# Total Synthesis of Myxalamide A REVISED

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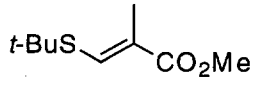
## SUPPORTING INFORMATION

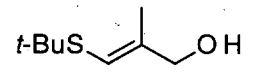
### Experimental Section.

**General.** All reactions involving air- and/or water-sensitive reagents were carried out under an atmosphere of $N_2$ using oven-dried glassware. Unless otherwise noted, starting materials and reagents were obtained from commercial suppliers and used without further purification. Diethyl ether, THF, and benzene-$d_6$ were distilled from Na/benzophenone ketyl immediately before use. Benzene, $CH_2Cl_2$, HMPA, $Et_3N$, diisopropylamine, diisopropylethylamine (DIPEA) and pyridine were distilled from calcium hydride. Unless otherwise indicated, organic extracts were dried over anhydrous magnesium sulfate and concentrated at aspirator pressure using a rotary evaporator. Purification by column chromatography was performed according to the method of Still, Kahn, and Mitra[1] using ICI SiliTech 32-63 D A silica gel as the stationary phase. $^1H$ and $^{13}C$ NMR spectra were measured in $CDCl_3$ and IR spectra were measured as thin films on NaCl plates unless otherwise indicated. Melting points are uncorrected. Optical rotations were measured at rt.




**11**

**(*E*)-3-(*t*-Butylthio)-2-methyl-2-propenoic acid methyl ester (11):** To a stirring slurry of NaH (224 mg of a 60% dispersion in oil, 5.59 mmol) in THF (10.0 mL) at rt was added bromide **10**[2] (834 mg, 4.65 mmol) followed by dropwise addition of *t*-butylthiol (0.520 mL, 4.65 mmol). After 40 min of stirring, the reaction mixture was diluted with ether (40 mL) and washed with 2 M KOH (2 x 20 mL) and brine (1 x 20 mL). The crude residue was purified by flash chromatography (8:1 petroleum ether:diethyl ether with 1% $Et_3N$) to yield 766 mg (87%) of ester **11** as a colorless oil. IR: 1708, 1585, 1236, 1111 $cm^{-1}$. $^1H$ NMR (400 MHz): δ 1.41 (s, 9), 1.82 (d, 3, $J$ = 1.0), 3.71 (s, 3), 7.65 (q, 1, $J$ = 1.0). $^{13}C$ NMR (100 MHz): δ 13.91 ($CH_3$), 31.12 ($CH_3$), 44.72 (C), 51.64 ($CH_3$), 122.23 (C), 138.73 (CH), 166.49 (C). Anal. Calcd. for $C_9H_{16}O_2S$: C, 57.41; H, 8.57. Found: C, 57.07; H, 8.56.



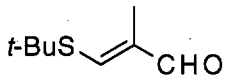

**12**

**(*E*)-3-(*t*-Butylthio)-2-methyl-2-propen-1-ol (12):** To a cool (0 °C) solution of methyl ester **11** (1.645 g, 8.13 mmol) in $CH_2Cl_2$ (10.0 mL) was added DIBALH (11.93 mL of a 1.5 M solution in toluene, 17.9 mmol) dropwise. After 70 min, MeOH (10.0 mL) followed by $H_2O$ (10 mL) was added and vigorous stirring was initiated. The heterogeneous mixture was then filtered through a pad of celite in a fritted glass

1. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

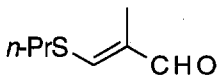
2. (a) Ford, M. C.; Waters, W. A. *J. Chem. Soc.* **1951**, 1851. (b) Aberhart, D. J.; Tann, C.-H. *J. Chem. Soc., Perkin Trans. I* **1979**, 939.

funnel, and the residue was rinsed thoroughly with diethyl ether. The mixture was partitioned and washed with brine (1 x 15 mL). The crude oil was purified by flash chromatography (4:1 petroleum ether:ether with 1% $Et_3N$) to yield thioether **12** (1.259 g, 97%) as a colorless oil. IR: 3351, 1624, 1458, 1365, 1163, 1008 $cm^{-1}$. $^1H$ NMR (400 MHz): δ 1.35 (s, 9), 1.43 (s, 1), 1.75 (s, 3), 4.07 (d, 2, $J$ = 5.8), 6.16 (s, 1). $^{13}C$ NMR (100 MHz): δ 15.52, 30.99, 43.65, 68.26, 117.74, 136.03. Anal. Calcd. for $C_8H_{16}OS$: C, 59.95; H, 10.06. Found: C, 59.79; H, 10.11.




**13**

**(*E*)-3-(*t*-Butylthio)-2-methyl-2-propen-1-al (13):** To a solution of vinyl sulfide **12** (4.20 g, 26.2 mmol) in 45 mL hexanes was added $MnO_2$ (11.4 g, 131 mmol) and vigorous stirring was initiated. After 15 h, the mixture was filtered through a plug of Florisil in a fritted glass funnel, and the residue was rinsed thoroughly with diethyl ether. The filtrate was concentrated to provide a yellow oil which was purified by flash chromatography (4:1 hexanes:diethyl ether). The product-containing fractions were concentrated to afford a colorless oil which upon standing solidified to afford white needles (3.39 g, 86%) of aldehyde **13**, mp 43-35 °C. IR: 1662, 1578, 1334, 1176, 1017 $cm^{-1}$. $^1H$ NMR (400 MHz): δ 1.46 (s, 9), 1.74 (s, 3), 7.43 (s, 1), 9.29 (s, 1). $^{13}C$ NMR (100 MHz): δ 10.41, 30.97, 45.50, 134.71, 150.61, 190.03. The spectral data matched that previously reported.[3]




**15**

**(*E*)-3-(Propylthio)-2-propen-1-al (15):** To a cool (0 °C) slurry of vinyl bromide **14**[4] (1.510 g, 10.00 mmol), NMO (1.760 g, 15.00 mmol), and powdered 4Å molecular sieves (5.0 g) in $CH_2Cl_2$ (20 mL)was added TPAP (100 mg, 0.285 mmol). After 2 h, the ice bath was replaced with a –78 °C bath and propanethiol (10.0 mL, 110 mmol) followed by $Et_3N$ (10.0 mL, 720 mmol) was added. The cold bath was removed after 15 min and stirring was continued for 2 h. The mixture was then filtered through a short plug of Florisil, and the residue was rinsed thoroughly with diethyl ether. The filtrate (~80 mL) was washed with 2 M NaOH (2 x 40 mL) and $H_2O$ (1 x 40 mL). The crude oil was purified by flash chromatography (4:1 hexanes:ether) to yield aldehyde **15** (988 mg, 69%) as a colorless oil. IR: 1662, 1578, 1333, 1185, 1019, 810 cm–1. $^1H$ NMR (400 MHz): δ 1.02 (t, 3, $J$ = 7.3), 1.74 (dt, 2, $J$ = 7.3, 7.3), 1.75 (s, 3), 2.86 (t, 2, $J$ = 7.3), 7.25 (s, 1), 9.25 (s, 1). $^{13}C$ NMR (100 MHz): δ 10.3 ($CH_3$), 12.9 ($CH_3$), 23.8 ($CH_2$), 36.9 ($CH_2$), 135.0 (C), 154.9 (CH), 189.9 (CH). Anal. Calcd. for $C_7H_{12}OS$: C, 58.29; H, 8.39. Found: C, 57.93; H, 8.48.

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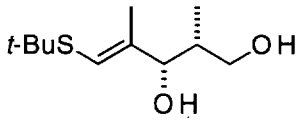
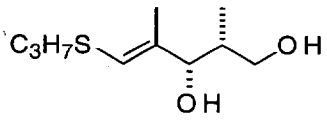
3. Michael J. Munchhof, Ph.D. thesis (University of California at Berkeley, 1994).

4. Preparation of bromide **14**: (a) Caubere, P. *Bull. Soc. Chim. Fr.* **1964**, *45*, 3584. (b) Brande, E. A.; Evans, E. A. *J. Chem. Soc.* **1955**, 3324. (c) Fischetti, W.; Mak, K. T.; Stakem, G.; Kim, J. -I.; Rheinhold, A. L.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 948.



