Chapter 5. Design, synthesis and biological evaluation of simplified and fluorescently labeled discodermolide analogs

5.1 Introduction

The structure of discodermolide is unique, because unlike other tubulin binding agents with polycyclic or large ring skeletons, discodermolide consists of a flexible chain. Discodermolide can thus adopt a seemingly infinite number of conformations when binding to tubulin, which brings us the question: which conformation is the most bioactive one among all possibilities? This could be resolved by examining the 3D structure of the discodermolide tubulin complex, but this complex has never been crystallized. Some NMR studies on the conformation of free discodermolide in solid state or in various solvents and tubulin-bound discodermolide have been conducted.[1] These studies show that the conformations of free discodermolide in the solid state and tubulin bound discodermolide in solution are quite similar except for the lactone moiety.[1b] It was also observed that when bound to microtubules, the orientation of the lactone ring relative to the backbone is nearly identical to that observed in the free state, and the bound discodermolide shows no significant distortions in the area of C5-C24 from the major conformer in water.[1a]

In addition of the NMR studies described above, indirect evidence of the orientation of discodermolide in the tubulin binding pocket can be obtained from the fluorescence spectroscopy of the discodermolide tubulin complex,[2] since fluorescence spectroscopy is widely used to study ligand-receptor interactions.[3] To use this technique, a fluorophore

must be incorporated into the discodermolide structure, since discodermolide does not have a natural fluorophore. In previous studies in our group, a small environmentally sensitive fluorophore, such as an aminobenzoyl group, was successfully used to explore the local environment of the paclitaxel binding site on microtubules.[4] However, the addition of such a fluorophore to discodermolide must inevitably cause major structural changes, which could lead to the loss of activity. Therefore, the fluorophore incorporation needs to be carefully designed to preserve the tubulin binding activity.

5.2 Design and synthesis of fluorescently labeled discodermolide analogs

5.2.1 SAR-based design of fluorescently labeled discodermolide analogs

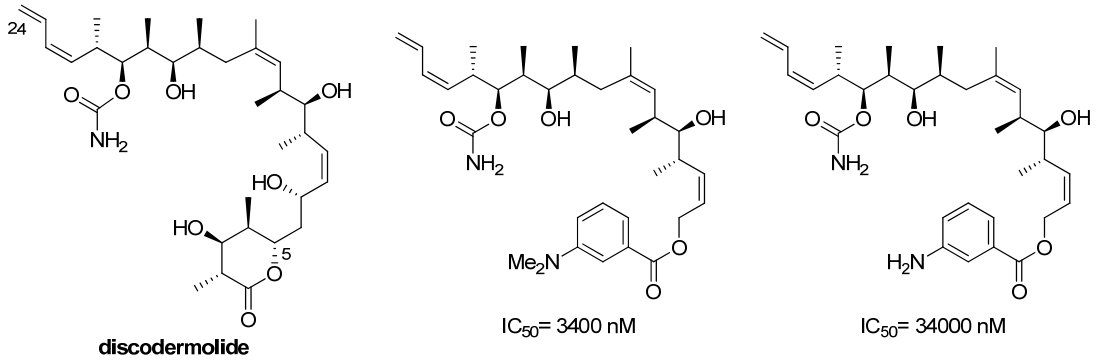


Figure 5.1 The structures of discodermolide and previous fluorescently labeled analogss

Previously, two simplified fluorescently labeled discodermolide analogs were designed and successfully synthesized in our group (Figure 5.1). The design of the two analogs was based on the SAR studies that the replacement of the δ-lactone by aromatic ring could preserve the cytotoxicity of discodermolide if it maintained the appropriate orientation.[5] Therefore, it was expected that the replacement of the δ-lactone by an

aromatic fluorophore, such as an aminobenzoyl group or a dimethylaminobenzoyl group, would not adversely interfere with the interaction of the analog with microtubules. Additionally, the C7 hydroxyl group was removed for structural simplication and synthetic convenience. Unfortunately, the antiproliferative activities of the two analogs were found to be reduced significantly, in comparison with discodermolide (Figure 5.1). This might result from the removal of C7 hydroxyl group, since previous SAR studies revealed that the absence of the hydroxyl group at C7 resulted in an apparent reduction in bioactivity.[6] Besides, it was noticeable that the dimethylaminobenzoate analog was ten-fold better than the aminobenzoate analos in its antiproliferative activity, suggesting that the dimethylaminobenzoate fluorophore could be a better choice.

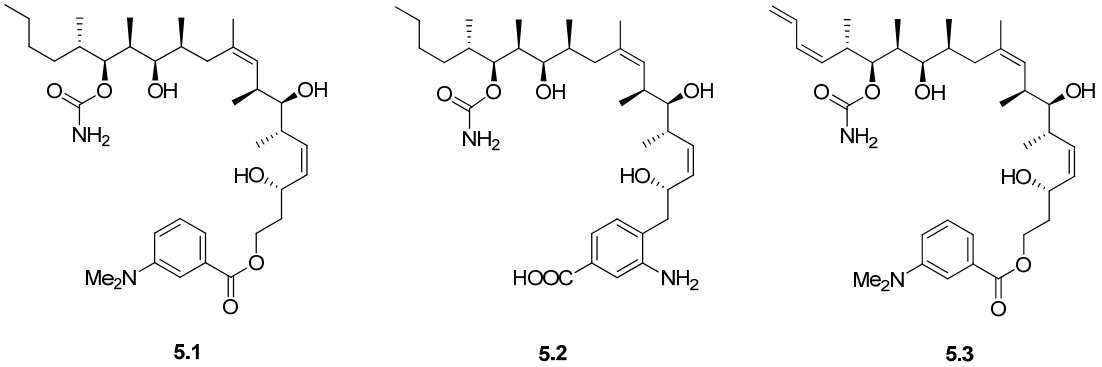


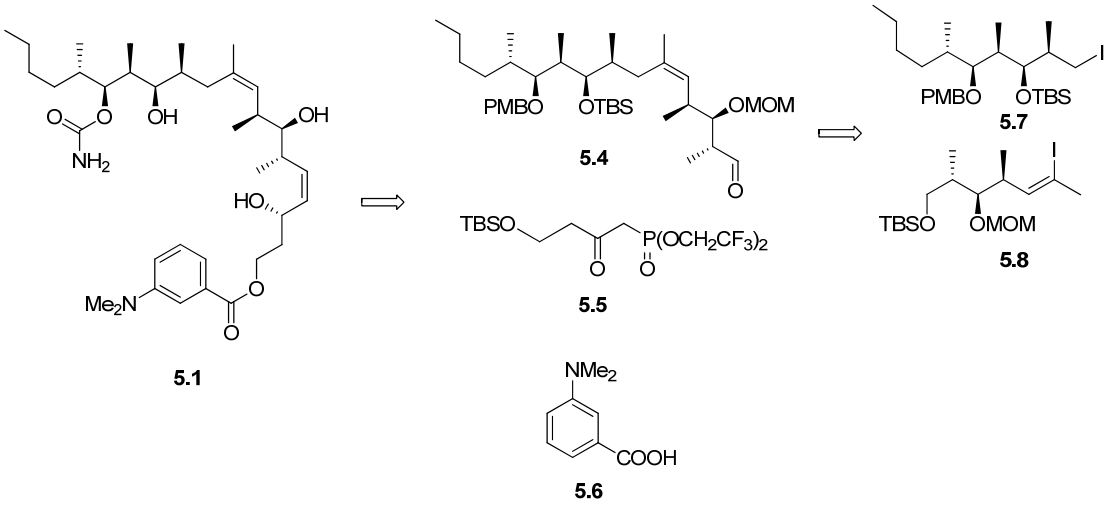
Figure 5.2 The structures of the new fluorescently labeled discodermolide analogs

According to the information above, three new simplified and fluorescently labeled discodermolide analogs were designed, as shown in Figure 5.2. These analogs avoided the possibility of the activity reduction by keeping the C7 hydroxyl group, and they took advantage of the dimethylaminobenzoyl fluorophore. Plus, in two of the analogs, the terminal diene was replaced by a saturated butyl group to simplify the structures, since

the terminal conjugated diene system does not contribute significantly to the cytotoxicity of discodermolide.[5b,7] Therefore, it was expected that these analogs would preserve the activity better than the previous ones.

5.2.2 Synthesis of analog 5.1

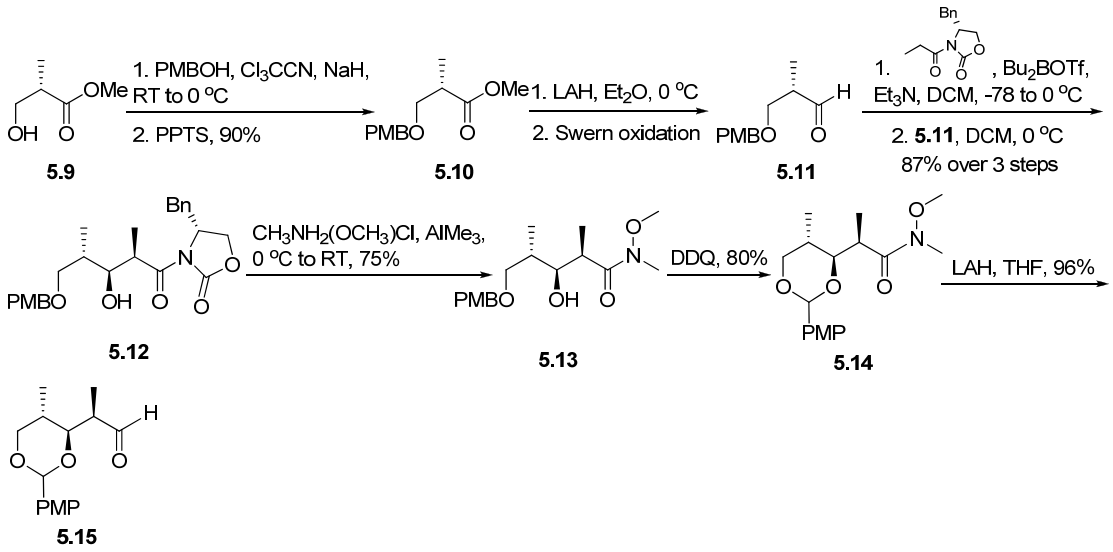
The retrosynthetic analysis is shown in Scheme 5.1. The synthesis of analog **5.1** involved the final installation of the fluorophore **5.6** and HWE coupling of the phosphonate **5.5** and aldehyde **5.4**, which was prepared from iodide **5.7** and vinyl iodide **5.8** by Suzuki coupling.



Scheme 5.1 Retrosynthesis of **5.1**

The precursors **5.7** and **5.8** were synthesized via the convergent approach developed in Smith's group.[5b,8] The synthesis of **5.7** started from the commercially available ester **5.9**, which was first protected as its PMB ether. Reduction and Swern oxidation converted ester **5.10** to aldehyde **5.11**, which subsequently underwent the Evans-aldol reaction to

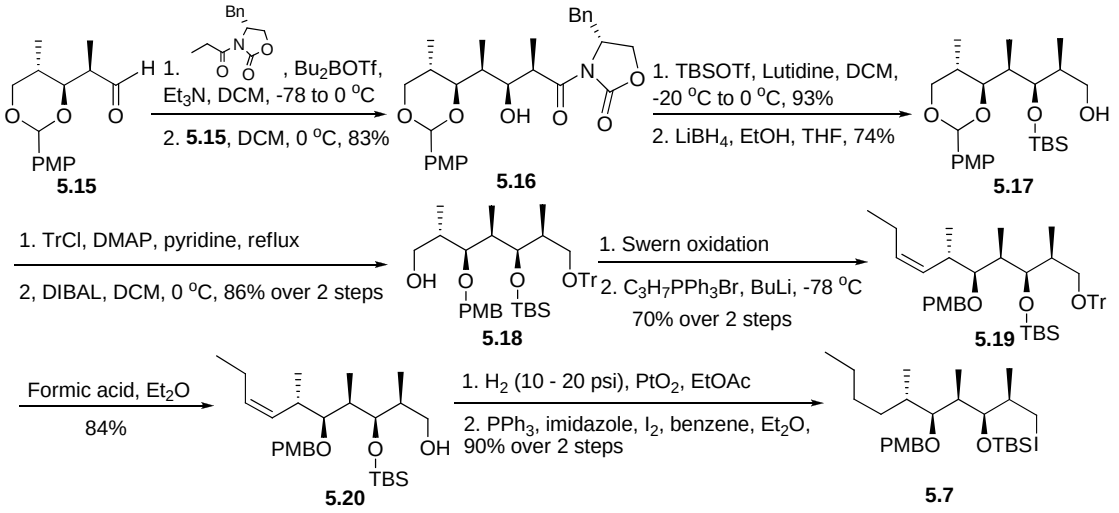
establish two chirality centers with the *syn* relative configuration. The resulted amide



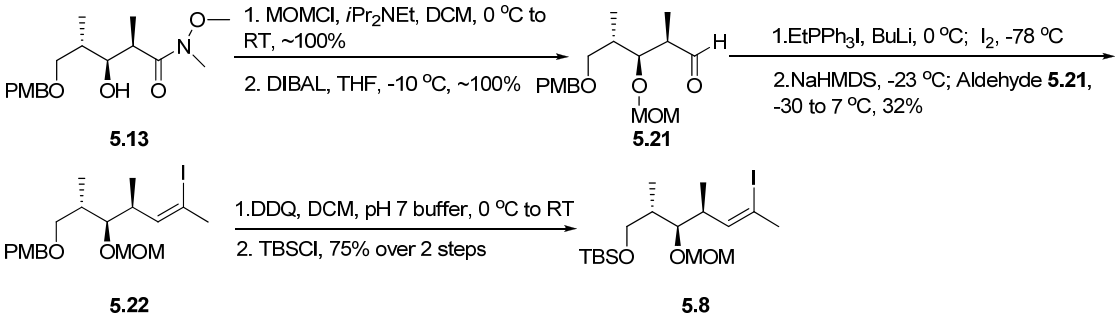
Scheme 5.2 Synthesis of aldehyde **5.15**

5.12 was treated with N,O-dimethylhydroxylamine hydrochloride and $AlMe_3$ in THF at 0 ^oC to afford the Weinreb amide **5.13** (Scheme 5.2), which was used as a common precursor to prepare both fragments **5.7** and **5.8**.

