JOC*Article*

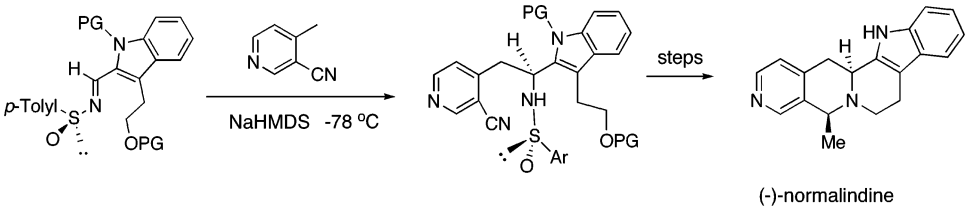
Total Synthesis of (−)-Normalindine via Addition of Metalated 4-Methyl-3-cyanopyridine to an Enantiopure Sulfinimine

Franklin A. Davis,* Jeffrey Y. Melamed, and Steven S. Sharik

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122

fdavis@temple.edu

Received July 11, 2006



A concise total asymmetric synthesis of the tetrahydronaphthyridine alkaloid (−)-normalindine has been accomplished via the addition of a laterally metalated 4-methyl-3-cyanopyridine to a sulfinimine (*N*-sulfinyl imine) as the key step.

Enantiopure tetrahydroisoquinolines and tetrahydronaphthyridines represent a large class of naturally occurring alkaloids which possess a broad range of biological activities.[1,2] Generally the synthesis of these compounds involves an intramolecular electrophilic aromatic cyclization step to form the nitrogen-containing ring of the isoquinoline. Examples include the Bischler−Napieralski,[3] Pictet−Spengler,[4] and Pomeranz−Fritch[5] reactions. Although these methods have been extensively exploited for this purpose, the success of these procedures is greatly enhanced when the aromatic ring is electron rich. Furthermore, these procedures often require harsh reaction conditions and suffer from unreliable regio- and stereoselectivity. Side reactions involving the reactive nitrilium ion intermediates can also be an issue. While some methods have been devised to circumvent these limitations, these procedures are largely target specific.[6]

An attractive alternative to the Bischler−Napieralski and Pictet−Spengler protocols is the addition of laterally lithiated amides and nitriles **1** to imines, such as enantiopure sulfinimines (*N*-sulfinyl imines) **2** (Scheme 1).[7] Indeed, this methodology has the promise of overcoming many of the problems of the electrophilic cyclization processes and to provide isoquinolines with substitution patterns not easily accessible by other means. The nitrogen-containing ring is formed via a nucleophilic cyclization step of the sulfinamide intermediate **3** with the aromatic ring amide or nitrile substituent. The resulting isoquinolone **4** and cyclic imine **5** can be readily elaborated to tetrahydroisoquinolines. Using this methodology, we have described highly stereoselective asymmetric syntheses of (2*R*,4*S*)-(−)-6-methoxy-*N*-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline-4-ol (**6**),[8] *trans*-(1*R*,3*R*)-(−)-6,8-dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**7**),[9] the isoquinoline segment of the anti-HIV michellamines, and (−)-xylopinine (**8**), the prototypical member of the protoberberine alkaloids.[10] In these studies, it was found that the addition of laterally lithiated nitriles to enantiopure sulfinimines was preferred over laterally lithiated

(1) (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, p 252. (b) Bringman, G.; Pokorny, F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1995; Vol. 46, p 128. (c) Bhakuni, D. S.; Jain, S. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 28, p 95.

