Supplemental Materials for:

# Enantioselective Total Synthesis of Nicandrenones

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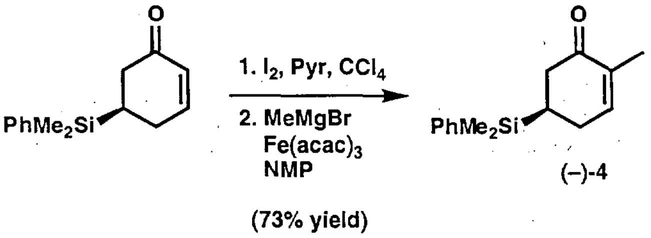
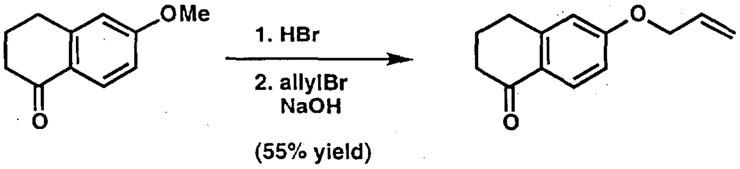
**Material and Methods.** Unless stated otherwise, reactions were performed in flame-dried glassware under a nitrogen or an argon atmosphere, using freshly distilled solvents. LiCl was dried at 120 °C under high vacuum (0.4 mmHg) for 15 h and stored over $CaSO_4$. CuCl was recrystallized from concentrated HCl, and dried under high vacuum for 15 h. *N,N*-Dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and *N*-methylpyrrolidone (NMP) were stirred over flame–dried $CaSO_4$ powder overnight and vacuum distilled with the bath temperature not higher than 80 °C. All other commercially obtained reagents were used as received. Reaction temperature was controlled by a Scientific Instruments temperature modulator model 2230. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm). Silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. $^1$H and $^{13}$C NMR chemical shifts are reported relative to $Me_4Si$ ($\delta$ 0.0), and $^{19}$F NMR chemical shifts relative to $CF_3COOH$ ($\delta$ -76.53). High resolution mass spectra were performed at The Harvard University Mass Spectrometry Center.



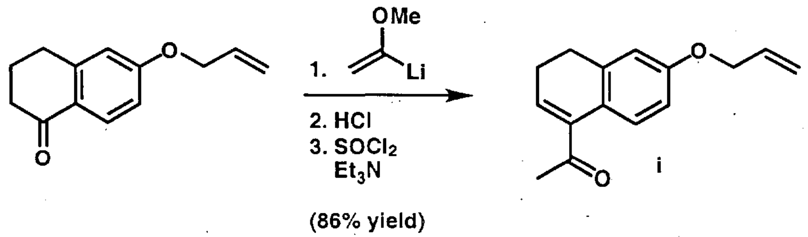
**Enone (–)-4.** To a cooled (0 °C) solution of (–)-5-phenyldimethylsilylcyclohex-2-en-1-one (3.00 g, 13.0 mmol) in $CCl_4$–pyridine (1:1, 50 mL) was added a solution of iodine (7.60 g, 30.0 mmol) in $CCl_4$–pyridine (1:1, 50 mL) in a dropwise fashion over 15 min. Following addition, the cold bath was removed and the reaction mixture was allowed to stand for 1 h. The crude mixture was poured into $Et_2O$ (300 mL) and washed sequentially with $H_2O$ (120 mL), 1 N HCl (120 mL), $H_2O$ (120 mL), 20% aq $Na_2S_2O_3$ (120 mL), and brine (120 mL). The organic layer was dried over $MgSO_4$ and evaporated to a solid which was recrystallized from $Et_2O$-pentane at -20 °C to provide (–)-2-iodo-5-phenyldimethylsilylcyclohex-2-en-1-one (4.06 g, 87% yield) as a yellow solid: mp 62-3 °C ($Et_2O$/pentane); $R_F$ 0.17 (6:1 hexanes/EtOAc); $[\alpha]_D^{25}$ –58 (*c* 1.0, $CHCl_3$); FTIR (film) 1686 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.75 (app.t, *J* = 4.3 Hz, 1H), 7.50-7.47 (m, 2H), 7.44-7.37 (m, 3H), 2.77 (dd, *J* = 3.4, 16.2 Hz, 1H), 2.41-2.31 (m, 3H), 1.80-1.71 (m, 1H), 0.35 (s, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 192.4, 160.1, 135.5, 133.8, 129.6, 128.1, 103.2, 37.9, 31.2, 23.3, -5.4, -5.5; HRMS (EI) *m/z* calcd for $[C_{14}H_{17}IOSi]^+$: 356.0094, found 356.0107.

A cooled (15 °C) solution of (–)-2-iodo-5-phenyldimethylsilylcyclohex-2-en-1-one (1.0 g, 2.81 mmol) in THF (3.4 mL) was treated with NMP (2.43 mL, 25.3 mmol), $Fe(acac)_3$ (9.9 mg, 0.028 mmol), and MeMgBr (3.0 M in $Et_2O$, 1.3 mL, 3.9 mmol) in a dropwise fashion over 20 min. After stirring for an additional 15 min, the reaction mixture was cooled to 0 °C, quenched by addition of 1 N HCl (10 mL), and extracted with $Et_2O$ (3 x 25 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (25 mL), $H_2O$ (25 mL), and brine (25 mL), dried over $MgSO_4$, and evaporated to an oil which was purified by flash chromatography on silica gel (10:1 hexanes/EtOAc eluent) to provide enone **(–)-4** (589 mg, 86% yield) as a reddish oil: $R_F$ 0.67 ($CH_2Cl_2$); $[\alpha]_D^{25}$ –21.0 (*c* 1.00, $CHCl_3$); FTIR (film) 1671 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.51-7.49 (m, 2H), 7.43-7.36 (m, 3H), 6.75-6.73 (m, 1H), 2.47 (dd, *J* = 3.5, 16.3 Hz, 1H), 2.31-2.15 (m, 3H), 1.75 (s, 3H), 1.70-1.61 (m, 1H), 0.33 (s, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.3, 146.2, 136.4, 135.2, 133.9, 129.3, 127.9, 38.8, 27.1, 23.5, 16.0, -5.4, -5.5; HRMS (EI) *m/z* calcd for $[C_{15}H_{20}OSi]^+$: 245.1362, found 245.1374.



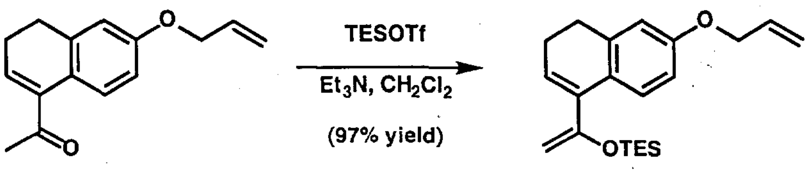
**6-Allyloxytetralone.** A solution of 6-methoxy-1-tetralone (40.0 g, 230 mmol) in 48% aq HBr (412 mL) was heated to reflux for 12 h. The reaction mixture was cooled to 0 °C and the precipitate was collected by vacuum filtration washing thoroughly with $H_2O$ (2 L) to give a brown solid which was used without further purification.

The crude phenol obtained above was dissolved in THF (460 mL) and treated with allyl bromide (22 mL, 250 mmol), $H_2O$ (150 mL), NaOH (46.0 g, 1140 mmol), and tetrabutylammonium bromide (730 mg, 2.3 mmol) and stirred at 25 °C for 12 h. The reaction mixture was diluted with $H_2O$ (500 mL) and extracted with $Et_2O$ (500 mL). The organic layer was washed sequentially with $H_2O$ (500 mL) and brine (500 mL), dried over $MgSO_4$, and evaporated to give a brown solid which was recrystallized from EtOAc-hexanes (1:6) to give 6-allyloxy tetralone as a yellow solid (25 g, 55% yield): mp 44-5 °C (EtOAc/hexanes); $R_F$ 0.56 (3:1 hexanes/EtOAc); FTIR (film) 1670 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.95 (d, $J$ = 8.8 Hz, 1H), 6.78 (dd, $J$ = 2.6, 8.8 Hz, 1H), 6.68 (d, $J$ = 2.6 Hz, 1H), 6.01 (m, 1H), 5.39 (d, $J$ = 17.2 Hz, 1H), 5.28 (d, $J$ = 10.6 Hz, 1H), 4.55 (s, 2H), 2.87 (app.t, $J$ = 5.9 Hz, 2H), 2.56 (app.t, $J$ = 6.2 Hz, 2H), 2.06 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 196.6, 162.1, 146.6, 132.2, 129.2, 126.0, 117.8, 113.3, 113.1, 68.6, 38.8, 30.0, 23.3; HRMS (EI) *m/z* calcd for $[C_{13}H_{14}O_2]^+$: 202.0994, found 202.0996.



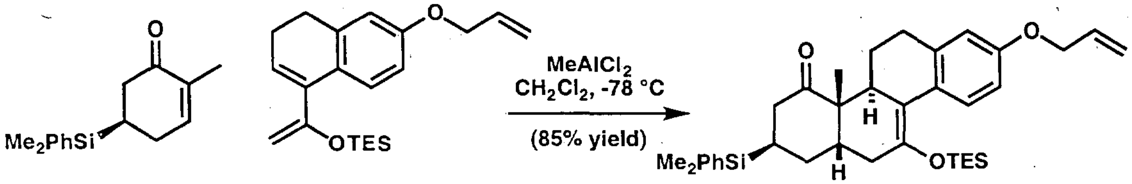
**Enone i.** To a solution of methyl vinyl ether (50 mL) in THF (150 mL) cooled to -78 °C was added *t*-BuLi (1.70 M in pentane, 146 mL, 250 mmol) via syringe in a dropwise fashion over 20 min. The yellow solution was stirred at -78 °C for 5 min, warmed to 0 °C for 5 min, and the resulting clear colorless solution was cooled again to -78 °C and stirred for 15 min. A solution of 6-allyloxytetralone (10.0 g, 49.5 mmol) in THF (80 mL) was added via an addition funnel over 10 min. The reaction mixture was stirred at -78 °C for 10 min and warmed to 0 °C for 20 min. The mixture was carefully treated with 3 M HCl (250 mL) [*caution: gas evolution!*] slowly over 30 min. After warming to ambient temperature, the mixture was extracted with EtOAc (300 mL), dried over $MgSO_4$, and evaporated to an oil which was used without further purification.

The crude oil obtained above was dissolved in $CH_2Cl_2$ (250 mL), cooled to 0 °C and treated sequentially with $SOCl_2$ (7.20 mL, 99.0 mmol) and $Et_3N$ (27.6 mL, 198 mmol). After stirring for 15 min, the thick brown suspension was warmed to 25 °C for 1 h, diluted with $H_2O$ (500 mL) and extracted with $CH_2Cl_2$ (3 x 250 mL). The combined organic layers were washed with brine (300 mL), dried over $MgSO_4$, and evaporated to an oil which was purified by flash chromatography on silica gel (10:1 hexanes/EtOAc eluent) to give enone **i** as a dark brown oil (9.66 g, 86% yield): $R_F$ 0.57 (3:1 hexanes/EtOAc); FTIR (film) 1671 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.68 (d, $J$ = 8.4 Hz, 1H), 6.90 (app.t, $J$ = 5.1 Hz, 1H), 6.75 (m, 1H), 6.73 (s, 1H), 6.04 (m, 1H), 5.39 (d, $J$ = 17.2 Hz, 1H), 5.27 (d, $J$ = 10.6 Hz, 1H), 4.53 (s, 1H), 4.52 (s, 1H), 2.70 (app.t, $J$ = 7.7 Hz, 2H), 2.44 (s, 3H), 2.40 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 199.1, 157.6, 138.3, 138.1, 137.2, 133.0, 127.7, 123.7, 117.3, 114.2, 111.6, 68.5, 27.8, 27.6, 23.5; HRMS (CI) *m/z* calcd for $[C_{14}H_{16}O_2+NH_4]^+$: 246.1494, found 246.1500.



i 5

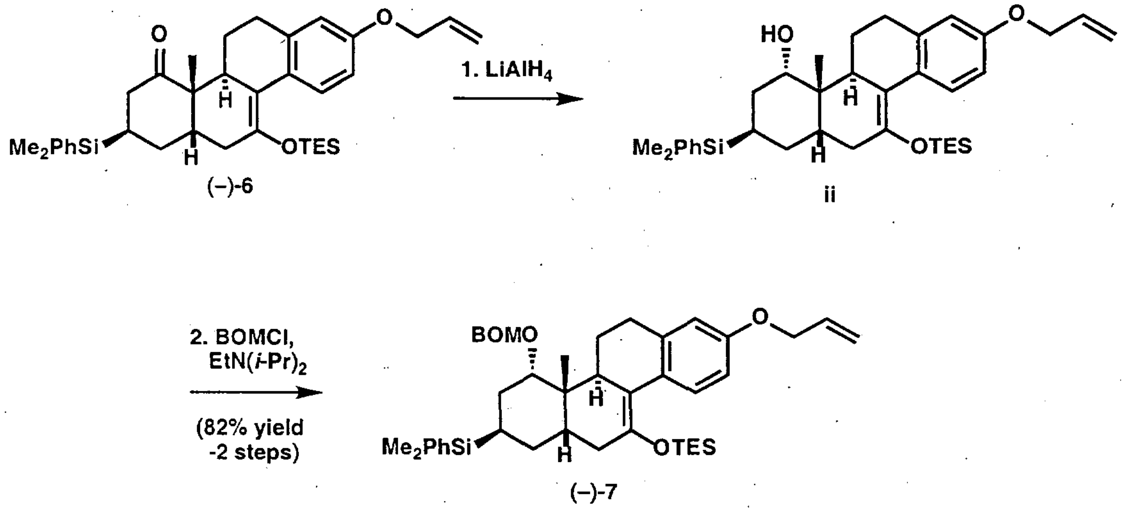
**Silyl enol ether 5.** To a cooled (0 °C) solution of enone **i** (2.0 g, 8.8 mmol) in $CH_2Cl_2$ (88 ml) was added TESOTf (2.4 mL, 11 mmol) followed by $Et_3N$ (2.4 mL, 17 mmol). After 10 min the reaction mixture was quenched with saturated aq $NaHCO_3$ solution (80 mL), and extracted with $CH_2Cl_2$ (3 x 30 mL). The combined organic layers were dried over $Na_2SO_4$, and evaporated to an oil which was purified by flash chromatography on silica gel (20:1 hexanes/EtOAc + 1% $Et_3N$ eluent) to give silyl enol ether **5** as a yellow oil (2.9 g, 97% yield): $R_F$ 0.59 (6:1 hexanes/EtOAc + 1%$Et_3N$); FTIR (film) 2954, 1608 $cm^{-1}$; $^1H$ NMR (300 MHz, benzene-$d_6$) δ 7.65 (d, *J* = 9.0 Hz, 1H), 6.73 (m, 2H), 6.20 (t, *J* = 4.8 Hz, 1H), 5.82 (m, 1H), 5.23 (d, *J* = 18.9 Hz, 1H), 5.02 (d, *J* = 10.5 Hz, 1H), 4.71 (s, 1H), 4.62 (s, 1H), 4.16 (s, 1H), 4.14 (s, 1H), 2.50 (app.t, *J* = 8.1 Hz, 2H), 2.00 (m, 2H), 1.00 (t, *J* = 8.1 Hz, 9H), 0.69 (q, *J* = 7.5 Hz, 6H); $^{13}C$ NMR (75 MHz, benzene-$d_6$) δ 158.2, 157.6, 138.7, 138.1, 133.9, 129.3, 128.5, 125.6, 125.2, 116.7, 114.8, 112.0, 94.5, 68.5, 28.8, 23.3, 5.3; HRMS (EI) *m/z* calcd for $[C_{21}H_{30}O_2Si]^+$: 342.2015, found 342.2016.



