Chapter 6. Bridged discodermolide analog for conformational study

6.1 Design of conformationally constrained discodermolide analogs

As mentioned in Chapters 4 and 5, conformational studies of discodermolide indicated that discodermolide in the β-tubulin binding site likely adopts a hairpin shaped conformation,[1] which is similar to those observed in the solid state and in solution.[2] If the conformational studies are correct, then a locked into its tubulin-binding hairpin shape would be expected to bind more strongly to tubulin than discodermolide itself, since it would not have to pay an entropic price to adopt the binding conformations. We thus collaborated with James P. Snyder of Emory University on the design of a bridged discodermolide analog which would be locked into the hairpin conformation. The resulting conformationally constrained discodermolide analog **6.1** (Figure 6.1) has a bridge between the C3 and C17 positions.

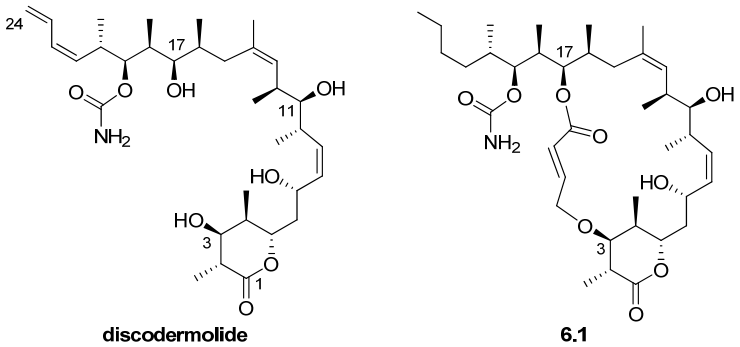


Figure 6.1 The structure of discodermolide and bridged analog **6.1**

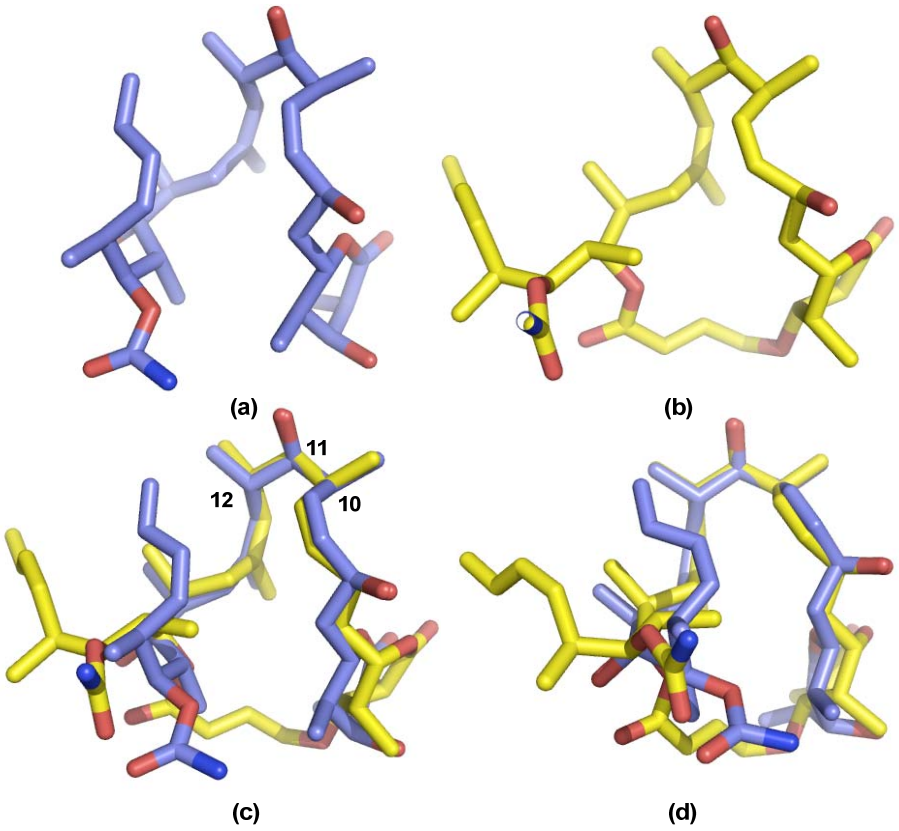


Figure 6.2 Computational modeling of discodermolide and bridged analog **6.1**. (a) Stereoscopic view of discodermolide; (b) Stereoscopic view of bridged analog **6.1**; (c) (d) discodermolide (blue) and bridged analog **6.1** (yellow) superimpose around the C10-C12 bend in the molecule. (Figure created by Dr. J. P. Snyder)

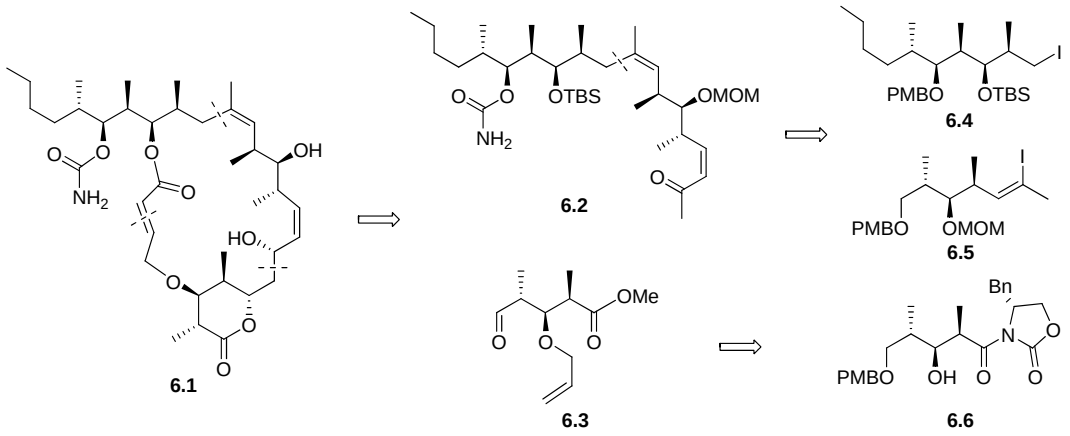
In addition**,** the terminal diene was replaced with an *n*-butyl group, since SAR studies indicate that the terminal diene is not essential for the tubulin assembly activity of discodermolide. The modeling study carried out by Professor Snyder shows that the bridge between the C3 and C17 positions constrains the conformation of the analog into a close analog of the hairpin shape (Figure 6.2). Therefore, if the bridged analog displays similar or better tubulin assembly activity, the hairpin shape conformation will have been confirmed as the bioactive conformation of discodermolide, and it is possible that a better

drug candidate will have been discovered.

6.2 Synthesis of the bridged analog

6.2.1 The first synthetic approach

The retrosynthetic analysis of the bridged analog **6.1** is shown in Scheme 6.1. According to Paterson's second generation synthetic strategy,[3] the target molecule can be formed from the two subunits ketone **6.2** and aldehyde **6.3** via an aldol reaction. Fragment **6.2** can be prepared from precursors **6.4** and **6.5**, and fragment **6.3** can be formed from precursor **6.6**. The synthesis of these precursors has been described in Chapter 5.

