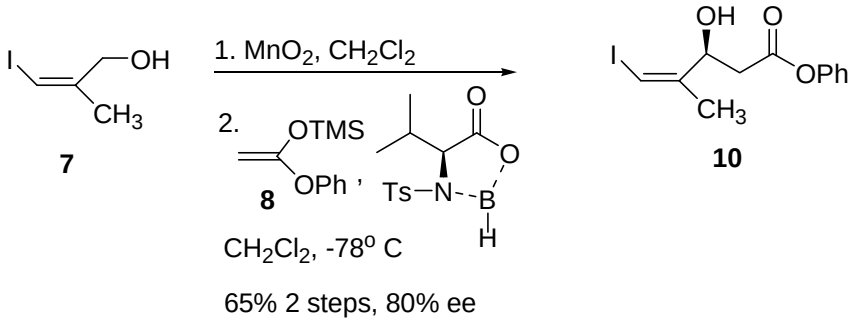
Synthesis of *ent*-Haterumalide NA (Oocydin A) Methyl Ester

Yonghong Gu and Barry B. Snider*

Department of Chemistry MS 015, Brandeis University, Waltham, MA 02454-9110

Experimental Procedures

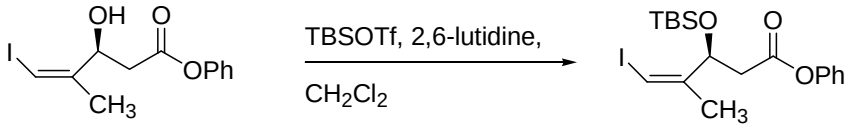
General Procedures. NMR spectra were recorded at 400 MHz, chemical shifts are reported in δ, and coupling constants are reported in Hz. IR spectra were obtained as thin films and are reported in cm^{-1}.



Phenyl (3*S*)-3-Hydroxy-5-iodo-4-methyl-4*Z*-pentenoate (10). MnO_2 (6.0 g, 60.6 mmol) was added to a solution of iodoalkenol **7**[9] (0.60 g, 3.03 mmol) in dry CH_2Cl_2 (30 mL), the reaction mixture was stirred at room temperature for 2 h and filtered. The filtrate was concentrated to give the very unstable aldehyde,[10] which was immediately used in next step.

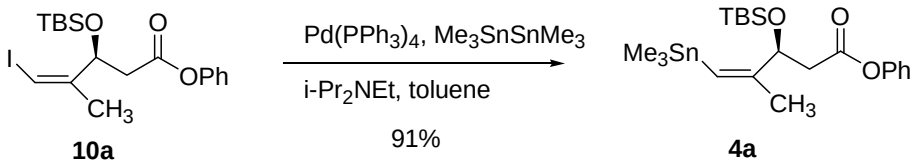
BH_3·THF (1.0 M in THF, 3.03 mL, 3.03 mmol) was added dropwise to a solution of *N*-Ts-L-valine[22] (0.724 g, 3.33 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C under N_2. The reaction mixture was allowed to stir for 30 min at 0 °C and an additional 30 min at room temperature and cooled to -78 °C. A solution of the above aldehyde in CH_2Cl_2 (3 mL) was added slowly over 5 min and the solution was stirred for 5 min. Silyl ketene acetal **8**[23] (0.69 g, 3.33 mmol) was added over 5 min. The reaction mixture was stirred at -78 °C for 4 h. The reaction was quenched at –78 °C by adding saturated $NaHCO_3$ (30 mL) and the aqueous layer was extracted with CH_2Cl_2

(3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (25:1 hexanes/EtOAc) gave 0.653 g (65%, 80%ee, Chiralpak AD, 9:1 hexanes/2-propanol, 1.0 mL/min, λ 254 nm, t_R = 8.8 min, (S, major isomer), t_R = 11.5 min, (R, minor isomer)) of alcohol **10**: ^{1}H NMR 7.40 (dd, 2, *J* = 7.9, 7.3), 7.26 (t, 1, *J* = 7.9), 7.12 (d, 2, *J* = 7.3), 6.06 (q, 1, *J* = 1.2), 5.13 (ddd, 1, *J* = 9.8, 3.7, 3.1)**,** 2.86 (dd, 1, *J* = 16.5, 9.8), 2.85 (d, 1, *J* = 3.1, OH), 2.76 (dd, 1, *J* = 16.5, 3.7), 1.95 (d, 3, *J* = 1.2); ^{13}C NMR 170.5, 150.3, 146.7, 129.5 (2 C), 126.1, 121.5 (2 C), 75.2, 72.6, 38.8, 19.0; IR 3459, 1748; $[\alpha]^{20}_D$ -15.9 (c 1.32, $CHCl_3$); HRMS (CI/NH_3) calculated for $C_{12}H_{17}NO_3I$ (MNH_4^+) 350.0253, found 350.0240.



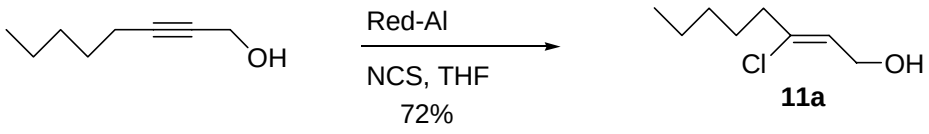
10 **10a**

Phenyl (3*S*)-3-*t*-Butyldimethylsilyloxy-5-iodo-4-methyl-4*Z*-pentenoate (10a). TBSOTf (0.368 g, 1.39 mmol) was added to a solution of alcohol **10** (0.257 g, 0.774 mmol) and 2,6-lutidine (0.315 g, 2.94 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (50:1 hexanes/EtOAc) gave 0.317 g (92%) of **10a**: ^{1}H NMR 7.38 (dd, 2, *J* = 8.5, 7.3), 7.23 (t, 1, *J* = 7.3), 7.11 (d, 2, *J* = 8.5), 5.99 (s, 1), 5.19 (dd, 1 *J* = 9.2, 4.3)**,** 2.83 (dd, 1, *J* = 14.7, 9.2), 2.61 (dd, 1, *J* = 14.7, 4.3), 1.92 (s, 3), 0.90 (s, 9), 0.13 (s, 3), 0.07 (s, 3); ^{13}C NMR 168.8, 150.7, 147.7, 129.4 (2 C), 125.8, 121.5 (2 C), 74.3, 73.9, 41.0, 25.7 (3 C), 18.7, 18.0, -4.8, -5.0; IR 1764, 1594; $[\alpha]^{20}_D$ +15.6 (c 1.50, $CHCl_3$); HRMS (CI/NH_3) calculated for $C_{18}H_{28}IO_3Si$ (MH^+) 447.0853, found 447.0835.



10a **4a**

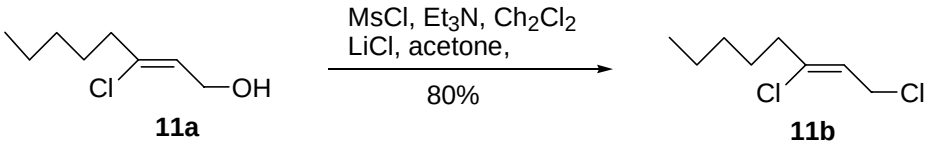
Phenyl (3*S*)-3-*t*-Butyldimethylsilyloxy-4-methyl-5-trimethylstannyl-4*Z*-pentenoate (4a). $Me_3SnSnMe_3$ (0.440 g, 1.34 mmol) was added to a solution of vinyl iodide **10a** (0.200 g, 0.448 mmol), *i*-Pr_2NEt (0.0116 g, 0.0897 mmol) and $Pd(PPh_3)_4$ (0.0518 g, 0.0448 mmol) in toluene (3 mL) at room temperature. The reaction mixture was heated in an 80 °C oil bath for 30 min. The reaction was quenched with H_2O (5 mL) and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on Florisil (hexanes with 3% Et_3N) gave 0.200 g (91%) of **4a** containing 10-20% Ph_3P. ^{1}H NMR 7.39-7.09 (m, 5), 5.63 (s, 1), 4.75 (dd, 1, *J* = 9.8, 3.1)**,** 2.91 (dd, 1, *J* = 14.7, 9.8), 2.53 (dd, 1, *J* = 14.7, 3.1), 1.92 (d, 3, *J* = 1.8), 0.89 (s, 9), 0.21 (s, 9), 0.07 (s, 3), 0.04 (s, 3); ^{13}C NMR 169.5, 155.9, 150.7, 129.3 (2 C), 125.7, 125.4, 121.5 (2 C), 75.0, 43.3, 25.7 (3 C), 20.3, 18.0, -4.7, -5.1, -8.6 (3 C); IR 1763, 1594; $[\alpha]^{20}_D$ +1.8 (c 1.0, $CHCl_3$); HRMS (CI/NH_3) calculated for $C_{21}H_{37}O_3SiSn$ (MH^+) 485.1534, found, 485.1512.



