

Regiospecific and Stereoselective Syntheses of (\pm)- and (-)-Reserpine

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Supporting Information

All reported NMR spectra were taken in in CDCl_3 solution.

Bromoacetal of Methyl 3-hydroxymethyl-5-tbutyldimethylsiloxy-3,6-dihydrobenzoate (10). The mixed acetal **7** was made in the usual way by reaction of NBS on an equimolar mixture of ethyl vinyl ether and allyl alcohol. ^1H NMR δ 5.91 (ddt, J = 6, 10.5, 17.1 Hz, 1H), 5.31 (d, J = 17.1 Hz, 1H), 5.20 (d, J = 10.5 Hz, 1H), 4.72 (t, J = 5. 5 Hz, 1H), 4.15 (dd, J = 6.13 Hz, 1H), 4.10 (dd, J = 6.13 Hz, 1H), 3.54-3.74 (m, 2H), 3.38 (d, J = 5.4 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H).

Ozone was bubbled through a solution of **7** (5.62 g, 26.9 mmol) in 100 mL of methylene chloride at -60 °C until saturated. After removal of excess ozone with oxygen, the solution was allowed to come to room temperature. Zinc dust (4 g) and a mixture of 3.4 mL of acetic acid and 0.6 mL of water was added in small portions, with vigorous stirring, keeping the temperature at 25-30 °C by occasional cooling in a water bath. The mixture was stirred for 2 h, was then filtered though Celite, washed with saturated sodium bicarbonate (2x30 mL), brine (30 mL), dried (magnesium sulfate) and concentrated. Distillation (kugelrohr, 90 °C / 1mm) gave 2.85 g (50%) of the mixed acetal of hydroxyacetaldehyde. ^1H NMR δ 9.73 (s, 1H), 4.75-4.79 (m, 1H), 4.16 (bs, 1H), 3.45-3.74 (m, 3H), 3.42 (d, J = 5.4 Hz, 2H), 1.22 (t, J = 7.0 Hz, 3H).

A solution of the above aldehyde (479 mg, 2.27 mmol) and 759 mg (2.38 mmol, 1.05 equiv) of triphenylphosphoranylideneacetone in tetrahydrofuran was refluxed under argon for 1.5 h. Concentration, followed by flash chromatography (1:2 ether/petroleum ether) gave 500 mg (88%) of the pure enone. ^1H NMR δ 6.80 (dt, J = 16.1, 4.4 Hz, 1H), 6.36 (d, J = 16.1 Hz, 1H), 4.75 (t, J = 5.5 Hz, 1H), 4.27-4.34 (m, 2H), 3.60-3.69 (m, 2H), 3.40 (d, J = 5.5 Hz, 2H), 2.28 (s, 3H), 1.23 (t, J = 7.0, 3H).

The above enone (2.26 g, 9.0 mmol in 10 mL of tetrahydrofuran) was then transformed into the siloxydiene **8** by addition to a solution of LDA (1.0.8 mmol, 1.2 equiv) in 25 mL of tetrahydrofuran), at -78 °C, over 10 min. After 5 more min, a solution of TBSCl (1.76 g, 11.7 mmol, 1.3 equiv) in 8 mL of hexamethylphosphoramide (HMPA) and 3 mL of tetrahydrofuran was added dropwise, with rapid stirring, at such a rate that most of the HMPA dissolved. After stirring for another 10 min, the mixture was allowed to warm to 0 °C over 2 h. Petroleum ether (150 mL) was added, and the reaction mixture was washed with water (2x40 mL) and with pH 7 buffer (40 mL), and dried. Concentration gave an oil which was flash chromatographed (1/19 ether/petroleum ether) to give 2.64 g (80%) of siloxydiene **8**, suitable for the subsequent 4+2 cycloaddition. ¹H NMR δ 6.12 (d, *J* = 15 Hz, 1H), 6.05 (dt, *J* = 5, 15 Hz, 1H), 4.73 (t, *J* = 5.4 Hz, 1H), 4.32 (bs, 2H), 4.17-4.23 (m, 2H), 3.59-3.70 (m, 2H), 3.39 (d, *J* = 5.4 Hz, 2H), 1.24 (t, *J* = 7.0 Hz, 3H), 0.965 (s, 9H), 0.18 (2 overlapping singlets, 6H).

A solution of the above siloxydiene **8** (2.63 g, 7.2 mmol), ethyl 2-nitroacrylate (0.93 g, 6.4 mmol) and ~20 mg of 3-*tert*butyl-4-hydroxy-5-methylphenyl sulfide in 15 mL of dry benzene was stirred in the dark, under argon, for 14 h. The crude material remaining after removal of volatile material (rotary evaporator, then high vacuum) was dissolved in 20 mL of tetrahydrofuran. The solution was cooled to 0 °C, and DBU (0.96 mL, 6.4 mmol, 1 equiv) was added dropwise, with stirring, under argon. After completion of the addition, the solution was kept for another 1.25 h. Concentration (water pump, then high vacuum at 0 °C), followed by flash chromatography (1:9 ether/petroleum ether) gave 1.75 g (59%) yield of clean dihydrobenzoate **10**, followed by 280 mg of the desired **10**, contaminated with some diene starting material. The whole 1.97 g was used in the subsequent hydroboration step. ¹HNMR δ 6.95 (bs, 1H), 4.80-4.84 (m, 1H), 4.15-4.79 (overlapping q and m, 3H), 3.42-3.72 (m, 4H), 3.34-3.37 (dd, *J* = 5.4, 2.0 Hz, 2H), 2.90-2.92 (m, 2H), 1.20-1.30 (2 overlapping t's, 6H), 0.928, 0.911 (s,s, in 6:1.7 ratio, 9H), 0.159 (s, 6H).