(–)-4 5 (–)-6

**Diels–Alder adduct (–)-6.** A solution of enone **(–)-4** (1.00 g, 4.10 mmol) in $CH_2Cl_2$ (41 mL) was cooled to 0 °C and treated with $MeAlCl_2$ solution (1.00 M in hexane, 4.30 mL, 4.30 mmol) in a dropwise fashion over 5 min. The pale yellow solution was stirred for 30 min, cooled to -78 °C and treated with a solution of silyl enol ether **5** (1.47 g, 4.30 mmol) in $CH_2Cl_2$ (8 mL) slowly over 2.5 h via syringe drive. Following this addition, the solution was stirred for an additional 60 min. The reaction mixture was quenched by sequential addition of $Et_3N$ (10 mL), saturated aq $NaHCO_3$ solution (20 mL), and saturated aq sodium potassium tartrate solution (40 mL), and allowed to thaw at ambient temperature over 1 h. The mixture was extracted with $CH_2Cl_2$ (3 x 75 mL), and the combined organic layers were dried over $Na_2SO_4$ and evaporated to a crude oil which consisted of Diels-Alder adduct **(–)-6** (2.45 g, >85% purity as measured by $^1H$ NMR analysis of the crude reaction product in $C_6D_6$ at 500 MHz) and was used without further purification.

An analytically pure sample of Diels-Alder adduct **(–)-6** was obtained by oxidation of alcohol **ii** (obtained by $LiAlH_4$ reduction of **(–)-6**, *vide infra*), using the following procedure. A solution of alcohol **ii** (25 mg, 0.043 mmol) in $CH_2Cl_2$ (0.43 mL) was treated with Dess-Martin periodinane (37 mg, 0.085 mmol), and stirred for 20 min at 25 °C. The crude reaction mixture was purified directly by flash chromatography on silica gel (10:1 hexanes/EtOAc eluent) to give ketone **(–)-6** as a clear colorless oil (25 mg, 98% yield): $R_F$ 0.48 (3:1 hexanes/EtOAc); $[\alpha]_D^{24}$ –53 (*c* 1.0, $CH_2Cl_2$); FTIR (film) 1700 $cm^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) δ 8.55 (d, *J* = 8.8 Hz, 1H), 7.40 (m, 2H), 7.20 (m, 3H), 6.88 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 5.83 (m, 1H), 5.22 (dd, *J* = 2.0, 17.1 Hz, 1H), 5.02 (dd, *J* = 2.0, 10.8 Hz, 1H), 4.16 (s, 1H), 4.15 (s, 1H), 2.74 (d, *J* = 10.8 Hz, 1H), 2.65-2.51 (comp m, 3H), 2.43 (ddd, *J* = 2.9, 6.4, 18.1 Hz, 1H), 2.36 (dd, *J* = 5.9, 15.6 Hz, 1H), 2.03-1.97 (comp m, 2H), 1.62 (ddd, *J* = 5.9, 11.2, 23.9 Hz, 1H), 1.55 (dt, *J* = 4.4, 13.7 Hz, 1H), 1.40 (m, 1H), 1.20 (s, 3H), 0.94 (t, *J* = 7.8 Hz, 9H), 0.61 (q, *J* = 7.8 Hz, 6H), 0.20 (s, 3H), 0.19 (s, 3H); $^{13}$C NMR (100 MHz, benzene-$d_6$) δ 212.8, 157.1, 141.6, 138.3, 137.6, 134.2, 134.0, 131.5, 129.5, 128.5, 116.6, 114.1, 112.6, 112.5, 68.5, 50.4, 40.3, 38.3, 37.6, 35.4, 31.2, 27.7, 25.0, 21.3, 17.2, 7.1, 6.0, -3.6, -3.7; HRMS (CI) *m/z* calcd for $[C_{36}H_{50}O_3Si_2+H]^+$: 587.3377, found 587.3349.



(–)-6

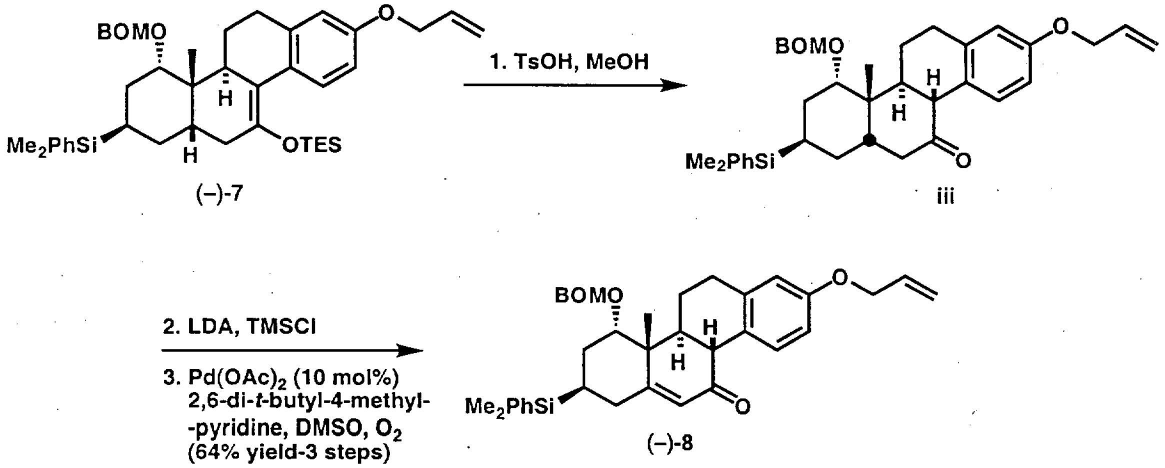
ii

(–)-7

**Alcohol ii.** To a cooled (-78 °C) solution of crude Diels-Alder adduct **(–)-6** (3.6 g, 85% purity, 5.2 mmol) in $Et_2O$ (62 mL) was added $LiAlH_4$ (1.0 M solution in $Et_2O$, 6.5 mL, 6.5 mmol) in a dropwise fashion over 5 min. The resulting solution was stirred for 30 min at -78 °C, warmed to 0 °C and treated sequentially with $H_2O$ (0.25 mL), 15% aq NaOH solution (0.25 mL) and $H_2O$ (0.74 mL). After 30 min the stirred mixture was filtered, and the filter cake washed thoroughly with $Et_2O$ (200 mL). The filtrate was evaporated to an oil which was purified by flash chromatography on silica gel (6:1 hexanes/EtOAc eluent) to provide alcohol **ii** (2.8 g, 90% yield) as a colorless oil: $R_F$ 0.26 (3:1 hexanes/EtOAc); $[\alpha]_D^{23}$ –38 (*c* 1.0, $CH_2Cl_2$); FTIR (film) 3450 cm$^{-1}$; $^1$H NMR (500 MHz, benzene-$d_6$) δ 8.38 (dd, *J* = 1.5, 8.8 Hz, 1H), 7.46 (d, *J* = 7.0 Hz, 2H), 7.22 (m, 3H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.68 (d, *J* = 1.5 Hz, 1H), 5.84 (m, 1H), 5.25 (dd, *J* = 1.5, 17.6 Hz, 1H), 5.03 (dd, *J* = 1.5, 10.3 Hz, 1H), 4.18 (s, 1H), 4.17 (s, 1H), 5.33 (m, 1H), 2.90-2.80 (comp m, 2H), 2.56 (m, 1H), 2.50-2.47 (comp m, 2H), 2.25 (d, *J* = 17.1 Hz, 1H), 1.84-1.20 (comp m, 8H), 1.04 (s, 3H), 0.96 (t, *J* = 7.8 Hz, 9H), 0.62 (q, *J* = 7.8 Hz, 6H), 0.26 (s, 3H), 0.26 (s, 3H); $^{13}$C NMR (100 MHz, benzene-$d_6$) δ 157.0, 142.1, 139.1, 137.7, 134.1, 131.5, 129.2, 129.1, 128.5, 128.1, 127.9, 116.6, 114.7, 114.1, 112.1, 78.0, 68.5, 39.4, 38.9, 38.1, 38.9, 31.3, 31.1, 28.1, 28.0, 21.6, 19.8, 7.3, 6.0, -2.5, -2.6; HRMS (CI) *m/z* calcd for $[C_{36}H_{52}O_3Si_2+H]^+$: 589.3533, found 589.3526.

**Ether (–)-7.** A solution of alcohol **ii** (2.3 g, 3.9 mmol) in $CH_2Cl_2$ (39 mL) was treated with $EtN(i\text{-}Pr)_2$ (1.7 mL, 9.8 mmol) and BOMCl (0.95 mL, 7.8 mmol) and stirred at 25 °C for 46 h. The reaction mixture was diluted with $H_2O$ (40 mL) and extracted with $CH_2Cl_2$ (2 x 30 mL). The combined organic layers were washed with $H_2O$ (30 mL), and brine (30 mL), dried over $Na_2SO_4$ and evaporated to an oil which was purified by flash chromatography on silica gel (10:1

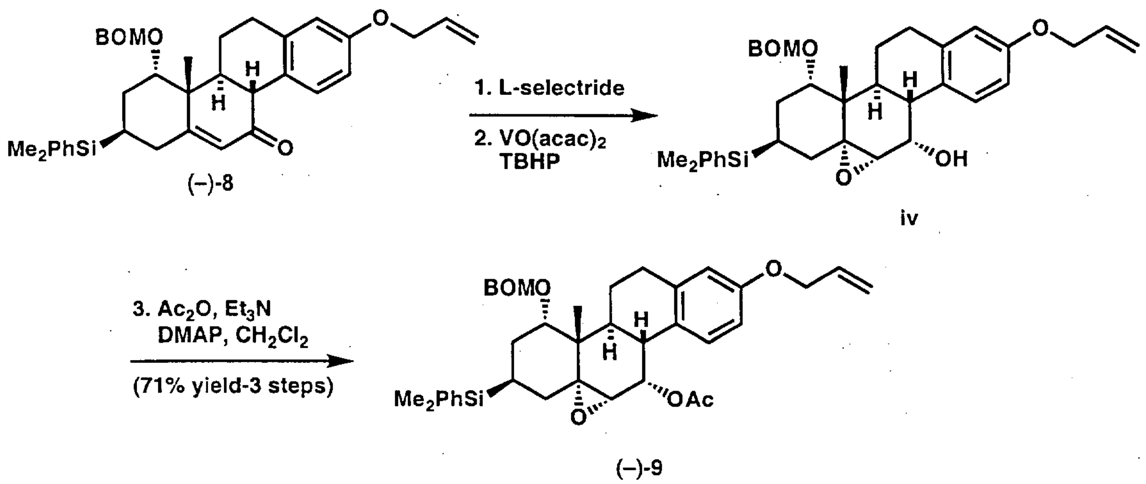
hexanes/EtOAc eluent) to provide ether **(–)-7** (2.6 g, 92% yield) as a clear colorless oil: $R_F$ 0.44 (6:1 hexanes/EtOAc); $[\alpha]_D^{24}$ –43 (*c* 1.0, $CH_2Cl_2$); FTIR (neat) 2952, 2930 $cm^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) δ 8.56 (d, *J* = 8.8 Hz, 1H), 7.50 (m, 2H), 7.32-7.10 (m, 8H), 6.90 (dd, *J* = 2.0, 8.8 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 5.83 (m, 1H), 5.24 (d, *J* = 17.1 Hz, 1H), 5.02 (d, *J* = 10.3 Hz, 1H), 4.67 (d, *J* = 6.8 Hz, 1H), 4.56 (d, *J* = 6.8 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.50 (d, *J* = 12.2 Hz, 1H), 4.17 (d, *J* = 1.5 Hz, 1H), 4.16 (d, *J* = 1.5 Hz, 1H), 3.44 (dd, *J* = 3.9, 11.2 Hz, 1H), 2.94 (ddd, *J* = 5.4, 16.6, 28.8 Hz, 1H), 2.88 (dd, *J* = 3.9, 16.6 Hz, 1H), 2.77 (bd, *J* = 9.3 Hz, 2H), 2.56 (dd, *J* = 4.9, 17.6 Hz, 1H), 2.13 (d, *J* = 17.6 Hz, 1H), 2.01 (d, *J* = 13.2 Hz, 1H), 1.92-1.84 (comp m, 2H), 1.74 (ddd, *J* = 5.4, 12.2, 24.4 Hz, 1H), 1.46-1.22 (comp m, 3H), 1.11 (s, 3H), 0.97 (t, *J* = 7.8 Hz, 9H), 0.64 (q, *J* = 7.8 Hz, 6H), 0.29 (s, 3H), 0.29 (s, 3H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) δ 157.0, 141.3, 139.4, 138.8, 137.8, 134.3, 134.2, 134.2, 131.7, 129.2, 128.5, 128.5, 128.1, 127.6, 116.6, 114.1, 114.0, 112.3, 94.2, 84.4, 69.6, 68.5, 40.7, 39.3, 36.7, 36.1, 31.6, 28.3, 27.6, 27.4, 21.6, 21.1, 7.2, 6.0, -2.3, -2.4; HRMS (FAB) *m/z* calcd for $[C_{44}H_{60}O_4Si_2+K]^+$: 747.3667, found 747.3645.



