# Efficient, Stereoselective Synthesis of *trans*-2,5-Disubstituted Morpholines

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**Supporting Information**

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## General Experimental Procedures

All reactions were performed in oven- or flame-dried glassware fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred by syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation (house vacuum, ~25–40 Torr) at 23 °C, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV), then were stained by submersion in aqueous ceric ammonium molybdate solution (CAM), ethanolic phosphomolybdic acid solution (PMA), or acidic ethanolic *p*-anisaldehyde solution (anis), followed by brief heating on a hot plate (~200 °C, 10–15 s). Flash chromatography was performed as described by Still et al.,[1] employing silica gel (60 Å pore size, 230–400 mesh, Merck KGA; or 60 Å pore size, 32–63 μm, standard grade, Sorbent Technologies).

## Materials

Commercial reagents and solvents were used as received with the following exceptions. Dichloromethane, ethyl ether, hexanes, methanol, pyridine, and tetrahydrofuran were purified by the method of Pangborn et al.[2] Chlorotrimethylsilane, 1,1,1,3,3,3-hexamethyldisilazane, and triethylamine were distilled under a dinitrogen atmosphere from calcium hydride at 760 Torr.

## Instrumentation

Proton magnetic resonance ($^{1}$H NMR) spectra and carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on Varian Mercury 400 (400 MHz), Varian INOVA 500 (500 MHz), or Varian INOVA 600 (600 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm; δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, $C_6D_5H$: δ 7.16). Carbon chemical shifts are expressed in parts per million (ppm; δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the NMR solvent ($CDCl_3$: δ 77.0, $C_6D_6$: δ 128.1). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, br = broad), integration, and coupling constant (*J*) in Hertz (Hz). Infrared (IR) spectra were obtained as neat films by evaporation from dichloromethane using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption ($cm^{-1}$), and intensity of absorption (s = strong, m = medium, w = weak, br = broad). Mass spectra were obtained at the Harvard University Mass Spectrometry Facility.

## $^{1}$H NMR Chemical shift assignments; Stereochemical determinations

$^{1}$H NMR resonances were assigned on the basis of COSY decoupling experiments. Relative stereochemical assignments of morpholine products were established by 1D NOESY experiments.

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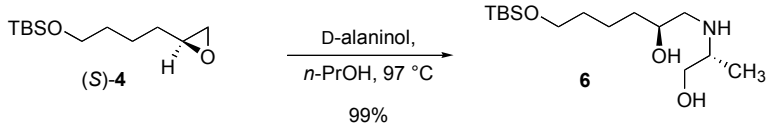
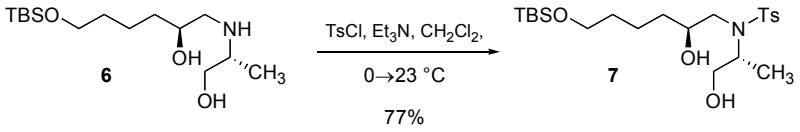
[1] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
[2] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.



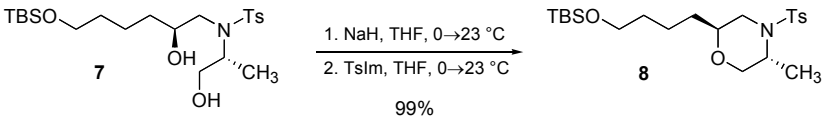

**Amino Diol 6:** (*S*)-2-[4-(*tert*-Butyldimethylsiloxy)-1-butyl]oxirane[3] ((*S*)-**4**, 143.9 μL, 548.2 μmol, 1 equiv) was added by syringe to a solution of D-alaninol (97% ee, 164.6 mg, 2.19 mmol, 4.0 equiv) in 1-propanol (550 μL) at 23 °C. The resulting light yellow solution was heated at reflux for 16 h, then was allowed to cool to 23 °C. The cooled product solution was partitioned between ethyl acetate (30 mL) and a 1:1 solution of brine and saturated aqueous sodium bicarbonate solution (30 mL). The organic layer was separated and washed with a 1:1 solution of brine and saturated aqueous sodium bicarbonate solution (30 mL). The combined aqueous layers were extracted with dichloromethane (2×40 mL) and all of the organic extracts were then combined and dried over sodium sulfate. Concentration of the dried extracts in vacuo afforded amino diol **6** (166.0 mg, 99%) as a clear oil.

$^1$H NMR (600 MHz, $CDCl_3$), δ 3.65 (m, 1H, C**H**OH), 3.60 (app t, 3H, J = 6.6 Hz, TBSOC**H**$_2$, C**H**$_2$OH), 3.36 (dd, 1H, J = 7.5, 11.1 Hz, C**H**$_2$OH), 2.83 (dd, 1H, J = 2.4, 12.0 Hz, C**H**$_2$NH), 2.80 (m, 1H, C**H**NH), 2.39 (dd, 1H, J = 9.3, 11.7 Hz, C**H**$_2$NH), 1.57–1.49 (m, 2H, TBSOCH$_2$C**H**$_2$), 1.49–1.42 (m, 2H, C**H**$_2$CHOH), 1.42–1.35 (m, 2H, TBSOCH$_2$CH$_2$C**H**$_2$), 1.05 (d, 3H, J = 6.0 Hz, CHC**H**$_3$), 0.88 (s, 9H, SiC(C**H**$_3$)$_3$), 0.04 (s, 6H, Si(C**H**$_3$)$_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 70.5, 65.8, 63.2, 55.2, 52.9, 35.1, 32.9, 26.1, 22.1, 18.5, 16.9, –5.1. FTIR (neat film), cm$^{-1}$: 3378 (br, s, OH), 2930 (m, CH), 2858 (m, CH), 1472 (m), 1386 (w), 1361 (w), 1255 (m), 1101 (m), 1045 (m), 836 (m), 775 (m), 661 (w). HRMS (TOF ES$^+$) calcd for $C_{15}H_{36}NO_3Si^+$ $(M+H)^+$: 306.2464, found: 306.2470. TLC (50% ethyl acetate–hexanes), $R_f$ 0.09.




**Sulfonamide 7:** Triethylamine (1.38 mL, 9.90 mmol, 2.0 equiv) was added to a solution of amino diol **6** (1.51 g, 4.94 mmol, 1 equiv) in dichloromethane (150 mL) at 0 °C. *p*-Toluenesulfonyl chloride (1.04 g, 5.46 mmol, 1.1 equiv) was then added in one portion, and the resulting clear solution was stirred at 0 °C for 20 min. The ice bath was then removed, and the reaction solution was allowed to warm to ambient temperature (23 °C) while stirring for an additional 20 min. The reaction solution was subsequently concentrated in vacuo (final volume, 5 mL) and the concentrate was loaded directly onto a column of silica gel (packed in dichloromethane). The product was eluted with 50% ethyl acetate–hexanes; after pooling and concentrating the requisite column fractions, the sulfonamide **7** was obtained as a colorless oil (1.49 g, 77%).

$^1$H NMR (600 MHz, $CDCl_3$), δ 7.72 (d, 2H, J = 8.4 Hz, 2×SO$_2$CC**H**), 7.31 (d, 2H, J = 8.4 Hz, 2×SO$_2$CCHC**H**), 4.09 (m, 1H, C**H**CH$_3$), 3.73 (m, 1H, C**H**OH), 3.61 (app t, 2H, J = 6.6 Hz, TBSOC**H**$_2$), 3.59–3.54 (m, 2H, C**H**$_2$OH), 3.36 (d, 1H, J = 4.8 Hz, CHO**H**), 3.18 (dd, 1H, J = 9.6, 15.6 Hz, C**H**$_2$NSO$_2$), 3.11 (dd, 1H, J = 3.6, 15.0 Hz, C**H**$_2$NSO$_2$), 2.87 (t, 1H, J = 5.7 Hz, CH$_2$O**H**), 2.43 (s, 3H, ArC**H**$_3$), 1.56–1.50 (m, 2H, TBSOCH$_2$C**H**$_2$), 1.47–1.38 (m, 4H, C**H**$_2$C**H**$_2$CHOH), 0.90 (d, 3H, J = 7.2 Hz, CHC**H**$_3$), 0.88 (s, 9H, SiC(C**H**$_3$)$_3$), 0.04 (s, 6H, Si(C**H**$_3$)$_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 143.7, 137.7, 130.0, 127.2, 70.8, 65.6, 63.2, 56.5, 50.2, 35.4, 32.9, 26.1, 22.0, 21.7, 18.5, 13.8, –5.1. FTIR (neat film), cm$^{-1}$ 3448 (br, s, OH), 2930 (m, CH), 2858 (m, CH), 1472 (m), 1388 (w), 1333 (m), 1256 (m), 1155 (s), 1091 (m), 836 (m), 814 (w), 776 (m), 658 (m). HRMS (TOF ES$^+$) calcd for $C_{22}H_{42}NO_5SSi^+$ $(M+H)^+$: 460.2553, found: 460.2555. TLC (50% ethyl acetate–hexanes), $R_f$ 0.71.

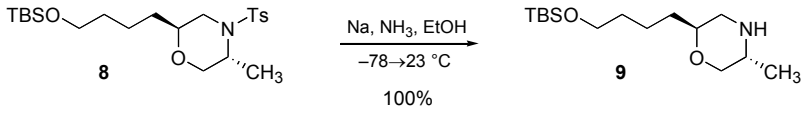



***N*-Tosyl Morpholine 8:** An ice-cooled solution of sulfonamide **7** (1.49 g, 3.24 mmol, 1 equiv) in tetrahydrofuran (160 mL) was transferred by cannula to a flask containing sodium hydride (oil free, 195.0 mg, 8.13 mmol, 2.5 equiv). The resulting white suspension was stirred vigorously at 0 °C for 5 min, then was allowed to warm to 23 °C with continued stirring. After 1 h, the reaction suspension was cooled in an ice bath and 1-(*p*-toluenesulfonyl)imidazole (722.2 mg, 19.6 μmol, 1.0

[3] Prepared as previously reported in Myers, A. G.; Lanman, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 12969–12971.

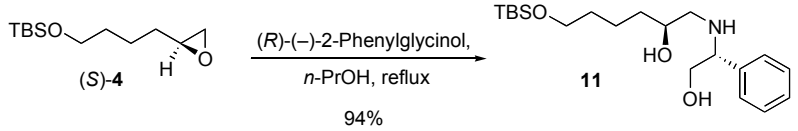
equiv) was added in one portion. The resulting white suspension was stirred at 0 °C for 15 min. The ice bath was then removed, and the reaction suspension was allowed to warm to ambient temperature (23 °C) with vigorous stirring. After stirring for 14 h at 23 °C, the reaction suspension was cooled to 0 °C and excess sodium hydride was CAREFULLY quenched by the dropwise addition of saturated aqueous ammonium chloride solution (50 mL). The resulting biphasic mixture was allowed to warm to 23 °C, and the warmed solution was then diluted with ethyl acetate (500 mL). The resulting solution was washed with a 1:1 mixture of brine and saturated aqueous sodium bicarbonate solution (2×400 mL). The organic layer was separated and dried over sodium sulfate, and the dried solution was concentrated in vacuo to afford the *N*-tosyl morpholine **8** as a clear oil (1.42 g, 99%; single diastereomer by $^1$H NMR).

$^1$H NMR (600 MHz, $CDCl_3$), δ 7.65 (d, 2H, J = 7.8 Hz, 2×$SO_2CC\mathbf{H}$), 7.33 (d, 2H, J = 8.4 Hz, 2×$SO_2CCHC\mathbf{H}$), 3.69 (dd, 1H, J = 3.6, 12.0 Hz, C$\mathbf{H}_2$OCH), 3.66 (dd, 1H, J = 2.4, 11.4 Hz, C$\mathbf{H}_2NSO_2$), 3.59 (app t, 3H, J = 6.6 Hz, TBSOC$\mathbf{H}_2$, C$\mathbf{H}$O$CH_2$), 3.29 (dd, 1H, J = 7.8, 11.4 Hz, C$\mathbf{H}_2$OCH), 2.91 (m, 1H, C$\mathbf{H}CH_3$), 2.47 (dd, 1H, J = 7.8, 12.0 Hz, C$\mathbf{H}_2NSO_2$), 2.44 (s, 3H, ArC$\mathbf{H}_3$), 1.57–1.47 (m, 2H, TBSO$CH_2$C$\mathbf{H}_2$), 1.45–1.39 (m, 2H, C$\mathbf{H}_2$CHOH), 1.37–1.31 (m, 2H, TBSO$CH_2CH_2$C$\mathbf{H}_2$), 1.25 (d, 3H, J = 6.6 Hz, CHC$\mathbf{H}_3$), 0.89 (s, 9H, SiC(C$\mathbf{H}_3$)$_3$), 0.04 (s, 6H, Si(C$\mathbf{H}_3$)$_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 143.8, 134.6, 129.9, 127.7, 74.9, 70.7, 63.0, 52.0, 49.9, 32.8, 31.8, 26.1, 21.7 (2), 18.5, 16.0, –5.1. FTIR (neat film), cm$^{-1}$ 2952 (m, CH), 2930 (m, CH), 2858 (m, CH), 1459 (w), 1352 (m), 1256 (w), 1170 (s), 1100 (m), 837 (m), 776 (m), 724 (m), 656 (w). HRMS (TOF ES$^+$) calcd for $C_{22}H_{40}NO_4SSi^+$ $(M+H)^+$: 442.2447, found: 442.2442. TLC (50% ethyl acetate–hexanes), $R_f$ 0.68.



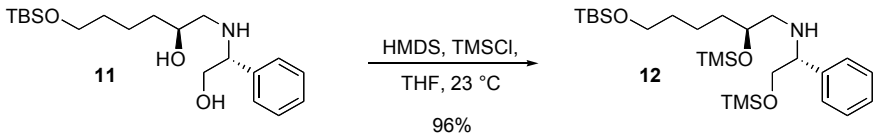

**(2*S*,5*R*)-2-[4-(*tert*-Butyldimethylsiloxy)-1-butyl]-5-methyl-morpholine (9):** Ammonia (450 mL) was condensed using a cold-finger condenser (–78 °C) into a flask containing a solution of *N*-tosyl morpholine **8** (8.16 g, 18.47 mmol, 1 equiv) in absolute ethanol (150 mL) cooled to –78 °C. The condenser was then replaced with a rubber septum and a needle affixed to an argon-filled balloon was inserted through the septum. Sodium (12.1 g, 0.53 mol, 28.5 equiv; washed free of mineral oil with hexanes) was added in three equal portions to the vigorously stirred reaction solution over 5 min. The resulting blue-tinged, cloudy white solution with suspended bronze globules was stirred for 10 min at –78 °C. A mineral oil-filled bubbler was then attached to the reaction flask, and the dry ice/acetone bath was removed. The reaction mixture was allowed to warm to 23 °C with continued stirring (steady gas evolution observed), then was stirred at 23 °C for 15 h (continued slow gas evolution), affording a white suspension. Ethyl ether (500 mL) and saturated aqueous ammonium chloride solution (100 mL) were added sequentially to this suspension, and the resulting biphasic mixture was stirred at 23 °C for 10 min. The biphasic mixture was then partitioned between ethyl acetate (1 L) and a 1:1 solution of brine and saturated aqueous sodium bicarbonate solution (500 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (1 L). The organic extracts were combined and dried over sodium sulfate. The dried solution was concentrated in vacuo to provide (2*S*,5*R*)-2-[4-(*tert*-butyldimethylsiloxy)-1-butyl]-5-methyl-morpholine (**9**) as a light yellow oil (5.36 g, 100%).