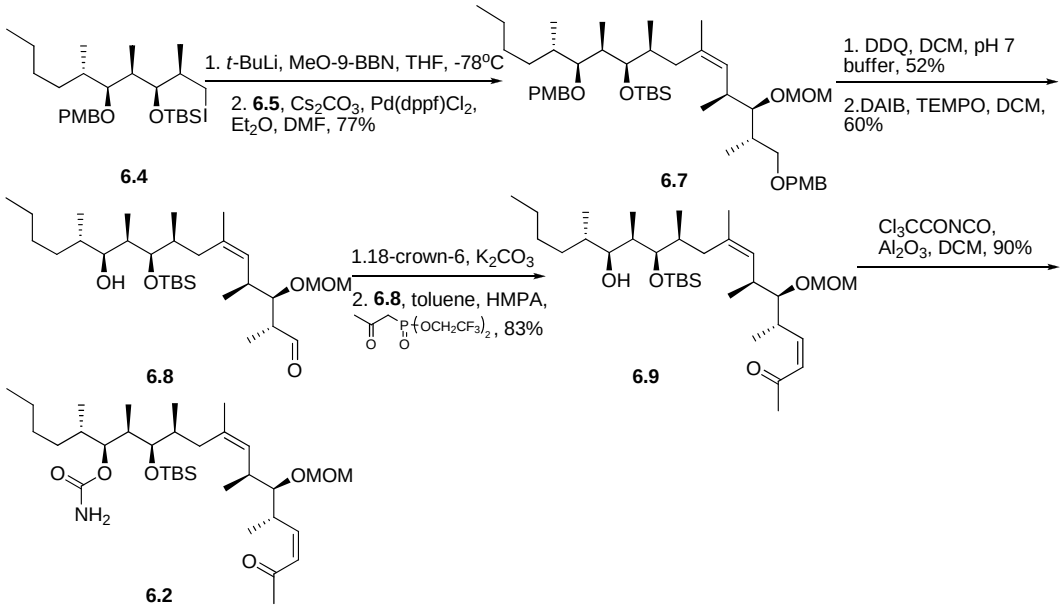


Scheme 6.1 The retrosynthetic analysis of analog **6.1**

The synthesis of fragment **6.2** began with the Suzuki coupling of precursors **6.4** and **6.5**, and their synthesis was described in Chapter 5. The resulting alkene **6.7** was treated

with DDQ in DCM to remove the PMB protecting groups and the following oxidation provided aldehyde **6.8** in 31% yield over two steps. The HWE coupling of aldehyde **6.8** and the appropriate phosphonate reagent afforded ketone **6.9**. The subsequent PMB deprotection and the installation of the carbamate finished the synthesis of fragment **6.2**.

To synthesize the other fragment **6.3**, the precursor **6.6** was first reduced to diol **6.10** upon treatment with lithium borohydride (Scheme 6.3). After selective protection of its primary hydroxyl group as a TBS ether, alcohol **6.11** was treated with sodium

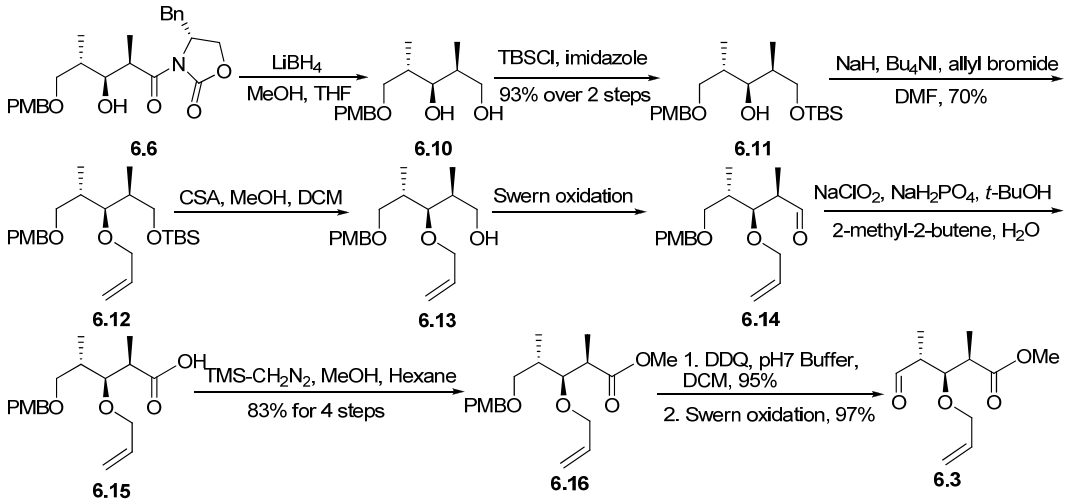


Scheme 6.2 The synthesis of fragment **6.2**

hydride, tetrabutylamonium iodide and allyl bromide to provide allyl ether **6.12** in 70% yield. Subsequent acidic removal of the TBS group followed by oxidation and methylation provided methyl ester **6.16** in 83% yield over four steps. After oxidative deprotection of the PMB group and Swern oxidation, PMB ether **6.16** was converted to

fragment **6.3** in 92% yield over two steps.

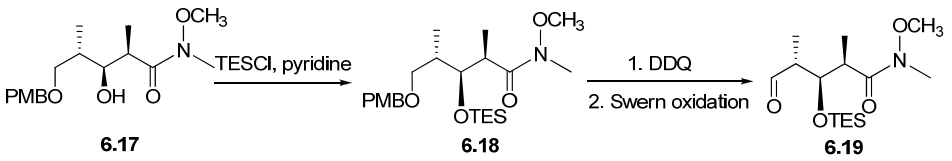
Before running the next step, we found that aldehyde **6.3** was readily epimerized at the α position of the aldehyde carbonyl group even on storage in the freezer. Therefore, we revised the structure of this fragment as shown in Scheme 6.4, in the expectation that the bulky TES group at the β position would block the epimerization at the α position. The synthesis of fragment **6.19** began with a previously synthesized precursor **6.17**, which was converted to fragment **6.19** in good yield after protection as its



Scheme 6.3 Synthesis of the fragment **6.3**

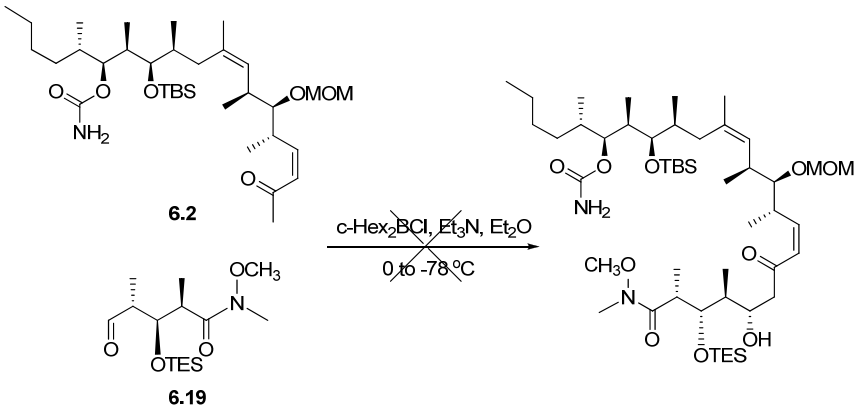
TES ether, oxidative removal of the PMB group, and Swern oxidation. As expected, fragment **6.19** was stable in the freezer.

