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Synthesis of the C1-C23 Fragment of Spirastrellolide A.

authored by

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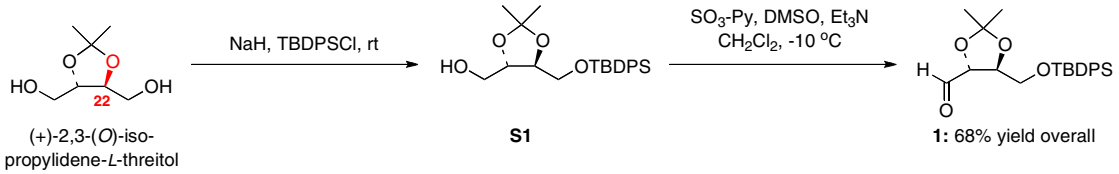
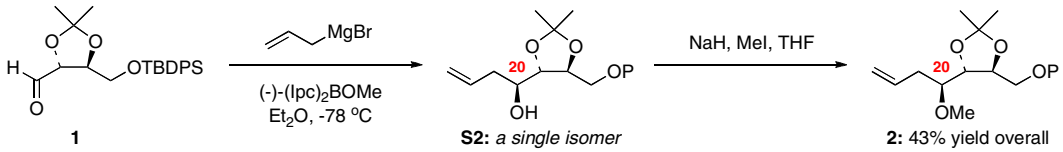
Synthesis Aldehyde 1 from (+)-2,3-(*O*)-Isopropylidene-*L*-Threitol.



TBDPS-Silyl Ether S1. To a solution of commercially available (+)-2,3-(*O*)-isopropylidene-*L*-threitol (1.03 g, 6.30 mmol) in THF (30 mL) was added NaH (252 mg, 6.3 mmol) at -10 °C. The mixture was gradually warmed up to rt and stirred for 1 h before being cooled back down to -10 °C and TBDPSCl (1.77 mL, 6.90 mmol) was added. After 2 h at rt, the reaction was quenched with H_2O (20 mL). The organic solvent was evaporated and the aqueous fraction was extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were combined, washed with sat aq NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [gradient eluent: 8-25% EtOAc in hexanes] to provide silyl ether **S1** in 83% yield (2.09 g) as yellow oil. **S1:** R_f = 0.60 [30% EtOAc in hexanes]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.42 (s, 3H), 1.45 (s, 3H), 3.67-3.88 (m, 4H), 3.97-4.03 (m, 1H), 4.09-4.14 (m, 1H), 7.40-7.49 (m, 6H), 7.68-7.72 (m, 4H); mass spectrum (ESI): m/e (% relative intensity) 423.2 $(M+Na)^+$ (100), 321.1 $(M+H)^+$ (100); m/e calcd for $C_{23}H_{32}O_4Si$ 423.1962, found 423.1966.

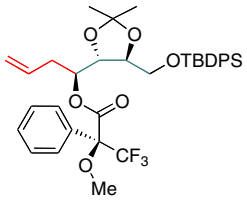
To a solution of silyl ether **S1** (2.09 g, 5.20 mmol), anhydr DMSO (7.38 mL, 104.0 mmol) and anhyd Et_3N (3.62 mL, 25.9 mmol) in CH_2Cl_2 (21 mL) was added SO_3-pyridine (3.31 g, 20.8 mmol) at -10 °C. The solution was stirred at -10 °C for 2 h and was quenched with H_2O at -10 °C. The organic phase was separated and the aqueous fraction was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [gradient eluent: 10-30% EtOAc in hexanes] to provide aldehyde **1** as colorless oil in 82% yield (1.69 g). **1:** R_f = 0.35 [50% EtOAc in hexanes]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.45 (s, 3H), 1.52 (s, 3H), 3.84 (dd, J = 4.2, 11.1 Hz, 4H), 3.90 (dd, J = 4.5, 11.1 Hz, 1H), 4.22 (dt, J = 4.2, 6.9 Hz, 1H), 4.48 (dd, J = 1.8, 7.2 Hz, 1H), 7.41-7.48 (m, 6H), 7.69-7.74 (m, 4H), 9.83 (d, J = 1.5 Hz, 1H).

Synthesis of Homoallyl Ether 2.



Homoallylic Alcohol S2. To a solution of (-)-(Ipc)$_2$BOMe (1.80 g, 5.69 mmol) in Et_2O (15 mL) was added allylmagnesium bromide (1.0 *M*, 4.93 mL, 4.93 mmol) at 0 °C. The solution was warmed up to rt and stirred for an additional 1 h to give a white suspension. The suspension was cooled to 0 °C and allowed to settle for 0.5 h. The upper supernatant was transferred to a solution of aldehyde **1** (1.51 g, 3.79 mmol) in ether (10 mL) *via* cannula at -78 °C and the mixture was stirred at -78 °C for 3 h before it was quenched with aq NaOH (3.0 *M*, 20 mL) and 30% H_2O_2 (8 mL) at -78 °C. The mixture was reflux overnight. The organic phase was separated and the aqueous fraction was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [gradient eluent: 10-20% EtOAc in hexanes] followed by removing isopinocampheol (Ipc-OH) byproduct through Kugelrohr distillation at 50 °C [1.0 mmHg] to provide homoallyl alcohol **S2** as colorless oil in 72% yield (1.20 g). **S2:** R_f = 0.60 [25% EtOAc in hexanes]; $[\alpha]_D^{23}$ = - 3.83 [c 0.31, $CHCl_3$]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 9 H), 1.41 (s, 3H), 1.42 (s, 3H), 2.23 (ddd, *J* = 7.5, 7.5, 14.5 Hz, 1H), 2.41 (m, 1H), 2.52 (d, *J* = 3.0 Hz, 1H), 3.78 (m, 1H), 3.80 (d, *J* = 4.5 Hz, 2H), 3.82 (dd, *J* = 7.0, 7.0 Hz, 1H), 4.08 (ddd, *J* = 4.5, 4.5, 7.0 Hz, 1H), 5.15 (d, *J* = 10.5 Hz, 1H), 5.16 (d, *J* = 17.0 Hz, 1H), 5.92 (dddd, *J* = 7.0, 7.0, 10.5, 17.0 Hz, 1H), 7.41-7.44 (m, 6H), 7.70-7.72 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 26.8, 27.0, 27.1, 37.7, 64.7, 71.4, 79.1, 80.5, 109.0, 118.0, 127.8, 127.8, 129.9, 129.9, 132.8, 132.9, 134.4, 135.7, 135.7; IR (film) cm^{-1} 3470 brs, 3072m, 2933s, 2859m, 1112s; mass spectrum (ESI): m/e (% relative intensity) 463.2 $(M+Na)^+$ (100); m/e calcd for $C_{26}H_{36}O_4Si$ 463.2275, found 463.2270.

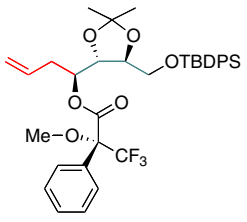
(*S*)-Mosher Ester of S2.



(S)-(-)-Mosher's ester

To a solution of homoallyl alcohol **S2** (9.60 mg, 0.022 mmol) in anhyd CH_2Cl_2 (0.22 mL) were added (*R*)-α-Methoxy-α-trifluoromethylphenylacetyl chloride ((*R*)-MTPA) (8.06 mL, 0.044 mmol) and DMAP (4.90 mg, 0.44 mmol) at 0 ^{o}C. The solution was warmed up to rt and stirred for an additional 2 h before it was quenched with H_2O (2 mL). The mixture was diluted with CH_2Cl_2 (3 mL). The organic phase was separated and the aqueous fraction was extracted with CH_2Cl_2 (3 × 3 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [gradient eluent: 5-8% EtOAc in hexanes] to provide the *(S)*-Mosher's ester as colorless oil in 93% yield (13.4 mg). R_f = 0.70 [20% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9 H), 1.41 (s, 6H), 2.44 (t, *J* = 7.0 Hz, 2H), 3.50 (s, 3H), 3.62 (dd, *J* = 4.0, 11.5 Hz, 1H), 3.81 (dd, *J* = 4.0, 11.5 Hz, 1H), 3.98 (ddd, *J* = 4.0, 4.0, 7.5 Hz, 1H), 4.28 (dd, *J* = 4.0, 8.0 Hz, 1H), 5.01 (d, *J* = 16.0 Hz, 1H), 5.02 (d, *J* = 12.0 Hz, 1H), 5.35 (ddd, *J* = 4.5, 6.0, 6.0 Hz, 1H), 5.62-5.70 (m, 1H), 7.34-7.43 (m, 9H), 7.53-7.54 (m, 2H), 7.67-7.71 (m, 4H).

