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Articles

Total Synthesis of SR 121463 A, a Highly Potent and Selective Vasopressin V_2 Receptor Antagonist

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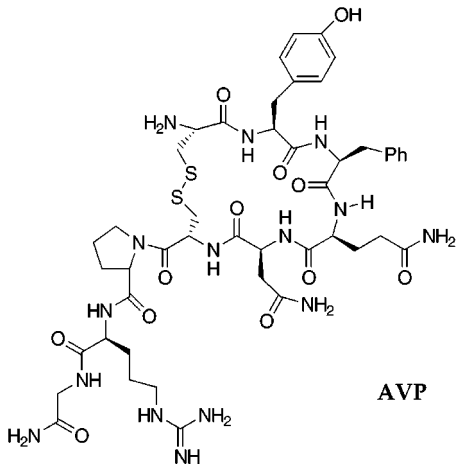
SR 121463 A, **1**, is a promising nonpeptide prototype for potent and selective antagonism of the vasopressin V_2 receptor subtype and, thus, a candidate for control of the clinically debilitating condition of hyponatremia and its associated syndromes. In the present work, we present a novel and stereoselective synthesis that stems from the preparation of three key intermediates: the substituted benzenesulfonyl chloride **2**, the N-protected oxindole **3**, and protected dibromide **4**. The synthesis of **1** has been achieved in good overall yield, each step proceeding in greater than 80% yield. In addition, intermediate **2** and the syn isomer of **1** were prepared with complete control of stereochemistry. The latter reduction appears to proceed by lithium cation mediated chelation control. Molecular mechanics calculations with the MM3* and MMFF force fields underscore geometric and energetic aspects of the reaction.

Introduction

Arginine vasopressin (AVP) is a cyclic nonapeptide containing a disulfide linkage between cysteines at position 1 and 6 and a three amino acid tail with arginine at the 8 position.[1] Several crucial physiological actions for AVP have been identified. These actions are mediated through three different receptor subtypes referred to as V_2, V_{1a}, and V_{1b}.[2]



AVP

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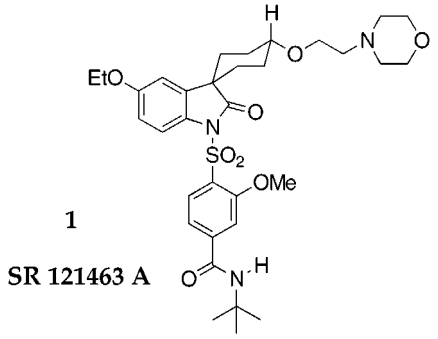
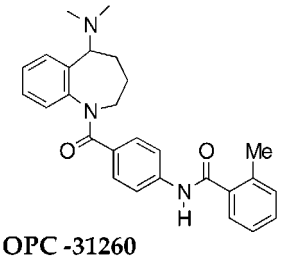
In the kidney, the primary function of AVP is to increase the water permeability of the luminal membranes present in the collecting ducts, leading to water reabsorption.[3] The antidiuretic action of AVP is mediated through specific binding of AVP to V_2 receptors.[4] Vasopressin levels are found to be high for patients with congestive heart failure, liver cirrhosis, central nervous system injuries, and syndrome of the inappropriate release of antidiuretic hormone (SIADH). The presence of excess vasopressin leads to water retention. Typical diuretic agents used to treat these diseases result in loss of essential cations, such as sodium and potassium, resulting in hyponatremia. It has been proposed that compounds which specifically block the action of AVP on V_2 receptors may result in specific water excretion without causing deleterious side effects sometimes associated with diuretic agents.[5] Intensive research has been carried out in the past several years to design selective ligands for AVP receptors. Both peptide and non-peptide analogues have been synthesized and evaluated.[6] SR 121463 A (**1**), a recently characterized V_2 receptor antagonist that is orally active in the rat, was reported to be more potent than the first reported nonpeptidyl V_2 antagonist, OPC-31260.[6]





OPC -31260

We have initiated a program directed at the discovery of novel non-peptide V_2 receptor antagonists using a rational drug design approach.[7] In brief, this approach involves construction of a minireceptor (a 3-D mimic of the binding site), development of a quantitative correlation between experimental and calculated K_is (and the associated ΔGs), and predictions of binding constants for novel candidate antagonists.[8] To compare the in vitro efficacy of the newly designed and synthesized compounds with a known standard, we chose to synthesize the very selective V_2 receptor antagonist SR 121463 A. Although this interesting molecule has no stereogenic centers, it embodies two important structural features: the spiro cyclohexyl ring α to the carbonyl in the oxindole ring, and the "syn" disposition of the ethoxy morpholino group in the cyclohexane ring with respect to the carbonyl group of the oxindole ring.

The synthesis reported in the patent literature lacks details with respect to both experimental procedures and yields.[9] In that work, the oxindole ring was constructed via a classical Fischer indole synthesis (Figure 1) using two separately prepared precursors, **A** and **B**. In addition, the conditions for the reaction were harsh, requiring high temperature (180 °C). The morpholino group was introduced via a two-step sequence involving reductive ring opening of the ketal. Importantly, the selectivity achieved in this process was not reported. Furthermore, the synthesis involves a tedious separation of a mixture of syn and anti isomers in the final step. We wish to report herein a novel stereoselective approach to the total synthesis of SR 121463 A (**1**) that circumvents these problems.

Retrosynthetic Strategy

A reasonable and efficient retrosynthetic disconnection was devised as shown in Figure 2. Retrosynthetic cleavage of the SR 121463 A bonds highlighted in Figure 2 furnishes the substituted benzenesulfonyl chloride **2**, the N-protected oxindole **3**, and a protected dibromide **4** as the three key intermediates. The synthesis of oxindoles has been studied extensively by several groups.[10] Of the available methods, we chose to employ the strategy of C−H insertion into α-diazo keto esters.[11] The spiro cyclohexane was envisioned to be accessible by enolate alkylation of the protected oxindole.

