Asymmetric Synthesis of *Cis*-Fused Bicyclic Pyrrolidines and Pyrrolidinones *via* Chiral Polycyclic Lactams

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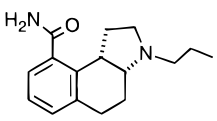
Condensation of racemic keto-ester **2** and 1.1 equiv of (*R*)-(−)-phenylglycinol in toluene with azeotropic removal of water and methanol gave rise to a tetracyclic lactam in greater than 90% yield. Examination of the crude reaction product by ^{1}H and ^{13}C NMR, capillary GC, and HPLC revealed this product to be a single isomer, the absolute configuration of which was determined to be that illustrated by structure **3**. The tetracyclic lactam **3** was stereospecifically reduced to either the *cis*-fused bicyclic pyrrolidine **4** or the *cis*-fused bicyclic pyrrolidinone **9**. The chiral auxiliaries in both **4** and **9** were removed using different, novel methodologies. This highly stereoselective reaction establishes two contiguous chiral centers *via* the deracemization of an achiral keto-ester. This methodology has been applied to the synthesis of (1*R*,5*R*)-2-azabicyclo[3.3.0]octane **15**. This important amine is now readily available from commercial materials in only three steps.

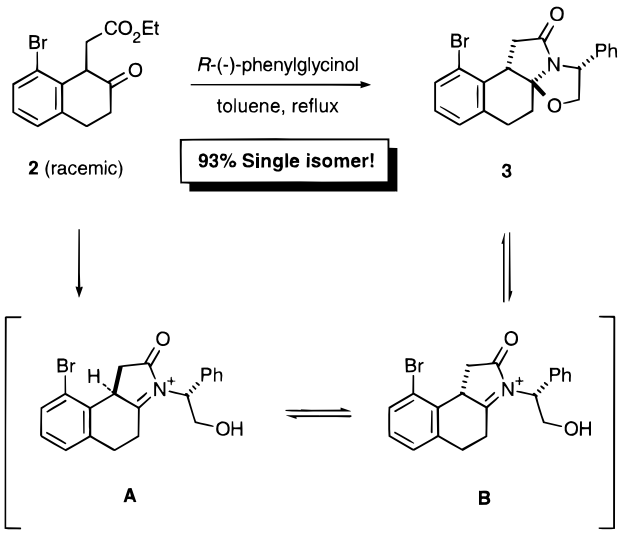
Introduction

The seminal contributions of Meyers have firmly established the synthetic usefulness of chiral bicyclic lactams.[1] Among the numerous applications of bicyclic lactam methodology are the preparation of nonracemic, substituted pyrrolidines and pyrrolidinones.[2] Recently, this methodology has been extended to include the preparation of enantiomerically-pure piperidines as well.[3] These nitrogen heterocycles are widespread among both natural products and medicinally-important synthetic compounds. In addition, nonracemic polysubstituted pyrrolidines serve as useful auxiliaries in several important chirality-transfer reactions. The prevalence of these small-ring nitrogen heterocycles has encouraged the development of numerous routes for their preparation.[4] We wish to describe herein our extension of bicyclic lactam chemistry that allows for the preparation of *cis*-fused bicyclic pyrrolidines and pyrrolidinones with complete stereochemical control. The development of this new methodology emerged from the need for a practical asymmetric synthesis of U-93385 (**1**), a potent serotonin-1A agonist.[5] A key feature of our synthesis is the simultaneous establishment of two contiguous stereogenic centers *via* the deracemization of an achiral keto-ester.



1, U-93385

Scheme 1



Results and Discussion

***Cis*-Fused Pyrrolidines: Synthesis of U-93385.** Examination of **1** revealed an imbedded pyrrolidine, and consideration of bicyclic lactam chemistry for its construction led to an intriguing hypothesis. We felt that condensation of *racemic* keto-ester **2** with (*R*)-(−)-phenylglycinol would produce a pair of diastereomeric *N*-acyliminium ion intermediates **A** and **B** (Scheme 1). We speculated that if equilibration between **A** and **B** (perhaps *via* an enamide intermediate; see ref 7) was a facile process, then intramolecular cyclization might proceed under thermodynamic control with selectivity for the desired tetracycle **3**. In the event, refluxing a solution of **2**[5] and 1.1 equiv of (*R*)-(−)-phenylglycinol in toluene with azeotropic removal of water and methanol gave rise to a tetracyclic lactam in greater than 90% yield.[6]

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1996.

(1) (a) Meyers, A. I.; Romo, D. *Tetrahedron* **1991**, *47*, 9503−9569. (b) Meyers, A. I.; Lefker, B. A. *Tetrahedron* **1987**, *43*, 5663−5676.

(2) (a) Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294−2296. (b) Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc.* **1991**, *113*, 9858−9859. (c) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656−1662. (d) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814−3819. (e) Westrum, L. J.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 973−976. (f) Tschantz, M. A.; Burgess, L. E.; Meyers, A. I. *Org. Synth.* **1994**, *73*, 221−230. (g) Bienz, S.; Busacca, C.; Meyers, A. I. *J. Am. Chem. Soc.* **1989**, *111*, 1905−1907.

(3) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084−7085.

(4) See Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1995**, *60*, 3221−3235 for an excellent overview of the enantioselective synthesis of substituted pyrrolidines.

