:* A 10 mL round bottom flask was filled with (*S*)-BINOL (36 mg, 0.12 mmol) and dichloromethane (0.5 mL), followed by the addition of Ti(*i*-PrO)$_4$ (35 mg, 0.12 mmol). The solution was stirred for several minutes, and 2-propanol (633 μL, 8.3 mmol) followed by aldehyde **4** (100 mg, 0.4 mmol) dissolved in dichloromethane (1 mL) were added together with tetraallyltin (150 μL, 0.6 mmol). The color of the reaction mixture changed from brown to yellow after several minutes and stirring was continued for 2 h at RT.

The reaction was quenched with a saturated NH$_4$Cl solution and the aqueous layer was extracted with diethyl ether (2x). The combined organic fractions were dried over MgSO$_4$, and the solution was concentrated and the crude mixture was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 9:1 to yield homoallylic alcohol (**R**)-**5** (160 mg, 85 %) as a waxy solid.
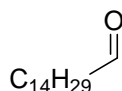
Pentadecanal (4):

A 100 mL round bottom flask was filled with dry dichloromethane (120 mL) followed by n-pentadecanol (15.03 g, 66.4 mmol), to this solution was added Et$_3$N (52 mL, 372 mmol) followed by DMSO (140 mL). The solution was cooled to 0 °C and a solution of PySO$_3$ complex (29.6 g, 186 mmol) in DMSO (100 mL) was added slowly. The reaction mixture was allowed to warm up to RT and stirred vigorously for 2 h. The reaction mixture was quenched with a 0.1 M aqueous solution of HCl and the organic layer was extracted with diethyl ether (2x). After drying over MgSO$_4$, the solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 97:3 to yield *n*-pentadecanal **4** (14.53 g, 96 %) as a waxy solid. ^{1}H-NMR (300 MHz, CDCl$_3$) δ 9.74 (t, *J* = 1.6 Hz, 1H), 2.40 (td, *J* = 7.4, 1.8 Hz, 2H), 1.89-1.12 (m, 24H), 0.86 (t, *J* = 6.6 Hz, 3H).
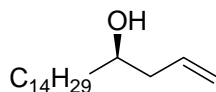
A 25 mL round bottom flask was filled with Ti(i-PrO)$_4$ (88 µL, 0.3 mmol) followed by TiCl$_4$ (0.1 mL, 1M) and dissolved in dichloromethane (2 mL). The solution was cooled to 0 °C and was stirred for 1 h and AgO (46 mg, 0.2 mmol) was added and the flask was protected from light with aluminium foil. The reaction was stirred at RT for another 5 h and then (*S*)-BINOL (114 mg, 0.4 mmol), dissolved in dichloromethane (1 mL), was added, followed by continuous stirring for 2 h. Aldehyde **4** (452 mg, 2 mmol) dissolved in dichloromethane (5 mL) was added slowly to the solution and after 5 min, allylBu$_3$Sn (680 µL, 2.2 mmol) was added and the reaction was stirred at RT for 48 h. The reaction was quenched by addition of water and the aqueous layer was extracted with diethyl ether (2x). The combined organic fractions were dried over MgSO$_4$, the solution was concentrated and the crude mixture was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 9:1 to yield homoallylic alcohol **(R)-5** (172 mg, 91 %, >99.5:0.5 *er*) as a waxy solid: [α]$_D$ +2.9 (*c* 0.8, CHCl$_3$); ^{1}H-NMR (300 MHz, CDCl$_3$) δ 5.96 (ddt, *J* = 19.7, 12.4, 7.8 Hz, 1H), 5.28 (dd, *J* = 19.7, 4.3 Hz, 1H), 5.27 (dd, *J* = 12.4, 4.3 Hz, 1H), 3.60 (tt, *J* = 7.0, 5.7 Hz, 1H), 2.28 (dd, *J* = 7.8, 6.1 Hz, 1H), 2.11 (dd, *J* = 7.8, 6.1 Hz, 1H), 1.44-1.46 (m, 2H), 1.36-1.22 (m, 24H), 0.86 (t, *J* = 6.7 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 134.9, 118.1, 70.7, 41.9, 36.8, 31.9, 29.7(x8), 29.5, 25.7, 22.7, 14.1 ppm.
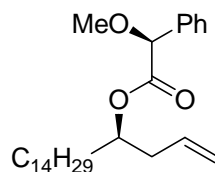
(S)-((R)-Octadec-1-en-4-yl) 2-methoxy-2-phenylacetate ((RS)-33):

A 25 mL round bottom flask was filled with dichloromethane (1 mL), followed by addition of homoallylic alcohol **(R)-5** (27 mg, 0.1 mmol) and (2*S*)-methoxy-2-phenyl acetic acid

(25 mg, 0.15 mmol). DMAP (18 mg, 1.5 mmol) was added and the solution was cooled to 0 °C

and DCC (41 mg, 0.2 mmol) was then added and the reaction was warmed to RT overnight. The

white precipitate was filtered on a plug of celite, and after evaporation of the solvent the crude

product was quickly purified by silica gel flash chromatography eluting with hexanes/ethyl

acetate 9:1 to yield **(RS)-33** (49 mg, 95 %) as a clear oil: $[\alpha]_D$ +14.3 (*c* 0.5, CHCl$_3$); IR (thin

film) 3054, 1741, 1265 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.59-7.56 (m, 2H), 7.50-7.47 (m,

3H), 5.55 (ddt, *J* = 17.0, 10.0, 7.1 Hz, 1H), 5.04 (d, *J* = 17.9 Hz, 1H), 5.02 (d, *J* = 9.6 Hz, 1H),

4.96 (tt, *J* = 6.3, 6.3 Hz, 1H), 4.73 (s, 1H), 3.42 (s, 3H), 2.31 (t, *J* = 6.6 Hz, 2H), 1.46-1.37 (m,

4H), 1.30-0.98 (m, 24H), 0.86 (t, *J* = 6.5 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 170.4, 136.5,

133.6, 128.6, 128.5, 127.2, 117.7, 82.7, 74.2, 57.3, 38.7, 33.5, 31.9, 29.7(x8), 29.4, 24.8, 22.7,

14.1 ppm; HRMS exact mass calcd for C$_{27}$H$_{44}$O$_3$: 516.3292, found: 516.3284. The analysis to

determine the *er* was done by HPLC on a silica-pak column, with isocratic elution 99:1

hexanes:isopropanol at 0.7 mL/min. T$_R$ = 7.5 min.
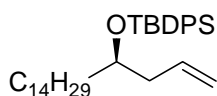
(R)-*tert*-Butyl(octadec-1-en-4-yloxy)diphenylsilane ((R)-43):

A 50 mL round bottom flask was filled with dry DMF (3 mL) followed by TBDPSCl

(1.9 ml, 7.1 mmol) and imidazole (964 mg, 14.2 mmol). Homoallylic alcohol **(R)-5** (1.46 g, 6.38

mmol) was then added portion wise to the solution, and after 4 h of vigorous stirring, the solution

was diluted by addition of dichloromethane and 1M aqueous solution of HCl was added for

hydrolysis. The aqueous layer was extracted with diethyl ether (2x) and the combined organic

fractions were dried over MgSO$_4$, and the solution was concentrated and the crude mixture was

purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 99.5:0.5 to yield

(**R**)-**43** (2.95 g, 92 %) as a clear oil: $[\alpha]_D$ +12.1 (*c* 0.9, CHCl$_3$); IR (thin film) 3072, 3052, 2927,

2856, 1639, 1589, 1469, 1110, 1058, 920 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.65 (dd, *J* = 7.6,

1.5 Hz, 4H), 7.40-7.30 (m, 6H), 5.78 (ddt, *J* = 19.7, 12.4, 7.8 Hz, 1H), 5.00 (d, *J* = 17.3 Hz, 1H)

4.97 (d, *J* = 9.9 Hz, 1H), 3.78 (tt, *J* = 5.7, 5.5 Hz, 1H), 2.23 (dd, *J* = 7.3, 6.2 Hz, 2H), 1.42-1.34

(t, *J* = 5.5 Hz, 2H), 1.30-1.05 (m, 26H), 1.03 (s, 9H), 0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C-NMR (75

MHz, CDCl$_3$) δ 135.9, 135.1, 134.6, 129.4, 127.4, 116.6, 72.8, 41.0, 36.0, 31.9, 29.7(x8), 29.4,

27.0(x3), 24.8, 22.7, 19.4, 14.1 ppm; HRMS exact mass calcd for C$_{34}$H$_{54}$O$_1$Si: 506.3949, found:

506.3931.
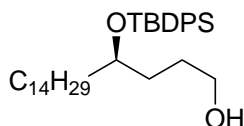
(R)-4-(*tert*-Butyldiphenylsilyloxy)octadecan-1-ol ((R)-44):

TBS ether (**R**)-**43** (2.43 g, 4.8 mmol) was dissolved in dry THF (48 mL) under argon

atmosphere and cooled to 0 °C. 0.5 M 9-BBN (29 ml, 57.6 mmol) was added to the reaction

dropwise, and the reaction was stirred continuously for 3 h. The reaction was quenched by the

addition of ethanol (10 mL), followed by phosphate buffer pH = 7 (10 mL) and slow addition of

30 % wt H$_2$O$_2$ (15 mL). The ice-bath was removed and the solution was stirred at RT overnight.

The solution was cooled to 0 °C before saturated Na$_2$SO$_3$ aqueous solution was added slowly.

The layers were separated and the aqueous layer was extracted with dichloromethane (2x). After

drying over MgSO$_4$, the solution was concentrated and the crude product was purified by silica

gel chromatography eluting with hexanes/ethyl acetate 92:8 to yield primary alcohol (**R**)-**44**

(2.10 g, 83 %) as a clear oil: $[\alpha]_D$ +9.5 (c 1.1, CHCl₃); IR (thin film) 3150, 3054, 2985, 1421, 1305 cm⁻¹; ¹H-NMR (300 MHz, CDCl₃) δ 7.66 (dd, J = 7.6, 1.5 Hz, 4H), 7.43-7.32 (m, 6H), 3.78 (t, J = 5.2 Hz, 1H), 3.52 (t, J = 5.5 Hz, 2H), 2.43 (t, J = 6.4 Hz, 1H), 1.98-1.94 (m, 2H), 1.79-1.75 (m, 2H), 1.57-1.46 (m, 8H), 1.35-1.10 (m, 24H), 1.04 (s, 9H), 0.86 (t, J = 6.6 Hz, 3H); ¹³C-NMR (75 MHz, CDCl₃) δ 135.9, 134.4, 129.5, 127.4, 72.9, 63.1, 41.9, 36.0, 32.3, 31.9, 29.7(x8), 27.0(x3), 25.6, 24.7, 22.7, 19.3, 14.1 ppm; HRMS exact mass calcd for $C_{34}H_{56}O_2SiNa$: 547.3947, found: 547.3965.
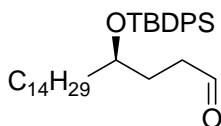
(R)-4-(*tert*-butyldiphenylsilyloxy)-octadecanal ((R)-12):

A 100 mL round bottom flask was filled with dichloromethane (20 mL) followed by alcohol **(R)-44** (832 mg, 1.6 mmol). The solution was cooled to 0 °C and TEMPO (2.5 mg, 1 mol%) was added. To the mixture was added KBr (4 mL, 2.25 M) and KHCO₃ (10 mL, 1.6 M), followed by slow addition of NaOCl (8 mL, 6.15%). The mixture was stirred until the dark orange color disappeared. The reaction was quenched with saturated aqueous solution of Na₂SO₃, and the reaction was stirred at 0 °C for 1 h. The layers were separated and the aqueous layer was extracted with dichloromethane (2x). After drying over MgSO₄, the solution was concentrated and the crude product was purified by silica gel chromatography eluting with hexanes/ethyl acetate (10:1) to yield aldehyde **(R)-12** (757 mg, 91%) as a clear oil: $[\alpha]_D$ +13.6 (c 0.8, CHCl₃); IR (thin film) 3049, 2989, 2887, 1720, 1620, 1612, 1260, 1110, 960 cm⁻¹; ¹H-NMR

(500 MHz, CDCl$_3$) δ 9.65 (s, 1H), 7.64 (dd, J = 8.4, 1.8 Hz, 4H), 7.43-7.35 (m, 6H), 3.79 (t, J = 5.6 Hz, 1H), 2.45 (td, J = 6.0, 1.5 Hz, 2H), 1.81 (ddt, J = 6.0, 5.6 Hz, 1H), 1.71 (ddt, J = 7.6, 5.6 Hz, 1H), 1.43-1.39 (m, 2H), 1.30-1.05 (m, 24H), 1.03 (s, 9H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 202.6, 135.9, 134.3, 129.6, 127.5, 72.1, 39.4, 36.2, 31.9, 29.7(x8), 29.5, 28.1, 27.0(x3), 25.0, 22.7, 19.4, 14.1 ppm; LRMS m/z 521 ((M − H), 21%), 368 (100%), 223 (35%).
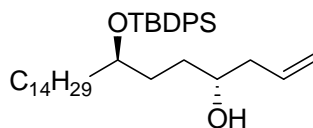
(4R,7R)-7-(*tert*-Butyldiphenylsilyloxy)henicos-1-en-4-ol ((*RR*)-34):

Titanocene **(R,R)-23** (676 mg, 1.1 mmol) was dissolved in dry diethyl ether (12 mL) under an argon atmosphere. The solution was cooled to 0 °C and allylMgCl 2M (0.4 ml, 0.8 mmol) was added dropwise over 10 min. The mixture was stirred at 0 °C for 1.5 h, before the solution was cooled to −78 °C. Aldehyde **(R)-12** (511 mg, 0.98 mmol) was dissolved in diethyl ether (1 mL) and added. After 3 h, a 45% aqueous NH$_4$F solution was added and the mixture was stirred overnight allowing it to warm up to RT. The mixture was diluted with water and diethyl ether. The layers were separated and the aqueous layer was extracted with dichloromethane (2x). After drying over MgSO$_4$, the solution was concentrated and the crude product was purified by silica gel chromatography eluting with hexanes/ethyl acetate 9:1 to yield homoallylic alcohol **(RR)-34** (162 mg, 73 %, 1:99 dr) as a light yellow oil: [α]$_D$ +21.4 (*c* 0.6, CHCl$_3$); IR (thin film) 3463, 3085, 2983, 1741, 1556, 1465, 1373, 1299, 1099 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.66 (dd, J = 8.4, 1.8 Hz, 4H), 7.41-7.33 (m, 6H), 5.75 (ddt, J = 16.4, 10.8, 7.8 Hz, 1H), 5.10 (d, J = 10.9 Hz,

1H), 5.09 (d, $J = 16.4$ Hz, 1H), 3.76 (tt, $J = 5.4, 5.3$ Hz, 1H), 3.50 (ddt, $J = 7.7, 7.4, 4.8$ Hz, 1H), 2.18 (ddd, $J = 7.8, 7.0, 6.5$ Hz, 1H), 2.09 (ddd, $J = 7.8, 7.5, 6.5$ Hz, 1H), 1.65-1.59 (m, 2H), 1.49-1.38 (m, 6H), 1.36-1.09 (m, 24H), 1.04 (s, 9H), 0.86 (t, $J = 6.6$ Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 135.9, 134.9, 134.5, 129.5, 127.4, 117.7, 73.2, 71.0, 41.7, 36.1, 32.3, 32.0, 31.9, 29.7(x8), 29.4, 27.0(x3), 24.9, 22.7, 19.4, 14.1 ppm; HRMS exact mass calcd for C$_{37}$H$_{60}$O$_2$Si: 564.4368, found: 564.4544.
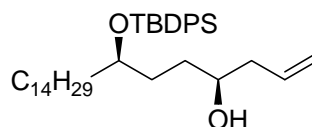
(4*S*,7*R*)-7-(*tert*-Butyldiphenylsilyloxy)henicos-1-en-4-ol ((*SR*)-34):

The synthesis of this compound was done by same the procedure as **(RR)-34**, using allyltitanocene **(S,S)-23** with **(R)-12** (528 mg, 1.01 mmol). The purification was done by silica gel flush chromatography eluting with hexanes/ethyl acetate (95:5) to yield **(SR)-34** (468 mg, 75%, 99:1 *dr*) as a slightly yellow oil: [α]$_D$ -4.3 (*c* 0.5, CHCl$_3$); IR (thin film) 3450, 3085, 2940, 1741, 1448, 1370, 1160 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.66 (dd, $J = 8.4, 1.8$ Hz, 4H), 7.40-7.32 (m, 6H), 5.75 (ddt, $J = 17.2, 10.0, 7.6$ Hz, 1H), 5.11 (d, $J = 10.0$ Hz, 1H), 5.10 (d, $J = 16.4$ Hz, 2H), 3.78 (tt, $J = 5.4, 5.2$ Hz, 1H), 3.48 (ddt, $J = 7.9, 7.4, 4.0$ Hz, 1H), 2.19 (ddd, $J = 7.7, 7.1, 6.7$ Hz, 1H), 2.07 (ddd, $J = 7.9, 7.3, 6.7$ Hz, 1H), 1.55-1.39 (m, 8H), 1.35-1.02 (m, 24H), 1.01 (s, 9H), 0.87 (t, $J = 6.6$ Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 135.9, 134.9, 134.6, 129.5, 127.4, 117.9, 72.9, 70.7, 41.8, 36.2, 31.9, 31.8, 31.6, 29.7(x8), 29.4, 27.1(x3), 25.0, 22.7, 19.4, 14.1 ppm; HRMS exact mass calcd for C$_{37}$H$_{60}$O$_2$Si: 564.4368, found: 564.4442.
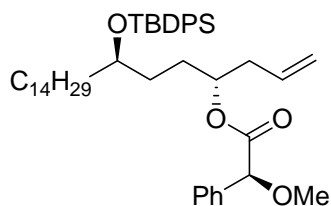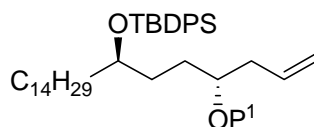
(S)-((4R,7R)-7-(tert-Butyldiphenylsilyloxy)henicos-1-en-4-yl)2-methoxy-2-phenylacetate ((SRR)-28):

The synthesis of this compound was done by same method as **(R)-26**, with **(RR)-27** (57 mg, 0.1 mmol). The purification was done by silica gel chromatography eluting with hexanes/ethyl acetate (95:5) to yield **(SRR)-28** (70 mg, 97 %) as a clear oil: $[\alpha]_D$ +17.8 (c 0.5, CHCl$_3$); IR (thin film) 3061, 2927, 1740, 1569, 1456 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.63 (dd, J = 8.4, 1.8 Hz, 4H), 7.43-7.29 (m, 11H), 5.37 (ddt, J = 17.0, 10.4, 6.7 Hz, 1H), 4.87 (tt, J = 6.6, 5.9 Hz, 1H), 4.79 (d, J = 8.6 Hz, 1H), 4.76 (d, J = 16.8 Hz, 1H), 3.70 (tt, J = 5.6, 5.5 Hz, 1H), 3.39 (s, 3H), 2.06 (t, J = 6.6, 2H), 1.62-1.45 (m, 4H), 1.42-1.38 (m, 6H), 1.36-1.08 (m, 26H), 1.07 (s, 9H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 170.3, 136.4, 135.9, 134.6, 132.9, 129.5, 128.5, 127.4, 127.2, 117.7, 82.6, 74.3, 72.7, 57.3, 38.3, 36.3, 31.9, 31.6, 29.7(x8), 29.4, 28.7, 27.1(x3), 24.8, 22.7, 19.4, 14.1 ppm; HRMS exact mass calcd for C$_{46}$H$_{68}$O$_4$SiNa: 735.4785, found: 735.4801. The analysis to determine the dr was done by HPLC on a silica-pak column, with isocratic elution 99:1 hexanes:isopropanol at 0.7 mL/min. T$_R$ = 10.18 min.
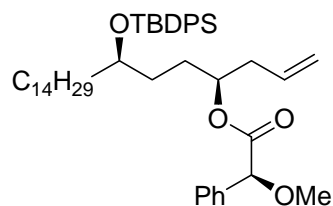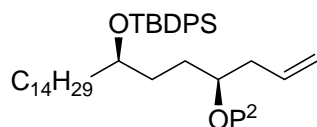
(S)-((4S,7R)-7-(tert-Butyldiphenylsilyloxy)henicos-1-en-4-yl)2-methoxy-2-phenylacetate ((SSR)-28):

The synthesis of this compound was done by same method as **(R)-26**, with **(SR)-27** (54 mg, 0.1 mmol). The crude mixture was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate (95:5) to yield **(SSR)-28** (63 mg, 93 %) as a clear oil: $[\alpha]_D$ -9.2 (*c* 0.4, CHCl$_3$); IR (thin film) 3065, 2985, 1744, 1560, 1421 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.60 (dd, *J* = 8.4, 1.8 Hz, 4H), 7.41-7.30 (m, 11H), 5.60 (ddt, *J* = 15.5, 10.7, 6.9 Hz, 1H), 5.00 (d, *J* = 15.5 Hz, 1H), 4.99 (d, *J* = 10.7 Hz, 1H), 4.84 (tt, *J* = 6.7, 5.4 Hz, 1H), 4.69 (s, 1H), 3.51 (tt, *J* = 5.7, 5.5 Hz, 1H), 3.40 (s, 3H), 2.22 (t, *J* = 6.9 Hz, 2H), 1.56-1.46 (m, 2H), 1.36-1.10 (m, 28H), 1.09 (s, 9H), 0.86 (t, *J* = 6.6 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 170.3, 136.4, 135.9, 134.6, 134.5, 129.4, 128.5, 127.4, 127.1, 117.7, 82.7, 74.7, 73.0, 57.3, 38.6, 36.4, 31.9, 31.7, 29.7(x8), 29.5, 29.4, 27.0(x3), 24.5, 22.7, 19.4, 14.1 ppm; HRMS exact mass calcd for C$_{46}$H$_{68}$O$_4$SiNa: 735.4785, found: 735.4818. The analysis to determine the dr was done by HPLC on a silica-pak column, with isocratic elution 99:1 hexanes:isopropanol at 0.7 mL/min. T$_R$ = 12.61 min.

OTBDPS

$C_{14}H_{29}$ ⟍＼／＼＼／＼═

ŌP¹

P¹ = (i-Pr)₂SiCH₂CH₂**C₃F₇**

1-(*tert*-Butyl((4R,7R)-4-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)henicos-1-en-7-yloxy)(phenyl)silyl)benzene ((RR)-39):

Trifluoromethanesulfonic acid (1.3 ml, 15.1 mmol) was added to (3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilane (5.53 g, 17.7 mmol) at 0 °C, and the solution was stirred overnight. The mixture was cooled to 0 °C before a solution of secondary alcohol **(RR)-27** (5 g, 8.9 mmol) and 2,6-lutidine (3.4 ml, 30.2 mmol) dissolved in dry dichloromethane (13 mL) was added. The resulting mixture was stirred for 30 min at 0 °C and 1 h at RT. The solution was diluted with dichloromethane and quenched with a saturated NH_4Cl solution and water. The layers were separated and the aqueous layer was extracted with dichloromethane (2x). After drying over $MgSO_4$, the solution was concentrated and the crude product was purified by silica gel chromatography eluting with pure hexanes followed by hexanes/ethyl acetate 95:5 to yield **(RR)-39** (7.36 g, 95 %) as a slightly yellow liquid: $[\alpha]_D$ +16.2 (*c* 1.3, $CHCl_3$); IR (thin film) 3068, 2977, 1459, 1365, 1230, 1110, 1050, 960 cm⁻¹; ¹H-NMR (300 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 8.4, 1.8 Hz, 4H), 7.39-7.30 (m, 6H), 5.68 (ddt, *J* = 17.7, 9.3, 7.1 Hz, 1H), 5.00 (d, *J* = 9.3 Hz, 1H), 4.99 (d, *J* = 17.7 Hz, 1H), 3.75-3.60 (m, 2H), 2.15-1.99 (m, 4H), 1.55-1.38 (m, 8H), 1.37-1.03 (m, 28 H), 1.02 (s, 9H), 0.98 (s, 14H), 0.89 (t, *J* = 6.6 Hz, 3H), 0.85-079 (m, 2H); ¹⁹F-NMR (282 MHz, $CDCl_3$) δ -79.4 (3F), -116.3 (2F), -126.4 (2F); ¹³C-NMR (75 MHz, $CDCl_3$); δ 135.9, 134.8, 134.7, 129.4, 127.4, 117.1, 73.3, 72.7, 41.4, 36.3, 31.9(x3), 31.7, 29.7(x8), 29.4, 27.0(x3), 25.4 , 24.8, 22.7, 21.3, 19.4, 17.7 (x4), 17.4 (t, J_{CF}= 4.5 Hz), 14.1, 12.9, 12.4, 0.5 ppm; HRMS exact mass calcd for $C_{48}H_{77}F_7O_2Si_2$: 874.5352, found: 874.5358.

OTBDPS

$C_{14}H_{29}$

OP^2

$P^2 = (i\text{-}Pr)_2SiCH_2CH_2\textbf{\textit{C}}_{\textbf{\textit{4}}}\textbf{\textit{F}}_{\textbf{\textit{9}}}$

1-(*tert*-Butyl((4*S*,7*R*)-4-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)henicos-1-en-7-yloxy)(phenyl)silyl)benzene ((*SR*)-39):

The synthesis of this compound was done by the same method used for **(SR)-39**, with (3,3,4,4,5,5,6,6,6-nonafluorohexyl)silane (6.42 g, 17.7 mmol) and alcohol **(SR)-27** (5 g, 8.8 mmol) The crude product was purified by silica gel flash chromatography eluting with pure hexanes followed by hexanes/ethyl acetate 95:5 to yield **(SR)-39** (6.63 g, 81 %) as a slightly yellow oil: $[\alpha]_D$ -21.2 (*c* 1.4, CHCl$_3$); IR (thin film) 3050, 2975, 1459, 1365, 1288, 1180, 1070, 912 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.63 (dd, *J* = 8.4, 1.8 Hz, 4H), 7.39-7.30 (m, 6H), 5.67 (ddt, *J* = 16.7, 10.8, 7.1 Hz, 1H), 5.04 (d, *J* = 10.8 Hz, 1H), 5.03 (d, *J* = 16.7 Hz, 1H), 3.78-3.60 (m, 2H), 2.16-2.05 (m, 4H), 1.48-1.40 (m, 8H), 1.32-1.00 (m, 28 H), 0.99 (s, 9H), 0.95 (s, 14H), 0.91 (t, *J* = 6.3 Hz, 3H), 0.86-0.80 (m, 2H); ^{19}F-NMR (282 MHz, CDCl$_3$) δ -79.8 (3F), -115.6 (2F), -123.1 (2F), -124.9(2F); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 135.9, 134.7, 134.6, 129.4, 127.4, 117.1, 73.3, 72.8, 41.3, 36.2, 31.9(x3), 31.7, 29.7(x8), 29.4, 27.6, 27.0(x3), 25.5 (t, J_{CF}= 24.4 Hz), 24.8, 22.7, 19.4, 18.6, 17.6(x4), 14.1, 12.9, 0.5 ppm; HRMS exact mass calcd for C$_{49}$H$_{77}$F$_9$O$_4$Si$_2$: 924.5328, found: 924.5351.

P^1 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_3$F$_7$**

P^2 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_4$F$_9$**
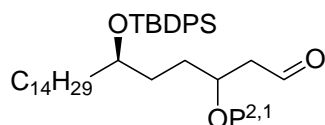
(6R)-6-(*tert*-Butyldiphenylsilyloxy)-3-((perfluoroalkylethyl)diisopropylsilyloxy)icosanal (M13):
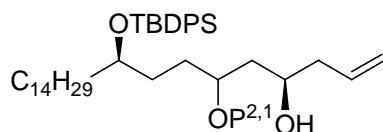
Alkene mixture **M47** (695 mg, 0.77 mmol) was suspended under vigorous stirring in acetone/water 4:1 (5 mL) and cooled to 0 °C. NMO (181 mg, 1.5 mmol) was added, followed by OsO$_4$ (9 mg, 0.04 mmol). Stirring was continued for 30 min, the ice bath was removed and stirring was continued overnight at RT. The mixture was diluted with ether and a saturated Na$_2$SO$_3$ aqueous solution was added. The layers were separated and the aqueous layer was extracted with dichloromethane (3x). After drying over MgSO$_4$, the solution was concentrated and the crude product (394 mg, 0.42 mmol) was suspended in acetone/water 4:1 (3 mL), to the resulting solution was added NaIO$_4$ (540 mg, 2.53 mmol) portion-wise at RT. After 6 h diethyl ether and water were added and the layers were separated. The aqueous layer was extracted two times with dichloromethane and the combined organic layers were dried over MgSO$_4$, the resulting solution was concentrated and the crude product was purified over silica gel flash chromatography eluting with hexanes/ethyl acetate 8:2 to yield **M13** (506 mg, 73 %) as a clear, slightly yellow oil: ^{1}H-NMR (300 MHz, CDCl$_3$) δ 9.76-9.73 (m, 1H), 7.68 (dd, J = 7.7, 1.6 Hz, 4H), 7.47-7.36 (m, 6H), 4.22 (tt, J = 5.6, 5.4 Hz, 1H), 4.1 (tt, J = 5.5, 5.4 Hz, 1H), 3.82-3.68 (m, 2H), 2.44-2.39 (m, 2H), 2.20-1.97 (m, 2H), 1.57-1.39 (m, 6H), 1.34-1.09 (m, 28H), 1.07 (s, 9H), 1.03-0.98 (m, 14H), 0.91 (t, J = 6.7 Hz, 3H), 0.86-0.80 (m, 2H); ^{19}F-NMR (282 MHz, CDCl$_3$): δ = -79.4 (3F), -79.8 (3F), -115.5 (2F), -116.2 (2F), -123.0 (2F), -124.8 (2F), -126.4 (2F) ppm;

LCMS (APCI, positive mode) *m/z* for **M13**: **(RR)-13** = 918.5 (M + K), 799.5 (M − Ph), 662.5, 471.5, 275.2; **(SR)-13** = 966.5 (M + K), 849.5 (M − Ph), 671.3, 471.4, 293.2, 275.2.

P^1 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_3$F$_7$**

P^2 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_4$F$_9$**
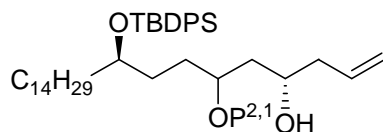
(4S,9R)-9-(*tert*-Butyldiphenylsilyloxy)-6-((perfluoroalkylethyl)diisopropylsilyloxy)tricos-1-en-4-ol ((SMR)-29):
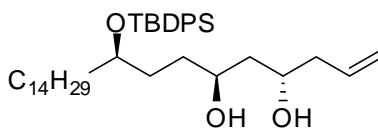
The synthesis of this compound was done by the same method used for **(RR)-34**, using **M13** (840 mg, 0.93 mmol). The crude product was purify by silica gel flash chromatography over silica gel eluting with hexanes/ethyl acetate (95:5) to yield **(SMR)-36** (815 mg, 88%) as a slightly yellow oil: ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.64 (dd, *J* = 8.5, 2.1 Hz, 4H), 7.41-7.35 (m, 6H), 5.76 (ddt, *J* = 15.8, 9.6, 7.1 Hz, 1H), 5.13 (d, *J* = 17.0, 9.6, 7.1 Hz, 1H), 5.10 (d, *J* = 15.8 Hz, 1H), 4.01-3.81 (m, 2H), 3.78-3.59 (m, 1H), 2.24-1.98 (m, 4H), 1.54-1.38 (m, 8H), 1.38-0.99 (m, 30 H), 0.93 (s, 24H), 0.88 (t, *J* = 6.5 Hz, 3H), 0.86-079 (m, 2H); ^{19}F-NMR (282 MHz, CDCl$_3$) δ -79.4 (3F), -79.8 (3F), -115.6 (2F), -116.3 (2F), -123.0 (2F), -124.8 (2F), -126.3 (2F) ppm; LCMS (APCI, positive mode) *m/z* for **(SMR)-36**: **(SRR)-36A** = 969.5 (M + 1), 713.5, 335.4, 317.5; **(SSR)-36B** =1020.5 (M + 1), 840.5, 663.5, 513.5, 317.5.

OTBDPS

C₁₄H₂₉

OP²,¹ OH

P^1 = (i-Pr)₂SiCH₂CH₂**C₃F₇**

P^2 = (i-Pr)₂SiCH₂CH₂**C₄F₉**

(4R,9R)-9-(tert-Butyldiphenylsilyloxy)-6-((perfluoroalkylethyl)diisopropylsilyloxy)tricos-1-en-4-ol ((RMR)-29):

The synthesis of this compound was done by the same method used for **(RR)-34**, using **M13** (840 mg, 0.93 mmol). The crude product was purify by silica gel flash chromatography over silica gel eluting with hexanes/ethyl acetate (95:5) to yield **(RMR)-36** (835 mg, 91%) as a slightly yellow oil: ¹H-NMR (300 MHz, CDCl₃) δ 7.63 (dd, J = 8.4, 1.8 Hz, 4H), 7.39-7.30 (m, 6H), 5.68 (ddd, J = 17.2, 11.7, 7.5 Hz, 1H), 5.13 (d, J = 11.7 Hz, 1H), 5.11 (d, J = 17.2 Hz, 1H), 3.95-3.60 (m, 3H), 2.20-2.01 (m, 4H), 1.53-1.36 (m, 8H), 1.34-1.01 (m, 30 H), 0.97 (s, 23H), 0.89 (t, J = 6.3 Hz, 3H), 0.85-0.80 (m, 2H); ¹⁹F-NMR (282 MHz, CDCl₃) δ -79.4 (3F), -79.8 (3F), -115.6 (2F), -116.3 (2F), -123.0 (2F), -124.8 (2F), -126.3 (2F) ppm; LCMS (APCI, positive mode) m/z for**(RMR)-36**: **(RRR)-36A** = 969.5 (M + 1), 724.5, 513.5, 317.5; **(RSR)-36B** =1020.5 (M + 1), 848.5, 663.5, 335.4, 317.5.

OTBDPS

C₁₄H₂₉

ŌH   ŌH
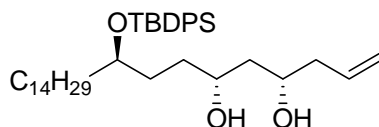
(4S,6R,9R)-9-(tert-butyldiphenylsilyloxy)tricos-1-ene-4,6-diol ((SRR)-37A):

Semiprep HPLC separation was carried out on a 600E waters HPLC system. The mixture **(SMR)-36** (40 mg, 0.04 mmol) of 2 compounds was filtered trough a Whatman filter paper (0.45 μM pore size) before injection. The separation was done on a FluoroFlash HPLC column (20mm

x 250 mm), and was achieved by gradient elution with isocratic 100% acetonitrile for 40 minutes with a flow rate of 10 mL/min. UV detector (254 nm, 230 nm) was used to identify the peaks. The injection of 40 mg of **(SMR)-36** provided in 78% yield **(SRR)-36A** (15 mg, 13.2 min) and **(SSR)-36B** (16 mg, 17.0 min), as clear oils. **(SRR)-36A** (15 mg, 15.0 µmol) was dissolved in ethanol (1.5 mL) followed by addition of 1 M HCl/Ethanol (1.5 mL). Stirring was continuous for 2 h at RT, then NaHCO$_3$ was added followed by removal of the solvent under vacuum. The crude reaction mixture was extracted with dichloromethane and filtered on a plug of celite. The organic layer was concentrated and the residue was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate (20:1) to yield **(SRR)-37A** (8 mg, 41%) as a clear oil: $[\alpha]_D$ -3.1 (*c* 0.9, CHCl$_3$), IR (thin film) 3054, 2987, 2925, 1421, 1361, 1255, 1222.65, 896, 734 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.68 (dd, *J* = 8.4, 1.8 Hz, 4H), 7.43-7.35 (m, 6H), 5.80 (ddt, *J* = 17.6, 10.8, 7.2, Hz, 1H), 5.15 (d, *J* = 17.6 Hz, 1H), 5.14 (d, *J* = 10.8 Hz, 1H), 3.86-3.76 (m, 2H), 3.73-3.69 (m, 1H), 3.00 (s, 1H), 2.89 (s, 1H), 2.24-2.21 (m, 2H), 1.51-1.45 (m, 4H), 1.43-1.39 (m, 4H), 1.29-1.09 (m, 27H), 1.06 (s, 9H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C-NMR (126 MHz, CDCl$_3$); δ 135.9, 134.5, 134.4, 129.5, 127.5, 118.2, 73.0, 72.8, 71.8, 42.5, 42.3, 36.1, 32.8, 31.9, 31.3, 29.7(x8), 29.4, 27.1(x3), 25.0, 22.7, 19.4, 14.1 ppm.

(4S,6S,9R)-9-(tert-butyldiphenylsilyloxy)tricos-1-ene-4,6-diol ((SSR)-37B):

The synthesis of this compound was done by the same method used for **(SRR)-37A**, with alcohol **(SSR)-36B** (16 mg) obtained from the demixing. The residue was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate (20:1) to yield **(SSR)-37B** (7 mg, 39%)

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as a clear oil: $[\alpha]_D$ -24.5 (*c* 0.8, CHCl$_3$), IR (thin film) 3060, 2971, 2893, 1452, 1360, 1158, 1220, 1066, 960 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.69 (dd, *J* = 8.4, 1.8 Hz, 4H), 7.43-7.36 (m, 6H), 5.80 (ddt, *J* = 13.7, 12.4, 7.2 Hz, 1H), 5.14 (dd, *J* = 13.7, 12.4 Hz, 2H), 3.93 (t, *J* = 5.8 Hz, 1H), 3.85-3.77 (m, 2H), 2.36 (s, 2H), 2.24 (dd, *J* = 7.0, 6.9 Hz, 2H), 1.55 (t, *J* = 5.4 Hz, 2H), 1.52-1.48 (m, 4H), 1.45-1.41 (m, 2H), 1.28-1.10 (m, 27H), 1.07 (s, 9H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C-NMR (126 MHz, CDCl$_3$); δ 135.9, 134.7, 134.5, 129.5, 127.4, 118.1, 73.0, 69.2, 68.2, 42.0, 41.7, 36.1, 32.2, 31.9, 31.8, 29.7(x8), 29.3, 27.1(x3), 25.0, 22.7, 19.4, 14.1 ppm.
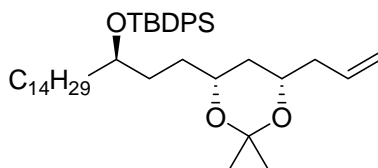
((*R*)-1-((4*R*,6*S*)-6-allyl-2,2-dimethyl-1,3-dioxan-4-yl)heptadecan-3-yloxy)(*tert*-butyl)diphenylsilane (38):

To a solution of diol (***SRR***)-**37A** (8 mg, 0.02 mmol) in acetone (0.3mL) was added sequentially 2,2-dimethoxypropane (0.3mL) and CSA (2 mg, 0.01 mmol). After 30 min at 25 °C, the reaction mixture was quenched with Et$_3$N (17 μL) and then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 20:1 to yield **38** (8 mg, 95%) as a clear oil: $[\alpha]_D$ -12.9 (*c* 0.5, CHCl$_3$), IR (thin film) 2999, 2927, 2854, 1643, 1469, 1378, 1224, 910 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.65 (dd, *J* = 8.4, 1.8 Hz, 4H), 7.41-7.32 (m, 6H), 5.78 (ddt, *J* = 18.6, 9.3, 7.0 Hz, 1H), 5.10 (d, *J* = 9.3 Hz, 1H), 5.08 (d, *J* = 18.6 Hz, 1H), 3.76-3.72 (m, 2H), 3.53-3.46 (m, 1H), 2.32-2.19 (m 2H), 2.14-2.05 (m, 2H), 1.97-1.83 (m, 2H), 1.77-1.72 (m, 2H), 1.33 (s, 3H), 1.31 (s, 3H), 1.21-1.09 (m, 30H), 1.02 (s, 9H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$); δ 135.9,

134.7, 134.3, 129.4, 127.4, 116.9, 98.3, 72.6, 68.6(x2), 40.8, 36.3, 36.1, 31.9, 31.1, 31.0, 30.2, 29.7(x8), 29.4, 27.1(x3), 24.9, 22.7, 19.7, 19.4, 14.1 ppm.
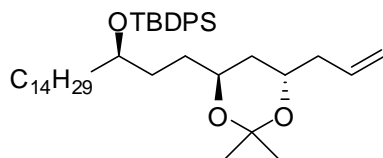

((R)-1-((4S,6S)-6-allyl-2,2-dimethyl-1,3-dioxan-4-yl)heptadecan-3-yloxy)(tert-butyl)diphenylsilane (39):

The synthesis of this compound was done by the same method used for **38**, with **(SSR)-37A** (8 mg, 0.02 mmol). The crude was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate (20:1) to yield **39** (7 mg, 92%) as a clear oil: $[\alpha]_D$ -25.1 (*c* 0.8, CHCl$_3$), IR (thin film) 3003, 2927, 2824, 1640, 1378, 1230, 1108, 991, 730 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.66 (dd, *J* = 8.4, 1.8 Hz, 4H), 7.43-7.35 (m, 6H), 5.78 (ddt, *J* = 18.6, 9.3, 7.0 Hz, 1H), 5.10 (d, *J* = 9.3 Hz, 1H), 5.08 (d, *J* = 18.6 Hz, 1H), 3.80-3.76 (m, 2H), 3.59-3.50 (m, 1H), 2.31-2.14 (m 4H), 1.49-1.39 (m, 8H), 1.31 (s, 3H), 1.27-1.09 (m, 30H), 1.06 (s, 9H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$); δ 135.9, 134.7, 134.5, 129.4, 127.4, 116.7, 100.1, 72.7, 66.5, 66.1, 40.1, 37.9, 36.2, 31.9, 31.7, 30.7, 29.7(x8), 29.4, 27.1(x3), 24.9, 24.8, 24.7, 22.7, 19.4, 14.1 ppm.
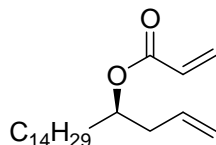
(*R*)-octadec-1-en-4-yl acrylate ((*R*)-40):

Homoallylic alcohol (*R*)-5 (100 mg, 0.37 mmol) was dissolved in dry dichloromethane (3 mL) under argon atmosphere. The resulting mixture was cooled to 0 °C and DIPEA (142 mg, 1.1 mmol) was added, followed by addition of freshly distilled acryloyl chloride (67 mg, 0.74 mmol) by syringe. After continuous stirring for 1 h at 0 °C the ice bath was removed and the mixture continued stirring overnight at RT. The reaction mixture was filtered over a pad of silica gel, and washed with dichloromethane (2x). The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate (10:1) to yield (*R*)-40 (74 mg, 78 %) as clear oil: $[\alpha]_D$ +6.7 (*c* 0.8, CHCl$_3$), ^{1}H-NMR (300 MHz, CDCl$_3$) δ 6.39 (dd, *J* = 17.3, 1.6 Hz, 1H), 6.11 (dd, *J* = 17.3, 10.3 Hz, 1H), 5.79 (dd, *J* = 10.3, 1.6 Hz, 1H), 5.76 (ddt, *J* = 17.1, 8.8, 7.0 Hz, 1H) 5.08 (d, *J* = 8.8 Hz, 1H), 5.07 (d, *J* = 17.1 Hz, 1H), 5.00 (tt, *J* = 6.4, 6.1 Hz, 1H), 2.34 (ddd, *J* = 7.1, 5.9, 1.9 Hz 2H), 1.61-1.55 (m, 2H), 1.26-1.05 (m, 24H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.2, 134.0, 130.6, 129.2, 117.9, 73.9, 38.9, 33.9, 32.2, 29.9, 29.7(x8), 25.5, 22.9, 14.4 ppm.
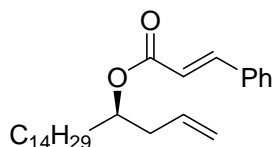
(*R*)-octadec-1-en-4-yl cynnamate ((*R*)-41):

Homoallylic alcohol (*R*)-5 (495 mg, 0.4 mmol) was dissolved in dry dichloromethane (3 mL) under argon atmosphere. The resulting mixture was cooled to 0 °C and DMAP (173 mg,
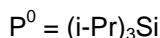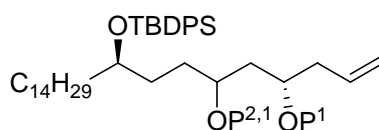
1.42 mmol) was added, followed by a solution of cynnamoyl chloride (169 mg, 1 mmol) in dry dichloromethane (1 mL). After continuous stirring for 1 h at 0 °C the ice bath was removed and the mixture continued stirring overnight at RT. The mixture was filtered over a small pad of silica gel, and washed with dichloromethane (2x). The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate (98:2) to yield (R)-41 (426 mg, 89 %) as clear oil: $[\alpha]_D$ +7.8 (c 1.3, CHCl$_3$), ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.69 (d, J = 16.0 Hz, 1H), 7.54 (d, J = 3.9 Hz, 2H), 7.41-7.37 (m, 3H), 6.45 (d, J = 16.0 Hz, 1H), 5.83 (ddt, J = 17.1, 10.0, 7.1 Hz, 1H), 5.19-4.97 (m, 3H), 2.40 (t, J = 6.5 Hz, 2H), 1.67-1.61 (m, 2H), 1.27-1.09 (m, 27H), 0.89 (t, J = 6.7 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.8, 144.7, 134.7, 134.0, 130.4, 129.0, 128.2, 118.7, 117.8, 73.7, 38.9, 33.9, 32.1, 29.7(x8), 29.6, 25.5, 22.9, 14.3 ppm.
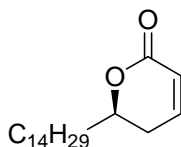
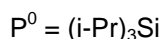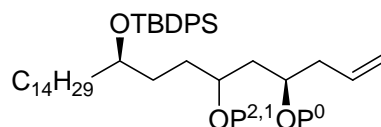**(R)-6-tetradecyl-5,6-dihydropyran-2-one ((R)-42):**

Cinnamate ester (R)-41 (390 mg, 0.3 mmol) was dissolved in dry toluene (30 mL) under an argon atmosphere and heated at reflux. To the refluxing solution Grubbs II catalyst (24 mg, 10 mol%) dissolved in dry toluene (1 mL) was added. After continuous stirring at reflux for 6 h, the reaction mixture was allowed to warm up to RT. The resulting mixture was concentrated and filtered with diethyl ether trough a small pad of Celite. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 9:1 to yield (R)-42 (336 mg, 89%) as a yellow oil: $[\alpha]_D$ +13.3 (c 0.6, CHCl$_3$), IR (thin film) 3055,

2985, 2927, 2854, 1465, 1390, 1421, 1265 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 6.86 (ddd, J = 9.6, 5.9, 3.2 Hz, 1H), 6.11 (d, J = 9.6 Hz, 1H), 4.39 (tt, J = 5.4, 5.3 Hz, 1H), 2.29 (ddd, J = 6.9, 5.4, 3.1 Hz, 2H), 1.79-1.75 (m, 1H), 1.66-1.60 (m, 1H), 1.26-1.09 (m, 4H), 0.85 (t, J = 6.5 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 164.5, 145.0, 121.3, 77.9, 34.8, 31.8, 29.6(x8), 29.3, 29.2, 24.7, 22.6, 14.0 ppm.

$$P^1 = (i\text{-Pr})_2SiCH_2CH_2\textbf{\textit{C}}_3\textbf{\textit{F}}_7$$

$$P^2 = (i\text{-Pr})_2SiCH_2CH_2\textbf{\textit{C}}_4\textbf{\textit{F}}_9$$

$$P^0 = (i\text{-Pr})_3Si$$

1-(*tert*-Butyl((4*S*,9*R*)-6-((perfluoroalkylethyl)diisopropylsilyloxy)-4-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)tricos-1-en-9-yloxy)(phenyl)silyl)benzene((*SMR*)-49):
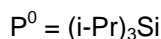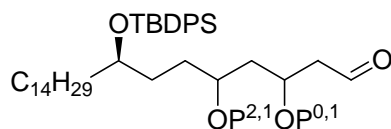
The synthesis of this compound was done by the same method used for **(*SR*)-39**, with **(*SMR*)-36** (2.6 g, 2.6 mmol). The crude mixture was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate (95:5) to yield **(*SMR*)-49** (3.1 g, 94 %) as a clear, slightly yellow liquid: ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.66 (dd, J = 8.4, 1.8 Hz, 4H), 7.42-7.28 (m, 6H), 5.74 (ddt, J = 18.9, 10.4, 6.9 Hz, 1H), 5.08 (d, J = 10.4 Hz, 1H), 5.06 (d, J = 18.9 Hz, 2H), 3.94-3.61 (m, 3H), 2.12-2.03 (m, 6H), 1.66-1.55 (m, 6H), 1.38-0.99 (m, 30H), 0.93 (s, 37H), 0.88 (t, J = 6.7 Hz, 3H), 0.86-0.79 (m, 4H); ^{19}F-NMR (282 MHz, CDCl$_3$) δ -79.5 (3F), -79.9 (6F), -115.6 (2F), -116.3 (4F), -123.0 (2F), -124.8 (2F), -126.4 (4F) ppm; LCMS (APCI, positive mode) *m/z* for **(*SMR*)-49**: **(*SRR*)-49A** = 1228.7 (M$^+$), 1192.7, 949.6; **(*SSR*)-49B** =1278.7 (M$^+$), 1262.3, 1099.9, 944.3.

