Enantiospecific Synthesis of (*R*)-4-Amino-5-oxo-1,3,4,5-tetrahydrobenz[*cd*]indole, an Advanced Intermediate Containing the Tricyclic Core of the Ergots

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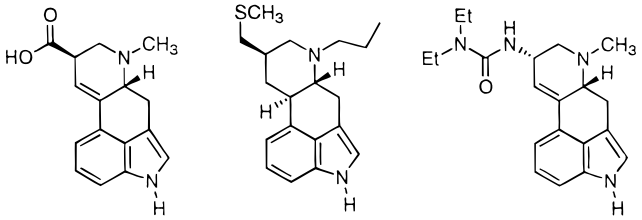
We report a new strategy for the enantiospecific synthesis of (*R*)-4-amino-5-oxo-1,3,4,5-tetrahydrobenz[*cd*]indole. This compound is an advanced intermediate which contains the tricyclic core of many of the tetracyclic ergot alkaloids. Our method involves the initial synthesis of D-4-bromotryptophan from the coupling of an indolyllithium species with a masked serinal. The α-amino position was protected with an *N*-trityl group, ensuring the enantiomeric integrity of this position during the ensuing organometallic cyclization reaction. Stabilization of the tricycle was accomplished by protecting the indole nitrogen with a BOC group or by reducing the α-amino ketone to the corresponding *β*-amino alcohol.

Introduction

Of interest due to their remarkable pharmacological properties, the ergot alkaloids[1] have often been the source for the development of new drugs.[2] Lysergic acid (**1**) (Chart 1) has been a major synthetic target since it possesses the fundamental nucleus of this class of alkaloids as do analogous derivatives, e.g., pergolide (**2**, an anti-Parkinson's drug) and lisuride (**3**, an anti-prolactin drug).

This existence of useful drugs and the potential for discovery of new ergot-based therapeutics has sustained much interest in the development of an enantiospecific synthesis of the ergot template. The majority of synthetic approaches have utilized the method first developed by Uhle to effect an intramolecular Friedel−Crafts cyclization in which the indole was masked as an indoline moiety.[3] These strategies imposed the necessity of reoxidizing the indoline to an indole at a later stage in the synthesis,[2] usually a difficult and inefficient process. Several groups attempted to avoid the problems associated with the reoxidation of an advanced indoline intermediate by maintaining the indole moiety while effecting the formation of the tricyclic system through intramolecular cyclizations employing a Diels−Alder reaction,[4] an electrophilic cyclization,[5] or a tandem radical reaction.[6] More recently, 1-pivaloylindole-3-propionic acid was used as a substrate for intramolecular Friedel−Crafts cyclization.[7] The pivaloyl group in the 1-position prevented cyclization at the 2-position and led to the formation of Uhle's ketone. In our hands, this methodology failed when applied to various tryptophan derivatives.[8]

Chart 1



1, Lysergic Acid 2, Pergolide 3, Lisuride

We now report an efficacious route to the tricyclic core of the ergot nucleus. We describe the racemic and enantiospecific syntheses of 4-amino-5-oxo-1,3,4,5-tetrahydrobenz[*cd*]indole (**C**), a key precursor for lysergic acid and some of its derivatives.[9] The formation of ketone **C** results from the intramolecular cyclization of 4-bromotryptophan **B**. In the racemic version, 4-bromogramine served as the intermediate[10] which was then converted to (±)-4-bromotryptophan. The enantiospecific pathway involved the formation of D-4-bromotryptophan from 4-bromoindole and L-serine (Figure 1). Previous methods for the asymmetric synthesis of 4-bromotryptophan have relied on either resolution of the racemic mixture[11] or an enzymatic coupling of indoles and serine.[12]

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(7) (a) Teranishi, K.; Hayashi, S.; Nakatsuka, S.; Goto, T. *Tetrahedron Lett.* **1994**, *35*, 8173. (b) Teranishi, K.; Hayashi, S.; Nakatsuka, S.; Goto, T. *Synthesis* **1994**, 506.
(8) Similar results were reported by Tani, M.; Matsumoto, S.; Aida, Y.; Arikawa, S.; Nakane, A.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull.* **1994**, *42*, 443.
(9) (a) Flaugh, M. E.; Mullen, D. L.; Fuller, R. W.; Mason, N. R. *J. Med. Chem.* **1988**, *31*, 1746. (b) Leanna, M. R.; Martinelli, M. J.; Varie, D. L.; Kress, T. J. *Tetrahedron Lett.* **1989**, *30*, 3935. (c) Martinelli, M. J.; Leanna, M. R.; Varie, D. L.; Peterson, B. C.; Kress, T. J.; Wepsiec, J. P.; Khau, V. V. *Tetrahedron Lett.* **1990**, *31*, 7579. (d) Varie, D. L. *Tetrahedron Lett.* **1990**, *31*, 7583.
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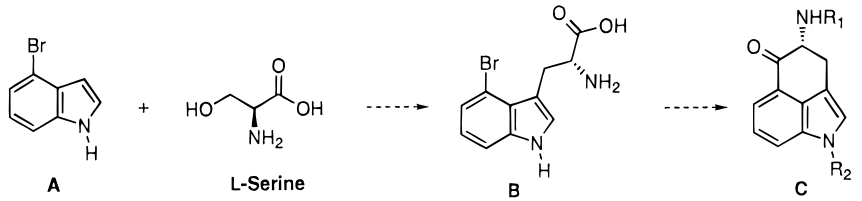
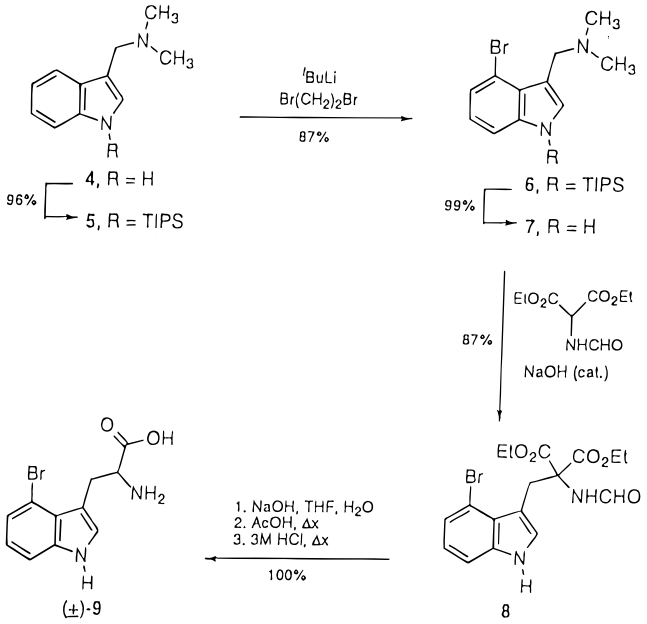


Figure 1. Proposed synthesis of protected (*R*)-4-amino-5-oxo-1,3,4, 5-tetrahydrobenz[*cd*]indole.

Scheme 1. Synthesis of (±)-4-Bromotryptophan



Results and Discussion

Synthesis of Racemic 4-Bromotryptophan. The synthesis of racemic tryptophan analogues has been discussed on a number of occasions, but rarely have the 4-halogen-substituted compounds been presented.[13] One method that showed considerable promise employed gramine to direct the substitution of electrophiles into the 4-position through an intermediate organometallic reagent.[10] This method provided a practical route to the synthesis of (±)-4-bromotryptophan (Scheme 1), with gramine as an inexpensive, readily available starting material. The indole nitrogen of gramine was protected with TIPSCl to give gramine **5** in a 96% yield. Gramine **5** then was treated with *t*-BuLi in Et_2O, leading to anion formation at the 4-position; quenching with 1,2-dibromoethane gave an 87% yield of bromogramine **6**. The silyl protecting group was then removed with a THF solution of TBAF leading to bromogramine **7** in a 99% yield. Thus our yields leading to the formation of 4-bromogramine were somewhat higher than those reported.[10]

4-Bromogramine (**7**) was treated with diethyl *N*-formamidomalonate and a catalytic amount of sodium hydroxide to give indolyl malonate **8** in an 87% yield. Through a series of deprotection reactions, (±)-4-bromotryptophan (**9**) was realized in quantitative yield. Ester hydrolysis was carried out with an aqueous NaOH/THF solution to give the corresponding carboxylate salts. Acidification and subsequent mono-decarboxylation resulted from slowly adding AcOH and heating the reaction at reflux for 24 h. The final removal of the formyl group from the α-amino nitrogen was effected by heating the suspension in aqueous 3 M HCl for 24 h. At this point the pH of the reaction mixture was slowly adjusted to 6.0 with aqueous 1 M KOH, leading to precipitation of (±)-4-bromotryptophan (**9**) in quantitative yield. The overall yield of (±)-4-bromotryptophan from gramine was 72%.

Preparation of Serinal 12. Our plan for the synthesis of enantiopure tryptophan derivatives required an indole with the potential for attachment at the 3-position of a side chain which possessed (a) a configurationally stable α-amino group and (b) a carboxylic acid surrogate at the terminus. The use of L-serine-derived reagents to introduce the required functionality appeared to be an obvious solution.[14] L-Serine would provide the three-carbon unit possessing an α-amino group, and it would be joined via its carbonyl to a 3-lithioindole derivative, thus providing D-tryptophan-configured derivatives. To ensure enantiomeric integrity at the α-amino position, the amine was protected with a 9-phenylfluorenyl group (Pf), and the reported isoxazolidide **10** was prepared.[15] The primary alcohol was then protected as its MOM ether in 96% yield to give isoxazolidide **11**. Direct reaction of **11** with the 3-lithioindole to form the ketone was unsuccessful;[16] however, serinal **12**, prepared in 96% yield by reduction of **11** with LAH, reacted readily with the 3-lithioindoles.