With fragments **6.2** and **6.19** in hand, the next step was to couple them through an aldol reaction (Scheme 6.5). But the aldol reaction turned out to be a major issue.



Scheme 6.4 Synthesis of the fragment **6.19**

Three attempts at the aldol reaction were made, but each time the fragment **6.2** was recovered and compound **6.19** had decomposed. One of the reasons why the aldol reaction did not work may be that the reaction is extremely sensitive to moisture, and furthermore, each batch was run on a small scale (less than 10 mg) due to the limited amount of **6.2**, which made the reaction even more sensitive to traces of moisture.

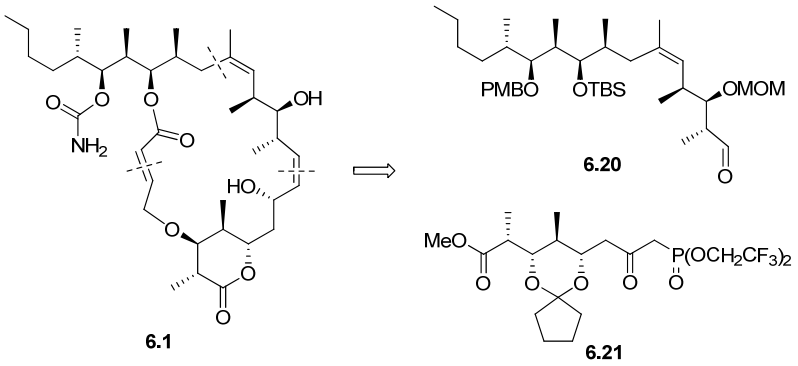


Scheme 6.5 Union of fragments **6.2** and **6.19**

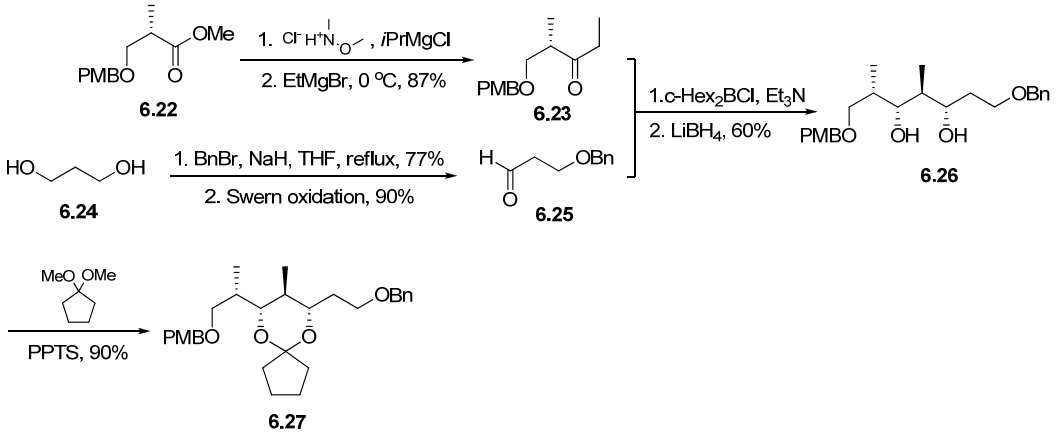
6.2.2 The revised synthetic approach

Since the original synthetic approach was not successful, we revised our synthetic strategy. The revised retrosynthetic analysis is shown in Scheme 6.6. The backbone of the target molecule **6.1** can be formed via HWE coupling of fragment **6.20** and **6.21**,

according to Paterson's third generation synthesis.[4]

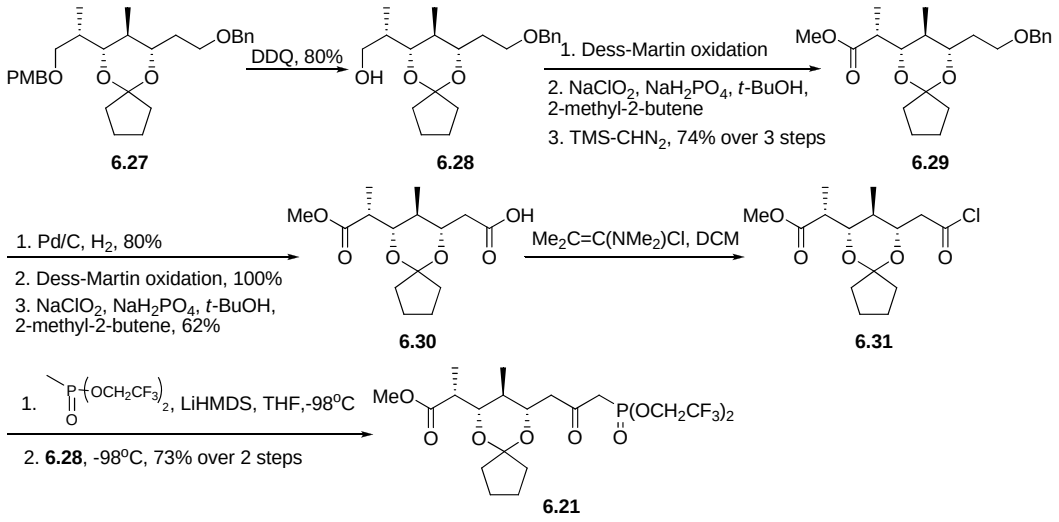


Scheme 6.6 The revised retrosynthetic analysis of analog **6.1**



Scheme 6.7 Synthesis of the intermediate **6.27**

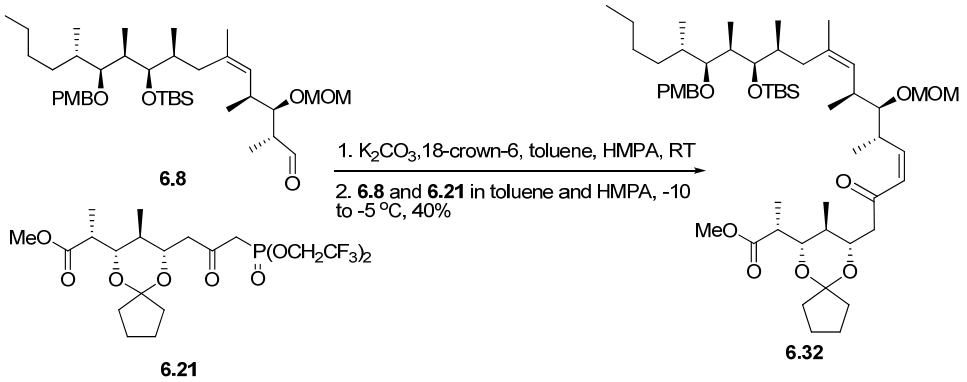
The synthesis of fragment **6.20** was described previously in Chapter 5, while the synthesis of fragment **6.21** began with PMB ether **6.22** (Scheme 6.7), which was first converted to ketone **6.23**. The following aldol coupling between ketone **6.23** and aldehyde **6.25** gave diol **6.26** in 60% yield, which was then protected as acetal **6.27** in 90% yield.



