A Practical Synthesis of the Kappa Opioid Receptor Selective Agonist (+)-5*R*,7*S*,8*S*-*N*-Methyl-*N*-[7-(1-pyrrolidinyl)-1-oxospiro[4,5]dec-8-yl]benzeneacetamide (U69,593)

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Abstract: A novel approach to the synthesis of the kappa opioid receptor agonist U69,593 has been developed. This approach improves upon current literature methods by substituting stable and isolable cyclic sulfates for the unstable epoxides. The new approach provides access to gram quantities of the target compound and displays excellent control of the relative stereochemistry. The absolute stereochemistry as well as biological activity of the U69,593 produced by this new method was verified using X-ray crystal structure analysis and binding assays for the kappa opioid receptor.

Key words: U69,593, kappa opioid agonist, X-ray crystal structure, synthesis, receptors

Morphine has been the treatment of choice for relief of severe pain for decades, but its side-effect profile, including respiratory depression and addiction, has prompted researchers to seek alternative remedies.[1] One approach to this problem has been the development of receptor subtype selective analgesics, reasoning that eliminating the action at multiple receptors might also eliminate unwanted side-effects. The arylacetamides first reported by Szmuszkovicz U50,488 (**1**), spiradoline (**2**), and (5*R*,7*S*,8*S*)-(+)-*N*-methyl-2-phenyl-*N*-(7-pyrrolidin-1-yl-1-oxospiro[4,5]dec-8-yl)acetamide (U69,593; **3**) (Figure 1), are a class of opioid agonist compounds selective for the kappa opioid receptor.[2,3] In animal models, these compounds were found to display potent analgesic activity, but unfortunately they also showed an unacceptable side-effect profile that included hallucinations and psychotomimesis.[4] While these compounds were not a suitable replacement for morphine, they have provided valuable research tools to identify the role of the kappa opioid receptors in both normal and disease states.[5]

Recently we required gram quantities of **3**, but found the synthesis provided in the patent literature to be both vague and provided the product in very low yield.[6] We, therefore, undertook a study to develop an improved synthetic approach to the title compound. The retrosynthetic analysis in Scheme 1 shows the key synthetic transformations of the previously reported methods compared to the modified methods described herein. The reported synthesis involved the conversion of 1-oxaspiro[4,5]dec-7-ene (**6**) to the resolved diamine **4** via the intermediate epoxides **5**. In our hands, this method gave an intractable mixture of **4** in <1% yield from **6** with the handling of the epoxides **5** being particularly troublesome. In order to avoid this problem, we developed an alternative approach to **4** that did not proceed through this intermediate.

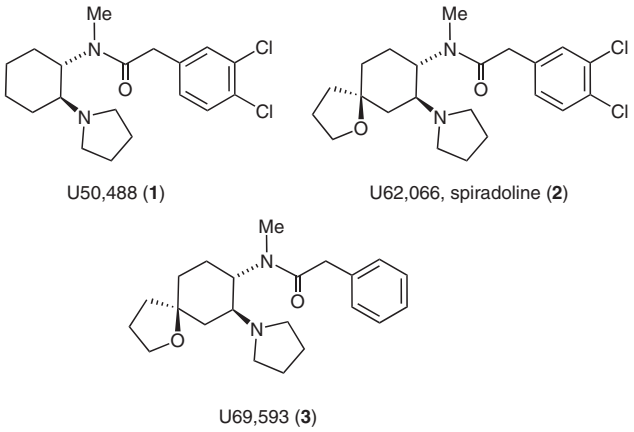

Figure 1 Structures of compounds **1**–**3**

The synthesis began with (±)-1-oxaspiro[4,5]dec-7-ene [(±)-**6**], which was available following the procedures described in the patent literature (Scheme 2).[6] A Sharpless one-pot procedure[7,8] provided a direct conversion of (±)-**6** into a mixture of diols (±)-**7a**,**b** (74%, 1:4, *cis*/*trans*) with diol (±)-**7b** being the major product. This procedure was chosen because the $K_2OsO_2(OH)_4$ is an easily handled crystalline solid. Without separation, the mixture of diols was converted into their corresponding stable and easily isolable cyclic sulfates (±)-**8a**,**b** in 77% yield. In stark contrast to our experience with the epoxides **5**, the chromatographic separation of cyclic sulfates (±)-**8a**,**b** was easily conducted on a greater than 100 g scale. X-ray crystal structure analysis revealed that the spirocyclic oxygen and the oxygen atoms of the cyclic sulfate (±)-**8b** occupied opposite faces of the cyclohexyl scaffold (Figure 2), and thus, was used to synthesize (+)-**3**.