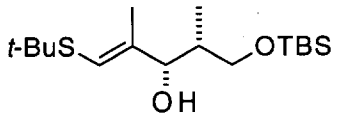

**19**

**(*E*)-(2*R*, 3*S*)-5-(*t*-Butylthio)-2,4-dimethyl-4-pentene-1,3-diol (19):** To a cool (0 °C) solution of oxazolidinone **16** (708 mg, 3.04 mmol) in $CH_2Cl_2$ (7.0 mL) was added $Bu_2BOTf$ (0.750 mL, 3.00 mmol) followed by $Et_3N$ (0.640 mL, 4.56 mmol). After 11 min the solution was cooled to –78 °C and aldehyde **13** (370 mg, 2.34 mmol) dissolved in $CH_2Cl_2$ (3.00 mL) was added over 7 min. The resulting yellow solution was kept at –78 °C for 30 min at which time the solution was warmed in an ice bath for 2 h. The ice bath was then removed and stirring was continued for a further 10 min. Methanol (2 mL) and pH 7 buffer (10 mL) were added to the reaction, and the mixture was stirred vigorously for 10 min. The mixture was poured into brine (10 mL) and partitioned, and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 15 mL). The crude yellow oil was dissolved in $CH_2Cl_2$ (40.0 mL), and Amberlite™ IRA-743 resin (25 mL) was added. The heterogeneous mixture was stirred vigorously for 22 h after which time the solids were removed by filtration through a fritted glass funnel, and the filtrate was concentrated to a yellow oil (1.30 g). The oil was then dissolved in diethyl ether (50.0 mL) and cooled in an ice bath. To this solution $H_2O$ (110 μL, 6.00 mmol) was added followed by $LiBH_4$ (3.00 mL of a 2 M solution in THF, 6.00 mmol). After 1.5 h, 50 mL of 1 M NaOH was added and the mixture was stirred vigorously until both layers were clear. The mixture was partitioned and the aqueous layer was extracted with $CH_2Cl_2$ (2 x 75 mL). The crude oil was purified by flash chromatography (1:1 hexanes:EtOAc) to yield diol **19** as a clear, colorless oil. Gentle heating (~45 °C) under vacuum (0.25 mm Hg) was necessary to remove all EtOAc from the diol (441 mg, 90%). $[\alpha]_D$: –10.76 (*c* 0.92, $CH_2Cl_2$). IR: 3380, 1625, 1162, 1086, 1033 $cm^{-1}$. $^1H$ NMR (400 MHz): δ 0.90 (d, 3, $J$ = 7.0), 1.36 (s, 9), 1.68 (dd, 3, $J$ = 0.9, 1.0), 1.89 (m, 1), 2.03 (br s, 1), 2.23 (br s, 1), 3.67 (m, 2), 4.24 (br d, 1, $J$ = 4.2), 6.19 (m, 1). $^{13}C$ (100 MHz): δ 10.4 ($CH_3$), 15.3 ($CH_3$), 31.0 ($CH_3$), 37.8 (CH), 43.7 (C), 66.7 ($CH_2$), 78.5 (CH), 117.1 (CH), 137.2 (C). Anal. Calcd. for $C_{11}H_{22}SO_2$: C 60.15; H 10.16. Found: C, 60.32; H, 10.29.



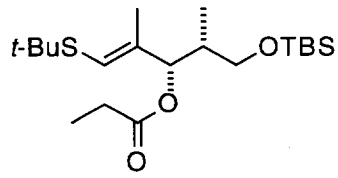

**20**

**(*E*)-(2*R*, 3*S*)-2,4-dimethyl-5-(propylthio)-4-pentene-1,3-diol (20):** The aldol reaction between oxazolidinone **16** (787 mg, 3.38 mmol) and aldehyde **15** followed by reduction of the aldol was carried out in an analogous procedure to that described above. This yielded 537 mg (90%) of diol **20** as a colorless oil. $[\alpha]_D$: –20.8 (*c* 0.48, $CH_2Cl_2$). IR: 3367, 1627, 1456, 1013 $cm^{-1}$. $^1H$ NMR (400 MHz): δ 0.90 (d, 3, $J$ = 7.0), 1.00 (t, 3, $J$ = 7.3), 1.64 (tq, 2, $J$ = 7.3, 7.3), 1.67 (s, 3), 1.86-1.91 (m, 1), 2.35 (br s, 1), 2.50 (br s, 1), 2.67 (t, 3, $J$ = 7.3), 3.66-3.68 (m, 2), 4.14 (d, 1, $J$ = 7.1), 5.99 (s, 1). $^{13}C$ NMR (100 MHz): δ 10.4, 13.2, 15.2, 23.8, 35.9, 37.7, 66.7, 78.3, 121.2, 135.0. Anal. Calcd. for $C_{10}H_{20}O_2S$: C, 58.78; H, 9.87. Found: C, 58.60; H, 9.67.



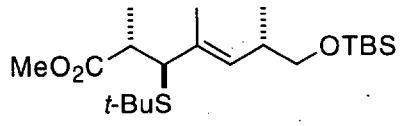

**21**

**(*E*)-(2*R*, 3*S*)-1-(*t*-Butyldimethylsilyloxy)-5-(*t*-butylthio)-3-hydroxy-2,4-dimethyl-4-pentene (21):** To a stirring solution of diol **19** (958 mg, 4.40 mmol) in $CH_2Cl_2$ (17.6 mL) was added $Et_3N$ (4.90 mL, 35.0 mmol), TBSCl (750 mg, 4.98 mmol), and imidazole (30 mg, 0.44 mmol). The solution was stirred at ambient temperature for 18 h after which time an additional 116 mg (0.77 mmol) TBSCl was added. After 6 h, $H_2O$ (10 mL) was added and the mixture was partitioned with diethyl ether (25 mL). The ethereal layer was washed with $H_2O$ (1 x 10 mL) and brine (1 x 10 mL). The crude oil was purified by flash chromatography (4:1 petroleum ether:diethyl ether containing 1% $Et_3N$) to yield 1.283 g (88%) of thioether **21** as a clear, colorless oil. $[\alpha]_D$: –16.31 (*c* 1.25, $CH_2Cl_2$). IR: 3464, 1624, 1471, 1364, 1256, 1093 $cm^{-1}$. $^1H$ NMR (400 MHz): δ 0.06 (s, 6), 0.85 (d, 3, *J* = 7.0), 0.90 (s, 9), 1.36 (s, 9), 1.67 (s, 3), 1.81-1.84 (m, 1), 3.03 (d, 1, *J* = 2.6), 3.65 (dd, 1, *J* = 4.8, 9.8), 3.7 (dd, 1, *J* = 3.9, 9.8), 4.27 (br s, 1), 6.20 (m, 1). $^{13}C$ NMR (100 MHz): δ –5.63 ($CH_3$), –5.58 ($CH_3$), 10.05 ($CH_3$), 15.45 ($CH_3$), 18.18 (C), 25.85 ($CH_3$), 31.03 ($CH_3$), 37.48 (CH), 43.53 (C), 67.72 ($CH_2$), 78.34 (CH), 116.4 (CH), 137.03 (C). Anal. Calcd. for $C_{17}H_{36}O_2SSi$: C, 61.39; H, 10.91. Found: C, 61.59; H, 11.24.



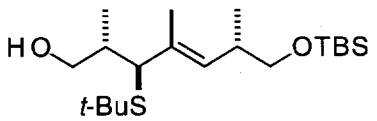

**22**

**3-[(*E*)-(2*R*, 3*S*)-1-(*t*-Butyldimethylsilyloxy)-5-(*t*-butylthio)-2,4-dimethyl-4-penten-3-ol] propanate (22):** To a stirring solution of alcohol **21** (980 mg, 2.95 mmol) in $CH_2Cl_2$ (8.0 mL) at rt was added pyridine (1.20 ml, 14.8 mmol), followed by propionyl chloride (380 μL, 4.40 mmol). After stirring for 2.5 h, 3.0 mL of MeOH was added to consume the remaining propionyl chloride, and the reaction mixture was diluted with diethyl ether (15 mL) and washed with ice cold 1 N HCl (2 x 10 mL) and $H_2O$ (1 x 10 mL). The crude oil which was purified by flash chromatography (4:1 petroleum ether:diethyl ether) to yield ester **22** (1.051 g, 92%) as a thick, colorless oil. $[\alpha]_D$: –36.74 (*c* 1.075, $CH_2Cl_2$). IR: 1742, 1472, 1365, 1183, 1092 $cm^{-1}$. $^1H$ NMR (500 MHz): δ 0.00 (s, 6), 0.87 (s, 9), 0.90 (d, 3, *J* = 6.8), 1.13 (t, 3, *J* = 7.6), 1.32 (s, 9), 1.69 (d, 3, *J* = 1.1), 1.94 (m, 1), 2.31 (dd, 1, *J* = 7.5, 7.5), 2.33 (dd, 1, *J* = 7.6, 7.6), 3.37 (dd, 1, *J* = 5.8, 9.9), 3.44 (dd, 1, *J* = 5.5, 9.9), 5.21 (d, 1, *J* = 7.1), 6.09 (m, 1). $^{13}C$ NMR (100 MHz): δ –5.56, –5.48, 9.29, 12.34, 14.56, 18.25, 25.88, 27.86, 30.96, 37.80, 43.82, 64.55, 78.72, 119.68, 134.19, 173.30. Anal. Calcd. for $C_{20}H_{40}O_3SSi$: C, 61.80; H, 10.37. Found: C, 61.85; H 10.61.