Bicyclic Acetals 5. A 0.95 M solution of diborane in THF (4.6 mL, 1.0 equiv) was added dropwise to a stirred solution of 4.38 mmol of crude **10** in 4.5 mL of THF, under argon, at -23 °C. The solution was sealed and kept at -12 °C for 4 h. After another hour at 0 °C, a mixture of 2 mL of 3 M sodium acetate and 2 mL of 30% hydrogen peroxide was added carefully at 0 °C, and the mixture was stirred for 3 h. Addition of water (40 mL), extraction with methylene chloride (3x20 mL), drying and concentration left a residue which was flash chromatographed (3:17 ether/petroleum ether) to give cyclohexanol **11** in 69% yield. ¹H NMR δ 6.85 (bs, 1H), 4.72 (t, *J* = 4.6 Hz, 1H), 4.18 (q, 2H), 3.40-3.80 (m, 6H), 3.38-3.39 (dd, *J* = 5.6, 5.4 Hz, 2H), 2.10-2.72 (m, 4H), 1.206, 1.24 (overlapping t's, *J* = 7.0, 7.2 Hz, 6H), 0.92 (0.902/0.919 *ca* 7:1, s 9H), 0.129 (s, 6H).

Methylation of the secondary hydroxyl of **11** was accomplished by refluxing a benzene solution of the latter with 3 equiv of methyl triflate, in the presence of 5 equiv of 2,6 ditert-butylpyridine to yield the methyl ether **12** in 80% yield. ¹H NMR δ 6.8 (bs, 1H), 4.70 (t, *J* = 5.4 Hz, 1H), 4.18 (q, 2H), 3.45-3.91 (m, 4H), 3.54 (t, 3H), 3.37, 3.38 (dd, *J* = 5.6 Hz, 2H), 3.21 (t, *J* = 8.0 Hz, 1H), 2.0-2.3 (m, 4H), 1.27, 1.24 (overlapping t's, *J* = 7.2 Hz, 3H; *J* = 7.0 Hz, 3H), 0.904 (s, 9H), 0.109 (s, 3H), 0.094 (s, 3H).

A solution of bromoacetal **12** (1.33 g, 2.84 mmol), tributylstannane (0.98 mL, 3.64 mmol, 1.28 equiv) and AIBN (25 mg, 0.05 equiv) in 150 mL of benzene was refluxed under argon for 3.5 h. The reaction mixture was washed with 3% aqueous ammonia (50mL), and the aqueous extracts were back extracted with 20 mL of ether. The combined organic solutions were dried, concentrated, and the residue was flash chromatographed (1:3, ether/petroleum ether) to give the cyclization prduct (954 mg, 86%) as a clean mixture (4-5:1) of the desired α -carbethoxy compound **5** (as 2 separable ethoxy acetal epimers, **5a** and **5b**), together with the unwanted α -carbethoxy epimer(s). ¹H NMR (**5a**) δ 4.42 (dd, *J* = 2.4, 8.0 Hz, 1H), 4.20-4.30 (m, 2(?)H), 4.13 (q, 2H), 3.85-4.03 (m, 1(?)H), 3.58 (s, 3H), 3.35-3.55 (m, 4H), 2.35-2.70 (m, 2H), 1.28-1.90 (m, 4H), 1.249 (t, *J* = 7.0, 3H), 1.220 (t, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.083 (s, 3H). (**5b**) δ 4.85

(bs, 1H), 4.00-4.20 (m, 1(?)H), 4.13 (q, 2H), 3.65-3.85 (m, 3(?)H), 3.59 (s, 3H), 3.30-3.50 (m, 4H), 2.45-2.80 (m, 2H), 1.65-1.90 (m, 4H), 1.25 (t, $J = 7.0$ Hz, 3H), 1.22 (t, $J = 7.0$ Hz, 3H), 0.90 (s, 9H), 0.10 (s, 3H), 0.083 (s, 3H).

6-Trimethylsilyl-5-hexynal (18). To a solution of 20g of 5-hexynol in 100 mL of ether was added 23.4 mL (1.2 equiv) of ethyl vinyl ether and a trace of p-toluenesulfonic acid (pTSA). Additional 10 mL portions of ethyl vinyl ether were added every 2 h until TLC indicated completion. After washing (satd. sodium bicarbonate; brine) and drying (MgSO_4), the solution was concentrated under reduced pressure, the residue was dissolved in 200 mL of dry THF and cooled to -78 °C. A hexane solution of nBuLi (0.250 M) was added and the solution was stirred for 30 min, and allowed to warm to room temperature after addition of 30 mL of chlorotrimethylsilane. Washing the reaction solution with water, drying (MgSO_4) and concentration gave a crude product which was dissolved in 150 mL of methanol, and the solution was refluxed in the presence of a trace of pTSA until completion (TLC). After removal of the methanol under reduced pressure, the crude product was dissolved in ether and the organic layer was washed (satd. sodium bicarbonate; brine), dried (MgSO_4), and concentrated. Distillation of the residue gave the desired 6-trimethylsilyl-5-hexynol (30.3 g; bp 78-81 °C / 0.6 mm). ^1H NMR δ 3.64 (t, $J = 6$ Hz, 2H), 2.25 (t, $J = 7$ Hz, 2H), 1.62 (m, 5H), 0.12 (s, 9H); TLC: R_f 0.5 (20% ethyl acetate/hexane).