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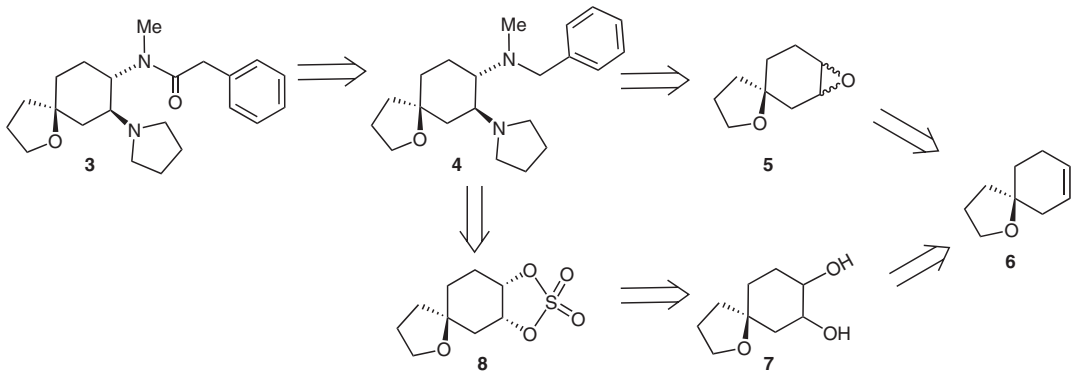
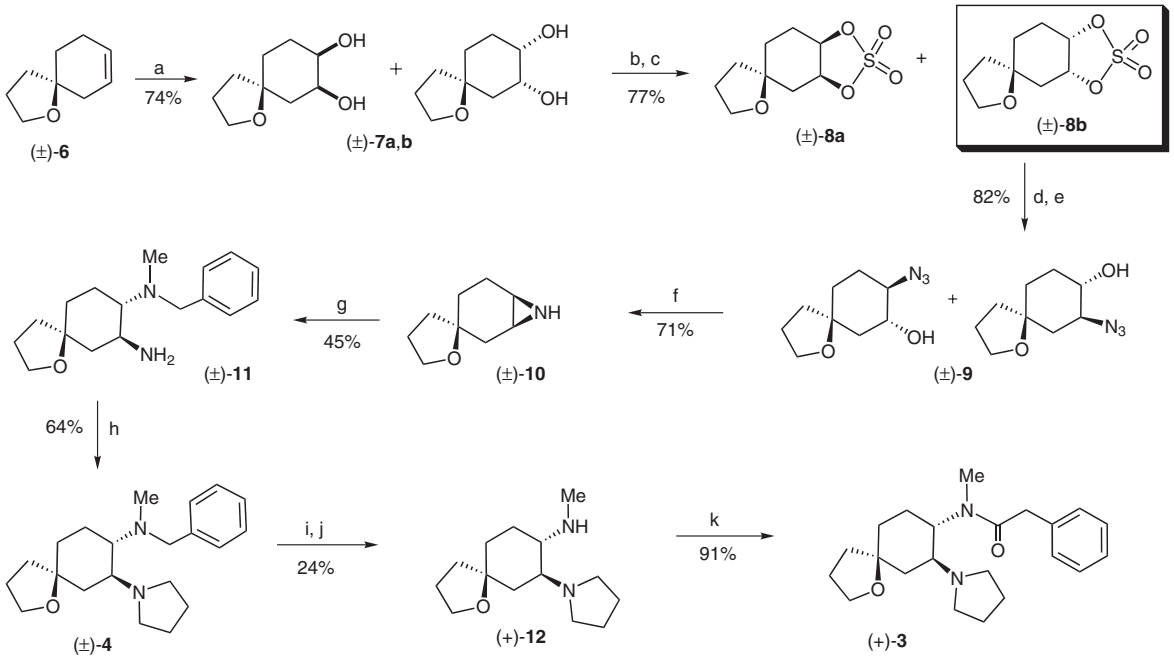