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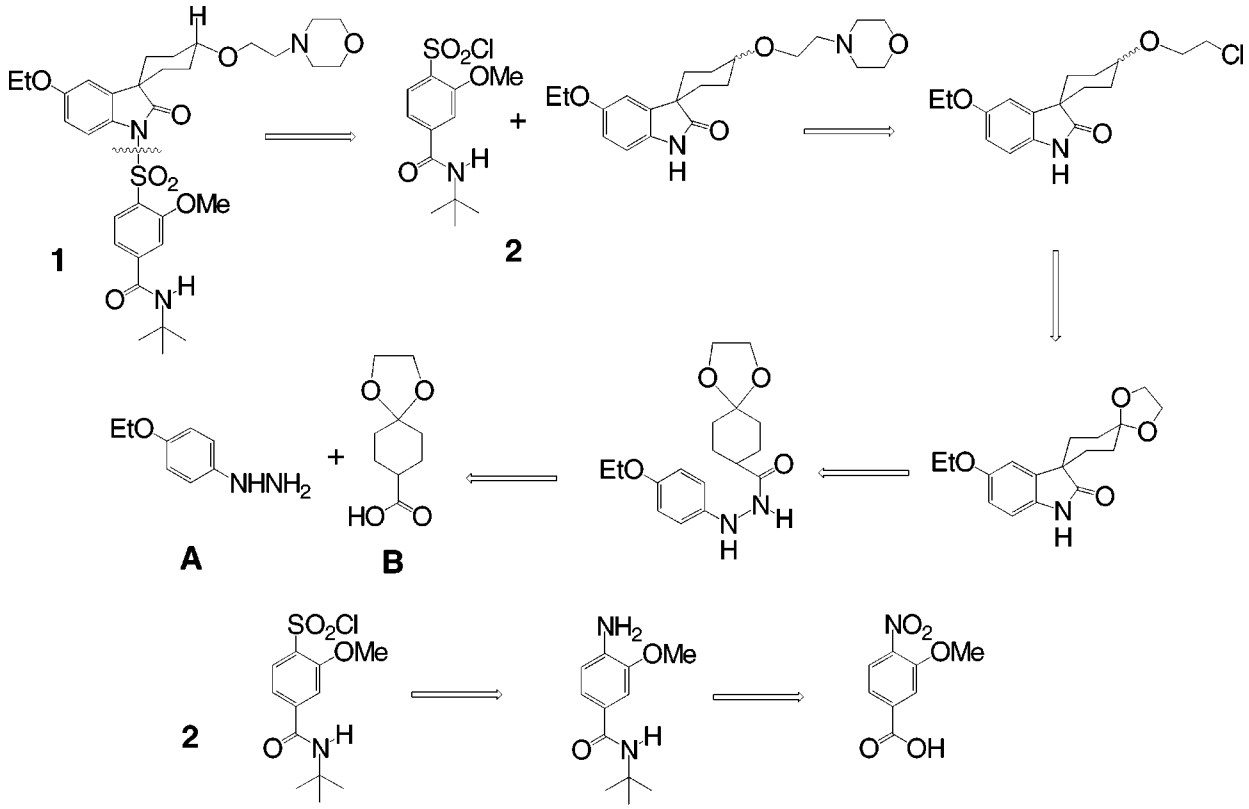


Figure 1. Patented synthesis of SR 121463 A, **1**.

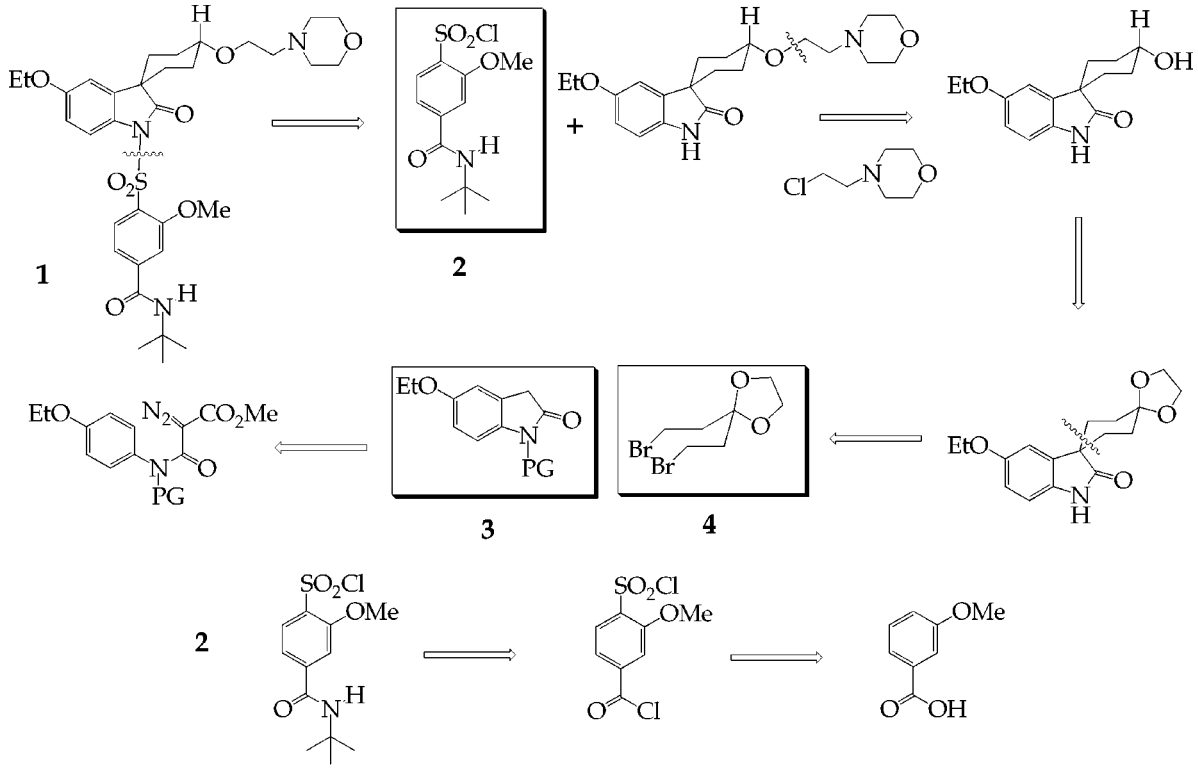
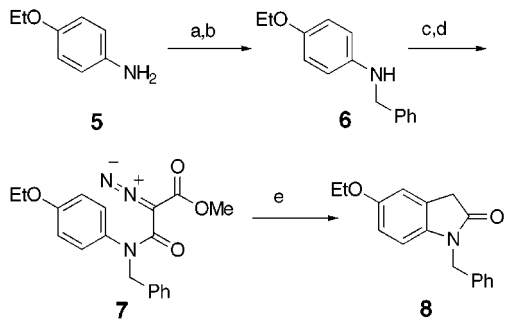


Figure 2. Retrosynthetic analysis of SR 121463 A; PG = protecting group.

Hydrolysis of the spirane ketal and subsequent reduction of the corresponding ketone should provide access to an alcohol, which can be alkylated with 2-chloroethylmorpholine. We expected that intermediate **2** could be synthesized in a regioselective manner by allowing 4-chloro-3-methoxy-sulfonylbenzoyl chloride[12] to react with *tert*-butylamine.

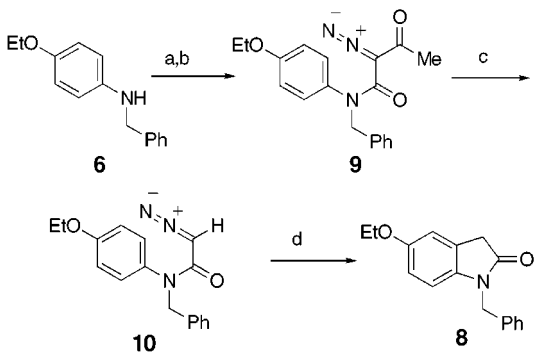
(12) Fedyunyaeva, I. A.; Shershukov, V. M. *Chem. Heterocycl. Compd. (Engl. Transl.)* 1993, *29* (2), 204.