To a solution of 37.8 mL of oxalyl chloride in 500 mL of methylene chloride, cooled to -78 °C, was added 61.6 mL of DMSO in 300 mL of methylene chloride, dropwise over 50 min. After another 10 min, 67 g of the above silylhexynol was added, dropwise, over 40 min. After stirring for another 10 min, 275 mL of triethylamine was added to the stirred solution which was then allowed to warm to room temperature. The solution was washed with water, dried, and concentrated. The remaining material was dissolved in hexane and filtered to remove solids. Concentration gave a crude product which was distilled to give the required 6-

trimethylsilyl-5-hexynal (**18**) as a colorless liquid, bp \sim 60 °C /0.45 mm, in 87% yield from the starting 5-hexynol. ^1H NMR δ 9.7 (s, 1H), 2.55 (t, J = 7 Hz, 2H), 2.3 (t, J = 7 Hz, 2H), 1.81 (t, J = 7 Hz, 2H), 0.12 (s, 9H). R_f 0.28 (15% ethyl acetate/hexane).

Methyl Ester of 2-Methoxy-8-trimethylsilyl-oct-2-en-7-yneic acid (19). Methylmethoxyacetate (38 mL, 0.383 mole) was added dropwise, over 30 min, to a solution of 0.402 mol LDA in 600 mL of THF, at -78 °C. After an additional 30 min, the above trimethylsilylhexynal (**18**) (64.4 g, 0.383 mol) was added dropwise, over 20 min, to the stirred solution. After an additional 20 min, 59 mL (1.2 equiv) of benzenesulfonyl chloride was added, and the solution was allowed to warm to room temperature. Following the usual work-up (addition of ether, water wash, MgSO_4 drying, and concentration), the crude product was dissolved in 400 mL of THF, and 69 mL (1.2 equiv) of DBU was added. After 2h reflux, TLC indicated completion of the reaction. Workup (addition of ether, extraction with 1N HCl, drying and concentration) was followed by vacuum distillation to yield 69 g (69%) of a 5:1 mixture of Z/E isomers, bp 110-115 °C /0.7mm. Although not necessary for the further elaboration, samples of the pure Z and E isomers of **19** were isolated by flash chromatography for characterization. Z-isomer: (**19Z**; major): R_f 0.3 (10% ethyl acetate/hexane); ^1H NMR δ 6.32 (t, J = 8 Hz, 1H), 3.85 (s, 3H), 3.74 (s, 3H), 2.4 (q, J = 7 Hz, 2H), 2.34 (t, J = 7 Hz, 2H), 1.7 (t, J = 7 Hz, 2H), 0.21 (s, 9H). E-isomer (**19E**; minor): R_f 0.22 (ethyl acetate/hexane); ^1H NMR δ 5.17 (t, J = 8 Hz, 1H), 3.78 (s, 3H), 3.57 (s, 3H), 2.52 (q, J = 7 Hz, 2H), 2.25 (t, J = 7 Hz, 2H), 1.64 (t, J = 7 Hz, 2H), 0.12 (s, 3H).

Trimethylsiloxy Ketene Acetals 20. A 250 mg (1 mmol) sample of the pure major Z-isomer **19Z** in the above mixture was added to a solution of 1.05 equiv of LDA at -78 °C. After stirring for 30 min, chlorotrimethylsilane (1.1 equiv) was added and the solution was allowed to come to room temperature, and worked up as usual to give, essentially exclusively, the 3,4 E-isomer **20**. ^1H NMR δ 6.1 (d, J =15Hz, 1H), 5.5 (m, 1H), 3.5 (s, 3H), 3.4 (s, 3H), 2.3 (s, 4H), 0.21 (s, 9H). The minor E isomer **19E** gave, under identical treatment, an isomeric ketene acetal (3,4

Z?) that gave no detectable 4+2 cycloaddition upon refluxing for 24 h with maleic anhydride in benzene.