(*R*)-Mosher ester of **S2.**

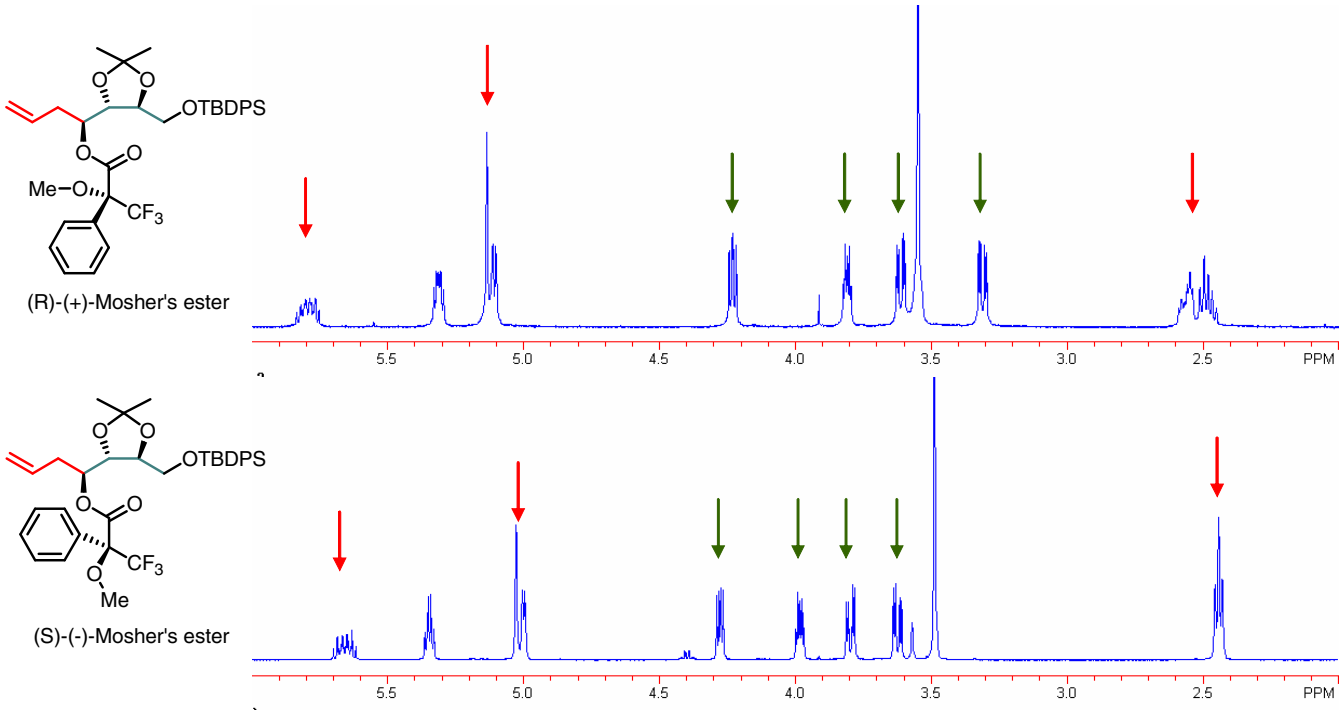


(R)-(+)-Mosher's ester

R_f = 0.70 [20% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 9 H), 1.32 (s, 3H), 1.37 (s, 3H), 2.48 (ddd, *J* = 7.5, 7.5, 15.5 Hz, 1H), 2.56 (ddd, *J* = 4.5, 4.5, 15.5 Hz, 1H), 3.31 (*J* = 3.5, 11.5 Hz, 1H), 3.55 (s, 3H), 3.61 (dd, *J* = 3.5, 11.5 Hz, 1H), 3.81 (ddd, *J* = 3.5, 3.5, 7.0 Hz, 1H), 4.23 (dd,

J = 5.5, 7.5 Hz, 1H), 5.13 (d, *J* = 10.0 Hz, 1H), 5.27 (d, *J* = 17.0 Hz, 1H), 5.31 (ddd, *J* = 4.5, 5.5, 7.5 Hz, 1H), 5.75-5.84 (m, 1H), 7.26-7.27 (m, 3H), 7.38-7.46 (m, 8H), 7.64-7.67 (m, 4H).

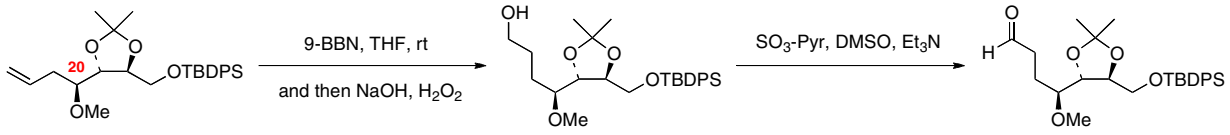
Mosher's Ester Analysis.



To a solution of homoallylic alcohol **S2** (1.20 g, 2.72 mmol) in THF (14 mL) was added NaH (163.2 mg, 4.08 mmol) at -10 ^{o}C. The solution was warmed up to rt and stirred for an additional 1 h before MeI (0.34 mL, 5.44 mmol) was added. The mixture was stirred at rt for 12 h and quenched with H_2O (15 mL). The organic phase was evaporated and the aqueous fraction was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [gradient eluent: 2-3% EtOAc in hexanes] to provide methyl ether **2** as colorless oil in 59% yield (725.0 mg). **2:** R_f = 0.70 [16% EtOAc in hexanes]; $[\alpha]_D^{23}$ = - 7.54 [c 0.93, $CHCl_3$]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 9 H), 1.45 (s, 3H), 1.46 (s, 3H), 2.33-2.45 (m, 2H), 2.39 (s, 3H), 3.40 (m, 1H), 3.79 (dd, *J* = 4.0, 11.0 Hz, 1H), 3.90 (dd, *J* = 3.5, 11.0 Hz, 1H), 4.08 (ddd, *J* = 4.0, 4.0, 7.0 Hz, 1H), 4.12 (dd, *J* = 5.0, 8.0 Hz, 1H), 5.11 (d, *J* = 10.0 Hz, 1H), 5.15 (dd, *J* = 1.5, 17.0 Hz, 1H), 5.91 (dddd, *J* = 7.0, 7.0, 10.0, 17.0 Hz, 1H),

7.40-7.45 (m, 6H), 7.73-7.76 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 26.9, 27.2, 27.3, 34.7, 58.1, 64.8, 77.9, 79.6, 81.5, 109.2, 117.2, 127.7, 127.7, 129.7, 129.7, 133.3, 133.5, 134.6, 135.5, 135.7, 135.8; IR (film) cm^{-1} 3072m, 2933s, 2861m, 1108s; mass spectrum (ESI): m/e (% relative intensity) 477.2 $(M+Na)^+$ (100); m/e calcd for $C_{27}H_{38}O_4SiNa$ 477.2432, found 477.2418.

Synthesis of Methoxy Aldehyde 3.



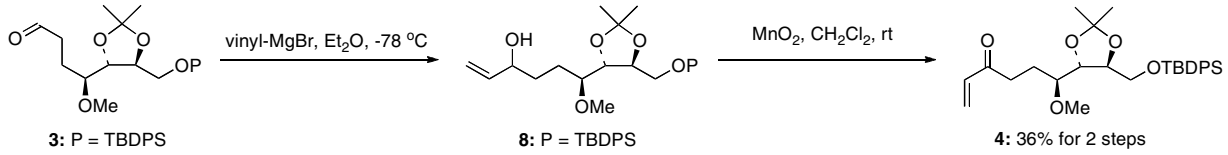
2 **S3** **3:** 71% yield overall

Alcohol S3. To a solution of methyl ether **2** (91.6 g, 0.20 mmol) in THF (2 mL) was added 9-BBN (0.5 *M*, 0.81 mL, 0.4 mmol) at 0 °C. The solution was warmed up to rt and stirred for 5 h before aq NaOH (3.0 *M*, 2 mL) and 30% H_2O_2 (1 mL) were added. The mixture was refluxed for 2 h. The organic phase was evaporated and the aqueous fraction was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [gradient eluent: 30-40% EtOAc in hexanes] to provide alcohol **S3** as colorless oil in 71% yield (66.9 mg). **S3:** R_f = 0.30 [30% EtOAc in hexanes]; $[\alpha]_D^{23}$ = -18.0 [c 0.75, $CHCl_3$]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.42 (s, 3H), 1.43 (s, 3H), 1.60-1.75 (m, 4H), 1.89 (br, 1H), 3.35 (m, 1H), 3.39 (s, 3H), 3.64 (m, 1H), 3.76 (dd, *J* = 4.5, 10.5 Hz, 1H), 3.87 (dd, *J* = 3.7, 11.0 Hz, 1H), 4.01 (ddd, *J* = 4.0, 4.0, 8.0 Hz, 1H), 4.12 (dd, *J* = 5.0, 7.5 Hz, 1H), 7.38-7.41 (m, 6H), 7.69-7.72 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 26.6, 26.8, 27.1, 27.2, 28.5, 58.1, 62.9, 64.7, 78.0, 79.4, 81.6, 109.1, 127.7, 127.7, 129.7, 129.7, 133.3, 133.3, 135.7, 135.7; IR (film) cm^{-1} 3425brs, 3072m, 2936s, 2864m, 1109s; mass spectrum (ESI): m/e (% relative intensity) 495.3 $(M+Na)^+$ (100); m/e calcd for $C_{27}H_{40}O_5SiNa$ 495.2537, found 495.2541.