(5) Lin, C.-H.; Haadsma-Svensson, S. R.; Phillips, G.; McCall, R. B.; Piercey, M. F.; Smith, M. W.; Svensson, K.; Carlsson, A.; Chidester, C. G.; VonVoigtlander, P. F. *J. Med. Chem.* **1993**, *36*, 2208−2218.

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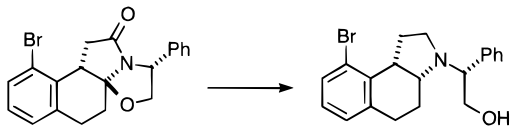
Table 1. Survery of Reductants



3 **4**

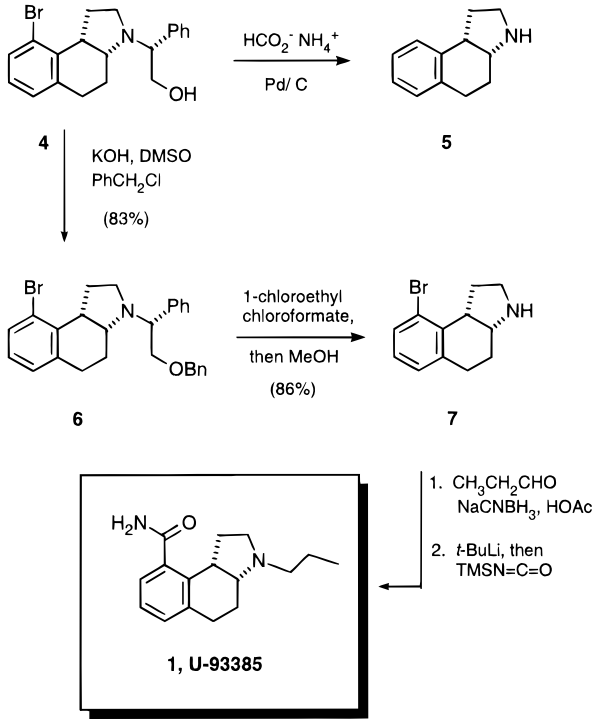
conditions (solvent, temp)	% yield of **4**
LAH, $AlCl_3$ (THF, −78 °C → 0 °C)	76
LAH (THF, −78 °C → RT)	62[a]
DIBAL (THF, −78 °C → RT)	89
BH_3·THF (THF, −78 °C → reflux)	93

[a] A small amount (ca. 15%) of the trans-isomer was obtained from this reaction.

Examination of the crude reaction product by ^1H and ^{13}C NMR, capillary GC, and HPLC revealed this product to be a single isomer! We were subsequently able to verify the absolute configuration of this product as that depicted in Scheme 1 (vide infra). The stereochemical disposition at the oxazolidine center is consistent with ample precedent from Meyers' studies.[1−3] That **3** represents the thermodynamically favored product is supported by molecular mechanics calculations, which place the two possible trans-ring junction isomers at substantially higher energy relative to **3**.[7] This remarkably selective reaction has been carried out without event on scales exceeding 100 kg.[8]

Although the extraordinary selectivity of this condensation provided the requisite stereochemical relationship for the imbedded pyrrolidine ring of U-93385, further elaboration was necessary to complete the synthesis. Specifically, reduction of the lactam function in **3** along with a stereoselective replacement of the oxazolidine C−O bond with a hydrogen atom was needed to establish the desired *cis*-fused pyrrolidine framework. Meyers has reported that tandem reductions of this type can be achieved using alane at −78 °C[2] or DIBAL in refluxing toluene.[3] In both cases, the reductant serves as a Lewis acid and coordinates with the oxazolidine oxygen to promote iminium ion formation. Delivery of hydride is directed by this departing oxygen and results in retention of configuration. For noncoordinating reducing agents, allylic 1,3-interactions also predict a stereoselective reduction with retention of configuration.[2b,c] We too found both alane and DIBAL effective at carrying out this transformation, but in anticipation of production scale processes, we briefly explored alternative reagents. As can be seen in Table 1, we found that several reductants could cleanly effect the stereospecific conversion of **3** to the *cis*-fused pyrrolidine **4**. Only when lithium aluminum hydride was used did we witness erosion of stereochemical integrity and generation of significant amounts of the *trans*-ring fusion isomer (ca. 15%).[9] For overall efficiency and practicality, we found borane, another Lewis acidic reagent, to be the reagent of choice for this transformation. The reduced stereoselectivity witnessed when using the noncoordinating reagent (LAH) may reflect a lesser ability for the allylic 1,3-interactions to direct hydride delivery relative to chelation control.

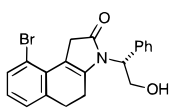
Scheme 2



To intersect with the previous synthetic route to U-93385 (and thereby confirm the absolute configuration), all that remained was removal of the chiral auxiliary from **4**. Typically, removal of the phenylglycinol-based auxiliary takes advantage of the benzylic nature of the N−C bond and is accomplished using hydrogenolytic conditions (Pd or $Pd(OH)_2$, 3 atm H_2 or ammonium formate).[2] Unfortunately, the aromatic bromide present in **4** (there as a synthetic handle for later conversion to the carboxamide in **1**) precluded the use of the normal hydrogenolytic conditions for this cleavage. Indeed, treatment of **4** with ammonium formate in the presence of 10 mol % Pd/C cleanly generated the overreduced pyrrolidine **5** in excellent yield (Scheme 2). After considerable experimentation, we found conditions which effectively removed the chiral auxiliary while allowing for retention of the required aryl bromide. Following protection of the primary alcohol of **4** as the benzyl ether

(6) All new compounds have been fully characterized by ^1H NMR (300 MHz) and ^{13}C NMR (75.5 MHz), IR, and possess satisfactory elemental analysis.

