Synthetic Studies toward the Partial Ergot Alkaloid LY228729, a Potent $5HT_{1A}$ Receptor Agonist

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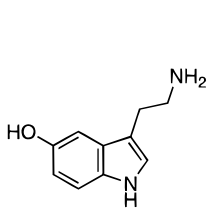
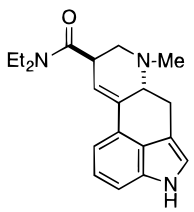
Synthetic studies on LY228729 (**3**) afforded two innovative approaches for the construction of this class of partial ergoline $5HT_{1a}$ receptor agonists. The first synthesis is based upon a diastereoselective epoxidation of racemic olefin **5**, followed by ring opening and covalent resolution to furnish the key amino alcohol **8**. Aziridination of amino alcohol **8**, with subsequent tandem hydrogenolysis of the benzylic aziridine and auxiliary bonds, provided access to the optically active primary amine **13**. A novel catalytic carboxamidation reaction installed the requisite side chain. Alternatively, the chiral pool was drawn upon for the single stereogenic center by virtue of L-tryptophan, albeit by a more circuitous route than expected. L-Tryptophan was differentially protected and reduced to the indoline diastereomers **26a,b** which were separated by fractional crystallization. The two indoline diastereoisomers were independently cyclized by a Friedel−Crafts protocol, which under thermodynamic control afforded enantiomeric ketones **30a**. The ketone was deoxygenated with a two-step reduction protocol to intersect the initial route and complete the second total synthesis. The two routes offer complementary access to this exciting class of partial ergot alkaloids.

Introduction

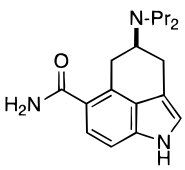
Serotonin is an important neurotransmitter, responsible for signal transduction and ultimately, for example, muscle control. The receptors for serotonin are accountable for a variety of functions and have thus been the target for a number of therapeutic reagents. The serotonin (5-HT, **1**) receptors are divided into families and subtypes, including $5HT_1$, $5HT_2$, $5HT_3$, $5HT_4$, $5HT_5$, $5HT_6$, and $5HT_7$. Both agonists and antagonists for many serotonin receptors have been identified and developed into valuable therapeutic reagents. Lysergic acid diethylamide (LSD, **2**) is an agonist for serotonin receptors, but is not very specific at any given receptor. Although this activity may not be surprising, the lack of specificity is intriguing on the basis of its conformational rigidity. The minor structural similarities of an indole tethered with an amine moiety suggested that the conformationally more fixed compound **3** should provide unique activity. SAR revealed the optimal structure with a di-*n*-propylamino substituent and the 5-carbamoyl moiety in LY228729 (**3**) for $5HT_{1a}$ receptor agonism. Thus, this molecule became the target drug candidate for further preclinical and clinical evaluations requiring synthetic methods for its construction.



5 HT (**1**)



LSD (**2**)



LY228729 (**3**)

The first generation synthesis was designed for optimal versatility in order to access a wide variety of analogues. However this approach, involving amino tetralin chemistry, was not sufficiently efficient for larger scale pursuit.[1] The second- and third-generation syntheses are discussed here in detail, with particular focus on some of the key transformations that enabled the synthesis of LY228729 for clinical trials. Also, based upon the Jacobsen catalytic asymmetric epoxidation,[2] it was possible to achieve kinetic resolution in the epoxidation of olefin **5** and hence afford a fourth-generation synthetic option. However, competing aromatization proved to be a difficult problem in this asymmetric epoxidation and it will not be discussed further.

Second-Generation Synthetic Route. Diastereoselective Epoxidation. The first total synthesis of lysergic acid was published by Kornfeld, Woodward, and colleagues from the Lilly Research Laboratories in 1954.[3] This elegant campaign was originally meant to address the difficulty in obtaining meaningful quantities from nature and stood the test of time for several decades which followed as the sole total synthesis. A critical intermediate in the Kornfeld−Woodward synthesis was a compound which became affectionately known as Kornfeld's ketone (**4**). $NaBH_4$ reduction of the ketone and subsequent dehydration afforded the crystalline olefin **5** in excellent overall yield (Scheme 1). The epoxidation of this olefin with peracids was known since the early lysergic acid synthesis days of Kornfeld. However, the stereochemical outcome of this epoxidation remained unknown for the four decades that followed the first disclosure. In any event, these molecules were success-

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1997.

(1) (a) Flaugh M. E.; Murdoch G. L. *Total Synthesis of LY228729, a Novel 5-HT$_{1A}$ Agonist,* presented at the 20th National Meeting of the American Chemical Society, Washington, DC; August 26, 1990. (b) For the synthesis of racemic LY228729, see: Flaugh, M. E.; Mullen, D. L.; Fuller, R. W.; Mason, N. R. *J. Med. Chem.* **1988**, *31*, 1746.

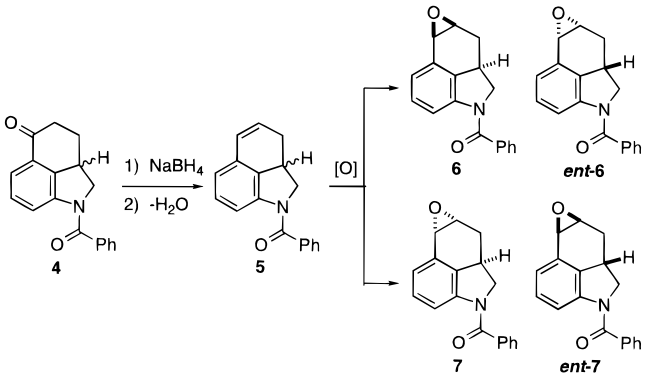
(2) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.

(3) Kornfeld, E. C.; Fornfeld, E. J.; Kline, G. B.; Mann, M. J.; Morrison, D. E.; Jones, R. G.; Woodward, R. B. *J. Am. Chem. Soc.* **1956**, *78*, 3087.

(4) Nichols, D. E.; Robinson, J. M.; Li, G. S.; Cassady, J. M.; Floss, H. G. *Org. Prep. Proc. Int.* **1985**, *17*, 391.

S0022-3263(97)01256-5 CCC: $14.00

Scheme 1

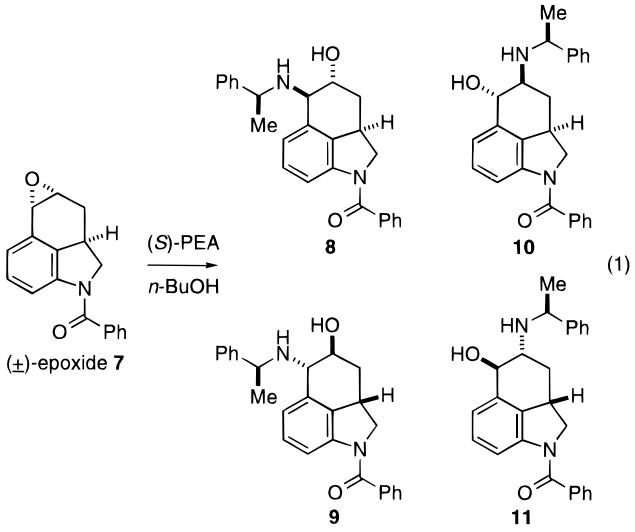


fully employed as valuable intermediates in a total synthesis of that complex natural product.

In late 1989, we had the opportunity to reinvestigate the epoxidation of the olefin,[4] believing that a mixture of diastereomeric epoxides (eg., **6**, **7**) would result. To our surprise, we determined that the epoxidation of olefin **5** was highly diastereoselective, affording primarily the anti-epoxides **7** with >96% de.[5] The rationale for this result was based upon a torsional model combined with transition state modeling.[6] The importance of this insight into the chemical process suggested that the epoxidation stereochemistry should be reagent independent. In other words, *m*-CPBA, NBS/H_2O, MMPP (monomagnesium peroxyphthalate) or OsO_4 should provide the same stereofacially selective oxidation with respect to selectivity sense and magnitude. That this was indeed the case allowed us the flexibility to choose the optimal oxidant with confidence that the reaction could be reliably scaled-up.

Interestingly, *m*-CPBA was employed in the initial epoxidation studies with great success in a variety of solvents including CH_2Cl_2, toluene, and ethereal solvents. During that time, the availability of relatively pure *m*-CPBA became difficult, being replaced with a somewhat more stable but less pure grade of the reagent (~50% potency). Also coincident with this transition was the introduction of monomagnesiumperoxyphthalate (MMPP)[7] as a potential replacement of the former oxidant. Since we believed the epoxidation was reagent and solvent independent, our incorporation of this new reagent into the process met only with the difficulties inherent to using the reagent itself. Namely, the relative insolubility of MMPP limited our solvent choice. Nonetheless, this resulted in the development of a 50% aqueous *n*-BuOH biphasic reaction medium. With substrate and reagent soluble under these conditions, the reaction proceeded smoothly. Upon complete reaction, the layers were separated to effect efficient removal of the spent oxidant. The organic phase contained the desired epoxide with an isomer profile identical with that derived from *m*-CPBA. The solvent choice resulted partly from a survey but equally importantly from consideration of how the epoxidation reaction would dovetail into the subsequent process (vide infra).

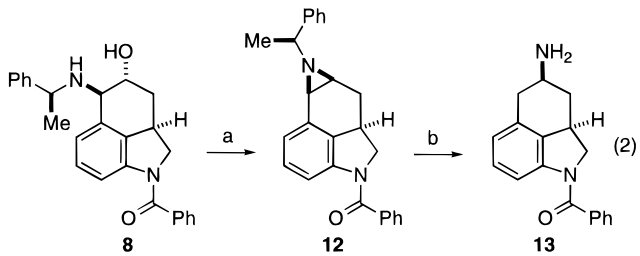
The epoxide opening of trisubstituted epoxide substrates (related to **7**) with a variety of amine nucleophiles



(1)

was previously studied by Kornfeld and shown to be regioselective for attack at the 4-position.[3] Thus, we concluded that amine would open epoxide **7** to afford amino alcohol **10**, which, in principle, could be deoxygenated to provide the correct relative stereochemistry (eq 1). However, it was disappointing (but rational)[8a] that attack occurred at the more electrophilic benzylic position to afford the amino alcohol **8**.[8b] Contrasted with the earlier Kornfeld results with trisubstituted epoxides, the amine opening of these disubstituted epoxides occurs at the less hindered side. A wide variety of 1° and 2° amines were reported to open this racemic epoxide in excellent yield. These epoxide openings were best conducted in *n*-BuOH at 110 °C, thus fitting very well with the epoxide-forming step above in the same solvent. Consequently, a solution of the racemic epoxide when reacted with an optically pure amine, such as (*S*)-α-phenethylamine, produced an equal mixture of diastereomers **8** and **9**. This mixture upon cooling provided the single isomer **8**[8b] in 43% yield, thus affording an efficient means for separation of optically enriched material. Simple reslurry of this crude material in warm 2-propanol effectively removed the more soluble undesired isomer **9**.

As noted above, it was disappointing due to the structural attributes of the target molecule that the epoxide opening had occurred at the benzylic position. Transposition of the nitrogen around the ring through the intermediacy of the aziridine **12** was then considered. Initially, a Mitsunobu reaction[9] furnished this aziridine in high yield, but concomitant with the production of highly crystalline contaminants, triphenylphosphine oxide, and the reduced form of DEAD (diethyl) or DIAD (diisopropyl azodicarboxylate) (eq 2). While chromato-



(2)

a. MsCl, Et_3N, CH_2Cl_2. b. Pd/C, H_2, THF, H_3PO_4, 0 °C - 55 °C.

graphic removal of these impurities was feasible on a

(5) Leanna, M. R.; Martinelli, M. J.; Varie, D. L.; Kress, T. J. *Tetrahedron Lett.* **1989**, *30* 3935.

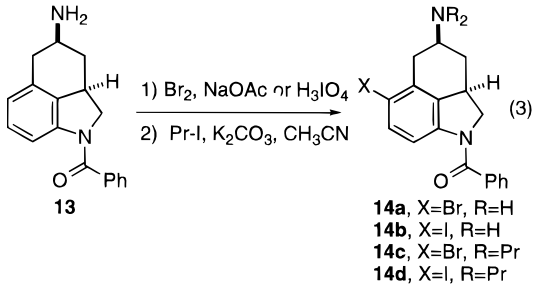
(6) Martinelli, M. J.; Peterson, B. C.; Khau, V. V.; Hutchison, D. R.; Leanna, M. R.; Audia, J. E.; Droste, J. J.; Wu, Y−D.; Houk, K. N. *J. Org. Chem.* **1994**, *59*, 2204.

(7) Brougham, P.; Cooper, M. S.; Heaney, H.; Thompson, N. *Synthesis* **1987**, 1015.

small scale, it was less likely at the larger scale. The aziridine could likewise be formed with Ph_3PCl_2, Ph_3PBr_2, and other similar reagents but with the same purification liabilities. A new procedure employing methanesulfonyl chloride and triethylamine was serendipitously discovered and then implemented to overcome this purification requirement, securing the aziridine **12** as a viable intermediate. That mesyl chloride could be utilized for this transformation is remarkable since *N*-mesylation was the expected primary course of reaction. It was not possible to isolate any sulfonamide derivative, nor mesylate from this reaction. However, application of this protocol to substrates without *N*-alkyl branching resulted only in *N*-mesylation.