To a solution of alcohol **S3** (66.9 mg, 0.14 mmol), anhyd DMSO (0.20 mL, 2.82 mmol), and anhyd Et_3N (0.11 mL, 0.79 mmol) in CH_2Cl_2 (2 mL) was added SO_3·pyridine (89.8 mg, 0.56 mmol) at -10 °C. The solution was stirred at -10 °C for 2 h and was quenched with H_2O at -10 °C. The organic

phase was separated and the aqueous fraction was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [gradient eluent: 5-15% EtOAc in hexanes] to provide aldehyde **3** as colorless oil in 99% yield (65.5 mg). **3:** R_f = 0.70 [30% EtOAc in hexanes]; $[\alpha]_D^{23}$ = - 23.5 [c 5.56, $CHCl_3$]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.42 (s, 6H), 1.92 (dt, *J* = 7.0, 7.5 Hz, 2H), 2.54 (dt, *J* = 1.5, 7.0 Hz, 2H), 3.32 (s, 3H), 3.33 (m, 1H), 3.77 (dd, *J* = 4.5, 11.5 Hz, 1H), 3.87 (dd, *J* = 3.5, 11.0 Hz, 1H), 4.00 (ddd, *J* = 4.0, 4.0, 7.0 Hz, 1H), 4.10 (dd, *J* = 5.0, 12.0 Hz, 1H), 7.39-7.42 (m, 6H), 7.69-7.72 (m, 4H), 9.75 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 22.8, 26.8, 27.1, 27.2, 39.6, 58.0, 64.6, 76.8, 77.1, 77.3, 77.7, 79.5, 80.8, 109.3, 127.7, 127.7, 129.7, 129.8, 133.2, 133.3, 135.7, 135.7, 202.1; IR (film) cm^{-1} 3071m, 2935s, 2861m, 1726s, 1108s; mass spectrum (ESI): m/e (% relative intensity) 493.2 $(M+Na)^+$ (100); m/e calcd for $C_{27}H_{38}O_5SiNa$ 493.2381, found 493.2372.

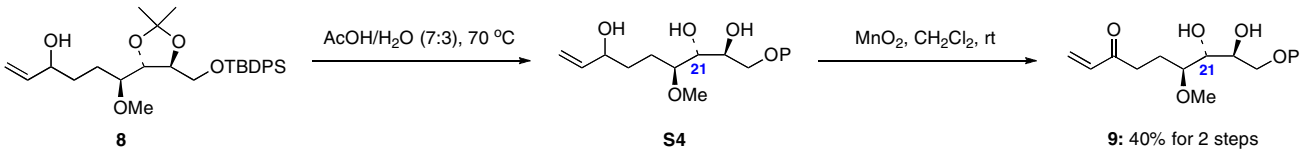
Synthesis of Enone 4.



Allyl Alcohol 8. To a solution of aldehyde **3** (534.3 mg, 1.14 mmol) in Et_2O (10 mL) was added vinyl magnesium bromide (1.0 *M*, 2.28 mL, 2.28 mmol) dropwise at -78 °C. The solution was stirred for 3 h at -78 °C and quenched with sat aq $NaHCO_3$ (10 mL). The organic phase was separated and the aqueous fraction was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [gradient eluent: 15-20% EtOAc in hexanes] to provide allyl alcohol **8** as a mixture of diastereomers in 68% yield (385.2 mg). **8:** R_f = 0.30 [25% EtOAc in hexanes]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.43 (s, 6H), 1.63-1.71 (m, 4H), 3.33-3.63 (m, 1H), 3.38 (s, 3H), 3.75 (dd, *J* = 4.5, 11.1 Hz, 1H), 3.88 (dd, *J* = 3.3, 11.1 Hz, 1H), 4.02 (ddd, *J* = 4.2, 4.2, 8.1 Hz, 1H), 4.12 (dd, *J* = 7.2, 7.2 Hz, 1H), 5.11 (dd, *J* = 1.2, 10.5 Hz, 1H), 5.24 (dt, *J* = 17.1, 1.5, 1.5 Hz, 1H), 5.88 (dddd, *J* = 1.6, 8.0, 11.5, 17.1 Hz, 1H), 7.36-7.45 (m, 6H), 7.69-7.74 (m, 4H).

To a solution of the above allyl alcohol **8** (385.2 mg, 0.77 mmol) in CH_2Cl_2 (10 mL) was added MnO_2 (669.4 mg, 7.7 mmol) at rt. The solution was sonicated at rt for 6 h. The mixture was filtered through Celite^{TM} and the residue was washed with CH_2Cl_2 several times. Then the filtrate was collected and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [gradient eluent: 10-15% EtOAc in hexanes] to provide enone **4** in 53% yield (157.7 mg) based on starting material recovered (85.6 mg). **4:** R_f = 0.50 [25% EtOAc in hexanes]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9H), 1.44 (s, 6H), 1.83-1.08 (m, 2H), 2.73 (dd, *J* = 2.1, 8.4 Hz, 1H), 2.78 (dd, *J* = 2.1, 8.4 Hz, 1H), 3.36 (s, 3H), 3.34-3.40 (m, 1H), 3.78 (dd, *J* = 4.2, 11.1 Hz, 1H), 3.89 (dd, *J* = 3.6, 11.1 Hz, 1H), 4.04 (ddd, *J* = 4.2, 4.2, 7.8 Hz, 1H), 4.15 (dd, *J* = 5.4, 7.8 Hz, 1H), 5.86 (dd, *J* = 1.5, 10.2 Hz, 1H), 6.26 (dd, *J* = 17.4, 1.5 Hz, 1H), 6.39 (dd, *J* = 10.2, 17.7 Hz, 1H), 7.41-7.47 (m, 6H), 7.71-7.76 (m, 4H).

Synthesis of Diol Enone 9 and Isolation of Bicyclic Acetal 10.



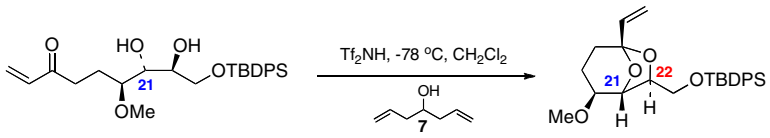
8 **S4** **9:** 40% for 2 steps

Triol S4. A solution of theallylic alcohol (200.0 mg, 0.40 mmol) in mixture of AcOH (5.60 mL) and H_2O (2.40 mL) was heated to 70 °C for 1.5 h. Then the solution was cooled to rt and sat aq $NaHCO_3$ was added slowly until pH is about 7. The mixture was diluted with EtOAc (20 mL). Then organic solvents were separated and the aqueous fraction was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with sat aq NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [gradient eluent: 40-60% EtOAc in hexanes] to provide triol **S4** in 86% yield (233.8 mg). **S4:** R_f = 0.25 [50 % EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.54-1.80 (m, 4H), 2.75-2.95 (br, 3H), 3.38 (m, 1H), 3.38 (s, 3H), 3.67 (dt, *J* = 6.5, 1.5 Hz, 1H), 3.77 (dd, *J* = 5.5, 10.0 Hz, 1H), 3.81 (dd, *J* = 5.5, 10.0 Hz, 1H), 3.90 (ddd, *J* = 1.0, 5.5, 5.5 Hz, 1H), 3.082-4.13 (m, 2H), 5.09 (d, *J* = 10.5 Hz, 1H), 5.22 (dd, *J* = 17.5 Hz, 1H), 5.86 (dddd, *J* = 3.5, 6.0, 9.5, 16.5 Hz, 1H), 7.38-7.44 (m, 6H), 7.67-7.70 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.2, 25.5 (25.7), 26.9, 32.0 (32.2), 58.3 (58.4), 66.2 (66.3), 69.9 (66.9), 71.7

(71.8), 72.8 (72.9), 82.2 (82.3), 114.6, 127.9, 129.9, 132.8 (132.9), 135.6 (135.6), 141.1 (141.1); IR (film) cm^{-1} 3415brs, 3073m, 2935s, 2861m, 1109s.

Triol **S4** was oxidized to diol enone **9** using the procedure described above for MnO_2 oxidation of allyl alcohol **8.**

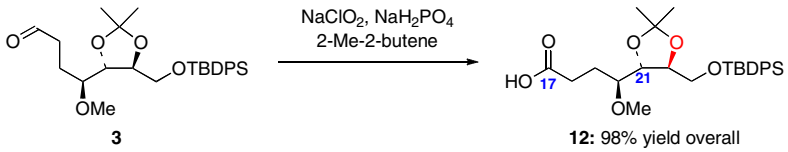
Isolation of Bicyclic Acetal 10.



9 **10:** 81% yield

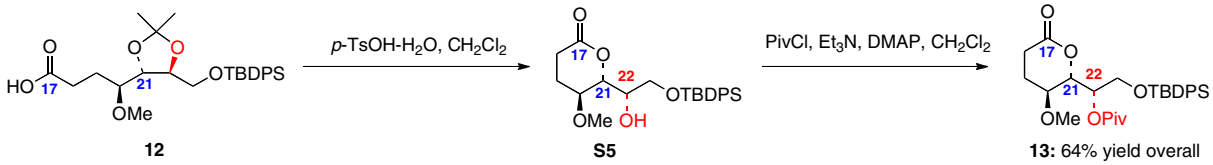
To a solution of the above diol-enone (7.76 mg, 0.017 mmol) and the alcohol **7** (3.90 mg, 0.034 mmol) in CH_2Cl_2 (0.5 mL) was added Tf_2NH (0.1 *M* in CH_2Cl_2, 0.34 mL, 0.034 mmol) at –78 °C. The solution was stirred at -78 °C for 5 min before quenched with Et_3N (0.2 mL) at –78 °C. The mixture was warmed to rt and filtered through Celite.™ After concentrating the filtrate under reduced pressure, the resulting crude residue (in 81% yield) showed a clean and pure NMR spectrum that could be assigned as bicyclic acetal **10**. **10:** R_f = 0.70 [10% EtOAc in hexanes]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.93-1.95 (m, 4H), 3.41-3.42 (m, 1H), 3.46 (s, 3H), 3.54(dd, *J* = 9.5, 9.5 Hz, 1H), 3.66 (dd, *J* = 5.0, 10.0 Hz, 1H), 3.99 (d, *J* = 5.0, 8.5 Hz, 1H), 4.65 (m, 1H), 5.20 (d, *J* = 11.0 Hz, 1H), 5.45 (d, *J* = 17.5 Hz, 1H), 5.87 (dd, *J* = 10.5, 17.5 Hz, 1H), 7.38-7.43 (m, 6 H), 7.64-7.66 (m, 4H).