**23**

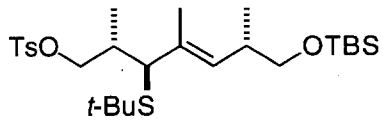
**(*E*)-(2*R*, 3*S*, 6*S*)-7-( *t*-Butyldimethylsilyloxy)-3-(*t*-butylthio)-2,4,6-trimethyl-4-heptenoic acid methyl ester (23):** To a cold (–78 °C) stirring solution of diisopropylamine (117 μL, 0.830 mmol) in THF (1.40 mL) was added *n*-BuLi (483 μL of a 1.6 M solution in hexanes, 0.770 mmol). After 5 min the cold bath was removed and stirring was continued for a further 15 min after which time the solvent was removed by bubbling $N_2$ through the reaction vessel to provide a white powdery solid. The white solid was dissolved in THF (0.200 mL), cooled to –78 °C, and stirring was initiated. To the cold solution was added a solution of ester **22** (212 mg, 0.545 mmol) in THF (200 μL) followed by a 200 μL THF rinse over a period of 11 min. After an additional 3 min of stirring, TBSCl (116 mg, 0.77 mmol) in a mixture of 320 μL of HMPA and 450 μL of THF was added dropwise. The pale yellow solution was kept at –78 °C for 45 min after which time the cold bath was removed and the reaction was allowed to slowly warm to rt. After 3 h 20 min the reaction solution was diluted with petroleum ether (10 mL) and washed with ice cold 5% HCl (1 x 5 mL) and $H_2O$ (3 x 5 mL). The organic extract was concentrated without drying, and the colorless residue was dissolved in THF (6.0 mL), cooled in an ice bath, and 1 M $K_2CO_3$ (6.0 mL) was added. The resulting mixture was stirred vigorously for 2 h then concentrated *in vacuo* to remove the volatiles. The aqueous mixture was cooled in an ice bath and acidified to the methyl orange endpoint with concentrated HCl. The acidifed aqueous mixture was extracted with diethyl ether (2 x 10 mL) and the organic extracts were treated with ethereal diazomethane until a yellow color persisted. The excess diazomethane was decomposed with $MgSO_4$, and the solution was filtered and concentrated. The yellow oil thus obtained was purified by flash chromatography (8:1 petroleum ether:diethyl ether) to yield 189 mg (86%) of ester **23** as a colorless oil. $[\alpha]_D$: +37.07 (*c* 0.99, $CH_2Cl_2$). IR: 1743, 1471, 1364, 1257, 1089, 776 $cm^{-1}$. $^1H$ NMR (400 MHz): δ 0.01 (s, 6), 0.87 (s, 9), 0.93 (d, 3, *J* = 6.7), 0.99 (d, 3, *J* = 7.0), 1.25 (s, 9), 1,62 (d, 3, *J* = 1.2), 2.46 (qd, 1, *J* = 7.0, 11.5), 2.53 (m, 1), 3.34 (dd, 1, *J* = 7.0, 9.6), 3.47 (dd, 1, *J* = 5.6, 9.6), 3.50 (d, 1, *J* = 11.5), 3.68 (s, 3), 5.20 (d, 1, *J* = 9.1). $^{13}C$ NMR (100 MHz): δ –5.42 ($CH_3$), –5.39 ($CH_3$), 12.00 ($CH_3$), 16.41 ($CH_3$), 17.27 ($CH_3$), 18.36 (C), 25.94 ($CH_3$), 31.20 ($CH_3$), 35.51 (CH), 43.31 (CH), 43.90 (C), 51.58 ($CH_3$), 54.34 (CH), 67.42 ($CH_2$), 132.26 (CH), 134.29 (C), 175.80 (C). Anal. Calcd. for $C_{21}H_{42}O_3SiS$: C, 62.63; H, 10.51. Found: C, 62.94; H, 10.82.




**24**

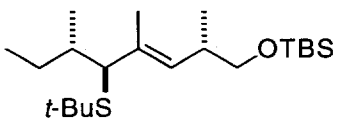
**(*E*)-(2*R*, 3*S*, 6*S*)-7-(*t*-Butyldimethylsilyloxy)-3-(*t*-butylthio)-2,4,6-trimethyl-4-hepten-1-ol (24):** To a cool (0 °C) slurry of $LiAlH_4$ (22.0 mg, 0.590 mmol) in diethyl ether (0.600 mL) was added ester **23** (118.0 mg, 0.290 mmol) dissolved in diethyl ether (1.20 mL). After 30 min the ice bath was removed,

and the reaction was allowed to stir at ambient temperature for 2 h. The reaction was quenched by the addition of 22 μL $H_2O$, 22 μL 15% NaOH, and 66 μL $H_2O$, causing some evolution of gas. When the evolution ceased, $MgSO_4$ was added to the mixture which was then filtered and concentrated to afford a colorless oil (123 mg). The oil was purified by flash chromatography (4:1 petroleum ether:diethyl ether) to yield 109.5 mg (99%) of alcohol **24** as a colorless oil. $[\alpha]_D$: –4.34 (*c* 0.415, $CH_2Cl_2$). IR: 3394, 1650, 1456, 1162, 1035 $cm^{-1}$. $^1H$ NMR (500 MHz): δ 0.02 (s, 6), 0.82 (d, 3, *J* = 6.8), 0.88 (s, 9), 0.93 (d, 3, *J* = 6.7), 1.30 (s, 9), 1.66 (s, 3), 1.72 (m, 1), 2.03 (br s, 1), 2.53 (m, 1), 3.19 (d, 1, *J* = 10.3), 3.34 (dd, 1, *J* = 7.1, 9.6), 3.47 (dd, 1, *J* = 5.7, 9.6 ), 3.68 (d, 1, *J* = 4.7), 5.12 (d, 1, *J* = 9.0). $^{13}C$ NMR (100 MHz): δ –5.41 ($CH_3$), –5.38 ($CH_3$), 12.65 ($CH_3$), 16.21 ($CH_3$), 17.19 ($CH_3$), 18.38 (C), 25.95 ($CH_3$), 31.36 ($CH_3$), 35.41 (CH), 37.93 (CH), 44.02 (C), 56.38 (CH), 67.51 ($CH_2$), 67.60 ($CH_2$), 130.68 (CH), 136.01 (C). Anal. Calcd. for $C_{20}H_{42}O_2SSi$: C, 64.11; H, 11.30. Found: C, 64.46; H, 11.54.