Scheme 1[a]



[a] (a) PhCHO, EtOH; (b) $NaBH_4$, MeOH; (c) $ClCOCH_2COOMe$, Et_3N, CH_2Cl_2; (d) $MeSO_2N_3$, Et_3N; (e) Nafion H.

Scheme 2[a]



[a] (a) Diketene, Et_3N, THF; (b) $MeSO_2N_3$, Et_3N, THF; (c) KOH, CH_3CN; (d) Rh_2OAc_4, CH_2Cl_2.

Synthesis of the Intermediates

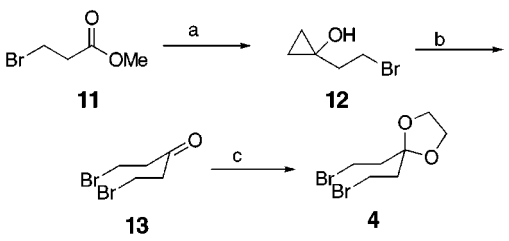
Recently it was reported that Nafion-H, a perfluorinated ion-exchange resin, could efficiently catalyze decarboxylative cyclization of α-carbomethoxy-α-diazoacetanilides.[11] We investigated this method for the construction of the protected oxindole intermediate as shown in Scheme 1. Reductive amination of *p*-phenetidine with benzaldehyde yielded 6 (95%). Treatment of **6** with methylmalonyl chloride, followed by diazo transfer with mesyl azide, yielded **7** (90%). However, much to our disappointment, the key reaction involving decarboxylative cyclization using Nafion H proceeded in only 20−30% yield. Substituting H for the carbomethoxy group in **7** circumvented this problem.

Compound **10** could easily be prepared using Doyle's procedure (Scheme 2).[11a] Thus, treatment of *N*-benzyl-*p*-phenetidine with diketene, followed by diazo transfer using methanesulfonyl azide and subsequent deacylation using KOH, resulted in the cyclization substrate **10**. Rhodium(II) acetate catalyzed decomposition of the diazo compound furnished the desired *N*-benzyl-protected oxindole **8** in high overall yield (70%).

Parallel with this, the protected dibromide was easily assembled using an established procedure in good overall yield (Scheme 3).[1]

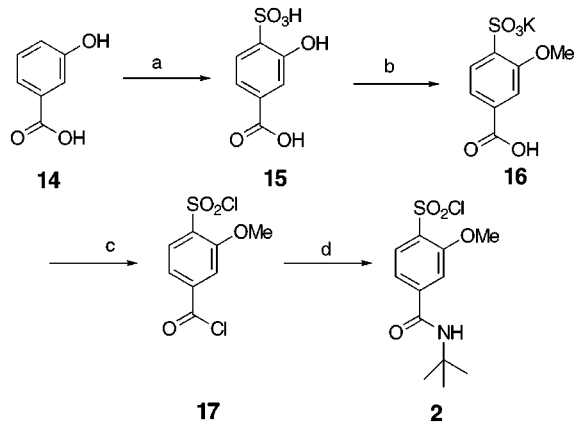
Synthesis of the substituted sulfonyl chloride moiety **2** commenced with *m*-hydroxybenzoic acid **14** (Scheme 4).[14] Sulfonylation using sulfuric acid containing 3% SO_3 proceeded smoothly to furnish the benzenesulfonic acid derivative **15**. Selective methylation of the phenoxyl group using KOH and Me_2SO_4 yielded the potassium salt of 4-sulfo-3-methoxybenzoic acid, **16**. The methylation reaction proved to be more difficult than reported previously. Great care had to be taken in monitoring the course of the reaction, which proceeded most effectively when the reagents were added 5 times in succession with a 0.5 h interval between each addition. We have reproduced this reaction on a 20-g scale without observing other products.

Scheme 3[a]



[a] (a) $Ti(iPrO)_4$, EtMgBr; (b) NBS, CCl_4; (c) ethylene glycol, PPTS, $HC(OEt)_3$.

Scheme 4[a]



[a] (a) H_2SO_4, 3% SO_3; (b) KOH, Me_2SO_4; (c) PCl_5; (d) Et_3N, $^tBuNH_2$.

Treatment of potassium salt **16** with PCl_5 yielded 4-chlorosulfonyl-3-methoxybenzoyl chloride **17** in good overall yield (40%). As expected, treatment of the dichloride with Et_3N and *tert*-butylamine at −78 °C and slow warming to room temperature produced **2** in good yield (80%). It is important to note that selective addition to the carbonyl chloride was achieved.

Convergent Synthesis of 1

Having completed the syntheses of the three intermediates, the final operations to complete the molecular skeleton of SR 121463 A were undertaken. Treatment of the *N*-protected oxindole **8** with 2 equiv of LHMDS and 1 equiv of dibromide **4**, either in the presence or absence of HMPA, did not produce the spiro derivative in acceptable yields. Instead, difficultly separated mixtures of **18**, the monoalkylated species, and other products were obtained. However, treatment of **8** with 4 equiv of NaH and 1.5 equiv of the dibromide in DME furnished the desired spiro compound **18** in excellent yield (90%, Scheme 5).

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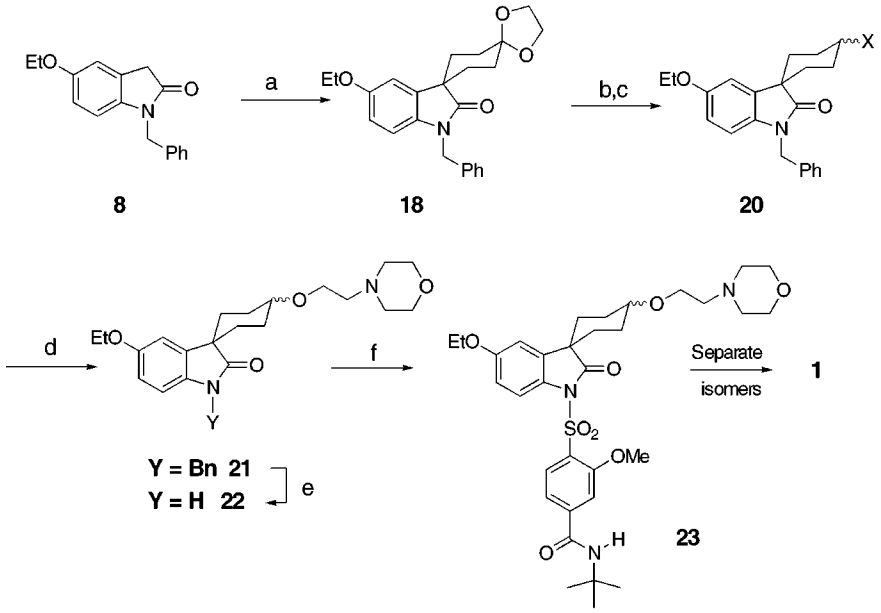
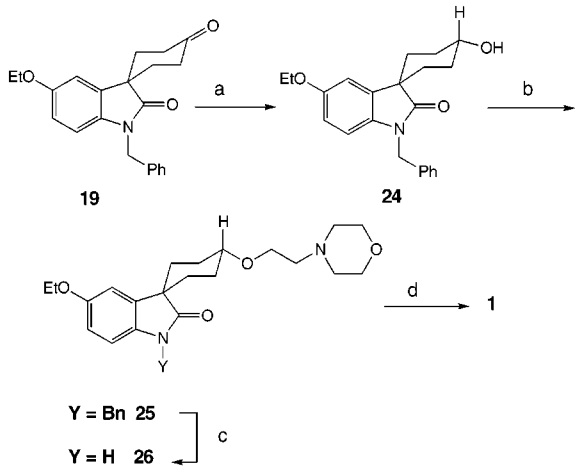
Scheme 5[a]