**Ketone iii.** A solution of enol ether **(–)-7** (2.62 g, 3.70 mmol) in $CH_2Cl_2$–MeOH (1:1, 74 mL) was treated with *p*-toluenesulfonic acid (422 mg, 2.22 mmol) and stirred for 5 min at 25 °C. The solution was diluted with $CH_2Cl_2$ (150 mL), followed by half-saturated aq $NaHCO_3$ (100 mL) and stirred for 10 min. The layers were separated and the aq layer was further extracted with $CH_2Cl_2$ (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to an oil which was purified by flash chromatography on silica gel (6:1 hexanes/EtOAc eluent) to provide ketone **iii** (1.96 g, 89% yield) as a clear colorless oil: $R_F$ 0.17 (6:1 hexanes/EtOAc); $[\alpha]_D^{25}$ –79 (*c* 1.0, $CH_2Cl_2$); FTIR (film) 1716 $cm^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) δ 7.59 (d, *J* = 8.8 Hz, 1H), 7.45 (m, 2H), 7.24-7.15 (comp m, 7H), 7.09 (app.t, *J* = 6.8 Hz, 1H), 6.95 (d, *J* = 8.8 Hz, 1H), 6.73 (s, 1H), 5.88 (m, 1H), 5.29 (d, *J* = 17.6 Hz, 1H), 5.05 (d, *J* = 10.7 Hz, 1H), 4.43-4.23 (comp m, 6H), 3.46 (d, *J* = 13.7 Hz, 1H), 3.42 (s, 1H), 3.11 (dd, *J* = 14.2, 17.6 Hz, 1H), 2.60 (app.t, *J* = 12.7 Hz, 1H), 2.50 (s, 1H), 2.48 (s, 1H), 1.99 (dd, *J* = 2.9, 17.6 Hz, 1H), 1.75 (dd, *J* = 2.0, 13.7 Hz, 1H), 1.58-1.48 (comp m, 3H), 1.35 (dd, *J* = 2.0, 12.7 Hz, 1H), 1.27 (d, *J* = 13.2 Hz, 1H), 1.21 (m, 2H), 0.61 (s, 3H), 0.22 (s, 3H), 0.21 (s, 3H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) δ 208.8, 157.4, 139.0, 138.5, 137.9, 134.2, 133.9, 129.3, 128.5, 128.1, 127.7, 127.6, 124.7, 116.6, 114.4, 112.5, 93.8, 77.8, 69.7, 68.6, 47.2, 43.5, 38.6, 37.2, 36.0, 31.4, 28.0, 27.1, 23.6, 19.7, 13.1, -4.8, -5.1; HRMS (FAB) *m/z* calcd for $[C_{38}H_{46}O_4Si+Na]^+$: 617.3141, found 617.3169.

**Enone (–)-8.** A solution of LDA in THF was prepared by dropwise addition of 1.58 M *n*-BuLi solution in hexanes (6.66 mL, 10.5 mmol) to diisopropylamine (1.63 mL, 11.6 mmol) in THF (39.0 mL) at 0 °C followed by srirring for 30 min. Upon cooling the solution to -78 °C, TMSCl (2.67 mL, 21.0 mmol) was introduced followed after 5 min by the addition of a solution of ketone **iii** (1.25 g, 2.10 mmol) in THF (7.0 mL) via cannula over 20 min. After stirring for 20 min, the reaction mixture was quenched at -78 °C by the addition of $Et_3N$ (7 mL) followed by saturated aq $NaHCO_3$ (20 mL). The mixture was allowed to thaw at 25 °C, diluted with $H_2O$ (50 mL) and extracted with $Et_2O$ (3 x 60 mL). The combined organic layers were washed with $H_2O$ (50 mL), and brine (50 mL), dried over $K_2CO_3$, and evaporated to give an oil which was used without further purification.

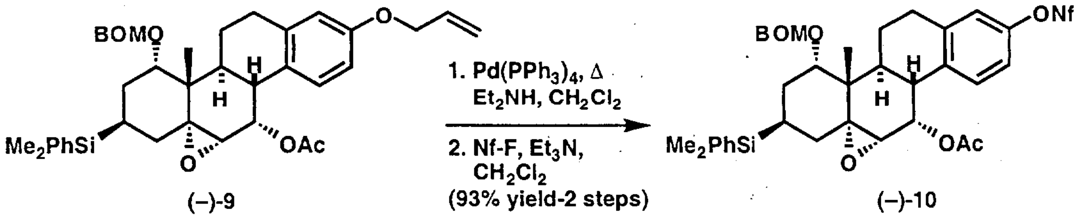
The crude oil prepared above was dissolved in DMSO (20 mL) and treated with 2,6-di-*t*-butyl-4-methyl pyridine (622 mg, 3.03 mmol) and $Pd(OAc)_2$ (45 mg, 0.20 mmol) under an atmosphere of $O_2$. The dark suspension was stirred at 25 °C for 12 h, diluted with hexanes–EtOAc (6:1, 10 mL), and purified directly by flash chromatography on silica gel (6:1 hexanes/EtOAc eluent) to provide enone **(–)-8** (856 mg, 72% yield) as a white solid: mp 127 °C (EtOAc/hexanes); $R_F$ 0.13 (6:1 hexanes/EtOAc); $[\alpha]_D^{24}$ –218 (*c* 1.00, $CH_2Cl_2$); FTIR (film) 1678 $cm^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) δ 7.92 (d8.8, 1H), 7.39 (m, 2H), 7.23-7.15 (comp m, 7H), 7.09 (app.t, *J* = 7.3 Hz, 1H), 6.92 (dd, *J* = 2.4, 8.3 Hz, 1H), 6.73 (d, *J* = 2.9 Hz, 1H), 6.00 (s, 1H), 5.88 (m, 1H), 5.29 (dd, *J* = 2.0, 17.1 Hz, 1H), 5.05 (dd, *J* = 1.5, 10.7 Hz, 1H), 4.49 (d, *J* = 7.3 Hz, 1H), 4.38 (d, *J* = 6.8 Hz, 1H), 4.35 (d, *J* = 12.2 Hz, 1H), 4.31 (d, *J* = 12.7 Hz, 1H), 4.24 (s, 1H), 4.23 (s, 1H), 3.55 (bs, 1H), 3.49 (d, *J* = 13.7 Hz, 1H), 2.77 (ddd, *J* = 2.0, 13.2, 14.2 Hz, 1H), 2.56-2.45 (comp m, 2H), 2.04 (s, 1H), 2.03 (dd, *J* = 14.6, 19.5 Hz, 1H), 1.79 (d, *J* = 14.2 Hz, 1H), 1.60-1.51 (comp m, 2H), 1.39 (dd, *J* = 12.7, 26.9 Hz, 1H), 1.07 (ddd, *J* = 4.9, 12.7, 24.9 Hz, 1H), 0.62 (s, 3H), 0.16 (s, 3H), 0.15 (s, 3H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) δ 196.1, 163.8, 157.3, 138.8, 138.4, 137.1, 134.2, 134.2, 134.1, 129.5, 128.6, 128.2, 127.6, 126.6, 124.6, 116.6, 114.6, 112.4, 93.3, 77.9, 69.8, 68.6, 46.4, 44.5, 40.5, 32.6, 30.9, 26.6, 22.5, 18.9, 15.6, -5.1, -5.4; HRMS (FAB) *m/z* calcd for $[C_{38}H_{44}O_4Si+Na]^+$: 615.2906, found 615.2922.



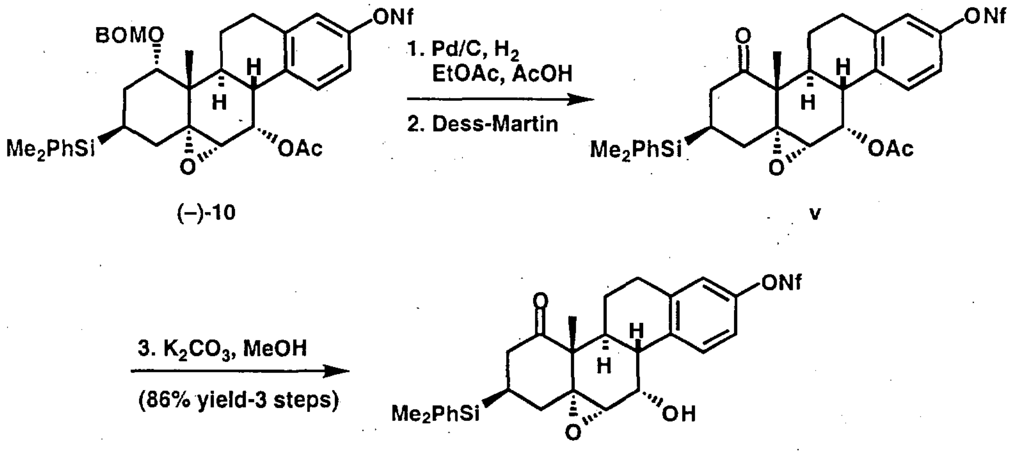
**Epoxy alcohol iv.** To a solution of enone **(–)-8** (750 mg, 1.27 mmol) in THF (15.8 mL) was added L-selectride (1.0 M solution in THF, 1.9 mL, 1.9 mmol) in a dropwise fashion over 5 min at -78 °C. The resulting solution was stirred for 20 min, quenched by addition of saturated aq $NH_4Cl$ (25 mL), and allowed to thaw at ambient temperature. The colorless mixture was extracted with $Et_2O$ (3 x 50 mL), and the combined organic extracts were dried over $MgSO_4$ and evaporated to an oil which was used without further purification.

A solution of the colorless oil obtained above in $CH_2Cl_2$ (12.7 mL) was cooled to 0 °C and treated with *t*-butylhydroperoxide (5.0-6.0 M solution in decane, 0.480 mL, 2.4 mmol) followed by $VO(acac)_2$ (95 mg, 0.37 mmol). The resulting dark red solution was stirred at 0 °C for 20 h, and purified directly by flash chromatography on silica gel (3:1 hexanes/EtOAc eluent) to provide epoxy-alcohol **iv** (564 mg, 73% yield-2 steps) as a slightly yellow oil: $R_F$ 0.24 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$ –94 (*c* 1.0, $CH_2Cl_2$); FTIR (film) 3552, 1502 $cm^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) δ 7.44 (d, *J* = 7.3 Hz, 2H), 7.30 (d, *J* = 7.3 Hz, 2H), 7.26-7.07 (comp m, 7H), 6.90 (dd, *J* = 2.5, 8.3 Hz, 1H), 6.68 (d, *J* = 2.4 Hz, 1H), 5.88 (m, 1H), 5.29 (dd, *J* = 1.5, 17.1 Hz, 1H), 5.05 (dd, *J* = 1.5, 10.7 Hz, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.60 (d, *J* = 7.3 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.52 (d, *J* = 12.7 Hz, 1H), 4.25 (m, 1H), 4.22 (s, 1H), 4.21 (s, 1H), 3.62 (s, 1H), 2.85 (d, *J* = 5.4 Hz, 1H), 2.72 (td, *J* = 3.9, 13.7 Hz, 1H), 2.58 (s, 1H), 2.57-2.50 (comp m, 2H), 2.12 (d, *J* = 10.3 Hz, 1H), 1.97 (comp m, 2H), 1.79 (app.t, *J* = 13.7 Hz, 1H), 1.65 (d, *J* = 11.7 Hz, 1H), 1.47 (app.t, *J* = 13.2 Hz, 1H), 0.98 (d, *J* = 10.3 Hz, 1H), 0.95 (m, 1H), 0.56 (s, 3H), 0.20 (s, 3H), 0.20 (s, 3H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) δ 156.8, 139.5, 138.8, 137.5, 134.3, 129.6, 129.4, 128.8, 128.5, 128.1, 127.6, 116.6, 114.5, 113.3, 93.8, 77.7, 69.9, 68.6, 66.9, 65.0, 60.6, 40.7, 40.4, 31.3, 31.2, 30.9, 26.7, 21.8, 16.1, 16.0, -5.0, -5.1; HRMS (FAB) *m/z* calcd for $[C_{38}H_{46}O_5Si+Na]^+$: 633.3012, found 633.2986.

**Acetate (–)-9.** A solution of epoxy-alcohol **iv** (310 mg, 0.51 mmol) in $CH_2Cl_2$ (5.1 mL) was treated sequentially with $Et_3N$ (0.711 mL, 5.1 mmol), $Ac_2O$ (0.260 mL, 2.54 mmol), and DMAP (62 mg, 0.51 mmol) at 25 °C. After stirring for 3 h, the crude solution was purified directly by flash chromatography on silica gel (3:1 hexanes/EtOAc eluent) to provide epoxyacetate **(–)-9** (324 mg, 97% yield) as a white foam: $R_F$ 0.40 (3:1 hexanes/EtOAc); $[\alpha]_D^{26}$ –90.9 (*c* 1.00, $CH_2Cl_2$); FTIR (film) 1732 $cm^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) δ 7.44 (d, *J* = 7.3 Hz, 2H), 7.27-7.06 (comp m, 9H), 6.77 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.64 (d, *J* = 2.5 Hz, 1H), 5.85 (m, 1H), 5.66 (app.t, *J* = 4.9 Hz, 1H), 5.26 (dd, *J* = 2.0, 17.6 Hz, 1H), 5.04 (dd, *J* = 1.5, 10.3 Hz, 1H), 4.70 (d, *J* = 6.8 Hz, 1H), 4.55 (d, *J* = 6.8 Hz, 1H), 4.50 (d, *J* = 12.7 Hz, 1H), 4.43 (d, *J* = 12.7 Hz, 1H), 4.17 (d, *J* = 1.5 Hz, 1H), 4.16 (d, *J* = 1.5 Hz, 1H), 3.62 (s, 1H), 3.15 (d, *J* = 4.4 Hz, 1H), 2.91 (app.t, *J* = 12.7 Hz, 1H), 2.76 (comp m, 2H), 2.47 (d, *J* = 15.6 Hz, 1H), 1.97 (m, 1H), 1.96 (d, *J* = 14.2 Hz, 1H), 1.78 (app.t, *J* = 13.7 Hz, 1H), 1.64 (d, *J* = 11.2 Hz, 1H), 1.55 (s, 3H), 1.47 (app.t, *J* = 15.1 Hz, 1H), 0.97-0.86 (comp m, 2H), 0.55 (s, 3H), 0.19 (s, 6H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) δ 170.5, 156.8, 139.3, 138.9, 137.5, 134.2, 134.1, 129.4, 128.5, 128.5, 128.5, 128.1, 127.5, 127.5, 116.7, 114.6, 113.2, 93.5, 77.6, 69.8, 68.6, 67.9, 64.5, 57.0, 40.5, 37.9, 32.0, 31.2, 31.0, 26.6, 21.7, 20.6, 16.1, 15.7, -5.0, -5.1; HRMS (FAB) *m/z* calcd for $[C_{40}H_{48}O_6Si+Na]^+$: 675.3118, found 675.3089.



