General Procedures. NMR spectra were recorded at 400 MHz in $CDCl_3$ unless otherwise indicated, chemical shifts are reported in δ, coupling constants in Hz, and IR spectra in cm^{-1}.

Methyl (*S*)-*O*-Benzyltyrosine (9). A solution of (*S*)-*N*-BOC-tyrosine methyl ester (2.95 g, 10 mmol) in 20 of mL of acetone was treated with Cs_2CO_3 (3.26 g, 10 mmol) and then benzyl bromide (1.19 mL, 10 mmol) at 25 °C. The reaction mixture was stirred at 65 °C for 2 h, cooled to 25 °C, and taken up in 50 mL of EtOAc. The mixture was filtered through celite, which was washed with 2×20 mL of EtOAc. The combined filtrates were concentrated under reduced pressure to dryness and the residue was dissolved in 20 mL of CH_2Cl_2. TFA (5 mL) was added to this solution and the resulting mixture was stirred at 25 °C for 1 h, and concentrated under reduced pressure to dryness. The residue was taken up in 20 mL of 0.1 N HCl, which was washed with Et_2O (3×20 mL). The combined organic layers were washed with 20 mL of 0.1 N HCl, and the combined aqueous layers was carefully neutralized with Na_2CO_3 at 0 °C to pH 8~9. The resulting mixture was extracted with CH_2Cl_2 (5×30 mL), and the combined organic layers were washed with brine, and dried (Na_2SO_4). Removal of the solvent provided 2.85 g (100%) of crude **9**.

Methyl (*S*)-*N*-Hydroxy-*O*-benzyltyrosine (10). A solution of amine **9** (2.85 g, 10 mmol) and anisaldehyde (1.22 mL, 10 mmol) in 12 mL of dry MeOH was stirred at 25 °C for 6 h. A white precipitate formed and the solvent was evaporated to dryness and the residue was taken up in 10 mL of CH_2Cl_2. The solution was cooled to -15 °C, and a solution of *m*-CPBA (2.88 g, 70%, 10 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise. The reaction mixture was stirred at 25 °C overnight and the precipitate was filtered off. The filtrate was washed with saturated $NaHCO_3$ solution and water and dried ($MgSO_4$). The solvent was evaporated and the residue was dissolved in MeOH (10 mL). Hydroxylamine hydrochloride (690 mg, 20.3 mmol) was added and the mixture was stirred at 25 °C overnight. The solvent was evaporated, water (20 mL) was added and the oily oxime was removed by filtration through celite. The filtrate was extracted with Et_2O (3×25 mL) and the extract was washed with 0.1 N HCl. The combined

aqueous solution was carefully saturated with $NaHCO_3$ and the free hydroxylamine was extracted with CH_2Cl_2 (5 × 25 mL). The organic layer was dried (Na_2SO_4). Removal of the solvent and flash chromatography of the residue on silica gel (3:2 hexane/EtOAc) gave 1.594 g (53%) of pure hydroxylamine **10**: mp 72.0-72.5 °C; ^{1}H NMR 7.43-7.29 (m, 5), 7.09 (d, 2, *J* = 8.8), 6.90 (d, 2, *J* = 8.8), 6.07 (br, 1, NH or OH), 5.46 (br, 1, NH or OH), 5.03 (s, 2), 3.83 (dd, 1, *J* = 7.9, 6.1), 3.71 (s, 3), 2.94 (dd, 1, *J* = 14.0, 6.1), 2.82 (dd, 1, *J* = 14.0, 7.9); ^{13}C NMR 173.3, 157.8, 136.9, 130.0 (2 C), 128.7, 128.5 (2 C), 127.9, 127.4 (2 C), 115.0 (2 C), 70.0, 66.3, 52.0, 34.6; IR (KBr) 3246, 1751, 1512; $[\alpha]_D$ +4.5 (*c* 0.47, $CHCl_3$). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.56; H, 6.12; N, 4.51.

Methyl (α*S*,3*R*)-3-(Ethoxycarbonyl)-α-[[4-(phenylmethoxy)phenyl]methyl]-2,9,14-trioxa-1-azadispiro[4.2.6.2]hexadecane-1-acetate (13). A mixture of ketone **11 (**819 mg, 4.45 mmol), hydroxylamine **10** (1.34 g, 4.45 mmol) and ethanol (7 mL) was stirred at 25 °C for 48 h. The ethanol was removed and the resulting nitrone **12** was taken up in 10 mL of toluene. Ethyl acrylate (0.48 mL, 4.45 mmol) was added and the resulting mixture was heated for 4 h at 100 °C and concentrated. The resulting isoxazolidine **13** contained a 6:1 mixture of diastereomers as determined by analysis of the ^{1}H NMR spectrum. The crude mixture was purified by flash chromatography on silica gel (1:1 hexane/EtOAc) to give 1.72 g (68%) of **13** as an inseparable 6:1 mixture of diastereomers.

The data for the major diastereomer was determined from the early fractions which contain the major isomer and less than 5% of an unidentified byproduct: ^{1}H NMR 7.43-7.29 (m, 5), 7.10 (d, 2, *J* = 8.8), 6.87 (d, 2, *J* = 8.8), 5.03 (s, 2), 4.67 (dd, 1, *J* = 9.2, 5.5), 4.23 (q, 2, *J* = 6.7), 3.76 (dd, 1, *J* = 10.4, 4.9), 3.65-3.60 (m, 4), 3.51 (s, 3), 3.30 (dd, 1, *J* = 13.4, 4.9), 3.12 (dd, 1, *J* = 13.4, 10.4), 2.43 (dd, 1, *J* = 12.8, 9.2), 2.38 (dd, 1, *J* = 12.8, 5.5), 1.92-1.70 (m, 5), 1.65-1.43 (m, 7), 1.29 (t, 3, *J* = 6.7); ^{13}C NMR 172.4, 171.9, 157.5, 137.1, 130.3 (2 C), 129.5, 128.5 (2 C), 127.9, 127.4 (2 C), 114.7 (2 C), 100.1, 75.9, 69.9, 67.5, 66.5, 61.9, 61.7, 61.3, 51.7, 41.3, 37.4, 31.3, 31.0, 30.6, 29.7, 29.6, 29.0, 14.2; IR (neat) 1738, 1612, 1512, 1239, 1201, 1113; $[\alpha]_D$ -18 (*c* 0.71, MeOH); HRMS (DEI) calcd for $C_{32}H_{41}NO_8$ 568.2910, found 568.2928.