Synthesis of *N*-BOC-4-bromo-3-lithioindole and Reaction with Serinal 12. The synthesis of the indole portion of the tryptophan derivatives required the ability to selectively generate an anion at C-3 of the nitrogen-protected 4-bromoindole, which would react with serine aldehyde **12**. The halogenation of 4-bromoindole (**13**) appeared to offer a possible solution. Bromoindole **13** was prepared as described;[17] however, attempts to brominate **13** at C-3 with bromine under a variety of conditions failed to produce the desired 3,4-dibromoindole.[18] Alternatively, when **13** was treated with pyridinium bromide perbromide, the unstable 3,4-dibromoindole (**14**) was produced.[19] The crude material was immediately N-

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(15) Lubell, W. D.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 3824.
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(17) Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106.
(18) Bocchi, V.; Palla, G. *Synthesis* **1982**, 1096.

protected with BOC_2O, and an 80% yield of **15** over the two steps was realized.

Regioselective metal−halogen exchange at the C-3 bromide then became the hurdle. Several factors were examined in order to achieve this selective exchange. Of primary importance was the rate of addition, as almost complete kinetic control was realized by bolus addition of *n*-BuLi to the reaction mixture containing dibromoindole **15**. Formation of the 3-lithio species proceeded with greater than 95% regioselectivity.[20] When the rate of addition of the alkyllithium was decreased, a methanol quench led to a mixture of three products: *N*-BOC-indole, *N*-BOC-3-bromoindole, and *N*-BOC-4-bromoindole.

The second factor which influenced the selectivity of the halogen−metal exchange was temperature control. Significant exothermic problems with reactions of more than 1 mmol were overcome by direct addition of liquid nitrogen to the reaction mixture, along with an external dry ice−acetone bath. Under this protocol, as the bolus addition of *n*-BuLi was initiated, the internal temperature of the reaction mixture gradually rose to −82 °C, but never exceeded −78 °C. In this way, the anion was generated exclusively at the 3-position from the 3,4-dibromoindole without recourse to the 3-iodo-4-bromoindole derivative.[21] The 3-lithio anion of **15** then reacted readily with serinal **12** to give an 85% yield of a 2.5:1 mixture of diastereomeric alcohols **16**.

D-4-Bromotryptophan. With the diastereomeric mixture of alcohols in hand, two transformations remained: reduction of the β-secondary alcohol to methylene and oxidation of the primary alcohol to carboxyl. Initially, we planned to oxidize the diastereomeric alcohols to the corresponding ketone **18**, followed by reductive deoxygenation with BH_3·THF to give methylene intermediate **20**.[22] Oxidizing the mixture of alcohols **16** with chromium trioxide produced ketone **18** in an 86% yield; however, removal of the *N*-BOC group from **18** led to the unexpected loss of bromide at C-4 and formation of **19**. The N-deprotection of ketone **18** was carried out with methanolic sodium methoxide at room temperature. When an acidic medium was used, again bromide was lost along with cleavage of the MOM and BOC groups. Since deprotection of the BOC group can lead to the generation of *tert*-butyl radicals[23] which might be responsible for the loss of the bromide, free radical scavengers[24] were introduced prior to initiation of the reaction; debromination still occurred. The same conditions for deprotection of the *N*-BOC group of 1-BOC-4-bromoindole led to a 1:1 mixture of 4-bromoindole and indole; addition of free radical scavengers totally prevented debromination. We have no explanation for this dramatic difference in behavior.

Failure to convert the keto group of **18** to methylene necessitated direct reductive replacement of the secondary alcohol, with or without derivatization. In contrast to the behavior of ketone **18**, when the alcohols **16** were treated with a methanolic solution of NaOMe, the aromatic bromide was retained and the yield was nearly quantitative. With the effective deprotection of the *N*-BOC group, the original deoxygenation conditions were invoked with alcohols **17** and gave 50−60% of the desired bromoindole **20**. Speculating that deprotonation of the indole nitrogen would enhance the deoxygenation process, we added 120 mol % of DMAP to the reaction of alcohol **17** with BH_3·THF, increasing the yield of bromoindole to 91%.

Proceeding to the target tryptophan **9**, bromoindole **20** was reprotected with BOC_2O and the MOM group was removed selectively from **21** with anhydrous 1 M HCl in EtOAc to give primary alcohol **22**. Alcohol **22** was oxidized stepwise to aldehyde and then to carboxylic acid. Initial attempts to oxidize the primary alcohol directly to the carboxylic acid led to poor yields;[25] however, oxidation [26] of **22** gave aldehyde **23** in 86% yield. The carboxylic acid **24** was then realized in 69% yield by oxidation with $NaClO_2$.[27] D-(+)-4-Bromotryptophan was obtained through the deprotection of both the BOC and the phenylfluorenyl protecting groups[28] on treatment with TMSOTf/Et_3SiH in refluxing dichloroethane to give a 95% yield of D-(+)-4-bromotryptophan. This process is delineated in Scheme 2.

Cyclization to 4-Amino-5-oxo-1,3,4,5-tetrahydrobenz[*cd*]indole. Since it had already been established that protection of the indole nitrogen was not necessary for the generation of regioisomerically pure lithiated indoles by metal−halogen exchange,[17] protecting groups on the α-amino group were evaluated for their effect on yield and maintenance of enantiomeric integrity (Scheme 3). Having previously examined a variety of N-protecting groups at the α-amino position for the intramolecular cyclization reaction,[29] we found the trityl group to be the most effective, as it not only aided in maintaining the solubility of the trianion which was formed but it also provided total protection of the stereocenter.

To attach the trityl group, (+)-4-bromotryptophan ((+)-**9**) was treated with excess TrBr in the presence of triethylamine to give the bis-*O*,*N*-trityl derivative **25**. Selective cleavage of the *O*-trityl ester to *N*-trityl acid **26** was achieved in 80% yield by simply heating at 50 °C in THF/MeOH/H_2O. Alternatively, (+)-**9** was esterified with TMSCl and MeOH to provide a 96% yield of the methyl ester **27** as its hydrochloride,[30] which then was treated with TrCl and *N*-methylmorpholine to give a 96% yield of the *N*-trityl α-amino-protected methyl ester **28**. Hydrolysis of the methyl ester with LiOH·H_2O in dioxane and water required refluxing and gave acid **26** after 96 h in quantitative yield. Both methods were employed for preparing (*R*)-4-bromo-α-*N*-trityltryptophan (**26**) since it was our key intermediate and total enantiomeric integrity was required. Although the α-*N*-trityl group should be sufficient to avoid epimerization during ester hydroly-

(19) Brennan, M. R.; Erickson, K. L.; Szmalc, F. S.; Tansey, M. J.; Thornton, J. M. *Heterocycles* **1986**, *24*, 2879.

(20) The alkyllithium was added via cannula with a rapid stream of nitrogen over a period of 5−30 s.

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(23) (a) Perkins, M. J.; Roberts, B. P. *J. Chem. Soc, Chem. Commun.* **1973**, 173. (b) Evans, C. A. *Aldrichimica Acta* **1979**, *12*, 23.

(24) The free radical scavengers employed were *N*-nitrosobenzene and *N*-*tert*-butyl-α-phenylnitrone purchased from Aldrich.