**25**

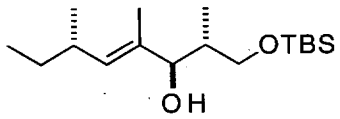
**(*E*)-(2*S*, 3*R*, 6*S*)-7-(*t*-Butyldimethylsilyloxy)-3-(*t*-butylthio)-2,4,6-trimethyl-4-hepten-1-*p*-toluenesulfonate (25):** To a stirring solution of alcohol **24** (500 mg, 1.33 mmol) in $CH_2Cl_2$ (5.0 mL) at rt was added $Et_3N$ (560 μL, 4.00 mmol), TsCl (279 mg, 1.46 mmol), and DMAP (16 mg, 0.13 mmol). After stirring for 21 h, $H_2O$ (5 mL) was added and the mixture was partitioned with diethyl ether (10 mL). The ethereal layer was washed with 10% HCl (1 x 5 mL) and $H_2O$ (1 x 5 mL). The combined aqueous layers were back-extracted with diethyl ether (1 x 10 mL). The crude oil was purified by flash chromatography (3:1 petroleum ether:diethyl ether) to yield 660 mg (94 %) of tosylate **25** as a colorless oil. Attempts at combustion analysis were unsuccessful and tosylate **25** appeared to undergo significant decomposition when stored. It was therefore used immediately in the next reaction. $[\alpha]_D$ +10.24 (*c* 1.06, $CH_2Cl_2$). IR: 1599, 1363, 1256, 1189, 1178, 1097, 777 $cm^{-1}$. $^1H$ NMR (500 MHz): δ 0.00 (s, 6), 0.82 (d, 3, *J* = 6.9), 0.86 (s, 9), 0.89 (d, 3, *J* = 6.7), 1.20 (s, 9), 1.58 (d, 3, *J* = 1.2), 1.69-1.73 (m, 1), 2.42 (s, 3), 2.48-2.51 (m, 1), 3.15 (d, 1, *J* = 10.5), 3.31 (dd, 1, *J* = 7.1, 9.6), 3.44 (dd, 1, *J* = 5.6, 9.6), 4.16 (dd, 1, *J* = 3.5, 9.2), 4.22 (dd, 1, *J* = 5.2, 9.2), 5.10 (d, 1, *J* = 9.2), 7.30 (d, 2, *J* = 8.4), 7.80 (d, 2, *J* = 8.3). $^{13}C$ NMR (100 MHz): δ –5.40 ($CH_3$), 12.3 ($CH_3$), 15.3 ($CH_3$), 17.1 ($CH_3$), 18.3 (C), 21.6 ($CH_3$), 25.9 ($CH_3$), 31.2 ($CH_3$), 35.4 (CH), 35.6 (CH), 43.8 (C), 53.4 (CH), 67.4 ($CH_2$), 73.5 ($CH_2$), 127.9 (CH), 129.7 (CH), 131.3 (CH), 133.0 (C), 135.0 (C), 144.5 (C).




**26**

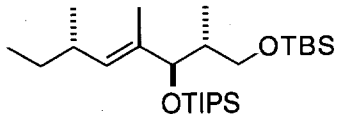
**(*E*)-(2*S*, 5*R*, 6*S*)-1-(*t*-Butyldimethylsilyloxy)-5-(*t*-butylthio)-2,4,6-trimethyl-3-octene (26):** To a cool (0 °C) stirring slurry of CuCN (138 mg, 1.54 mmol) in diethyl ether (2.0 mL) was added MeLi (1.90 mL of a 1.6 M solution in diethyl ether, 3.08 mmol). Stirred was continued for 15 min at which time all of the CuCN had dissolved. Tosylate **25** (265 mg, 0.501 mmol) dissolved in diethyl ether (1.0 mL) was

added to the solution followed by a 1.5 mL diethyl ether rinse. After 3 h 15 min, the reaction mixture was poured into 15 mL of a 9:1 mixture of sat. aq. $NH_4Cl$:$NH_4OH$ and vigorous stirring was initiated. After 2 h the mixture was partitioned and the ethereal layer was washed with brine (1 x 10 mL). The crude oil was purified by flash chromatography (8:1 petroleum ether:ether) to yield 176 mg (94%) of thioether **26** as a colorless oil. $[\alpha]_D$: –2.74 (*c* 1.76, $CH_2Cl_2$). IR: 1661, 1256, 1086, 775 $cm^{-1}$. $^1H$ NMR (400 MHz): δ 0.02 (s, 6), 0.78 (d, 3, *J* = 6.7), 0.86-0.89 (m, 12), 0.93 (d, 3, *J* = 6.7), 1.11-1.15 (m, 1), 1.27 (s, 9), 1.41 (m, 1), 1.65 (d, 3, *J* = 1.2), 2.55 (m, 1), 3.04 (d, 1, *J* = 9.5), 3.32 (dd, 1, *J* = 7.4, 9.7), 3.48 (dd, 1, *J* = 5.5, 9.7), 5.08 (br d, 1, *J* = 9.1). $^{13}C$ NMR (100MHz): δ –5.39 ($CH_3$), –5.34 ($CH_3$), 11.27 ($CH_3$), 13.05 ($CH_3$), 17.07 ($CH_3$), 17.25 ($CH_3$), 18.39 (C), 25.97 ($CH_2$), 27.06 ($CH_3$), 31.40 ($CH_3$), 35.44 (CH), 37.05 (CH), 43.15 (C), 58.18 (CH), 67.57 ($CH_2$), 130.07 (CH), 136.65 (C). Anal. Calcd. for $C_{21}H_{44}OSSi$: C, 67.67; H, 11.90. Found: C, 67.95; H, 12.07.



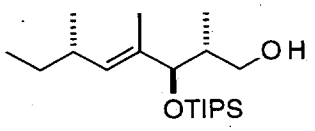

**27**

**(*E*)-(2*R*, 3*R*, 6*S*)-1-(*t*-Butyldimethylsilyloxy)-2,4,6-trimethyl-4-octen-3-ol (27):** To a cold (-78 °C) stirring solution of sulfide **26** (196 mg, 0.530 mmol) $CH_2Cl_2$ (1.50 mL) was added *m*-CPBA (101 mg of *m*-CPBA of 90% purity, 0.530 mmol). After 25 min an additional 6.0 mg (0.03 mmol) of *m*-CPBA was added. Stirring was continued for an additional 10 min after which time sat. $NaHCO_3$ (1 mL) was added and the mixture was partitioned. The aqueous layer was extracted with $CH_2Cl_2$ (2 x 5 mL). The combined organic extracts were dried, filtered and concentrated to afford a colorless oil (226 mg) which was used immediately without further purification. $^1H$ NMR analysis of the crude product revealed it to be a ~2:1 mixture of sulfoxide diastereomers. The mixture of sulfoxides was dissolved in MeOH (5.30 mL) which had been freshly distilled from $CaH_2$. $P(OMe)_3$ (1.56 mL, 13.25 mmol) was added and the mixture was heated at 55 °C for 8.5 h. After the reaction has cooled to rt, sat. $NH_4Cl$ (5 mL) was added. The mixture was partitioned with diethyl ether (15 mL) and washed with $H_2O$ (1 x 10 mL). The crude oil thus isolated was placed under high vacuum (~ 2 mm Hg) for 16 h to remove residual $P(OMe)_3$. The oil was purified by flash chromatography (8:1 petroleum ether:diethyl ether) to yield 126 mg (80%) of alcohol **27** as a colorless oil. $[\alpha]_D$: –9.36 (*c* 0.47, $CH_2Cl_2$). IR: 3491, 1255, 1089, 777 $cm^{-1}$. $^1H$ NMR (400 MHz): δ 0.08 (s, 6), 0.70 (d, 3, *J* = 7.0), 0.85 (t, 3, *J* = 7.4), 0.89-0.91 (m, 12), 1.21-1.34 (m, 2), 1.60 (d, 3, *J* = 1.3), 1.83-1.87 (m, 1), 2.29 (m, 1), 3.56 (dd, 1, *J* = 8.0, 9.9), 3.78 (dd, 1, *J* = 4.0, 9.9), 3.81 (d, 1, *J* = 8.6), 5.14 (d, 1, *J* = 9.4). $^{13}C$ NMR (100 MHz): δ –5.67, –5.60, 11.39, 12.00, 13.63, 18.11, 20.62, 25.82, 30.21, 33.70, 37.32, 68.77, 84.02, 134.35. Anal. calc. for $C_{21}H_{44}SiSO$: C, 67.94; H, 12.07. Found: C, 67.84; H, 12.14.