Methyl (α*S*,13*R*)-13-Hydroxy-α-[(4-hydroxyphenyl)methyl]-12-oxo-1,6-dioxa-11-azadispiro[4.2.6.2]hexadecane-11-acetate (14). A 6:1 mixture of isoxazolidines **13** and the diastereomer (1.31 g, 2.31 mmol) and 10% Pd/C (220 mg) in 8 mL of AcOH was shaken under 45 PSI of H_2 at 25 °C for 6 h. The Pd/C was filtered off and the filtrate was taken up in 100 ml of CH_2Cl_2, which was carefully neutralized with Na_2CO_3 solution, washed with water and brine and dried (Na_2SO_4). The solvent was evaporated and the residue was dissolved in 110 mL of 10/1 CH_2Cl_2/HOAc and stirred at 25 °C overnight. The solution was carefully neutralized with saturated Na_2CO_3 aqueous solution and then washed with water and brine, dried (Na_2SO_4), and concentrated to give a 6:1 mixture of diastereomers as determined by analysis of the ^{1}H NMR spectrum. Flash chromatography (CH_2Cl_2/MeOH 95:5) of the residue on silica gel provided 697 mg (67.5%) of a 6:1 mixture of **14** and the diastereomer, and 190 mg (16.8%) of debenzylated **13**.

Data for **14** was determined from the mixture of diastereomers: ^{1}H NMR 7.04 (d, 2, *J* = 8.5), 6.73 (d, 2, *J* = 8.5), 5.58 (s, 1, OH), 4.20 (dd, 1, *J* = 7.9, 7.9), 3.83 (dd, 1, *J* = 11.4, 4.9), 3.77 (s, 3), 3.65-3.55 (m, 5), 3.33 (dd, 1, *J* = 14.0, 4.9), 3.09 (s, 1, OH), 2.35 (dd, 1, *J* = 12.8, 7.9), 1.91-1.85 (m, 1), 1.82 (dd, 1, *J* = 12.8, 7.9), 1.71-1.54 (m, 7), 1.40 (ddd, 1, *J* = 14, 14, 4), 1.27 (ddd, 1, *J* = 14, 14, 4), 0.93 (ddd, 1 *J* = 14, 13, 4), 0.28-0.22 (m, 1); ^{13}C NMR 175.1, 170.5, 155.2, 130.7 (2 C), 129.2, 115.3 (2 C), 99.4, 68.3, 62.1, 62.0, 61.8, 56.6, 52.6, 37.7, 33.1, 32.9, 30.6, 30.0, 29.9, 29.6, 29.4; IR (neat) 3356, 1738, 1682; HRMS (DEI) calcd for $C_{23}H_{31}NO_7$ 433.2101, found 433.2110.

Partial data for the minor diastereomer: ^{1}H NMR 5.72 (s, 1, OH), 4.36 (dd, 1, *J* = 9.2, 8.8), 3.76 (s, 3), 3.43 (s, 1, OH), 2.64 (dd, 1, *J* = 12.8, 8.8).

Methyl (α*S*,13*R*)-13-Hydroxy-α-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methyl]-12-oxo-1,6-dioxa-11-azadispiro[4.2.6.2]hexadecane-11-acetate (15). A 6:1 mixture of **14** and the diastereomer (544 mg, 1.26 mmol), Cs_2CO_3 (594 mg, 1.89 mmol), 1-bromo-3-methyl-2-butene (0.30 mL, 2.64 mmol) and 12 mL of acetone was stirred at 50 °C for 2 h and cooled to 25 °C. The mixture was filtered through celite, which was washed with CH_2Cl_2 (2 × 10 mL). The

combined filtrates were concentrated and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/EtOAc) to give 538 mg (86%) of a 6:1 mixture of **15** and the diastereomer.

Data for **15** was determined from the mixture of diastereomers: ^{1}H NMR 7.08 (d, 2, *J* = 8.5), 6.81 (d, 2, *J* = 8.5), 5.47 (m, 1), 4.47 (m, 2), 4.24 (ddd, 1, *J* = 8.5, 8.5, 2.4), 3.83 (dd, 1, *J* = 10.4, 4.9), 3.76 (s, 3), 3.65-3.55 (m, 5), 3.38 (s, 1, OH), 3.35 (dd, 1, *J* = 13.4, 4.9), 2.34 (dd, 1, *J* = 13.4, 8.5), 1.91-1.82 (m, 2), 1.79 (s, 3), 1.74 (s, 3), 1.70-1.52 (m, 7), 1.40 (ddd, 1, *J* = 13.4, 13.4, 4.3), 1.27 (ddd, 1, *J* = 14.0, 13.4, 3.7), 0.92 (ddd, 1, *J* = 13.4, 13.4, 4.3), 0.26-0.21 (m, 1); ^{13}C NMR 174.7, 170.4, 157.7, 138.1, 130.6 (2 C), 130.0, 119.6, 114.6 (2 C), 99.2, 68.3, 64.8, 61.9, 61.8, 61.7, 56.6, 52.6, 37.7, 33.2, 33.0, 30.7, 30.1, 29.9, 29.6, 29.5, 25.8, 18.1; IR (neat) 3378, 1742, 1682; HRMS (DEI) calcd for $C_{28}H_{40}NO_7$ (MH^+) 502.2805, found 502.2812.