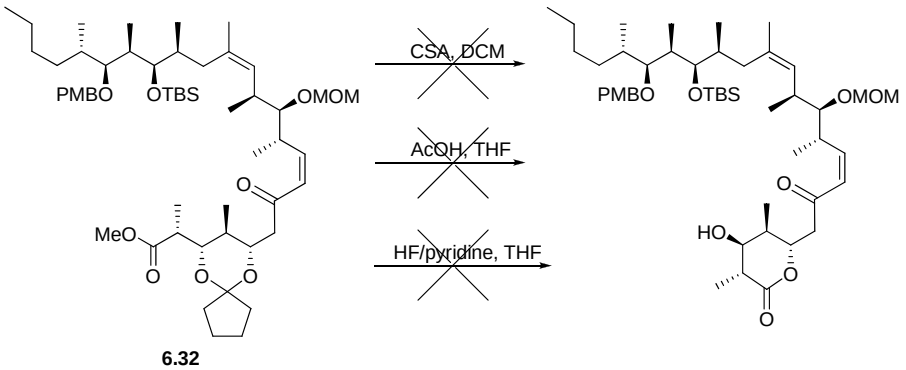
Scheme 6.8 Synthesis of the intermediate **6.21**

Removal of the PMB protecting group from **6.27** gave primary alcohol **6.28**. This was then converted to methyl ester **6.29** in 60% yield by oxidation and methylation (Scheme 6.8). Subsequent debenzylation and oxidations afforded carboxylic acid **6.30** in 49% yield, which was then transformed to acid chloride **6.31** in quantitative yield. Subsequently, acid chloride **6.31** was converted to phosphonate **6.21** in 73% yield.

The following step to connect aldehyde **6.20** to phosphonate **6.21** via the HWE reaction established the backbone successfully to afford **6.32** in 40% yield. Unfortunately, the subsequent deprotection and ring closure reactions could not be achieved under acidic conditions (Scheme 6.9). Three acids (CSA, AcOH and HF) were tested, but none of them yielded any product. Therefore, this project has been deferred. Currently, 100 mg of key intermediate **6.20** and 200 mg of the key intermediate **6.21** are available for future use.



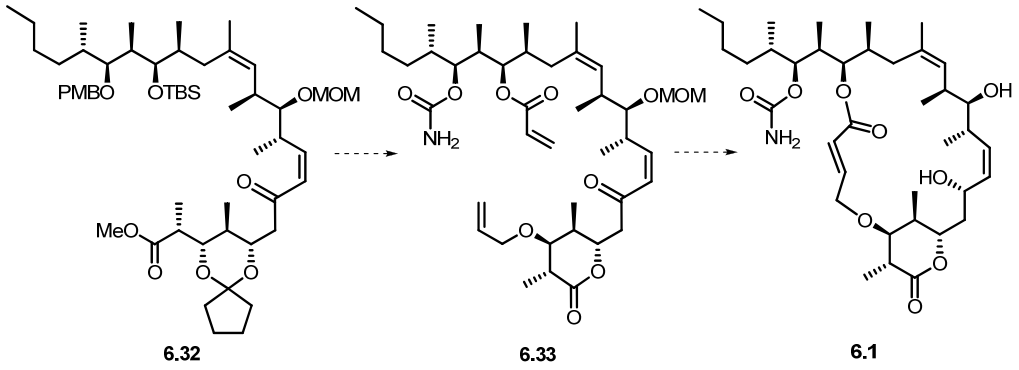
Scheme 6.9 The HWE reaction between **6.8** and **6.21**



Scheme 6.10 The ring closure reaction of intermediate **6.32**

6.3 Future work

In the future, other acids need to be tested to find out the optimized condition for the ring closure reaction. Once this is done, allylation at the C3 position, the installation of the carbamate moiety, and the acryloylation at the C17 position will provide **6.33**. Following reduction of the carbonyl group at C7 position, Grubb's metathesis, and the final removal of the MOM protecting group will afford the bridged discodermolide analog **6.1** (Scheme 6.10).



Scheme 6.11 Future work

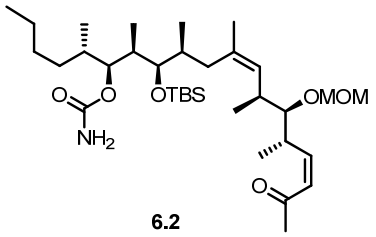
6.4 Experimental section

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.

(5*S*,6*S*,7*R*,8*R*,9*S*,11*Z*,13*S*,14*S*,15*S*,16*Z*)-8-(*tert*-Butyldimethylsilyloxy)-14-(methoxymethoxy)-5,7,9,11,13,15-hexamethyl-18-oxononadeca-11,16-dien-6-ylcarbamate (6.2)



6.2

Removal of PMB protecting groups

To a vigorously stirring solution of **6.7** (50 mg, 0.065 mmol) in DCM (1.5 mL) and pH 7 buffer (0.15 mL) was added DDQ (37 mg, 0.16 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 30 mL), washed with brine, dried over Na_2SO_4 and concentrated to yield a diol (18 mg, 52%) as a colorless oil, which was used for the next step without purification.

Oxidation

To a solution of the diol from last step (17 mg, 0.032 mmol) in DCM (0.5 mL) was

added DAIB (28 mg, 0.096 mmol) and TEMPO (1 mg, 0.0064 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 **6.8** (10 mg, 60%) as a colorless oil.

HWE reaction

A solution of 18-crown-6 (285 mg, 1.08 mmol) and K_2CO_3 (75 mg, 0.54 mmol) in toluene (1 mL) and HMPA (0.1 mL) was stirred at RT for 3 hours. The solution was cooled to -10 ^{o}C and a solution of aldehyde **6.8** (47 mg, 0.09 mmol) and bis(2,2,2-trifluoroethyl) methylphosphonate (109 mg, 0.36 mmol) in toluene (1 mL) and HMPA (0.1 mL) was added. The resulting solution was stirred at -5 ^{o}C for 16 hours. After addition of ammonium chloride solution, the solution was extracted with EtOAc (3 x 10 mL), washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified via flash chromatography (10% EtOAc in hexanes) to give ketone **6.9** (40 mg, 83%) as a colorless oil.

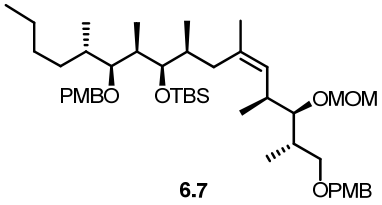
Installation of the carbamate moiety

To a solution of the product **6.9** from last step (40 mg, 0.071 mmol) in DCM (1.26 mL) was added trichloroacetyl isocyanate (12.6 μL, 0.106 mmol) and the solution was stirred at RT for 1.5 hours. Then the solution was loaded onto a neutral Al_2O_3 plug. After