(25) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

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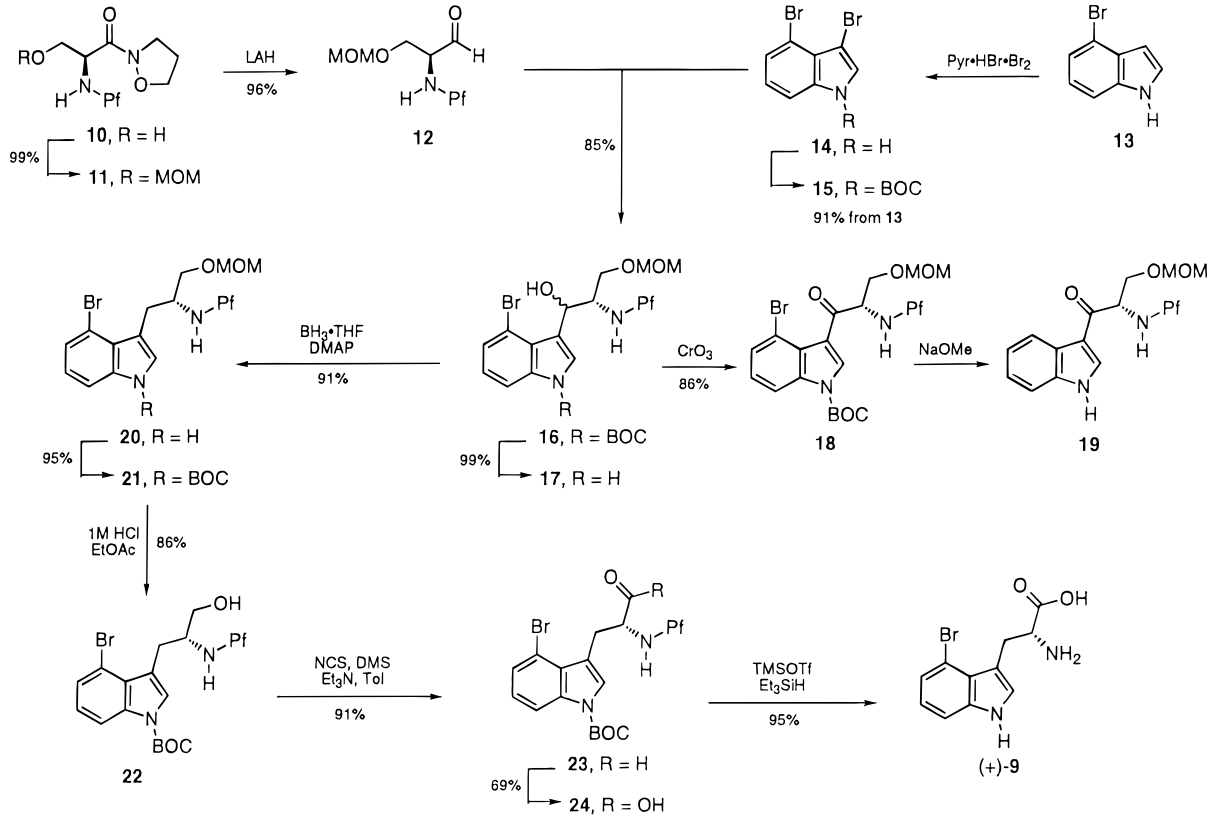
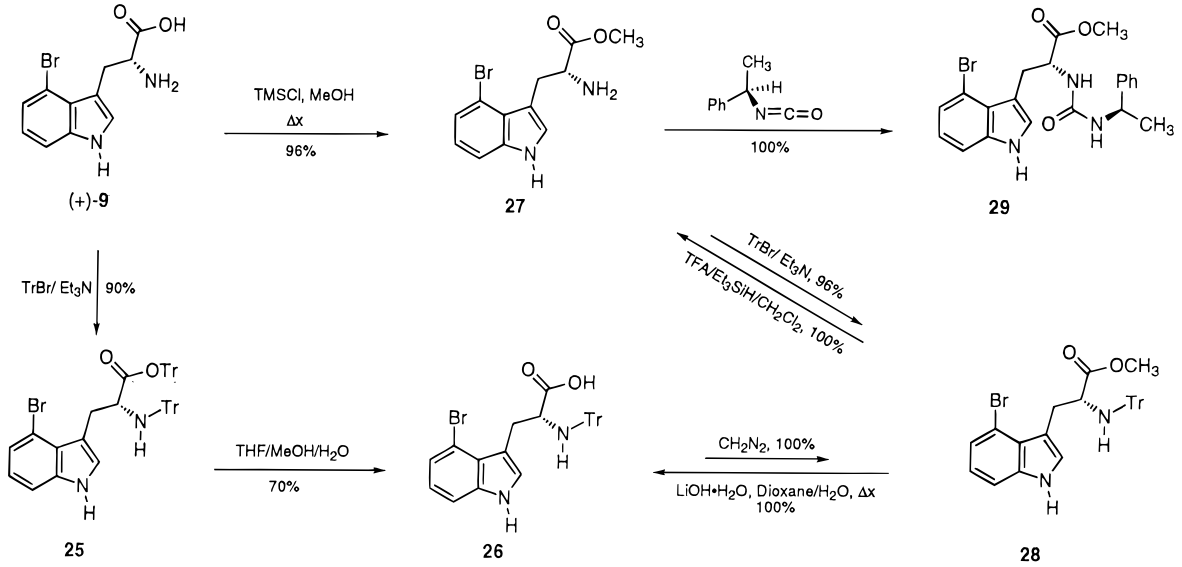
(29) The protecting groups employed were Pf, BOC, acetyl, and Bs. Low yields were obtained with the acetyl, BOC and Bs ranging from 15 to 50%. The Pf-protected system did not cyclize. Initial reactions with the *N*-acetyl compound were performed by R. Häner, this laboratory.

(30) Brook, M. A.; Chan, T. H. *Synthesis* **1983**, 201.

Scheme 2. Synthesis of D-(+)-4-Bromotryptophan



Scheme 3. Synthesis and Analysis of D-(+)-4-Bromotryptophan Derivatives[a]

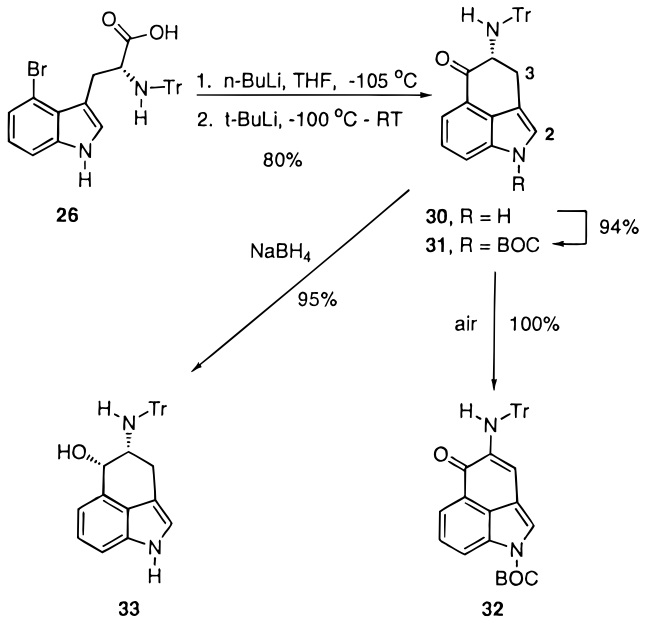


[a] Both racemic and *R* compounds were prepared; only the *R* forms are shown.

sis,[28] the drastic conditions required for the generation of acid **26** from ester **28** led us to develop the alternative path, (+)-**9** → **25** → **26**. The enantiomeric purity of each of the intermediates was examined by derivatization of common intermediate **27** with (*R*)-(+)-α-methylbenzylisocyanate to form **29** as a diastereomeric mixture, separable on HPLC analysis. For example, compound **26** was first transformed to **28** quantitatively by reaction with CH_2N_2 and then to **27**, also quantitatively, by selective deprotection with TFA. The enantiomeric purity of **26** obtained by the second approach was found to range from 97 to 99% er, while that obtained by the first approach was found to be 99% er on the basis of HPLC analysis of derivatives **29**. These results were consistent with independent chiral HPLC analysis of compound **28**.

Initially, bromotryptophan **26** was deprotonated at −78 °C with approximately 250 mol % of *n*-BuLi to remove the three acidic protons. With the trityl group on the α-amino group, the reaction remained homogeneous. Addition of 250 mol % of *t*-BuLi at −78 °C initiated the metal−halogen exchange for formation of the 4-lithio species, which in turn led to the cyclization to ketone **30**. The reaction was allowed to warm slowly to room temperature before it was quenched to give ketone **30** in

Scheme 4. Synthesis of Tricyclic α-Amino Ketone[a]



[a] Both (±) and (+) compounds were prepared; only the (+) form is shown.

60−65% yield. To avoid any deprotonation at the benzylic position, the reaction temperature was lowered to −100 °C.[31] Thus, by deprotonating, followed by the metal−halogen exchange of bromotryptophan **26** at −105 °C, the yield of ketone **30** was increased to 80% (Scheme 4).

The desamino tricyclic ketone (Uhle's ketone) related to **30** has been shown to be unstable.[32] We found α-amino ketone **30** to be very susceptible to air oxidation; it is better stored as its relatively stable BOC derivative **31** (prepared in 94% yield). The enantiomeric ratio of **31** was found to be 99.5/0.5 by chiral HPLC analysis, established by comparison with the corresponding racemic material. Exposure of BOC ketone **31** to air slowly transformed it in 100% yield to the corresponding α-amino α,*β*-unsaturated ketone **32** with a half-life ($t_{1/2}$) of 14 days based on ^{1}H NMR analysis in $CDCl_3$. The completely deprotected racemic amino ketone corresponding to **30** has been reported to be unstable.[33] Thus, the tricyclic α-amino ketone **30** should be used directly after preparation; it was converted to the corresponding *β*-amino alcohol **33**, prepared by reducing the α-amino ketone **30** stereospecifically with $NaBH_4$. The cis configuration of the *β*-amino alcohol **33** was assigned on the basis of the assumption that the α-*N*-trityl group would direct nucleophilic attack from the opposite side and was supported by the observed small coupling constant on the two adjacent protons. The various forms **30**, **31**, and **33** of the tricyclic ketone afford attractive and versatile intermediates, from which the synthesis of a variety of ergot derivatives can be envisaged.

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(32) (a) Grob, C. A.; Voltz, J. *Helv. Chim. Acta* **1950**, *33*, 1796. (b) Grob, C. A.; Hofer, B. *Helv. Chim. Acta* **1952**, *35*, 2095. (c) Grob, C. A.; Payot, P. *Helv. Chim. Acta* **1953**, *36*, 839. (d) Grob, C. A.; Hofer, B. *Helv. Chim. Acta* **1953**, *36*, 847.

(33) Stoll, A.; Rutschmann, J.; Petrzilka, T. *Helv. Chim. Acta* **1950**, *33*, 2257.

Conclusion

We have developed a direct and efficient strategy for the enantiospecific snthesis of (*R*)-4-amino-5-oxo-1,3,4,5-tetrahydrobenz[*cd*]indole, the tricyclic core of the ergot alkaloids. This route relies upon the ability to perform an intramolecular cyclization reaction via metal−halogen exchange with the substrate D-4-bromotryptophan, which was synthesized in an enantiospecific fashion from L-serine. We have also established the racemic syntheses of both 4-bromotryptophan and the corresponding tricyclic ketone. These new routes allow for the enantiospecific syntheses of ergot derivatives and avoid the previously commonly employed intermediacy of indolines and their subsequent reoxidation to indoles.

Experimental Section

General. Glassware was flame dried before use and cooled to room temperature under a nitrogen atmosphere. THF and Et_2O were distilled from sodium/benzophenone; CH_3CN, DIEA, TEA, CH_2Cl_2, 1,2-DCE, toluene, and TMSCl were distilled from CaH_2; MeOH was distilled from Mg; *N*-methylmorpholine (NMM) and 1,2-dibromoethane were distilled prior to use. Final solutions before evaporation were dried over $MgSO_4$, and chromatography was carried out using (a) 70−230 or (b) 230−400 mesh silica gel. IR spectra were taken in $CHCl_3$, and NMR spectra were taken in $CDCl_3$, unless otherwise noted. ^{1}H coupling constants, *J*, are reported in hertz.