Synthesis of Acid 12.



To a solution of aldehyde **3** (4.20 g, 8.90 mmol), 2-methyl-2-butene (4.7 mL, 44.5 mmol), and NaH_2PO_4 (2.46 g, 19.7 mmol) in the mixture of *t*-BuOH (30 mL) and H_2O (15 mL) was added $NaClO_2$ (3.22 g, 35.6 mmol) at -10 °C in 3 portions. The solution was warmed up to rt and stirred for 1 h to give a pale green solution. Then the reaction was quenched with sat aq $Na_2S_2O_3$ (30 mL). The organic phase was separated and the aqueous fraction was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [gradient eluent: 30-80% EtOAc in hexanes] to provide the carboxylic acid **12** as colorless oil in 98% yield (4.29 g). **12:** R_f = 0.40 [50% EtOAc in hexanes]; $[\alpha]_D^{23}$ = - 15.9 [c 4.37, $CHCl_3$]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.42 (s, 6H), 1.86-1.94 (m, 2H), 2.49 (ddd, *J* = 7.0, 16.5, 16.5 Hz, 2H), 2.52 (ddd, *J* = 7.0, 16.5, 16.5 Hz, 2H), 3.37 (s, 3H), 3.38 (m, 1H), 3.77 (ddd, *J* = 1.5, 4.5, 11.5 Hz, 1H), 3.88 (ddd, *J* = 1.5, 4.0, 11.0 Hz, 1H), 4.02 (m, 1H), 4.11 (m, 1H), 7.38-7.43 (m, 6H), 7.70-7.73 (m, 4H), 11.1 (br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 25.1, 16.8, 27.1, 27.2, 29.6, 58.2, 64.6, 77.8, 79.5, 80.6, 109.3, 127.7, 127.7, 129.7, 129.7, 133.2, 133.3, 135.7, 135.7, 179.5; IR (film) cm^{-1} 3010brs, 3071m, 2934s, 2861m, 1710s, 1109s; mass spectrum (ESI): m/e (% relative intensity) 509.2 $(M+Na)^+$ (100); m/e calcd for $C_{27}H_{38}O_6SiNa$ 509.2330, found 509.2335.

Synthesis of Lactone 13.

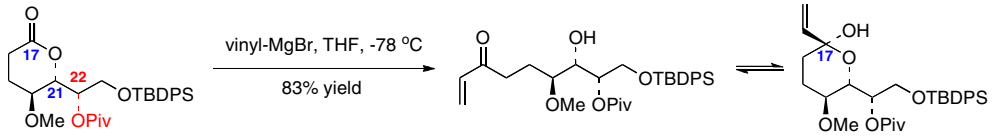


C22-Unprotected Lactone S5. To a solution of acid **12** (4.20 g, 8.63 mmol) in CH_2Cl_2 (45 mL) was added *p*-TsOH-H_2O (4.92 g, 25.9 mmol) at 0 °C. The solution was warmed up to rt and stirred for 3

h before quenched with sat aq $NaHCO_3$ (30 mL). The organic phase was separated and the aqueous fraction was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [gradient eluent: 40-50% EtOAc in hexanes] to provide the unprotected lactone **S5** as colorless oil in 83% yield (3.08 g). **S5:** R_f = 0.20 [50% EtOAc in hexanes]; $[\alpha]_D^{23}$ = 48.3 [c 5.24, $CHCl_3$]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09(s, 9H), 1.82 (ddd, *J* = 3.9, 6.9, 12.9 Hz, 1H), 2.04-2.16 (m, 1H), 2.36 (dt, *J* = 18.6, 6.3 Hz, 1H), 2.55 (ddd, *J* = 17.1, 6.3, 6.3 Hz, 1H), 3.31 (s, 3H), 3.68 (dd, *J* = 6.0, 10.8 Hz, 1H), 3.79-3.85 (m, 1H), 3.90-3.97 (m, 1H), 4.46 (d, *J* = 6.0 Hz, 1H), 7.36-7.37 (m, 6H), 7.70-7.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 20.8, 23.2, 26.8, 56.4, 63.9, 70.6, 72.9, 80.0, 127.7, 129.8, 133.0, 135.4, 170.9; IR (film) cm^{-1} 3440brs, 3071m, 2936s, 2861m, 1738s, 1110s; mass spectrum (ESI): m/e (% relative intensity) 451.2 $(M+Na)^+$ (100); m/e calcd for $C_{24}H_{32}O_5SiNa$ 451.1911, found 451.1912.

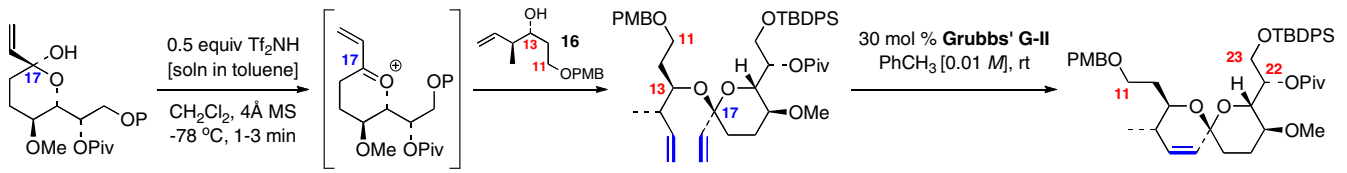
To a solution of the C22-unprotected lactone **S5** (805.7 mg, 1.88 mmol), pyridine (1.6 mL, 18.8 mmol) in CH_2Cl_2 (10 mL) was added $(CH_3)_3COCl$ (0.46 mL, 3.8 mmol) followed by DMAP (45.9 mg, 0.38 mmol) at rt. The solution was stirred for overnight and quenched with H_2O (10 mL). The organic phase was separated and the aqueous fraction was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [gradient eluent: 10-20% EtOAc in hexanes] to provide the pivalate-protected lactone **13** as colorless oil in 77% yield (737.0 mg). **13:** R_f = 0.65 [50 % EtOAc in hexanes]; $[\alpha]_D^{23}$ = 26.8 [c 3.45, $CHCl_3$]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H), 1.24 (s, 9H), 2.06 (dddd, *J* = 5.1, 5.7, 9.0, 13.8 Hz, 2H), 2.46 (ddd, *J* = 6.0, 6.0, 17.0 Hz, 1H), 2.69 (ddd, *J* = 6.6, 9.0, 17.1 Hz, 1H), 3.39 (s, 3H), 3.42 (m, 1H), 3.88 (d, *J* = 6.6 Hz, 2H), 4.55 (dd, *J* = 2.4, 6.6 Hz, 1H),5.33 (dt, J = 2.4, 6.6 Hz, 1H), 7.43-7.48 (m, 6H), 7.69-7.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 23.1, 26.6, 26.9, 27.0, 38.8, 56.7, 61.4, 71.3, 72.3, 78.6, 127.7, 127.7, 129.7, 129.8, 132.7, 132.8, 135.4, 135.5, 170.4, 177.5; IR (film) cm^{-1} 3071m, 2936s, 2862m, 1741s, 1151s; mass spectrum (APCI): m/e (% relative intensity) 513.3 $(M+H)^+$ (100); m/e (ESI) calcd for $C_{29}H_{40}O_6SiNa$ 535.2486, found 535.2489.

Synthesis of Vinyl Ketone and Lactol Mixture 14a/b.



To a solution of lactone **13** (131.2 mg, 0.256 mmol) in THF (2 mL) was added vinyl magnesium bromide (1.0 *M*, 0.51 mL, 0.51 mmol) dropwise at -78 °C. The solution was stirred for 1 h at -78 °C and quenched with sat aq $NaHCO_3$ (5 mL) and diluted with CH_2Cl_2 (5 mL). The organic phase was separated and the aqueous fraction was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography [gradient eluent: 15-20% EtOAc in hexanes] to provide an inseparable mixture of vinyl ketone and lactol **14a/b** as colorless oil in 83% yield (114.7.0 mg) and the recovered starting material (19.5 mg). **14a/b:** R_f = 0.65 [50 % EtOAc in hexanes]; $[\alpha]_D^{23}$ = 9.79 [c 3.36, $CHCl_3$]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.25 (s, 9H), 1.45 (d, *J* = 2.7 Hz, 1H), 1.98-2.06 (m, 2H), 2.62-2.80 (m, 2H), 3.17-3.21 (m, 1H), 3.28 (s, 3H), 3.81 (m, 1H), 3.90 (d, *J* = 4.5 Hz, 1H), 5.29 (dt, *J* = 2.5, 7.0 Hz, 1H), 5.83 (d, J = 11.5 Hz, 1H), 6.24 (d, *J* = 18.0 Hz, 1H), 6.37 (dd, *J* = 11.0, 18.0 Hz, 1H), 7.40-7.48 (m, 6H), 7.68-7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.9, 22.3, 26.6, 27.1, 33.7, 38.9, 57.3, 64.1, 71.3, 78.9, 103.6, 127.7, 127.7, 128.1, 129.8, 129.8, 132.4, 132.6, 135.4, 135.5, 136.3, 177.6, 201.0; IR (film) cm^{-1} 3506brs, 3071m, 2932s, 2858m, 1731s, 1112s; mass spectrum (ESI): m/e (% relative intensity) 563.3 $(M+Na)^+$ (100); m/e calcd for $C_{31}H_{44}O_6SiNa$ 563.2799, found 563.2810.