**Nonaflate (–)-10.** A solution of epoxy acetate **(–)-9** (540 mg, 0.83 mmol) in $CH_2Cl_2$ (16.5 mL) was treated with diethylamine (0.790 mL, 8.28 mmol) and $Pd(PPh_3)_4$ (48 mg, 0.041 mmol) and heated to reflux for 3 h. After cooling to ambient temperature, the reaction mixture was evaporated, azeotroped from benzene (3 x 15 mL), and used without further purification.
The residue obtained above was dissolved in $CH_2Cl_2$ (16.5 mL) and treated with $Et_3N$ (2.30 mL, 16.6 mmol) and nonafluorobutanesulfonyl fluoride (2.97 mL, 16.6 mmol) and stirred at 25 °C for 18 h. The reaction mixture was cooled to 0 °C, diluted with hexanes–EtOAc (6:1, 5 mL) and treated with $SiO_2$ (5 g). After stirring for 10 min, the slurry was purified directly by flash chromatography on silica gel (6:1 hexanes/EtOAc eluent) to provide nonaflate **(–)-10** (690 mg, 93% yield) as a white solid: $R_F$ 0.46 (3:1 hexanes/EtOAc); $[\alpha]_D^{26}$ –76.0 (*c* 1.00, $CH_2Cl_2$); FTIR (film) 1737 $cm^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) δ 7.43 (dd, *J* = 2.0, 7.8 Hz, 2H), 7.24-7.08 (comp m, 8H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 6.75 (s, 1H), 5.48 (app.t, *J* = 5.4 Hz, 1H), 4.67 (d, *J* = 7.3 Hz, 1H), 4.51 (d, *J* = 7.3 Hz, 1H), 4.46 (d, *J* = 12.2 Hz, 1H), 4.41 (d, *J* = 12.2 Hz, 1H), 3.54 (s, 1H), 3.07 (d, *J* = 4.4 Hz, 1H), 2.78 (td, *J* = 2.0, 12.2 Hz, 1H), 2.55 (dd, *J* = 5.9, 12.2 Hz, 1H), 2.44 (td, *J* = 3.9, 16.6 Hz, 1H), 2.16 (d, *J* = 16.6 Hz, 1H), 1.96-1.90 (comp m, 2H), 1.77 (app.t, *J* = 13.7 Hz, 1H), 1.51-1.42 (comp m, 2H), 1.48 (s, 3H), 0.94 (d, *J* = 12.7 Hz, 1H), 0.62 (ddd, *J* = 4.4, 12.7, 25.9 Hz, 1H), 0.48 (s, 3H), 0.20 (s, 6H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) δ 170.3, 147.7, 140.9, 138.7, 137.4, 136.7, 134.2, 129.4, 129.4, 128.5, 128.1, 127.6, 127.5, 121.6, 118.5, 93.5, 77.5, 69.9, 67.5, 64.5, 56.7, 40.3, 38.1, 31.5, 31.1, 30.3, 26.6, 21.0, 20.2, 16.1, 15.5, -5.1, -5.2; $^{19}F$ NMR (400 MHz, benzene-$d_6$) δ -81.60 (t, 9.2), -109.90 (t, 12.2), -121.30 (m), -126.3 (t, 13.7); HRMS (FAB) *m/z* calcd for $[C_{41}H_{43}SSiO_8F_9+Na]^+$: 917.2202, found 917.2173.



(–)-10

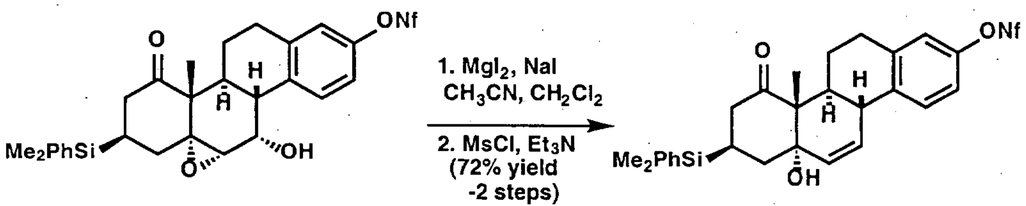
v

(–)-11

**Ketone v.** A mixture of ether **(–)-10** (680 mg, 0.76 mmol) and 10% Pd/C (340 mg) in EtOAc–AcOH (10:1, 8.4 mL) was stirred under an atmosphere of $H_2$ while monitoring by $^1H$ NMR analysis of crude aliquots periodically removed from the reaction mixture. Upon completion (after 7 h), the reaction mixture was filtered through a pad of $SiO_2$, and the filtrate evaporated and used directly in the next step.
A solution of the crude alcohol obtained above in $CH_2Cl_2$ (15.2 mL) was treated with Dess-Martin periodinane (1.93 g, 4.56 mmol) at 25 °C and stirred for 2 h. The crude reaction mixture was purified directly by silica gel chromatography (6:1→3:1 hexanes/EtOAc eluent) to provide

ketone **v** (560 mg, 95% yield-2 steps) as a clear colorless oil: $R_F$ 0.35 (3:1 hexanes/EtOAc); $[\alpha]_D^{23}$ –17.1 (*c* 1.00, $CH_2Cl_2$); FTIR (film) 1738, 1711 cm$^{-1}$; $^1$H NMR (500 MHz, benzene-$d_6$) δ 7.31 (d, *J* = 5.4 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.21 (m, 3H), 6.83 (d, *J* = 8.8 Hz, 1H), 6.78 (dd, *J* = 2.4, 8.3 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 5.34 (app.t, *J* = 4.9 Hz, 1H), 3.24 (d, *J* = 4.9 Hz, 1H), 2.73 (td, *J* = 2.0, 12.2 Hz, 1H), 2.62 (td, *J* = 3.4, 16.6 Hz, 1H), 2.36 (d, *J* = 14.2 Hz, 1H), 2.32 (app.t, *J* = 5.9 Hz, 1H), 2.25 (dd, *J* = 4.4, 13.7 Hz, 1H), 2.18 (bd, *J* = 16.6 Hz, 1H), 2.10 (bd, *J* = 10.8 Hz, 1H), 1.95 (app.t, *J* = 13.7 Hz, 1H), 1.72 (app.t, *J* = 4.4, 14.2 Hz, 1H), 1.46 (s, 3H), 0.86 (dd, *J* = 3.9, 13.2 Hz, 1H), 0.67 (s, 3H), 0.62 (ddd, *J* = 3.9, 12.7, 24.9 Hz, 1H), 0.07 (s, 6H); $^{13}$C NMR (100 MHz, benzene-$d_6$) δ 209.9, 170.3, 147.8, 141.7, 136.1, 135.9, 134.2, 129.8, 128.9, 128.5, 121.8, 118.5, 69.5, 67.0, 60.0, 52.2, 38.4, 38.0, 31.7, 30.3, 29.9, 24.1, 22.9, 20.0, 15.0, -5.2, -5.6; $^{19}$F NMR (500 MHz, benzene-$d_6$) δ -81.61 (t, 9.2), -110.11 (t, 15.3), -121.51 (s), -126.60 (s); HRMS (FAB) *m/z* calcd for $[C_{33}H_{33}O_7SiF_9S+Na]^+$: 795.1470, found 795.1466.

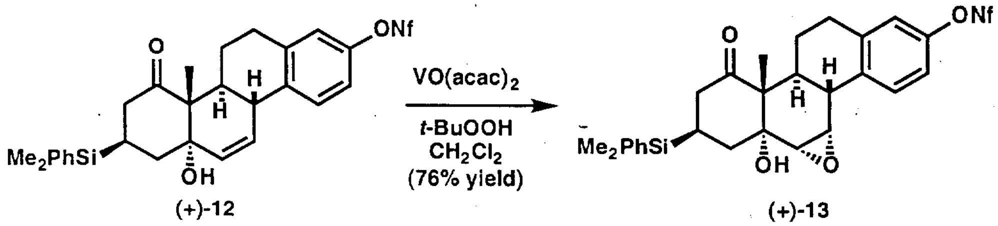
**Alcohol (–)-11.** To a solution of acetate **v** (560 mg, 0.73 mmol) in $CH_2Cl_2$ (2.5 mL) was added a mixture of MeOH–$H_2O$ (10:1, 16.0 mL) followed by $K_2CO_3$ (1.0 g, 7.3 mmol) at 25 °C, and the resulting mixture was stirred for 2.5 h. The reaction mixture was diluted with $CH_2Cl_2$ (80 mL) and $H_2O$ (25 mL), and extracted with $CH_2Cl_2$ (3 x 60 mL). The combined organic layers were washed with brine (25 mL), dried over $Na_2SO_4$ and purified by flash chromatography on silica gel (3:1 hexanes/EtOAc eluent) to provide alcohol **(–)-11** (480 mg, 91% yield) as a white solid: mp 167-8 °C (EtOAc/heptane); $R_F$ 0.10 (3:1 hexanes/EtOAc); $[\alpha]_D^{24}$ –8.6 (*c* 1.0, $CH_2Cl_2$); FTIR (film) 3439, 1709 cm$^{-1}$; $^1$H NMR (500 MHz, benzene-$d_6$) δ 7.32-7.21 (comp m, 5H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.93 (dd, *J* = 2.0, 8.3 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 3.95 (app.dt, *J* = 5.4, 10.7 Hz, 1H), 2.84 (d, *J* = 4.9 Hz, 1H), 2.61 (app.t, *J* = 12.7 Hz, 1H), 2.36-2.22 (comp m, 4H), 2.10 (dd, *J* = 3.9 Hz, 12.7H,), 2.04 (bd, *J* = 12.2 Hz, 1H), 1.93 (app.t, *J* = 13.7 Hz, 1H), 1.71 (app.tt, *J* = 4.4, 14.2 Hz, 1H), 1.63 (d, *J* = 10.7 Hz, 1H), 0.88 (m, 2H), 0.66 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); $^{13}$C NMR (100 MHz, benzene-$d_6$) δ 210.5, 147.7, 141.7, 136.6, 136.2, 134.2, 130.3, 129.8, 121.4, 118.4, 71.7, 64.2, 63.6, 52.5, 40.4, 38.3, 30.5, 30.5, 30.1, 24.2, 22.9, 15.2, -5.2, -5.6; $^{19}$F NMR (500 MHz, benzene-$d_6$) δ -81.69 (t, 9.2), -110.22 (t, 12.2), -121.58 (s), -126.68 (s); HRMS (CI) *m/z* calcd for $[C_{31}H_{31}O_6SSiF_9+H]^+$: 731.1545, found 731.1518.



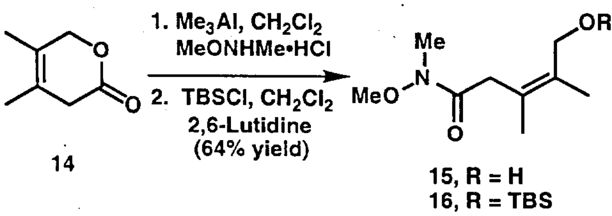
(–)-11 (+)-12

**Olefin (+)-12.** To a solution of epoxy alcohol **(–)-11** (0.100 g, 0.137 mmol) in a mixture of $CH_2Cl_2$–$CH_3CN$ (1:1, 16.2 mL) was added NaI (123 mg, 0.822 mmol) and $MgI_2$ (228 mg, 0.822 mmol) at 0 °C. The yellow solution was stirred for 10 min and filtered directly through a pad of $SiO_2$ (3:1 hexanes/EtOAc eluent). The filtrate was evaporated to a residue which was used immediately without further purification.

The crude residue was dissolved in $CH_2Cl_2$ (1.4 mL), cooled to -66 °C, and treated sequentially with methanesulfonyl chloride (0.078 mL, 0.69 mmol) and, after 5 min, a solution of $Et_3N$ (0.115 mL, 0.822 mmol) in $CH_2Cl_2$ (0.55 mL) slowly over 10 min. After stirring for 1 h, the reaction mixture was allowed to warm to 25 °C over 30 min and quenched by addition of $Et_3N$ (0.020 mL). The reaction mixture was evaporated onto $SiO_2$ and chromatographed on silica gel (6:1 hexanes/EtOAc eluent) to provide olefin **(+)-12** (70 mg, 72% yield-2 steps) as a slightly yellow foam: $R_F$ 0.37 (3:1 hexanes/EtOAc); $[\alpha]_D^{25}$ +69.6 (*c* 1.00, $CH_2Cl_2$); FTIR (film) 3510, 1709 $cm^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) δ 7.36-7.20 (comp m, 5H), 6.86 (d, *J* = 8.3 Hz, 1H), 6.77 (d, *J* = 7.3 Hz, 1H), 6.77 (s, 1H), 11.5 (d, *J* = 10.3 Hz, 1H), 5.36 (dd, *J* = 2.5, 9.8 Hz, 1H), 2.66 (m, 1H), 2.54 (m, 1H), 2.50 (d, *J* = 11.2 Hz, 1H), 2.38 (m, 1H), 2.34 (d, *J* = 14.2 Hz, 1H), 2.16 (dd, *J* = 5.9, 14.2 Hz, 1H), 2.05-1.97 (comp m, 2H), 1.83 (app.t, *J* = 13.7 Hz, 1H), 1.37 (dd, *J* = 4.9, 13.7 Hz, 1H), 1.06 (comp m, 2H), 0.70 (s, 3H), 0.13 (s, 6H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) δ 211.5, 148.3, 140.5, 139.9, 136.8, 134.2, 132.8, 129.5, 128.7, 125.7, 121.7, 118.2, 76.3, 54.0, 39.5, 37.5, 36.1, 32.6, 29.7, 23.9, 19.7, 14.7, -5.1, -5.4; $^{19}F$ NMR (500 MHz, benzene-$d_6$) δ -81.64 (t, 9.2), -110.06 (t, 13.7), -121.54 (s), -126.60 (s); HRMS (FAB) *m/z* calcd for $[C_{31}H_{31}O_5SSiF_9+Na]^+$: 737.1415, found 737.1406.

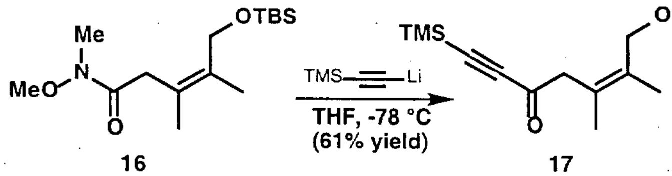


**Epoxy-alcohol (+)-13.** A solution of olefin **(+)-12** (155 mg, 0.217 mmol) in $CH_2Cl_2$ (2.2 mL) was cooled to 0 °C and treated with *t*-butylhydroperoxide (5.0-6.0 M solution in decane, 0.065 mL, 0.326 mmol) followed by $VO(acac)_2$ (6.0 mg, 0.022 mmol). The resulting dark red solution was stirred at 0 °C for 44 h, and purified by evaporation onto $SiO_2$ and flash chromatography on silica gel (6:1 hexanes/EtOAc eluent) to provide epoxy-alcohol **(+)-13** (121 mg, 76% yield) as a white foam: $R_F$ 0.34 (3:1 hexanes/EtOAc); $[\alpha]_D^{24}$ +61.7 (*c* 1.00, $CH_2Cl_2$); FTIR (film) 3531, 1711, 1427 $cm^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) δ 7.36 (m, 2H), 7.22 (m, 3H), 7.04 (d, *J* = 8.8 Hz, 1H), 6.89 (dd, *J* = 2.4, 8.3 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 3.09 (app.t, *J* = 3.4 Hz, 1H), 2.79 (s, 1H), 2.55 (m, 1H), 2.51 (d, *J* = 3.9 Hz, 1H), 2.45 (m, 1H), 2.29 (d, *J* = 13.7 Hz, 1H), 2.28 (m, 1H), 2.13 (comp m, 3H), 1.71 (comp m, 2H), 1.51 (dd, *J* = 4.9, 13.7 Hz, 1H), 0.93 (m, 1H), 0.49 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) δ 210.5, 148.6, 140.5, 138.8, 136.7, 134.2, 129.6, 128.5, 126.5, 121.5, 118.3, 74.6, 57.5, 54.5, 54.4, 38.6, 37.6, 33.4, 31.4, 29.2, 24.0, 19.6, 14.3, -5.1, -5.5; $^{19}F$ NMR (400 MHz, benzene-$d_6$) δ -81.62 (t, 9.2), -109.89 (t, 12.2), -121.31 (s), -126.36 (s); HRMS (FAB) *m/z* calcd for $[C_{31}H_{31}O_6SSiF_9+K]^+$: 769.1104, found 769.1072.