11a

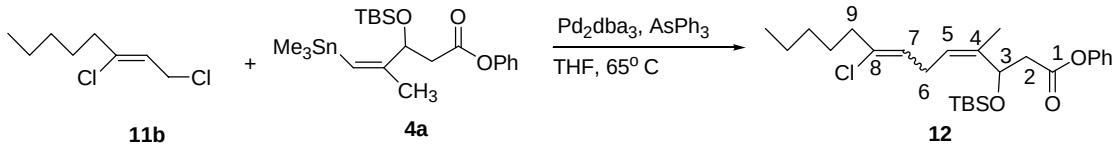
3-Chloro-2*Z*-octen-1-ol (11a). Red-Al (1.21 mL, 4.0 mmol) was added slowly to a solution of 2-octyn-1-ol (0.315 g, 2.5 mmol) in THF (15 mL) at room temperature. The resulting mixture was stirred at room temperature for 8 h and cooled to -78 °C. A solution of *N*-chlorosuccinimide (1.0 g, 7.5 mmol) in THF (15 mL) was added and the resulting mixture was slowly warmed to room temperature overnight. The reaction was quenched with saturated NH_4Cl (10 mL) and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue

on silica gel (25:1 hexanes/EtOAc) gave 0.261 g (72%) of **11a**: ^{1}H NMR 5.72 (t, 1, *J* = 6.1), 4.30 (d, 2, *J* = 6.1), 2.33 (t, 2, *J* = 7.9), 1.60-1.53 (m, 2), 1.40-1.24 (m, 4), 0.90 (t, 3, *J* = 6.7).



11a **11b**

1,3-Dichloro-2*Z*-octene (11b). MsCl (0.288 g, 2.51 mmol) was added slowly to a solution of alcohol **11a** (0.240 g, 1.477 mmol) and Et_3N (0.187 g, 1.846 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C. The reaction was stirred for 20 min at 0 °C, a solution of LiCl (0.626 g, 14.77 mmol) in acetone (5 mL) was added. The resulting mixture was stirred at room temperature for 6 h. The reaction was quenched with saturated NH_4Cl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (hexane) gave 0.214 g (80%) of **11b**: ^{1}H NMR 5.72 (t, 1, *J* = 7.3), 4.20 (d, 2, *J* = 7.3), 2.36 (t, 2, *J* = 7.3), 1.61-1.53 (m, 2), 1.35-1.26 (m, 4), 0.90 (t, 3, *J* = 6.7).



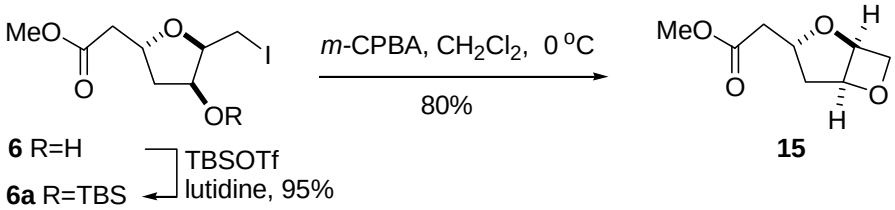
11b **4a** **12**

Phenyl (3*S*)-3-(*t*-Butyldimethylsilyloxy)-8-Chloro-4-methyl-4*Z*,7*Z*-tridecadienoate (12). $AsPh_3$ (5.1 mg, 0.0166 mmol) and Pd_2dba_3 (3.8 mg, 4.15 μmol) were added to a solution of allylic chloride **11b** (26.3 mg, 0.083 mmol) in dry THF (0.5 mL) at room temperature. The reaction was stirred at room temperature for 10 min and a solution of vinyltin **4a** (40 mg, 0.083 mmol) in THF (0.5 mL) was added. The reaction mixture was heated at 65 °C for 19 h and concentrated. Flash chromatography of the residue on silica gel (hexane) gave 8 mg of a 1:1 mixture of (***7E***)-and (***7Z***)-**12** followed by 27 mg (70%) of (***7Z***)-**12**.

Data for (***7Z***)-**12**: ^{1}H NMR 7.39-7.02 (m, 5), 5.39 (dd, 1, *J* = 6.7, 6.7); 5.22-5.18 (m, 2), 3.07-2.90 (m, 2), 2.89 (dd, 1, *J* = 14.7, 8.5), 2.58 (dd, 1, *J* = 14.7, 4.9), 2.27 (t, 2, *J* = 7.3), 1.75

(s, 3), 1.56-1.48 (m, 2), 1.32-1.23 (m, 4), 0.90 (t, 3, *J* = 6.7), 0.88 (s, 9), 0.08 (s, 3), 0.04 (s, 3). The stereochemistry of (***Z***)-**12** was established by a 1D NOESY experiment. Irradiation of H-7 at δ 5.39 showed a cross peak to H-9 at δ 2.27.

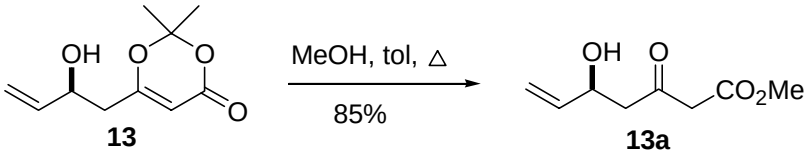
Partial data for (***7E***)-**12**: ^{1}H NMR 5.52 (dd, 1, *J* = 7.3, 7.3), 2.32 (t, 2, *J* = 7.3).



Methyl *cis*-2,6-Dioxabicyclo[3.2.0]heptane-3-acetate (15). TBSOTf (0.281 g, 1.065 mmol) was added to a solution of alcohol **6**[8] (0.168 g, 0.56 mmol) and 2,6-lutidine (0.178 g, 1.658 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was stirred at room temperature for 12 h and quenched with H_2O (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (25:1 hexanes/EtOAc) gave 0.22 g (95%) of **6a**: ^{1}H NMR 4.67-4.60 (m, 1), 4.48-4.46 (m, 1), 4.22-4.18 (m, 1), 3.69 (s, 3), 3.27 (dd, 1, *J* = 9.2, 9.2), 3.20 (dd, 1, *J* = 9.2, 4.9), 2.63 (dd, 1, *J* = 15.3, 6.7), 2.49 (dd, 1, *J* = 15.3, 6.1), 2.15 (dd, 1, *J* = 13.1, 5.5), 1.80 (ddd, 1, *J* = 13.1, 10.1, 3.7), 0.91 (s, 9), 0.16 (s, 3), 0.12 (s, 3); ^{13}C NMR 171.3, 83.7, 75.1, 72.4, 51.7, 41.7, 40.4, 25.8 (3 C), 17.9, 2.4, -4.4, -4.8.

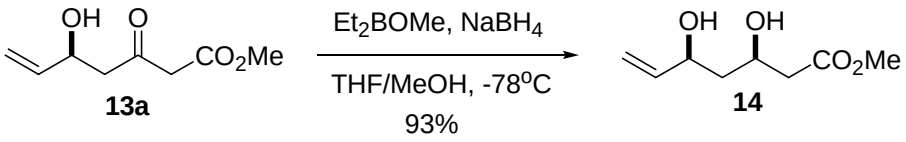
m-CPBA (77%, 89 mg, 0.398 mmol) was added to a solution of iodide **6a** (110 mg, 0.265 mmol) in CH_2Cl_2 (5 mL) at 0 °C and the mixture was stirred at 0 °C for 3 h. The reaction was quenched with saturated $Na_2S_2O_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with 5% $NaHCO_3$ (10 mL) and dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (3:1 hexanes/EtOAc) gave 36.5 mg (80%) of **15**: ^{1}H NMR 5.40 (dd, 1, *J* = 4.3, 3.0), 4.95 (dd, 1, *J* = 4.9, 3.0, 3.0), 4.90-4.84 (m, 1), 4.74 (dd, 1, *J* = 7.9, 4.9), 4.42 (dd, 1, *J* = 7.9, 3.0), 3.69 (s, 3), 2.72 (dd, 1, *J* = 15.9, 7.3), 2.66 (dd, 1, *J* = 15.9, 6.1), 2.26 (dd, 1, *J* = 13.7, 4.6), 1.38 (ddd, 1,

J = 13.7, 10.3, 4.3); ^{13}C NMR 171.2, 88.6, 77.8, 77.4, 74.6, 51.8, 39.4, 38.9; MS (DCI/NH_3) calculated for $C_8H_{12}O_4$ (MH^+) 173, found 173.