Partial data for the minor diastereomer: ^{1}H NMR 4.38 (ddd, 1, *J* = 8.7, 8.7, 2.4), 3.74 (s, 3), 2.64 (dd, 1, *J* = 12.5, 8.7), 0.10-0.07 (m, 1).

Methyl (α*S*,13*S*)-13-Azido-α-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methyl]-12-oxo-1,6-dioxa-11-azadispiro[4.2.6.2]hexadecane-11-acetate (16). The 6:1 mixture of **15** and the diastereomer (512 mg, 0.904 mmol), Et_3N (0.30 mL, 2.15 mmol), DMAP (121 mg, 0.99 mmol) and TsCl (284 mg, 1.49 mmol) in 10 mL of CH_2Cl_2 were stirred at 25 °C for 6 h. The reaction was diluted with 50 mL of EtOAc, washed with 20 mL of 0.1 N HCl, 20 mL of water, and 20 mL of brine, dried ($MgSO_4$), and concentrated to give 589 mg of the crude tosylate.

A solution of the crude tosylate and NaN_3 (150 mg, 2.31 mmol) in 5 mL of dry DMF was stirred at 25 °C for 12 h. The reaction mixture was diluted with 50 mL of EtOAc, washed with H_2O and brine, and dried ($MgSO_4$). Evaporation of the solvent, followed by flash chromatography of the residue on silica gel (1:1 CH_2Cl_2/EtOAc) gave 61 mg (12%) of the diastereomer of **16** followed by 0.426 g (79%) of pure **16**.

Data for the diastereomer of **16**: ^{1}H NMR 7.08 (d, 2, *J* = 8.5), 6.82 (d, 2, *J* = 8.5), 5.49-5.45 (m, 1), 4.52-4.44 (m, 2), 4.06 (dd, 1, *J* = 8.5, 5.5), 3.82 (dd, 1, *J* = 10.3, 4.9), 3.78 (s, 3), 3.66-3.52 (m, 5), 3.37 (dd, 1, *J* = 14.0, 4.9), 2.03 (dd, 1, *J* = 14.0, 8.5), 1.90 (dddd, 1, *J* = 13.7, 3.7, 3.1, 3), 1.84 (dd, 1, *J* = 14.0, 5.5), 1.79 (s, 3), 1.74 (s, 3), 1.70-1.54 (m, 7), 1.41-1.32 (m, 1),

1.20 (ddd, 1, *J* = 14.0, 13.4, 3.7), 1.02 (ddd, 1, *J* = 13.8, 13.4, 3.7), 0.15 (br d, 1, *J* = 13.8); ^{13}C NMR 170.6, 170.1, 157.7, 138.1, 130.7 (2 C), 130.0, 119.6, 114.6 (2 C), 99.1, 64.8, 62.4, 62.0, 61.8, 57.9, 56.7, 52.6, 35.3, 33.4, 32.0, 31.1, 30.3, 30.2, 29.6, 29.5, 25.8, 18.2; IR (neat) 2111, 1745, 1698; HRMS (DEI) calcd for $C_{28}H_{38}N_4O_6$ (MH^+) 527.2870, found 527.2871.

Data for **16**: ^{1}H NMR 7.09 (d, 2, *J* = 8.5), 6.83 (d, 2, *J* = 8.5), 5.49-5.45 (m, 1), 4.53-4.44 (m, 2), 4.15 (dd, 1, *J* = 8.9, 8.9), 3.79 (dd, 1, *J* = 11.0, 4.9), 3.77 (s, 3), 3.62-3.55 (m, 5), 3.35 (dd, 1, *J* = 14.0, 4.9), 2.49 (dd, 1, *J* = 12.8, 8.9), 1.91 (dddd, 1, *J* = 14.0, 3.7, 3.1, 3), 1.79 (s, 3), 1.74 (s, 3), 1.66-1.63 (m, 1), 1.59-1.52 (m, 5), 1.48-1.43 (m, 1), 1.38 (ddd, 1, *J* = 14.0, 4.3, 4.3), 1.30 (dd, 1, *J* = 12.8, 8.9), 1.21-1.10 (m, 2), 0.06-0.04 (m, 1); ^{13}C NMR 171.5, 170.1, 157.7, 138.0, 130.8 (2 C), 129.8, 119.6, 114.6 (2 C), 99.1, 64.8, 62.0, 61.8, 61.4, 57.8, 56.6, 52.6, 35.2, 33.8, 32.0, 30.7, 30.5, 29.9, 29.6, 29.5, 25.8, 18.2; IR (neat) 2109, 1745, 1698; $[\alpha]_D$ –143 (*c* 0.34, $CHCl_3$); HRMS (DEI) calcd for $C_{28}H_{38}N_4O_6$ (MH^+) 527.2870, found 527.2884.

(13*S*)-1-[(1*S*)-2-Hydroxy-1-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methyl]-3-methylamino-1,6-dioxa-11-azadispiro[4.2.6.2]hexadecane (17). LAH (2.3 mL, 1.0 M in THF) was added to a solution of **16** (400 mg, 0.76 mmol) in dry THF (7.5 mL) dropwise at -78 °C. The resulting mixture was warmed to 0 °C and stirred at 0 °C for 15 min and at reflux for 2 h, and was cooled to 0 °C. Excess EtOAc was added to quench the LAH. Water (87 μL), 15% NaOH (87 μL) and water (262 μL) were added. The granular precipitate was removed by filtration and the filtrate was concentrated to give 360 mg of the crude amino alcohol.

Formic acid (98%, 0.81 mL) was added to acetic acid (1.34 mL) at 0 °C. The mixture was heated at 60 °C for 1 h and cooled to 25 °C. A solution of 360 mg of crude amine in 2 mL of THF was added to the above mixture dropwise. The formylation was complete in 30 min. The reaction mixture was concentrated under reduced pressure and the residue was taken up in 50 mL of CH_2Cl_2, which was washed with Na_2CO_3 solution and brine and dried. Removal of the solvent gave 368 mg of the crude formate.