For the synthesis of iodide **5.7**, the common precursor **5.13** was oxidized by DDQ to give acetal **5.14** in 80% yield, which was then reduced directly to aldehyde **5.15** in 96% yield (Scheme 5.2). Subsequently, a second Evans-aldol reaction built two more chirality centers with the *syn* relative configuration, which finished the construction of the repeating stereotriad sequence of the backbone of **5.7** (Scheme 5.3). The resulting amide **5.16** was then protected as its TBS ether, followed by treatment with $LiBH_4$ to afford alcohol **5.17**. After protection as its trityl ether, acetal **5.17** was converted to PMB ether **5.18** by treatment with DIBAL. Swern oxidation, Wittig olefination and trityl deprotection then afforded alcohol **5.20** in 59% yield over 3 steps, and this was hydrogenated by H_2 and Pt_2O, and then iodinated to give iodide **5.7** in 90% over 2 steps.



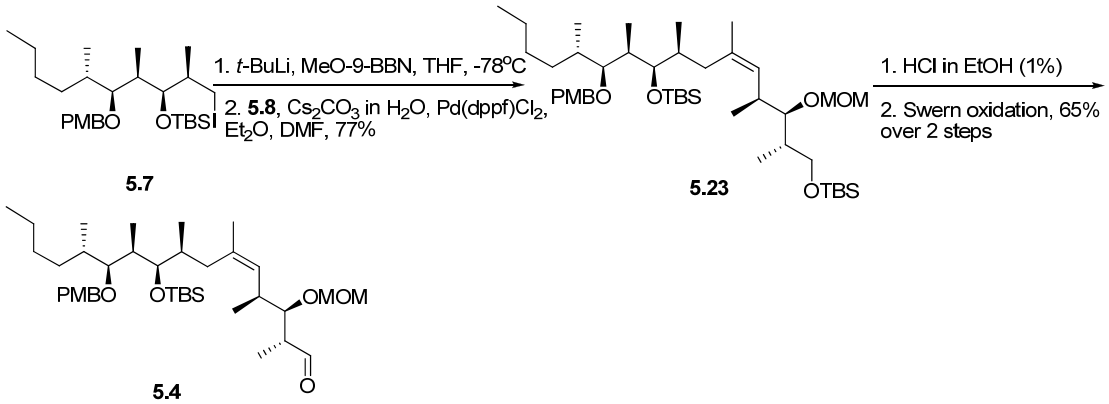
Scheme 5.3 Synthesis of iodide **5.7**



Scheme 5.4 Synthesis of vinyl iodide **5.8**

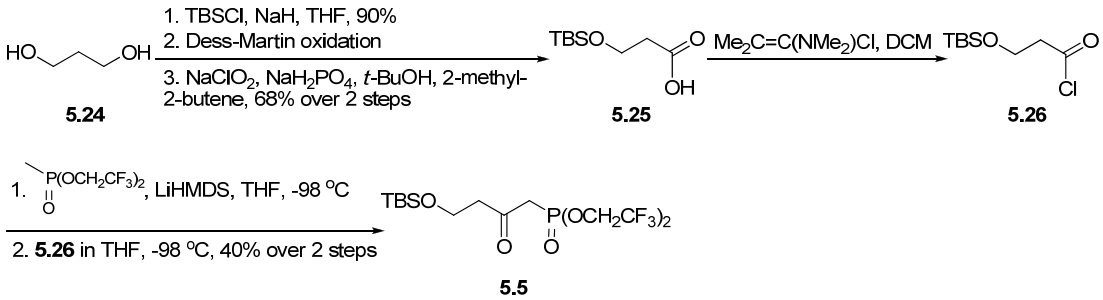
For the synthesis of vinyl iodide **5.8**, the common precursor **5.13** was protected as its MOM ether and reduced by DIBAL to give aldehyde **5.21**, which was subsequently iodo-olefinated to vinyl iodide **5.22** in 32% yield. After oxidative deprotection of the PMB group, vinyl iodide **5.22** was then protected as its TBS ether to afford subunit **5.8**, as shown in Scheme 5.4.

The connection of subunit **5.7** to **5.8** was achieved via Suzuki coupling to afford TBS ether **5.23** in 77% yield. Subsequent TBS deprotection and Swern oxidation provided aldehyde **5.4** in 65% yield (Scheme 5.5).



Scheme 5.5 Synthesis of aldehyde **5.4**

The synthesis of subunit **5.5** began with propane-1,3-diol, which was mono protected as its TBS ether. After Swern oxidation and further oxidation by $NaClO_2$ and NaH_2PO_4, the resulting acid was converted to acid chloride **5.26** by treatment with 1-chloro-N,N,2-trimethyl-1-propenylamine.[9] Subsequently, acid chloride **5.26** was transformed to phosphonate **5.5** at -98 °C in 40% yield over 2 steps (Scheme 5.6).



Scheme 5.6 Synthesis of phosphonate **5.5**

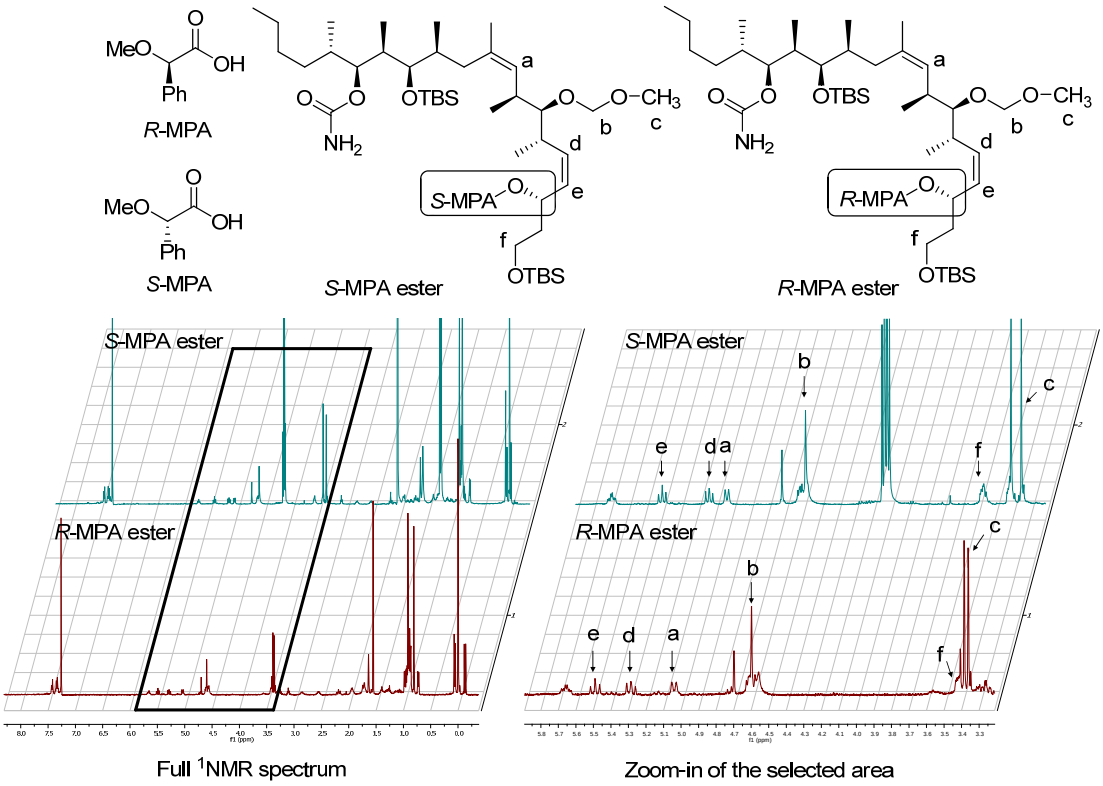
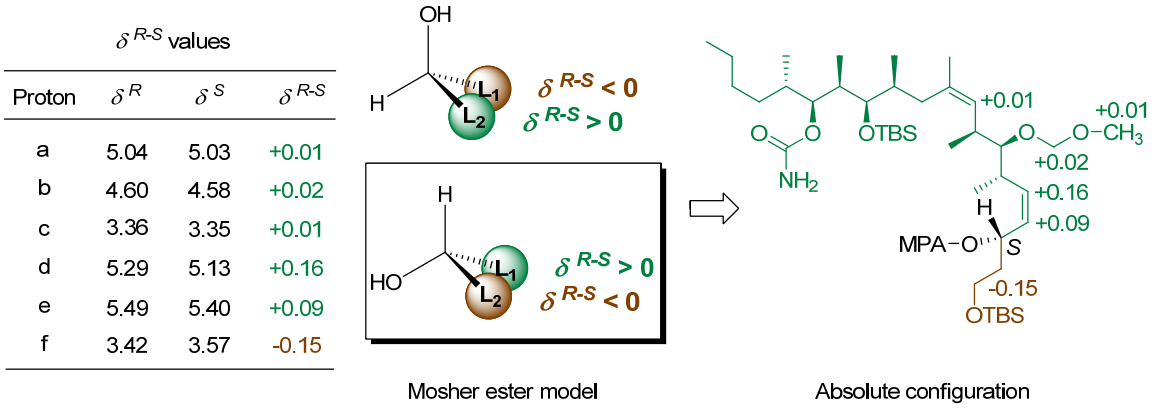


Figure 5.3 ^{1}H NMR spectra of the MPA esters

As shown in Scheme 5.7, HWE coupling between subunit **5.4** and subunit **5.5** afforded TBS ether **5.27** in 85% yield, which was then subjected to oxidation with DDQ to remove the PMB protecting group. The subsequent installation of the carbamate moiety on the resulting alcohol gave ketone **5.29**, which was reduced by K-selectride^{TM} to give alcohol **5.30** with the desired configuration. The configuration was determined by Mosher ester analysis. Alcohol **5.30** was coupled separately with *R*-PMA and *S*-PMA to

form two Mosher esters (Figure 5.3) via EDC coupling. Their ^{1}H NMR spectra were obtained and the $\delta^{R\text{-}S}$ values were calculated for adjacent protons to the chiral cencer. The results are summarized in Figure 5.4, where the $\delta^{R\text{-}S}$ values of the top part of the structure were positive, while the values for the bottom part were negative. According to the Mosher ester model (Figure 5.4), the configuration was confirmed to be the desired one.

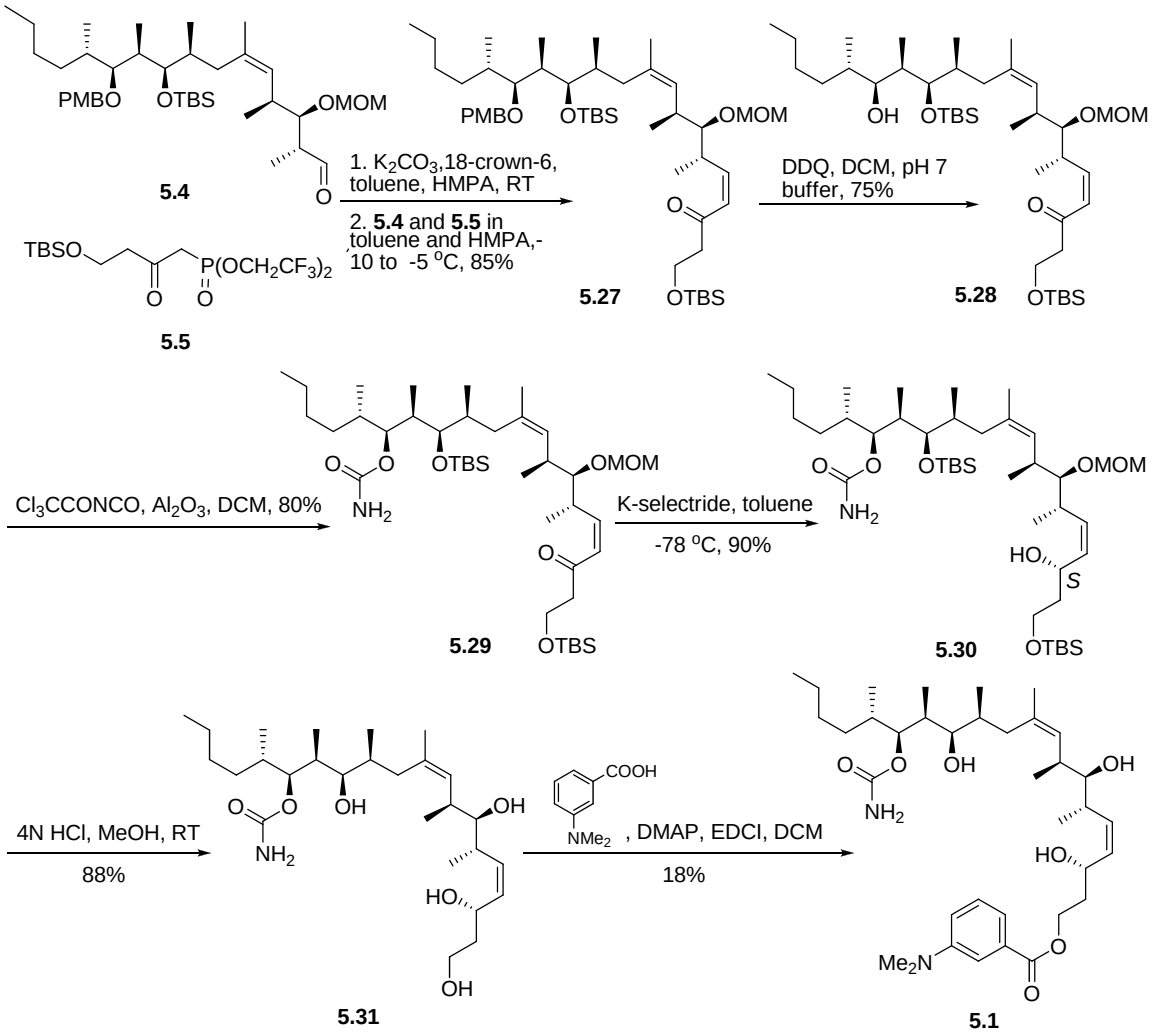
The alcohol **5.30** was then treated with HCl (4 N) in small portions over 4 hours to remove all the protecting groups, and the resulting alcohol was coupled with 3-dimethylaminobenzoic acid via EDCI coupling to give the final product **5.1** in 10% yield over 2 steps.