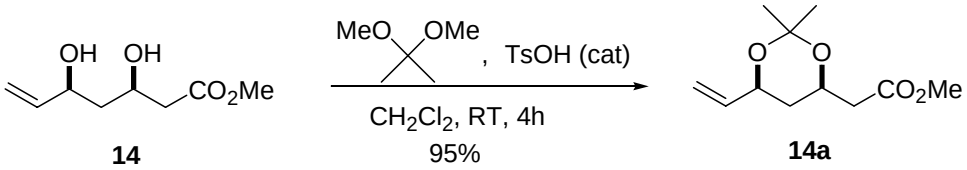
13 **13a**

Methyl (5*S*)-5-Hydroxy-3-oxo-6-heptenoate (13a). A mixture of allyl alcohol **13**[15,16] (7.0 g, 35.3 mmol) and MeOH (40 mL, 98.9 mmoL) in toluene (200 mL) was refluxed for 2 days and concentrated. Flash chromatography of the residue on silica gel (3:1 hexanes/EtOAc) gave 5.16 g (85%) of keto ester **13a**:[24] ^{1}H NMR 5.87 (ddd, 1, J = 17.1, 11.0, 6.1), 5.32 (d, 1, J = 17.1), 5.16 (d, 1, J = 11.0), 4.65-4.58 (m, 1), 3.75 (s, 3), 3.52 (s, 2), 2.82-2.76 (m, 2); ^{13}C NMR 202.6, 167.2, 138.6, 115.4, 68.4, 52.4, 49.7, 49.2; IR 3497, 1746, 1714, 1658, 1643; $[\alpha]^{20}_D$ -23.6 (c 0.46, $CHCl_3$).



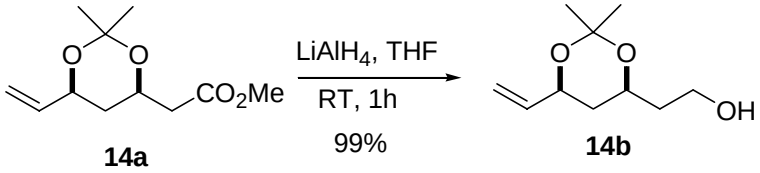
13a **14**

Methyl (3*R*,5*S*)-3,5-Dihydroxy-6-heptenoate (14). Et_2BOMe (5.06 g, 50.67 mmol) was added to a solution of **13a** (8.3 g, 48.26 mmol) in THF (192 mL) and MeOH (48 mL) at –78 °C. The mixture was stirred at that temperature for 15 min. $NaBH_4$ (1.92 g, 50.67 mmol) was added and the resulting mixture was stirred at –78 °C for 4 h, quenched with HOAc (10 mL), and neutralized with saturated $NaHCO_3$ (150 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated. The residue was taken up in MeOH (250 mL) and most of the MeOH (ca 200 mL) was distilled of to remove the boron-containing byproducts. The residue was concentrated to give 7.8 g (93%) of diol **14**[25] that was used without purification. ^{1}H NMR 5.86 (ddd, 1, J = 17.1, 10.4, 6.1), 5.26 (d, 1, J = 17.1), 5.10 (d, 1, J = 10.4), 4.42-4.36 (m, 1), 4.34-4.26 (m, 1), 3.71 (s, 3), 2.57-2.47 (m, 2), 1.72-1.64 (m, 2); ^{13}C NMR 172.6, 140.2, 114.6, 72.5, 68.1, 51.7, 42.2, 41.5; IR 3408, 1736, 1645; $[\alpha]^{20}_D$ -17.8 (c 0.73, $CHCl_3$).



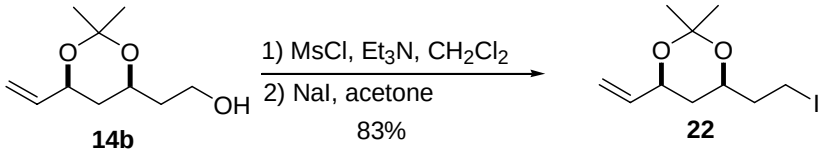
14 **14a**

Methyl (4*R*,6*S*)-6-Ethenyl-2,2-dimethyl-1,3-dioxane-4-acetate (14a). A mixture of diol **14** (5.5 g, 31.61 mmol), 2,2-dimethoxypropane (32.9 g, 0.316 mol) and $TsOH \cdot H_2O$ (0.301 g, 1.58 mmol) was stirred at room temperature for 4 h. The reaction was quenched with 5% $NaHCO_3$ (20 mL) and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give 6.43 g (95%) of acetonide **14a**[26] that was used without purification. ^{1}H NMR 5.82 (ddd, 1, *J* = 17.1, 10.4, 6.1), 5.27 (d, 1, *J* = 17.1), 5.13 (d, 1, *J* = 10.4), 4.41-4.32 (m, 2), 3.69 (s, 3), 2.57 (dd, 1, *J* = 15.3, 7.3), 2.41 (dd, 1, *J* = 15.3, 6.1), 1.67 (ddd, 1, *J* = 12.8, 2.4, 2.4), 1.50 (s, 3), 1.41 (s, 3), 1.31 (ddd, 1, *J* = 12.8, 12.8, 12.8); ^{13}C NMR 171.3, 138.3, 115.5, 98.9, 69.9, 65.6, 51.6, 41.1, 36.2, 30.0, 19.6; IR 1741, 1648; $[\alpha]^{20}_D$ -2.8 (c 1.43, $CHCl_3$).

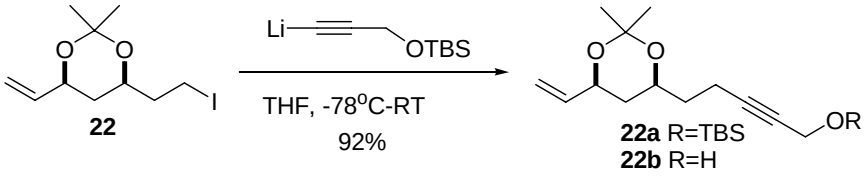


14a **14b**

(4*S*,6*S*)-6-Ethenyl-2,2-dimethyl-1,3-dioxane-4-ethanol (14b). $LiAlH_4$ (1.60 g, 42.06 mmol) was added to a solution of ester **14a** (6.0 g, 28.03 mmol) in THF (200 mL) at 0 °C and the mixture was stirred at room temperature for 1.5 h. The reaction was cooled to 0 °C and quenched by adding H_2O (100 mL) dropwise to the reaction mixture. The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated to give 4.95 g (95%) of alcohol **14b**: ^{1}H NMR 5.83 (ddd, 1, *J* = 17.1, 10.4, 6.1), 5.27 (d, 1, *J* = 17.1), 5.14 (d, 1, *J* = 10.4), 4.41-4.36 (m, 1), 4.20-4.14 (m, 1), 3.85-3.74 (m, 2), 1.78-1.72 (m, 2), 1.55 (ddd, 1, *J* = 12.8, 3.1, 3.1), 1.51 (s, 3), 1.43 (s, 3), 1.46-1.37 (m, 1); ^{13}C NMR 138.4, 115.4, 98.7, 70.0, 68.6, 60.4, 38.0, 36.4, 30.1, 19.7; IR 3415, 1648; $[\alpha]^{20}_D$ -29.0 (c 1.73, $CHCl_3$).



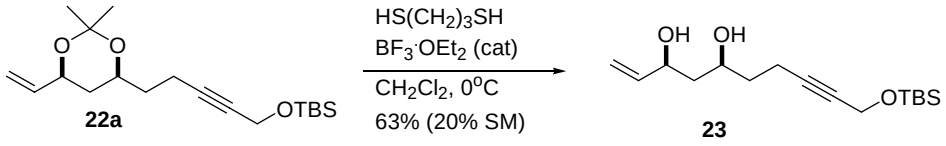
(4*R*,6*S*)-6-Ethenyl-4-(2-iodoethyl)-2,2-dimethyl-1,3-dioxane (22). MsCl (4.53 g, 39.52 mmol) was added to a solution of alcohol **14b** (4.90 g, 26.34 mmol) and Et_3N (4.66 g, 46.10 mmol) in CH_2Cl_2 (50 mL) at 0 °C and the resulting mixture was stirred at room temperature for 15 min. Acetone (200 mL), NaI (23.64 g, 0.158 mol) and $NaHCO_3$ (39.52 mmol) were added and the mixture was heated at 40 °C in an oil bath for 6 h. The reaction was quenched with saturated $Na_2S_2O_3$ (50 mL) and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (100:1 hexanes/EtOAc) gave 6.47 g (83%) of iodide **22**: ^{1}H NMR 5.82 (ddd, 1, *J* = 17.1, 10.4, 6.1), 5.27 (d, 1, *J* = 17.1), 5.14 (d, 1, *J* = 10.4), 4.41-4.37 (m, 1), 4.02 (ddd, 1, *J* = 12.8, 6.1, 3.7) 3.34-3.24 (m, 2), 1.99-1.86 (m, 2), 1.54 (ddd, 1, *J* = 12.8, 3.7, 2.4), 1.51 (s, 3), 1.42 (s, 3), 1.33 (ddd, 1, *J* = 12.8, 12.8, 12.8); ^{13}C NMR 138.5, 115.5, 98.8, 70.0, 68.2, 39.4, 36.0, 30.1, 19.8, 2.5; IR 1648; $[\alpha]^{20}_D$ -43.5 (c 1.83, $CHCl_3$); HRMS (CI/NH_3) calculated for $C_{10}H_{18}IO_2$ (MH^+) 297.0352, found 297.0362.



