Supporting Information

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Experimental Protocols. Unless otherwise noted, NMR spectra were recorded in $CDCl_3$ at 300 MHz for ^1H and 75 MHz for ^{13}C, respectively. Chemical shift (δ) are in ppm, and coupling constants (*J*) are in Hz. Multiplicities are reported as: "s" (singlet), "d" (doublet), "dd" (doublet of doublets), "t" (triplet), "q" (quartet), "m" (multiplet), "c" (complex), "br" broad. IR spectra (cm^{-1}) were measured on a Perkin Elmer 1720-X FTIR from $CHCl_3$ solutions. Low- and high resolution mass spectra [m/e (%)]were obtained on a Finnigan-MAT 95 XL in the CI (CH_4), EI (70 eV) or LSIMS (Cs^+) mode, as specified. Optical rotation were measured in $CHCl_3$, with concentrations (*c*) expressed in g/100 mL. All reactions were run under Ar, and monitored by TLC. All reagents and solvents were commercial products used as received except: THF (freshly dist. Na/benzophenone); CH_2Cl_2, Et_3N (dist. CaH_2).

(*S*)-3-(4-Hydroxyphenyl)-2-[(methoxycarbonyl)amino] propionic acid (A): Methyl chloroformate (8.5 mL, 0.11 mmol) was added to a solution of L-tyrosine (18.1 g, 0.1 mol) and $NaHCO_3$ (25 g, 0.3 mol) in a mixture of H_2O/THF (500 mL/500 mL). After stirring at rt overnight the mixture was diluted with H_2O and washed with Et_2O. The aqueous layer was acidified and extracted with EtOAc (3 × 60 mL). The combined extracts were washed (H_2O), dried ($MgSO_4$) and concentrated to afford 23.65 g (99%) of **A**, white foam, $[\alpha]_D^{25}$ +21.5° (*c* 2.375, MeOH). ^1H (acetone-d_6): 7.25 (2H, d, *J* = 8.3), 6.90 (2H, d, *J* = 8.3), 6.41 (1H, d, *J* = 7.4, NH), 4.60-4.50 (1H, m), 3.67 (3H, s), 3.24 (1H, dd, *J* = 14.0, 4.6), 3.04 (1H, dd, *J* = 14.0, 8.8). ^{13}C (acetone-d_6): 173.68, 157.41, 157.03, 131.08, 128.84, 115.97, 56.40, 52.05, 37.36. EI-MS: 239 (1) $[M]^+$, 164 (17) , 147 (1), 107 (100), 77 (6), 69 (1). HREI-MS: $C_{11}H_{13}NO_5$ $[M]^+$: calcd. 239.0794; found: 239.0794.

Methyl (*S*)-2-[(methoxycarbonyl)amino]-3-(4-methoxyphenyl) propanoate (B): To a solution of **A** (17.95 g, 75 mmol) and K_2CO_3 (25.9 g, 187.5 mmol) in dry acetone (150 mL) was added dimethyl sulfate (15.6 mL, 165 mmol) dropwise during 30 minutes. The mixture was warmed at reflux for 2 h, then cooled to rt, diluted with H_2O and extracted with EtOAc (3 × 50 mL). The combined extracts were washed (H_2O, sat. $NaHCO_3$ solution and brine), dried ($MgSO_4$) and concentrated. Filtration of the residue through silica gel (EtOAc/hexane: 50/50) afforded 19.8 g (99%) of **B**, colorless oil, $[\alpha]_D^{25}$ +14.4° (*c* 1.11, EtOH). ^1H: 7.00 (2H, d, *J* = 8.7), 6.80 (2H, d, *J* = 8.7), 5.25 (1H, d, *J* = 8.0, NH), 4.63-4.52 (1H, m), 3.75 (3H, s), 3.69 (3H, s), 3.63 (3H, s), 3.09-2.93 (2H, m). ^{13}C: 172.29, 158.68, 156.40, 130.21, 127.88, 113.97, 55.10, 52.20, 37.26. IR: 3437, 1723. EI-MS: 267 (1) $[M]^+$, 236 (1), 208 (4), 192 (21), 176 (4), 161 (6), 134 (2), 121 (100), 107 (1), 91 (4), 77 (5), 65 (2). HREI-MS: $C_{13}H_{17}NO_5$, $[M]^+$: calcd. 267.1107; found: 267.1103.

(*S*)-2-[(Methoxycarbonyl)amino]-3-(4-methoxyphenyl) propan-1-ol (C): To a solution of $LiAlH_4$ (7.3 g, 192 mmol) in THF (240 mL) was added dropwise a solution of **B** (25.6 g, 96 mmol) in THF (240 mL) at 0°C under Ar for 2 h. The mixture was stirred overnight at rt, cooled to 0°C and acidified with 4*N* HCl. The layers were separated and the aqueous layer was extracted with EtOAc. The combined extracts were washed (H_2O and brine),

dried ($MgSO_4$) and concentrated. Filtration of the residue over silica gel (EtOAc/hexane: 60/40) afforded 19.5 g (85%) of **C**, colorless oil, $[\alpha]_D^{25}$ -23.1° (*c* 1.95, EtOH). ^{1}H: 7.11 (2H, d, *J* = 8.5), 6.82 (2H, d, *J* = 8.5), 5.20 (1H, s, NH), 3.97-3.78 (1H, m), 3.76 (3H, s), 3.63 (1H, dd, *J* = 11.2, 4.0), 3.62 (3H, s), 3.52 (1H, dd, *J* = 11.2, 5.0), 3.1 (1H, s, OH), 2.77 (2H, d, *J* = 7.0). ^{13}C: 158.15, 157.16, 130.08, 129.69, 113.81, 63.37, 55.04, 54.14, 51.99, 36.29. IR: 3437, 1713. CI-MS: 240 (100) $[M+H]^+$, 222 (2), 208 (26), 164 (3), 121 (2), 81 (1), 69 (2). HRCI-MS: $C_{12}H_{17}NO_4$ $[M+H]^+$: calcd. 240.1236; found: 240.1236.