2 hours, the plug was eluted with EtOAc (200 mL), and the eluent was concentrated and purified by flash chromatography (30% EtOAc in hexanes) to give ketone **6.2** (34 mg, 80%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (1H, dd, *J* = 11.6, 9.4 Hz), 6.07 (1H, d, *J* = 11.6 Hz), 4.87 (1H, d, *J* = 10.2 Hz), 4.73 (2H, dd, *J* = 38.6, 6.7 Hz), 4.68 (2H, br s), 4.60 (1H, m), 3.66 (1H, ddd, *J* = 17.3, 8.6, 5.4 Hz), 3.43 (1H, dd, *J* = 5.6, 3.1 Hz), 3.41 (3H, s), 3.22 (1H, dd, *J* = 7.9, 3.4 Hz), 2.47 – 2.42 (1H, m), 2.17 (3H, s), 1.97 – 1.85 (3H, m), 1.74 – 1.67 (2H, m), 1.60 (3 H, s), 1.44 – 1.27 (4H, m), 1.12 (1H, ddd, *J* = 7.2, 6.7, 4.3 Hz), 1.10 – 1.04 (1H, m), 1.03 (3H, d, *J* = 6.9 Hz), 0.96 (3H, d, *J* = 6.6 Hz), 0.91 (9H, s), 0.90-0.86 (9H, m), 0.70 (3 H, d, *J* = 6.8 Hz), 0.07 (3 H, s), 0.05 (3H, s); ^{13}C NMR (500 Hz, $CDCl_3$) δ 198.8, 157.4, 150.9, 133.6, 129.78, 126.1, 98.0, 87.3, 80.2, 77.0, 56.3, 37.3, 36.4, 36.3, 36.2, 35.4, 35.1, 31.7, 31.1, 29.5, 26.4, 26.3, 23.1, 23.1, 18.6, 17.9, 17.2, 16.3, 14.3, 13.5, 10.7, -3.3, -3.7; HRMS (ESI+) calcd for $C_{34}H_{66}NO_6Si$ $[M + H]^+$ 612.4659, found 612.4638.

(5R,6S,10S,11R,Z)-11-((2R,3S,4S)-3-(4-Methoxybenzyloxy)-4-methyloctan-2-yl)-5-((S)-1-(4-methoxybenzyloxy)propan-2-yl)-6,8,10,13,13,14,14-heptamethyl-2,4,12-triox

a-13-silapentadec-7-ene (6.7)

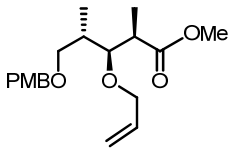


6.7

To a solution of alkyl iodide **6.4** (87 mg, 0.15 mmol) in ether (1.74 mL) was added *tert*-butyl lithium (0.18 mL, 1.7 M in pentane), MeO-9-BBN (0.30 mL, 1.0 M in hexane) and THF (1.74 mL) at -78 ^{o}C. After stirring at RT for one hour, Cs_2CO_3 (0.13 mL, 3M in H_2O) was added, followed by the addition of vinyl iodide **6.5** (66.6 mg, 0.151 mmol) in DMF (1.40 mL) and Pd(dppf)Cl_2 (6.2 mg). The reaction mixture was covered with aluminum foil and stirred at RT for 20 hours. The resulting solution was diluted with H_2O (5 mL) and ether (5 mL) and extracted with ether (3 x 10 mL). The combined organic phase was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (5% EtOAc in hexanes) to give **6.7** (86 mg, 77%) as a colorless oil. $[\alpha]_D^{25}$ +4.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.20 (4H, m), 6.89 – 6.81 (4H, m), 5.06 (1H, d, *J* = 10.1 Hz), 4.62 (2H, dd, *J* = 15.3, 6.6 Hz), 4.48 (2H, dd, *J* = 42.4, 10.8 Hz), 4.39 (2H, dd, *J* = 17.4, 11.6 Hz), 3.80 – 3.79 (1H, m), 3.79 (3H, s), 3.79 (3H, s), 3.54 – 3.45 (2H, m), 3.37 (3H, s), 3.29 (1H, dd, *J* = 9.0, 7.9 Hz), 3.21 (1H, t, *J* = 5.8 Hz), 3.14 (1H, t, *J* = 5.2 Hz), 2.64 – 2.55 (1H, m), 2.21 (1H, t, *J* = 12.3 Hz), 2.05 – 1.96 (1H, m), 1.92 – 1.82 (2H, m), 1.66 – 1.61 (2H, m), 1.60 (3H, d, *J* = 0.7 Hz), 1.55 – 1.48 (1H, m), 1.34 – 1.26 (2H, m), 1.19 – 1.13 (2H, m), 0.99 (3H, d, *J* =

6.8 Hz), 0.98 (3H, d, J = 6.9 Hz), 0.97 – 0.87 (9H, m), 0.93 (3H, s), 0.74 (3H, d, J = 6.7 Hz), 0.06 (6H, d, J = 5.1 Hz); ^{13}C NMR (500 Hz, $CDCl_3$) δ 159.0, 159.0, 132.7, 131.4, 130.9, 130.5, 129.2, 129.1, 113.7, 113.7, 98.2, 85.4, 85.3, 77.5, 74.5, 72.6, 72.4, 56.1, 55.3, 55.3, 38.9, 36.7, 35.9, 35.2, 34.5, 31.0, 29.9, 26.3, 26.2, 23.2, 23.1, 18.5, 17.2, 16.4, 14.8, 14.2, 13.6, 11.4, -3.3, -3.4; HRMS (ESI+) calcd for $C_{46}H_{78}O_7SiNa$ $[M + Na]^+$ 793.5415, found 793.5419.

(2*R*,3*S*,4*S*)-Methyl 3-(allyloxy)-5-(4-methoxybenzyloxy)-2,4-dimethylpentanoate (6.16)



6.16

A solution of PMB ether **6.6** (3.1 g, 7.1 mmol) in THF (80 mL) was treated with MeOH (0.9 mL) followed by $LiBH_4$ (7.1 mL, 4 M in THF) at -30 ^{o}C. After stirring at 0 ^{o}C for 1 hour and RT for 12 hours, the mixture was diluted with EtOAc (100 mL). NaOH solution was added and stirred for another 2 hours before the solution was extracted with EtOAc (3 x 100 mL), washed with brine, dried over Na_2SO_4, concentrated to give crude diol **6.10**.

To a solution of the crude diol **6.10** in DCM (26 mL) was added imidazole (1.82 g,

26.8 mmol) and TBSCl (1.1 g, 7.3 mmol) at 0 ^{o}C. After stirring at 0 ^{o}C for 1 hour, the solution was diluted with MeOH, concentrated and purified by flash chromatography (15-30% EtOAc in hexanes) to give TBS ether **6.11** (2.663 g, 92% over 2 steps) as a colorless oil.

A solution of alcohol **6.11** (0.51 g, 1.3 mmol) in DMF (2.6 mL) was treated with NaH (80 mg, 60%, 2 mmol) at 0 ^{o}C. After 30 minutes stirring at 0 ^{o}C, Bu_4NI (25 mg, 0.063 mmol) and allyl bromide (0.18 mL, 2 mmol) were added successively. The resulting mixture was stirred at RT for 24 hours. After the addition of water, the mixture was extracted with EtOAc (3 x 30 mL), washed with brine, dried over Na_2SO_4, concentrated and purified by chromatography (2% EtOAc in hexanes) to give allyl ether **6.12** (360.2 mg, 70%) as a colorless oil.

To a solution of allyl ether **6.12** (340 mg, 0.763 mmol) in DCM (3.1 mL) and MeOH (3.1 mL) was added CSA (34 mg, 0.15 mmol) at RT. After stirring for 1 hour, the reaction was quenched with $NaHCO_3$ solution, extracted with DCM (3 x 20 mL), dried over Na_2SO_4 and concentrated to give crude alcohol **6.13** as a colorless oil.