(2) (a) Massiot, G.; Thepenier, P.; Jacquier, M. J.; Men-Olivier, L. L.; Verpoorte, R.; Delaude, C. *Phytochemistry* **1987**, *26*, 2839. (b) Jahangir; Brook, M. A.; MacLean, D. B.; Holland, H. L. *Tetrahedron* **1987**, *43*, 5761. (c) Phillipson, J. D.; Hemingway, S. R. *Phytochemistry* **1974**, *13*, 973. (d) Erdelmeier, C. A.; Regenass, U.; Rali, T.; Sticher, O. *Planta Med.* **1992**, *58*, 43. (e) Abreu, P.; Pereira, A. *Heterocycles* **1998**, *48*, 885. (f) Arbain, D.; Putra, D. P.; Sargent, M. V. *Aust. J. Chem.* **1993**, *46*, 977. (g) Caprasse, M.; Tavernier, D.; Anteunis, M. J. O.; Angenot, L. *Planta Med.* **1984**, *50*, 27. (h) Arbain, D.; Lajis, N. H.; Putra, D. P.; Sargent, M. V.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1993**, *46*, 969. (i) Arbain, D.; Byrne, L. T.; Dachriyanus; Sargent, M. V. *Aust. J. Chem.* **1997**, *50*, 1109.

(3) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 74.

(4) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1951**, *6*, 151.

(5) Gensler, W. J. *Org. React.* **1951**, *6*, 191.

(6) (a) Mendelson, W. L.; Spainhour, C. B., Jr.; Jones, S. S.; Lam, B. L.; Wert, K. L. *Tetrahedron Lett.* **1980**, *21*, 1393. (b) Subimoto, A.; Shinba-Tanaka, H.; Ishikawa, M. *Synthesis* **1995**, 431. (c) Quallich, G. J.; Makowski, T. W.; Sander, A. F.; Urban, F. J.; Vazquez, E. *J. Org. Chem.* **1998**, *63*, 4116.

(7) For reviews on lateral lithiation reactions, see: (a) Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 5. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

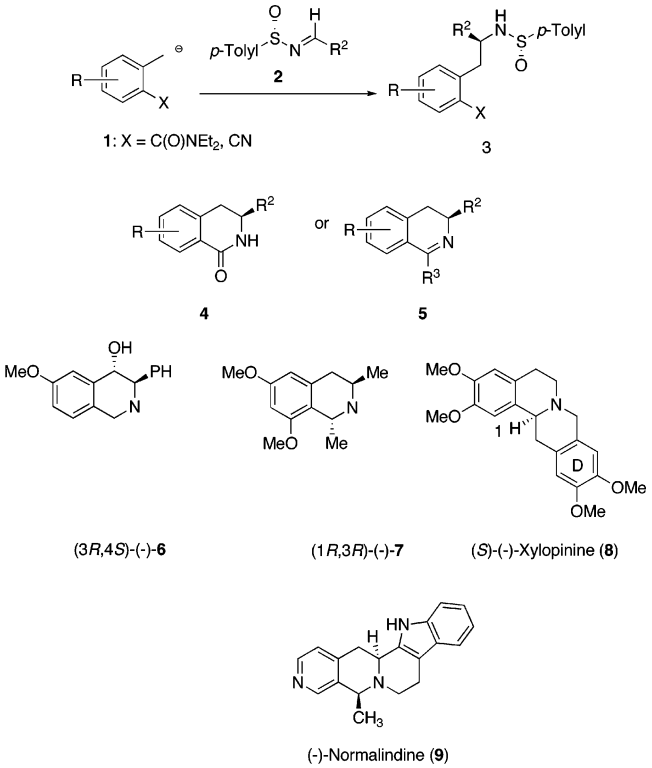
(8) Davis, F. A.; Andemichael, Y. W. *J. Org. Chem.* **1999**, *64*, 8627.

(9) Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett.* **2000**, *2*, 3901.

(10) Davis, F. A.; Mohanty, P. K. *J. Org. Chem.* **2002**, *67*, 1290.

10.1021/jo061443+ CCC: $33.50
Published on Web 10/18/2006

SCHEME 1



amides because the cyclic imine is formed in one pot. Furthermore, the formation of atropisomers in the sulfinamide derived from the laterally lithiated amides made it difficult to determine the diastereoselectivity of the reaction.