(4*S*,6*S*)-6-Ethenyl-2,2-dimethyl-1,3-dioxane-4-pent-2-yn-1-yl *t*-Butyldimethylsilyl Ether (22a). *n*-BuLi (1.6 M in hexane, 22 mL, 35.12 mmol) was added to a solution of *tert*-butyldimethylsilyl propargyl ether (5.70 g, 33.45 mmol) in THF (40 mL) and HMPA (16 mL) at –78 °C. The resulting mixture was slowly warmed to –40 °C over 1 h and cooled to –78 °C. A solution of iodide **22** (3.96 g, 13.38 mmol) in THF (20 mL) was added to the mixture, which was slowly warmed to room temperature. The reaction was quenched with saturated NH_4Cl and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried

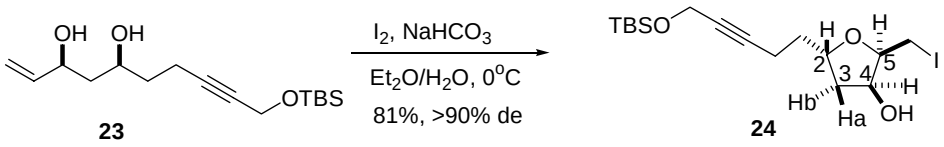
over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (100:1 hexanes/EtOAc) gave 3.17 g (70%) of alkyne **22a** followed by 0.60 g (22%) of alcohol **22b**, which could be readily resilylated to give **22a**.

A mixture of **22b** (0.6 g, 2.67 mmol), TBSCl (0.48 g, 3.21 mmol) and imidazole (0.27 g, 4.0 mmol) in CH_2Cl_2 (5 mL) was stirred at room temperature for 1h. The reaction was quenched with H_2O (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give 0.90 g (100%) of **22a**: ^{1}H NMR 5.82 (ddd, 1, *J* = 17.1, 10.4, 6.1), 5.26 (d, 1, *J* = 17.1), 5.13 (d, 1, *J* = 10.4), 4.38-4.33 (m, 1), 4.29 (t, 2, *J* = 2.4), 4.05-3.98 (m, 1) 2.34-2.30 (m, 2), 1.73-1.59 (m, 2), 1.55 (ddd, 1, *J* = 12.8, 2.4, 2.4), 1.48 (s, 3), 1.41 (s, 3), 1.27 (ddd, 1, *J* = 12.8, 12.8, 12.8), 0.91 (s, 9), 0.12 (s, 6); ^{13}C NMR 138.7, 115.4, 98.7, 84.6, 78.8, 70.2, 67.2, 51.9, 36.5, 34.9, 30.2, 25.8 (3 C), 19.8, 18.3, 14.5, -5.1 (2 C); IR 2232, 1648; $[\alpha]^{20}_D$ -21.6 (c 1.23, $CHCl_3$); HRMS (CI/NH_3) calculated for $C_{19}H_{35}O_3Si$ (MH^+) 339.2355, found 339.2362.



(3*S*,5*S*)-10-(*t*-Butyldimethylsilyloxy)-1-decen-8-yne-3,5-diol (23). $BF_3{\cdot}OEt_2$ (81.8 mg, 0.576 mmol) was added to a mixture of **22a** (2.787 g, 8.23 mmol) and 1,3-propanedithol (2.317 g, 21.41 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The mixture was stirred at 0 °C for 1.5 h and quenched with 5% $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (100:1 to 5:1 hexanes/EtOAc) gave recovered 0.56 g (20%) of acetonide **22a**, followed by 1.52 g (63%) of diol **23**: ^{1}H NMR 5.91 (ddd, 1, *J* = 17.1, 10.4, 6.1), 5.29 (d, 1, *J* = 17.1), 5.14 (d, 1, *J* = 10.4), 4.45-4.39 (m, 1), 4.33 (t, 2, *J* = 2.4), 4.10-4.03 (m, 1), 3.60 (br s, 1, OH), 3.38 (br s, 1, OH), 2.38 (br t, 2, *J* = 7.3), 1.76-1.60 (m, 4), 0.94 (s, 9), 0.15 (s, 6); ^{13}C NMR 140.5, 114.5, 84.6, 79.2, 73.6, 71.1, 51.9, 42.6, 36.3, 25.8 (3 C),

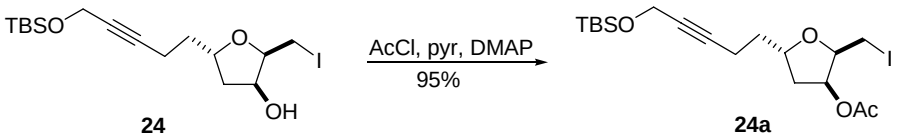
18.3, 14.9, -5.2 (2 C); IR 3358, 2231, 1644; $[\alpha]^{20}_{D}$ -6.9 (c 0.83, $CHCl_3$); HRMS (CI/NH_3) calculated for $C_{16}H_{31}O_3Si$ (MH^+) 299.2042, found 299.2038.



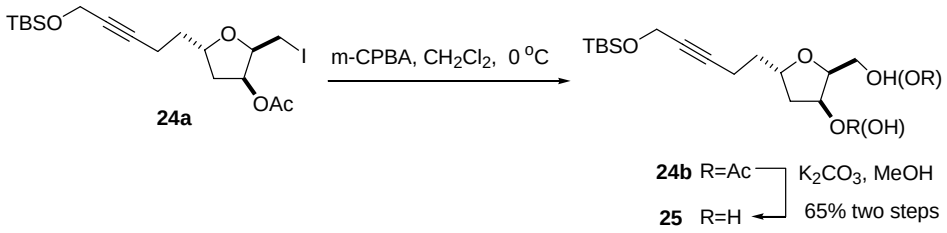
5-[(2*S*,4*S*,5*R*)-Tetrahydro-4-hydroxy-5-iodomethyl-2-furanyl]-2-pentyn-1yl *t*-Butyldimethylsilyl Ether (24). $NaHCO_3$ (0.97 g, 11.52 mmol) and I_2 (1.75 g, 6.91 mmol) were added to a solution of **23** (1.72 g, 5.76 mmol) in Et_2O (200 mL) and H_2O (80 mL) at 0 °C. The mixture was stirred at 0 °C for 4 h and quenched with saturated $Na_2S_2O_3$ (50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (9:1 hexanes/EtOAc) gave 1.98 g (81%) of iodide **(5*R*)-24**, followed by 0.10 g (4%)of diastereomer **(5*S*)-24**. The stereochemistry of **(5*R*)-24** was established by 1D NOESY studies. Irradiation of H-5 at δ 4.17 showed a cross peak to H-4 at δ 4.55, but not to H-2 at δ 4.40. Irradiation of H-4 at δ 4.55 showed cross peaks to H-5 at δ 4.17 and to H-3b at δ 1.81. Irradiation of H-2 at δ 4.40 showed a cross peak to H-3a at δ 2.18, but not to H-5 at δ 4.17 and H-4 at δ 4.55.

Data for **(5*R*)-24**: ^{1}H NMR 4.55 (ddd, 1, *J* = 3.7, 3.7, 3.7), 4.44-4.37 (m, 1), 4.29 (t, 2, *J* = 2.4), 4.17 (ddd, 1, *J* = 9.7, 6.1, 3.7), 3.29-3.21 (m, 2), 2.34-2.28 (m, 2), 2.18 (dd, 1, *J* = 13.4, 5.5), 1.82-1.63 (m, 3), 0.91 (s, 9), 0.11 (s, 6); ^{13}C NMR 84.4, 82.1, 79.0, 78.0, 72.7, 51.9, 41.2, 34.9, 25.8 (3 C), 18.3, 15.6, 2.0, -5.1 (2 C); IR 3442, 2231; $[\alpha]^{20}_{D}$ +29.7 (c 1.60, $CHCl_3$); HRMS (CI/NH_3) calculated for $C_{16}H_{33}INO_3Si$ (MNH_4^+) 442.1275, found 442.1284.

Data for **(5*S*)-24**: ^{1}H NMR 4.32-4.25 (m, 2), 4.29 (t, 2, *J* = 2.4), 3.84-3.80 (m, 1), 3.27 (dd, 1, *J* = 10.4, 4.3), 3.12 (dd, 1, *J* = 10.4, 7.3), 2.33 (dt, 2, *J* = 7.3, 2.4), 2.00 (ddd, 1, *J* = 13.4, 5.5, 2.4), 1.87-1.71 (m, 3), 0.91 (s, 9), 0.12 (s, 6); ^{13}C NMR 85.6, 84.4, 79.0, 77.9, 76.7, 51.9, 40.4, 34.5, 25.8 (3 C), 18.3, 15.6, 7.4, -5.1 (2 C).