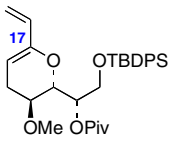
Synthesis of Vinyl Cyclic Acetal 17 and the C11-23 Fragment 18 [Fragment B] via RCM.



Vinyl Cyclic Acetal 17. To a solution of the vinyl ketone and lactol mixture **14a/b** (2.60 mg, 0.0048 mmol) in CH_2Cl_2 (0.1 mL) was added MS 4Å (10.0 mg), alcohol **16** (4.80 mg, 0.019 mmol)

followed by Tf_2NH (0.5 *M* in toluene, 0.012 mL, 0.0024 mmol) at –78 °C. The solution was stirred at -78 °C for 2 min before quenched with Et_3N (0.05 mL) at –78 °C. The mixture was warmed to rt and filtered through Celite.™ After evaporating the solvent under reduced pressure, the resulting crude residue was purified by silica gel flash column chromatography [gradient eluent: 10-25% EtOAc in hexanes] to provide the key vinyl cyclic acetal **17** in 56% yield based on starting material recovered. **17:** R_f = 0.80 [25% EtOAc in hexanes]; $[\alpha]_D^{23}$ = 23.5 [c 0.46, $CHCl_3$]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 9H), 1.28 (s, 9H), 1.37-1.40 (m, 1H), 1.50-1.59 (m, 1H), 1.71-1.81 (m, 2H), 1.91-2.00 (m, 2H), 2.89-2.92 (m, 1H), 3.23-3.28 (m, 2H), 3.32 (s, 3H), 3.69-3.75 (m, 2H), 3.80-3.82 (m, 1H0, 3.83 (s, 3H), 4.04 (m, 1H), 4.07 (d, *J* = 11.7 Hz, 1H), 4.19 (d, *J* = 11.4 Hz, 1H), 4.87 (d, *J* = 17.1 Hz, 1H), 4.92 (d, *J* = 9.9 Hz, 1H), 5.18 (d, *J* = 12.9 Hz, 1H), 5.46 (d, *J* = 17.1 Hz, 1H), 5.59-5.62 (m, 1H), 5.78 (dd, *J* = 10.5, 17.1 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.7 Hz, 2H), 7.38-7.43 (m, 6 H), 7.70-7.72 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 19.0, 23.0, 26.5, 27.3, 31.5, 34.8, 38.8, 40.3, 55.1, 56.2, 63.7, 66.4, 71.5, 71.8, 73.6, 74.4, 77.1 97.0, 113.5, 114.4, 115.8, 127.5, 127.6, 129.0, 129.5, 133.3, 135.5, 139.5, 140.5, 158.8, 170.4; IR (film) cm^{-1} 3071m, 2932s, 2859m, 1731s, 1513m, 1112s; mass spectrum (ESI): m/e (% relative intensity) 795.6 $(M+Na)^+$ (100); m/e calcd for $C_{46}H_{64}O_6SiNa$ 795.4263, found 795.4251.

***Minor Side Product Diene S6*:**



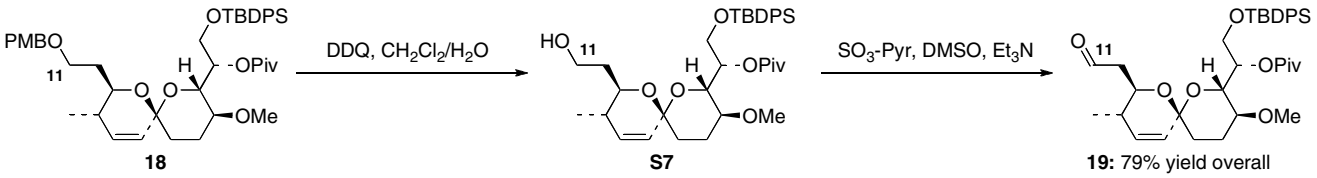
S6

R_f = 0.80 [25% EtOAc in hexanes]; $[\alpha]_D^{23}$ = 27.3 [c 0.40, $CHCl_3$]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9H), 1.24 (s, 9H), 2.16 (ddd, *J* = 3.0, 7.5, 17.7, 1H), 2.52 (ddd, *J* = 2.4, 2.4, 17.7 Hz, 1H), 3.40 (s, 3H), 3.47 (ddd, *J* = 5.7, 7.5, 7.5 Hz, 1H), 3.90 (d, *J* = 6.0 Hz, 2H), 4.18 (dd, *J* = 3.6, 7.5 Hz, 1H), 4.78 (dd, *J* = 4.2, 4.2 Hz, 1H), 5.02 (d, *J* = 10.8 Hz, 1H), 5.38 (d, *J* = 17.1 Hz, 1H), 5.47 (ddd, *J* = 3.6, 6.0, 6.0 Hz, 1H), 6.07 (dd, *J* = 10.8, 17.1 Hz, 1H), 7.30-7.47 (m, 6 H), 7.70-7.73 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.0, 22.4, 26.4, 26.5, 27.1, 56.5, 61.7, 70.4, 71.6, 74.5, 99.0, 112.7, 127.6, 129.6, 131.3,

133.1, 135.4, 149.9, 170.4; IR (film) cm^{-1} 3069m, 2960s, 2856m, 1732s, 1279m, 1157s; mass spectrum (ESI): m/e (% relative intensity) 545.3 $(M+Na)^+$ (100); m/e calcd for $C_{31}H_{42}O_5SiNa$ 545.2694, found 545.2691.

The C11-23 Fragment 18 [Fragment B]. To a 0.01 *M* solution of cyclic acetal **17** (34.8 mg, 0.45 mmol) in toluene was added Grubbs Generation-II Ru-catalyst (0.30 equiv) at rt and the mixture was stirred for 8 h until cyclic ketal **17** was consumed. The suspension was concentrated under reduced pressure and the residue was purified with silica gel flash column chromatography [isocratic eluent: 15% EtOAc in hexanes] to provide C11-23 fragment **18**, colorless oil, in 95% yield. The product yield was based on the amount of cyclic ketal compound **18** and the ratio between cyclic ketal and side product was figured out by ^1H NMR analysis. **18:** R_f = 0.50 [20% EtOAc in hexanes]; $[\alpha]_D^{23}$ = - 9.88 [c 0.24, $CHCl_3$]; ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (d, *J* = 9Hz, 3H), 1.02 (s, 9H), 1.26 (s, 9H), 1.52-1.66 (m, 2H), 1.68-1.75 (m, 2H), 1.82-1.87 (m, 1H), 1.97-2.02 (m, 2H), 2.94 (ddd, *J* = 2.5, 10.5, 10.5 Hz, 1H), 3.27 (s, 3H), 3.28-3.34 (m, 1H), 3.51 (ddd, *J* = 5.0, 9.0, 9.0 Hz, 1H), 3.57 (dd, *J* = 2.5, 9.5 Hz, 1H), 3.76 (ddd, *J* = 3.5, 10.5, 10..5 Hz, 1H), 3.79 (s, 3H), 3.92 (d, *J* = 9.0, 11.0 Hz, 1 H), 4.12 (d, *J* = 11.5 Hz, 1H), 4.16 (d, *J* = 11.5 Hz, 1H), 5.48 (dd, *J* = 2.5, 10.0 Hz, 1H), 5.54 (ddd, *J* = 3.0, 3.0, 8.5 Hz, 1H), 5.61 (dd, *J* = 1.5, 10.0 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 7.32-7.37 (m, 6 H), 7.67-7.68(m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.9, 19.4, 23.9, 26.9, 27.7, 33.3, 33.8, 34.5, 39.2, 55.5, 56.5, 64.3, 67.0, 71.2, 71.9, 72.7, 74.6, 93.5, 113.9, 113.9, 127.8, 127.8, 127.9, 128.6, 129.6, 129.7, 130.0, 130.9, 133.7, 133.9, 134.7, 135.8, 135.9, 159.3, 177.8; IR (film) cm^{-1} 3070m, 2959s, 2859m, 1731s, 1513m, 1101s; mass spectrum (ESI): m/e (% relative intensity) 767.4 $(M+Na)^+$ (100); m/e calcd for $C_{44}H_{60}O_6SiNa$ 767.3950, found 767.3947.

Synthesis of Aldehyde 19.