(−)-Normalindine (**9**) is an unusual 1,3-*cis*-disubstituted tetrahydronaphthyridine alkaloid which was isolated from the root bark of *Strychnos johnsonii*.[2a] This alkaloid has been the subject of several racemic syntheses[11] but only one asymmetric synthesis. In their preparation of (−)-**9**, Ohba and co-workers employed an intramolecular oxazole−olefin Diels−Alder cyclization to form the key tetrahydronaphthyridine core.[12] Although their synthesis confirmed the absolute configuration of the natural product, it required 16 steps with an overall yield of less than 0.1%. Here we describe a highly efficient asymmetric synthesis of (−)-**9**, requiring 8 steps with an overall yield of 14%, using our laterally lithiated nitrile sulfinimine technology.

In earlier work, we attributed the high diastereoselectivities for the addition of laterally lithiated *ortho*-tolylnitriles to sulfinimines based on the *o*-quinonedimethane structure which was chelated through a lithium cation to the sulfinyl oxygen.[9] On the basis of this hypothesis, one would predict that the diastereoselectivity for sulfinimine addition could be poor (Scheme 2) if in the *o*-quinonedimethane structure **12** generated from 3-cyano-4-methylpyridine (**11**) the anion is localized at the pyridine nitrogen. For this reason, we first carried out a model study for the addition of **12** to sulfinimine (*S*)-(+)-**13** before pursuing the synthesis (−)-normalindine (**9**).

3-Cyano-4-methylpyridine (**11**) was prepared in 80% yield by the catalytic palladium(0) coupling of zinc cyanide with

SCHEME 2

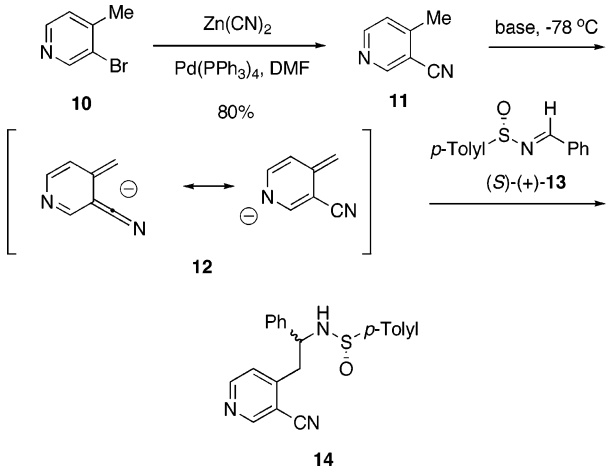


TABLE 1. Addition of Metalated 11 to (*S*)-(+)-13 at −78 °C

entry	base[a]	solvent	**14** % isolated yield[b] (% de)[c]
1	LDA	THF	56 (18)
2	LDA	toluene	no reaction
3	LDA	ether	23 (16)
4	LiHMDS	THF	32 (16)
5	NaHMDS	THF	22 (60)
6	NaHMDS[d]	THF	87 (58)
7	KHMDS	THF	68 (34)

[a] Anion aged for 30 min before adding to **13**. [b] Yields correspond to the diastereomeric mixtures. [c] Determined by ^{1}H NMR on the crude reaction mixtures. [c] Anion aged for 2 min before adding to **13**.

3-bromo-4-methylpyridine (**10**) (Scheme 2).[10] The laterally metalated species were generated by the addition of **11** to a solution of base in THF at −78 °C and resulted in an intense orange colored solution of the anion. After 0.5 h, (*S*)-(+)-**13** was added dropwise to the base solution. The reaction was complete as determined by TLC of the solution (typically 15 min) and was quenched with a saturated aqueous NH_4Cl solution. Flash chromatography afforded the sulfinamide products **14** as an inseparable mixture of diastereomers. These results are summarized in Table 1.