4-Bromogramine (7). Bromogramine **6** (3.5 g, 8.55 mmol)[10] was dissolved in THF (75 mL) and stirred under nitrogen as a solution of TBAF (9.00, 1.0 M in THF, 9.00 mmol) was added dropwise over 5 min. The reaction was stirred at room temperature for 4 h before it was poured into ice water (100 mL) and extracted with EtOAc (3 × 100 mL) and dried. The organic layer was filtered and evaporated to give the crude product (2.12 g, 99%) which was used directly in the next reaction.

α-*N*-Formyl-α-(ethoxycarbonyl)-4-bromotryptophan (8). 4-Bromogramine (**7**, 16.8 g, 66.4 mmol) was suspended in toluene (300 mL) followed by addition of a catalytic amount of NaOH (300 mg, 7.5 mmol) while stirring under nitrogen. To this mixture was added diethyl formamidomalonate (15.5 g, 76.3 mmol), and the reaction mixture was heated at reflux for 24 h and then cooled to room temperature and dissolved in EtOAc (500 mL). The organic layer was washed with 1 M H_3PO_4 (3 × 300 mL) and brine (2 × 300 mL), dried, filtered, and evaporated. The residue was titurated in hot MeOH (150 mL), allowed to cool to room temperature, filtered, and dried under vacuum to give 25.1 g (92% yield) of **8** as a beige solid: mp 204−205 °C; ^{1}H NMR (DMSO-d_6) δ 1.08 (t, J = 7.1, 6H), 3.98 (s, 2H), 4.04−4.14 (m, 4H), 6.94 (t, J = 7.76, 7.9, 1H), 7.15 (d, J = 7.6, 1H), 7.19 (s, 1H), 7.37 (d, J = 1.33, 1H), 8.04 (s, 1H), 8.8 (s, 1H), 11.4 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 13.6, 27.8, 61.7, 66.1, 107.5, 111.3, 112.8, 121.9, 123.3, 124.8, 126.0, 137.2, 160.7, 167.1. Anal. Calcd for $C_{17}H_{19}BrN_2O_5$: C, 49.7; H, 4.7; N, 6.8. Found: C, 49.8; H, 4.6; N, 6.9.

(±)-4-Bromotryptophan [(±)-9]. To indolylmalonate **8** (3.00 g, 7.27 mmol) in THF (18 mL) was added a solution of NaOH (1.02 g, 25.5 mmol) in water (30 mL), and the mixture was stirred at room temperature for 24 h. Acetic acid (6 mL) was added dropwise over 5 min, the resulting mixture was heated at reflux for 24 h and then cooled to room temperature, and the organic phase was evaporated. To the remaining aqueous layer was added 3 M HCl (30 mL), and the reaction mixture was refluxed for 24 h and then cooled to room temperature, whereupon a white precipitate formed. The suspension was placed in an ice bath, and the pH was adjusted to 6.0 with 2 M KOH. The white solid formed was filtered off, washed with water, and then dried overnight under vacuum to give 2.05 g (99% yield) of (±)-**9** as a beige solid: mp 287−289 °C; ^{1}H NMR (DMSO-d_6) δ 3.18−3.24 (dd, J = 9.65, 5.13, 1H), 3.65−3.7 (dd, J = 9.65, 5.13, 1H), 3.65−3.7 (dd, J = 5.41,

9.36, 1H), 4.13 (br, 1H), 7.00 (d, J = 7.83, 1H), 7.2 (d, J = 7.48, 1H), 7.35 (d, J = 2.33, 1H), 7.42 (d, J = 8.06, 1H), 8.34 (s, 1H), 11.5 (d, J = 2.04, 1H); ^{13}C NMR (DMSO-d_6) δ 27.3, 53.9, 107.6, 111.7, 112.7, 122.5, 122.9, 124.8, 127.7, 138.2, 170.8. Anal. Calcd for $C_{11}H_{11}BrN_2O_2$: C, 46.7; H, 3.9; N, 9.9. Found: C, 46.5; H, 4.1; N, 9.6.

3-*O*-(Methoxymethyl)-2-*N*-(9-phenyl-9-fluorenyl)amino-L-serine Isoxazolidide (11). The isoxazolidide 10 (8.5 g, 21.3 mmol)[15] was dissolved in CH_2Cl_2 (250 mL) and stirred under nitrogen as DIEA (23.0 mL, 145 mmol) was added dropwise. The resulting solution was stirred for 5 min, MOMCl (6.82 mL, 89.5 mmol) was added dropwise over 5 min, and the reaction was stirred at room temperature for another 20 h. The reaction mixture was washed with 1 M H_3PO_4 (3 × 200 mL), and the combined aqueous layers were washed with CH_2Cl_2 (2 × 200 mL). The organic layers were combined and washed with saturated NaCl (2 × 300 mL), dried, filtered, and evaporated. Chromatography (EtOAc) of the residue gave 9.37 g (99% yield) as a light yellow oil: $[\alpha]^{24}_D$ −189° (*c* 2.15, $CHCl_3$); ^{1}H NMR δ 1.75−2.10 (m, 2H), 2.50−2.70 (m, 1H), 3.10−3.40 (m, 2H), 3.28 (s, 3H), 3.52−3.60 (m, 5H), 4.52 (s, 2H), 7.17−7.45 (m, 11H), 7.66 (t, J = 7.16, 2H); ^{13}C NMR δ 26.7, 42.8, 52.5, 55.0, 68.1, 70.4, 73.0, 96.1, 119.4, 119.6, 125.4, 126.0, 127.0, 127.9, 128.1, 128.2, 139.5, 141.3, 149.3, 149.7, 173.5. Anal. Calcd for $C_{27}H_{28}N_2O_4$: C, 73.0; H, 6.4; N, 6.3. Found: C, 72.9; H, 6.5; N, 6.5.

3-*O*-(Methoxymethyl)-2-*N*-(9-phenyl-9-fluorenyl)amino-L-serinal (12). To isoxazolidide **11** (3.00 g, 6.78 mmol) dissolved in THF (100 mL) and cooled to 0 °C with stirring under nitrogen was added dropwise a solution of LAH (300 mg, 7.9 mmol) dissolved in THF (40 mL) over 15 min at 0 °C. This mixture was stirred for an additional 30 min at 0 °C, then poured over ice cold saturated $KHSO_4$ (100 mL) and ice (50 g), and extracted with Et_2O (3 × 100 mL). The combined organic layer was washed successively with ice cold $KHSO_4$ (2 × 200 mL), saturated $NaHCO_3$ (2 × 200 mL), H_2O (200 mL), and brine (250 mL), then dried, filtered, and evaporated. Chromatography (EtOAc) of the residue gave 2.42 g (96% yield) of aldehyde **12** as a yellow oil: $[\alpha]^{24}_D$ −32.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 2.72 (dt, J = 4.5, 0.7, 1H), 3.24 (s, 3H), 3.23−3.50 (m, 2H), 3.59 (dd, J = 10.0, 4.5, 1H), 4.4 (s, 2H), 7.20−7.69 (m, 13H), 9.4 (d, J = 0.7, 1H); ^{13}C NMR δ 55.2, 61.8, 67.5, 72.8, 96.3, 119.9, 120.0, 125.2, 125.3, 126.1, 127.3, 127.9, 128.0, 128.3, 128.5, 128.7, 140.4, 140.6, 144.3, 148.9, 149.3, 202.6. Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.2; H, 6.2; N, 3.8. Found: C, 76.9; H, 6.5; N, 3.8.

***N*-BOC-3,4-dibromoindole (15).** 4-Bromoindole (**13**, 23.5 g, 120 mmol)[17] was dissolved in pyridine (470 mL) and cooled to 0 °C as it was stirred under nitrogen. After 10 min, a solution of pyridinium bromide perbromide (45.4 g, 127 mmol, 90% techical grade) in pyridine (235 mL) was added dropwise over 15 min. Upon completion of the addition, ice water (600 mL) was added and the reaction mixture was extracted with Et_2O (3 × 800 mL). The organic layer was washed with 3 M phosphoric acid (3 × 800 mL), followed by saturated $NaHCO_3$ (3 × 800 mL) and brine (2 × 800 mL). The organic layer was dried, filtered, and evaporated to give **14** as a dark oil (31.0 g). Dibromide **14** is unstable, especially on warming, and should be used directly after isolation: ^{1}H NMR δ 7.02 (t, J = 7.88, 1H), 7.24 (d, J = 2.74, 1H), 7.31 (dd, 2H), 8.32 (br, 1H); ^{13}C NMR δ90.7, 111.1, 113.8, 123.2, 123.7, 125.5, 125.6, 136.2.

The above freshly prepared **14** was immediately dissolved in THF (590 mL), and the resulting solution was stirred under nitrogen. Triethylamine (4.00 mL), DMAP (2.94 g, 24.4 mmol), and $(BOC)_2O$ (34.7 g, 159 mmol) were added successively, and the reaction mixture was stirred under nitrogen for 14 h. Evaporation under reduced pressure was followed by resolution of the residue in Et_2O (1200 mL) which was washed with saturated NH_4Cl (2 × 800 mL) followed by saturated $NaHCO_3$ (3 × 800 mL) and brine (2 × 800 mL). The organic layer was dried, filtered, and evaporated. Chromatography (5% EtOAc/hexanes) of the oily residue led to 40.8 g (91% yield from **13**) of **15** as a white solid: mp 80 °C; ^{1}H NMR δ 1.66 (s, 9H), 7.16 (t, J = 8.18, 1H), 7.43 (d, J = 7.76, 1H), 7.69 (s, 1H), 8.22 (d, J = 8.36, 1H); ^{13}C NMR 100 MHz) δ 28.1, 84.9, 114.0, 114.6, 125.4, 125.9, 127.2, 135.8, 148.2; IR ($CDCl_3$) 3050, 2980, 1735, 1460, 1412 cm^{-1}. Anal. Calcd for $C_{13}H_{13}Br_2NO_2$: C, 41.6; H, 3.5; N, 3.7. Found: C, 41.7; H, 3.4; N, 3.7.