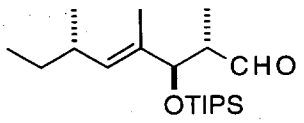

**28**

**(*E*)-(2*R*, 3*R*, 6*S*)-1-(*t*-Butyldimethylsilyloxy)-3-(triisopropylsilyloxy)-2,4,6-trimethyl-4-octene (28):** To a cool (0 °C) stirring solution of alcohol **27** (51.6 mg, 0.172 mmol) in $CH_2Cl_2$ (1.00 mL) was added $Et_3N$ (140 μL, 1.02 mmol) followed by TIPSOTf (140 μL, 0.530 mmol). After 20 min a few drops of MeOH were added to consume the remaining TIPSOTf. The reaction mixture was diluted with diethyl ether (5 mL) and washed with 10% HCl (1 x 5 mL) and brine (1 x 5 mL). The crude oil was purified by flash chromatography (5:1 petroleum ether:diethyl ether) to yield 73.9 mg (94%) of silylether **28** as a colorless oil. $[\alpha]_D$: +13.39 (*c* 1.1, $CH_2Cl_2$). IR: 1251, 1060, 777 $cm^{-1}$. $^1H$ NMR (400 MHz): δ 0.02 (s, 6), 0.73 (d, 3, *J* = 6.9), 0.84 (t, 3, *J* = 7.4), 0.88 (m, 12), 1.03 (br s, 21), 1.27 ( m, 2), 1.57 (d, 3, *J* = 1.2), 1.77 (m, 1), 2.26 (m, 1), 3.46 (dd, 1, *J* = 6.9, 9.6), 3.69 (dd, 1, *J* = 4.9, 9.5), 3.99 (d, 1, *J* = 7.7), 5.04 (d, 1, *J* = 9.0). $^{13}C$ NMR (100 MHz): δ –5.39 ($CH_3$), –5.33 ($CH_3$), 11.89 ($CH_3$), 12.66 (CH), 13.39 ($CH_3$), 18.22 ($CH_3$), 18.27 ($CH_3$), 18.34 (C), 20.40 ($CH_3$), 25.97 ($CH_3$), 30.04 ($CH_2$), 33.73 (CH), 41.16 (CH), 65.47 ($CH_2$), 79.82 (CH), 133.86 (CH), 134.48 (C). Anal. Calcd. for $C_{26}H_{56}O_2Si_2$: C, 68.35; H, 12.35. Found: C, 68.37; H, 12.24.




**29**

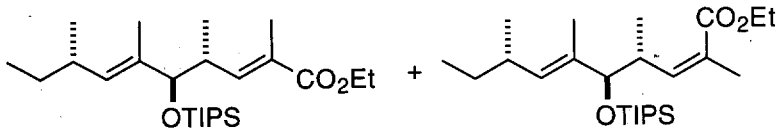
**(*E*)-(2*R*, 3*R*, 6*S*)-3-(Triisopropylsilyloxy)-2,4,6-trimethyl-4-octen-1-ol (29):** Silylether **28** (73.9 mg, 0.162 mmol) was dissolved in THF (1.45 mL) and 0.33 mL of 5% $H_2SO_4$ was added. This mixture was stirred vigorously for 7.5 h after which time the reaction mixture was diluted with diethyl ether (5 mL) and washed with sat. $NaHCO_3$ (1 x 2 mL) and brine (1 x 2 mL). The crude oil was purified by flash chromotography (5:1 petroleum ether:diethyl ether) to yield 51.8 mg (94%) of alcohol **29** and 4.2 mg (5%) of silylether **28**. $[\alpha]_D$: +14.71 (*c* 0.51, $CH_2Cl_2$). IR: 3390, 1251, 1060, 777 $cm^{-1}$. $^1H$ NMR (400 MHz): δ 0.78 (d, 3, *J* = 7.0), 0.85 (t, 3, *J* = 7.4), 0.89 (d, 3, *J* = 6.7), 1.04-1.12 (m, 21), 1.24-1.33 (m, 2), 1.60 (d, 3, *J* = 1.3), 1.83 (m, 1), 2.27 (m, 1), 3.61 (dd, 1, *J* = 4.0, 10.8), 3.67 (dd, 1, *J* = 6.7, 10.8), 4.01 (d, 1, *J* = 7.7), 5.14 (d, 1, *J* = 9.2). $^{13}C$ NMR (100 MHz): δ 11.82 ($CH_3$), 11.96 ($CH_3$), 12.80 (CH), 14.31 ($CH_3$), 18.14 ($CH_3$), 18.23 ($CH_3$), 20.15 (CH), 29.89 ($CH_2$), 33.74 (CH), 39.20 (CH), 66.85 ($CH_2$), 84.51 (CH), 134.22 (CH), 134.45 (C). Anal. Calcd. for $C_{20}H_{42}O_2Si$: C, 70.11; H, 12.36. Found: C, 69.96; H, 12.08.




**30**

**(*E*)-(2*S*, 3*R* 6*S*)-3-(Triisopropylsilyloxy)-2,4,6-trimethyl-4-octen-1-al (30):** Alcohol **29** (110 mg, 0.321 mmol), NMO (53.0 mg, 0.450 mmol), and 4 Å powdered molecular sieves (~ 250 mg) were

combined in $CH_2Cl_2$ (2.50 mL) and stirred for 20 min at rt. TPAP (2.3 mg, 0.064 mmol) was added, and the slurry was stirred for 20 min. Diethyl ether (5.0 mL) was added and the mixture was filtered through a plug of Florisil, rinsing with ether. The filtrate was concentrated to provide aldehyde **30** as a colorless oil (105 mg, 96%) which was of sufficient purity to be used in the subsequent reaction. IR: 1729, 1060 $cm^{-1}$. $^1H$ NMR (400 MHz): δ 0.84 (t, 3, $J$ = 7.4), 0.87 (d, 3, $J$ = 7.1), 0.89 (d, 3, $J$ = 6.8), 1.02 (m, 21), 1.23-1.33 (m, 2), 1.60 (d, 3, $J$ = 1.3), 2.24-2.31 (m, 1), 2.56 (dqd, 1, $J$ = 2.9, 7.0, 8.1), 4.26 (d, 1, $J$ = 8.1), 5.17 (d, 1, $J$ = 9.4), 9.81 (d, 1, $J$ = 2.9). $^{13}C$ NMR (100 MHz): δ 10.96 ($CH_3$), 11.48 ($CH_3$), 11.84 ($CH_3$), 12.60 (CH), 18.11 ($CH_3$), 18.14 ($CH_3$), 20.30 ($CH_3$), 29.88 ($CH_2$), 33.82 (CH), 51.09 (CH), 80.50 (CH), 133.26 (C), 135.34 (CH), 205.36 (CH).

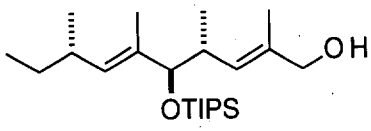



**35** **36**

**Enoates 35 and 36:** To a solution of $Bu_3P$ (1.42 mL, 5.7 mmol) in benzene (3.5 mL) was added ethyl 2-bromopropionate (0.74 mL, 5.7 mmol). After 7 h, $Et_3N$ (0.78 mL, 5.6 mmol) was added. To aldehyde **30** (100.0 mg, 0.290 mmol) was added 3.5 mL of the ylide solution. The mixture was then heated at 73 °C for 12.5 h. After that time an additional 1.0 mL of the ylide solution was added and heating was continued for a further 3.5 h. The reaction mixture was then cooled to rt, diluted with diethyl ether (10 mL) and washed with $H_2O$ (1 x 5 mL) and brine (1 x 5 mL). The crude oil (589 mg) was purifed by flash chromatography (4:1 petroleum ether:$CH_2Cl_2$) to provide 113.3 mg (92%) of a 2:1 mixture of enoates **35** and **36**. The olefin isomers were separated by a second submission to flash chromatography (5:1 petroleum ether:$CH_2Cl_2$) to yield 68.0 mg (56%) of the *E* isomer **35** and 32.0 mg (26%) of the *Z* isomer **36**. Anal. Calcd. for $C_{25}H_{48}O_3Si$: C, 70.70; H, 11.39. Found: C, 70.45; H, 11.34.