$\delta^{R\text{-}S}$ values

Proton	δ^{R}	δ^{S}	$\delta^{R\text{-}S}$
a	5.04	5.03	+0.01
b	4.60	4.58	+0.02
c	3.36	3.35	+0.01
d	5.29	5.13	+0.16
e	5.49	5.40	+0.09
f	3.42	3.57	-0.15

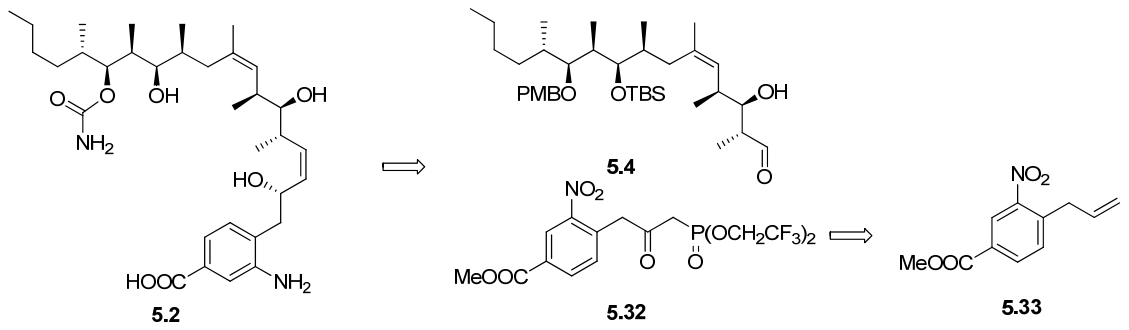
Figure 5.4 Determination of the absolute configuration of **5.30**



Scheme 5.7 Finale of the Synthesis of **5.1**

5.2.3 Synthesis towards analog 5.2

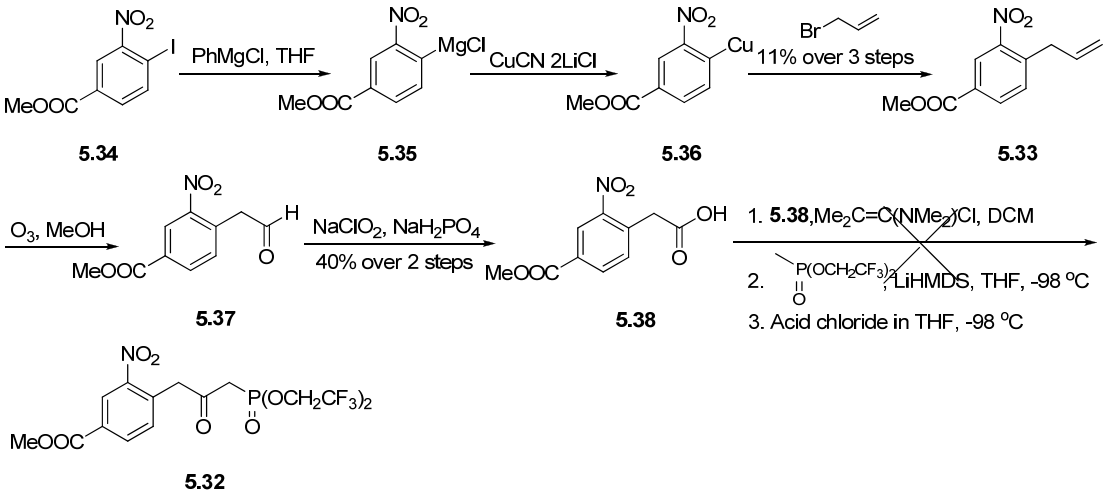
From a structure-activtity viewpoint, an analog such as **5.2** was predicted to have higher activity than analog **5.1**, based on the known SAR of discodermolide. It was thus an attractive target for synthesis. According to a retrosynthetic analysis, analog **5.2** could be synthesized via HWE coupling between the known subunit **5.4** and phosphonate **5.32**.



Scheme 5.8 Retrosynthesis of analog **5.2**

We began with the synthesis of phosphonate **5.32**, since the subunit **5.4** was prepared previously. Stille coupling was first tested as the method to connect the side chain to the commercially available material methyl 3-nitro-4-iodobenzoate, but this reaction did not proceed as desired. Later, we found a convenient method to prepare allylbenzene **5.33** as a starting point via halogen-magnesium exchange, followed by transmetalation and allylation.

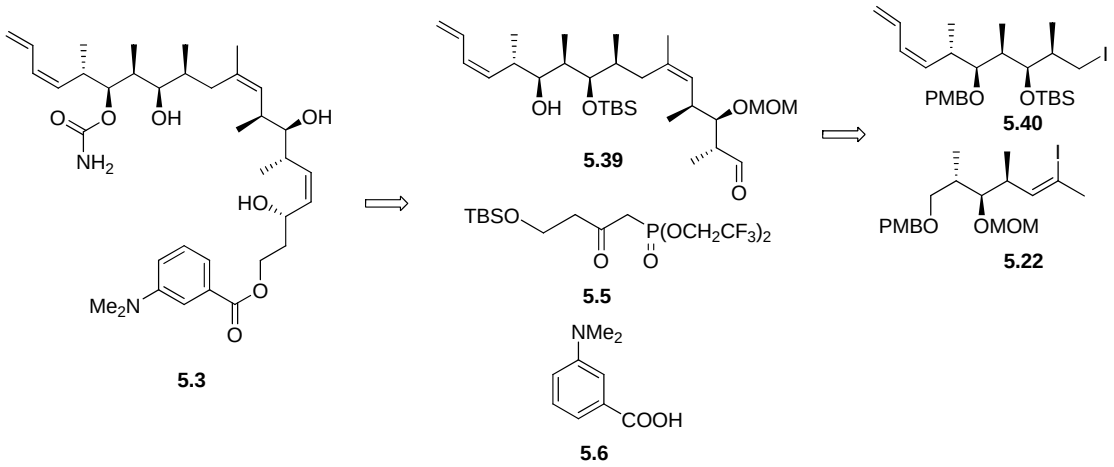
The commercially available methyl 3-nitro-4-iodobenzoate was treated with PhMgCl, followed by CuCN·2LiCl and allyl bromide at -40 ^{o}C to give allylbenzene **5.33** in 11% yield over 3 steps. Ozonolysis of **5.33** produced phenylacetaldehyde **5.37**, which was subsequently oxidized to give acid **5.38** in 40% yield over 2 steps. Unfortunately, the transformation of acid **5.38** to phosphonate **5.32** via the previous method was not successful, probably due to the interference of the ester carbonyl moiety and nitro group in the structure. So a method to convert acid **5.38** to subunit **5.32** needs to be explored in the future.



Scheme 5.9 Synthesis towards analog **5.32**

5.2.4 Synthesis towards analog 5.3

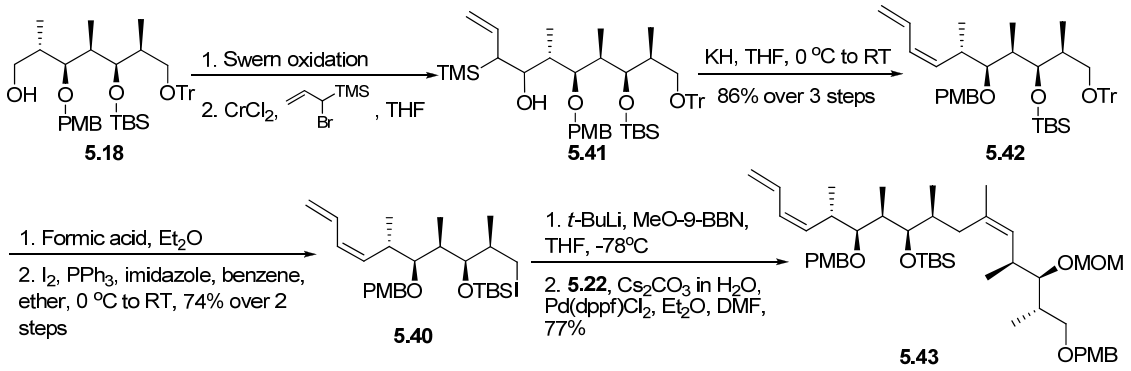
Similar to the synthesis of analog **5.1**, the synthesis of analog **5.3** involved a Suzuki coupling between iodide **5.40** and vinyl iodide **5.22** and an HWE reaction to establish the backbone of the structure, as shown in Scheme 5.10.



Scheme 5.10 Retrosynthesis of **5.3**

The synthesis of fragment **5.40** was begun with alcohol **5.18** which was prepared in

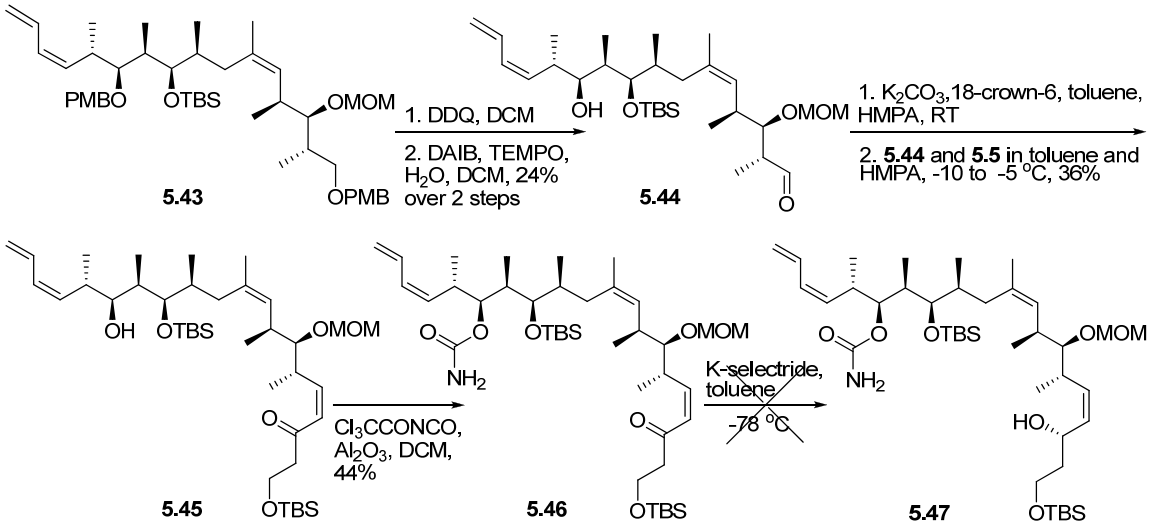
the synthesis of analog **5.1**. After Swern oxidation, alcohol **5.18** was converted to an aldehyde, which was then treated with 1-bromo-1-trimethylsilyl-2-propene and chromium(II) chloride in THF to give intermediate anti-α-hydroxysilanes **5.41** (Scheme 5.11). Treatmemt of **5.41** with KH in THF led to the formation of the terminal diene moiety. Subsequently, the resulting diene **5.42** was transformed to iodide **5.40** via trityl deprotection and iodination, and Suzuki coupling of **5.40** and **5.22** provided PMB ether **5.43**.



Scheme 5.11 Synthesis of **5.43**

After the reductive deprotection of the PMB groups of **5.43** by DDQ and TEMPO oxidation, the PMB ether **5.43** was converted to aldehyde **5.44**, which was coupled to phosphonate **5.5** via the HWE reaction to yield TBS ether **5.45**. Then the carbamate moiety was installed at C19 position to provide amide **5.46**. However, the first attempt to reduce ketone **5.46** to alcohol **5.47** by K-selectride™ failed in the first batch. Fortunately, a successful procedure was later found for the K-selectride reduction in the synthesis of analog **5.1**, which could be used to synthesize analog **5.3**. But due to the limited amount of intermediate **5.46**, this project was temporarily placed on hold. The good thing is that all the steps to synthesize analog **5.3** have been well explored to give good or acceptable

yields.



Scheme 5.12 Synthesis towards **5.3**

5.3 Biological evaluations of the simplified fluorescently labeled discodermolide analog

Table 5.1 The bioassay results of analog **5.1**

Compound	IC_{50} in A2780 bioassay (uM)	EC_{50} in tubulin assembly bioassay (uM)
Paclitaxel	0.014 ± 0.002	0.5
5.1	5.4 ± 2.2	5

The simplified fluorescently labeled discodermolide analog **5.1** was submitted to the A2780 bioassay for antiproliferative activity and to Susan L. Bane at SUNY at Binghamton for tubulin assembly activity. The bioassay results are summarized in Table 5.1. The analog **5.1** was active in both bioassays, but it was nearly 400 times less active than paclitaxel in A2780 bioassay. Fortunately, it showed much better activity in the

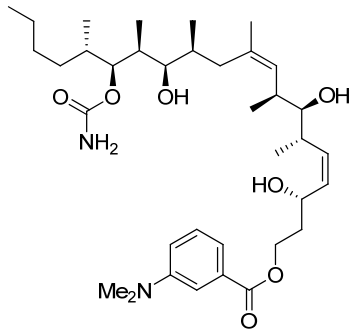
tubulin assembly bioassay, only 10 times less active than paclitaxel, indicating that it binds tubulin in a similar way to discodermolide. Further biological investigations are currently in progress.