Methoxycyclohexenone 22. The 5:1 mixture of Z/E isomers of 2-methoxy conjugated esters **19** (vide supra) was transformed into the mixture of trimethylsiloxy ketene acetals as described above for the pure Z-isomer. After the reaction mixture had come to room temperature, following reaction with TMSCl , pentane was added and the organic layer was washed with 100 mL of 3M pH 7 phosphate buffer. The organic layer was dried over potassium carbonate and concentrated under reduced pressure. The resulting crude ketene acetal mixture was dissolved in 50 mL of benzene, and, after addition of 6g of maleic anhydride, the mixture was refluxed until completion (NMR) of the reaction (~ 8 h). A sample of the (unstable) purified adduct **21** was obtained, as a low-melting white solid, via concentration and flash chromatography, for NOE studies. ^1H NMR δ 4.6 (d, J = 3 Hz, 1H) 3.6 (d, J = 9 Hz, 1H), 3.51 (s, 3H), 3.3 (dd, J = 9.3 Hz, 1H) 3.16 (s, 3H), 2.9 (m, 1H), 2.4 (m, 2H), 1.9-2.2 (m, 2H), 0.23 (s, 9H), 0.12 (s, 9H). The bulk of the reaction mixture was concentrated, dissolved in 80 mL of a 5:1 mixture of THF/water, and refluxed for 12 h. After addition of ether, the organic layer was extracted (4 times) with saturated sodium bicarbonate, the aqueous extracts were acidified with 2.5 M HCl , and repeatedly extracted with ether. Drying and concentration gave the crude acid, which was dissolved in 50 mL of DMF. Potassium carbonate (15 g) was added to the solution, followed, after stirring 20 min, by 10 g of benzyl bromide. TLC showed esterification to be complete after 2 h. Potassium fluoride (4 equiv) was added, followed by another 4 equiv after 24 h. The mixture was stirred for 2 days to complete desilylation. Dilution of the DMF solution with ether was followed by washing five times with water, and extraction of the aqueous extracts with ether. The combined organic layers were washed with brine and concentrated to give the crude product. Flash chromatography gave purified **22**, a 5:1 mixture of cis/trans isomers, as a yellow viscous oil (9.3 g, 62% based on the amount of the reactive 3,4-E isomer in the ketene acetal mixture used for the cycloaddition with maleic anhydride. ^1H NMR *cis* **22**: δ 5.75 (d, J = 5 Hz, 1H), 3.57 (s,

3H); *trans*: **22** □ 5.67 (d, J = 4 Hz, 1H), 3.56 (s, 3H), 7.3 (s, 5H), 5.2 (d, J = 5 Hz, 2H), 3.3 (m, 1H), 3.2 (m, 1H), 2.7-3.0 (m, 2H), 2.4 (m, 2H), 2.1 (t, J = 3 Hz, 1H), 1.7 (m, 2H).

Free Radical Cyclization of 22 and Conversion to 25. To a solution of the 5/1 mixture of *cis* and *trans* vicinally substituted isomers **22** (3.9 g, 12.5 mMol) in 625 mL of *tert*-butanol was added 4 mL (1.2 equiv) of tributylstannane and 200 mg of AIBN. The solution was refluxed for 24 h, and additional 200 mg portions of AIBN were added every 4 h until completion of the cyclization (TLC). After removal of the *tert*-butanol by distillation, and removal of the remaining solvent by co-distillation with benzene, the crude product was dissolved in methylene chloride (500 mL), and the solution was stirred overnight with 80 g of silica gel. The silica gel was filtered off, washed with 1 L of ethyl acetate, the solution was concentrated and the residue dissolved in 50 mL of methylene chloride, and 0.5 equiv of PCC was added. After stirring for 5 h the solution was filtered through 10 g of silica gel, and the resulting crude product was purified by flash chromatography to give 2.15 g of **23** (55%), as a yellowish thick oil. R_f 0.42, 30% ethyl acetate/hexane. ^1H NMR □ 7.3 (s, 5H), 5.1 (br, 2H), 4.9-5.1 (m, 2H), 3.4 (s, 3H), 3.3 (s, 3H), 1.3-4.4 (m, 7H).

Equilibration to the required more stable α -methoxycyclohexanone **24** was achieved by treatment of 0.646 g of the above mixture of methoxy epimers in 20 mL of THF with 10 drops of a 25% solution of sodium benzyloxide in benzyl alcohol. After stirring overnight, the solution was cooled to -78 °C. L-selectride (1.2 equiv) was added to the solution of equilibrated methoxyketone, and, after stirring for 30 min, the solution was quenched with 12 mL of 3M sodium hydroxide solution, allowed to come to room temperature, and 30% aqueous hydrogen peroxide was added until the solution became colorless. Ether extraction and usual workup gave crude **25** which was submitted to flash chromatography to give material which still contained traces of the carbobenzyloxy epimer. Crystallization from 95% ethanol gave 0.468 g of pure **25** (72%) as a white crystalline solid, mp 106-107 °C, R_f 0.26 (40% ethyl acetate/hexane). ^1H NMR □ 7.32 (s, 5H), 5.1 (s, 2H), 5.0 (s, 1H), 4.83 (s, 1H), 4.17 (s, 1H),

3.35 (s, 3H), 3.2 (dt, J = 13, 5 Hz, 1H), 2.81 (dd, J = 10, 3 Hz, 1H), 2.5 (m, 3H), 2.2 (m, 3H), 1.8 (t, J = 5 Hz, 1H), 1.45 (m, 2H). Found: C, 72,17, H, 7.66.

Benzyl Ester Acetate 26. A solution of 0.5 g of cyclohexanol **25** and 0.182 mL of methanesulfonyl chloride in 10 mL of pyridine was stirred for 4 h. Dilution with ether, washing (1M HCl, brine), drying ($MgSO_4$), and concentration was followed by removal of pyridine under vacuum. The resulting mesylate was dissolved in 30 mL of benzene, 3 g (10 equiv) of cesium acetate and 0.5 g (1.5 equiv) of 18-crown-6 were added, and after refluxing for 2 days, another 3 g of cesium acetate was added, and the mixture was refluxed an additional 3 days. Ether extraction, washing (sodium bicarbonate, brine), drying ($MgSO_4$) and concentration, gave the crude product which gave purified **26** as a colorless thick oil, in 96% yield, R_f 0.25 (20% ethyl acetate/hexane), following flash chromatography. 1H NMR δ 7.32 (s, 5H), 5.08 (bs, 3H), 4.85 (s, 1H), 4.7 (ddd, J = 11, 9 , 4.4 Hz, 1H), 3.42 (s, 3H) 2.99 (m, 2H) 2.05 (bs, 4H), 1.5-1.8 (m, 3H), 1.2-1.6 (m, 4H).