Tandem benzylic hydrogenolysis of the aziridine bond and the auxiliary bond was achieved by exposure to hydrogen in the presence of a palladium catalyst. Thus, cleavage of the aziridine bond occurred at 0 °C under 1 atm of H_2 gas. Upon complete conversion to the 2° amine, the benzylic auxiliary bond was cleaved at 55 °C in the same vessel. The only detectable side product from these reactions was the desamino compound in which the exocyclic nitrogen was completely lost. This unwanted pathway could be minimized by careful temperature control to conduct the endocyclic reductive ring opening at low temperatures, followed by auxiliary cleavage at the elevated temperature. To prevent competing solvolytic reactions, nucleophilic solvents such as acetic acid or alcohols were avoided. With those solvents, aziridine opening could be observed to afford the corresponding acetate or methyl ether derivatives. The optimal binary solvent medium selected for this hydrogenolysis was therefore THF and phosphoric acid. To further prevent hydrolysis of the benzamide protecting group, the pH was adjusted to 3 prior to temperature elevation. Under these conditions, both diastereomeric amino alcohols could be converted to the enantiomers of **13** with equal but opposite signs of rotation ($[\alpha]_D = 59°$ ($c = 1$, THF)).

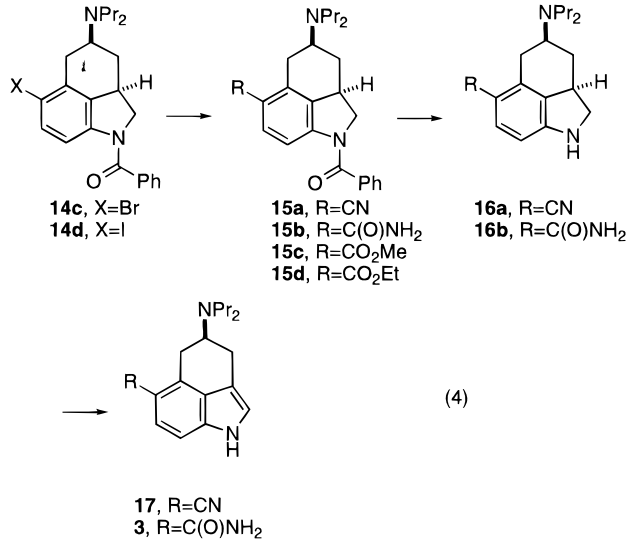
Regioselective aromatic electrophilic *para*-substitution on an indoline moiety is well precedented,[10] although many reaction conditions were not compatible with the existing functionality. The mildly directing and activating effects of the *p*-benzamide and *o*-alkyl moieties were essential for regiocontrol. The primary amine **13** thus obtained could undergo aromatic electrophilic substitution reaction with bromine in a carefully buffered NaOAc/HOAc[10] reaction medium, thereby preventing oxidation of the amine moiety, to afford the aryl bromide **14a** in 89% yield (eq 3). Alternatively, iodination with iodine and periodic acid furnished the aryl iodide **14b** in 85% yield.[11] Subsequent alkylation with excess iodopropane and K_2CO_3 in acetonitrile at 80 °C afforded the tertiary amine **14d** in 80% yield. Quaternization of the amine group, rather than incomplete alkylation, was the preferred option since the quaternary ammonium salt could be easily removed by aqueous extraction.



13

14a, X=Br, R=H
14b, X=I, R=H
14c, X=Br, R=Pr
14d, X=I, R=Pr

To introduce the requisite carboxamide moiety, several options were available. It was expected that Friedel–Crafts acylation followed by amide formation would be problematic. However, the bromide moiety offered several possibilities for aromatic substitution or metal-catalyzed replacement. Rosenmund–von Braun reaction of the bromide **14c** with CuCN in NMP (*N*-methylpyrrolidinone) at 200 °C gave the nitrile **15a** in 76% yield (eq 4). An alternative to NMP included DMF at reflux, but the reaction was much slower even in the presence of CuI. A competing side reaction was the cleavage of an *N*-propyl group under these extreme conditions. Conversion of the nitrile into the corresponding amide **15b** was accomplished quite smoothly with neat polyphosphoric acid (PPA) at 90 °C in excellent yield. Although this reaction was run quite concentrated, large volumes of water were required in the workup procedure to break the intermediate complex. This latter fact presented us with a throughput issue, suggesting a search for alternatives (*vide infra*).



14c, X=Br
14d, X=I

15a, R=CN
15b, R=C(O)NH2
15c, R=CO2Me
15d, R=CO2Et

16a, R=CN
16b, R=C(O)NH2

17, R=CN
3, R=C(O)NH2

Deprotection of the nitrile **15a** could be accomplished with a variety of reagents. In the early phases of the project during an attempt to transmetalate the aryl bromide, we noted the facile amide cleavage with *n*-BuLi. In fact, the cleavage was so efficient that we actually implemented this protocol to prepare initial quantities of the desired indoline **16a**. On a small scale, however, we also noted the indole as the major byproduct. This could perhaps be formed from autoxidation of a dipole-stabilized α-anion and was noted in the Rebek lysergic acid synthesis.[12] The suspected autoxidation could not be developed into an efficient process for net oxidation.

(8) (a) Nedelec, L; Brown, N. L.; Plassard, G. French Patent FR2522-658-A 82 03726. (b) 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.

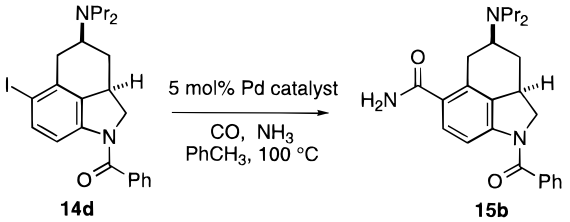
(9) Mitsunobu, O. *Synthesis* **1981**, 1.

(10) (a) Russell, H. F.; Harris, B. J.; Hood, D. B.; Thompson, E. G.; Watkins, A. D.; Williams, R. D. *Org. Prep. Proc. Int.* **1985**, *17*, 391. (b) Johnson, H. E.; Crosby, D. G. *J. Org. Chem.* **1963**, *55*, 2794. (c) Borror, A. L.; Chinoporos, E.; Filosa, M. P.; Herchen, S. R.; Petersen, C. P.; Stern, C. A.; Onan, K. D. *J. Org. Chem.* **1988**, *53*, 2047.

(11) (a) Suzyuki, H. *Org. Synth.* **1971**, *51*, 94. (b) Suzuki, H. *Bull Chem. Soc. Jpn.* **1970**, *43*, 481. (c) Suzuki, H.; Nakamura, K.; Goto, R. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 128.

(12) (a) Rebek, J.; Tai, D. F.; Shue, Y. K. *J. Am. Chem. Soc.* **1984**, *106*, 1813–1819. (b) Rebek, J.; Shue, Y. K.; Tai, D. F. *J. Org. Chem.* **1984**, *49*, 3540–3545.

Table 1. Palladium-Catalyzed Carboxamidation of Iodide 14d



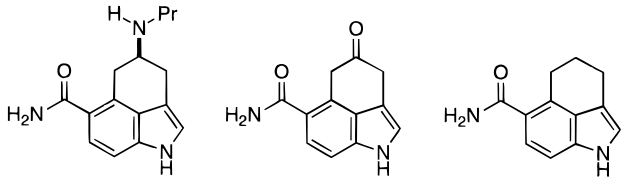
14d **15b**

palladium source	added ligand (equiv)	reaction time (h)	% yield, amide **15b**
$Pd(PPh_3)_2Cl_2$		6	66
$Pd(PPh_3)_2Br_2$		5	76
Pd black	PPh_3 (4)	14	89
Pd black	$Ph_2P(CH_2)_3PPh_2$ (2)	8	84

Later, it was found that the more conventional KOH/EtOH conditions were well-suited for benzamide cleavage, and these were the conditions ultimately implemented for our large scale work. The deprotection workup incorporated an acid−base extraction to separate the benzoic acid and neutral impurities. Thus, deprotection could occur at either the nitrile or amide stage with equal efficiency to provide a substrate compatible with subsequent oxidation conditions.

Two alternative strategies for introduction of the primary amide functionality utilized Heck carbonylation technology. Two potential precursors to amide **15b** were envisioned to be esters or secondary amides, which could be prepared by the reaction of an aryl halide with carbon monoxide in the presence of a palladium catalyst (eq 4).[13] While the aryl bromide **14c** proved to be an unreactive substrate for carbonylation, the iodide **14d** reacted with carbon monoxide and $Pd(PPh_3)_2Cl_2$ catalyst in methanol and ethanol to give methyl and ethyl esters **15c**,**d** in high yields. Both esters were extremely resistant toward amidation with ammonia. Under forcing conditions ($NaNH_2$) only cleavage of the benzoyl group occurred. We were pleased to find, however, that iodide **14d** smoothly underwent carboxamidation in the presence of carbon monoxide/ammonia with 0.05 equiv of $Pd(PPh_3)_2Cl_2$ to give the desired primary amide **15b** in 65−75% yield. A variety of palladium sources gave acceptable results in this reaction (Table 1). Fortunately a very convenient catalyst precursor, palladium black with added triphenylphosphine, gave the best yields (consistently greater than 80%) of **15b**. Toluene was found to be an optimal solvent for this process as the residual palladium was easily removed by filtering the warm reaction mixture, and the amide product was then crystallized directly from the cooled reaction mixture. We believe this reaction was the first reported example of preparation of a primary amide via this methodology.[14]

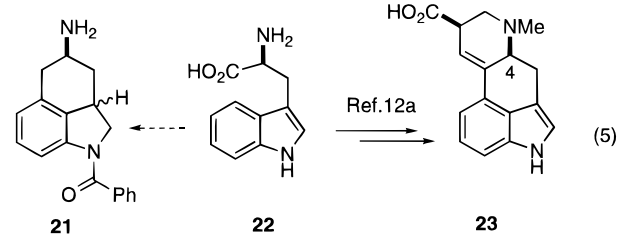
With access to the optically enriched indoline, our attention was now focused on the indole oxidation. The literature offers many suggestions for this thermodynamically favored conversion.[15] Manganese dioxide in CH_2Cl_2 was initially quite effective but required a large excess of reagent, often >25 molar equiv. Solvent exchange to acetic acid resulted in a dramatic rate acceleration even at 1.5−2 equiv of MnO_2. This oxidative protocol seemed reasonable at first, but the workup revealed some hidden troubles. Filtration of the manganese waste at the end of the reaction was problematic, due presumably to a myriad of acetate salts. The filtrate obtained after these lengthy separations contained a new species (**18**), derived from *N*-depropylation. Employing $Mn(OAc)_2$ or $Mn(OAc)_3$ itself as the primary oxidant also proved successful and avoided dealkylation since it is a much milder oxidant.[16]



18 **19** **20**

Alternatives to the manganese-based oxidations included DDQ,[17] which was less effective at completing the oxidation. Swern oxidation[18] of the indoline provided the indole very efficiently and concomitantly dehydrated the amide to the nitrile. Palladium on carbon[19] in MeOH at reflux smoothly transformed the indoline to the indole in 75−85% yield. As with the manganese procedure, scale-up proved that *N*-dealkylation was the major byproduct. Potentially, coordination with either nitrogen could lead to an oxidative insertion across a carbon−nitrogen bond. Reductive elimination would then provide the desired indole, or the undesired propyl-cleaved secondary amine. Additional new components in the reaction mixture were characterized as the transposed "Uhle's" ketone **19** and the saturated compound **20**. These were rationalized as arising from oxidative addition to form an enamine, which produced the ketone. This ketone, when isolated and resubjected to the reaction conditions, afforded the corresponding saturated material. The reaction profile varied with various lots of catalyst. Catalyst water content and age played a significant role in securing the optimal catalytic system. Isolation of LY228729 as the hippurate salt[20] offered a convenient method for purification by recrystallization (Scheme 2).

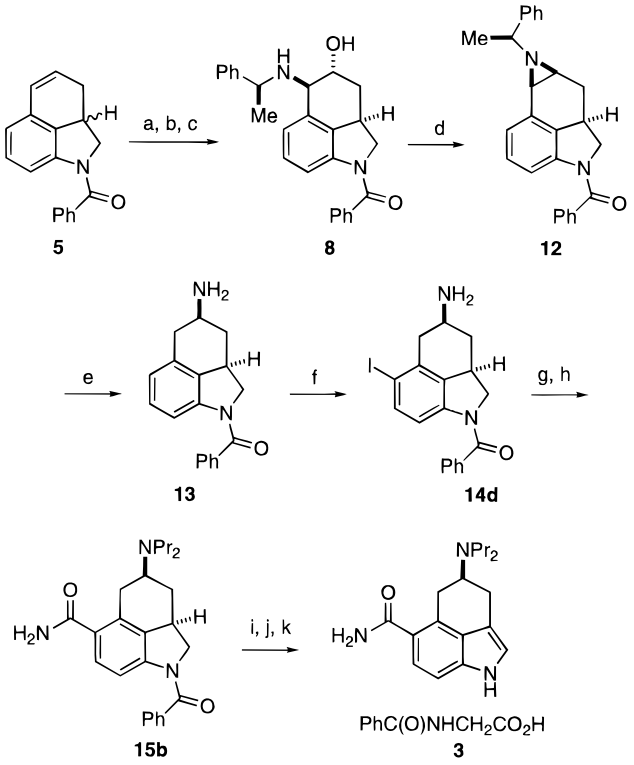
Tryptophan Route. L-Tryptophan (**22**) contains the carbon framework and an appropriately positioned stereocenter, with the desired absolute configuration needed for LY228729. In 1984, Rebek reported the synthesis of lysergic acid and its C-4 epimer (**23**) from L-tryptophan.[12] These factors and the ready availability of L-tryptophan lead us to pursue it as a starting material for the synthesis of LY228729.[21] On the basis of Rebek's work, we believed there was a high probability that L-tryptophan could be converted to tricyclic amine **21** and thus intersect with the synthetic route described in the previous section (eq 5). As will be discussed, we were less certain this "chiral pool" based synthesis could be developed into an efficient, manufacturable process.