(7) These calculations were performed using MM2. A similar ordering of relative energies was calculated for the 1-azabicyclo[3.3.0]octane system. A reviewer recommended experimental support for the thermodynamically driven equilibration we propose as the mechanism for this condensation. Our suggestion of an equilibrium-based rationale is founded upon a number of observations. The facile formation of *N*-acyliminium ions (such as **B**) from bicyclic lactams has been repeatedly described, as has the generation of enamides derived therefrom.[2g] We postulate the equilibration of **A** and **B** proceeds via a similar enamide (**ii**). In support of this, when a solution of **3** in toluene/CH_3OD is treated with a catalytic amount of *p*-TsOH (0.1 equiv) at room temperature, one observes a gradual diminution of the benzylic proton resonance. While it is possible that iminium ion **B** is in equilibrium with **ii** whereas **A** is not, we have no evidence to suggest that.

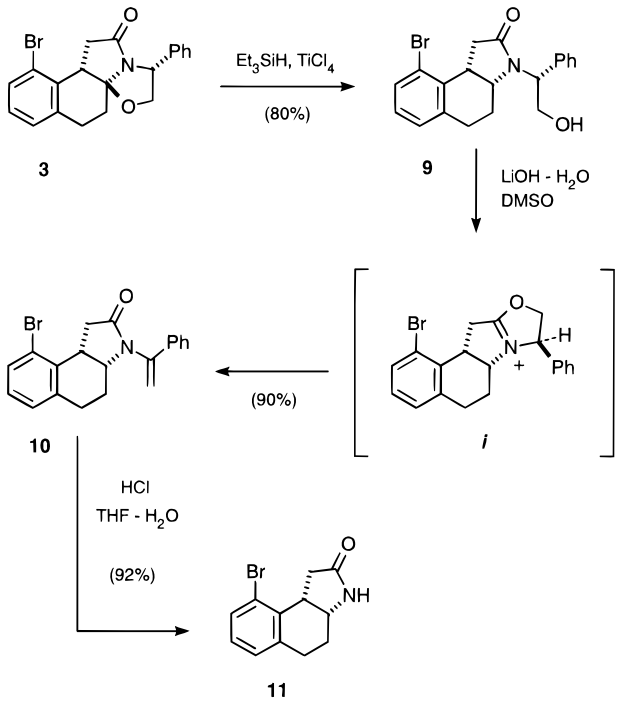


ii

(8) The scale-up of this condensation was carried out by Dr. Thomas A. Runge, Chemical Research Preparations, Pharmacia and Upjohn, Inc.

(9) Meyers has also observed that using LAH alone is less clean than using alane for these reductions (see ref 2a).

Scheme 3

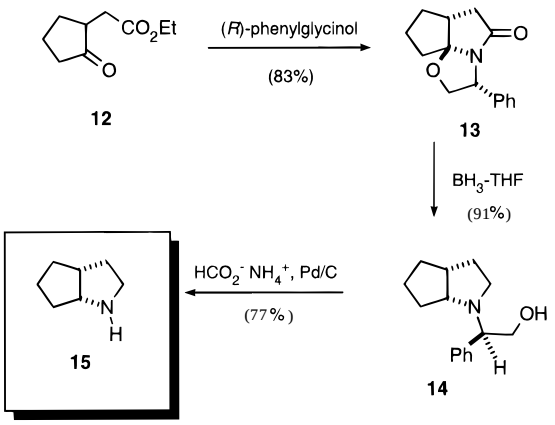


6,[10] treatment with 2-chloroethyl chloroformate[11] in warm toluene and subsequent methanolysis provided the sought after secondary amine **7** in 71% overall yield.[12]

The *cis*-fused pyrrolidine **7** is a common intermediate with the previously-reported synthesis of **1**.[5] Conversion of **7** into U-93385 (**1**) requires only addition of an *n*-propyl group onto the secondary nitrogen followed by transformation of the aryl bromide into the carboxamide. This overall process for the preparation of U-93385 has been carried out as described herein on scales providing over 25 kg of final product.[13]

Cis*-Fused Pyrrolidinones.** Meyers has demonstrated the utility of chiral bicyclic lactams for the preparation of pyrrolidinones based upon a selective reduction with triethylsilane.[2c,f] We have also shown that **3** can be selectively reduced to the pyrrolidinone **9** using triethylsilane and titanium tetrachloride (Scheme 3). Again, only the *cis*-ring fusion was detected in this reaction. Cleavage of the chiral auxiliary in Meyers's monosubstituted pyrrolidinones is typically accomplished using dissolving metal reductions (Li, ammonia),[2] conditions which we again wished to avoid in order to retain our aryl bromide. For our case, we developed a novel, base-induced dehydration for removal of the chiral auxiliary in **9**. Treatment of **9** with lithium hydroxide in DMSO at room temperature affords an excellent yield of the enamide **10**. We speculate the intermediacy of ***i as the progenitor for the observed enamide **10**.[14] Simple hydrolysis of **10** provides the lactam **11** in 83% overall yield. Thus, the versatile intermediate **3** can serve as an entry point into either *cis*-fused pyrrolidines or pyrrolidinones.