Diol Monotosylate 27. A solution of 235 mg (0.0066 mol) of benzyl ester acetate **26** in 5 mL of THF at -78 °C was added dropwise to 0.787 mL of a 1M solution of LAH in 10 mL of ether. After warming to room temperature, the reaction was diluted with ether and carefully quenched with 1M HCl. The solution was extracted with several portions of ethyl acetate, and the combined organic layers were dried ($MgSO_4$) and concentrated. Flash chromatography gave the purified diol as a thick colorless liquid in quantitative yield. R_f 0.15 (ethyl acetate); 1H NMR δ 5.1 (s, 1H), 4.85 (s, 1H), 3.5 (m, 5H), 2.85 (t, J = 9 Hz, 1H), 1.0-2.6 (m, 12H).

To a solution of 90 mg of the above diol in a mixture of 3 mL of methylene chloride and 3 mL of pyridine was added 95 mg (1.2 equiv) of p-toluenesulfonyl chloride. Additional portions of toluenesulfonyl chloride were required to complete the reaction (TLC). After 12 h stirring, ether extraction, washing of the extract with 1M HCl and brine, followed by drying ($MgSO_4$), concentration and chromatography gave the purified tosylate **27** (142 mg, 91% yield) as a

white crystalline solid, mp 93-94 °C. R_f 0.26 (60% ethyl acetate/hexane); ^1H NMR δ 7.75 (d, J = 8 Hz, 2H), 7.33 (d, J = 8 Hz, 2H), 5.07 (s, 1H), 4.84 (s, 1H), 3.85 (dd, J = 8, 6 Hz, 2H) 3.49 (s, 3H), 3.42 (ddd, J = 11, 9, 4.4 Hz, 1H) 2.8 (t, J = 9 Hz, 1H), 2.4 (s, 3H), 1.2-2.5 (m, 10H).

TBS Derivative 17. To a solution of 130 mg (0.00355 mol) of the above tosylate **27** in 3 mL of DMF was added 100 mg of TBSCl and a trace of imidazole. The solution was stirred 3 h, and was then diluted with ether, washed with 3M pH 7 phosphate buffer, dried (MgSO_4) and concentrated. Chromatography gave purified **17** as a white solid mp 88-89 °C, in quantitative yield. R_f 0.23 (10% ethyl acetate/hexane); ^1H NMR δ 7.76 (d, J = 8 Hz, 2H), 7.32 (d, J = 8 Hz, 2H), 5.06 (s, 1H), 4.8 (s, 1H), 3.84 (dd, J = 7, 3 Hz, 2H), 3.4 (bs, 4H), 2.7 (t, J = 9 Hz, 1H), 2.4 (s, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 1.2-2.2 (m, 9H).

Indenone 28. Ozone was bubbled at -78 °C through a solution of 208 mg of **17** (4.33 mmol) in a mixture of 5 mL each of methanol and methylene chloride, until a blue color persisted. After purging the excess ozone with argon, 2 mL of dimethyl sulfide was added, and the solution was allowed to warm to room temperature. The solvent was removed under reduced pressure, and the crude ketone was purified by chromatography to give 206 mg (98% yield) of **28**, mp 99-101 °C. R_f 0.33 (30% ethyl acetate/hexane). ^1H NMR δ 7.76 (d, J = 8 Hz, 2H), 7.33 (d, J = 8 Hz, 2H), 3.9 (d, J = 8 Hz, 2H), 3.5 (ddd, J = 11, 9, 4.4 Hz, 1H), 3.4 (s, 3H), 2.95 (t, 9 Hz, 1H), 2.45 (bs, 4H), 0.85 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H), 1.3-1.8 (m, 6H).

(\pm) Aldehydotosylate 30. To a solution of 208 mg (4.3 mmol) of **28** and 0.11 mL (2 equiv) of TMSCl in 10 mL of THF, at -78 °C, was added 0.516 mL of 1M lithium hexamethyldisilazide (1.2 equiv), and the solution was stirred for 25 min. After addition of pentane, the organic layer was washed with 3M pH 7 phosphate buffer. The solvent was removed under reduced pressure and the crude silyl enol ether **29** was dissolved in 20 mL of methylene chloride. After cooling to -78 °C, ozone was bubbled through the solution until a blue color persisted. Excess ozone was purged with argon, 1.2 equiv of triphenylphosphine was added, and the solution

was allowed to come to room temperature and stirred for 2 h. The organic layer was diluted with ether, washed with 0.1M HCl, and treated with excess diazomethane. Drying (MgSO_4) and concentration, followed by chromatography gave 156 mg (68%) of purified (\pm) -30. R_f 0.33 (25% ethyl acetate/hexane). $^1\text{H NMR}$ δ 9.5 (s, 1H), 7.76 (d, J = 8 Hz, 2H), 7.33 (d, J = 8 Hz, 2H), 3.8 (m, 2H), 3.6 (s, 3H), 3.5 (s, 3H), 3.25 (t, J = 9 Hz, 1H), 2.95 (bs, 1H), 2.85 (dd, J = 15, 7 Hz, 1H), 2.4 (s, 3H), 2.2 (dd, J = 15, 7 Hz, 1H), 0.85 (s, 9H), 0.06 (s, 3H), 0.03 (s, 3H), 1.2-2.0 (m, 6H).