21 **22** **23** (5)

(13) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. *J. Org. Chem.* **1974**, *39*, 3327.
(14) Kress, T. J.; Wepsiec, J. P. U.S. Patent 5039820, 1991.
(15) Sundberg, R. J. In *The Chemistry of Indoles*; Academic Press: New York, 1970.

Scheme 2. Synthesis of LY228729 from Olefin 5 ("Kornfeld Ketone Route")[a]

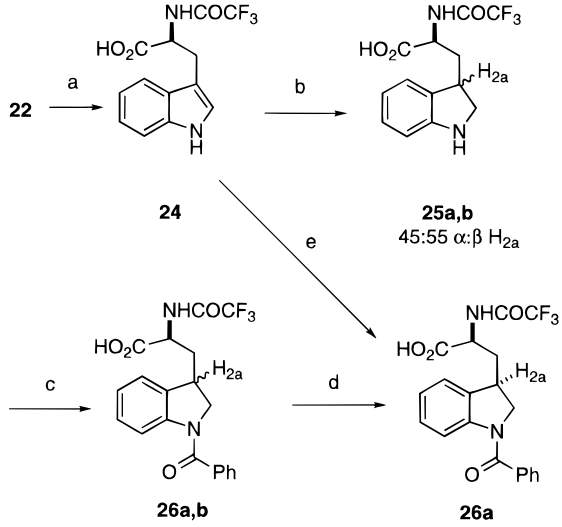


[a] (a) MMPP, *n*-BuOH; (b) (*S*)-phenethylamine, *n*-BuOH; (c) crystallize from *i*-PrOH; (d) MsCl, NEt_3; (e) 10% Pd−C, H_2, THF/H_3PO_4; (f) H_5IO_6, I_2; (g) *n*-PrI K_2CO_3; (h) CO, NH_3, Pd black, PPh_3; (i) NaOH, EtOH; (j) 10% Pd-C, MeOH; (k) hippuric acid.

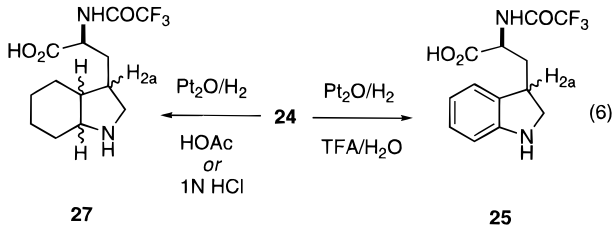
Reduction and Protection of L-Tryptophan. We planned to form the C-ring of LY228729 using an intramolecular Friedel−Crafts acylation reaction, as precedented by Rebek. The *N*-protected indoline[22] we required was prepared by trifluoroacetylation[23] of L-tryptophan, followed by ionic hydrogenation of the C-2 double bond (TFA/Et_3SiH) and benzoylation of the indoline nitrogen (Scheme 3). Using this scheme, a 45:55 mixture of diastereomeric indolines (**26a:26b**) was obtained in 67% yield from **24**. Fractional crystallization of the mixture from $CHCl_3$ provided what was eventually shown to be indoline diastereomer having the α C-2a hydrogen (**26a**) with >96% de in 21% overall yield from **24**.

The Et_3SiH reduction required TFA as solvent. Although convenient for small scale work, more economical catalytic hydrogenation methods were investigated. Optimal catalytic hydrogenation conditions for **24** were found to be effected by 5% PtO_2 catalyst in water with 10−20 equiv of TFA at 10 psi of hydrogen. The catalytic hydrogenation had processing advantages over the ionic hydrogenation, namely that indolines **25a,b** were not isolated. Upon complete hydrogenation, the PtO_2 was filtered and aqueous $NaHCO_3$ was added to the reaction mixture followed by PhC(O)Cl. This process was coupled with the $CHCl_3$ fractional crystallization to provide indoline **26a** in 18% overall yield from **24**. Notably, when the hydrogenation was performed in acetic acid or 1 N HCl, extensive overreduction of the aromatic ring occurred (eq 6). Even with the TFA/H_2O reaction medium, the reaction had to be carefully monitored to prevent overreduction. Unfortunately, regardless of which indole reduction and benzoylation sequence was used, consistent crystallization of acid **26a** was difficult (even with seeding) and $CHCl_3$ proved to be the optimal crystallization solvent.

Scheme 3. Reduction and Protection of L-Tryptophan[a]



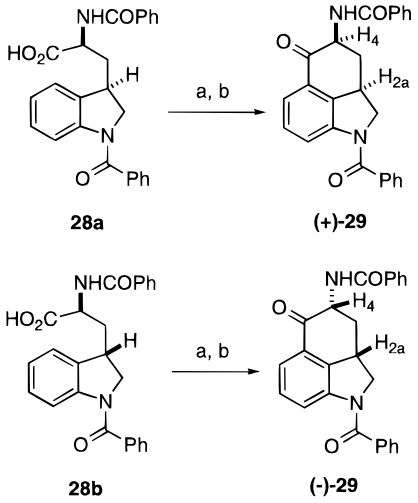
[a] (a) CF_3CO_2Et, MeOH, NEt_3; (b) Et_3SiH, TFA; (c) PhCOCl, NEt_3, THF; (d) $CHCl_3$ crystallization; (e) 1.5% PtO_2, H_2, H_2O, TFA; 2. $NaHCO_3$, PhCOCl; 3. $CHCl_3$.



Friedel−Crafts Acylation Reaction and Stereochemistry. Preserving the configuration of the C-4 stereocenter during the Friedel−Crafts acylation reaction was essential for using this strategy to prepare LY228729. While several enantiomerically pure α-amido 1-tetralones have been prepared via Friedel−Crafts cyclizations,[24] Rebek's work suggested the desired tricyclic ketone and/or the cyclization precursor (e.g. acid chloride, activated ester) would be more prone to epimerization at C-4. As shown in Scheme 4,[12] the azalactones derived from indo-

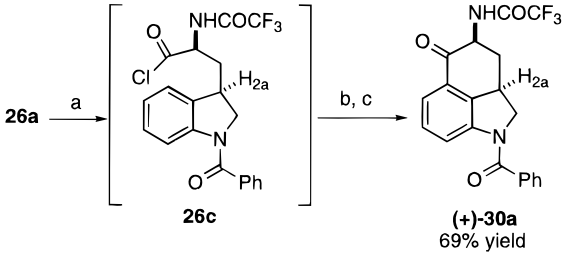
(16) Ketcha, D. *Tetrahedron Lett.* **1988**, *29*, 2151.
(17) Hagen, T. J.; Narayanan, K.; Names, J.; Cook, J. M. *J. Org. Chem.* **1989**, *54*, 2170.
(18) Keirs, D.; Overton, K. *J. Chem. Soc., Chem. Commun.* **1987**, 1660.
(19) Kiguchi, T.; Kuninobu, N.; Takahashi, Y.; Yoshida, Y.; Naito, T.; Ninomiya, I. *Synthesis* **1989**, 778.
(20) Kress, T. J.; Varie, D. L. U.S. Patent 5397799, 1995.
(21) For a preliminary account of ths work, see: Varie, D. L. *Tetrahedron Lett.* **1990**, *31*, 7583.
(22) Friedel−Crafts cyclizations of indole propionic acid derivatives typically occur on the 2-position rather than the 4-position. For leading references and a report of Friedel−Crafts cyclization conditions of indole propionic acids which occur on the 4-position, see: Teranishi, K; Hayashi S.; Nakatsuka, S.; Goto, T. *Synthesis* **1995**, 506.
(23) Curphey, T. J. *J. Org. Chem.* **1979**, *44*, 2805−2807.
(24) Examples of intramolecular acylations of α-amino acid derivatives: (a) Melillo, D. G.; Larsen, R. D.; Mathre, D. J.; Shukis, W. F.; Wood, A. W.; Colleluori, J. R. *J. Org. Chem.* **1987**, *52*, 5143−50. (b) Buckley, T. F.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 4222−4232. (c) McClure, D. E.; Lumma, P. K.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1983**, *48*, 2675−2679. (d) McClure, D. E.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1981**, *46*, 2431−2433.

Scheme 4. Friedel–Crafts Cyclization Precedent[12,a]



[a] (a) Ac_2O, 100 °C; (b) 4 equiv of $AlCl_3$, $EtCl_2$, 80 °C.

Scheme 5[a]



[a] (a) 2 equiv of $(COCl)_2$, cat. DMF, −5 °C, CH_2Cl_2; (b) 4 equiv of $AlCl_3$, 22 °C; (c) *n*-BuOH cryst.

line diastereomers **28a** and **28b** cyclized in the presence of $AlCl_3$ at 80 °C to give enantiomers of a single ketone diastereomer **29**, having the C-2a and C-4 hydrogens on the same face of the molecule. As expected, cyclization of 50:50 mixture of acid diastereomers (**28a**, **28b**) gave racemic ketone **29**. In short, the configuration at C-2a (which was not controlled) dictated the configuration at C-4.

Considering this precedent, we desired to determine if the Friedel–Crafts cyclization reaction of indoline **26** could be performed under (milder) conditions that would enable us to use both diastereomers and avoid epimerization at C-4 in the product ketones. If so, the covalent resolution of acid **26** could be omitted from the synthesis, providing a much more efficient large scale process. Indeed we found that the single diastereomer of the carboxylic acid **26a** could be converted to the tricyclic ketone **30a** under relatively mild conditions. The acid was treated with 2 equiv of oxalyl chloride and catalytic DMF at −5 °C, and the resulting acid chloride (**26c**, not isolated) was treated with 4 equiv of $AlCl_3$ at 22 °C for 20–30 h. The crude ketone **30** was obtained as a 98:2 mixture of diastereomers and was recrystallized from *n*-BuOH to provide **(+)-30a** in 70% overall yield with >99% ee (Scheme 5). Other Lewis acids were examined in this reaction. $TiCl_4$ and $FeCl_3/MeNO_2$ gave no reaction at ambient temperature. Reactions with $AlBr_3$ gave the desired ketone product but offered no advantage over $AlCl_3$.

When a 45:55 mixture of indolines **26a:26b** was subjected to the above Friedel–Crafts cyclization conditions, we were pleased to find that a 42:58 ratio of ketones **(+)-30a:30b** was formed. However, chiral HPLC assay of the crude reaction product showed that the enantiomeric purity of ketone **(+)-30a** in this crude mixture was unacceptable (82% ee). When the reaction was repeated at 0 °C/27 h both ketone diastereomers were again isolated, with ketone **(+)-30a** having 91% ee. In this experiment 50% of the carboxylic acid starting materials **26a**, **26b** was recovered as well. This reaction essentially stopped after 4 h at which time the reaction became heterogeneous. Additionally, the majority of the loss in enantiomeric purity of ketone **(+)-30a** (from 98.5% ee to 93% ee) occurred over the first 4 h (while the reaction mixture was homogeneous). The amorphous residue that precipitated from the reaction mixture appeared to be aluminum complexes of the acid chloride and the ketone product. Although performing the reaction at 0 °C slowed the rate of epimerization at C-4, these reaction conditions were not synthetically useful.

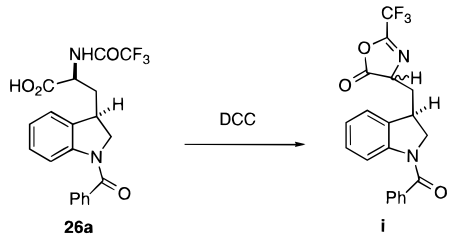
Table 2. Isomerization of Mixtures of Ketones 30a/30b

entry	initial ratio[a] **30a:30b**	conditions[b]	final ratio **30a:30b**
1	63:37	4 equiv of $AlCl_3$ powder;[c] CH_2Cl_2; 24 h	66:34
2	63:37	4 equiv of $AlCl_3$ powder; CH_2Cl_2; 55 h	69:31
3	63:37	4 equiv of $AlCl_3$ flakes;[d] CH_2Cl_2; 55 h	73:27
4	63:37	4 equiv of $AlCl_3$ powder; 0.05 equiv DMF; CH_2Cl_2; 55 h	85:15
5	76:24	2 equiv of NEt_3; CH_3CN; 1 h	98:2
6	76:24	1 equiv $NaHCO_3$; CH_3CN/H_2O: 24 h	98:2
7	76:24	1 equiv 1 N HCl; CH_3CN; 24 h	77:23

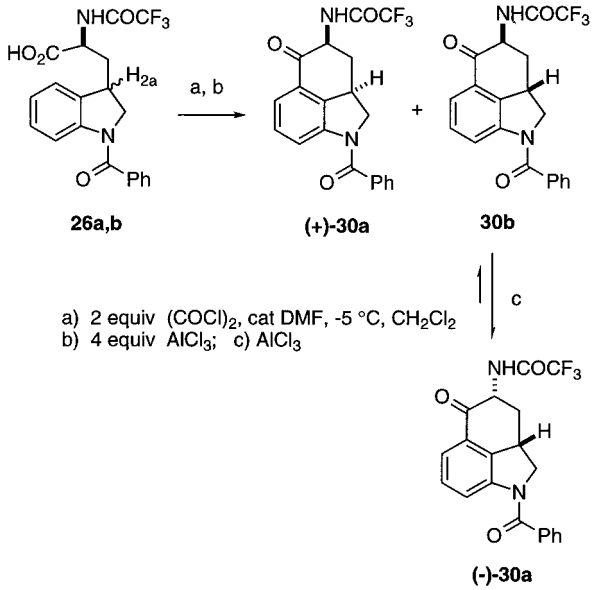
[a] Determined by HPLC (see Experimental Section). [b] All reactions performed at 22 °C. [c] Aldrich 99.9%. [d] Witco technical grade.