OTBDPS

C$_{14}$H$_{29}$

OP^{2,1}OP^0

P^1 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_3$F$_7$**

P^2 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_4$F$_9$**

P^0 = (i-Pr)$_3$Si

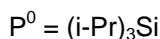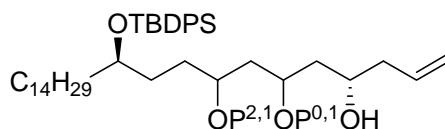## 1-(*tert*-Butyl((4*R*,9*R*)-6-((perfluoroalkylethyl)diisopropylsilyloxy)-4-(triisopropylsilyloxy)tricos-1-en-9-yloxy)(phenyl)silyl)benzene ((*RMR*)-51):

A 25 mL round bottom flask was filled with dichloromethane (5 mL), followed by **(RMR)-36** (2 g, 1 mmol). The solution was cooled to 0 ^{o}C, and 2,6-lutidine (2 equiv) was added. To the solution TIPSOTf (2 equiv.) was added, and stirring was continued for 3 hours. The reaction was quenched with saturated NH$_4$Cl solution. The layers were separated and the aqueous layer was extracted with dichloromethane (2x). The combined organic layers were dried over MgSO$_4$, the resulting solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 95:5 to yield **(RMR)-51** (2.28 g, 90 %) as a clear, slightly yellow oil: ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.64 (dd, *J* = 8.4, 1.8 Hz, 4H), 7.44-7.28 (m, 6H), 5.74 (ddt, *J* = 17.0, 9.9, 7.1 Hz, 1H), 5.07-5.01 (m, 2H), 3.91-3.61 (m, 3H), 2.15-2.07 (m, 4H), 1.63-1.57 (m, 6H), 1.38-0.99 (m, 30 H), 0.93 (s, 44H), 0.88 (t, *J* = 6.7 Hz, 3H), 0.85-0.79 (m, 4H); ^{19}F-NMR (282 MHz, CDCl$_3$) δ -79.5 (3F), -79.9 (3F), -115.6 (2F), -116.3 (2F), -123.0 (2F), -124.8 (2F), -126.4 (2F) ppm; LCMS (APCI, positive mode) *m/z* for **(RMR)-51**: **(RRR)-51** = 1074.7 (M$^+$), 1039.7, 837.7; **(RSR)-51** =1124.7 (M$^+$), 1082.9, 1030.6, 970.8.

$$P^1 = \text{(i-Pr)}_2\text{SiCH}_2\text{CH}_2\textbf{\textit{C}}_{\textbf{\textit{3}}}\textbf{\textit{F}}_{\textbf{\textit{7}}}$$

$$P^2 = \text{(i-Pr)}_2\text{SiCH}_2\text{CH}_2\textbf{\textit{C}}_{\textbf{\textit{4}}}\textbf{\textit{F}}_{\textbf{\textit{9}}}$$
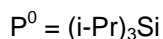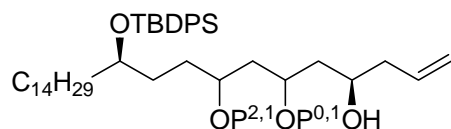
$$P^0 = \text{(i-Pr)}_3\text{Si}$$

(8*R*)-8-(*tert*-Butyldiphenylsilyloxy)-5-((perfluoroalkylethyl)diisopropylsilyloxy)-3-((perfluoroalkylethyl)diisopropylsilyloxy)docosanal (M14):

The synthesis of this compound was done by the same method used for **M13**. Using **M50B** (2.5 g, 2.02 mmol). The crude was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate (8:2) to yield **M14** (1.83 g, 73 %) as a clear, slightly yellow oil: ^{1}H-NMR (300 MHz, CDCl$_3$) δ 9.8-9.77 (m, 1H), 7.63 (dd, J = 8.4, 1.8 Hz, 4H), 7.46-7.36 (m, 6H), 4.41-4.34 (m, 1H), 3.81-3.62 (m, 2H), 2.68-2.39 (m, 2H) 2.16-1.94 (m, 4H), 1.63-1.52 (m, 6H), 1.38-0.99 (m, 30 H), 0.95 (s, 41H), 0.86 (t, J = 6.7 Hz, 3H), 0.84-0.77 (m, 4H); ^{19}F NMR (282.4 MHz, CDCl$_3$) δ -79.4(12F), -79.8(6F), -115.6(4F), -116.2(4F), -123.0(4F), -124.9(4F), -126.4(8F) ppm; LCMS (APCI, positive mode) *m/z* for **M14**: **(*SRR*)-14** = 1145.8 (M + H), 1067.8 (M − Ph), 896.6; **(*SSR*)-14** =1212.8 (M + H$_2$O), 1195.8 (M + H), 1117.8 (M − Ph), 939.7; **(*RRR*)-14** = 1299.7 (M + 1), 1221.7 (M − Ph), 1043.7; **(*RSR*)-14** = 1349.7 (M + H), 1271.7 (M − Ph), 1093.6.

P^1 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_3$F$_7$**

P^2 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_4$F$_9$**
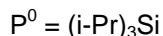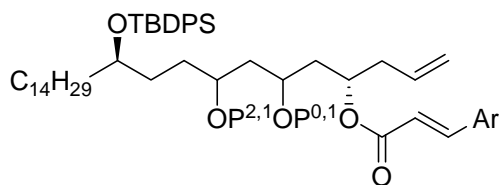
P^0 = (i-Pr)$_3$Si

(4*S*,11*R*)-11-(*tert*-Butyldiphenylsilyloxy)-8-((perfluoroalkylethyl)diisopropylsilyloxy)-6-((perfluoroalkylethyl)diisopropylsilyloxy)pentacos-1-en-4-ol ((*S*)-M52):

The synthesis of this compound was done by the same method used for **(*RR*)-34**, with **M14** (733 mg, 0.6 mmol). The crude was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate (10:1) to yield **(*S*)-M52** (498 mg, 80 %) as a colourless oil: ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.63 (dd, *J* = 8.4, 1.8 Hz, 4H), 7.43-7.36 (m, 6H), 5.76 (ddt, *J* = 16.7, 9.3, 6.5, Hz, 1H), 5.16-5.08 (m, 2H), 4.01-3.91 (m, 2H), 3.83-3.69 (m, 2H), 2.33-1.99 (m, 4H) 1.59-1.46 (m, 6H), 1.38-0.96 (m, 30H), 0.93 (s, 41H), 0.86 (t, *J* = 6.7 Hz, 3H), 0.90-0.73 (m, 4H); ^{19}F NMR (282.4 MHz, CDCl$_3$) δ -79.4(12F), -79.8(6F), -115.6(4F), -116.2(4F), -123.0(4F), -124.9(4F), -126.4(8F) ppm; LCMS (APCI, positive mode) *m/z* for **(*S*)-M52**: **(*SRRR*)-52** = 1117.7 (M − H), 1059.7, 896.6, 749.6, 697.4; **(*SRSR*)-52** = 1167.7 (M − H), 1109.7, 935.6, 871.5, 749.6; **(*SSRR*)-52** = 1271.7 (M − H), 1213.7, 975.5, 647.4, 629.3; **(*SSSR*)-52** = 1321.7 (M − H), 1264.7, 1191.6, 1025.5, 697.4, 629.3.

P^1 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_3$F$_7$**

P^2 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_4$F$_9$**
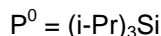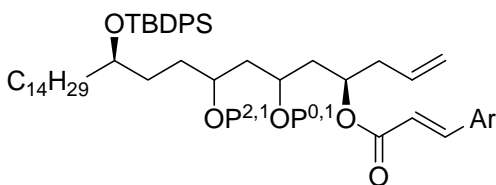
P^0 = (i-Pr)$_3$Si

(4*R*,11*R*)-11-(*tert*-Butyldiphenylsilyloxy)-8-((perfluoroalkylethyl)diisopropylsilyloxy)-6-((perfluoroalkylethyl)diisopropylsilyloxy)pentacos-1-en-4-ol ((*R*)-M52):

The synthesis of this compound was done by the same method used for **(*RR*)-34**, with **M14** (603 mg, 0.493 mmol). The crude mixture was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate (10:1) to yield **(*R*)-M52** 580 mg (0.459 mmol, 93 %) as a colourless oil: ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.65 (dd, *J* = 8.4, 1.8 Hz, 4H), 7.40-7.36 (m, 6H), 5.78 (ddt, *J* = 16.7, 9.3, 6.5, Hz, 1H), 5.13-5.05 (m, 2H), 4.39-3.65 (m, 4H), 2.38-1.98 (m, 6H), 1.59-1.46 (m, 6H), 1.38-0.96 (m, 30H), 0.93 (s, 41H), 0.86 (t, *J* = 6.7 Hz, 3H), 0.90-0.73 (m, 4H); ^{19}F NMR (282.4 MHz, CDCl$_3$) δ -79.4(12F), -79.8(6F), -115.6(4F), -116.2(4F), -123.0(4F), -124.9(4F), -126.4(8F) ppm; LCMS (APCI, positive mode) *m/z* for **(*R*)-M52**: **(*RRRR*)-52** = 1117.7 (M - H), 1059.7, 821.5, 769.6, 647.4; **(*RRSR*)-52** = 1167.7 (M - H), 1109.7, 935.6, 899.5, 679.5; **(*RSRR*)-52** = 1271.7 (M - H), 1213.7, 885.5, 647.4, 629.3; **(*RSSR*)-52** = 1321.7 (M - H), 1264.7, 1191.6, 1055.5, 647.4, 629.4.

OTBDPS

C$_{14}$H$_{29}$

OP^{2,1}OP^{0,1}O

Ar

O

P^1 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_3$F$_7$**

P^2 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_4$F$_9$**
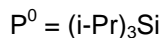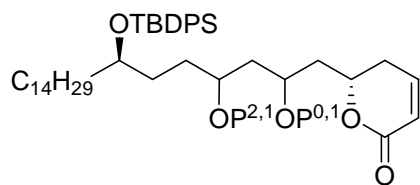
P^0 = (i-Pr)$_3$Si

(4*S*,11*R*)-11-(*tert*-Butyldiphenylsilyloxy)-8-((perfluoroalkylethyl)diisopropylsilyloxy)-6-((perfluoroalkylethyl)diisopropylsilyloxy)pentacos-1-en-4-yl cynnamate ((*S*)-M15):

The synthesis of this compound was done by the same method used for **(R)-41**, with **(S)-M52** (479 mg, 0.39 mmol). The crude was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate (98:2) to yield **(S)-M15** (426 mg, 78 %) as a clear oil: ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.66-7.56 (m, 5H), 7.50-7.25 (m, 10H), 6.34 (dd, *J* = 15.9, 4.3 Hz, 1H), 5.75 (ddt, *J* = 15.7, 10.2, 6.5, Hz, 1H), 5.23-5.15 (m, 1H), 5.09 (d, *J* = 15.7 Hz, 1H), 5.08 (d, *J* = 10.2 Hz, 1H), 4.12-3.57 (m, 3H), 2.39 (m, 4H), 2.06 (m, 6H), 1.27 (m, 29H), 1.19-0.97 (m, 41H), 0.89 (t, *J* = 6.7 Hz, 3H), 0.86-0.78 (m, 4H); ^{19}F NMR (282.4 MHz, CDCl$_3$) δ -79.4(12F), -79.8(6F), -115.6(4F), -116.2(4F), -123.0(4F), -124.9(4F), -126.4(8F) ppm; LCMS (APCI, positive mode) *m/z* for **(S)-M15**: **(SRRR)-15** = 1266.8 (M + H2O), 1076.8, 993.8, 819.8, 665.5; **(SRSR)-15** = 1316.8 (M + H$_2$O), 1126.8, 921.7, 870.5, 665.5; **(SSRR)-15** = 1420.8 (M + H$_2$O), 1325.8 (M − Ph), 1147.6, 1076.6, 689.4; **(SSSR)-15** = 1453.8 (M + H), 1376.8 (M − Ph), 1197.6, 819.5, 689.4.

OTBDPS

C$_{14}$H$_{29}$

OP^{2,1}OP^{0,1}O

Ar

O

$P^1 = (\text{i-Pr})_2\text{SiCH}_2\text{CH}_2\textbf{\textit{C}}_3\textbf{\textit{F}}_7$

$P^2 = (\text{i-Pr})_2\text{SiCH}_2\text{CH}_2\textbf{\textit{C}}_4\textbf{\textit{F}}_9$
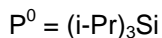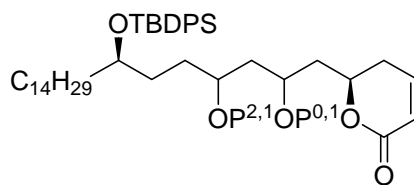
$P^0 = (\text{i-Pr})_3\text{Si}$

(4*R*,11*R*)-11-(*tert*-Butyldiphenylsilyloxy)-8-((perfluoroalkylethyl)diisopropylsilyloxy)-6-((perfluoroalkylethyl)diisopropylsilyloxy)pentacos-1-en-4-yl cynnamate ((*R*)-M15):

The synthesis of this compound was done by the same method used for **(*R*)-41**, with **(*R*)-M52** (517 mg, 0.42 mmol). The crude mixture was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate (98:2) to yield **(*R*)-M15** (490 mg, 83 %) as a clear oil: ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.67-7.62 (m, 5H), 7.53-7.27 (m, 10H), 6.36 (dd, *J* = 15.7, 4.4 Hz, 1H), 5.77 (ddt, *J* = 15.9, 10.5, 6.5, Hz, 1H), 5.28-5.13 (m, 1H), 5.09 (d, *J* = 15.9 Hz, 1H), 5.08 (d, *J* = 10.5 Hz, 1H), 4.25-3.95 (m, 3H), 2.41-2.37 (m, 2H), 2.09-2.05 (m, 5H), 1.27-1.05 (m, 30H), 0.99 (s, 43H), 0.89 (t, *J* = 6.7 Hz, 3H), 0.87-0.79 (m, 4H); ^{19}F NMR (282.4 MHz, CDCl$_3$) δ -79.4(12F), -79.9(6F), -115.6(4F), -116.2(4F), -123.0(4F), -124.9(4F), -126.4(8F) ppm; LCMS (APCI, positive mode) *m/z* for **(*R*)-M15**: **(*RRRR*)-15** = 1266.8 (M + H$_2$O), 1076.8, 993.8, 854.8; **(*RRSR*)-15** = 1316.8 (M + H$_2$O), 1126.8, 1043.7, 918.3, 879.5; **(*RSRR*)-15** = 1420.8 (M +H$_2$O), 1325.8 (M − Ph), 1140.6, 1096.6, 779.4; **(*RSSR*)-15** = 1453.8 (M + H), 1376.8 (M − Ph), 1197.6, 829.5, 750.5.

P^1 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_3$F$_7$**

P^2 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_4$F$_9$**
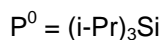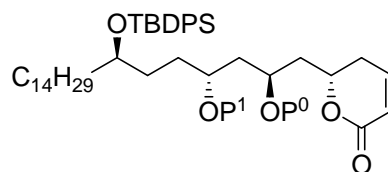
P^0 = (i-Pr)$_3$Si

(*S*)-6-((7*R*)-7-(*tert*-Butyldiphenylsilyloxy)-4-((perfluoroalkylethyl)diisopropylsilyloxy)-2-((perfluoroalkylethyl)diisopropylsilyloxy)henicosyl)-5,6-dihydropyran-2-one ((*S*)-M16):

The synthesis of this compound was done by the same method used for **(*R*)-42**, with **(*S*)-M15** (381 mg, 0.28 mmol). The crude mixture was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate (9:1) to yield **(*S*)-M16** (336 mg, 92%) as a yellow oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.67 (dd, *J* = 8.4, 1.8 Hz, 4H), 7.43-7.33 (m, 6H), 6.85 (ddd, *J* = 9.7, 5.9, 2.9 Hz, 1H), 6.02 (d, *J* = 9.8 Hz, 1H), 4.69-4.65 (m, 0.5H), 4.59-4.55 (m, 0.5H), 4.32-4.28 (m, 0.5H), 4.17-4.13 (m, 0.5H), 4.04-3.98 (m, 0.5H), 3.79-3.65 (m, 1.5H), 2.35-3.27 (m, 2H), 2.18-1.95 (m, 4H), 1.27-1.09 (s, 25H), 1.03 (s, 43H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{19}F NMR (282.4 MHz, CDCl$_3$) δ -79.4(12F), -79.8(6F), -115.5(4F), -116.2(4F), -123.0(4F), -124.8(4F), -126.3(8F) ppm; LCMS (APCI, positive mode) *m/z* for **(*S*)-M16**: **(*SRRR*)-16** = 1145.8 (M + H), 1067.8 (M − Ph), 896.6; **(*SRSR*)-16** =1212.8 (M + H$_2$O), 1195.8 (M + H), 1117.8 (M − Ph), 939.7; **(*SSRR*)-16** = 1299.7 (M + H), 1221.7 (M − Ph), 1043.7; **(*SSSR*)-16** = 1349.7 (M + H), 1271.7 (M − Ph), 1093.6.

$P^1 = (i\text{-}Pr)_2SiCH_2CH_2\mathbf{\mathit{C_3F_7}}$

$P^2 = (i\text{-}Pr)_2SiCH_2CH_2\mathbf{\mathit{C_4F_9}}$

$P^0 = (i\text{-}Pr)_3Si$

(R)-6-((7R)-7-(tert-Butyldiphenylsilyloxy)-4-((perfluoroalkylethyl)diisopropylsilyloxy)-2-((

perfluoroalkylethyl)diisopropylsilyloxy)henicosyl)-5,6-dihydropyran-2-one ((R)-M16):
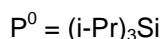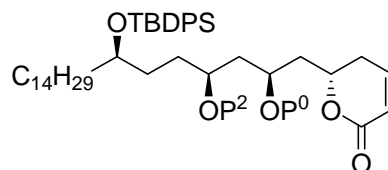
The synthesis of this compound was done by the same method used for **(R)-42**, with **(R)-M15** (465 mg, 0.346 mmol). The crude mixture was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate (9:1) to yield **(R)-M16** (379 mg, 85%) as a yellow oil: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.67 (dd, $J = 8.4$, 1.8 Hz, 4H), 7.42-7.27 (m, 6H), 6.86 (ddd, $J = 9.8$, 5.9, 2.8 Hz, 1H), 6.03 (d, $J = 9.8$ Hz, 1H), 4.66-4.40 (m, 1H), 4.23-4.19 (m, 0.5H), 4.14-4.10 (m, 0.5H), 3.91-3.87 (m, 0.5H), 3.79-3.65 (m, 1.5H), 2.40-2.31 (m, 2H), 2.18-2.05 (m, 4H), 1.29-1.09 (m, 25H), 1.06 (s, 46H), 0.87 (t, $J = 6.7$ Hz, 3H); ^{19}F NMR (282.4 MHz, CDCl$_3$) δ -79.4(12F), -79.8(6F), -115.5(4F), -116.2(4F), -123.0(4F), -124.8(4F), -126.3(8F) ppm; LCMS (APCI, positive mode) m/z for **(R)-M16**: **(RRRR)-16** = 1145.8 (M + H), 1067.8 (M − Ph); **(RRSR)-16** = 1212.8 (M + H$_2$O), 1195.8 (M + H), 1117.8 (M − Ph); **(RSRR)-16** = 1299.7 (M + H), 1221.7 (M − Ph); **(RSSR)-16** = 1349.7 (M + H), 1271.7 (M − Ph).

P^1 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_3$F$_7$**

P^2 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_4$F$_9$**

P^0 = (i-Pr)$_3$Si

(*S*)-6-((2*R*,4*R*,7*R*)-7-(*tert*-Butyldiphenylsilyloxy)-4-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-2-(triisopropylsilyloxy)henicosyl)-5,6-dihydropyran-2-one ((*SRRR*)-16):
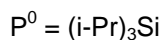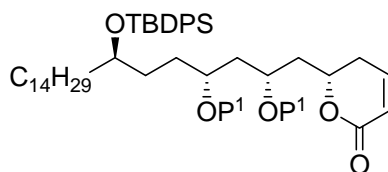
Semiprep HPLC separation was carried out on a 600E waters HPLC system. The mixture **(*S*)-M16** (336 mg, 0.26 mmol) of 4 compounds was filtered trough a Whatman filter paper (0.45 µM pore size) before injection. The separation was done on a FluoroFlash HPLC column (20mm x 250 mm). The separation was achieved by gradient elution with 95:5 acetonitrile/water to 100% acetonitrile in 30 minutes then isocratic acetonitrile for 60 min with a flow rate of 10 mL/min. UV detector (254 nm, 230nm) was used to manually identify the peaks. Aliquots (33 mg/mL) of **(*S*)-M16** were injected per run. The yield of the demixing was 85%, collecting the first peak **(*SRRR*)-16** (61 mg) at 30.9 min as a clear oil: [α]$_D$ -17.3 (*c* 0.6, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.67 (dd, *J* = 9.8, 1.9 Hz, 4H), 7.42-7.31 (m, 6H), 6.87 (ddd, *J* = 9.8, 5.9, 3.1 Hz, 1H), 6.02 (d, *J* = 9.8 Hz, 1H), 4.68-4.64 (m, 1H), 4.15-4.11 (m, 1H), 3.74-4.70 (m, 2H), 2.34-2.29 (m, 2H), 2.19-2.01 (m, 4H), 1.85-1.76 (m, 4H), 1.63-1.51 (m, 8H), 1.27-1.09 (m, 27H), 1.08-1.01 (m, 35H), 1.00 (s, 9H), 0.88 (t, *J* = 6.7 Hz, 3H), 0.85-0.79 (m, 2H); ^{19}F NMR (282.4 MHz) δ -79.4 (3F), -116.2 (3F), -126.3 (3F); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 163.9, 144.9, 135.9, 134.7, 134.4, 129.4, 127.4, 121.6, 74.5, 73.2, 71.0, 66.6, 46.6, 43.1, 36.5, 31.9, 31.8, 30.0, 29.7(x8), 29.5, 29.4, 27.0(x3), 25.3 (t, *J*$_{CF}$= 24.4 Hz), 24.8, 22.7, 19.3, 18.6, 18.2(x5), 18.1(x5),

17.7(x3), 14.1, 13.1, 13.0, 12.8(x3), 0.8 ppm; LCMS (APCI, positive mode) m/z = 1145.8 (M + H), 1067.8 (M − Ph).

P^1 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_3$F$_7$**

P^2 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_4$F$_9$**
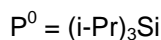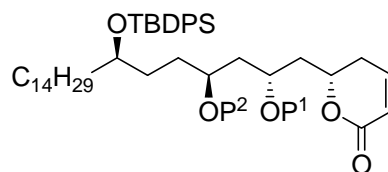
P^0 = (i-Pr)$_3$Si

(S)-6-((2R,4S,7R)-7-(*tert*-Butyldiphenylsilyloxy)-4-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-2-(triisopropylsilyloxy)henicosyl)-5,6-dihydropyran-2-one ((*SRSR*)-16):

From the demixing of **(S)-M16**, the second peak **(SRSR)-16** (72 mg) at 45.1 min was isolated as a clear oil: [α]$_D$ -5.0 (*c* 1.2, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.66 (dd, J = 9.8, 1.9 Hz, 4H), 7.42-7.23 (m, 6H), 6.85 (ddd, J = 9.7, 6.1, 3.0 Hz, 1H), 6.02 (d, J = 9.7 Hz, 1H), 4.67-4.63 (m, 1H), 4.31-4.27 (m, 1H), 3.80-3.78 (m, 1H), 3.74-3.71 (m, 1H), 2.31-2.27 (m, 2H), 2.25-1.98 (m, 4H), 1.77-1.68 (m, 2H), 1.61-1.53 (m, 8H), 1.27-1.11 (m, 27H), 1.10-1.03 (m, 35H), 1.01 (s, 9H), 0.89 (t, J = 6.7 Hz, 3H), 0.84-0.80 (m, 2H); ^{19}F NMR (282.4 MHz) δ -79.8 (3F), -115.4 (2F), 123.0 (2F), 124.8 (2F); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 163.8, 144.6, 135.8, 134.7, 134.4, 129.5, 127.4, 121.7, 74.6, 73.0, 70.4, 66.1, 45.3, 42.7, 35.9, 33.0, 31.9, 31.5, 30.0, 29.7(x8), 29.5, 29.4, 27.0(x3), 25.5 (t, J_{CF} = 24.4 Hz), 24.9, 22.7, 19.3, 18.1(x10), 17.7(x3), 14.1, 13.0, 12.8(x3), 0.8 ppm; LCMS (APCI, positive mode) m/z = 1212.8 (M + H$_2$O), 1195.8 (M + H), 1117.8 (M − Ph).
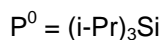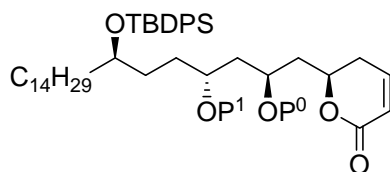
P^1 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_3$F$_7$**

P^2 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_4$F$_9$**

P^0 = (i-Pr)$_3$Si

(*S*)-6-((2*S*,4*R*,7*R*)-7-(*tert*-Butyldiphenylsilyloxy)-2,4-bis((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)henicosyl)-5,6-dihydropyran-2-one ((*SSSR*)-16):

From the demixing of **(*S*)-M16**, the third peak **(*SSRR*)-16** (73 mg) at 53.3 min was isolated as a clear oil: [α]$_D$ +9.7 (*c* 0.4, CHCl$_3$); ^{1}H NMR (300 MHz) δ 7.67 (dd, *J* = 9.8, 1.9 Hz, 4H), 7.41-7.29 (m, 6H), 6.86 (ddd, *J* = 9.8, 6.5, 3.4 Hz, 1H), 6.49 (d, *J*= 9.8 Hz, 1H), 4.57-4.53 (m, 1H), 4.17-4.13 (m, 1H), 3.85-3.81 (m, 1H), 3.73-3.69 (m, 1H), 2.37-2.31 (m, 2H), 2.25-1.96 (m, 5H), 1.83-1.79 (m, 2H), 1.65-1.59 (m, 6H), 1.47-1.39 (m, 8H), 1.26-1.16 (m, 27H), 1.12-1.05 (m, 28H), 1.03 (s, 9H), 0.86 (t, *J* = 6.7 Hz, 3H), 0.84-0.79 (m, 4H); ^{19}F NMR (282.4 MHz) δ -79.4 (6F), -116.2 (4F), -126.3 (4F); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 163.6, 144.4, 135.9, 134.7, 134.5, 129.4, 127.4, 121.7, 74.5, 73.3, 70.3, 67.1, 43.7, 41.6, 36.3, 33.2, 31.9(x3), 31.3, 31.2, 30.0, 29.7(x8), 29.5, 29.4, 27.0(x3), 25.0 (t, *J*$_{CF}$= 24.4 Hz), 24.9, 22.7, 19.4, 17.7(x5), 17.6(x5), 14.1, 13.0, 12.8(x3), 12.7(x3), 1.2, 0.9 ppm; LCMS (APCI, positive mode) *m/z* = 1299.7 (M + H), 1221.7 (M − Ph).

P^1 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_3$F$_7$**

P^2 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_4$F$_9$**

P^0 = (i-Pr)$_3$Si

(*S*)-6-((2*S*,4*S*,7*R*)-7-(*tert*-Butyldiphenylsilyloxy)-4-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-2-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)henicosyl)-5,6-dihydropyran-2-one ((*SSSR*)-16):
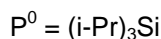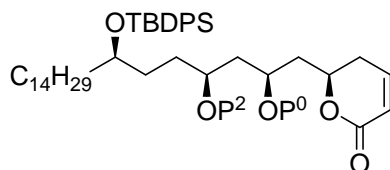
From the demixing of **(*S*)-M16**, the fourth peak **(*SSSR*)-16** (80 mg) at 69.7 min was isolated as a clear oil: [α]$_D$ +13.5 (*c* 0.6, CHCl$_3$); ^{1}H NMR (300 MHz) δ 7.67 (dd, *J* = 9.8, 1.9 Hz, 4H), 7.44-7.34 (m, 6H), 6.83 (ddd, *J* = 9.7, 6.3, 3.5 Hz, 1H), 6.03 (dd, *J* = 9.7, 1.9 Hz, 1H), 4.58-4.54 (m, 1H), 4.02-3.98 (m, 1H), 3.79-3.75 (m, 1H), 3.73-3.69 (m, 1H), 2.38-2.28 (m, 2H), 2.21-1.97 (m, 6H), 1.74-1.65 (m, 4H), 1.63-1.56 (m, 6H), 1.41-1.35 (m, 5H), 1.26-1.13 (s, 27H), 1.10-1.05 (m, 28H), 1.02 (s, 9H), 0.87 (t, *J* = 6.7 Hz, 3H), 0.83-0.78 (m, 4H); ^{19}F NMR (282.4 MHz) δ -79.4 (3F), -79.9 (3F), -115.5 (2F), -116.3 (2F), -123.0 (F), -124.9 (2F), -126.4 (2F); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 163.6, 144.3, 135.9, 134.7, 134.4, 129.4, 127.4, 121.7, 74.5, 73.4, 70.6, 67.4, 45.1, 42.0, 36.4, 32.8, 31.9, 31.6, 30.0, 29.7(x8), 29.5, 29.4, 26.8(x5), 25.6 (t, *J*$_{CF}$= 24.4 Hz), 24.8, 22.7, 19.4, 17.7(x5), 17.6 (x5), 14.1, 13.1, 13.0, 12.8(x5), 1.1, 0.9 ppm; LCMS (APCI, positive mode) *m/z* = 1349.7 (M + H), 1271.7 (M − Ph).

OTBDPS

C₁₄H₂₉ ... ŌP¹ ŌP⁰ O

O

P¹ = (i-Pr)₂SiCH₂CH₂**C₃F₇**

P² = (i-Pr)₂SiCH₂CH₂**C₄F₉**

P⁰ = (i-Pr)₃Si

(*R*)-6-((2*R*,4*R*,7*R*)-7-(*tert*-Butyldiphenylsilyloxy)-4-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)-2-(triisopropylsilyloxy)henicosyl)-5,6-dihydropyran-2-one ((*RRRR*)-16):
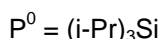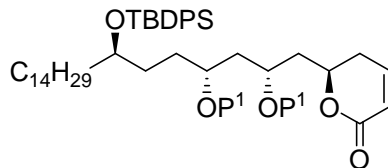
Semiprep HPLC separation was carried out on a 600E waters HPLC system. The mixture (*R*)-**M16** (336 mg, 0.26 mmol) of 4 compounds was filtered trough a Whatman filter paper (0.45 µM pore size) before injection. The separation was done on a FluoroFlash HPLC column (20mm x 250 mm). The separation was achieved by gradient elution with 95:5 acetonitrile/water to 100% acetonitrile in 30 minutes then isocratic acetonitrile for 60 min with a flow rate of 10 mL/min. UV detector (254 nm, 230nm) was used to manually identify the peaks. Aliquots (33 mg/mL) of (*R*)-**M16** were injected per run. The yield of the demixing was 85%, collecting the first peak (*RRRR*)-**16** (56 mg) at 33.5 min as a clear oil [α]$_D$ -11.3 (*c* 0.8, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.65 (dd, *J* = 9.8, 1.9 Hz, 4H), 7.42-7.30 (m, 6H), 6.85-6.81 (ddd, *J* = 9.8, 5.6, 2.5 Hz, 1H), 6.01 (dd, *J* = 9.8, 2.5 Hz, 1H), 4.67-4.63 (m, 1H), 4.05-4.01 (m, 1H), 3.77-3.73 (m, 2H), 2.38-2.26 (m, 2H), 2.11-1.96 (m, 4H), 1.85-1.72 (m, 5H), 1.46-1.37 (m, 8H), 1.26-1.15 (m, 27H), 1.06-1.04 (m, 35H), 1.00 (s, 9H), 0.88 (t, *J* = 6.7 Hz, 3H), 0.85-0.79 (m, 2H); ¹⁹F NMR (282.4 MHz) δ -79.4 (3F), -116.2 (2F), -126.3 (2F); ¹³C-NMR (75 MHz, CDCl₃) δ 164.0, 144.7, 135.8, 134.7, 134.4, 129.5, 127.4, 121.6, 74.8, 73.3, 70.4, 67.0, 44.8, 41.5, 36.6, 32.0, 31.9, 31.4,

31.2, 30.0, 29.7(x8), 29.5, 29.4, 27.0(x3), 25.3 (t, J_{CF}= 24.4 Hz), 24.9, 22.7, 19.4, 18.2(x10), 17.7(x3), 14.1, 12.9(x3), 12.7(x3), 0.8 ppm; LCMS (APCI, positive mode) m/z = 1145.8 (M + H), 1067.8 (M − Ph).
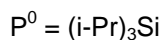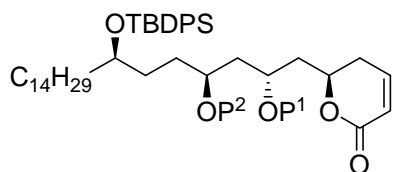

P^1 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_3$F$_7$**

P^2 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_4$F$_9$**

P^0 = (i-Pr)$_3$Si

(*R*)-6-((2*R*,4*S*,7*R*)-7-(*tert*-Butyldiphenylsilyloxy)-4-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-2-(triisopropylsilyloxy)henicosyl)-5,6-dihydropyran-2-one ((*RRSR*)-16):

From the demixing of **(*R*)-M16**, the second peak **(*RRSR*)-16** (70 mg) at 47.0 min was isolated as a clear oil: [α]$_D$ +23 (*c* 1.1, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.66 (dd, *J* = 9.8, 1.9 Hz, 4H), 7.43-7.230 (m, 6H), 6.86 (ddd, *J* = 9.8, 6.6, 2.5 Hz, 1H), 6.03 (d, *J* = 9.8 Hz, 1H), 4.67-4.63 (m, 1H), 4.23-4.19 (m, 1H), 3.91-3.87 (m, 1H), 3.76-3.72 (m, 1H), 2.41-2.32 (m, 2H), 2.10-2.01 (m, 4H), 1.89-1.84 (m, 2H), 1.69-1.64 (m, 3H), 1.52-1.48 (m, 5H), 1.26-1.13 (m, 27H), 1.10-1.05 (m, 35H), 1.01 (s, 9H), 0.88 (t, *J* = 6.7 Hz, 3H), 0.82-0.79 (m, 2H); ^{19}F NMR (282.4 MHz) δ -79.8 (3F), -115.5 (2F), -123.0 (2F), -124.9 (2F); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 163.9, 144.6, 135.9, 134.8, 134.5, 129.5, 127.4, 121.6, 74.7, 73.2, 70.6, 66.7, 43.7, 41.3, 36.1, 33.2, 31.9, 31.4, 30.1, 29.7(x8), 29.4, 27.0(x3), 25.6 (t, J_{CF}= 24.4 Hz), 24.9, 22.7, 19.3, 18.1(x10), 17.7(x3), 14.1(x3), 13.1, 13.0, 12.8(x3), 0.8 ppm; LCMS (APCI, positive mode) m/z = 1212.8 (M + H$_2$O), 1195.8 (M + H), 1117.8 (M − Ph).

P^1 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_3$F$_7$**

P^2 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_4$F$_9$**

P^0 = (i-Pr)$_3$Si

(*R*)-6-((2*S*,4*R*,7*R*)-7-(*tert*-Butyldiphenylsilyloxy)-2,4-bis((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)henicosyl)-5,6-dihydropyran-2-one ((*RSRR*)-16):

From the demixing of **(*R*)-M16**, the third peak **(*RSRR*)-16** (69 mg) at 54.3 min was isolated as a clear oil: $[\alpha]_D$ +16.2 (*c* 0.5, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.67 (dd, *J* = 9.8, 1.9 Hz, 4H), 7.43-7.30 (m, 6H), 6.86 (ddd, *J* = 9.6, 6.9, 2.4 1H), 6.49 (d, *J* = 9.6 Hz, 1H), 4.60-4.57 (m, 1H), 4.30-4.26 (m, 1H), 3.72-3.67 (m, 2H), 2.31-2.26 (m, 2H), 2.18-1.96 (m, 6H), 1.71-1.67 (m, 3H), 1.52-1.49 (m, 5H), 1.44-1.37 (m, 5H), 1.27-1.17 (m, 27H), 1.10-1.03 (m, 28H), 1.01 (s, 9H), 0.88 (t, *J* = 6.7 Hz, 3H), 0.83-0.77 (m, 4H); ^{19}F NMR (282.4 MHz) δ -79.4 (6F), -116.2 (4F), -126.3 (4F); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 163.6, 144.6, 135.9, 134.7, 134.6, 129.6, 127.5, 121.7, 74.2, 73.2, 70.2, 66.2, 45.2, 42.5, 36.3, 33.5, 31.9, 31.6, 30.0, 29.7(x8), 29.6, 29.4, 27.0(x3), 25.3 (t, J_{CF}= 24.4 Hz), 24.8, 22.7, 19.4, 17.6(x13), 14.1, 12.9(x5), 12.7, 0.8 ppm; LCMS (APCI, positive mode) *m/z* = 1299.7 (M + H), 1221.7 (M − Ph).

P^1 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_3$F$_7$**

P^2 = (i-Pr)$_2$SiCH$_2$CH$_2$**C$_4$F$_9$**

P^0 = (i-Pr)$_3$Si

(*R*)-6-((2*S*,4*S*,7*R*)-7-(*tert*-Butyldiphenylsilyloxy)-4-(diisopropyl(3,3,4,4,5,5,6,6,6-nonafluorohexyl)silyloxy)-2-((3,3,4,4,5,5,5-heptafluoropentyl)diisopropylsilyloxy)henicosyl)-5,6-dihydropyran-2-one ((*RSSR*)-16):

From the demixing of **(*R*)-M16**, the fourth peak **(*RSSR*)-16** (75 mg) at 68.6 min was isolated as a clear oil: [α]$_D$ -3.8 (*c* 1.2, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.66 (dd, *J* = 9.8, 1.9 Hz, 4H), 7.43-7.30 (m, 6H), 6.89-6.84 (ddd, *J* = 9.9, 6.0, 3.0 Hz, 1H), 6.02 (d, *J* = 9.9 Hz, 1H), 4.59-4.55 (m, 1H), 4.10-4.06 (m, 1H), 3.72-4.68 (m, 2H), 2.33-2.28 (m, 2H), 2.19-1.96 (m, 6H), 1.83-1.71 (m, 2H), 1.57-1.51 (m, 5H), 1.43-1.35 (m, 5H), 1.26-1.16 (m, 27H), 1.15-1.03 (m, 28H), 1.01 (s, 9H), 0.86 (t, *J* = 6.7 Hz, 3H), 0.85-0.80 (m, 4H); ^{19}F NMR (282.4 MHz) δ -79.4 (3F), -79.8 (3F), -115.5 (2F), -116.3 (2F), -123.0 (2F), -124.9 (2F), -126.4 (2F); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 163.6, 144.6, 135.9, 134.7, 134.4, 129.4, 127.4, 121.6, 74.1, 73.2, 71.7, 66.8, 46.4, 42.8, 36.3, 32.6, 31.9, 31.6, 30.0, 29.7(x8), 29.5, 29.4, 27.0(x3), 25.3 (t, *J*$_{CF}$= 24.4 Hz), 24.8, 22.7, 19.3, 17.6(x19), 14.1, 13.0, 12.8, 0.9 ppm; LCMS (APCI, positive mode) *m/z* = 1349.7 (M + H), 1271.7 (M − Ph).
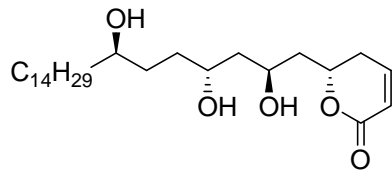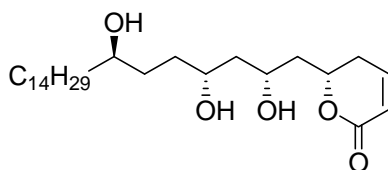
(*S*)-6-((2*S*,4*R*,7*R*)-2,4,7-Trihydroxyhenicosyl)-5,6-dihydropyran-2-one ((*SSRR*)-3):

Quasiisomer **(*SRRR*)-16** (60 mg, 0.04 mmol) was dissolved in ethanol (1 mL), and 3N HCl/ethanol (1.5 mL, 12 equiv.) was added. Stirring was continued for 40 hours or until TLC indicated completion of the reaction by consumption of starting material. The reaction was quenched with solid NaHCO$_3$ and the organic product was dried over with MgSO$_4$. The solution was concentrated and dissolved in 1:1 ACN/THF (0.5 mL), and then injected in C18 semi-prep HPLC column for purification. The purification was done by isocratic elution with 80:20 ACN/H$_2$O for 30 min with a flow rate of 10 mL/min. UV detector (210 nm, 254 nm) was used to identify the peaks. The reaction after purification by C18 HPLC column yielded in 48% (12 mg, 9 min) **(*SSRR*)-3** as a white solid. **(*SSRR*)-3** was dissolved in a 1:1 mixture of THF:ethanol (0.2 mL), and then injected in a Chiracel OD semi-prep HPLC column for purification. The purification was done by isocratic elution with 86:14 hexanes/isopropanol for 30 min with a flow rate of 10 mL/min. UV detector (210 nm, 254 nm) was used to identify the peaks. The yield of the purification was 72% (8 mg, 7.9 min), obtaining **(*SSRR*)-3** as a white solid: [α]$_D$ -15.8 (*c* 0.93, MeOH); ^{1}H NMR (600 MHz) δ 6.90 (ddd, *J* = 9.6, 6.5, 3.4 Hz, 1H), 6.03 (d, *J* = 9.6 Hz, 1H), 4.79-4.75 (m, 1H), 4.35-4.31 (m, 1H), 4.01-3.97 (m, 1H), 3.65-3.63 (m, 1H), 2.41-2.39 (m, 2H), 1.91-1.87 (m, 1H), 1.81-1.77 (m, 1H), 1.69-1.65 (m, 4H), 1.47 (t, *J* = 7.1 Hz, 2H), 1.29-1.21 (m, 27H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 164.7, 145.5, 121.3, 75.1, 73.6, 71.9, 68.1, 42.5, 42.3, 38.2, 34.1, 31.9, 30.1, 29.7(x8), 29.5, 29.4, 25.3, 22.7, 14.1 ppm; LCMS (APCI, positive mode) *m/z* = 509 (M + 3Na), 486 (M + 2Na), 463 (M + Na), 440 (M$^+$), 422 (M − H$_2$O), 404 (M − 2XH$_2$O), 386 (M − 3XH$_2$O).
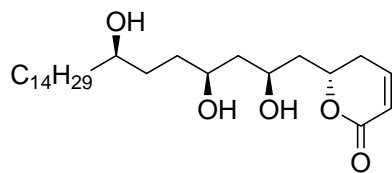
(*S*)-6-((2*S*,4*S*,7*R*)-2,4,7-Trihydroxyhenicosyl)-5,6-dihydropyran-2-one ((*SSSR*)-3):

The synthesis of this compound was done by the same method used for **(*SSRR*)-3**, with

(*SRSR*)-16 (69 mg, 0.04 mmol). The crude after Chiracel OD purification provided **(*SSSR*)-3** (7

mg, 32%) as a white solid: $[\alpha]_D$ -21.5 (*c* 0.7, MeOH); ^{1}H NMR (600 MHz) δ 6.90 (ddd, *J* = 9.8,

6.5, 3.4 Hz, 1H), 6.03 (d, *J* = 9.8 Hz, 1H), 4.78-4.74 (m, 1H), 4.27-4.23 (m, 1H), 3.95-3.91 (m,

1H), 3.66-3.63 (m, 1H), 2.39-2.35 (m, 2H), 1.87 (t, *J* = 12.1 Hz, 1H), 1.75-1.68 (m, 4H), 1.58-

1.56 (m, 2H), 1.49-1.46 (m, 2H), 1.41-1.38 (m, 1H), 1.27 (m, 24H), 0.88 (t, *J*= 6.9 Hz, 3H); ^{13}C-

NMR (75 MHz, CDCl$_3$) δ 164.6, 145.5, 121.4, 74.8, 73.1, 72.5, 68.0, 43.7, 43.2, 37.9, 35.3, 33.9,

31.9, 30.0, 29.7(x8), 29.4, 25.8, 22.7, 14.1 ppm; LCMS (APCI, positive mode) *m/z* = 509 (M +

3Na), 486 (M + 2Na), 463 (M + Na), 440 (M$^+$), 422 (M − H$_2$O), 404 (M − 2XH$_2$O), 386 (M −

3XH$_2$O).

(*S*)-6-((2*R*,4*R*,7*R*)-2,4,7-Trihydroxyhenicosyl)-5,6-dihydropyran-2-one ((*SRRR*)-3):
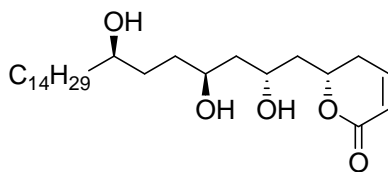
The synthesis of this compound was done by the same method used for **(*SSRR*)-3**, with

(*SSRR*)-16 (70 mg, 0.04 mmol). The crude after Chiracel OD purification provided **(*SRRR*)-3** (6

mg, 327%) as a white solid: $[\alpha]_D$ -26.8 (*c* 0.8, MeOH); ^{1}H NMR (600 MHz) δ 6.90 (ddd, *J* = 9.0,

6.5, 3.4 Hz, 1H), 6.03 (d, *J* = 8.8 Hz, 1H), 4.72-4.66 (m, 1H), 4.22-4.19 (m, 1H), 4.02-3.95 (m,

1H), 3.73-3.66 (m, 1H), 2.51-2.38 (m, 2H), 2.09-2.01 (m, 1H), 1.82-1.75 (m, 1H), 1.75-1.55 (m,

4H), 1.53-1.45 (m, 2H), 1.43-1.36 (m, 1H), 1.32-1.20 (m, 25H), 0.89 (t, J=6.9 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 164.3, 145.1, 121.4, 76.3, 72.5, 71.9, 69.3, 42.6, 42.2, 37.5, 34.1, 32.7, 32.0, 29.7(x8), 29.5, 29.4, 25.9, 22.7, 14.1 ppm; LCMS (APCI, positive mode) m/z = 509 (M + 3Na), 486 (M + 2Na), 463 (M + Na), 440 (M$^+$), 422 (M − H$_2$O), 404 (M − 2XH$_2$O), 386 (M − 3XH$_2$O).

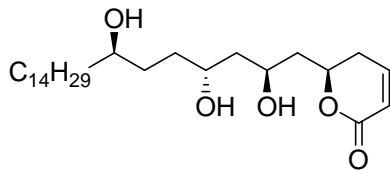**(S)-6-((2R,4S,7R)-2,4,7-Trihydroxyhenicosyl)-5,6-dihydropyran-2-one ((SRSR)-3):**

The synthesis of this compound was done by the same method used for **(SSRR)-3**, with **(SSSR)-16** (78 mg, 0.04 mmol). The crude after Chiracel OD purification provided **(SRSR)-3** (6 mg, 28%) as a white solid: [α]$_D$ +15.3 (c 0.8, MeOH); ^{1}H NMR (600 MHz) δ 6.90 (ddd, J = 8.5, 6.5, 3.4 Hz, 1H), 6.03 (d, J = 8.1 Hz, 1H), 4.79-4.74 (m, 1H), 4.38-4.34 (m, 1H), 4.06-4.02 (m, 1H), 3.73-3.69 (m, 1H), 2.47-2.31 (m, 2H), 2.08-1.86 (m, 2H), 1.77-1.63 (m, 2H), 1.62-1.53 (m, 1H), 1.52-1.44 (m, 2H), 1.42-1.37 (m, 1H), 1.34-1.27 (m, 25H), 0.88 (t, J=6.9 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 164.6, 145.5, 121.6, 75.1, 73.5, 72.8, 68.4, 43.8, 43.3, 38.1, 34.0, 32.1, 30.2, 29.8(x8), 29.5, 29.4, 25.9, 22.9, 14.3 ppm; LCMS (APCI, positive mode) m/z = 509 (M + 3Na), 486 (M + 2Na), 463 (M + Na), 440 (M$^+$), 422 (M − H$_2$O), 404 (M − 2XH$_2$O), 386 (M − 3XH$_2$O).
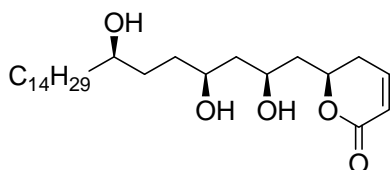
(R)-6-((2S,4R,7R)-2,4,7-Trihydroxyhenicosyl)-5,6-dihydropyran-2-one ((RSRR)-3):

The synthesis of this compound was done by the same method used for **(SSRR)-3**, with **(RRRR)-16** (53 mg, 0.04 mmol). The crude after Chiracel OD purification provided **(RSRR)-3** (8 mg, 40%) as a white solid: $[\alpha]_D$ +3.4 (*c* 0.31, MeOH); ^{1}H NMR (600 MHz) δ 6.91 (ddd, *J* = 10.3, 6.6, 3.1 Hz, 1H), 6.03 (d, *J* = 10.7 Hz, 1H), 4.85-4.67 (m, 1H), 4.40-4.28 (m, 1H), 4.26-4.16 (m, 1H), 3.94-3.82 (m, 1H), 2.57-2.26 (m, 2H), 1.91-1.82 (m, 1H), 1.83-1.75 (m, 1H), 1.73-1.53 (m, 4H), 1.52-1.42 (m, 2H), 1.42-0.96 (m, 27H), 0.89 (t, *J*=6.9 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 164.3, 145.1, 121.4, 76.3, 72.5, 71.9, 69.3, 42.6, 42.2, 37.5, 34.1, 32.7, 32.0, 29.7(x8), 29.5, 29.4, 25.9, 22.7, 14.1 ppm; LCMS (APCI, positive mode) *m/z* = 509 (M + 3Na), 486 (M + 2Na), 463 (M + Na), 440 (M$^+$), 422 (M – H$_2$O), 404 (M – 2XH$_2$O), 386 (M − 3XH$_2$O).

(R)-6-((2S,4S,7R)-2,4,7-Trihydroxyhenicosyl)-5,6-dihydropyran-2-one ((RSSR)-3):
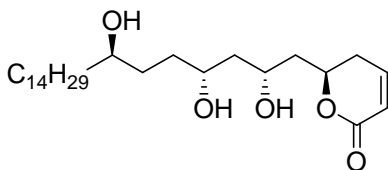
The synthesis of this compound was done by the same method used for **(SSRR)-3**, with **(RRSR)-16** (68 mg, 0.04 mmol). The crude after Chiracel OD purification provided **(RSSR)-3** (4 mg, 22%) as a white solid: $[\alpha]_D$ +12.2 (*c* 0.9, MeOH); ^{1}H NMR (600 MHz) δ 6.92 (ddd, *J* = 10.3, 6.5, 3.1 Hz, 1H), 6.04 (d, *J* = 10.5 Hz, 1H), 4.79-4.75 (m, 1H), 4.29-4.25 (m, 1H), 4.02-3.98 (m, 1H), 3.72-3.68 (m, 1H), 2.54-2.36 (m, 2H), 1.93-1.85 (m, 1H), 1.78-1.74 (m, 1H), 1.63-1.56 (m, 4H), 1.53-1.46 (m, 2H), 1.29-1.24 (m, 27H), 0.89 (t, *J*=6.9 Hz, 3H); ^{13}C-NMR (75 MHz,

CDCl$_3$) δ 164.1, 145.1, 121.6, 76.1, 73.2, 72.3, 69.4, 43.0, 42.3, 37.9, 35.2, 33.8, 31.9, 29.7(x8), 29.5, 29.4, 25.8, 22.7, 14.1 ppm; LCMS (APCI, positive mode) m/z = 509 (M + 3Na), 486 (M + 2Na), 463 (M + Na), 440 (M$^+$), 422 (M – H$_2$O), 404 (M – 2XH$_2$O), 386 (M − 3XH$_2$O).