$^1$H NMR (500 MHz, $CDCl_3$), δ 3.78 (dd, 1H, J = 3.3, 10.8 Hz, C$\mathbf{H}_2$OCH), 3.59 (app t, 2H, J = 6.8 Hz, TBSOC$\mathbf{H}_2$), 3.31 (m, 1H, $CH_2$OC$\mathbf{H}$), 3.12 (t, 1H, J = 10.8 Hz, C$\mathbf{H}_2$OCH), 2.90 (dd, 1H, J = 1.8, 12.3 Hz, C$\mathbf{H}_2$NH), 2.85 (ddd, 1H, J = 3.3, 6.5, 9.8 Hz, C$\mathbf{H}CH_3$), 2.59 (dd, 1H, J = 10.8, 11.8 Hz, C$\mathbf{H}_2$NH), 1.56–1.48 (m, 2H, TBSO$CH_2$C$\mathbf{H}_2$), 1.48–1.41 (m, 2H, C$\mathbf{H}_2$CHOH), 1.41–1.33 (m, 2H, TBSO$CH_2CH_2$C$\mathbf{H}_2$), 0.95 (d, 3H, J = 6.5 Hz, CHC$\mathbf{H}_3$), 0.88 (s, 9H, SiC(C$\mathbf{H}_3$)$_3$), 0.03 (s, 6H, Si(C$\mathbf{H}_3$)$_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 76.4, 74.2, 63.2, 51.6, 50.2, 33.4, 33.0, 26.1, 21.8, 18.5, 17.7, –5.1. FTIR (neat film), cm$^{-1}$ 3324 (w, NH), 2954 (m, CH), 2931 (m, CH), 2858 (m, CH), 1473 (m), 1256 (m), 1097 (s), 836 (m), 775 (m). HRMS (TOF ES$^+$) calcd for $C_{15}H_{34}NO_2Si^+$ $(M+H)^+$: 288.2359, found: 288.2352. TLC (10% methanol–dichloromethane, triethylamine-washed plate), $R_f$ 0.53.



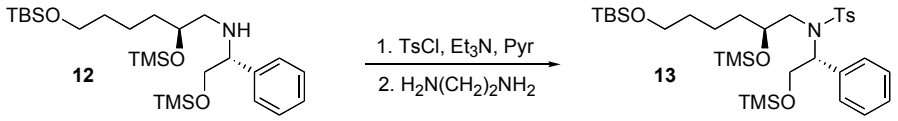
**Amino Diol 11:** A solution of (*S*)-2-[4-(*tert*-butyldimethylsiloxy)-1-butyl]oxirane[4] ((*S*)-**4**, 0.878 g/mL, 600.0 μL, 2.29 mmol, 1 equiv) and (*R*)-(–)-2-phenylglycinol (99% ee, 1.25 g, 9.11 mmol, 3.98 equiv) in 1-propanol (2.29 mL) was heated at reflux for 19.5 h. The resulting yellow solution was concentrated in vacuo, and the oily residue was purified by flash column chromatography (8% methanol–ethyl acetate initially, grading to 12% methanol–ethyl acetate), providing amino diol **11** as a waxy, off-white solid (792.6 mg, 94%).

$^1$H NMR (500 MHz, $CDCl_3$), δ 7.36 (t, 2H, J = 7.0 Hz, Ar**H**), 7.31–7.27 (m, 3H, Ar**H**), 3.76 (m, 1H, C**H**OH), 3.74 (dd, 1H, J = 4.5, 10.5 Hz, C**H**$_2$OH), 3.63 (dd, 1H, J = 8.0, 10.0 Hz, C**H**$_2$OH), 3.58 (t, 2H, J = 6.0 Hz, C**H**$_2$OTBS), 3.55 (m, 1H, C**H**Ph), 2.68 (dd, 1H, J = 3.0, 12.0 Hz, C**H**$_2$NH), 2.40 (dd, 1H, J = 8.5, 12.0 Hz, C**H**$_2$NH), 2.17 (br, s, 3H, CHO**H**, CH$_2$O**H**, N**H**), 1.55–1.46 (m, 2H, C**H**$_2$CH$_2$OTBS), 1.46–1.37 (m, 3H, C**H**$_2$C**H**$_2$CH$_2$CH$_2$OTBS), 1.37–1.29 (m, 1H, C**H**$_2$CH$_2$CH$_2$OTBS), 0.88 (s, 9H, C(C**H**$_3$)), 0.03 (s, 6H, Si(C**H**$_3$)$_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 140.4, 128.8, 127.8, 127.4, 70.9, 67.0, 65.6, 63.2, 53.8, 35.2, 32.9, 26.1, 22.0, 18.5, –5.2. FTIR (neat film), cm$^{-1}$ 3356 (br s, OH), 3064 (w), 3030 (w), 2930 (s), 2858 (s), 1472 (m), 1462 (m), 1388 (w), 1361 (w), 1256 (m), 1100 (m), 1027 (m), 836 (m), 775 (m), 758 (m). HRMS (TOF ES$^+$) calcd for $C_{20}H_{38}NO_3Si^+$ (M+H)$^+$: 368.2621, found: 368.2613. TLC (10% methanol–ethyl acetate), $R_f$ 0.37.




**Bis-trimethylsilyl ether 12:** 1,1,1,3,3,3-Hexamethyldisilazane (5.07 mL, 24.03 mmol, 2.04 equiv) and chlorotrimethylsilane (600.0 μL, 4.72 mmol, 0.4 equiv) were added sequentially to a solution of amino diol **11** (4.33 g, 11.78 mmol, 1 equiv) in tetrahydrofuran (115 mL) at 23 °C. The resulting suspension was stirred for 1 h, then was partitioned between ethyl acetate (400 mL) and a 1:1 mixture of aqueous phosphate buffer solution (0.05 M monobasic sodium phosphate, 0.05 M dibasic potassium phosphate, pH = 7) and brine (400 mL). The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate (300 mL). The combined organic extracts were dried over sodium sulfate, and the dried solution was concentrated in vacuo, affording bis-trimethylsilyl ether **12** as a yellow oil (5.79 g, 96%).

$^1$H NMR (600 MHz, $CDCl_3$), δ 7.36 (d, 2H, J = 7.8 Hz, Ar**H**), 7.31 (t, 2H, J = 7.8 Hz, Ar**H**), 7.24 (t, 1H, J = 7.2 Hz, Ar**H**), 3.76 (m, 1H, C**H**OTMS), 3.73 (dd, 1H, J = 3.6, 9.6 Hz, C**H**$_2$OTMS), 3.59 (dd, 1H, J = 3.6, 9.6 Hz, C**H**$_2$OTMS), 3.56 (t, 2H, J = 6.6 Hz, C**H**$_2$OTBS), 3.47 (t, 1H, J = 9.6 Hz, C**H**Ph), 2.41 (dd, 1H, J = 4.2, 12.0 Hz, C**H**$_2$NH), 2.37 (dd, 1H, J = 8.4, 11.4 Hz, C**H**$_2$NH), 2.29 (br, s, 1H, N**H**), 1.50–1.43 (m, 2H, C**H**$_2$CH$_2$OTBS), 1.43–1.37 (m, 2H, C**H**$_2$C**H**$_2$CH$_2$CH$_2$OTBS), 1.37–1.28 (m, 1H, C**H**$_2$CH$_2$CH$_2$CH$_2$OTBS), 1.28–1.18 (m, 1H, CH$_2$C**H**$_2$CH$_2$CH$_2$OTBS), 0.87 (s, 9H, C(C**H**$_3$)$_3$), 0.15 (s, 9H, Si(C**H**$_3$)$_3$), 0.10 (s, 9H, Si(C**H**$_3$)$_3$), 0.02 (s, 6H, Si(C**H**$_3$)$_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 141.3, 128.4, 127.9, 127.4, 73.0, 68.2, 65.5, 63.2, 53.9, 36.0, 33.2, 26.1, 22.0, 18.5, 0.79, –0.42, –5.1. FTIR (neat film), cm$^{-1}$ 3342 (w, NH), 3064 (w), 3026 (w), 2955 (s), 2930 (s), 2902 (m), 2859 (s), 1459 (m), 1388 (w), 1362 (w), 1252 (s), 1094 (s), 883 (m), 840 (s), 775 (m), 758 (m), 701 (m). HRMS (TOF ES$^+$) calcd for $C_{26}H_{54}NO_3Si_3^+$ (M+H)$^+$: 512.3411, found: 512.3409. TLC (50% ethyl acetate–hexanes), $R_f$ 0.82.

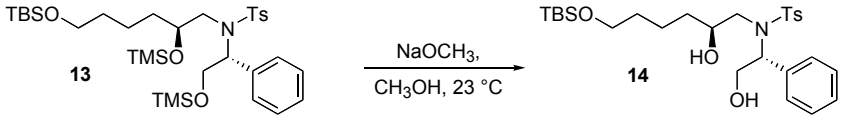



**Sulfonamide 13:** Triethylamine (1.12 mL, 8.04 mmol, 8.0 equiv) and *p*-toluenesulfonyl chloride (765.3 mg, 4.01 mmol, 4.0 equiv) were added sequentially to a solution of bis-trimethylsilyl ether **12** (513.8 mg, 1.00 mmol, 1 equiv) in pyridine (5.0 mL) at 23 °C. The resulting yellow-orange solution was stirred at 23 °C for 15 h, during which time the reaction solution turned dark red. Ethylene diamine (268.4 μL, 4.01 mmol, 4.0 equiv) was added, and the resulting solution was stirred at 23 °C for 2.5 h. The reaction solution was then diluted with ethyl acetate (100 mL). The resulting solution was washed sequentially with saturated aqueous ammonium chloride solution (100 mL) and a 1:1 mixture of saturated aqueous sodium bicarbonate solution and brine (100 mL). The organic layer was separated, and the aqueous washes were combined

[4] Prepared as previously reported in Myers, A. G.; Lanman, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 12969–12971.

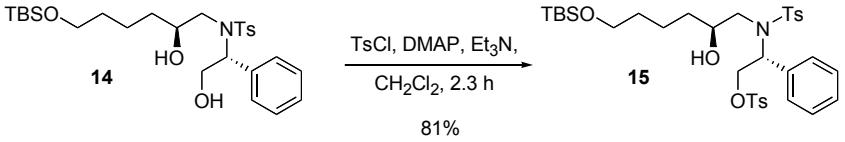
and extracted with ethyl acetate (150 mL). The combined organic extracts were then dried over sodium sulfate, and the dried extracts were concentrated in vacuo. Chromatographic purification of the oily residue (loaded onto a silica column in dichloromethane, eluted with 15% ethyl acetate–hexanes) provided sulfonamide **13** as a yellow oil (662.9 mg, 99%).

$^1$H NMR (600 MHz, $CDCl_3$), δ 7.72 (d, 2H, J = 7.8 Hz, $SO_2CC\mathbf{H}$), 7.27–7.25 (m, 4H, Ar**H** (Ph)), 7.25–7.23 (m, 1H, Ar**H** (Ph)), 7.23 (d, 2H, J = 7.8 Hz, $SO_2CCHC\mathbf{H}$), 5.08 (t, 1H, J = 6.6 Hz, C**H**Ph), 4.06 (dd, 1H, J = 7.2, 10.2 Hz, $C\mathbf{H}_2$OTMS), 3.89 (dd, 1H, J = 7.2, 10.2 Hz, $C\mathbf{H}_2$OTMS), 3.49 (t, 2H, J = 6.6 Hz, $C\mathbf{H}_2$OTBS), 3.38 (m, 1H, C**H**OTMS), 2.99 (d, 2H, J = 6.6 Hz, $C\mathbf{H}_2$NTs), 2.40 (s, 3H, Ar$C\mathbf{H}_3$), 1.44 (m, 1H, $C\mathbf{H}_2CH_2CH_2CH_2$OTBS), 1.29 (p, 2H, J = 6.6 Hz, $C\mathbf{H}_2CH_2CH_2$OTBS), 1.26–1.20 (m, 1H, $C\mathbf{H}_2CH_2CH_2$OTBS), 1.15–1.08 (m, 1H, $C\mathbf{H}_2CH_2CH_2CH_2$OTBS), 0.87 (s, 9H, $C(C\mathbf{H}_3)_3$), 0.76–0.70 (m, 1H, $C\mathbf{H}_2CH_2CH_2$OTBS), 0.02 (s, 18H, $2\times Si(C\mathbf{H}_3)_3$), 0.00 (s, 6H, $Si(C\mathbf{H}_3)_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 143.1, 138.6, 137.7, 129.5, 128.6, 128.5, 127.9, 127.7, 70.7, 63.4, 61.9, 61.7, 51.3, 34.3, 33.1, 26.1, 22.2, 21.6, 18.5, 0.48, –0.51, –5.1. FTIR (neat film), cm$^{-1}$ 3065 (w), 3032 (w), 2955 (s), 2930 (m), 2900 (m), 2859 (m), 1599 (w), 1498 (w), 1344 (m), 1252 (m), 1163 (m), 1104 (s), 879 (m), 841 (s), 775 (m), 750 (w), 698 (w), 660 (m). LRMS (TOF ES$^+$) calcd for $C_{33}H_{60}NO_5SSi_3^+$ $(M+H)^+$: 666, found: 666. TLC (20% ethyl acetate–hexanes), $R_f$ 0.64.




**Diol 14:** Sodium methoxide (99.9 mg, 1.85 mmol, 0.2 equiv) was added in one potion to a solution of sulfonamide **13** (6.16 g, 9.24 mmol, 1 equiv) in methanol (92.5 mL) at 23 °C. The resulting solution was stirred for 1 h, then was concentrated in vacuo (final volume, 15 mL). The concentrate was partitioned between ethyl acetate (400 mL) and a 1:1 mixture of saturated aqueous ammonium chloride solution and brine (300 mL). The organic layer was separated, and the aqueous layer was extracted with additional ethyl acetate (300 mL). The combined organic extracts were then dried over sodium sulfate, and the dried solution was concentrated in vacuo. Purification of the residue by flash column chromatography (40% ethyl acetate–hexanes) provided diol **14** as an orange oil (4.69 g, 97%).

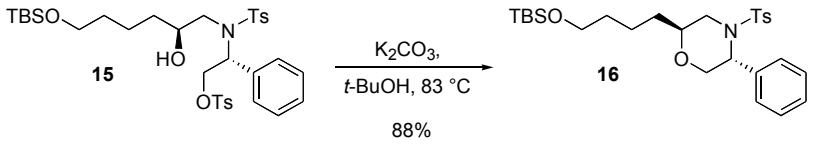
$^1$H NMR (600 MHz, $CDCl_3$), δ 7.61 (d, 2H, J = 7.8 Hz, $SO_2CC\mathbf{H}$), 7.28–7.24 (m, 3H, Ar**H** (Ph)), 7.22 (t, 2H, J = 7.2 Hz, Ar**H** (Ph)), 6.95 (d, 2H, J = 7.2 Hz, $SO_2CCHC\mathbf{H}$), 5.13 (dd, 1H, J = 5.4, 9.6 Hz, C**H**Ph), 4.23 (ddd, 1H, J = 6.0, 9.6, 12.0 Hz, $C\mathbf{H}_2$OH), 4.12 (ddd, 1H, J = 6.0, 12.0, 12.6 Hz, $C\mathbf{H}_2$OH), 3.76 (m, 1H, C**H**OH), 3.57 (t, 2H, J = 6.0 Hz, $C\mathbf{H}_2$OTBS), 3.19 (dd, 1H, J = 10.2, 15.6 Hz, $C\mathbf{H}_2$NTs), 3.16 (d, 1H, J = 6.6 Hz, CHO**H**), 3.08 (t, 1H, J = 6.6 Hz, $CH_2O\mathbf{H}$), 2.97 (dd, 1H, J = 3.6, 15.6 Hz, $C\mathbf{H}_2$NTs), 2.43 (s, 3H, Ar$C\mathbf{H}_3$), 1.52–1.42 (m, 3H, $C\mathbf{H}_2CH_2C\mathbf{H}_2CH_2$OTBS), 1.40–1.34 (m, 1H, $C\mathbf{H}_2CH_2CH_2CH_2$OTBS), 1.34–1.28 (m, 2H, $C\mathbf{H}_2CH_2CH_2$OTBS), 0.88 (s, 9H, $C(C\mathbf{H}_3)_3$), 0.03 (s, 6H, $Si(C\mathbf{H}_3)_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 143.8, 137.4, 135.5, 129.8, 128.9, 128.6, 128.3, 127.5, 70.7, 63.4, 63.2, 63.1, 51.8, 35.4, 32.8, 26.1, 21.9, 21.7, 18.5, –5.1. FTIR (neat film), cm$^{-1}$ 3448 (br, s, OH), 2929 (s), 2858 (s), 1459 (w), 1333 (m), 1255 (m), 1157 (s), 1090 (s), 938 (m), 836 (m), 775 (m), 698 (m), 662 (m). HRMS (TOF ES$^+$) calcd for $C_{27}H_{44}NO_5SSi^+$ $(M+H)^+$: 522.2709, found: 522.2691. TLC (50% ethyl acetate–hexanes), $R_f$ 0.40.