Subsequent experiments showed that ketone diastereomer **(+)-30a** is the themodynamically favored diastereomer and that epimerization of **30b** to **(−)-30a** during the reaction is the likely cause for the decrease in ee of **(+)-30a** (Scheme 6).[25] When mixtures of ketones **30a:30b** were treated with 4 equiv of $AlCl_3$ and 0.05 equiv of DMF in CH_2Cl_2 at 22 °C, ketone **30b** isomerized to **30a** with a half-life of approximately 33 h (see Table 2). The fact that a catalytic amount of DMF increased the rate of epimerization (compare entries 2 and 4) indicated that a variety of reaction parameters, such as the amount of HCl present and $AlCl_3$ solubility, may be significant for isomerization catalysis. (Some differences in the rates of both the cyclization and epimerization reactions were also observed when different grades of $AlCl_3$ were used.) Ketone **30b** was more rapidly (2 h) isomerized with 1 equiv of triethylamine in CH_2Cl_2 and was stable in the

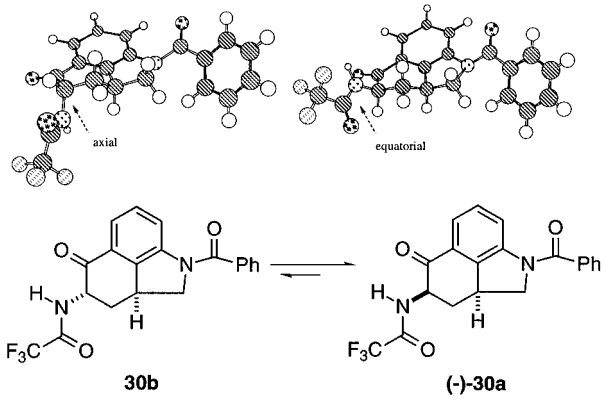
(25) The data do not exclude the possibilty of azalactone formation and epimerization prior to cyclization or epimerization of the acid chloride. While small amounts (<5% yield) of azalactone **i** were isolated from some of the cyclization reactions, it is not clear that any of the azalactone cyclized. Treatment of **26a** or a mixture of **26a** and **26b** with DCC gave an identical (by NMR and HPLC) 1:1 mixture of diastereomeric azalactones **i.** Cyclization of **i** with $AlCl_3$ at 22 °C in CH_2Cl_2 was much slower than the cyclization of the acid chloride. Less than 5% ketone **30** was formed after 7 h, whereas 80% of the acid chloride **26c** was converted to **30** in the same time.



Scheme 6. Intramolecular Friedel–Crafts Acylation Reaction: Stereochemistry



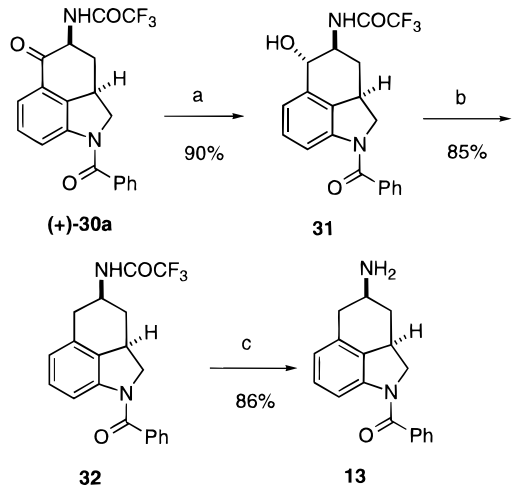
Scheme 7. Possible Conformations of Ketone Diastereomers



presence of aqueous acid (e.g. acetonitrile containing 1 equiv of 1 N HCl/24 h). We found that any mixture of the ketone diastereomers could be isomerized to an equilibrium 98:2 ratio of diastereomers, **30a:30b**, respectively. Extensive isomerization of **30b** also occurred on silica gel flash chromatography columns, making it impossible to isolate pure samples in this fashion. Ketone **30b** was eventually isolated in 97% purity by rapid preparative HPLC on a silica gel column (see Experimental Section). The thermodynamic preference for diastereomer **30a** versus **30b** can be rationalized as the difference between equatorial and axial C-4 amide substituents, respectively (Scheme 7). With the above data in hand we concluded that the Friedel–Crafts cyclization of the mixture of diastereomeric acids **26** would not be a suitable process for the preparation of enantiomerically pure LY228729.

Intersection with the Kornfeld Ketone Route. Focusing on ketone **(+)-30a**, all that remained to intersect the Kornfeld ketone route was deoxygenation of C-5 and deprotection of the primary amide. Deoxygenation of the ketone proved to be nontrivial. Catalytic reduction of **(+)-30a** with 10% Pd/C gave the fully reduced compound (**32**) in 47% yield but required TFA as solvent. The most efficient deoxygenation method was a two-step protocol (Scheme 8). Ketone **(+)-30a** was reduced with $NaBH_4$ to give alcohol **31** as an 8:1 mixture of epimers

Scheme 8. Completion of the Synthesis of Amine 13 from L-Tryptophan[a]



[a] (a) $NaBH_4$, MeOH, THF, 0 °C; (b) TFAA, THF, H_2, 10% Pd–C; (c) NaOH, THF, H_2O.

at C-5 in 90% yield. Alcohol **31** was then trifluoroacetylated *in situ* with TFAA under hydrogenolysis conditions (10% Pd–C, 50 psi of H_2, THF) to give amide **32** in 86% yield. Simple base hydrolysis of the trifluoroacetamide gave amine **13** identical with that prepared from the Kornfeld ketone.

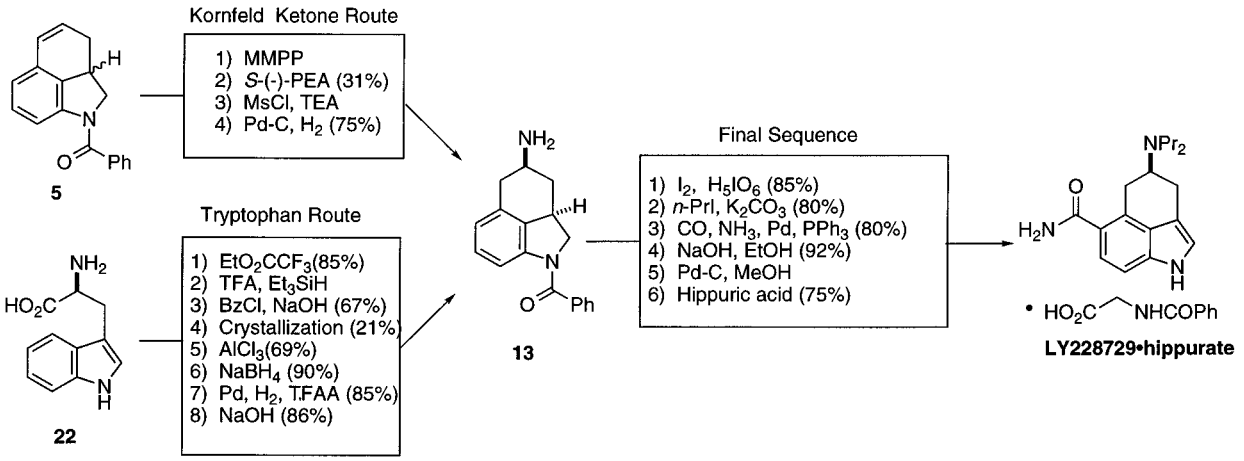
In summary, we demonstrated that a key intermediate in the LY228729 synthesis (amine **13**) could be prepared in seven steps and 8% overall yield from L-tryptophan. However, due to the stereochemical consequences of the Friedel–Crafts acylation reaction, this strategy still required a difficult covalent resolution which detracted from its large scale viability.

Comparison of Synthetic Routes. Our route selection was guided by our laboratory and pilot plant experiences on all three synthetic approaches, including the tetralone approach. Strategically, all three routes produced enantiomerically pure product *via* a covalent resolution. A comparison of the syntheses of the key intermediate, amine **13**, from commercially available materials is shown in Scheme 9. In summary, the synthesis of LY228729 was accomplished in nine steps in 9% overall yield from commercially available olefin **5**. While L-tryptophan cost is approximately one-tenth that of olefin **5**, the synthesis of LY228729 from L-tryptophan required 13 steps and proceeded in 3% overall yield. In addition to requiring fewer steps, the conversion of olefin **5** to amine **13** was operationally much simpler and more reliable than the conversion of L-tryptophan to **13**. Notably the fractional crystallization of amino alcohol **8** was much more robust than the fractional crystallization of the tryptophan-derived acid **26a**. These factors all pointed to the Kornfeld ketone route as the most viable long-term route of choice.

Experimental Section

Melting points are uncorrected. Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. TLC was performed on Kieselgel 60 F254 plates (Merck) using reagent grade solvents. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh). ^1H NMR spectra were recorded at 500 or 300 MHz or ^{13}C NMR spectra were recorded at 75 or 125 MHz, respectively, in $CDCl_3$ unless otherwise

Scheme 9. Comparison of Synthetic Routes



noted. Chemical shifts are in ppm downfield from internal tetramethylsilane. Concentrations were made using a rotary evaporator at a bath temperature <40 °C. Mass spectral analysis and combustion analysis were performed by the Eli Lilly and Co. Physical Chemistry Department.

1-Benzoyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indol-5-ol (A). The ketone[3] (947.9 g, 3.42 mol) was suspended in absolute EtOH (3 L) in a 5-L, 3-neck round-bottom flask equipped with a condenser topped with a drying tube, a mechanical stirrer, and a thermocouple. $NaBH_4$ (126.6 g, 3.35 mol) was then added portionwise at rt over a 15 min period. The internal temperature rose from 23 to 66 °C and began to cool slowly, whereupon the reaction mixture became nearly homogeneous and then formed a precipitate. When the exotherm subsided, the reaction mixture was heated to reflux for 30 min to consume the last 5−10% of starting ketone and then cooled to rt. The resulting thick slurry was added to water (5 L) and the pH adjusted to 7 with 6 N HCl. The precipitate was filtered, washed well with 4:1 water:EtOH,and dried to vacuo to afford 832.2 g (87.1%) as an off-white solid. The crude reaction mixture was analyzed by reverse phase HPLC, acetonitrile/water 1/1, and the ratio of epimers determined to be 6:1. The NMR data given represent the chemical shifts for the major isomer, although the minor isomer is also apparent by NMR: mp 190.5−191.5 °C; IR (KBr) 3437 (br), 1637 (s), 1468 (s), 1466 (s), 1395 (s), 1249 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (m, 1H), 1.74 (m, 1H), 2.17 (m, 1H); 2.42 (m, 1H), 2.52 (br s, 1H), 3.31 (m, 1H), 3.58 (t, 1H, J = 10.8 Hz), 4.24 (br s, 1H), 4.86 (m, 1H), 6.98−7.64 (m, 8H), ^{13}C NMR ($CDCl_3$) δ 26.9, 33.9, 37.5, 59.5, 68.4, 127.4, 128.3, 128.6, 130.6, 141.3, 168; EI-MS m/z = 279, 105 (parent); UV (EtOH) λ_{max} = 293 (ϵ = 8600), 266 (ϵ = 11 000); TLC R_f = 0.44 (two spots, SiO_2, 4:1 toluene:acetone). Anal. Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.10; H, 6.17; N, 5.01.

1-Benzoyl-1,2,2a,3-tetrahydrobenz[*cd*]indole (5). Into a 5-L, 3-neck round-bottom flask were placed Amberlyst 15 ion-exchange resin (228 g) and toluene (2.5 L). The flask was equipped with a mechanical stirrer, a Dean−Stark water separator topped with a condenser, a N_2 inlet, and a thermocouple. The mixture was stirred at reflux for 15−20 min and cooled to 95 °C (internal temperature). The alcohol **A** (432.5 g, 1.55 mol) was then carefully added and the mixture brought to reflux under N_2. Water collected in the trap at a steady rate, and the dehydration was complete after 3 h. The cooled reaction mixture was filtered through a small plug of SiO_2 and rinsed first with toluene and then with toluene:acetone (1:1) until the filtrates were colorless. Filtration through a plug of silica gel removes some of the color and a base line impurity as well as the resin. The filtrates were concentrated to dryness and then dried in vacuo, causing crystallization of the olefin (317.8 g, 78.7%). The olefin was used directly in the subsequent epoxidation, although an analytical sample was prepared by recrystallization from EtOAc/hexanes: mp 97−98.5 °C; IR (KBr) 3030 (m), 1639 (s), 1623 (s), 1607 (m), 1460 (s), 1456 (s), 1395 (s), 1233 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14 (m, 1H); 2.54 (m, 1H), 3.50 (m, 1H), 3.78 (t, 1H, J = 10.2 Hz), 4.32 (br s, 1H), 6.01 (m, 1H), 6.54 (dd, 1H, J = 3, 7.2 Hz), 6.75 (br s, 1H), 7.36−7.66 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 28.1, 34.5, 59.7, 119.6, 126.3, 127.3, 128.3, 128.4, 128.6, 130.5, 140.7, 168.8; EI-MS m/z = 261; UV (EtOH) λ_{max} = 265 (ϵ = 21 400), 235 (ϵ =15 800); TLC R_f = 0.75 (SiO_2, 4:1 toluene:acetone). Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.49; H, 5.73; N, 5.24.