[a] (a) NaH, DME, then **4**; (b) PPTS, acetone/H_2O; (c) $NaBH_4$, MeOH; (d) NaH, toluene, 2-chloroethylmorpholine, 100 °C; (e) Li/NH_3, −78 °C; (f) KO^{t}Bu, then **2**.

Scheme 6[a]



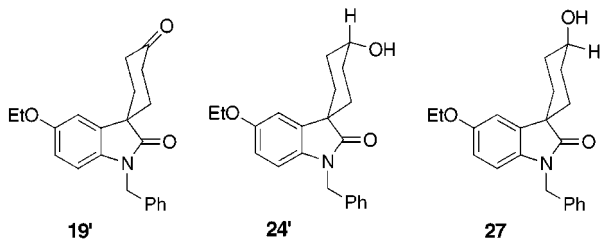
[a] (a) L-Selectride, THF, −78 °C; (b) NaH, toluene, 2-chloroethylmorpholine; (c) Li, NH_3, −78 °C; (d) KO^{t}Bu, then **2**.

Deprotection of the ketal with PPTS and subsequent reduction of the ketone **19** with $NaBH_4$ yielded the alcohol **20** as a 2:1 mixture of syn and anti isomers (90%). Exposure of the alcohol to NaH in toluene at 100 °C for 1.5 h, followed by the treatment with freshly distilled 2-chloroethylmorpholine[15] and refluxing for 14 h, resulted in the desired product **21** in 80% yield. Deprotection of the *N*-benzyl group in **21** proved to be more difficult than anticipated. Standard catalytic hydrogenolysis conditions at 40 or 80 psi of H_2 or heating with ammonium formate or cyclohexadiene in the presence of Pd/C resulted in complete recovery of the starting material. However, treatment of **21** with 4−5 equiv of Li/NH_3 furnished the deprotected compound **22** in excellent yield (90%).[16] The final step in the total synthesis was accomplished easily by treatment of **22** with *t*-BuOK and the sulfonyl chloride **2**. Although the transformation was efficient, separation of the syn and anti isomers proved to be tedious and time-consuming. Nevertheless, SR 121463 A was isolated in 50% yield. The anti isomer was also isolated in 25% yield.

To improve selectivity in the overall process, we reinvestigated the crucial reduction step in the synthesis (**19** → **20**). The use of $NaBH_4$/LiBr, $LiAlH_4$, and N-Selectride led to selectivities of 3:1, 4:1, and 4:1, respectively, in favor of the syn isomer. Even better, we succeeded in synthesizing the syn isomer **24** selectively (66:1) in good yield (85%) when L-Selectride was used as the reducing agent (Scheme 6). Clearly, both the bulky selectride reagent and the Li cation combine to effect the larger stereoselective outcome. Addition of the morpholino moiety, deprotection of the benzyl group without oxindole reduction to give **26**, and subsequent coupling with the sulfonyl chloride as before yielded SR 121463 A in good overall yield.

Regiospecific L-Selectride Reduction of 19 to 24

While ^{13}C NMR indicated the presence of a single isomer from the L-Selectride reduction of **19**, definitive



proof that it was the desired syn epimer **24** was obtained from X-ray crystallography. The substance crystallizes in the alternative chair cyclohexane conformation and, surprisingly, the OH group is axial, **24′**.

The latter can be understood by an examination of nonbonded interactions in the solid state. Figure 3 illustrates that two symmetry-related intermolecular

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(16) Webster, F. X.; Millar, J. G.; Silverstein, R. M. *Tetrahedron Lett.* **1986**, 27 (41), 4941.

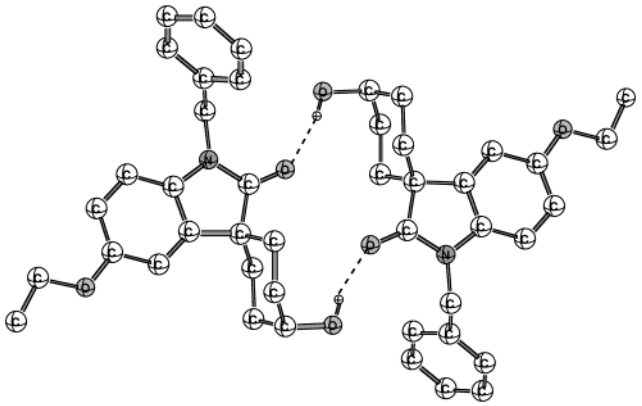

Figure 3. The pairwise intermolecular hydrogen bonds between C_2 dimers of axial **24′** found in the solid state.

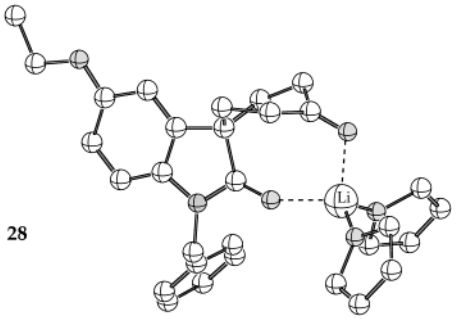

Figure 4. Oxindole **19/19′** with the cyclohexanone ring in a twist-boat conformation, **28**. Both the cyclohexanone and the amide C═O moieties are coordinated to a tetrahedral lithium cation further coordinated by two molecules of tetrahydrofuran solvent. Shaded atoms are oxygen and nitrogen.

hydrogen bonds between the amide carbonyl and the axial OH link pairs of molecules of **24′** in the crystal. The observation is compatible with *A*-value determinations for cyclohexanol and substituted cyclohexyl ethers and acetates. In solution the axial isomers are less stable than the equatorial forms by only $\Delta G = 0.5-1.0$ kcal/mol, corresponding to axial populations of 15−30%.[18] In reasonable accord, the MM3* and MMFF force fields implemented in MacroModel[19] posit axial-**24′** to be less stable than **24** by 2.0 and 1.1 kcal/mol, respectively. All things considered, the solid state H-bonds are clearly more than sufficient to override the 1,3-diaxial interactions in the cyclohexane portion of **24′**.