(*S*)-2-Amino-3-(4-methoxyphenyl)-1-propanol (2): A solution of **C** (24.75 g, 103 mmol) in 25% aq. KOH was stirred at 50°C overnight. The mixture was then extracted with EtOAc (3 × 50 mL). The combined extracts were washed (H_2O), dried ($MgSO_4$) and concentrated. The crude product was recrystallized (EtOAc/Et_2O) to yield 16 g (86%) of **2**, white crystals, m.p. 94-96°C, $[\alpha]_D^{25}$ -21.5° (*c* 1.00, EtOH). ^{1}H: 7.10 (2H, d, *J* = 8.8), 6.84 (2H, d, *J* = 8.8), 5.20 (1H, s, NH), 3.78 (3H, s), 3.61 (1H, dd, *J* = 11.0, 3.7), 3.52 (1H, dd, *J* = 11.0, 7.4), 3.10-3.02 (1H, m), 2.72 (1H, dd, *J* = 14.0, 5.2), 2.45 (1H, dd, *J* = 14.0, 8.8), 2.05 (1H, s, NH_2). ^{13}C: 158.26, 130.65, 130.16, 114.03, 66.13, 55.30, 54.33, 39.79. IR: 3450, 3170. EI-MS: 181 (3) $[M]^+$, 161 (3), 150 (7), 134 (8), 122 (54), 121 (100), 118 (13), 108 (5), 107 (9), 91 (10), 78 (13), 77 (18), 65 (6), 60 (66). HREI-MS: $C_{10}H_{15}NO_2$ $[M]^+$: calcd.: 181.1103; found: 181.1103.

Ethyl (*S*)-2-[*N*-(4-methylphenyl)sulfonylamino]-3-(4-hydroxyphenyl) propion-ate (D): L-tyrosine ethyl ester hydrochloride (36.9 g, 150 mmol) was dissolved in a solution of Na_2CO_3 (7.5 g, 71 mmol) in H_2O (37.5 mL) and $CHCl_3$ (225 mL) was added. The mixture was stirred for 10 minutes and a solution of *p*-toluenesulfonyl chloride (29.9 g, 157 mmol, 1.05 eq) in $CHCl_3$ (100 mL) was added at rt. The mixture was stirred for 2 h. Then a solution of Na_2CO_3 (7.5 g, 71 mmol) in H_2O (37.5 mL) was added. The mixture was stirred for further 4 h, then it was cooled to 0°C and acidified to pH 2-3 with 3*M* HCl. The layers were separated and the aqueous phase was extracted with $CHCl_3$ (2 × 75 mL). The combined extracts were washed (H_2O, 75 mL), dried ($MgSO_4$) and concentrated to afford 53.4 g (98%) of **D**, white solid, m.p. 111-113°C (lit. 114°C), $[\alpha]_D^{25}$ +5.3° (*c* 1.05, EtOH). ^{1}H: 7.64 (2H, d, *J* = 8.1), 7.24 (2H, d, *J* = 8.1), 6.94 (2H, d, *J* = 8.1), 6.68 (2H, d, *J* = 8.1), 5.07 (1H, d, *J* = 8.8, NH), 4.13 (1H, td, *J* = 9.5, 5.9), 3.91 (2H, q, *J* = 7.4), 2.96 (2H, d, *J* = 5.9), 2.40 (3H, s), 1.07 (3H, t, *J* = 7.4). ^{13}C: 171.48, 155.38, 143.83, 136.53, 130.58, 129.70, 127.15, 126.63, 115.56, 61.87, 57.24, 38.46, 21.49, 13.88. IR: 3363, 1735. CI-MS: 364 (100)

$[M+H]^+$, 290 (2), 192 (4). HRCI-MS: $C_{18}H_{21}NO_5S$ $[M+H]^+$: calcd. 364.1219; found: 364.1217.

(*S*)-2-[*N*-(4-Methylphenyl)sulfonylamino]-3-(4-hydroxyphenyl)propionic acid (3): Compound **D** (9.8 g, 27 mmol) was suspended in a 5*M* NaOH solution (20 mL) and warmed for 30 minutes in a water bath. H_2O (35 mL) was added and the mixture was acidified to pH 2-3 with 5*M* HCl and warmed for further 5 min, then cooled to 0°C. Stirring was

continued for 10 min and the product was vacuum-filtered to afford 8.87 g (98%) of **3**, white solid, m.p. 185-187°C (lit. m.p. 187-188°C), $[\alpha]_D^{25}$ +1.90° (*c* 1.05, EtOH). ^{1}H (DMSO-d_6): 12.63 (1H, s, COOH), 9.19 (1H, s, OH), 8.09 (1H, d, *J* = 8.8, NH), 7.44 (2H, d, *J* = 8.8), 7.24 (2H, d, *J* = 8.1), 6.87 (2H, d, *J* = 8.8), 6.56 (2H, d, *J* = 8.8), 3.73 (1H, m), 2.78 (1H, dd, *J* = 13.2, 5.9), 2.57 (2H, dd, *J* = 13.2, 8.8), 2.34 (3H, s). ^{13}C (DMSO-d_6): 172.42, 155.96, 142.19, 138.11, 130.09, 129.18, 126.89, 126.29, 114.85, 57.83, 37.18, 20.90. IR (KBr): 3567, 3409, 3280, 1732. CI-MS: 336 (100) $[M+H]^+$, 290 (6), 289 (2), 288 (11), 164 (3), 157 (4). HRCI-MS: $C_{16}H_{17}NO_5S$ $[M+H]^+$: calcd. 336.0906; found: 336.0905.