**Tosylate 15:** Triethylamine (4.64 mL, 33.29 mmol, 3.7 equiv) was added to a solution of diol **14** (4.69 g, 8.99 mmol, 1 equiv) in dichloromethane (90 mL) at 23 °C. *p*-Toluenesulfonyl chloride (2.14 g, 11.22 mmol, 1.25 equiv) and *N*,*N*-dimethylaminopyridine (439.2 mg, 3.59 mmol, 0.4 equiv) were then added sequentially, and the resulting solution was stirred at 23 °C for 1 h. The reaction solution was then diluted with ethyl acetate (500 mL), and the resulting solution was washed sequentially with saturated aqueous ammonium chloride solution (300 mL) and a 1:1 mixture of saturated aqueous sodium bicarbonate solution and brine (300 mL). The organic layer was separated and dried over sodium sulfate, and the dried solution was concentrated in vacuo to afford tosylate **15** as an orange oil (6.08 g, 100%; 4.4:1 mixture of **15** and bis-*O*-tosylated **14** (~81% yield of the monotosylate)). This mixture was employed directly in the subsequent reaction.

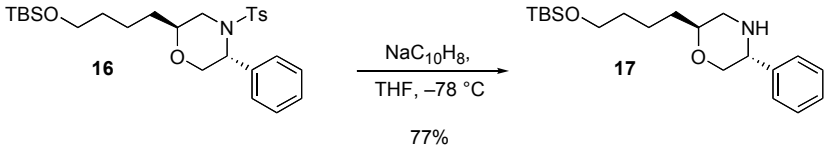
$^1$H NMR (400 MHz, $CDCl_3$), δ 7.75 (d, 2H, J = 8.4 Hz, $OSO_2CC\mathbf{H}$), 7.62 (d, 2H, J = 8.4 Hz, $NSO_2CC\mathbf{H}$), 7.35 (d, 2H, J = 8.4 Hz, $OSO_2CCHC\mathbf{H}$), 7.30–7.20 (m, 5H, Ar**H** (Ph)), 6.96 (d, 2H, J = 6.4 Hz, $NSO_2CCHC\mathbf{H}$), 5.21 (t, 1H, J = 8.0 Hz,

C**H**Ph), 4.58 (dd, 1H, J = 8.4, 10.4 Hz, C**H**$_2$OTs), 4.51 (dd, 1H, J = 6.4, 10.4 Hz, C**H**$_2$OTs), 3.56 (m, 1H, C**H**OH), 3.55 (t, 2H, J = 6.4 Hz, C**H**$_2$OTBS), 2.99 (dd, 1H, J = 9.2, 15.2 Hz, C**H**$_2$NTs), 2.79 (dd, 1H, J = 2.4, 15.2 Hz, C**H**$_2$NTs), 2.47 (s, 3H, ArC**H**$_3$ (OTs)), 2.44 (s, 3H, ArC**H**$_3$ (NTs)), 2.30 (d, 1H, J = 4.0 Hz, CHO**H**), 1.49–1.38 (m, 2H, C**H**$_2$CH$_2$OTBS), 1.37–1.28 (m, 1H, C**H**$_2$CH$_2$CH$_2$CH$_2$OTBS), 1.28–1.14 (m, 3H, C**H**$_2$C**H**$_2$CH$_2$CH$_2$OTBS), 0.88 (s, 9H, C(C**H**$_3$)$_3$), 0.03 (s, 6H, Si(C**H**$_3$)$_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 145.3, 144.0, 136.7, 134.2, 132.5, 130.1, 129.9, 129.0, 128.9, 128.4, 128.3, 127.6, 71.0, 68.4, 63.1, 59.9, 52.0, 34.8, 32.8, 26.1, 21.8, 21.8, 21.7, 18.5, –5.1. FTIR (neat film), cm$^{-1}$ 3541 (br, s, OH), 3066 (w), 3035 (w), 2951 (s), 2930 (s), 2857 (s), 1598 (m), 1462 (m), 1367 (m), 1344 (m), 1256 (w), 1190 (m), 1177 (s), 1160 (m), 1096 (m), 976 (m), 837 (m), 814 (m), 774 (m), 661 (m). LRMS (TOF ES$^+$) calcd for $C_{34}H_{50}NO_7S_2Si^+$ (M+H)$^+$: 676, found: 676. TLC (40% ethyl acetate–hexanes), $R_f$ 0.44.



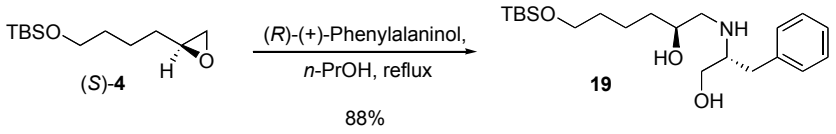

***N*-Tosyl Morpholine 16:** Solid potassium carbonate (2.02 g, 14.62 mmol, 2.0 equiv) was added to a solution of tosylate **15** (6.33 g (a 4.4:1 mixture of **15** and bis-*O*-tosylated **14**), 7.73 mmol (of **15**), 1 equiv) in *tert*-butyl alcohol (150 mL). The resulting white suspension was heated at reflux for 12.5 h, then was partitioned between ethyl acetate (400 mL) and a 1:1 mixture of saturated aqueous ammonium chloride solution and brine (400 mL). The organic layer was separated and the aqueous layer was extracted with additional ethyl acetate (400 mL). The combined organic extracts were then dried over sodium sulfate, and the dried solution was concentrated in vacuo. The residue was purified by flash column chromatography (12% ethyl acetate–hexanes initially, grading to 40% ethyl acetate–hexanes), yielding *N*-tosyl morpholine **16** as a yellow oil (3.24 g, 71% from **14**, two steps).

$^1$H NMR (600 MHz, $CDCl_3$), δ 7.41 (d, 2H, J = 7.8, $SO_2CC$**H**), 7.28–7.25 (m, 5H, Ar**H** (Ph)), 7.24 (d, 2H, J = 7.8 Hz, $SO_2CCHC$**H**), 3.82 (dd, 1H, J = 2.4, 12.0 Hz, C**H**$_2$NTs), 3.71 (dd, 1H, J = 3.6, 9.0 Hz, C**H**Ph), 3.70 (m, 1H, C**H**OCH$_2$), 3.68 (dd, 1H, J = 4.2, 12.6 Hz, C**H**$_2$OCH), 3.60 (t, 2H, J = 6.6 Hz, C**H**$_2$OTBS), 3.55 (dd, 1H, J = 10.2, 12.6 Hz, C**H**$_2$OCH), 2.45 (dd, 1H, J = 9.6, 11.4 Hz, C**H**$_2$NTs), 2.42 (s, 3H, ArC**H**$_3$), 1.58–1.50 (m, 3H, C**H**$_2$C**H**$_2$CH$_2$OTBS), 1.50–1.43 (m, 2H, C**H**$_2$CH$_2$CH$_2$CH$_2$OTBS), 1.43–1.35 (m, 1H, C**H**$_2$CH$_2$CH$_2$OTBS), 0.89 (s, 9H, C(C**H**$_3$)$_3$), 0.04 (s, 6H, Si(C**H**$_3$)$_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 143.8, 137.0, 133.2, 129.5, 128.6, 128.4, 128.2, 128.1, 75.6, 72.2, 63.0, 61.5, 50.9, 32.8, 32.8, 26.1, 21.7, 21.7, 18.5, –5.1. FTIR (neat film), cm$^{-1}$ 3064 (w), 3033 (w), 2952 (s), 2929 (s), 2857 (s), 1598 (m), 1494 (m), 1472 (m), 1360 (s), 1255 (m), 1170 (s), 1097 (s), 940 (m), 837 (s), 776 (m), 761 (m), 737 (m), 701 (m), 679 (w), 659 (m). HRMS (TOF ES$^+$) calcd for $C_{27}H_{42}NO_4SSi^+$ (M+H)$^+$: 504.2604, found: 504.2605. TLC (20% ethyl acetate–hexanes), $R_f$ 0.45.



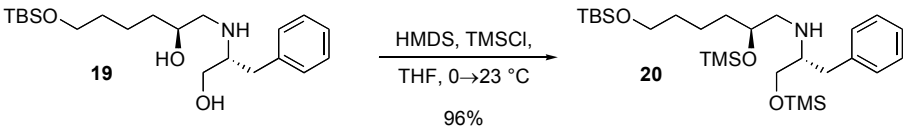

**(2*S*,5*R*)-2-[4-(*tert*-Butyldimethylsiloxy)-1-butyl]-5-phenyl-morpholine (17):** Naphthalene (4.79 g, 37.37 mmol, 6.25 equiv) was added in one portion to a vigorously stirred suspension of sodium (686.8 mg, 29.87 mmol, 5.0 equiv; washed free of oil in hexanes) in tetrahydrofuran (14.9 mL) at 23 °C. The resulting green suspension was stirred for 2 h at 23 °C, then was transferred in portions (by cannula) to a solution of *N*-tosyl morpholine **16** (3.01 g, 5.97 mmol, 1 equiv) in tetrahydrofuran (60 mL) cooled in a dry ice/acetone bath; portionwise addition of this suspension to the reaction solution was ceased upon formation of a persistent, dark-green reaction solution. The dark-green solution was stirred at –78 °C for 5 min. Saturated aqueous ammonium chloride solution (24 mL; added in eight portions) was then CAREFULLY added to this solution at –78 °C. The resulting suspension was stirred at –78 °C for 2 min, then was allowed to warm to ambient temperature (23 °C). The suspension was then partitioned between ethyl acetate (400 mL) and a 1:1 mixture of brine and saturated aqueous sodium bicarbonate solution (300 mL). The organic layer was separated, and the aqueous later was extracted with additional ethyl acetate (400 mL). The organic extracts were then combined and dried over sodium sulfate, and the dried extracts were concentrated in vacuo. The residue was purified by flash column chromatography (hexanes initially, grading to 30% ethyl acetate–hexanes), affording (2*S*,5*R*)-2-[4-(*tert*-butyldimethylsiloxy)-1-butyl]-5-phenyl-morpholine (**17**) as a yellow-orange oil (1.60 g, 77%).

$^1$H NMR (400 MHz, $CDCl_3$), δ 7.40–7.25 (m, 5H, Ar**H**), 3.90–3.85 (m, 2H, C**H**$_2$OCH, C**H**Ar), 3.62 (t, 2H, J = 6.4 Hz, C**H**$_2$OTBS), 3.53 (m, 1H, C**H**OCH$_2$), 3.44 (t, 1H, J = 5.6 Hz, C**H**$_2$OCH), 3.07 (dd, 1H, J = 2.4, 12.0 Hz, C**H**$_2$NH), 2.74 (dd, 1H, J = 10.4, 11.6 Hz, C**H**$_2$NH), 1.87 (br, s, 1H, N**H**), 1.62–1.36 (m, 6H, C**H**$_2$C**H**$_2$C**H**$_2$CH$_2$OTBS), 0.89 (s, 9H, SiC(C**H**$_3$)$_3$), 0.05 (s, 6H, Si(C**H**$_3$)$_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 140.6, 128.6, 127.9, 127.3, 76.3, 74.0, 63.2, 60.5, 51.9, 33.5, 33.0, 26.1, 21.8, 18.5, –5.1. FTIR (neat film), cm$^{-1}$ 3326 (w, NH), 3030 (w), 2950 (s), 2932 (s), 2856 (s), 1473 (w), 1256 (m), 1099 (s), 836 (s), 775 (m), 756 (w), 700 (m), 660 (w). HRMS (TOF ES$^+$) calcd for $C_{20}H_{36}NO_2Si^+$ (M+H)$^+$: 350.2515, found: 350.2508. TLC (50% ethyl acetate–hexanes), $R_f$ 0.09.




**Amino Diol 19:** A solution of (*S*)-2-[4-(*tert*-butyldimethylsiloxy)-1-butyl]oxirane[5] ((*S*)-**4**, 0.878 g/mL, 600.0 μL, 2.29 mmol, 1 equiv) and (*R*)-(+)-2-amino-3-phenyl-1-propanol (97% ee, 1.38 g, 9.13 mmol, 4.0 eq) in 1-propanol (2.29 mL) was heated at reflux for 17 h. The resulting yellow solution was concentrated in vacuo, and the oily residue purified by flash chromatography (10% methanol–ethyl acetate initially, grading to 20% methanol–ethyl acetate), affording amino diol **19** as a waxy, off-white solid (770.5 mg, 88%).

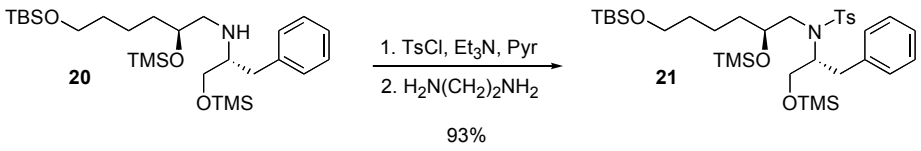
$^1$H NMR (400 MHz, $CDCl_3$), δ 7.31 (t, 2H, J = 7.2 Hz, Ar**H**), 7.25–7.21 (m, 1H, Ar**H**), 7.21–7.17 (m, 2H, Ar**H**), 3.64 (dd, 1H, J = 3.6, 10.8 Hz, C**H**$_2$OH), 3.60 (t, 3H, J = 6.0 Hz, C**H**$_2$OTBS, C**H**OH), 3.44 (dd, 1H, J = 5.2, 10.8 Hz, C**H**$_2$OH), 3.01–2.88 (m, 4H, C**H**CH$_2$Ph, CHO**H**, CH$_2$O**H**, N**H**), 2.86–2.75 (m, 3H, C**H**$_2$NH, C**H**$_2$Ph), 2.48 (dd, 1H, J = 8.8, 12.0 Hz, C**H**$_2$NH), 1.57–1.46 (m, 2H, C**H**$_2$CH$_2$OTBS), 1.46–1.31 (m, 4H, C**H**$_2$C**H**$_2$CH$_2$CH$_2$OTBS), 0.89 (s, 9H, C(C**H**$_3$)$_3$), 0.04 (s, 6H, Si(C**H**$_3$)$_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 138.3, 129.3, 128.8, 126.7, 70.2, 63.2, 62.7, 60.8, 52.8, 37.8, 34.8, 32.9, 26.1, 22.0, 18.5, –5.1. FTIR (neat film), cm$^{-1}$ 3333 (br, s, OH), 3063 (w), 3028 (w), 2934 (s), 2858 (s), 1496 (m), 1256 (m), 1098 (br, s), 1040 (m), 835 (m), 775 (m), 745 (m), 700 (m), 662 (w). HRMS (TOF ES$^+$) calcd for $C_{21}H_{40}NO_3Si^+$ (M+H)$^+$: 382.2777, found: 382.2785. TLC (10% methanol–ethyl acetate), $R_f$ 0.46.