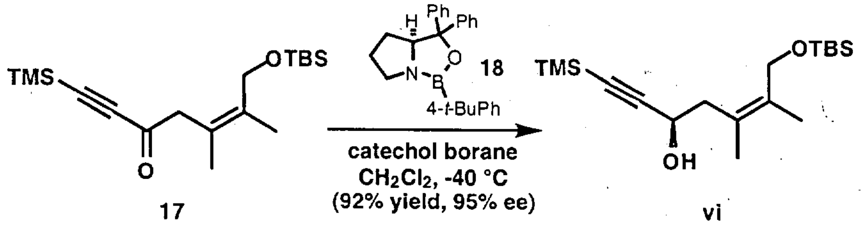


**Amide 16.** A flame-dried flask (3-neck 2L) fitted with 2 addition funnels and a $N_2$ inlet tube was charged with *N,O*-dimethylhydroxyamine•HCl (29.1 g, 298 mmol) in $CH_2Cl_2$ (600 mL),

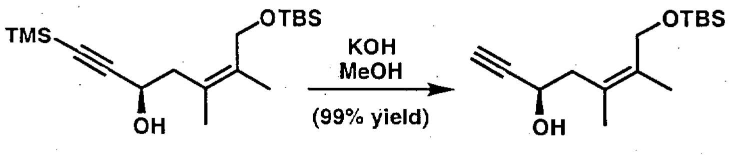
and the reaction mixture stirred at -5 °C. A solution of $Me_3Al$ (28.6 mL, 298 mmol) in toluene (150 mL) was added in a dropwise fashion over 30 min to the *N,O*-dimethylhydroxyamine•HCl solution. Evolution of thick smoke was followed by stirring the solution for 1 h. To this solution was added the lactone **14** (15.0 g, 119 mmol) as a solution in $CH_2Cl_2$ (40 mL) over 10 min. After stirring for 30 min, the reaction mixture was quenched by slowly pouring into saturated aq $NaHCO_3$ (600 mL) and extracted with $CH_2Cl_2$ (3 x 200 mL). The combined organic layers were washed with brine (500 mL), dried over $Na_2SO_4$, and concentrated in vacuo. The crude oil (containing **15**) was dissolved in $CH_2Cl_2$ (200 mL), cooled to 0 °C and treated with 2,6-lutidine (15.2 mL, 131 mmol) followed by TBSOTf (27.3 mL, 119 mmol). The reaction mixture was stirred at 0 °C for 10 min, then washed sequentially with saturated aq $NH_4Cl$ (300 mL), saturated aq $NaHCO_3$ (300 mL) and brine (300 mL). The organic layer was dried over $Na_2SO_4$, filtered and concentrated *in vacuo* to afford the desired amide **16** (22.9 g, 64% yield-2 steps) as a colorless oil: FTIR (film) 1674 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 4.17 (s, 2H), 3.70 (s, 3H), 3.30 (s, 2H), 3.20 (s, 3H), 1.77 (s, 3H), 1.75 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 172.8, 131.8, 124.3, 63.7, 61.1, 37.1, 32.2, 25.9, 25.6, 19.4, 18.3, 16.1, -5.3; HRMS (CI) *m/z* calcd for $[C_{15}H_{31}O_3NSi+H]^+$: 302.2151, found 302.2164.



**Ketone 17.** To a stirred solution of trimethylsilylacetylene (0.205 mL, 1.45 mmol) in THF (4.5 mL) at -78 °C was added *n*-BuLi solution in hexane (1.46 M, 0.904 mL, 1.32 mmol) in a dropwise fashion. The mixture was warmed to 0 °C, stirred for 1 h, and cooled to -20 °C. The resulting alkynyl lithium reagent was added dropwise to a solution of amide **16** (200 mg, 0.66 mmol) in THF (9 mL) at -20 °C. Stirring continued as the temperature was gradually raised to -10 °C over 1 h. The reaction mixture was cooled to -78 °C, quenched by slowly pouring into 0.25 N HCl aq solution (16 mL) at 0 °C, and extracted with $Et_2O$ (2 x 16 mL). The combined organic layers were washed with brine (50 mL), dried over $Na_2SO_4$, and then evaporated to an oil. The resultant oil was subjected to silica gel chromatography (40:1 hexanes/EtOAc eluent) to provide ketone **17** (138 mg, 61%) as a colorless oil: FTIR (film) 1682 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 4.16 (s, 2H), 3.37 (s, 2H), 1.78 (s, 3H), 1.76 (s, 3H), 0.92 (s, 9H), 0.25 (s, 9H), 0.09 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 185.2, 133.8, 122.6, 102.0, 98.1, 63.8, 50.5, 25.9, 19.9, 18.4, 16.3, -0.8, -5.3; HRMS (CI) *m/z* calcd for $[C_{18}H_{34}O_2Si_2+H]^+$: 339.2175, found 339.2191.

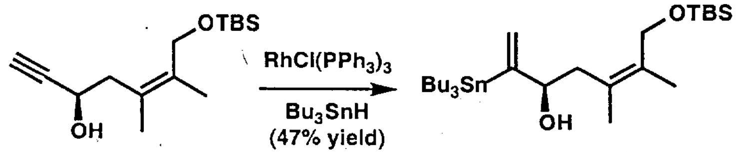


**TMS-propargyl alcohol vi.** A flame-dried flask was charged with a toluene solution of (*S*)-*B*-4-*t*-butylphenyl oxazaborolidine catalyst **18** (0.2 M, 1.48 mL, 0.30 mmol), the solvent was removed *in vacuo* and a solution of TMS-ethynyl ketone **17** (2.0 g, 5.9 mmol) in $CH_2Cl_2$ (12 mL) was added. The solution was cooled to -40 °C and treated with catecholborane (0.76 mL, 7.10 mmol) in $CH_2Cl_2$ (4.8 mL) over 30 min. After 40 h, MeOH (5 mL) was added and the solution was warmed to ambient temperature. The reaction mixture was diluted with ether (280 mL), washed with pH 13 buffer until the aq washings were colorless, washed with brine (20 mL), dried over $MgSO_4$, and concentrated to an oil which was purified by flash chromatography on silica gel (6:1 hexanes/EtOAc eluent) to provide propargyl alcohol **(+)-vi** (1.85 g, 92% yield, 95% ee) as a clear oil: $[\alpha]_D^{23}$ +82.9 (*c* 1.00, $CHCl_3$); FTIR (film) 3410 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 4.43-4.39 (m, 1H), 4.28 (d, $J$ = 11.1 Hz, 1H), 3.98 (d, $J$ = 11.1 Hz, 1H), 3.35 (d, $J$ = 5.6 Hz, 1H), 2.72 (dd, $J$ = 8.8, 13.6 Hz, 1H), 2.45 (dd, $J$ = 4.5, 13.6 Hz, 1H), 1.76 (s, 6H), 0.94 (s, 9H), 0.18 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 132.0, 128.4, 107.5, 88.2, 64.1, 60.2, 42.6, 26.0, 19.1, 18.4, 17.9, -0.2, -5.3; HRMS (CI) *m/z* calcd for $[C_{18}H_{36}O_2Si_2+NH_4]^+$: 358.2598, found 358.2598. Conversion of the alcohol to the *p*-nitrobenzoate (*p*-nitrobenzoylchloride, DMAP, $CH_2Cl_2$, 25 °C) and HPLC analysis (Whelk-O1, 0.2% *i*-PrOH in hexane, 0.25 mL/min, λ=254 nm) showed the product to be of 95% ee ($t_{fast}$ = 31.3 min, major; $t_{slow}$ = 33.6 min, minor).



(+)-vi (+)-19

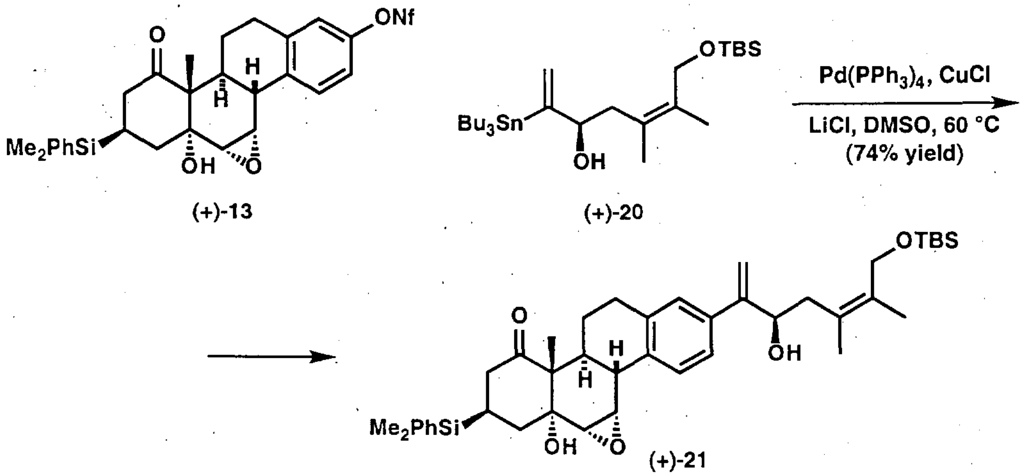
**Propargyl alcohol (+)-19.** To a solution of TMS-propargyl alcohol **(+)-vi** (5.35 g, 15.7 mmol, 95% ee) in $Et_2O$ (270 mL) at 25 °C was added a 3 M KOH–MeOH solution (135 mL) and stirred for 10 min. The reaction mixture was washed with $H_2O$ (300 mL), saturated aq $NH_4Cl$ (300 mL) and brine (300 mL), dried over $MgSO_4$ and concentrated to an oil which was purified by flash chromatography on silica gel (6:1 hexane/EtOAc) to provide propargyl alcohol **(+)-19** (4.21 g, 99% yield) as a colorless liquid: $[\alpha]_D^{23}$ +83.4 (*c* 1.0, $CHCl_3$); FTIR (film) 3402, 3313 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 4.45-4.40 (m, 1H), 4.29 (d, $J$ = 11.0 Hz, 1H), 3.96 (d, $J$ = 11.0 Hz, 1H), 3.55 (d, $J$ = 5.4 Hz, 1H), 2.78 (dd, $J$ = 9.2, 13.7 Hz, 1H), 2.44 (dd, $J$ = 4.0, 13.7 Hz, 1H), 2.44 (d, $J$ = 2.1 Hz, 1H), 1.77 (s, 6H), 0.93 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 132.1, 128.3, 85.5, 71.9, 64.0, 59.5, 42.5, 25.9, 19.0, 18.3, 17.9, -5.4; HRMS (CI) *m/z* calcd for $[C_{15}H_{28}O_2Si+NH_4]^+$: 286.2202, found 286.2215.



(+)-19 (+)-20

**Vinyl stannane (+)-20.** To a suspension of propargyl alcohol **(+)-19** (80 mg, 0.30 mmol) and $(PPh_3)_3RhCl$ (13 mg, 0.031 mmol) was added $Bu_3SnH$ (0.121 mL, 0.45 mmol) at 25

°C under $N_2$. After stirring for 20 h, the reaction mixture was subjected to silica gel chromatography (15:1 hexane/EtOAc eluent) to provide vinyl stannane **(+)-20** (78 mg, 47% yield) as a colorless oil: $[\alpha]_D^{23}$ +41.5 (*c* 0.80, $CHCl_3$); FTIR (film) 3481 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): δ 5.86 (s, $J_{SnH}$ = 67.6 Hz, 1H), 5.23 (s, $J_{SnH}$ = 32.2 Hz, 1H), 4.28 (d, *J* = 10.8 Hz, 1H), 4.24 (d, *J* = 8.5 Hz, 1H), 3.96 (d, *J* = 10.8 Hz, 1H), 3.01 (s, 1H), 2.52 (dd, *J* = 10.4, 13.4 Hz, 1H), 2.01 (d, *J* = 13.4 Hz, 1H), 1.77 (s, 6H), 1.56-1.47 (m, 6H), 1.38-1.29 (m, 6H), 0.98-0.89 (m, 6H), 0.93 (s, 9H), 0.91 (t, *J* = 7.3 Hz, 9H), 0.11 (s, 6H); $^{13}C$ NMR (400 MHz, $CDCl_3$): δ 160.0, 131.2, 130.0, 122.7, 75.3, 63.7, 43.9, 29.2, 27.4, 25.9, 19.2, 18.3, 17.8, 13.7, 10.2, -5.3; HRMS (EI) *m/z* calcd for $[C_{23}H_{47}O_2SiSn{-}C_4H_9]^+$: 503.2367, found 503.2378.