4-Bromo-1-(*tert*-butyloxycarbonyl)-3-[1(*RS*)-hydroxy-2(*R*)-((9-phenyl-9-fluorenyl)amino)-3-(methoxymethoxy)-propyl]indole (16). Dibromoindole **15** (1.7 g, 4.0 mmol) was dissolved in 50 mL of THF, and the solution was cooled to −78 °C. Liquid nitrogen was introduced directly into the reaction mixture over a period of 2−5 min, reducing the internal temperature to −95 °C. When the reaction mixture had become homogeneous, *n*-BuLi (2.04 mL, 4.4 mmol), precooled to −78 °C in 5 mL of THF, was added over a 2−5 min interval. The internal temperature of the reaction immediately rose to −78 °C, and after 90 min at this temperature, a solution of aldehyde (**12**, 1.5 g, 4.0 mmol) in 5 mL of THF, precooled to −78 °C, was added via cannula. After 4 h at −75 °C, the reaction was poured into saturated NH_4Cl (50 mL) and extracted with Et_2O (3 × 75 mL). The combined organic layer was washed with brine (100 mL), dried, filtered, and evaporated to give an oil. Chromatography (4:1, hexanes/EtOAc) led to 2.19 g (82%, diastereomer ratio, 2.5:1) in several fractions. First diastereomer **16a**: 1.56 g; mp 102−103 °C; $[\alpha]^{25}_D$ +111° (*c* 1.02, $CHCl_3$); ^{1}H NMR δ 1.62 (2, 9H), 2.92 (dd, J = 3.98, 5.82, 1H), 3.23 (s, 3H), 3.37−3.30 (m, 2H), 4.42 (dd, J = 6.46, 27.1, 2H), 4.66 (br, 1H), 4.81 (d, J = 4.56, 1H), 6.99 (t, J = 8.15, 1H), 7.67−7.14 (m, 15H), 7.73 (d, J = 7.46, 1H), 8.11 (d, J = 8.11, 1H); ^{13}C NMR δ 28.1, 55.4, 55.5, 66.4, 66.7, 72.7, 83.9, 96.5, 113.7, 114.2, 119.9, 120.8, 124.7, 124.9, 125.2, 125.6, 125.8, 126.7, 127.2, 127.6, 127.7, 128.1, 128.4, 128.6, 137.1, 139.9, 141.6, 145.4, 149.1, 149.5; IR ($CDCl_3$): 3400, 3100, 2940, 1725, 1465, 1440, 1360 cm^{-1}. Anal. Calcd for $C_{37}H_{37}BrN_2O_5$: C, 66.4, H, 5.6, N, 4.2. Found: C, 66.6; H, 5.8; N, 4.1. Second diastereomer **16b**: 630 mg; $[\alpha]^{25}_D$ +151° (*c* 1.02, $CHCl_3$); mp 101−103 °C; ^{1}H NMR δ 1.68 (s, 9H), 2.8−2.75 (m, 2H), 3.31 (s, 3H), 4.43 (AB, J = 6.3, 57.6, 2H), 4.72 (s, 1H), 5.59 (d, J = 2.97, 1H), 6.37 (d, J = 7.53, 1H), 6.48 (t, J = 7.48, 1H), 7.50−6.98 (m, 12H), 7.66−7.55 (m, 2H), 8.21 (d, J = 7.87, 1H); ^{13}C NMR δ 28.1, 55.5, 69.4, 69.7, 72.0, 83.9, 96.6, 113.2, 114.3, 119.3, 119.9, 121.8. 124.1, 124.7, 125.0, 125.8, 126.1, 127.0, 127.1, 127.3, 127.4, 127.5, 127.7, 128.1, 128.3, 137.2, 139.7, 140.4, 145.0, 148.1, 149.0, 150.9.

4-Bromo-3-[1(*RS*)-hydroxy-2(*R*)-((9-phenyl-9-fluorenyl)amino)-3-(methoxymethoxy)propyl]indole (17). To alcohol **16** (500 mg, 0.77 mmol) dissolved in THF (20 mL) and stirred under nitrogen at room temperature was added a solution of NaOMe (generated from Na, 88 mg, 3.85 mmol, in MeOH, 3 mL) via cannula. The reaction was stirred for 1 h at room temperature, after which saturated NH_4Cl (5 mL) and brine (5 mL) were added, the mixture was extracted with Et_2O (2 × 25 mL), and the organic layer was washed with brine (50 mL), dried, filtered, and evaporated. Chromatography (50% EtOAc/hexanes) of the residue led to 430 mg (99% yield) of a mixture of isomers. Diastereomer **17a**: 307 mg; mp 102−103 °C; $[\alpha]^{25}_D$ +101° (*c* 1.02, $CHCl_3$); ^{1}H NMR δ 2.89 (dd, J = 4.18, 5.62, 1H), 3.23 (m, 3H), 3.41−3.29 (m, 2H), 4.41 (q, J = 6.45, 18.7, 2H), 4.66 (br, 1H), 4.86 (d, J = 3.58, 1H), 6.85 (t, J = 7.87, 1H), 7.01 (dd, J = 0.82, 6.79, 1H), 7.47−7.14 (m, 13H),7.67 (d, J = 7.54, 1H), 7.74 (d, J = 7.55, 1H), 8.38 (s, 1H); ^{13}C NMR δ 55.4, 56.0, 60.4, 66.7, 72.8, 96.5, 110.2, 113.8, 116.2, 119.8, 120.0, 122.3, 123.4, 123.5, 124.7, 125.2, 125.6, 125.8, 127.2, 127.6, 128.1, 128.4, 128.5, 128.6, 137.5, 140.0, 141.7, 145.7, 149.3, 149.4. Anal. Calcd for $C_{32}H_{29}BrN_2O_3$: C, 67.5; H, 5.1; N, 4.9. Found: C, 66.9; H, 5.5; N, 4.5. Diastereomer **17b**: 123 mg; mp 101−103 °C; $[\alpha]^{25}_D$ +167.5° (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 2.65 (dd, J = 3.44, 6.35, 1H), 2.74 (br, 1H), 3.07 (br, 1H), 3.17 (d, J = 9.6, 1H), 3.25 (s, 3H), 4.31 (br, 1H), 4.40 (AB, J = 6.45, 47.1, 2H), 5.63 (d, J = 5.33, 1H), 6.47 (d, J = 7.43, 1H), 6.57 (t, J = 7.52, 1H), 6.89 (t, J = 7.91, 1H), 6.95 (d, J = 2.11, 1H), 7.44−7.07 (m, 10H), 7.56 (d, J = 7.55, 1H), 7.65 (d, J = 7.94, 1H), 8.53 (s, 1H); ^{13}C NMR δ 55.5, 56.9, 68.6, 72.3, 96.7, 110.4, 113.5, 117.5, 119.4, 119.9, 122.4, 124.1, 124.2, 125.0, 125.1, 125.2, 126.1, 127.1, 127.5, 127.6, 127.9, 128.2, 128.3, 137.6, 140.1, 140.4, 145.1, 148.4, 151.0.

4-Bromo-1-(*tert*-butyloxycarbonyl)-3-[1-oxo-2(*R*)-((9-phenyl-9-fluorenyl)amino)-3-(methoxymethoxy)propyl]-indole (18). To a solution of CrO_3 (1.5 g) in H_2O (1.5 mL), cooled to 5 °C, was added pyridine (10 mL) over 20 min to give an orange solution. Alcohol **16** (500 mg, 0.75 mmol) was dissolved in pyridine (10 mL), the cold bath was removed from the CrO_3 solution, and the alcohol solution was added dropwise. The mixture was stirred for 96 h at room temperature and then cooled to 0 °C, and 2 M H_3PO_4 (20 mL) was added. The mixture was washed with EtOAc (3 × 30 mL), and the combined organic layer was then washed with brine (2 × 100 mL), dried, filtered, and evaporated to give an oil. Chromatography (hexanes/EtOAc, 2:1) led to 430 mg (86% yield) of a yellow oil that solidified: $[\alpha]^{23}_D$ −77.8 (*c* 1.02, $CHCl_3$); mp 74−76 °C; ^{1}H NMR δ 1.71 (s, 9H), 3.18 (s, 3H), 3.38 (t, J = 5.52, 1H), 3.52 (d, J = 5.7, 2H), 3.87 (br, 1H), 4.43 (q, J = 6.42, 5.28, 2H), 6.84 (s, 1H), 6.97 (t, J = 7.5, 1H), 7.5−7.1 (m, 13H), 7.72 (d, J = 7.41, 1H), 8.11 (d, J = 8.4, 1H); ^{13}C NMR δ 28.0, 55.2, 61.1, 70.5, 73.1, 85.2, 96.5, 114.1, 114.5, 119.4, 119.7, 121.1, 125.7, 126.0, 126.3, 126.6, 127.1, 127.7, 128.0, 128.1, 128.2, 128.4, 129.0, 130.3, 136.8, 139.7, 140.9, 144.2, 148.1, 149.2, 149.7, 198.1; IR ($CDCl_3$) 3300, 2920, 1740, 1680, 1560, 1460, 1415, 1255 cm^{-1}. Anal. Calcd for $C_{37}H_{35}BrN_2O_5$: C, 66.6; H, 5.3; N, 4.2. Found: C, 66.5; H, 5.3; N, 4.1.