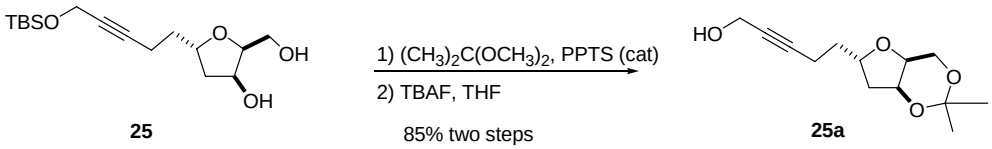


5-[(2*S*,4*S*,5*R*)-4-Acetoxy-tetrahydro-5-iodomethyl-2-furanyl]-2-pentyn-1yl *t*-Butyldimethylsilyl Ether (24). AcCl (0.208 g, 2.651 mmol) was added to a mixture of iodide **24** (0.450 g, 1.060 mmol), pyridine (0.210 g, 2.651 mmol) and DMAP (6.5 mg, 0.053 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was stirred at room temperature for 2 h and the reaction was quenched with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (25:1 hexanes/EtOAc) gave 0.470 g (95%) of acetate **24a**: ^{1}H NMR 5.46 (dd, 1, *J* = 3.7, 3.7), 4.35-4.26 (m, 2), 4.29 (t, 2, *J* = 2.4), 3.21 (d, 2, *J* = 7.9), 2.34-2.30 (m, 2), 2.21 (dd, 1, *J* = 14.0, 5.5), 2.11 (s, 3), 1.88 (ddd, 1, *J* = 14.0, 9.5, 3.7), 1.82-1.63 (m, 2), 0.91 (s, 9), 0.11 (s, 6); ^{13}C NMR 170.1, 84.2, 80.6, 79.1, 77.8, 74.8, 51.9, 39.3, 34.7, 25.8 (3 C), 20.9, 18.3, 15.6, 0.7, -5.1 (2 C); IR 2232, 1743; $[\alpha]^{20}_D$ +39.0 (c 1.23, $CHCl_3$); HRMS (CI/NH_3) calculated for $C_{18}H_{35}INO_4Si$ (MNH_4^+) 484.1380, found 484.1365.



5-[(2*S*,4*S*,5*S*)-Tetrahydro-4-hydroxy-5-hydroxymethyl-2-furanyl]-2-pentyn-1yl *t*-Butyldimethylsilyl Ether (25). *m*-CPBA (77%, 0.389 g, 1.738 mmol) was added to a solution of iodide **24a** (0.405 g, 0.869 mmol) in CH_2Cl_2 (20 mL) at 0 °C and the mixture was stirred at 0 °C for 3 h. The reaction was quenched with saturated $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with 5% $NaHCO_3$ (30 mL) and dried over $MgSO_4$ and concentrated to give 0.398 g of a 1:1 mixture of acetoxy alcohols **24b**.

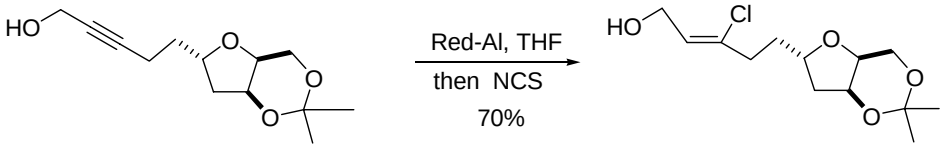
A solution of crude **24b** (0.398 g, 1.116 mmol) and K_2CO_3 (0.154 g, 1.116 mmol) in MeOH (2 mL) was stirred at room temperature for 30 min. The solvent was evaporated and the residue was diluted with EtOAc (10 mL). The organic layer was washed with saturated NH_4Cl (10 mL), dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (1:1 hexanes/EtOAc) gave 0.118 g (65%) of diol **25**: ^{1}H NMR 4.53 (br s, 1), 4.42-4.34 (m, 1), 4.29 (t, 2, *J* = 2.4), 3.97-3.92 (m, 3), 3.50-2.95 (br s, 2, OH), 2.36-2.31 (m, 2), 2.13 (dd, 1, *J* = 14.7, 6.5), 1.83-1.65 (m, 3), 0.91 (s, 9), 0.12 (s, 6); ^{13}C NMR 84.5, 80.3, 78.9, 77.1, 74.3, 61.8, 51.9, 41.9, 34.7, 25.8 (3 C), 18.3, 15.7, -5.2 (2 C); IR 3404, 2232; $[\alpha]^{20}_D$ -3.8 (c 0.58, $CHCl_3$); HRMS (CI/NH_3) calculated for $C_{16}H_{34}NO_4Si$ (MNH_4^+) 332.2257, found 332.2262.



25 **25a**

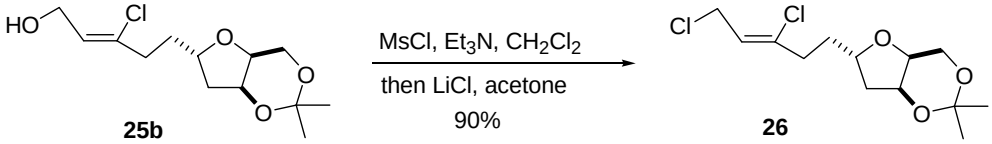
Acetonide 25a. A mixture of diol **25** (0.64 g, 2.04 mmol), 2,2-dimethoxypropane (4.2 g, 40.7 mmol) and PPTS (25.6 mg, 0.102 mmol) was stirred at room temperature overnight. The reaction was diluted with CH_2Cl_2 (20 mL) and quenched with 5% $NaHCO_3$ (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give 0.70 g of crude dioxane.

TBAF (1.0 M in THF, 2 mL, 2 mmol) was added to a solution of the above crude dioxane in THF (10 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min and quenched with saturated NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (3:1 hexanes/EtOAc) gave 0.417 g (85%) of alcohol **25a:** ^{1}H NMR 4.43(dd, 1, *J* = 3.7, 3.1), 4.44-4.36 (m, 1), 4.26 (br s, 2), 4.01 (dd, 1, *J* = 12.8, 3.7), 3.89 (dd, 1, *J* = 12.8, 2.4), 3.83 (ddd, 1, *J* = 3.7, 3.1, 2.4), 2.41-2.28 (m, 2), 2.15 (dd, 1, *J* = 13.4, 5.5), 1.84-1.65 (m, 3), 1.44 (s, 3), 1.39 (s, 3); ^{13}C NMR 97.6, 85.7, 78.6, 77.5, 73.7, 71.1, 60.8, 51.2, 39.9, 34.9, 28.2, 19.8, 15.7; IR 3440, 2222; $[\alpha]^{20}_D$ -1.5 (c 0.85, $CHCl_3$); HRMS (CI/NH_3) calculated for $C_{13}H_{24}NO_4$ (MNH_4^+) 258.1705, found 258.1704.



25a **25b**

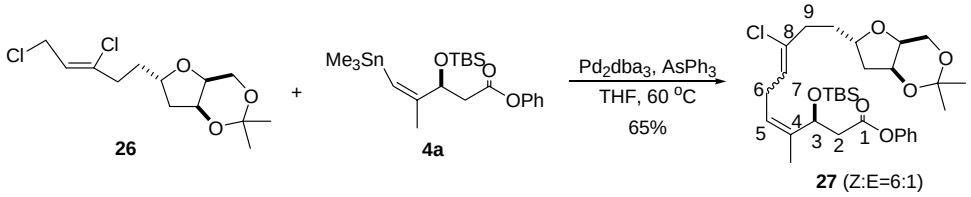
Chloroalkenol 25b. Red-Al (3.3 M in toluene, 0.45 mL, 1.50 mmol) was added to a solution of **25a** (180 mg, 0.748 mmol) in THF (3 mL). The mixture was stirred at room temperature for 8 h and cooled to –78 °C. A solution of *N*-chlorosuccinimide (0.50 g, 3.74 mmol) in THF (10 mL) was added and the resulting mixture was slowly warmed to room temperature overnight. The reaction was quenched with saturated NH_4Cl (10 mL) and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (2:1 hexanes/EtOAc) gave 145 mg (70%) of allylic alcohol **25b**: ^{1}H NMR 5.78 (t, 1, *J* = 6.7), 4.43 (dd, 1, *J* = 3.7, 3.7), 4.37-4.29 (m, 1), 4.29 (d, 2, *J* = 6.7), 4.01 (dd, 1, *J* = 12.8, 3.7), 3.88 (dd, 1, *J* = 12.8, 3.1), 3.87-3.84 (m, 1), 2.57-2.37 (m, 2), 2.13 (dd, 1, *J* = 13.4, 5.5), 1.84-1.78 (m, 2), 1.72-1.60 (m, 1), 1.44 (s, 3), 1.39 (s, 3); ^{13}C NMR 136.5, 124.8, 97.6, 77.6, 73.7, 71.1, 60.8, 59.7, 40.0, 36.3, 33.7, 28.2, 19.9; IR 3444, 1662; $[\alpha]^{20}_D$ +11.1 (c 1.45, $CHCl_3$); HRMS (CI/NH_3) calculated for $C_{13}H_{22}O_4Cl$ (MH^+) 277.1207, found 277.1201.