**Bis-Trimethylsilyl Ether 20:** 1,1,1,3,3,3-Hexamethyldisilazane (786.5 μL, 3.73 mmol, 2.05 equiv) and chlorotrimethylsilane (46.2 μL, 364.0 μmol, 0.2 equiv) were added sequentially to a solution of amino diol **19** (694.0 mg, 1.82 mmol, 1 equiv) in tetrahydrofuran (18.2 mL) at 0 °C. After 2 min, the ice bath was removed, and the resulting white suspension was stirred at 23 °C for 70 min. Additional chlorotrimethylsilane (92.4 μL, 728.0 μmol, 0.4 equiv) was then added, and the resulting suspension was stirred at 23 °C for 25 min. The suspension was then partitioned between ethyl ether (200 mL) and a 1:1 mixture of aqueous phosphate buffer solution (0.05 M monobasic sodium phosphate, 0.05 M dibasic potassium phosphate, pH = 7) and brine (200 mL). The organic layer was separated, and the aqueous layer was extracted with additional ethyl ether (200 mL). The combined organic extracts were then dried over sodium sulfate, and the dried solution was concentrated in vacuo, providing bis-trimethylsilyl ether **20** as a light-yellow oil (920.6 mg, 96%).

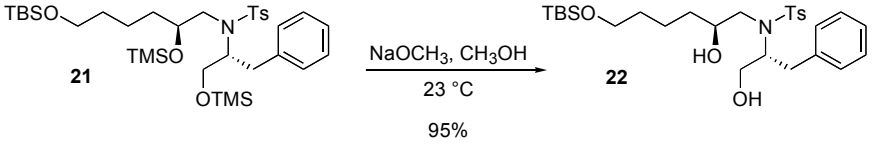
$^1$H NMR (400 MHz, $CDCl_3$), δ 7.27 (t, 2H, J = 8.0 Hz, Ar**H**), 7.22–7.16 (m, 3H, Ar**H**), 3.74 (p, 1H, J = 5.6 Hz, C**H**OTMS), 3.59 (t, 2H, J = 6.8 Hz, C**H**$_2$OTBS), 3.47 (dd, 1H, J = 4.8, 10.4 Hz, C**H**$_2$OTMS), 3.41 (dd, 1H, J = 6.4, 10.4 Hz, C**H**$_2$OTMS), 2.84–2.73 (m, 2H, C**H**CH$_2$Ph, CHC**H**$_2$Ph), 2.67–2.61 (m, 2H, CHC**H**$_2$Ph, C**H**$_2$NH), 2.54 (dd, 1H, J = 6.8, 10.8 Hz, C**H**$_2$NH), 1.79 (br, s, 1H, N**H**), 1.53–1.41 (m, 4H, C**H**$_2$CH$_2$C**H**$_2$CH$_2$OTBS), 1.41–1.22 (m, 2H, C**H**$_2$CH$_2$CH$_2$OTBS), 0.89 (s, 9H, C(C**H**$_3$)$_3$), 0.09 (s, 9H, CH$_2$OSi(C**H**$_3$)$_3$), 0.08 (s, 9H, CHOSi(C**H**$_3$)$_3$), 0.04 (s, 6H, Si(C**H**$_3$)$_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 139.6, 129.4, 128.4, 126.2, 72.7, 64.0, 63.2, 61.4, 53.9, 38.2, 35.9, 33.1, 26.1, 22.1, 18.5, 0.64, –0.37, –5.1. FTIR (neat film), cm$^{-1}$ 3336 (w, NH), 3028 (w), 2955 (m), 2859 (m), 1472 (m), 1252 (s), 1101 (br s), 839 (s), 775 (m), 746 (m), 700 (m). HRMS (TOF ES$^+$) calcd for $C_{27}H_{56}NO_3Si_3^+$ (M+H)$^+$: 526.3568, found: 526.3560. TLC (50% ethyl acetate–hexanes), $R_f$ 0.71.

[5] Prepared as previously reported in Myers, A. G.; Lanman, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 12969–12971.



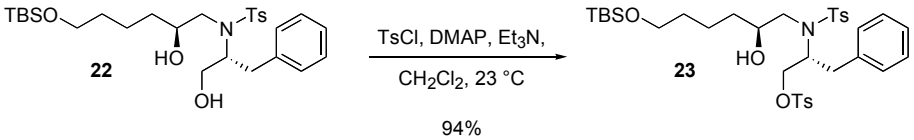

**Sulfonamide 21:** Triethylamine (1.53 mL, 10.98 mmol, 6.0 equiv) and *p*-toluenesulfonyl chloride (1.05 g, 5.51 mmol, 3.0 equiv) were added sequentially to a solution of bis-trimethylsilyl ether **20** (962.6 mg, 1.83 mmol, 1 equiv) in pyridine (9.2 mL) at 23 °C. The resulting red-orange solution was stirred at 23 °C for 80 min. Ethylene diamine (367.0 μL, 5.49 mmol, 3.0 equiv) was then added, and the resulting solution was stirred at 23 °C for 12 h. The solution was then diluted with ethyl acetate (200 mL), and the resulting solution was washed sequentially with saturated aqueous ammonium chloride solution (200 mL) and a 1:1 mixture of saturated aqueous sodium bicarbonate solution and brine (200 mL). The organic layer was separated, and the aqueous washes were combined and extracted with ethyl acetate (250 mL). The organic extracts were then combined and dried over sodium sulfate, and the dried solution was concentrated in vacuo. Chromatographic purification of the oily residue (loaded onto a silica column in dichloromethane, eluted with 10% ethyl acetate–hexanes) provided sulfonamide **21** as a light-yellow oil (1.16 g, 93%).

$^1$H NMR (400 MHz, $CDCl_3$), δ 7.71 (d, 2H, J = 8.0 Hz, $SO_2CC\mathbf{H}$), 7.28–7.20 (m, 4H, Ar**H** (Ph), $SO_2CCHC\mathbf{H}$), 7.20–7.15 (m, 3H, Ar**H** (Ph)), 3.99 (m, 2H, C**H**OTMS, C**H**$CH_2$Ph), 3.59 (t, 2H, J = 6.0 Hz, C$\mathbf{H}_2$OTMS), 3.48 (dd, 1H, J = 7.2, 11.2 Hz, C$\mathbf{H}_2$OTMS), 3.39 (dd, 1H, J = 4.4, 11.2 Hz, C$\mathbf{H}_2$OTMS), 3.21 (d, 2H, J = 6.4 Hz, C$\mathbf{H}_2$Ph), 2.91 (dd, 1H, J = 4.4, 13.6 Hz, C$\mathbf{H}_2$NTs), 2.82 (dd, 1H, J = 10.4, 13.6 Hz, C$\mathbf{H}_2$NTs), 2.39 (s, 3H, ArC$\mathbf{H}_3$), 1.64–1.55 (m, 1H, C$\mathbf{H}_2$$CH_2CH_2CH_2$OTBS), 1.51–1.40 (m, 3H, C$\mathbf{H}_2$C$\mathbf{H}_2$$CH_2CH_2$OTBS), 1.40–1.30 (m, 1H, C$\mathbf{H}_2$$CH_2CH_2CH_2$OTBS), 1.27–1.16 (m, 1H, C$\mathbf{H}_2$$CH_2CH_2$OTBS), 0.89 (s, 9H, C(C$\mathbf{H}_3$)$_3$), 0.16 (s, 9H, Si(C$\mathbf{H}_3$)$_3$), 0.05 (s, 6H, Si(C$\mathbf{H}_3$)$_2$), –0.12 (s, 9H, Si(C$\mathbf{H}_3$)$_3$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 143.0, 138.8, 138.1, 129.5, 129.3, 128.6, 127.6, 126.5, 72.2, 63.3, 62.3, 61.3, 51.2, 38.2, 34.9, 33.3, 26.1, 22.0, 21.6, 18.5, 0.72, –0.72, –5.1. FTIR (neat film), cm$^{-1}$ 3029 (w), 2955 (s), 2931 (m), 2859 (m), 1459 (m), 1343 (m), 1252 (s), 1160 (m), 1103 (s), 841 (s), 775 (m), 748 (m), 700 (m), 658 (m). HRMS (TOF ES$^+$) calcd for $C_{34}H_{62}NO_5SSi_3^+$ $(M+H)^+$: 680.3656, found: 680.3646. TLC (10% ethyl acetate–hexanes), $R_f$ 0.50.



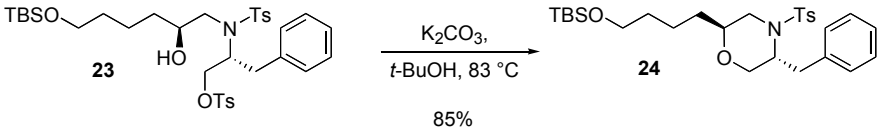

**Diol 22:** Sodium methoxide (18.4 mg, 340.6 μmol, 0.2 equiv) was added in one potion to a solution of sulfonamide **21** (1.16 g, 1.71 mmol, 1 equiv) in methanol (17.0 mL) at 23 °C. The resulting solution was stirred for 40 min, then was concentrated in vacuo (final volume, 5 mL). The concentrate was partitioned between ethyl acetate (160 mL) and a 1:1 mixture of saturated aqueous ammonium chloride solution and brine (160 mL). The organic later was separated, and the aqueous layer was extracted with additional ethyl acetate (160 mL). The combined organic extracts were then dried over sodium sulfate, and the dried extracts were concentrated in vacuo to provide diol **22** as a yellow oil (867.4 mg, 95%).

$^1$H NMR (400 MHz, $CDCl_3$), δ 7.65 (d, 2H, J = 8.4 Hz, $SO_2CC\mathbf{H}$), 7.26–7.18 (m, 5H, Ar**H** (Ph)), 7.03 (dd, 2H, J = 8.4 Hz, $SO_2CCHC\mathbf{H}$), 4.14 (m, 1H, C$\mathbf{H}_2$OH), 3.74 (m, 1H, C**H**OH), 3.69 (dd, 1H, J = 4.4, 10.4 Hz, C$\mathbf{H}_2$OH), 3.62 (t, 2H, J = 6.8 Hz, C$\mathbf{H}_2$OTBS), 3.28 (dd, 1H, J = 3.2, 15.2 Hz, C$\mathbf{H}_2$NTs), 3.18 (dd, 1H, J = 10.0, 15.2 Hz, C$\mathbf{H}_2$NTs), 2.72 (dd, 2H, J = 8.4, 13.6 Hz, C$\mathbf{H}_2$Ph, C**H**$CH_2$Ph), 2.66 (dd, 1H, J = 6.0, 13.6 Hz, C$\mathbf{H}_2$Ph), 2.41 (s, 3H, ArC$\mathbf{H}_3$), 1.56–1.47 (m, 3H, C$\mathbf{H}_2$C$\mathbf{H}_2$$CH_2$OTBS), 1.47–1.36 (m, 3H, C$\mathbf{H}_2$C$\mathbf{H}_2$$CH_2CH_2$OTBS), 0.90 (s, 9H, C(C$\mathbf{H}_3$)$_3$), 0.05 (s, 6H, Si(C$\mathbf{H}_3$)$_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 143.7, 137.7, 137.6, 129.9, 129.1, 128.8, 127.4, 126.9, 70.8, 63.6, 63.2, 51.9, 51.0, 36.0, 35.2, 32.8, 26.1, 22.0, 21.7, 18.5, –5.1. FTIR (neat film), cm$^{-1}$ 3439 (br, s, OH), 3064 (w), 3028 (w), 2953 (s), 2930 (s), 2858 (s), 1743 (m), 1599 (m), 1496 (m), 1462 (m), 1334 (m), 1256 (m), 1155 (m), 1091 (m), 1043 (m), 836 (m), 814 (m), 777 (m), 701 (m), 660 (m). LRMS (TOF ES$^+$) calcd for $C_{28}H_{46}NO_5SSi^+$ $(M+H)^+$: 536, found: 536. TLC (30% ethyl acetate–hexanes), $R_f$ 0.28.



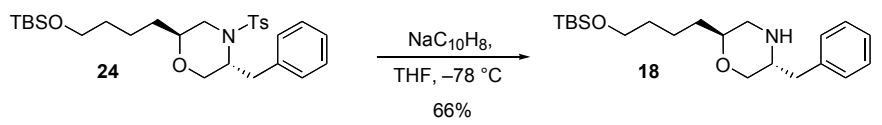
**Tosylate 23:** Triethylamine (429.1 μL, 3.08 mmol, 4.0 equiv) was added to a solution of diol **22** (412.4 mg, 769.7 μmol, 1 equiv) in dichloromethane (9.6 mL) at 23 °C. *p*-Toluenesulfonyl chloride (183.4 mg, 962.0 μmol, 1.25 equiv) and *N*,*N*-dimethylaminopyridine (37.6 mg, 307.8 μmol, 0.4 equiv) were then added sequentially, and the resulting solution was stirred for 3.2 h. The reaction solution was then diluted with ethyl acetate (100 mL), and the resulting solution washed sequentially with saturated aqueous ammonium chloride solution (80 mL) and a 1:1 mixture of saturated aqueous sodium bicarbonate solution and brine (80 mL). The organic layer was dried over sodium sulfate, and the dried solution concentrated in vacuo to provide tosylate **23** as an orange oil (496.8 mg, 103%; 10:1 mixture of **23** and bis-*O*-tosylated **22** (~94% yield of the monotosylate)). This mixture was employed directly in the subsequent reaction.

$^1$H NMR (400 MHz, $CDCl_3$), δ 7.65 (d, 2H, J = 8.4 Hz, $OSO_2CC\mathbf{H}$), 7.61 (d, 2H, J = 8.4 Hz, $NSO_2CC\mathbf{H}$), 7.31 (d, 2H, J = 8.4 Hz, $OSO_2CCHC\mathbf{H}$), 7.23 (d, 2H, J = 7.6 Hz, $NSO_2CCHC\mathbf{H}$), 7.20 (app t, 3H, Ar**H** (Ph)), 7.04–7.01 (m, 2H, Ar**H** (Ph)), 4.20–4.11 (m, 2H, $C\mathbf{H}_2OTs$, $C\mathbf{H}CH_2Ph$), 3.99 (dd, 1H, J = 3.2, 9.2 Hz, $C\mathbf{H}_2OTs$), 3.66 (m, 1H, C**H**OH), 3.62 (t, 2H, J = 6.4 Hz, $C\mathbf{H}_2OTBS$), 3.12 (dd, 1H, J = 2.8, 15.6 Hz, $C\mathbf{H}_2NTs$), 3.01 (dd, 1H, J = 8.8, 15.6 Hz, $C\mathbf{H}_2NTs$), 2.92 (dd, 1H, J = 8.4, 14.0 Hz, $C\mathbf{H}_2Ph$), 2.83 (dd, 1H, J = 6.0, 14.0 Hz, $C\mathbf{H}_2Ph$), 2.61 (d, 1H, J = 4.0 Hz, CHO**H**), 2.45 (s, 3H, $ArC\mathbf{H}_3$ (OTs)), 2.41 (s, 3H, $ArC\mathbf{H}_3$ (NTs)), 1.58–1.41 (m, 3H, $C\mathbf{H}_2C\mathbf{H}_2CH_2OTBS$), 1.41–1.30 (m, 3H, $C\mathbf{H}_2C\mathbf{H}_2CH_2CH_2OTBS$), 0.90 (s, 9H, $C(C\mathbf{H}_3)_3$), 0.06 (s, 6H, $Si(C\mathbf{H}_3)_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 145.3, 143.9, 136.9, 136.6, 132.4, 130.1, 129.9, 129.1, 128.9, 128.1, 127.6, 127.0, 70.8, 69.6, 63.2, 60.0, 52.3, 36.4, 34.9, 32.9, 26.1, 21.9, 21.8, 21.7, 18.5, –5.1. FTIR (neat film), cm$^{-1}$ 3528 (br w, OH), 3060 (w), 3032 (w), 2949 (m), 2929 (m), 2858 (m), 1364 (m), 1340 (m), 1256 (m), 1189 (m), 1178 (s), 1157 (m), 1096 (m), 974 (m), 836 (s), 814 (m), 777 (m), 666 (m). LRMS (TOF ES$^+$) calcd for $C_{35}H_{52}NO_7S_2Si^+$ $(M+H)^+$: 690, found: 690. TLC (30% ethyl acetate–hexanes), $R_f$ 0.34.