What remains unexplained is the unusual improvement in the stereoselectivity of **24** relative to **27** as the reducing agent is varied from $NaBH_4$ to $LiAlH_4$ and then to L-Selectride ($LiBH(sec\text{-}Bu)_3$). The latter is known to reduce cyclohexanones by approaching from the less hindered equatorial face of the ring.[20] Were conformations **19** and **19′** attacked from this face, compounds **27** and **24/24′** would result, respectively. Given that the three *sec*-butyl groups on boron are undoubtedly distant from the oxindole rings in C═O-localized transition states stemming from **19** or **19′**, the origin of the observed selectivity must arise from a source unrelated to the bulk of the *sec*-butyl substitutents. One possibility is that conformer **19′** is considerably more stable than **19** and thereby competes effectively with the reducing agent to give **24/24′**. This would not, of course, explain why **19′** would not be equally effective at interacting with $LiAlH_4$ and $NaBH_4$. Indeed, MM3* and MMFF optimizations for **19** and **19′** suggest the latter to be less stable than the former by 2.3 and 2.6 kcal/mol, respectively. Thus, if relative conformational stability were operating as the guide to product, the *anti*-epimer **27**, not **24/24′**, is expected to be the reduction product.

We propose that *syn*-alcohol **24/24′** arises from preorganization of **19** to give **28** as pictured in Figure 4. The powerful lithium cation Lewis acid coordinates to both the ketone and amide carbonyl groups, capturing the cyclohexanone in a twist-boat conformation. The latter is only 2.7 kcal/mol above the chair conformer, while the activation barrier for inversion is 4.0 kcal/mol.[21] Both values are considerably lower than for cyclohexane.

The situation is reminiscent of many reported cases of stereocontrol promoted by cationic coordination.[22] Complex **28** not only presents the appropriate ring face to the reducing agent but also establishes a highly polarized carbonyl group to facilitate rapid reduction. Mediation of the reaction by such a complex likewise explains why $LiAlH_4$, but not $NaBH_4$, shows selectivity.

To verify that complex **28** is energetically reasonable, we subjected ligand **19** to MacroModel calculations in which the methylammonium cation ($CH_3NH_3^+$) serves as a surrogate for Li^+. The cation substitution was necessitated by the lack of Li^+ parameters in the MM3* and MMFF force fields. Optimizations were performed on chelated structures virtually identical in geometry to **28** (i.e. **29**) and on **19** hydrogen bonded to $CH_3NH_3^+$ through the amide carbonyl (**30**) (cf. Figure 5). With the MM3*/GBSA/$CHCl_3$ and MMFF/GBSA/$CHCl_3$ protocols (the $CHCl_3$ continuum model used as a THF replacement and a charge damping factor), complex **29** is more stable than **30** by 3.7 and 6.7 kcal/mol, respectively. When $CH_3NH_3^+$ is placed at the cyclohexanone carbonyl, the system is competitive with the chelated species **29**; i.e. −0.6 and 1.6 kcal/mol for MM3* and MMFF, respectively. We believe these values to be on the order of magnitude that Li^+ stabilizes **28** relative to single-center coordination alternatives. Complex **28** thus serves as both a geometric and energetic model to explain the advantageous regioselectivity of L-Selectride reduction of **19**.

Conclusion

The synthesis of SR 121463 A has been achieved in good overall yield. Although the number of steps employed is large, the yield in each step in the total synthesis is greater than 80%. The construction of the spiro ring does not require harsh conditions. Intermediate

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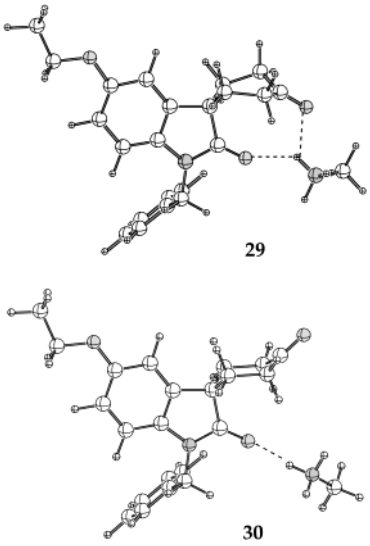

Figure 5. Oxindole **19** coordinated to $CH_3NH_3^+$ by chelation of the two carbonyl groups (**29**) and by hydrogen bonding to the amide carbonyl group alone (**30**); MM3* optimized structures. Shaded atoms are oxygen and nitrogen.

2 was synthesized in only four steps using simple, cheap reagents with complete control of regioselectivity. In addition, the selective formation of the syn isomer of **1** via **24** was achieved. This avoids the necessity of a tedious separation of a mixture of isomers as reported in the patent literature. This strategy can potentially be employed to construct other analogues in a general manner.

Experimental Section

General Methods. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are reported uncorrected. Proton and carbon NMR spectra were obtained on General Electric QE−300 (300 MHz) or Varian Inova-400 (400 MHz) spectrometers. Single-crystal X-ray analysis for compound **24** was carried out with a Siemens P4RA automated diffractometer with a rotating-anode Cu X-ray source, FRS scintillation and Hi-Star area detectors, and an LT-2 low-temperature system.

TLC was performed on precoated, glass-backed plates (silica gel 60 F_{254}; 0.25-mm thickness) from EM Science and was visualized by UV lamp. Chromatography was performed with silica gel 60 (230−400 mesh ASTM) from EM Science using the "flash" method. Atlantic Microlab Inc. Norcross, Georgia performed elemental analyses. All solvents and reagents were purchased from Aldrich Chemical Co., Milwaukee. The solvents were either dried with molecular sieves (4A) or distilled before use. The reagents were used as received. Methanesulfonyl azide[17] and **4**[13] were prepared by published procedures. **CAUTION:** Working with mesyl azide is extremely dangerous. Distillation of up to 25 mL of the compound was routinely carried out behind a blast shield. All reactions were performed under anhydrous nitrogen atmosphere in oven-dried glassware.

Potassium Hydrogen 4-Sulfo-3-hydroxybenzoate Monohydrate (15). To a magnetically stirred solution of **14** (20 g, 145 mmol) in concentrated H_2SO_4 (27 mL) heated to 90 °C was added dropwise 30% SO_3 in concentrated H_2SO_4 (3 mL). After 12 h of stirring, a precipitate formed and stirring became difficult. The mixture was heated at 90 °C further while mechanically stirred for another 1 h. The reaction was then cooled to room temperature and H_2O (100 mL) was added to dissolve the reaction mixture. The mixture was stirred while 25% KOH (32.5 mL) was added dropwise. The resulting precipitate of the title compound was collected by filtration and recrystallized from H_2O (29.36 g, 79%): mp >250 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.5 (s, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.4 (d, J = 6.9 Hz, 1H), 7.3 (s, 1H), 3.85 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.98, 153.38, 134.56, 133.36, 127.77, 119.80, 117.56. Anal. Calcd for $C_7H_5O_6K\cdot H_2O$: C, 30.65; H, 2.55; S, 11.68. Found: C, 31.09; H, 2.51; S, 11.9.