Scheme 4



Non-Tetralone Based Systems. The chemistry described above pertains to a specialized case involving keto-tetralones and originated from a specific need for construction of U-93385. We have shown, however, that the remarkable control of adjacent stereocenters *via* polycyclic lactams is available in other, simpler systems as well. To illustrate, we examined the condensation of (*R*)-(−)-phenylglycinol with the 2-substituted cycloalkanone **12** (Scheme 4).[15] We found the same high level of stereoselectivity for **12** as we had observed for **2**, again obtaining a single isomer **13** in 83% yield. Stereoselective reduction of **13** with borane afforded the pyrrolidine **14**, and hydrogenolytic removal of the chiral auxiliary provided (1*R*,5*R*)-2-azabicyclo[3.3.0]octane (**15**) in enantiomerically pure form. Thus, our new methodology has allowed for the synthesis of this *cis*-fused bicyclic amine *in only three steps*! This amine, only recently prepared in optically-active form, has been used as a chiral auxiliary in Michael-type reactions of enamines.[16]

Conclusion

We have described an extension of chiral bicyclic lactam chemistry which allows for the preparation of *cis*-fused bicyclic pyrrolidines and pyrrolidinones. This new methodology simultaneously establishes the two contiguous asymmetric centers of the bicyclic system in a single, high-yielding reaction of a racemic starting keto-ester. Novel transformations of the initial cyclodehydration product provide alternatives to published procedures for chiral auxiliary removal. These new transformations provide access to both pyrrolidines and pyrrolidinones containing reducible functional groups which would be reactive under standard hydrogenolytic conditions. The tetracyclic lactam **3** has proven rich in synthetic potential, and we have explored a number of facets of this chemistry. Results of these studies will be the subject of future reports from our laboratory.

(10) We chose to protect the primary hydroxyl of **4** as a benzyl for convenience and cost reasons. We have carried out this sequence with success using a number of other alcohol derivatives, including *tert*-butyldimethylsilyl and methyl ethers as well as acetates.

(11) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2795−2799.

(12) Meyers provides an alternative procedure for auxiliary removal for compounds intolerant of hydrogenolytic conditions. This involves transformation of the primary alcohol of the auxiliary to a thiophenyl derivative using triethylphosphine and diphenyl disulfide and then treatment with lithio di-*tert*-butylbiphenyl (51% overall yield; see ref 2a).

(13) The multi-kilogram preparation of U-93385 by this chemistry was carried out by Dr. Michael F. Lipton and his associates Michael A. Mauragis and Michael F. Veley, Chemical Research Preparations, Pharmacia and Upjohn, Inc.

(14) For a related reaction, see Vedejs, E.; Wilde, R. G. *J. Org. Chem.* **1986**, *51*, 117−119.

(15) During the preparation of this manuscript, an example of condensations similar to these appeared: Ragan, J. A.; Claffey, M. C. *Heterocycles* **1995**, *41*, 57−70. We thank Dr. Ragan for alerting us to these results.

Experimental Section

Proton and carbon magnetic resonance spectra were recorded in $CDCl_3$ at 300 and 75.5 MHz, respectively, and are reported in ppm on the δ scale from internal tetramethylsilane. Infrared spectra, combustion analysis, optical rotation, and mass spectra were determined by Physical and Analytical Chemistry, The Upjohn Company. When necessary, solvents and reagents were dried prior to use. Anhydrous tetrahydrofuran refers to material that was distilled from sodium metal/benzophenone ketyl. Dichloromethane was dried over activated 4 Å molecular sieves. Unless otherwise noted, all nonaqueous reactions were carried out under an atmosphere of dry nitrogen using oven-dried glassware.

Condensation of Keto-Ester 2 and (*R*)-Phenylglycinol: Preparation of Tetracyclic Lactam (3). A 1-L round bottom flask was charged with keto-ester **2** (29.18 g, 0.098 mol), toluene (490 mL), and (*R*)-2-phenylglycinol (20.21 g, 0.147 mol) and fitted with a Dean−Stark trap. The reaction suspension was heated to reflux, and after approximately 1 h the reaction became homogenous. Heating was continued for 18 h, by which time the trap contained approximately 2.0 mL of water (theory = 1.8 mL). The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting crude product was purified by chromatography on a Waters Prep 500 using 20% ethyl acetate/hexane to give 34.75 g (92%) of **3** as a pale yellow solid, mp 123.0−125.5 °C: R_f 0.24 (20% ethyl acetate/hexane); IR (mull) 2949, 2926, 2855, 1710, 1447, 1364, 1025, 786, 718, 702 cm^{-1}; ^1H NMR δ 7.37 (m, 6H), 7.12 (d, J = 6.7 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 5.33 (t, J = 7.3 Hz, 1H), 4.70 (dd, J = 8.7, 8.1 Hz, 1H), 4.23 (dd, J = 8.8, 6.6 Hz, 1H), 3.84 (t, J = 9.8, 1H), 3.51 (dd, J = 17.1, 9.5 Hz, 1H), 2.84 (t, J = 6.0 Hz, 2H), 2.57 (dd, J = 17.1, 10.3 Hz, 1H), 2.09 (m, 1H), 1.85 (m, 1H); ^{13}C NMR δ 176.9, 139.8, 138.7, 136.3, 131.2, 128.8, 128.1, 127.6, 125.5, 124.7, 101.2, 73.4, 57.5, 44.9, 41.1, 30.7, 27.3; $[\alpha]^{25}_D$ −265 (*c* 0.961, methanol). Anal. Calcd for $C_{20}H_{18}NO_2Br$: C, 62.51; H, 4.72; N, 3.65. Found: C, 62.55; H, 4.76; N, 3.61.