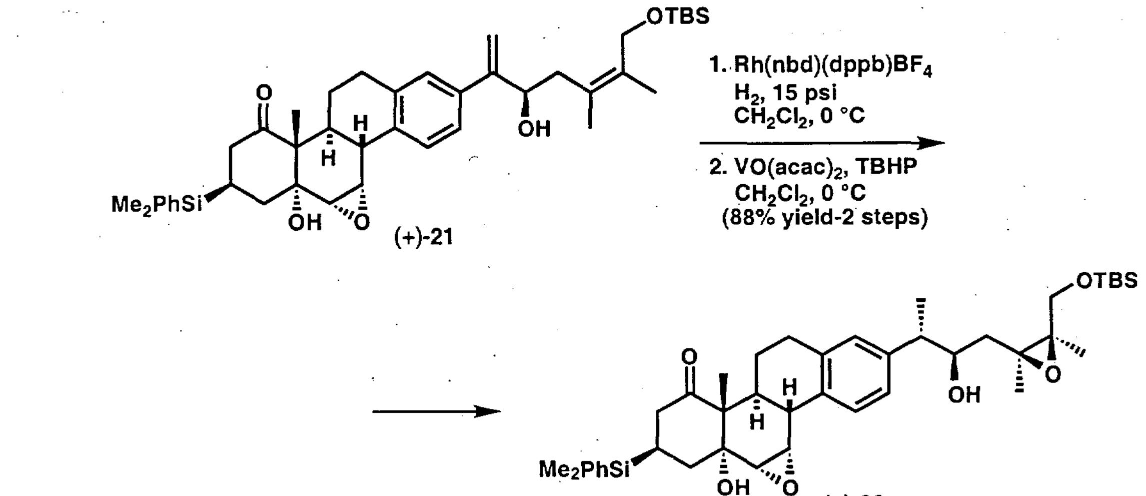


(+)-13

(+)-20

(+)-21

**Stille product (+)-21.** To a solution of nonaflate **(+)-13** (azeotroped from PhH, 14 mg, 0.020 mmol) in DMSO (0.77 mL) under Ar in a Schlenk tube (25 mL) was added LiCl (flame dried under vacuum, 24 mg, 0.58 mmol), $Pd(PPh_3)_4$ (11 mg, 0.0095 mmol) and CuCl (48 mg, 0.48 mmol), and the mixture was degassed (4 x) under high vacuum with an Ar purge. Vinyl stannane **(+)-20** (0.069 mL, 75 mg, 0.14 mmol) was added and the resulting mixture was rigorously degassed (4 x) by the freeze/pump-thaw process (-78 → 25 °C, Ar). The reaction mixture was stirred at room temperature for 1 h, then heated to 60 °C for the 45 h. Following completion of the coupling as monitored by TLC, the reaction mixture was cooled, diluted with $Et_2O$ (10 mL), and washed with a mixture of brine (12 mL) and 5% aq $NH_4OH$ (3 mL). The combined aq layers were further extracted with $Et_2O$ (2 x 7 mL), and the combined organic layers were washed with water (2 x 12 mL) then brine (2 x 12 mL), dried over $Na_2SO_4$, and concentrated to a residue which was purified by flash chromatography on silica gel (6:1→4:1 hexanes/EtOAc eluent) to provide **(+)-21** (10 mg, 74% yield) as a slightly yellow oil: $R_F$ 0.22 (3:1 hexanes/EtOAc); $[\alpha]_D^{22}$ +72.7 (*c* 1.00, $CH_2Cl_2$); FTIR (film) 3527, 1712 $cm^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) δ 7.36 (m, 3H), 7.25-7.22 (m, 5H), 5.83 (s, 1H), 5.46 (s, 1H), 4.82 (d, *J* = 9.3 Hz, 1H), 4.20 (d, *J* = 10.7 Hz, 1H), 3.75 (d, *J* = 10.7 Hz, 1H), 3.34 (bs, 2H), 2.95 (dt, *J* = 7.8, 17.6 Hz, 1H), 2.90 (s, 1H), 2.68 (comp m, 2H), 2.58 (d, *J* = 8.3 Hz, 1H), 2.55 (d, *J* = 12.2 Hz, 1H), 2.49 (d, *J* = 11.2 Hz, 1H), 2.32 (comp m, 2H), 2.14 (comp m, 2H), 1.97 (td, *J* = 2.9, 11.2 Hz, 1H), 1.73 (d, *J* = 13.7 Hz, 1H), 1.69 (s, 3H), 1.58 (s, 3H), 1.53 (d, *J* = 17.2 Hz, 1H), 1.00 (s, 9H), 0.89 (m, 1H), 0.58 (s, 3H), 0.12 (s, 6H), 0.11 (s, 3H), 0.09 (s, 3H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) δ 210.6, 152.8, 139.3, 137.6, 137.5, 136.8, 134.2, 131.3, 130.7, 129.5, 128.5, 124.9, 124.3, 112.0, 74.7, 71.0, 64.2, 57.6, 55.1, 54.5, 42.6, 39.0, 37.6, 33.4, 32.0, 29.8, 26.2, 24.9, 19.6, 19.0, 18.7, 18.2, 14.5, -5.0, -5.1, -5.4; HRMS (FAB) *m/z* calcd for $[C_{42}H_{60}O_5Si_2+Na]^+$: 723.3877, found 723.3853.

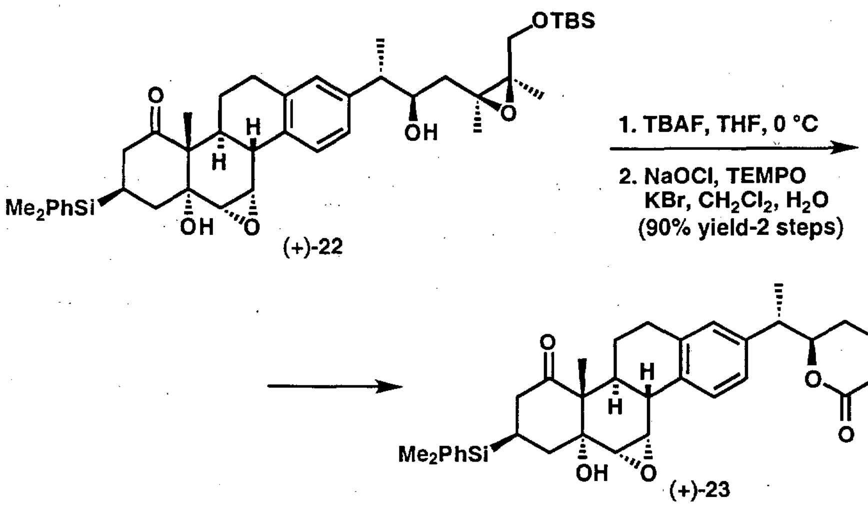


(+)-21

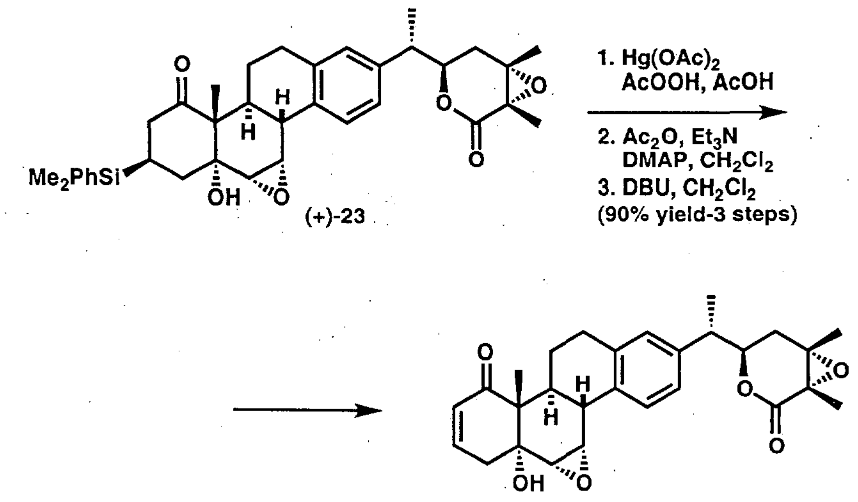
(+)-22

**Epoxy alcohol (+)-22.** A flame-dried one dram vial capped with a serum stopper was charged with $[Rh(nbd)dppb]BF_4$ (8.2 mg, 0.012 mmol) under an atmosphere of $N_2$ (glove-bag). The catalyst was transferred as a solution in $CH_2Cl_2$ (0.57 mL) to a Schlenk tube containing azeotropically dried (PhH, 4 x 1 mL) alcohol **(+)-21** (20 mg, 0.029 mmol). The resulting reaction mixture was rigorously degassed (4 x) by the freeze/pump-thaw process (-196 °C → 25 °C, Ar– and in the final thawing under an atmosphere of $H_2$) and stirred at 0 °C for 45 h under $H_2$ (balloon). Following completion of the reaction as monitored by TLC, the solution was diluted with EtOAc (2 mL) and filtered through a pad of silica gel (EtOAc eluent). The filtrate was concentrated to a residue which was used without further purification.

The above residue was dissolved in $CH_2Cl_2$ (0.30 mL), cooled to 0 °C, and treated with *t*-butylhydroperoxide (5.0-6.0 M solution in decane, 0.009 mL, 0.044 mmol) followed by $VO(acac)_2$ (0.8 mg, 0.003 mmol). The resulting dark red solution was stirred at 0 °C for 2 h, and purified directly by flash chromatography on silica gel (3:1 hexanes/EtOAc eluent) to provide a single diastereomer of epoxy-alcohol **(+)-22** (18 mg, 88% yield-2 steps) as a colorless oil: $R_F$ 0.17 (3:1 hexanes/EtOAc); $[\alpha]_D^{22}$ +55.1 (*c* 1.00, $CH_2Cl_2$); FTIR (film) 3523, 1712 cm$^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) δ 7.36 (comp m, 3H), 7.22-7.17 (comp m, 5H), 4.27 (dd, *J* = 4.4, 10.3 Hz, 1H), 3.50 (s, 2H), 3.41 (app.t, *J* = 3.4 Hz, 1H), 3.35 (s, 1H), 3.02 (m, 1H), 3.00 (s, 1H), 2.72 (m, 3H), 2.60 (d, *J* = 3.9 Hz, 1H), 2.54 (d, *J* = 11.2 Hz, 1H), 2.34 (app.t, *J* = 15.1 Hz, 1H), 2.14 (m, 2H), 2.04 (td, *J* = 3.4, 11.2 Hz, 1H), 1.74 (app.t, *J* = 13.2 Hz, 1H), 1.63 (app.t, *J* = 10.3 Hz, 1H), 1.54 (m, 2H), 1.47 (d, *J* = 7.3 Hz, 3H), 1.28 (s, 3H), 1.21 (m, 1H), 1.16 (s, 3H), 0.93 (s, 9H), 0.59 (s, 3H), 0.13 (s, 3H), 0.12 (s, 3H), 0.00 (s, 3H), -0.01 (s, 3H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) δ 210.6, 141.8, 137.2, 136.8, 136.1, 134.2, 129.5, 129.4, 128.5, 126.2, 124.6, 74.8, 73.7, 66.5, 65.3, 64.3, 57.6, 55.3, 54.5, 46.2, 38.9, 37.6, 36.8, 33.4, 32.1, 29.9, 26.1, 25.0, 20.2, 19.7, 18.5, 17.9, 16.2, 14.5, -5.0, -5.2, -5.3, -5.4; HRMS (FAB) *m/z* calcd for $[C_{42}H_{62}O_6Si_2+Na]^+$: 741.3983, found 741.4012.



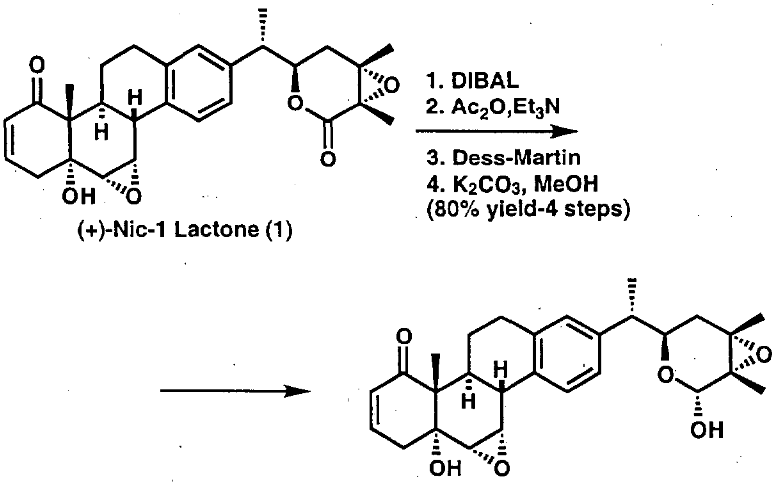
**Lactone (+)-23.** To a cooled (0 °C) solution of silyl ether **(+)-22** (8.0 mg, 0.011 mmol) in THF (0.110 mL) was added a solution of TBAF in THF (1.0 M, 0.036 mL, 0.036 mmol). After 5 min, the reaction mixture was diluted with $CH_2Cl_2$ (2 mL), evaporated onto $SiO_2$ and filtered through a pad of silica gel (1:1 hexanes/EtOAc eluent). The filtrate was evaporated, dissolved in $CH_2Cl_2$ (0.11 mL), and treated with $H_2O$ (0.002 mL), KBr (0.1 mg, 0.0008 mmol), TEMPO (0.1 mg, 0.0006 mmol), and 0.95 M aq NaOCl solution (adjusted to pH 9 by treatment with $NaHCO_3$ immediately prior to use, 0.035 mL, 0.037 mmol). After 10 min, the reaction mixture was diluted with $CH_2Cl_2$ (2 mL), evaporated onto $SiO_2$ and chromatographed on silica gel (2:1 hexanes/EtOAc eluent) to provide lactone **(+)-23** (6.0 mg, 93% yield) as a slightly yellow foam: $R_F$ 0.50 (1:1 hexanes/EtOAc); $[\alpha]_D^{25}$ +62 (*c* 0.50, $CH_2Cl_2$); FTIR (film) 3542, 1732, 1683 $cm^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) $\delta$ 7.35 (m, 3H), 7.21 (m, 3H), 7.04 (d, $J$ = 8.3 Hz, 1H), 7.00 (s, 1H), 4.50 (td, $J$ = 3.9, 7.8 Hz, 1H), 3.35 (app.t, $J$ = 3.4 Hz, 1H), 2.96 (m, 1H), 2.82 (s, 1H), 2.66 (m, 2H), 2.57 (d, $J$ = 3.9 Hz, 1H), 2.50 (m, 2H), 2.31 (app.t, $J$ = 13.7 Hz, 1H), 2.11 (m, 2H), 1.92 (td, $J$ = 3.4, 11.2 Hz, 1H), 1.71 (app.t, $J$ = 13.7 Hz, 1H), 1.50 (dd, $J$ = 4.4, 13.7 Hz, 1H), 1.41 (d, $J$ = 7.8 Hz, 2H), 1.35 (s, 3H), 1.24 (d, $J$ = 7.3 Hz, 3H), 1.14 (m, 1H), 0.68 (s, 3H), 0.56 (s, 3H), 0.11 (s, 3H), 0.11 (s, 3H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) $\delta$ 210.5, 168.9, 139.7, 137.6, 137.0, 136.8, 134.2, 129.5, 129.4, 126.1, 124.9, 77.4, 74.7, 62.4, 59.4, 57.6, 55.1, 54.4, 43.0, 39.0, 37.6, 33.4, 33.0, 32.1, 29.7, 24.9, 19.6, 17.2, 17.1, 14.4, 13.8, -5.0, -5.4; HRMS (FAB) *m/z* calcd for $[C_{36}H_{44}O_6Si+Na]^+$: 623.2805, found 623.2800.



(+)-Nic-1 Lactone (1)

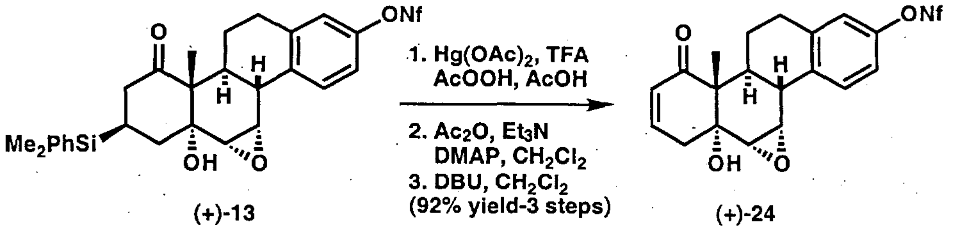
**(syn)-(+)-Nic-1-lactone (1).** To a solution of lactone (+)-**23** (10 mg, 0.017 mmol) in 35% AcOOH–AcOH (0.83 mL) at 25 °C was added $Hg(OAc)_2$ (26 mg, 0.082 mmol), and the clear solution was stirred for 3 h. The reaction mixture was diluted with $Et_2O$ (5 mL), washed sequentially with 10% aq $Na_2S_2O_3$ (7 mL), $H_2O$ (7 mL), saturated aq $NaHCO_3$ (7 mL), and brine (7 mL), dried over $MgSO_4$, and evaporated to a white solid which was used without further purification.