25b **26**

Dichloride 26. Et_3N (95 mg, 0.939 mmol) and MsCl (107.5 mg, 0.939 mmol) were added to a solution of alcohol **25b** (130 mg, 0.469 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred at room temperature for 20 min. Acetone (12 mL) and LiCl (199 mg, 4.69 mmol) were added and the mixture was stirred at room temperature overnight. The reaction was quenched with H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (25:1 hexanes/EtOAc) gave 124.6 mg (90%) of chloride **26**: ^{1}H NMR 5.78 (t, 1, *J* = 7.3), 4.43 (dd, 1, *J* = 3.1, 3.1), 4.35-4.28 (m, 1), 4.19 (d, 2, *J* = 7.3), 4.01 (dd, 1, *J* = 12.2,

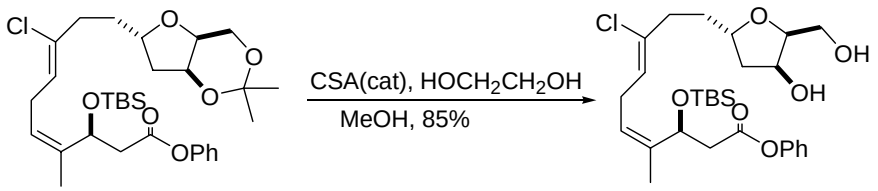
3.1), 3.88-3.84 (m, 1), 3.87 (dd, 1, *J* = 12.2, 3.1), 2.61-2.40 (m, 2), 2.12 (dd, 1, *J* = 13.4, 5.5), 1.86-1.78 (m, 2), 1.68 (ddd, 1, *J* = 13.4, 9.8, 3.7), 1.43 (s, 3), 1.39 (s, 3); ^{13}C NMR 139.6, 121.5, 97.6, 77.5, 73.8, 71.1, 60.8, 40.2, 40.0, 36.3, 33.6, 28.1, 19.9; IR 1654; $[\alpha]^{20}_{D}$ +8.6 (c 0.86, $CHCl_3$); HRMS (CI/NH_3) calculated for $C_{13}H_{24}NO_3Cl_2$ (MNH_4^+) 312.1133, found 312.1128.



Stille Product 27. $AsPh_3$ (29 mg, 0.0948 mmol) and Pd_2dba_3 (21.7 mg, 0.0237 mmol) were added to a solution of allylic chloride **26** (70 mg, 0.237 mmol) in THF (3 mL). The mixture was stirred at room temperature for 10 min and a solution of vinyltin **4a** (137 mg, 0.285 mmol) in THF (1 mL) was added. The reaction mixture was heated to 60 °C for 18 h and concentrated. Flash chromatography of the residue on silica gel (25:1 hexanes/EtOAc) gave 15 mg (10%) a 2:1 mixture of (***7E***)- and (***7Z***)-**27** followed by 89 mg (65%) of (***7Z***)-**27**: The stereochemistry of (***7Z***)-**27** was established by a 1D NOESY study. Irradiation of H-7 at δ 5.45 showed a cross peak to H-9 at δ 2.52-2.31.

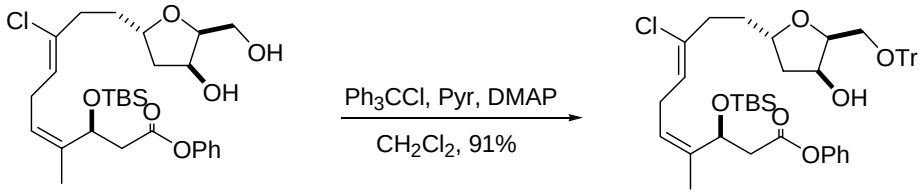
Data for (***7Z***) -**27**: ^{1}H NMR 7.37 (dd, 2, *J* = 7.9, 7.3), 7.22 (t, 1, *J* = 7.3), 7.08 (d, 2, *J* = 7.9), 5.45 (dd, 1, *J* = 7.3, 6.7), 5.21-5.16 (m, 2), 4.42 (dd, 1, *J* = 3.7, 3.1), 4.33-4.26 (m, 1), 3.99 (dd, 1, *J* = 12.8, 3.7), 3.87 (dd, 1, *J* = 12.8, 3.1), 3.87-3.84 (m, 1), 3.07-2.90 (m, 2), 2.89 (dd, 1, *J* = 14.7, 8.5), 2.58 (dd, 1, *J* = 14.7, 4.9), 2.52-2.31 (m, 2), 2.10 (dd, 1, *J* = 13.4, 5.5), 1.80-1.75 (m, 2), 1.75 (s, 3), 1.66 (ddd, 1, *J* = 13.4, 9.8, 3.7), 1.43 (s, 3), 1.39 (s, 3), 0.88 (s, 9), 0.08 (s, 3), 0.04 (s, 3); ^{13}C NMR 169.4, 150.7, 137.6, 134.7, 129.3 (2 C), , 125.7, 123.4, 123.1, 121.5 (2 C), 97.6, 77.7, 73.8, 71.2, 67.1, 60.9, 41.9, 40.0, 36.3, 33.9, 28.1, 27.2, 25.7 (3 C), 20.0, 18.0, 17.5, -4.9, -5.1; IR 1760, 1593; $[\alpha]^{20}_{D}$ +6.2 (c 1.6, $CHCl_3$).

Partial Data for ***(7E)***-**27**: ^{1}H NMR 5.53 (dd, 1, *J* = 7.3, 7.3), 4.39 (dd, 1, *J* = 3.7, 3.1).



27 **27a**

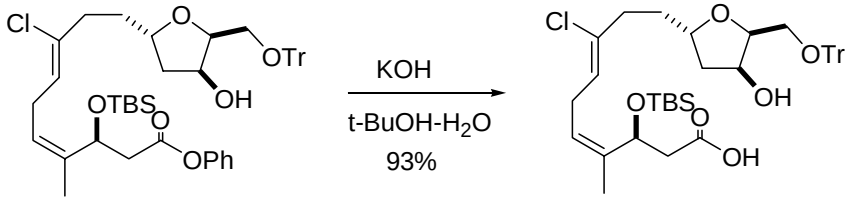
Phenyl (*3S*,*4Z*,*7Z*)-3-(*t*-Butyldimethylsilyloxy)-8-chloro-4-methyl-10-[(2*S*,4*S*,5*S*)-tetrahydro-4-hydroxy-5-(hydroxymethyl)-2-furanyl]-4,7-decadienoate (27a). CSA (2.3 mg, 0.01 mmol) was added to a solution of **27** (82 mg, 0.142 mmol) and ethylene glycol (439 mg, 7.08 mmol) in MeOH (2 mL). The mixture was stirred to room temperature for 2 h. The reaction was quenched with H_2O (2 mL). The aqueous layer was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (3:1 to 1:1 hexanes/EtOAc) gave 65 mg (85%) of diol **27a**: ^{1}H NMR 7.37 (dd, 2, *J* = 8.4, 7.3), 7.22 (t, 1, *J* = 7.3), 7.08 (d, 2, *J* = 8.4), 5.44 (dd, 1, *J* = 7.3, 6.7), 5.22-5.15 (m, 2), 4.51 (br s, 1), 4.28-4.21 (m, 1), 3.96-3.90 (m, 3), 3.24 (dd, 1, *J* = 12.8, 3.7, OH), 3.07-2.92 (m, 2), 2.89 (dd, 1, *J* = 14.7, 8.5), 2.59 (ddd, 1, *J* = 14.7, 4.9, 1.2), 2.50-2.32 (m, 2), 2.07 (ddd, 1, *J* = 13.4, 3.7, 3.7), 1.80-1.69 (m, 3), 1.76 (s, 3), 0.89 (s, 9), 0.09 (s, 3), 0.04 (s, 3); ^{13}C NMR 169.5, 150.7, 137.6, 134.5, 129.4 (2 C), 125.7, 123.6, 123.1, 121.5 (2 C), 80.2, 77.3, 74.4, 67.1, 61.9, 42.1, 41.9, 36.1, 33.7, 27.2, 25.7 (3 C), 18.0, 17.5, -4.9, -5.1; IR 3406, 1760, 1658, 1594; $[\alpha]^{20}_D$ +5.5 (c 1.0, $CHCl_3$); HRMS (MALDI) calculated for $C_{28}H_{43}O_6NaSiCl$ (MNa^+) 561.2410, found 561.2447.