Scheme 1



Scheme 2 *Reagents and conditions*: (a) $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3 and $K_2OsO_2(OH)_4$; (b) $SOCl_2$, CH_2Cl_2; (c) $NaIO_4$, $RuCl_3$, H_2O; (d) NaN_3, MeOH; (e) dil H_2SO_4, MeOH; (f) PPh_3, toluene, heat; (g) *N*-methylbenzylamine, NH_4Cl and H_2O; (h) 1,4-dibromobutane, Na_2CO_3, THF; (i) H_2, 10% Pd/C, MeOH; (j) DTTA; (k) phenylacetyl chloride, Et_3N, CH_2Cl_2.

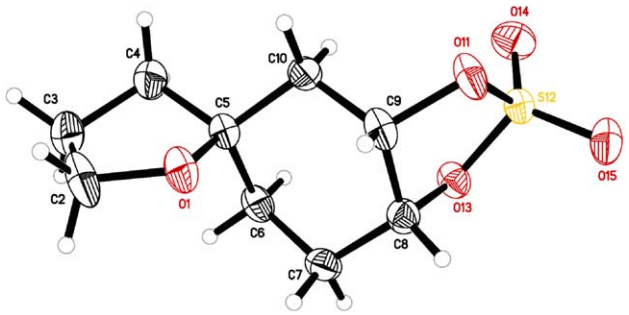


Figure 2 Structure of compound (±)-**8b** showing labeling of the nonhydrogen atoms. Displacement ellipsoids are at the 30% probability level.

Our attempts to open the cyclic sulfates (±)-**8b** with various amines, proved to be unsuccessful. Eventually, we found that cyclic sulfates (±)-**8b** could be opened with sodium azide. Acid hydrolysis of the sulfate esters gave a mixture of azidoalcohols (±)-**9** in 82% yield. Subsequent treatment of this mixture with triphenylphosphine in refluxing toluene provided the reactive aziridine intermediate (±)-**10** in 71% yield on a 50 g scale. Opening of the aziridine (±)-**10** with *N*-methylbenzylamine using ammonium chloride as the acid catalyst[9] gave exclusively the diamine (±)-**11** in 43% yield. Use of other acids to catalyze the reaction, including HCl and trifluoroacetic acid gave a mixture of regioisomers. The key intermediate (±)-**4** was then prepared in 64% yield by cycloalkylation of (±)-**11** with 1,4-dibromobutane and sodium carbonate. Removal of the benzyl group from racemic (±)-**4** under catalytic hydrogenation conditions followed by resolution of the resulting racemic diamines [(±)-**12**] using di-*p*-toluoyltartaric acid[10,11] gave (+)-**12** and (–)-**12** in 24% yield. The absolute stereochemistry of (–)-**12** was shown to have the 5*S*,7*R*,8*R*-stereochemistry by X-ray crystal structure anal-

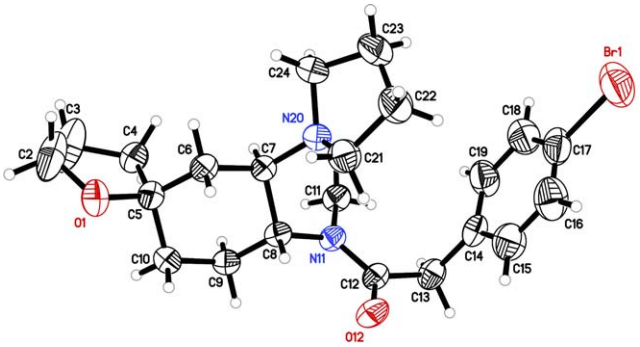
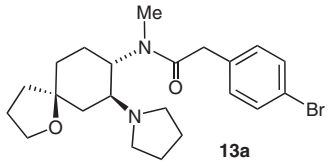
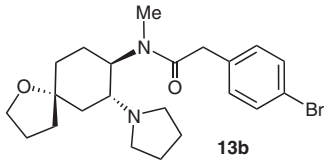


Figure 3 Structure of compound **13b** showing labeling of the non-hydrogen atoms. Displacement ellipsoids are at the 30% probability level.