(R)-6-((2R,4R,7R)-2,4,7-Trihydroxyhenicosyl)-5,6-dihydropyran-2-one (($RRRR$)-3):
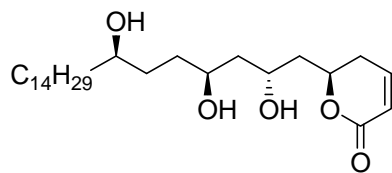
The synthesis of this compound was done by the same method used for (**SSRR**)-3, with (**RSRR**)-16 (66 mg, 0.04 mmol). The crude after Chiracel OD purification provided (**RRRR**)-3 (4 mg, 21%) as a white solid: [α]$_D$ -34.1 (c 0.46, MeOH); ^{1}H NMR (600 MHz) δ 6.90 (ddd, J = 9.8, 6.5, 3.4 Hz, 1H), 6.03 (d, J = 9.7 Hz, 1H), 4.76 (t, J = 10.8 Hz, 1H), 4.25 (t, J = 9.4 Hz, 1H), 4.00-3.96 (m, 1H), 3.69-3.65 (m, 1H), 2.43-2.32 (m, 2H), 1.87 (t, 1H), 1.73 (t, 1H), 1.63 (t, J = 13.2 Hz, 2H), 1.57 (t, J = 14.1 Hz, 2H), 1.49-1.45 (m, 2H), 1.43-1.38 (m, 1H), 1.27 (m, 25H), 0.89 (t, J=6.9 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 164.6, 145.5, 121.6, 75.0, 72.9, 72.3, 68.5, 43.5, 43.3, 37.4, 34.3, 32.4, 32.1, 30.2, 29.7(x8), 29.5, 25.9, 22.9, 14.1 ppm; LCMS (APCI, positive mode) m/z = 509 (M + 3Na), 486 (M + 2Na), 463 (M + Na), 440 (M$^+$), 422 (M – H$_2$O), 404 (M – 2XH$_2$O), 386 (M − 3XH$_2$O).

(_R_)-6-((2_R_,4_S_,7_R_)-2,4,7-Trihydroxyhenicosyl)-5,6-dihydropyran-2-one ((_RRSR_)-3):

The synthesis of this compound was done by the same method used for **(_SSRR_)-3**, with **(_RSSR_)-16** (71 mg, 0.04 mmol). The crude after Chiracel OD purification provided **(_RRSR_)-3** (5 mg, 29%) as a white solid: $[\alpha]_D$ +19.2 (_c_ 0.39, MeOH); ^{1}H NMR (600 MHz) δ 6.90 (ddd, _J_ = 9.8, 6.5, 3.4 Hz, 1H), 6.03 (d, _J_ = 9.8 Hz, 1H), 4.78-4.74 (m, 1H), 4.27-4.23 (m, 1H), 3.95-3.91 (m, 1H), 3.67-3.63 (m, 1H), 2.39-2.35 (m, 2H), 1.93-1.83 (m, 1H), 1.78-1.65 (m, 2H), 1.63-1.53 (m, 2H), 1.52-1.44 (m, 2H), 1.43-1.37 (m, 1H), 1.36-1.13 (m, 26H), 0.89 (t, _J_ = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 164.4, 145.3, 121.3, 74.9, 73.3, 72.6, 68.1, 43.6, 43.1, 37.8, 35.3, 33.8, 31.9, 29.7(x8), 25.7, 22.7, 14.1 ppm; LCMS (APCI, positive mode) _m/z_ = 509 (M + 3Na), 486 (M + 2Na), 463 (M + Na), 440 (M$^+$), 422 (M − H$_2$O), 404 (M − 2XH$_2$O), 386 (M − 3XH$_2$O).

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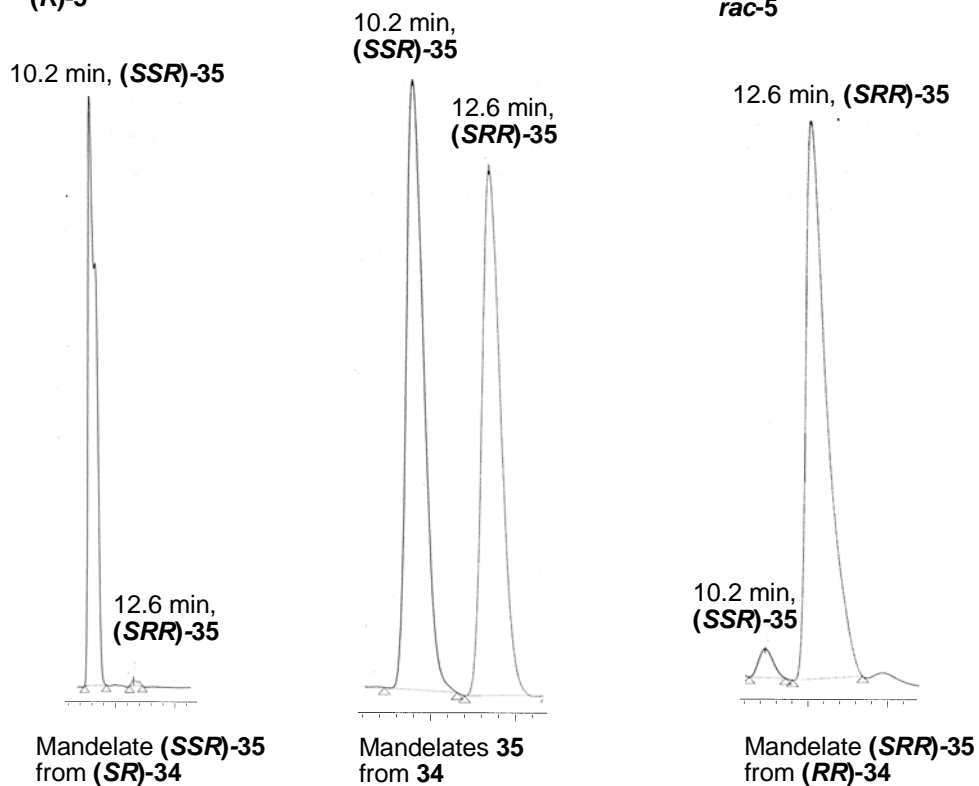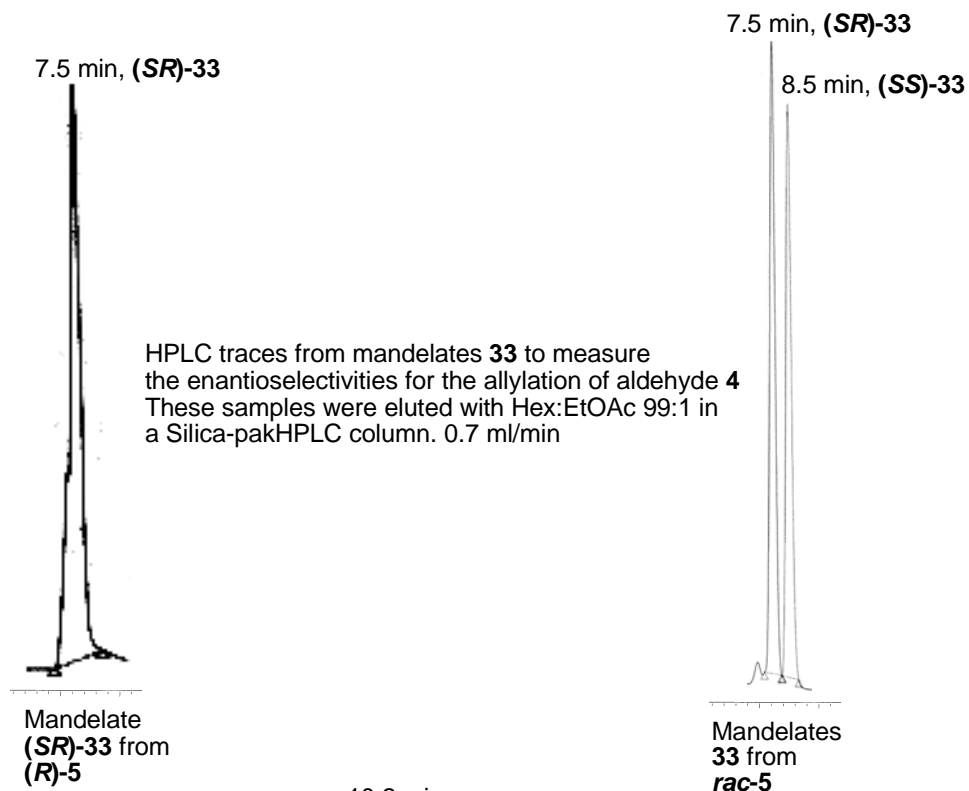
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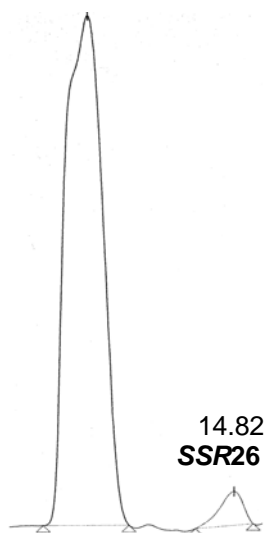42. Scouten, C. G.; Brown, H. C. *J. Org. Chem.* **1973**, *38*, 4092.

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45. Mixture synthesis utilizes LC (HPLCor LCMS) and NMR (^{1}H or ^{19}F NMR) to analyze the purity of the mixtures. The yields in mixture synthesis are calculated assuming that all components in the mixture are equimolar to each other, then the yield shown is the average yield for the mixture.

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2.6 APPENDIX A

HPLC traces for allylation derivatives for the first, second and third allylation. HPLC traces for relevant fluorous mixtures.
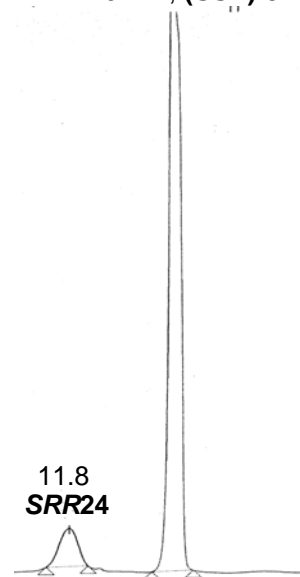
7.5 min, (*SR*)-33

7.5 min, (*SR*)-33

8.5 min, (*SS*)-33

HPLC traces from mandelates **33** to measure
the enantioselectivities for the allylation of aldehyde **4**
These samples were eluted with Hex:EtOAc 99:1 in
a Silica-pakHPLC column. 0.7 ml/min

Mandelate
(*SR*)-**33** from
(*R*)-**5**

Mandelates
33 from
rac-**5**

10.2 min,
(*SSR*)-35

10.2 min, (*SSR*)-35

12.6 min,
(*SRR*)-35

12.6 min, (*SRR*)-35

12.6 min,
(*SRR*)-35

10.2 min,
(*SSR*)-35

Mandelate (*SSR*)-**35**
from (*SR*)-**34**

Mandelates **35**
from **34**

Mandelate (*SRR*)-**35**
from (*RR*)-**34**

HPLC traces from mandelates **35** to measure
the diastereoselectivities for the allylation of aldehyde **12**
These samples were eluted with Hex:EtOAc 99:1 in
a Silica-pakHPLC column. 0.7 ml/min
dr for (*SR*)-**34 =** 99:1, *dr* for (*RR*)-**34 =** 1:99

115

11.7 min, (*SRR*)-37A

14.9 min, (*SSR*)-37B

14.82
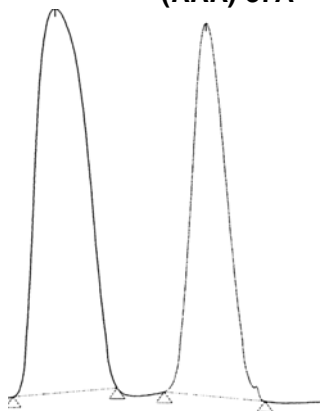**SSR26**

11.8
SRR24

Diols **37** after
deprotection of
(**SRR**)-36A

Diols **37** after
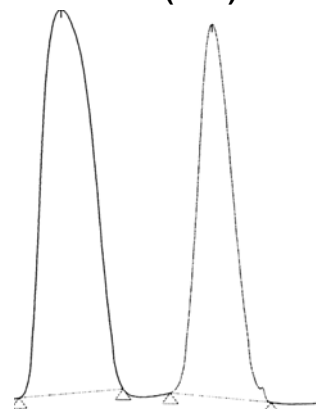deprotection of
(**SSR**)-36B

HPLC traces for diol **37** fto measure the diastereoselectivities for the allylation of aldehydes **M13**. The
samples were eluted with Hex:EtOAc 9:1 in a Silica-pak HPLC column. 0.7 ml/min
dr for mixtures *R*m*R*25M = 97:3 *RSR*25:*SSR*25 and 5:95 *SRR*25:*RRR*25

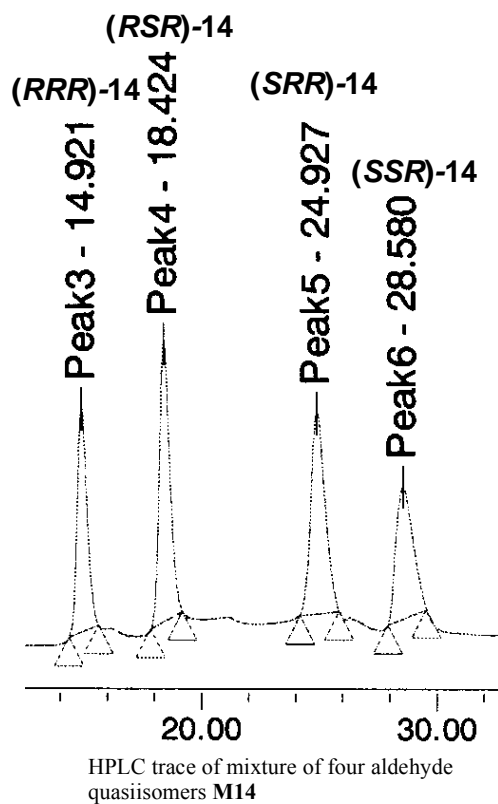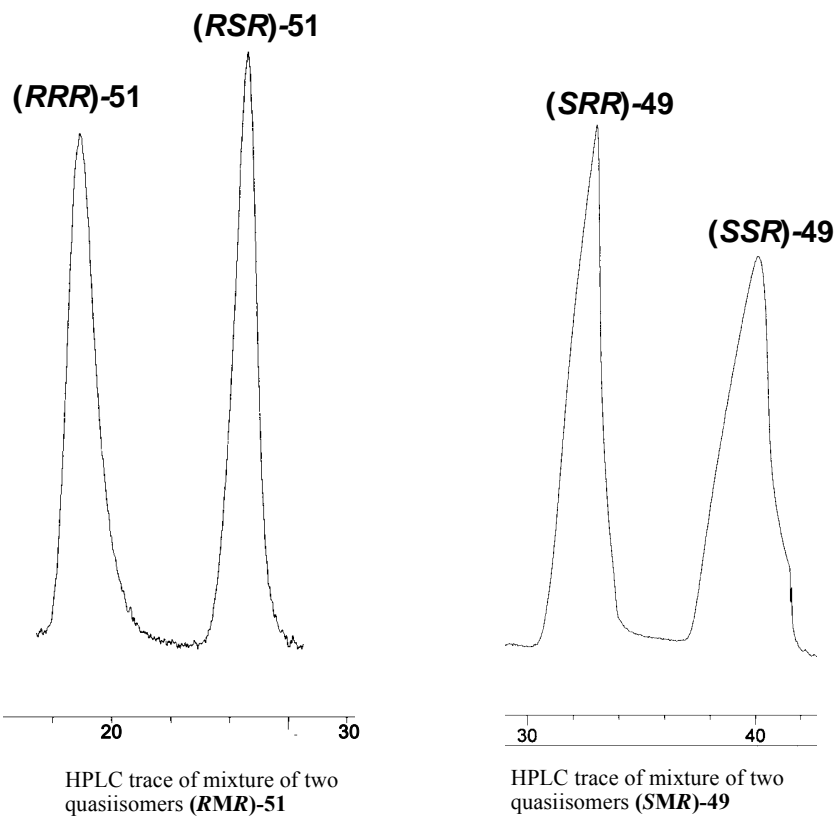11.7 min,
(**SRR**)-37A

14.8 min,
(**RRR**)-37A

11.8 min,
(**RSR**)-37B

14.9 min,
(**SSR**)-37B

Diols **37** after
deprotection of
36A

Diols **37** after
deprotection of
36B

116

(RRR)-51 **(RSR)-51**

20   30

HPLC trace of mixture of two
quasiisomers **(RMR)-51**

(SRR)-49 **(SSR)-49**

30   40

HPLC trace of mixture of two
quasiisomers **(SMR)-49**

(RRR)-14 **(RSR)-14** **(SRR)-14** **(SSR)-14**

Peak3 - 14.921
Peak4 - 18.424
Peak5 - 24.927
Peak6 - 28.580

20.00   30.00

HPLC trace of mixture of four aldehyde
quasiisomers **M14**

These are analytical HPLC traces (gradient elution 95:5 ACN:H_2O to 100% ACN in 30 min + 100% ACN for 30 min)
from injections in a fluoroflash column.

117
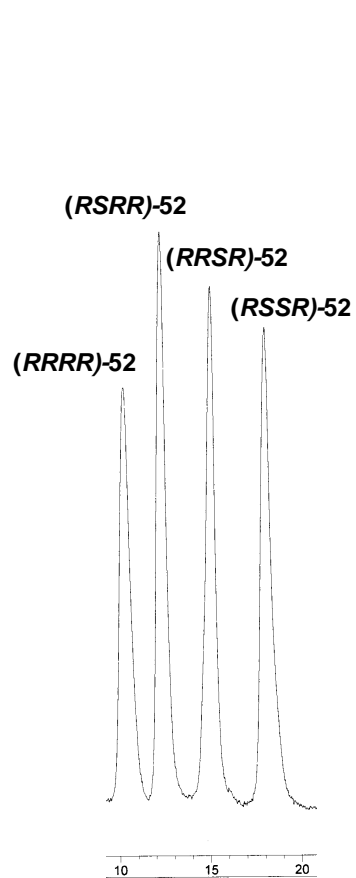
HPLC trace of **(R)-M52** from
the allylation of M**14** with (**S,S**)-**23**
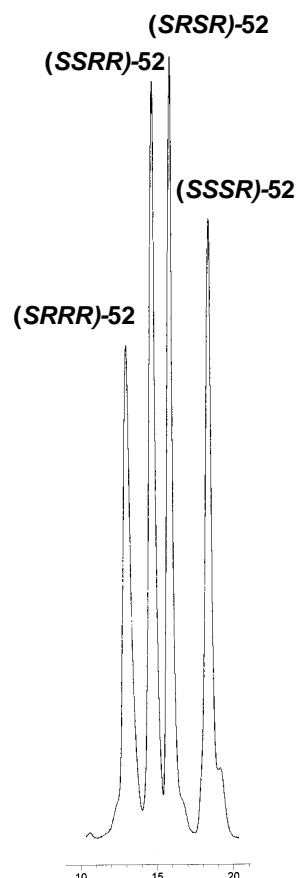
HPLC trace of **(S)-M52** from
the allylation of M**14** with (**R,R**)-**23**

HPLC trace of **(R)-M15** from
the acylation of **(R)-M52**

These are analytical HPLC traces (gradient elution 95:5 ACN:H_2O to 100% ACN in 30 min
+ 100% ACN for 30 min)from injections in a fluoroflash column.

118
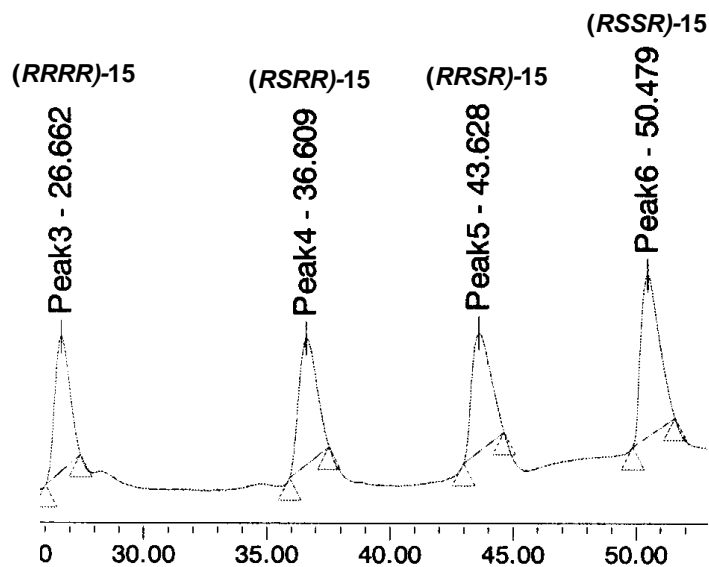
HPLC trace of (S)-M15 from
the acylation of (S)-M52

This is a analytical HPLC trace (gradient elution 95:5 ACN:H$_2$O to 100% ACN in 30 min + 100% ACN for 30 min) from an injection in a fluoroflash column.
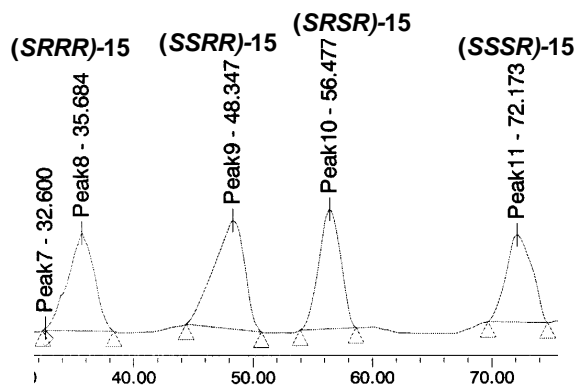

HPLC trace of (R)-M16 from
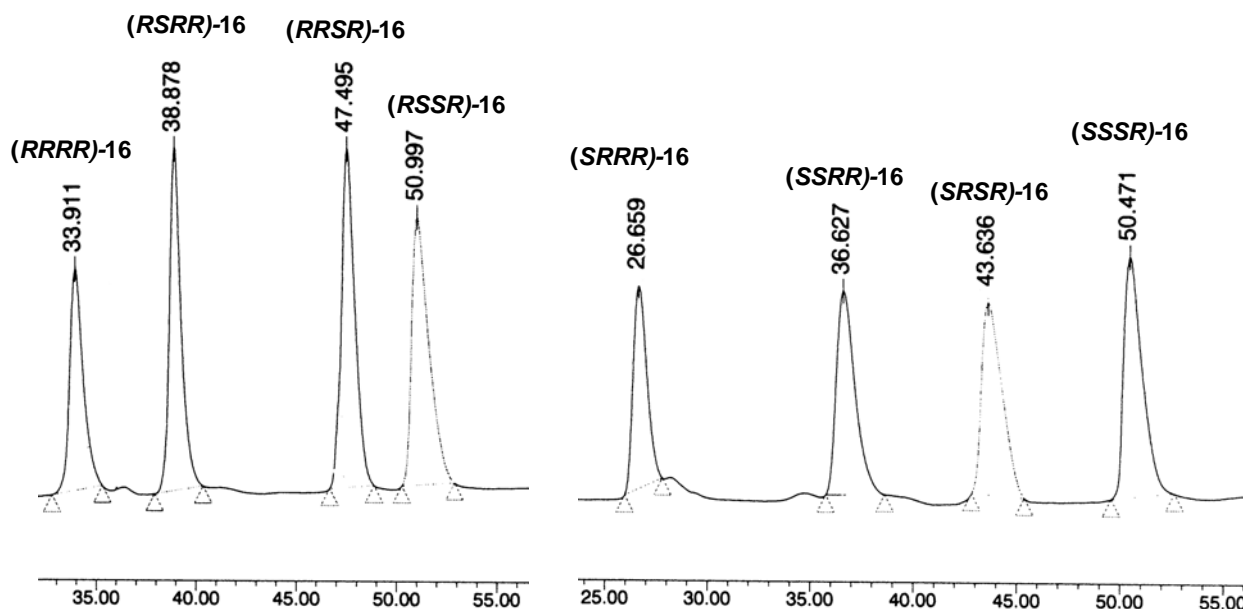the RCM reaction of (R)-M16

HPLC trace of (S)-M16 from
the RCM reaction of (S)-M16

These are analytical HPLC traces (gradient elution 95:5 ACN:H$_2$O to 100% ACN in 30 min + 100% ACN for 30 min) from injections in a fluoroflash column.

119

3.0   SELECTIVE SYNTHESIS OF (2*Z*,4*E*)-DIENYL ESTERS BY ENE-DIENE
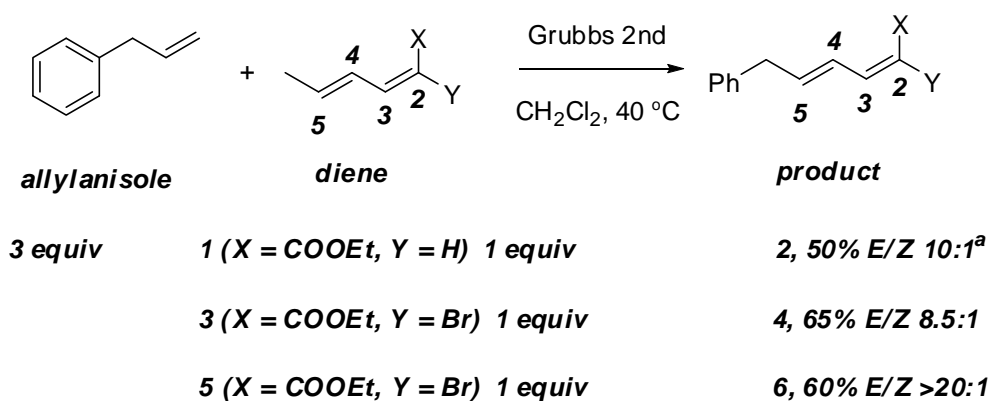
CROSS METATHESIS

3.1   INTRODUCTION

Dienyl esters and conjugated esters are recurrent functionalities in chemotherapeutic agents.[1] For example, the (2*Z*, 4*E*)-dienyl ester moiety (in lactone form) is one of the key structural features that differentiates the potent dictyostatin family of anti-cancer agents from its relatives in the discodermolide family.[2] SAR studies on dictyostatin and analogs has proven that the (2*Z*,4*E*)-dienyl ester moiety plays an important role in activity.[3]

The construction of the (2*Z*,4*E*)-dienyl ester functionality in all the reported syntheses of dictyostatin and analogs has relied on a late-stage coupling reaction to complete that part of the molecule.[3] Recently, our group developed a multi-step approach to incorporate the (2*Z*,4*E*)-diene before fragment coupling through a sequence of cross metathesis, olefination and reduction reactions for the synthesis of 16-*epi*-15,16-dehydrodictyostatin (Figure 11).[3,7]

The Curran group has spent the last 8 years focusing on the synthesis of discodermolide and dictyostatin analogues with great success.[4] Because of the need for developing a short and efficient synthetic approach for dictyostatin, we engaged in experiments directed towards obtaining a rapid and general approach to substituted (2*Z*,4*E*)-dienyl esters (*cis,trans*) by ene-diene cross metathesis.

Cross metathesis reactions of two alkenes have seen increasing use in synthesis in the last years,[5] and ene-diene cross metathesis reactions have recently gained attention.[5c] Our starting point was a recent report by Grubbs and coworkers on cross metathesis of alkenes with (2E,4E)-dienyl esters (*trans,trans*).[6] Grubbs proposed that it should be feasible to obtain cross-metathesis products from the reaction of only one of the olefins in a diene. His strategy was based on shielding one of the olefins in the conjugated diene by attaching either electron-withdrawing substituents or steric bulk (Scheme 16). The reaction of allylanisole and diene **1** promoted by Grubbs second generation catalyst provided diene product **2** in 50% yield and 10:1 E/Z ratio for the C4-C5 olefin. The reaction using bulkier and more electron poor diene **3** provided diene **4** in 65% yield and 8.5:1 *E/Z* ratio. Moreover, the cross metathesis reaction with dibromo diene **5** provided diene product **6** in 60% yield and much better >20:1 *E/Z* ratio. This report showed that the formation of the new double bond at C4-C5 occurred with modest to good *E*-selectivity, for a broad range of substrates.

allylanisole   diene   product

3 equiv   *1 (X = COOEt, Y = H) 1 equiv*   *2, 50% E/Z 10:1[a]*

           3 (X = COOEt, Y = Br) 1 equiv   *4, 65% E/Z 8.5:1*

           5 (X = COOEt, Y = Br) 1 equiv   *6, 60% E/Z >20:1*

a) C4-C5 olefin ratio

Scheme 16. Grubbs' studies on ene-diene metathesis

Inspired by these results, we proposed that methyl-(2Z,4E)-dienyl ester are perfect substrates to obtain functionalized dienyl esters like bottom fragment **8** for a more convergent coupling strategy in the synthesis of (−)-dictyostatin **7**. The key open question for the intended use in dictyostatin and analogues syntheses was the fate of the "spectator" double bond at C2-C3 of the dienyl ester during the cross metathesis reaction. We also envisioned applying this methodology for the multi-gram scale synthesis of bottom fragment **8**.
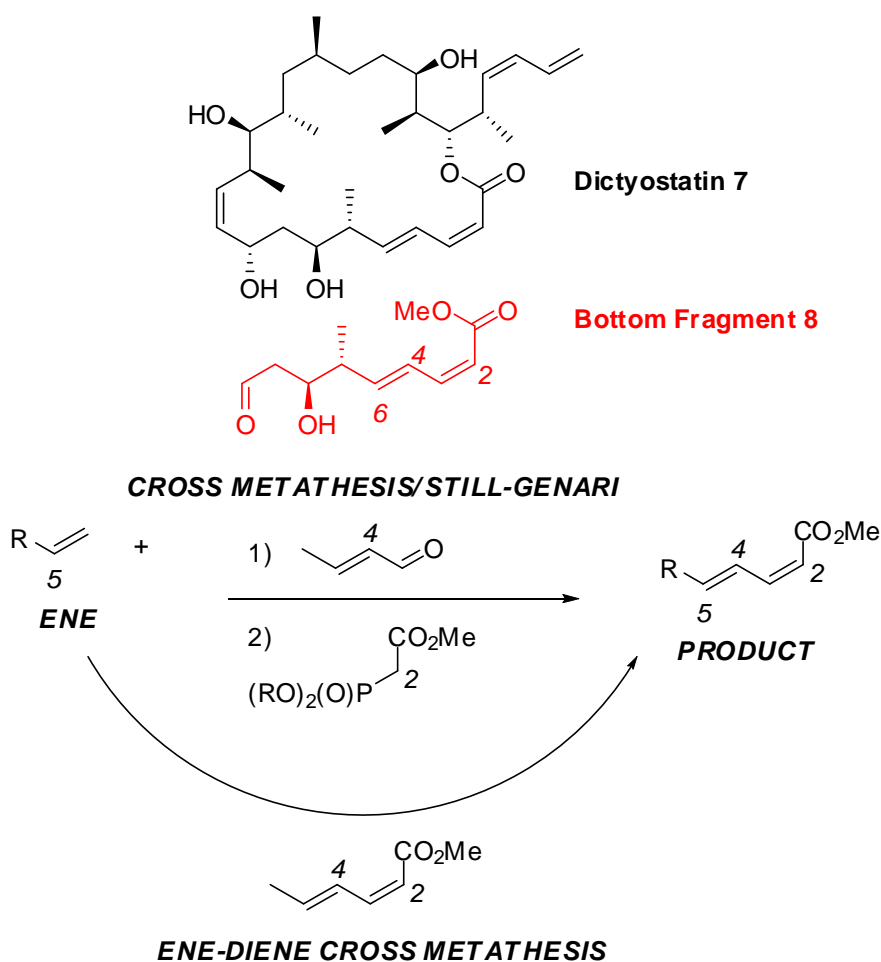

Figure 11. Ene-diene metathesis reaction for the synthesis of bottom fragment 8

3.1.1   Cross-metathesis catalysts

The commercial availability of well-defined catalysts; such as the molybdenum alkoxyimido alkylidene **9a** developed by Schrock,[8] and the ruthenium benzylidene catalysts **9b** and **9c** developed by Grubbs,[9] have made the olefin metathesis reaction practical for small molecule synthesis (Figure 12). The availability of more air-stable and compatible catalysts like the phophine-free Hoveyda-Grubbs catalyst (**10a**)[10] and the Grela catalyst (**10b**)[11] for the cross-metathesis of more electron deficient olefins has contributed to increase the generality of the cross metathesis reaction. However, the high cost of these catalysts is a limitation, even for small scale reactions. Therefore, the introduction of reusable cross metathesis catalysts has become an important alternative for more traditional catalysts.[13]
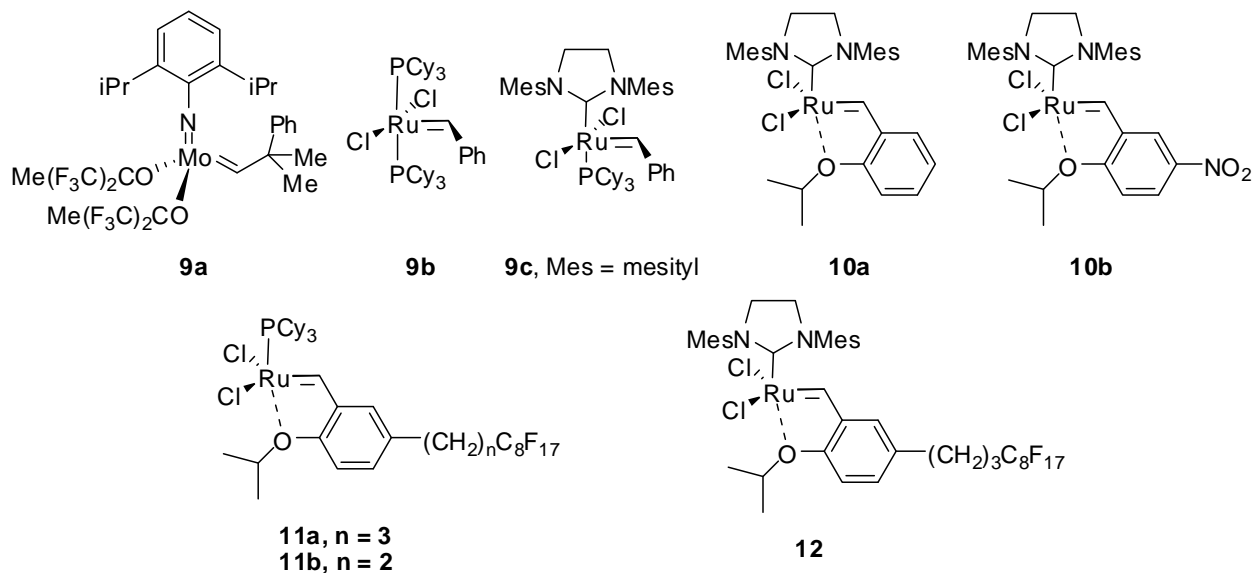

Figure 12. Metathesis catalysts

Light fluorous catalysts are especially convenient since they typically promote the reaction of organic substrates like their nonfluorous relatives, but are reliably removed from the

crude reaction products by fluorous solid-phase extraction (FSPE).[12] Our group recently developed a family of fluorous olefin metathesis catalysts (**11a** and **11b**) that are highly active towards cross metathesis and show high levels of recovery and recycling.[13] Due to our interest in the ene-diene metathesis at a multi-gram scale, we decided to prepare the fluorous Hoveyda-Grubbs (FHG) 2nd-generation catalyst **12**, to evaluate the ene-diene cross metathesis reaction.

3.2   RESULTS AND DISCUSSION

The synthesis of FHG catalyst **12** was based on previous chemistry developed in the Curran group.[13] We started by reacting fluorous iodide ($C_8F_{17}I$) and 1-allyl-3-methoxybenzene mediated by $Pd(PPh_3)_4$ to provide a secondary iodide intermediate in 64% yield.[14] The resulting iodide was then reduced with Zn dust to provide **13** in 95% yield,[15] followed by demethylation reaction to provide phenol intermediate[16] and protection with an isopropyl group to provide **14** in 91% yield over 2 steps. Intermediate **14** was brominated[17] and the resulting bromide was coupled with vinyl tributyltin[18] to provide ligand **16** in 79% overall yield. Trans-metathesis with catalyst **9c** provided catalyst **12** in 92% yield as green crystals (mp 141-142 °C) after recrystalization. Catalyst **12** was characterized by ^1H, ^{13}C, and ^{19}F NMR spectroscopy. However, crystals suitable for X-ray analysis were not obtained.
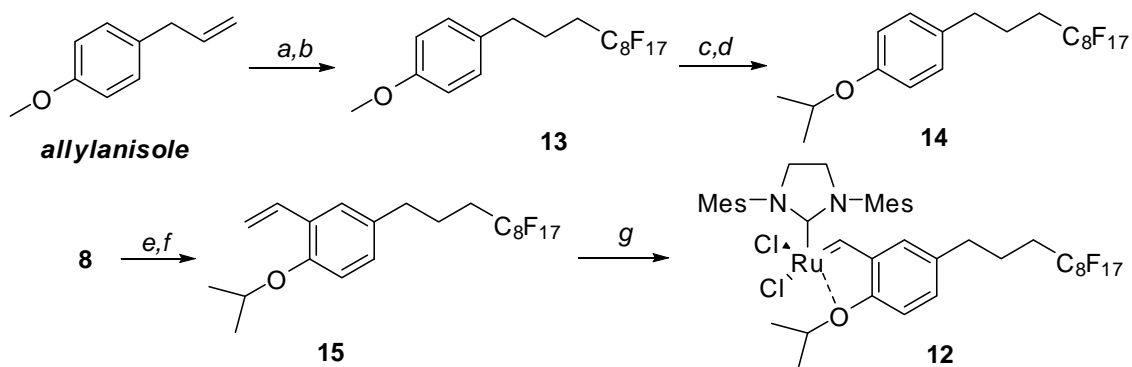
Reagents and conditions: a) 2.2 equiv of $C_8F_{17}I$, 1 equiv of Me_3Al, 5 mol% of $Pd(PPh_3)_4$, CH_2Cl_2, rt 64%; b) $NiCl_2$, Zn, THF, 95%; c) 4 equiv of $BBr_3S(CH_3)_2$, dichloroethane, reflux, 88%, d) 1.5 equiv of NaH, 2 equiv of iPrI. THF/DMF, rt, 94%;e) 1.1 equiv of Br_2, 0.04 equiv of AcOH, CH_2Cl_2, rt, 94%; f) 50 mol% of $Pd(PPh_3)_4$, 3 equiv of tributylvinylstannane,toluene, reflux, 64%; g) 1.1 equiv of catalyst **9c**, 1.25 equiv CuCl, CH_2Cl_2, rt, 71%.

Scheme 17. Synthesis of third generation FHG catalyst 12

Next, we tested the ene-diene cross metathesis reaction for terminal olefins. We initially surveyed catalysts and solvents for the cross metathesis reaction of readily available alkene (*R*,*S*)-**16** (C5-C9 of dictyostatin) and methyl (2*Z*,4*E*)-hexadienoate **17** (C1-C4), as summarized in Table 10. In a typical reaction, a mixture of 1 equiv of **16**, 1 equiv of **17** and 5 mol% of Grubbs second generation catalyst **9c** dissolved in CH_2Cl_2 (0.2 M) was refluxed for 8 h. The solvent was then removed and the crude mixture was purified twice by silica gel flash chromatography to provide **18a** in a promising 47% yield (Entry 1). Moreover, diene **18a** was a single compound resulting from metathesis at C4-C5 olefin, and there was no evidence of metathesis products at the C2-C3 olefin in **17**.[19] We also isolated a fraction containing starting material alkene **16** and its homodimerized byproduct **18b**. Careful chromatography provided pure homodimer **18b** as the less polar fraction from the mixture of compounds.

Table 10. Initial solvent and catalyst survey
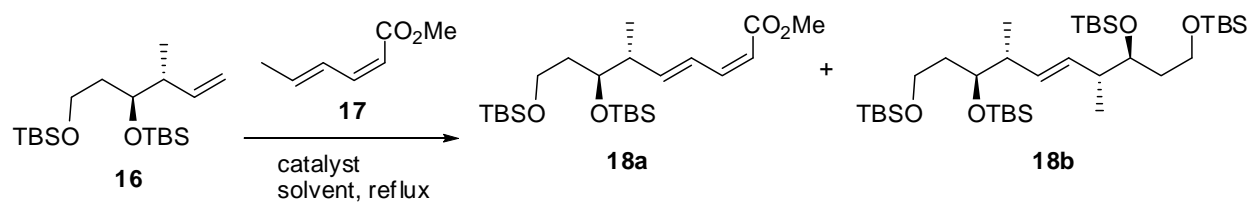
| entry	catalyst	solvent	concentration	yield[a]
1	**9c**	CH$_2$Cl$_2$	0.2 M	47%
2	**9c**	CH$_2$Cl$_2$	0.15 M	58%
3	**9c**	CH$_2$Cl$_2$	0.1 M	43%
4	**9c**	Toluene	0.1 M	23%
5	**9c**	Toluene	0.2 M	25%
6	**10a**	CH$_2$Cl$_2$	0.15 M	62%
7	**12**	CH$_2$Cl$_2$	0.15 M	64%

a Isolated yields as single isomers.
Conditions: a) 1 equiv **16**, 1 equiv **17**, 5 mol% of catalyst, 8h.

Further optimization of the reaction conditions showed that diluting the mixture to 0.15M provided **18a** in a better 58% yield; however, when the reaction mixture was further diluted to 0.1M, **18a** was isolated in a lower 43% yield (Entries 2 and 3). The reaction using refluxing toluene at 110 $^{\circ}$C provided **18a** in only 23% yield when the concentration was 0.1M, and 25% yield when it was 0.2M (Entries 4 and 5). We tried the reaction using 5 mol% of catalyst **10a** and refluxing CH$_2$Cl$_2$ at 0.15M concentration, to obtain **18a** in 62% yield (Entry 6). Finally, the reaction with 5 mol% of FHG catalyst **12** under the same conditions provided **18a** in 64% yield (Entry 7).

Next, we investigated the stoichiometry of the ene-diene metathesis in an attempt to further optimize the yield of the product. We conducted a series of model reactions using *p*-allylanisole **19** (1.2, 1.5, 2 equiv) and methyl (2*Z*,4*E*)-hexadienoate **17** (1.2, 1.5 and 2 equiv) at

different molar ratios, as summarized in Table 11. The reaction of 2 equiv of methyl (2*Z*,4*E*)-

hexadienoate **17** and 1 equiv of **19** promoted by 5 mol% of **9c** provided **20** in 64% yield as a

single olefin isomer (Entry 1). The reaction with 1.5 equiv of **17** provided **20** in 65% yield, and

with 1.2 equiv of **17** provided **20** in a slightly better 68% yield (Entries 2 and 3). The reaction of

1.2 equiv of **19** and 1 equiv of **17** provided **20** in 71% yield also as a single olefin isomer (Entry

4).

Table 11. Ene/diene stoichiometry survey
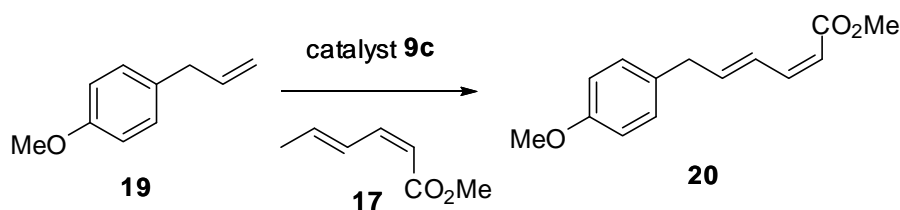
entry	**19** equiv	**17** equiv	Yield **20**[a,b]
1	1	2	64%
2	1	1.5	65%
3	1	1.2	68%
4	1.2	1	71%
5	1.5	1	76%
6	2	1	79%

a) Reactions run at 0.15 M in refluxing CH_2Cl_2 with 5 mol% of catalyst **9c**.
b) Isolated yields as a single olefin isomer.

Similarly, the reaction with 1.5 equiv of **19** provided **20** in 76% yield, and with 2 equiv of

19 provided **20** in a comparable 79% yield. In addition to the target product **20**, these reaction

mixtures exhibited a second, less polar spot on TLC. This spot was deduced to contain a mixture
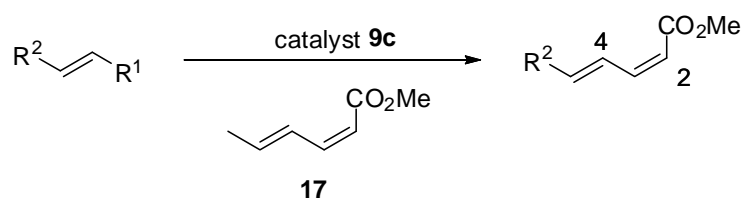
of products resulting from self-metathesis of alkene **19** (no methyl esters or conjugated alkene protons in the ^{1}H NMR spectrum). A similar mixture of products was obtained when the metathesis of **19** was attempted in the absence of **17**. These results implied that the competing reactions cannot be completely suppressed by using a modest excess of one of the components, and therefore a 1:1 stoichiometry is satisfactory for most applications.

3.2.1 Scope of the ene-diene cross metathesis

Because of the success found in the ene-diene metathesis reaction of olefin **16** and **19**, we decided to investigate the scope of ene-diene cross metathesis reaction for diene **17** with different alkenes, as summarized in Table 12.

The reaction of 1 equiv of alkene **16** and 1 equiv of diene **17** promoted by 5 mol% of catalyst **9c** in refluxing CH_2Cl_2 provided **18a** in 58% yield as a single olefin isomer (Entry 1). Under the same conditions, the reaction of diene **17** with MOM-protected alkene provided the desired product in 65% yield, and the reaction with PMB-protected alkene provided the product in 62% yield (Entries 2 and 3). Similarly, the reaction of unprotected alkene with **17** provided the respective product in 61% yield (Entry 4). The reaction of simple *p*-allylanisole with **17** provided the desired diene in 69% yield (Entry 5). Allylbenzene reacted with **17** under the same conditions to give the desired product in a very good 76% yield as a 10:1 ratio of *E/Z* olefin isomers (Entry 6).

Table 12. Scope of the ene-diene cross metathesis for the ene component

Entry	R^1	R^2	yield[a]	Entry	R^1	R^2	yield
1	H	(TBSO, OTBS)	58%	4	H	(OH, OTBS)	61%
2	H	(TBSO, OMOM)	65%	5	H	CH_2PhOMe	69%
				6	H	CH_2Ph	76%[b]
				7	CH_2OAc	CH_2OAc	68%
3	H	(TBSO, OPMB)	62%	8	CH_2Cl	CH_2Cl	63%
				9	H	(complex structure)	76%[c]

Conditions: 1 equiv ene, 1 equiv **17**, 5 mol% **9c**, 0.15M, CH_2Cl_2, 40 °C, 8h.
a) Isolated yield as single isomer. b) E/Z ratio = 10:1.
c) E/Z ratio = 8:1 .

The ene-diene metathesis reaction with symmetrical 1,2-disubstituted alkenes (entries 7 and 8) provided dienes in good yields (68% and 63%, respectively). Moreover, the reaction with complex triene[20] (Entry 9) provided tetraene in 76% yield as an 8:1 ratio of *E/Z* isomers at the C4 alkene. All products isolated from these ene-diene metathesis reactions were exclusively *Z*-isomers at the spectator C2 alkene.

The success of the ene-diene metathesis for simple olefins encouraged us to investigate the reaction with dienes with different substitution patterns, as summarized in Table 13. The reaction of 1 equiv of allylbenzene and 1 equiv of methyl (2Z,4E)-4-methyl-hexadienoate **21**

(trisubstituted C4-C5 alkene) promoted by 5 mol% of catalyst **9c** in refluxing CH_2Cl_2 and at 0.25M concentration provided diene **23a** in 68% yield as a single olefin isomer (Entry 1). The reaction with *p*-allylanisole provided diene **23b** in 63% yield (Entry 2).

Table 13. Scope of the ene-diene cross metathesis for the diene component

entry	R	diene	product	yield[a]
1	CH_2PhOMe	**21**	**23a**	68%
2	CH_2Ph	**21**	**23b**	63%
3	CH_2PhOMe	**22**	**24a**	71%
4	CH_2Ph	**22**	**24b**	73%
5	Ph	**22**	**24c**	73%

Conditions: a) 1 equiv ene, 1 equiv diene, 5 mol% **9c**, 0.25M, CH_2Cl_2, 40 °C, 8h.
a) Isolated yield as single isomer.

The ene-diene metathesis reaction with modified ethyl (2*Z*, 4*E*)-3-methyl-hexadienoate **22 (**trisubstituted C2-C3 alkene) and allylbenzene provided dienoate **24a** in 71% yield (Entry 3). The reaction with *p*-allylanisole and **22** provided dienoate **24b** in 73% yield, and the reaction

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with styrene provided dienoate **24c** in 73% yield. All these products were single stereoisomers at both the reacting (4*E*) and spectator (2*Z*) alkenes.

3.2.2   Multi-gram scale synthesis of bottom fragment for 6-*epi*-dictyostatin

The final goal was to implement a multi-gram scale ene-diene metathesis process with catalyst removal and recycle for potential use in the synthesis of dictyostatin or analogs. Based on structure activity relationships (SAR) studies, recently synthesized 6-epimer analog (6-*epi*-dictyostatin) proved to be four times more active than dictyostatin.[4c]

Based on these results, we focused on the scale-up synthesis of the bottom fragment for 6-*epi*-dictyostatin. We made the olefin starting material with the desired stereochemistry at C6 by reacting aldehyde **25** with (+)-*cis*-crotyl-di*iso*pinocampheylborane in diethyl ether at −78 °C to provide alcohol **26** in 63% yield as a single diastereomer, followed by protection of the resulting alcohol **26** with TBSCl and imidazole to provide starting material **27** in 95% yield.

The big-scale ene-diene metathesis reaction for olefin **27** was performed in three different batches. We used the FHG catalyst **12** in 3 mol% instead of the usual 5 mol% to increase catalyst turnover, as summarized in Table 14. In the first cycle, we reacted alkene **27** (15 g, 42 mmol) and diene **17** (42 mmol) with 3 mol% of catalyst **12** in refluxing CH_2Cl_2 at 0.15 M concentration for 8 h. After cooling we removed the solvent and the crude product was loaded onto a 50 g fluorous spe cartridge that was eluted in a first pass with 9/1 MeOH/H_2O followed by second pass with THF. The MeOH/H_2O fraction yielded 10.9 g (59%) of diene **28** after silica gel flash chromatography, and the THF fraction yielded 74% of catalyst **12** after recrystallization. The crude catalyst recovery was nearly quantitative; however, ^{1}H NMR analysis showed small but significant impurities. During the purification of **28**, the less polar fraction accounted for

37% of the mass balance and contained a substantial amount of **27** (~50%) along with other

unidentified products derived from **27**.