1-Benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz-[*cd*]indole (6). The olefin **5** (455.0 g, 1.74 mol) was dissolved in CH_2Cl_2 (2.5L) and cooled to −2 °C with stirring. *m*-Chloroperbenzoic acid (300.6 g, 1.74 mol) was then added, and a strong exotherm was noted after a 5 min induction period. After 2 h, another portion of *m*-chloroperbenzoic acid (150.3 g, 0.87 mol) was added with continued stirring for another 2 h. The precipitated *m*-chlorobenzoic acid was filtered and washed with CH_2Cl_2. The filtrate was then successively washed with cold 2 N NaOH (1 L), water (1 L), 2 N NaOH (1 L), water (1 L), and brine (1 L). The organic phase was dried over Na_2SO_4, filtered through HyFlo, and concentrated to dryness. The residue was azeotroped several times from toluene and used directly in the next step without further purification. An analytical sample was prepared by recrystallization from EtOAc/hexanes: mp 109−110 °C; IR (KBr) 3035 (m), 1640 (s), 1619 (m), 1475 (s), 1406 (s), 1392 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (dd, 1H, J = 12.0, 13.8 Hz), 2.68 (m, 1H), 3.36 (m, 1H), 3.70 (m, 2H), 3.86 (d, 1H, J = 3.9 Hz), 4.38 (br s, 1H), 7.10 (br s, 1H), 7.20−7.42 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 26.2, 32.0, 50.2, 55.1, 57.8, 123.0, 127.4, 128.0, 128.6, 130.7, 141.6, 168.7; EI-MS m/z = 277; UV (EtOH) λ_{max} = 295 (ϵ = 7100), 265 (ϵ = 12 000), 216 (ϵ = 30 000); TLC R_f = 0.44 (SiO_2, 1:1 hexanes:EtOAc). Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.79; H, 5.20; N, 4.98.

1-Benzoyl-5-(1-(*S*)-phenethylamino)-1,2,2a,3,4,5-hexahydrobenz[*cd*]indol-4-ol (8). The epoxide **7** (482.5

g, 1.74 mol) was dissolved in *n*-BuOH (4400 mL) in a 12-L 3-neck flask equipped with a mechanical stirrer, a thermocouple, and a condenser topped with a N_2 inlet. The (S)-(−)-α-methylbenzylamine (900 mL, 14.0 mol) was added, and the solution was stirred at 90 °C overnight. After 24 h, the reaction mixture was allowed to cool to rt, whereupon the desired amino alcohol crystallized directly from the reaction mixture. The crystalline material was filtered, washed with Et_2O (2 L), and dried. The first crop weighed 168.26 g (24.3%) and was used directly in the subsequent reaction. A second crop could be obtained by concentrating the filtrates to dryness and dissolution in toluene (200 mL) followed by the addition of hexanes (100 mL) and Et_2O (100 mL). The resulting solution was allowed to stand in the refrigerator overnight to provide an additional 39.2 g (5.7%) after filtration. Recrystallization from *i*-PrOH affords the amino alcohol as colorless fibrous needles: mp 192−193 °C; IR (KBr) 3480 (br), 1638 (s), 1610 (w), 1470 (s), 1457 (s), 1394 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.02−7.56 (m, 13H), 4.21 (q, 1H, J = 6.6 Hz), 4.25 (br s, 1H), 3.63 (m, 2H), 3.42 (m, 2H), 2.72 (br s, 1H, exhanges with D_2O), 1.99 (m, 1H), 1.80 (m, 1H), 1.47 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 168.8, 145.4, 141.1, 136.5, 130.6, 128.6, 128.2, 127.3, 126.9, 120.3, 71.1, 59.2, 57.5, 30.7, 24.9; EI-MS m/z = 398, 355, 249, 145, 105; UV (EtOH) λ_{max} = 292 (ϵ = 8900), 265 (ϵ = 11 400); TLC R_f = 0.68 (SiO_2, 42:42:16 EtOAc:hexane:triethylamine) = desired diastereomer, R_f = 0.62 undesired diastereomer. Anal. Calcd for $C_{26}H_{26}N_2O_2$: C, 78.37; H, 6.58; N, 7.03. Found: C, 78.14; H, 6.67; N, 6.77.

(−)-4-Benzoyl-5,5a,6,6a,7,7a-hexahydro-7-(1-(*S*)-phenethyl)-4*H*-azirino[*f*]benz[*cd*]isoindole (12). Mitsunobu Protocol. The amino alcohol **8** (278.0 g, 0.698 mol) was placed into a 5-L 3-neck round-bottom flask equipped with a mechanical stirrer, a thermocouple, and an addition funnel topped with a N_2 inlet. Anhydrous THF (3.0 L) was added followed by triphenylphosphine (228 g, 0.873 mol, 1.25 molar equiv), and the resulting solution was stirred at rt under N_2. Diethyl azodicarboxylate (DEAD, 150.1 g, 0.873 mol) dissolved in THF (100 mL) was added dropwise over a 5 h period. A slight exotherm was also noted during the course of the addition: 21−30.4 °C. The reaction mixture was stirred vigorously at rt overnight and monitored by TLC showing steady progress but requiring in excess of 16 h for complete reaction. The reaction was then filtered through Celite (HyFlo) and silica gel (ca. 60 g), and the solution was washed with THF (500 mL). The solvent was removed in vacuo, and the resulting semisolid (715 g) was triturated with MeOH (100 mL) and Et_2O (600 mL) and refrigerated overnight. The solid was filtered, washed well with Et_2O (3 × 100 mL to remove DEAD−H_2), and dried. The fairly crystalline sold (279.4 g, >100%) was triturated again with MeOH (100 mL) and Et_2O (500 mL), filtered, washed, and dried to yield 248.0 g that appeared to be >90% pure by NMR. The calculated chemical yield was 84.5%. The thus obtained material could be recrystallized from *i*-PrOH (approximately 20 volumes): mp 184−186 °C; IR (KBr) 2978 (m), 1638 (s), 1468 (s), 1455 (s), 1385 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18−7.56 (m, 13H), 4.17 (br m, 1H), 3.55 (t, 1H, J = 10.7 Hz), 3.41 (m, 1H), 2.75 (q, 1H, J = 6.5 Hz), 2.56 (br m, 1H), 2.50 (d, 1H, J = 6.3 Hz), 2.08 (m, 1H), 1.59 (m, 1H), 1.53 (d, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 168.6, 144.4, 141.6, 136.5, 132.8, 130.5, 128.6, 128.3, 127.3, 127.0, 126.7, 124.1, 69.9, 59.0, 38.6, 37.7, 34.5, 31.6, 23.6; MS m/z = 380, 275, 261, 105, 77; UV (EtOH) λ_{max} = 294 (ϵ = 8400), 265 (ϵ = 11 200); TLC R_f = 0.72 (SiO_2, hexane:ethyl acetate 1:1) = desired diastereomer, R_f = 0.60 undesired diastereomer. Anal. Calcd for $C_{26}H_{24}N_2O$: C, 82.07; H, 6.37; N, 7.36. Found: C, 81.79; H, 6.34; N, 7.28. $[\alpha]_D$ = −41.1 (589 nm); $[\alpha]_D$ = −249.4 (365 nm).

Mesylation Protocol. Methanesulfonyl chloride (438 g, 3.8 mol) was added over 55 min to a −10 °C solution of amino alcohol **8** (1015 g, 2.55 mol) and triethylamine (800 g, 7.9 mol) in 8.1 L of CH_2Cl_2. The reaction mixture was allowed to warm to 25 °C and then stirred for 2 h. The reaction mixture was then extracted sequentially with 8.1 L each of water, a 5% $NaHCO_3$ solution, and brine. The organic layer was dried with Na_2SO_4 and added to 4 L of acetonitrile. The solution was concentrated in vacuo, and an additional 4 L of acetonitrile was added. The solution was concentrated to a total volume of 2 L, cooled to 0−5 °C for 18 h, and filtered. The solid was washed with 2 L of cold acetonitrile and vacuum-dried to give 855 g (88% yield) of aziridine **12** as a white solid.

Physical data (for undesired aziridine diastereomer derived from **9**): mp 196−199 °C; IR (KBr) 3010 (m), 1636 (s), 1612 (s), 1596 (s), 1459 (s) 1398 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00−7.58 (m, 13H), 4.21 (br m, 1H), 3.59 (t, 1H, J = 10.7 Hz), 3.47 (m, 1H), 2.77 (br m, 2H), 2.37 (d, 1H, J = 6.3 Hz), 2.24 (m, 1H), 1.47 (d, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 168.6, 144.3, 141.2, 130.4, 128.5, 128.4, 128.3, 128.0, 127.4, 127.3, 127.0, 126.9, 70.0, 59.0, 39.3, 36.9, 31.6, 23.2; EI-MS m/z = 381, 277, 262, 105, 77; UV (EtOH) λ_{max} = 294 (ϵ = 8780), 264 (ϵ = 1600). Anal. Calcd for CHNO: C, 82.07; H, 6.37; N, 7.36. Found: C, 82.32; H, 6.54; N, 7.28. $[\alpha]_D$ = −34.4 (*c* 1.0, THF).

(+)-1-Benzoyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole-4-amine (13). To a mixture of 12 g of 10% Pd−C and 20 mL of water under nitrogen was added 600 mL of a 3:1 THF:85% phosphoric acid solution. The mixture was cooled to 5 °C, and 60 g (0.15 mol) of aziridine **12** was added. The reaction vessel was evacuated and back-filled with H_2 three times. The reaction mixture was stirred under 1 atm of H_2 for 6 h, at which time HPLC analysis showed complete aziridine hydrogenolysis. The pH of the reaction mixture was then increased to 3 by the addition of 127 mL of a 45% KOH solution. The reaction vessel was again evacuated and back-filled with H_2 (3×). The reaction mixture was heated to 55 °C and stirred under 1 atm of H_2 for 17 h. The reaction mixture was then cooled to ambient temperature, vented, and diluted with 450 mL of CH_2Cl_2 and 50 mL of water. The pH was then adjusted to 10 with 45% KOH. This mixture was stirred for 90 min and filtered through a pressure filter. The catalyst was washed with 2 × 150 mL of CH_2Cl_2 and 2 × 50 mL of water. The (upper) CH_2Cl_2 layer was separated, and the water layer was extracted with 200 mL of CH_2Cl_2. The product was extracted from the combined CH_2Cl_2 layers by the addition of 350 mL of 0.5 M HCl. The layers were separated, and the pH of the aqueous layer was adjusted to 11 with 45% KOH solution. The milky solution was extratcted with 300 mL of CH_2Cl_2. The organic layer was separated and concentrated by atmospheric distillation. To the residual warm oil were added 98 mL of *i*-PrOH and 196 mL of water. After being cooled to 0 °C for 2 h the resulting slurry was filtered. The solid was washed with cold 1:2 *i*-PrOH:water (100 mL) and vacuum-dried to provide 31.1 g (71% yield) of amine **13** as short needles: mp 147−150 °C; IR (KBr) 1225 (w), 1396 (s), 1457 (s),

1488 (m), 1597 (m), 1612 (s), 1637 (s), 3009 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38−7.57 (m, 5H), 6.99 (m, 1H), 6.78 (m, 2H), 4.25 (br m, 1H), 3.62 (t, 1H, J = 11.5 Hz), 3.29 (m, 2H), 3.12 (dd, 1H, J = 6.1, 16.7 Hz), 2.39 (dd, 1H, J = 10.3, 16.7 Hz), 2.17 (m, 1H), 1.49 (br s, 2H), 1.31 (q, 1H, J = 11.5 Hz); ^{13}C NMR ($CDCl_3$) δ 168.5, 141.4, 136.6, 133.3, 132.6, 130.7, 130.1, 128.8, 128.1, 127.7, 127.6, 127.1, 123.1, 122.6 58.2, 48.6, 37.3, 37.2, 36.9; EI-MS m/z = 278, 261, 235, 130, 105, 77; UV (EtOH) λ_{max} = 291 (ϵ = 8150), 266 (ϵ = 10 600); TLC R_f = 0.19 (SiO_2, CH_2Cl_2:MeOH 4:1), R_f = 0.86 = 2° amine. Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.76; H, 6.55; N, 9.61. $[\alpha]_D$ = +57.4 (EtOH). $[\alpha]_{365}$ = +341.6.