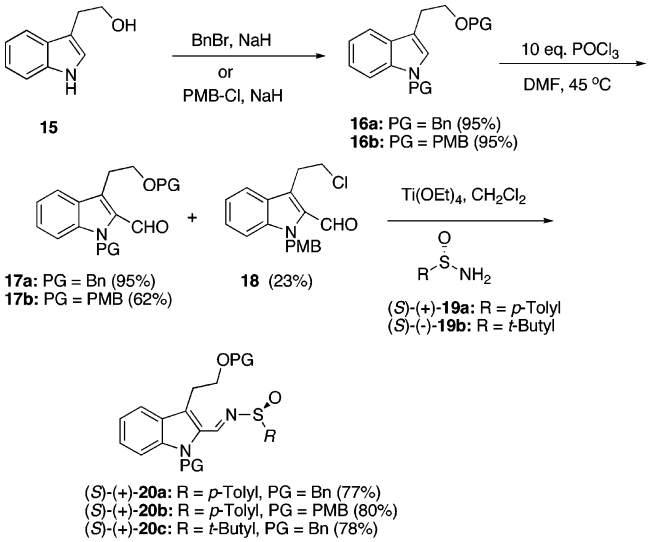
The results summarized in Table 1 reveal that LDA, the base of choice for the generation of laterally lithiated *o*-tolunitriles,[6b,c] gave poor diastereomeric excesses of the desired product with **11** (Table 1, entry 1). Diethyl ether gave lower yields, probably due to the poor solubility of the laterally lithiated species in this solvent (Table 1, entry 3). No improvement in the yield or diastereomeric excess was noted with LiHMDS or KHMDS (Table 1, entries 4 and 7). However, NaHMDS resulted in a diastereomeric excess of 60%, but the yield was poor (Table 1, entry 5). The isolated yield was dramatically improved when the anion was formed and subsequently quenched with sulfinimine within 2 min. Apparently longer reaction times resulted in product decomposition. Although results using NaHMDS as the base were promising, the product diastereoisomers **14** proved to be inseparable. However, an advantage of our synthetic methodology is that modification of the sulfinimine often not only improves the diastereoselectivity but also results in chromatographically separable products.

The synthesis of (−)-normalindine (**9**) begins with the preparation of the requisite sulfinimines **20a**−**c** as outlined in Scheme 3. Commercially available tryptophol (**15**) was protected with either a benzyl or *p*-methoxy benzyl (PMB) to give **16a**

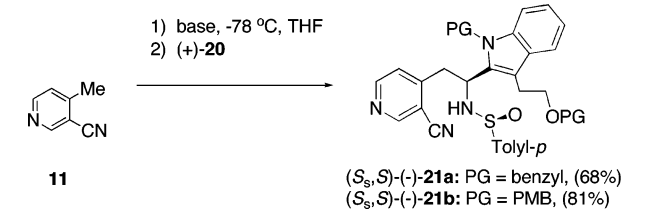
(11) (a) Maiti, B. C.; Giri, V. S.; Pakrashi, S. C. *Heterocycles* **1990**, *31*, 847. (b) Rey, A. W.; Szarek, W. A.; MacLean, D. B. *Heterocycles* **1991**, *32*, 1143.

(12) (a) Ohba, M.; Kubo, H.; Fujii, T.; Ishibashi, H.; Sargent, M. V.; Arbain, D. *Tetrahedron Lett.* **1997**, *38*, 6697. (b) Ohba, M.; Kubo, H.; Ishibashi, H. *Tetrahedron* **2000**, *56*, 7751.

SCHEME 3



SCHEME 4



and **16b**, respectively, in excellent yields. The Vilsmeier formylation reaction of the protected indoles **16** with $POCl_3$ in DMF afforded the corresponding aldehydes **17a** and **17b** in moderate to excellent yields.[14] Apparently, in the course of this reaction with **17b**, some hydrolysis of the PMB group occurs, resulting in the formation of alkyl chloride **18**, which was isolated in 23% yield (Scheme 3). The optimal conditions for the Vilsmeier reaction proved to be 10 equiv of $POCl_3$ in DMF at 45 °C for 3 h. Sulfinimines **20a**−**c** were prepared in 77−80% yields in the usual manner by condensing the aldehydes with either (*S*)-(+)-*p*-toluenesulfinamide (**19a**) or (*S*)-(−)-*tert*-butanesulfinamide (**19b**) in the presence of $Ti(OEt)_4$ in refluxing CH_2Cl_2 for 24 h.[15]