3-[1-Oxo-2(*R*)-((9-phenyl-9-fluorenyl)amino)-3-(methoxymethoxy)propyl]indole (19). Ketone **18** (350 mg, 0.527 mmol) was dissolved in THF (10 mL) and stirred under nitrogen as a solution of $NaOCH_3$ (generated from Na, 37 mg, 1.6 mmol, in 5 mL of CH_3OH) was added via cannula. The reaction was stirred at room temperature for 2 h before it was diluted with EtOAc (25 mL) and hydrolyzed with 1 M H_3PO_4 (20 mL). The aqueous layer was washed with EtOAc (2 × 30 mL), and the combined organic layer was washed with brine (75 mL), dried, and filtered. The solvent was evaporated to give a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.12 (s, 3H), 3.35−3.6 (m, 3H), 4.4 (d, J = 2.0, 2H), 6.52 (d, J = 3.0, 1H), 6.8 (t, J = 7.5, 1H)6.9 (t, J = 7.8, 1H), 7.0−7.7 (m, 14H), 8.3 (m, 2H), 9.4 (s, 1H).

4-Bromo-3-[2(*R*)-((9-phenyl-9-fluorenyl)amino)-3-(methoxymethoxy)propyl]indole (20). Alcohol **17** (2.5 g, 4.4 mmol) and DMAP (670 mg, 5.5 mmol) were dissolved in THF (90 mL), and the resulting solution was stirred under nitrogen and cooled to 0 °C. To this mixture was added a solution of BH_3·THF (22.0 mL, 22.0 mmol, 1 M) dropwise over 1 h after which the reaction was stirred at 0 °C for 72 h. Ten milliliters of H_2O/AcOH (1:1) were slowly added to the reaction mixture at 0 °C, and it was then allowed to warm to room temperature and heated at reflux for 2 min. The mixture was poured into ice water (100 mL) and extracted with Et_2O (3 × 75 mL). The combined organic layer was washed with saturated $NaHCO_3$ (4 × 150 mL) and brine (2 × 100 mL), dried, filtered, and evaporated to a residue which was chromatographed (50% EtOAc/hexanes) to give 2.20 (91% yield) of **20** as a white solid: mp 69−72 °C; $[\alpha]^{25}_D$ +98 °C (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 2.91−2.72 (m, 3H), 3.11−3.07 (m, 2H), 3.27 (s, 3H), 4.40 (q, J = 6.33, 1.89, 2H), 6.56 (q, J = 6.51, 0.98, 1H), 7.39−6.92 (m, 13H), 7.58 (d, J = 7.49, 1H), 7.65 (d, J = 7.44, 1H), 8.07 (s, 1H); ^{13}C NMR δ 14.1, 30.9, 53.7, 55.3, 70.4, 72.8, 96.6, 110.3, 114.5, 114.6, 119.4, 119.9, 122.6, 123.9, 124.9, 125.0, 125.5, 126.0, 126.2, 126.9, 127.4, 127.7, 128.0, 128.1, 137.6, 140.2, 140.5, 145.9, 149.6, 150.9. Anal. Calcd for $C_{32}H_{29}BrN_2O_2$: C, 69.4; H, 5.3; N, 5.1. Found: C, 69.8; H, 5.5; N, 4.9.

4-Bromo-1-(*tert*-butyloxycarbonyl)-3-[2(*R*)-((9-phenyl-9-fluorenyl)amino)-3-(methoxymethoxy)propyl]indole (21). To a solution of bromoindole **20** (900 mg, 1.62 mmol) in THF (20 mL) stirred under nitrogen were added DMAP (470 mg, 0.54 mmol), Et_3N (4.0 mL, 28.7 mmol), and $(BOC)_2O$ (600 mg, 2.89 mmol) successively, and the reaction was stirred for 4 h at room temperature. The solvent was evaporated, and the residue was dissolved in Et_2O (100 mL) which was washed with saturated NH_4Cl (2 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL), and brine (75 mL). Drying, filtering, and evaporating left a residue which was chromatographed (20% EtOAc/hexanes), giving 1.02 g (95% yield) of **21** as a white solid: $[\alpha]^{23}_D$ +144.7° (*c* 1.03, $CHCl_3$); mp 62−64 °C; ^{1}H NMR δ 1.69 (s, 9H), 2.87−2.69 (m, 3H), 3.02−2.89 (m, 2H), 3.15−3.06 (m, 1H), 3.29 (s, 3H), 4.42 (q, J = 6.36, 21.2, 2H), 6.51 (d, J = 7.51, 1H), 6.66 (t, J = 6.76, 1H), 7.43−7.04 (m, 12H), 7.58 (d, J = 7.54, 1H), 7.67 (d, J = 6.85, 1H), 8.18 (d, J = 8.2, 1H); ^{13}C NMR δ 28.2, 31.0, 53.2, 55.2, 70.2, 72.6, 83.8, 96.6, 114.2, 114.3, 118.6, 119.4, 119.9, 124.7, 124.9, 125.3, 126.1, 126.4, 126.9, 127.0, 127.4, 127.5, 127.7, 128.0, 128.2, 128.9, 136.9, 139.9, 140.7, 145.7, 149.1, 149.5, 150.9. Anal. Calcd for $C_{37}H_{37}BrN_2O_4$: C, 68.0; H, 5.7; N, 4.3. Found: C, 67.7; H, 5.8; N, 4.4.

4-Bromo-1-(*tert*-butyloxycarbonyl)-3-[2(*R*)-((9-phenyl-9-fluorenyl)amino)-3-hydroxypropyl]indole (22). Bromoindole **21** (5.0 g, 7.65 mmol) was dissolved in 1 M HCl in EtOAc (200 mL) precooled to 0 °C, and the solution was stirred under nitrogen. The reaction mixture was allowed to warm to room temperature over 1 h, stirred for 4 h, and poured into ice and saturated $NaHCO_3$ (150 mL). The EtOAc layer was separated, and the aqueous phase was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL), dried, filtered, and evaporated. Chromatography (33% EtOAc/hexanes) of the residue led to 4.00 g (86% yield) of **22** as a white foam: $[\alpha]^{23}_D$ −14.9° (*c* 1.00, $CHCl_3$); ^{1}H NMR δ 1.66 (s, 9H), 2.75 (m, 3H), 2.92 (d, J = 7.15, 2H), 3.03 (d, J = 9.13, 1H), 6.34 (d, J = 7.52, 1H), 6.63 (dt, J = 1.1, 6.46, 1H), 7.37−7.02 (m, 12H), 7.73−7.59 (m, 2H), 8.15 (d, J = 8.25, 1H); ^{13}C NMR δ 28.1, 55.0, 62.8, 72.8, 84.2, 114.2, 114.3, 117.2, 119.7, 120.1, 124.6, 125.1, 125.4, 125.9, 126.5, 127.1, 127.4, 127.7, 128.1, 128.4, 128.8, 137.1, 140.1, 140.7, 143.7, 148.2, 148.9. Anal. Calcd for $C_{35}H_{33}N_2BrO_3$: C, 69.0; H, 5.5; N, 4.6. Found: C, 68.5; H, 5.9; N, 4.2.

4-Bromo-1-(*tert*-butyloxycarbonyl)-3-[2(*R*)-((9-phenyl-9-fluorenyl)amino)-3-oxopropyl]indole (23). A solution of NCS (300 mg, 2.24 mmol) in toluene (10 mL) was cooled to 0 °C and stirred under nitrogen as DMS (0.2 mL, 2.72 mmol) was added dropwise. The mixture was stirred for another 30 min at 0 °C and then cooled to −25 °C, and bromo alcohol **22** (400 mg, 0.66 mmol), dissolved in toluene (10 mL), was added via cannula. The reaction mixture was stirred at −25 °C for 6 h, Et_3N (0.32 mL, 2.22 mmol) was added dropwise over 5 min, and the mixture was stirred for an additional 10 min at −25 °C. After being warmed to room temperature and stirred for 1 h, it was poured into H_2O (50 mL) and extracted with brine (100 mL), dried, filtered, and evaporated. Chromatography of the residue (20% EtOAc/hexanes) led to 340 mg (86% yield) of **23** as a white solid consisting of rotamers: $[\alpha]^{23}_D$ +41.3° (*c* 1.00, $CHCl_3$); mp 73−74 °C; ^{1}H NMR δ major 1.68 (s), minor 1.64 (s, 9H), 3.64−3.28 (m, 4H), 7.18 (t, J = 7.59, 1H), 7.96−7.53 (m, 12H), major 8.69 (d, J = 8.07), minor 8.60 (d, J = 8.0, 1H), 9.87 (d, J = 1.7, 1H); ^{13}C NMR δ 28.0, 28.2, 62.2, 72.8, 83.8, 84.2, 114.1, 114.3, 114.4, 115.8, 118.4, 119.1, 119.6, 119.8, 119.9, 124.3, 124.7, 125.1, 125.7, 125.8, 126.1, 126.6, 126.8, 126.9, 127.0, 127.1, 127.2, 127.5, 127.7, 127.9, 128.0, 128.1, 128.3, 128.4, 128.7, 137.1, 140.3, 140.7, 143.9, 148.7, 148.8, 148.9, 203.5. Anal. Calcd for $C_{35}H_{31}N_2BrO_3$: C, 69.2; H, 5.1; N, 4.6. Found: C, 69.5; H, 5.5; N, 4.4.