***cis*-(−)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-(2(*R*)-1-hydroxypheneth-2-yl)-1*H*-benz[*e*]indole (4).** A solution of **3** (0.769 g, 2.00 mmol) in anhydrous THF (10 mL) was cooled to −78 °C and treated dropwise with a 1 M solution of borane in THF (6.0 mL, 6.00 mmol). The reaction was stirred for 2 h at −78 °C and then for 2 h at room temperature and then finally brought to reflux for 3 h. After stirring at room temperature overnight, the reaction was treated dropwise with 1 M aqueous HCl (5 mL), causing vigorous gas evolution. The reaction was again brought to reflux for 1 h and then cooled to room temperature and poured into brine (30 mL). The aqueous phase was basified to pH 10 with 5 N NaOH and extracted with dichloromethane (3 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to a colorless oil. The resulting crude product was purified by flash chromatography on 60 g silica gel using 20% ethyl acetate/hexane to give 692 mg (93%) of **4** as a colorless, tacky solid: R_f 0.20 (15% ethyl acetate/hexane); IR (neat) 2936, 1453, 1442, 1177, 1081, 1060, 1035, 1029, 767, 703 cm^{-1}; ^1H NMR δ 7.36 (m, 4H), 7.23 (m, 2H), 7.05 (d, J = 7.4 Hz, 1H), 6.69 (t, J = 7.7 Hz, 1H), 4.07 (m, 2H), 3.69 (dd, J = 9.2, 4.1 Hz, 1H), 3.42 (dd, J = 18.4, 9.1 Hz, 1H), 3.10 (m, 2H), 2.95 (t, J = 7.8 Hz, 1H), 2.79 (m, 1H), 2.51 (m, 2H), 2.30 (m, 1H), 2.18 (d of q, J = 13.7, 3.5 Hz, 1H), 1.48 (m, 1H), 1.33 (m, 1H); ^{13}C NMR δ 140.2, 139.4, 134.7, 130.3, 129.2, 128.0, 127.7, 127.3, 126.5, 124.5, 62.7, 61.1, 56.4, 44.6, 41.0, 31.6, 26.0, 25.9; $[\alpha]^{25}_D$ −127 (*c* 0.566, methanol). Anal. Calcd for $C_{20}H_{22}NOBr \cdot 0.5\ H_2O$: C, 63.00; H, 6.08; N, 3.67. Found: C, 63.02; H, 5.83; N, 3.60.

***cis*-(−)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-(2(*R*)-1-hydroxypheneth-2-yl)-1*H*-benz[*e*]indole (6).** To a solution of amino-alcohol **5** (16.50 g, 44.3 mmol) in anhydrous DMSO (148 mL) was added freshly-powdered potassium hydroxide (11.71 g of 85% KOH, 0.18 mol). The reaction was stirred at room temperature for 10 min prior to the dropwise addition of benzyl chloride (10.2 mL, 88.7 mmol), and then stirring was continued for an additional 50 min, during which time the reaction color gradually changed from dark-orange to yellow. At this point, the reaction was added to ice−water (300 mL), and the resulting milky aqueous suspension was extracted with dichloromethane (3 × 400 mL). The combined organic phases were washed once with brine (300 mL), dried over $MgSO_4$, filtered, and concentrated to give 21.17 g of a yellow syrup. This crude product was purified by chromatography on a Waters Prep 500 using 5% ethyl acetate/hexane to give 16.99 g (83%) of the desired benzyl ether as a pale yellow syrup: R_f 0.28 (5% ethyl acetate/hexane); IR (mull) 2966, 2944, 2924, 2888, 2861, 2807 1453, 1110, 734, 695 cm^{-1}; ^1H NMR δ 7.28 (m, 11H), 7.01 (d, J = 7.4 Hz, 1H), 6.92 (t, J = 7.7 Hz, 1H), 4.50 (dd, J = 15.7, 12.2 Hz, 2H), 4.07 (t, J = 6.3 Hz, 1H), 3.87 (dd, J = 9.7, 6.1 Hz, 1H), 3.77 (dd, J = 9.7, 6.6 Hz, 1H), 3.40 (q, J = 8.4 Hz, 2H), 3.07 (m, 1H), 2.83 (m, 2H), 2.56 (m, 3H), 1.93 (m, 1H), 1.53 (m, 1H), 1.38 (m, 1H); ^{13}C NMR δ 140.4, 139.9, 138.7, 138.4, 130.4, 128.8, 128.3, 128.0, 127.5, 127.4, 127.2, 126.2, 125.0, 73.2, 73.1, 63.8, 58.0, 47.9, 41.7, 31.4, 27.3, 24.8; $[\alpha]^{25}_D$ −92 (*c* 0.9895, methanol). Anal. Calcd for $C_{27}H_{28}NOBr$: C, 70.13; H, 6.10; N, 3.03. Found: C, 69.94; H, 6.01; N, 2.87.