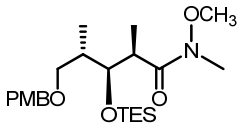
A solution of DMSO (0.2 mL) in DCM (3.7 mL) was treated with oxalyl chloride (0.11 mL, 1.2 mmol) at -78 ^{o}C. After 30 minutes stirring at -78 ^{o}C, a solution of crude alcohol **6.13** in DCM (0.3 mL) was added and the solution was stirred for 45 minutes at -78 ^{o}C. Then Et_3N (0.75 mL, 5.4 mmol) was added slowly. After stirring at -78 ^{o}C for another 30 minutes, the solution was warmed to 0 ^{o}C slowly, quenched with $NaHSO_4$

solution, extracted with EtOAc (3 x 20 mL), washed with water and brine and concentrated to give crude aldehyde **6.14** as a colorless oil.

A solution of the crude aldehyde **6.14** in *t*-BuOH (3.6 mL) and 2-methyl-2 butene (0.5 mL) was treated dropwise with a solution of $NaClO_2$ (173 mg) and NaH_2PO_4 (880 mg) in water (2.7 mL) at 0 ^oC. After stirred at RT for 3 hours, the mixture was partitioned between brine and Et_2O. The organic layer was dried over Na_2SO_4 and concentrated to give crude carboxylic acid **6.15** as a colorless oil. To a solution of this crude acid in hexane (4.5 mL) and MeOH (0.45 mL) was added TMS-CHN_2 (2 M in Et_2O) dropwise until no bubbles came out and the color of solution stayed no change. After the addition of one or two drops of acetic acid, the solution was concentrated and purified by flash chromatography (5%-15% EtOAc in hexanes) to give methyl ester **6.16** (226 mg, 82% over 4 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.6 Hz), 6.87 (2H, d, *J* = 8.6 Hz), 5.89 – 5.67 (1H, m), 5.18 (1H, dq, *J* = 17.2, 1.7 Hz), 5.09 (1H, ddd, *J* = 10.4, 2.8, 1.4 Hz), 4.42 (2H, ABq, *J* = 11.7, 4.1 Hz), 3.98 – 3.89 (2H, m), 3.80 (3H, s), 3.74 – 3.69 (1H, m), 3.66 (3H, s), 3.50 (1H, dd, *J* = 8.9, 3.8 Hz), 3.44 (1H, dd, *J* = 8.9, 5.9 Hz), 2.67 (1H, qd, *J* = 7.0, 4.3 Hz), 1.90 (1H, m), 1.16 (3H, d, *J* = 7.1 Hz), 0.98 (3H, d, *J* = 6.9 Hz); ^{l3}C NMR (500 MHz, CDCl3) δ 176.3, 159.4, 135.3, 131.1, 129.5, 116.7, 114.0, 82.3, 73.8, 73.1, 72.1, 55.6, 51.9, 42.0, 37.5, 15.1, 10.8; HRMS (ESI+) calcd for $C_{19}H_{29}O_5$ $[M + H]^+$ 337.2015, found 337.2028.

(2*R*,3*S*,4*S*)-3-(Triethylsilyloxy)-5-(4-methoxylbenzyloxy)-2,4-dimethylpentanoic acid

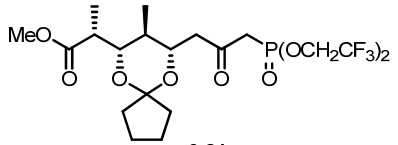
methoxymethyl amide (6.18)



6.18

To a solution of alcohol **6.17** (110 mg, 0.34 mmol) in DMF (1.8 mL) was added imidazole (60 mg) and TESCl (0.12 mL) at RT. After stirring overnight, the solution was extracted with EtOAc (3 x 40 mL), washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (30% EtOAc in hexanes) to give TES ether **6.18** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.7 Hz), 6.86 (2H, d, *J* = 8.7 Hz), 4.39 (2H, s), 3.93 (1H, dd, *J* = 8.3, 3.1 Hz), 3.80 (3H, s), 3.59 – 3.55 (1H, m), 3.57 (3H, s), 3.17 (1H, dd, *J* = 9.1, 7.9 Hz), 3.11 (3H, s), 1.94 – 1.82 (1H, m), 1.12 (3H, d, *J* = 6.9 Hz), 1.00 (3H, d, *J* = 6.9 Hz), 0.96 (9H, t, *J* = 7.9 Hz), 0.62 (6H, q, *J* = 7.9 Hz); ^{13}C NMR (500 MHz, CDCl3) δ 177.1, 159.4, 131.3, 129.6, 114.0, 73.0, 72.2, 61.6, 55.6, 39.6, 38.8, 15.9, 15.1, 7.4, 5.7; HRMS (ESI+) calcd for $C_{23}H_{42}NO_5Si$ $[M + H]^+$ 440.2832, found 440.2820.

(*R*)-Methyl 2-((7*S*,8*S*,9*S*)-9-(3-(bis(2,2,2-trifluoroethoxy)phosphoryl)-2-oxo- propyl)-8-methyl-6,10-dioxaspiro[4.5]decan-7-yl)propanoate (6.21)

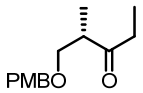


6.21

1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine (0.17 mL, 1.3 mmol) was added to a solution of acid **6.30** (174 mg, 0.58 mmol) in DCM (7.1 mL). The solution was stirred at RT for 1 hour before being concentrated. The crude acid chloride was dried under high vacuum for another hour. At the same time, to a solution of bis(2,2,2-trifluoroethyl)methylphosphonate (493 mg) in THF (1.42 mL) was added LiHMDS (1.86 mL, 1 M in THF) at -98 ^{o}C. After stirring at -98 ^{o}C for 30 minutes, a solution of the crude acid chloride in THF (4.16 mL) was added to the reaction mixture. The resulting solution was stirred at -98 ^{o}C for 1 hour before the addition of aqueous NH_4Cl solution. The mixture was warmed to RT, diluted with aqueous NH_4Cl solution, extracted with DCM (3 x 30 mL), dried over Na_2SO_4, concentrated, and purified by flash chromatography (30% EtOAc in hexanes) to give phosphonate **6.21** (230 mg, 73%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.49 – 4.36 (4H, m), 3.99 (1H, dd, *J* = 10.3, 3.1 Hz), 3.90 (1H, ddd, *J* = 10.0, 8.4, 3.7 Hz), 3.68 (3H, s), 3.39 (1H, s), 3.35 (1H, s), 2.70 (3H, ddd, *J* = 10.2, 9.8, 3.5 Hz), 1.94 – 1.75 (3H, m), 1.74 – 1.66 (1H, m), 1.64 – 1.50 (5H, m), 1.14 (3H, d, *J* = 7.1 Hz), 0.77 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 200.1, 174.4, 122.5, 110.6, 75.9, 73.5, 62.3, 51.7, 47.8, 43.3, 42.0, 40.8, 39.7,

35.7, 30.8, 24.2, 22.4, 11.5, 8.7; HRMS (ESI+) calcd for $C_{20}H_{30}O_8F_6P$ $[M + H]^+$ 543.1583, found 543.1578. Spectroscopic data agreed with the literature data.[4]

(*S*)-1-(4-Methoxybenzyloxy)-2-methylpentan-3-one (6.23)



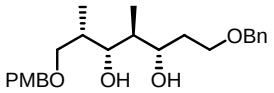
6.23

To a solution of ester **6.22** (2.0115 g, 8.45 mmol) and N,O-dimethylhydroxylamine hydrochloride (1.23 g, 12.6 mmol) in THF (14 mL) was added iPrMgCl (12.6 mL, 2.0 M in THF) at -15 ^{o}C. After stirring for 30 minutes, the solution was partitioned between NH_4Cl and ether (3 x 50 mL). The combined organic solution was washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (30% EtOAc in hexanes) to give the Weinreb amide as a yellow oil.