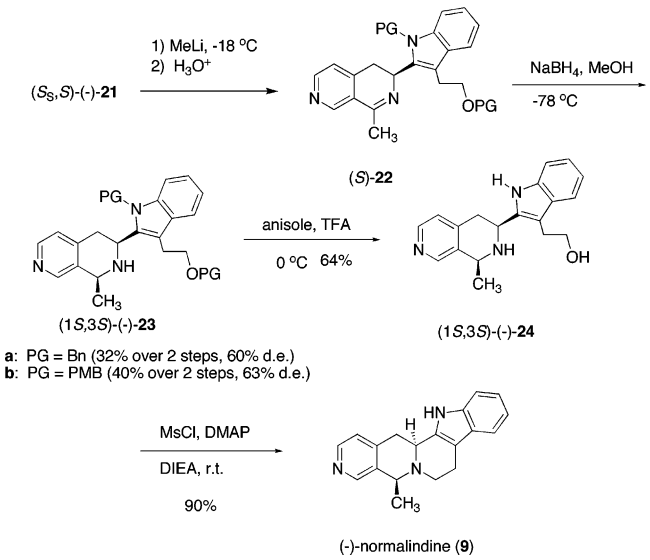
Next, 3-cyano-4-methylpyridine (**11**) was treated with the appropriate base at −78 °C in THF, affording the orange colored solution of the anion (Scheme 4). Addition of the sulfinimines **20a**−**c** to the anion solution quenched the color, producing the diastereomeric sulfinamides **21a**,**b** (Table 2). The results revealed in Table 2 indicated that while LiHMDS and KHMDS gave moderated diastereomeric excess values of 40 and 60%, respectively, the yields were poor to modest (Table 2, entries 1 and 2). However, when NaHMDS was employed as the base, the diastereomeric excesses were better than 80%. Furthermore, the diastereoisomers were easily separated, affording the major isomers (S_S,*S*)-(−)-**21a** and (S_S,*S*)-(−)-**21b** in 68 and 81% isolated yields, respectively (Table 2, entries 3 and 4). Decomposition occurred upon addition of the anion of **11** to the (*S*)-(−)-*tert*-butanesulfinimine **20c** (Table 2, entry 5). The major

TABLE 2. Addition of the Anion of 11 to (+)-20 at −78 °C in THF

entry	(+)-**20** R =	(+)-**20** PG =	conditions, base, time[a]	sulfinamide (−)-**21** % isolated yield[b] (% de)[c]
1	**20a** (*p*-tolyl)	Bn	LiHMDS, 30 min	27 (40)
2	**20a** (*p*-tolyl)	Bn	KHMDS, 30 min	50 (64)
3	**20a** (*p*-tolyl)	Bn	NaHMDS, 2 min	68 (80)
4	**20b** (*p*-tolyl)	PMB	NaHMDS, 2 min	81 (82)
5	**20c** (*t*-Bu)	Bn	NaHMDS, 2 min	no reaction

[a] Time for anion formation, before adding **20**. [b] Isolated yield of major diastereoisomer. [c] Determined by ^1H NMR on the crude reaction mixture.

SCHEME 5



diastereoisomer is predicted to have the (*S*)-configuration at the newly created chiral center in sulfinamide **21**, based on our earlier proposed chelated transition state hypothesis.[8,9] Indeed, this was confirmed in the total synthesis of (−)-normalindine (**9**).

Reaction of sulfinamides (−)-**21** with MeLi, followed by addition of aqueous HCl, accomplishes four operations in one pot: (i) installation of the 1-methyl group, (ii) removal of the sulfinyl auxiliary, (iii) hydrolysis of the resulting ketimine to the methyl ketone, and (iv) formation of the cyclic imines **22** (Scheme 5). The resulting imines were unstable to silica gel chromatography and therefore were immediately reduced with sodium borohydride to give the corresponding disubstituted tetrahydronaphthyridines (1*S*,3*S*)-(−)-**23a** and (1*S*,3*S*)-(−)-**23b** in modest 60 and 63% de, respectively.[16] Other reducing reagents, such as Super-Hydride or $LiBH_4$, failed to improve the diastereoselectivity. Chromatographic separation of the diastereoisomers afforded (−)-**22a** and (−)-**22b** in 46 and 65% isolated yields, respectively, for the two-step reaction sequence (Scheme 5).