Table 14. Preparative cross metathesis for the multi-gram synthesis of bottom fragment 30
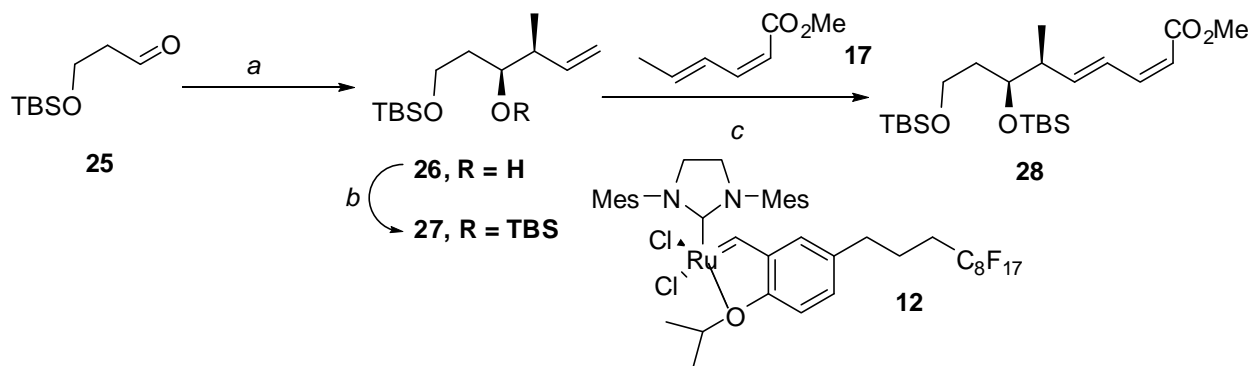
cycle	yield 28	weight 12	scale	recovered 12	
1	10.9 g 59%	1.3g	42 mmol	1.0g	74 %
2	8.1 g 60%	1.0g	31 mmol	0.7g	70%
3	5.2 g 56%	0.7g	21 mmol	0.4g	70%[i]
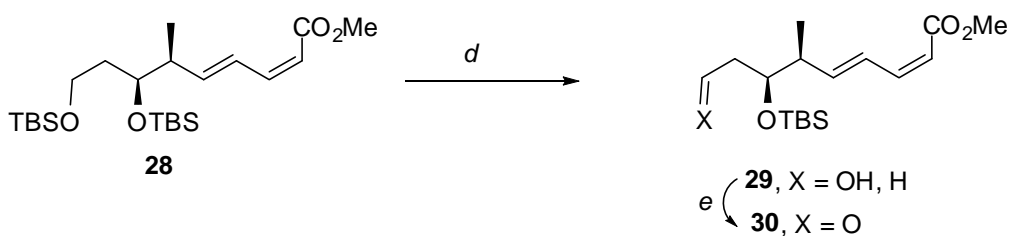
i) The recovered catalyst was recrystalized twice in hexanes to obtain it pure.
Conditions: a) (+)-cis-crotyl-diisopinocampheylborane, diethyl ether, −78 °C, 63%;
b) TBSCl, imidazole, CH$_2$Cl$_2$, 95%. c) 1 equiv **27**, 1 equiv **17**, 3 mol% **12**, 0.15M, CH$_2$Cl$_2$, 40 °C, 8h,
followed by fspe. d) HFPy/Py/THF, THF, RT (88%).
e) PySO$_3$, DMSO, Et$_3$N, CH$_2$Cl$_2$, 0 °C (89%).

As a separate exercise, the entire less polar fraction isolated from the first cycle was directly

reused in a cross metathesis with **17** to provide an additional 20% of pure **28** after FSPE and

flash chromatography. Including the recycling of the less polar fraction, the overall yield of **28** based on **27** for the first cycle was 79%.

The recrystallized catalyst **12** from cycle 1 was reused for cycle 2 ene-diene metathesis reaction. The reaction of **27** (11.1 g, 31 mmol), **17** (3.9 g, 31 mmol) and **12** (1 g, 0.93 mmol) for cycle 2 provided **28** (8.1 g, 18.6 mmol) in 60% yield and the recovered catalyst **12** (0.7 g, 0.65 mmol) in 70% yield. Similarly, cycle 3 provided **28** (5.2 g, 10.4 mmol) in 56% yield and the recovered catalyst **12** (0.4 g, 0.37mmol) in 70% yield. Overall, the initial lot of 1.3 g (1.3 mmol) of **12** was used to metathesize 33.5 g (94 mmol) of **27** into 24.2 g of pure **28** as a single diastereomer in 59% yield. This yield does not include the recycling of the less polar fraction out of the cross metathesis in the first cycle.

Finally, diene **28** (24.2 g, 55 mmol) reacted with HF·Py/Py/THF for the selective deprotection of the primary TBS ether to provide primary alcohol **29** (12 g, 35 mmol) in 88% yield. The last step was the Parikh-Doering oxidation of **29** (12 g, 35 mmol) to provide aldehyde **30** (10 g, 30 mmol) in 89% yield.

3.3   CONCLUSIONS

The ene-diene cross metathesis reaction for monosubstituted or symmetrical 1,2-disubstituted alkenes with methyl (2*Z*, 4*E*)-hexadienoate and related dienyl esters provided substituted (2*Z*,4*E*)-dienyl esters in good yields and stereoselectivities.

The *Z*-geometry of the spectator alkene of the dienyl ester (C2-C3) is strictly retained in the product, while the newly formed alkene (C4-C5) is mainly or exclusively the *E*-isomer.

The synthesis and characterization of third generation FHG catalyst **12** was achieved efficiently. Catalyst **12** proved to promote the cross metathesis of enes with dienes in good yields with almost complete stereoselectivity.

Large scale reactions are conveniently conducted with 3 mol% of the third generation FHG catalyst **12**, which can be recovered and recycled as illustrated by the rapid preparation of 10 g of bottom fragment **30** for the synthesis of 6-epi-dictyostatin.

3.4   EXPERIMENTAL

All reactions were performed under an atmosphere of argon unless otherwise specified or the reaction solvent contained water. The reaction times reported are dictated by TLC analysis of the reaction mixture in comparison to the starting material. Reaction solvents were freshly dried either by distillation or passing through an activated alumina column. CH_2Cl_2 was distilled from CaH. Commercially available reagents were used a received from supplier. Reactions were monitored using thin layer chromatography (TLC) using Kieselgel 60 F_{254} silica gel plates. Flash chromatography was performed over silica gel 60, 230-400 mesh, with the designated solvents. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-300 or a Bruker DPX-500 spectrometer using residual solvent peaks as internal standard: $CDCl_3$ 7.23 ppm (^{1}H NMR) and 77.00 ppm (^{13}C NMR). Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane and proton-proton coupling constants (J) in Hz. Infrared spectra (IR) were recorded on a ATI Mattson genesis series FTIR spectrometer and are reported in reciprocal centimetres (cm^{-1}). Optical rotations were measured with a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature. HPLC analysis was performed on a Waters 600E system with UV

detector. Low and high resolution mass spectra were obtained on a VG 70-G or Micromass Autospec double focusing instrument using EI, ESI, or CI.

Typical procedure for the ene-diene metathesis: To a solution of (3R,4S)-4,6-bis(*tert*-butyldimethylsilyloxy)-3-methylhex-1-ene **16** (100 mg, 0.279 mmol) in CH_2Cl_2 (1.5 mL) was added (2Z,4E)-methyl hexa-2,4-dienoate **17** (35.2 mg, 0.279 mmol), and the solution was heated to reflux. At that temperature was added catalyst **9c** (12.1 mg, 0.014 mmol) dissolved in CH_2Cl_2 (0.4 mL). The reaction was stirred at reflux for 10 h and then the solvent was removed by rotary evaporation. The crude mixture was purified twice by silica gel flash chromatography eluting with hexanes:EtOAc 10:1 to provide **18a** (71.6 mg, 58%) as a colorless oil.

Typical procedure for the big scale ene-diene metathesis: To a solution of (3S,4S)-4,6-bis(*tert*-butyldimethylsilyloxy)-3-methylhex-1-ene **27** (15 g, 42 mmol) in CH_2Cl_2 (260 mL) was added (2Z,4E)-methyl hexa-2,4-dienoate **11** (5.3 g, 42 mmol), and the solution was heated to reflux. At that temperature was added catalyst **12** (1.37 g, 1.26 mmol) dissolved in CH_2Cl_2 (29 mL). The reaction was stirred at reflux for 10 h and the solvent was removed by rotary evaporation. The crude mixture was purified by fluorous solid phase extraction in a 50 g cartridge with 100 mL of 9:1 MeOH, followed by 100 mL of pure MeOH to give the organic fraction. Silica gel flash chromatography with 20:1 Hexanes/EtOAc furnished **28** (10.9 g, 59%) as a colorless oil. FHG catalyst **12** was recovered by flushing the cartridge with 200 mL of THF. The fraction was concentrated and the dark green residue was recrystalized from a hexanes/CH_2Cl_2 mixture to furnish **12** (1005 mg, 74%) as light green crystals.
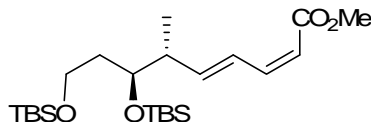
(2Z,4E,6R,7S)-Methyl 7,9-bis(*tert*-butyldimethylsilyloxy)-6-methylnona-2,4-dienoate (18a):

[α]$_D$ -6.1 (*c* 0.4, CHCl$_3$); IR (thin film) 2954, 2857, 1721, 1424, 1165, 1101, 830, 751 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.35 (dd, *J* = 15.4, 11.3 Hz, 1H), 6.58 (t, *J* = 11.3 Hz, 1H), 6.04 (dd, *J* = 15.4, 8 Hz, 3H), 5.59 (d, *J* = 11.3 Hz, 1H), 3.82-3.77 (m, 1H), 3.73 (s, 3H), 3.64 (t, *J* = 6.6 Hz, 1H), 2.51-2.46 (m, 1H), 1.66-1.54 (m, 2H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 18H), 0.06 (s, 6H), 0.04 (s, 6H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 167.1, 147.6, 145.8, 127.1, 115.6, 72.6, 60.0, 51.2, 42.9, 37.4, 26.1, 18.5, 8.3, 15.7, -4.1, -5.0 ppm; HRMS (ESI) calcd for C$_{23}$H$_{46}$O$_4$Si$_2$ = 442.2899, found = 442.2897.
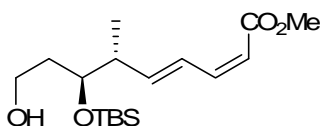
(2Z,4E,6R,7S)-Methyl 7-(*tert*-butyldimethylsilyloxy)-9-hydroxy-6-methylnona-2,4-dienoate (Table 11, Entry 4):

[α]$_D$ -14.9 (*c* 0.25, CHCl$_3$); IR (thin film) 3421, 2953, 2857, 1719, 1412, 1190, 1167, 837 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.37 (dd, *J* = 15.4, 11.3 Hz, 1H), 6.56 (t, *J* = 11.3 Hz, 1H), 6.01 (dd, *J* = 15.4, 8 Hz, 3H), 5.61 (d, *J* = 11.3 Hz, 1H), 3.87-3.83 (m, 1H), 3.75-3.71 (m, 5H), 2.59-2.52 (m, 1H), 1.85 (bs, 1H), 1.70-1.66 (m, 2H), 1.08 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 6H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.8, 147.2, 145.5, 126.8, 115.5, 73.2, 59.4, 51.0, 42.7, 36.0, 25.8, 18.0, 15.0, -4.4 ppm; HRMS (ESI) calcd for C$_{17}$H$_{32}$O$_4$Si = 328.2097, found = 328.2092.
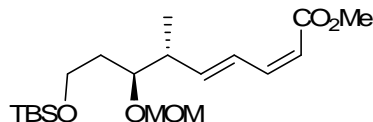
(2*Z*,4*E*,6*R*,7*S*)-Methyl 9-(*tert*-butyldimethylsilyloxy)-7-(methoxymethoxy)-6-methylnona-2,4-dienoate (Table 11, Entry 2):

$[\alpha]_D$ -7.8 (*c* 0.5, CHCl$_3$); IR (thin film) 3053, 2955, 2930, 2857, 2254, 1713, 1637, 1463, 1439, 1265, 1198, 1096, 909, 736 cm^{-1};^{1}H-NMR (600 MHz, CDCl$_3$) δ 7.36 (dd, *J* = 15.4, 11.3 Hz, 1H), 6.54 (t, *J* = 11.3 Hz, 1H), 6.02 (dd, *J* = 15.4, 7.7 Hz, 1H), 5.58 (d, *J* = 11.3 Hz, 1H), 4.64 (dd, *J* = 21.3, 6.8 Hz, 2H), 3.71 (s, 3H), 3.68-3.64 (m, 4H), 3.36 (s, 3H), 2.63-2.60 (m, 1H), 1.67-1.58 (m, 2H), 1.10 (d, *J* = 6.8 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C-NMR (125.8 MHz, CDCl$_3$) δ 166.8, 146.9, 145.4, 127.0, 115.6, 96.5, 78.6, 78.4, 59.6, 55.7, 51.1, 40.9, 34.9, 25.9, 18.2, 15.3, 5.4 ppm; HRMS (ESI) calcd for C$_{18}$H$_{33}$O$_5$Si = 357.2097, found = 357.2098.
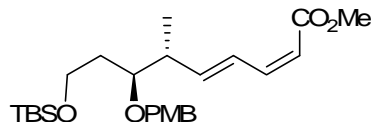
**(2*Z*,4*E*,6*R*,7*S*)-Methyl 7-(4-methoxybenzyloxy)-9-(*tert*-butyldimethylsilyloxy)-6-methylnona-2,4-dienoate (Table 11, Entry 3):**

$[\alpha]_D$ -13.3 (*c* 0.41, CHCl$_3$), IR (thin film) 3055, 2985, 2927, 2854, 1465, 1390, 1421, 1265 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.44 (dd, *J* = 15.1, 11.4 Hz, 1H), 7.07 (d, *J* = 6.7 Hz, 2H), 6.80 (d, *J* = 6.7 Hz, 2H), 6.53 (t, *J* = 11.4 Hz, 1H), 6.11 (dt, *J* = 15.2, 7.2 Hz, 1H), 5.59 (d, *J* = 11.4 Hz, 1H), 4.72 (d, *J* = 6.7 Hz, 2H), 3.77-3.75 (m, 1H), 3.72 (s, 3H), 3.65-3.58 (m, 2H), 3.41 (s, 3H), 2.53-2.49 (m, 1H), 1.60-1.50 (m, 2H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.83 (s, 9H), 0.02 (s, 6H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.7, 158.0, 144.9, 143.7, 130.9, 129.5, 127.1, 115.8,

113.8, 73.2, 59.5, 55.0, 51.0, 42.7, 36.1, 25.9, 18.0, 15.0, -4.5 ppm. HRMS (ESI) calcd for $C_{25}H_{40}O_5Si = 448.2613$, found = 448.2628.
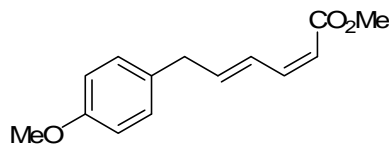

(2Z,4E)-Methyl 6-(4-methoxyphenyl)hexa-2,4-dienoate (Table 11, Entry 5):

IR (thin film) 3052, 2986, 2959, 2872, 2253, 1720, 1610, 1511, 1439, 1265, 1175, 909, 734 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.44 (dd, J = 15.1, 11.4 Hz, 1H), 7.07 (d, J = 6.7 Hz, 2H), 6.80 (d, J = 6.7 Hz, 2H), 6.53 (t, J = 11.4 Hz, 1H), 6.11 (dt, J = 15.2, 7.2 Hz, 1H), 5.59 (d, J = 11.4 Hz, 2H), 3.74 (s, 3H), 3.69 (s, 3H), 3.43 (d, J = 6.7 Hz, 2H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.7, 158.0, 144.9, 143.7, 130.9, 129.4, 127.2, 115.8, 113.8, 55.0, 50.9, 38.4 ppm; HRMS (ESI) calcd for $C_{14}H_{16}O_3 = 232.1099$, found = 232.1094.
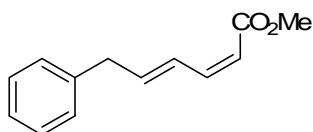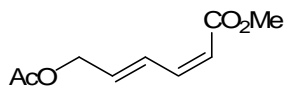

(2Z,4E)-Methyl 6-phenylhexa-2,4-dienoate (Table 11, Entry 6):

IR (thin film) 3053, 2985, 2959, 2928, 2253, 1717, 1456, 1265, 909, 735 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.40 (dd, J = 15.2, 11.4 Hz, 1H), 7.23-7.10 (m, 5H), 6.49 (t, J = 11.4 Hz, 1H), 6.09 (dt, J = 15.2, 7.2 Hz, 2H), 5.54 (d, J = 11.4, 1H), 3.64 (s, 3H), 3.45(d, J = 7.2 Hz, 2H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.8, 144.9, 143.2, 139.0, 128.5, 127.5, 126.3, 116.0, 51.0, 39.3 ppm; HRMS (ESI) calcd for $C_{13}H_{14}O_2 = 202.0993$, found = 202.0984.
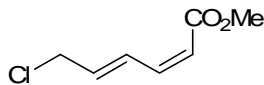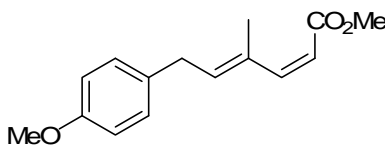
(2Z,4E)-Methyl 6-chlorohexa-2,4-dienoate (Table 11, Entry 7):

IR (thin film) 3053, 2986, 2953, 2249, 1712, 1638, 1602, 1439, 1265, 1177, 908 cm^{-1};

^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.58 (ddt, J = 15.2, 11.3, 1.2 Hz, 1H), 6.57 (t, J = 11.3 Hz, 2H),

6.09 (ddt, J = 15.2, 7.2, 0.7 Hz, 1H), 4.10 (d, J = 7.2 Hz, 2H), 3.73 (s, 3H); ^{13}C-NMR (75 MHz,

CDCl$_3$) δ 166.3, 142.8, 137.2, 129.5, 119.0, 51.3, 44.1 ppm; HRMS (ESI) calcd for C$_7$H$_9$O$_2$Cl =

160.0291, found = 232.0286.

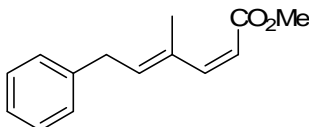**(2Z,4E)-Methyl 6-acetoxyhexa-2,4-dienoate (Table 11, Entry 9):**

IR (thin film) 3053, 2986, 2955, 2872, 2254, 1739, 1648, 1607, 1438, 1377, 1265, 1232,

909, 735 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.54 (dd, J = 15.5, 11.3 Hz, 1H), 6.54 (t, J = 11.3

Hz, 1H), 6.04 (dt, J = 15.5, 5.9 Hz, 1H), 5.68 (d, J = 11.3 Hz, 1H), 4.67 (d, J = 5.8 Hz, 2H), 3.69

(s, 3H), 2.05 (s, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 170.5, 166.3, 143.2, 136.1, 128.7, 127.2,

118.2, 63.8, 51.1, 20.7 ppm; HRMS (ESI) calcd for C$_9$H$_{12}$O$_4$ = 184.0735, found = 184.0741.

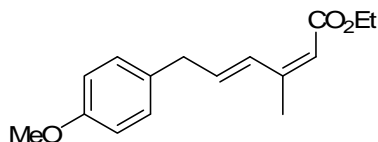**(2Z,4E)-Methyl 6-(4-methoxyphenyl)-4-methylhexa-2,4-dienoate (Table 12, Entry 1):**

IR (thin film) 3052, 2986, 2959, 2872, 2254, 1720, 1610, 1511, 1439, 1265, 1175, 909,

734 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.27 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.60

(d, J = 12.5 Hz, 1H), 6.02 (t, J = 7.4 Hz, 1H), 5.82 (d, J = 12.5 Hz, 1H), 4.67 (d, J = 5.8 Hz,

2H), 3.95 (s, 3H), 3.87 (s, 3H), 3.60 (d, J = 7.4 Hz, 2H), 2.12 (s, 3H); ^{13}C-NMR (75 MHz,

CDCl$_3$) δ 166.9, 157.8, 145.4, 136.4, 132.8, 131.8, 129.1, 116.6, 113.7, 54.9, 51.0, 33.5, 14.9

ppm; HRMS (ESI) calcd for C$_{15}$H$_{18}$O$_3$ = 246.1255, found = 246.1259.

(2Z,4E)-Methyl 4-methyl-6-phenylhexa-2,4-dienoate (Table 12, Entry 2):

IR (thin film) 3053, 2986, 2959, 2929, 2872, 2253, 1710, 1626, 1453, 1265, 903, 735 cm$^-$

^{1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.38-7.21 (m, 5H), 6.47 (d, J = 12.5 Hz, 1H), 5.90 (t, J = 7.4

Hz, 2H), 5.70 (d, J = 12.5 Hz, 1H), 3.72 (s, 3H), 3.52 (d, J = 7.4 Hz, 2H); ^{13}C-NMR (75 MHz,

CDCl$_3$) δ 167.1, 145.5, 140.0, 135.9, 133.3, 128.5, 126.1, 116.9, 51.3, 34.6, 15.1 ppm; HRMS

(ESI) calcd for C$_{14}$H$_{16}$O$_2$ = 216.1150, found = 216.1145.

(2Z,4E)-Ethyl 6-(4-methoxyphenyl)-3-methylhexa-2,4-dienoate (Table 12, Entry 3):

IR (thin film) 3051, 2991, 2879, 2872, 2249, 1720, 1610, 1512, 1439, 1265, 1175, 912,

734 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.06 (d, J = 8.7 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 6.22

(dt, J = 15.6, 6.5 Hz, 1H), 6.08 (d, J = 15.4 Hz, 1H), 5.69 (s, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.78

(s, 3H), 3.40 (d, J = 6.5 Hz, 2H), 2.2 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz,

CDCl$_3$) δ 167.2, 158.2, 152.2, 135.8, 134.4, 131.3, 129.6, 118.4, 114.0, 59.6, 55.2, 38.4, 29.7 ppm; HRMS (ESI) calcd for C$_{16}$H$_{20}$O$_3$ = 260.1255, found = 260.1257.

(2Z,4E)-Ethyl 3-methyl-6-phenylhexa-2,4-dienoate (Table 12, Entry 4):
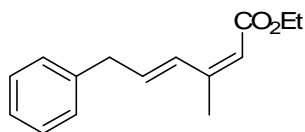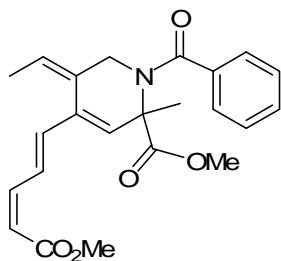
IR (thin film) 3055, 2986, 2959, 2929, 2872, 2253, 1710, 1626, 1453, 1265, 903, 735 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.38-7.21 (m, 5H), 6.24 (dt, J = 15.6, 6.5 Hz, 1H), 6.12 (d, J = 15.4 Hz, 1H), 5.69 (s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.54 (d, J = 6.5 Hz, 2H), 2.02 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 167.1, 152.2, 135.8, 135.8, 134.3, 129.6, 121.7, 114.4, 55.3, 38.4, 29.7, 14.3 ppm; HRMS (ESI) calcd for C$_{15}$H$_{18}$O$_2$ = 230.1150, found = 230.1143.

(E)-Methyl 1-benzoyl-5-ethylidene-4-((1E,3Z)-5-methoxy-5-oxopenta-1,3-dienyl)-2-methyl-1,2,5,6-tetrahydropyridine-2-carboxylate (Table 12, Entry 9):

IR (thin film) 3606, 2971, 2306, 1741, 1712, 1422, 1265, 1160, 1128, 948, 738 cm^{-1}; ^{1}H-NMR (600 MHz, CDCl$_3$) δ 7.67 (dd, J = 15.5, 11.4 Hz, 1H), 7.43-7.41 (m, 5H), 6.60 (t, J = 11.4 Hz, 1H), 6.46 (d, J = 15.5 Hz, 1H), 5.83 (q, J = 7.0 Hz, 1H), 5.74 (s, 1H), 5.69 (d, J = 11.4 Hz, 1H), 3.70 (s, 3H), 3.74 (s, 3H), 3.66 (d, J = 14.6 Hz, 1H), 3.14 (d, J = 14.6 Hz, 1H), 1.72 (s, 3H), 1.61 (d, J = 7.0 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 171.8, 171.0, 166.6, 144.4, 138.0, 135.8,

135.7, 130.3, 129.4, 128.5, 127.9, 127.6, 127.4, 123.6, 117.9, 63.0, 52.9, 51.3, 43.6, 20.7, 13.5

ppm; HRMS (ESI) calcd for $C_{23}H_{25}NO_5$ = 395.1732, found = 395.1717.
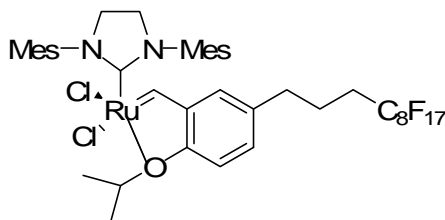
Fluorous Hoveyda Grubbs 2nd-generation catalyst (12):

Green solid; mp: 140-141 °C; IR (thin film) 1625, 1490, 1315, 1242, 1215, 1115, 752,

720, 561 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 17.01 (s, 1H), 7.27 (dd, J = 8.4, 2 Hz, 1H), 7.04

(s, 4H), 6.70-6.67 (m, 2H), 4.83 (q, J = 6.1 Hz, 1H), 4.15 (s, 4H), 2.66 (t, J = 7.4 Hz, 1H), 2.49-

2.34 (m, 18H), 2.15-1.95 (m, 2H), 1.87-1.79 (m, 1H), 1.22 (d, J = 6.1 Hz, 1H); ^{13}C-NMR (75

MHz, CDCl$_3$) δ 211.4, 150.9, 145.3, 138.8, 134.1, 129.4, 129.2, 122.2, 112.9, 75.0, 33.6, 21.0;

^{19}F-NMR (282 MHz, CDCl$_3$) δ -81.1 (3F), -114.4 (2F), -122.3 (6F), -123.9 (2F), -123.7 (2F), -

126.5 (3F) ppm.
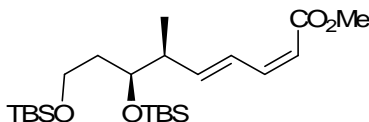
(2Z,4E,6R,7S)-Methyl 7,9-bis(*tert*-butyldimethylsilyloxy)-6-methylnona-2,4-dienoate (28):

[α]$_D$ +10.1 (*c* 0.87, CHCl$_3$); IR (thin film) 2954, 2857, 1721, 1424, 1165, 1101, 830, 751

cm^{-1}; ^{1}H-NMR (600 MHz, CDCl$_3$) δ 7.31 (dd, J = 15.4, 11.3 Hz, 1H), 6.54 (t, J = 11.3 Hz, 1H),

6.13 (dd, J = 15.4, 8 Hz, 3H), 5.55 (d, J = 11.3 Hz, 1H), 3.76-3.72 (m, 1H), 3.69 (s, 3H), 3.64-

3.58 (m, 2H), 2.49-2.44 (m, 1H), 1.62-1.50 (m, 2H), 1.02 (d, J = 6.9 Hz, 3H), 0.84 (s, 18H), 0.02

(s, 4H), 0.01 (s, 8H); ^{13}C-NMR (125.8 MHz, CDCl$_3$) δ 166.9, 148.3, 145.3, 126.3, 115.3, 72.7, 59.8, 50.9, 42.5, 36.8, 25.9, 18.2, 14.5, -4.4, -5.3 ppm; HRMS (ESI) calcd for C$_{23}$H$_{46}$O$_4$Si$_2$ = 442.2897, found = 442.2895.
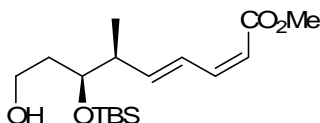
(2Z,4E,6S,7S)-Methyl 7-(*tert*-butyldimethylsilyloxy)-9-hydroxy-6-methylnona-2,4-dienoate (29):

To a solution of diene **28** (5 g, 11 mmol) in THF (20 mL) was added HF·Py/Py/THF (90 mL, 13.2 mmol). The resulting mixture was stirred at 0 °C for 20 min and then at RT for 3 h. The reaction was quenched with saturated aqueous NaHCO$_3$ and the aqueous phase was extracted with CH$_2$Cl$_2$ The combined organic phase was washed with brine and dried over MgSO$_4$, the solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 4:1 to yield alcohol **29** (12 g, 88%) as a colorless oil: [α]$_D$ +18.4 (*c* 0.35, CHCl$_3$); IR (thin film) 3421, 2953, 2857, 1719, 1412, 1190, 1167, 837 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.33 (dd, *J* = 15.4, 11.3 Hz, 1H), 6.52 (t, *J* = 11.3 Hz, 1H), 6.09 (dd, *J* = 15.4, 8 Hz, 1H), 5.53 (d, *J* = 11.3 Hz, 1H), 3.77-3.65 (m, 6H), 2.80-2.2.76 (m, 1H), 2.52 (bs, 1H), 1.69-1.64 (m, 2H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.06 (s, 6H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.6, 147.0, 145.3, 126.4, 115.2, 73.6, 59,4, 50.8, 42.2, 35.5, 25.6, 17.8, 14.8, -4.8 ppm; HRMS (ESI) calcd for C$_{17}$H$_{32}$O$_4$Si = 328.2097, found = 328.2092.
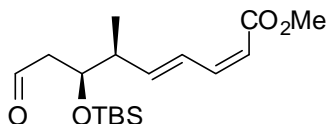
(2Z,4E,6S,7S)-Methyl 7-(*tert*-butyldimethylsilyloxy)-6-methyl-9-oxonona-2,4-dienoate (30):

To a solution of alcohol **29** (5 g, 15.2 mmol) and Et$_3$N (3.07 g, 30.4 mmol) in CH$_2$Cl$_2$ (20 mL) and DMSO (20 mL) was added a solution of Py·SO$_3$ (3.60 g, 22.8 mmol) in DMSO (20 mL) at 0 °C under Ar atmosphere. The resulting mixture was stirred at 0 °C for 20 min and then quenched with aqueous HCl (0.1 M). The aqueous phase was extracted with CH$_2$Cl$_2$, and the combined organic phase was washed with brine and dried over MgSO$_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 10:1 to yield aldehyde **30** (4.35 g, 89%) as a colorless oil: IR (thin film) 3031, 2953, 2857, 1760, 1719, 1412, 1190, 1167, 837 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 9.76 (t, *J* = 2.1 Hz, 1H), 7.37 (dd, *J* = 15.6, 11.4 Hz, 1H), 6.54 (t, *J* = 11.2 Hz, 1H), 6.06 (dd, *J* = 15.6, 7.2 Hz, 1H), 5.60 (d, *J* = 11.4 Hz, 1H), 4.15 (dt, *J* = 6.6, 5.1 Hz, 1H), 3.77 (s, 3H), 2.50 (m, 1H), 2.47 (d, *J* = 5.1 Hz, 2H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.96 (s, 9H), 0.04 (s, 6H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 201.2, 166.4, 145.4, 144.6, 126.8, 115.8, 71.0, 50.7, 47.8, 42.2, 42.8, 25.3, 17.6, 14.6, -4.8, -5.1 ppm.

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4.0 STUDIES ON A VERY POTENT MICROTUBULE-STABILIZING AGENT: A CONVERGENT SYNTHESIS OF 6-EPI-DICTYOSTATIN

4.1 INTRODUCTION

Microtubules are tube-shape protein polymers that are the key components in all eukaryotic cells. These polymers are involved in many cellular processes including transport of vesicles, mitochondria, cell signaling, and more important mitosis. Microtubules are composed of α-tubulin and β-tubulin heterodimers. The crucial role that microtubules have in cell division makes them and important target for anticancer drugs.[1] Microtubules are the targets of a chemically diverse group of antimitotic drugs that have been used with great success in the treatment of cancer. These protein polymers represent the best cancer target to be identified so far. It is also likely that these drugs will continue to be chemotherapeutic agents for the treatment of cancer.[2]

The polymerization of microtubules takes place by a nucleation-elongation mechanism. The mechanism is described as the slow formation of a short microtubule followed by a fast elongation of the microtubule at its ends by the reversible and non-covalent addition of tubulin dimers. The microtubule shows a dynamic behavior (dynamic instability), where the individual microtubule ends switch between phases of polymerization and depolymerization (Figure 13).[3a]

A large number of chemically diverse substances bind to either soluble tubulin or tubulin in the microtubules. Most of these compounds are antimitotic agents which inhibit cell proliferation by acting on the polymerization dynamics of the spindle microtubules.[3b] Microtubule-targeted antimitotic drugs are usually classified into two main groups. The first one, known as the microtubule-destabilizing agents, inhibits microtubule polymerization when the agent is at high concentrations. This group includes the Vinca alkaloids (vinblastine, vincristine, and vinflunine), cryptophycins, halichondrins, estramustrine, and combretastanins. Most of these are under clinical investigation and some are already used clinically for the treatment of cancer.[4]
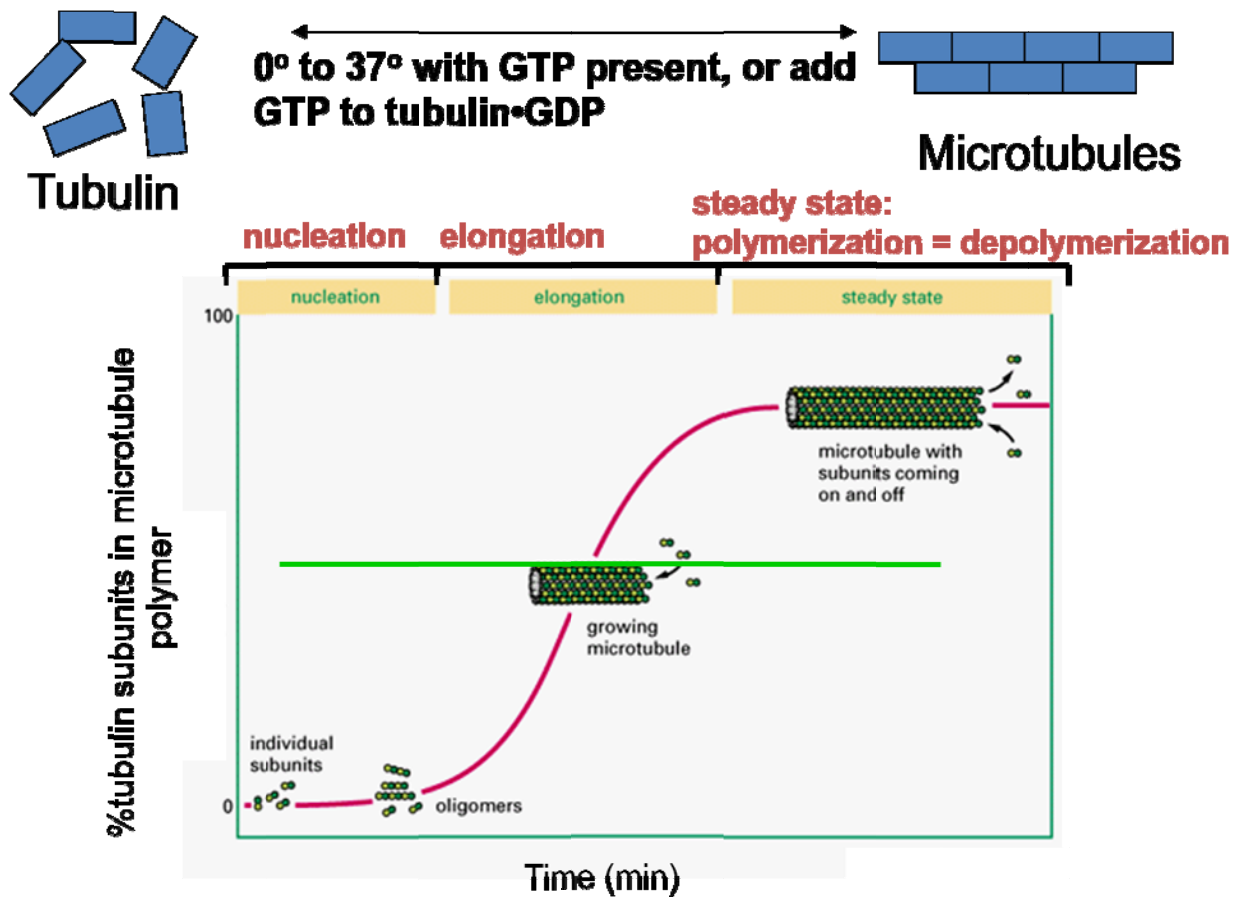

Figure 13. Tubulin polymerization dynamics

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The second group of microtubule-targeted antimitotic drugs is known as the microtubule-stabilizing agents. These compounds stimulate microtubule polymerization and include paclitaxel (the first agent in this class), docetaxel, the epothilones, the eleutherobins, sarcodyctins, laulimolide, rhazinalam, discodermolide, and dictyostatin (Figure 14).[2] Some of these microtubule-stabilizing agents bind to and act directly on the microtubule or on soluble tubulin. As a consequence, the specific binding of these compounds onto tubulin and the microtubule greatly affects the response of the microtubule system to the drug.[5]
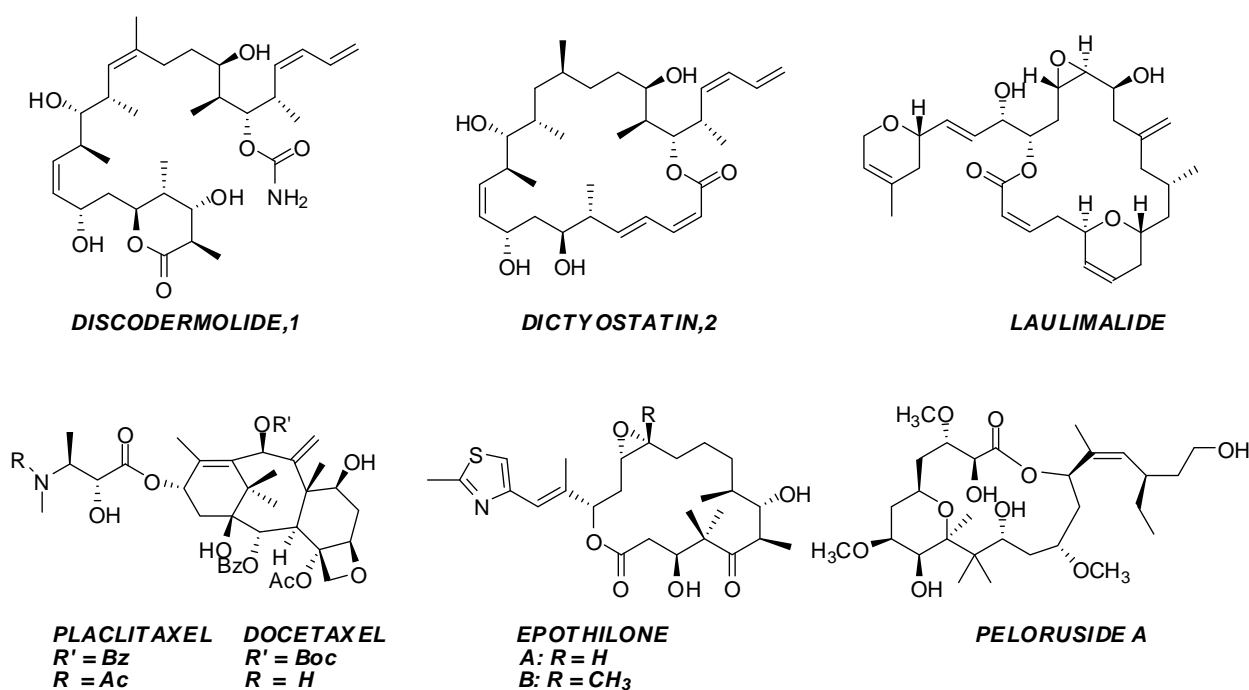
Figure 14. Selective microtubule-stabilizing agents from natural sources

The main family of the microtubule-stabilizing group of compounds is the taxanes. These agents bind poorly to soluble tubulin itself, but instead bind directly, with high affinity, to the assembled tubulin along the length of the microtubule. The taxane binding site is in the β-subunit on the inside surface of the microtubule. When the compound is bound, microtubule

depolymerization decreases and polymerization increases. There is one taxane-binding site per molecule of tubulin. The binding of a very small number of paclitaxel molecules per tubulin subunit strongly decreases microtubule depolymerization without enhancing microtubule polymerization.[6] The clinical success of taxanes has led to the discovery of other families of drugs that enhance microtubule polymerization such as epothilones, discodermolides, laulimolides, and dictyostatins.[7]

Discodermolide and Dictyostatin

(+)-Discodermolide (**1**) is a marine sponge-derived polyketide δ-lactone. It is known to have activity as a microtubule-stabilizing agent.[8a] The discovery of discodermolide taxane-like mechanism of action and its limited natural supply prompted the scientific community to synthesize **1** and its analogs via a number of routes.[8] Discodermolide activity is in the low nanomolar range (Figure 15). It has proven to induce tumor regression and suppression of angiogenesis in animal models as good as paclitaxel.[9]

(−)-Dictyostatin **2** is a marine sponge-derived macrolactone, isolated from *Spongia sp.* by Pettit in 1994[10] and later by Wright from *Corallistidia* sponges.[11] Structurally **2** resembles **1**. **2** has 11 stereocenters, one external (*Z,E*)-diene (C23-C26), and one internal (*E,Z*)-dienyl lactone moiety (C2-C5). Dictyostatin also contains a synthetically challenging internal *Z*-allylic alcohol (C10-C11), as well as, an isolated methyl group attached to a chiral sp^3 carbon (C16).

DISCODERMOLIDE 1   DICTYOSTATIN 2
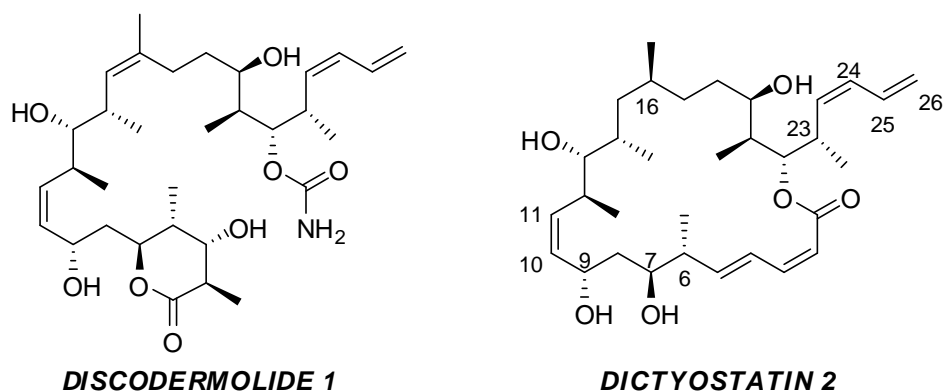
	cell line (GI$_{50}$)	
COMPOUND	T47D	MDA-MB231
DISCODERMOLIDE	3.6	9.8
PACLITAXEL	1.5	5.5
DICTYOSTATIN	0.5	5.3
EPOTHILONE B	<0.2	1.2

Figure 15. Antiproliferative activity in breast carcinoma cells

Biological testing showed that **2** displays high levels of toxicity for a wide range of human cancer cell lines.[12] As a consequence, **2** has emerged as a new microtubule-stabilizing agent with promising anticancer properties (Figure 15). The strong structural similarity with **1** helped to discover that **2** also interacts with the paclitaxel binding site on β-tubulin.[12] The cytotoxicity of **2** is more pronounced than that for paclitaxel, and it is also retained against paclitaxel-resistant cell lines. Moreover, **2** displays selectivity for the taxane binding site over paclitaxel and even discodermolide.[13] Dictyostatin's potency and selectivity over the taxane binding domain has prompted many scientists to synthesize **2** in an efficient and enantiomerically pure fashion.[14] Paterson's and Curran's group published back to back their

independent syntheses of **2**.[14a,b] Later, Phillips[14c] and Ramachandran[14d] published their syntheses of **2**, and many others have published syntheses of different fragments.[15]

4.1.1   Dictyostatin syntheses

The evolution of synthetic knowledge towards dictyostatin/discodermolide type of molecules has moved from simple linear syntheses to highly convergent routes. The synthetic plan that our group designed for **2** was based on the efficient coupling of fragments **3** and **4** through an alkyne addition/*cis*-selective reduction reaction sequence to establish the C10-C11 *Z*-alkene in advanced intermediate **6** (Figure 16).[14b]

The coupling reaction started with the lithiation of fragment **3**, followed by the addition to bottom fragment **4** to provide a ketone, followed by stereoselective reduction with (*S*,*S*)-Noyori catalyst to provide propargyl alcohol **7** in 73% yield for the 2 steps as a single diastereomer. Selective *cis*-reduction of **7** with Lindlar catalyst provided key C10-C11 *Z*-alkene, followed by TBS protection of allylic alcohol, selective deprotection of primary TBS, and Dess-Martin oxidation to provide aldehyde **8** in 78% yield for 4 steps.

Final coupling of top fragment **5** with **8** provided an enone, followed by selective reduction of conjugated alkene with NiB_2. The resulting ketone was then reduced with sodium borohydride to give a readily separable epimeric mixture of alcohols **9β** and **9α** in a 2.4:1 ratio. The major β-epimer was protected with a TBS group to obtain advanced intermediate **6** in 42% yield from **8**. The longest linear sequence of 34 steps in this total synthesis ran through fragment **3** and provided **2** in 1% overall yield from (2*S*)-3-hydroxy-2-methylpropionic acid methyl ester.
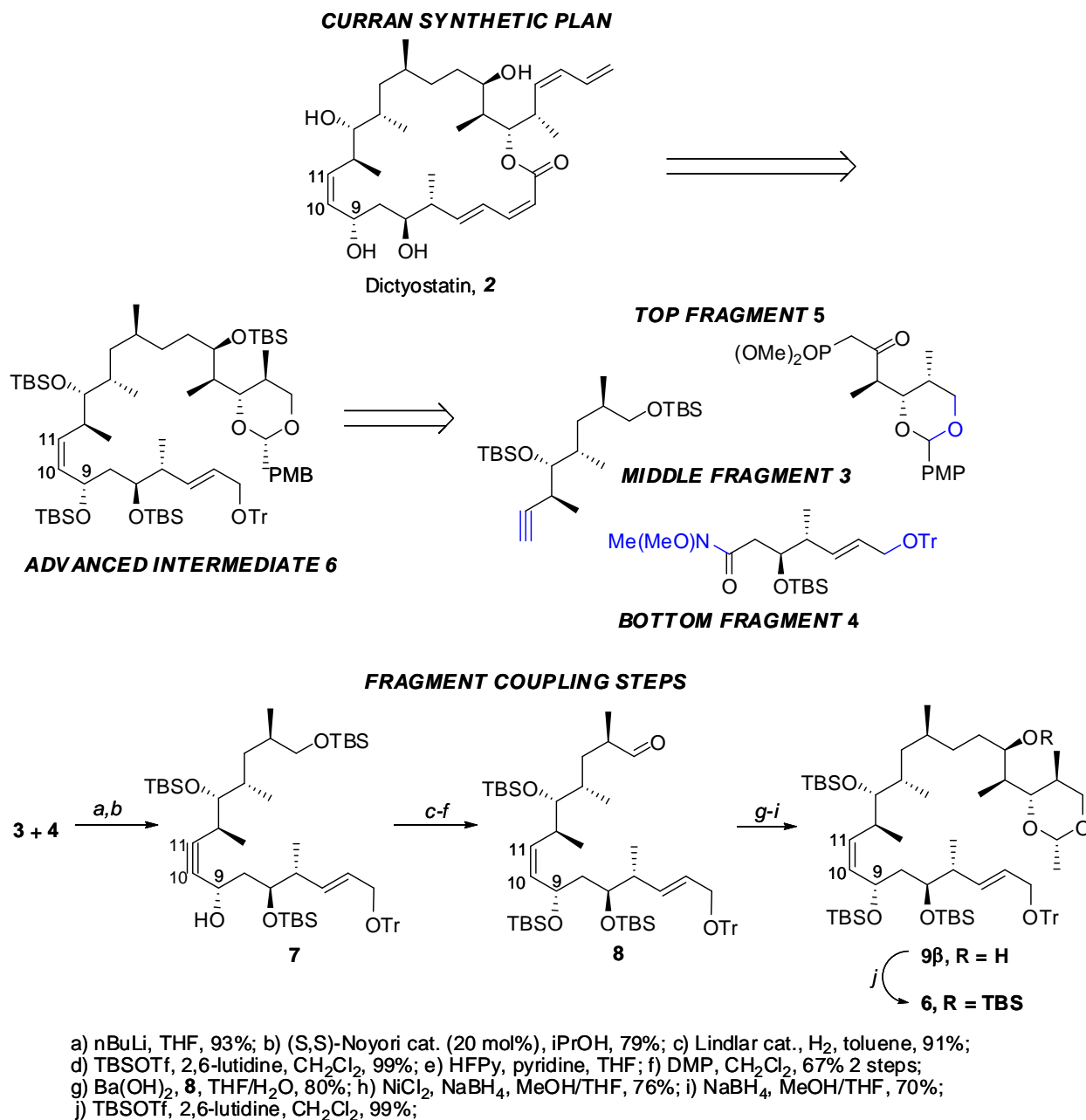
CURRAN SYNTHETIC PLAN

Dictyostatin, **2**

TOP FRAGMENT 5

MIDDLE FRAGMENT 3

BOTTOM FRAGMENT 4

ADVANCED INTERMEDIATE 6

FRAGMENT COUPLING STEPS

9β, R = H

6, R = TBS

a) nBuLi, THF, 93%; b) (S,S)-Noyori cat. (20 mol%), iPrOH, 79%; c) Lindlar cat., H_2, toluene, 91%;
d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 99%; e) HFPy, pyridine, THF; f) DMP, CH_2Cl_2, 67% 2 steps;
g) Ba(OH)$_2$, **8**, THF/H_2O, 80%; h) NiCl$_2$, NaBH$_4$, MeOH/THF, 76%; i) NaBH$_4$, MeOH/THF, 70%;
j) TBSOTf, 2,6-lutidine, CH_2Cl_2, 99%;

Figure 16. First generation coupling of fragments: Synthesis of (−)-dictyostatin 2

Similarly, Paterson's synthesis of dictyostatin relied on the synthesis of advanced intermediate **10** through the coupling of highly functionalized fragments by a Still-Genari olefination reaction to establish the key C10-C11 *Z*-alkene (Figure 17).[14a] The olefination reaction of **11** and **12** in the presence of K_2CO_3 and 18-crown-6 provided key enone **14** in 77%

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yield and 5:1 *Z:E* ratio. Then the enone was coupled with stannane **13** followed by removal of

TIPS group with KF to obtain seco-acid **10** in 83% overall yield from enone **14**. The longest

linear sequence of 24 steps in Paterson's synthesis ran through fragment **11** and provided **2** in

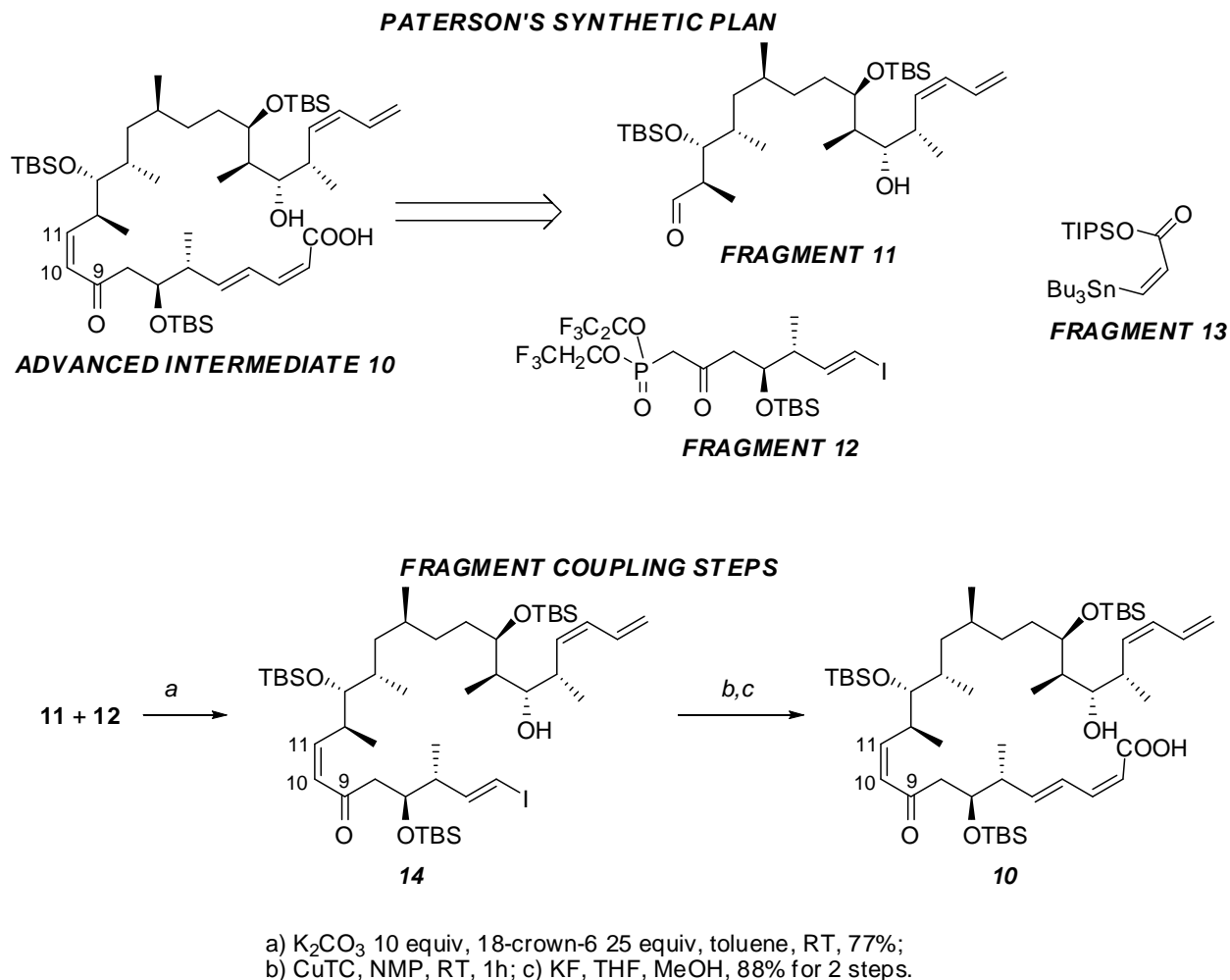3.8% overall yield from (*S*)-1-(4-methoxybenzyloxy)-2-methylpentan-3-one.