4-Benzylloxymethyl-2-cyclohexenone (33) A mixture of 3-ethoxy-2-cyclohexenone (10 mL, 68.8 mmol) in 10 mL of hexamethylphosphoramide was added dropwise, at -78 °C, under argon, to a stirred solution of lithium diisopropylamide (1.3 equiv) in 80 mL of anhydrous tetrahydrofuran. The mixture was allowed to warm to -35 °C. After 1 h, benzyl chloromethyl ether (10.1 mL) was added, and the mixture was stirred at -35 °C for 1.5 h. The reaction was quenched with aqueous ammonium chloride solution, and allowed to warm to room temperature, with stirring. Extraction with ether, washing the organic layer with brine, drying (MgSO_4) and concentrating gave a residue which was chromatographed on silica gel (10:3 hexane-ethyl acetate) to give 183 mg of starting material and 16.6 g of the desired 6-benzylloxymethyl alkylation intermediate in 94% yield. Conversion to the desired 4-benzylloxymethyl 2-cyclohexenone 33 was carried out by dropwise addition of a solution of the above alkylation product (16.5g, 63.5 mmol) in 30 mL of ether to a suspension of 1.2 g lithium aluminum hydride (31.6 mmol) in 150 mL of ether, at room temperature, with stirring. After 1.5 h, water (1.2 mL) was added, followed by 1.2 mL of 15% sodium hydroxide solution and an additional 3.6 mL of water. After 0.5 h, magnesium sulfate (5 g) was added, the white precipitate was filtered off and the filtrate was concentrated to give a residue that was then dissolved in 80 mL of tetrahydrofuran. To that solution was added 5 mL of 1N hydrochloric acid, while stirring at room temperature. After addition of 50 mL of saturated sodium bicarbonate solution at 0 °C, the mixture was extracted with ether, the organic layer was washed with brine, dried (magnesium sulfate), and evaporated to give a residue which was

chromatographed on silica to yield the desired 4-benzyloxymethyl 2-cyclohexenone **33** as an oil (11.8 g, 83%). ¹H NMR: δ 7.25-7.45 (m, 5H), 6.90-7.00 (m, 1H), 6.03 (dd, J = 2.6, 2.6 Hz, 1H), 4.51 (s, 2H), 3.48 (dq, J = 4.0, 2.6 Hz, 2H), 2.65-2.85 (m, 1H), 2.30, 2.60 (m, 2H), 2.05-2.20 (m, 1H), 1.70-1.90 (m, 1H).

Methyl 3-(dimethyl-2-furyl)silyl)acrylate (32). Dimethyl 2-furylsilane was prepared by treating a solution of furan (10 mL) in 100 mL of ether, at -25 °C, under argon, with 1 equiv of butyl lithium. The mixture was allowed to come to room temperature, and was then refluxed for 4 h. Cooling to -25 °C was followed by addition of chlorodimethylsilane (15.3 mL), followed by refluxing for 4 h. Cooling to room temperature, filtration through Celite, and distillation at 53 °C gave 14.7g (85%) of dimethyl 2-furylsilane.

To a stirred solution of the above furylsilane (8.56 g) and methyl acrylate (30.56 mL) in 90 mL of dry benzene, at room temperature, was added dicobaltoctacarbonyl (1.106 g). After keeping 2 h at 45-47 °C, solvent and excess acrylate was removed, and the residue was chromatographed on silica (100:3 hexane : ethyl acetate) to yield 7.026 g of a 2:1 mixture of the desired silyl acrylate **32** and of the corresponding reduction product. Removal of the latter from the mixture was not necessary because only **32** takes part in the following double Michael reaction. ¹H NMR: δ 7.66 (bs, 1H), 7.29 (d, J = 18.8 Hz, 1H), 6.69 (d, J = 3.6, 1 H), 6.38-6.40 (m, 1H), 6.30 (d, J = 18.8 Hz, 1H), 3.74 (s, 3H), 0.397 (s, 3H).

Bicyclo [2,2,2]-octanone 34. The 4-benzyloxymethyl cyclohexenone **33** (3.34 g) was added, dropwise, under argon, to a stirred solution of lithium diisopropylamide (1.3 equiv) in 50 mL of anhydrous tetrahydrofuran at -78 °C. The reaction mixture was allowed to warm to -35 °C, stirred for 1 h, followed by dropwise addition of the silyl acrylate **32** (3.41 g) (either the chromatographically separated pure silyl acrylate was used, or, more simply, the unseparated mixture of acrylate and propionate, after the amount of mixture had been adjusted for its acrylate content by NMR). The reaction mixture was allowed to warm to 0 °C, and after

another 2 h, the mixture was quenched by the addition of 50 mL of saturated aqueous ammonium chloride solution, and extracted with ether. The organic layer was washed with brine, dried (magnesium sulfate), and evaporated to give a residue which was chromatographed on silica with hexane-ethyl acetate (10:3) to yield the bicyclooctanone **34** as an oil (5.8 g; 88%). ¹H NMR δ 7.66 (d, *J* = 1.4 Hz, 1H), 7.20-7.40 (m, 5H), 6.69 (d, *J* = 3.2 Hz, 1H), 6.39 (dd, *J* = 1.4, 3.2 Hz, 1H), 4.35-4.50 (m, 2H), 3.65 (s, 3H), 3.15-3.30 (m, 2H), 2.70-2.80 (m, 1H), 2.56 (bs, 1H), 2.15-2.40 (m, 2H), 1.70-1.95 (m, 2H), 1.05-1.20 (m, 1H), 0.345 (s, 3H), 0.280 (s, 3H).