(*R*)-4-Bromo-1-(*tert*-butyloxycarbonyl)-α-*N*-(9-phenyl-9-fluorenyl)tryptophan (24). A solution of aldehyde **23** (1.00 g, 1.65 mmol) in CH_3CN (15 mL), *t*-BuOH (51 mL), and 2-methyl-2-butene (10 mL) was stirred rapidly as it was cooled to 0 °C. A solution of $NaClO_2$ (1.15 g, 12.7 mmol) and NaH_2PO_4 (1.81 g, 1.28 mmol) in H_2O (20 mL) was added dropwise over a period of 10 min at 0 °C, and the mixture was then partitioned between EtOAc (100 mL) and brine (60 mL). The organic layer was washed with 1 M $Na_2S_2O_4$ (2 × 75 mL), dried, filtered, and evaporated. Purification of the residue by chromatography (2:1:0.3, hexanes/EtOAc/AcOH) led to 700 mg (69% yield) of **24** as a tan solid: mp 123−125 °C; $[\alpha]^{22}_D$ +55.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 1.67 (s, 9H), 3.21−3.00 (m, 3H), 6.18 (d, J = 7.34, 1H), 6.49 (t, J = 7.38, 1H), 7.35−7.01 (m, 12H), 7.51 (d, J = 7.48, 1H), 7.60 (d, J = 7.45, 1H), 8.19 (d, J = 7.88, 1H); ^{13}C NMR δ 13.9, 15.1, 22.3, 28.2, 30.1, 34.1, 57.4, 65.8, 72.7, 84.2, 114.0, 144.4, 116.2, 119.4, 119.9, 123.9, 125.1, 125.7, 125.9, 126.1, 126.7, 127.2, 127.3, 127.6, 127.9, 128.3, 128.5, 128.8, 136.9, 140.2, 140.8, 143.7 147.1, 148.3, 148.9, 177.6. Anal. Calcd for $C_{35}H_{31}N_2BrO_4$: C, 67.4; H, 5.0; N, 4.5. Found: C, 67.4; H, 5.4; N, 4.6.

(*R*)-4-Bromotryptophan [(*R*)-9]. Tryptophan **24** (4.0 g, 6.4 mmol) was dissolved in DCE (100 mL) and stirred under nitrogen as Et_3SiH (3.16 mL, 22.4 mmol) and TMSOTf (5.6 mL, 32.1 mmol) were added successively. The mixture was heated at reflux for 1 h and then cooled to room temperature. The solvent was evaporated, the residue was suspended in hexane (350 mL) which was decanted, and the resulting residue was suspended in 1 M HCl (75 mL) and heated at reflux for 2 h. The mixture was cooled to room temperature and then cooled in an ice bath as a solution of 1 M KOH was added dropwise until the pH was 6.0. The water was evaporated, and the residue was suspended in hot MeOH and then filtered. The filtrate was evaporated, and the solid was titurated with EtOAc, filtered off, and dried under vacuum overnight to give 1.72 g (95% yield) as a light brown solid. The spectroscopic properties were identical to those of (±)-**9**: $[\alpha]^{24}_D$ +27.6 (*c* 1.02, 1 M HCl); mp 288−290 °C.

(*R*)-4-Bromo-α-*N*-trityltryptophan Trityl Ester (25). Bromotryptophan [(***R***)-**9**] (906 mg, 3.2 mmol) was dissolved in dry DMF (5.0 mL) with stirring under nitrogen at room temperature. After cooling to 0 °C, Et_3N (1.78 mL, 12.8 mmol) was then added dropwise. To the resultant solution was further added a solution of trityl bromide (2.28 g, 7.04 mmol) in $CHCl_3$ (10 mmol). The reaction mixture was stirred for 15 min and then allowed to warm to room temperature. After stirring at room temperature for 2 h, the mixture was evaporated. The crude product could be directly subjected to selective hydrolysis of the trityl ester to give compound **26**. By column chromatography with EtOAc/hexane, 1:3, pure **25** could be obtained as a white foam (2.60 g, 90%): ^{1}H NMR δ 2.42 (dd, J = 6.4m 15.3, 1H), 2.56 (d, 1H), 3.25 (dd, J = 6.9, 15.3, 1H), 3.94 (m, 1H), 6.61 (s, 1H), 6.90−7.45 (m, 33H), 8.26 (s, 1H); ^{13}C NMR δ 30.2, 58.0, 71.5, 90.5, 110.5, 111.8, 114.2, 122.4, 123.7, 124.9, 125.5, 126.4, 127.1, 127.2, 127.5, 127.7, 127.9, 128.3, 128.7, 137.3, 142.8, 146.1, 146.8, 172.8.

(*R*)-4-Bromo-α-*N*-trityltryptophan (26). From (*R*)-25. To a solution of **25** (0.72 g, 0.94 mmol) in THF (35 mL) were added MeOH (10 mL) and H_2O (10 mL). The resultant THF (35 mL) was stirred at 50−55 °C for 14 h and evaporated, and the residue was chromatographed with EtOAc/hexane, 1:1, to give acid **26** (395 mg, 80%): mp 181 °C (dec); $[\alpha]^{24}_D$ −20.2° (*c* 1.0, THF); ^{1}H NMR (DMSO-d_6) δ 3.12−3.26 (m, 2H), 3.38 (br, 1H), 3.56 (m, 1H), 6.98 (t, J = 7.8, 1H), 7.03−7.07 (m, 1H), 7.14 (d, J = 7.45, 1H), 7.22−7.25 (m, 1H), 7.38 (d, J = 2.3, 1H), 7.42 (d, J = 7.7, 1H), 11.3 (s, 1H), 11.55 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 31.8, 57.8, 70.2, 110.9, 111.1, 113.2, 121.8, 122.6, 125.5, 126.0, 127.3, 127.4, 128.5, 137.7, 146.1, 176.1. Anal. Calcd for $C_{30}H_{25}BrN_2O_2$: C, 68.6; H, 4.8; N, 5.3. Found: C, 68.2; H, 5.0; N, 5.2.

From (*R*)-28. The ester (*R*)-**28** (6.9 g, 12.84 mmol) was dissolved in 1,4-dioxane (160 mL) and stirred rapidly at room temperature as a solution of $LiOH\cdot H_2O$ (5.5 g, 141 mmol) in water (60 mL) was added. The resulting mixture was heated at reflux for 96 h and then cooled to room temperature, and the organic layer was evaporated. The remaining aqueous phase was cooled to 0 °C, ice cold 1.0 M H_3PO_4 (100 mL) was added, and the resulting mixture was extracted with a mixture of $CHCl_3$/IPA (4:1, 3 × 100 mL). The combined organic layer was washed with 1 M H_3PO_4 (3 × 100 mL), water (2 × 100 mL), and brine (2 × 100 mL). Drying, filtering, and evaporating gave 6.75 g (100% yield) of **26**.

Esterification of acid **26** with CH_2N_2 gave a quantitative yield of methyl ester **28** with an er identical to that of ester **28** prepared from **27**.

(*R*)-4-Bromotryptophan Methyl Ester Hydrochloride (27). Bromotryptophan [(*R*)-**9**] (3.00 g, 10.6 mmol) was suspended in MeOH (50 mL) with stirring under nitrogen at room temperature as TMSCl (3.00 mL, 23.3 mmol) was added dropwise. The now homogeneous reaction mixture was heated at reflux for 48 h, after which it was cooled to room temperature and evaporated. The solid residue was dissolved in hot MeOH (20 mL), then Et_2O (180 mL) was added, and a white precipitate formed. After being cooled in an ice bath, the solid was filtered off and washed with Et_2O. Drying overnight under vacuum gave 3.39 g (96% yield) of ester hydrochloride **27**: mp 246−247 °C; $[\alpha]^{24}_D$ +8.7° (*c* 1.0, MeOH); ^{1}H NMR (DMSO-d_6) δ 3.23 (AB, J = 6.65, 7.97, 49.4, 8.4, 6.2, 8.45, 2H), 3.65 (s, 3H), 4.17 (t, J = 7.44, 1H), 6.99 (t, J = 7.85, 1H), 7.18 (d, J = 7.85, 1H), 7.18 (d, J = 7.4, 1H), 7.40 (m, 2H), 8.7 (br, 1H), 11.6 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 27.0, 52.6, 53.9, 107.1, 111.5, 112.4, 122.3, 122.8, 124.6, 127.6, 137.9, 169.5. Anal. Calcd for $C_{12}H_{14}ClN_2O_2$: C, 43.2; H, 4.2; N, 8.4. Found: C, 43.2; H, 4.3; N, 8.3.

(*R*)-4-Bromo-α-*N*-trityltryptophan Methyl Ester (28). 4-Bromotryptophan methyl ester hydrochloride [(*R*)-**27**, 4.6 g, 13.79 mmol] was suspended in 1,2-dichloroethane (200 mL) and stirred under nitrogen as Et_3N (9.24 mL, 65.84 mmol) was added dropwise at room temperature. To this mixture was added TrCl (4.0 g, 14.32 mmol) in dichloroethane (30 mL) via cannula, and the resulting mixture was stirred for 48 h at room temperature. Methanol (3.0 mL) was added, and stirring was continued for 1 h at room temperature before the organic layer was evaporated. The residue was dissolved in a mixture of $CHCl_3$/IPA (3:1, 250 mL) washed with water (3 × 150 mL) and brine (2 × 150 mL), dried, filtered, and evaporated. The residue was chromatographed (33% EtOAc/hexanes) to give 7.1 g (96% yield) of **28** as a white solid: mp 205−206 °C; $[\alpha]^{24}_D$ −31.2° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 2.74 (d, J = 10.8, 1H), 2.9 (s, 3H), 3.36 (AB, J = 8.1, 6.0, 5.59, 6.9, 7.3, 2H), 3.85 (m, 1H), 6.96 (t, J = 7.84, 1H), 7.0 (d, J = 2.3, 1H), 7.07−7.09 (m, 9H), 7.10−7.23 (m, 2H), 7.36−7.38 (m, 6H), 8.21 (s, 1H); ^{13}C NMR δ 32.3, 51.1, 58.4, 70.8, 110.4, 112.4, 114.3, 122.7, 123.9, 125.5, 125.8, 126.2, 127.5, 128.9, 137.41, 145.9, 175.9. Anal. Calcd for $C_{31}H_{27}BrN_2O_2$: C, 69.0; H, 5.0; N, 5.2. Found: C, 69.0; H, 5.2; N, 5.0.