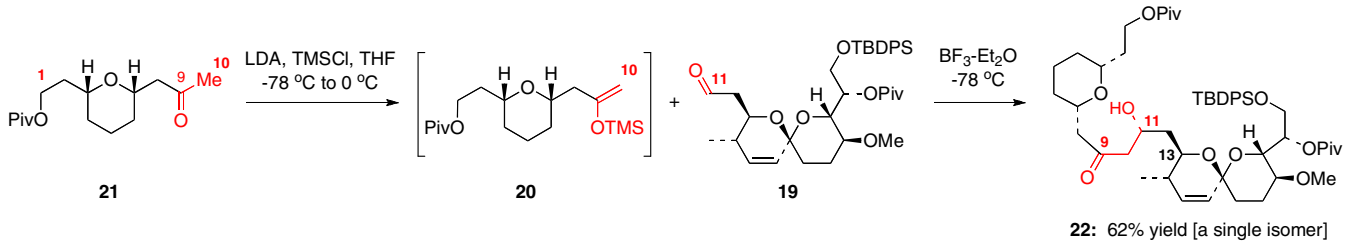


PMB Deprotected Sprioketal Alcohol S7. To a solution of **18** (130.4 mg, 0.17 mmmol) in CH_2Cl_2 : H_2O (10:1) was added DDQ (0.25 mmol, 1.5 equiv) at rt. After being stirred for 1.5 h, the mixture was quenched by sat aq $NaHCO_3$. The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by silica gel flash column chromatography [gradient eluent: 33-50% EtOAc in hexanes] to provide **S7** (94.8 mg, 0.15 mmol) in 88% yield as a colorless oil. **S7:** R_f = 0.30 [33% EtOAc/hexanes]; $[\alpha]_D^{23}$ = + 3.50 [c 0.84, CH_2Cl_2]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.087 (d, *J* = 9.0 Hz, 3H), 1.04 (s, 9H), 1.25 (s, 9H), 1.51-1.69 (m, 6H), 1.72-1.89 (m, 1H), 2.01-2.12 (m, 2H), 2.05 (s, 1H), 2.96 (ddd, *J* = 4.0, 10.0, 10.0 Hz, 1H), 3.25 (s, 3H), 3.45 (dt, *J* = 2.8, 9.6 Hz, 1H), 3.61 (t, *J* = 4.4 Hz, 2H), 3.69 (dd, *J* = 2.8, 9.6 Hz, 1H), 3.80 (dd, *J* = 4.4, 10.8 Hz, 1H), 3.88 (dd, *J* = 8.0, 10.8 Hz, 1H), 5.45 (ddd, *J* = 2.4, 4.4, 7.2 Hz, 1H), 5.49 (dd, *J* = 2.8, 10.0 Hz, 1H), 5.64 (dd, *J* = 2.0, 10.0 Hz, 1H), 7.32-7.37 (m, 6 H), 7.67-7.68(m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 19.4, 24.0, 27.0, 27.6, 33.7, 34.2, 35.0, 39.2, 56.4, 60.1, 63.8, 71.6, 72.5, 72.7, 74.5, 93.8, 127.8, 128.6, 129.7, 129.8, 133.8, 133.9, 134.7, 135.8, 135.9, 177.9; IR (neat) cm^{-1} (neat) 3524w, 3073w, 2958s, 2933s, 2858brs, 2361s, 2342s, 1731s, 1699w, 1160s, 1107s; mass spectrum (MALDI): m/e (% relative intensity) 647.3 $(M+Na)^+$ (100); m/e calcd for $C_{36}H_{52}O_7SiNa$ 647.3375, found 647.3352.

The Spiroketal Aldehyde 19. To a solution of primary alcohol **S7** (94.8 mg, 0.15 mmol) in DMSO/CH_2Cl_2 were added SO_3·Pyr (96.8 mg, 0.61 mmol) and Et_3N (0.12 mL, 0.76 mmol) sequentially in this order at 0 ºC and the resulting mixture was subsequently stirred for 2 h at that temperature. The residue was purified by silica gel flash column chromatography [isocratic eluent: 25% EtOAc in hexanes] to provide C11-23 fragment aldehyde **19** (101.2 mg, 0.132 mmol) in 90% yield. **19:** R_f = 0.50 [25% EtOAc/hexanes]; $[\alpha]_D^{23}$ = + 7.50 [c 0.24, CH_2Cl_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.086 (d, *J* = 7.2 Hz, 3H), 1.04 (s, 9H), 1.24 (s, 9H), 1.55 (dd, *J* = 4.4, 13.2 Hz, 1H), 1.61-1.69 (m, 1H), 1.73 (ddd, *J* = 3.2,

3.2, 8.4, 1H), 1.96-2.01 (m, 1H), 2.05-2.10 (m, 1H), 2.37 (ddd, *J* = 3.2, 8.4, 16.0 Hz, 1H), 2.48 (ddd, *J* = 1.2, 3.6, 16.0 Hz, 1H), 2.96 (ddd, *J* = 4.4, 10.0, 10.0 Hz, 1H), 3.24 (s, 3H), 3.67 (dd, *J* = 2.4, 9.6 Hz, 1H), 3.77 (ddd, *J* = 3.6, 8.4, 9.6 Hz, 1H), 3.96 (dd, *J* = 4.0, 7.2 Hz, 2H), 5.47 (ddd, *J* = 2.8, 5.6, 8.0 Hz, 1H), 5.53 (dd, *J* = 2.8, 10.0 Hz, 1H), 5.64 (dd, *J* = 1.6, 10.0, Hz, 1H), 7.35-7.41 (m, 6H), 7.66-7.69 (m 4H), 9.61 (dd, *J* = 1.2, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6, 19.5, 23.6, 27.1, 27.7, 33.7, 34.1, 39.2, 46.8, 56.4, 60.1, 63.5, 69.7, 71.7, 72.0, 74.4, 93.9, 127.8, 127.9, 128.9, 129.8, 133.7, 133.8, 135.8, 177.7, 201.1; IR (neat) cm^{-1} (neat) 3457w, 3074w, 2962s, 2935s, 2860brs, 2724w, 2362w, 2345w, 1733s, 1163s, 1108s; mass spectrum (MALDI): m/e (% relative intensity) 645.3 $(M+Na)^+$ (100); m/e calcd for $C_{36}H_{50}O_7SiNa$ 645.3218, found 645.3250.

Mukaiyama Methyl Ketone Enolate *Anti*-Aldol Connecting C10-11.



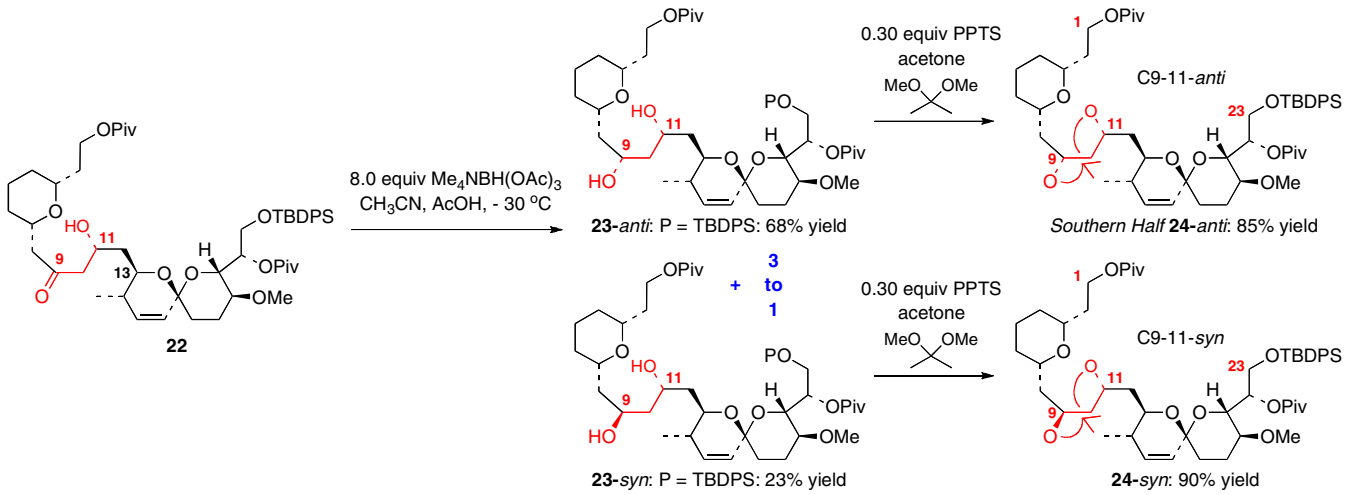
The Pivaloyl-Protected Pyran 21. R_f = 0.40 [25% EtOAc/hexanes]; $[\alpha]_D^{23}$ = - 22.5 [c 1.87, CH_2Cl_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 9H), 1.53-1.63 (m, 2H), 1.53-1.63 (m, 3H), 1.75 (dd, *J* = 7.0, 13.0Hz), 1.82-1.85 (m, 1H), 2.18 (s, 3H), 2.41 (dd, *J* = 5.0, 15.0Hz, 1H), 2.66 (dd, *J* = 7.5, 15.0Hz, 1H), 3.42 (dddd, *J* = 1.5, 7.0, 10.5, 13.0Hz, 1H), 3.75 (dddd, *J* = 2.0, 5.0, 8.0, 11.0Hz, 1H), 4.12 (ddd, *J* = 6.0, 10.5, 11.0Hz, 2H)**;** ^{13}C NMR (125MHz, $CDCl_3$) δ 23.7, 27.4, 27.4, 27.4, 31.2, 31.5, 31.6, 35.6, 39.0, 50.6, 61.3, 74.7, 74.8, 178.7, 207.8; IR (neat) cm^{-1} 3420brs, 2929s, 2857s, 2360s, 2341s 1710s; mass spectrum (APCI): m/e (% relative intensity) 293 $(M+Na)^+$ (14), 271 $(M+H)^+$ (100), 253 (71), 213 (85), 169 (50), 151 (89), 133 (19), 129 (6), 111 (42).