A solution of the above solid in $CH_2Cl_2$ (0.83 mL) was treated with $Et_3N$ (0.025 mL, 0.17 mmol), $Ac_2O$ (0.008 mL, 0.084 mmol), and DMAP (2 mg, 0.017 mmol). After stirring for 15 min, the crude solution was diluted with $CH_2Cl_2$ (2 mL), evaporated onto $SiO_2$, and filtered through a pad of silica gel (1:1 hexanes/EtOAc eluent) to provide a colorless residue. The crude material was dissolved in $CH_2Cl_2$ (0.5 mL), treated with DBU (0.015 mL, 0.10 mmol) and stirred at 25 °C for 2.5 h. The reaction mixture was diluted with $CH_2Cl_2$ (3.0 mL), evaporated onto $SiO_2$ and chromatographed (1:1 hexanes/EtOAc eluent) to provide (+)-Nic-1-lactone (**1**, 7.0 mg, 90% yield) as a white solid which was indistinguishable from a sample of (nat)-(+)-Nic-1-lactone: mp 230 °C (EtOAc/hex) ; $R_F$ 0.53, 0.37, 0.21 (1:1 acetone/hexanes, 2:1 EtOAc/hexanes, 1:1 EtOAc/hexanes); $[\alpha]_D^{26}$ +7 (*c* 0.1, $CH_2Cl_2$); FTIR (film) 3500, 1731, 1688 $cm^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) δ 7.34 (d, *J* = 7.8 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.96 (s, 1H), 5.92 (ddd, *J* = 2.0, 4.9, 10.3 Hz, 1H), 5.80 (dd, *J* = 2.9, 9.8 Hz, 1H), 4.50 (m, 1H), 3.38 (app.t, *J* = 2.9 Hz, 1H), 3.11 (m, 1H), 2.90 (m, 1H), 2.80 (d, *J* = 1.0 Hz, 1H), 2.67 (ddd, *J* = 3.9, 6.8, 17.1 Hz, 1H), 2.56 (bd, *J* = 11.2 Hz, 1H), 2.53 (d, *J* = 3.9 Hz, 1H), 2.50 (m, 1H), 2.04 (dd, *J* = 4.9, 18.6 Hz, 1H), 1.91 (bd, *J* = 19.5 Hz, 1H), 1.85 (td, *J* = 3.4, 10.8 Hz, 1H), 1.41 (d, *J* = 7.3 Hz, 2H), 1.38 (m, 1H), 1.35 (s, 3H), 1.24 (d, *J* = 6.8 Hz, 3H), 0.71 (s, 3H), 0.69 (s, 3H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) δ 201.4, 168.9, 139.7, 139.4, 137.6, 136.8, 129.4, 128.9, 126.1, 124.9, 77.4, 72.5, 62.4, 59.4, 56.8, 55.3, 51.7, 43.0, 39.0, 36.9, 33.0, 32.1, 29.7, 24.9, 17.2, 13.8, 13.8; HRMS (FAB) *m/z* calcd for $[C_{28}H_{32}O_6{+}Na]^+$: 487.2097, found 487.2092.



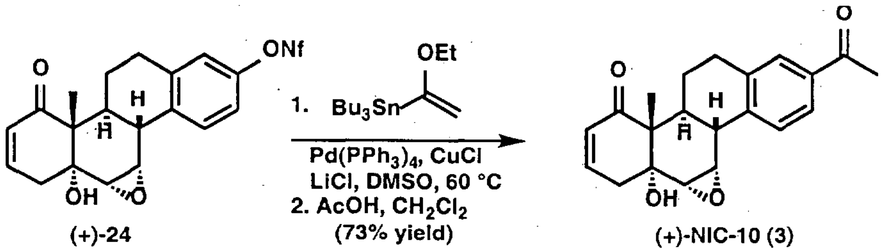
**(syn)-(+)-Nic-1 (2).** To a cooled (-78 °C) solution of Nic-1-lactone (**1**, 8.0 mg, 0.017 mmol) in toluene (1.5 mL) was added a solution of DIBAL in toluene (1.0 M, 0.051 mL, 0.051 mmol) in a dropwise fashion. After 5 min, the reaction mixture was treated with MeOH (0.05 mL) followed by the addition of $Na_2SO_4 \cdot 10H_2O$ (300 mg) and celite (60 mg). The mixture was allowed to thaw at ambient temperature, stirred for 15 min, and filtered through a pad of celite (EtOAc eluent). The filtrate was evaporated to a residue which was used without further purification.

The residue obtained above was dissolved in $CH_2Cl_2$ (1.0 mL) and treated with $Et_3N$ (0.024 mL, 0.17 mmol), $Ac_2O$ (0.008 mL, 0.09 mmol), and DMAP (2 mg, 0.02 mmol). After stirring for 45 min, the crude solution was diluted with $CH_2Cl_2$ (2 mL), evaporated onto $SiO_2$ , and filtered through a pad of silica gel (1:1 hexanes/EtOAc eluent) to provide a colorless residue. The crude material was dissolved in $CH_2Cl_2$ (0.85 mL), treated with Dess-Martin periodinane (36 mg, 0.085 mmol) and heated to reflux for 14 h. The reaction mixture was diluted with $CH_2Cl_2$ (3.0 mL), evaporated onto $SiO_2$ and filtered through a pad of silica gel (1:1 hexanes/EtOAc). The filtrate was evaporated to provide a residue which was dissolved in a mixture of MeOH–$H_2O$ (9:1, 0.50 mL), treated with $K_2CO_3$ (20 mg, 0.14 mmol), and stirred at 25 °C for 15 min. The reaction mixture was diluted with $CH_2Cl_2$ (2 mL), evaporated onto $SiO_2$ and purified by flash chromatography on silica gel (2:1 EtOAc/hexanes eluent) to provide (+)-Nic-1 (**2**, 6.3 mg, 80% yield-4 steps) as a white solid which was indistinguishable from a sample of (nat)-(+)-Nic-1: mp 119 °C (PhH/$CHCl_3$); mixed mp 119 °C (PhH/$CHCl_3$); $R_F$ 0.28, 0.39, 0.39 (2:1 EtOAc/hexanes, 4:1 EtOAc/hexanes, 1:1 acetone/hexanes); $[\alpha]_D^{24}$ +35 (*c* 0.10, $CH_2Cl_2$); FTIR (film) 3465, 1687 $cm^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) $\delta$ 7.40 (d, $J$ = 7.8 Hz, 1H), 7.15 (d, $J$ = 7.8 Hz, 1H), 7.07 (s, 1H), 5.94 (ddd, $J$ = 2.0, 4.9, 9.8 Hz, 1H), 5.81 (dd, $J$ = 2.4, 10.3 Hz, 1H), 4.96 (d, $J$ = 9.8 Hz, 1H), 3.89 (m, 1H), 3.46 (d, $J$ = 10.7 Hz, 1H), 3.41 (bs, 1H), 3.11 (m, 1H), 2.94 (m, 1H), 2.85 (s, 1H), 2.72 (ddd, $J$ = 4.4, 6.3, 16.6 Hz, 1H), 2.66 (m, 1H), 2.57 (bd, $J$ = 11.7 Hz, 1H), 2.54 (d, $J$ = 3.4 Hz, 1H), 2.05 (dd, $J$ = 4.9, 18.6 Hz, 1H), 1.92 (bd, $J$ = 18.6 Hz, 1H), 1.85 (td, $J$ = 3.4, 10.7 Hz, 1H), 1.57 (dd, $J$ = 2.0, 14.2 Hz, 1H), 1.43 (d, $J$ = 14.4 Hz, 1H), 1.40 (d, $J$ = 7.3 Hz, 1H), 1.34 (d, $J$ = 6.8 Hz, 3H), 0.97 (s, 3H), 0.88 (s, 3H), 0.72 (s, 3H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) $\delta$ 201.5, 141.7, 139.4, 137.2, 136.0, 129.4, 128.9, 126.1, 124.6, 91.8, 72.5, 67.5, 64.6, 63.7, 56.8, 55.4, 51.7, 43.7, 39.0, 36.9, 34.6, 32.1, 29.9, 24.9, 18.6, 18.2, 16.4, 13.8; HRMS (FAB) *m/z* calcd for $[C_{28}H_{34}O_6{+}Na]^+$: 489.2253, found 489.2255.



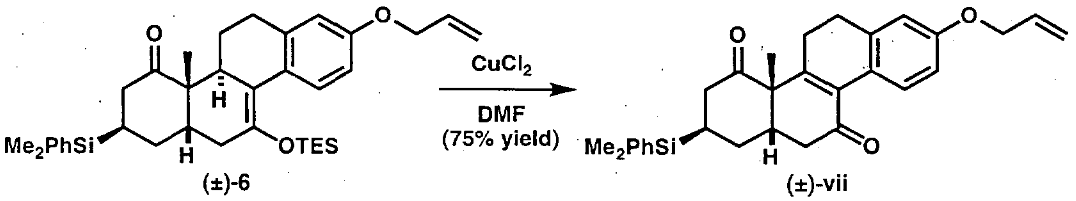
**Enone (+)-24.** To a solution of nonaflate **(+)-13** (20 mg, 0.027 mmol) in 35% AcOOH–AcOH (1.3 mL) and TFA (0.66 mL) at 25 °C was added $Hg(OAc)_2$ (44 mg, 0.14 mmol), and the clear solution was stirred for 3 h. The reaction mixture was diluted with $Et_2O$ (10 mL), washed sequentially with 10% aq $Na_2S_2O_3$ (15 mL), $H_2O$ (15 mL), saturated aq $NaHCO_3$ (15 mL), and brine (15 mL), dried over $MgSO_4$, and evaporated to a white solid which was used without further purification.

A solution of the above solid in $CH_2Cl_2$ (1.0 mL) was treated with $Et_3N$ (0.037 mL, 0.27 mmol), $Ac_2O$ (0.013 mL, 0.14 mmol), and DMAP (3.0 mg, 0.027 mmol). After stirring for 5 min, the crude solution was evaporated onto $SiO_2$, and filtered through a pad of silica gel (1:1 hexanes/EtOAc eluent) to provide a colorless residue. The crude material was dissolved in $CH_2Cl_2$ (1.0 mL), treated with DBU (0.040 mL, 0.27 mmol) and stirred at 25 °C for 2 h. The reaction mixture was diluted with $CH_2Cl_2$ (3.0 mL), evaporated onto $SiO_2$ and chromatographed (1:1 hexanes/EtOAc eluent) to provide enone **(+)-24** (15 mg, 92% yield) as a white foam: $R_F$ 0.26 (1:1 hexanes/EtOAc); $[\alpha]_D^{25}$ +16 (*c* 0.50, $CH_2Cl_2$); FTIR (film) 3461, 1687 $cm^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) δ 7.04 (d, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.74 (s, 1H), 5.94 (ddd, *J* = 2.4, 5.4, 10.3 Hz, 1H), 5.81 (2.4, *J* = 10.3 Hz, 1H), 3.13 (bs, 1H), 2.90 (m, 1H), 2.74 (bs, 1H), 2.49 (m, 2H), 2.88 (dt, *J* = 5.4, 16.6 Hz, 1H), 2.20 (d, *J* = 11.2 Hz, 1H), 2.04 (dd, *J* = 4.9, 18.6 Hz, 1H), 1.90 (d, *J* = 18.6 Hz, 1H), 1.63 (td, *J* = 3.9, 10.7 Hz, 1H), 1.17 (m, 1H), 0.65 (s, 3H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) δ 201.1, 148.6, 140.6, 139.5, 138.5, 128.8, 126.4, 121.4, 118.4, 72.4, 56.7, 54.7, 51.7, 38.6, 36.9, 31.4, 29.2, 24.0, 13.7; $^{19}F$ NMR (400 MHz, benzene-$d_6$) δ -81.45 (t, 9.2), -109.70 (t, 12.2), -121.12 (s), -126.16 (s); HRMS (FAB) *m/z* calcd for $[C_{23}H_{19}O_6SF_9+Na]^+$: 617.0656, found 617.0652.

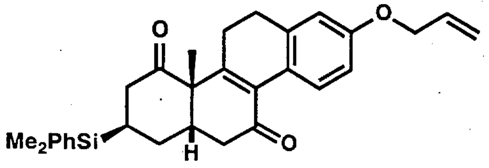


**(syn)-(+)-Nic-10 (3).** To a solution of nonaflate **(+)-24** (azeotroped from PhH, 12 mg, 0.020 mmol) in DMSO (0.81 mL) under Ar in a Schlenk tube (25 mL) was added LiCl (flame dried under vacuum, 26 mg, 0.61 mmol), $Pd(PPh_3)_4$ (12 mg, 0.010 mmol) and CuCl (50 mg, 0.51 mmol), and the mixture was degassed (4 x) under high vacuum with an Ar purge. Ethoxyvinyltributylstannane (0.048 mL, 51 mg, 0.14 mmol) was added and the resulting mixture was rigorously degassed (4 x) by the freeze/pump-thaw process (-78 → 25 °C, Ar). The reaction mixture was stirred at room temperature for 1 h, then heated to 60 °C for 22 h. Following completion of the coupling as monitored by TLC, the reaction mixture was cooled, diluted with