(*S*)-2-{(*S*)-1-[*N*-(4-Methylphenyl)sulfonylamino]-2-(4-hydroxyphenyl)ethyl}-4-methoxybenzyl-2-oxazoline (4): Compound **3** (3.35 g, 10 mmol) was dissolved in acetonitrile/pyridine(10mL/10 mL), then compound **2** (1.81 g, 10 mmol), NEt_3 (3.05 g, 30 mmol) and CCl_4 (6.22 g, 40 mmol) were added. A solution of triphenylphosphine (8 g, 30 mmol) in acetonitrile/pyridine (10mL/10 mL) (warming necessary) was added dropwise over 3 h. Stirring was continued for 24 h at 27-30°C followed by addition of a 0.5 *M* NaOH (200 mL). After extraction, the aqueous layer was successively washed with Et_2O (2 × 50 mL) and CH_2Cl_2 (2 × 50 mL). Then EtOAc (50 mL) was added to the aqueous layer and the mixture was acidified with solid NH_4Cl to pH 6. The layers were separated and the aqueous layer was extracted with EtOAc (4 × 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated to yield 3.5 g (73%) of **4**, orange foam, $[\alpha]_D^{25}$ +13.3° (*c* 1.00, EtOH). ^{1}H: 7.73 (2H, d, *J* = 8.5), 7.26 (2H, d, *J* = 8.5), 6.92 (2H, d, *J* = 8.5), 6.83 (2H, d, *J* = 8.5), 6.76 (2H, d, *J* = 8.5), 6.44 (2H, d, *J* = 8.5), 5.51 (1H, d, *J* = 9.6, NH), 4.40-4.25 (1H, m), 4.15-4.00 (2H, m), 3.87-3.80 (1H, m), 3.73 (3H, s), 2.93 (2H, d, *J* =5.5), 2.60 (1H, dd, *J* = 13.8, 5.5), 2.39 (3H, s), 2.10 (1H, dd, *J* = 13.8, 7.7). ^{13}C: 166.23, 158.39, 155.53, 143.39, 137.30, 130.51, 129.90, 129.50, 129.10, 127.41, 125.69, 115.37, 114.05, 72.52, 66.69, 55.21, 52.23, 40.25, 38.94, 21.47. IR: 3260, 1515, 1445, 1340, 1305. CI-MS: 481 (2) $[M+H]^+$, 451 (2), 417 (1), 391 (1), 364 (18), 325 (10), 295 (15), 279 (6), 185 (8), 157 (100), 139 (30), 107 (3), 93 (5). HRCI-MS: $C_{26}H_{28}N_2O_5S$ $[M+H]^+$: calcd. 481.1797; found: 481.1770.

(3*S*,1*S*')-1-[2'-Acetoxy-1'-(4-methoxybenzyl)-ethyl]-3-[*N*-acetyl-*N*-(4-methyl phenyl)sulfonylamino]-1-azaspiro[4.5]deca-6,9-dien-2,8-dione (6): To a solution of oxazoline **4** (0.96 g, 2 mmol) in 2,2,2-trifluoroethanol (10 mL) was added dropwise a

solution of DIB (0.74 g, 2.3 mmol) in 2,2,2-trifluoroethanol (10 mL) over 5 minutes. The mixture was stirred for 30 minutes at rt; then solid $NaHCO_3$ (0.50 g, 6 mmol) was added. The suspension was filtered through glass wool and evaporated under reduced pressure. The crude product was acetylated under standard conditions [pyridine (1.58 g, 20 mmol), acetic anhydride (2.03 g, 20 mmol), DMAP (24.4 mg, 0.2 mmol), r.t., stirring overnight]. The solution was diluted with EtOAc and washed with a saturated NH_4Cl solution (3 × 15 mL). The organic layer was dried ($MgSO_4$) and concentrated. Chromatography of the residue (10% → 60% EtOAc/hexane) afforded 0.48 g (41%) of **6**, yellow foam, $[\alpha]_D^{25}$ -22.7° (*c* 1.21). ^{1}H: 8.04 (2H, d, *J* = 8.1), 7.42 (2H, d, *J* = 8.1), 7.10 (2H, d, *J* = 8.5), 6.83 (3H, m), 6.24 (1H,

dd, *J* = 9.9, 1.8), 6.17 (1H, dd, *J* = 10.3, 2.8), 6.07 (1H, dd, *J* = 10.3, 1.8), 5.24 (1H, t, *J* = 8.8), 4.57 (1H, dd, *J* = 11.3, 8.3), 4.28 (1H, dd, *J* = 11.3, 4.4), 3.78 (3H, s), 3.18 (1H, dd, *J* = 12.1, 7.0), 3.23-3.05 (1H, m), 3.00 (1H, dd, *J* = 12.1, 5.5), 2.54 (1H, dd, *J* = 13.2, 5.5), 2.47 (3H, s), 2.42 (1H, dd, *J* = 13.2, 5.2), 2.28 (3H, s), 2.03 (3H, s). ^{13}C: 184.10, 170.26, 169.76, 169.65, 158.61, 148.96, 148.56, 145.49, 136.22, 130.84, 130.23, 130.10, 129.56, 128.93, 127.63, 113.93, 62.49, 59.96, 57.48, 55.25, 34.74, 34.38, 25.07, 21.67, 20.93. IR: 1745, 1705, 1675, 1635, 1615, 1515, 1370, 1355. EI-MS: 580 (3) $[M]^+$, 562 (2), 520 (1), 501 (2), 459 (1), 408 (2), 407 (2), 375 (16), 323 (10), 206 (100), 163 (11), 147 (12), 121 (30), 91 (19), 43 (12). HRCI-MS: $C_{26}H_{28}N_2O_5S$ $[M]^+$: calcd. 580.1879; found: 580.1884.