The Silyl Enol Ether 20. To a cooled solution of *i*-Pr_2NH (12.0 μL, 0.57 mmol) in THF (2 mL) was added *n*-BuLi (1.6 *M* in hexanes, 0.033 mL, 0.53 mmol) at 0 °C. This resulting solution was stirred for 10 min to prepare LDA (0.5 *M* in THF) in *situ* for next step.

The LDA solution was cooled to -78 ^{o}C. To this solution was added pyran **21** (52.0 mg, 0.19 mmol) *via* cannula and the mixture was stirred for 30 min. TMSCl (35.0 μL, 294 mmol) was then added and the resulting reaction mixture was stirred for 30 min. The reaction mixture was gradually warmed up to 0 ^{o}C and the reaction was quenched with sat aq $NaHCO_3$ solution. The organic phase was extracted with EtOAc, dried over Na_2SO_4, and concentrated under reduced pressure. The crude yellow residue was used for the next step without further purification.

The C1-23 Fragment 22. To a cooled mixture of the silyl enol ether **20** prepared above (0.189 mmol) and **19** (101.0 mg, 0.13 mmol) in CH_2Cl_2 (1 mL) was added BF_3-Et_2O (47.3 μL, 0.37 mmol) at -78 ^{o}C dropwise. The reaction was stirred at -78 ^{o}C for 1 h and then sat aq $NaHCO_3$ (3 mL) was added to quench the reaction. After the mixture was warmed up to room temperature, the organic phase was separated and the aqueous fraction was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified with silica gel flash column chromatography [gradient eluent: 2-10% EtOAc in hexanes] to provide the desired C1-23 fragment **22** (62.4 mg, 0.069 mmol) in 62% yield (colorless oil) as a single isomer. **22:** R_f = 0.50 [33% EtOAc/hexanes]; $[\alpha]_D^{23}$ = - 15.2 [c 0.43, CH_2Cl_2]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.086 (d, *J* = 7.0 Hz, 3H), 1.02 (s, 9H), 1.18 (s, 9H), 1.18-1.2 (m, 2H), 1.24 (s, 9H), 1.40-1.47 (m, 1H), 1.50-1.78 (m, 9H), 1.9-1.96 (m, 1H), 1.97-2.04 (m, 1H), 2.10 (dd, *J* = 2.5, 8.0 Hz, 1H), 2.42 (dd, *J* = 5.5, 16.0, 1H), 2.54 (d, *J* = 5.5 Hz, 2H), 2.65 (dd, *J* = 7.5, 15.5 Hz, 1H), 2.94 (ddd, *J* = 4.5, 10.0, 10.0 Hz, 1H), 3.03 (d, *J* = 3.0 Hz, 1H), 3.23 (s, 3H), 3.41 (dddd, *J* = 1.0, 7.5, 7.5, 7.5 Hz, 1H), 3.53 (td, *J* = 1.0, 8.0 Hz, 1H), 3.69 (dd, *J* = 2.0, 9.5, 1H), 3.76 (dddd, *J* = 5.5, 5.5, 5.5, 5.5 Hz, 1H), 3.86 (dd, *J* = 4.0, 11.0 Hz, 1H), 3.88 (dd, *J* = 4.0, 9.5 Hz, 1H), 4.12 (t, *J* = 6.5 Hz, 2H), 4.24 (m, 1H), 5,.45 (ddd, *J* = 2.0, 4.0, 4.0Hz, 1H), 5.47 (dd, *J* = 2.5, 10.0 Hz, 1H), 5.63 (d, *J* = 10.0 Hz, 1H), 7.35-7.41 (m, 6H), 7.66-7.69 (m 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.9, 19.5, 23.7, 24.0, 27.1, 27.5, 27.7, 31.5, 31.6, 33.7, 33.9, 35.6, 39.0, 39.2, 39.3, 50.5, 51.2, 56.4, 61.3, 63.9, 64.3, 71.4, 71.7, 72.6, 74.4, 74.5, 74.9, 93.8, 110.0, 127.8, 127.9, 128.5, 129.7, 129.8, 133.9, 134.1, 134.8, 135.8, 135.9, 178.0, 178.7, 209.4; IR (neat) cm^{-1} 2957brs, 2933s, 2860brs, 2361s, 2342s, 1728s,1157s; mass spectrum (ESI): m/e (% relative intensity) 915.7 $(M+Na)^+$ (80), 910.7 (60), 640.6 (50), 563.5 (100).

Directed Reduction and Acetonide Formation: Synthesis of C1-23 Fragment – Southern Half.



The Diol 23. To a solution of tetramethylammonium triacetoxyborohydride (85.1 mg, 0.036 mmol) in anhyd acetonitrile (1.8 mL) and anhyd acetic acid (1.8 mL) at -30 ºC was added a solution of *β*–hydroxy ketone **22** (40.5 mg, 0.045 mmol) in anhyd acetonitrile (1 mL). After the stirring for 12 h, the reaction mixture was quenched with sat aq $NaHCO_3$ with an additional stirring of 30 min. The mixture was extracted with CH_2Cl_2. The combined organic layers are dried over Na_2SO_4, filtered, concentrated under reduced pressure and the desired diol **23**-*anti* was isolated by silica gel flash column chromatography [gradient eluent: 25-50% EtOAc in hexanes]. However, the undesired diol **23**-*syn* was also isolated. The combined yield was 91% with the *anti:syn* ratio being 3:1. The *dr* reflects the isolated ratio. We tried to figure out the ratio according to the crude proton NMR but it was not clear by integration.

23-*Anti*: R_f= 0.40 [25% EtOAc/hexanes]; $[\alpha]_D^{23}$ = - 7.69 [c 0.52, CH_2Cl_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, *J* = 9.0 Hz, 3H), 1.02 (s, 9H), 1.19 (s, 9H), 1.19-1.20 (m, 2H) , 1.23 (s, 9H), 1.45-1.60 (m, 8H), 1.63-1.70 (m, 3H), 1.72-1.89 (m, 4H), 1.98-2.02 (m, 1H), 2.14-2.18 (ddd, *J* = 2.0, 5.6, 5.6 Hz, 1H), 2.96 (ddd, *J* = 4.8, 4.8, 4.8 Hz, 1H), 3.35 (dddd, *J* = 6.0, 6.0, 11.6, 11.6 Hz, 1H), 3.56-3.61 (m, 2H), 3.77 (dd, *J* = 2.8, 9.6 Hz, 1H), 3.87 (d, *J* = 5.2, 1H), 3.88 (d, *J* = 6.8 Hz, 1H), 4.07 (ddd, *J* = 5,6, 5.6, 11.2 Hz, 1H), 4.14-4.22 (m, 2H), 4.32 (ddd, *J* = 6.0, 6.0, 10.8 Hz, 1H), 5.40 (ddd, *J* = 2.4, 5.2, 5.2 Hz, 1H), 5.48 (dd, *J* = 2.4, 10.0 Hz, 1H), 5.65 (dd, *J* = 2.0, 9.6 Hz, 1H), 7.34-7.40 (m, 6H), 7.66-7.68 (m,

4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.0, 19.5, 21.3, 23.9, 24.0, 27.1, 27.5, 27.7, 31.5, 31.8, 33.4, 33.8, 35.9, 39.3, 39.5, 43.3, 44.6, 56.3, 60.7, 61.1, 63.6, 65.4, 65.8, 71.4, 71.9, 72.9, 74.6, 74.8, 75.7, 93.9, 127.8, 127.9, 128.4, 129.7, 129.8, 134.0, 135.0, 135.9, 135.9, 178.0, 178.9; IR (neat) cm^{-1} 2934 brs, 2859brs, 2361s, 2341s, 1728s, 1157s, 1105s; mass spectrum (MALDI): m/e (% relative intensity) 917.7 $(M+Na)^+$ (100); m/e calcd for $C_{51}H_{78}O_{11}SiNa$ 917.5206, found 917.5192.

23-*Syn*: R_f = 0.50 [25% EtOAc/hexanes]; $[\alpha]_D^{23}$ = - 4.18 [c 0.41, CH_2Cl_2]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85(d, *J* = 9.0 Hz, 3H), 1.02 (s, 9H), 1.19 (s, 9H), 1.19-1.22 (m, 3H), 1.24 (s, 9H), 1.46-1.62 (m, 7H), 1.63-1.90 (m, 5H), 1.99-2.05 (m, 2H), 2.92 (ddd, *J* = 6.0, 12.5, 12.5 Hz, 1H), 3.24 (s, 3H), 3,46-3.53 (m, 2H), 3.56-3.60 (m, 2H), 3.70 (dd, *J* = 3.5, 12.5 Hz, 1H), 3.91 (d, *J* = 7.0 Hz, 1H), 3.92 (d, *J* = 8.0 Hz, 1H), 3.97-4.03 (m, 2H), 4.12 (m, 1H), 4.15 (dd, *J* = 15.0, 15.0 Hz, 1H), 4.17 (dd, *J* = 15.0, 15.0 Hz, 1H), 7.33-7.39 (m, 6H), 7.65-7.68 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.0, 19.4, 23.5, 27.0, 27.4, 27.7, 31.3, 32.0, 34.0, 35.6, 38.9, 39.2, 56.4, 61.2, 64.1, 68.5, 71.4, 71.7, 72.3, 72.6, 74.6, 75.2, 76.9, 79.0, 93.6, 127.7, 127.8, 128.5, 129.6, 129.7, 133.9, 134.1, 134.8, 135.8, 135.9, 178.5, 178.7; IR (neat) cm^{-1} 2934 brs, 2859brs, 2361s, 2341s, 1728s, 1157s, 1105s; mass spectrum (MALDI): m/e (% relative intensity) 917.8 $(M+Na)^+$ (100); m/e calcd for $C_{51}H_{78}O_{11}SiNa$ 917.5206, found 917.5164.