Removal of the alcohol and indole benzyl protecting groups from (−)-**23a** was explored next. Dissolving metal reduction with sodium and liquid ammonia led to only trace amounts of (−)-**24**. Catalytic hydrogenation with 10% Pd−C with or without acetic acid at 350 psi in a Parr high-pressure reactor

(13) Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887.
(14) Walkup, R. E.; Linder, J. *Tetrahedron Lett.* **1985**, *26*, 2155.
(15) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403.
(16) Bringmann, G.; Weirich, R.; Reuscher, H.; Jansen, J. R.; Kinzinger, L.; Ortmann, T. *Liebigs Ann. Chem*. **1993**, 877.

produced none of the desired product, and starting materials were recovered. Aluminum chloride, anisole-mediated deprotection of the benzyl groups led to molecular destruction, again with only trace amounts of **24** being detected.

Fortunately, we were able to remove the PMB protecting group in (−)-**23b** using a modification of the procedure reported by Forbes and co-workers.[17] They reported that PMB deprotection of a protected indole could be accomplished in high yield with trifluoroacetic acid (TFA) in the presence of concentrated sulfuric acid and anisole. However, when **23b** was submitted to these reaction conditions, only low yields of the desired product (−)-**24** were obtained; ca. 15% and numerous other impurities was observed. The elimination of sulfuric acid led to cleaner conversion to **24**. Here the TFA and 10 equiv of anisole solution were cooled to 0 °C followed by addition of **23b**. The reaction turned deep green and after 30 min was complete, affording (−)-**24** in 64% isolated yield. Monitoring the reaction by TLC indicated that deprotection of the alcohol occurred first followed by a slower removal of the protecting group on the indole nitrogen. This represents the first simultaneous deprotection of an alcohol and indole protecting groups.

Cyclization was easily accomplished by reaction of (−)-**24** with methanesulfonyl chloride, (dimethylamino)pyridine, and Hunigs base, resulting in a 90% yield of (−)-normalindine (**9**). This concise synthesis provided (−)-**9** in 8 steps with an overall yield of 14% from commercially available starting materials. The spectral properties, specific rotation, and melting point of (−)-normalindine (**9**) were in agreement with literature values.[2f] Importantly, this methodology suggests that it will find applications in the asymmetric synthesis of other electron-deficient tetrahydroisoquinolines and tetrahydronaphthyridines.

Experimental Section

(*S*)-(−)-*N*-(Benzylidene)-*p*-toluenesulfinamide (**13**) was prepared as previously described.[15]