***cis*-(−)-2,3,3a,4,5,9b-Hexahydro-9-bromo-1*H*-benz[*e*]indole (7).** A solution of benzyl ether **6** (16.96 g, 36.7 mmol) in chlorobenzene (70 mL) was treated with 1-chloroethyl chloroformate (20.0 mL, 0.183 mol) and heated to reflux (bath temp 150 °C). During the initial minutes of heating the reaction darkened to a deep emerald green. After 18 h at reflux, the now-brown reaction mixture was cooled to room temperature and treated with a second portion of the chloroformate reagent (20 mL), and refluxing was continued for an additional 4 h. The reaction was then cooled, treated with methanol (500 mL), and reheated to reflux for 1 h. At this point, the reaction was cooled to room temperature and concentrated to a brown oil. This material was dissolved in dichloromethane (300 mL) and washed with 1 M HCl (3×). The combined aqueous washes were cooled in an ice bath and adjusted to pH > 13 with 50% sodium hydroxide, forming a milky solution. This basic aqueous phase was extracted with dichloromethane (2 × 600 mL), and the combined organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo* to give 7.91 g (86%) of **7** as a light tan oil: IR (neat) 2961, 2934, 2862, 2841, 1560, 1453, 1440, 1400, 1176, 774 cm^{-1}; ^1H NMR δ 7.40 (d, J = 7.7 Hz, 1H), 7.05 (d, J = 7.3 Hz), 6.95 (t, J = 7.7 Hz, 1H), 3.51 (m, 2H), 3.06 (m, 1H), 2.92 (m, 1H), 2.76 (m, 1H), 2.65 (m, 2H), 2.23 (bs, 1H), 1.80 (m, 1H), 1.65 (m, 1H), 1.41 (m, 1H); ^{13}C NMR δ 139.8, 139.5, 130.6, 127.7, 126.8, 125.6, 56.2, 45.3, 42.6, 33.8, 28.4, 27.3; $[\alpha]^{25}_D$ −113 (*c* 0.6461, methanol). For the hydrochloride salt: IR (mull) 2802, 2772, 2741, 2644, 2602, 2589, 2485, 2476, 1443, 771 cm^{-1}; $[\alpha]^{25}_D$ −84 (*c* 0.8539, methanol). Anal. Calcd for $C_{12}H_{15}NBrCl$: C, 49.94; H, 5.24; N, 4.85. Found: C, 49.81; H, 5.32; N, 4.87.

***cis*-(−)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-(2(*R*)-1-hydroxypheneth-2-yl)-1*H*-benz[*e*]indol-2-one (9).** A solution of **3** (15.0 g, 39.03 mmol) in CH_2Cl_2 (176 mL) was cooled to −78 °C and treated with triethylsilane (13.72 mL, 85.88 mmol) *via* syringe. After 15 min, $TiCl_4$ (9.42 mL, 85.88 mmol) was added dropwise *via* syringe. The reaction was stirred for another 2 h at −78 °C and then warmed to room temperature and quenched with saturated aqueous NH_4Cl (400 mL). The organics were separated, and the aqueous layer was extracted with CH_2Cl_2 (2x). The organics were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to give 22.4 g of a crude product. This material was purified on a Waters Prep 500 using 40% ethyl acetate in hexane as the eluent to give 12.0 g (80%) of **9** as a white foam: R_f 0.15 (40% ethyl acetate in hexane); $[\alpha]^{25}_D$ −227 (*c* 1, ethanol); IR (mull) 3371, 1666, 1443, 1424, 1367, 1259, 1064, 1060, 777, 702 cm^{-1}; ^1H NMR δ 7.42−7.32 (m, 6H), 7.06−6.98 (m, 2H), 4.58−4.54 (m, 2H), 4.39−4.30 (m, 1H), 4.00−3.93 (m, 1H), 3.75−3.61 (m, 2H), 3.39 (q, J = 8.8 Hz, 1H), 2.84 (t of d, J_a = 5.4 Hz, J_b = 16.8 Hz, 1H), 2.62 (d of t, J_a = 4.6 Hz, J_b = 10.5 Hz, 1H), 2.41 (q, J = 9.3 Hz, 1H), 1.94 (m, 1H), 1.82 (m, 1H); ^{13}C NMR δ 175.2, 138.5, 137.3, 136.0, 131.2, 128.9, 128.1, 127.9, 127.86, 127.82, 127.1, 125.1, 64.4, 62.7, 58.7, 38.6, 37.1, 27.4, 24.2. Anal. Calcd for $C_{20}H_{20}N_1O_2Br_1$: C, 62.19; H, 5.22; N, 3.63. Found: C, 61.80; H, 5.17; N, 3.39. HRMS Calcd for $C_{20}H_{20}NO_2Br$: 386.0756. Found: 386.0759.