(3*S*,1*S*')-1-[2'-Acetoxy-1'-(4-methoxybenzyl)-ethyl]-3-[*N*-(4-methylphenyl) sulfonylamino]-1-azaspiro[4.5]decan-2,8-dione (7): A solution of **6** (0.548 g, 0.95 mmol) and PtO_2 (22 mg) in EtOAc (5 mL) was stirred at rt under 1 atm of H_2 overnight. Filtration (Celite) and concentration afforded 0.530 g (96%) of **7**, white foam, $[\alpha]_D^{25}$ -53.2° (*c* 1.25). ^{1}H: 8.07 (2H, d, *J* = 8.1), 7.42 (2H, d, *J* = 8.1), 7.15 (2H, d, *J* = 8.5), 6.82 (2H, d, *J* = 8.5), 5.20-5.06 (1H, m), 4.66 (1H, dd, *J* = 11.0, 8.1), 4.31 (1H, dd, *J* = 11.0, 5.5), 3.77 (3H, s), 3.41-3.28 (1H, m), 3.14 (2H, dd, *J* = 7.0, 3.3), 2.79 (1H, dd, *J* = 12.3, 10.1), 2.56-2.20 (5H, m), 2.46 (3H, s), 2.27 (3H, s), 2.18-2.07 (1H, m), 1.99 (3H, s), 1.89-1.54 (3H, m). ^{13}C: 208.26, 169.69, 169.57, 158.45, 145.30, 130.56, 130.45, 130.19, 127.61, 127.26, 113.98, 62.91, 60.17, 57.43, 55.37, 55.24, 37.97, 37.25, 35.20, 35.02, 33.94, 33.67, 25.19, 21.66, 20.90. IR: 3377, 1715, 1695, 1429, 1353. CI-MS: 585 (67) $[M+H]^+$, 563 (48), 467 (67), 409 (38), 370 (100), 342 (34), 157 (83). HRCIMS: $C_{30}H_{36}N_2O_8S$ $[M+H]^+$: calcd. 585.2271; found: 585.2285.

(3*S*,1*S*')-1-[2'-Hydroxy-1'-(4-methoxybenzyl)-ethyl]-3-[*N*-(4-methylphenyl) sulfonylamino]-1-azaspiro[4.5]decan-2,8-dione (8): A solution of **7** (0.530 g, 0.91 mmol) and K_2CO_3 (0.025 g, 0.18 mmol) in MeOH (18 mL) was stirred overnight. The solution was concentrated and the residue was diluted in EtOAc (30 mL) and acidified with 1*M* HCl (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined extracts were washed (brine, 30 mL) and dried ($MgSO_4$).

Concentration afforded 0.360 g (79%) of **8**, yellow foam, $[\alpha]_D^{25}$ +2.7° (*c* 1.1). ^{1}H: 7.80 (2H, d, *J* = 8.5), 7.32 (2H, d, *J* = 8.5), 7.02 (2H, d, *J* = 8.5), 6.79 (2H, d, *J* = 8.5), 5.84 (1H, s, NH), 3.98 (1H, dd, *J* = 11.1, 7.0), 3.87-3.72 (1H, m), 3.75 (3H, s), 3.69 (1H, dd, *J* = 11.1, 3.3), 3.28-3.16 (1H, m), 3.11 (1H, dd, *J* = 14.0, 8.1), 2.98 (1H, dd, *J* = 14.0, 6.6), 2.88 (1H, dd, *J* = 13.2, 8.1), 2.53-2.15 (4H, m), 2.43 (3H, s), 2.13-1.91 (1H, m), 1.90-1.56 (3H, m), 0.81-0.65 (1H, m). ^{13}C: 208.11, 171.78, 158.54, 144.04, 135.95, 130.39, 129.99, 129.94, 127.22, 114.01, 62.77, 61.48, 58.26, 55.25, 52.45, 37.99, 37.64, 37.07, 35.15, 33.84, 32.94, 21.53. IR: 3261, 1715, 1682, 1325. CI-MS: 501 (100) $[M+H]^+$, 345 (36), 157 (24), 93 (31). HRCI-MS: $C_{26}H_{32}N_2O_6S$ $[M+H]^+$: calcd. 501.2059; found: 501.2058.

(3*S*,1*S*')-1-[2'-Hydroxy-1'-(4-methoxybenzyl)-ethyl]-3-[*N*-methyl-*N*-(4-methylphenyl)sulfonylamino]-1-azaspiro[4.5]decan-2,8-dione (9): To a solution of **8** (0.785 g, 1.60 mmol) in DMF (16 mL) was added K_2CO_3 (0.261 g, 1.92 mmol) and iodomethane (0.68 g, 4.8 mmol) The mixture was stirred overnight then the solvent was evaporated under reduced pressure. The residue was diluted with EtOAc (40 mL), washed with 1*M* HCl (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield 0.780 g (97%) of **9**, yellow foam, $[\alpha]_D^{25}$ -76.0° (*c* 1.0). ^{1}H: 7.84 (2H, d, *J* = 8.5), 7.31 (2H, d, *J* = 8.5), 7.02 (2H, d, *J* = 8.5), 6.75 (2H, d, *J* = 8.5), 5.03 (1H, dd, *J* = 10.7, 9.2), 4.12 (1H, dd, *J* = 11.2, 7.2), 3.74 (3H, s), 3.72 (1H, dd, *J* = 11.2, 3.3), 3.31-3.19 (1H, m), 3.13 (1H, dd, *J* = 13.6, 8.8), 2.98 (1H, dd, *J* = 13.6, 5.9), 2.76 (3H, s), 2.57 (1H, dd, *J* = 12.7, 9.2); 2.45-2.35 (2H, m), 2.42 (3H, s), 2.21-2.09 (2H, m), 2.02-1.91 (2H, m), 1.74-1.63 (1H, m), 1.56 (1H, dd, *J* = 12.7, 10.7), 0.68-0.57 (1H, m). ^{13}C: 208.40, 171.41, 158.51, 143.78, 136.14, 130.58, 130.42, 129.79, 127.62, 113.85, 63.15, 60.24, 58.50, 57.18, 55.32, 38.17, 37.20, 35.70, 34.06, 32.90, 31.76, 29.80, 21.61. IR: 3415, 1703, 1426, 1342. CI-MS: 515 (100) $[M+H]^+$, 513 (19), 499 (13), 361 (16), 359 (49), 186 (19), 157 (36), 141 (15). HRCI-MS: $C_{27}H_{34}N_2O_6S$ $[M+H]^+$: calcd. 515.2216; found: 515.2215.