13a



13b

Figure 4 Structures of **13a** and **13b**

ysis of the highly crystalline (–)-*p*-bromophenylacetyl derivative (**13b**, Figure 3 and Figure 4). By deduction, (+)-**12** possessed the 5*R*,7*S*,8*S*-stereochemistry. Acylation of (+)- and (–)-**12** with phenylacetyl chloride gave the title compound (+)-(5*R*,7*S*,8*S*)-*N*-methyl-2-phenyl-*N*-(7-pyrrolidin-1-yl-1-oxospiro[4,5]dec-8-yl)acetamide [U69,593, (+)-**3**] and (–)-**3**. To confirm which of the compounds was the active isomer, both (+)- and (–)-**3** isomers were assayed for their ability to compete with [^{3}H]U69,593 in an opioid receptor binding assay. The result was that (+)-**3** displaced the radioligand, whereas (–)-**3** showed no inhibition of binding (Figure 5).

In summary, a novel approach to the synthesis of the kappa opioid receptor agonist U69,593 has been developed. The new approach provides access to gram quantities of the target compound and displays excellent control of the relative stereochemistry. The absolute stereochemistry as well as biological activity of the U69,593 produced by this new method was verified using X-ray crystal structure analysis and binding assays for the kappa opioid receptor.

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 125 MHz, respectively, using a Bruker Avance 300 spectrometer. Chemical shift data for the proton resonances were reported in parts per million (δ) relative to internal TMS (δ = 0.0). Optical rotations were measured on an AutoPol III polarimeter, purchased from Rudolf Research. Elemental analyses were performed by Atlantic Microlab, Norcross, GA. Analytical TLC was carried out on plates precoated with silica gel GHLF (250 µm thickness). TLC visualization

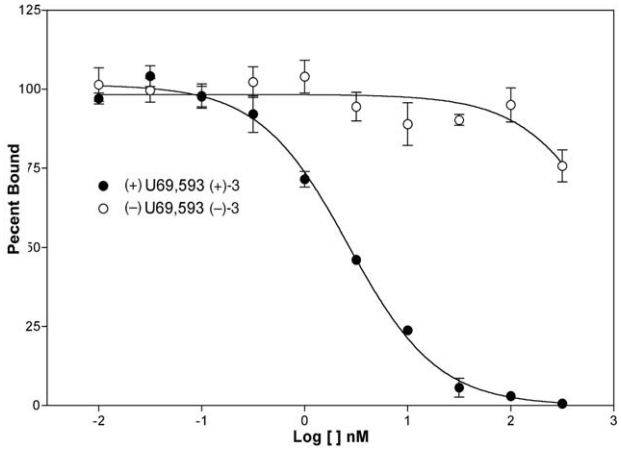


Figure 5 [^{3}H]U69,593 competition binding isotherms showing (+)-U69,593 [(+)-**3**] is the active enantiomer. The competition binding assays were performed in 0.5 mL using a 50 mM Tris buffer (pH 7.4 at 4 °C). Each sample was run in duplicate and contained 21 µg crude membrane homogenate prepared from CHO cells expressing the human kappa opioid receptor (hKOR), 4 nM [^{3}H]U69,593 (K_d = 2 nM), and one of ten different concentrations of test compound. Samples were incubated for 1 h at 4 °C before rapid filtration over GF/B filters and trapped radioactivity determined by standard liquid scintillation counting techniques. The K_i value for the active enantiomer of U69,593 was 0.9 nM ± 0.1 nM (mean ± SEM).

was accomplished with a UV lamp, in an iodine chamber or PMA stain (5% phosmolibdic acid in EtOH). All moisture sensitive reactions were performed under a positive pressure of nitrogen maintained by a direct line from a nitrogen source. Flash chromatography was preformed on Silica gel 60 (EDM Chemical particle size 0.040–0.063 mm; 230–400 mesh ASTM). 3-Phenylpropan-1-ol was obtained from Aldrich Chemical Company. Petroleum ether (PE) refers to the fraction boiling in the range 38.5–54.5 °C.

(±)-1-Oxaspiro[4,5]dec-7-ene (6)

Following the patent procedure,[6] 3-phenylpropan-1-ol was treated with Na metal in liquid NH_3 to obtain a mixture of starting material and 3-(cyclohexa-1,4-dienyl)propan-1-ol. Treatment of this mixture with *p*-TsOH at 120 °C under vacuum gave the title compound, which was distilled from the mixture to give **6** as a fragrant oil: bp 50–55 °C/5 mm Hg.