***cis*-(−)-2,3,3a,4,5,9b-Hexahydro-9-bromo-3-(1-phenylethylene)-3a-(3-propenyl)-1*H*-benz[*e*]indol-2-one (10).** A

250 mL round bottom flask equipped with a reflux condenser was charged with **9** (5.02 g, 13.0 mmol), $LiOH·H_2O$ (2.18 g, 52.0 mmol), and DMSO (100 mL). The reaction was heated to 100 °C for 72 h. The brown mixture was cooled to room temperature and poured into 1 L of H_2O. The aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL), dried over Na_2SO_4, filtered, and concentrated to a crude brown oil. The mixture was purified on a Waters Prep 500 using 20% ethyl acetate as the eluent to give 4.33 (90%) of the enamide **10** as a white foam: R_f 0.44 (40% ethyl acetate in hexane); IR (mull) 1700, 1445, 1396, 1367, 1331, 1304, 1243, 1178, 775, 698 cm^{-1}; ^1H NMR δ 7.45−7.32 (m, 6H), 7.07−6.98 (m, 2H), 5.68 (s, 1H), 5.44 (s, 1H), 4.15−4.04 (m, 1H), 3.89 (q, 1H, J = 8.4 Hz), 3.47 (q, 1H, J = 9.5 Hz), 2.86−2.77 (m, 1H), 2.62−2.53 (m, 1H), 2.46 (q, 1H, J = 8.4 Hz), 1.87−1.74 (m, 2H); ^{13}C NMR δ 173.3, 140.9, 138.7, 136.4, 135.5, 131.1, 128.6, 128.5, 127.8, 127.6, 126.2, 125.1, 113.2, 57.7, 38.4, 35.7, 26.5, 25.0; $[\alpha]^{25}_D$ −55 (*c* 1, ethanol); HRMS calcd for $C_{20}H_{18}NOBr$: 367.0572. Found: 367.0587.

***cis*-(−)-2,3,3a,4,5,9b-Hexahydro-9-bromo-1*H*-benz[*e*]-indol-2-one (11).** A solution of enamide **10** (8.88 g, 24.05 mmol) in THF (200 mL) and 1 N aqueous HCl (36.08 mL) was heated to reflux for 8 h and then cooled to room temperature and diluted with H_2O (250 mL). After concentration *in vacuo*, the residue was extracted with CH_2Cl_2 (3×), and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to a tan solid. The solid was triturated with hot hexane (4×) to give 5.88 g (92%) of **11** as an off-white solid: mp 189−190 °C; R_f 0.26 (50% acetone in hexane); IR (mull) 3159, 3083, 3055, 1700, 1647, 1437, 1328, 1303, 816, 771 cm^{-1}; ^1H NMR δ 7.45 (d, 1H, J = 7.5 Hz), 7.05 (quintet, 2H, J = 7.5 Hz), 6.18 (broad s, 1H), 4.11 (d of d, 1H, J_a = 7.1 Hz, J_b = 11.6 Hz), 3.93 (d of d, 1H, J_a = 7.6 Hz, J_b = 17.3 Hz), 3.18 (q, 1H, J = 9.8 Hz), 2.94−2.84 (m, 1H), 2.72−2.63 (m, 1H), 2.21 (d of d, 1H, J_a = 7.5 Hz, J_b = 17.4 Hz), 1.92−1.84 (m, 2H); ^{13}C NMR δ 177.5, 139.0, 136.9, 131.0, 127.7, 127.5, 125.1, 53.0, 37.7, 37.6, 27.7, 26.1; $[\alpha]^{25}_D$ −291 (*c* 1, ethanol). Anal. Calcd for $C_{12}H_{12}NOBr$: C, 54.16; H, 4.54; N, 5.26; Br, 30.02. Found: C, 53.93; H, 4.34; N, 5.17; Br, 29.64.

Preparation of Tricyclic Lactam 13. A mixture of ethyl 2-cyclopentanoneacetate (**12**) (7.00 g, 41.1 mmol) and (*R*)-(−)-2-phenylglycinol (8.46 g, 61.7 mmol) was refluxed in toluene (125 mL) in a flask fitted with a Dean−Stark trap. After 16 h, the reaction was cooled and concentrated *in vacuo* to an orange solid which was purified by chromatography of silica gel (25% ethyl acetate/hexane) to give **13** (8.31 g, 83% yield) as a light yellow solid, mp 43.5−44.0 °C: IR (mull) 1708, 1451, 1356, 1330, 1234, 1058, 1020, 972, 731, 702 cm^{-1}; ^1H NMR δ 7.38−7.24 (m, 5H), 5.16 (t, J = 7.7, 1H), 4.62 (t, J = 8.3, 1H), 3.99 (t, J = 7.6, 1H), 2.90 (dd, J = 17.3, 10.4, 1H), 2.77−2.68 (m, 1H), 2.49 (dd, J = 17.3, 6.6, 1H), 2.07−1.91 (m, 2H), 1.85−1.70 (m, 3H), 1.68−1.55 (m, 1H); ^{13}C NMR δ 180.3, 139.7, 128.7, 127.4, 125.5, 110.8, 73.4, 57.8, 41.4, 40.6, 36.6, 32.3, 24.5; $[\alpha]^{25}_D$ −168.5 (*c* 0.995, EtOH) (lit. $[\alpha]_D$ −161, c 2.0, CH_2Cl_2).[15] Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.66; H, 6.98; N, 5.67.