(+)-1-Benzoyl-6-bromo-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole-4-amine (14a). The 1° amine **13** (29.4.g, 0.106 mol) was placed into a 500-mL, 3-neck round-bottom flask equipped with a mechanical stirrer, a N_2 inlet, and a constant addition funnel. The substrate was dissolved in glacial HOAc (250 mL), and NaOAc (34.7 g, 0.423 mol, 4 molar equiv) was then added. A solution of bromine (5.45 mL, 0.106 mol) in HOAc (20 mL) was then added dropwise over a 1 h period with vigorous stirring and then stirred at rt overnight. The resulting thick slurry was diluted with Et_2O, filtered, and washed well with Et_2O. The material thus obtained was slurried in H_2O (400 mL) and the pH adjusted to 11−12 with 5 N NaOH. The solid was filtered, washed well with H_2O (2 × 200 mL), and dried in vacuo to provide 33.6 g (88.8%) of the bromo 1° amine. An analytical sample could be prepared by recrystallization from *i*-PrOH or 50% aqueous EtOH: mp 169−173 °C; IR (KBr) 3010, 2934, 1640, 1580, 1468, 1454, 1384 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42−7.58 (m, 7H), 4.27 (br s, 1H), 3.68 (t, 1H, J = 11.1 Hz), 3.33 (m, 2H), 3.16 (dd, 1H, J = 6.3, 17.3 Hz), 2.28 (dd, 1H, J = 9.6, 17.3 Hz), 2.17 (m, 1H), 1.44 (br s, 2H), 1.32 (q, 1H, J = 11.6 Hz); ^{13}C NMR (CD_3OD) δ 170.6, 141.9, 137.3, 136.4, 134.1, 132.1, 132.0, 129.8, 128.1, 118.8, 116.2, 59.5, 49.3, 37.8, 37.1, 35.4; EI-MS m/z = 356, 358, 339, 341, 105, 77; UV (EtOH) λ_{max} = 272 (ϵ = 14 400); TLC R_f = 0.28 (SiO_2, MeOH); HPLC Supelco C-18 25 cm column, 2 mL/min, 35.65 acetonitrile: chloroacetic acid buffer t_R = 6.3 min (product); t_R = 4.2 min (intermediate 2° amine); t_R = 4.6 min (desbromo). Anal. Calcd for $C_{18}H_{17}N_2OBr$: C, 65.31; H, 6.62; N, 6.35; Br, 18.10. Found: C, 65.15; H, 6.70; N, 6.36; Br, 18.31. $[\alpha]_D$ = +11.64 (EtOH).

(+)-1-Benzoyl-6-bromo-*N*,*N*-dipropyl-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole-4-amine (14c). Amine **14a** (9.82 g, 0.0275 mol) was placed in a 500-mL, round-bottom flask equipped with a mechanical stirrer, a condenser topped with a N_2 inlet, and a thermocouple. Acetonitrile (175 mL) and K_2CO_3 (0.275 mol) were added, followed by the addition of iodopropane (13.2 mL, 0.137 mol) with vigorous stirring. The reaction mixture was stirred at 75 °C under N_2 overnight. After being cooled to rt, the reaction mixture was diluted with CH_2Cl_2 (200 mL), washed successively with H_2O, $NaHCO_3$ solution, H_2O, and brine, and dried over Na_2SO_4. After filtration, the volatiles were removed in vacuo to provide 11.5 g (94%) of crude product. This material was then recrystallized from 95% EtOH to provide the desired product as colorless needles, 9.7 g (80.0%): mp 93 °C; IR (KBr) 2958, 1655, 1464, 1453, 1381 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41−7.58 (m, 7H), 4.27 (m, 1H), 3.34 (m, 1H), 3.19 (m, 1H), 2.92 (dd, 1H, J = 5.6, 18.1 Hz), 2.48 (m, 5H), 2.16 (m, 1H), 1.47 (m, 4H), 1.40 (m, 1H), 0.90 (t, 6H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 168.9, 140.9, 134.7, 131.3, 130.0, 128.9, 127.7, 118.6, 57.8, 53.1, 30.6, 29.2, 22.9, 12.1; EI-MS m/z = 440/442; UV (EtOH) λ_{max} = 272 (ϵ = 15 600); TLC R_f = 0.46 (SiO_2, Hex:EtOAc:TEA 60:35:5); HPLC Supelco C-18 25 cm column, 2 mL/min, 35.65 acetonitrile: chloroacetic acid buffer t_R = 2.9 min (product), t_R = 2.0 min (starting material). Anal. Calcd for $C_{24}H_{29}N_2OBr$: C, 60.52; H, 4.80; N, 7.82. Found: C, 60.33; H, 4.89; N, 7.72. $[\alpha]_D$ = +20.73 (EtOH).

(+)-1-Benzoyl-4-(dipropylamino)-1,2,2a,3,4,5-hexahydro[*cd*]indole-6-carbonitrile (15a). The bromide **14c** (154.48 g, 0.35 mol) was dissolved in *N*-methylpyrrolidinone (NMP, 850 mL) to which CuCN (37.6 g, 0.42 mol, 1.2 molar equiv) was added. The flask was equipped with a condenser topped with a Firestone valve, a thermocouple, and a mechanical stirrer. The mixture was degassed five times (vacuum/N_2 purge) and slowly brought to 200 °C (internal temperature). After 1 h, TLC indicated that the reaction was nearly complete. After a total of 2.5 h, TLC showed that no starting material present. The resulting dark reaction mixture had precipitated Cu on the flask walls and was then cooled to rt. The mixture was diluted with CH_2Cl_2 (1 L) and washed with 15% NH_4OH. The combined organic layers were washed with H_2O (4 x l L), and brine (1 L) and dried over Na_2SO_4. The desiccant was removed by filtration and the filtrate concentrated to dryness. The crude residue was chromatographed in several small portions over silica gel with a hexane/EtOAc gradient to provide 10.27 g of the nitrile (75.7%). This material was used in the subsequent deprotection step without crystallization but could be recrystallized from 50% aqueous EtOH or EtOH: mp 109−111 °C; IR (KBr) 2959, 2213, 1661, 1616, 1470, 1453, 1368, 1355 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34−7.58 (m, 7H), 4.35 (m, 1H), 3.72 (t, 1H, J = 11.2 Hz), 3.30 (m, 2H), 3.13 (m, 1H), 2.72 (m, 1H), 2.45 (m, 4H), 2.27 (m, 1H), 1.46 (m, 5H), 0.90 (t, 6H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 169.0, 145.0, 138.2, 135.8, 134.1, 133.2, 131.0, 128.6, 127.3, 117.5, 113.9, 106.3, 58.4, 56.9, 52.7, 37.7, 29.3, 27.9, 22.5, 11.7; EI-MS m/z = 387; UV (EtOH) λ_{max} = 304 (ϵ = 19 600), 287 (ϵ = 19 800), 225 (ϵ = 23 000); TLC R_f= 0.38 (SiO_2, Hex:EtOAc:TEA 65:35:5). Anal. Calcd for $C_{25}H_{29}N_3O$: C, 77.47; H, 7.55; N, 10.85. Found: C, 77.09; H, 7.65; N, 10.74. $[\alpha]_D$ = +1.59 (EtOH).

(−)-4-(Dipropylamino)-1,2,2a,4,5-hexahydrobenz[*cd*]indole-6-carbonitrile (16a). The benzamide **15a** (41.02 g, 0.106 mol) was dissolved in freshly distilled THF (375 mL) and cooled to −78 °C under N_2. *n*-BuLi (59.3 mL, 0.148 mol, 1.4 molar equiv, 2.5 M) was then added dropwise at a rate to maintain the temperature below −65 °C. When TLC analysis indicated complete reaction, glacial HOAc (10 mL) was added carefully and the reaction mixture was warmed to rt. Et_2O (250 mL) and 1 N HCl (250 mL) were added and the layers separated. The organic phase was extracted with additional 1 N HCl (2 × 100 mL) and the combined aqueous phase washed with Et_2O (2 × 250 mL); 5 N NaOH (100 mL) was added dropwise with stirring followed by extraction with CH_2Cl_2 (250 + 2 × 150 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated to dryness. The resulting light tan, highly crystalline material was dried in vacuo to a constant weight (28.4 g, 94.5%). This material was recrystallized from hot aqueous EtOH (EtOH:H_2O 75:25), cooled, filtered, and washed with ice cold solvent: mp 114.5−115.5 °C; IR (KBr) 3336, 2934, 2210, 1625, 1586, 805 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (1H, d, J = 9.0 Hz), 6.39 (1H, d, J = 9.0 Hz), 4.12 (1H, br s), 3.75 (1H, m),

3.20 (1H, m), 3.03 (1H, dd, J = 18, 6.0 Hz), 2.63 (1H, ddd, J = 18, 12, 2.0 Hz), 2.45 (4H, t, J = 9.0 Hz), 2.19 (1H, dt, J = 6.0, 3.0 Hz), 1.45 (5H, m), 0.89 (6H, t, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$) δ 154.0, 137.4, 134.0, 130.7, 119.2, 105.7, 99.6, 57.4, 55.7, 52.8, 38.9, 29.7, 27.6, 22.6, 11.8; EI-MS m/z = 283, 254, 240, 183, 156, 128, 98, 72; UV (EtOH) λ_{max} = 296 (ϵ = 16 500), 231 (ϵ = 14 100), 205 (ϵ = 16 300) in EtOH; TLC R_f = 0.30 (SiO_2, Hex:EtOAc:TEA 65:35:5). Anal. Calcd for $C_{18}H_{25}N_3$: C, 76.28; H, 8.89; N, 14.83. Found: C, 76.56; H, 8.85; N, 14.71. $[\alpha]_D$ = −34.0 (THF, c = 1). $[\alpha]_{365}$ = −217.7.

(−)-4-(Dipropylamino)-1,2,2a,3,4,5-hexahydro-[*cd*]indole-6-carboxamide (16b). Polyphosphoric acid (PPA, 300 mL) was placed into a 500-mL, 3-neck flask equipped with a mechanical stirrer, a stopper, and a condenser topped with a N_2 inlet. The reaction vessel was degassed by vacuum/purge cycles (5×) and then heated to 85−90 °C (internal temperature) while the nitrile **16a** (22.65 g, 0.080 mol) was added portionwise. The reaction mixture became homogeneous as the hydrolysis occurred. After all of the nitrile had been added, the mixture was stirred at this temperature for an additional 2.0 h to ensure complete hydrolysis. The reaction mixture was then carefully poured onto crushed ice and stirred vigorously. After the ice had melted, the pH was adjusted with 5 N NaOH to 11/12, and the solution was extracted with several portions of CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered, and concentrated to afford 23.53 g of the amide as a foam: mp 161−164 °C; IR (KBr) 3381 (s), 3377 (s), 2956 (m), 2932 (m), 1645 (s), 1616 (s), 1585 (m), 1379 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (d, 1H, J = 8.0 Hz), 6.40 (d, 1H, J = 8.0 Hz), 5.67 (br s, 2H), 3.92 (br s, 1H), 3.70 (m, 1H), 3.24 (m, 1H), 3.18 (m, 3H), 2.82 (dd, 1H, J = 10.1, 17.0 Hz), 2.46 (m, 4H), 2.17 (m, 1H), 1.46 (m, 5H), 0.87 (t, 6H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 171.2, 152.4, 133.9, 130.6, 128.4, 122.8, 104.8, 57.5, 55.5, 52.5, 39.2, 29.0, 27.8, 22.3, 11.5; EI-MS m/z = 301 (fd); UV (EtOH) λ_{max} = 273 (ϵ = 15 400), 214 (ϵ = 22 300); TLC R_f = 0.44 (SiO_2, CH_2Cl_2:MeOH, 1:1). Anal. Calcd for $C_{18}H_{27}N_3O$: C, 71.72; H, 9.02; N, 13.94. Found: C, 71.44; H, 8.88; N, 13.75. $[\alpha]_D$ = −70.5 (c = 1.02, MeOH).

(2a*S*,4*S*)-1-Benzoyl-4-amino-6-iodo-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (14b). H_2SO_4 (4.4 g, 45 mmol) was added dropwise to a solution of amine **13** (10.0 g, 36 mmol) in 1:1 acetic acid/water (50 mL). Periodic acid (2.2 g, 9.6 mmol) and I_2 (4.8 g, 18.9 mmol) were added in rapid succession. The solution was heated to 60 °C for 1 h. With vigorous agitation, a 20% $NaHSO_3$ solution (10 mL) was added to the warm mixture. After the solution was cooled with an ice bath, CH_2Cl_2 (50 mL) was added and the pH adjusted to 12 with a 10 N NaOH solution (60 mL). The two-phase mixture was warmed to 25 °C, and 50 mL of CH_2Cl_2 was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried with Na_2SO_4·CH_3CN (70 mL) was added, and a solvent exchange to CH_3CN was affected. A mixture with a yellow precipitate resulted, which was cooled to −15 °C overnight. The cold mixture was filtered, and the solid was washed with cold CH_3CN (2 × 30 mL). After vacuum-drying, 13.1 g (90% yield) of **14b** was obtained as a white solid; mp 178−80 °C. $[\alpha]_D$ = 5.0 (c = 1, THF). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 7H), 4.27 (bs, 1H), 3.70 (t, J = 15 Hz, 1H), 3.30 (m, 2H), 3.05 (dd, J = 17, 6 Hz, 1H), 2.18 (m, 2H), 1.30 (q, J = 12 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 141.8, 137.7, 136.8, 136.2, 136.2, 134.5, 130.8, 128.6, 127.4, 115.9, 92.4, 58.1, 49.2, 42.8, 38.1, 36.8. IR (KBr) 1640 cm^{-1}; FD mass spectrum m/z 404 (M^+). Anal. Calcd for $C_{18}H_{17}IN_2O$: C, 53.48; H, 4.24; N, 6.93. Found: C, 53.20, H, 4.11; N, 6.64.