LAH (1.5 mL, 1.0 M in THF) was added to a solution of 368 mg of the crude formate in dry THF (7 mL) dropwise at -78 °C. The resulting mixture was warmed up to 0 °C and stirred at

0 °C for 15 min and at reflux for 2 h, and was cooled to 0 °C. Excess EtOAc was added to quench the LAH. Water (57 μL), 15% NaOH (57 μL) and water (171 μL) were added. The granular precipitate was removed by filtration and the filtrate was concentrated to dryness followed by flash chromatography of the residue on silica gel (CH_2Cl_2/MeOH/Et_3N 95:5:2) to give 207 mg of **17**: ^{1}H NMR 7.05 (d, 2, *J* = 8.5), 6.83 (d, 2, *J* = 8.5), 5.51-5.47 (m, 1), 4.48 (d, 2, *J* = 6.7), 3.71-3.68 (m, 4), 3.31-3.26 (m, 1), 3.21-3.09 (m, 4), 2.94 (d, 1, *J* = 12.8), 2.66-2.61 (m, 1), 2.45 (s, 3), 2.46-2.40 (m, 1), 2.18 (dd, 1, *J* = 12.2, 7.9), 2.01-1.93 (m, 2), 1.86-1.80 (m, 1), 1.80 (s, 3), 1.74 (s, 3), 1.66-1.39 (m, 9), 1.18-1.13 (m, 1); ^{13}C NMR 157.3, 138.0, 131.0, 129.7 (2 C), 119.7, 114.7 (2 C), 100.1, 64.7, 62.8, 61.9, 61.8, 60.5, 57.7, 56.0, 49.4, 42.5, 36.2, 35.2, 34.7, 31.9, 31.0, 30.8, 29.8, 29.6, 25.8, 18.2; IR (neat) 3411, 1611, 1510; $[\alpha]_D$ -3.6 (*c* 0.34, MeOH); HRMS (DEI) calcd for $C_{28}H_{44}N_2O_4$ (MH^+) 473.3379, found 473.3365.

(5*S*)-4-Methyl-2-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methyl]-dispiro[1,4-diazabicyclo[3.2.1]oct[2]en-7,1'-cyclohexane-4',2''-[1,3]dioxepane] (18). $(F_3CCO)_2O$ (23 μL, 0.079 mmol) was added to a solution of DMSO (15 μL, 0.20 mmol) in 0.5 mL of CH_2Cl_2 at -78 °C and the resulting mixture was stirred at this temperature for 20 min. A solution of **17** (31 mg, 0.066 mmol) in 0.5 mL of CH_2Cl_2 was added to the mixture and stirred for 30 min. Et_3N (32 μL, 0.23 mmol) was added and the mixture was allowed to warm to 0 °C, stirred for 30 min and was taken up in 5 mL of CH_2Cl_2, which was washed with water and brine and dried (Na_2SO_4). The solvent was evaporated to give the crude aldehyde as a mixture of diastereomers.

A mixture of the crude aldehydes, K_2CO_3 (18 mg, 0.13 mmol), 0.6 mL of MeOH and 0.4 mL of water was stirred at 25 °C for 2 h and concentrated under reduced pressure. The residue was taken up in 5 mL of CH_2Cl_2, which was washed with water and brine and dried (Na_2SO_4). Removal of the solvent followed by flash chromatography of the residue on silica gel (1:1 CH_2Cl_2/EtOAc) gave 18 mg (60%) of **18**: ^{1}H NMR 7.09 (d, 2, *J* = 8.6), 6.82 (d, 2, *J* = 8.6), 5.52-5.47 (m, 1), 5.07 (d, 1, *J* = 1.2), 4.48 (d, 2, *J* = 6.7), 3.47-3.66 (m, 4), 3.29 (dd, 1, *J* = 6.1, 2.5), 3.22 (s, 2), 3.15 (dd, 1, *J* = 11.6, 2.5), 2.72 (dd, 1, *J* = 11.6, 1.8), 2.45 (s, 3), 2.06-1.92 (m, 3), 1.85 (dddd, 1, *J* = 13.4, 4, 3, 3), 1.79 (3, 3), 1.75 (1, dd, *J* = 13.4, 6.1), 1.74 (s, 3), 1.69-1.57 (m,

7), 1.50-1.42 (m, 1), 1.35 (ddd, 1, *J* = 13.4, 4, 4, 3); ^{13}C NMR 157.1, 137.9, 132.1, 130.1 (2 C), 129.3, 127.1, 120.0, 114.3 (2 C), 100.6, 72.5, 64.7, 61.8, 61.7, 59.2, 51.5, 42.5, 41.5, 40.5, 34.2, 32.5, 31.8, 30.4, 29.8, 29.0, 25.8, 18.2; IR (neat), 1680, 1640, 1111.