Fluorosilyl Tosylate 36. To a stirred solution of **34** (694 mg) in 7 mL of anhydrous tetrahydrofuran was added 1.63 mL of a tetrahydrofuran solution of tetrabutylammonium fluoride (1.63 mmol). After 2 minutes at room temperature, the mixture was cooled to 0 °C, and stirred with saturated sodium chloride solution. Extraction with ether, drying (magnesium sulfate) and evaporation gave, after silica chromatography (5 : 3 hexane : ethyl acetate), the desired fluorosilane as an oil (542 mg; 84%). It was stirred in ethyl acetate with 10% Pd-C under hydrogen, at atmospheric pressure, for 30 h to give the fluorosilyl alcohol **35** (2.07 g; 98%), after chromatography (1 : 4 hexane : ethyl acetate). Conversion to the tosylate **36** was achieved by stirring a mixture of the above alcohol (2 g; 6.95 mmol) with 1.59 g (1.2 equiv) tosyl chloride, 1.69 mL (3 equiv) pyridine, and 25 mg (0.03 equiv) of 4-dimethylaminopyridine in 20 mL of methylene chloride for 10 h at 55 °C. Cooling to room temperature, addition of saturated aqueous potassium bisulfate solution, and extraction with methylene chloride was followed by washing the organic layer with potassium bisulfate solution, drying (magnesium sulfate), and evaporation to give a residue which was chromatographed on silica with 1 : 1 hexane : ethyl acetate to give the desired tosylate **36** as an oil (2.21 g; 72%). ¹H NMR δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 3.71-3.90 (m, 3H), 3.70 (s, 3H), 2.50-2.80 (m, 3H), 2.44 (s, 3H), 2.05-2.35 (m, 3H), 1.55-1.65 (m, 1H), 1.00-1.15 (m, 1H), 0.174 (s, 3H), 0.127 (s, 3H).

Methoxylactone 31. A mixture of the above fluorosilyl tosylate **36** (2.04 g), m-chloroperbenzoic acid (2.0 g; 2 equiv) and Na_2PO_4 (1.97 g; 3 equiv) in 30 mL methylene chloride was stirred at room temperature for 15 h. Washing twice with saturated aqueous Na_2CO_3 solution, then with brine, drying (MgSO_4) and evaporation, gave a residue which was purified by chromatography on silica (1 : 2 hexane : ethyl acetate) to give the intermediate hydroxylactone **37** as an oil (1.07 g; 60.5% yield). ^1H NMR δ 7.76 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 4.55-4.65 (m, 1H), 4.31 (bs, 1H), 3.75 (s, 3H), 3.20 (d, J = 4.2 Hz, 1H), 2.45-2.70 (m, 5H), 2.44 (s, 3H), 2.10-2.35 (m, 1H), 1.55-1.75 (m, 1H).

Methylation of the secondary hydroxyl was achieved by stirring a mixture of 1.0 g of **37**, silver oxide (6.12 g; 10 equiv), and CaSO_4 (7.2 g) in 25 mL of methyl iodide for 20 h. The mixture was then filtered through Celite, and evaporated to a residue which was chromatographed on silica (1 : 1 hexane : ethyl acetate) to give the desired methyl ether **31** as an oil (1 g; 96%). ^1H NMR δ 7.77 (d, J = 5.6 Hz, 2H), 7.37 (d, J = 5.6 Hz, 2H), 4.39-4.43 (m, 1H), 4.15-4.19 (m, 1H), 3.97-4.05 (m, 1H), 3.75-3.90 (m, 1H), 3.76 (s, 3H), 3.38 (s, 3H) 2.50-2.75 (m, 5H), 2.46 (s, 3H), 2.10-2.25 (m, 1H), 1.55-1.70 (m, 1H).

Aldehyde Tosylate 39 (4, R=H). A stirred solution of the above lactone **31** (261 mg; 0.66 mmol) in 5.5 mL of 10 : 1 ether/tetrahydrofuran, under argon, was cooled to -78 °C, and treated with 103 mg of diisobutylaluminum hydride (0.72 mmol). After 30 min, 1 mL of water was added and the mixture was allowed to warm to room temperature. After 1 h, addition of 0.5 g of MgSO_4 and filtration gave a filtrate which was evaporated. Chromatography of the residue on silica (1 : 2 hexane : ethyl acetate) gave the purified aldehyde tosylate **39 (4, R=H)**, (220 mg; 84%). ^1H NMR δ 9.56 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 3.80-3.88 (m, 2H), 3.63 (s, 3H), 3.51 (s, 3H), 3.45-3.55 (m, 1H), 3.20-3.35 (m, 1H), 2.90-3.05 (m, 1H), 2.65-2.85 (m, 1H), 2.50-2.55 (m, 1H), 2.44 (s, 3H), 2.00-2.30 (m, 3H), 1.70-1.90 (m, 1H), 1.05-1.30 (m, 1H).