PATERSON'S SYNTHETIC PLAN

ADVANCED INTERMEDIATE 10

FRAGMENT 11

FRAGMENT 13

FRAGMENT 12

FRAGMENT COUPLING STEPS

11 + 12 → *a* → **14** → *b,c* → **10**

a) K$_2$CO$_3$ 10 equiv, 18-crown-6 25 equiv, toluene, RT, 77%;
b) CuTC, NMP, RT, 1h; c) KF, THF, MeOH, 88% for 2 steps.

Figure 17. Synthesis of (−)-dictyostatin 2 by Paterson

Phillips's synthesis relied on the coupling of fragments **15** and **16** through a RCM

reaction to establish the C10-C11 *Z*-alkene in advanced intermediate **17** (Figure 18).[14c] The

acylation reaction of fragment **15** with fragment **16** under Yamaguchi conditions provided ester **18** in 90% yield. Ester **18** reacted with 15 mol% of Grubbs second generation catalyst to provide lactone **19** in 75% yield as a single *Z*-alkene isomer. Lactone **19** was reduced to the lactol with DIBAL-H and then reacted with Ph$_3$PCHCO$_2$Et. The resulting ester was reduced again with DIBAL-H and then the alcohol was protected as a TBS ether to obtain advanced intermediate **17** in 70% yield from **19**. The longest linear sequence of 26 steps in Phillips synthesis ran through fragment **15** and provided **2** in 2.8% overall yield from 2-(*S*)-3-hydroxy-2-methylpropionic acid methyl ester.

Ramachandran's approach for the construction of C10-C11 *Z*-alkene was based on the addition reaction of *Z*-vinylzincates to aldehydes like fragment **21** to provide advanced intermediate **22** (Figure 18).[14d] The coupling reaction began with lithiation of fragment **20**. Then undergoing transmetallation with Me$_2$Zn to yield *Z*-vinylzincate, which was added to fragment **21** to provide advanced intermediate **22** in 80% as a single diastereomer. The longest linear sequence of 28 steps in Ramachandran synthesis ran through fragment **20** and provided **2** in 3.6% overall yield from 2-(*S*)-3-hydroxy-2-methylpropionic acid methyl ester.

PHILLIPS SYNTHESIS

ADVANCED INTERMEDIATE 17

FRAGMENT 15 + FRAGMENT 16

15 + 16 → 18 → 19 → 17
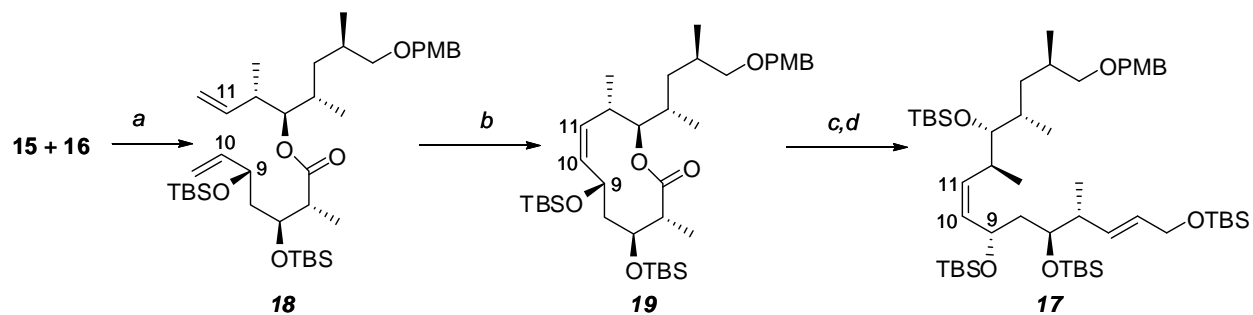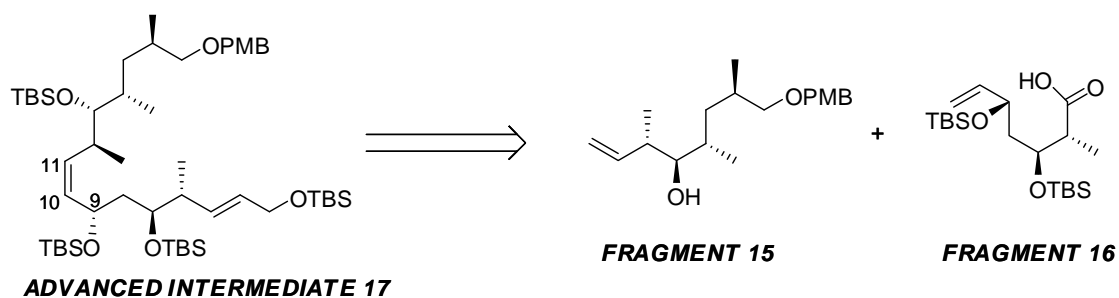
a) 2,4,6-trichlorobenzoyl chloride, Et$_3$N, DMAP, toluene, 90%; b) 15 mol% Grubbs II, toluene, 110 ^{o}C, 76%; c) DIBALH, CH$_2$Cl$_2$ then Ph$_3$PCHCO$_2$Et, 73%; d) DIBALH then TBSOTf, 2,6-Lutidine, 95%.

RAMACHANDRAN SYNTHESIS

FRAGMENT 20

i) t-BuLi
ii) Me$_2$Zn

FRAGMENT 21
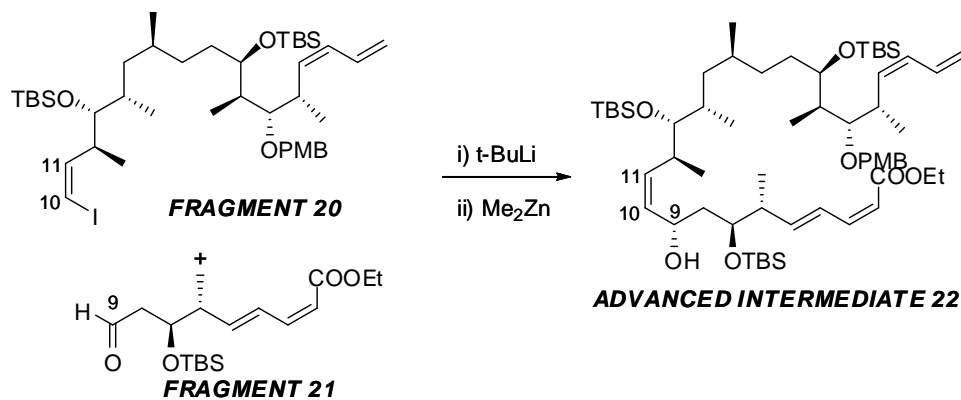
ADVANCED INTERMEDIATE 22

Figure 18. Syntheses of dictyostatin 2 done by Phillips and Ramachandran

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4.1.2   Second generation coupling of fragments: Synthesis of 16-normethyl-15,16-dehydrodictyostatin

The synthesis of analogs along the different fragments has been an important goal in our synthetic studies towards microtubule-stabilizing agents. Structure-activity relationships (SAR) studies, obtained from discodermolide models, suggested that loss of C16 methyl group and gain of C15-C16 alkene may retain cytotoxicity.[16] Therefore, our group proposed the synthesis of a simpler analog C16-normethyl-15,16-dehydro-dictyostatin **23**.

For the synthesis of analog **23** our group envisioned the construction of the C10-C11 *Z*-alkene by the coupling of top-middle fragment **30**, as a *Z*-vinyl zincate, with bottom fragment **33** to obtain advance intermediate **24**.[17] This approach introduced some new key reactions for the synthesis of the fragments, as described in Scheme 17. The synthesis of middle fragment **28** began with the oxidation of alcohol **25** (derived from commercially available (*S*)-Roche ester) followed by Roush *anti*-crotylation reaction to obtain allylic alcohol.[18] This product was protected as a TBS ether and the alkene underwent oxidative cleavage followed by Corey-Fuchs reaction to furnish alkyne **26** in 39% overall yield. Formation of *Z*-vinyl iodide was done by iodolysis of alkyne **26** with *n*-BuLi and I_2, followed by *cis*-selective reduction with NBSH and triethylamine to provide enantiomerically pure **27** in 94% yield. Final removal of PMB and Dess-Martin oxidation provided **28** in 36% yield over 10 steps. The coupling reaction to obtain C15-C16 alkene was done by the Wittig reaction of middle fragment **28** and top fragment **29** in the presence of NaHMDS to provide **30** in 70% yield.

C16-NORMETHYL-15,6-DEHYDRODICTYOSTATIN 23   **ADVANCED INTERMEDIATE 24**
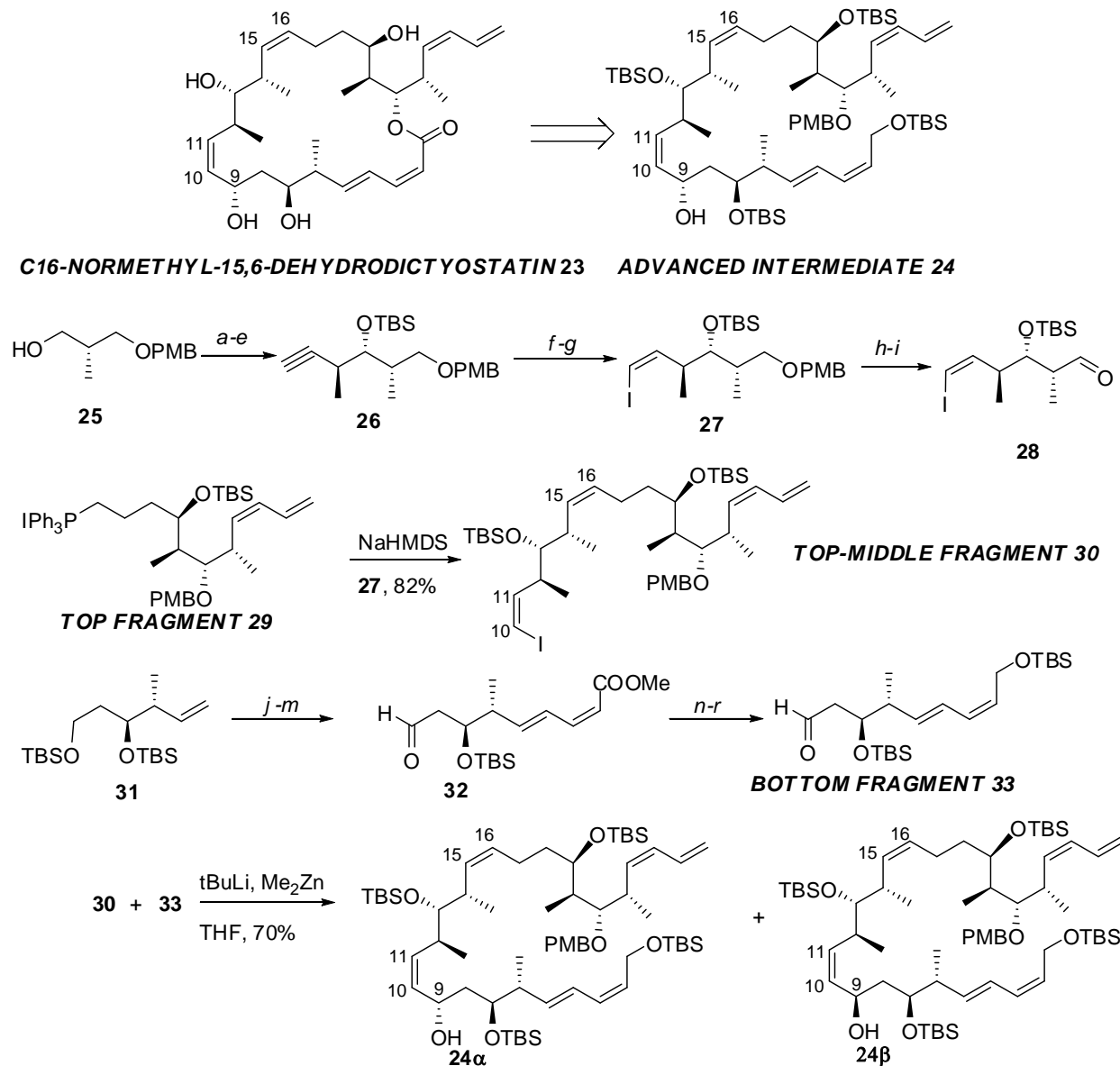
a) Roush-reagent, THF, 67% 2 steps; b) TBSOTf, 2,6-Lutidine, CH$_2$Cl$_2$, 82%; c) OsO$_4$ (10mol%), NaIO$_4$, Et$_2$O, H$_2$O;
d) Ph$_3$P, CBr$_4$, 2,6-lutidine, 74% 2 steps; e) BuLi, THF, 96%; f) BuLi, I$_2$, THF, 99%; g) NBSH, TEA, 95%. h) DDQ,
98%; i) Dess-Martin, 100%.
k) crotonaldehyde, Grubbs II (10 mol%), CH$_2$Cl$_2$, reflux, 91%; l) (CF$_3$CH$_2$O)$_2$P(O)CH$_2$CO$_2$Me, KHMDS,
18-crown-6, THF, 98%; m) HFPy, pyridine, THF, 92%; n) SO$_3$Py, Et$_3$N, DMSO, CH$_2$Cl$_2$, 91%;
o) NaClO$_2$, NaHPO$_4$, 2-methyl-2-butene, THF/H$_2$O; p) NH(OMe)MeHCl, DCC, Et$_3$N, DMAP, CH$_2$Cl$_2$, 70% 2 steps;
q) DIBALH, CH$_2$Cl$_2$; r) TBSOTf, 2,6-Lutidine, CH$_2$Cl$_2$, 96% 2 steps; s) PySO$_3$, DMSO, Et$_3$N, CH$_2$Cl$_2$;

Scheme 18. Synthesis of 16-normethyl-15,16-dehydrodictyostatin 23

Synthesis of bottom fragment **33** started with the cross-metathesis reaction of a known

intermediate **31** with crotonaldehyde and Grubbs second generation catalyst to provide

conjugated aldehyde.[19] This step was followed by Still-Genari olefination to set the *Z*-alkene then selective deprotection of primary TBS ether and finally Parikh-Doering oxidation of the resulting alcohol to provide intermediate **32** in 75% overall yield. Aldehyde **32** was oxidized with $NaClO_2$ to the acid and then transformed to the Weinreb amide. The amide was reduced with DIBALH and the resulting alcohol was protected as a TBS ether to obtain **33** in 50% overall yield and 8 steps. Advanced intermediate **24** was prepared by reacting middle fragment **30** and *t*-BuLi 1.7M in THF to obtain *Z*-vinyl lithium, followed by transmetallation with Me_2Zn and addition of bottom fragment **33** to provide a 1:1.6 mixture of **24α:24β** epimers at C9 in 70% yield. Advanced intermediate **24α** was isolated by silica gel flash chromatography and used to complete the synthesis of **23**.
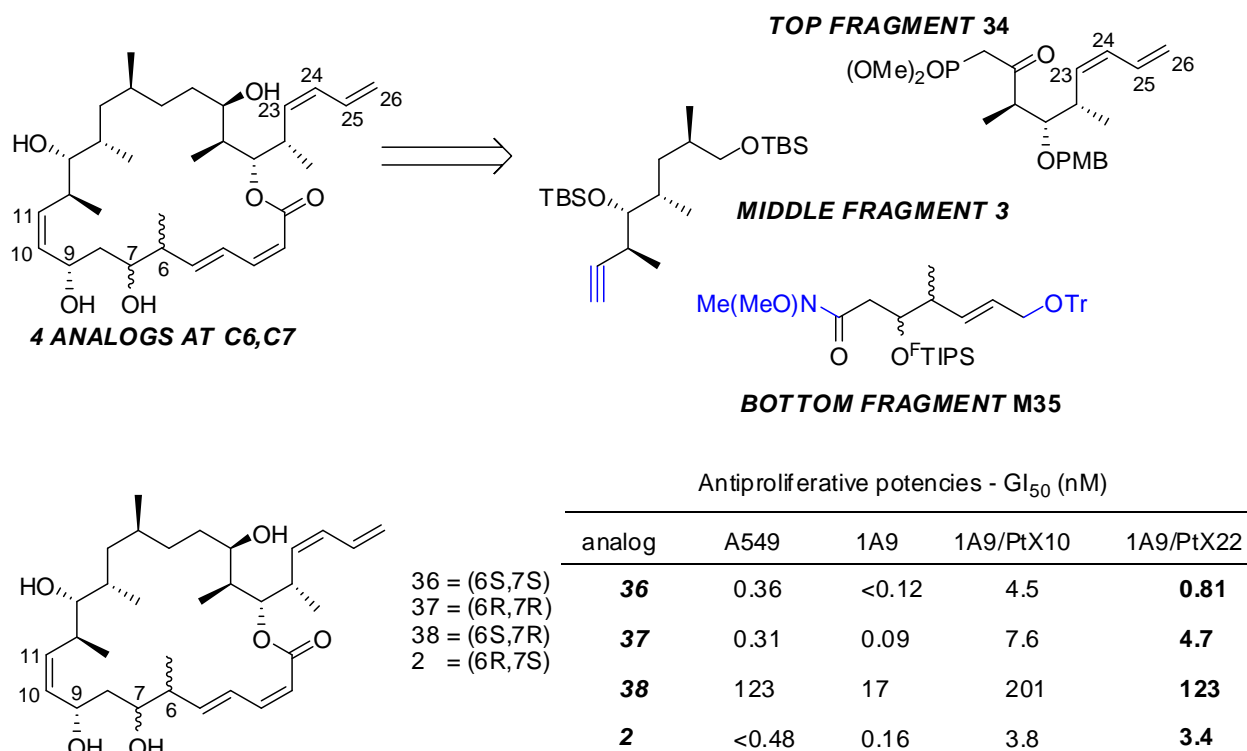
4.1.3 Third generation coupling of fragments: Synthesis of 6-*epi*-dictyostatin

The continuous production of discodermolide/dictyostatin analogs has led us to search based on structure-activity relationships (SAR) for the minimum structural elements that contribute to cytotoxicity and retain affinity for the taxane binding site.[20] Subsequently, our group next hypothesized that changes to the C6 and C7 stereocenters of **2** may lead to no loss of activity. We proposed a fluorous mixture synthesis (FMS) approach to obtain all possible diastereomers for C6 and C7 stereocenters (Scheme 18).[21] The synthetic strategy was similar to our group's original synthesis of **2**. However, new top fragment **34**, including the C23-C26 diene, and bottom fragment **M35** (fluorous mixture of four quasiisomers using fluorous silanes as fluorous tags) were prepared. The coupling strategy relied on a previously developed alkyne addition/*cis*-selective reduction reaction sequence to provide the C10-C11 *Z*-alkene. This FMS

provided 2-4 mg of each desired analog (6-*epi*-dictyostatin **36**, 7-*epi*-dictyostatin **37**, 6,7-*bisepi*-dictyostatin **38** and dictyostatin **2**).
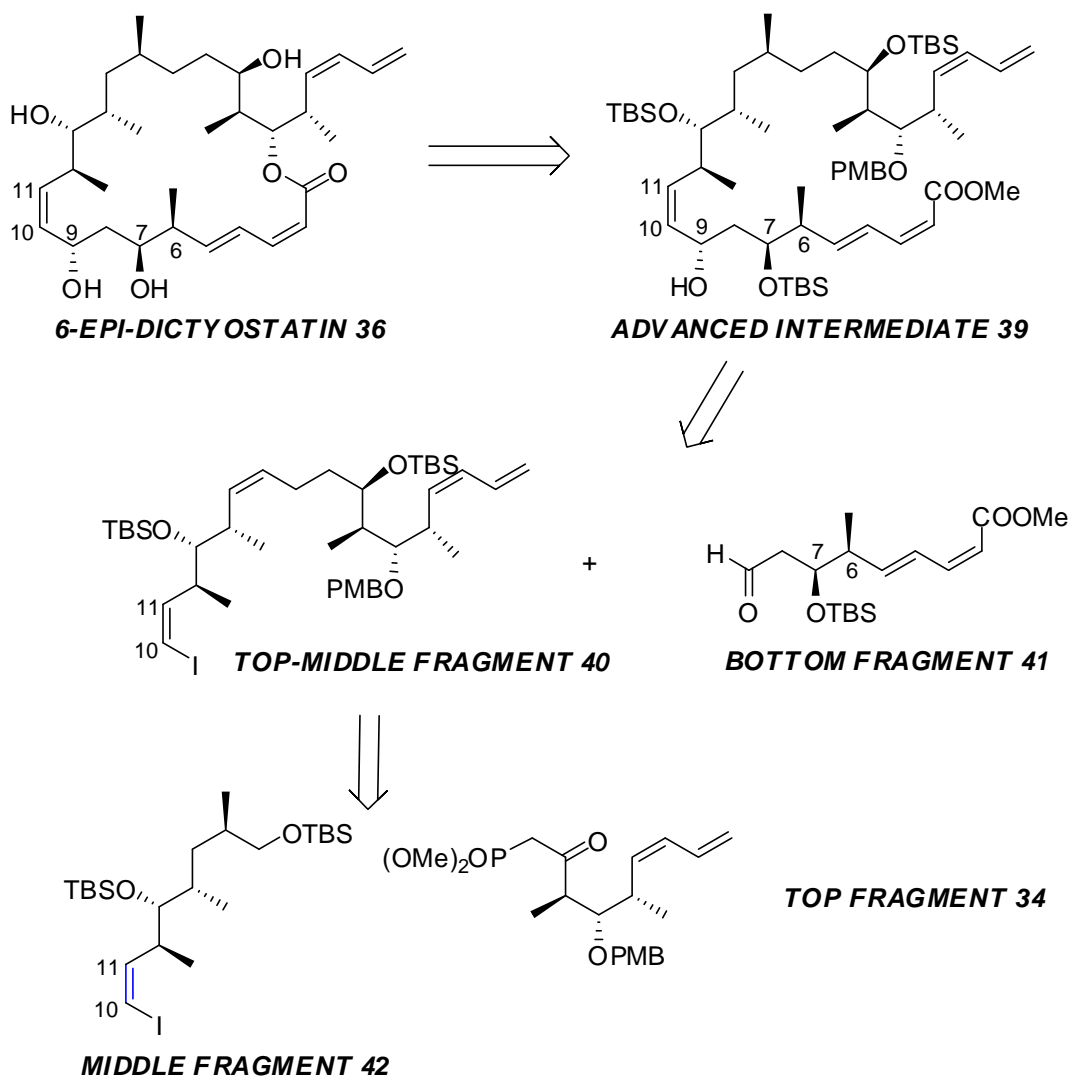
The antiproliferative effects of these compounds against human ovarian carcinoma cells were tested and the results showed that 6,7-*epi*-dictyostatin **38** was considerably less active than **2**. However, 7-*epi*-dyctiostatin **37** showed to have comparable activity to **2** and 6-*epi*-dyctiostatin **36** showed to be four times more potent than **2** (Scheme 19).[21]

Recent biological studies revealed that **36** and **37** have high levels of affinity to isolated tubulin and proved to be effective competitors of [^{14}C]-epothilone B for the binding site. 6-*Epi*-dictyostatin **36** has also shown to be active against paclitaxel-resistant cell lines compared to 16-normethyl analogs that were inactive.[20] These experiments clearly showed that **36** not only improves *in vitro* potency, but may maintain potency *in vivo*.

	Antiproliferative potencies - GI$_{50}$ (nM)			
analog	A549	1A9	1A9/PtX10	1A9/PtX22
36	0.36	<0.12	4.5	**0.81**
37	0.31	0.09	7.6	**4.7**
38	123	17	201	**123**
2	<0.48	0.16	3.8	**3.4**

Scheme 19. Fluorous Mixture Synthesis of 6-*epi*-dictyostatin

After these promising results, we decided to focus on making 6-*epi*-dictyostatin **36** in large scale for further *in vivo* testing. It was envisioned an even more convergent approach so the scale-up could be achieved in a reasonable time frame.

6-EPI-DICTYOSTATIN 36

ADVANCED INTERMEDIATE 39

TOP-MIDDLE FRAGMENT 40

BOTTOM FRAGMENT 41

MIDDLE FRAGMENT 42

TOP FRAGMENT 34

Scheme 20. Synthetic plan for scale-up of 6-*epi*-dictyostatin 36

As depicted in Scheme 18, we envisioned obtaining large amounts of **36** by designing an efficient coupling strategy to obtain advance intermediate **39**. This compound will come from the coupling of top-middle fragment **40** and bottom fragment **41** *via* the *in-situ* formation of Z-vinyl

metal intermediate. The top-middle fragment will be obtained from the Still-Genari olefination of middle fragment **42** and top fragment **34**. The synthetic route for bottom fragment **41** has been recently improved by the ene-diene metathesis reaction of functionalized olefins and substituted (*E,Z*)-dienyl ester recently developed in our laboratory (Chapter 3).[22]

4.2   RESULTS AND DISCUSSION

4.2.1   Fourth generation synthesis and coupling of fragments

The application of the ene-diene metathesis reaction for the quick synthesis of bottom fragments **41/32** (see Chapter 3, Table 14) encouraged us to investigate different coupling strategies for the synthesis of 6-*epi*-dictyostatin. Because of our previous success with the coupling of Weinreb amide **4** with alkyne **3**, we next investigated the coupling of alkynes with aldehyde **32**. Due to the unknown reactivity towards nucleophiles of the dienyl ester moiety in aldehyde **32**, we did the model addition reaction of 4-phenyl-1-propyne with aldehyde **32**. The results are summarized in Table 15A. The lithium alkynoate, obtained from the addition of *n*-BuLi to 4-phenyl-1-propyne reacted with aldehyde **32** at −78 ^{o}C in a 1:1 ratio, yielded a promising 51% of propargyl alcohol **43** after silica gel flash chromatography (Entry 1). Increasing the equivalents of lithium alkynoate to 1.5 equiv provided **43** in 78% yield; and, when we use 2 equiv we obtained **43** in 80% yield (Entry 2 and 3).

Because of the promising results, we investigated the selective reduction of propargyl alcohol **43** to *cis*-allylic alcohols, as summarized in Table 15B. The selective reduction of alkynes has been successfully applied previously in our group (Figure 16).[23] However, activated

dienes, like **43**, are not inert to selective hydrogenation catalysts like Lindlar, Rh complexes, or Raney nickel.[24] Moreover, the reduction of conjugated propargyl alcohols in the presence of Rieke zinc and at elevated temperatures is known to provide *cis*-dienols in high yields.[26]

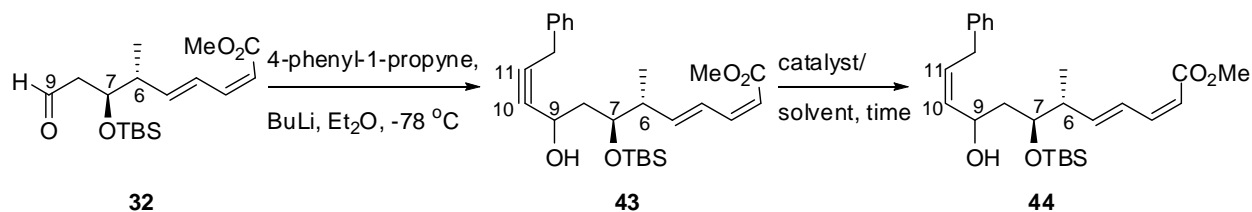**Table 15. Alkyne addition (15A) and selective reduction (15B) reactions**

TABLE 15A			
entry	alkyne (equiv)	product[a]	yield[b]
1	1	**43**	51%
2	1.5	**43**	78%
3	2	**43**	80%

TABLE 15B				
entry	catalyst/solvent	product[a]	time	yield[b]
1	Lindlar/toluene	**44**	3 h	>10%
2	Lindlar/toluene	**44**	1 h	15%
3	Rieke zinc/THF[c]	**44**	24h	SM

a) Isolated as a mixture of diastereomers.
b) Isolated yields after silica gel flash chromatography.
c) Reaction temperature was 65 °C.

We next decided to try the selective reduction of **43** using Lindlar catalyst in toluene for 3 h. We obtained **44** in <10 % isolated yield after silica gel flash chromatography (Entry 1). Reduced product **44** was a separable mixture of diastereomers at C9 by TLC. ^{1}H NMR analysis of **44** showed that it was a mixture of epimers at C9 in a 1:1 ratio. We then tried running the same reaction for only 1 h and we only obtained **44** in 15% isolated yield (Entry 2). We also attempted the selective reduction of **43** with Rieke zinc in THF at 65 °C for 24 h. We recovered the starting material out of the reaction mixture (Entry 3).

Because of the low yields in the selective reduction of propargyl alcohol **43**, we tried the addition reaction of *Z*-vinyl metal species to aldehyde **33** to obtain vinyl alcohol **44** directly. The

addition of these species to α- or β-alkoxy aldehydes sometimes gave good levels of stereoselectivity for the allylic alcohols due to substrate induction.[27] Evans has shown that the stereoselectivity increases when a Z-vinyl lithium is transmetallated to a Z-vinyl magnesium halide along with a chelating group in the α or β position.[28] In planning this reaction, we considered important to test the addition reaction of aldehydes with chelating protected ethers (**45** = MOM ether, **46** = PMB ether) and with a non-chelating protected ether (**33** = TBS ether) in the β-position and model substrate (Z)-(3-iodoallyl)-benzene, as summarized in Table 16.

**Table 16. Addition reaction of Z-vinyl metal compound to aldehydes**
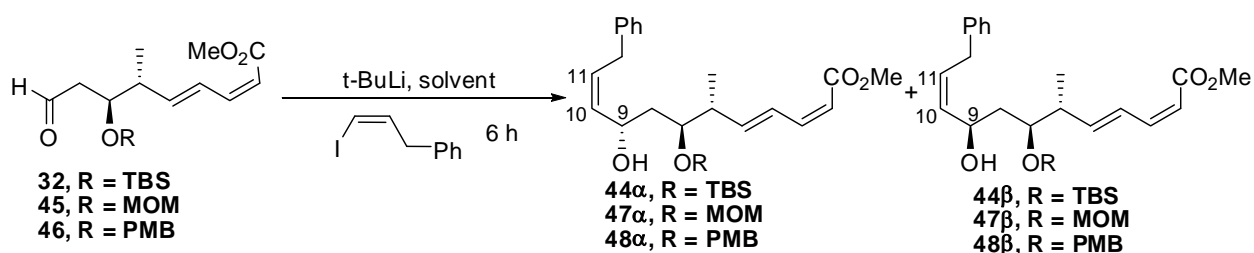
entry	equiv vinyl iodide/tBuLi	CHO	solvent	yield[a]	product	α:β
1	2/2	**32**	Et$_2$O	55%	**44**	1:1
2	1.5/1.5	**32**	Et$_2$O	59%	**44**	1:1
3	1.5/3	**32**	Et$_2$O	79%	**44**	1:1
4	1.5/3	**32**	Et$_2$O	79%	**44**	1:1
5	1.5/3	**32**	CH$_2$Cl$_2$	67%	**44**	1:1
6	1.5/3	**45**	CH$_2$Cl$_2$	66%	**47**	1.5:1
7	1.5/3	**46**	CH$_2$Cl$_2$	63%	**48**	1.7:1

a) The combined isolated yield of α,β after silica gel flash chromatography

In a typical experiment, we reacted 2 equiv of (Z)-(3-iodoallyl)-benzene and 2 equiv of t-BuLi at −78 °C, followed by addition of 1 equiv of aldehyde **32**. The crude mixture was purified

by silica gel flash chromatography to provide **44** in 51% yield (Entry 1). The reaction provided **44** as a separable 1:1 mixture of diastereomers at C9 (**44α/44β**). However, we reported the yield as the combined yields of **44α** and **44β** and the diastereoselectivity as the ratio of isolated **44α** (more polar) and **44β** (less polar). We then tried the reaction with 1.5 equiv of (*Z*)-(3-iodoallyl)-benzene and 1.5 equiv of *t*-BuLi to obtain **44** in 59% yield and 1:1 *dr*; and, then with 1.5 equiv of (*Z*)-(3-iodoallyl)-benzene and 3 equiv of *t*-BuLi to obtain **44** in 79% yield and 1:1 *dr* (Entry 2 and 3).

The reaction using conditions for entry 3 and 2 equiv of $MgBr_2$ in diethyl ether provided **44** in 79% yield and 1:1 *dr* (Entry 4). Similarly, the reaction using CH_2Cl_2, as a transmetallating solvent, provided **44** in 79% yield and 1:1 *dr* (Entry 5). In turn, the reaction (Entry 5) with MOM-protected aldehyde **45** provided **47** in 66% yield and 1.5:1 *dr* (Entry 6). When we used PMB-protected aldehyde **46** as the substrate for the reaction, we obtained **48** in 66% yield and 1.7:1 *dr* (Entry 7). Alcohols **47** and **48** were also obtained as a separable mixtures of epimers at C9 (**47α**:**47β** and **48α**:**48β**) and the combined isolated yields are given. The addition reaction using *Z*-vinyl lithium and aldehyde **32** provided alcohol **44** in very good yields; however, the reactions were not very diastereoselective with aldehydes bearing β-chelating or non-chelating ethers.
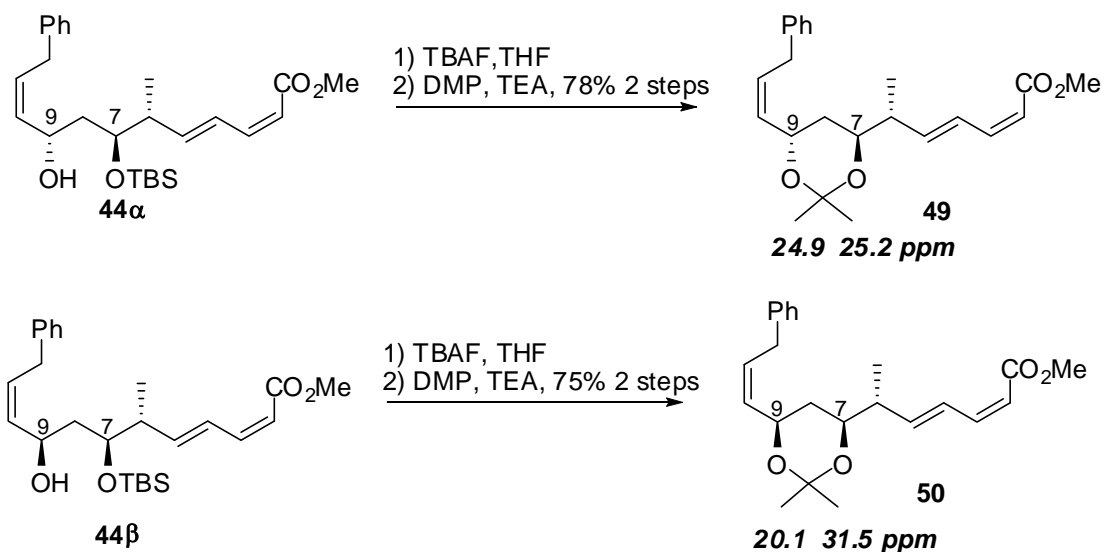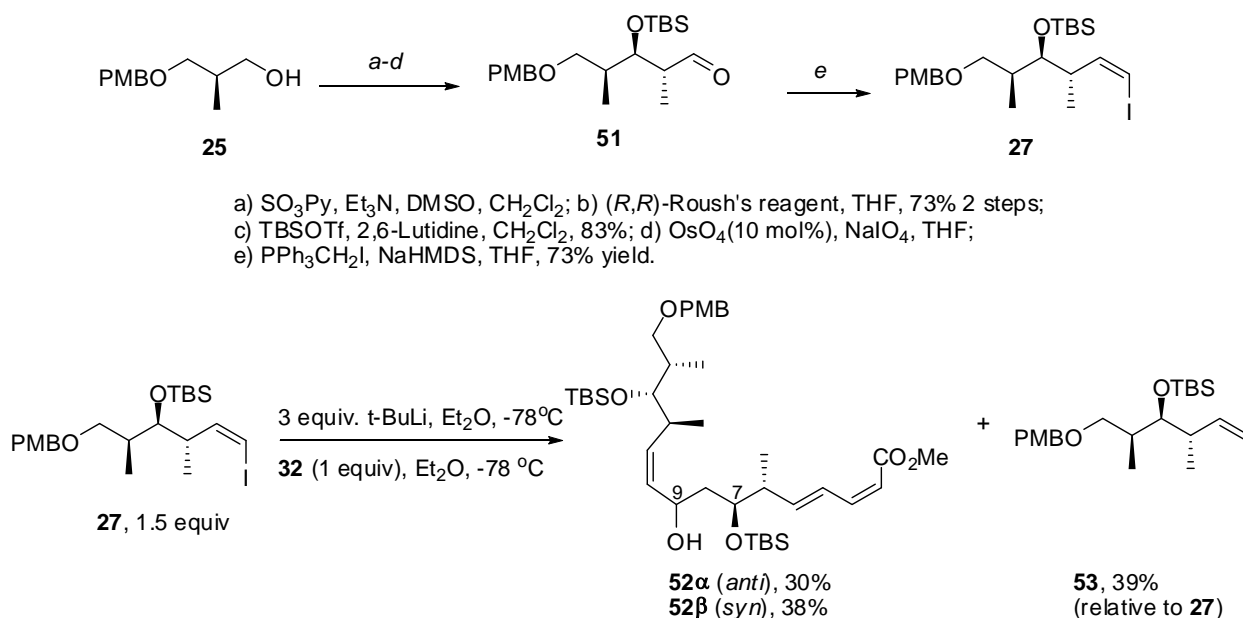
Scheme 21. Stereochemical assignment of the C9 stereocenter

The next step was to assign the stereochemistry for epimers **44α/44β**, **47α/47β** and **48α/48β**. To achieve this task, we prepared acetonides from isolated **44α** and **44β**.[29] First, we removed the TBS group of alcohol **44α** with TBAF in THF to obtain the crude diol. This was reacted with 2,2-dimethoxypropane and Et₃N to provide acetonide **49** in 78% overall yield after isolation by silica gel flash chromatography. The same reaction sequence was done for **44β**, to provide acetonide **50** in 75% overall yield. Analysis of ^{13}C NMR spectrum of **49** showed acetal methyl carbons resonances at 24.9 and 25.2 ppm and acetal quaternary carbon resonance at 101.1 ppm. The same analysis for the spectrum of **50** showed acetal methyl carbons resonances at 20.1 and 31.5 ppm and acetal quaternary carbon resonance at 97.9 ppm. These results indicated that acetonide **49** (from **44α**) had a *syn* relationship between C9 and C7 and that acetonide **50** (from **44β**) had an *anti* relationship between C9 and C7.[29] Moreover, analysis of the ^{1}H NMR spectrum of alcohol **44α** revealed that the C9 proton resonance was more down field (4.81 ppm) than the one for alcohol **44β** (4.67 ppm). The same trend in the C9 proton resonances was found for epimers **47α/47β** and **48α/48β**.

The results from the addition of *Z*-vinyl lithium to aldehyde **32** encouraged us to try the reaction with middle fragment **27** (Scheme 22). The synthesis of fragment **27** was developed earlier in our group in 9 steps from (*S*)-Roche Ester.[17] However, we found that the reaction of aldehyde **51** with ICH$_2$PPh$_3$ and NaHMDS provided fragment **27** in 76% yield as a single *Z*-alkene isomer.[30] The development of this step reduced the synthesis of fragment **27** to 7 steps from (*S*)-Roche Ester in 44% overall yield.

The addition reaction of vinyl iodide **27** to aldehyde **32**, in the presence of *t*-BuLi and THF, furnished allylic alcohol **52** as a mixture of *anti/syn* diastereomers in 1:1.3 ratio. Alcohols **52** were isolated by silica gel flash chromatography yielding **52α** (*anti,* more polar) and **52β** (*syn,* less polar) in a 68% combined yield, along with reduced product **53** in 39% yield (relative to **27**). Stereochemical assignment of **52α**, as the *anti* epimer, and **52β**, as the *syn* epimer, was performed by comparing C9 proton resonance patterns found in alcohols **44α** and **44β** with the ones found for alcohols **52**.


a) SO$_3$Py, Et$_3$N, DMSO, CH$_2$Cl$_2$; b) (*R,R*)-Roush's reagent, THF, 73% 2 steps;
c) TBSOTf, 2,6-Lutidine, CH$_2$Cl$_2$, 83%; d) OsO$_4$(10 mol%), NaIO$_4$, THF;
e) PPh$_3$CH$_2$I, NaHMDS, THF, 73% yield.

Scheme 22. Synthesis and coupling of bottom fragment 32 and middle fragment 27

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The successful coupling of middle fragment **27** and bottom fragment **32** on small scale encouraged us to scale-up the coupling of fragments towards the synthesis of 6-*epi*-dictyostatin **36**. Mr. Won-Huyk Jung prepared 6 g of top-middle fragment **40** and I prepared 10 g of bottom fragment **41** (Chapter 3, Table 14, Synthesis of fragment **2**). Mr. Jung did the coupling of **40** and **41** in the presence of *t*-BuLi in two batches (batch 1 = 1 g of **40**, batch 2 = 5 g of **40**). He obtained **39** (**39α**) in 20% for batch 1 and 8% for batch 2 (Scheme 23). The reaction produced a mixture of **39α** and **39β** that was separated by silica gel flush chromatography. The yields reported above are of isolated **39α**. The low yields of the scale-up coupling were disappointing. It was decided to focus on investigating better ways to couple the bottom and middle fragment.

	40		**39α**	**39β**
scale-up batch 1	*1g*		*165 mg, 20%*	*248 mg, 30%*
scale-up batch 2	*5g*		*331 mg, 8%*	*498 mg, 12%*
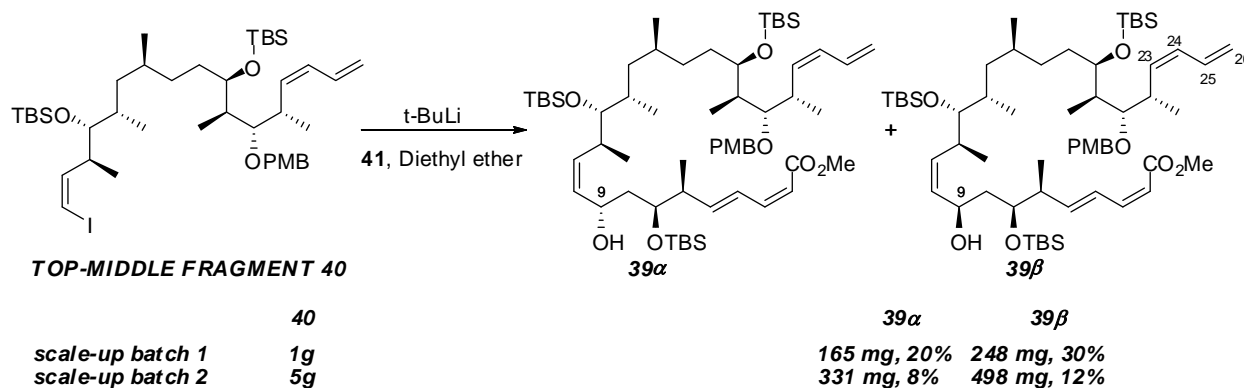
Scheme 23. Scale-up coupling reaction for 6-*epi*-dictyostatin 23

Before the scale-up addition reaction of top-middle fragment **40** and aldehyde **41** by Mr. Jung, we investigated a more direct route for the synthesis of top fragment **34** (Scheme 24). Because the previous synthetic approach towards **34** had some low yielding steps (PMB transfer from a secondary to a primary alcohol, stoichiometric CrCl$_3$-mediated coupling, and Peterson-type olefination to build (C23-C26)-*Z,E*-diene), we envisioned the construction of (C23-C26)-*Z,E*-diene *via* a simple one step *Z*-selective Wittig reaction with allyltriphenylphosphine.[32]
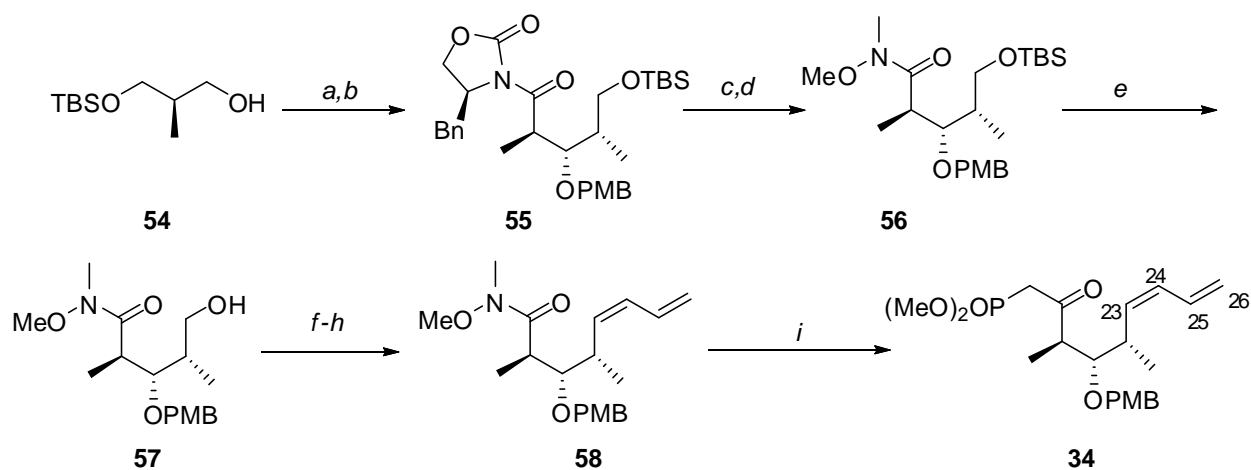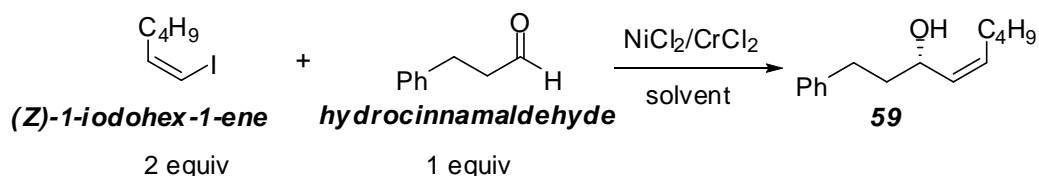
a) TEMPO (5 mol%), Bleach, KBr, K_2CO_3, CH_2Cl_2/H_2O; b) oxazolidinone, Bu_2BOTf, DIPEA, CH_2Cl_2; 67% in 2 steps; c) MeN(H)OMe·HCl, $AlMe_3$, THF, 75%; d) PMBOC(NH)CCl$_3$, BF_3OEt_2, CH_2Cl_2, 83%; e) TBAF•3H_2O, DMF, 51%; f) $PySO_3$, DMSO, Et_3N, CH_2Cl_2, 86%; g) AllylPPh$_3$, Ti(i-PrO)$_4$, t-BuLi, MeI, 62%; h) phenyl triazole dione, 86%; i) $(MeO)_2POCH_3$, n-BuLi, THF, 90%.

Scheme 24. Synthesis of top fragment 34

We started the synthesis by oxidation of alcohol **54** with catalytic TEMPO and bleach. The crude aldehyde then was reacted with (*S*)-4-benzyl-3-propionyloxazolidin-2-one to provide *syn* aldol adduct **55** in 67% overall yield. Adduct **55** underwent reductive cleavage of chiral auxiliary and PMB protection in the presence of BF_3·Et_2O[31] to obtain Weinreb amide **56** as a single isomer in 62% yield for the 2 steps. The removal of the sterically hindered primary TBS was done by the reaction of **56** with anhydrous TBAF in DMF to provide after 6 h **57** in 51% yield. Primary alcohol **57** underwent Parikh-Doering oxidation followed by a highly selective Wittig-type olefination[32] with allyltriphenylphosphine, Ti(iPrO)$_4$, and *t*-BuLi to furnish **58** as a 10:1 mixture of *Z/E*-olefin isomers at C23-C24. The major *Z*-olefin isomer was purified by reacting the mixture with phenyl triazole dione to remove the minor but more reactive *E,E*-diene isomer.[33] The resulting Diels-Alder adduct was removed from the desired *Z,E*-diene isomer by silica gel flash chromatography to provide **58** in 46% yield in 2 steps as a single *Z*-olefin isomer. Finally, reaction of **58** with dimethyl methylphosphonate and *n*-BuLi in THF provided top

fragment **34** in 90% yield. Top fragment **34** was obtained in 9% overall yield and 9 linear steps from TBS ether **54**. This approach was 5 steps shorter than the previous synthesis of **34**.