5.4 Experimental section

General experimental methods

All chemicals obtained from commercial sources were used without further purification. The anhydrous reactions were performed under nitrogen or argon. All solvents were of reagent grade or HPLC grade. Tetrahydrofuran (THF) was distilled over sodium/benzophenone, and dichloromethane (DCM) was distilled over calcium hydride. The reactions were monitored by the analytical thin layer chromatography (TLC) plates (silica gel 60 GF) and analyzed with 254 nm UV light, $KMnO_4$ stain, and/or vanillin/sulfuric acid spray. Preparative thin layer chromatography (PTLC) plates were purchased from Analtech. All NMR spectral data were obtained on JEOL Eclipse spectrometer at 500 MHz, Varian Unity or Varian Inova spectrometer at 400 MHz. Chemical shifts reported as δ-values relative to known solvent residue peaks. High-resolution mass spectra (HRMS) were obtained in the analytical service in the Department of Chemistry at Virginia Tech. Known compounds were prepared through the reported procedures, and the NMR data of these compounds matched the literature values. All compounds were more than 95% pure as judged by the TLC and ^{1}H NMR.

(3*S*,4*Z*,6*S*,7*S*,8*S*,9*Z*,12*S*,13*R*,14*S*,15*S*,16*S*)-15-(Carbamoyloxy)-3,7,13-trihydroxy-6,8,10,12,14,16-hexamethylicosa-4,9-dienyl 3-(dimethylamino)benzoate (5.1)



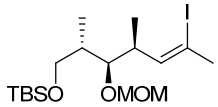
5.1

TBS ether **5.30** (18 mg, 0.024 mmol) was dissolved in MeOH (3.6 mL). After stirring for 15 minutes, HCl solution (3.6 mL, 4M in water) was added to the solution in small portions (0.15 mL per 10 minutes in 4 hours) at RT before $NaHCO_3$ was added carefully to quench reaction. The solution was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (80% EtOAc in hexanes) to give alcohol **5.31** (10 mg, 88%) as a colorless oil.

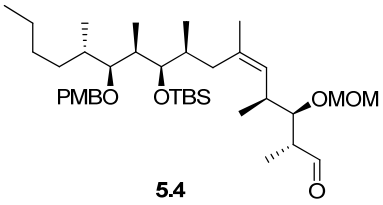
To a solution of 3-(dimethylamino)benzoic acid (2.8 mg, 17 μmol) and DMAP (1.5 mg, 12.3 μmol) in DCM (0.6 mL) was added a solution of alcohol **5.31** (4.2 mg, 8.7 μmol) in DCM (0.6 mL), followed by EDCI (3.9 mg, 20 μmol). After stirring at RT for 12 hours, water was added and the mixture was extracted with EtOAc. The organic layer was then washed by brine, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (50% EtOAc in hexanes) to give **5.1** (1 mg, 18%) as a colorless oil. $[\alpha]_D^{25}$ -12.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (1H, dd, *J* = 2.6, 1.4 Hz), 7.35 (1H, dd, *J* = 7.6, 1.2 Hz), 7.29 (1H, t, *J* = 7.9 Hz), 7.00 (1H, ddd, *J* = 8.2, 2.7, 0.9

Hz), 5.60 (1H, d, J = 10.3 Hz), 5.42 (1H, dd, J = 10.7, 9.2 Hz), 5.03 (1H, d, J = 10.0 Hz), 4.65 (1H, t, J = 5.9 Hz), 4.53 (1H, td, J = 8.6, 3.6 Hz), 4.42 (2H, dd, J = 7.3, 5.6 Hz), 3.20 (1H, t, J = 5.7 Hz), 3.14 (1H, dd, J = 7.7, 3.8 Hz), 2.99 (6H, s), 2.72 – 2.67 (1H, m), 2.52 – 2.37 (2H, m), 2.18 – 2.08 (2H, m), 1.97 – 1.89 (3H, m), 1.88 – 1.78 (2H, m), 1.74 (1H, dd, J = 11.6, 2.6 Hz), 1.59 (3H, s), 1.46 – 1.41 (2H, m), 1.22 – 1.11 (4H, m), 1.07 (3H, d, J = 7.0 Hz), 0.95 (3H, d, J = 6.6 Hz), 0.93 (3H, t, J = 7.2 Hz), 0.91 – 0.89 (6H, m), 0.78 (3H, d, J = 6.6 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 167.6, 159.1, 150.8, 133.0, 132.9, 132.1, 130.7, 130.2, 128.8, 117.4, 117.0, 112.9, 79.2, 76.4, 64.1, 61.6, 48.3, 39.5, 36.8, 36.5, 36.3, 36.1, 35.6, 34.4, 32.8, 30.4, 29.1, 22.7, 22.2, 18.2, 16.4, 15.3, 13.2, 13.0, 8.3; HRMS (ESI+) calc for $C_{36}H_{60}N_2O_7Na$ $[M + Na]^+$ 655.4298, found 655.4306.

(2*R*,3*R*,4*S*,5*Z*,8*S*,9*R*,10*R*,11*S*,12*S*,*Z*)-9-(*tert*-Butyldimethylsilyloxy)-11-(4-methoxy benzyl-oxy)-3-(methoxymethoxy)-2,4,6,8,10,12-hexamethylhexadec-5-enal (5.4)



5.8



5.4

To a vigorously stirred solution of PMB ether **5.22** (400 mg, 0.9 mmol) in DCM (6.4 mL) and water (0.3 mL) was added DDQ (250 mg, 1.1 mmol) at 0 ^{o}C. After stirring for 1.5 hours, $NaHCO_3$ solution was added and the mixture was extracted with DCM, washed by $Na_2S_2O_3$ solution, water and brine, dried over Na_2SO_4, filtered and concentrated to give the crude alcohol without purification. The crude alcohol was dissolved in DCM (4 ml) and then imidazole (123 mg, 1.8 mmol) and TBSCl (210 mg,

1.35 mmol) were added at RT. After stirring for 15 hours, the reaction was quenched by brine. The mixture was then extracted with DCM, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (10% EtOAc in hexanes) to afford TBS ether **5.8** (300 mg, 75% over 2 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.46 (1H, dd, *J* = 8.7, 1.5 Hz), 4.68 (2H, dd, *J* = 16.7, 6.5 Hz), 3.69 (1H, dd, *J* = 9.8, 4.0 Hz), 3.59 (1H, dd, *J* = 9.8, 6.5 Hz), 3.47 – 3.43 (1H, m), 3.44 (3H, s), 2.54 (d, *J* = 1.4 Hz, 10H), 1.85 (1H, dtd, *J* = 13.6, 6.8, 4.0 Hz), 1.04 (3H, d, *J* = 6.9 Hz), 1.04 (3H, d, *J* = 6.9 Hz), 0.94 (9H, s), 0.09 (6H, s). Spectroscopic data agreed with the literature data.[10]

To a solution of iodide **5.7** (87 mg, 0.15 mmol) in ether (1.74 mL) was added *t*-BuLi (0.18 mL, 1.7 M in pentane, 0.3 mmol), followed by MeO-9-BBN (0.3 mL, 1 M in hexane, 0.3 mmol) and THF (1.74 mL) at -78 ^{o}C. After stirring at RT for 1 hour, Cs_2CO_3 solution (0.13 mL, 3 M in water, 0.38 mmol), a solution of vinyl iodide **5.8** (67 mg, 0.15 mmol) in DMF (1.4 mL) and Pd(dppf)Cl_2 (6.2 mg) were added successively. The resulting solution was covered with aluminum foil and stirred at RT for 20 hours. After dilution with water and ether, the mixture was extracted with ether, washed by brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (5% EtOAc in hexanes) to afford TBS ether **5.23** (86 mg, 77%) as a colorless oil. $[\alpha]_D^{23}$ +4.0 (*c* 10.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (2H, d, *J* = 7.2 Hz), 6.87 (2H, d, *J* = 8.3 Hz), 5.12 (1H, d, *J* = 10.2 Hz), 4.64 (2H, q, *J* = 6.5 Hz), 4.49 (2H, dd, *J* = 33.5, 10.7 Hz), 3.80 (3H, s), 3.64 (1H, dd, *J* = 10.0, 3.8 Hz), 3.52 – 3.47 (2H, m), 3.41 (3H, s), 3.21 (1H, t, *J* = 5.8 Hz), 3.14 (1H, t, *J* = 5.3 Hz), 2.64 – 2.49 (1H, m), 2.22 (1H, t, *J* = 13.3 Hz), 1.95 – 1.80 (3H, m), 1.80 – 1.73 (2H, m), 1.63 (3H, s), 1.45 – 1.23 (4H, m), 1.20 – 1.12 (2H, m),

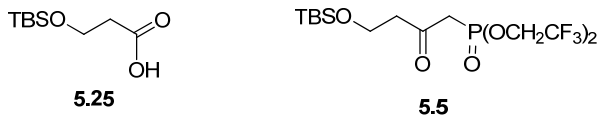
0.99 (3H, d, J = 6.6 Hz), 0.96 (3H, d, J = 6.8 Hz), 0.95 – 0.87 (9H, m), 0.94 (9H, s), 0.89 (9H, s), 0.75 (3H, d, J = 6.7 Hz), 0.07 (3H, s), 0.06 (3H, s), 0.03 (6H, s). Spectroscopic data agreed with the literature data.[5b]

This TBS ether (86 mg, 0.11 mmol) was dissolved in HCl/EtOH (1:99, 3.8 mL) at RT and stirred for 20 minutes. The reaction was quenched with $NaHCO_3$ and extracted with DCM, dried over Na_2SO_4, filtered, and concentrated to give the crude alcohol without purification.

To the crude alcohol (50 mg, 0.077 mmol) in DCM (0.4 mL) and DMSO (0.4 mL) was added Et_3N (0.11 mL, 0.77 mmol) and pyridinium sulfurtrioxide (122 mg, 0.77 mmol) at 0 ^{o}C. After stirring at 0 ^{o}C for 1 hour, NH_4Cl solution and water was added. The mixture was extracted with DCM, washed by water and brine, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (15% EtOAc in hexanes) to afford aldehyde **5.4** (33 mg, 65% over 2 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.62 (1H, d, J = 1.2 Hz), 7.27 (2H, d, J = 8.0 Hz), 6.88 (2H, d, J = 8.6 Hz), 4.85 (1H, d, J = 10.5 Hz), 4.67 (2H, dd, J = 8.2, 7.1 Hz), 4.53 (1H, d, J = 10.8 Hz), 4.43 (1H, d, J = 10.8 Hz), 3.80 (3H, s), 3.62 (1H, dd, J = 8.1, 4.0 Hz), 3.46 (1H, dd, J = 5.2, 3.5 Hz), 3.37 (3H, s), 3.13 (1H, t, J = 5.2 Hz), 2.69 – 2.59 (2H, m), 2.18 (1H, t, J = 12.4 Hz), 1.95 – 1.81 (2H, m), 1.77 – 1.65 (2H, m), 1.58 – 1.56 (3H, m), 1.52 (1H, ddd, J = 10.3, 7.6, 3.1 Hz), 1.45 – 1.23 (3H, m), 1.19 – 1.13 (2H, m), 1.09 (3H, d, J = 7.0 Hz), 1.01 (3H, d, J = 6.6 Hz), 0.98 (3H, d, J = 6.9 Hz), 0.96 (3H, d, J = 6.8 Hz), 0.93 (9H, s), 0.89 (3H, t, J = 7.2 Hz), 0.72 (3H, d, J = 6.7 Hz), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 202.7, 159.0, 135.7, 131.3, 129.1, 128.6, 113.7, 97.4, 85.3, 84.1, 77.5, 74.5, 56.0, 55.3,

49.5, 39.0, 37.3, 35.9, 35.2, 35.1, 31.1, 29.9, 26.3, 23.1, 18.5, 17.4, 17.2, 14.2, 13.5, 11.4, 9.9, -3.4, -3.4; HRMS (APCI+) calc for $C_{38}H_{69}O_6Si$ $[M + H]^+$ 649.4863, found 649.4865.

1-(Bis(2,2,2-trifluoroethyl)phosphoryl)-4-(*tert*-butyldimethylsilyloxy)butan-2-one (5.5)



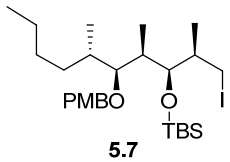
5.25 **5.5**

To a solution of 1,3-propanediol (3 mL, 40 mmol) in THF (60 mL) was added NaH (1.2 g, 60%, 20 mmol) at RT. After stirring for 2.5 hours, TBSCl (630 mg, 4.3 mmol) was added and the mixture was stirred overnight before the addition of $NaHCO_3$ solution in MeOH. The solution was then extracted with DCM, washed with water and brine, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (30% EtOAc in hexanes) to afford TBS ether (800 mg, 90% based on TBSCl) as a colorless oil. To a solution of this TBS ether (590 mg, 3.11 mmol) in DCM (29 mL) was added $NaHCO_3$ and Dess-Martin periodinane at RT. After stirring for 30 minutes, the solution was concentrated, diluted with hexane to participate byproduct, filtered and concentrated carefully to give the crude aldehyde without purification. A solution of this crude aldehyde in *t*-BuOH (13 mL) and 2-methyl-2-butene (1.5 mL) was treated with a solution of $NaClO_2$ (500 mg, 5.5 mmol) and NaH_2PO_4 (1.85 g, 15.4 mmol) in water (12 mL) dropwise. After stirring for 1 hour, the reaction was partitioned between brine and DCM. The organic layer was dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (30% EtOAc in hexanes) to afford acid **5.25** (431 mg, 68% over 2 steps)

as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (2H, t, *J* = 6.1 Hz), 2.58 (2H, t, *J* = 6.1 Hz), 0.89 (9H, s), 0.09 (6H, s).