^{1}H NMR ($CDCl_3$): δ = 1.72 (4 H, m), 1.76–2.21 (6 H, m), 3.88 (2 H, m), 5.60–5.68 (2 H, m).

Cyclic Sulfates (±)-8a and (±)-8b

A mixture of hydroquinidine 1,4-phthalazinediyl diether [$(DHQD)_2PHAL$] (8.0 g, 0.010 mol), $K_3Fe(CN)_6$ (1.0 kg, 3.89 mol), K_2CO_3 (430 g, 3.12 mol) and $K_2OsO_2(OH)_4$ (1.1 g, 0.0038 mol) in H_2O (4 L) and *t*-BuOH (4 L) was stirred at r.t. until a solution had formed. The solution was cooled in an ice bath (some precipitate formed) and (±)-1-oxaspiro[4,5]dec-7-ene [(±)-**6**, 142 g, 1.0 mol] was added in one portion. The resultant mixture was stirred for 5 h at low temperature, then for 12 h at r.t. After this time, Na_2SO_3 (500 g, 3.4 mol) was added, and the mixture was stirred an additional 30 min. The mixture was then extracted with EtOAc (2.00 L, then 4 × 1.00 L). The combined organic layers were dried ($MgSO_4$) and evaporated to give a purple-brown oil [a mixture of diols (±)-**7a**,**b**]. Further purification was accomplished by flash chromatograph on SiO_2 utilizing EtOAc–PE (1:9) → EtOAc. The chromatography provided the diol mixture (1:4 *cis*/*trans*) as a white solid (132 g, 74%); mp 35–37 °C.

Diol Mixture (±)-7a,b

^{1}H NMR ($CDCl_3$): δ = 1.72 (4 H, m), 1.76–2.12 (6 H, m), 3.77–3.96 (4 H, m).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.80; H, 9.30. Found: C, 62.29; H, 9.29.

The diol mixture was divided into two equal batches (66 g, 0.38 mol). Each batch was dissolved in CH_2Cl_2 (500 mL) and cooled in an ice bath. A solution of $SOCl_2$ (30 mL, 0.42 mol) in CH_2Cl_2 (300 mL) was added dropwise over 2 h to each chilled solution of the diol mixture. Following the addition, the ice bath was removed and the resultant mixture stirred for 3 h at r.t. The solvent and excess $SOCl_2$ were then evaporated. Aq sat. K_2CO_3 (300 mL) was added to each batch and each mixture extracted with EtOAc (3 × 100 mL). The combined organic extracts from both batches were dried ($MgSO_4$) and evaporated to give a thick oil (139 g, 83%) that by ^{1}H NMR contained two components. This mixture was used in the next reaction with no further purification.

A solution of the above mixture (139 g, 0.63 mol) in MeCN (5.00 L) was treated with $NaIO_4$ (254 g, 0.90 mol) and $RuCl_3{\cdot}3H_2O$ (0.55 g, 0.0023 mol), followed by H_2O (1.00 L). (It is important to add the H_2O last to avoid clumping of the $NaIO_4$.) The resultant heterogeneous mixture was stirred for 5 h at r.t., then diluted with Et_2O (6.00 L) and H_2O (1.00 L). After separation of the layers, the aqueous layer was extracted with Et_2O (3 × 1.00 L). The combined organic extracts were washed with brine (500 mL), dried ($MgSO_4$), and evaporated to give 145 g of a brown oil containing a mixture of cyclic sulfates (±)-**8a**,**b**. The mixture was chromatographed on SiO_2 utilizing EtOAc–PE (4:1) to obtain 87 g (59%) of sulfate (±)-**8b** and 27.8 g (18%) of sulfate (±)-**8a**. Crystallization of cyclic sulfate (±)-**8b** from Et_2O–benzene afforded a white solid; mp 65–69 °C.

Anal. Calcd for $C_9H_{14}O_5S$: C, 46.12; H, 5.98; S, 13.70. Found: C, 46.26; H, 5.95; S, 13.80.