**N-Tosyl Morpholine 24:** A mixture of anhydrous potassium carbonate (111.8 mg, 808.9 μmol, 2.0 equiv), tosylate **23** (313.4 mg (a 10:1 mixture of **23** and bis-*O*-tosylated **22**), 404.6 μmol (of **23**), 1 equiv), and *t*-butanol (20.2 mL) was stirred at reflux (83 °C) for 28.5 h. The mixture was then partitioned between ethyl acetate (80 mL) and a 1:1 mixture of saturated aqueous ammonium chloride and brine (20 mL), and the organic layer was separated. The aqueous layer was extracted with additional ethyl acetate (80 mL), and the organic layers were then combined and dried over sodium sulfate. The dried solution was then concentrated in vacuo. Chromatographic purification of the oily residue (15% ethyl acetate–hexanes) afforded *N*-tosyl morpholine **24** as a clear oil (178.3 mg, 80% from **22**, two steps).

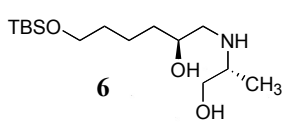
$^1$H NMR (600 MHz, $CDCl_3$), δ 7.21 (d, 2H, J = 8.4 Hz, $SO_2CC\mathbf{H}$), 7.31 (d, 2H, J = 7.8 Hz, $SO_2CCHC\mathbf{H}$), 7.26 (t, 2H, J = 8.4 Hz, Ar**H** (Ph)), 7.19 (t, 1H, J = 7.2 Hz, Ar**H** (Ph)), 7.12 (d, 2H, J = 7.2 Hz, Ar**H** (Ph)), 3.76 (m, 1H, $C\mathbf{H}OCH_2$), 3.66 (dd, 1H, J = 3.0, 11.4 Hz, $C\mathbf{H}_2Ph$), 3.58 (dd, 1H, J = 3.0, 11.4 Hz, $C\mathbf{H}_2OCH$), 3.57 (t, 2H, J = 8.4 Hz, $C\mathbf{H}_2OTBS$), 3.53 (dd, 1H, J = 9.0, 13.2 Hz, $C\mathbf{H}_2NTs$), 3.32 (dd, 1H, J = 2.4, 11.4 Hz, $C\mathbf{H}_2OCH$), 3.18 (dd, 1H, J = 3.6, 13.2 Hz, $C\mathbf{H}_2NTs$), 3.01 (t, 1H, J = 12.6 Hz, $C\mathbf{H}CH_2Ph$), 2.82 (dd, 1H, J = 3.0, 13.2 Hz, $C\mathbf{H}_2Ph$), 2.42 (s, 3H, $ArC\mathbf{H}_3$), 1.76–1.69 (m, 1H, $C\mathbf{H}_2CH_2CH_2CH_2OTBS$), 1.51–1.43 (m, 2H, $C\mathbf{H}_2CH_2OTBS$), 1.43–1.38 (m, 1H, $C\mathbf{H}_2CH_2CH_2CH_2OTBS$), 1.38–1.31 (m, 1H, $C\mathbf{H}_2CH_2CH_2OTBS$), 1.30–1.21 (m, 1H, $C\mathbf{H}_2CH_2CH_2OTBS$), 0.87 (s, 9H, $C(C\mathbf{H}_3)_3$), 0.03 (s, 6H, $Si(C\mathbf{H}_3)_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 143.7, 137.9, 136.8, 129.9, 129.5, 128.8, 127.3, 126.7, 72.5, 63.1, 61.7, 55.7, 45.1, 34.6, 32.7, 29.5, 26.1, 21.8, 21.7, 18.5, –5.1. FTIR (neat film), cm$^{-1}$ 3062 (w), 3028 (w), 2948 (m), 2930 (m), 2857 (m), 1599 (w), 1462 (m), 1352 (m), 1256 (m), 1165 (s), 1093 (s), 953 (m), 837 (m), 776 (m), 701 (m), 685 (m), 657 (w). HRMS (TOF ES$^+$) calcd for $C_{28}H_{44}NO_4SSi^+$ $(M+H)^+$: 518.2760, found: 518.2756. TLC (20% ethyl acetate–hexanes), $R_f$ 0.43.




**(2*S*,5*R*)-2-[4-(*tert*-Butyldimethylsiloxy)-1-butyl]-5-benzyl-morpholine (18):** Naphthalene (1.61 g, 12.56 mmol, 6.25 equiv) was added in one portion to a vigorously stirred suspension of sodium (230.5 mg, 10.03 mmol, 5.0 equiv; washed free of oil in hexanes) in tetrahydrofuran (5.0 mL) at 23 °C. The resulting green suspension was stirred at 23 °C for 2 h, then was transferred in portions (by cannula) to a solution of *N*-tosyl morpholine **24** (250.0 mg, 482.8 mmol, 1 equiv) in tetrahydrofuran (5.1 mL) cooled in a dry ice/acetone bath; portionwise addition of this suspension to the reaction solution

was ceased upon formation of a persistent, dark-green reaction solution. The dark-green solution was stirred at –78 °C for 5 min; saturated aqueous ammonium chloride solution (3 mL) was then SLOWLY added to this solution at –78 °C. The resulting suspension was stirred at –78 °C for 2 min, then was allowed to warm to ambient temperature (23 °C). The solution was then partitioned between ethyl acetate (70 mL) and a 1:1 mixture of saturated aqueous sodium bicarbonate solution and brine (30 mL). The organic layer was separated, and the aqueous later was extracted with additional ethyl acetate (70 mL). The combined organic extracts were dried over sodium sulfate, and the dried extract was concentrated in vacuo. The residue was purified by flash column chromatography (50% ethyl acetate–hexanes initially, grading to 100% ethyl acetate–hexanes, followed by 10% methanol–ethyl acetate), affording (2*S*,5*R*)-2-[4-(*tert*-butyldimethylsiloxy)-1-butyl]-5-benzyl-morpholine (**18**) as a clear orange oil (115.9 mg, 66%).