Potassium Hydrogen 4-Sulfo-3-methoxybenzoate Monohydrate (16). To a magnetically stirred solution of **15** (27.61 g, 100 mmol) in H_2O (61 mL) was added KOH (11.2 g, 200 mmol) in H_2O (10 mL) with vigorous stirring, followed by dimethyl sulfate (9.47 mL, 100 mmol), and the mixture stirred for 20 min. The sequence was repeated four times, after which the reaction was heated to 80 °C for 10 min. The reaction was cooled to room temperature., neutralized with concentrated H_2SO_4, and finally acidified to pH 1 with concentrated HCl. Upon standing, the title compound precipitated and was filtered (12.75 g, 44%): mp >250 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.8 (d, J = 8.25 Hz, 1H), 7.49 (m, 2H), 3.82 (s, 3H), 3.7 (bs, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 167.13, 156.23, 139.03, 132.95, 128.91, 120.74, 112.34, 55.83. Anal. Calcd for $C_8H_7O_6SK\cdot H_2O$: C, 33.33; H, 3.12. Found: C, 33.29; H, 3.16

4-Chlorosulfonyl-3-methoxybenzoyl Chloride (17). A mixture of **16** (11.75 g, 40 mmol) and phosphorus pentachloride (27 g, 131 mmol) were heated for 1 h at 80 °C, after which all solid dissolved. The mixture was cooled to room temperature and 50 mL of ice and water was added. The title compound was filtered, dried, and recrystallized from CCl_4 (10.5 g, 96%): mp 85 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.1 (d, J = 8.5 Hz, 1H), 7.85 (dd, J = 1.7 Hz, 8.3 Hz, 1H), 7.8 (s, 1H), 4.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.41, 157.44, 140.29, 136.68, 130.49, 122.98, 115.08, 57.38. Anal. Calcd for $C_8H_6O_4SCl_2$: C, 35.82; H, 2.24; Cl, 26.12. Found: C, 35.53; H, 2.24; Cl, 26.38.

4-Chlorosulfonyl-3-methoxy-*tert*-butylaminobenzamide (2). To a stirred solution of **17** (1 g, 3.7 mmol) and triethylamine (0.52 g, 3.7 mmol) in CH_2Cl_2 (5 mL) cooled to −78 °C was added dropwise *tert*-butylamine (0.27 g, 3.7 mmol). The reaction was allowed to warm to room temperature over 1 h and then poured into 10 mL of ice water. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3 × 4 mL). The combined organic phases were dried ($MgSO_4$) and evaporated in vacuo to a white solid. The solid was chromatographed (CH_2Cl_2) to obtain the title compound (0.85 g, 75%): mp 150−3 °C (CH_2Cl_2/CCl_4); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94, (d, J = 8.1 Hz, 1H), 7.59 (s, 1H), 7.23 (dd, J = 1.4 Hz, 8.0 Hz, 1H), 6.05 (bs, 1H), 4.1 (s, 3H), 1.5 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.8, 157.75, 144.35, 133.49, 130.1, 117.3, 112.99, 57.11, 52.58, 28.88. Anal. Calcd for $C_{12}H_{16}NO_4SCl$: C, 47.21; H, 5.25; N, 4.56. Found: C, 47.17; H, 5.31; N, 4.51.

***N*-Benzyl-4-ethoxyaniline (6).** To a magnetically stirred solution of **5** (16 g, 116 mmol) in 200 mL of MeOH at room temperature was added dropwise benzaldehyde (11.85 mL, 116 mmol) over 0.5 h. The mixture was heated to reflux for 2 min. After cooling to room temperature $NaBH_4$ (4.8 g, 127 mmol) was added in portions with vigorous stirring over 1 h. The reaction was stirred for another 2 h and then quenched with H_2O (200 mL). After 0.5 h the title compound precipitated and was filtered and dried (23.31 g, 97%): mp 44−6 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.3−7.2 (m, 5H), 6.77 (d, J = 9.2 Hz, 2H), 6.61 (d, J = 8.9 Hz, 2H), 4.28 (s, 2H), 3.95 (q, J = 7 Hz, 2H), 1.37 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.65, 142.56, 139.85, 128.77, 127.75, 127.35, 115.93, 114.29, 64.27, 49.44, 15.22. Anal. Calcd for $C_{15}H_{17}NO$: C, 79.30; H, 7.49; N, 6.17. Found: C, 79.31; H, 7.57; N, 6.08.

***N*-Benzyl-*N*-(4-ethoxyphenyl)-2-diazo-3-oxobutanamide (9).** To a magnetically stirred solution of **6** (10 g, 44 mmol) in THF (25 mL) at room temperature. was added dropwise diketene (4.07 mL, 52.8 mmol) over 1 h. The reaction was then heated to reflux for 0.5 h, after which diketene (0.5 mL, 6.5 mmol) was added again and the reaction was refluxed for 1 h. The reaction was cooled and an additional 0.5 mL (6.5 mmol) of diketene was added and the reaction was heated to reflux for 4 h. After this time no **9** was present by TLC (CH_2-

Cl_2/MeOH). The reaction was cooled, and the volatiles were evaporated in vacuo. The remaining thick brown oil was dissolved in 25 mL of acetonitrile, and triethylamine (6.4 mL, 46 mmol) was added. To this mixture at room temperature was added dropwise methanesulfonyl azide (7.05 g, 58 mmol) dissolved in 20 mL of acetonitrile over 1 h. After stirring for 12 h, the volatiles were evaporated in vacuo and the remaining residue was partitioned between H_2O and Et_2O. The organic phase was separated, dried ($MgSO_4$), and evaporated in vacuo. The remaining oil was subjected to chromatography to obtain the title compound as a yellow oil (13.75 g, 93%) that slowly crystallized on standing: mp 54−6 °C (hexanes/Et_2O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.3−7.1 (m, 5H), 6.92 (d, J = 9.2 Hz, 2H), 6.81 (d, J = 8.9 Hz, 2H), 4.92 (s, 2H), 3.95 (q, J = 7 Hz, 2H), 2.55 (s, 3H), 1.41 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.32, 161.21, 159.07, 137.06, 133.75, 129.16, 128.98, 128.7, 127.83, 115.83, 63.99, 54.25, 28.98, 14.87. Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.66; H, 5.64; N, 12.46. Found: C, 67.72; H, 5.73; N, 12.41.