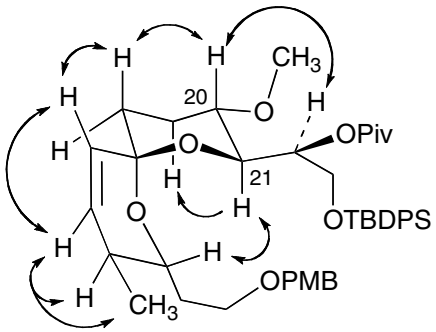
The Southern Half 24-Anti/Syn Acetonide. To a solution of diol **23**-*anti* (18.3 mg, 0.021 mmol) in acetone (4.8 mL) was added a catalytic amount of pyridinium *p*-toluene sulfonate (1.76 mg, 0.007 mmol) and 2,2-dimethoxypropane (10.0 μL, 0.063 mmol) and the resulting mixture was stirred over 1 h. The reaction was quenched by sat aq $NaHCO_3$ and the organic layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The desired the southern half **24**-*anti* acetonide was isolated by silica gel flash column chromatography [gradient eluent: 20-50% EtOAc in hexanes] in 85 % yield (15.7 mg, 0.018 mmol).

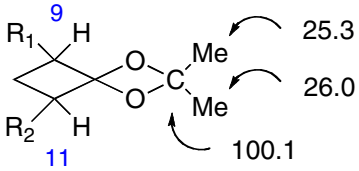
Also, diol **23**-*syn* (7.20 mg, 0.008 mmol) was transformed into the respective acetonide **24**-*syn* using the same reaction protocol in 90% yield (6.95 mg, 0.007 mmol).

The Southern Half 24-*Anti* Acetonide. R_f = 0.50 [20% EtOAc/hexanes]; $[\alpha]_D^{23}$ = - 2.70 [c 0.08, CH_2Cl_2]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (d, *J* = 7.2 Hz, 3H), 1.00, (s, 9H), 1.10 (s, 3H), 1.11 (s, 3H), 1.15-1.19 (m, 2H), 1.19 (s, 9H), 1.26 (s, 9H), 1.37-1.45 (m, 3H), 1.50-1.75 (m, 10H), 1.83-2.01 (m, 3H), 1.98 (m, 1H), 2.90 (ddd, *J* = 4.4, 9.6, 9.6 Hz, 1H), 3.17 (s, 3H), 3.32 (ddd, *J* = 2.0, 10.0, 10.0 Hz), 3.35-3.39 (m, 1H), 3.44 (m, 1H), 3.57 (dd, *J* = 3.2, 9.6 Hz, 1H), 3.76 (dd, *J* = 2.8, 11.2 Hz, 1H), 3.92 (dd, *J* = 9.6, 11.2 Hz, 1H), 3.95-4.04 (m, 2H), 4.13 (ddd, *J* = 6.8, 6.8, 10.8 Hz, 1H), 4.22 (ddd, *J* = 6.8, 6.8, 10.4 Hz, 1H), 5.47 (dd, *J* = 2.4, 10.0 Hz, 1H), 5.52 (ddd, *J* = 3.2, 3.2, 9.6 Hz, 1H), 5.58 (dd, *J* = 2.0, 10.0 Hz, 1H), 7.33-7.39 (m, 6H), 7.64-7.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.3, 19.4, 23.6, 23.9, 25.3, 26.0, 27.0, 27.5, 27.8, 32.1, 32.3, 33.9, 34.9, 36.0, 39.0, 39.2, 39.8, 42.0, 42.9, 56.2, 61.5, 62.7, 63.7, 64.5, 70.4, 71.9, 72.8, 74.1, 74.6, 74.7, 92.9, 100.1, 127.8, 127.9, 128.5, 129.7, 129.8, 133.8, 134.0, 135.9, 136.0, 177.8, 178.7; IR (neat) cm^{-1} 3454brs, 3048s, 2934s 2858m, 2363s, 2341s, 1661w, 1730s, 1284s, 1159s, 1106s, 1032s, 996s, 935s, 740s, 704s; mass spectrum (MALDI): m/e (% relative intensity) 957.5 $(M+Na)^+$ (100); calcd for $C_{54}H_{81}O_{11}SiNa$ 957.5519, found 957.5507.

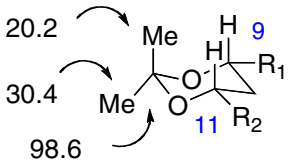
The Southern Half 24-*Syn* Acetonide: R_f = 0.50 [20% EtOAc/hexanes]; $[\alpha]_D^{23}$ = + 2.54 [c 0.14, CH_2Cl_2]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (d, *J* = 7.0 Hz, 3H), 0.99 (s, 9H), 1.00 (s, 3H), 1.09 (m, 1H), 1.14-1.23 (m, 3H), 1.18 (s, 9H), 1.24 (s, 3H), 1.27 (s, 9H), 1.30-1.42 (m, 2H), 1.44 (m, 1H), 1.50-1.57 (m, 5H), 1.70-1.86 (m, 7H), 2.01 (m, 1H), 2.90 (ddd, *J* = 4.5, 10.5, 10,5 Hz, 1H), 3.20 (s, 3H), 3.33-3.42 (m, 2H), 3.37 (dd, *J* = 1.5, 10.0 Hz, 1H), 3.56 (dd, *J* = 3.0, 9.5 Hz, 1H), 3.77 (dd, *J* = 2.5, 10.5 Hz, 1H), 3.94 (m, 1H), 3.98 (dd, *J* = 10.0, 10.0 Hz, 1H), 4.09 (ddd, *J* = 2.0, 9.5, 9.5, Hz, 1H), 4.14 (dd, *J* = 6.0, 6.0 Hz, 1H), 4.15 (dd, *J* = 6.0, 6.0 Hz, 1H), 5.47 (dd, *J* = 2.0, 10.0 Hz, 1H), 5.58 (m, 1H), 5.58 (dd, *J* = 2.0, 10.0 Hz, 1H) ,7.32-7.38 (m, 6H), 7.65-7.69 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.2, 19.4, 20.2, 23.7, 23.9, 26.9, 26.9, 26.9, 27.5, 27.5, 27.5, 27.9, 27.9, 27.9, 30.4, 31.5, 31.9, 33.8, 35.2, 35.8, 38.2, 39.0, 39.3, 42.0, 43.2, 56.4, 61.5, 64.6, 64.7, 65.7, 69.1, 71.9, 72.5, 74.2, 74.5, 74.6, 92.9, 98.6, 127.8, 127.8, 127.9, 127.9, 128.5, 129.7, 129.8, 133.8, 134.2, 135.9, 135.9, 136.0, 136.0, 177.0, 177.8; IR (neat) cm^{-1} 3454brs, 3048s, 2934s 2858m, 2363s, 2341s, 1730s, 1284s, 1159s, 1106s, 1032s, 935s, 740s, 703s; mass spectrum (MALDI): m/e (% relative intensity) 957.6 $(M+Na)^+$ (100); calcd for $C_{54}H_{81}O_{11}SiNa$ 957.5519, found 957.5516.

NOE OF C11-23 Fragment B: Spiroketal 18.



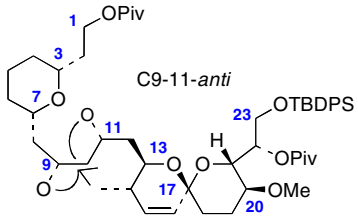


Southern Half **24-***anti*

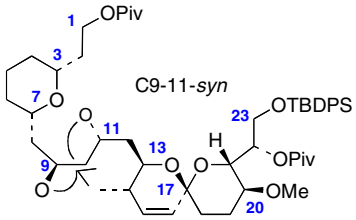


Southern Half **24-***syn*

24-Anti- *and* ***24-syn****-acetonide determination of* ^{13}C *NMR Resonances at* C_9 *and* C_{11} *with* ***Rychonovsky acetal analysis***



Southern Half **24-***anti*



24-*syn*

	^{1}H (ppm)	^{13}C (ppm)	^{1}H (ppm)	^{13}C (ppm)
Acetonide C_9 and C_{11}	1.10 (s, 3H) 1.11 (s, 3H)	25.3 26.0 100.1	1.00 (s, 3H) 1.24 (s, 3H)	20.2 30.4 98.6

24-Anti *and* ***24-Syn*** *- Acetonide determination with* ***Rychonovsky acetal analysis***