$^1$H NMR (400 MHz, $CDCl_3$), δ 7.31 (t, 2H, J = 6.8 Hz, Ar**H**), 7.24 (dt, 1H, J = 2.0, 7.2 Hz, Ar**H**), 7.20 (dd, 2H, J = 2.0, 6.4 Hz, Ar**H**), 3.86 (dd, 1H, J = 3.2, 11.2 Hz, C**H**$_2$OCH), 3.59 (t, 2H, J = 6.4 Hz, C**H**$_2$OTBS), 3.40 (dddd, 1H, J = 2.8, 5.2, 5.2, 7.2 Hz, C**H**OCH$_2$), 3.30 (t, 1H, J = 10.8 Hz, C**H**$_2$OCH), 2.96 (dddd, 1H, J = 3.2, 4.8, 9.2, 12.4 Hz, C**H**CHPh), 2.87 (dd, 1H, J = 2.4, 11.6 Hz, C**H**$_2$NH), 2.66 (dd, 1H, J = 4.8, 13.2 Hz, C**H**$_2$Ph), 2.47 (dd, 1H, J = 10.4, 12.0 Hz, C**H**$_2$NH), 2.43 (dd, 1H, J = 9.2, 13.2 Hz, C**H**$_2$Ph), 1.56–1.42 (m, 3H, C**H**$_2$CH$_2$C**H**$_2$CH$_2$OTBS), 1.42–1.28 (m, 3H, C**H**$_2$C**H**$_2$CH$_2$CH$_2$OTBS), 0.88 (s, 9H, C(C**H**$_3$)$_3$), 0.03 (s, 6H, Si(C**H**$_3$)$_2$). $^{13}$C NMR (100 MHz, $CDCl_3$), δ 138.1, 129.3, 128.8, 126.7, 76.6, 72.8, 63.2, 56.0, 51.7, 38.9, 33.4, 32.9, 26.1, 21.8, 18.5, –5.1. FTIR (neat film), cm$^{-1}$ 3026 (w), 2930 (m), 2856 (m), 1458 (m), 1256 (m), 1101 (s), 836 (m), 775 (m), 700 (m). HRMS (TOF ES$^+$) calcd for $C_{21}H_{38}NO_2Si^+$ $(M+H)^+$: 364.2672, found: 364.2665. TLC (50% ethyl acetate–hexanes), $R_f$ 0.17.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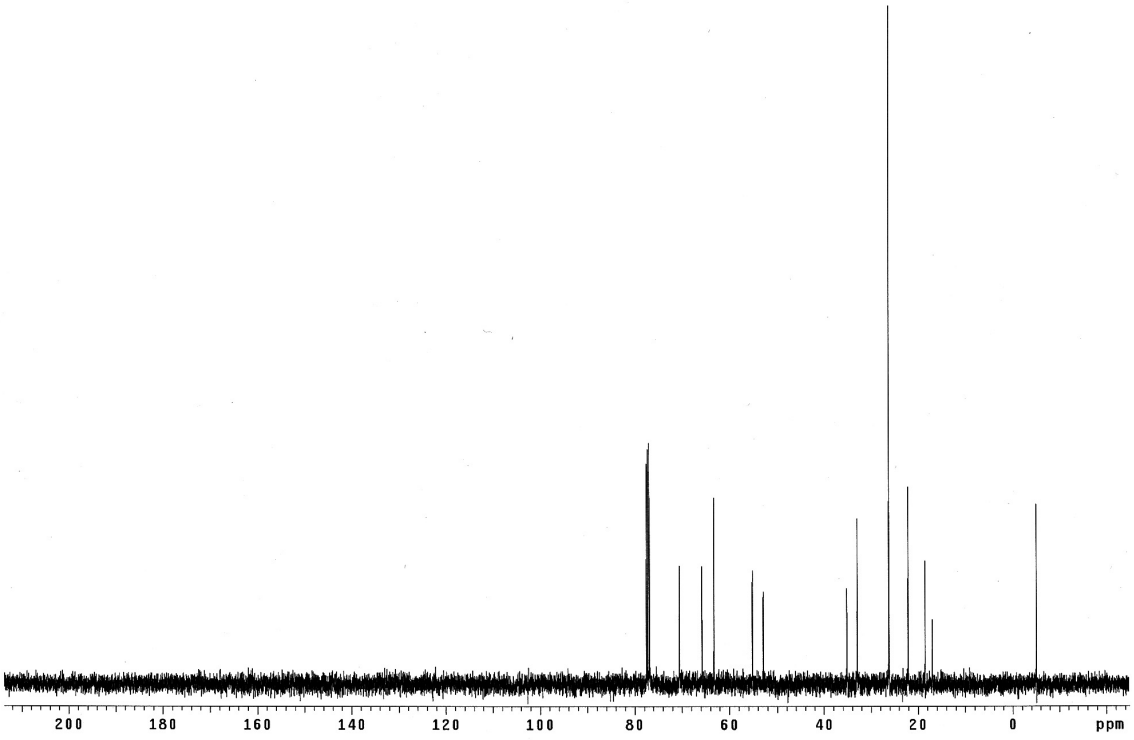
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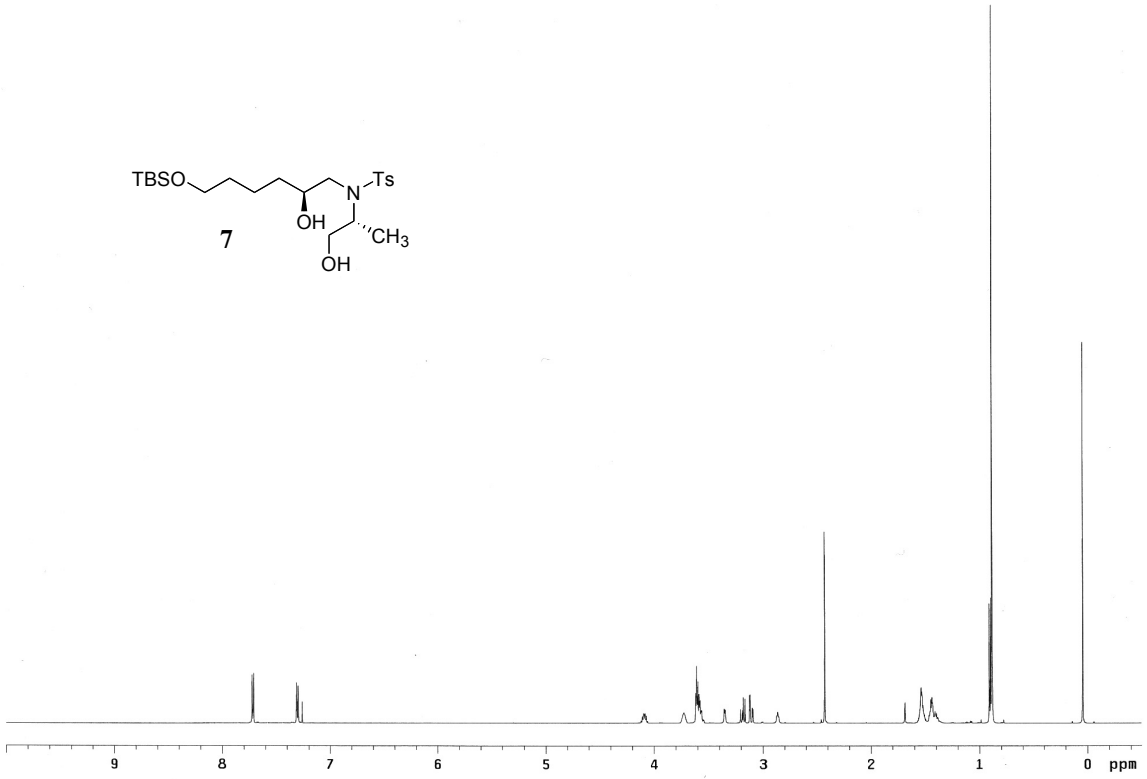
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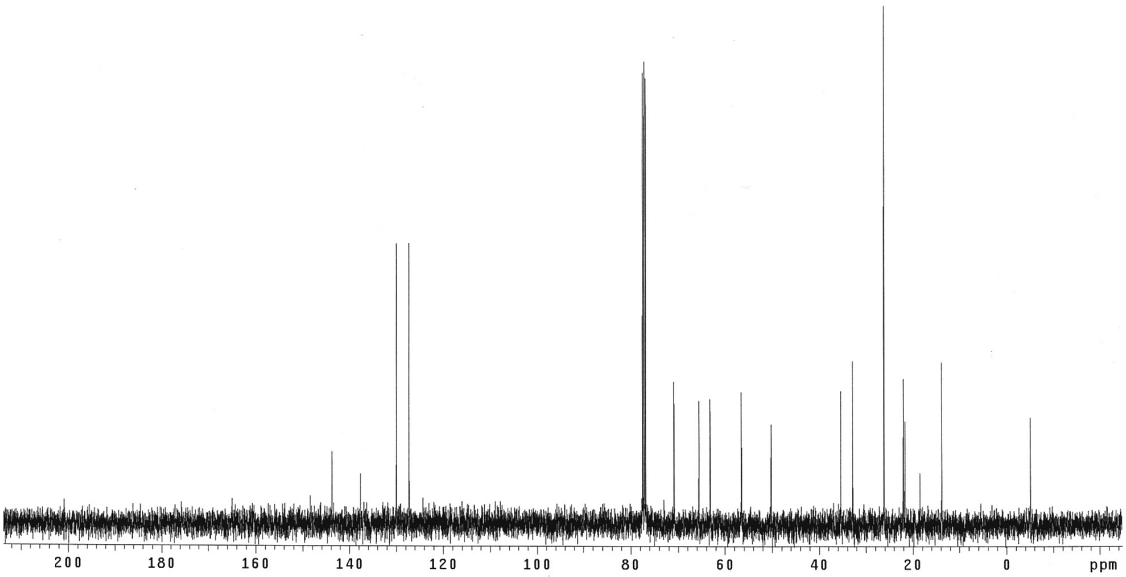
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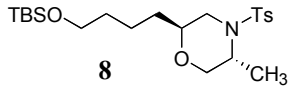
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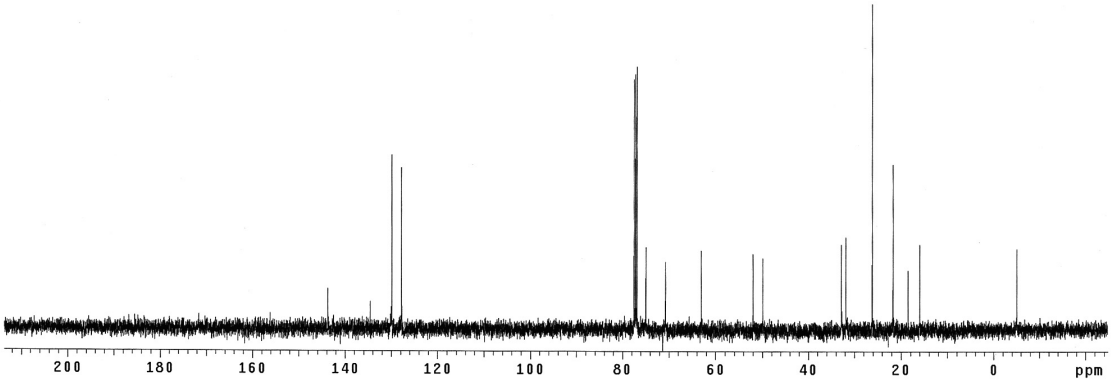
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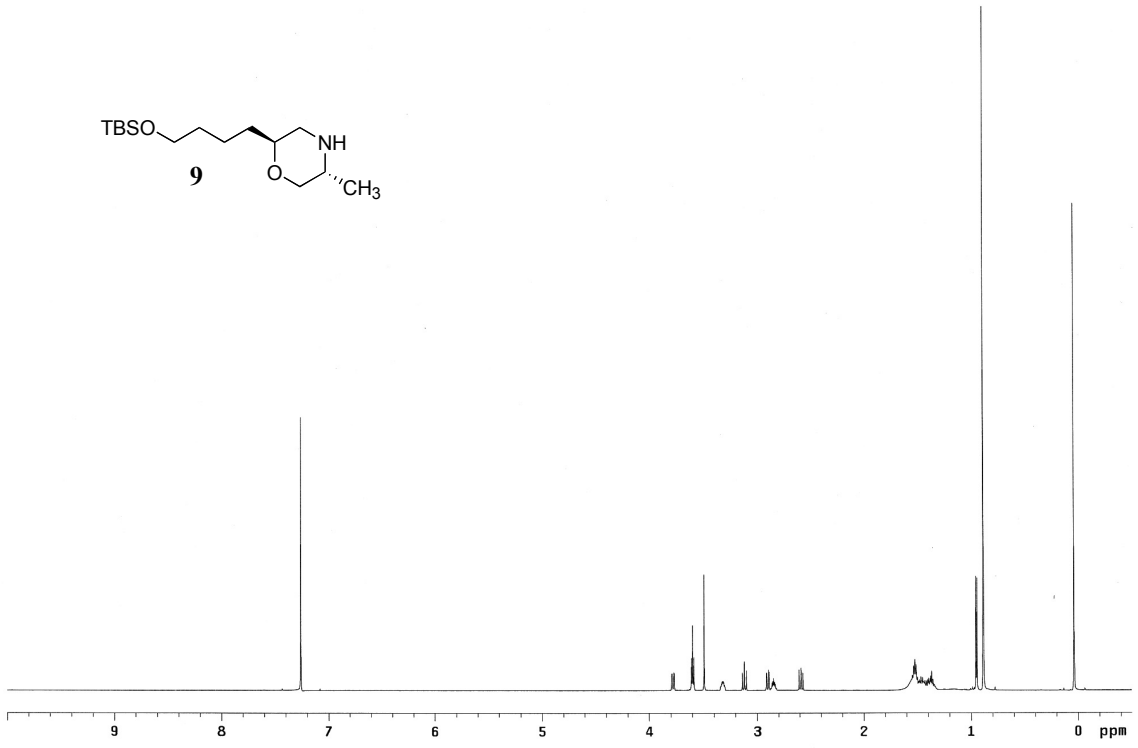
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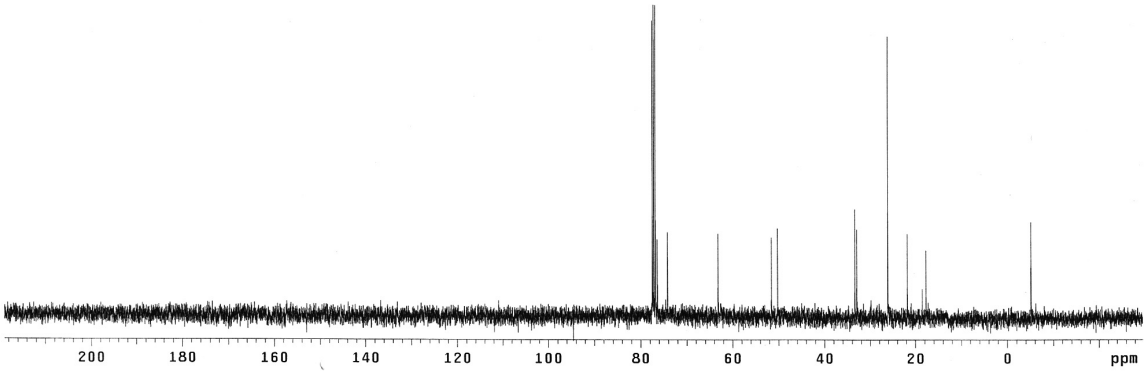
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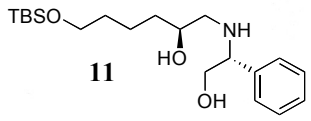
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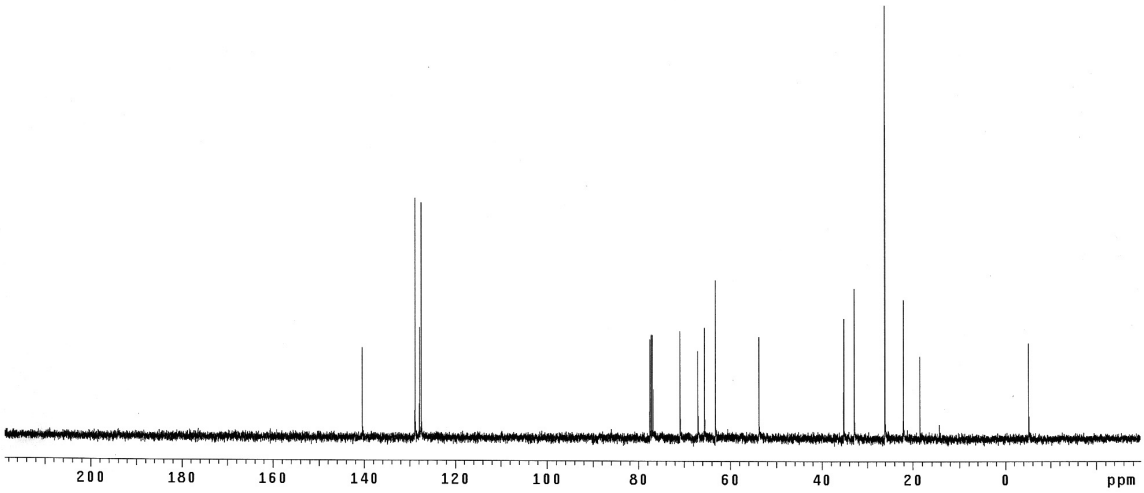
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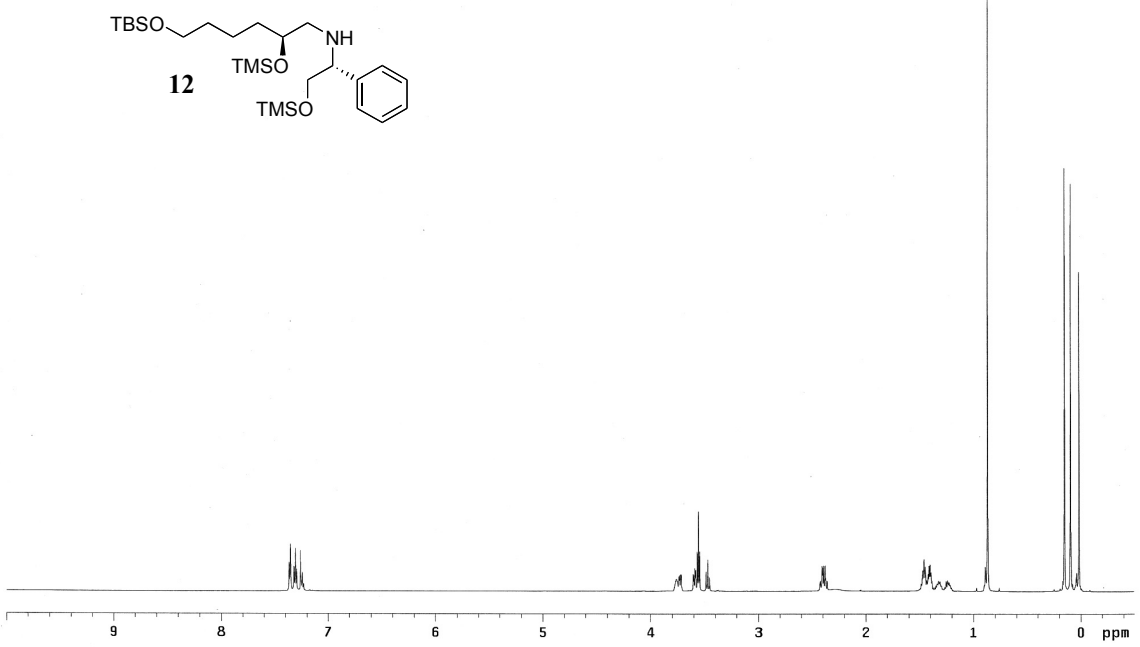
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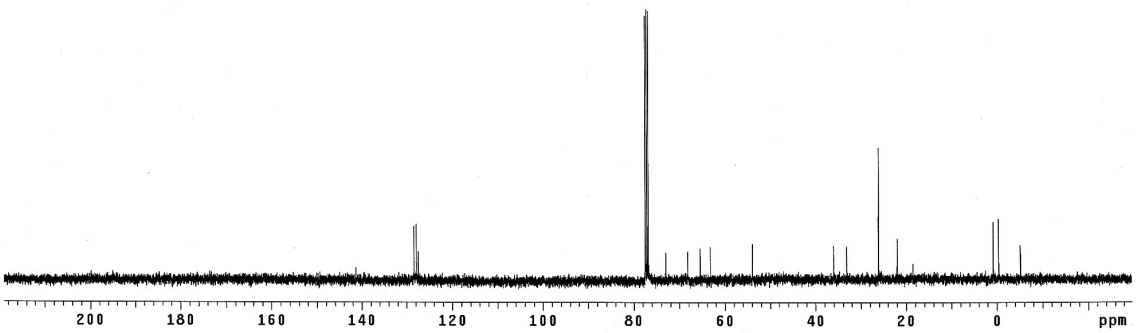
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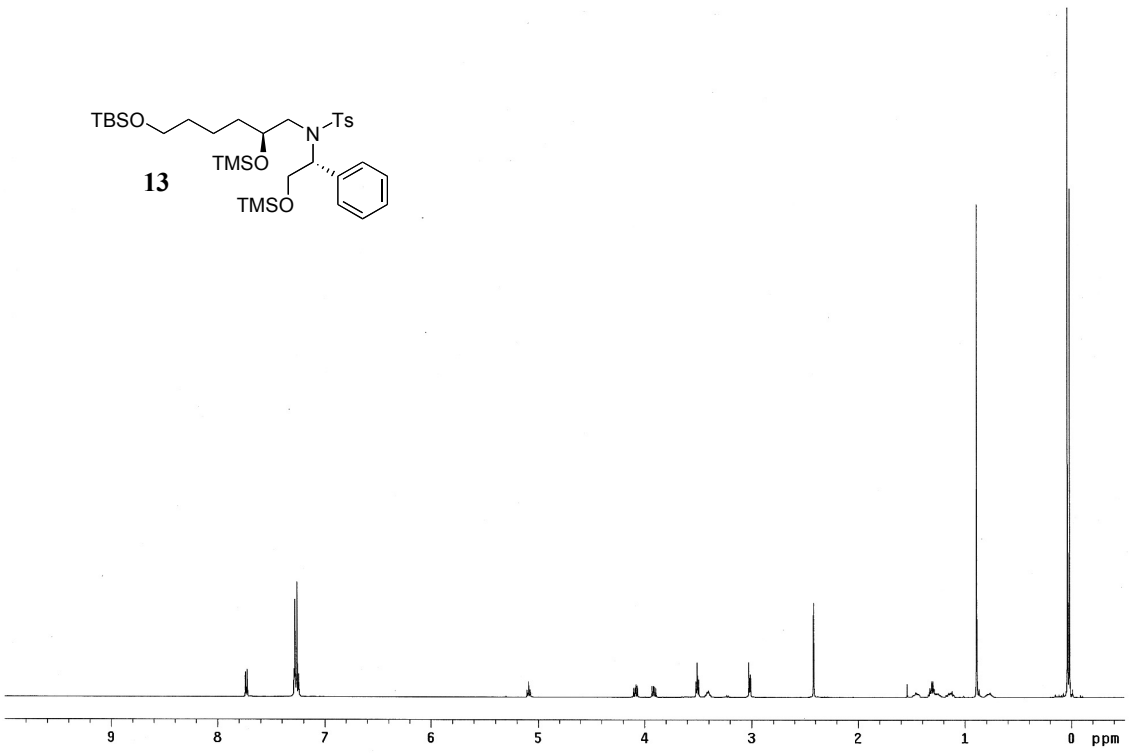
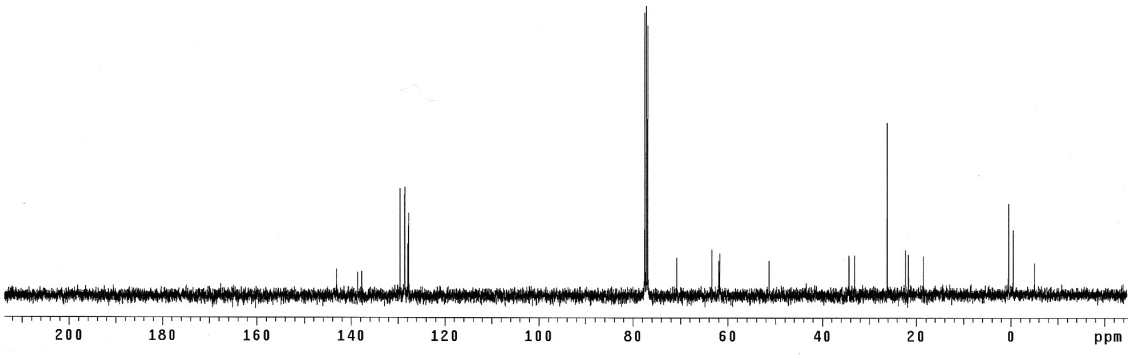
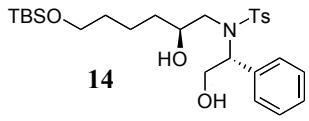
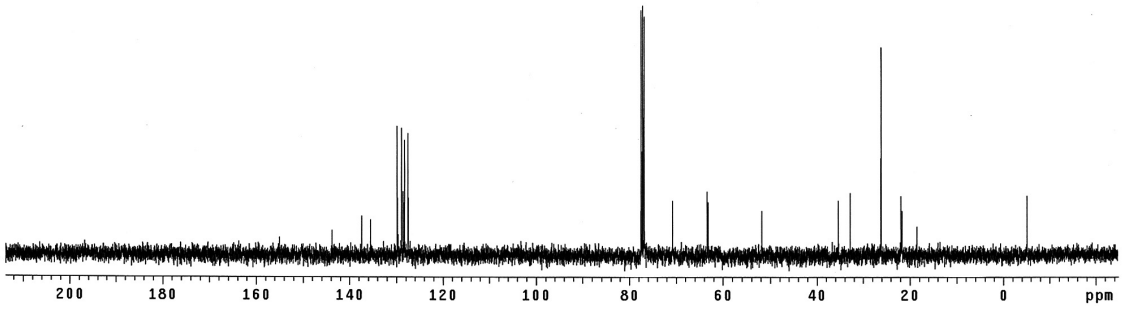