(5'*S*)-4'-Methyl-2'-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methyl]-spiro[cyclohexane-1,7'-[1,4]diazabicyclo[3.2.1]oct[2]en-4-one (3, TAN1251C). A solution of **18** (9.5 mg, 0.021 mmol) and 50 μL of 1 N HCl (aq.) in 0.5 mL of acetone was stirred at 25 °C for 3 h and neutralized with Na_2CO_3 solution. The acetone was evaporated and the residue was taken up in 5 mL of CH_2Cl_2 which was washed with Na_2CO_3 solution and brine and dried (Na_2SO_4). Removal of the solvent followed by flash chromatography of the residue on silica gel (CH_2Cl_2/EtOAc 1:1) gave 6 mg (75%) of **3**: ^{1}H NMR 7.08 (d, 2, *J* = 8.6), 6.83 (d, 2, *J* = 8.6), 5.52-5.47 (m, 1), 5.24 (d, 1, *J* = 1.2), 4.48 (d, 2, *J* = 6.7), 3.40-3.38 (m, 1), 3.21 (s, 2), 3.20 (dd, 1, *J* = 11.3, 3.1), 2.78 (dd, 1, *J* = 11.3, 1.5), 2.63-2.18 (m, 7), 2.51 (s, 3), 1.97 (ddd, 1, *J* = 13.4, 10.4, 4.9), 1.87 (dd, 1, *J* = 13.1, 5.2), 1.84-1.81 (m, 1), 1.79 (s, 3), 1.74 (s, 3); ^{13}C NMR 211.6, 157.1, 137.9, 131.9, 129.8 (2 C), 128.2, 127.8, 119.9, 114.4 (2 C), 71.4, 64.7, 59.0, 52.2, 42.9, 41.4, 40.3, 39.5, 37.8, 37.3, 34.6, 25.8, 18.2; IR (neat) 1716, 1681, 1642; $[\alpha]_D$ +23 ° (*c* 0.45, MeOH) (lit. $[\alpha]_D$ +24 ° (*c* 0.44, MeOH)); HRMS (DEI) calcd for $C_{24}H_{32}N_2O_2$ 380.2464, found 380.2454.

(1*S*,2'*Z*,5*S*)-4-Methyl-2-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methylene]-dispiro[1,4-diazabicyclo[3.2.1]octan-7,1'-cyclohexane-4',2''-[1,3]dioxepane] (20). A suspension of DDQ (7.0 mg, 0.031 mmol) in 0.2 mL of dry (freshly redistilled from CaH_2) CH_2Cl_2 was added dropwise to a solution of **18** (14 mg, 0.031 mmol) in 0.3 mL of CH_2Cl_2, which was stirred at 25 °C for 2 h. The solvent was evaporated and the residue was taken up in 0.5 mL of MeOH, to which $NaCNBH_3$ (10 mg, 0.15 mmol), and a drop of 2% bromocresol green in MeOH were added. A few drops of HOAc were added to this mixture till the solution turned yellow. The resulting mixture was stirred at 25 °C for 1 h and neutralized with Na_2CO_3 solution. The MeOH was removed under reduced pressure and the residue was taken up in 10 mL of CH_2Cl_2 which was washed with Na_2CO_3 solution and brine and dried (Na_2SO_4). Removal of the solvent

followed by flash chromatography (CH_2Cl_2/MeOH 95:5) of the residue on silica gel gave 11 mg (79%) of **20**: ^{1}H NMR 7.88 (d, 2, *J* = 8.6) 6.83 (d, 2, *J* = 8.6), 5.91 (s, 1), 5.51-5.48 (m, 1), 4.50 (d, 2, *J* = 6.7), 3.70-3.56 (m, 4), 3.24-3.19 (m, 3), 2.88 (d, 2, *J* = 13.4), 2.17 (s, 3), 1.95-1.56 (m, 13), 1.79 (s, 3), 1.74 (s, 3), 1.46 (dd, 1, *J* = 13.2, 5.2); ^{13}C NMR 157.6, 141.8, 137.9, 130.9 (2 C), 129.1, 122.3, 119.9, 114.0 (2 C), 100.5, 64.8, 64.6, 61.62, 61.58, 61.1, 58.0, 55.9, 42.5, 35.2, 33.4, 31.3, 30.9, 29.8, 29.6, 28.6, 25.8, 18.2; IR (neat) 1659, 1605, 1506, 1112; $[\alpha]_D$ -81 (*c* 0.315, MeOH).

(1'*S*,2'*Z*,5'*S*)-4'-Methyl-2'-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methylene]-spiro[cyclohexane-1,7'-[1,4]diazabicyclo[3.2.1]octan]-4-one (1, TAN1251A). A solution of **20** (16 mg, 0.035 mmol) and 50 μL of 1 M HCl (aq.) in 0.5 mL of acetone was stirred at 25 °C for 3 h and neutralized with Na_2CO_3 solution. The acetone was evaporated and the residue was taken up in 10 mL of CH_2Cl_2 which was washed with Na_2CO_3 solution and brine and dried (Na_2SO_4). Removal of the solvent followed by flash chromatography of the residue on silica gel (CH_2Cl_2/MeOH 95:5) gave 12 mg (89%) of **1**: mp 112-114 °C (lit. 118.5-120 °C); ^{1}H NMR 7.76 (d, 2, *J* = 9.2), 6.80 (d, 2, *J* = 9.2), 6.03 (s, 1), 5.48 (m, 1), 4.47 (m, 2), 3.30-3.27 (m, 3), 3.03 (dd, 1, *J* = 11.7, 2.0), 2.95 (d, 1, *J* = 14.0), 2.81-2.72 (m, 1), 2.20 (s, 3), 2.20-2.12 (m, 3), 2.11-2.07 (m, 1), 2.01-1.95 (m, 1), 1.86 (dd, 1, *J* = 14.0, 1.6), 1.86-1.70 (m, 2), 1.79 (s, 3), 1.74 (m, 3), 1.49 (dd, 1, *J* = 14.0, 5.2); ^{13}C NMR 212.1, 157.8, 141.4, 138.2, 130.7 (2 C), 128.5, 122.9, 119.6, 114.0 (2 C), 64.6, 64.0, 61.1, 58.4, 55.6, 42.5, 38.59, 38.54, 38.2, 34.5, 32.2, 25.8, 18.2; IR (KBr) 1712, 1606, 1508; $[\alpha]_D$ –9.1 (*c* 0.40, MeOH) (lit. $[\alpha]_D$ –8.1 (*c* 0.42, MeOH)); HRMS (DEI) calcd for $C_{24}H_{32}N_2O_2$ 380.2464, found 380.2460.