Because of the disappointing yields in the scale-up addition reaction of top-middle fragment **40** to bottom fragment **41**, we investigated the addition reaction of *Z*-vinyl chromium to aldehydes also known as the Nozaki-Hiyama-Kishi (NHK) reaction.[34]

(Z)-1-iodohex-1-ene   **hydrocinnamaldehyde**   **59**
2 equiv   1 equiv

Stoichometric: 4 equiv of $CrCl_2$, 0.2 equiv of $NiCl_2$, DMF.
Asymmetric: 3 equiv of $CrCl_2$, 3 equiv of **60**, 3 equiv Base, 1 equiv $NiCl_2$, DMF, 76% yield and 40% *ee*

Catalytic 1: 10 mol% $CrCl_2$, 10 mol% **60**, 10 mol% DIPEA, 10mol% $NiCl_2$, 2 equiv Mn,
2 equiv TMSCl, 20 mol% $(Bn)(Bu)_3NCl$, 2 equiv LiCl, THF, 87% yield and 80% *ee*.
Catalytic 2: 5 mol% $CrCl_2$, 5 mol% **60**, 5 mol% DIPEA, 1 mol% $NiCl_2(dppp)$, 2 equiv Mn,
1 equiv $Zr(Cp)_2Cl_2$, 2 equiv LiCl, THF, 90% yield and 92% *ee*.

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60, R = Me, 58%
**62**, R = Naphthyl, 42%
63, R = tolyl, 40%
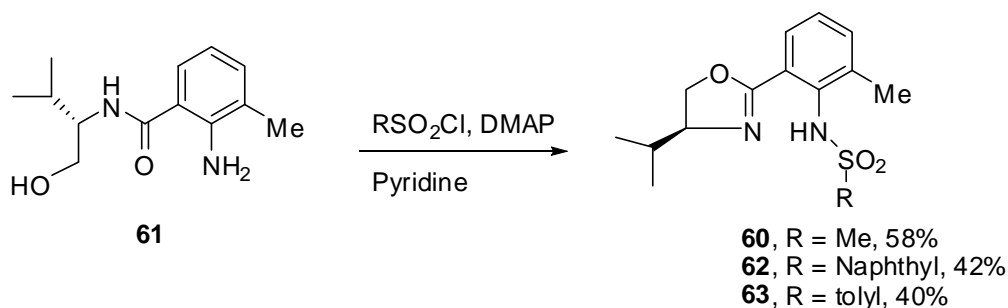
Figure 19. Stoichiometric and catalytic NHK reaction

Kishi has found that the reaction of (*Z*)-1-iodohex-1-ene in the presence of $NiCl_2$, $CrCl_2$, and stoichiometric amounts of chiral sulfonamide **60** with hydrocinnamaldehyde provided allylic alcohol **59** in 76% yield and 40% *ee* (Figure 19).[34] Kishi found that when the reaction of (*Z*)-1-iodohex-1-ene and hydrocinnamaldehyde was set up with 1 equiv of Mn, 10 mol% of $NiCl_2$, 10 mol% of $CrCl_2$, 10 mol% of **60**, and 2 equiv of TMSCl. **59** was obtained in 87 yield and 80%

ee.[35] Moreover, by replacing TMSCl with $Zr(Cp)_2Cl_2$ in the reaction, they obtained **59** in 90% yield and 92% *ee*.[36]

Table 17. NHK reaction for the coupling of 41 and 42
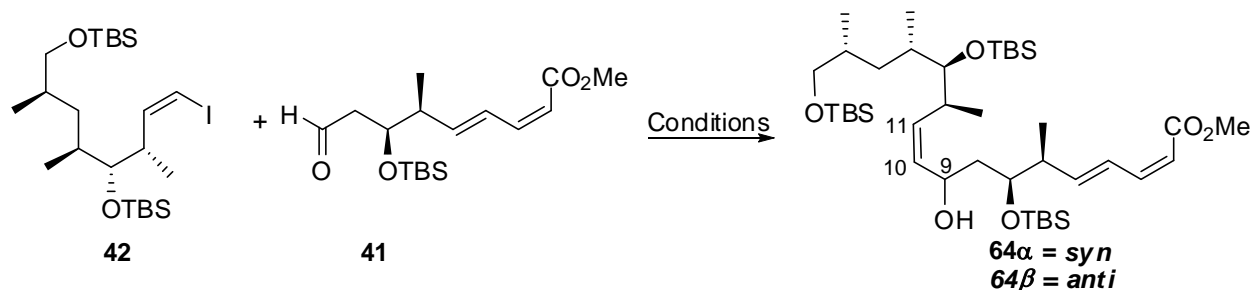
entry	ligand	conditions[c]	base	yield[a]	ratio (**64α:64β**)[b]
1	-	stoichiometric		61%	1:1
2	**60**	asymmetric	Et_3N	50%	1:1
3	**62**	asymmetric	Et_3N	54%	1.5:1
4	**63**	asymmetric	Et_3N	45%	1.2:1
5	**62**	catalytic 1[d]	DIPEA	35%	1.7:1
6	**62**	catalytic 2[d]	DIPEA	34%	2:1

a) Isolated yields. b) isomer distribution determined after isolating each diastereomer. d) ~40% of unreacted **41** was recovered.
c) Conditions: Stoichiometric: 4 equiv of $CrCl_2$, 0.2 equiv of $NiCl_2$, DMF.
Asymmetric: 3 equiv of $CrCl_2$, 3 equiv of ligand, 3 equiv Base, 1 equiv $NiCl_2$, DMF.
Catalytic 1: 10 mol% $CrCl_2$, 10 mol% ligand, 10 mol% DIPEA,10mol% $NiCl_2$, 2 equiv Mn, 2 equiv TMSCl, 20 mol% $(Bn)(Bu)_3NCl$, 2 equiv LiCl, THF.
Catalytic 2: 5 mol% $CrCl_2$, 5 mol% ligand, 5 mol% DIPEA, 1 mol% $NiCl_2(dppp)$, 2 equiv Mn, 1 equiv $Zr(Cp)_2Cl_2$, 2 equiv LiCl, THF.

Chiral sulfonamides are not commercially available. However, due to the ease of their synthesis and the need to search for a chiral ligand that would give high levels of diastereoselectivity, we made three different chiral sulfonamides: a known sulfonamide **60** and

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two new sulfonamides **62** and **63** (Figure 19). The reaction of aniline **61** with MeSO$_2$Cl and DMAP in pyridine provided chiral sulfonamide **60** in 58% yield.[37] Under the same conditions we then reacted aniline **61** with tolylsulfonyl chloride and naphthylsulfonyl chloride to obtain bulkier chiral sulfonamides **62** and **63** in 42 and 40% yield, respectively. The next step was to test the coupling reaction of bottom fragment **41** with middle fragment **42** under NHK conditions, as summarized in Table 17.

In a typical reaction, we weighted NiCl$_2$ and CrCl$_2$ in a reaction flask in a glove box. The middle fragment **42** was added in DMF, followed by the addition of aldehyde **41** after 1 h. After 6 h the crude mixture was filtered through celite to provide crude alcohol **64** as a separable 1:1 mixture of diastereomers at C9. Alcohols **64** were purified by silica gel flash chromatography to provide **64α** (more polar) in 31% yield and **64β** (less polar) in 30% yield (Entry 1). Stereochemical assignment of **64α** and **64β** was performed by comparison of C9 proton resonance patterns found in alcohols **44α** and **44β** with the ones found for alcohols **64**. The reaction, under the same conditions, using ligand **60** provided **64** in 50% yield and 1:1 ratio of **64α**:**64β** (Entry 2). Moreover, the reaction with ligand **62** provided **64** in 45% yield and 1.5:1 ratio of **64α**:**64β**. The reaction with ligand **63** provided **64** in 54% yield and 1.2:1 ratio of **64α**:**64β** (Entries 3 and 4). We next tried the reaction, under catalytic conditions, with ligand **62** and TMSCl to obtain **64** in 35% yield and 1.7:1 ratio of **64α**:**64β**. The same reaction but using Zr(Cp)$_2$Cl$_2$ provided **64** in 34% yield and 2:1 ratio of **64α**:**64β**. Because of the moderate yield and selectivities, no further optimization of this reaction was tried.

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4.2.2　　　Fifth generation synthesis and coupling of fragments

The application of convergent strategies for the coupling of bottom and middle fragment in which the C9 stereocenter was formed together with the C10-C11 Z-alkene gave unsatisfactory results. We hypothesized that incorporation of C9 stereocenter before coupling could make coupling of fragments more efficient and convergent.

Our group has recently reported the ring-closing metathesis (RCM) reaction of ester **65** (already has C9 stereocenter) with Grubbs first generation catalyst to provide lactone **66** in 76% yield as a single olefin isomer (Figure 20).[38] Phillips's synthesis of dictyostatin also utilized a ring-closing metathesis (RCM) reaction strategy to incorporate the C10-C11 Z-alkene (Figure 18). Intermediate ester **18** (already has C9 stereocenter)[39] reacted with Grubbs second generation catalyst to provide lactone **19** in 76% yield as a single olefin isomer.[14c] These results suggested that the RCM reaction might be a good approach to make the C10-C11 Z-alkene in a fragment coupling.
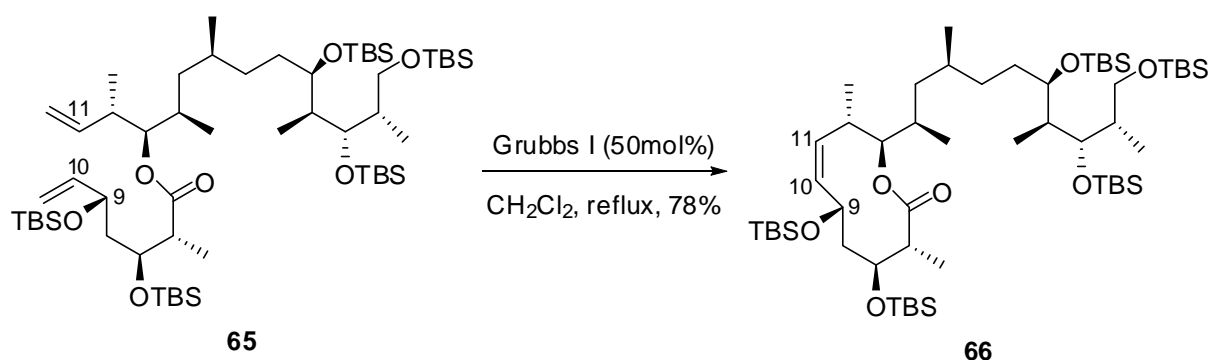
Figure 20. RCM strategy for the synthesis of C10-C11 Z-alkene

RCM reactions of silaketals of different sizes is also a recurrent strategy for the synthesis of encumbered *Z*-alkenes (Figure 20).[40] In order to provide medium-size rings (7, 8 or 9 membered rings), RCM reactions of silicon-tethered substrates need preorganization of the substrate into a cyclic-like conformation to overcome the substantial enthalpic barrier.[41] The RCM reactions of diisopropyl and diphenyl silaketals to give seven-membered rings have been applied successfully for the total synthesis of (−)-muccocin[42] and (+)-gigantecin.[43]
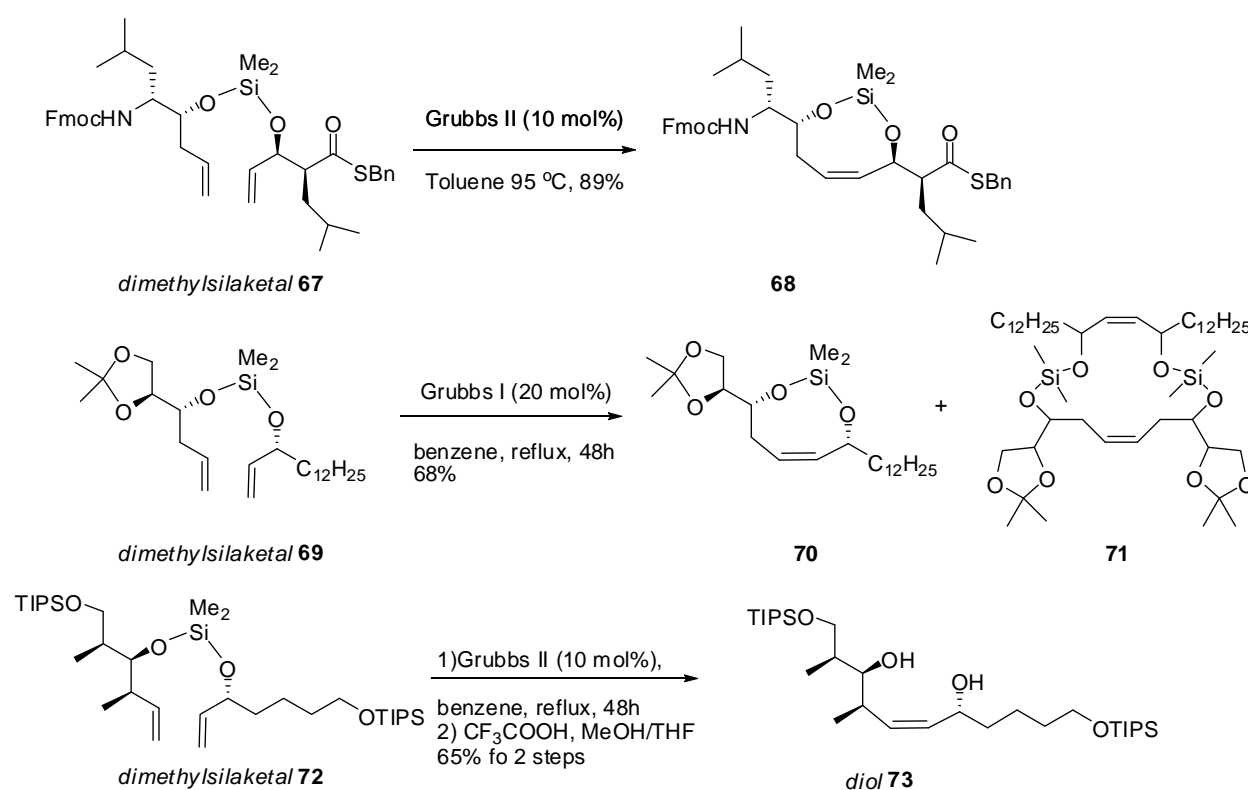
Figure 21. RCM of dimethylsilaketals for the synthesis of eight-member rings

Furthermore, the RCM reaction of dimethylsilaketal **67** promoted by Grubbs second generation catalyst provided eight-membered ring product **68** in 89% as a single *Z*-olefin isomer.[44] Likewise, the RCM reaction of similar dimethylsilaketal **69** with Grubbs first generation catalyst provided eight-membered ring product **70** in 68% yield. In contrast, when **69**

was reacted with Grubbs second generation catalyst (5 to 10 mol%), large amounts of cross-metathesized dimeric byproduct **71** were isolated.[45] Comparatively, when dimethylsilaketal **72** (bearing methyl group in allylic position) reacted with Grubbs second generation catalyst followed by addition of CF₃COOH in MeOH/THF to remove dimethylsilyl group, diol **73** was isolated in 65% overall yield (Figure 21).[46]

Based on those results, we envisioned the application of the RCM reaction of silaketals for the construction of C10-C11 *Z*-alkene for the synthesis of 6-*epi*-dyctiostatin **36**. We proposed the RCM reaction of dimethylsilaketal **74** for the synthesis of key middle-bottom fragment **75**. In turn, dimethylsilaketal **74** was synthesized by the coupling of middle fragment **76** and bottom fragment **77** (Figure 22).
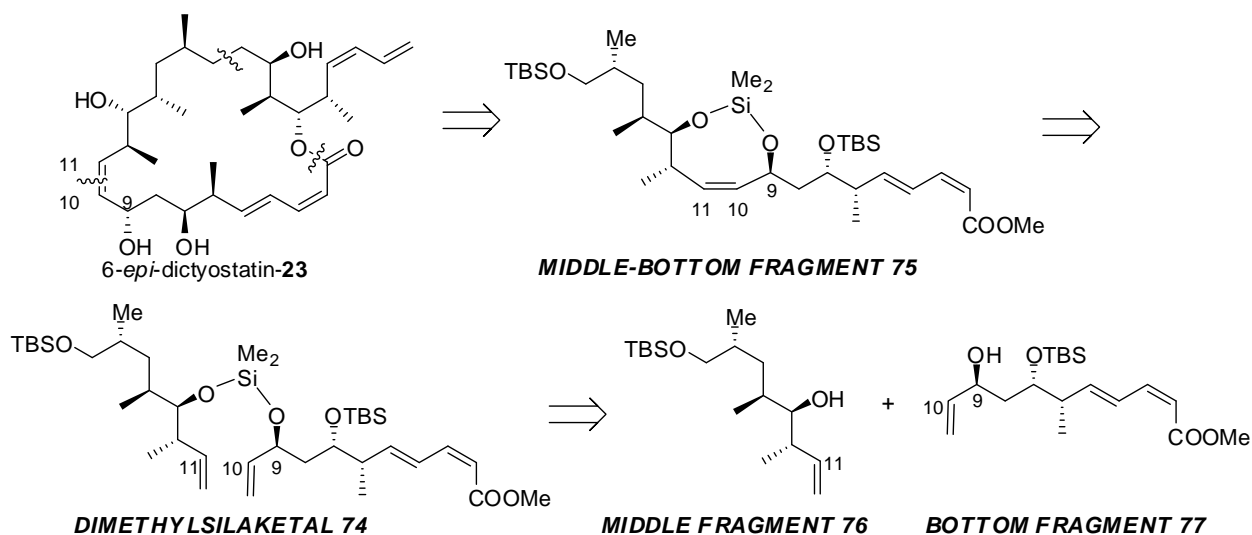
Figure 22. Fifth generation synthetic plan and coupling of fragments

The first task to implement this plan was the synthesis of fragments **76** and **77** (Scheme 23). The synthesis of middle fragment **76** started with the desilylation of primary alcohol **78** with

HCl 3N in THF to provide crude diol. The diol was selectively protected with TBSCl in CH_2Cl_2 to provide alcohol **76** in 75% yield over 2 steps. Bottom fragment **77** was synthesized by the addition of vinyl magnesium bromide to aldehyde **41** followed by Parikh-Doering oxidation and (*S*)-CBS reduction of the resulting ketone to provide a 5:1 mixture of C9 epimers **77α/β** in 74% overall yield over the 3 steps. The diastereoselectivity for the CBS reduction was measured by integrating the C9 proton resonances in the ^{1}H NMR spectra (*anti* **77α** 4.23 ppm, *syn* **77β** 4.08 ppm). The same chemical shift pattern was seen for the *anti* and *syn* compounds synthesized from the previous generations coupling experiments. Since the diastereomers coeluted during flash chromatography and the desired **77α**-isomer was the major product, this mixture was used directly. From here on, all the compounds made with this mixture (**77α/β**) will be labeled as **α/β**; although, we will only show the **α**-epimer.

**MIDDLE FRAGMENT SYNTHESIS**
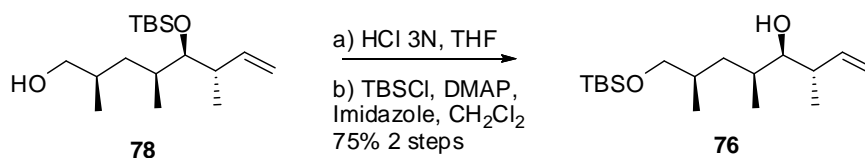
BOTTOM FRAGMENT SYNTHESIS
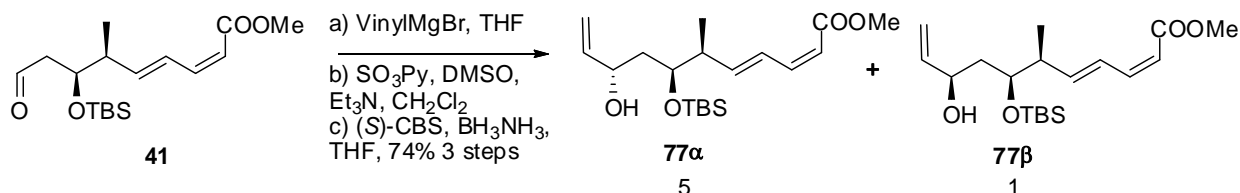
Scheme 25. Sixth generation synthesis of fragments

In planning the RCM reaction sequence, we considered that having groups of different size (Me, iPr, Ph) on the silaketal might affect the outcome of the RCM. The results for the synthesis of silaketals bearing different groups are summarized in Table 18. We tested several

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reagent and base combinations for the synthesis of silaketals **74α/β**, **79α/β** and **80α/β**. In a typical coupling reaction, 12 equiv of diisopropyldichlorosilane were added to a mixture of 1.2 equiv of **76** and 1.5 equiv of imidazole in CH_2Cl_2. The excess silane and solvent were removed under vacuum and a mixture of 1 equiv of **77α/β** and 1.5 equiv of imidazole in CH_2Cl_2 were added. After 24 h, the crude mixture was purified by silica gel flash chromatography to provide silaketal **79α/β** in 53% yield (Entry 1). The reaction adding *n*-BuLi 1.6M to **76** at −78 ^{o}C and then 5 equiv of diisopropyldichlorosilane instead provided **79α/β** in 69% yield (Entry 2).

In another typical reaction, a mixture of 2.5 equiv of diisopropylbis-(3-methoxyprop-1-ynyl)-silane and 1.2 equiv of **76** in hexanes reacted with 10 mol% of NaH for 1 h. The monosilane was then mixed with 1 equiv of **77α/β** in hexanes followed by the addition of 10 mol% of NaH. After 3 h, the crude product was purified by silica gel flash chromatography to provide silaketal **79α/β** in 46% yield (Entry 3).[47] Silaketal bearing phenyl groups was made by coupling **76** and **77α/β** using diphenyldichlorosilane and *n*-BuLi/imidazole to provide **80α/β** in 28% yield (Entry 4). When the coupling was done using diphenylbis-(3-methoxyprop-1-ynyl)-silane and NaH, **80α** was obtained in 75% yield (Entry 5). Silaketal **74α/β** (bearing methyl groups) was obtained by coupling **76** and **77α/β** using dimethyldichlorosilane and *n*-BuLi/imidazole in 91% yield. In contrast, coupling using dimethylbis-(3-methoxyprop-1-ynyl)-silane and NaH provided **74α/β** in 49% yield (Entries 6 and 7). Silaketals **74α/β**, **79α/β** and **80α/β** were isolated as a 5:1 mixtures of epimers at C9.

Table 18. Silaketal synthesis
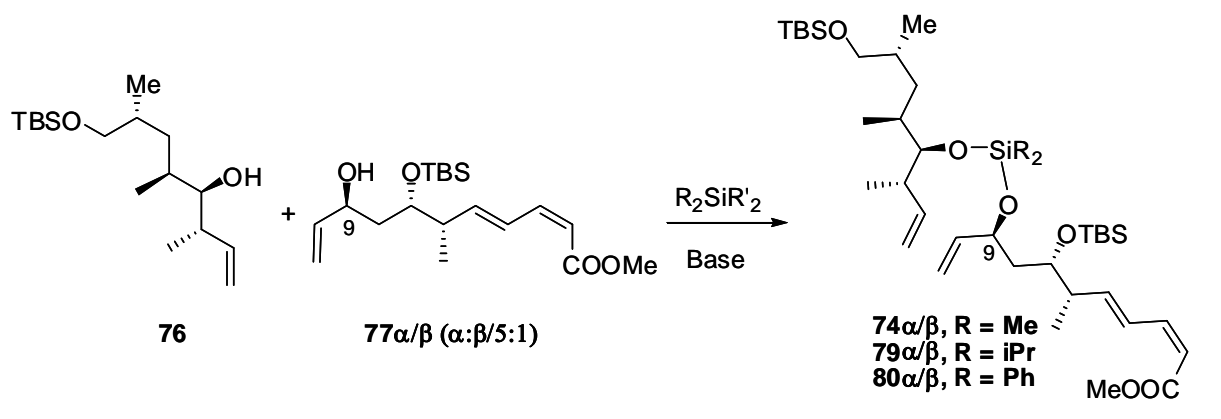
Entry	R'	R	Base	Time	Product[a]	Yield
1	Cl	i-Pr	Imid.	24h	**79α/β**	53%
2	Cl	i-Pr	BuLi/Imid.	16h	**79α/β**	69%
3	≡—CH₂OMe	i-Pr	NaH	4h	**79α/β**	46%
4	Cl	Ph	BuLi/Imid.	16h	**80α/β**	28%
5	≡—CH₂OMe	Ph	NaH	4h	**80α/β**	75%
7	Cl	Me	BuLi/Imid.	16h	**74α/β**	91%
6	≡—CH₂OMe	Me	NaH	4h	**74α/β**	49%

a) all products were isolated as 5:1 α:β mixtures after silica gel flash chromatography

With the three different silaketals in hand, we tested the RCM reactions with the different catalysts (Grubbs second generation and first generation, Hoveyda-and Grubbs catalyst), as summarized in Table 19. In a typical experiment silaketal, **74α/β** was dissolved in benzene at 0.01 M concentration. At reflux, was added 10 mol% of Grubbs II catalyst. After 24 h, the crude product was purified by silica gel chromatography to provide **75α/β** in 63% yield (Entry 1). However, isolation of **75α/β** was cumbersome and the ¹H NMR spectrum of the product showed small unidentified impurities. The reaction of silaketal **74α/β** with 10 mol% of Hoveyda-Grubbs

catalyst in benzene for 24 h provided impure **75α/β** in 25% yield. Moreover, when **74α/β** reacted under the same conditions for only 4 h, **75α/β** was isolated in 43% yield (entries 2 and 3). Furthermore, reaction of silaketal **74α/β** with 25 mol% of Grubbs I catalyst in benzene for 3 h provided **75α/β** in 44% yield together with 40% of unreacted **74α/β** (Entry 4). Reaction of **74α/β** under the same conditions for 48 h in refluxing CH_2Cl_2 provided **75α/β** and recovered **74α/β** in 31 and 50% yield, respectively (Entry 5). In turn, the reaction of **74α/β** under the same conditions for 1 h in refluxing toluene provided **75α/β** in 59% yield along with 15% of recovered **74α/β** (Entry 6).

Finally, in an attempt to reach a complete conversion of silaketal, we reacted **74α/β** with 10 mol% of Hoveyda-Grubbs catalyst in benzene for 1 h. We isolated **75α/β** in 61% yield without significant amounts of **74α/β** (Entry 7). Reaction of diisopropylsilaketal **79α** with the last conditions (Entry 7) provided **81α/β** in 30% along with other unidentified impurities (Entry 8). The reaction of diphenylsilaketal **80α/β** with the last conditions provided **82α/β** in 45% yield with 15% of recovered **80α/β** (Entry 9). The combination of silaketal formation using dimethyldichlorosilane with *n*-BuLi/imidazole and RCM reaction using dimethylsilaketal **74α/β** and 10 mol% of Grubbs-Hoveyda catalyst is the best reaction sequence for the coupling of fragments **76** and **77α/β** (Table 19).

Table 19. RCM reaction of silaketals 74α/β, 79α/β and 80α/β

74α/β, R = Me
79α/β, R = iPr
80α/β, R = Ph

RCM catalyst
refluxing solvent
0.01 M

75α/β, R = Me
81α/β, R = iPr
82α/β, R = Ph
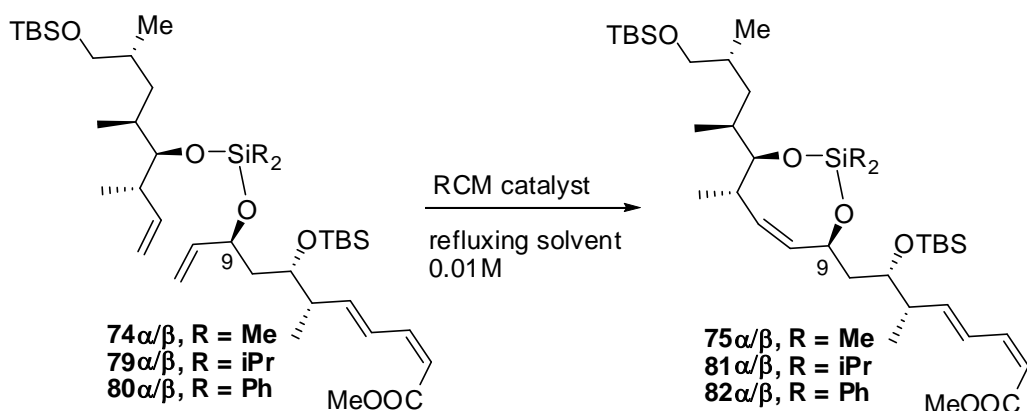
Entry	Catalyst	Substrate	Solvent	Time	Product[d]	Yield % PDT(RSM)[a]
1	Grubbs II 10%	74α/β	Benzene	24h	75α/β	69
2	Hoveyda-Grubbs 10%	74α/β	Benzene	24h	75α/β	25[b]
3	Hoveyda-Grubbs 10%	74α/β	Benzene	4h	75α/β	43[b]
4	Grubbs I 25%	74α/β	Benzene	3h	75α/β	44 (40)
5	Grubbs I 25%	74α/β	DCM	48h	75α/β	31 (50)
6	Grubbs I 25%	74α/β	Toluene	1h	75α/β	59 (15)
7	Hoveyda-Grubbs 10%	74α/β	Toluene	1h	75α/β	61 (0)
8	Hoveyda-Grubbs 10%	79α/β	Toluene	1h	81α/β	30 (ND)
9	Hoveyda-Grubbs 10%	80α/β	Toluene	1h	82α/β	45 (15)

a) mixture of epimers at C9 in 5:1 ratio. Yields of product (PDT) and
in () yield of recovered starting material (RSM)
b) Isolated yields with small unidentified impurities

Because of the promising results in the RCM reaction, we investigated a more direct route of **41** to a suitable bottom fragment alcohol. The current 3-step sequence could, in principle, be replaced by a single step *via* an asymmetric addition to **41**. Wipf has shown that vinyl-zirconium species added to aldehydes to provide internal allylic alcohols in high yields and high levels of stereoselectivity if promoted by a chiral ligand (Scheme 26).[48]

The application of internal olefins, bearing a silyl ether in the allylic position, as suitable substrates for the RCM reaction, led us to investigate a reductive addition of 1-hexyne and aldehyde **41** using chiral ligands **83**, **84**, and **85**. The diastereoselectivities were measured the same way as for the synthesis of bottom fragment **77α/β**. The results for this reaction are summarized in Scheme 26.

In a typical experiment, 1.2 equiv of 1-hexyne was added to 1.2 equiv of Cp_2ZrHCl in CH_2Cl_2. The solvent was then removed under vacuum. At $-78\ ^oC$, toluene was added followed by 1.2 equiv of Me_2Zn 2M. Then, 10 mol% of chiral ligand **85**[49] was added. At $-30\ ^oC$, aldehyde **41** was added and the resulting solution was stirred for 15 h. The crude mixture was purified by silica gel flash chromatography to provide **86** in 81% yield and 6:1 *dr* of **86α:86β** (Entry 1). Reaction of **41** with 10 mol% of ligand **83** provided alcohol **86** in 75% yield and 4:1 *dr* of **86α:86β** (Entry 2). However, reaction using 10 mol % of ligand **84**[50] provided **86** in 87% yield and 7:1 *dr* of **86α:86β** (Entry 3). In an attempt to optimize the diastereoselectivity, we changed the ligand loading using conditions for Entry 3. When we used 5 mol % of **84**, we obtained **86** in 79% yield and 5:1 *dr* of **86α:86β**. While, the reaction with 20 mol% of **84** provided **86** in 75% yield and 2.5:1 *dr* of **86α:86β**. Ligand **84** was easily synthesized from L-proline in 3 steps and 85% overall yield and provided the best yields and diastereoselectivities for the asymmetric reductive addition of 1-hexyne and aldehyde **41**. From here on, all the compounds made with the mixture (**86α/β**) will be labeled as **α/β**; although, we will only show the **α**-epimer.
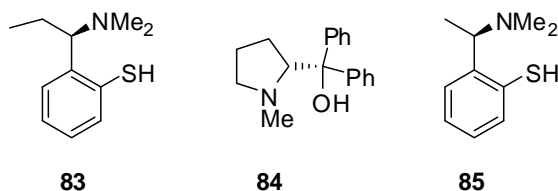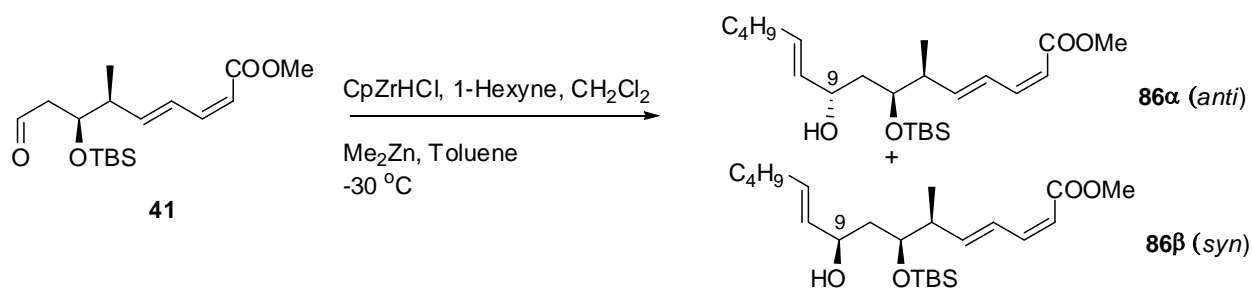
| Entry	Ligand	Mol%	ratio (86α:86β)[b]	Yield[a]
1	**85**	10	**6:1**	81%
2	**83**	10	**4:1**	75%
3	**84**	10	**7:1**	87%
4	**84**	5	**5:1**	76%
5	**84**	20	**2.5:1**	79%

a) isolated yields after silica gel flash chromatography. b) ratios determined by ^{1}H NMR.

Scheme 26. Reductive alkyne coupling reaction for the synthesis of fragment 86α

Because of the isolation problems found in the RCM reaction using middle fragment **76** and bottom fragment **77α/β**, we next investigated alternative protecting groups for the middle fragment. RCM catalysts are known to have low reactivity towards olefins bearing a methyl group in the allylic position (fragment **76**).[51] Similarly, alkenes bearing free hydroxyl groups or chelating protecting groups (PMB, MOM) have enhanced reactivity towards RCM catalysts.[52] We hypothesized that changing the primary TBS ether (**76**) to a primary PMB ether (**87**) in the middle fragment will increase the reactivity of the more hindered alkene, as well as, decrease formation of the undesired byproducts during the RCM reaction. The synthesis of middle

fragment **87** started with the reaction of primary alcohol **78** with PMB trichloroimidiate in cyclohexane/CH$_2$Cl$_2$ and 0.05 equiv of BF$_3$·OEt$_2$ to provide PMB ether. This product was then reacted with TBAF in THF at 50 ^{o}C to provide **87** in 84% yield for 2 steps (Scheme 27).
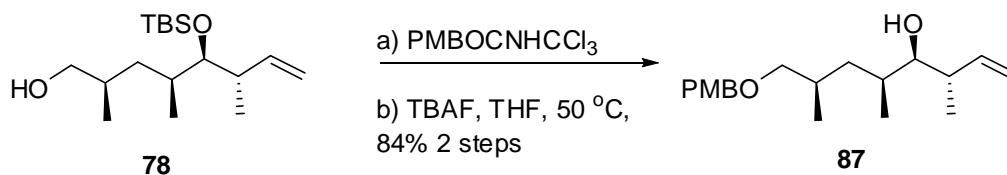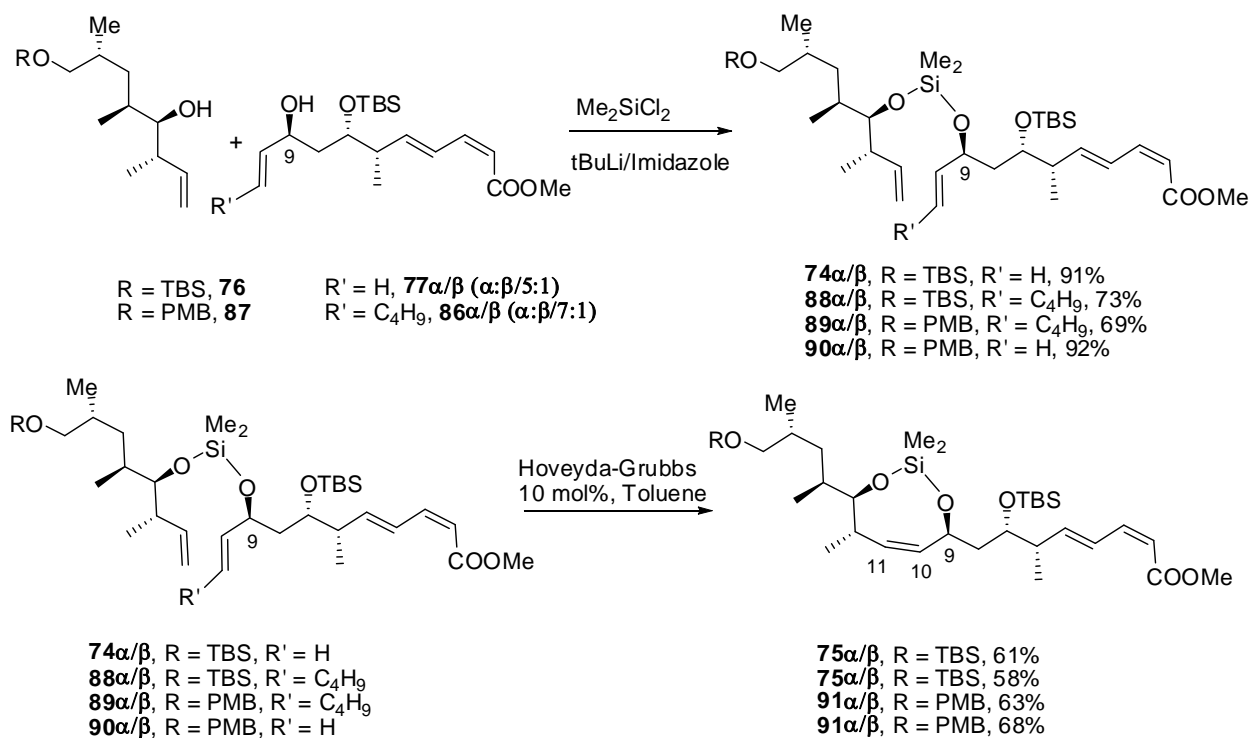

Scheme 27. Synthesis of middle fragment 87

The availability of new fragments **86α/β** and **87** with previous fragments **76** and **77α/β**, allowed us to investigate the RCM reaction of all possible dimethylsilaketals obtained by coupling the fragments (Scheme 28). The coupling reaction of bottom fragment **86α/β** (internal allylic alcohol) with middle fragment **76** (primary TBS ether) using dimethyldichlorosilane and *n*-BuLi/imidazole (see Entry 6, Table 18), provided silaketal **88α/β** in 73% yield (7:1 mixture of epimers **86α/β** at C9). The combination of bottom fragment **86α/β** (internal allylic alcohol) and middle fragment **87** (primary PMB ether) under the same coupling conditions provided silaketal **89α/β** in 69% yield along with 15% of recovered **86α/β**. The last coupling combination with **77α/β** (terminal allylic alcohol) and **87** (primary PMB ether) under the same conditions provided silaketal **90α/β** in 92% yield. The ratio of C9 epimers **89α/β** and **90α/β** was not measured because PMB ether proton resonance overlapped with C9 proton resonance from the minor β-isomer in the ^{1}H NMR spectrum. However, we presume that it is similar to the ratio from the respective bottom fragment.

RCM reaction of silaketal **88α/β** with 10 mol% of Hoveyda-Grubbs catalyst in refluxing toluene (see Entry 7, Table 19) provided **75α/β** in 58% yield after 2 purifications by silica gel

flash chromatography (no recovered **88α/β** was isolated). Reaction of silaketal **89α/β** under the same conditions provided **91α/β** in 63% yield along with 10% of recovered **89α/β**. Finally, RCM reaction of silaketal **90α/β** and Hoveyda-Grubbs catalyst under previous conditions provided **91α/β** in 68% yield along with 15% of recovered **90α/β**. The results showed that the RCM, as well as, the silaketal formation reactions were higher yielding with middle fragment **87**. In turn, bottom fragment **86α/β** was produced in a better 7:1 ratio of epimers at C9 compared to bottom fragment **77α/β** that was obtained in a 5:1 ratio of epimers. The good results from the optimization experiments for a better synthetic route to C9 stereocenter and C10-C11 *Z*-alkene led us to scale up the synthesis of bottom fragment **86α/β** and middle fragment **87** for an approach using the silaketal formation/RCM reaction sequence for a multi-gram synthesis of 6-*epi*-dictyostatin **36**.

Scheme 28. Synthesis and RCM reaction of silaketals

4.2.3   Application of fifth generation fragment coupling for final steps in the synthesis of 6-*epi*-dictyostatin.

Because of the success in the small-scale bottom fragment and middle fragment coupling reactions (silaketal reaction/RCM reaction), we followed up with a scale-up reductive addition reaction of 1-hexyne and bottom fragment **41** and obtained 3 g of **86α/β** in 73% yield and 8:1 ratio of diastereomers (Scheme 29). Similarly, we obtained 3 g of middle fragment **87** (This experiment was done by Mr. Jung). The coupling of 2.5 g of bottom fragment **86α/β** and 2.2 g of middle fragment **87** with dimethyldichlorosilane provided 3 g of **89α/β** in 65% yield. The RCM reaction of 1 g of **89α/β** using 10 mol% of Hoveyda-Grubbs catalyst in refluxing toluene provided 552 mg of **91α/β** in 62% yield along with 150 mg of recovered **89α/β**.

We next investigated the selective removal of the dimethylsilicon group. At the same time, we expected to remove the diastereomeric impurity in **91α/β**. Small-scale reaction of **91α/β** with $Cl_2CHCOOH$ in $MeOH/CH_2Cl_2$ produced diol **92** in 69% yield as a 8:1 ratio of **92α:92β** (epimers at C9) after silica gel flash chromatography. After scanning different combinations of TLC solvents, Hexanes/EtOAc 4:1 with 2% of MeOH showed separation of the epimers on TLC. Silica gel flash chromatography of **92α/92β** mixture eluting with hexanes/EtOAc 4:1 with 2% of MeOH provided **92α** in 54% overall yield as a single diastereomer (Scheme 29). We identified the isolated product as the desired mayor epimer (**92α**) by comparing the C9 proton resonance in the ^{1}H NMR spectrum with the C9 proton resonances from diastereomerically pure **52α** (Scheme 20) and **62α** (Table 17). We then protected diol **92α** in small-scale with TBSOTf to obtain **93α** in 78% yield. We then removed the PMB group with DDQ to obtain primary alcohol **94α** in 65% yield. Initial attempts to oxidize **94α** using Parikh-Doering conditions gave impure aldehyde **95α**. However, the reaction with Dess-Martin reagent produced **95α** in 86% yield after silica gel flash

chromatography. We next tried to scale-up the sequence of reactions up to aldehyde **95α**. However, the results were unsuccessful.
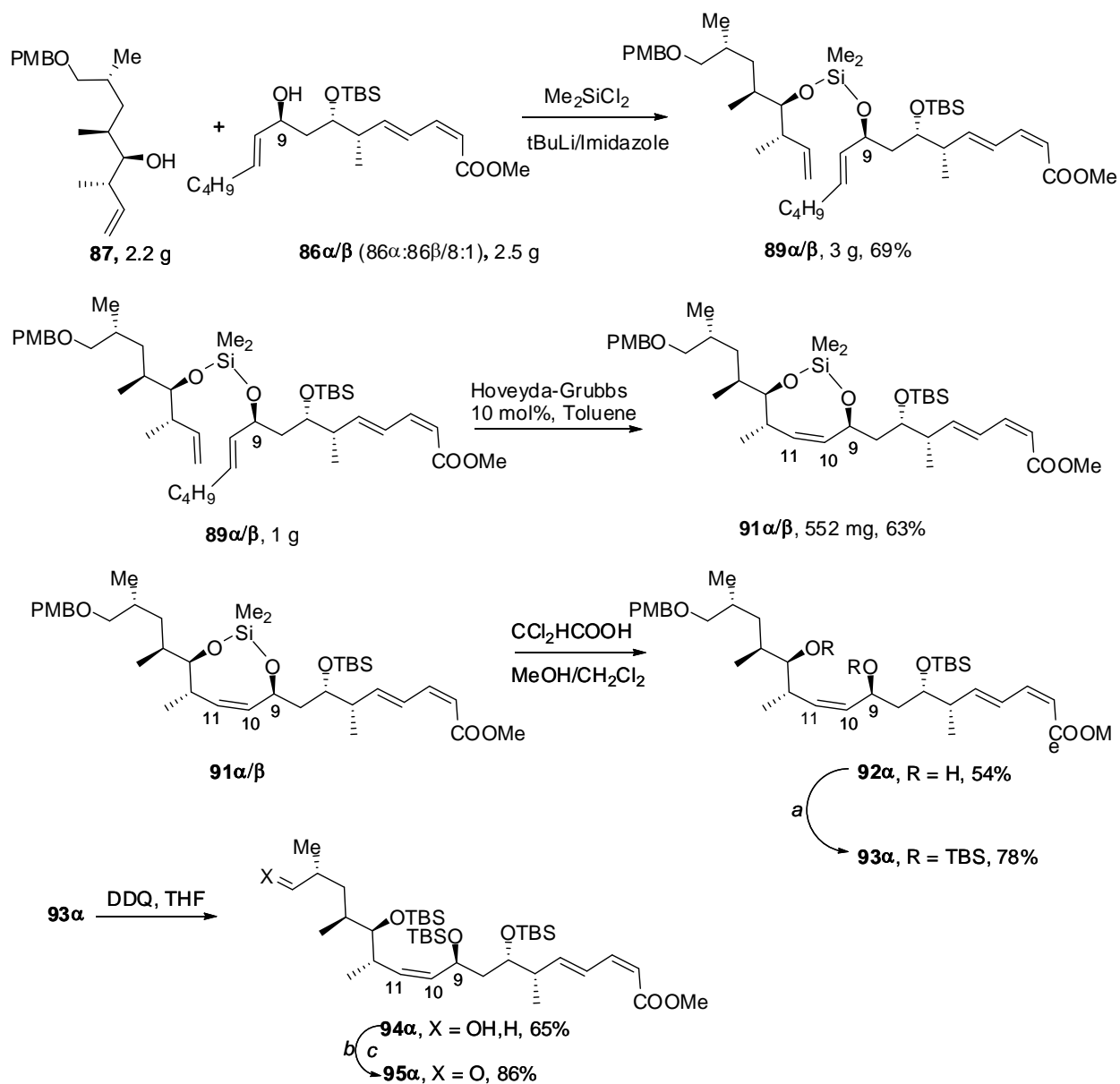
a) TBSOTf, 2,6-Lutidine, CH$_2$Cl$_2$, 78%; b) SO$_3$Py, DMSO, Et$_3$N, CH$_2$Cl$_2$; b) DMP, CH$_2$Cl$_2$.

Scheme 29. Synthesis of key intermediate 95α
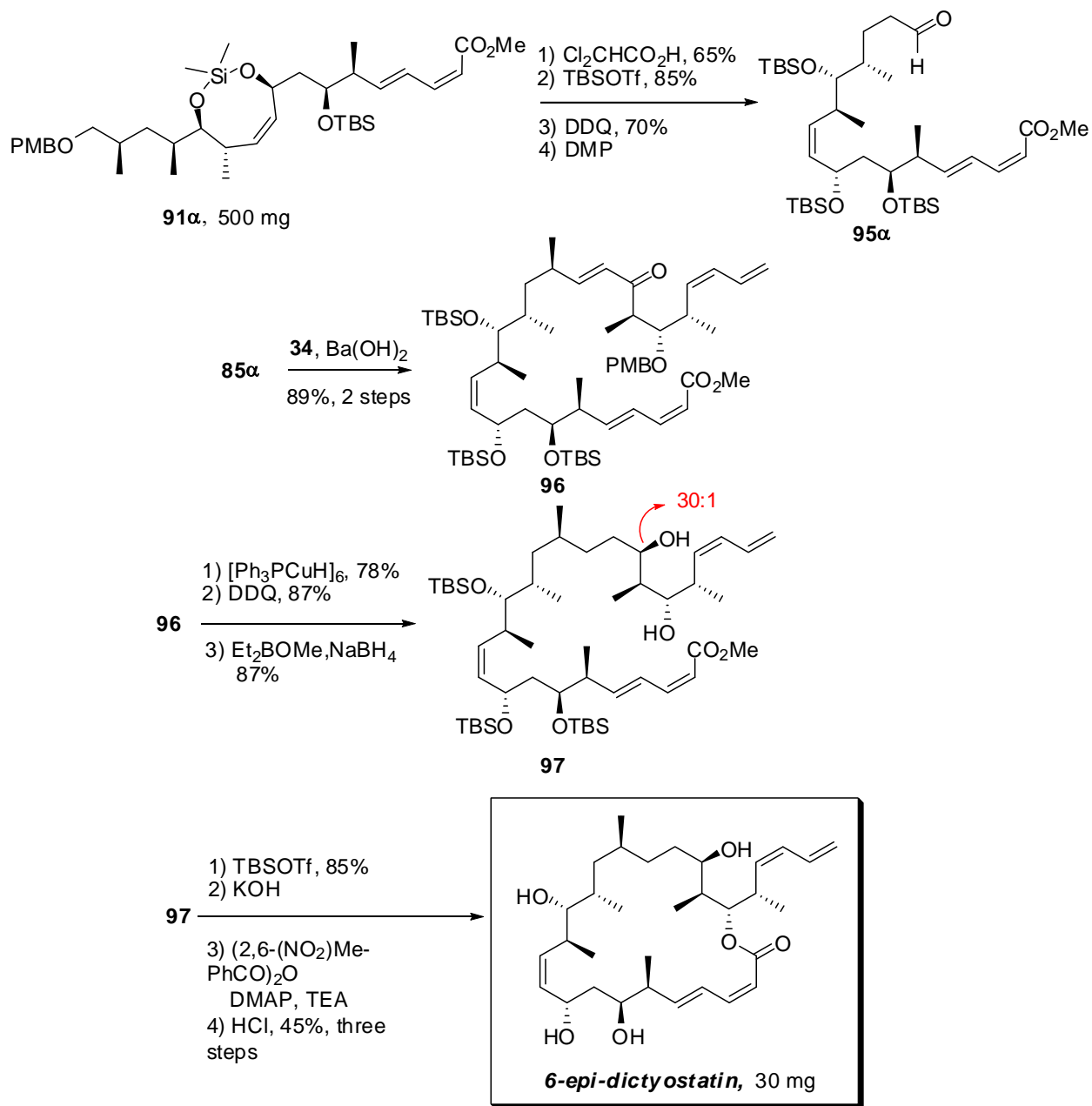
Scheme 30. Final steps for the synthesis of 6-*epi*-dictyostatin 36

Mr. Jung was provided with the remaining material of **89α/β** to attempt the scale-up synthesis of **95α**. Mr. Jung's results on the scale-up synthesis of **95α** and the remaining steps to obtain 6-*epi*-dictyostatin are summarized in Scheme 30. He obtained 208 mg of primary alcohol

94α and did Dess-Martin oxidation to provide crude aldehyde **95α**. The crude mixture was reacted with top fragment **34** in the presence of Ba(OH)$_2$ to provide advanced intermediate **96** in 89% yield for the 2 steps. Enone **96** was reduced with Stryker's reagent, followed by removal of PMB with DDQ and *syn*-selective reduction. Intermedaite **97** was obtained in 59% yield after 3 steps. Alcohol **97** was selectively protected as a TBS ether then the ester was transformed to the acid followed by macrolactonization under Yamaguchi's conditions. The final global deprotection Yielded 30 mg 6-*epi*-dictyostatin **36** in 45% yield for the last 3 steps.