To a solution of acid **5.25** (166 mg, 0.81 mmol) in DCM (9 mL) was added 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (0.24 mL, 1.8 mmol). After stirring for 1 hour, the solution was concentrated and the crude acid chloride was dried in vacuo for 30 minutes. Meanwhile, LiHMDS (2.7 mL, 1.0 M in THF, 2.7 mmol) was added dropwise to a solution of methylphosphonic acid bis(2,2,2-trifluoroethyl) ester (700 mg, 2.67 mmol) in THF (2 mL) at -98 ^{o}C. After stirring for 15 minutes, a solution of the crude acid chloride in THF (5.8 mL) was added at -98 ^{o}C. The resulting solution was stirred for 1 hour at -98 ^{o}C before adding NH_4Cl solution to quench the reaction. The solution was then warmed to RT, and more NH_4Cl solution was added. The mixture was extracted with DCM, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (30% EtOAc in hexanes) to afford phosphonate **5.5** (135 mg, 40% over 2 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 – 4.39 (4H, m), 3.90 (2H, t, *J* = 6.0 Hz), 3.38 (1H, s), 3.34 (1H, s), 2.74 (2H, td, *J* = 6.0, 0.8 Hz), 0.88 (9H, s), 0.06 (6H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 200.7, 122.6 (dd, *J* = 551.5, 16.6 Hz), 62.5 (dq, *J* = 75.8, 11.1 Hz), 58.6, 47.2 (d, *J* = 10.4 Hz), 42.8, 41.7, 25.9, 18.3, -5.5; HRMS (ESI+) calc for $C_{14}H_{26}F_6O_5PSi$ $[M + H]^+$ 447.1191, found 447.1186.

***tert*-Butyl((2*R*,3*S*,4*R*,5*S*,6*S*)-1-iodo-5-(4-methoxybenzyloxy)-2,4,6-trimethyldecan-3-yloxy)dimethylsilane (5.7)**



5.7

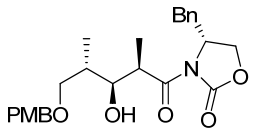
To a solution of trityl ether **5.19** (626 mg, 0.89 mmol) in ether (20 mL) was added a solution of formic acid (20 mL) in ether (20 mL) dropwise at RT. After stirring for 12 hours, the reaction was diluted with water and quenched carefully with solid K_2CO_3. The aqueous layer was extracted with ether and the combined organic phases were concentrated, dissolved in MeOH and treated with K_2CO_3. After stirring for 20 minutes, the solution was diluted with water and ether. The aqueous layer was extracted with ether and the combined organic phases were washed with water and brine, concentrated and purified by flash chromatography (5%-10% EtOAc in hexanes) to give the alcohol (346 mg, 84%) as a colorless oil. Spectroscopic data agreed with the literature data.[5b]

This alcohol (346 mg, 0.75 mmol) was dissolved in EtOAc (5 mL) and PtO_2 (15 mg, on carbon) was added. The mixture was submitted to a hydrogen pressure (10-15 psi) and stirred for 4 hours. After filtration and concentration, the residue was purified by flash chromatography (10% EtOAc in hexanes) to afford the hydrogenated alcohol as a colorless oil which was used in the next step without purifications.

To a solution of this hydrogenated alcohol, PPh_3 (380 mg, 1.43 mmol) and imidazole (100 mg, 1.43 mmol) in benzene/ether (1:2, 15 mL) was added a solution of iodine (290 mg, 1.13 mmol) in ether (3 mL) at 0 ^{o}C. After stirring for 1 hour at RT, $NaHCO_3$ solution

was added and the mixture was extracted with ether, washed by $Na_2S_2O_3$ solution, water and brine, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (5% EtOAc in hexanes) to afford iodide **5.7** (476.4 mg, 90% over 2 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (2H, d, *J* = 8.6 Hz), 6.89 (2H, d, *J* = 8.7 Hz), 4.52 (2H, dd, *J* = 30.1, 10.8 Hz), 3.81 (3H, s), 3.63 (1H, dd, *J* = 6.2, 3.0 Hz), 3.15 (1H, dd, *J* = 9.5, 6.1 Hz), 3.09 (2H, dt, *J* = 9.5, 5.0 Hz), 1.95 (1H, ddd, *J* = 13.3, 6.8, 3.0 Hz), 1.87 – 1.81 (1H, m), 1.79 – 1.71 (1H, m), 1.59 – 1.52 (1H, m), 1.46 – 1.25 (3H, m), 1.24 – 1.12 (2H, m), 0.99 (3H, d, *J* = 6.8 Hz), 0.97 (3H, d, *J* = 7.0 Hz), 0.94 (3H, d, *J* = 6.8 Hz), 0.92 (9H, s), 0.90 (3H, t, *J* = 7.2 Hz), 0.08 (3H, s), 0.08 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.2, 131.5, 129.3, 113.9, 84.7, 75.6, 74.4, 55.4, 40.9, 39.4, 36.2, 31.7, 30.0, 26.4, 23.3, 18.7, 17.1, 15.3, 14.5, 14.4, 11.6, -3.3, -3.4; HRMS (ESI+) calc for $C_{46}H_{63}O_4Si$ $[M + H]^+$ 577.2574, found 577.2578. Spectroscopic data agreed with the literature data.[5b]

(*R*)-4-Benzyl-3-((2*R*,3*S*,4*S*)-3-hydroxy-5-(4-methoxybenzyloxy)-2,4-dimethylpentan-oyl)oxazolidin-2-one (5.12)



5.12

To a suspension of NaH (275 mg, 60%, 6.83 mmol) in Et_2O (45 mL) was added a solution of PMBOH (8.5 mL, 68.3 mmol) in Et_2O (35 mL) at RT. After stirring for 1 hour, the mixture was cooled to 0 ^oC and Cl_3CCN (6.8 mL, 68.3 mmol) was added. The

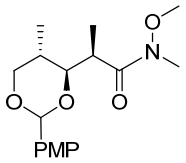
mixture was then stirred at 0 ^{o}C for 5 minutes and at RT for 20 minutes before adding $NaHCO_3$ solution. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was dissolved in DCM (90 mL), and ester **5.9** (5 mL, 45.5 mmol) and PPTS (500mg) was added. After the mixture had stirred at RT for 22 hours, $NaHCO_3$ was added and the organic layer was washed with $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (5% EtOAc in hexanes) to give PMB ether **5.10** (9.65 g, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (2H, dd, *J* = 8.7, 0.5 Hz), 6.87 (2H, d, *J* = 8.7 Hz), 4.49 – 4.41 (2 H, ABq, *J* = 11.8, 2.5 Hz), 3.80 (3H, s), 3.69 (3H, s), 3.62 (1H, dd, *J* = 9.1, 7.3 Hz), 3.45 (1H, dd, *J* = 9.2, 5.9 Hz), 2.81 – 2.72 (1H, m), 1.66 (3H, d, *J* = 7.1 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 175.2, 159.1, 130.2, 129.1, 113.6, 72.6, 71.6, 55.01, 51.6, 40.1, 13.9. Spectroscopic data agreed with the literature data.[8b]

$LiAlH_4$ (310 mg) was added to a solution of ester **5.10** (1.9 g, 8.1 mmol) in Et_2O (40 mL) at 0 ^{o}C. After stirring at 0 ^{o}C for 4 hours, small amount of cold water was added carefully and slowly and the mixture was diluted with EtOAc before being dried over Na_2SO_4, filtered and concentrated to give crude alcohol as a colorless oil.

To a solution of DMSO (1.9 mL) in DCM (39 mL) was added oxalyl chloride (1.14 mL, 13 mmol) at -78 ^{o}C. After stirring for 30 minutes, a solution of the crude alcohol in DCM (3 mL) was added to the solution. The resulting solution was stirred at -78 ^{o}C for 45 minutes before adding iPr_2NEt (9.2 mL, 53 mmol). After stirring at -78 ^{o}C for another 30 minutes, the solution was warmed slowly to 0 ^{o}C, and $NaHCO_3$ solution was added. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, filtered and concentrated to give crude aldehyde **5.11** as a colorless oil.

Bu_2BOTf (9.7 mL, 1.0 M in DCM, 9.7 mmol) and Et_3N (1.5 mL, 10.5 mmol) was added successively to a solution of (*R*)-4-benzyl-3-propionyloxazolidin-2-one[8b] (2.2 g, 9.33 mmol) in DCM (23 mL) at 0 ^oC. The resulting light yellow solution was stirred at 0 ^oC for 30 minutes and then cooled to -78 ^oC before slowly adding a solution of crude aldehyde **5.11** in DCM (5 mL). After stirring at -78 ^oC for 2 hours and at 0 ^oC for another 2 hours, pH 7 buffer was added, followed by the addition of H_2O_2 in MeOH (1: 2) at 0 ^oC. The mixture was warmed to RT slowly and stirred overnight. The mixture was then extracted with EtOAc (3x50 mL), washed with $NaHCO_3$, water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (25%-30% EtOAc in hexanes) to give amide **5.12** (3.1 g, 87% over 3 steps) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (2H, m), 7.30 – 7.27 (1H, m), 7.25 – 7.18 (4H, m), 6.86 (2H, d, *J* = 8.7 Hz), 4.70 – 4.63 (1H, m), 4.44 (2H, s), 4.19 – 4.16 (2H, m), 3.93 (1H, qd, *J* = 7.0, 3.1 Hz), 3.89 – 3.84 (1H, m,), 3.80 (3H, s), 3.57 (1H, dd, *J* = 9.2, 4.4 Hz), 3.52 (1H, dd, *J* = 9.2, 7.3 Hz), 3.32 (1H, dd, *J* = 13.3, 3.2 Hz), 2.76 (1H, dd, *J* = 13.3, 9.7 Hz), 2.01 – 1.91 (1H, m), 1.25 (3H, d, *J* = 6.9 Hz), 0.94 (3H, d, *J* = 7.0 Hz). Spectroscopic data agreed with the literature data.[8b]

(2*R*)-N-Methoxy-2-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-methyl-1,3-dioxan-4-yl)-N-methylpropanamide (5.14)



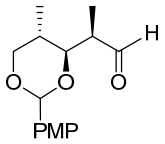
5.14

To a solution of N,O-dimethylhydroxylamine hydrochloride (2.3 g, 23.1 mmol) in THF (17 mL) was slowly added $AlMe_3$ (11.55 mL, 2.0 M in hexane, 23.1 mmol) at 0 ^oC (venting required). After stirring at 0 ^oC for 30 minutes and at RT for 90 minutes, a solution of PMB ether **5.12** (3.39 g, 7.7 mmol) in THF (17 mL) was introduced slowly at -20 ^oC and the solution was stirred at -20 ^oC for 90 minutes before pouring the solution into HCl solution (1 N, 50 mL) and DCM (50 mL). After stirring at 0 ^oC for another 90 minutes, the mixture was extracted with DCM (3 x 50 mL). The combined organic phases were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (30% EtOAc in hexanes) to give Weinreb amide **5.13** (1.88 g, 75%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (3H, d, *J* = 8.6 Hz), 6.87 (2H, d, *J* = 8.7 Hz), 4.45 (2H, dd, *J* = 17.2, 11.6 Hz), 4.02 (1H, d, *J* = 2.7 Hz), 3.80 (3H, s), 3.73 – 3.67 (1H, m), 3.67 (3H, s), 3.62 (1H, dd, *J* = 9.1, 4.0 Hz), 3.53 (1H, dd, *J* = 9.1, 5.9 Hz), 3.18 (3H, s), 3.08 – 2.99 (1H, m), 1.93 – 1.80 (1H, m), 1.17 (3H, d, *J* = 7.0 Hz), 0.97 (3H, d, *J* = 6.9 Hz). Spectroscopic data agreed with the literature data.[8b]

To the mixture of this amide **5.13** (2.7 g, 8.3 mmol) and molecular sieves (3.2g, 4 Å) in DCM (63 mL) was added DDQ (2.26 g, 9.97 mmol) at -10 ^oC. After stirring at 0 ^oC for 90 minutes, the mixture was filtered through celite pad and the filtrate was washed by NaOH solution (1 N) and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (30% EtOAc in hexanes) to give acetal **5.14** (2.15 g, 80%) as a colorless liquid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.4 Hz), 6.87 (2H, d, *J* = 8.9 Hz), 5.47 (1H, s), 4.05 (1H, dd, *J* = 11.3, 4.7 Hz), 3.82 (1H, dd, *J* = 9.7, 6.5 Hz), 3.80 (3H, s), 3.71 (3H, s), 3.52 (1H, t, *J* = 11.2 Hz), 3.19 (3H, s),

3.19 – 3.15 (1H, m), 1.95 (1H, m), 1.27 (3H, d, J = 7.0 Hz), 0.76 (3H, d, J = 6.7 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.8, 131.3, 127.3, 113.6, 100.8, 82.9, 72.9, 61.5, 55.4, 39.0, 33.9, 13.2, 12.5; HRMS (ESI+) calc for $C_{17}H_{26}NO_5$ $[M + H]^+$ 324.1810, found 324.1821. Spectroscopic data agreed with the literature data.[8b]