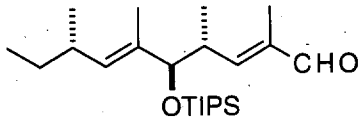
**(2*E*, 6*E*)-(3*R*, 4*R*, 7*S*)-4-(Triisopropylsilyloxy)-2,4,6,8-tetramethyl-2,6-decadienoic acid ethyl ester (35):** IR: 1716, 1654, 1212, 1090, 1061 $cm^{-1}$. $^1H$ NMR (400 MHz): δ 0.83 (t, 3, $J$ = 7.5), 0.83 (d, 3, $J$ = 7.1), 0.89 (d, 3, $J$ = 6.7), 1.00-1.05 (br s, 21), 1.21-1.32 (m, 2), 1.26 (t, 3, $J$ = 7.1), 1.59 (d, 3, $J$ = 1.3), 1.83 (d, 3, $J$ = 1.4), 2.24-2.28 (m, 1), 2.66 (qdd, 1, $J$ = 7.0, 7.4, 10.2), 3.95 (d, 1, $J$ = 7.5), 4.08-4.21 (m, 2), 5.09 (d, 1, $J$ = 9.4), 6.69 (dd, 1, $J$ = 1.4, 10.2). $^{13}C$ NMR (100 MHz): δ 11.81, 12.52, 12.68, 14.26, 16.47, 18.14, 18.17, 20.37, 29.69, 29.97, 33.74, 38.81, 60.21, 82.82, 127.09, 134.30, 134.45, 146.19, 168.30. $[\alpha]_D$: +18.98 ( *c* 0.295, $CH_2Cl_2$).

**(2*Z*, 6*E*)-(3*R*, 4*R*, 7*S*)-4-(Triisopropylsilyloxy)-2,4,6,8-tetramethyl-2,6-decadienoic acid ethyl ester (36):** IR: 1714, 1651, 1260, 1091 $cm^{-1}$. $^1H$ NMR (400 MHz, $C_6D_6$): δ 0.87 (t, 3, $J$ = 7.4), 0.91 (d, 3, $J$ = 6.7), 0.99 (t, 3, $J$ = 7.1), 1.06 (d, 3, $J$ = 6.9), 1.11-1.17 (m, 21), 1.24-1.35 (m, 2), 1.66 (d, 3, $J$ = 1.3), 1.98 (d, 3, $J$ = 1.4), 2.18-2.24 (m, 1), 3.84 (qdd, 1, $J$ = 6.8, 6.9, 10.1), 3.98-4.04 (m, 3), 5.15 (d, 1, $J$ = 9.4), 5.92 (dd, 1, $J$ = 1.3, 10.1). $^{13}C$ NMR (100 MHz, $C_6D_6$): δ 12.08, 12.61, 13.07, 13.13, 14.27, 17.49, 18.49, 20.67, 21.24, 30.46, 34.03, 39.01, 59.86, 83.23, 127.12, 133.86, 135.39, 146.67, 167.49.



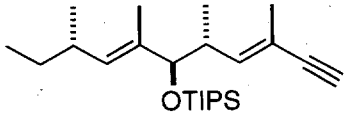

**37**

**(2*E*, 6*E*)-(3*R*, 4*R*, 7*S*)-4-(Triisopropylsilyloxy)-2,4,6,8-tetramethyl-2,6-decadien-1-ol (37):** To a cool (0 °C) stirring solution of enoate **35** (66.0 mg, 0.16 mmol) in $CH_2Cl_2$ (1.0 mL) was added DIBALH (0.218 mL of a 1.5 M solution in toluene, 0.330 mmol). After 25 min, MeOH (1 mL) was added followed by $H_2O$ (1 mL). The mixture was stirred vigorously until colorless salts had formed and it was then filtered through Celite, rinsing the residue thoroughly with diethyl ether. The filtrate was partitioned and the aqueous layer was back-extracted with diethyl ether (1 x 5 mL). The combined organic extracts were washed with brine (1 x 5 mL). The crude oil was chromatographed (4:1 petroleum ether:diethyl ether) to yield alcohol **37** as a colorless oil (56.3 mg, 95%). $[\alpha]_D$: +9.02 (*c* 0.255, $CH_2Cl_2$). IR: 3340, 1458, 1247, 1085 $cm^{-1}$. $^1H$ NMR (500 MHz): δ 0.80 (d, 3, *J* = 6.9), 0.83 (t, 3, *J* = 7.5), 0.89 (d, 3, *J* = 6.7), 1.02-1.04 (m, 21), 1.18-1.31 (m, 2), 1.58 (d, 3, *J* = 1.3), 1.66 (d, 3, *J* = 1.3), 2.23-2.28 (m, 1), 2.57 (qdd, 1, *J* = 6.9, 9.7, 9.7), 3.88 (d, 1, *J* = 7.2), 3.97 (s, 2), 5.05 (d, 1, *J* = 9.4), 5.28 (d, 1, *J* = 9.7). $^{13}C$ NMR (100 MHz): δ 11.85, 12.13, 12.73, 13.91, 17.35, 18.17, 18.21, 20.39, 30.05, 33.73, 37.68, 69.34, 82.89, 130.78, 133.81, 134.76. Anal. Calcd. for $C_{23}H_{46}O_2Si$: C, 72.18; H, 12.11. Found: C, 72.01; H, 11.88.




**38**

**(2*E*, 6*E*)-(3*R*, 4*R*, 7*S*)-4-(Triisopropylsilyloxy)-2,4,6,8-tetramethyl-2,6-decadien-1-al (38):** Allylic alcohol **37** (55.0 mg, 0.144 mmol), NMO (18.5 mg, 0.158 mmol), and 4 Å powdered molecular sieves (~70 mg) were combined in $CH_2Cl_2$ (2.0 mL) and the slurry was stirred for 20 min at rt. TPAP (5.0 mg, 0.0142 mmol) was then added. After 10 min the mixture was diluted with diethyl ether (5 mL) and Florisil was added. The mixture was then filtered through a plug of Florisil. The filtrate was concentrated to a heterogeneous mixture (68 mg) which was filtered through a plug of glass wool, rinsing with diethyl ether, and concentrated to yield 55.0 mg (100%) of aldehyde **38** as a colorless oil which was of sufficient purity to be used in the subsequent reaction. IR: 1691, 1642, 1263, 1082 $cm^{-1}$. $^1H$ NMR (400 MHz): δ 0.82 (t, 3, *J* = 7.4), 0.90 (d, 3, *J* = 6.8), 0.93 (d, 3, *J* = 6.9), 0.97-1.07 (m, 21), 1.20-1.32 (m, 2), 1.60 (s, 3), 1.74 (s, 3), 2.24-2.29 (m, 1), 2.87 (qdd, 1, *J* = 6.9, 7.0, 10.1), 4.03 (d, 1, *J* = 7.0), 5.13 (d, 1, *J* = 9.3), 6.44 (d, 1, *J* = 10.2). $^{13}C$ NMR (100 MHz): δ 9.41, 11.79, 12.07, 12.73, 16.59, 18.16, 18.19, 20.32, 29.94, 33.77, 39.15, 82.44, 134.11, 134.60, 138.65, 158.57, 195.52.




**39**

**(3*E*, 7*E*)-(5*R*, 6*R*, 8*S*)-6-(Triisopropylsilyloxy)-3,5,7,9-tetramethyl-3,7-decadien-1-yne (39):** To a cold (-78 °C) slurry of KO*t*-Bu (34.0 mg, 0.304 mmol) in THF (0.500 mL) was added dimethyl(diazomethyl)phosphonate[5] dissolved in THF (0.500 mL) and the solution immediately became dark orange-brown in color. After 15 min, a solution of aldehyde **38** (59.9 mg, 0.16 mmol) in THF (1.0 mL) was added slowly to the solution. The reaction was then packed in dry ice and allowed to stir for 16 h after which time it had warmed to rt. The reaction mixture was partitioned with diethyl ether (5 mL) and $H_2O$ (3 mL) and the ethereal layer was washed with $H_2O$ (1 x 3 mL). The organic extract was dried, filtered, and concentrated to a colorless oil which was resubmitted to the same reaction conditions. The crude oil thus isolated was purified by flash chromatography (4:1 petroleum ether:diethyl ether) to yield 54.7 mg (91%) of enyne **39** as a colorless oil. $[\alpha]_D$: +24.1 (*c* 0.56, $CH_2Cl_2$). IR: 2942, 1468, 1260, 1023 cm–1. $^1H$ NMR (400 MHz): δ 0.81 (d, 3, *J* = 6.9), 0.84 (t, 3, *J* = 7.4), 0.89 (d, 3, *J* = 6.7), 1.03 (br s, 1), 1.20-1.34 (m, 2), 1.59 (d, 3, *J* = 1.3), 1.79 (d, 3, *J* = 1.5), 2.22-2.30 (m, 1), 2.60 (dqd, 1, *J* = 6.9, 7.1, 10.1), 2.72 (s, 1), 3.88 (d, 1, *J* = 7.2), 5.08 (d, 1, *J* = 9.4), 5.82 (dd, 1, *J* = 1.4, 10.1). $^{13}C$ NMR (100 MHz): δ 11.86, 11.97, 12.67, 16.81, 17.28, 18.17, 18.22, 20.37, 30.02, 33.76, 38.63, 73.27, 82.63, 87.17, 116.22, 134.21, 134.45, 143.84. Anal. Calcd. for $C_{24}H_{44}OSi$: C, 76.53; H, 11.77. Found: C, 76.71; H, 11.49.