***N*-Benzyl-*N*-(4-ethoxyphenyl)diazoacetamide (10).** To a magnetically stirred solution of **9** (13.75 g, 41 mmol) dissolved in 40 mL of acetonitrile at room temperature was added dropwise 16% KOH (30 mL) over 1 h. Stirring was continued for another 12 h, after which the reaction was complete by TLC. The volatiles were evaporated in vacuo, and the remaining residue was partitioned between Et_2O and H_2O. The organic phase was separated, dried ($MgSO_4$), and evaporated in vacuo to an orange oil. Chromatography yielded the title compound as a yellow oil (10.06 g, 84%) that slowly crystallized: mp 49−52 °C (hexanes/Et_2O); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.3−7.19 (m, 5H), 6.89 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.9 Hz, 2H), 4.87 (s, 2H), 4.44 (s, 1H), 3.9 (q, J = 7 Hz, 2H), 1.4 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 158.75, 137.85, 134.01, 129.84, 129.0, 128.58, 127.54, 115.34, 63.88, 53.21, 47.4, 14.97. Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.15; H, 5.76; N, 14.24. Found: C, 69.31; H, 5.87; N, 14.15.

1-Benzyl-5-ethoxy-2-indolinone (8). To a magnetically stirred solution of rhodium(II) acetate dimer (95.5 mg, 0.2 mmol) in 127 mL of CH_2Cl_2 at room temperature. was added dropwise over 1 h a solution of **10** (7.5 g, 25.5 mmol) in 20 mL of CH_2Cl_2. The evolution of N_2 gradually occurred and the reaction was stirred for 12 h. The reaction was filtered through neutral Al_2O_3 (5 g), then solvent was evaporated in vacuo, leaving a yellow solid. A single recrystallization (hexanes/EtOAc) furnished **8** (5.96 g, 88%): mp 108−11 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.2 (m, 5H), 6.87 (s, 1H), 6.68 (d, J = 8.8 Hz, 1H), 6.58 (d, J = 8.6 Hz, 1H), 4.89 (s, 2H), 3.95 (q, J = 7 Hz, 2H), 3.6 (s, 2H), 1.37 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.00, 155.30, 137.92, 136.14, 128.93, 127.75, 127.52, 125.91, 113.15, 112.70, 109.53, 64.28, 44.01, 36.37, 15.09. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.4; H, 6.37; N, 5.24. Found: C, 76.45; H, 6.41; N, 5.17.

1′-Benzyl-5′-ethoxyspiro[cyclohexane-1,3′-indoline]-4,2′-dione Cyclic 4-Ethylene Ketal (18). To a magnetically stirred solution of **8** (2.67 g, 10 mmol) in DME (70 mL) at 0 °C was added NaH (0.96 g, 40 mmol). After 15 min of stirring, dibromide **4** (4.3 g, 15 mmol) was added at 0 °C and the reaction allowed to warm to room temperature. After 16 h the reaction was quenched with water (30 mL) at 0 °C and extracted with ethyl acetate (3 × 60 mL). The combined organics were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography using 20% EtOAc/methylene chloride yielded 3.5 g (90%) of **18**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.2−7.3 (m, 5H), 6.95 (d, J = 2.4 Hz, 1H), 6.65 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 4.85 (s, 2H), 4.0 (t, J = 2.1 Hz, 4H), 3.9 (q, J = 6.8 Hz, 2H), 2.3 (m, 2H), 2.0 (m, 1H), 2.2 (m, 1H), 1.8−1.95 (m, 4H), 1.35 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 179.64, 155.03, 150.17, 136.15, 135.67, 135.19, 128.67, 127.38, 127.02, 112.34, 111.55, 109.14, 108.13, 64.36, 64.28, 64.05, 46.30, 43.34, 31.51, 30.17, 14.86. Anal. Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.30; H, 6.95; N, 3.58.

1′-Benzyl-5′-ethoxyspiro[cyclohexane-1,3′-indoline]-4,2′-dione (19). A magnetically stirred solution of **18** (4.64 g, 11.8 mmol), PPTS (0.88 g), 10 mL of H_2O, and 100 mL of acetone was refluxed for 20 h, after which time no ketal remained by TLC (CH_2Cl_2/MeOH). The mixture was cooled, evaporated in vacuo, and subjected to chromatography to obtain the title compound (3.7 g, 90%) as a pale brown oil that slowly crystallized: mp 125−8 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.2 (m, 5H), 6.85 (d, J = 2.5 Hz, 1H), 6.69 (d, J = 8.6 Hz, 2H), 6.64 (d, J = 8.6 Hz, 1H), 4.9 (s, 2H), 3.95 (q, J = 7 Hz, 2H), 3.26−3.18 (m, 2H), 2.95−2.55 (m, 2H), 2.25−2.12 (m, 4H), 1.4 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 210.92, 179.2, 155.55, 136.1, 135.38, 134.67, 129.06, 127.87, 127.32, 112.79, 111.34, 109.84, 64.31, 46.08, 43.75, 37.13, 33.99, 15.08. Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.64; H, 6.59; N, 4.01. Found: C, 75.36; H, 6.63; N, 3.95.

1′-Benzyl-5′-ethoxy-4-hydroxyspiro[cyclohexane-1,3′-indolin]-2′-one (24). To a magnetically stirred solution of **19** (415 mg, 1.2 mmol) dissolved in 5 mL of THF at −78 °C was added dropwise 1 M L-Selectride (1.78 mL, 1.8 mmol) in THF over 1 h. The reaction was stirred at −78 °C for an additional 2 h and then 0.2 mL of H_2O was added. The volatiles were removed in vacuo, and the residue partitioned between H_2O and CH_2Cl_2. The organic layer was separated, dried (Na_2SO_4), and evaporated in vacuo. ^{1}H NMR analysis demonstrated a 66:1 ratio of syn and anti alcohols. Chromatography afforded the title compound as a colorless oil (0.38 g, 90%) that slowly crystallized: mp 125−7 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.2−7.3 (m, 5H), 6.85 (d, J = 2.4 Hz, 1H), 6.65 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 4.85 (s, 2H), 3.95 (q, J = 6.8 Hz, 2H), 3.9 (m, 1H), 2.3−2.1 (m, 3H), 2.1−1.9 (m, 3H), 1.8−1.6 (m, 2H), 1.4 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.72, 155.04, 135.89, 128.96, 127.69, 127.32, 112.27, 111.42, 109.38, 69.28, 64.26, 46.33, 43.58, 31.52, 29.96, 15.12. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.21; H, 7.12; N, 3.99. Found: C, 75.35; H, 7.25; N, 3.98.

Other carbonyl reducing agents were employed as follows: A solution of **19** (140 mg, 0.4 mmol) in 5 mL of absolute EtOH at 0 °C was treated with solid $NaBH_4$ (23.3 mg, 0.6 mmol). After 1 h the reaction was warmed at room temperature and the solvent evaporated. The residue was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine and dried with Na_2SO_4, and the solvent was evaporated. The product was purified with flash chromatography using EtOAc/hexane (2:3). A final purification with EtOAc/hexane (3:2) gave the diastereomeric mixture of **24** (2:1 syn:anti by NMR).