(2*R*)-2-((4*S*,5*S*)-2-(4-methoxyphenyl)-5-Methyl-1,3-dioxan-4-yl)propanal (5.15)

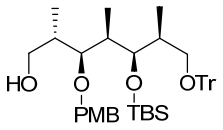


5.15

A solution of acetal **5.14** (2.15 g, 6.7 mmol) in THF (13 mL) was added to a solution of $LiAlH_4$ (430 mg, 11.3 mmol) in THF (50 mL) slowly at -60 ^{o}C. After stirring at -60 ^{o}C for 2 hours and 0 ^{o}C for 1 hour, glacial acetic acid (2 mL) was added to the solution, followed by sodium potassium tartrate solution (66 mL) and the mixture was stirred at RT for another 1 hour before diluted with hexanes. The mixture was then extracted with DCM and the organic phase was washed by brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (20% EtOAc in hexanes) to give aldehyde **5.15** (1.7 g, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (1H, s), 7.34 (2H, d, J = 8.4 Hz), 6.86 (2H, d, J = 8.9 Hz), 5.49 (1H, s), 4.15 (1H, dd, J = 11.3, 4.7 Hz), 4.07 (1H, dd, J = 10.1, 2.3 Hz), 3.79 (3H, s), 3.58 (1H, t, J = 11.1 Hz), 2.58 (1H, ddd, J = 7.2, 6.1, 4.1 Hz), 2.17 – 2.05 (1H, m), 1.24 (3H, d, J = 7.1 Hz), 0.82 (3H, d, J = 6.7 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 204.3, 160.1, 130.9, 127.4, 113.7, 101.1, 81.8, 73.0, 55.4,

47.5, 30.5, 12.1, 7.2; HRMS (ESI+) calc for $C_{15}H_{21}O_4$ $[M + H]^+$ 265.1440, found 265.1443. Spectroscopic data agreed with the literature data.[8b]

(2*S*,3*S*,4*R*,5*R*,6*S*)-5-(*tert*-butyldimethylsilyloxy)-3-(4-methoxybenzyloxy)-2,4,6-trimethyl-7-trityloxy-heptan-1-ol (5.18)



5.18

Bu_2BOTf (4.04 mL, 1 M in DCM, 4.04 mmol) and Et_3N (0.74 mL, 5.3 mmol) was added successively to a solution of (*R*)-4-benzyl-3-propionyloxazolidin-2-one (1.02 g, 4.35 mmol) in DCM (6 mL) at 0 ^oC. The resulting light yellow solution was stirred at 0 ^oC for 30 minutes and then cooled to -78 ^oC before adding a solution of aldehyde **5.15** (821 mg, 3.11 mmol) in DCM (2 mL) slowly. After stirring at -78 ^oC for 2 hours and at 0 ^oC for another 2 hours, pH 7 buffer was added, followed by the addition of H_2O_2 in MeOH (1: 2) at 0 ^oC. The mixture was warmed to RT slowly and stirred overnight. The mixture was then extracted with EtOAc (3 x 50 mL), washed with $NaHCO_3$, water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (20% EtOAc in hexanes) to give amide **5.16** (1.34 g, 86%) as a colorless oil. Spectroscopic data agreed with the literature data.[8b]

To a solution of alcohol **5.16** (1.33 g, 2.6 mmol) and 2,6-lutidine (0.61 mL, 5.2 mmol) in DCM (7.4 mL) was added TBSOTf (1 mL, 3.9 mmol) at -20 ^oC. After stirring at 0 ^oC for 2 hours, the solution was diluted with ether, washed with $NaHSO_4$ and brine, dried

over Na_2SO_4, filtered, concentrated and purified by flash chromatography (10% EtOAc in hexanes) to give TBS ether (1.52 g, 93%) as a colorless oil. Spectroscopic data agreed with the literature data.[8b]

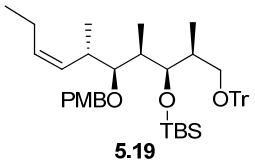
This TBS ether (1.52 g, 2.4 mmol) was dissolved in THF (27 mL). EtOH (0.3 mL) and $LiBH_4$ (2.4 mL, 2 M in THF, 4.8 mmol) added to the solution at -30 ^oC. After stirring at 0 ^oC for 1 hour and RT for 12 hours, the solution was diluted with Et_2O. Then NaOH solution (1 N) was added and the mixture was stirred for additional 2 hours. The organic phase was washed by brine, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (20% EtOAc in hexanes) to give alcohol **5.17** (820 mg, 74%) as a colorless oil. Spectroscopic data agreed with the literature data.[8b]

To a solution of alcohol **5.17** (820 mg, 1.8 mmol) in pyridine (18 mL) was added TrCl (1.06 g, 3.8 mmol) and DMAP (464 mg, 3.8 mmol). After refluxing for 18 hours, the solution was cooled to RT and citric acid was added. The mixture was extracted with DCM and the organic phase was washed with citric acid, water and $NaHCO_3$ solution, dried over Na_2SO_4, filtered and concentrated to give crude trityl ether as a white solid which was used in the next step without purifications.

This trityl ether was dissolved in DCM (11 mL). DIBAL-H (9 mL, 1 M in toluene, 9 mmol) was added at 0 ^oC. After stirring for 3 hours, MeOH was added dropwise, followed by potassium sodium tartrate and EtOAc. The solution was stirred for another 1 hour. The mixture was then extrated with DCM, and the organic phase was washed by water, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (20% EtOAc in hexanes) to give alcohol **5.18** (1.09 g, 86% over 2 steps)

as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.40 (6 H, m), 7.28 – 7.16 (11 H, m), 6.83 (2 H, d, *J* 8.7), 4.47 (2 H, dd, *J* 30.1, 10.4), 3.79 (3 H, s), 3.73 – 3.65 (2 H, m), 3.56 (1 H, dt, *J* 11.0, 5.5), 3.32 (1 H, dd, *J* 6.3, 4.6), 3.07 (1 H, dd, *J* 9.1, 6.5), 3.01 (1 H, dd, *J* 9.0, 7.3), 2.70 (1 H, dd), 2.04 – 1.99 (1 H, m), 1.91 (1 H, ddd, *J* 13.1, 6.3, 3.5), 1.84 (1 H, td, *J* 6.9, 4.6), 0.99 (3 H, d, *J* 7.0), 0.93 (3 H, d, *J* 7.0), 0.91 (3 H, d, *J* 6.8), 0.79 (8 H, s), -0.03 (3 H, s), -0.25 (2 H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.35, 144.42, 130.48, 129.37, 128.82, 127.82, 127.00, 113.96, 100.00, 86.77, 86.07, 75.24, 73.83, 67.22, 66.05, 55.36, 40.69, 38.36, 37.96, 26.25, 18.53, 15.60, 11.80, 11.51, -3.40, -3.89.; HRMS (ESI+) calc for $C_{43}H_{59}O_5Si$ $[M + H]^+$ 683.4131, found 683.4128.

***tert*-Butyl((2*S*,3*R*,4*R*,5*S*,6*S*,*Z*)-5-(4-methoxybenzyloxy)-2,4,6-trimethyl-1-(trityloxy) dec-7-en-3-yloxy)dimethylsilane (5.19)**



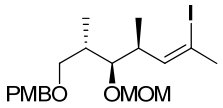
5.19

To a solution of DMSO (0.41 mL) in DCM (7.5 mL) was added oxalyl chloride (0.22 mL, 2.5 mmol) at -78 ^{o}C. After stirring for 30 minutes, a solution of alcohol **5.18** (1.09 g, 1.55 mmol) in DCM (1 mL) was added. The resulting solution was stirred at -78 ^{o}C for 45 minutes before adding Et_3N (1.5 mL, 11 mmol). After stirring at -78 ^{o}C for another 30 minutes, the solution was warmed to 0 ^{o}C slowly, and $NaHCO_3$ solution was added. The organic layer was separated, washed with water and brine, dried over Na_2SO_4, filtered

and concentrated to give crude aldehyde as a colorless oil which was used in the next step without purification.

Propyltriphenylphosphonium bromide (1.1 g, 2.9 mmol) was suspended in THF (6 mL). *n*-BuLi solution (1.14 mL, 2.5 M in hexane, 2.9 mmol) was added dropwise at -78 ^{o}C. After stirring at RT for 40 minutes, the resulting orange solution was added to a solution of the above crude aldehyde in THF (8 mL) at -78 ^{o}C until the orange color persisted. Then the solution was warmed to -10 ^{o}C, stirred for 1 hour and quenched with saturated NH_4Cl solution. The mixture was then diluted with hexane and the layers separated. The combined organic layers were washed with water (2 x 20 mL) and brine (20 mL), dried (MgSO4), concentrated and purified by flash chromatography (5% EtOAc/hexanes) to afford trityl ether **5.19** (766 mg, 70% over 2 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.41 (6H, m), 7.28 – 7.17 (11H, m), 6.81 (2H, d, *J* = 8.7 Hz), 5.36 (1H, dd, *J* = 10.9, 9.6 Hz), 5.28 (1H, dt, *J* = 11.0, 7.1 Hz), 4.45 (2H, dd, *J* = 80.0, 10.6 Hz), 3.79 (3H, s), 3.52 (1H, dd, *J* = 5.7, 3.3 Hz), 3.16 (1H, t, *J* = 5.2 Hz), 3.06 (1H, dd, *J* = 8.8, 5.5 Hz), 2.85 (1H, t, *J* = 8.8 Hz), 2.77 – 2.71 (1H, m), 2.05 – 1.99 (2H, m), 1.90 (1H, ddd, *J* = 15.6, 11.0, 4.6 Hz), 1.70 (1H, dd, *J* = 12.5, 5.7 Hz), 0.99 (3H, d, *J* = 6.9 Hz), 0.96 (3H, d, *J* = 6.9 Hz), 0.91 – 0.87 (6H, m), 0.79 (9H, s), -0.03 (3H, s), -0.24 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.0, 144.6, 131.7, 131.6, 129.1, 128.9, 128.1, 127.8, 127.0, 113.7, 86.6, 84.5, 74.7, 74.2, 67.2, 55.4, 40.1, 38.8, 35.3, 26.3, 21.0, 18.9, 18.6, 14.5, 12.6, 11.1, -3.3, -3.9; HRMS (ESI+) calc for $C_{46}H_{63}O_4Si$ $[M + H]^+$ 707.4496, found 707.4499. Spectroscopic data agreed with the literature data.[5b]

1-(((2*S*,3*R*,4*S*,*Z*)-6-Iodo-3-(methoxymethoxy)-2,4-dimethylhept-5-enyloxy)methyl)-4-methoxybenzene (5.22)



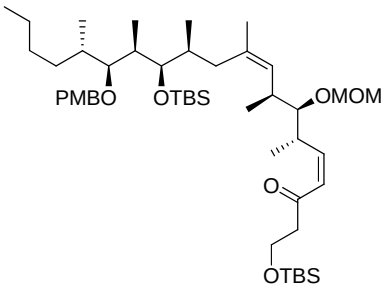
5.22

To a solution of Weinreb amide **5.13** (420 mg, 1.14 mmol) in THF (11.4 mL) was added DIBAL-H (1.4 mL, 1 M in toluene, 1.4 mmol) dropwise at -10 ^{o}C. After stirring for 3 hours, the solution was poured into Rochelle's solution, diluted with ether and stirred for another 30 minutes. Two layers formed and the organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated to give the crude aldehyde without purification.

To a solution of ethyltriphenylphosphonium iodide (326 mg, 0.78 mmol) in THF (2 mL) was added *n*-BuLi (0.30 mL, 2.5 M in hexane, 0.75 mmol) at 0 ^{o}C. After stirring for 10 minutes, the solution was cooled to -78 ^{o}C, and a pre-cooled (-78 ^{o}C) solution of iodine (198 mg, 0.78 mmol) in THF (4.5 mL) was added. The resulting slurry mixture was stirred at -70 ^{o}C for 15 minutes before warmed to -23 ^{o}C. NaHMDS (0.7 mL, 1 M in THF, 0.7 mmol) was added. After stirring at -23 ^{o}C for 10 minutes, the red solution was cooled to -33 ^{o}C and the crude aldehyde in THF (0.5 mL) was added and the solution was stirred at -33 ^{o}C for 30 minutes before warming to RT and addition of MeOH. The mixture was then concentrated and purified by flash chromatography (5-10% EtOAc in hexanes) to give vinyl iodide **5.22** (38 mg, 32%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (2H, d, J = 8.7 Hz), 6.87 (2H, d, J = 8.7 Hz), 5.35 (1H, dq, J = 8.9, 1.4 Hz), 4.60 (2H, dd, J = 14.8, 6.6 Hz), 4.42 (2H, s), 3.80 (3H, s), 3.52 (1H, dd, J = 9.1, 4.3 Hz),

3.41 – 3.37 (1H, m), 3.37 (3H, s), 3.34 (1H, dd, *J* = 9.1, 7.1 Hz), 2.65 – 2.53 (1H, m), 2.46 (3H, d, *J* = 1.4 Hz), 2.03 – 1.92 (1H, m), 1.04 (3H, d, *J* = 6.9 Hz), 0.99 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ159.2, 138.7, 131.0, 129.4, 113.9, 99.8, 98.3, 84.0, 72.9, 72.2, 56.2, 55.4, 43.8, 36.9, 33.7, 15.0, 14.5; HRMS (ESI+) calc for $C_{19}H_{29}IO_4Na$ $[M + Na]^+$ 471.1008, found 471.1001. Spectroscopic data agreed with the literature data.[8b]