TBSO
N
Ts
TMSO
TMSO
13
9
8
7
6
5
4
3
2
1
0
ppm

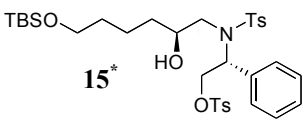

200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
HO
N
Ts
OH

**14**


9
8
7
6
5
4
3
2
1
0 ppm

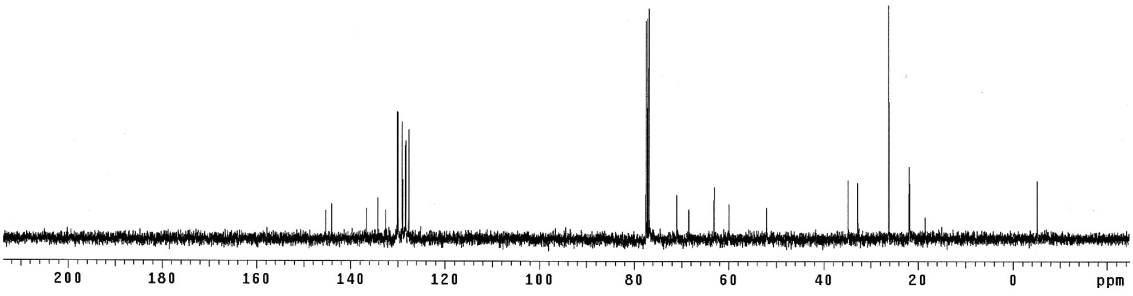

200
180
160
140
120
100
80
60
40
20
0
ppm



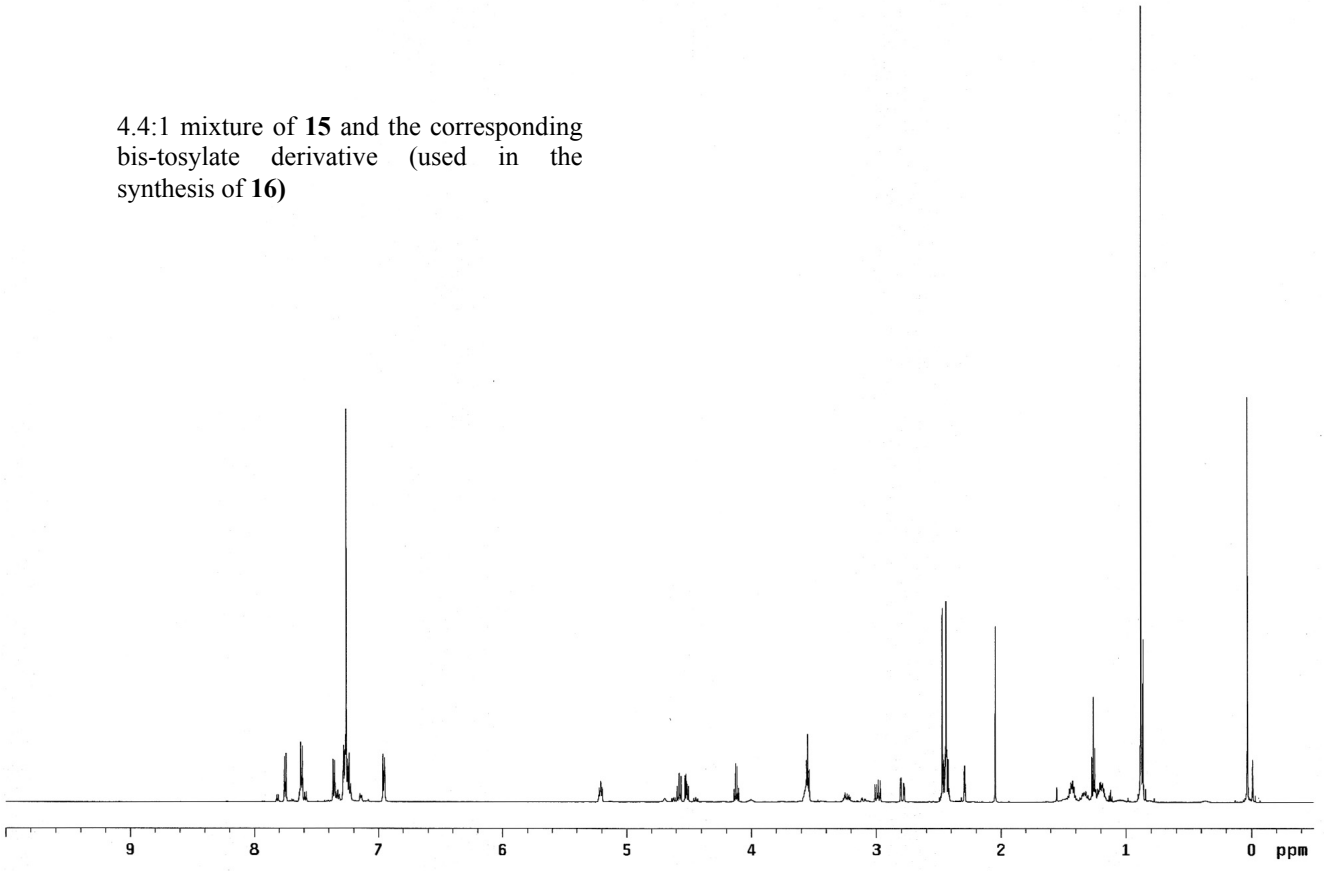

**15**[*]

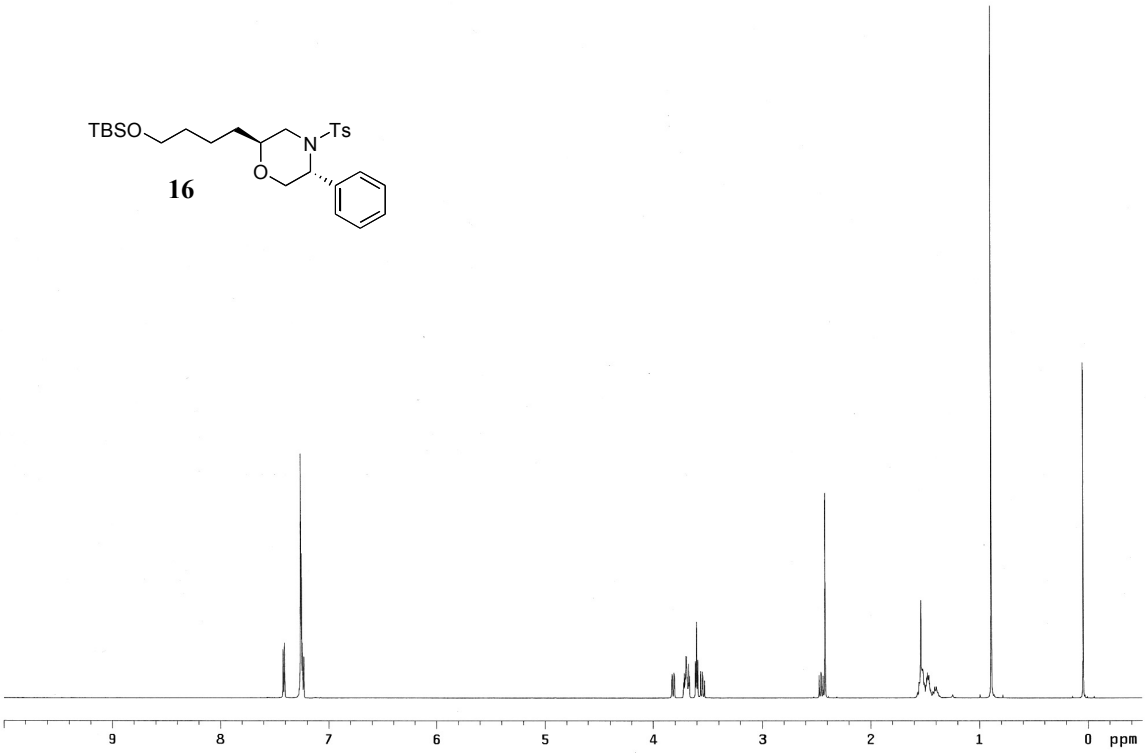



[*] Chromatographically purified: silica gel, 25% ethyl acetate–hexanes.

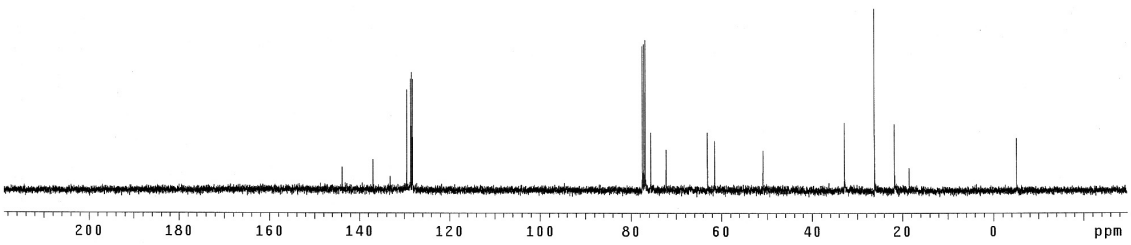


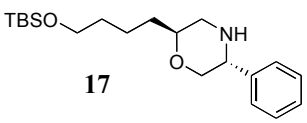
4.4:1 mixture of **15** and the corresponding bis-tosylate derivative (used in the synthesis of **16)**