(1'*R*,2'*R*, 5'*S*)-4'-Methyl-2'-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methyl]-spiro[cyclohexane-1,7'-[1,4]diazabicyclo[3.2.1]octan]-4-one (5, *epi*-TAN1251D). A solution of **18** (23 mg, 0.050 mmol) and $NaBH(OAc)_3$ (32 mg, 0.15 mmol) in 0.5 mL of HOAc was stirred at 25 °C for 30 min, carefully neutralized with Na_2CO_3 solution, and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with Na_2CO_3 solution and brine and dried (Na_2SO_4). Removal of the solvent afforded a 1:9 mixture of **23** and **24** as determined

by analysis of the ^{1}H NMR spectrum. The mixture was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 9:1) to give 21 mg (91%) of **24**, which contained less than 2% of **23**: ^{1}H NMR 7.15 (d, 2, *J* = 8.5), 6.84 (d, 2, *J* = 8.5), 5.51-5.47 (m, 1), 4.47 (d, 2, *J* = 6.7), 3.69 (m, 4), 3.23 (d, 1, *J* = 12.2), 3.08-3.06 (m, 1), 3.02-2.88 (m, 3), 2.86 (dd, 1, *J* = 12.2, 3.0), 2.46 (d, 1, *J* = 12.2), 2.07 (s, 3), 1.98 (dd, 1, *J* = 12.2, 5.5), 1.92-1.51 (m, 9), 1.79 (s, 3), 1.74 (s, 3), 1.61 (m, 4), 1.31 (dd, 1, *J* = 14.0, 5.5); ^{13}C NMR 157.2, 137.9, 132.9, 130.3 (2 C), 119.8, 114.4 (2 C), 100.6, 64.7, 64.1, 61.7, 61.6, 61.0, 56.0, 52.3, 49.4, 43.2, 39.6, 35.3, 32.7, 31.7, 30.7, 29.8, 29.7, 28.0, 25.8, 18.1.

A solution of **24** (20 mg, 0.044 mmol) and 40 μL of 1 N HCl in 0.4 mL of acetone was stirred at 25 °C for 5 h, carefully neutralized with Na_2CO_3 solution, and concentrated under the reduced pressure. The residue was dissolved in 0.4 mL of 0.1 N HCl, which was extracted with ether (2 × 0.4 mL). The combined organic layers were washed with 0.4 mL of 0.1 N HCl one more time and the ether layer was discarded. The combined aqueous layers were treated with Na_2CO_3 solution and extracted with CH_2Cl_2 (3 × 2 mL), which was washed with brine and dried (Na_2SO_4). Removal of the solvent followed by flash chromatography of the residue on silica gel (CH_2Cl_2/MeOH 9:1) gave 14 mg (83%) of **5** (*epi*-TAN1251D): ^{1}H NMR 7.13 (d, 2, *J* = 8.8), 6.83 (d, 2, *J* = 8.8), 5.51-5.46 (m, 1), 4.47 (d, 2, *J* = 6.7), 3.34 (dd, 1, *J* = 12.8, 1.2), 3.15 (dd, 1, *J* = 5.5, 3.6), 3.02-3.95 (m, 3), 2.89 (dd, 1, *J* = 12.8, 3.6), 2.70 (ddd, 1, *J* = 14.0, 12.2, 5.5), 2.56 (d, 1, *J* = 12.2), 2.37-1.94 (m, 7), 2.11 (s, 3), 1.79 (dd, 1, *J* = 14.0, 2), 1.79 (s, 3), 1.74 (s, 3), 1.72-1.65 (m, 1), 1.36 (dd, 1, *J* = 14.0, 5.5); ^{13}C NMR 211.8, 157.3, 138.0, 132.6, 130.1 (2 C), 119.8, 114.5 (2 C), 64.7, 63.0, 61.0, 56.3, 52.3, 50.4, 43.2, 39.7, 38.7, 38.4, 38.3, 33.7, 31.1, 25.8, 18.2; IR (neat) 1714, 1612, 1510, 1237; $[\alpha]_D$ +35 (*c* 0.12, MeOH); HRMS (DEI) calcd for $C_{24}H_{34}N_2O_2$ 382.2620, found 382.2607.

(1'*R*,2'*S*, 5'*S*)-4'-Methyl-2'-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methyl]-spiro[cyclohexane-1,7'-[1,4]diazabicyclo[3.2.1]octan]-4-one (4, TAN1251D). A few drops of HOAc were added to a mixture of **18** (10 mg, 0.026 mmol), $NaCNBH_3$ (9 mg, 0.14 mmol), a drop of 2% bromocresol green in $(CF_3)_2CHOH$, and 0.5 mL of $(CF_3)_2CHOH$. The resulting