27a **27b**

Phenyl (*3S*,*4Z*,*7Z*)-3-(*t*-Butyldimethylsilyloxy)-8-chloro-4-methyl-10-[(2*S*,4*S*,5*S*)-tetrahydro-4-hydroxy-5-(triphenylmethoxymethyl)-2-furanyl]-4,7-decadienoate (27b). A mixture of diol **27a** (56 mg, 0.104 mmol), triphenylmethyl chloride (37.7 mg, 0.135 mmol), pyridine (21.4 mg, 0.27 mmol), and DMAP (1.3 mg, 0.0104 mmol) in CH_2Cl_2 (3 mL) was stirred

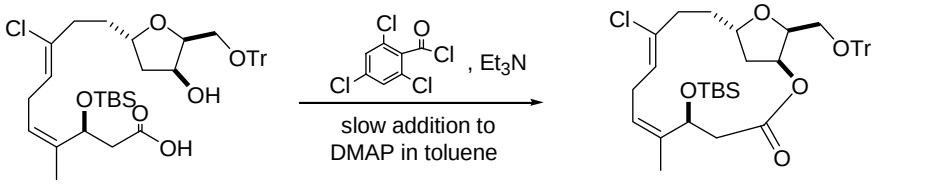
at room temperature for 12 h. The solvent was evaporated and flash chromatography of the residue on silica gel (9:1 hexanes/EtOAc) gave 74 mg (91%) of **27b**: ^{1}H NMR 7.45-7.06 (m, 20), 5.43 (dd, 1, *J* = 7.3, 6.7), 5.18-5.14 (m, 2), 4.54 (ddd, 1, *J* = 3.7, 3.7, 3.7), 4.25-4.18 (m, 1), 4.16-4.12 (m, 1), 3.45 (dd, 1, *J* = 9.7, 4.9), 3.29 (dd, 1, *J* = 9.7, 7.3), 3.04-2.89 (m, 2), 2.87 (dd, 1, *J* = 14.7, 9.2), 2.61 (d, 1, *J* = 3.1, OH), 2.57 (dd, 1, *J* = 14.7, 4.3), 2.50-2.30 (m, 2), 2.09 (dd, 1, *J* = 13.4, 5.5), 1.78-1.66 (m, 3), 1.73 (s, 3), 0.88 (s, 9), 0.07 (s, 3), 0.02 (s, 3); ^{13}C NMR 169.4, 150.7, 143.5 (3 C), 137.6, 134.7, 129.3 (2 C), 128.4 (6 C), 128.0 (6 C), 127.2 (3 C), 125.7, 123.7, 123.2, 121.5 (2 C), 87.2, 80.1, 77.3, 73.6, 67.1, 62.6, 41.9, 41.2, 36.2, 33.8, 27.2, 25.7 (3 C), 18.0, 17.5, -4.9, -5.1; IR 3460, 1750, 1652; $[\alpha]^{20}_{D}$ +5.8 (c 0.31, $CHCl_3$); HRMS (MALDI) calculated for $C_{47}H_{57}O_6NaSiCl$ (MNa^+) 803.3505, found 803.3537.



27b **28**

(*3S,4Z,7Z*)-3-(*t*-Butyldimethylsilyloxy)-8-chloro-4-methyl-10-[(2*S*,4*S*,5*S*)-tetrahydro-4-hydroxy-5-(triphenylmethoxymethyl)-2-furanyl]-4,7-decadienoic Acid (28). KOH (0.95 mL, 0.5 M in H_2O, 0.474 mmol) was added to a solution of phenyl ester **27b** (74 mg, 0.0947 mmol) in *t*-BuOH (4 mL). The mixture was stirred at room temperature for 6 h. The reaction was quenched with saturated NaH_2PO_4 (5 mL). The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (3:1 to 1:1 hexanes/EtOAc) gave 62 mg (93%) of acid **28**: ^{1}H NMR 7.45-7.22 (m, 15), 5.50 (t, 1, *J* = 7.3), 5.29 (t, 1, *J* = 7.9), 4.98 (dd, 1, *J* = 7.4, 6.7), 4.43 (dd, 1, *J* = 3.7, 3.7), 4.24-4.17 (m, 1), 4.09-4.05 (m, 1), 3.47-3.27 (m, 2), 2.88 (dd, 2, *J* = 7.9, 7.3), 2.58 (dd, 1, *J* = 13.4, 6.7), 2.52-2.35 (m, 2), 2.44 (dd, 1, *J* = 13.4, 7.4), 2.15 (dd, 1, *J* = 13.4, 6.1), 1.77-1.71 (m, 3), 1.69 (s, 3), 0.88 (s, 9), 0.08 (s, 3), 0.03 (s, 3); ^{13}C NMR 174.8, 143.5 (3 C), 137.2, 133.8, 128.5 (6 C), 127.9 (6 C), 127.2 (3 C), 124.3, 123.1, 87.1, 80.5,

76.3, 73.4, 67.0, 62.3, 41.7, 41.1, 36.0, 33.2, 26.8, 25.6 (3 C), 18.0, 17.2, -4.9, -5.2; IR 3459, 1712, 1560; $[\alpha]^{20}_{D}$ +28.9 (c 0.58, $CHCl_3$).



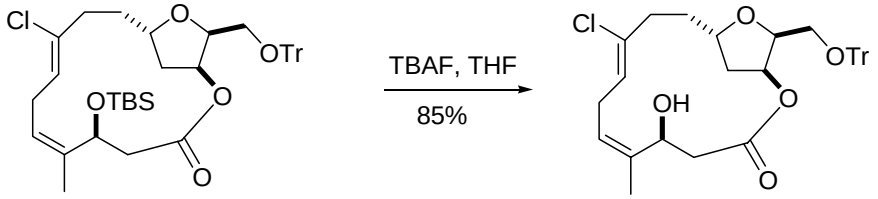
28 **29** (65%) + 15% dimer **29a**

(1*S*,5*S*,6*Z*,9*Z*,13*S*,15*S*)-5-(*t*-Butyldimethylsilyloxy)-10-chloro-15-[(triphenylmethoxy)methyl]-6-methyl-2,14-Dioxabicyclo[11.2.1]hexadeca-6,9-dien-3-one (29). Et_3N (31 mg, 0.307 mmol) and 2,4,6-trichlorobenzoyl chloride (62.3 mg, 0.256 mmol) were added to a solution of acid **28** (18 mg, 0.0256 mmol) in THF (1 mL). The mixture was stirred at room temperature for 2 h and diluted with toluene (9 mL). The resulting mixture was added slowly to a solution of DMAP (78 mg, 0.64 mmol) in toluene (80 mL) through a syringe pump over 15 h. After stirring for additional 2 h at room temperature, the reaction was quenched with saturated NH_4Cl (10 mL). The organic layer was separated and aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (25:1 hexanes/EtOAc) gave 2.8 mg (15%) of dimer **29a**, followed by 11.5 mg (65%) of macrolide **29**.

Data for **29**: ^{1}H NMR 7.43-7.22 (m, 15), 5.45 (br dd, 1, *J* = 10.8, 6.7), 5.32 (dd, 1, *J* = 3.7, 3.7), 5.20 (br d, 1, *J* = 6.7), 4.50 (dd, 1, *J* = 11.6, 4.3), 4.38-4.34 (m, 1), 3.76 (dddd, 1, *J* = 11.0, 11.0, 3.7, 3.7), 3.43 (dd, 1, *J* = 8.6, 5.5), 3.23-3.14 (m, 1), 3.16 (dd, 1, *J* = 8.6, 8.6), 2.56 (dd, 1, *J* = 11.6, 11.6), 2.54-2.46 (m, 2), 2.40-2.34 (m, 1), 2.23 (dd, 1, *J* = 11.6, 4.3), 2.20-2.15 (m, 1), 2.09 (dd, 1, *J* = 12.8, 3.7), 1.82 (s, 3), 1.47 (ddd, 1, *J* = 12.8, 3.7, 3.7), 1.44-1.40 (m, 1), 0.86 (s, 9), 0.02 (s, 3), 0.00 (s, 3); MS (MALDI) calculated for $C_{41}H_{51}ClO_5NaSi$ (MNa^+) 709, found 709.

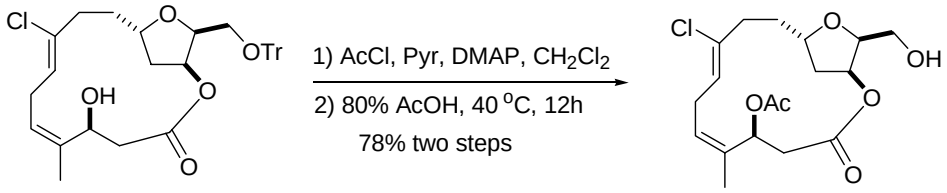
Data for dimer **29a**: ^{1}H NMR 7.44-7.22 (m, 30), 5.45-5.32 (m, 4), 5.09 (dd, 2, *J* = 7.3, 6.7), 4.71 (dd, 2, *J* = 8.6, 6.1), 4.22 (ddd, 2, *J* = 9.8, 5.5, 5.5), 4.15-4.10 (m, 2), 3.35 (dd, 2, *J* = 9.8, 5.5), 3.12 (dd, 2, *J* = 9.8, 5.5), 2.95-2.86 (m, 2), 2.80-2.74 (m, 2), 2.43-2.30 (m, 6), 2.09-

2.03 (m, 2), 1.90-1.85 (m, 2), 1.80-1.70 (m, 4), 1.61 (s, 6), 0.83 (s, 18), -0.05 (s, 6), -0.06 (s, 6); MS (MALDI) calculated for $C_{82}H_{102}Cl_2O_{10}NaSi_2$ (MNa^+) 1396, found 1397.