Aziridine (±)-10

A solution of cyclic sulfate (±)-**8b** (146 g, 0.62 mol) and NaN_3 (80.60 g, 1.25 mol) in MeOH (5.00 L) was heated under reflux for 36 h. The MeOH was then removed and the residue chromatographed on SiO_2 utilizing $CHCl_3$–MeOH–concd NH_4OH (80:18:2) to obtain a white solid. This solid was dissolved in MeOH (5.00 L) and 10% H_2SO_4 (2.00 L), and the mixture was heated under reflux for 6 h. Afterwards, it was cooled in an ice bath, neutralized with $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 2.00 L). The combined organic extracts were dried (Na_2SO_4) and evaporated to yield 100 g (82%) of azidoalcohols (±)-**9**. A solution of the azidoalcohols (±)-**9** (100 g, 0.51 mol) in toluene (2.50 L) was cooled in an ice bath and treated with a solution of PPh_3 (134 g, 0.51 mol) in toluene (500 mL), added dropwise. Following the addition, the mixture was heated under reflux for 12 h, cooled to r.t., and the toluene was removed under vacuum. Vacuum distillation of the residue (oil bath: 150 °C) yielded 55.4 g (71%) of the title compound; bp 89–95 °C/5 mm Hg.

^{1}H NMR ($CDCl_3$): δ = 1.13–1.89 (11 H, m), 3.34–4.04 (4 H, m).

A fumarate salt was prepared for elemental analysis.

Anal. Calcd for $C_{13}H_{19}NO_5{\cdot}0.5H_2O$: C, 57.53; H, 7.09; N, 5.16. Found: C, 57.49; H, 7.08; N, 5.10.

(±)-(5*S*,7*R*,8*R*)-*N*^{8}-Benzyl-*N*^{8}-methyl-1-oxospiro[4,5]decane-7,8-diamine [(±)-11]

A mixture of aziridine (±)-**10** (55 g, 0.36 mol), *N*-methylbenzylamine (250 mL, 1.90 mol), NH_4Cl (2.0 g, 0.035 mol) and H_2O (250 mL) was heated under reflux for 14 h. After this time, the H_2O and excess *N*-methylbenzylamine were removed by vacuum distillation. The residual oil was distilled bulb-to-bulb to obtain 43.9 g (43%) of (±)-**11** as a thick oil; bp 170 °C/5 mm Hg. This material was used without further characterization.

(±)-(5*S*,7*R*,8*R*)-*N*-Benzyl-*N*-methyl-7-pyrrolidin-1-yl-1-oxospiro[4,5]decan-8-amine [(±)-4]

A mixture of (±)-**11** (43.9 g, 0.16 mol), 1,4-dibromobutane (33.7 g, 0.16 mol) and Na_2CO_3 (49.5 g, 0.4 mol) in THF (1.75 L) was heated under reflux for 16 h. The mixture was then filtered and the solvent removed by evaporation. The residue was dissolved in aq half sat. K_2CO_3 (900 mL) and extracted with EtOAc (2 × 1.00 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Subsequent chromatography of the residue on SiO_2 using PE–Et_2O–Et_3N (67:30:3) yielded 33 g (64%) of the title compound as a clear oil.

^{1}H NMR ($CDCl_3$): δ = 1.32–1.95 (16 H, m), 2.19 (3 H, s, NCH_3), 2.67–2.73 (4 H, m), 3.69–3.83 (2 H, dd, *J* = 6, 6 Hz), 4.05 (2 H, t, *J* = 6 Hz), 6.98–7.61 (5 H, m, ArH).

(+)-(5*S*,7*R*,8*R*)-*N*-Methyl-7-pyrrolidin-1-yl-1-oxospiro[4,5]decan-8-amine [(+)-12]

A mixture of intermediate (±)-**4** (33 g, 0.100 mol) and 10% Pd/C (30 g) in MeOH (300 mL) was hydrogenated at 50 psig H_2 for 36 h. The mixture was filtered through a Celite pad and washed with MeOH (2 × 200 mL). The combined filtrates and washings were concentrated to yield 23.9 g (99%) of (±)-**12** as a white solid.