(2a*S*,4*S*)-1-Benzoyl-4-(di-*n*-propylamino)-6-iodo-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (14d). Primary amine **14b** (100 g, 0.25 mol), potassium carbonate (137 g, 1.0 mol), and 1-iodopropane (97 mL, 1.0 mol) were slurried together in 1 L of CH_3CN. The heterogeneous reaction mixture was warmed to approximately 75 °C and stirred for 17 h. The mixture was cooled to room temperature, and water (500 mL) and *tert*-butyl methyl ether (500 mL) were added. The organic layer was separated and washed with water. CH_3CN (500 mL) was added to the organic layer, and the volume was reduced in half by evaporation. A small amount of precipitated black solids was removed by hot gravity filtrataion. The filtrate was cooled to room temperature, and orange crystals formed. The mixture was cooled in an bath and filtered. The solid was washed with cold CH_3CN (2 × 75 mL) and vacuum-dried to give 100 g (83% yield) of tertiary amine **14d**: mp 109−110 °C; $[\alpha]_D$ = 17.0 (c = 1, THF); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 7H), 4.28 (bs, 1H), 3.66 (t, J = 11 Hz, 1H), 3.34 (m, 1H), 3.20 (m, 1H), 3.05 (dd, J = 18, 6 Hz, 1H), 2.47 (m, 5H), 2.16 (m, 1H), 1.38 (m, 5H), 0.91 (t, J = 7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 141.7, 137.9, 137.6, 137.6, 136.3, 130.7, 127.4, 106.8, 93.3, 58.0, 52.9, 38.5, 35.1, 29.1, 22.6, 11.9; IR (KBr) 1638 cm^{-1}; FD mass spectrum m/z 488 (M^+). Anal. Calcd for $C_{24}H_{29}IN_2O$: C, 59.02; H, 5.99; N, 5.74. Found: C, 59.03, H, 5.87; N, 5.64.

(2a*S*,4*S*)-1-Benzoyl-4-(di-*n*-propylamino)-6-(aminocarbonyl)-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (15b). To a 500-mL stainless stell autoclave were added 10.0 g (20.5 mmol) of iodoindoline **14d**, 0.12 g (1.1 mmol) of Pd black, 1.07 mmol of triphenylphosphine, and 150 mL of toluene. The autoclave was sealed, purged with anhydrous ammonia (3 × 50 psi), and then pressured to 50 psi with ammonia. Carbon monoxide was added to bring the final pressure to 85 psi. The stirred mixture was heated to 110 °C for 14 h and then cooled to 35 °C and vented. The warm reaction mixture was filtered, and the autoclave was rinsed with an additional 50 mL of toluene. The filtrate was concentrated to 50 mL, and then 10 mL of hexane was added. The resulting slurry was cooled to −15 °C for 24 h and filtered. The filter cake was rinsed with cold toluene (25 mL) and hexanes (2 × 30 mL) and then vacuum-dried at 50 °C to give 7.39 g (89% yield) of the product as a white crystalline solid: mp 120−122 °C; $[\alpha]_D$ = −14.5 (c = 1, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 7.0 Hz, 2H), 7.51 (m, 1H), 7.47 (m, 3H), 7.31 (bs, 1H), 5.81 (bs, 2H), 4.30 (bs, 1H), 3.69 (t, 1H, J = 7.3 Hz), 3.34 (m, 1H), 3.27 (dd, J = 17.5, 6.0 Hz), 3.19 (m, 1H), 2.89 (dd, 1H, J = 17.5, 10.0 Hz), 2.47 (m, 4H), 2.19 (m, 1H), 1.48 (m, 4H), 0.90 (t, J = 5.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 168.9, 143.3, 138.2, 134.6, 134.2, 130.8, 129.2, 128.6, 127.7, 127.4, 57.4, 52.9, 38.4, 29.2, 27.9, 22.6, 11.8; IR (KBr) 3347, 3177, 2958, 2932, 2871, 1676, 1639, 1579, 1465, 1450, 1368 cm^{-1}; FD mass spectrum m/z 405 (M^+). Anal. Calcd for $C_{25}H_{31}N_3O_2$: C, 74.03; H, 7.70; N, 10.36. Found: C, 74.33, H, 7.90; N, 10.48.

(2a*S*,4*S*)-4-(Di-*n*-propylamino)-6-(aminocarbonyl)-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (16b). To a solution of 71.95 g (177 mmol) of indoline **15b** in 720 mL of EtOH were added 650 mL of deionized water and 47 mL of 50% NaOH. The solution was heated to 80 °C for

4 h at which time HPLC analysis showed the reaction to be complete. EtOH was removed by distillation under vacuum, and 720 mL of CH_2Cl_2 was added to the remaining aqueous mixture. The organic layer was isolated and washed with water. Ethyl acetate (360 mL) was added, and the organic layer was concentrated to approximately 400 mL total volume by atmospheric distillation. The solution was cooled to room temperature and stirred for 2 h to initiate crystallization. The slurry was then cooled to 5 °C, stirred for 2 h, and filtered. The solid was washed with 200 mL of cold ethyl acetate and vacuum-dried at 50 °C to obtain 43.69 g (82% yield) of white solid: mp 163−64 °C. $[\alpha]_D = -48.5$ ($c = 1$, THF); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.29 (bs, 1H), 7.21 (d, J = 8.0 Hz, 1H), 6.76 (bs, 1H), 6.27 (d, J = 8.0 Hz, 1H), 5.69 (s, 1H), 3.55 (m, 1H), 3.01 (m, 4H), 2.67 (dd, J = 17, 10.3 Hz, 1H), 2.42 (m, 4H), 2.06 (d, J = 6.8 Hz, 1H), 1.40 (m, 4H), 1.30 (q, J = 11.0 Hz, 1H), 0.86 (t, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.35, 153.7, 134.1, 131.1, 129.4, 123.8, 104.9, 58.2, 55.8, 53.0, 29.4, 23.1, 12.6.7; IR (KBr) 3392, 3180, 2957, 2934, 2870, 2810, 1654, 1584, 1457, 1380 cm^{-1}; FD mass spectrum m/z 301 (M^+). Anal. Calcd for $C_{18}H_{27}N_3O$: C, 71.72; H, 9.03; N, 13.94. Found: C, 71.48, H, 9.15; N, 13.75.

Preparation of LY228729. (4*R*)-4-(Di-*n*-propylamino)-6-(aminocarbonyl)-1,3,4,5-tetrahydrobenz[*cd*]indole (3). Pd/C Oxidation. To a slurry of 1.25 g of 10% Pd/C in 100 mL of deionized water was added 4.1 g (41.8 mmol) of concentrated H_2SO_4. To this mixture was aded 25.0 g (83.1 mmol) of indoline **16b** in 125 mL of MeOH. The mixture was heated to reflux (approximately 80 °C) for 7 h. The reaction mixture was cooled to 25 °C and filtered to remove the catalyst. The catalyst was washed with water (2 × 60 mL) and ethyl acetate (125 mL). An additional 125 mL of ethyl acetate was added to the filtrate, and the layers were separated. The aqueous phase was diluted with 100 mL of H_2O and then extracted with 2 × 200 mL of ethyl acetate. The aqueous phase was combined with 500 mL of ethyl acetate, and then 75 mL of 5 M NaOH solution was added to the mixture. The organic layer was separated, washed with 250 mL of H_2O, dried with Na_2SO_4, and concentrated in vacuo to approximately 100 mL total volume. The resulting slurry was cooled (with stirring) to 5 °C for 2 h and filtered. The filter cake was washed with cold ethyl acetate and vacuum-dried at 50 °C to give 17.13 g (69% yield) of LY228729 as a white solid: mp 178−80 °C (500 MHz, DMSO-d_6) δ 10.74 (s, 1H), 7.41 (s, 1H), 7.28 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 8.4 Hz, 1H), 7.0 (s, 1H), 3.38 (d, J = 14.1 Hz, 1H), 3.32 (s, 1H), 2.99 (m, 1H), 2.87 (dd, J = 14.2, 3.2 Hz), 2.6.8 (d, J = 13.7 Hz, 1H), 2.52 (m, 4H), 1.40 (m, 4H), 0.88 (t, J = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 171.6, 135.1, 132.3, 127.4, 123.9, 123.0, 120.7, 113.9, 108.6, 59.21, 53.2, 29.9, 24.7, 24.7, 23.1, 12.6; IR (KBr) 3320, 2960, 2880, 1645, 1602, 1591, 1467, 1447 cm^{-1}; EI-MS m/z = 300 (M + 1), 199, 156, 129; UV (EtOH) λ_{max} = 243 (ϵ = 34 700), 284 (ϵ = 5600); TLC R_f = 0.11 (SiO_2, 42:42:16 EtOAc:Hex:TEA). Anal. Calcd for $C_{18}H_{25}N_3O$: C, 72.33; H, 8.16; N, 13.83. Found: C, 72.21; H, 8.42; N, 14.03. $[\alpha]_D = -104.03$ (589 nm), 29.76 mg/3.0 mL THF; 5.0 cm path. $[\alpha]_D = -480.04$ (365 nm). pK_a = 8.6, DMF/H_2O.

Preparation of LY228729 (3). Manganese Dioxide Oxidation. Acetic acid (88 mL) was added to a slurry of indoline **16b** (21.0 g, 70 mmol) in 88 mL of CH_2Cl_2 at −10 °C. Solid MnO_2 (9.1 g, 104 mmol) was added, and the mixture was stirred for 5.5 h. The cold mixture was filtered through diatomaceous earth filter aid, and the filter pad was washed with CH_2Cl_2 (6 × 50 mL). The filtrate was placed in a flask with an overhead stirrer, and 100 mL of water was added. The mixture was cooled to 0 °C, and 50% NaOH (75 mL) was added dropwise over 20 min. The two-phase mixture was filtered through a filter aid to remove precipiated manganese salts. The organic layer was isolated from the filtrate, and the aqueous layer was extratcted with 200 mL of CH_2Cl_2. The combined CH_2Cl_2 layers were washed with 200 mL of brine, dried (Na_2SO_4), and concentrated in vacuo to give 18.0 g of crude LY228729 as an amber foam. The foam was flash chromatographed on silica gel (eluent 1:1 EtOAc:hexane) to give 13.06 g (62% yield) of purified product as a yellow foam.

Preparation of LY228729 Hippurate (3). To a slurry of 5.0 g of 10% Pd/C in 100 mL of deionized water was added 9.9 g (33 mmol) of indoline **16b** in 50 mL of MeOH. An additional 50 mL of MeOH was added, and the mixture was heated to reflux for 2 h. The reaction mixture was cooled to 25 °C and filtered to remove the catalyst. The catalyst was washed with ethyl acetate (3 × 50 mL). The filtrate was concentrated in vacuo to remove most of the MeOH and ethyl acetate. The remaining residue was partitioned between 200 mL of ethyl acetate and 100 mL of 1 N HCl. The lower acid layer was isolated, and the pH was adjusted to appproximately 11 by adding 55 mL of 2 N NaOH. The basic aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated in vacuo to give 7.0 g of LY228729 as a tan foam. The foam was dissolved in 30 mL of *i*-PrOH and added to a 70 °C solution of hippuric acid (4.19 g, 23.4 mmol) in 30 mL of *i*-PrOH maintaining the temperature at 65−70 °C. The solution was allowed to cool to 25 °C and stirred for 2 h. The resulting slurry was cooled to 5 °C for 2 h and filtered. The solid was washed with cold *i*-PrOH (3 × 25 mL) and vacuum-dried at 40 °C to give 9.63 g (61% overall yield) of the hippurate salt as a white solid: mp 187−88 °C; $[\alpha]_D = -39.4$ (c = 1, MeOH); ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.80 (s, 1H), 8.73 (t, J = 5.6 Hz, 1H), 7.88 (d, J = 7.1 Hz, 2H), 7.54 (m, 1H), 7.48, (m, 3H), 7.31 (d, J = 8.5 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 7.06 (s, 1H), 7.02 (1H, s), 3.92 (d, J = 5.8 Hz, 2H), 3.46 (dd, J = 16.0, 2.4 Hz, 1H), 3.13 (m, 1H), 3.02 (m, 1H), 2.92 (dd, J = 14.5, 3.3 Hz, 1H), 2.76 (t, J = 13 Hz, 1H), 2.61 (m, 4H), 1.46 (m, 4H), 0.89 (t, J = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 172.3, 171.6, 167.2, 135.2, 134.9, 132.7, 131.8, 129.2, 128.1, 127.3, 123.9, 123.0, 120.3, 113.4, 108.7, 62.9, 59.5, 53.2, 42.4, 29.7, 26.3, 24.4, 22.5, 12.5. IR (KBr) 3458, 3134, 2975, 1655, 1604, 1545, 1457, 1384 cm^{-1}; FAB mass spectrum m/z 300 (M + 1 for amine). Anal. Calcd for $C_{27}H_{34}N_4O_4$: C, 67.76; H, 7.16; N, 11.71. Found: C, 67.96, H, 7.18; N, 11.61.