TBSO
N
Ts
O
9
8
7
6
5
4
3
2
1
0 ppm

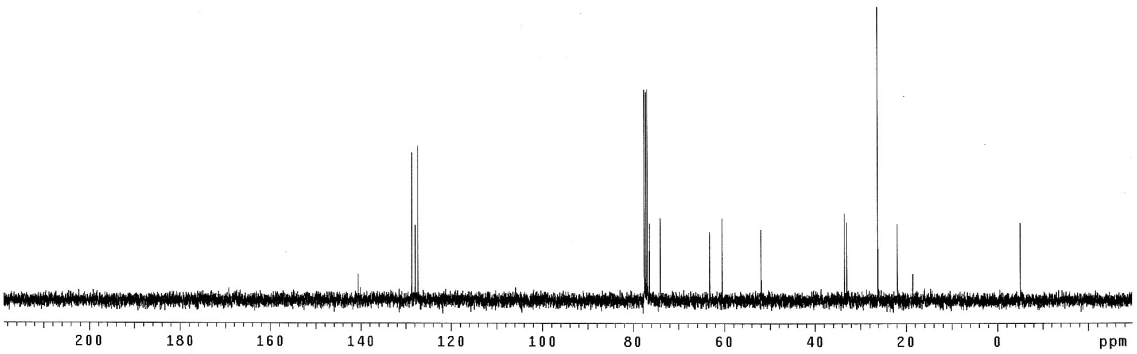
**16**

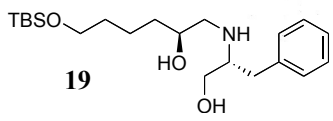

200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
NH
O

**17**

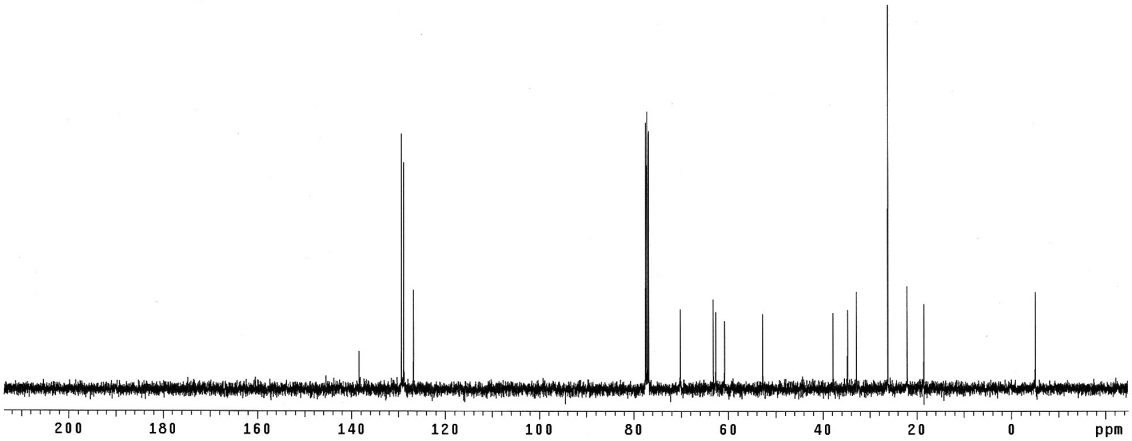

9
8
7
6
5
4
3
2
1
0
ppm

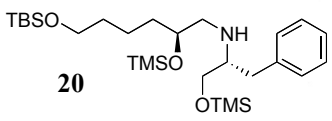

200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
NH
HO
OH

**19**

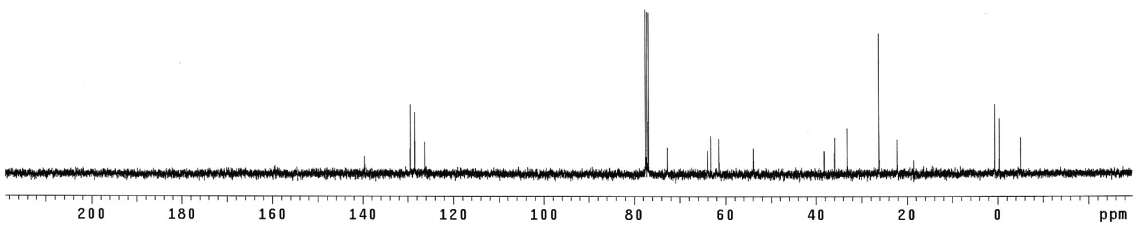

9
8
7
6
5
4
3
2
1
0
ppm

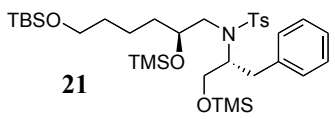

200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
NH
TMSO
OTMS

**20**

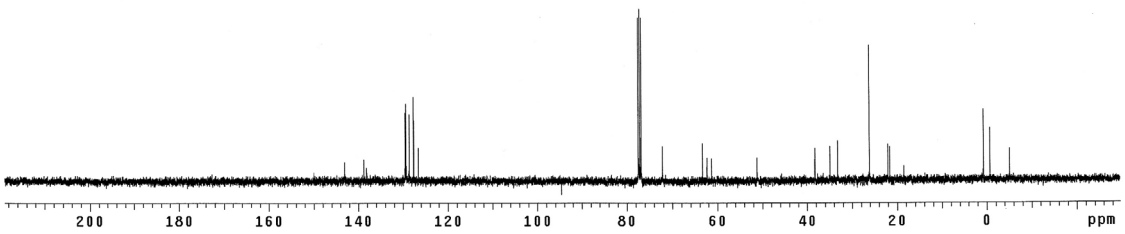

9
8
7
6
5
4
3
2
1
0
ppm

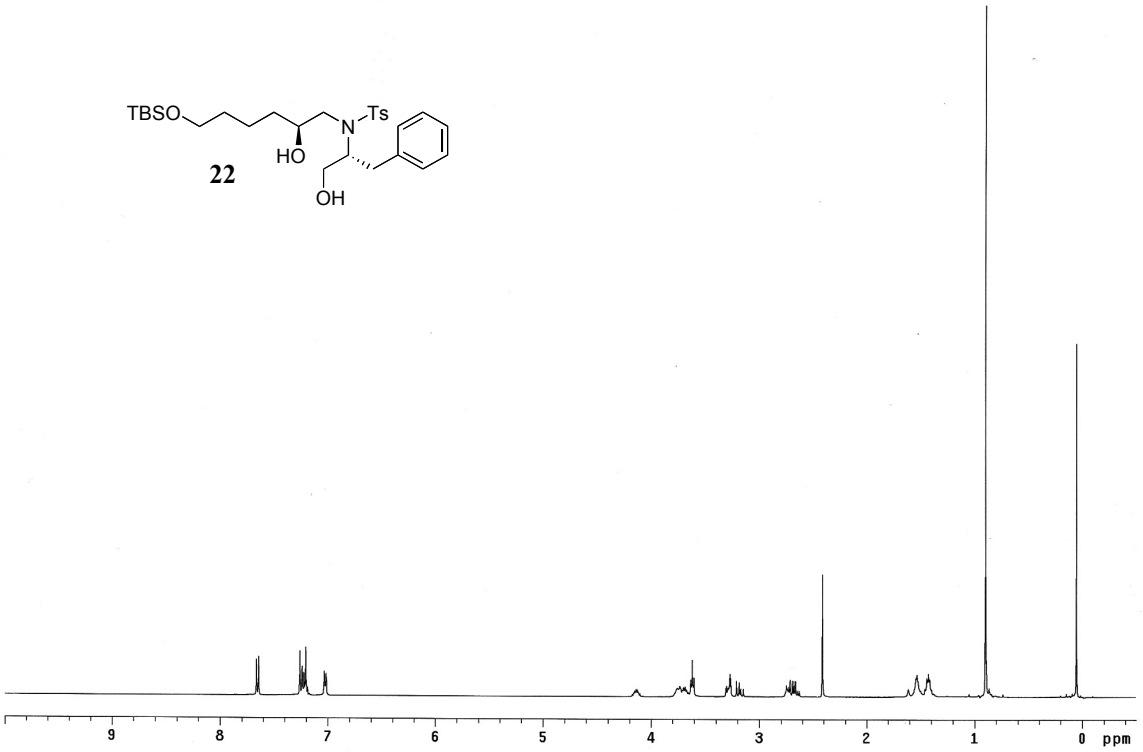

200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
N
Ts
TMSO
OTMS

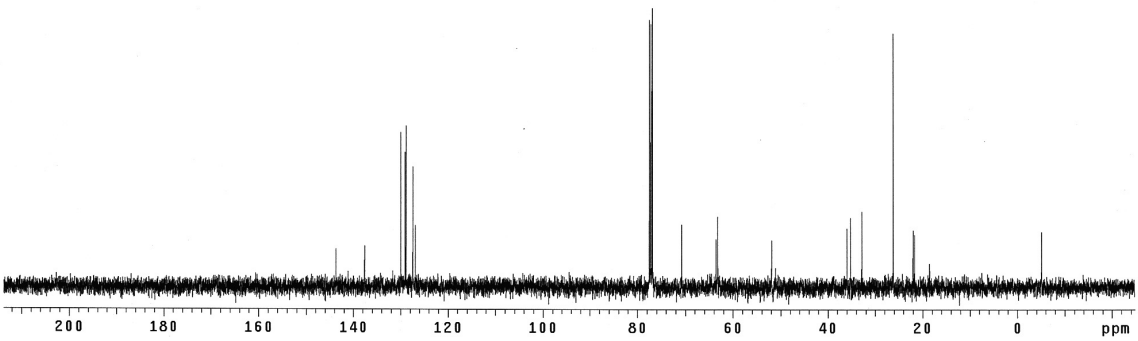
**21**

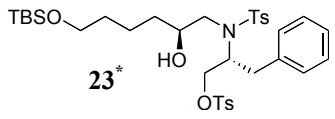

9
8
7
6
5
4
3
2
1
0
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm

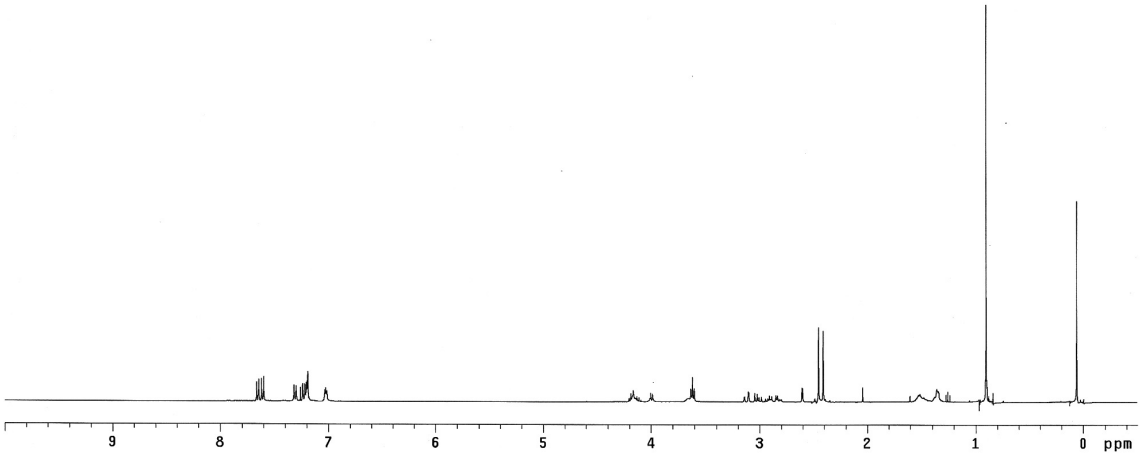

TBSO
HO
N
Ts
OH
9
8
7
6
5
4
3
2
1
0
ppm

**22**

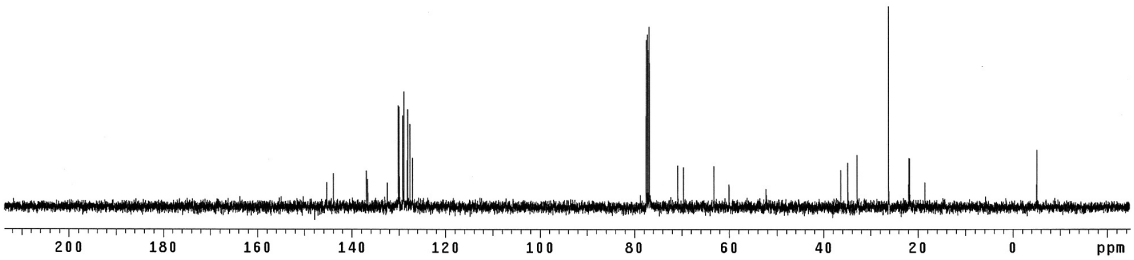

200
180
160
140
120
100
80
60
40
20
0
ppm



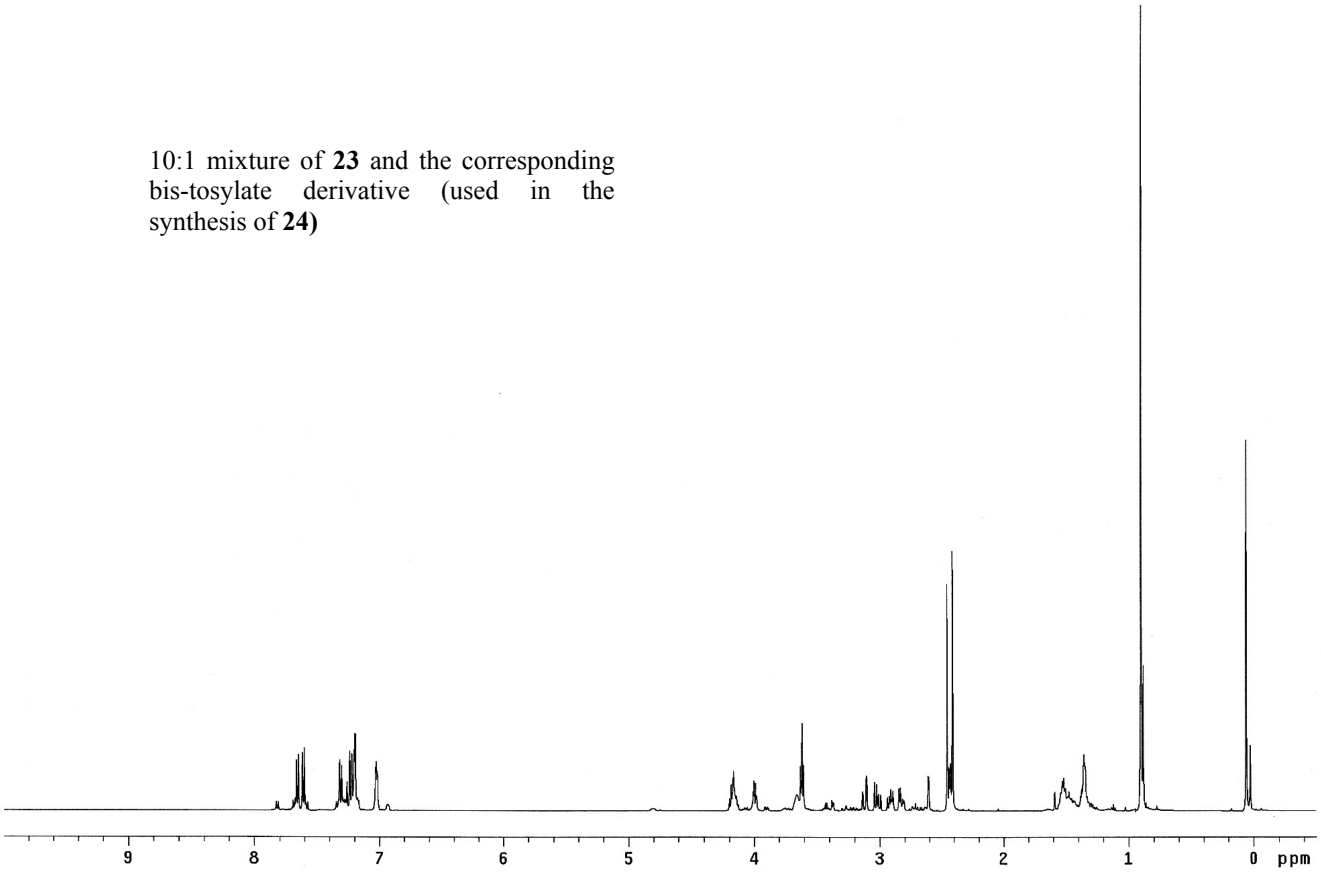

**23**[*]

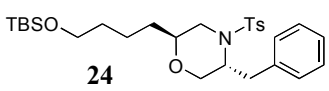



[*] Chromatographically purified: silica gel, 30% ethyl acetate–hexanes.



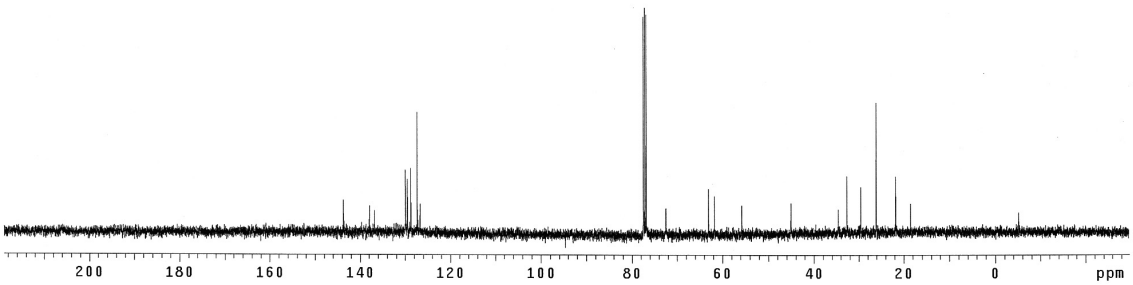
10:1 mixture of **23** and the corresponding bis-tosylate derivative (used in the synthesis of **24)**

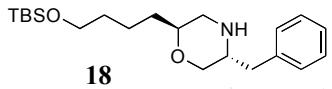



TBSO
Ts
N
O

**24**

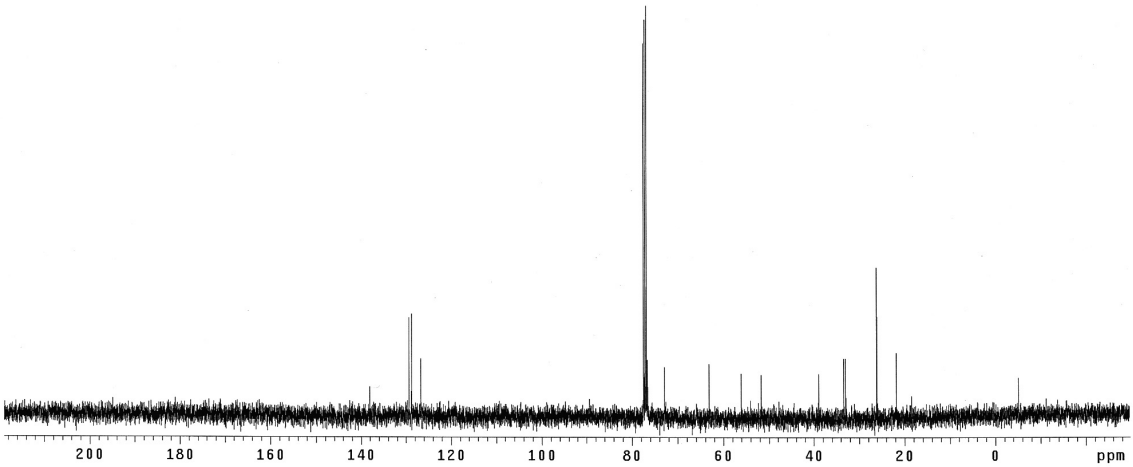

9
8
7
6
5
4
3
2
1
0
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm


TBSO
NH
O

**18**


9
8
7
6
5
4
3
2
1
0
ppm


200
180
160
140
120
100
80
60
40
20
0
ppm