^{1}H NMR ($CDCl_3$): δ = 0.89–2.18 (18 H, overlapping m), 2.23 (3 H, s, NCH_3), 2.25–2.80 (2 H, m), 3.73 (2 H, q, *J* = 3 Hz).

The resolution of (±)-**12** was achieved utilizing di-*p*-toluoyl-L-tartaric acid according to the literature procedure.[11] The resolution afforded 5.76 g of (+)-**12** as a freebase. The other enantiomer (–)-**12** was isolated as well using di-*p*-toluoyl-D-tartaric acid. The ee of these samples was found to be >97% according to the method of Pirkle and Hoover.[10]

(5*S*,7*R*,8*R*)-(–)-2-(4-Bromophenyl)-*N*-methyl-*N*-(7-pyrrolidin-1-yl-1-oxospiro[4,5]dec-8-yl)acetamide [(–)-13b]

A solution of 4-bromophenylacetic acid (0.806 g, 0.0037 mol) in CH_2Cl_2 (5 mL) was treated with oxalyl chloride (2 mL of 2 M solution in CH_2Cl_2) and one drop of DMF was added. The mixture was stirred at r.t. for 3 h and concentrated. The residue was dissolved in CH_2Cl_2 (10 mL) and added dropwise to (–)-**12** (0.10 g, 0.0042 mol) in CH_2Cl_2 (5 mL) cooled in an ice bath. Following this addition, the mixture was stirred an additional 10 min. Et_3N (3 mL, 0.021 mol) was added by pipette below the surface of the reaction mixture, and the resulting mixture was stirred 16 h at r.t. The mixture was diluted with 50% NH_4OH (10 mL), the layers separated, and the aqueous layer extracted with CH_2Cl_2 (500 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. The resultant residue was purified by column chromatography on SiO_2 utilizing PE–EtOAc–Et_3N (10:9:1) to obtain the title compound as a white solid. The compound was then crystallized from Et_2O–hexane to obtain 0.12 g (69%) of **13b** as white needles; mp 122–123 °C; R_f = 0.30 [single spot on SiO_2 utilizing hexane–EtOAc–Et_3N (10:9:1)].

1H NMR ($CDCl_3$): δ = 1.06–1.96 (14 H, overlapping m), 2.45–2.68 (6 H, overlapping m), 2.77 (3 H, s, NCH_3), 3.67–4.55 (4 H, m), 7.08–7.49 (5 H, m, ArH).

Anal. Calcd for $C_{22}H_{31}BrN_2O_2$: C, 60.69; H, 7.18; N, 6.43; Br, 18.35. Found: C, 60.68; H, 7.21; N, 6.44; Br, 18.35.

(5*R*,7*S*,8*S*)-(+)-*N*-Methyl-2-phenyl-*N*-(7-pyrrolidin-1-yl-1-oxospiro[4,5]dec-8-yl)acetamide [(+)-3]

A mixture of intermediate (+)-**12** (5.70 g, 0.021 mol) in CH_2Cl_2 (500 mL) was cooled in an ice bath. Phenylacetyl chloride (5.25 mL, 0.038 mol) was added dropwise. Following this addition, the mixture was stirred 10 min and Et_3N (10 mL, 0.071 mol) was added by pipette below the surface of the reaction mixture. Afterwards, the mixture was stirred for 16 h at r.t. and diluted with 50% NH_4OH (100 mL). The layers were separated, and the aqueous layer extract-

ed with CH_2Cl_2 (500 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. The resultant residue was purified by column chromatography on SiO_2 utilizing PE–EtOAc–Et_3N (50:45:5) to obtain 6.5 g (91%) of the title compound as a white solid; mp 120–123 °C; $[\alpha]_D^{20}$ +7.5 (*c* 1.2, MeOH); R_f = 0.50 [single spot on SiO_2 utilizing Et_2O–Et_3N (9:1)].

^{1}H NMR ($CDCl_3$): δ = 1.00–1.96 (14 H, overlapping m), 2.45–2.78 (6 H, overlapping m), 2.80 (3 H, s, NCH_3), 3.74–3.84 (4 H, m), 7.08–7.49 (5 H, m, ArH).

Anal. Calcd for $C_{22}H_{32}N_2O_2$: C, 74.12; H, 9.05; N, 7.86. Found: C, 73.88; H, 9.04; N, 7.68.

Acknowledgment

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