The er was shown to be 99:1 by chiral HPLC (Chirobiotic V column, 80% methyl *tert*-butyl ether/20% hexane/0.05% DMF; 1.0 mL/min at 245 nm, 45 °C, t_R 9.6 min for D-enantiomer, t_R 10.3 min for L-enantiomer).

Detritylation of **28** to amino ester **27** was effected by treating **28** (40 mg, 74 μmol), dissolved in CH_2Cl_2 (2 mL) and stirred under nitrogen, with Et_3SiH (14 mL, 0.089 mmol) and TFA (35 mL, 0.445 mmol), added successively. The reaction mixture was stirred at room temperature for 30 min, evaporated, and chromatographed, eluting with 5% MeOH/EtOAc to give **27** (22 mg, 100%), identical to **27** obtained from (+)-**9**.

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Formation of Urea 29. Alternative evidence for enantiomeric purity was obtained by adding to a solution of amino ester **27** (18 mg, 64 μmol) in THF (1 mL) under nitrogen (*R*)-(+)-α-methylbenzyl isocyanate (9.0 mg, 65 μmol). The reaction mixture was stirred at room temperature for 30 min and then evaporated, and the residue was directly subjected to HPLC analysis (EtOAc/hexane, 2:1, 1 mL/min at 254 nm, t_R 16 min for D-enantiomer, t_R 18 min for l-enantiomer): ^{1}H NMR δ 1.32 (d, 3H), 3.36 (dd, 1H), 3.62 (dd, 1H), 3.68 (s, 3H), 4.56 (d, 1H), 4.69 (t, 1H), 4.79 (m, 1H), 4.83 (d, 1H), 6.98 (s, 1H), 7.00 (t, 1H), 7.10−7.40 (m, 7H), 8.4 (br, 1H).

For the determination of HPLC efficacy, (±)-**27**, (±)-**28**, and (±)-**29** were prepared as described above for the single enantiomers to provide HPLC controls.

4(*R*)-*N*-Tritylamino-5-oxo-1,3,4,5-tetrahydrobenz[*cd*]-indole [(*R*)-30]. (*R*)-Bromo-α-*N*-trityltryptophan **26** (1.00 g, 1.90 mmol) was dissolved in THF (25 mL) and cooled to −100 °C (liquid nitrogen, pentane bath) with stirring under nitrogen. To this solution was added *n*-BuLi (2.6 mL, 2.14 M in hexanes, 5.7 mmol) dropwise over 5 min, maintaining the temperature below −100 °C. After the reaction mixture was stirred at −105 °C for 2 h, a solution of *t*-BuLi (2.3 mL, 1.7 M in pentane, 3.9 mmol) was added dropwise over 8 min, maintaining the internal temperature at −100 °C by direct addition of liquid N_2. The resulting reaction mixture was stirred at −100 °C for 1 h before it was allowed to slowly warm to −78 °C, where it was stirred for 1 h and then allowed to slowly warm to 0 °C. After remaining at 0 °C for 1 h, the reaction was allowed to warm to room temperature and the solution was stirred for an additional 4 h, then poured into saturated $NaHCO_3$ (25 mL) and extracted with EtOAc (3 × 40 mL). The organic layers were combined, washed with brine (2 × 50 mL), dried, filtered, and evaporated. The residue was chromatographed (33%

EtOAc/hexane) to give 650 mg (80% yield) of (*R*)-**30** as an off-white solid: mp 194−196 °C; $[\alpha]^{24}_D$ −73.2° (*c* 1.0, THF); ^{1}H NMR δ 2.53 (dd, J = 6.7, 15.4, 1H), 2.80 (m, 1H), 3.73 (dd, J = 6.7, 11.6, 1H), 4.2 (br, exchangeable with D_2O, 1H), 6.67 (s, 1H), 7.05−7.28 (m, 1H), 7.45 (d, J = 6.9, 1H), 7.57 (d, J = 7.3, 6H), 8.39 (s, 1H); ^{13}C NMR δ 30.2, 61.0, 71.3, 109.8, 115.6, 115.7, 120.7, 122.6, 126.4, 126.6, 127.7, 127.8, 128.0, 128.9, 131.0, 134.2, 146.4, 148.5, 198.5.

1-(*tert*-Butyloxycarbonyl)-4(*R*)-*N*-tritylamino-5-oxo-1,3,4,5-tetrahydrobenz[*cd*]indole [(*R*)-31]. To tricyclic ketone (*R*)-**30** (950 mg, 2.21 mmol), dissolved in THF (20 mL) and stirred rapidly under nitrogen, were added successively NMM (1.0 mL, 9.10 mmol), DMAP (20 mg, 0.16 mmol), and BOC_2O (550 mg, 2.52 mmol). The resulting solution was stirred at room temperature for 2 h, then diluted with Et_2O (50 mL) and washed with 1 M H_3PO_4 (3 × 50 mL), $NaHCO_3$ (2 × 70 mL), and brine (2 × 50 mL). The organic layer was dried, filtered, and evaporated. Chromatography (25% EtOAc/hexane) of the residue led to 1.10 g (94% yield) of (*R*)-**31** as a light yellow solid: mp 106−108 °C; $[\alpha]^{24}_D$−81.2° (*c* 0.95, $CHCl_3$); ^{1}H NMR δ 1.64 (s, 9H), 2.47 (dd, J = 6.6, 9.3, 1H), 2.73 (m, 1H), 3.67 (q, J = 6.6, 5.1, 1H), 4.17 (s, 1H), 7.2 (t, J = 7.2, 1H), 7.26−7.6 (m, 17H), 8.05 (br, 1H); ^{13}C NMR δ 28.2, 29.9, 60.4, 71.3, 84.0, 114.4, 118.8, 120.0, 121.7, 125.2, 125.8, 126.5, 127.9, 128.9, 133.7, 146.3, 149.6, 197.4. Anal. Calcd for $C_{35}H_{32}N_2O_3$: C, 79.5; H, 6.1; N, 5.3. Found: C, 79.4; H, 6.4; N, 5.1.

Chiral HPLC: er 99.5/0.5 (Chirobiotic T column, 50% hexane/methyl *tert*-butyl ether, 0.5 mL/min at 250 nm, ambient temperature, t_R 11.8 min for D-enantiomer, t_R 13.3 for L-enantiomer). To provide a sample for development of the HPLC protocol, (±)-**31** was prepared in exactly the same way.

Upon standing exposed to the atmosphere, **31** was slowly oxidized to the corresponding α,β-unsaturated ketone, **1-(*tert*-butyloxycarbonyl)-4-*N*-tritylamino-5-oxo-1,5dihydrobenz[*cd*]indole (32):** mp 180−182 °C (dec); ^{1}H NMR δ 1.64 (s, 9H), 5.82 (s, 1H), 6.84 (s, 1H), 7.20−7.40 (m, 17H), 8.10 (d, J = 7.6, 1H); ^{13}C NMR δ 28.1, 71.0, 84.2, 102.7, 114.7, 119.9, 122.3, 124.3, 126.1, 126.5, 126.9, 127.9, 128.0, 128.3, 128.9, 129.1, 141.0, 144.6, 146.3, 179.9. Anal. Calcd for $C_{35}H_{30}N_2O_3$: C: 79.8; H, 5.7; N, 5.3. Found: C, 79.9; H, 5.8; N, 5.2.

(4*R*,5*S*)-4-*N*-Tritylamino-5-hydroxy-1,3,4,5-tetrahydrobenz[*cd*]indole [(4*R*,5*S*)-33]. (*R*)-4-Bromo-α-*N*-trityltryptophan (**26**, 0.25 g, 0.48 mmol) was dissolved in THF (6.3 mL) and cooled to −100 °C (liquid nitrogen, pentane bath) with stirring under nitrogen. To this solution was added *n*-BuLi (250 mol %, 0.48 mL, 2.5 M in hexane, 1.20 mmol) dropwise over 5 min maintaining the temperature below −100 °C by direct addition of liquid N_2. After the reaction mixture was stirred at −105 °C for 2 h, a solution of *t*-BuLi (0.70 mL, 1.7 M in pentane, 1.20 mmol) was added dropwise over 10 min. The resulting reaction mixture was stirred at −100 °C for 1 h before it was allowed to slowly warm to −78 °C, where it was stirred for 5 h and then allowed to slowly warm to −15 °C over a period of 2 h. After stirring at −15 °C for 5 h, the reaction mixture was poured into a cooled pH 7.0 buffer solution (10 mL) and extracted with CH_2Cl_2 (3 × 40 mL), and the combined organic layer was dried, filtered, and evaporated. The residue was dissolved in MeOH (5.0 mL), the resultant solution was cooled to −40 °C, and to this solution was added 150 mg of $NaBH_4$ portionwise over 10 min. The reaction mixture was then allowed to warm to room temperature over 1 h, poured into a cooled pH 7.0 phosphate buffer solution, and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was dried, filtered, evaporated, and chromatographed (33% EtOAc/hexane) to give 144 mg (70% yield) of (4*R*,5*S*)-**33**. Recrystallization from $CHCl_3$/hexane afforded a white solid which by HPLC and NMR was found to be a single diastereomer: mp 182−183 °C; $[\alpha]^{22}_D$ −28.4° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 1.57 (br, exchangeable with D_2O, 1H), 1.93 (dd, J = 5.1, 15.4, 1H), 2.55 (dd, J = 3.4, 15.5, 1H), 3.21 (m, 1H), 4.65 (d, J = 5.0, 1H), 6.61 (s, 1H), 7.05−7.59 (m, 18H), 7.85 (s, 1H); ^{13}C NMR δ 24.5, 55.0, 71.0, 71.7, 110.2, 110.3, 116.8, 119.4, 123.0, 125.9, 126.3, 127.8, 127.9, 128.7, 130.7, 133.7, 146.9. Anal. Calcd for $C_{30}H_{26}N_2O$: C, 83.7; H, 6.1; N, 6.5. Found: C, 83.3; H, 6.4; N, 6.5.

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