(8*Z*,10*S*,11*S*,12*S*,13*Z*,16*S*,17*R*)-17-((2*R*,3*S*,4*S*)-3-(4-methoxybenzyloxy)-4-methyloctan-2-yl)-11-(methoxymethoxy)-2,2,3,3,10,12,14,16,19,19,20,20-dodecamethyl-4,18-dioxa-3,19-disilahenicosa-8,13-dien-7-one (5.27)

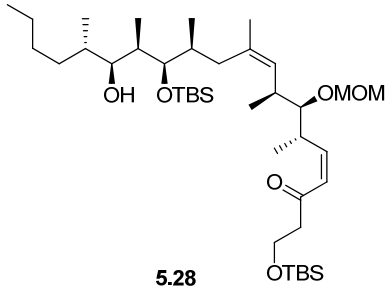


5.27

K_2CO_3 (60 mg, 0.43 mmol) and 18-crown-6 (228 mg, 0.86 mmol) were dissolved in toluene (0.6 mL) and HMPA (0.06 mL) at RT and the mixture was stirred for 3 hours before adding a solution of aldehyde **5.4** (38 mg, 0.07 mmol) and phosphonate **5.5** (103 mg, 0.23 mmol) in toluene (0.6 mL) and HMPA (0.06 mL) at -10 ^{o}C. After stirring at -5 ^{o}C for 18 hours, NH_4Cl solution was added to quench the reaction and the mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (20% EtOAc in hexanes) to afford the new TBS ether

5.27 (51 mg, 85%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.5 Hz), 6.87 (2H, d, *J* = 8.7 Hz), 6.15 – 6.08 (2H, m), 4.90 (1H, d, *J* = 10.3 Hz), 4.73 (2H, dd, *J* = 36.7, 6.7 Hz), 4.48 (2H, dd, *J* = 36.0, 10.8 Hz), 3.95 – 3.84 (2H, m), 3.80 (3H, s), 3.75 – 3.64 (1H, m), 3.49 – 3.46 (1H, m), 3.41 (3H, s), 3.25 (1H, d, *J* = 7.3, 3.8 Hz), 3.13 (1H, t, *J* = 5.4 Hz), 2.73 – 2.55 (2H, m), 2.54 – 2.42 (1H, m), 2.16 (1H, t, *J* = 12.5 Hz), 1.95 – 1.80 (2H, m), 1.74 – 1.65 (2H, m), 1.57 (3H, s), 1.51 (1H, ddd, *J* = 10.7, 8.0, 2.7 Hz), 1.45 – 1.25 (3H, m), 1.20 – 1.13 (2H, m), 1.02 (3H, d, *J* = 6.9 Hz), 0.98 (3H, d, *J* = 6.9 Hz), 0.96 (3H, d, *J* = 6.8 Hz), 0.96 (3H, d, *J* = 6.6 Hz), 0.93 (9H, s), 0.89 (3H, t, *J* = 7.3 Hz), 0.87 (9H, s), 0.72 (2H, d, *J* = 6.7 Hz), 0.07 (3H, s), 0.06 (3H, s), 0.04 (3H, s), 0.04 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 199.6, 159.0, 151.1, 133.0, 131.4, 130.0, 129.0, 125.7, 113.7, 97.6, 86.9, 85.6, 77.5, 74.6, 59.1, 56.2, 55.3, 47.2, 38.8, 36.7, 36.2, 35.9, 35.6, 35.4, 30.9, 29.9, 29.7, 26.3, 25.9, 23.1, 18.5, 18.3, 17.5, 17.3, 16.9, 14.2, 14.0, 11.4, -3.4, -3.5, -5.4, -5.4; HRMS (ESI+) calc for $C_{48}H_{88}O_7Si_2Na$ $[M + Na]^+$ 855.5966, found 855.5944.

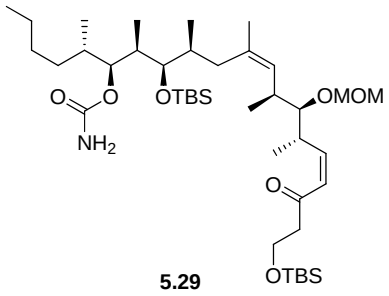
(8*Z*,10*S*,11*S*,12*S*,13*Z*,16*S*,17*R*)-17-((2*R*,3*S*,4*S*)-3-hydroxy-4-methyloctan-2-yl)-11-(methoxymethoxy)-2,2,3,3,10,12,14,16,19,19,20,20-dodecamethyl-4,18-dioxa-3,19-disilahenicosa-8,13-dien-7-one (5.28)



5.28

To a vigorously stirred solution of PMB ether **5.27** (45 mg, 0.06 mmol) in DCM (2.7 mL) and pH 7 buffer (0.3 mL) was added DDQ (25 mg, 0.11 mmol) at 0 ^{o}C. After stirring for 1.5 hours, $NaHCO_3$ solution was added and the mixture was extracted with DCM, washed by $Na_2S_2O_3$ solution, water and brine, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (20% EtOAc in hexanes) to give alcohol **5.28** (28 mg, 75%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 – 6.08 (2H, m), 4.92 (1H, d, *J* = 10.2 Hz), 4.73 (2H, dd, *J* = 24.2, 6.7 Hz), 3.90 (2H, qt, *J* = 10.3, 6.6 Hz), 3.71 (1H, ddd, *J* = 9.0, 6.9, 3.7 Hz), 3.65 (1H, t, *J* = 3.9 Hz), 3.41 (3H, s), 3.26 (2H, dd, *J* = 7.2, 3.8 Hz), 2.70 (1H, dt, *J* = 15.9, 6.7 Hz), 2.60 (1H, dt, *J* = 15.9, 6.4 Hz), 2.54 – 2.45 (1H, m), 2.14 (1H, t, *J* = 12.1 Hz), 1.90 – 1.79 (3H, m), 1.70 (1H, br s), 1.66 – 1.61 (1H, m), 1.59 (3H, d, *J* = 0.9 Hz), 1.55 – 1.50 (1H, m), 1.43 – 1.26 (3H, m), 1.24 – 1.15 (1H, m), 1.13 – 1.05 (1H, m), 1.03 (3H, d, *J* = 6.9 Hz), 0.97 (3H, d, *J* = 6.6 Hz), 0.92 (9H, s), 0.90 (3H, t, *J* = 7.3 Hz), 0.89 (3H, d, *J* = 7.0 Hz), 0.87 (9H, s), 0.84 (3H, d, *J* = 6.7 Hz), 0.74 (3H, d, *J* = 6.9 Hz), 0.10 (3H, s), 0.10 (3H, s), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 199.6, 151.0, 133.3, 130.0, 125.8, 97.8, 87.1, 79.7, 79.1, 59.0, 56.2, 47.2, 36.9, 36.4, 36.2, 36.0, 35.8, 35.3, 31.9, 29.2, 26.2, 25.9, 23.2, 23.2, 18.4, 18.3, 17.5, 17.1, 16.0, 14.5, 14.2, 8.8, -3.2, -4.1, -5.4, -5.4; HRMS (ESI+) calc for $C_{40}H_{80}O_6Si_2Na$ $[M + Na]^+$ 735.5391, found 735.5401.

(5*S*,6*S*,7*R*,8*R*,9*S*,11*Z*,13*S*,14*S*,15*S*,16*Z*)-8,20-bis(*tert*-butyldimethylsilyloxy)-14-(methoxymethoxy)-5,7,9,11,13,15-hexamethyl-18-oxoicosa-11,16-dien-6-yl carbamate (5.29)

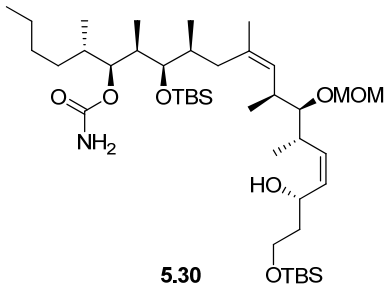


5.29

To a solution of alcohol **5.28** (28 mg, 0.04 mmol) in DCM (3.7 mL) was added $Cl_3CCONCO$ (24 µL, 0.2 mmol) at RT. After stirring for 1.5 hours, the solution was loaded onto a neutral Al_2O_3 plug and left for 2 hours. The Al_2O_3 plug was then flushed with EtOAc (100 mL) and the solution was concentrated and purified by flash chromatography (30% EtOAc in hexanes) to afford carbamate **5.29** (24 mg, 82%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.17 – 6.06 (2H, m), 4.86 (1H, d, *J* = 10.3 Hz), 4.73 (2H, dd, *J* = 33.8, 6.7 Hz), 4.69 (2H, br s), 4.61 (1H, dd, *J* = 7.2, 4.6 Hz), 3.91 (2H, t, *J* = 6.8 Hz), 3.68 (1H, dqd, *J* = 10.3, 6.9, 3.6 Hz), 3.40 (3H, s), 3.40 – 3.38 (1H, m), 3.22 (1H, dd, *J* = 7.8, 3.5 Hz), 2.67 (2H, td, *J* = 6.8, 2.7 Hz), 2.50 – 2.41 (1H, m), 2.15 (1H, t, *J* = 12.4 Hz), 1.96 – 1.87 (2H, m), 1.73 – 1.62 (2H, m), 1.59 (3H, s), 1.45 – 1.23 (4H, m), 1.17 – 1.03 (2H, m), 1.01 (3H, d, *J* = 7.0 Hz), 0.94 (3H, d, *J* = 6.6 Hz), 0.91 (9H, s), 0.90 – 0.85 (9H, m), 0.86 (9H, s), 0.69 (3H, d, *J* = 6.8 Hz), 0.07 (3H, s), 0.06 (3H, s), 0.04 (3H, s), 0.04 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 199.4, 157.1, 151.1, 133.4, 129.6, 125.7, 97.8, 87.2, 79.9, 77.1, 59.1, 56.2, 47.1, 37.4, 36.6, 36.3, 36.0, 34.9, 34.9,

31.1, 29.4, 26.2, 25.9, 23.0, 22.9, 18.5, 18.3, 17.7, 17.0, 16.1, 14.1, 13.0, 10.5, -3.4, -3.6, -5.4; HRMS (ESI+) calc for $C_{41}H_{81}NO_7Si_2Na$ $[M + Na]^+$ 778.5449, found 778.5462.

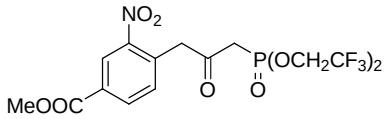
(5*S*,6*S*,7*R*,8*R*,9*S*,11*Z*,13*S*,14*S*,15*S*,16*Z*,18*S*)-8,20-bis(*tert*-butyldimethylsilyloxy)-18-hydroxy-14-(methoxymethoxy)-5,7,9,11,13,15-hexamethylicosa-11,16-dien-6-yl carbamate (5.30)



A solution of ketone **5.29** (15 mg, 0.02 mmol) in toluene (3.7 mL) was treated with K-selectride™ (40 µL, 1 M in THF, 0.04 mmol) at -78 °C. After stirring for 2 hours, one drop of AcOH was added to quench the reaction. The solution was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography (15% EtOAc in hexanes) to give alcohol **5.30** (14 mg, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 – 5.38 (2H, m), 5.03 (1H, d, *J* = 10.1 Hz), 4.63 (2H, s), 4.62 – 4.54 (3H, m), 3.91 (1H, dt, *J* = 10.3, 5.3 Hz), 3.88 – 3.81 (1H, m), 3.43 (1H, dd, *J* = 5.9, 3.0 Hz), 3.39 (3H, s), 3.14 – 3.07 (1H, m), 2.81 (1H, dd, *J* = 13.8, 6.8 Hz), 2.58 – 2.50 (1H, m), 2.19 (1H, t, *J* = 12.3 Hz), 1.98 – 1.90 (2H, m), 1.79 – 1.66 (4H, m), 1.64 (3H, s), 1.44 – 1.27 (4H, m), 1.19 – 1.04 (2H, m), 1.02 (3H, d, *J* = 6.9 Hz), 0.95 (3H, d, *J* = 6.7 Hz), 0.92 (9H, s), 0.90 (9H, s), 0.90 – 0.85 (9H, m), 0.73

(3H, d, J = 6.8 Hz), 0.08 (3H, s), 0.07 (3H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.1, 134.3, 132.9, 131.8, 130.3, 98.2, 87.3, 80.0, 77.2, 68.2, 62.4, 56.1, 38.8, 37.3, 36.4, 35.7, 35.1, 35.0, 31.1, 29.7, 29.4, 26.2, 25.9, 23.1, 23.0, 18.5, 18.3, 18.2, 16.6, 16.1, 14.1, 13.1, 10.5, -3.4, -3.7, -5.5; HRMS (ESI+) calc for $C_{41}H_{83}NO_7Si_2Na$ [M + Na]$^+$ 780.5606, found 780.5615.

Methyl 4-(3-(bis(2,2,2-trifluoroethoxy)phosphoryl)-2-oxopropyl)-3-nitrobenzoate (5.32)



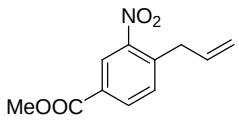
5.32

A solution of the aldehyde **5.37** (244 mg, 1.09 mmol) in t-BuOH (6 mL) and 2-methyl-2-butene (0.75 mL) was treated with a solution of NaClO2 (248 mg, 2.74 mmol) and NaH2PO4 (972 mg, 8.10 mmol) in water (6 mL) dropwise. After stirring for 1 hour, the reaction was partitioned between brine and DCM. The organic layer was dried over Na2SO4, filtered, concentrated to afford acid **5.38** which was used for the next step without purification.