(3*S*,1*S*')-1-[1'-Formyl-2'-(4-methoxyphenyl)-ethyl]-3-[*N*-methyl-*N*-(4-methyl phenyl)sulfonylamino]-1-azaspiro[4.5]decan-2,8-dione (10): To a solution of **9** (0.340g, 0.66 mmol) in CH_2Cl_2 (13.2 mL) were added dried molecular sieve 4Å (0.330 g, 0.5 g/mmol), 4-methylmorpholine *N*-oxide (0.154 g, 1.32 mmol) and tetrapropylammonium perruthenate (0.023 g, 66 μmol). The mixture was stirred for 15 min, filtered over silica gel (EtOAc) and concentrated to afford 0.263 g (77%) of **10**, colorless foam. $[\alpha]_D^{25}$ –56.6 (*c* 1.25). ^{1}H: 9.57 (1H, s), 7.84 (2H, d, *J* = 8.1), 7.32 (2H, d, *J* = 8.1); 7.01 (2H, d, *J* = 8.6), 6.75 (2H, d, *J* = 8.6), 5.01 (1H, dd, *J* = 11.0, 9.2), 3.76 (3H, s), 3.56-3.45 (1H, m), 3.36 (1H, d, *J* = 7.7), 2.77 (3H, s), 2.75-3.70 (1H, m), 2.47-2.37 (2H, m), 2.42 (3H, s), 2.31-1.65 (5H, m), 1.47-1.33 (1H, m), 0.60-0.46 (1H, m). ^{13}C: 207.65, 197.60, 170.44, 158.80, 143.81, 136.02, 132.35, 130.60, 129.77, 127.68, 114.08, 63.25, 59.19, 57.05, 55.37, 37.89, 37.11, 35.58, 32.93, 32.87, 32.66, 29.88, 21.67. IR: 1736, 1717, 1698, 1422, 1334. CI-MS: 513 (100) $[M+H]^+$, 485 (7), 359 (9), 357 (11), 351 (5), 316 (5), 157 (7), 93 (6). HRCIMS: $C_{27}H_{32}N_2O_6S$ $[M+H]^+$: calcd. 513.2059; found: 513.2054.

(1*S*, 3*S*, 6*S*, 7*S*, 8*R*)-7-Hydroxy-6-(4-methoxybenzyl)-3-[*N*-methyl-*N*-(4-methylphenyl)sulfonylamino]-5-azatricyclo[6.3.1.0^{1,5}]dodecan-4,9-dione (11): To a solution of aldehyde **10** (0.2 g, 0.39 mmol) in MeOH/H_2O (7.2 mL/0.8 mL, 9/1) was added sodium methoxide (0.042 g, 0.78 mmol). The mixture was stirred for 30 min then the solvent was evaporated. The residue was diluted with EtOAc (40 mL) and washed with 1*M* HCl (20 mL) and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the residue was purified by preparative TLC (EtOAc/hexane: 60/40) to afford 0.090 g (44%) of **11**, colorless foam, $[\alpha]_D^{25}$ -10.6° (*c* 1.41, EtOH). ^{1}H: 7.86 (2H, d, *J* = 8.1), 7.31 (2H, d, *J* = 8.1), 7.10 (2H, d, *J* = 8.8), 6.76 (2H, d, *J* = 8.8), 5.00 (1H, dd, *J* = 11.0, 8.8), 3.81-3.69

(2H, m), 3.75 (3H, s), 3.38 (1H, dd, *J* = 14.0, 8.8), 3.32-3.25 (1H, m), 2.82-2.76 (1H, m), 2.65-2.37 (3H, m), 2.61 (3H, s), 2.41 (3H, s), 2.29 (1H, dd, *J* = 12.9, 8.8), 2.25-1.90 (2H, m), 1.80 (1H, dd, *J* = 13.6, 3.3), 1.72 (1H, dd, *J* = 12.9, 11.0). ^{13}C: 211.77, 171.54, 158.14, 143.52, 136.33, 130.72, 129.92, 129.77, 127.59, 113.93, 68.47, 59.80, 58.36, 57.20, 55.20, 50.68, 36.92, 35.61, 33.14, 32.33, 29.64, 28.29, 21.56. IR: 3428, 1702, 1421, 1342. CI-MS: 513 (80) $[M+H]^+$, 497 (19), 358 (16), 357 (85), 343 (11), 157 (100). HRCIMS**:** $C_{27}H_{32}N_2O_6S$ $[M+H]^+$: calcd. 513.2059; found: 513.2061.