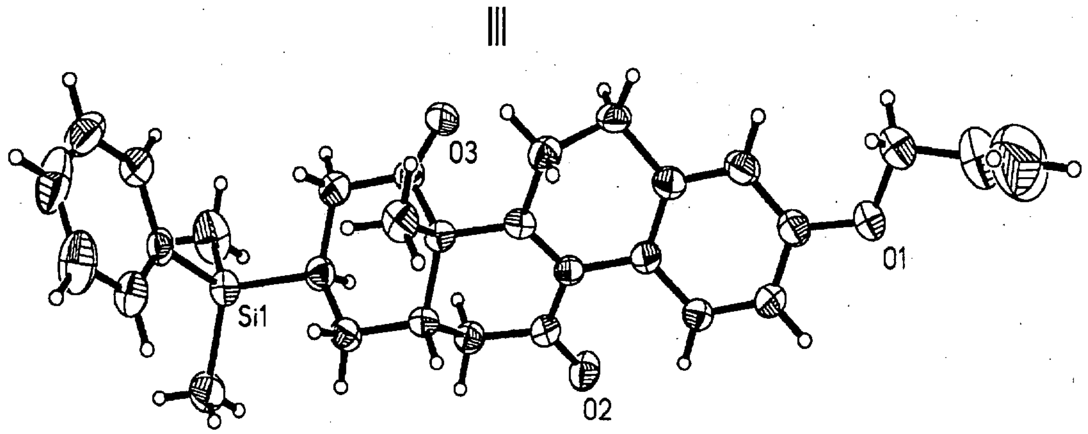
$Et_2O$ (10 mL), and washed with a mixture of brine (12 mL) and 5% aq $NH_4OH$ (3 mL). The aq layer was further extracted with $Et_2O$ (2 x 7 mL), and the combined organic layers were washed with water (2 x 12 mL) then brine (2 x 12 mL), and dried over $Na_2SO_4$. The resulting solution was concentrated to a residue which was dissolved in $CH_2Cl_2$ (0.75 mL) and treated with AcOH (0.050 mL). After 20 min at 25 °C the mixture was evaporated onto $SiO_2$ and purified by flash chromatography on silica gel (1:1 hexanes/EtOAc eluent) to provide (+)-Nic-10 (**3**, 5.0 mg, 73% yield) as a white solid. An analytically pure sample was obtained by preparative TLC (1:1 hexanes/EtOAc eluent): mp 207-8 °C (EtOH); $R_F$ 0.37, 0.30, 0.13 (1:1 acetone/hexanes, 2:1EtOAc/hexanes, 1:1 EtOAc/hexanes); $[\alpha]_D^{25}$ +21 (*c* 0.10, $CH_2Cl_2$); FTIR (film) 3451, 1687, 1682 $cm^{-1}$; $^1H$ NMR (500 MHz, benzene-$d_6$) δ 7.81 (d, *J* = 7.8 Hz, 1H), 7.63 (s, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 5.94 (ddd, *J* = 1.0, 3.9, 10.3 Hz, 1H), 5.82 (dd, *J* = 2.0, 10.3 Hz, 1H), 3.28 (s, 1H), 3.03 (m, 1H), 2.82 (s, 1H), 2.75 (m, 1H), 2.55 (app.t, *J* = 5.4 Hz, 1H), 2.55 (d, *J* = 4.6 Hz, 1H), 2.39 (d, *J* = 11.7 Hz, 1H), 2.19 (s, 3H), 2.08 (dd, *J* = 4.9, 18.6 Hz, 1H), 1.92 (d, *J* = 18.6 Hz, 1H), 1.81 (td, *J* = 4.4, 11.2 Hz, 1H), 1.32 (m, 1H), 0.70 (s, 3H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) δ 201.3, 201.2, 139.4, 132.4, 132.3, 131.5, 127.4, 125.8, 125.0, 72.4, 56.7, 55.0, 51.7, 39.2, 36.9, 31.6, 29.4, 26.3, 24.4, 13.8; HRMS (CI) *m/z* calcd for $[C_{21}H_{22}O_4+NH_4]^+$: 356.1862, found 356.1871.



**Enone (±)-vii.** A solution of ketone **(±)-6** (10.0 mg, 0.017 mmol) in DMF (0.17 mL) was treated with anhydrous $CuCl_2$ (9 mg, 0.068 mmol) and heated to 60 °C. After 15 min the reaction mixture was diluted with $CH_2Cl_2$ (1 mL) and purified directly by preparative TLC (3:1 hexanes/EtOAc eluent) to provide enone **(±)-vii** (6.0 mg, 75% yield) as a white solid. Crystals suitable for X-ray analysis were obtained by crystallization from EtOAc/heptane at 25 °C: mp 172-3 °C (EtOAc/heptane); $R_F$ 0.45 (3:1 hexanes/EtOAc); FTIR (film) 1699, 1670 $cm^{-1}$; $^1H$ NMR (400 MHz, benzene-$d_6$) δ 8.79 (d, *J* = 8.7 Hz, 1H), 7.30 (m, 2H), 7.21 (m, 3H), 6.83 (dd, *J* = 2.7, 8.7 Hz, 1H), 6.77 (d, *J* = 2.5 Hz, 1H), 5.83 (m, 1H), 5.25 (dd, *J* = 1.6, 17.3 Hz, 1H), 5.02 (dd, *J* = 1.0, 10.5 Hz, 1H), 4.16 (s, 1H), 4.15 (s, 1H), 2.97 (td, *J* = 5.3, 14.5 Hz, 1H), 2.36 (m, 2H), 2.22-1.07 (comp m, 9H), 0.91 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H); $^{13}C$ NMR (100 MHz, benzene-$d_6$) δ 211.5, 195.6, 158.3, 158.2, 138.9, 136.4, 134.2, 134.0, 130.7, 129.9, 129.7, 127.8, 124.8, 116.7, 114.1, 111.9, 68.5, 55.9, 44.6, 41.9, 38.8, 36.2, 28.3, 27.8, 22.8, 20.5, -5.0, -5.4; HRMS (FAB) *m/z* calcd for $[C_{30}H_{34}O_3Si+Na]^+$: 493.2175, found 493.2193.



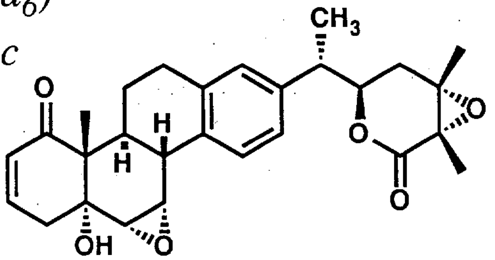
**(±)-vii**

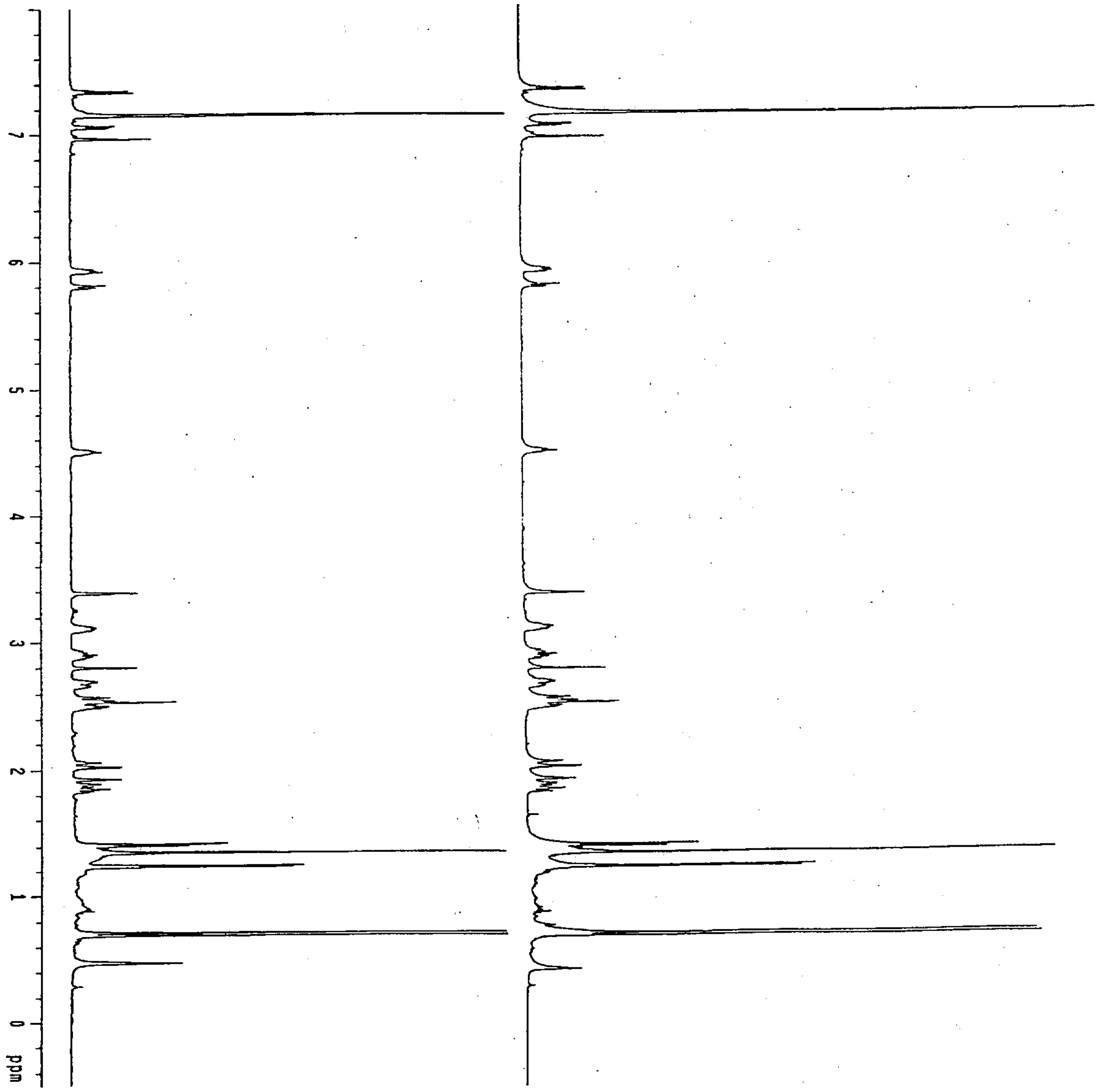


| | |
|---|---|
| chemical formula | $C_{30}H_{34}O_3Si$ |
| chemical formula weight | 470.66 |
| Temperature | 213 (2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Orthorhombic |
| Space group | Pccn |
| Unit Cell dimensions | a = 18.7297 (6) Å alpha = 90°<br>b = 37.2711 (1) Å beta = 90°<br>c = 7.3366 (3) Å gamma = 90° |
| Volume, Z | 5121.5 (3) Å$^3$, 8 |
| Density (calculated) | 1.221 Mg/m$^3$ |
| Absorbtion coefficient | 0.121 mm$^{-1}$ |
| F(000) | 2016 |

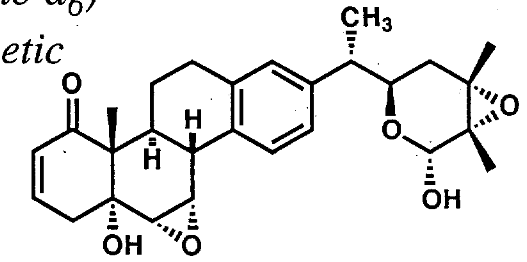
| | |
|---|---|
| Crystal Size | 0.125 x 0.125 x 0.075 mm |
| θ range for data collection | 1.09 to 28.35° |
| Limiting indices | $-21 \le h \le 24$, $-34 \le k \le 48$, $-4 \le l \le 8$ |
| Reflections collected | 14712 |
| Independent reflections | 5895 ($R_{int}$ = 0.0492) |
| Completeness to θ = 28.35° | 92.3% |
| Absorption coefficient | None |
| Max. and min. transmission | 0.000000 and 0.000000 |
| Refinement method | Full-matrix least squares on $F^2$ |
| Data / restraints / parameters | 5895 / 0 / 307 |
| Goodness–of–fit on $F^2$ | 1.044 |
| Final R indices [I>2σ (I)] | R1 = 0.0609, wR2 = 0.1465 |
| R indices (all data) | R1 = 0.1119, wR2 = 0.1779 |
| Largest diff. peak and hole | 0.646 and -0.410 eÅ$^{-3}$ |

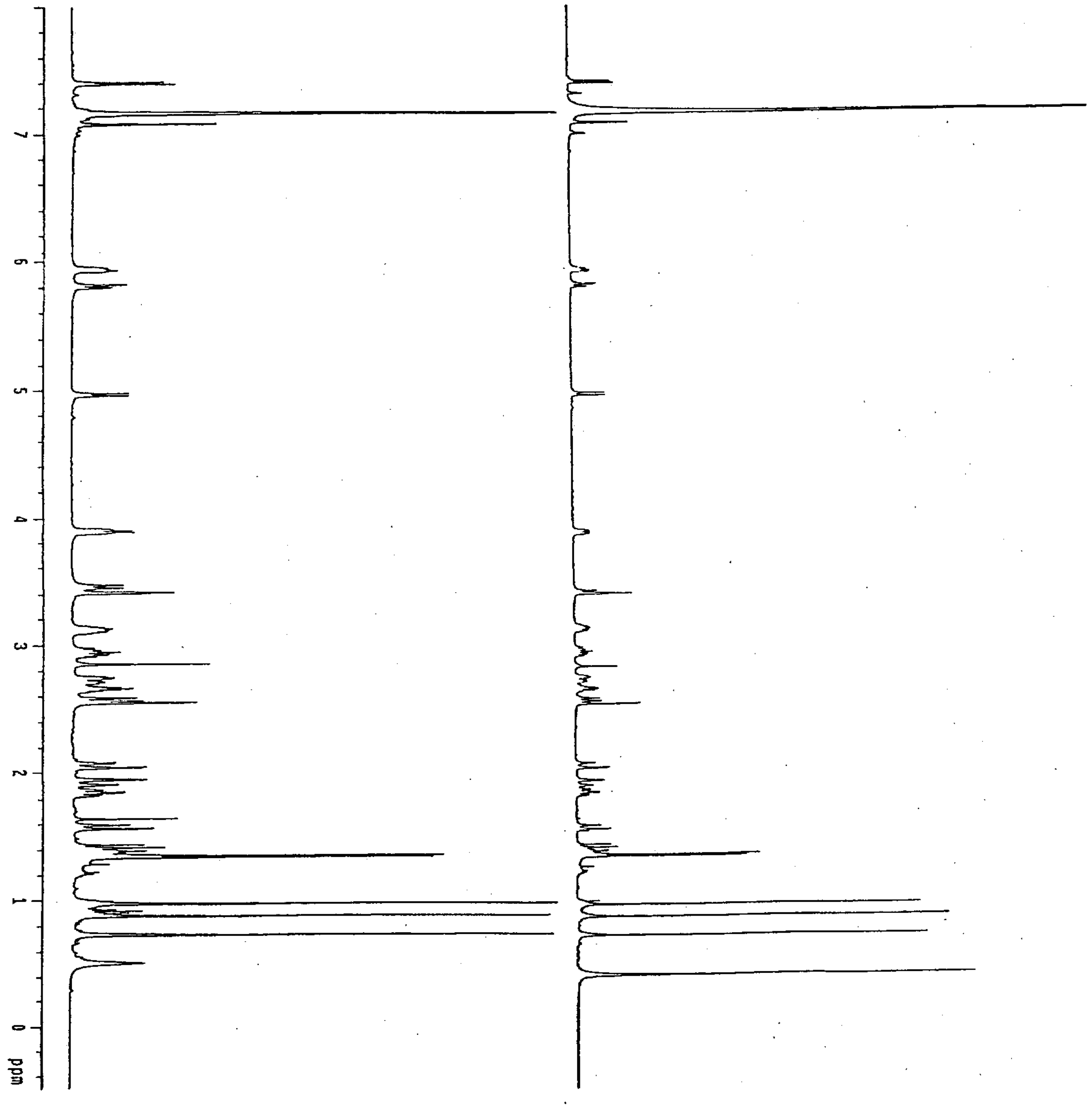
*(+)-NIC-1-lactone (**1**) comparison spectra*
*(500 MHz $^1H$ NMR, benzene-$d_6$)*
*top: natural, bottom: synthetic*





*(+)-NIC-1 (**2**) comparison spectra*
*(500 MHz $^1H$ NMR, benzene-$d_6$)*
*top: natural, bottom: synthetic*





*synthetic (+)-NIC-10 (**3**)*
*(500 MHz $^{1}$H NMR, benzene-$d_6$)*