(1*R*,5*R*)-2-(2(*R*)-1-Hydroxypheneth-2-yl)-2-azabicyclo-[3.3.0]octane (14). A solution of **13** (4.95 g, 20.3 mmol) in anhydrous THF (50 mL) was cooled to −78 °C and treated dropwise with a 1 M solution of borane in THF (61.0 mL). Stirring was continued at −78 °C for 1 h, at which point the cooling bath was removed and the reaction was stirred for an additional 1 h. The reaction was then heated to a gentle reflux for 2 h, after which it was cooled to room temperature and stirred for 48 h. The reaction was then placed in an ice-bath and treated dropwise with 1 N HCl (61 mL; vigorous gas evolution). When the addition was complete, the reaction was heated to reflux for 1.5 h and then cooled and poured into brine (200 mL). This mixture was concentrated *in vacuo* and the resulting aqueous layer was adjusted to pH > 10 with 5 N NaOH. The aqueous base layer was extracted with dichloromethane (4×) and the combined organics layers were dried over $MgSO_4$, filtered, and concentrated to an oil. This material was purified by chromatography on silica gel (40% ethyl acetate/hexane) to give the desired amino alcohol **14** (4.24 g, 91% yield) as a clear, colorless oil: IR (liquid) 2948, 2861, 2826, 1452, 1075, 1058, 1035, 1029, 767, 703 cm^{-1}; ^1H NMR δ 7.38−7.26 (m, 3H), 7.20−7.17 (m, 2H), 3.95−3.83 (m, 2H), 3.60 (dd, J = 8.4, 3.6, 1H), 3.06 (br t, J = 7.1, 2H), 2.82 (t, J = 7.5, 1H), 2.36−2.28 (m, 1H), 2.04−1.96 (m, 1H), 1.91−1.24 (m, 8H); ^{13}C NMR δ 135.4, 129.3, 128.0, 127.6, 64.7, 64.5, 61.1, 46.8, 41.3, 33.1, 32.0, 31.6, 24.0; $[\alpha]^{25}_D$ −56.2 (*c* 1.01, EtOH); HRMS calcd for $C_{15}H_{21}NO$: 231.1623. Found: 231.1619. Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.58; H, 9.13; N, 6.08.

(1*R*, 5*R*)-2-Azabicyclo[3.3.0]octane (15). A mixture of the amino alcohol **14** (4.16 g, 18.0 mmol) and ammonium formate (5.68 g, 90.0 mmol) in methanol (300 mL) was treated with 10% palladium on carbon (2.03 g) and stirred overnight at room temperature. The reaction mixture was treated with 5 M HCl (40 mL) and filtered through a pad of Celite, washing repeatedly with methanol. The filtrate and washings were combined and concentrated *in vacuo* to a yellow solid, which was dissolved in a minimum of 1 N HCl and extracted with ether (4×). The acidic aqueous phase was cooled in an ice bath and brought to pH > 12 with solid NaOH. This basic phase was then extracted with minimum amounts of ether (3×, total ether volume = 50 mL). The organic layers were combined and the ether, was removed by atmospheric distillation. The remaining residue was transferred to a smaller flask and distillation was continued. In this manner was obtained **15** (1.55 g, 77%) as a mobile, volatile oil, bp 115−117 °C: ^1H NMR δ 3.61−3.56 (m, 1H), 2.89−2.84 (m, 1H), 2.74−2.66 (m, 1H), 2.51−2.38 (m, 1H), 1.91−1.79 (m, 1H), 1.73 (br s, 1H), 1.75−1.52 (m, 3H), 1.48−1.40 (m, 2H), 1.36−1.24 (m, 2H); $[\alpha]^{20}_D$ = + 25.3 (*c* 4.04, $CHCl_3$) [lit.[16a] value +15.1 (*c* 3.51, $CHCl_3$)].[16c] Due to its volatility, this compound was characterized as the picrate salt, mp 205−206 °C (lit.[17] mp 201−203); IR (mull) 3114, 3093, 3027, 1646, 1623, 1540, 1347, 1328, 1081, 731 cm^{-1}; ^1H NMR δ 9.13 (d, J = 2.1, 2H), 9.09 (t, J = 2.2, 1H), 4.15 (m, 1H), 4.41−3.22 (m, 2H), 2.90 (m, 1H), 2.33−2.21 (m, 1H), 2.12−1.51 (m, 7H); ^{13}C NMR 168.0, 148.1, 141.6, 129.1, 119.9, 63.4, 45.6, 42.5, 32.3, 31.1, 31.2, 25.0; $[\alpha]_D$ −2.17° (*c* 0.8770, EtOH). Anal. Calcd for $C_{14}H_{17}N_3O_6$: C, 52.01; H, 5.30; N, 13.00. Found: C, 51.82; H, 5.28; N, 13.01.

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(16) (a) Wallbaum, S.; Mehler, T.; Martens, J. *Synth. Commun.* **1994**, *24*, 1381−1387. (b) Stingl, K.; Martens, J. *Liebigs Ann. Chem.* **1994**, 479−484. (c) Martens, J.; Lubben, S. *Tetrahedron* **1991**, *47*, 1205−1214. Interestingly, these authors report a rotation for the hydrochloride salt of **15** of $[\alpha]^{20}_D$ = −3.0 (*c* 1.2, methanol) (note the change in sign). It is possible that the discrepancy between the rotation value for **15** we obtained and that report by Wallbaum et. al. is due to the presence of HCl in the $CHCl_3$ used.

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