(1*S*, 3*S*, 6*S*, 7*S*, 8*R*)-7-Acetoxy-6-(4-methoxybenzyl)-3-[*N*-methyl-*N*-(4-methylphenyl)sulfonylamino]-5-azatricyclo[6.3.1.0^{1,5}]dodecan-4,9-dione (12): To a solution of **11** (0.140 g, 0.27 mmol) in CH_2Cl_2 (2.7 mL) were added acetic anhydride (0.033 g, 0.33 mmol), pyridine (0.064 g, 0.81 mmol) and catalytic amount of DMAP. The mixture was stirred for 3 h and concentrated. The residue was purified by preparative TLC (EtOAc/hexane: 60/40) to afford 0.140 g (93%) of **12**, colorless foam, $[\alpha]_D^{25}$ -27.8° (*c* 1.41). ^{1}H: 7.82 (2H, d, *J* = 8.1), 7.30 (2H, d, *J* = 8.1), 7.02 (2H, d, *J* = 8.8), 6.74 (2H, d, *J* = 8.8), 4.94-4.85 (2H, m), 3.80 (1H, dd, *J* = 14.0, 7.4), 3.73 (3H, s), 3.41-3.32 (1H, m), 3.05 (1H, dd, *J* = 14.0, 7.4), 2.92-2.86 (1H, m), 2.65-2.97 (2H, m), 2.57 (3H, s), 2.41 (3H, s), 2.30 (1H, dd, *J* = 12.8, 8.8), 2.19 (3H, s), 2.04-1.84 (2H, m), 1.77 (1H, dd, *J* = 12.8, 11.0). ^{13}C: 209.46, 170.39, 169.70, 158.26, 143.54, 136.27, 130.10, 129.70, 127.59, 113.93, 68.88, 58.30, 58.11, 56.58, 55.17, 47.55, 36.90, 35.25, 33.20, 32.12, 29.52, 28.89, 21.58, 21.03. IR: 3405, 1742, 1708, 1341. CI-MS: 555 (100) $[M+H]^+$, 554 (5), 401 (5), 399 (5). HRCI-MS: $C_{29}H_{34}N_2O_7S$ $[M+H]^+$: calcd.: 555.2165; found: 555.2163.

(1*S*, 3*S*, 6*S*, 7*S*, 8*S*, 9*R*)-7-Acetoxy-9-hydroxy-6-(4-methoxybenzyl)-3-[*N*-methyl-*N*-(4-methylphenyl)sulfonylamino]-5-azatricyclo[6.3.1.0^{1,5}]dodecan-4-one (13): To a solution of **12** (0.118 g, 0.21 mmol) in THF (0.85 mL) at -78°C was added dropwise a 1 *M* solution of L-selectride® in THF (0.25 mL, 0.25 mmol). The mixture was stirred for 5 h. The solution was warmed to 0°C and diluted with EtOAc (20 mL). Organoboron compounds were oxidized with 10% NaOH (10 mL) and H_2O_2 (5 mL). The layers were separated and

the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined extracts were washed with brine (20 mL), dried ($MgSO_4$) and concentrated to yield 0.111 g (0.20 mmol, 95%) of **13**, colorless crystals, m.p.: 159-161°C, $[\alpha]_D^{25}$ +46.5° (*c* 1.70). ^{1}H: 7.83 (2H, d, *J* = 8.1), 7.30 (2H, d, *J* = 8.1), 7.04 (2H, d, *J* = 8.8), 6.76 (2H, d, *J* = 8.8), 4.92-4.82 (2H, m), 4.24-4.16 (1H, m), 3.91 (2H, m), 3.73 (3H, s), 3.15 (1H, dd, *J* = 14.0, 8.8), 2.84 (1H, s, OH), 2.60 (3H, s), 2.40 (3H, s), 2.34-2.25 (1H, m), 2.14 (3H, s), 2.11-1.68 (6H, m), 1.60 (1H, dd, *J* = 13.2, 10.3), 1.30-1.20 (1H, m). ^{13}C: 170.45, 170.24, 158.08, 143.40, 136.42, 130.73, 129.64, 127.64, 113.97, 68.64, 68.19, 59.95, 58.39, 56.54, 55.17, 40.03, 36.82, 35.33, 33.20, 32.92, 29.91, 29.58, 21.58, 21.37. IR: 3421, 1734, 1698, 1417. LSI-MS (gycerol): 557 $[M+H]^+$. HRLSI-MS (glycerol): $C_{29}H_{36}N_2O_7S$ $[M+H]^+$: calcd. 557.2321; found: 557.2325.

(1*S*, 3*S*, 6*S*, 7*S*, 8*R*, 9*R*)-7-Acetoxy-6-(4-methoxybenzyl)-3-[*N*-methyl-*N*-(4-methylphenyl)sulfonylamino]-9-[(4-nitrophenyl)sulfonyloxy]-5-azatricyclo [6.3.1.0^{1,5}]dodecan-4-one (14): To a solution of **13** (0.032 g, 57.5 µmol), *p*-nitrobenzenesulfonyl chloride (0.019 g, 86.25 µmol) and DMAP (0.007 g, 57.5 µmol) in CH_2Cl_2 (0.6 mL), at -20°C was added NEt_3 (0.024 mL, 172.5 µmol). The reaction mixture was stirred for 2 h at 0°C and then diluted with EtOAc (10 mL). The solution was washed with 0.1*M* HCl (4 mL) and H_2O, and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by preparative TLC (silica gel, EtOAc/Hexane: 60/40) to give 0.031 g (72%) of nosylate **14**, colorless foam, $[\alpha]_D^{25}$ +65.0° (*c* 1.50). ^{1}H: 8.30 (2H, d, *J* = 8.5), 8.01 (2H, d, *J* = 8.5), 7.82 (2H, d, *J* = 8.5), 7.30 (2H, d, *J* = 8.5), 6.97 (2H, d, *J* = 8.5), 6.71 (2H, d, *J* = 8.5), 5.08-4.97 (1H, m), 4.90-4.81 (1H, m), 4.71-4.65 (1H, m), 4.16-4.08 (1H, m), 3.85 (1H, dd, *J* = 14.3, 5.5), 3.73 (3H, s), 3.18 (1H, dd, *J* = 14.3, 5.5), 2.61 (3H, s), 2.49-2.27 (3H, m), 2.40 (3H, s), 2.18-1.94 (3H, m), 2.13 (3H, s), 1.90-1.72 (1H, m), 1.71-1.60 (1H, m), 1.39-1.30 (1H, m). ^{13}C: 170.26, 169.63, 158.23, 150.76, 143.55, 136.27, 130.16, 129.68, 127.52, 129.07, 127.66, 124.41, 113.99, 78.78, 66.63, 59.77, 58.15, 55.77, 55.19, 37.57, 35.76, 35.13, 33.09, 32.44, 29.65, 28.74, 21.60, 21.10. IR: 1740, 1703. LSI-MS (glycerol): 742 $[M+H]^+$. HRLSI-MS: $C_{35}H_{39}N_3O_{11}S_2$ $[M+H]^+$: calcd. 742.2104; found: 742.2100.