***N*$^{\alpha}$-(Trifluoroacetyl)-*N*^{1}-benzoyl-2,3-dihydro-L-tryptophan (26a). Catalytic Hydrogenation Procedure.** *N*$^{\alpha}$-(Trifluoroacetyl)-L-tryptophan (**24**)[23] (20 g, 66.7 mmol), platinum oxide (1.0 g, 4.4 mmol), and a mixture of 100 mL of water and 100 mL of TFA were added sequentially to a Parr pressure bottle. The mixture was shaken under 10 psi of hydrogen at 25 °C for 2 h, at which time HPLC analysis showed that all starting material had been consumed. The catalyst was removed by filtration through diatomaceous earth. The filtrate was cooled to 0 °C, and the pH was adjusted to 8 by the addition of 150 mL of 25% NaOH solution. The resulting solution was diluted

with 120 mL of of 1 M $NaHCO_3$ solution, and benzoyl chloride (7.3 mL, 63 mmol) was added dropwise. After 30 min the solution was cooled to 0 °C and 25 mL of 6 N HCl was added to adjust the pH to 3. The precipitate was filtered, washed with water, and vacuum-dried to give 17.25 g of a mixture of diastereomers as a light brown solid. The solid was dissolved in 85 mL of $CHCl_3$ at 25 °C and then cooled to −20 °C. After 7 days, the precipitate was filtered, washed with cold $CHCl_3$, and vacuum-dried to give 4.34 g (18% yield) of a 98:2 mixture of amides. An analytical sample of the desired amide was obtained by recrystallization from 90:10 dichloroethane:EtOAc (8 mL/g): mp 175−78 °C; $[\alpha]_D = -36.1$ (*c* = 0.1, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.15 (s, 1H), 9.85 (d, J = 6 Hz, 1H), 7.5 (m, 6H), 7.32 (m, 2H), 7.05 (m, 1H), 4.40 (m, 1H), 4.15 (t, J = 10 Hz, 1H), 3.77 (m, 1H), 3.40 (m, 1H), 3.27 (m, 1H), 3.05 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.5, 167.9, 156.7, 156.2, 142.2, 136.8, 135.1, 130.1, 128.4, 127.6, 126.9, 124.3, 123.8, 117.6, 113.8, 56.2, 51.3, 45.0, 37.3, 34.8; IR (KBr) 3250, 3070, 2990, 2460, 1707, 1700, 1612, 1560, 1485, 1436 cm^{-1}; FD mass spectrum *m*/*z* 406 (M^+), 105. Anal. Calcd for $C_{20}H_{17}N_2O_4F_3$: C, 59.12; H, 4.22; N, 6.89. Found: C, 58.98, H, 4.30; N, 6.91.

***N*$^\alpha$-(Trifluoroacetyl)-*N*^{1}-benzoyl-2,3-dihydro-L-tryptophan (26a). Reduction with Triethylsilane.** *N*$^\alpha$-(Trifluoroacetyl-L-tryptophan (**24**)[23] (125 g, 0.42 mol) was added to a stirred mixture of 755 mL of TFA and triethylsilane (133 mL, 0.84 mol). The mixture was stirred for 40 min at 25 °C and concentrated in vacuo. The resulting oily residue was partitioned between 250 mL of 2 N HCl and 200 mL of EtOAc and 100 mL of EtOAc. The layers were separated, and the organic layer was extracted with 2 N HCl (5 × 100 mL). The pH of the aqueous layer was adjusted to 3.0 by the dropwise addition of a 50% NaOH solution. The cloudy solution was then extracted with EtOAc (6 × 200 mL). The combined EtOAc extracts were dried (Na_2SO_4) and concentrated in vacuo to give 125.9 g of a mixture of indoline diasteroemers as a tan foam.

To a solution of crude indoline (as prepared above, 100.0 g, 0.33 mol) and triethylamine (49 mL, 0.35 mol) in 700 mL of dry THF was added, dropwise, a solution of benzoyl chloride (36.5 mL, 0.31 mol) in 230 mL of THF. The reaction mixture was then stirred for 1 h, diluted with 1 L of Et_2O, and then added to 1 L of 2 N HCl. The resulting mixture was stirred for 5 min, and the layers were separated. The aqueous layer was extracted with 500 mL of Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give an oily brown foam. The foam was dissolved in 300 mL of hot $CHCl_3$ and cooled to 0 °C for 24 h. The resulting solid was filtered, washed with cold $CHCl_3$, and vacuum-dried to give 27.24 g (21% yield from tryptophan trifluoracetamide) of the carboxylic acid as a tan crystal. HPLC analysis showed this to be a 97:3 mixture of diastereomers. The mother liquor was concentrated to an an oil and redissolved in 150 mL of hot $CHCl_3$. Cooling to 0 °C for 24 h provided a second crop of 48.58 g. HPLC analalysis showed this to be a 44:56 ratio of diastereomers. Diastereomer ratios were determined by dissolving the indolines in HOAc and treating the solution with excess 1 M Br_2 in HOAc. The solution was stirred for 5 min, dissolved in pH 3.5 chloroacetic acid buffer, and treated with a 10% Na_2SO_3 solution to decompose the excess bromine. The resulting solution of the 7-bromoindolines was assayed by HPLC: Zorbax C-18 25 cm column; 35:65 CH_3CN:pH 3.5 chloroacetic acid buffer eluent; 2 mL/min; UV detection at 275 nm.

(2a*R*,4*S*)-1-Benzoyl-4-trifluoroacetamido-5-oxo-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole ((+)-30a). To a mixture of indolinecarboxylic acid **(26a)** (24.00 g, 59 mmol) and DMF (0.93 mL, 12 mmol) in 240 mL of CH_2Cl_2 at −10 °C was added a solution of oxalyl chloride (10.3 mL, 118 mmol) in 10 mL of CH_2Cl_2 over 8 min. The mixture was warmed to −5 °C and stirred 1 h, at which time all of the carboxylic acid had dissolved. The reaction mixture was cooled to −10 °C, and solid $AlCl_3$ (39.23 g, 295 mmol) was added. The mixture was stirred for 1 h at −10 °C, and the cooling bath was removed. After 22 h, the reaction mixture was added in a stream to a stirred mixture of 200 g of ice, 50 mL of concentrated HCl, and 100 mL of CH_2Cl_2. The reaction flask was rinsed with 100 mL of CH_2Cl_2 which was added to the quench mixture. The layers were separated, and the aqueous layer was extracted with 100 mL of CH_2Cl_2. The combine organic layers were washed with brine (250 mL), saturated $NaHCO_3$ solution (250 mL), and then brine (250 mL). After the solution was dried with Na_2SO_4, the organic layer was concentrated in vacuo to give 20.6 g of a light yellow foam. The foam was crystallized from 100 mL of boiling *n*-BuOH to give 15.70 g (69% yield) of the ketone as a white solid: mp 210−212 °C; $[\alpha]_D = 183$ (*c* = 0.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (bs, 1H), 7.58 (m, 5H), 7.49 (m, 2H), 7.28 (m, 1H), 4.69 (m, 1H), 4.43 (m, 1H), 3.87 (m, 1H), 3.77 (t, J = 10.6 Hz, 1H), 3.02 (m, 1H), 1.95 (q, J = 12.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.3, 169.3, 157.8 (q for CF_3), 142.7, 141.6, 135.9, 131.6, 129.8, 129.2, 128.5, 127.7, 121.4, 119.4, 117.2, 114.9, 57.1, 35.5. IR (KBr) 3290, 3070, 1730, 1721, 1691, 1643, 1634, 1595, 1470, 1393 cm^{-1}; FD mass spectrum *m*/*z* 388 (M^+). Anal. Calcd for $C_{20}H_{15}N_2O_3F_3$: C, 61.86; H, 3.89; N, 7.21. Found: C, 61.78, H, 3.88; N, 7.14. Chiral HPLC assay: SS Whelk 01 S/N 100022 column; 60:40 ethanol:hexane eluent; 1 mL/min; UV detection at 275 nm. Retention times: ketone diastereomer **30b**, 4.9 min; ketone diastereomer **30a**, (−)-enantiomer, 5.8 min; ketone diastereomer **30a**, (+)-enantiomer, 6.6 min.

(2a*S*,4*S*)-1-Benzoyl-4-trifluoroacetamido-5-oxo-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (30b). Friedel−Crafts reaction of 2.44 g of a 45:55 mixture of carboxylic acids, as described above, gave 1.82 g of crude ketone as a mixture of diastereomers. The mixture was flash chromatographed on silica gel (eluent 1:1:1 hexane:Et_2O:CH_2Cl_2) to give 1.05 g of ketone diastereomer **(+)-30a** and 0.34 g of a 65:35 mixture (by HPLC, conditions desribed above) of ketones diastereomers **30a**:**30b**. Ketone **30b** was isolated as a white foam from this mixture by preparative HPLC on silica gel (eluent 2.5% *i*-PrOH in hexane): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.4−8.0 (bs, 1H), 7.55 (m, 3H), 7.49 (m, 3H), 7.28 (m, 2H), 4.62 (t, J = 5.2 Hz, 1H), 4.42 (m, 1H), 3.78 (m, 2H), 2.67 (d, J = 13.2 Hz, 1H), 2.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.6, 169.4, 157.9 (q for CF_3), 142.3, 141.5, 135.9, 131.6, 129.7, 129.2, 129.1, 127.6, 121.6, 119.4, 117.1, 114.9, 112.6, 53.8, 33.7; IR (KBr) 3290, 3070, 1730, 1721, 1691, 1643, 1634, 1595, 1470, 1393 cm^{-1}; FD mass spectrum *m*/*z* 388 (M^+).

(4*S*)-1-Benzoyl-4-trifluoroacetamido-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (31). Solid $NaBH_4$ (0.50 g, 13.2 mmol) was added to a −10 °C suspension of ketone **(+)-30a** (13.90 g, 35.8 mmol) in 20 mL of THF. Methanol (20 mL) was added dropwise over

8 min, keeping the temperature below 2 °C. The reaction mixture was stirred for 1 h at 0 °C and then quenched by the addition of 70 mL of 1 N HCl over 20 min (the temperature was maintained below 5 °C). Water (50 mL) was added to preceipitate the product, and the mixture was stirred for an additional 1 h at 0 °C. After filtration the filter cake was washed with water (4 × 30 mL) and dried to give 12.59 g (90% yield) of alcohol as an 89:11 mixture of epimers at C-5. An analytical sample of the trans alcohol was obtained by recrystallization from *n*-BuOH: mp 250−253 °C; $[\alpha]_D = 93.7$ ($c = 0.1$, THF); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.50 (d, $J = 8.5$ Hz, 1H), 7.60 (m, 2H), 7.50 (m, 3H), 7.13 (m, 2H), 5.71 (d, $J = 7.3$ Hz, 1H), 4.73 (t, $J = 7.6$ Hz, 1H), 4.10 (m, 1H), 3.76 (m, 1H), 3.50 (m, 1H), 2.09 (m, 1H), 1.76 (q, $J = 12.1$ Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.5, 156.8 (q), 141.7, 137.4, 133.6, 131.3, 129.3, 128.8, 128.0, 123.1, 120.4, 118.1, 115.9, 70.5, 55.4, 33.7; IR (KBr) 3279, 1698, 1627, 1593, 1471, 1461, 1232, 1214 cm^{-1}; FD mass spectrum *m*/*z* 390 (M^+). Anal. Calcd for $C_{20}H_{17}N_2O_3F_3$: C, 61.54; H, 4.39; N, 7.18. Found: C, 61.80, H, 61.80; N, 7.24.

(4*S*)-1-Benzoyl-4-trifluoroacetamido-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (32). A solution of alcohol **31** (750 mg, 1.9 mmol) and trifluoroacetic anhydride (0.75 mL, 5.3 mmol) in 12 mL of THF was added to 375 mg of 10% Pd−C under N_2. The mixture was hydrogenated under 45 psi of hydrogen for 22 h at 25 °C. The catalyst was removed by filtration, and the filter cake was washed with 60 mL of EtOAc. The filtrate was concentrated to give the crude product as a white solid. The solid was chromatographed on silica gel (1:1:1 hexane:CH_2Cl_2:Et_2O eluent) to give 624 mg (86% yield) of white solid, mp 185−6 °C: $[\alpha]_D = 65$ ($c = 0.1$, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (m, 6H), 6.87 (m, 3H), 4.38 (m, 2H), 3.61 (t, $J = 11$ Hz, 1H), 3.40 (m, 1H), 3.28 (dd, $J = 16.8$, 6.5 Hz), 2.60 (dd, $J = 16.8$, 11 Hz), 2.36 (m, 1H), 1.47 (q, $J = 11$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 157.3 (q), 141.8, 136.6, 132.0, 131.3, 129.1, 128.7, 127.7, 123.3, 119.7, 117.4, 115.1, 112.8, 58.0, 47.5, 37.0, 32.9, 32.7; IR (KBr) 3290, 1693, 1652, 1555, 1458, 1390, 1205, 1164 cm^{-1}; FD mass spectrum *m*/*z* 374 (M^+). Anal. Calcd for $C_{20}H_{17}N_2O_2F_3$: C, 64.17; H, 4.58; N, 7.48. Found: C, 64.38, H, 4.50; N, 7.52.

(4*S*)-1-Benzoyl-4-amino-1,2,2a,3,4,5-hexahydrobenz[*cd*]indole (13). Amide **32** (480 mg, 1.28 mmol) was dissolved in a mixture of 7 mL of THF and 2 mL of 1 N NaOH. The reaction mixture was heated to reflux (70 °C) for 3 h, at which time HPLC indicated the reaction to be complete. To the cooled reaction mixture were added 10 mL of EtOAc and 10 mL of water. The layers were separated, and the aqueous layer was extracted with 10 mL of EtOAc. The combined organic layers were extracted with 10 mL of a saturated $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated in vacuo to obtain 327 mg (91% yield) of the amine as a white solid. This compound was identical by HPLC and NMR to amine **13** prepared from Kornfeld's ketone. An analytical sample was obtained by recrystallization of the solid from EtOAc: mp 146−48 °C; $[\alpha]_D = 61.6$ ($c = 0.1$, THF). Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.44, H, 6.52; N, 10.00. FD mass spectrum *m*/*z* 278 (M^+).

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