(S_S,*S*)-(+)-*N*-[(1)-2-(3-Cyanopyridin-4-yl)-1-phenylethyl]-4-methylbenzenesulfinamide (14). In a 100 mL, three-necked oven-dried round-bottom flask equipped with a magnetic stirring bar and rubber septum under argon were placed anhydrous THF (8 mL) and NaHMDS (8.47 mL, 1.0 M in THF, 8.47 mmol). The solution was cooled to −78 °C, and 4-methyl-3-cyanopyridine (**11**) (0.50 g, 4.2 mmol) in THF (3 mL) was added dropwise while keeping the internal temperature less than −76 °C. To the yellow solution was immediately added (*S*)-(+)-**13** (1.04 g, 4.23 mmol) in THF (5 mL) dropwise. After stirring for 2 min, the reaction mixture was quenched with aqueous NH_4Cl (10 mL) at −78 °C, and the solution was warmed to room temperature. After dilution with water (10 mL) and EtOAc (20 mL), the phases were separated, the aqueous layer was extracted with EtOAc (20 mL), and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography ($CHCl_3$/MeOH, 98:2) afforded 1.1 g (87%) of a mixture of diastereomers (79:21): $[\alpha]^{20}_D$ +9.5° (*c* 1.0, MeOH); ^{1}H NMR of the major diastereomer (DMSO-d_6) δ 8.78 (s, 1 H), 8.67 (d, J = 5.2 Hz, 1 H), 7.49 (m, 2 H), 7.30 (d, J = 5.2 Hz, 1 H), 7.27 (m, 5 H), 7.12 (m, 2 H), 4.75 (m, 1 H), 4.45 (d, J = 5.8 Hz, 1 H), 3.59 (dd, J = 7.2, 13.8 Hz, 1 H), 3.39 (dd, J = 7.6, 13.7 Hz, 1 H), 2.42 (s, 3 H); ^{13}C NMR (DMSO) δ 153.1, 151.1, 142.2, 140.9, 137.9, 129.1, 128.0, 127.1, 126.5, 125.5, 116.0, 110.3, 57.1, 42.3, 21.2. ES HRMS calcd for $C_{21}H_{19}N_3OS$ (M + H): 362.1319. Found: 362.1321.

1-Benzyl-3-(2-(benzyloxy)ethyl)-1*H*-indole (16a). In a 500 mL, round-bottom flask equipped with a stirring bar and rubber septum under an argon atmosphere were placed bromobenzene (13.26 g, 77.5 mmol) and NaH (1.48 g, 61.8 mmol) in DMF (250 mL) at 0 °C. Tryptophol (**15**) (20 mL, 15.5 M in DMF, 31.0 mmol) was then added to the reaction mixture at 0 °C. The reaction mixture was warmed to room temperature, stirred for 12 h, and quenched with water (100 mL). The organic phase was extracted with Et_2O (3 × 50 mL), dried (Na_2SO_4), and concentrated. Purification by flash chromatography (hexane/Et_2O 10:1) gave 7.30 g (95%) of an oil: ^{1}H NMR ($CDCl_3$) δ 7.71 (d, J = 7.2 Hz, 1 H), 7.38 (m, 8 H), 7.22 (m, 4 H), 7.07 (s, 1 H), 5.34 (s, 2 H), 4.65 (s, 2 H), 3.89 (d, J = 7.5 Hz, 2 H), 3.20 (d, J = 7.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 138.6, 137.8, 136.6, 128.8, 128.4, 128.3, 127.8, 127.6, 126.9, 126.3, 121.8, 119.1, 119.0, 112.2, 109.7, 73.0, 70.8, 50.0, 25.9. HRMS calcd for $C_{24}H_{23}NO$ (M + H): 342.1893. Found: 342.1835.

1-(4-Methoxybenzyl)-3-(2-(4-methoxybenzyloxy)ethyl)-1*H*-indole (16b). In a 250 mL, round-bottom flask equipped with a stirring bar and rubber septa under an argon atmosphere were placed *p*-methoxybenzyl chloride (2.43 g, 15.51 mmol) and NaH (0.37 g 77.5 mmol) in DMF (100 mL) at 0 °C. To the reaction mixture was added dropwise tryptophol (**15**) (10 mL, 6.2 M in DMF, 6.2 mmol) at 0 °C, and the solution was warmed to room temperature and stirred for 12 h. At this time, the reaction mixture was quenched with water (30 mL), and the organic phase was extracted with Et_2O (3 × 25 mL), dried (Na_2SO_4), and concentrated. Purification by flash chromatography (hexane/Et_2O, 10:1) gave 2.18 g (95%) of an oil: ^{1}H NMR ($CDCl_3$) δ 7.67 (d, J = 8.4 Hz, 1 H), 7.35 (m, 4 H), 7.19 (m, 4 H), 7.03 (s, 1 H), 6.92 (m, 4 H), 5.28 (s, 2 H), 4.57 (s, 2 H), 3.88 (s, 2 H), 3.85 (s, 3 H), 3.83 (t, J = 7.2 Hz, 2 H), 3.16 (t, J = 7.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 159.2, 159.1, 136.5, 130.7, 129.8, 129.4, 128.3, 128.3, 126.1, 121.7, 119.1, 118.9, 114.1, 113.8, 112.1, 109.7, 72.7, 70.5, 55.4, 55.3, 49.4, 25.9. HRMS calcd for $C_{26}H_{27}NO_3$ (M + H): 402.2064. Found: 402.2054.