(1*S*, 3*S*, 6*S*, 7*S*, 8*S*, 9*S*)-7,9-Diacetoxy-6-(4-methoxybenzyl)-3-[*N*-methyl-*N*-(4-methylphenyl)sulfonylamino]-5-azatricyclo[6.3.1.0^{1,5}]dodecan-4-one (15): A solution of **14** (0.112 g, 0.15 mmol), 18-crown-6 (0.048 g, 0.18 mmol) and CsOAc (0.087 g, 0.45 mmol) in benzene (2.5 mL) was stirred for 2 h at 80°C. The mixture was cooled to rt and diluted with EtOAc (25 mL), washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated. Purification by preparative TLC afforded 0.065 g (73%) of diacetate **15**, colorless crystals, m.p.: 195-197°C, $[\alpha]_D^{25}$ +44.8° (*c* 1.25). ^{1}H: 7.86 (2H, d, *J* = 8.1), 7.31 (2H, d, *J* = 8.1), 7.01 (2H, d, *J* = 8.8), 6.79 (2H, d, *J* = 8.8), 4.97-4.83 (2H, m), 4.62-4.56 (1H, m), 4.03-3.96 (1H, m), 3.86 (1H, dd, *J* = 14.0, 5.9), 3.77 (3H, s), 3.21 (1H, dd, *J* = 14.0, 9.6), 2.64 (3H, s), 2.41 (3H, s), 2.35-2.29 (1H, m), 2.23-2.10 (2H, m), 2.17 (3H, s), 2.02 (3H, s), 1.90-1.71 (5H, m), 1.65 (1H, dd, *J* = 13.2, 10.3). ^{13}C: 170.33, 169.87, 169.84, 158.36,

143.42, 136.43, 130.36, 129.65, 127.69, 114.20, 68.87, 68.22, 58.77, 58.32, 56.69, 55.24, 38.15, 36.39, 33.16, 32.74, 29.61, 28.40, 26.81, 21.60, 21.25, 21.21. IR: 1741, 1703. CI-MS: 599 (100) $[M+H]^+$, 445 (45), 314 (16), 157 (17), 93 (16). HRCI-MS: $C_{31}H_{38}N_2O_8S$ $[M+H]^+$: calcd. 559.2427; found: 599.2429.

(1*S*, 3*S*, 6*S*, 7*S*, 8*S*, 9*S*)-6-(4-Methoxybenzyl)-3-(*N*-methylamino)-5-azatricyclo[6.3.1.0^{1,5}]dodecane-7,9-diol (16): A solution of **15** (0.062 g, 104 µmol) and LAH (0.73 mmol) in THF (1 mL) was heated at reflux for 5 h. After cooling to 0°C EtOAc was added followed by H_2O (15 µl), 15% NaOH (15 µl) and H_2O (40 µL). The precipitate was filtered through Celite and rinsed with MeOH. The filtrates were concentrated to yield 0.036 g of the crude compound **16**, colorless foam. ^{1}H: 7.17 (2H, d, *J* = 8.1), 6.80 (2H, d, *J* = 8.1),

3.76 (3H, s), 3.67-3.59 (1H, m), 3.54-3.46 (1H, m), 3.27-3.17 (2H, m), 3.16-3.07 (1H, m), 2.84-2.56 (2H, m), 2.45 (1H, dd, *J* = 9.6, 5.9), 2.31 (3H, s), 2.08-2.02 (1H, m), 1.99-1.80 (4H, m), 1.70-1.50 (3H, m), 1.33 (1H, dd, *J* = 12.5, 3.0). ^{13}C: 157.96, 130.94, 130.37, 113.78, 67.07, 66.81, 60.04, 59.10, 56.60, 55.25, 54.80, 47.15, 47.15, 35.69, 34.95, 30.06, 27.78, 27.08. IR: 3384. CI-MS: 347 (100) $[M+H]^+$, 329, 281, 253, 239, 225, 209, 165, 151, 137, 113. HRCI-MS: $C_{20}H_{30}N_2O_3$ $[M+H]^+$: calcd. 347.2335; found: 347.2335.