To a solution of acid **5.38** (239 mg, 1.0 mmol) in DCM (13.5 mL) was added 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine (0.32 mL, 2.4 mmol). After stirring for 1 hour, the solution was concentrated and the crude dark red oil was dried in vacuo for 30 minutes. Meanwhile, LiHMDS (3.5 mL, 1.0 M in THF, 3.5 mmol) was added dropwise to a solution of methylphosphonic acid bis(2,2,2-trifluoroethyl) ester (935 mg, 3.63 mmol)

in THF (2.7 mL) at -98 ^{o}C. After stirring for 15 minutes, a solution of the dark red oil in THF (7.9 mL) was added at -98 ^{o}C. The resulting solution was stirred for 1 hour at -98 ^{o}C before adding NH_4Cl solution to quench the reaction. The solution was then warmed to RT, and more NH_4Cl solution was added. The mixture was extracted with DCM, dried over Na_2SO_4, filtered, concentrated. TLC plate and ^{1}H NMR spectrum of the crude mixture indicated that this reaction failed to yield the desired product **5.32**.

Methyl 4-allyl-3-nitrobenzoate (5.33)

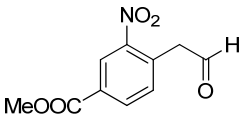


5.33

To a solution of methyl 4-iodo-3-nitrobenzoate **5.34** (1.0 g, 3.3 mmol) in THF (13 mL) was added PhMgCl (1.8 M in THF, 2.0 mL, 3.6 mmol) dropwise at -78 ^{o}C. After 10 minutes, CuCN·2LiCl (1.0 M in THF, 3.6 mL, 3.6 mmol) was added dropwise. The reaction mixture was stirred for 5 minutes before allyl bromide (0.60 mL, 6.5 mmol) was added. After stirring at -78 ^{o}C for 2 hours, the reaction mixture was quenched with saturated NH_4Cl solution was and poured into water. The aqueous layer was extracted with ethyl acetate (3 x 100 mL), and the combined organic phases were washed with brine, dried over Na2SO4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (1% EtOAc in hexanes) to yield alkene 5.33 (610 mg, 85%) as a yellow oil. ^{1}H NMR (500 MHz, CDCl3) δ 8.55 (1H, d, J = 1.6 Hz), 8.18 (1H, dd, J = 8.0, 1.7 Hz), 7.48 (1H, d, J = 8.0 Hz), 6.02 – 5.88 (1H, m), 5.20 – 5.03 (2H, m), 3.96 (3H, s),

3.74 (2H, d, J = 6.5 Hz); 13C NMR (500 MHz, CDCl3) δ 165.1, 139.8, 134.3, 133.6, 132.3, 129.9, 126.0, 118.1, 52.8, 37.1.

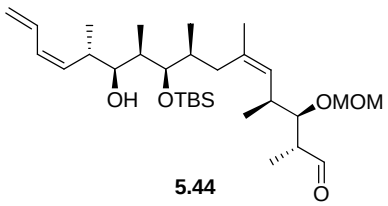
Methyl 3-nitro-4-(2-oxoethyl)benzoate (5.37)



5.37

A solution of alkene **5.33** (370 mg, 1.7 mmol) in MeOH (21 mL) was cooled to -78 ^{o}C, and O_3 was bubbled into the solution. When the solution turned light blue, O_3 was stopped and Me_2S was added to quench the reaction. The resulted solution was concentrated in vacuo, and the residue was purified by flash chromatography (2% EtOAc in hexanes) to give aldehyde 5.37 (244 mg, 65%) as a yellow oil. ^{1}H NMR (500 MHz, CDCl3) δ 9.86 (1H, s), 8.77 (1H, s), 8.26 (1H, dd, *J* = 7.9, 1.5 Hz), 7.43 (1H, d, *J* = 7.9 Hz), 4.22 (2H, s), 3.99 (3H, s); ^{13}C NMR (500 MHz, CDCl3) δ 195.8, 164.8, 134.3, 134.0, 133.1, 131.4, 126.5, 53.0, 48.7.

(2R,3R,4S,5Z,8S,9R,10R,11S,12S,13Z)-9-(*tert*-Butyldimethylsilyloxy)-11-hydroxy-3-(methoxymethoxy)-2,4,6,8,10,12-hexamethylhexadeca-5,13,15-trienal (5.44)

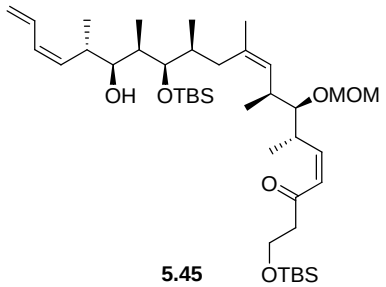


5.44

To a vigorously stirring solution of PMB ether **5.43** (130 mg, 0.17 mmol) in DCM (4.25 mL) and pH 7 buffer (0.43 mL) was added DDQ (118 mg, 0.425 mmol) at 0 ^{o}C. After stirring for 30 minutes at 0 ^{o}C and 45 minutes at RT, the mixture was diluted with pH 7 buffer and extracted with DCM (3 x 50 mL), washed with brine, dried over Na_2SO_4 and concentrated to give a crude diol as a colorless oil.

To a solution of this diol (45 mg, 0.085 mmol) in DCM (1.0 mL) and H_2O (0.6 μL) was added DAIB (163 mg, 0.51 mmol) and TEMPO (5.3 mg, 0.034 mmol) at RT. After stirring for 2 hours, $Na_2S_2O_3$ aqueous solution was added. The solution was extracted with EtOAc (3 x 15 mL), washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (15% EtOAc in hexanes) to give aldehyde **5.44** (21 mg, 24% over two steps) as a colorless oil. ^{1}H NMR (500 MHz, CDCl3) δ 9.63 (1H, d, *J* = 1.4 Hz), 6.63 (1H, dt, *J* = 17.1, 10.8 Hz), 6.15 (1H, t, *J* = 11.0 Hz), 5.33 (1H, t, *J* = 10.5 Hz), 5.25 (1H, dd, *J* = 16.9, 1.6 Hz), 5.16 (1H, d, *J* = 10.1 Hz), 4.86 (1H, d, *J* = 10.4 Hz), 4.67 (2H, s), 3.64 – 3.58 (2H, m), 3.37 (3H, s), 3.35 – 3.31 (1H, m), 2.85 – 2.76 (1H, m), 2.69 – 2.60 (2H, m), 2.17 (1H, t, *J* = 12.2 Hz), 1.94 – 1.84 (1H, m), 1.82 – 1.75 (2H, m), 1.61 (3H, s), 1.58 (1H, d, *J* = 3.1 Hz), 1.10 (3H, d, *J* = 7.0 Hz), 1.01 (3H, d, *J* = 6.6 Hz), 0.97 (3H, d, *J* = 6.7 Hz), 0.96 (3H, d, *J* = 7.0 Hz), 0.93 (9H, s), 0.74 (3H, d, *J* = 6.8 Hz), 0.09 (3H, s), 0.09 (3H, s); ^{13}C NMR (500 MHz, CDCl3) δ 202.9, 136.0, 134.6, 132.1, 131.1, 128.5, 118.5, 97.5, 84.2, 78.8, 76.2, 56.1, 49.5, 38.2, 36.9, 36.3, 35.2, 34.8, 26.2, 23.3, 18.5, 17.3, 17.2, 13.5, 10.1, 9.5, -3.3, -3.6.

(8Z,10S,11S,12S,13Z,16S,17R)-17-((2R,3S,4S,Z)-3-Hydroxy-4-methylocta-5,7-dien-2-yl)-11-(methoxymethoxy)-2,2,3,3,10,12,14,16,19,19,20,20-dodecamethyl-4,18-dioxa-3,19-disilahenicosa-8,13-dien-7-one (5.45)

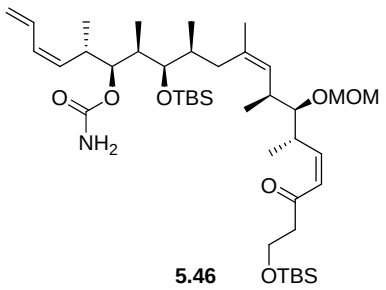


5.45

K_2CO_3 (34 mg, 0.24 mmol) and 18-crown-6 (127 mg, 0.48 mmol) were dissolved in toluene (0.4 mL) and HMPA (0.04 mL) at RT and the mixture was stirred for 3 hours before adding a solution of aldehyde **5.44** (20 mg, 0.040 mmol) and phosphonate **5.5** (17 mg, 0.040 mmol) in toluene (0.4 mL) and HMPA (0.04 mL) at -10 ^{o}C. After stirring at -5 ^{o}C for 18 hours, NH_4Cl solution was added to quench the reaction and the mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, concentrated and purified by flash chromatography (20% EtOAc in hexanes) to afford the TBS ether **5.45** (10 mg, 36%) as a colorless oil. ^{1}H NMR (500 MHz, CDCl3) δ 6.63 (1H, dt, *J* = 16.9, 10.6 Hz), 6.18 – 6.07 (3H, m), 5.34 (1H, t, *J* = 10.4 Hz), 5.25 (1H, dd, *J* = 16.8, 1.8 Hz), 5.16 (1H, d, *J* = 10.1 Hz), 4.90 (1H, d, *J* = 10.3 Hz), 4.73 (2H, dd, *J* = 27.0, 6.7 Hz), 3.90 (2H, qt, *J* = 10.3, 6.6 Hz), 3.73 – 3.65 (1H, m), 3.61 (1H, dd, *J* = 5.5, 3.3 Hz), 3.41 (3H, s), 3.33 (1H, dd, *J* = 7.8, 3.3 Hz), 3.25 (1H, dd, *J* = 7.4, 3.8 Hz), 2.85 – 2.76 (1H, m), 2.70 (1H, dt, *J* = 15.9, 6.8 Hz), 2.61 (1H, dt, *J* = 15.9, 6.4 Hz), 2.53 – 2.44 (1H, m), 2.15 (1H, t, *J* = 12.3 Hz), 1.93 – 1.83 (1H, m), 1.82 – 1.77 (1H, m), 1.72 (1H, d, *J* = 12.1 Hz), 1.58 (3H, d, *J* = 0.7 Hz), 1.03 (3H, d, *J* = 6.9 Hz), 0.97 (3H, d, *J* = 6.6 Hz), 0.95 (3H, d, *J*

= 6.4 Hz), 0.95 (3H, d, *J* = 7.0 Hz), 0.92 (9H, s), 0.87 (9H, s), 0.72 (3H, d, *J* = 6.8 Hz), 0.09 (3H, s), 0.09 (3H, s), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR (500 MHz, CDCl3) δ 199.6, 151.1, 134.7, 133.4, 132.1, 131.0, 129.8, 125.8, 118.5, 97.7, 87.1, 78.9, 76.5, 59.0, 56.2, 47.2, 37.9, 36.4, 36.3, 36.2, 35.7, 35.0, 26.2, 25.9, 23.2, 18.5, 17.5, 17.2, 17.1, 13.7, 9.4, -3.3, -3.7, -5.4, -5.4.

(3Z,5S,6S,7R,8R,9S,11Z,13S,14S,15S,16Z)-8,20-Bis(*tert*-butyldimethylsilyloxy)-14-(methoxymethoxy)-5,7,9,11,13,15-hexamethyl-18-oxoicosa-1,3,11,16-tetraen-6-yl carbamate (5.46)



To a solution of this alcohol (10 mg, 0.014 mmol) in DCM (1.25 mL) was added $Cl_3CCONCO$ (8.5 μL, 0.071 mmol) at RT. After stirring for 1.5 hours, the solution was loaded onto a neutral Al_2O_3 plug and left for 2 hours. The Al_2O_3 plug was then flushed with EtOAc (100 mL) and the solution was concentrated and purified by flash chromatography (30% EtOAc in hexanes) to afford carbamate **5.45** (4.6 mg, 44%) as a colorless oil. ^{1}H NMR (500 MHz, CDCl3) δ 6.60 (1H, dt, J = 16.9, 10.7 H), 6.19 – 6.07 (2H, m), 6.03 (1H, t, J = 11.1 Hz), 5.38 (1H, t, J = 10.5 Hz), 5.23 (1H, dd, J = 16.8, 1.9 Hz), 5.14 (1H, d, J = 10.1 Hz), 4.86 (1H, d, J = 10.3 Hz), 4.77 (1H, d, J = 6.7 Hz), 4.75 – 4.71 (1H, m), 4.70 (1H, d, J = 6.7 Hz), 4.58 (1H, s), 3.91 (2H, td, J = 6.9, 2.2 Hz), 3.73 –

3.64 (1H, m), 3.41 (3H, s), 3.22 (1H, dd, J = 7.7, 3.5 Hz), 3.03 – 2.94 (1H, m), 2.74 – 2.61 (2H, m), 2.48 – 2.40 (1H, m), 2.07 (1H, t, J = 12.4 Hz), 1.91 – 1.81 (2H, m), 1.62 (1H, d, J = 13.4 Hz), 1.58 (3H, s), 1.02 (3H, d, J = 7.0 Hz), 1.00 (3H, d, J = 6.8 Hz), 0.94 (3H, d, J = 4.9 Hz), 0.93 (9H, s), 0.92 (3H, d, J = 6.8 Hz), 0.87 (9H, s), 0.70 (3H, d, J = 6.8 Hz), 0.11 (3H, s), 0.08 (3H, s), 0.05 (3H, s), 0.05 (3H, s); 13C NMR (500 MHz, CDCl3) δ 199.4, 156.9, 151.1, 133.7, 133.3, 132.1, 129.8, 129.7, 125.7, 117.9, 97.8, 87.1, 78.8, 76.9, 59.1, 56.2, 47.2, 37.8, 36.3, 36.2, 35.9, 35.1, 34.4, 26.2, 25.9, 22.9, 18.5, 18.3, 17.6, 17.5, 17.0, 13.7, 10.2, -3.4, -3.6, -5.4.

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