mixture was stirred at 25 °C for 1 h, carefully treated with Na_2CO_3 solution, and concentrated under reduced pressure. The residue was taken up in 5 mL of CH_2Cl_2, which was washed with water and brine and dried (Na_2SO_4). Removal of the solvent afforded a >25:1 mixture of **23** and **24** as determined by analysis of the ^{1}H NMR spectrum. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 9:1) gave 9 mg (90%) of **23**: ^{1}H NMR 7.07 (d, 2, *J* = 8.5), 6.81 (d, 2, *J* = 8.5), 5.50-5.46 (m, 1), 4.47 (d, 2, *J* = 6.7), 3.72 (m, 2), 3.69 (m, 2), 3.31-3.23 (m, 2), 3.14 (m, 1), 3.08 (d, 1, *J* = 13.4), 2.94 (d, 1, *J* = 11.6), 2.70 (dd, 1, *J* = 13.4, 11.6), 2.60 (dd, 1, *J* = 11.6, 3.7), 2.16 (dd, 1, *J* = 11.6, 11.6), 2.10 (s, 3), 2.07-1.89 (m, 4), 1.79 (s, 3), 1.73 (s, 3), 1.69-1.42 (m, 6), 1.62 (m, 4); ^{13}C NMR 157.3, 138.0, 132.2, 129.8 (2 C), 119.8, 114.6 (2 C), 100.1, 65.9, 64.7, 61.9, 61.8, 61.4, 61.2, 52.2, 42.4, 41.3, 36.1, 32.4 (2 C), 30.7, 30.5, 29.8, 29.6, 25.8, 18.1, (quaternary C not observed). A drop (3 μL) of formic acid was added to the $CDCl_3$ solution: ^{1}H NMR 7.08 (d, 2, *J* = 8.5), 6.85 (d, 2, *J* = 8.5), 5.49-5.46 (m, 1), 4.48 (d, 2, *J* = 6.7), 3.92 (br t, 1, *J* = 11.6, 11.6), 3.79 (dd, 1, *J* = 12.8, 3.7), 3.72-3.64 (m, 5), 3.56 (d, 1, *J* = 12.8), 3.50 (d, 1, *J* = 13.4), 3.02 (dd, 1, *J* = 13.4, 3.7), 2.81 (dd, 1, *J* = 13.4, 11.6), 2.76 (dd, 1, *J* = 13.4, 11.6), 2.40 (s, 3), 2.29-2.03 (m, 7), 1.81 (m, 1), 1.79 (s, 3), 1.74 (s, 3), 1.62 (m, 4), 1.52-1.43 (m, 2). A 1D NOESY experiment with irradiation of the peak at δ 3.92 gave strong NOE peaks at δ 7.08 and δ 3.56, and small NOE peaks at δ 3.50 and δ 3.02.

A solution of **23** (9 mg, 0.020 mmol) and 20 μL of 1 N HCl in 0.2 mL of acetone was stirred at 25 °C for 5 h, carefully neutralized with Na_2CO_3 solution, and concentrated under reduced pressure. The residue was dissolved in 0.2 mL of 0.1 N HCl, which was extracted with ether (2 × 0.4 mL). The combined organic layers were washed with 0.2 mL of 0.1 N HCl one more time and the ether layer was discarded. The combined aqueous layers were treated with Na_2CO_3 solution and extracted with CH_2Cl_2 (3 × 2 mL), which was washed with brine and dried (Na_2SO_4). Removal of the solvent followed by flash chromatography of the residue on silica gel (CH_2Cl_2/MeOH 9:1) gave 6 mg (79%) of TAN1251D (**4**): ^{1}H NMR 7.07 (d, 2, *J* = 8.6), 6.82 (d, 2, *J* = 8.6), 5.50-5.46 (m, 1), 4.47 (d, 2, *J* = 6.7), 3.30 (dddd, *J* = 11.6, 11.6, 3.7, 3.7), 3.27 (dd, 1, *J* = 12.2, 3.3), 3.22-3.20 (m, 1), 3.03-2.92 (m, 2), 2.67-2.60 (m, 2), 2.59-2.32 (m, 5), 2.27-2.17

(m, 2), 2.17 (s, 3), 2.10-1.98 (m, 2), 1.86 (dd, 1, *J* = 13.4, 1.8), 1.79 (s, 3), 1.74 (s, 3), 1.64 (dd, 1, *J* = 13.4, 5.8); ^{13}C NMR 211.0, 157.4, 138.1, 131.9, 129.7 (2 C), 119.8, 114.7 (2 C), 65.8, 65.0, 64.7, 61.9, 61.3, 52.3, 42.4, 41.4, 39.6, 39.2, 38.0, 33.3, 33.0, 25.8, 18.2; IR (neat) 1715, 1607, 1510, 1236; $[\alpha]_D$ +22 (*c* 0.10, MeOH) (lit. $[\alpha]_D$ +24 (*c* 0.47, MeOH)); HRMS (DEI) calcd for $C_{24}H_{34}N_2O_2$ 382.2620, found 382.2607.

(1*R*,1'*S*,2'*Z*,3*S*,5'*S*)-3-Hydroxy-4'-methyl-2'-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methylene]-spiro[cyclohexane-1,7'-[1,4]diazabicyclo[3.2.1]octan]-4-one (25) and (1*S*,1'*S*,2'*Z*,3*R*,5'*S*)-3-Hydroxyl-4'-methyl-2'-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methylene]-spiro[cyclohexane-1,7'-[1,4]diazabicyclo[3.2.1]octan]-4-one (26). A solution of TAN1251A (**1**) (9 mg, 0.024 mmol) in 0.2 mL of dry THF was added to a solution of NaHMDS (48 μL, 1 M in THF) in THF at -78 °C. The resulting mixture was warmed to -40 °C, stirred at this temperature for 10 min, and cooled to -78 °C. A solution of (1*S*)+(10)-(camphorsulfonyl)oxaziridine (15 mg, 0.066 mmol) in THF (0.1 mL) was added to this reaction mixture, which was stirred for another 20 min. The reaction was quenched with Et_3N (13 μL, 0.095 mmol) at -78 °C, and then a drop of HOAc. The resulting mixture was taken up in 10 mL of CH_2Cl_2, which was washed with $NaHCO_3$, brine, and dried (Na_2SO_4). Removal of the solvent gave crude product whose ^{1}H NMR spectrum showed the formation of **25** and **26** in about a 2:3 ratio in 50% yield with the remainder being recovered **1**.

Partial data for **25** were determined from ^{1}H NMR, COSY, HSQC and 1D NOESY spectra of the crude reaction mixture: ^{1}H NMR 7.67 (d, 2, *J* = 8.6), 6.82 (d, 2, *J* = 8,6), 5.99 (s, 1), 4.07 (dd, 1, *J* = 10.8, 5.2), 2.38 (m, 1), 1.74 (dd, 1, *J* = 14, 5), 1.97 (m, 1); ^{13}C NMR 132.2, 122.8, 72.1; A 1D NOESY experiment with irradiation of the peak at δ 4.07 gave strong NOE peaks at δ 2.38 and δ 1.74.