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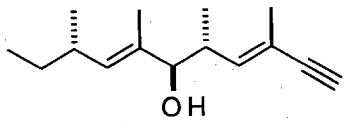
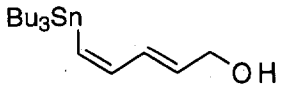
5. Brown, D. G.; Velthuisen, E. J.; Commerford, J. R.; Brisbois, R. G.; Hoye, T. R. *J. Org. Chem.* **1996**, *61*, 2540.




**40**

**(3*E*, 7*E*)-(5*R*, 6*R*, 8*S*)-3,5,7,9-Tetramethyl-3,7-decadien-1-yn-6-ol (40):** To a solution of alkyne **39** (23.2 mg, 0.0616 mmol) in THF (0.200 mL) was added TBAF (0.500 mL of a 1 M solution in THF, 0.500 mmol). After 10 h the solution was diluted with diethyl ether (5 mL) and washed with $H_2O$ (1 x 2 mL) and brine (1 x 2 mL). The crude oil was purified by flash chromatography (4:1 hexanes:diethyl ether) to yield 12.2 mg (90%) of alcohol **40**. $[\alpha]_D$: +28.4 (*c* 0.285, $CH_2Cl_2$). IR: 3377, 1632, 1463, 1263 $cm^{-1}$. $^1H$ NMR (500 MHz): δ 0.83(d, 3, *J* = 6.8), 0.85 (t, 3, *J* = 7.4), 0.91 (d, 3, *J* = 6.7), 1.19-1.34 (m, 2), 1.61 (d, 3, *J* = 1.2), 1.85 (d, 3, *J* = 1.4), 2.25-2.33 (m, 1), 2.64 (qdd, 1, *J* = 6.8, 8.4, 9.9), 2.78 (s, 1), 3.68 (d, 1, *J* = 8.4), 5.15 (d, 1, *J* = 9.4), 5.82 (d, 1, 10.0). $^{13}C$ NMR (125 MHz): δ 11.30, 11.92, 16.89, 17.49, 20.54, 30.09, 33.75, 37.14, 74.18, 82.20, 86.52, 118.55, 133.40, 135.50, 142.06.




**47**

**(2*E*)-1-(*t*-Butyldimethylsilyloxy)-5-(tri-*n*-butylstannyl)-2-penten-4-yne (47):** To a cold (-78 °C) stirring solution of KHMDS (5.60 mL of a 0.5 M solution in toluene, 2.80 mmol) was added enyne **46**[6] (439 mg, 2.24 mmol) in THF (5.60 mL). After 15 min the –78 °C bath was replaced with an ice bath and stirring was continued. After 45 min, $Bu_3SnCl$ (911 mg, 2.80 mmol) was added and the resulting mixture was allowed to slowly warm to rt over 13 h. The reaction mixture was partitioned with diethyl ether (25 mL) and $H_2O$ (10 mL), and the ethereal layer was washed with brine (1 x 10 mL). The combined organics were dried, filtered and concentrated to a dark yellow oil (1.348 g) which was dissolved in THF (5.0 mL) and added to a stirring slurry of $Cp_2ZrHCl$[7] (855 mg, 3.315 mmol) in THF (10.0 mL) at rt. After 70 min, the reaction mixture was diluted with 20.0 mL pentane and stirring was continued for 20 min at which time the mixture was transferred onto a column of silica gel and the product was eluted with 1% ether in hexanes. The resulting fractions were concentrated to yield 1.0521 g of a clear yellow oil which was used immediately. The oil was dissolved in THF (5 mL) and to this solution was added TBAF (2.00 mL of 1.0 M solution in THF, 2.0 mmol). After 30 min, the reaction was diluted with diethyl ether (25 mL) and washed with $H_2O$ (1 x 10 mL) and with brine (1 x 10 mL). The organic extract was dried, filtered, and concentrated to a brown oil which was purified by chromatography (4:1 hexanes:diethyl ether) to yield alcohol **47** (415.2 mg, 50%) as a pale yellow oil. IR: 3336, 1648, 1559, 1462, 1000 cm–1. $^1H$ NMR (400 MHz): δ 0.88 (t, 9, 7.2), 0.96 (tt, 6, *J* = 8.3, 25.1), 1.30 (tt, 6, *J* = 7.2, 7.4), 1.39-1.58 (m, 6), 4.20 (t, 2, *J* = 5.9), 5.82 (dt, 1, *J* = 15.1, 5.6), 6.12 (dt, 1, *J* = 12.8, 31.2), 6.15 (dd, 1, *J* = 10.4, 15.0), 7.05 (ddt, 1, *J* = 10.5, 12.7, 64.7). $^{13}C$

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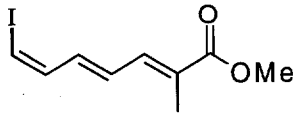
6. Crevisy, C.; Couturier, M; Dugave, C.; Dory, Y. L; Deslongchamps, P. *Bull. Chim. Soc. Fr.* **1995**, *132*, 360.

7. Buchwald, S. J.; Lamaire, S. J.; Neilsen, R. B.; Watson, B. T.; King, S. M. *J. Org. Chem.* **1992**, *71*, 77.

NMR (100 MHz): δ 10.44, 13.66, 27.23, 29.12, 63.45, 133.46, 134.00, 135.25, 145.49.[8] Although the preparation of this compound has been reported, no characterization data (spectral data, combustion analysis) was given.[9]




**44**

**(2*E*, 4*E*, 6*Z*)-7-Iodo-2-methyl-2,4,6-heptatrienoic acid ethyl ester (44):** To a stirring solution of diene **47** (48.9 mg, 0.13 mmol) in $CH_2Cl_2$ (1.0 mL) at rt which was shielded from light was added $I_2$ (33.2 mg, 0.13 mmol). After 5 min, 2.0 mL of sat. $Na_2S_2O_3$ was added, and the mixture was stirred for 1 h. Diethyl ether (10 mL) was added, and the mixture was partitioned. The ethereal layer was washed with brine (1 x 5 mL). The organic extract was dried, filtered, and concentrated to afford a yellow oil (61.3 mg) which was used immediately without further purification. The crude oil was dissolved in $CH_2Cl_2$ (2.0 mL) and shielded from light. To this solution was added $MnO_2$ (113 mg, 1.30 mmol), and the slurry was stirred vigorously for 13.5 h. After that time, additional $MnO_2$ (113 mg, 1.30 mmol) was added and stirring was continued for 11 h. The mixture was then filtered through a plug of Florisil in a fritted glass funnel, and the residue was rinsed thoroughly with diethyl ether. The resulting filtrate was concentrated to yield the aldehyde (23 mg) as a yellow semi-solid. To a cool (0 °C) stirring solution of triethyl 2-phosphonopropionate (61.9 mg, 0.26 mmol) in THF (1.0 mL) was added *n*-BuLi dropwise (102 μL of a 2.16 M solution in hexanes, 0.220 mmol). After 10 min a solution of the aldehyde in THF (1.0 mL) was added to the cool solution. Stirring was continued for 20 min at which time the reaction mixture was poured into brine (5 mL) and partitioned with diethyl ether (10 mL). The organic extract was dried, filtered, and concentrated to afford a yellow oil which was purified by flash chromatography (4:1 hexanes:diethyl ether) to give ester **44** (20.1 mg, 52% over 3 steps) as a colorless oil which quickly yellowed upon standing. IR: 1702, 1619, 1267, 1233 $cm^{-1}$. $^1H$ NMR (500 MHz): δ 1.31 (t, 3, $J$ = 7.1), 1.95 (s, 3), 4.22 (q, 2, $J$ = 7.1), 6.50 (d, 1, $J$ = 7.6), 6.64 (dd, 1, $J$ = 10.1, 14.8), 6.74 (dd, 1, $J$ = 11.4, 14.9), 6.86 (dd, 1, $J$ = 7.6, 10.0). $^{13}C$ NMR (125 MHz): δ 12.94, 14.30, 60.75, 86.26, 129.57, 131.58, 137.19, 138.04, 138.07, 168.11. Anal. Calcd. for $C_{10}H_{13}IO_2$: C, 41.12; H, 4.49. Found: C, 40.98; H, 4.42.