To a solution of this Weinreb amide (2.14 g) in THF (60 mL) was added EtMgBr (15.23 mL, 1 M in THF) dropwise at 0 ^{o}C. After 2 hours, NH_4Cl solution was added and the resulting mixture was extracted with ether (3 x 30 mL), washed with brine, dried over Na_2SO_4, concentrated, and purified by chromatography (5% EtOAc in hexanes) to give ketone **6.23** (1.726 g, 87%) as a colorless oil. $[\alpha]_D^{25}$ +20.2 (*c* 6.73, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (2H, d, *J* = 8.8 Hz), 6.86 (2H, d, *J* = 8.7 Hz), 4.40 (2H, ABq, *J* = 16.9, 11.6 Hz), 3.80 (3H, s), 3.59 (1H, dd, *J* = 9.1, 7.8 Hz), 3.43 (1H, dd, *J* = 9.1, 5.5 Hz),

2.96-2.78 (1H, m), 2.50 (2H, q, J = 7.3 Hz), 1.06 (3H, d, J = 7.0 Hz), 1.04 (3H, t, J = 7.3 Hz). Spectroscopic data agreed with the literature data.[3]

(2*S*,3*R*,4*S*,5*S*)-7-(Benzyloxy)-1-(4-methoxybenzyloxy)-2,4-dimethylheptane-3,5-diol (6.26)

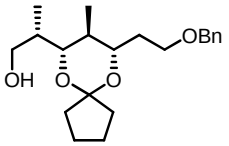


6.26

To a solution of c-Hex_2BCl (1.84 mL, 8.37 mmol) in Et_2O (20.5 mL) was added Et_3N (1.35 mL) and a solution of ketone **6.23** (1.517 g, 6.43 mmol) in Et_2O (10.7 mL) at 0 ^oC. After stirring at 0 ^oC for 2 hours, the solution was cooled to -78 ^oC, and a solution of aldehyde **6.25** (1.062 g, 6.48 mmol) in Et_2O (17.2 mL) was added. After stirring at -78 ^oC for 3 hours, $LiBH_4$ (15.03 mL, 2 M in THF) was added and the reaction was stirred at -78 ^oC for another 3 hours and then stirred at -23 ^oC for 20 hours. NH_4Cl solution was added to the cold solution and the solution was warmed to RT. The mixture was extracted with Et_2O (3 x 50 mL), and the combined organic layers was redissolved in MeOH (19.9 mL). At 0 ^oC, NaOH (19.9 mL, 10%) and H_2O_2 (19.9 mL, 30%) was added. After stirring at RT for 3 hours, the reaction was diluted with H_2O, extracted with Et_2O, washed with brine, dried over Na_2SO_4, concentrated and purified by flash chromatography (20% EtOAc in hexanes) to give diol **6.26** (1.7796 g, 70%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$)

δ 7.36-7.27 (5H, m), 7.26-7.23 (2H, m), 6.90-6.86 (2H, m), 4.53 (2H, s), 4.45(2H, s), 3.87-3.83 (1H, m), 3.80 (3H, s), 3.77-3.66 (3H, m),3.53 (2H, qd, *J* = 9.0, 5.4 Hz), 1.93-1.88 (2H, m), 1.78-1.72(1H, m), 1.70-1.64 (1H, m), 1.43 (1H), 1.21 (1H), 0.95 (3H, d, *J* = 7.0 Hz), 0.75 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (500 MHz, $CDCl_3$) δ 159.2, 138.0, 130.3, 129.2, 128.4, 127.7, 113.8, 77.9, 75.7, 75.1, 73.3, 73.1, 70.0, 55.3, 40.9, 35.2, 33.8, 30.3, 12.7, 9.3; HRMS (ESI+) calcd for $C_{24}H_{35}O_5$ $[M + H]^+$ 403.2479, found 403.2488. Spectroscopic data agreed with the literature data.[4]

(*S*)-2-((7*R*,8*S*,9*S*)-9-(2-(Benzyloxy)ethyl)-8-methyl-6,10-dioxaspiro[4.5]decan-7-yl)propan-1-ol (6.28)



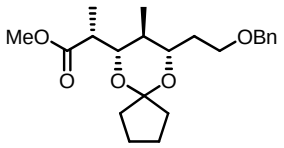
6.28

To a solution of diol **6.26** (800 mg, 1.99 mmol) and cyclopentylidene dimethyl acetal (5.5 mL) in DCM (3.3 mL) was added PPTS (8 mg). The mixture was stirred at 50 ^{o}C for 1.5 hours, then cooled to RT and concentrated. The residue was purified by flash chromatography (20% EtOAc in hexanes) to give PMB ether **6.27** (781 mg, 84%) as a colorless oil. Spectroscopic data agreed with the literature data.[4]

To a vigorously stirring solution of PMB ether **6.27** (781 mg, 1.67 mmol) in DCM

(43 mL) and pH 7 buffer (4.5 mL) was added DDQ (570 mg, 2.51 mmol) at RT. After stirring for 50 minutes, the mixture was diluted with pH 7 buffer, extracted with DCM (3 x 50 mL), dried over Na_2SO_4, concentrated, and purified by flash chromatography (30% EtOAc in hexanes) to give alcohol **6.28** (500 mg, 86%) as a colorless oil. ^{1}H NMR (500 MHz, CDCl3) δ 7.36-7.26 (5H, m), 4.53 (1H, d, *J* = 11.9 Hz), 4.47 (1H, d, *J* = 12.1 Hz), 3.73 (1H, dd, *J* = 10.6, 3.4 Hz), 3.68-3.47 (5H, m), 2.06-1.99 (1H, m), 1.94-1.70 (5H, m), 1.69-1.53 (6H, m), 0.98 (3H, d, *J* = 7.2 Hz), 0.75 (3H, d, *J* = 6.8 Hz). Spectroscopic data agreed with the literature data.[4]

(*R*)-Methyl 2-((7*S*,8*S*,9*S*)-9-(2-(benzyloxy)ethyl)-8-methyl-6,10-dioxaspiro[4.5] decan -7-yl)propanoate (6.29)



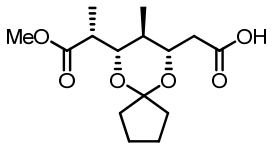
6.29

To a solution of alcohol **6.28** (500 mg, 1.44 mmol) in DCM (8.3 mL) was added $NaHCO_3$ (1.22 g, 14.52 mmol) and Dess-Martin periodinane (1.22 g, 2.88 mmol). After stirring at RT for 3 hours, the solution was diluted with Et_2O, aqueous $Na_2S_2O_3$ and $NaHCO_3$. The solution was stirred vigorously for another 30 minutes, and then extracted with Et_2O, washed with aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated to give a crude aldehyde.