Partial data for **26** were determined from ^{1}H NMR, COSY, HSQC and 1D NOESY spectra: ^{1}H NMR 7.79 (d, 2, *J* = 8.6), 6.80 (d, 2, *J* = 8.6), 5.92 (s, 1), 4.23 (dd, 1, *J* = 12.8, 6.0), 2.50 (m, 1), 2.05 (d, 1, *J* = 14), 1.61 (m, 1); ^{13}C NMR 134.5, 122.6, 72.6; A 1D NOESY experiment with irradiation of the peak at δ 4.23 gave strong NOE peaks at δ 2.50 and δ 2.05.

(1*R*,1'*S*,2'*Z*,3*R*,5'*S*)-3-Hydroxy-4'-methyl-2'-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methylene]-spiro[cyclohexane-1,7'-[1,4]diazabicyclo[3.2.1]octan]-4-one (2, TAN1251B) and (1*S*,1'*S*,2'*Z*,3*S*,5'*S*)-3-Hydroxyl-4'-methyl-2'-[[4-[(3-methyl-2-butenyl)oxy]phenyl]methylene]-spiro[cyclohexane-1,7'-[1,4]diazabicyclo[3.2.1]octan]-4-one (27). A solution of **1** (23 mg, 0.061 mmol) in 0.5 mL of dry THF was added to a solution of LDA (120 μL, 1 M in THF) in 0.4 mL of THF at -78 °C. The resulting mixture was warmed to -40 °C, stirred at this temperature for 10 min, and cooled to -78 °C. TMSCl (25 μL, 0.18 mmol) was added to this reaction mixture, which was stirred for another 20 min. The reaction was quenched with saturated $NaHCO_3$ solution, which was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated. The residue was dissolved in 0.15 mL of *t*-BuOH and 0.3 mL of H_2O, to which NMO (8 mg, 0.067 mmol) and OsO_4 (150 μL, 2.5% wt in *t*-BuOH, 0.012 mmol) was added at 0 °C. The resulting mixture was stirred at 0 °C for 5 min and quenched with 10% Na_2SO_3 solution. The reaction mixture was extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic layers were washed with brine and dried (Na_2SO_4). Removal of the solvent followed by flash chromatography of the residue on silica gel (CH_2Cl_2/MeOH 9:1 to 8:1) gave 12 mg of starting **1** and a 2:1:8:4 mixture of **25**, **26**, **2**, and **27**, followed by 6 mg (23%) of the mixture of the triols. The mixture of **1** and hydroxy isomers was further purified by PTLC to give 2 mg (9%) of unreacted **1**, 6 mg (25%) of the 2:1 mixture of **2** and **27** and 2 mg of the mixture of **25** and **26** containing other impurities.

Data for **3.2** were determined from the 2:1 mixture: ^{1}H NMR 7.68 (d, 2, *J* = 8.6), 6.81 (d, 2, *J* = 8.6), 6.05 (s, 1), 5.48 (m, 1), 4.54 (dd, 1, *J* = 12.2, 6.1), 4.47 (d, 2, *J* = 6.7), 3.44 (dd, 1, *J* = 12.1, 3.1), 3.34-3.27 (m, 2), 3.11 (d, 1, *J* = 12.2), 2.94 (d, 1, *J* = 13.4), 2.64-2.57 (m, 1), 2.30-2.24 (m, 1), 2.20 (s, 3), 2.10-2.06 (m, 2), 1.86 (dd, 1, *J* = 14.0, 1.8), 1.79 (s, 3), 1.74 (s, 3), 1.82-1.74 (m, 1), 1.49 (dd, 1, *J* = 13.4, 12.2), 1.48 (dd, 1, *J* = 14.0, 5.5); ^{13}C NMR 211.7, 157.9, 141.2, 138.2, 130.6 (2 C), 128.2, 123.1, 119.5, 114.1 (2 C), 72.4, 65.2, 64.6, 60.9, 58.8, 55.4, 47.1, 42.4, 36.2, 34.8, 33.0, 25.8, 18.2.

Data for **27** were determined from the 2:1 mixture: ^{1}H NMR 7.71 (d, 2, *J* = 8.6), 6.80 (d, 2, *J* = 8.6), 6.11 (s, 1), 5.48 (m, 1), 4.47 (d, 2, *J* = 6.7), 3.70 (dd, 1, *J* = 12.8, 6.7), 3.34-3.27 (m, 3), 3.08 (d, 1, *J* = 12), 3.02 (d, 1, *J* = 14.0), 2.87 (ddd, 1, *J* = 13.4, 13.4, 5.2), 2.64-2.57 (m, 1), 2.30-2.24 (m, 2), 2.21 (s, 3), 1.90 (dd, 1, *J* = 14.0, 1.8), 1.79 (s, 3), 1.74 (s, 3), 1.66 (dd, 1, *J* = 13.4, 12.8), 1.63 (ddd, 1, *J* = 14.0, 13.4, 4.0), 1.47 (dd, 1, *J* = 14.0, 5.7); ^{13}C NMR 211.7, 157.8, 141.1, 138.2, 130.7 (2 C), 128.3, 123.4, 119.5, 114.0 (2 C), 71.8, 65.1, 64.6, 60.8, 59.0, 55.5, 42.4, 41.6, 38.9, 36.3, 35.0, 25.8, 18.2.

Analytical separation of the 2:1 mixture of **2** and **27** was carried out on a Chiralpak AD column (4.6 mm × 250 mm). The eluent was 5:1 isopropanol/hexane containing 0.1% of Et_3N. The retention time was 21.5 min for **2** and 24.8 min for **27** with a flow rate of 0.3 mL/min. The ^{1}H NMR spectrum of **2** was identical to that of natural TAN1251B except for the coupling between the O*H* (δ 3.36, d, *J* = 3.4) and H_3, which was only observed in this very dilute sample.