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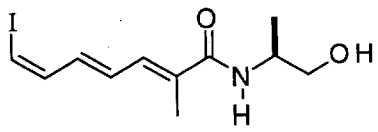
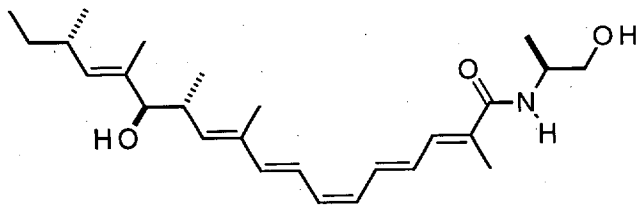
8. A sample of **47** was further purified by Kugelrohr distillation (bp ~240 °C @ 5 mm Hg) for combustion analysis (Calcd. for $C_{17}H_{34}OSn$: C, 54.72; H, 9.18). When combustion analysis was run immediately the results were C, 54.23; H, 9.07. When the analysis was repeated on the same sample after 3 h, the results were C, 53.48, H, 8.81 and it therefore appeared as if the compound underwent ready decomposition at rt.

9. (a) Andrus, M. B.; Lepore, S. D. *J. Am. Chem. Soc.* **1997**, *119*, 2327. (b) Andrus, M. B.; Lepore, S. D.; Turner, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 12159.



9

**(*S*)-7-Iodo-2-methyl-2,4,6-heptatrienoic alaninol amide (9):** Ester **44** was combined with LiOH (35.1 mg, 0.84 mmol) in *t*-BuOH (0.84 mL) and $H_2O$ (0.42 mL) and the resulting solution was stirred for 64 h. The reaction mixture was directly loaded onto a column of silica gel and the product was eluted with 2% MeOH in EtOAc to yield 42.3 mg of a powdery white solid. The solid was dissolved in $CH_2Cl_2$ (1.6 mL) and cooled in an ice bath. To this cool solution was added $Et_3N$ (109 μL, 0.78 mmol) followed by pivaloyl chloride (19.3 μL, 0.16 mmol). After 1.5 h an additional 5 μL of pivaloyl chloride was added. After 50 min (*S*)-2-amino-1-propanol (62.3 μL, 0.80 mmol) was added to the solution. After 2.5 h the reaction mixture was poured into $CH_2Cl_2$ (5 mL) and brine (2 mL) and partitioned. The crude residue which was purified by chromatography (0.5% MeOH in $CH_2Cl_2$) to yield amide **9** (38.4 mg, 71%) as a colorless oil. IR: 3357, 1638, 1602, 1529, 1450 1250 $cm^{-1}$. $^1H$ NMR (500 MHz): δ 1.27 (d, 3, *J* = 6.6), 1.96 (s, 3), 3.57 (dd, 1, *J* = 5.8, 11.0), 3.70 (dd, 1, *J* = 3.5, 11.0), 4.16 (m, 1), 6.44 (d, 1, *J* = 7.6), 6.58 (dd, 1, *J* = 10.1, 14.8), 6.69 (dd, 1, *J* = 11.3, 14.8), 6.83 (dd, 1, *J* = 7.7, 10.1), 6.95 (d, 1, *J* = 11.4). $^{13}C$ NMR (125 MHz): δ 13.29, 18.98, 48.02, 66.90, 85.49, 131.41, 132.49, 132.88, 169.1. HRMS (EI, 70 eV) calcd for $C_{11}H_{16}INO_2$: 321.0226. Found: 321.0222.



1

**Myxalamide A (1):** To a solution of alkyne **40** (5.1 mg, 0.023 mmol) in 0.800 mL of benzene-*d6* at rt was added catechol borane (6.2 μL, 0.058 mmol). After 90 min, $H_3B$•*N*, *N*-diethylaniline was added to the solution and the progress of the reaction was monitored by $^1H$ NMR. After 14 h an additional aliquot of catechol borane (6.2 μL, 0.058 mmol) was added and monitoring continued for 9 h. The solution was concentrated to an oily white solid which was dissolved in $CH_3CN$ (300 μL) and $H_2O$ (50 μL). To this was added iodide **9** (7.4 mg, 0.023 mmol) and 50 μL of diisopropylamine, and the resulting solution was degassed and shielded from light. $Pd(OAc)_2$ (22.8 μL of a 5.7 mg/mL solution in $CH_3CN$, 0.578 μmol) followed by TPPTS (51.5 μL of a 12.8 mg/mL solution in $H_2O$, 1.16 μmol) was added to the degassed solution. All subsequent manipulations were performed in the absence of light and with minimal exposure to oxygen. After 3.25 h, the reaction mixture was partitioned between degassed $CH_2Cl_2$ (2 mL) and brine (1 mL). The organic extract was concentrated without drying to afford a yellow oil which was purified by chromatography (degassed 4:1 EtOAc:hexanes) to yield a bright yellow oil (8.9 mg). The oil appeared by $^1H$ NMR spectral analysis to contain myxalamide A (**1**) as well as iodide **9**. The yellow oil was further purified by HPLC on a $SiO_2$ column using 1.5% MeOH in $CH_2Cl_2$ (λ = 340 nm, flow rate 5 mL/min) to yield 1.1 mg of

myxalamide A as well as a fraction containing 3.4 mg of a mixture of myxalamide A and iodotriene **9**. The mixed fraction was resubmitted to HPLC purification to yield 2.6 mg of myxalamide A (total weight = 4.5 mg, 44% for 2 steps). $[\alpha]_D$: –73 (*c* 0.05, MeOH) [lit. $[\alpha]_D$: –71.2 (*c* 0.5, MeOH)]. IR: 3357, 1636, 1603, 1523, 1455, 1380, 1252, 1153, 1097, 1050, 1041, 991 $cm^{-1}$. UV (EtOH): $\lambda_{max}$ 204, 265, 330 (sh), 358, 373 (sh). $^1H$ NMR (acetone-*d6*, 500 MHz): δ 0.81 (d, 3, *J* = 7.4), 0.89 (d, 3, *J* = 6.9), 0.90 (d, 3, *J* = 6.7), 1.16 (d, 3, *J* = 6.8), 1.19 (m, 1), 1.33 (m, 1), 1.61 (d, 3, *J* = 1.2), 1.85 (d, 3, *J* = 1.0), 1.95 (s, 3), 2.3 (1, m), 2.76 (m, 1, overlap with $H_2O$), 3.52 (2, m), 3.52 (d, 1, *J* = 3.6), 3.77 (dd, 1, *J* = 3.6, 7.1), 3.92 (t, 1, *J* = 5.6), 4.03 (m, 1), 5.13 (d, 1, *J* = 9.6), 5.57 (d, 1, *J* = 9.7), 6.12 (dd, 1, *J* = 10.7, 11.2), 6.17 (dd, 1, *J* = 10.4, 10.9), 6.37 (d, 1, *J* = 15.2), 6.58 (dd, 1, *J* = 11.6, 14.4), 6.79 (dd, 1, *J* = 10.9, 15.0), 6.83 (br s, 1), 6.99 (d, 1, *J* = 11.6), 7.10 (dd, 1, *J* = 11.0, 14.6). $^{13}C$ (acetone-*d6*, 125 MHz): δ 12.15, 12.18, 13.02, 13.16, 17.35, 18.09, 21.14, 31.03, 34.40, 37.83, 48.48, 66.53, 82.20, 122.48, 128.90, 129.13, 132.04, 133.32, 133.53, 133.69, 134.88, 136.31, 139.82, 141.3, 169.05. HRMS calcd for $C_{26}H_{41}NO_3$ 415.308644. Found: 415.308797.