4.3   CONCLUSIONS

Effective construction of C9 chiral center and *Z*-alkene at C10-C11 using the 3 steps procedure of alkynilation, Noyori reduction, and selective reduction was unsuccessful due to the reactivity of dienyl ester moiety in bottom fragment **41** to selective reduction catalysts.

The design of a *Z*-vinyl lithium addition reaction to aldehyde **41** for coupling of fragments proved to work in small scale. However, scale-up results showed that yields were not very reproducible. As a consequence, the route was not suitable for the synthesis of 6-*epi*-dictyostatin **36** in big-scale.

NHK reaction of middle fragment **42** and aldehyde **41** promoted by chiral sulfonamides (**60, 62, 63**) proved to provide coupling product **64** in good yield but moderate diastereoselectivity. However, the inherited toxicity of the reagents (especially if used in large scale) together with the poor results obtained with the catalytic NHK reaction made this approach not suitable for our goals.

We designed a quicker and more efficient approach for the synthesis of top fragment **34**. We obtained fragment **34** in 11 steps from alcohol **54** derived from (*S*)-Roche ester in 9% overall yield.

The coupling of middle fragments (**76** and **87**) and bottom fragments (**77α/β** and **86α/β**) as a dimethylsilaketal and subsequent RCM reaction using Hoveyda-Grubbs catalyst in toluene was the best route to establish the desired C10-C11 *Z*-alkene. Substrates (**79α/β** and **80α/β**) with bulkier groups on silicon center led to moderate yields together with multiple impurities that made purification very hard during the RCM reaction.

The Wipf coupling of alkynes and aldehydes proved to work with high levels of *dr* (7:1 for small-scale and 8:1 for big-scale) for the synthesis of C9 stereocenter in bottom fragment **86α/β**. Moreover, formation of silaketals and RCM reaction when using bottom fragment **86α/β** gave intermediate **91α/β** in good yields.

Small-scale synthesis of aldehyde **95α** allowed us to remove **β**-isomer impurity. However, when it was scale-up from **91α**, the results were unsuccessful. Mr. Jung completed the scale-up and the final steps of the synthesis to obtain 30 mg of 6-*epi*-dictyostatin **36**.

4.4   EXPERIMENTAL

All reactions were performed under an atmosphere of argon unless otherwise specified or the reaction solvent contained water. The reaction times reported are dictated by TLC analysis of the reaction mixture in comparison to the starting material. Reaction solvents were freshly dried either by distillation or passing through an activated alumina column. CH_2Cl_2 was distilled from CaH. Commercially available reagents were used a received from supplier. Reactions were

monitored using thin layer chromatography (TLC) using Kieselgel 60 F$_{254}$ silica gel plates. Flash chromatography was performed over silica gel 60, 230-400 mesh, with the designated solvents. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-300 or a Bruker DPX-500 spectrometer using residual solvent peaks as internal standard: CDCl$_3$ 7.23 ppm (^{1}H NMR) and 77.00 ppm (^{13}C NMR). Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane and proton-proton coupling constants (J) in Hz. Infrared spectra (IR) were recorded on a ATI Mattson genesis series FTIR spectrometer and are reported in reciprocal centimetres (cm^{-1}). Optical rotations were measured with Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature. HPLC analysis was performed on a Waters 600E system with UV detector. Low and high resolution mass spectra were obtained on a VG 70-G or Micromass Autospec double focusing instrument using EI, ESI, or CI.
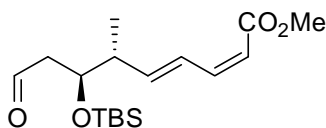
(2Z,4E,6R,7S)-Methyl 7-(*tert*-butyldimethylsilyloxy)-6-methyl-9-oxonona-2,4-dienoate (32):

To a solution of (2Z,4E,6R,7S)-methyl-7-(*tert*-butyldimethylsilyloxy)-9-hydroxy-6-methylnona-2,4-dienoate (5 g, 15.2 mmol) and Et$_3$N (3.07 g, 30.4 mmol) in CH$_2$Cl$_2$ (20 mL) and DMSO (20 mL) was added a solution of PySO$_3$ (3.60 g, 22.8 mmol) in DMSO (20 mL) at 0 ^{o}C under Ar atmosphere. The resulting mixture was stirred at 0 ^{o}C for 20 min and then quenched with aqueous HCl (0.1 M). The aqueous phase was extracted with CH$_2$Cl$_2$, and the combined organic phase was washed with brine and dried over MgSO$_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 10:1 to yield aldehyde **32** (4.51 g, 91%) as a colorless oil: [α]$_D$ −10.7 (c = 0.97, CHCl$_3$);

IR (thin film) 3421, 2953, 2857, 1760, 1719, 1412, 1190, 1167, 837 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 9.76 (t, J = 2.1 Hz, 1H), 7.37 (dd, J = 15.6, 11.4 Hz, 1H), 6.54 (t, J = 11.2 Hz, 1H), 6.06 (dd, J = 15.6, 7.2 Hz, 1H), 5.60 (d, J = 11.4 Hz, 1H), 4.15 (dt, J = 6.6, 5.1 Hz, 1H), 3.77 (s, 3H), 2.50 (m, 1H), 2.47 (d, J = 5.1 Hz, 2H), 1.05 (d, J = 6.6 Hz, 3H), 0.96 (s, 9H), 0.04 (s, 6H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 201.5, 166.8, 145.6, 144.9, 127.6, 116.3, 70.9, 51.1, 48.3, 43.8, 25.7, 18.0, 15.1, −4.5, −4.6 ppm.
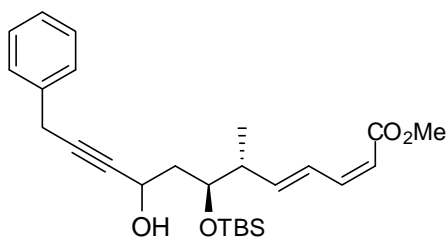
(2*Z*,4*E*,6*R*,7*S*)-Methyl-7-(*tert*-butyldimethylsilyloxy)-9-hydroxy-6-methyl-12-phenyldodeca-2,4-dien-10-ynoate (43):

To a solution of prop-2-ynylbenzene (72 mg, 0.62 mmol) in diethyl ether (3 mL) was added dropwise *n*-BuLi (387 μL, 1.6 M) at -78 °C under argon atmosphere. The resulting mixture was stirred for 1 h and a solution of aldehyde **32** (100 mg, 0.31 mmol) in diethyl ether (1 mL) was added. The resulting mixture was stirred at −78 °C for 3 h and then quenched at RT with sat. aqueous NH$_4$Cl. The aqueous phase was extracted with CH$_2$Cl$_2$, and the combined organic phase was washed with brine and dried over MgSO$_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 9:1 to yield alcohol **43** (110 mg, 80%) as a colorless oil. IR (thin film) 3399, 2954, 2857, 1721, 1424, 1165, 1101, 830, 751 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.39-7.22 (m, 6H), 6.54 (t, J = 11.3 Hz, 1H), 6.12 (dd, J = 15.0, 7.8 Hz, 1H), 5.56 (d, J = 11.3 Hz, 1H), 4.52-4.47 (m, 1H), 3.85 (t, J = 6.7 Hz, 1H), 3.68 (s, 3H), 3.60 (s, 2H), 2.56-2.51 (m, 1H), 1.84-1.71 (m, 2H),

1.09 (d, J = 6.7 Hz, 3H), 0.90 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ

166.9, 146.4, 145.5, 128.5, 127.9, 126.9, 126.7, 115.6, 83.7, 74.2, 61.3, 51.1, 42.5, 41.3, 25.8,

25.1, 18.1, 14.6, −4.2, −4.6 ppm.
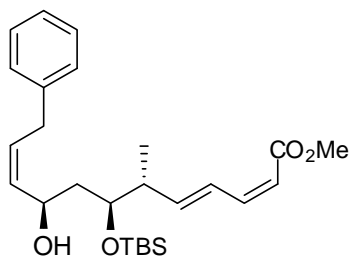
(2Z,4E,6R,7S,9R,10Z)-Methyl-7-(*tert*-butyldimethylsilyloxy)-9-hydroxy-6-methyl-12-

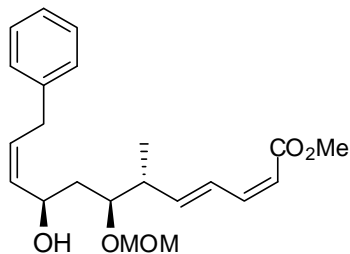**phenyldodeca-2,4,10-trienoate (44β):**

To a solution of (*Z*)-(2-iodovinyl)-benzene (107 mg, 0.47 mmol) in diethyl ether (3 mL)

was added dropwise *t*-BuLi (547 μL, 1.7M) at −78 °C and under argon atmosphere. The resulting

mixture was stirred for 1 h and a solution of aldehyde **32** (100 mg, 0.31 mmol) in diethyl ether (1

mL) was added. The resulting mixture was stirred at −78 °C for 3 h and then quenched at RT

with sat. aqueous NH$_4$Cl. The aqueous phase was extracted with diethyl ether, and the combined

organic phase was washed with brine and dried over MgSO$_4$. The solution was concentrated and

the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl

acetate 9:1 to provide a first less polar alcohol **44β** (55 mg, 39%) as a colorless oil: [α]$_D$ −2.5 (*c*

0.79, CHCl$_3$); IR (thin film) 3431, 3053, 2955, 2930, 2857, 2254, 1713, 1637, 1463, 1439, 1265,

1198, 1096, 909, 736 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.44 (dd, J = 15.0, 11.3 Hz, 1H), 7.29-

7.18 (m, 5H), 6.55 (t, J = 11.3 Hz, 1H), 5.98 (dd, J = 15.0, 7.8 Hz, 1H), 5.63-5.532 (m, 3H),

4.70-4.65 (m, 1H), 3.97 (dt, J = 7.2, 6.8 Hz, 1H), 3.65 (s, 3H), 3.44 (t, J = 8.9 Hz, 2H), 2.67-2.64

(m, 1H), 2.46 (s, 1H), 1.78-1.70 (m, 1H), 1.62-1.56 (m, 1H), 1.10 (d, J = 6.7 Hz, 3H), 0.93 (s,

9H), 0.14 (s, 3H), 0.09 (s, 3H); ^{13}C-NMR (125.8 MHz, CDCl$_3$) δ 166.7, 145.3, 144.9, 143.7, 139.0, 135.1, 128.5, 127.5, 126.3, 116.0, 79.5, 70.7, 51.0, 48.3, 43.2, 39.1, 25.7, 18.0, 15.1, −4.6, −4.7 ppm; HRMS (ESI) calcd for C$_{26}$H$_{40}$O$_4$Si =444.2696, found = 444.2683.
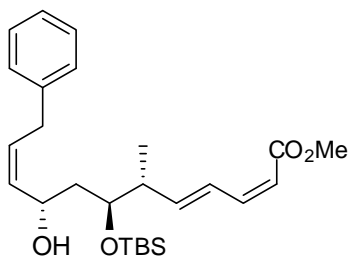

(2Z,4E,6R,7S,9S,10Z)-Methyl-7-(*tert*-butyldimethylsilyloxy)-9-hydroxy-6-methyl-12-phenyldodeca-2,4,10-trienoate (44α):

The crude product from **44** provided a second more polar alcohol **44α** (55 mg, 40%) as a colorless oil. [α]$_D$ −16.1 (*c* 0.71, CHCl$_3$); IR (thin film) 3421, 2953, 2857, 1719, 1412, 1190, 1167, 837 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.35 (dd, *J* = 15.0, 11.3 Hz, 1H), 7.29-7.18 (m, 5H), 6.57 (t, *J* = 11.3 Hz, 1H), 6.02 (dd, *J* = 15.0, 7.8 Hz, 1H), 5.63-5.53 (m, 3H), 4.80 (dt, *J* = 8.1, 6.8 Hz, 1H), 3.95 (dt, *J* = 7.2, 6.8 Hz, 1H), 3.73 (s, 3H), 3.45 (t, *J* = 8.9 Hz, 2H), 2.52-2.58 (m, 1H), 1.64-1.59 (m, 2H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.92 (s, 9H), 0.14 (s, 3H), 0.09 (s, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.8, 145.6, 144.9, 143.2, 139.0, 135.7, 128.5, 127.5, 126.3, 116.0, 78.1, 70.9, 51.0, 48.3, 43.8, 39.3, 25.7, 18.0, 15.1, −4.5, −4.6 ppm; HRMS (ESI) calcd for C$_{26}$H$_{40}$O$_4$Si =444.2696, found = 444.2687.
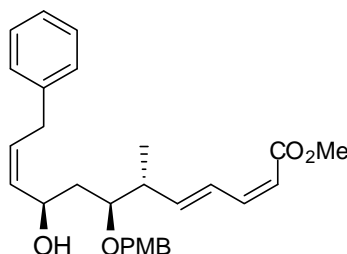
(2Z,4E,6R,7S,9R,10Z)-Methyl-9-hydroxy-7-(methoxymethoxy)-6-methyl-12-phenyldodeca-2,4,10-trienoate (47β):

Following the same procedure as **44β**, aldehyde **45** (100 mg, 0.39 mmol) provided first a less polar alcohol **47β** (39 mg, 26%) as a colorless oil. $[\alpha]_D$ −24.1 (*c* 0.69, CHCl$_3$); IR (thin film) 3311, 3052, 2986, 2959, 2872, 2253, 1720, 1610, 1511, 1439, 1265, 1175, 909, 734 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.37 (dd, *J* = 15.4, 11.3 Hz, 1H), 7.29-7.18 (m, 5H), 6.54 (t, *J* = 11.3 Hz, 1H), 6.02 (dd, *J* = 15.4, 7.7 Hz, 1H), 5.57-5.52 (m, 3H), 4.68 (dt, *J* = 8.2, 6.5 Hz, 1H), 4.64 (dd, *J* = 21.3, 6.8 Hz, 2H), 3.71 (s, 3H), 3.68-3.64 (m, 4H), 3.45 (t, *J* = 8.9 Hz, 2H), 3.36 (s, 3H), 2.63-2.60 (m, 1H), 1.79-1.72 (m, 1H), 1.65-1.60 (m, 1H), 1.09 (d, *J* = 6.8 Hz, 3H); ^{13}C-NMR (125.8 MHz, CDCl$_3$) δ 166.7, 145.6, 144.8, 143.2, 139.1, 135.6, 128.5, 127.5, 126.3, 116.2, 96.9, 79.1, 70.7, 55.7, 51.0, 48.3, 43.5, 39.3, 15.1 ppm; HRMS (ESI) calcd for C$_{25}$H$_{30}$O$_5$ = 374.2093, found = 374.2068.
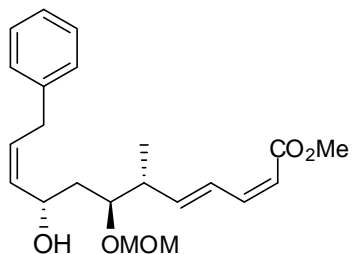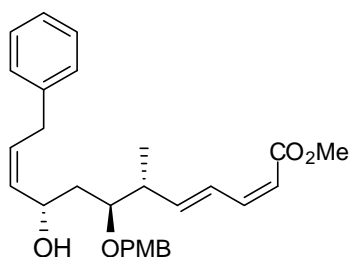
The crude product from **47** provided a second more polar alcohol **47α** (58 mg, 40%) as a colorless oil. $[\alpha]_D$ −19.3 (c 0.64, CHCl$_3$); IR (thin film) 3295, 3050, 2999, 2927, 2854, 1465, 1390, 1421, 1265 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.36 (dd, J = 15.4, 11.3 Hz, 1H), 7.29-7.18 (m, 5H), 6.54 (t, J = 11.3 Hz, 1H), 6.02 (dd, J = 15.4, 7.7 Hz, 1H), 5.59-5.53 (m, 3H), 4.72 (dt, J = 8.1, 6.8 Hz, 1H), 4.64 (dd, J = 21.3, 6.8 Hz, 2H), 3.71 (s, 3H), 3.68-3.64 (m, 4H), 3.45 (t, J = 8.9 Hz, 2H), 3.36 (s, 3H), 2.63-2.60 (m, 1H), 1.67-1.58 (m, 2H), 1.10 (d, J = 6.8 Hz, 3H); ^{13}C-NMR (125.8 MHz, CDCl$_3$) δ 166.9, 145.7, 144.9, 143.2, 139.1, 135.6, 128.5, 127.5, 126.3, 116.2, 96.9, 78.4, 70.3, 55.7, 51.0, 48.3, 43.8, 39.3, 15.1 ppm; HRMS (ESI) calcd for C$_{25}$H$_{30}$O$_5$ = 374.2093, found = 374.2045.

**(2Z,4E,6R,7S,9R,10Z)-Methyl-9-hydroxy-7-(4-methoxybenzyloxy)-6-methyl-12-phenyldodeca-2,4,10-trienoate (48β):**

Following the same procedure as **44β**, aldehyde **46** (100 mg, 0.30 mmol) provided first a less polar alcohol **48β** (31 mg, 23%) as a colorless oil. $[\alpha]_D$ −7.5 (c 0.6, CHCl$_3$); IR (thin film) 3345, 3053, 2986, 2953, 2249, 1712, 1638, 1602, 1439, 1265, 1177, 908 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.43 (dd, J = 15.1, 11.4 Hz, 1H), 7.15-1.05 (m, 7H), 6.81 (d, J = 6.7 Hz, 2H), 6.53 (t, J = 11.4 Hz, 1H), 6.11 (dt, J = 15.2, 7.2 Hz, 1H), 5.59-5.51 (m, 3H), 4.75-4.71 (m, 3H), 3.77-3.75 (m, 1H), 3.72 (s, 3H), 3.47 (t, J = 8.9 Hz, 2H), 3.41 (s, 3H), 2.55-2.47 (m, 1H), 1.81-1.76 (m, 1H), 1.70-1.66 (m, 1H), 1.04 (d, J = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.8,

145.3, 144.8, 143.5, 143.3, 139.0, 135.6, 129.5, 128.5, 127.5, 126.3, 116.0, 113.8, 78.9, 70.6, 55.6, 51.2, 49.6, 48.3, 43.8, 39.3, 25.7, 18.0, 15.1; HRMS (ESI) calcd for $C_{28}H_{34}O_5$ = 450.2406, found = 450.2423.


(2Z,4E,6R,7S,9S,10Z)-Methyl-9-hydroxy-7-(4-methoxybenzyloxy)-6-methyl-12-phenyldodeca-2,4,10-trienoate (48α):

The crude product from **48** provided a second more polar alcohol **48α** (54 mg, 40%) as a colorless oil. $[\alpha]_D$ +4.3 (*c* 0.9, CHCl$_3$); IR (thin film) 3321, 3053, 2985, 2959, 2928, 2253, 1717, 1456, 1265, 909, 735 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.44 (dd, *J* = 15.1, 11.4 Hz, 1H), 7.16-1.07 (m, 7H), 6.80 (d, *J* = 6.7 Hz, 2H), 6.53 (t, *J* = 11.4 Hz, 1H), 6.11 (dt, *J* = 15.2, 7.2 Hz, 1H), 5.59-5.51 (m, 3H), 4.82 (dt, *J* = 8.1, 6.8 Hz, 1H), 4.72 (d, *J* = 6.7 Hz, 1H), 3.77-3.75 (m, 1H), 3.72 (s, 3H), 3.47 (t, *J* = 8.9 Hz, 2H), 3.41 (s, 3H), 2.55-2.47 (m, 1H), 1.60-1.50 (m, 2H), 1.03 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.8, 145.6, 144.9, 143.7, 143.2, 139.0, 135.7, 129.5, 128.5, 127.5, 126.3, 116.0, 113.8, 77.8, 70.7, 55.6, 51.0, 49.6, 48.3, 43.8, 39.3, 25.7, 18.0, 15.1; HRMS (ESI) calcd for $C_{28}H_{34}O_5$ = 450.2406, found = 450.2379.
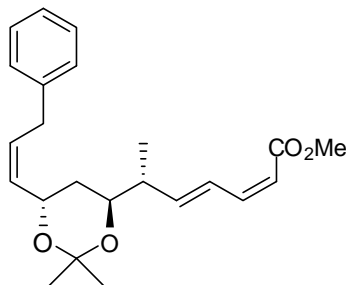
(*R*,2*Z*,4*E*)-Methyl-6-((4*S*,6*S*)-2,2-dimethyl-6-((*Z*)-3-phenylprop-1-enyl)-1,3-dioxan-4-yl)hepta-2,4-dienoate (49):

To a solution of vinyl alcohol **44α** (20 mg, 0.05 mmol) in THF (1 mL) was added TBAF (75 μL, 1M), and the resulting mixture was stirred for 1 h. The reaction was quenched with sat. aqueous NH$_4$Cl. The aqueous phase was extracted with diethyl ether, and the combined organic phase was washed with brine and dried over MgSO$_4$. The solution was concentrated and the crude mixture was dissolved in acetone (1 mL) and then was added Et$_3$N (10 mg, 0.1 mmol) and 2,2-dimethoxypropoane (26 mg, 0.25 mmol) at RT. The resulting mixture was stir for 30 min then the solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 5:1 to yield acetonide **49** (14 mg, 78% for 2 steps) as a colorless oil. [α]$_D$ −29.3 (*c* 0.52, CHCl$_3$); IR (thin film) 3053, 2986, 2955, 2872, 2254, 1739, 1648, 1607, 1438, 1377, 1265, 1232, 909, 735 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.40 (dd, *J* = 15.0, 11.3 Hz, 1H), 7.32-7.17 (m, 5H), 6.60 (t, *J* = 11.3 Hz, 1H), 6.11 (dd, *J* = 15.0, 7.8 Hz, 1H), 5.75-5.66 (m, 1H), 5.61 (d, *J* = 11.3 Hz, 1H), 5.56 (dd, 10.8, 8.1 Hz, 1H), 4.76 (dt, *J* = 8.5, 6.3 Hz, 1H), 3.77 (dt, *J* = 7.2, 6.8 Hz, 1H), 3.73 (s, 3H), 3.45 (t, *J* = 8.3 Hz, 2H), 2.43 (m, 1H), 1.79-1.1.72 (m, 2H), 1.41 (s, 3H), 1.26 (s, 3H), 1.09 (d, *J* = 6.7 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.8, 145.6, 144.9, 143.2, 139.0, 135.7, 128.5, 127.5, 126.3, 116.0, 100.3, 78.3, 69.1, 51.0, 48.3, 43.8, 39.3, 25.2, 24.9, 18.0, 15.1 ppm; HRMS (ESI) calcd for C$_{23}$H$_{30}$O$_4$ = 370.2144, found = 370.2119.
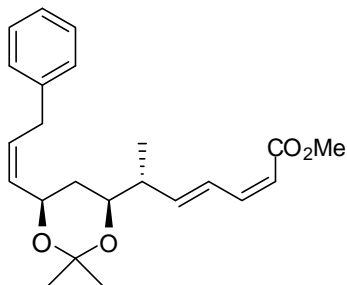
(*R*,2*Z*,4*E*)-Methyl-6-((4*S*,6*R*)-2,2-dimethyl-6-((*Z*)-3-phenylprop-1-enyl)-1,3-dioxan-4-yl)hepta-2,4-dienoate (50):

Following the same procedure for acetonide **49**, alcohol **44β** (20 mg, provided acetonide **50** (13 mg, 75% for 2 steps) as a colorless oil. $[\alpha]_D$ −11.8 (*c* 0.94, CHCl$_3$); IR (thin film) 3052, 2986, 2959, 2872, 2254, 1720, 1610, 1511, 1439, 1265, 1175, 909, 734 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.39 (dd, *J* = 15.0, 11.3 Hz, 1H), 7.30-7.18 (m, 5H), 6.60 (t, *J* = 11.3 Hz, 1H), 6.13 (dd, *J* = 15.0, 7.8 Hz, 1H), 5.74-5.68 (m, 1H), 5.62 (d, *J* = 11.3 Hz, 1H), 5.53 (dd, 10.8, 8.1 Hz, 1H), 4.70 (dt, *J* = 8.5, 6.3 Hz, 1H), 3.82 (dt, *J* = 7.2, 6.8 Hz, 1H), 3.74 (s, 3H), 3.47 (t, *J* = 8.3 Hz, 2H), 2.41 (m, 1H), 1.64-1.59 (m, 2H), 1.43 (s, 3H), 1.26 (s, 3H), 1.09 (d, *J* = 6.7 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.8, 145.4, 144.5, 143.3, 139.2, 135.9, 128.5, 127.5, 126.3, 116.0, 98.3, 79.1, 69.7, 51.0, 48.3, 43.8, 39.3, 31.5, 20.1, 18.0, 15.1 ppm; HRMS (ESI) calcd for C$_{23}$H$_{30}$O$_4$ = 370.2144, found = 370.2164.
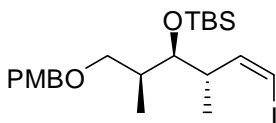
***tert*-Butyl((2*S*,3*S*,4*S*,*Z*)-6-iodo-1-(4-methoxybenzyloxy)-2,4-dimethylhex-5-en-3-yloxy)dimethylsilane (31):**

To a suspension of IPh$_3$PCH$_3$ (3.49 g, 8.65 mmol) in THF (15 mL) was added *n*-BuLi (5.15 mL, 1,6 M). The resulting mixture was transferred via cannula to a solution of I$_2$ (2.09 g,

8.24 mmol) in THF (5 mL) at −78 °C. The resulting brown suspension was stirred for ½ hour, and then NaHMDS (7.07 mL, 1M) was added dropwise at −78 °C. The red suspension was stirred for 15 min at −20 °C and then cooled back to −78 °C, followed by addition of a solution of aldehyde **51** (1.68 g, 4.42 mmol) in THF (5 mL). The resulting mixture was stirred at −78°C for 30 min and at −20 °C for 1 h. The reaction was quenched with sat. aqueous NH_4Cl, and the aqueous phase was extracted with diethyl ether, and the combined organic phase was washed with brine and dried over $MgSO_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 4:1 to yield vinyl iodide **31** (1.8 g, 81%) as a colorless oil. $[α]_D$ +18.4 (*c* 0.35, $CHCl_3$); IR (thin film) 2955, 2929, 2855, 1513, 1249, 1039, 837, 773 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.90 (dd, *J* = 8.8, 7.3 Hz, 1H), 5.13 (d, *J* = 7.3 Hz, 1H), 4.61 (s, 2H), 3.81 (s, 3H), 3.74 (t, *J* = 3.8 Hz, 2H), 3.40 (dd, *J* = 9.0, 5.8 Hz, 1H), 3.21 (dd, *J* = 9.0, 7.1 Hz, 1H), 2.71-2.67 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 159.2, 144.0, 130.9, 129.3, 113.8, 81.8, 76.0, 72.7, 55.3, 43.8, 38.9, 26.3, 18.5, 17.7, 13.4, −3.5, −3.7 ppm; HRMS (EI) calcd for $C_{22}H_{37}IO_3Si$ = 504.1557, found = 504.1563.
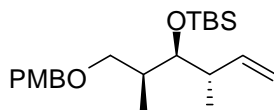
tert-Butyl((2S,3S,4S)-1-(4-methoxybenzyloxy)-2,4-dimethylhex-5-en-3-yloxy)dimethylsilane (53):

To a solution (Z)-vinyl iodide **31** (200 mg, 0.40 mmol) in diethyl ether (3 mL) was added dropwise *t*-BuLi (470 μL, 1.7M) at −78 °C and under argon atmosphere. The resulting mixture

was stirred for 1 h and a solution of aldehyde **32** (90 mg, 0.27 mmol) in diethyl ether (1 mL) was added. The resulting mixture was stirred at −78 °C for 3 h and then quenched at RT with sat. aqueous NH$_4$Cl. The aqueous phase was extracted with diethyl ether, and the combined organic phase was washed with brine and dried over MgSO$_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 9:1 to provide a first less polar olefin **53** (59 mg, 39%) as a colorless oil: [α]$_D$ −5.0 (*c* 0.20, CHCl$_3$); IR (thin film) 2957, 2929, 2856, 1513, 1249, 1039, 836 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.27 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.86 (ddd, *J* = 17.8, 10.2, 7.7 Hz, 1H), 4.97 (dd, *J* = 17.7, 10.2 Hz, 2H), 4.43 (d, *J* = 11.5 Hz, 1H), 4.38 (t, *J* = 11.2 Hz, 1H), 3.81 (s, 3H), 3.65 (dd, *J* = 4.6, 3.4 Hz, 1H), 3.37 (dd, *J* = 9.0, 6.6 Hz, 1H), 3.22 (dd, *J* = 6.8, 8.8 Hz, 1H), 2.37-2.33 (m 1H), 1.96-1.92 (m, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.91-0.89 (m, 12H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 159.1, 142.0, 130.9, 129.2, 114.1, 113.8, 76.0, 73.4, 72.5, 55.3, 42.9, 37.2, 26.2, 18.5, 17.4, 12.4, −3.5, −3.9 ppm; HRMS (ESI) calcd for C$_{22}$H$_{38}$O$_3$Si = 378.2590, found = 378.2587.
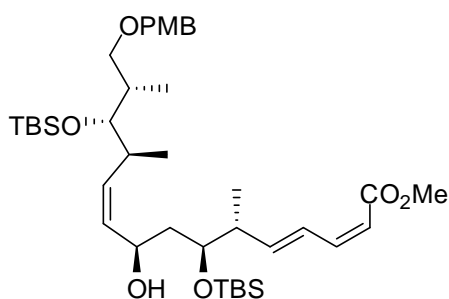
(2*Z*,4*E*,6*R*,7*S*,9*R*,10*Z*,12*S*,13*S*,14*S*)-Methyl-7,13-bis(*tert*-butyldimethylsilyloxy)-9-hydroxy-15-(4-methoxybenzyloxy)-6,12,14-trimethylpentadeca-2,4,10-trienoate (52β):

The crude product from **52** provided a second more polar alcohol **52β** (72 mg, 38%) as a colorless oil: [α]$_D$ −2.2 (*c* 0.39, CHCl$_3$); IR (thin film) 3367, 3053, 2991, 2959, 2929, 2872,

2253, 1710, 1626, 1453, 1265, 903, 735 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.38 (dd, J = 15.4, 11.3 Hz, 1H), 7.29 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 6.58 (t, J = 11.3 Hz, 1H), 6.05 (dd, J = 15.4, 8.0 Hz, 1H), 5.61 (d, J = 11.3 Hz, 1H), 5.33 (dd, J = 10.1, 9.3 Hz, 1H), 5.27 (t, J = 10.6 Hz, 1H), 4.45 (s, 2H), 4.44-4.41 (m, 1H), 3.83 (s, 3H), 3.80-3.76 (m, 1H), 3.75 (s, 3H), 3.67 (dd, J = 9.0, 7.1 Hz, 1H), 3.38 (dd, J = 7.5, 3 Hz, 1H), 3.21 (dd, J = 9, 6 Hz, 1H), 2.89 (ddq, J = 10, 7, 6.6 Hz, 1H), 2.53-2.49 (m, 1H), 2.11 (m, 1H), 1.70 (m, 1H), 1.646 (bs, 1H), 1.48 (m, 1H), 1.05 (d, J = 6.7 Hz, 3H), 0.91-0.86 (m, 24H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.7, 159.1, 147.1, 145.5, 135.6, 132.3, 130.3, 129.5, 127.0, 115.1, 113.8, 79.4, 73.5, 72.9, 72.2, 64.4, 55.2, 51.2, 42.2, 41.3, 37.2, 37.0, 26.2, 25.9, 18.4, 18.0, 16.4, 15.7, −3.6, −4.4 ppm; HRMS (ESI) calcd for C$_{39}$H$_{68}$O$_7$Si$_2$ = 704.4505, found = 704.4531.
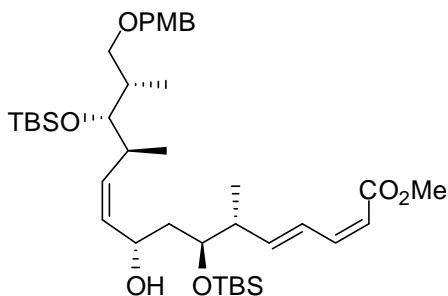
(2Z,4E,6R,7S,9S,10Z,12S,13S,14S)-Methyl-7,13-bis(*tert*-butyldimethylsilyloxy)-9-hydroxy-15-(4-methoxybenzyloxy)-6,12,14-trimethylpentadeca-2,4,10-trienoate (52α):

The crude product from **52** provided a third more polar alcohol **52α** (57 mg, 30%) as a colorless oil: [α]$_D$ +8.8 (*c* 0.45, CHCl$_3$); IR (thin film) 3367, 3051, 2991, 2879, 2872, 1720, 1610, 1512, 1439, 1265, 1175, 912, 734 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.38 (dd, J = 15.3, 11.2 Hz, 1H), 7.27 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 6.57 (t, J = 11.2 Hz, 1H), 6.04 (dd, J = 15.3, 7.6 Hz, 1H), 5.62 (d, J = 11.3 Hz, 1H), 5.38 (t, J = 11 Hz, 1H), 5.32 (dd, J = 11,

8.5 Hz, 2H), 4.66 (dt, J = 8.5, 6.0 Hz, 1H), 4.38 (d, J = 4.5 Hz, 2H), 3.96 (dt, J = 6, 5 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.48 (dd, J = 9.5, 5.5 Hz, 1H), 3.45 (t, J = 5.5 Hz, 1H), 3.24 (t, J = 8.5 Hz, 1H), 2.74 (m, 1H), 2.56 (m, 1H), 2.02-1.97 (m, 1H), 1.57 (t, J = 6 Hz, 2H), 1.08 (d, J = 6.5 Hz, 3H), 1.00 (d, J = 6.5 Hz, 3H), 0.98 (d, J = 6.5 Hz, 3H), 0.94 (s, 9H), 0.91 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.9, 159.1, 147.2, 145.6, 135.7, 131.3, 131.1, 129.1, 126.8, 115.7, 113.7, 77.9, 72.7, 72.6, 72.2, 64.4, 55.2, 51.1, 42.7, 40.1, 38.6, 35.6, 26.1, 26.0, 25.9, 25.4, 18.4, 18.0, 17.1, 14.8, 14.7, −3.9, −4.1, −4.5 ppm; HRMS (ESI) calcd for C$_{39}$H$_{68}$O$_7$Si$_2$ = 704.4505, found = 704.4519.
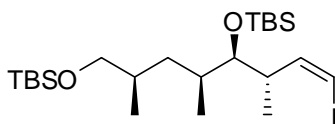
(5R,6S,8R)-5-((S,Z)-4-Iodobut-3-en-2-yl)-2,2,3,3,6,8,11,11,12,12-decamethyl-4,10-dioxa-3,11-disilatridecane (42):

Following the same procedure for vinyl iodide **31**, (2R,3R,4S,6R)-3,7-bis(*tert*-butyldimethylsilyloxy)-2,4,6-trimethylheptanal (1.84 g, 4.42 mmol) provided vinyl iodide **42** (1.65 g, 69%) as a colorless oil. [α]$_D$ +18.4 (*c* 0.35, CHCl$_3$); IR (thin film) 2955, 2929, 2855, 1513, 1249, 1039, 837, 773 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 6.24 (dd, J = 8.7, 7.2 Hz, 1H), 6.07 (d, J = 7.2 Hz, 1H), 3.49-3.43 (m, 2H), 3.20 (dd, J = 9.9, 7.5 Hz, 1H), 2.65 (ddq, J = 9.9, 6.8, 6.6 Hz, 1H), 1.63-1.57 (m, 3H), 1.39-1.31 (m, 1H) 0.92 (d, J = 6.6 Hz, 3H), 0.93-0.89 (m, 24H), 0.06 (s, 3H), 0.05 (s, 3H), 0.01 (s, 6H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 144.2, 80.9, 78.8, 68.1, 43.2, 37.5, 35.7, 33.4, 25.9, 18.2, 17.8, 16.0, −3.8, −4.0, −5.5 ppm; HRMS (EI) calcd for C$_{23}$H$_{49}$IO$_2$Si$_2$ = 540.2317, found = 540.2304.
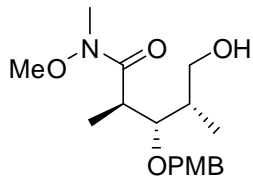
(2*R*,3*S*,4*S*)-5-Hydroxy-N-methoxy-3-(4-methoxybenzyloxy)-N,2,4-trimethylpentanamide (57):

To a solution of TBS ether **55** (2 g, 4.55 mmol) in DMF (10 mL) under argon atmosphere, was added portion wise solid TBAF·3H$_2$O (2.54 g, 9.10 mmol) and the resulting solution was stirred for 8 h. The reaction mixture was quenched by addition of aqueous solution of HCl 1N. The aqueous phase was extracted with diethyl ether, and the combined organic phase was washed with brine and dried over MgSO$_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate to provide alcohol **57** (754 mg, 51%) as a colorless oil: IR (thin film) 3367, 3063, 2991, 2986, 2872, 1769, 1688, 1607, 1438, 1377, 1265, 1232, 909, 745 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.28 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.57 (d, *J* = 10.3 Hz, 1H), 4.51 (d, *J* = 10.3 Hz, 1H), 3.8 (s, 3H), 3.79-3.69 (m ,4H), 3.42 (dd, *J* = 9.6, 6.8 Hz, 1H), 3.21 (s, 3H), 2.85 (dq, *J* = 6.9, 5.7 Hz, 1H), 1.95-1.88 (m, 1H), 1.27 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 164.1, 159.1, 130.6, 129.6, 113.6, 79.0, 72.1, 66.1, 61.2, 55.4, 39.6, 29.7, 26.0, 16.1, 11.3 ppm; HRMS (ESI) calcd for C$_{17}$H$_{27}$NO$_5$ = 325.1889, found = 325.1870.
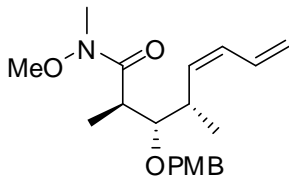
(2R,3S,4S,Z)-N-Methoxy-3-(4-methoxybenzyloxy)-N,2,4-trimethylocta-5,7-dienamide (58):

To a -78 °C solution of freshly distilled allyldiphenyl phospine (1.17 mL, 5.43 mmol) in THF (17 mL), was added *t*-BuLi (3.2 mL, 1.7M) and stirred for 5 min. The solution was warmed to 0 °C, stirred for 30 min and cooled to −78 °C. The solution was treated with Ti(i-PrO)$_4$ (1.6 mL, 5.43 mmol) and stirred for 30 min. A precooled solution of (2R,3S,4R)-N-methoxy-3-(4-methoxybenzyloxy)-N,2,4-trimethyl-5-oxopentanamide (879 mg, 2.72 mmol) in THF (10 mL) was added via cannula and stirred for 1 h, then warmed to 0 °C. Iodomethane (1.69 mL, 27.2 mmol) was added, and the solution was warmed to ambient temperature and stirred for 16 h. The solution was quenched with pH 7 buffer and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic phase was washed with brine and dried over MgSO$_4$ and the solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate to provide **58** (586 mg, 62%) as a 11:1 mixture of *Z:E* olefin isomers. To a solution of **58** (586 mg, 1.67 mmol) in THF (6 mL) at −78 °C was added phenyl triazole dione (87 mg, 0.5 mmol) and the resulting solution was stirred for 3 h. The reaction mixture was quenched with water and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic phase was washed with brine and dried over MgSO$_4$ and the solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate to provide **58** (504 mg, 86%) as a single olefin isomer: $[\alpha]_D^{20}$ +60.6° (*c* 11.2, CHCl$_3$); IR (thin film) 2962, 2937, 1657, 1612, 1514, 1462, 1250, 1061 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.31 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.50 (dt, *J* = 16.8, 10.6 Hz, 1H), 6.02 (t, *J* = 11.0

Hz, 1H), 5.62 (t, J = 10.7 Hz, 1H), 5.15 (d, J = 16.8 Hz, 1H), 5.06 (d, J = 10.2 Hz, 1H), 4.63 (d, J = 10.6 Hz, 1H), 4.59 (d, J = 10.6 Hz, 1H), 3.81 (s, 3H), 3.70-3.66 (m, 1H), 3.59 (s, 3H), 3.13 (s, 3H), 2.97-2.90 (m, 2H), 1.25 (d, J = 6.9 Hz, 3H), 1,14 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.7,159.5, 134.4, 132.9, 131.3, 129.9, 129.6 (2C), 117.4, 114.1 (2C), 84.8, 76.1, 61.2, 55.6, 40.9, 36.5, 32.4, 19.4, 15.1; HRMS (EI) calcd for C$_{20}$H$_{29}$NO$_4$ = 347.2097, found = 347.2099.
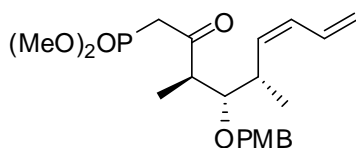
**Dimethyl-(3R,4S,5S,Z)-4-(4-methoxybenzyloxy)-3,5-dimethyl-2-oxonona-6,8-dienylphosphonate (34):**

To a solution of dimethoxy methylphosphonate (4.71 g, 38.0 mmol) in THF (24 mL) was added n-BuLi (21.6 mL, 1.6 M) at −78°C. The resulting solution was stirred for 1 h and a solution of Weinreb amide **58** (2.40 g, 6.91 mmol) in THF (12 mL) was added over 15 min. The resulting mixture was stirred at −78°C for 2 h. The mixture was quenched with sat. aqueous NH$_4$Cl solution and the aqueous phase was extracted with diethyl ether. The combined organic extracts were washed with brine and dried over MgSO$_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 1:1 to yield phosphonate **34** (1.65 g, 69%) as a colorless oil. $[\alpha]_D^{20}$ −1.7° (c 1.50, CHCl$_3$); IR (thin film) 2958, 2873, 1709, 1612, 1514, 1462, 1248, 1032, 810 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.29-7.24 (m, 2H), 6.89-6.84 (m, 2H), 6.50 (dt, J = 16.8, 11.0 Hz, 1H), 6.03 (t, J = 11.0 Hz, 1H), 5.51 (t, J = 10.4 Hz, 1H), 5.22 (d, J = 16.8 Hz, 1H), 5.13 (d, J = 10.1 Hz, 1H), 4.57 (d, J = 11.9 Hz, 1H), 4.52 (d, J = 11.9 Hz, 1H), 3.81 (s, 3H), 3.78 (d, J = 5.9 Hz, 3H), 3.74 (d, J = 5.9

Hz, 3H), 3.60-3.57 (m, 1H), 3.31 (dd, J = 22.0, 14.4 Hz, 1H), 3.04-2.91 (m, 2H), 2.86-2.75 (m, 1H), 1.21 (d, J = 7.0 Hz, 3H), 1,07 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ; 204.7 (d, J_{PC} = 6.3 Hz), 159.4, 133.7, 132.2, 130.6, 130.0, 129.5, 118.2, 113.8, 83.6, 74.3, 55.3, 53.1 (d, J_{PC} = 6.5 Hz), 52.9 (d, J_{PC} = 6.1 Hz), 50.7, 41.0 (d, J_{PC} = 129.3 Hz), 36.0, 19.0, 12.7; HRMS (EI) calcd for C$_{21}$H$_{31}$O$_6$P = 410.1858, found 410.1857.
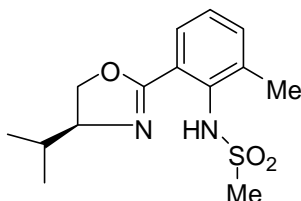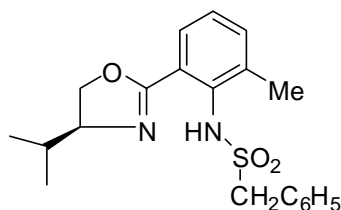

(S)-N-(2-(4-isopropyl-4,5-dihydrooxazol-2-yl)-6-methylphenyl)methanesulfonamide (60):

To a solution of aniline **61** (5 g, 21.2 mmol) in pyridine (100 mL) was added DMAP (145 mg) and mesityl chloride (11.42 mL, 146 mmol) at 0 °C. The resulting mixture was stirred for 1 h and then overnight at RT. The reaction mixture was evaporated and the residue dissolved in EtOAc (150 mL) and sat. aqueous NH$_4$Cl (60 mL). The organic phase was washed with brine and dried over MgSO$_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with 2% MeOH/CH$_2$Cl$_2$ to yield sulfonamide **60** (3.15 g, 58%) as a pale yellow solid. [α]$_D$ −5.8 (*c* 1.00, MeOH); ^{1}H-NMR (300 MHz, CDCl$_3$) δ 10.49 (br s, 1H), 7.40 (d, J = 7.5 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.20 (dd, J = 7.5, 7.5 Hz, 1H), 4.47-4.40 (m, 1H), 4.12-4.06 (m, 2H), 2.82 (s, 3H), 2.55 (s, 3H), 1.84-1.74 (m 1H), 1.09 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 164.3, 137.4, 136.3, 135.2, 127.2, 125.8, 120.5, 72.9, 69.7, 38.6, 33.2, 19.9, 19.1, 18.5 ppm; HRMS (ESI) calcd for C$_{14}$H$_{20}$N$_2$O$_3$S = 296.1194, found = 296.1170.
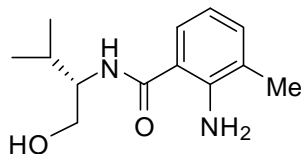
(*S*)-2-Amino-N-(1-hydroxy-3-methylbutan-2-yl)-3-methylbenzamide (61):

To a solution of 3-methyl-2-nitrobenzoic acid (30.0 g, 166 mmol) in CH$_2$Cl$_2$ (300 mL) was added DMF (1.2 mL) and oxalyl chloride (24.0 mL, 275 mmol) at 0 $^{\circ}$C, and the suspension was sitrred for 5 h. The resulting clear mixture was stirred overnight at RT and then concentrated to give a crude yellow solid acid chloride. The crude mixture was dissolved in CH$_2$Cl$_2$ (250 mL) and treated with (L)-valinol (14.3 g, 138 mmol) at 0 $^{\circ}$C, followed by Et$_3$N (42 mL, 300 mol), and the resulting mixture was stirred for ½ hour. The reaction mixture was stirred at RT for 6 h and then diluted with CH$_2$Cl$_2$ (150 mL) and quenched with sat. aqueous NH$_4$Cl (150 mL). The combined organic phases were washed with brine and dried over MgSO$_4$. The resulting solution was concentrated to provide crude alcohol that was dissolved in a mixture of MeOH (160 mL) and THF (64 mL). The solution was treated with 10% Pd-C (500 mg) and after 3 operations of evacuation-hydrogen fill, the reaction mixture was stirred under H$_2$ (balloon) at RT for 2 days. The reaction mixture was filtered through Celite and the filtrate was concentrated and the crude product was purified by silica gel flash chromatography eluting with 2% MeOH/CH$_2$Cl$_2$ to yield aniline **61** (17.6 g, 45%) as a white solid: $[\alpha]_D$ −23.8 (*c* 1.00, MeOH); IR (thin film) 3494, 3090, 3024, 2996, 2959, 2929, 2872, 1710, 1626, 1453, 1265, 903, 775 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.43-7.37 (m, 3H), 6.08 (d, *J* = 8.5 Hz, 1H), 4.05 (ddt, *J* = 8.5, 5.0, 3.5 Hz, 1H), 3.75 (t, *J* = 3.5 Hz, 2H), 2.41 (s, 3H), 1.98 (dq, *J* = 6.5, 5.0 Hz, 1H), 1.59 (bs, 1H), 1.00 (t, *J* = 6.5 Hz, 6H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 165.2, 133.7, 131.4, 130.6, 125.5, 55.7, 46.4, 29.4, 19.3, 18.9, 17.7 ppm; HRMS (ESI) calcd for C$_{13}$H$_{20}$N$_2$O$_2$ = 236.1525, found = 236.1512.