(1*S*, 3*S*, 6*S*, 7*S*, 8*S*, 9*S*)-3-(*N*-Benzyloxycarbonyl-*N*-methylamino)-6-(4-methoxybenzyl)-5-azatricyclo[6.3.1.0^{1,5}]dodecane-7,9-diol (17): To a solution of **16** (0.036 g, 104 µmol) and benzyl chloroformate (0.02 mL, 135 µmol) in CH_2Cl_2 (1 mL) was added NEt_3 (0.03 mL, 208 µmol). The mixture was stirred overnight. The solvent was evaporated and the residue was purified by preparative TLC (CH_2Cl_2/MeOH: 90/10) to afford 0.035 g (70% over 2 steps) of **17**, colorless oil, $[\alpha]_D^{25}$ -6.4° (*c* 1.5). ^{1}H: 7.38-7.31 (5H, m), 7.29 (2H, d, *J* = 8.8), 6.79 (2H, d, *J* = 8.8), 5.06 (2H, br s), 4.20 (1H, br s), 3.72 (3H, s), 3.79-3.64 (3H, m), 3.42-3.08 (4H, m), 3.05 (3H, s), 2.60-1.69 (11H, m). ^{13}C: 158.66, 156.82, 136.21, 130.66, 128.62, 128.26, 127.86, 114.23, 67.68; 66.90, 65.03, 63.85, 60.34, 55.28, 51.22, 50.64, 42.55, 40.33, 32.62, 30.55, 28.19, 27.24, 21.61. IR: 3361, 1693. LSI-MS (glycerol): 481 $[M+H]^+$. HRLSI-MS: $C_{28}H_{36}N_2O_5$ $[M+H]^+$: calcd. 481.2702; found: 481.2706.

(1*S*, 3*S*, 6*S*, 7*S*, 8*R*, 9*S*)-3-(*N*-Benzyloxycarbonyl-*N*-methylamino)-7-hydroxy-6-(4-methoxybenzyl)-5-azatricyclo[6.3.1.0^{1,5}]dodecan-9-yl dibenzyl phosphate (18): A solution of **17** (0.034 g, 70.8 µmol), 1-*H*-tetrazole (0.011 g, 163 µmol) and *N*,*N*-diisopropyldibenzylphosphoramidite (0.027 g, 78 µmol) in CH_2Cl_2 (1.4 mL) was stirred at 0°C for 1.5 h. The mixture was cooled at -78°C and *t*-BuOOH (17 µl, 92 µmol) in decane was added. The solution was stirred 1 h at –78°C. The reaction mixture was diluted with CH_2Cl_2 (5 mL), washed (Na_2SO_3, H_2O and brine) and dried (Na_2SO_4). The solvent was evaporated and the residue was purified by preparative TLC (5% MeOH / CH_2Cl_2) to

afford 0.010 g of starting diol **18** and 0.015 g (29%) of **19**, colorless oil. ^{1}H: 7.35 (5H, s), 7.32 (10H, s), 7.17 (2H, d, *J* = 8.8), 6.83 (2H, d, *J* = 8.8), 5.11 (2H, s), 5.03-4.95 (5H, m), 4.29 (1H, br s), 3.79 (3H, s), 3.19 (1H, br s), 2.83 (6H, br s), 2.15-1.44 (11H, m). ^{13}C: 158.14, 156.40, 136.89, 135.88, 130.66, 130.13, 128.63, 128.53, 128.02, 127.93, 113.93, 74.90, 69.37, 67.18, 66.88, 58.51, 55.32, 51.86, 50.17, 43.42, 42.85, 35.55, 29.74, 29.40, 29.07, 28.68, 22.72. LSI-MS (glycerol): 741 $[M+H]^+$. HRLSI-MS: $C_{42}H_{49}N_2O_8P$, $[M+H]^+$: calcd. 741.3305; found: 741.3281.

Synthetic FR901483 bis-hydrochloride (1*S*, 3*S*, 6*S*, 7*S*, 8*R*, 9*S*)-7-Hydroxy-3-(*N*-methylamino)-6-(4-methoxybenzyl)-5-azatricyclo[6.3.1.0^{1,5}]dodecan-9-yl dihydrogen phosphate, bis HCl salt: To a solution of **18** (0.013 g, 17.5 μmol) in MeOH (1 mL) was added 3*M* HCl (6 μL). The solvent was evaporated under reduced pressure

and the residue was dissolved in MeOH (0.2 mL). 10% Pd/C (5 mg) was added and the mixture was stirred at rt under 1 atm of H_2 for 3 h and filtered through Celite. The solvent was evaporated to yield 7.6 mg (94%) of FR901483 bis-hydrochloride, $[\alpha]_D^{25}$ +4.0° (*c* 0.35, CH_3OH, lit. +5° (B. B. Snider, H. Lin, *J. Am. Chem. Soc.* **1999**, *121*, 7778, rotation very sensitive to the amount of water and of residual HCl). ^{1}H (500 MHz, CD_3OD): 7.35 (2H, d, *J* = 8.6), 6.92 (2H, d, *J* = 8.6), 4.52 (1H, dd, *J* = 13.6, 9.9), 4.36 (1H, br d, *J* = 7.7), 4.33-4.26 (1H, m), 3.97 (1H, dd, *J* = 13.6, 2.9), 3.93-3.88 (1H, m), 3.80 (3H, s), 3.67 (1H, br s), 3.34 (1H, m), 3.10 (1H, dd, *J* = 12.4, 3.6), 2.81 (3H, s), 2.65 (1H, dd, *J* = 14.0, 8.9), 2.48 (1H, br s), 2.35-2.07 (6H, m), 1.93 (1H, br d, *J* = 14.2). ^{13}C (125 MHz, CD_3OD): 159.54, 130.66, 127.40, 114.35, 71.39, 67.86, 63.89, 61.01, 54.74, 54.13, 50.86, 41.79, 40.75, 33.04, 31.40 27.21, 26.64, 21.67. LSI-MS (glycerol): 427 $[M+H]^+$. HRLSI-MS: $C_{31}H_{38}N_2O_8S$ $[M+H]^+$: calcd. 427.1998; found: 427.2000.