A solution of this crude aldehyde in *t*-BuOH (8.5 mL) and 2-methyl-2 butene (1 mL) was treated dropwise with a solution of $NaClO_2$ (326 mg, 3.6 mmol) and NaH_2PO_4 (1.212 g, 10.1 mmol) in water (7.85 mL). After stirred at RT for 1 hour, the mixture was partitioned between brine and DCM. The organic layer was dried over Na_2SO_4 and concentrated to give the crude acid.

To a solution of this crude acid in hexane (13.4 mL) and MeOH (1.7 mL) was added TMS-CHN_2 (2 M in Et_2O) dropwise until no bubbles came out and the color of solution stayed unchanged. After the addition of one or two drops of acetic acid, the solution was concentrated and purified by flash chromatography (5%-15% EtOAc in hexanes) to give methyl ester **6.29** (548 mg, 95% over 3 steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.26 (5H, m), 4.53 (1H, d, *J* = 12.1 Hz), 4.47 (1H, d, *J* = 12.0 Hz), 3.95 (1H, dd, *J* = 10.4, 3.0 Hz), 3.68 (3H, s), 3.62-3.53 (3H, m), 2.69 (1H, dq, *J* = 7.2, 3.1 Hz), 2.06-1.98 (1H, m), 1.95-1.72 (4H, m), 1.65-1.48 (6H, m), 1.14 (3H, d, *J* = 7.1 Hz), 0.78 (3H, d, *J* = 6.7 Hz). Spectroscopic data agreed with the literature data.[4]

2-((7*S*,8*S*,9*S*)-9-((*R*)-1-Methoxy-1-oxopropan-2-yl)-8-methyl-6,10-dioxaspiro[4.5]decan-7-yl)acetic acid (6.30)



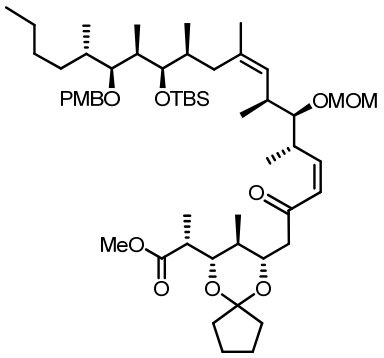
6.30

To a solution of benzyl ether **6.30** (548 mg, 1.44 mmol) in THF (25 mL) was added $Pd(OH)_2$ (421 mg, 20% on C). The mixture was stirred under hydrogen pressure (40-50 psi) overnight. The mixture was then filtered and concentrated to give the crude alcohol.

A solution of this crude alcohol in DCM (13.6 mL) was treated with $NaHCO_3$ (1.23 g, 14.6 mmol) and Dess-Martin periodinane (1.23 g, 2.9 mmol) at RT. After stirring for 30 minutes, the mixture was diluted with hexane, filtered, concentrated, and purified by flash chromatography (30% EtOAc in hexanes) to give aldehyde (266 mg, 65 % over 2 steps) as a colorless oil. Spectroscopic data agreed with the literature data.[4]

A solution of the aldehyde (266 mg, 0.94 mmol) in *t*-BuOH (11.2 mL) and 2-methyl-2 butene (0.71 mL) was treated dropwise with a solution of $NaClO_2$ (213 mg, 2.35 mmol) and NaH_2PO_4 (790 mg, 6.58 mmol) in water (11.2 mL). After stirring at RT for 1 hour, the mixture was partitioned between brine and DCM. The organic layer was dried over Na_2SO_4, concentrated, and purified by flash chromatography (30% EtOAc in hexanes) to give carboxylic acid **6.30** (174 mg, 62%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (1H, dd, J = 10.3, 3.1 Hz), 3.83 (1H, ddd, J = 10.1, 8.7, 3.1 Hz), 3.61 (3H, s), 2.67 – 2.57 (2H, m), 2.41 (1H, dd, J = 15.7, 8.6 Hz), 1.89 – 1.65 (4H, m), 1.52 (5H, m), 1.07 (3H, d, J = 7.1 Hz), 0.73 (3H, d, J = 6.7 Hz). Spectroscopic data agreed with the literature data.[4]

(*R*)-Methyl 2-((7*S*,8*S*,9*S*)-9-((3*Z*,5*S*,6*S*,7*S*,8*Z*,11*S*,12*R*,13*R*,14*S*,15*S*)-12-(*tert*-butyl-dimethylsilyloxy)-14-(4-methoxybenzyloxy)-6-(methoxymethoxy)-5,7,9,11,13,15-hexa methyl-2-oxononadeca-3,8-dienyl)-8-methyl-6,10-dioxaspiro[4.5]decan-7-yl)propano ate (6.32)



6.32

A solution of 18-crown-6 (110 mg, 0.41 mmol) and K_2CO_3 (30 mg, 0.21 mmol) in toluene (0.33 mL) and HMPA (0.033 mL) was stirred at RT for 3 hours. The solution was cooled to -10 ^{o}C and a solution of aldehyde **6.8** (22.2 mg, 0.034 mmol) and phosphonate **6.21** (26.5 mg, 0.048 mmol) in toluene (0.33 mL) and HMPA (0.033 mL) was added. The resulting solution was stirred at -5 ^{o}C for 48 hours. After addition of ammonium chloride solution, the resulting solution was extracted with EtOAc (3 x 20 mL), washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified via flash chromatography (20% EtOAc in hexanes) to give ketone **6.32** (13 mg, 40%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (2H, d, *J* = 8.7 Hz), 6.87 (3H, d, *J* = 8.7 Hz), 6.14 – 6.05 (2H, m), 4.90 (1H, d, *J* = 10.4 Hz), 4.73 (2H, dd, *J* = 31.2, 6.7 Hz), 4.48 (2H, dd, *J* = 36.8, 10.4 Hz), 3.98 (2H, dd, *J* = 10.4, 3.0 Hz), 3.80 (3H, s), 3.74 – 3.68 (1H, m), 3.68 (3H, s),

3.50 – 3.45 (2H, m), 3.40 (3H, s), 3.27 (1H, dd, *J* = 7.1, 3.9 Hz), 3.13 (1H, t, *J* = 5.2 Hz), 2.70 – 2.64 (1H, m), 2.65 – 2.50 (2H, m), 2.16 (1H, t, *J* = 12.5 Hz), 1.93 – 1.82 (5H, m), 1.80 – 1.65 (3H, m), 1.58 (3H, s), 1.62 – 1.48 (6H, m), 1.32 – 1.25 (3H, m), 1.18 – 1.13 (2H, m), 1.12 (3H, d, *J* = 7.1 Hz), 1.01 (3H, d, *J* = 6.9 Hz), 0.99 – 0.86 (12H, m), 0.93 (9H, s), 0.74 (3H, d, *J* = 6.7 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 199.0, 174.9, 159.1, 151.5, 133.2, 131.5, 130.1, 129.2, 125.7, 113.8, 110.3, 97.5, 94.6, 86.9, 85.6, 76.3, 74.7, 73.3, 56.3, 55.4, 51.9, 48.2, 41.0, 39.9, 39.0, 36.9, 36.2, 36.0, 35.9, 35.5, 35.4, 31.1, 31.0, 30.0, 26.4, 24.4, 23.3, 23.2, 22.5, 18.7, 17.6, 17.4, 17.0, 14.4, 14.0, 11.8, 11.5, 8.8, -3.2, -3.3. HRMS (ESI+) calcd for $C_{54}H_{93}O_{10}Si$ $[M + H]^+$ 929.6538, found 929.6525.

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