(*S*)-N-(2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)-6-methylphenyl)-1-

phenylmethanesulfonamide (63):

Following the same procedure for sulfonamide **60**, aniline **61** (5 g, 21.2 mmol) and α-toluenesulfonyl chloride (25 g, 146 mmol) provided sulfonamide **63** (3.15 g, 40%) as a clear solid: $[\alpha]_D$ +14.0 (*c* 1.2, CHCl$_3$); ^{1}H-NMR (300 MHz, CDCl$_3$) δ 12.1 (br s, 1H), 7.62-7.15 (m, 8H), 4.49-4.34 (m, 2H), 4.26-4.21 (m, 1H), 4.12-4.08 (m, 1H), 3.86 (dd, *J* = 10.0, 8.5 Hz, 1H), 2.33 (s, 3H), 1.86-1.79 (m 1H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 163.0, 133.6, 132.0, 130.9, 130.0, 129.1, 128.8, 128.7, 117.3, 75.7, 67.9, 57.9, 33.8, 2.60, 20.8, 18.5 ppm; HRMS (ESI) calcd for C$_{14}$H$_{20}$N$_2$O$_3$S = 372.1508, found = 372.1542.
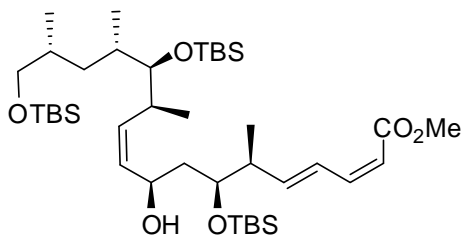
(2*E*,4*E*,6*S*,7*S*,9*R*,10*Z*,12*S*,13*R*,14*S*,16*R*)-Methyl-7,13,17-tris(*tert*-butyldimethylsilyloxy)-9-

hydroxy-6,12,14,16-tetramethylheptadeca-2,4,10-trienoate (64β):

In a glove box a round bottom flask (RBF) was weighted with CrCl$_2$ (151 mg, 1.24 mmol) and NiCl$_2$ (8 mg, 0.06mmol). The capped RBF was removed from the glove box and DMF (1 mL) was added and then stirred for 10 min. Vinyl iodide **42** (334 mg, 0.62 mmol) in DMF (1 mL) was added to the reaction mixture an stirred for 30 min at RT, then aldehyde **41**

(100 mg, 0.31 mmol) in DMF (1 mL) was added and the resulting mixture was stirred for 6 h at RT. The mixture was filtered through celite and washed with THF. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 6:1 to provide a first less polar alcohol **64β** (71 mg, 31%) as a colorless oil. $[\alpha]_D$ −17.2 (*c* 0.56, CHCl$_3$); IR (thin film) 3365, 3059, 2986, 2968, 2904, 2872, 2253, 1710, 1626, 1453, 1265, 903, 735 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.31 (dd, *J* = 15.3, 11.2 Hz, 1H), 6.50 (t, *J* = 11.2 Hz, 1H), 6.17 (dd, *J* = 15.3, 8.0 Hz, 1H), 5.51 (d, *J* = 11.2 Hz, 1H), 5.39-5.24 (m, 2H), 4.40-4.36 (m, 1H), 3.87-3.81 (m, 1H), 3.65 (s, 3H), 3.42 (dd, *J* = 9.0, 7.1 Hz, 1H), 3.34 (dd, *J* = 7.5, 3 Hz, 1H), 3.25 (dd, *J* = 9, 6 Hz, 1H), 2.65-2.54 (m, 2H), 1.65-1.59 (m, 2H), 1.54-1.45 (m, 2H), 1.39-1.32 (m, 2H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.89-0.86 (m, 12H), 0.85-0.83 (m, 17H), 0.75 (d, *J* = 6.8 Hz, 3H), 0.13 (s, 3H), 0.09 (s, 3H), -0.03 (s, 12H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.9, 147.2, 145.8, 133.9, 132.3, 127.0, 115.8, 79.7, 73.5, 68.9, 66.5, 52.3, 43.5, 42.7, 38.3, 35.7, 36.0, 33.5, 26.8, 26.6, 26.5, 25.9, 20.3, 18.3, 18.0, 16.2, 15.2, −2.1, −3.6, −3.9, -4.1, -4.4 ppm; HRMS (ESI) calcd for C$_{40}$H$_{80}$O$_6$Si$_3$ = 740.5263, found = 740.5279.
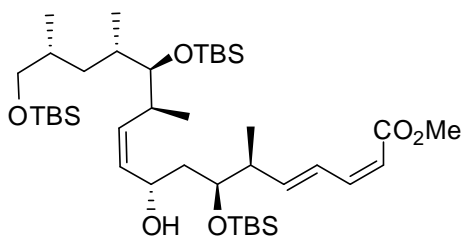
(2*E*,4*E*,6*S*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*R*)-Methyl-7,13,17-tris(*tert*-butyldimethylsilyloxy)-9-hydroxy-6,12,14,16-tetramethylheptadeca-2,4,10-trienoate (62α):

The crude product from **62** provided a second more polar alcohol **62α** (69 mg, 30%) as a colorless oil. $[\alpha]_D$ −11.1 (*c* 0.35, CHCl$_3$); IR (thin film) 3365, 3055, 2986, 2959, 2929, 2872,

1710, 1626, 1453, 1265, 903, 735 cm^{-1}; ^{1}H-NMR (500 MHz, CDCl$_3$) δ 7.35 (dd, J = 15.4, 11.3

Hz, 1H), 6.51 (t, J = 11.3 Hz, 1H), 6.12 (dd, J = 15.4, 8.0 Hz, 1H), 5.54 (d, J = 11.3 Hz, 1H),

5.46 (t, J = 10.5 Hz, 1H), 5.28 (dd, J = 10.5, 8.5 Hz, 1H), 4.57 (t, J = 8.5 Hz, 1H), 3.90-3.86 (m,

1H), 3.68 (s, 3H), 3.44 (dd, J = 9.0, 7.1 Hz, 1H), 3.31 (dd, J = 7.5, 3 Hz, 1H), 3.19 (dd, J = 9, 6

Hz, 1H), 2.62-2.59 (m, 2H), 2.08 (bs, 1H), 1.65-1.59 (m, 2H), 1.54-1.50 (m, 1H), 1.49-1.45 (m,

1H), 1.38-1.32 (m, 2H), 0.95 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.89-0.86 (m, 12H),

0.85-0.83 (m, 17H), 0.79 (d, J = 6.8 Hz, 3H), 0.11 (s, 3H), 0.08 (s, 3H), -0.04 (s, 12H); ^{13}C-

NMR (75 MHz, CDCl$_3$) δ 167.1, 147.3, 145.9, 133.9, 132.4, 126.9, 115.7, 80.2, 73.1, 68.6, 66.2,

52.1, 43.5, 42.7, 38.0, 35.9, 36.0, 33.8, 26.8, 26.6, 26.5, 25.9, 20.3, 18.9, 18.6, 16.2, 15.2, −2.9,

−3.5, −3.9, -4.1, -4.2 ppm; HRMS (ESI) calcd for C$_{40}$H$_{80}$O$_6$Si$_3$ = 740.5263, found = 740.5224.
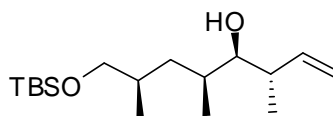
(3S,4R,5S,7R)-8-($tert$-Butyldimethylsilyloxy)-3,5,7-trimethyloct-1-en-4-ol (76):

To a solution of alcohol **78** (1.24 g, 4.13 mmol) in THF (5 mL) was added HCl 3N in

THF (5 mL). The resulting mixture was stirred for 3 h at RT and then quenched with sat.

aqueous NaHCO$_3$. The aqueous phase was extracted with diethyl ether, and the combined

organic phase was washed with brine and dried over MgSO$_4$. The solution was concentrated and

the crude mixture dissolved in CH$_2$Cl$_2$ (20 mL) and then reacted with TBSCl (747 mg, 4.96

mmol), imidazole (309 mg, 4.54 mmol) and DMAP (26 mg, 0.21 mmol). The resulting mixture

was stirred for 6 h at RT and then quenched with sat. aqueous NH$_4$Cl. The aqueous phase was

extracted with diethyl ether, and the combined organic phase was washed with brine and dried

over MgSO$_4$. The solution was concentrated and the crude product was purified by silica gel

flash chromatography eluting with hexanes/ethyl acetate 3:1 to yield alcohol **76** (930 mg, 75%) as a colorless oil. $[\alpha]_D$ +14.3 (*c* 1.3, CHCl$_3$); IR (thin film) 3325, 3015, 2993, 2968, 2872, 1769, 1648, 1623, 1438, 1395, 1265, 1232, 909, 735 cm^{-1}; ^{1}H-NMR (600 MHz, CDCl$_3$) δ 5.60 (ddd, *J* = 17.0, 10.2, 8.1 Hz, 1H) 4.95 (dd, *J* = 16.8, 10.2 Hz, 2H), 3.46 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.35 (dd, *J* = 9.9, 6.6 Hz, 1H), 3.09 (dd, *J* = 8.1, 6.3 Hz, 1H), 2.18 (m, 1H), 1.77 (m, 1H), 1.71 (m, 1H), 1.66 (m, 1H) 1.60-1.56 (m, 1H) 0.98 (s, 9H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 141.7, 116.1, 68.2, 42.0, 37.9, 32.8, 31.5, 25.9, 18.3, 17.7, 16.5, 13.2, −5.4 ppm; HRMS (ESI) calcd for C$_{17}$H$_{132}$O$_2$Si = 300.2485, found = 300.2464.
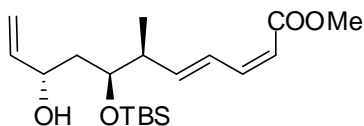
(2*Z*,4*E*,6*S*,7*S*,9*S*)-Methyl-7-(*tert*-butyldimethylsilyloxy)-9-hydroxy-6-methylundeca-2,4,10-trienoate (77α/β):

To a solution of aldehyde **41** (326 mg, 1 mmol) in THF (5 mL) was added vinylMgBr (1.5 mL, 1M in THF) at −78 °C. The resulting mixture was stirred for 4 h and for another 2 h at −30 °C. The mixture was quenched with sat. aqueous NH$_4$Cl and then the aqueous phase was extracted with diethyl ether, and the combined organic phase was washed with brine and dried over MgSO$_4$. The solution was concentrated and the crude product was dissolved in CH$_2$Cl$_2$ (5 mL) and reacted with Dess-Martin reagent (509 mg, 1.2 mmol) at RT. The resulting mixture was stirred for 2 h and then quenched with sat. aqueous Na$_2$S$_2$O$_3$. The aqueous phase was extracted with diethyl ether, and the combined organic phase was washed with brine and dried over MgSO$_4$. The solution was concentrated and the crude product was dissolved in toluene (5 mL)

and was added (*R*)-CBS (272 mg, 1 mmol) at RT. The resulting mixture was cooled to −78 °C and BH$_3$·SMe$_2$ (2 mL, 2 M) was added and then the mixture was stirred for 12 h and another 1 h at −30 °C. The resulting mixture was quenched at −78 °C with MeOH (200 μL) and then at RT was added sat. aqueous NaHCO$_3$. The aqueous phase was extracted with diethyl ether, and the combined organic phase was washed with brine and dried over MgSO$_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/diethyl ether 4:1 to yield alcohol **77α/β** (261 mg, 74% for 3 steps as a 5:1 mixture of **77α:77β**) as a pale yellow oil. IR (thin film) 3398, 3052, 2986, 2959, 2872, 1720, 1610, 1511, 1439, 1265, 1175, 909, 734 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.39 (dd, *J* = 15.3, 11.4 Hz, 1H), 6.57 (t, *J* = 11.3 Hz, 1H), 6.12 (dd, *J* = 15.3, 6.9 Hz, 1H), 5.86 (ddd, *J* = 17.1, 10.4, 8.1 Hz, 1H), 5.62 (dd, *J* = 11.4 Hz, 1H), 5.23 (d, *J* = 17.1 Hz, 1H), 5.07 (d, *J* = 10.4 Hz, 1H), 4.36 (dt, *J* = 8.1, 5.4 Hz, 1H), 3.85 (dt, *J* = 7.2, 5.4 Hz, 1H), 3.72 (s, 3H), 2.56 (m, 1H), 2.28 (d, *J* = 3.6 Hz, 1H), 1.57 (t, *J* = 5.4 Hz, 2H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 167.2, 147.6, 145.9, 142.3, 127.2, 116.0, 114.1, 73.5, 69.7, 51.4, 43.0, 40.8, 26.4, 26.3, 18.5, 15.5, −3.8, −4.0 ppm.
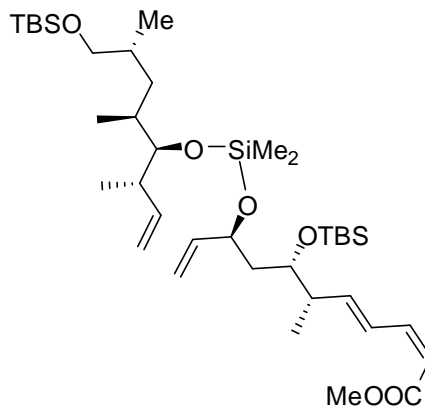
(6R,8S,9R,13S,15S,16S,17E,19Z)-Methyl-9-((S)-but-3-en-2-yl)-15-(tert-butyldimethylsilyloxy)-2,2,3,3,6,8,11,11,16-nonamethyl-13-vinyl-4,10,12-trioxa-3,11-disilahenicosa-17,19-dien-21-oate (74α/β):

To a solution of alcohol **76** (1.24 g, 4.13 mmol) in THF (40 mL) was added dropwise nBuLi (2.84 mL, 1.6 M) at −78 °C. The resulting mixture was stirred for 20 min and then was added dropwise dimethyldichlorosilane (2.49 mL, 20.65 mmol). The resulting mixture was warm up to RT and stirred for 2 h and then the solvent was removed under high vacuum until dryness for 4 h. A solution of **77α/β** (1.61 g, 4.54 mmol) in THF (10 mL) and imidazole (930 mg, 13.65 mmol) was added under argon atmosphere and the resulting solution was stirred for 16 h. The resulting mixture was quenched with sat. aqueous $NaHCO_3$. The aqueous phase was extracted with diethyl ether, and the combined organic phase was washed with brine and dried over $MgSO_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 9:1 to yield silaketal **74α/β** (2.67 g, 91%) as a colorless oil. $[\alpha]_D$ −12.9 (c 0.88, $CHCl_3$); IR (thin film) 3023, 2998, 2974, 2931, 2872, 1710, 1626, 1453, 1265, 9043, 735 cm^{-1}; ^{1}H-NMR (300 MHz, C_6D_6) δ 7.74 (dd, J = 15.3, 11.1 Hz, 1H), 6.28 (t, J = 11.1 Hz, 1H), 6.09-5.97 (m, 2H), 5.80 (ddd, J = 17.0, 10.2, 7.7 Hz, 1H), 5.56 (d, J = 11.1 Hz, 1H), 5.13-4.90 (m 4H), 4.38-4.36 (m, 1H), 3.88 (dt, J = 11.1 Hz, 1H), 3.50-3.47

(m, 2H), 3.37 (s, 3H), 3.14 (dd, J = 8.1, 6.3 Hz, 1H), 2.50 (m, 1H) 2.40 (m, 1H), 1.78-1.74 (m, 3H), 1.64-1.54 (m ,3H), 1.05-0.086 (m, 30H), 0.17-0.02 (m, 18H); ^{13}C-NMR (75 MHz, C$_6$D$_6$) δ 166.4, 147.6, 145.6, 142.4, 142.0, 127.3, 116.1, 114.6, 114.4, 80.8, 73.2, 72.2, 68.2, 62.3, 50.6, 44.8, 43.2, 42.7, 42.3, 38.6, 33.9, 33.6, 30.2, 29.6, 26.2, 26.1, 18.6, 17.9, 15.3, 14.0, −0.3, −0.7, −3.6, −4.4 ppm; HRMS (ESI) calcd for C$_{38}$H$_{74}$O$_6$Si$_3$ = 710.4793, found = 710.4786.
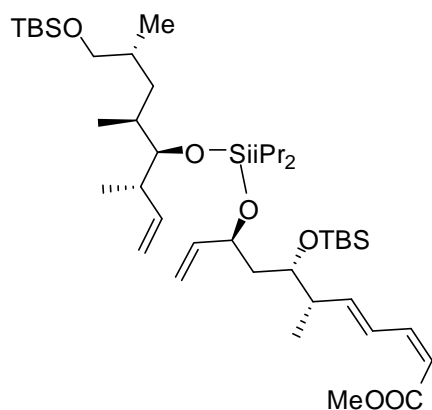
(6R,8S,9R,13S,15S,16S,17E,19Z)-Methyl-9-((S)-but-3-en-2-yl)-15-(*tert*-butyldimethylsilyloxy)-11,11-diisopropyl-2,2,3,3,6,8,16-heptamethyl-13-vinyl-4,10,12-trioxa-3,11-disilahenicosa-17,19-dien-21-oate (79α/β):

Following the same procedure for **74α/β**, alcohol **57** (124 mg, 0.41 mmol), diisopropyldichlorosilane (249 μL, 2.07 mmol) and alcohol **58** (161 mg, 0.45 mmol) provided silaketal **79α/β** (217 mg, 69%) as a colorless oil. [α]$_D$ −55.6 (*c* 0.31, CHCl$_3$); IR (thin film) 3050, 2981, 2959, 2929, 2843, 1710, 1620, 1453, 1265, 903, 735 cm^{-1}; ^{1}H-NMR (300 MHz, C$_6$D$_6$) δ 7.73 (dd, J = 15.3, 11.1 Hz, 1H), 6.27 (t, J = 11.1 Hz, 1H), 6.09-5.97 (m, 2H), 5.80 (ddd, J = 17.0, 10.2, 7.7 Hz, 1H), 5.56 (d, J = 11.1 Hz, 1H), 5.13-4.90 (m 4H), 4.38-4.36 (m, 1H), 3.88 (dt, J = 11.1 Hz, 1H), 3.50-3.47 (m, 2H), 3.37 (s, 3H), 3.14 (dd, J = 8.1, 6.3 Hz, 1H), 2.50 (m, 1H), 2.40 (m, 1H), 1.78-1.74 (m, 3H), 1.64-1.54 (m ,3H), 1.05-0.082 (m, 37H), 0.12-0.02 (m, 12H);

^{13}C-NMR (75 MHz, C$_6$D$_6$) δ 166.4, 147.6, 145.6, 142.4, 142.0, 127.3, 116.1, 114.6, 114.4, 80.8, 73.2, 72.2, 68.2, 62.3, 50.6, 44.8, 43.2, 42.7, 42.3, 38.6, 33.9, 33.6, 30.2, 29.6, 26.2, 26.1, 18.6, 17.9, 15.3, 14.0, −0.3, −0.7, −3.6, −4.4 ppm; HRMS (ESI) calcd for C$_{42}$H$_{82}$O$_6$Si$_3$ = 766.5419, found = 766.5402.
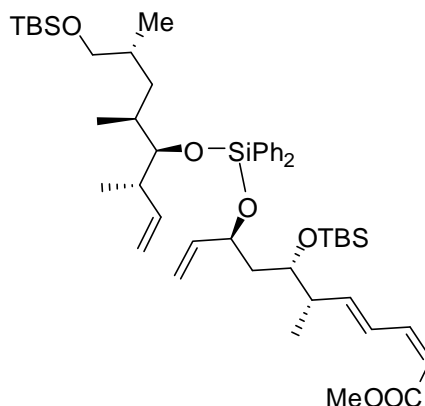
(6*R***,8***S***,9***R***,13***S***,15***S***,16***S***,17***E***,19***Z***)-Methyl-9-((***S***)-but-3-en-2-yl)-15-(***tert*-**

butyldimethylsilyloxy)-2,2,3,3,6,8,16-heptamethyl-11,11-diphenyl-13-vinyl-4,10,12-trioxa-

3,11-disilahenicosa-17,19-dien-21-oate (80α/β):

To a solution of bis(3-methoxyprop-1-ynyl)diphenylsilane (150 mg, 0.49 mmol) and alcohol **76** (60 mg, 0.20 mmol) in hexanes (1.5 mL) was added sodium hydride (60% dispersion in mineral oil, 1 mg, 0.02 mmol). The resulting mixture wad stirred for 10 min and then filtered through celite. The solution was concentrated and the crude product was purified on silica gel eluting with hexanes/diethyl ether 9:1 to yield silane (100 mg, 91%) as a colorless oil. To a solution of silane (100 mg, 0.18 mmol) and alcohol **77α/β** (64 mg, 0.18 mmol) in hexanes (1 mL) was added sodium hydride (60% dispersion in mineral oil, 1 mg, 0.02 mmol). The resulting mixture was stirred for 20 min and then filtered through celite. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with

hexanes/diethyl ether 9:1 to yield silaketal **80α/β** (123 mg, 82%) as a colorless oil. $[\alpha]_D$ −8.4 (*c* 0.31, CHCl$_3$); IR (thin film) 3053, 2986, 2959, 2929, 2872, 2253, 1710, 1626, 1453, 1265, 903, 735 cm^{-1}; ^{1}H-NMR (300 MHz, C$_6$D$_6$) δ 7.73 (dd, *J* = 15.3, 11.1 Hz, 1H), 7.65 (dd, *J* = 7.6, 1.5 Hz, 4H), 7.40-7.30 (m, 6H), 6.27 (t, *J* = 11.1 Hz, 1H), 6.09-5.97 (m, 2H), 5.80 (ddd, *J* = 17.0, 10.2, 7.7 Hz, 1H), 5.56 (d, *J* = 11.1 Hz, 1H), 5.13-4.90 (m 4H), 4.38-4.36 (m, 1H), 3.88 (dt, *J* = 11.1 Hz, 1H), 3.50-3.47 (m, 2H), 3.37 (s, 3H), 3.14 (dd, *J* = 8.1, 6.3 Hz, 1H), 2.50 (m, 1H), 2.40 (m, 1H), 1.78-1.74 (m, 3H), 1.64-1.54 (m ,3H), 1.05-0.082 (m, 30H), 0.12-0.02 (m, 12H); ^{13}C-NMR (75 MHz, C$_6$D$_6$) δ 166.4, 147.6, 145.6, 142.4, 142.0, 127.3, 116.1, 114.6, 114.4, 80.8, 73.2, 72.2, 68.2, 62.3, 50.6, 44.8, 43.2, 42.7, 42.3, 38.6, 33.9, 33.6, 30.2, 29.6, 26.2, 26.1, 18.6, 17.9, 15.3, 14.0, −0.3, −0.7, −3.6, −4.4 ppm; HRMS (ESI) calcd for C$_{48}$H$_{78}$O$_6$Si$_3$ = 834.5106, found = 834.5138.
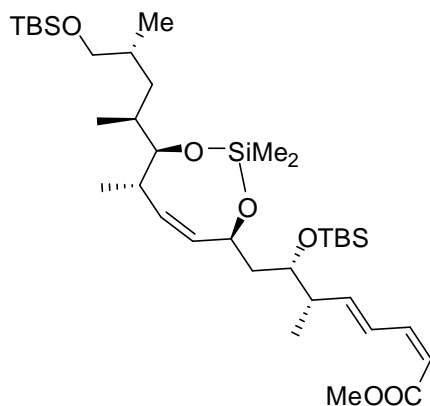
(2*Z*,4*E*,6*S*,7*S*)-Methyl-7-(*tert*-butyldimethylsilyloxy)-8-((4S,7S,8R,Z)-8-((2S,4R)-5-(tert-butyldimethylsilyloxy)-4-methylpentan-2-yl)-2,2,7-trimethyl-7,8-dihydro-4H-1,3,2-dioxasilocin-4-yl)-6-methylocta-2,4-dienoate (75α/β):

To a solution of silaketal **74α/β** (100 mg, 0.14 mmol) in toluene (13 mL, 0.01M) was added dropwise a solution of Hoveyda-Grubbs II (9 mg, 0.014 mmol) in toluene (1 mL) at 120

°C. The resulting mixture was stirred for 1 h at 120 °C and then the solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 15:1 to yield compound **75α/β** (68 mg, 61%) as a pale brown oil: [α]$_D$ −18.4 (*c* = 0.57, CHCl$_3$); ^{1}H-NMR (300 MHz, C$_6$D$_6$) δ 7.76 (dd, *J* = 15.3, 11.1 Hz, 1H), 6.26 (t, *J* = 11.1 Hz, 1H), 6.05 (dd, *J* = 15.4, 8.0 Hz, 1H), 5.61 (d, *J* = 11.3 Hz, 1H), 5.33 (t, *J* = 10.6 Hz, 1H), 5.27 (dd, *J* = 10.1, 9.3 Hz, 1H), 4.38-4.36 (m, 1H), 3.86 (dt, *J* = 11.1 Hz, 1H), 3.50-3.47 (m, 2H), 3.37 (s, 3H), 3.16 (dd, *J* = 8.1, 6.3 Hz, 1H), 2.57-2.52 (m, 1H), 2.46-2.40 (m, 1H), 1.78-1.78-1.74 (m, 3H), 1.64-1.54 (m, 3H), 1.05-0.086 (m, 30H), 0.17-0.02 (m, 18H); ^{13}C-NMR (75 MHz, C$_6$D$_6$) δ 166.4, 147.6, 145.6, 142.0, 127.3, 116.1, 114.4, 80.9, 73.4, 72.5, 68.2, 62.3, 50.7, 44.6, 43.1, 42.9, 42.8, 38.7, 33.9, 33.6, 30.2, 29.6, 26.2, 26.1, 18.6, 17.9, 15.3, 14.0, −0.3, −0.7, −3.6, −4.4 ppm.
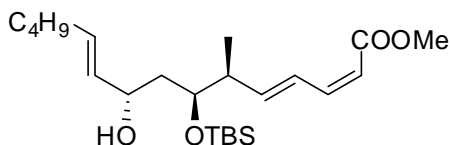
(2*Z*,4*E*,6*S*,7*S*,9*S*,10*E*)-Methyl-7-(*tert*-butyldimethylsilyloxy)-9-hydroxy-6-methylpentadeca-2,4,10-trienoate (86α/β):

To a suspension of zirconocene hydrochloride (500 mg, 1.93 mmol) in CH$_2$Cl$_2$ (4 mL) was added 1-hexyne (175 μL, 1.52 mmol) at RT and under argon atmosphere. The resulting mixture was stirred for 5 min and more 1-hexyne (80 μL, 0.7 mmol) was added. The resulting clear red solution was stirred for 10 min and then concentrated under high vacuum for ½ hour. To the resulting orange solid/oil was added toluene (4 mL) and then at −78 °C was added Me$_2$Zn (650 μL, 2M). The resulting mixture was stirred for 10 min and was added ligand **84** (50 mg, 0.19 mmol) and the mixture was allowed to warm up to −30 °C in 1 h. To the resulting mixture was added a solution of aldehyde **41** (421 mg, 1.29 mmol) in toluene (1 mL). The resulting

mixture was stirred for 12 h at −30 °C and then quenched with sat. aqueous NaHCO$_3$. The aqueous phase was extracted with EtOAc and the combined organic phase was washed with brine and dried over MgSO$_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/diethyl ether 8:1 to yield alcohol **86α/β** (460 mg, 87% as a 5:0.75 mixture of epimers **86α:86β**) as a pale yellow oil. [α]$_D$ −2.4 (c = 1.00, CHCl$_3$); IR (thin film) 3326, 2998, 2976, 1760, 1625, 1490, 1315, 1242, 1215, 1115, 752 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.34 (dd, J = 15.3, 11.4 Hz, 1H), 6.53 (t, J = 11.3 Hz, 1H), 6.09 (dd, J = 15.3, 6.9 Hz, 1H), 5.63-5.54 (m, 2H), 5.33 (dd, J = 15.3, 6.6 Hz, 1H), 5.27 (t, J = 10.6 Hz, 1H), 4.23 (dt, J = 8.1, 6.8 Hz, 1H), 3.85 (dt, J = 7.2, 6.8 Hz, 1H), 3.68 (s, 3H), 2.56 (m, 1H), 2.31 (bs, 1H), 1.99-1.95 (m, 2H), 1.54-1.43 (m, 2H), 1.29-1.27 (m, 4H), 1.03 (d, J = 6.6 Hz, 3H), 0.84 (s, 12H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.7, 147.0, 145.4, 133.0, 131.2, 126.6, 115.4, 73.3, 69.2, 50.9, 42.3, 40.4, 31.7, 31.2, 25.8, 26.7, 22.1, 18.0, 15.2, 13.8, −4.4, −4.6 ppm;; MS (ESI) m/z 353(100), 395(64), 410(12); HRMS (ESI) calcd for C$_{23}$H$_{42}$O$_4$Si = 410.2852, found = 410.2871.
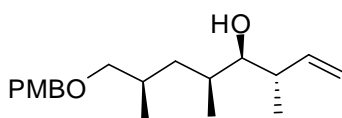
(3S,4R,5S,7R)-8-(4-Methoxybenzyloxy)-3,5,7-trimethyloct-1-en-4-ol (87):

To a solution of alcohol **78** (295 mg, 0.96 mmol) and 4-methoxybenzyl 2,2,2-trichloroacetimidate (413 mg, 1.45 mmol) in a mixture of CH$_2$Cl$_2$ (1 mL) and cyclohexane (2 mL) at 0 °C was added BF$_3$·Et$_2$O (6 µL). The resulting mixture was stirred for 2 h and for another 6 h at RT. The mixture was quenched with sat. aqueous NaHCO$_3$ and then the aqueous phase was extracted with CH$_2$Cl$_2$ and the combined organic phase was washed with brine and dried

over MgSO₄. The solution was concentrated and the crude product was purified on silica gel eluting with hexanes/diethyl ether 7:1 to yield PMB ether (355 mg, 88%) as a colorless oil. To a solution of PMB ether (355 mg, 0.85 mmol) in THF (1 mL) was added TBAF (2.55 mL, 1M). The resulting pale brown solution was heated to 50 °C and stirred at that temperature for 24 h. The mixture was quenched with sat. aqueous NH₄Cl and then the aqueous phase was extracted with CH₂Cl₂ and the combined organic phase was washed with brine and dried over MgSO₄. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/diethyl ether 3:1 to yield alcohol **87** (219 mg, 84%) as a colorless oil. $[\alpha]_D$ +28.8 (c = 1.6, CHCl₃); IR (thin film) 3310, 2954, 2857, 1721, 1424, 1165, 1101, 830, 751 cm⁻¹; ^{1}H-NMR (600 MHz, CDCl₃) δ 5.74 (ddd, J = 14.7, 10.5, 8.4 Hz, 1H), 5.13 (dd, J = 15.1, 10.5 Hz, 2H), 4.43 (s, 2H), 3.81 (s, 3H), 3.33 (dd, J = 9.0, 5.4 Hz, 1H), 3.24-3.18 (m, 2H), 2.27 (m, 1H), 1.92-1.84 (m, 1H), 1.80-1.73 (m, 1H), 1.59 (t, J = 5.4 Hz, 2H), 0.97 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H) 0.88 (d, J = 6.8 Hz, 3H); ^{13}C-NMR (75.5 MHz, CDCl₃) δ 159.7, 142.4, 131.4, 129.7, 116.4, 114.4, 76.8, 76.3, 73.3, 55.7, 42.5, 39.0, 32.5, 31.3, 18.8, 17.2, 14.1 ppm; HRMS (ESI) calcd for C₁₉H₃₀O₃ = 306.2195, found = 306.2192.
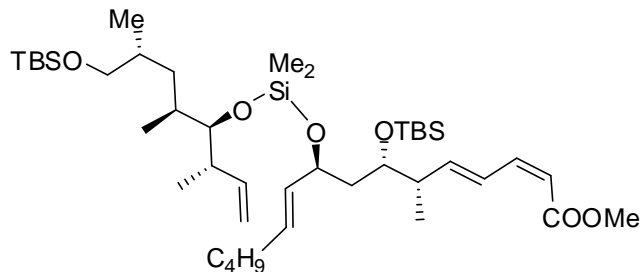
(6R,8S,9R,13S,15S,16S,17E,19Z)-Methyl-9-((S)-but-3-en-2-yl)-15-(*tert*-butyldimethylsilyloxy)-13-((E)-hex-1-enyl)-2,2,3,3,6,8,11,11,16-nonamethyl-4,10,12-trioxa-3,11-disilahenicosa-17,19-dien-21-oate (88α/β):

Following the same procedure for silaketal **84α**, alcohol **76** (124 mg, 0.41 mmol) and alcohol **77α/β** (186 mg, 0.45 mmol) provided **88α/β** (231 mg, 73%) as a colorless oil. $[\alpha]_D$ −23.2 (*c* 0.76, CHCl$_3$); IR (thin film) 3053, 2986, 2959, 2929, 2872, 1710, 1626, 1453, 1265, 903, 735 cm^{-1}; ^{1}H-NMR (300 MHz, C$_6$D$_6$) δ 7.74 (dd, *J* = 15.3, 11.1 Hz, 1H), 6.28 (t, *J* = 11.1 Hz, 1H), 6.09-5.97 (m, 2H), 5.80 (ddd, *J* = 17.0, 10.2, 7.7 Hz, 1H), 5.56 (d, *J* = 11.1 Hz, 1H), 5.13-4.90 (m 4H), 4.38-4.36 (m, 1H), 3.88 (dt, *J* = 11.1 Hz, 1H), 3.50-3.47 (m, 2H), 3.37 (s, 3H), 3.14 (dd, *J* = 8.1, 6.3 Hz, 1H), 2.50 (m, 1H), 2.40 (m, 1H), 1.78-1.74 (m, 3H), 1.64-1.54 (m ,3H), 1.05-0.086 (m, 30H), 0.17-0.02 (m, 18H); ^{13}C-NMR (125 MHz, CDCl$_3$) δ 166.9, 148.6, 145.8, 142.0, 133.3, 131.5, 126.1, 115.2, 114.1, 80.5, 72.6, 71.3, 67.9. 51.0, 42.9, 42.1, 41.7, 38.2, 33.5, 33.2, 31.8, 31.3, 29.7, 25.9, 22.3, 18.3, 17.8, 15.0, 13.9, 13.6, −4.2, −5.4 ppm; HRMS (ESI) calcd for C$_{42}$H$_{82}$O$_6$Si$_3$ = 766.5420, found = 766.5429.
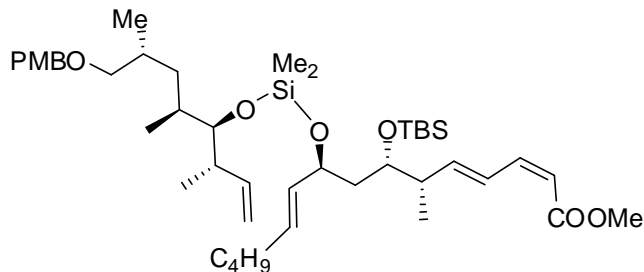
(4R,6S,7R,11S,13S,14S,15E,17Z)-Methyl-7-((S)-but-3-en-2-yl)-13-(*tert*-butyldimethylsilyloxy)-11-((E)-hex-1-enyl)-1-(4-methoxyphenyl)-4,6,9,9,14-pentamethyl-2,8,10-trioxa-9-silanonadeca-15,17-dien-19-oate (89α/β):

Following the same procedure for silaketal **74α/β**, alcohol **87** (126 mg, 0.41 mmol) and alcohol **77α/β** (186 mg, 0.45 mmol) provided silaketal **89α/β** (218 mg, 69%) as a colorless oil. [α]$_D$ −16.8 (*c* 0.88, CHCl$_3$); IR (thin film) 3053, 2986, 2959, 2929, 2872, 2253, 1710, 1626, 1453, 1265, 903, 735 cm^{-1}; ^{1}H-NMR (300 MHz, C$_6$D$_6$) δ 7.88 (dd, *J* = 15.0, 11.3 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.34 (t, *J* = 11.3 Hz, 1H), 6.18 (dd, *J* = 15.1, 6.6 Hz, 1H), 6.09 (ddd, *J* = 14.7, 10.5, 8.4 Hz, 1H), 5.62-5.59 (m ,2H) 5.11-5.09 (m, 3H), 4.49 (dt, *J* = 8.1, 6.8 Hz, 1H), 4.40 (d, *J* = 10.2 Hz, 2H), 4.15 (dt, *J* = 7.2, 6.8 Hz, 1H), 3.56 (dd, *J* = 8.5, 5.4 Hz, 1H), 3.39-3.37 (m, 4H), 3.32 (s, 3H), 3.23 (t, *J* = 7.2 Hz, 1H), 2.60 (m, 1H), 2.47 (m, 1H), 1.99-1.96 (m, 4H), 1.88-1.85 (m, 2H), 1.73-1.1.70 (m, 1H), 1.69-1.65 (m ,1H), 1.33-1.29 (m, 2H), 1.28-1.25 (m, 2H), 1.12 (d, *J* = 6.6 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 1.02 (s, 9H), 0.87 (t, *J* = 7.2 Hz, 3H) 0.41 (s, 3H), 0.29 (s, 3H), 0.17 (s, 3H), 0.12 (s, 3H); ^{13}C-NMR (75 MHz, C$_6$D$_6$) δ 166.7, 159.9, 148.3, 145.9, 142.8, 134.3, 132.0, 131.8, 129.6, 127.5, 116.3, 114.7, 114.3, 75.8, 73.6, 73.3, 72.1, 55.0, 50.9, 43.8, 42.9, 42.7, 39.4, 34.2, 32.5, 31.9, 31.8, 26.5, 22.9, 19.1, 18.2, 15.5, 14.4, 0.2, −0.3, −3.7 ppm.
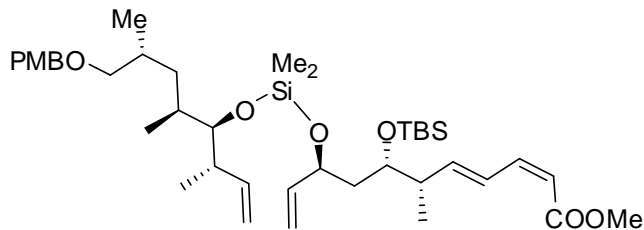
(4R,6S,7R,11S,13S,14S,15E,17Z)-Methyl-7-((S)-but-3-en-2-yl)-13-(*tert*-butyldimethylsilyloxy)-1-(4-methoxyphenyl)-4,6,9,9,14-pentamethyl-11-vinyl-2,8,10-trioxa-9-silanonadeca-15,17-dien-19-oate (90α/β):

Following the same procedure for silaketal **74α/β**; alcohol **87** (126 mg, 0.41 mmol) and alcohol **77α/β** (159 mg, 0.45 mmol) provided **90α/β** (270 mg, 92%) as a colorless oil: IR (thin film) 3021, 2991, 2879, 2872, 1720, 1610, 1512, 1439, 1265, 1175, 912, 734 cm^{-1}; ^{1}H-NMR (300 MHz, CDCl$_3$) δ 7.34 (dd, J = 15.6, 11.4 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.57 (t, J = 11.4 Hz, 1H), 6.14 (dd, J = 15.6, 6.9 Hz, 1H), 5.92-5.75 (m, 2H), 5.58 (d, J = 11.4 Hz, 1H) 5.16-4.95 (m ,4H), 4.42 (d, J = 4.8 Hz, 2H), 4.49 (dt, J = 7.8, 4.5 Hz, 1H), 3.83-3.79 (m, 4H), 3.72 (s, 3H), 3.39 (dd, J = 5.7, 4.5 Hz, 1H), 3.34 (t, J = 4.5 Hz, 1H), 3.14 (dd, J = 8.5, 7.5 Hz, 1H), 2.51 (m, 1H), 2.34 (m, 1H), 1.87-1.80 (m, 1H), 1.74-1.67 (m, 3H), 1.48-1.41 (m, 2H), 1.04 (d, J = 6.6 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 1.02 (s, 9H), 0.87 (d, J = 6.7 Hz, 3H) 0.1 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C-NMR (75 MHz, CDCl$_3$) δ 166.7, 159.0, 148.0, 145.6, 142.0, 141.6, 130.9, 129.0, 126.4, 115.4, 114.4, 114.1, 113.6, 80.2, 75.3, 72.6, 71.6, 55.1, 50.9, 42.7, 42.3, 41.8, 38.6, 33.4, 31.0, 25.9, 18.5, 18.1, 17.5, 14.8, 13.8, 1.0, −0.6, −1.0, −4.1 ppm.
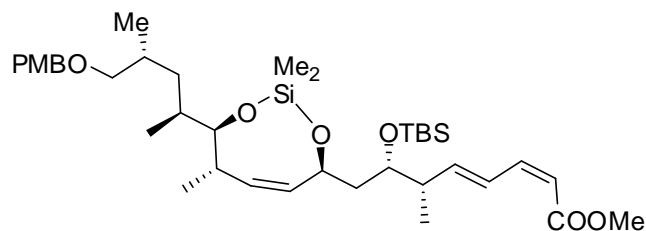
(2Z,4E,6S,7S)-Methyl-7-(*tert*-butyldimethylsilyloxy)-8-((4S,7S,8R,Z)-8-((2S,4R)-5-(4-methoxybenzyloxy)-4-methylpentan-2-yl)-2,2,7-trimethyl-7,8-dihydro-4H-1,3,2-dioxasilocin-4-yl)-6-methylocta-2,4-dienoate (91α/β):

Following the same procedure for **75α/β**. Silaketal **89α/β** (1 g, 1.30 mmol) provided **91α/β** (624 mg, 65%) as a pale brown oil: $[\alpha]_D$ −48.3 (*c* 0.08, CHCl₃); ¹H-NMR (600 MHz, C₆D₆) δ 7.88 (dd, *J* = 15.4, 11.3 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.35 (t, *J* = 11.4 Hz, 1H), 6.20 (dd, *J* = 15.3, 6.7 Hz, 1H), 5.59 (d, *J* = 11.4 Hz, 1H), 5.40 (t, *J* = 10.8 Hz, 1H), 5.23 (dd, *J* = 10.8, 8.4 Hz, 1H), 4.52 (t, *J* = 8.0 Hz, 1H), 4.41 (d, *J* = 6 Hz, 2H), 3.92-3.81 (m, 4H), 3.74 (s, 3H), 3.38-3.36 (m, 1H), 3.31 (dd, *J* = 9, 4.4 Hz, 1H), 3.17 (t, *J* = 8.4 Hz, 1H), 2.56-2.51 (m, 2H), 1.76-1.73 (m, 1H), 1.67-1.62 (m, 1H), 1.51-1.46 (m, 1H), 1.42-1.36 (m, 1H), 1.33-1.27 (m, 2H), 1.09 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 1.02 (s, 12H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.10 (s, 3H), 0.08 (s, 6H), 0.05 (m, 3H); ¹³C-NMR (151.1 MHz, C₆D₆) δ 166.8, 159.2, 146.9, 145.6, 132.8, 132.0, 130.8, 129.4, 126.7, 115.2, 112.9, 79.7, 75.5, 72.9, 72.1, 66.2, 55.4, 50.2, 42.1, 42.0, 38.2, 35.2, 35.3, 31.6, 31.2, 26.3, 26.2, 26.0, 25.9, 25.8, 25.7, 19.5, 18.5, 18.1, 17.5, 14.8, 13.8, 1.0, −0.6, −1.0, −4.1 ppm.
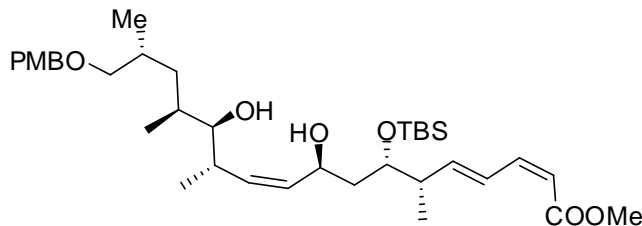
(2*Z*,4*E*,6*S*,7*S*,9*S*,10*Z*,12*S*,13*R*,14*S*,16*R*)-Methyl-7-(*tert*-butyldimethylsilyloxy)-9,13-dihydroxy-17-(4-methoxybenzyloxy)-6,12,14,16-tetramethylheptadeca-2,4,10-trienoate (92α):

To a solution of compound **91α/β** (600 mg, 0.87 mmol) in a mixture of CH_2Cl_2 (30 mL) and MeOH (30 mL) was added a solution of Cl_2CHCO_2H (361 μL, 4.35 mmol) in MeOH (5 mL) at 0 °C. The resulting mixture was stirred for 2 h and then quenched with sat. aqueous $NaHCO_3$. The aqueous phase was extracted with diethyl ether and the combined organic phase was washed with brine and dried over $MgSO_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 4:1 and 2% of MeOH to yield diol **92α** (303 mg, 54%) as a colorless oil. $[\alpha]_D$ −27.8 (*c* 0.1, CHCl$_3$); IR (thin film) 3406, 2983, 2971, 1765, 1684, 1641, 1512, 1422, 1265, 1160, 1128, 948, 738 cm^{-1}; ^{1}H-NMR (600 MHz, CDCl$_3$) δ 7.40 (dd, *J* = 15.6, 11.4 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.58 (t, *J* = 11.4 Hz, 1H), 6.16 (dd, *J* = 15.6, 6.9 Hz, 1H), 5.59 (d, *J* = 11.4 Hz, 1H), 5.51 (dd, *J* = 10.8, 7.8 Hz, 1H), 5.29 (t, *J* = 10.8 Hz, 1H), 4.65 (dt, *J* = 7.8, 4.5 Hz, 1H), 4.42 (d, *J* = 6 Hz, 2H), 3.90 (dt, *J* = 6.8, 4.5 Hz, 1H), 3.8 (s, 3H), 3.71 (s, 3H), 3.39 (dd, *J* = 9, 6 Hz, 1H), 3.21 (t, *J* = 6.6 Hz, 1H), 3.17 (dd, *J* = 7.2, 6.6 Hz, 1H), 2.72 (m, 1H), 2.65 (m, 1H), 1.86-1.83 (m, 1H), 1.76-1.73 (m, 1H), 1.65-1.59 (m, 2H), 1.54-1.49 (m, 2H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 1.02 (s, 9H), 0.85 (d, *J* = 6.7 Hz, 3H) 0.14 (s, 3H), 0.10 (s, 3H); ^{13}C-NMR (151.1 MHz, CDCl$_3$) δ 166.9, 159.1, 147.1, 145.6, 134.7,

133.9, 130.7, 129.1, 126.7, 115.5, 113.7, 76.2, 75.8, 72.6, 65.2, 55.2, 51.1, 42.2, 40.3, 38.4, 36.1, 31.4, 30.6, 25.9, 18.0, 17.9, 17.4, 15.5, 13.1, −4.4, −4.5 ppm.
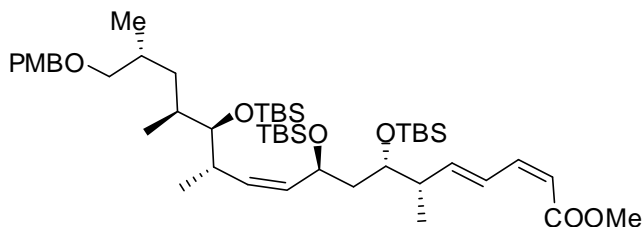
(2Z,4E,6S,7S,9S,10Z,12S,13R,14S,16R)-Methyl-7,9,13-tris(*tert*-butyldimethylsilyloxy)-17-(4-methoxybenzyloxy)-6,12,14,16-tetramethylheptadeca-2,4,10-trienoate (93α):

To a solution of diol **92α** (300mg, 0.47 mmol) in CH$_2$Cl$_2$ (6 mL) was added 2,6-lutidine (199 μL, 1.69 mmol) and TBSOTf (216 μL, 0.94 mmol) at −78 °C. The resulting mixture was warmed up to 0 °C and stirred for 2 h. The resulting mixture was quenched with water and the aqueous phase was extracted with diethyl ether. The combined organic phase was washed with brine and dried over MgSO$_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 10:1 yield TBS ether **93α** (315 mg, 78%) as a colorless oil. [α]$_D$ −72.2 (*c* 0.1, CHCl$_3$); IR (thin film) 2965, 2953, 2899, 1694, 1625, 1490, 1315, 1242, 1215, 1115, 720 cm^{-1}; ^{1}H-NMR (600 MHz, CDCl$_3$) δ 7.34 (dd, *J* = 15.6, 11.4 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.54 (t, *J* = 11.4 Hz, 1H), 6.21 (dd, *J* = 15.6, 6.9 Hz, 1H), 5.54 (d, *J* = 11.4 Hz, 1H), 5.38 (t, *J* = 10.8 Hz, 1H), 5.25 (dd, *J* = 10.8, 8.4 Hz, 1H), 4.54 (t, *J* = 8.6 Hz, 1H), 4.42 (d, *J* = 6 Hz, 2H), 3.92 (d, *J* = 7.2 Hz, 1H), 3.81 (s, 3H), 3.72 (s, 3H), 3.36-3.34 (m, 1H), 3.31 (dd, *J* = 9, 4.4 Hz, 1H), 3.17 (t, *J* = 8.4 Hz, 1H), 2.58-2.53 (m, 2H), 1.76-1.73 (m, 1H), 1.67-1.62 (m, 1H), 1.51-1.47 (m, 1H), 1.41-1.36 (m, 1H), 1.33-1.31 (m, 1H), 1.29-1.27 (m, 1H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 1.02 (s, 27H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.10 (s, 3H), 0.9 (s, 3H), 0.05 (s, 6H),

0.02 (s, 3H), 0.01 (s, 3H); ^{13}C-NMR (151.1 MHz, CDCl$_3$) δ 166.8, 159.1, 146.8, 145.7, 132.7, 132.4, 130.8, 129.0, 126.6, 115.1, 113.6, 79.8, 75.4, 72.8, 72.6, 66.4, 55.1, 50.8, 42.9, 42.2, 37.8, 35.6, 35.4, 31.6, 31.2, 26.3, 26.2, 26.0, 25.9, 25.8, 25.7, 19.5, 18.8, 18.4, 18.1, 15.5, 14.7, −2.8, −3.5, −3.8, −4.1, −4.2 ppm.
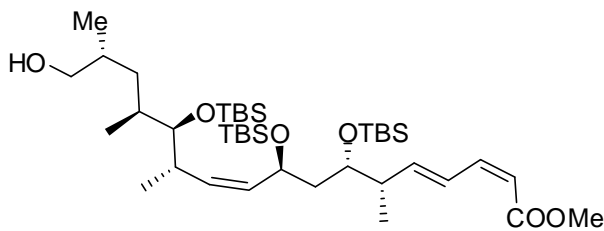
(2Z,4E,6S,7S,9S,10Z,12S,13R,14S,16R)-Methyl-7,9,13-tris(*tert*-butyldimethylsilyloxy)-17-hydroxy-6,12,14,16-tetramethylheptadeca-2,4,10-trienoate (94α):

To a solution TBS ether **93α** (200 mg, 0.23 mmol) in CH$_2$Cl$_2$ (4 mL) and PH 7 buffer (200 μL) was added DDQ (63 mg, 0.28 mmol). The resulting mixture was stirred for 2 h and then quenched with with sat. aqueous NaHCO$_3$. The aqueous phase was extracted with diethyl ether and the combined organic phase was washed with brine and dried over MgSO$_4$. The solution was concentrated and the crude product was purified by silica gel flash chromatography eluting with hexanes/ethyl acetate 3:1 t yield alcohol **94α** (111 mg, 65%) as a colorless oil. [α]$_D$ −96.1 (*c* 0.1, CHCl$_3$); IR (thin film) 3355, 2984, 2857, 1721, 1656, 1424, 1165, 1101, 830, 751 cm^{-1}; ^{1}H-NMR (600 MHz, CDCl$_3$) δ 7.35 (dd, *J* = 15.6, 11.4 Hz, 1H), 6.56 (t, *J* = 11.4 Hz, 1H), 6.22 (dd, *J* = 15.6, 6.9 Hz, 1H), 5.57 (d, *J* = 11.4 Hz, 1H), 5.44 (t, *J* = 10.8 Hz, 1H), 5.28 (dd, *J* = 10.8, 8.4 Hz, 1H), 4.56 (t, *J* = 8.6 Hz, 1H), 3.94 (d, *J* = 7.2 Hz, 1H), 3.72 (s, 3H), 3.52-3.48 (m, 1H), 3.37 (t, *J* = 7.2 Hz, 1H), 3.34-3.31 (m, 1H), 2.58-2.53 (m, 2H), 1.76-1.73 (m, 1H), 1.67-1.62 (m, 1H), 1.51-1.47 (m, 1H), 1.41-1.36 (m, 1H), 1.33-1.31 (m, 1H), 1.29-1.27 (m, 1H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 1.02 (s, 27H), 0.84 (d, *J* =

6.7 Hz, 3H), 0.10 (s, 3H), 0.9 (s, 3H), 0.05 (s, 6H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C-NMR (151.1 MHz, CDCl$_3$) δ 167.4, 147.5, 146.3, 133.4, 132.8, 127.1, 115.7, 80.5, 73.4, 68.1, 66.9, 51.5, 43.5, 42.7, 37.9, 36.1, 36.0, 33.9, 26.8, 26.7, 26.5, 26.4, 20.1, 19.0, 18.7, 16.2, 15.2, -2.8, -3.5, -3.8, −4.1, −4.2 ppm.

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