Compound **19** (414 mg, 1.2 mmol) was dissolved in 10 mL of absolute EtOH, and a solution of LiBr in 5 mL of absolute EtOH (161 mg, 1.2 mmol) was added. After cooling at 0 °C, solid $NaBH_4$ (70 mg, 1.2 mmol) was added in portions with vigorous stirring over 1 h. The reaction was stirred for another 2 h at room temperature and then quenched with 15 mL of H_2O. The volatiles were removed in vacuo, and the residue was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, and evaporated. The mixture was purified by flash chromatography as for $NaBH_4$ above to give a 3:1 syn:anti diastereomeric mixture of **24** (by NMR).

Compound **19** (100 mg, 0.3 mmol) in 2.0 mL of THF at 0 °C was treated with $LiAlH_4$ (3 mg, 0.3 equiv) in THF. After 5 min, an additional 3 mg of reducing agent was added. The reaction was stirred at 0 °C for 1 h, followed by quenching with 3 drops of saturated NH_4Cl. The latter was extracted with CH_2Cl_2. The dried organic layer was subjected to GCMS analysis to reveal two peaks of MW 351 in a ratio of 3:1.

Compound **19** (140 mg, 0.4 mmol) in 2.5 mL of THF at −78 °C was treated with 1M N-Selectride (0.6 mL, 0.6 mmol) in THF over 1 h. The reaction was stirred at −78 °C for an additional 2 h, and then 0.1 mL of H_2O was added. The volatiles were removed in vacuo and the residue partitioned between CH_2Cl_2 and H_2O. The organic layer was separated, dried with Na_2SO_4, and evaporated. Purification as above gave a 4:1 syn:anti diastereomeric mixture of **24** (by NMR).

1′-Benzyl-5′-ethoxy-4-[2-(4-morpholino)ethoxy]spiro-[cyclohexane-1, 3′-indolin]-2′-one (25). To a magnetically

stirred solution of **24** (0.3 g, 0.86 mmol) in toluene (5 mL) at room temperature was added NaH (31 mg, 1.28 mmol) and the reaction heated to 80 °C for 1.5 h. Freshly distilled 2-chloroethylmorpholine (0.19 g, 1.28 mmol) was then added as a solution in toluene (1 mL) to the refluxing solution. After 6 h, an additional equivalent of 2-chloroethylmorpholine was added and the reaction heated to 100 °C for 12 h. The reaction was cooled to 0 °C, quenched with water (20 mL), and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography using 4: 1 ethyl acetate/hexanes and subsequently increasing polarity with small amounts of MeOH yielded the desired product **25** (0.28 g, 70%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25−7.13 (m, 5H), 6.83 (d, J = 2.4 Hz, 1H), 6.57 (dd, J = 2.4 Hz, 8.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 4.79 (s, 2H), 3.88 (q, J = 6.8 Hz, 2H), 3.68 (t, J = 4.8 Hz, 3H), 3.62 (t, J = 5.6 Hz, 2H), 3.5 (m, 1H), 2.6 (t, J = 5.6 Hz, 2H), 2.5 (m, 4H), 2.15 (m, 2H), 2.0 (m, 2H), 1.87 (m, 2H), 1.75 (m, 1H), 1.55 (m, 2H), 1.3 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.93, 155.0, 136.39, 136.23, 135.47, 128.89, 127.61, 127.27, 111.96, 111.88, 109.26, 75.97, 67.1, 65.85, 64.21, 58.81, 54.39, 46.79, 43.56, 30.77, 26.33, 15.09. Anal. Calcd for $C_{28}H_{36}N_2O_4$: C, 72.39; H, 7.81; N, 6.03. Found: C, 72.13; H, 7.77; N, 5.97.

1′-[2-Methoxy-4-(*tert*-butylaminocarboxamido)benzenesulfonyl]-5′-ethoxy-4-[2-(4-morpholino)ethoxy]spiro-[cyclohexane-1,3′-indolin]-2′-one (1). To a magnetically stirred solution of liquid ammonia (10 mL) at −78 °C were added small pieces of Li (42 mg, 6 mmol), causing the solution to turn dark blue. A solution of **25** (0.54 g, 1.16 mmol) in THF (2 mL) was added and the blue color disappeared within minutes of stirring. The reaction was quenched with solid ammonium chloride and warmed to room temperature over 1 h. Water (30 mL) was added and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product **26** (0.39 g, 90%) was subjected to the next reaction without further purification.

To a magnetically stirred solution of **26** (302 mg, 0.8 mmol) in 5 mL of THF cooled to −78 °C was added potassium *tert*-butoxide (90 mg, 0.8 mmol), and then the mixture was allowed to warm to room temperature. After stirring for10 min, the reaction was cooled to −78 °C and **2** (246 mg, 0.8 mmol) was added in one portion. The cooling bath was removed and the reaction allowed to warm to room temperature over 1 h. After stirring an additional 2 h, the reaction was complete by TLC (CH_2Cl_2/MeOH). The volatiles were evaporated in vacuo, and the remaining residue was subjected to chromatography to provide the title compound (443 mg, 85%) as an oil that slowly crystallized: mp 210−2 °C (hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.13 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 1.2 Hz, 1H), 7.27 (m, 1H), 6.83 (dd, J = 2.4 Hz, 8.8 Hz, 1H), 6.6 (d, J = 2.4 Hz, 1H), 6.10 (s, 1H), 4.02 (q, 6.8 Hz, 2H), 3.73 (m, 4H), 3.62 (m, 5H), 3.45 (m, 1H), 2.6 (t, J = 5.2 Hz, 2H), 2.56 (bs, 4H), 2.0 (m, 2H), 1.85 (br m, 4H), 1.6 (m, 2H), 1.46 (s, 9H), 1.42 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.71, 165.21, 157.64, 156.3, 143.06, 134.54, 132.27, 132.05, 128.27, 117.53, 115.02, 112.96, 111.85, 110.14, 75.97, 67.05, 65.77, 64.06, 58.69, 56.24, 54.29, 52.35, 46.5, 31.8, 29.87, 28.82, 26.18, 15.0. Anal. Calcd for $C_{33}H_{45}N_3O_8S$: C, 61.68; H, 6.85; N, 6.54. Found: C, 60.63; H, 6.88; N, 6.31.

Molecular Mechanics Calculations. These were performed on a Silicon Graphics O2 workstation with MacroModel, v 6.5.[19] Geometry optimizations of **19**, **19′**, **24**, **24′**, **27**, **29**, and **30** were performed with the MM3* and MMFF force fields in combination with the GBSA/$CHCl_3$ continuum model.[23]

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Supporting Information Available: X-ray crystallographic data and an ORTEP drawing are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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