29 **29b**

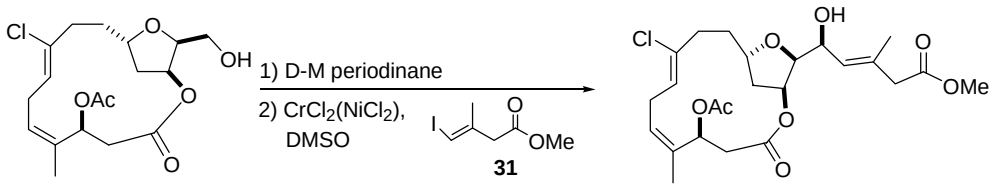
(1*S*,5*S*,6*Z*,9*Z*,13*S*,15*S*)-10-chloro-5-hydroxy-15-[(triphenylmethoxy)methyl]-6-methyl-2,14-Dioxabicyclo[11.2.1]hexadeca-6,9-dien-3-one (29b). TBAF (40 μL, 0.04 mmol) was added to a solution of **29** (11.2 mg, 0.016 mmol) in THF (1 mL) and the solution was stirred at room temperature for 2 h. The reaction was diluted with Et_2O (5 mL) and quenched with saturated NH_4Cl (3 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (5:1 hexanes/EtOAc) gave 7.9 mg (85%) of alcohol **29b**: ^{1}H NMR 7.43-7.21 (m, 15), 5.61 (br dd, 1, *J* = 9.8, 7.9), 5.37 (dd, 1, *J* = 3.1, 3.1), 5.18 (d, 1, *J* = 7.3), 4.56 (dd, 1, *J* = 11.6, 3.7), 4.32 (ddd, 1, *J* = 8.5, 5.5, 3.1), 3.77 (dddd, 1, *J* = 11.6, 11.6, 3.7, 3.7), 3.39 (dd, 1, *J* = 8.5, 5.5), 3.24-3.15 (m, 1), 3.20 (dd, 1, *J* = 8.5, 8.5), 2.58 (dd, 1, *J* = 11.6, 11.6), 2.58-2.46 (m, 2), 2.42-2.31 (m, 1), 2.39 (dd, 1, *J* = 11.6, 3.7), 2.15 (ddd, 1, *J* = 12.8, 5.5, 5.5), 2.03 (dd, 1, *J* = 12.8, 3.7), 1.87 (s, 3), 1.48 (ddd, 1, *J* = 12.8, 11.6, 3.7), 1.42 (ddd, 1, *J* = 11.6, 11.6, 5.5); ^{13}C NMR 168.8, 143.8 (3 C), 137.5, 131.8, 128.6 (6 C), 127.8 (6 C), 127.4, 127.0 (3 C), 125.6, 86.5, 79.2, 76.1, 75.0, 65.9, 61.2, 39.9, 37.7, 34.8, 27.9, 26.3, 17.6; IR (CH_2Cl_2) 3460, 1732, 1643; $[\alpha]^{20}_D$ +10.3 (c 0.3, $CHCl_3$); HRMS (MALDI) calculated for $C_{35}H_{37}O_5NaCl$ (MNa^+) 595.2227, found 595.2215.



29b **30**

(1*S*,5*S*,6*Z*,9*Z*,13*S*,15*S*)-5-Acetyloxy-10-chloro-15-hydroxymethyl-6-methyl-2,14-Dioxabicyclo[11.2.1]hexadeca-6,9-dien-3-one (30). Acetyl chloride (6.9 mg, 0.0873 mmol) was added to a solution of **29b** (5 mg, 8.73 μmol), pyridine (6.8 mg, 0.0873 mmol) and DMAP (0.2 mg, 1.75 μmol) in CH_2Cl_2 (0.5 mL). The resulting mixture was stirred at room temperature for 1 h. The reaction was quenched with H_2O (1 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give 5.0 mg (95%) of crude product.

The crude product was treated with 80% HOAc in H_2O (0.5 mL) at room temperature and heated at 40 °C for 12 h. The reaction was quenched with saturated $NaHCO_3$ (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and the organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (2:1 hexanes/EtOAc) gave 2.5 mg (78%) of alcohol **30**: ^{1}H NMR (CD_3OD) 5.76 (dd, 1, *J* = 9.3, 6.7), 5.69 (br dd, 1, *J* = 8.2, 8.2), 5.33 (br d, 1, *J* = 6.7), 5.26 (dd, 1, *J* = 3.7, 3.7), 4.15 (ddd, 1, *J* = 6.7, 6.7, 3.7), 3.91 (dddd, 1, *J* = 11.6, 11.6, 3.1, 3.1), 3.69 (dd, 1, *J* = 11.6, 6.7), 3.66 (dd, 1, *J* = 11.6, 6.7), 3.52-3.43 (m, 1), 2.77-2.74 (m, 2), 2.52-2.42 (m, 2), 2.32-2.28 (m, 2), 2.09 (dd, 1, *J* = 12.8, 3.1), 2.01 (s, 3), 1.87 (s, 3), 1.52 (ddd, 1, *J* = 12.8, 3.7, 3.7), 1.46-1.40 (m, 1); ^{13}C NMR (CD_3OD) 171.2, 169.4, 134.6, 133.2, 130.9, 127.0, 82.1, 77.5, 76.8, 68.7, 61.3, 38.72, 38.71, 35.5 29.0, 27.7, 20.9, 18.5; IR (CH_2Cl_2) 3417, 1732; $[\alpha]^{20}_D$ +10.7 (c 0.15, $CHCl_3$). The ^{1}H NMR spectrum is identical to that provided by Prof. Kigoshi.



30 **31** Haterumalide NA methyl ester (**32**)

Haterumalide NA Methyl Ester (32). Dess-Martin periodinane (12.3 mg, 29.0 μmol) was added to a solution of **30** (2.0 mg, 5.38 μmol) in CH_2Cl_2 (1 mL). The mixture was stirred at room temperature for 3.5 h and quenched with saturated Na_2SO_3 (5 mL) and saturated $NaHCO_3$ (5 mL). After stirring at room temperature for 1 h, the resulting mixture was extracted with Et_2O (3 × 5 mL). The organic layers were dried over $MgSO_4$ and concentrated to give aldehyde **2** (2 mg), which was used in the next experiment without purification.

A solution of aldehyde **2** (2 mg) and iodide **31** (41.0 mg, 0.170 mmol) in DMSO (0.5 mL) was added to $CrCl_2$ containing 1% $NiCl_2$ (58 mg, 0.472 mmol) under N_2 ($CrCl_2$ and $NiCl_2$ were handled in a glove box). After stirring at room temperature for 20 h, the reaction was diluted with Et_2O (5 mL) and poured into H_2O (5 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (9:1 to 2:1 hexane/EtOAc) gave 0.7 mg (30%) of product **32**. Further purification by HPLC (C18, 4.6 × 250 mm, 80% aqueous MeOH, 1 mL/min, UV 215 nm) gave haterumalide NA methyl ester (**32**) (ca. 0.5 mg): CD (MeOH) λ_{ext} 219 nm ($\Delta\varepsilon$ -0.8); ^{1}H NMR (CD_3OD) 5.79 (dd, 1, *J* = 11.4, 4.6), 5.70 (br dd, 1, *J* = 9.6, 6.4), 5.37 (br d, 1, *J* = 8.5), 5.31 (br d, 1, *J* = 6.7), 5.30 (dd, 1, *J* = 3.7, 3.7), 4.53 (dd, 1, *J* = 8.5, 8.5), 3.93 (dddd, 1, *J* = 11.4, 11.4, 3.6, 3.6), 3.90 (dd, 1, *J* = 8.5, 3.7), 3.67 (s, 3), 3.49 (m, 1), 3.08 (s, 2), 2.81 (dd, 1, *J* = 11.5, 4.6), 2.77 (dd, 1, *J* = 11.5, 11.4), 2.47 (m, 2), 2.29 (m, 2), 2.10 (dd, 1, *J* = 12.8, 3.6), 2.02 (s, 3), 1.88 (s, 3), 1.81 (d, 3, *J* = 1.3), 1.52 (ddd, 1, *J* = 12.8, 11.4, 3.7), 1.39 (m, 1). The ^{1}H NMR and CD spectra are identical to those reported by Prof. Kigoshi.[5]

References and Notes

(22) Berry, M. B.; Craig, D. *Synlett* **1992**, 41.

(23) Slougui, N.; Rousseau, G. *Synth. Commun.* **1987**, *17*, 1.

(24) Brussani, G.; Ley, S. V.; Wright, J. L.; Williams, D. J. *J. Chem. Soc. Perkin Trans. 1* **1986**, 303.

(25) Bertolini, G.; Casagrande, C.; Norcini, G.; Santangelo, F. S*ynth Commun.* **1994**, *24*, 1833.

(26) (a) Scialdone, M. A.; Johnson, C. R. *Tetrahedron Lett.* **1995**, *36*, 43. (b) Sliskovic, D. R.; Roth, B. D.; Wilson, M. W.; Hoefle, M. L.; Newton, R. S. *J. Med. Chem.* **1990**, *33*, 31.