Methyl Cyano seco-reserpate 41. A mixture of the above tosylate aldehyde **4** (R=H, 70 mg, 0.176mmol), 56 mg of KCN and 105 mg of MgSO₄ in 4mL of acetonitrile was stirred at room temperature for 10 min. To the stirred solution was added 67 mg of 6-methoxytryptamine (**40**). After 1h, the mixture was filtered through Celite and evaporated to a residue which was chromatographed on silica (1 : 3 hexane : ethyl acetate) to yield the crystalline aminonitrile **41** (67.5 mg; 87%). ¹H NMR δ 7.88 (bs, 1H), 7.42 (d, J = 8.6 Hz, 1H), 6.91 (d, J = 2.2 Hz, 1H), 6.83 (s, 1H), 6.79 (dd, J = 2.2, 8.6 Hz, 1H), 3.96 (bs, 1H), 3.84 (s, 3H), 3.72 (s, 3H), 3.55 (s, 3H), 3.30-3.50 (m, 1H), 2.55-2.90 (m, 7H), 2.25-2.40 (m, 2H), 1.80-2.10 (m, 4H), 1.50-1.80 (m, 2H).

(\pm)-Reserpine (1). A mixture of the above cyano compound **41** (53 mg; 0.12 mmol) and 0.1 mL of 1N aqueous HCl in 1 mL of tetrahydrofuran was stirred at room temperature for 30 h. Saturated aqueous Na₂CO₃ solution was added, the mixture was extracted with ether, and then with methylene chloride. The combined organic extacts were dried (MgSO₄), and evaporated to give a residue which was chromatographed on silica (10 : 1 chloroform : methanol) to give (46.1 mg; 92%) of (\pm)-methyl reserpate (**43**), mp 238-239 °C (reported^{1a}: mp 241-242 °C). ¹H NMR δ 7.33 (d, J = 4.40 Hz, 1H), 6.85 (s, 1H), 6.77 (dd, J = 1.2, 4.2 Hz, 1H), 4.45-4.50 (bs, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.59 (s, 3H), 3.50-3.55 (m, 2H), 3.15-3.25 (m, 2H), 2.85-3.07 (m, H). Esterification was carried out by stirring at room temperature, for 4 days, under argon, a mixture of the above hydroxyester (42 mg) and 117 mg of 3,4,5-trimethoxybenzoyl chloride in 2 mL of dry pyridine. Removal of solvent under reduced pressure, and addition of saturated Na₂CO₃ solution at 0 °C, with stirring, was followed by extraction with methylene chloride. The organic layer was washed with saturated aqueous Na₂CO₃ solution, then brine, dried over MgSO₄ and evaporated, to give a residue which was chromatographed on silica with 1:2 hexane : ethyl acetate to give 58.6 mg (95%) of synthetic (\pm)-reserpine, mp 256-258 °C (reported^{1a} mp: 260.5-262 °C (dec.). ¹H NMR identical with that of an authentic sample of natural (-)-reserpine.

(4S)-Benzylloxymethyl-2-cyclohexenone (45). Previously described⁴¹ (1R, 4S) 4-benzylloxymethyl-2-cyclohexen-1-ol **44**, $[\alpha]^{24}_D$ -5.68 (c 1.09, CHCl₃), 2.10 g, 9.63 mmol), derived from (-)(S)-3-cyclohexenecarboxylic acid,⁴² was oxidized to the desired cyclohexenone by stirring with a mixture of 4.153 g of pyridinium chlorochromate, 395 mg of sodium acetate and 5 g of Florisil in 30 mL of methylene chloride, for 3 h at room temperature. Removal of the Florisil by filtration through Celite, and concentration gave a residue which was chromatographed on silica (10 : 5 n-hexane-ethyl acetate) to give 1.74 g of the required 4(S)-benzylloxymethyl-2-cyclohexenone **45**, (-)33, as an oil, $[\alpha]^{26}_D$ - 109.4, (c 3.58, MeOH), in 83% yield.

(-)-Reserpine (-)-1. The identical procedures described above for the synthesis of racemic reserpine were followed, using the (-)4(S)-benzylloxymethyl-2-cyclohexenone (**45**) just described in the initial double Michael condensation with furyldimethylsilyl acrylate. The synthetic (-)-reserpine, (-)**1**, had mp 283-285 °C (recrystallized from methylene chloride; $[\alpha]^{24}_D$ -120.9 (c 0.642, CHCl₃); reported: 286-288 °C; $[\alpha]^{27}_D$ -118.9 (c 1.09, CHCl₃)). Rotations of intermediates in the enantioselective route to (-)-reserpine were: (+)-**34**: (oil) $[\alpha]^{21}_D$ + 80.9 (c 6.5, CHCl₃); (+)-**35**: (oil) $[\alpha]^{21}_D$ + 68.5 (c 2.0, CHCl₃); (+)-**36**: (oil) $[\alpha]^{21}_D$ + 61.0 (c 0.52, CHCl₃); (-)-**31**(oil) $[\alpha]^{21}_D$ - 36.7 (c 1.8, CHCl₃).