1-Benzyl-3-(2-(benzyloxy)ethyl)-1*H*-indole-2-carbaldehyde (17a). In a 250 mL, round-bottom flask equipped with a stirring bar and rubber septum under an argon atmosphere were placed phosphoryl chloride (53.9 g, 102.5 mmol) and **16a** (7.30 g, 21.39 mmol) in DMF (150 mL). The reaction mixture was heated to 60 °C and stirred for 12 h, cooled to 0 °C, and 1 M NaOH (1 M, 250 mL) was slowly added. The solution was warmed to room temperature, stirred for 1 h, and saturated NH_4Cl (100 mL) was added. The organic phase was extracted with Et_2O (3 × 70 mL), dried (Na_2SO_4), and concentrated. Purification by flash chromatography (hexane/EtOAc 10:1) gave 7.84 g (95%) of a yellow oil: ^{1}H NMR ($CDCl_3$) δ 10.25 (s, 1 H), 7.84 (d, J = 6.1 Hz, 1 H), 7.31 (m, 13 H), 5.91 (s, 2 H), 4.60 (s, 2 H), 3.86 (t, J = 7.1 Hz, 2 H), 3.52 (t, J = 6.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 182.0, 138.1, 131.4, 128.7, 128.6, 128.5, 128.0, 127.7, 127.7, 127.6, 127.5, 127.4, 127.3, 126.7, 126.6, 126.5, 121.5, 121.1, 120.7, 111.2, 111.0, 73.2, 70.7, 47.9, 24.8. HRMS calcd for $C_{25}H_{23}NO_2$ (M + H): 370.1802. Found: 370.1786.

1-(4-Methoxybenzyl)-3-(2-(4-methoxybenzyloxy)ethyl)-1*H*-indole-2-carbaldehyde (17b). In a 50 mL, round-bottom flask equipped with a stirring bar and rubber septum under an argon atmosphere were placed phosphoryl chloride (0.95 g, 6.2 mmol) and **16b** (0.25 g, 0.62 mmol) in DMF (1.5 mL, 0.4 molar) at room temperature. The reaction mixture was heated to 45 °C for 4.5 h. At this time, the reaction mixture was cooled to 0 °C in an ice bath, and NaOH (3 mL, 1 M) was added, and the solution was stirred for 1 h at room temperature. At this time, saturated NH_4Cl (3 mL) was added, and the organic phase was extracted with Et_2O (3 × 15 mL), dried (Na_2SO_4), and concentrated. Purification by flash chromatography (hexane:EtOAc, 10:1) gave 0.16 g (62%) of a yellow oil: ^{1}H NMR ($CDCl_3$) δ 10.21 (s, 1 H), 7.78 (dd, J = 1.2, 8.1 Hz, 1 H), 7.46 (m, 2 H), 7.55 (m, 1 H), 7.25 (m, 3 H), 7.13 (d, J = 8.1 Hz, 2 H), 6.87 (m, 4 H), 5.82 (s, 2 H), 4.51 (s, 2 H), 3.87 (m, 3 H), 3.81 (m, 6 H), 3.47 (t, J = 6.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 182.0, 159.2, 158.8, 139.6, 131.3, 130.3, 130.2, 129.2, 128.0, 128.0, 127.4, 126.7, 121.4, 120.6, 114.0, 114.0, 113.8,

(17) Forbes, I. T.; Johnson, C. N.; Thompson, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 275.

111.0, 72.8, 70.4, 55.3, 55.3, 47.3, 24.8. HRMS calcd for $C_{27}H_{27}NO_4$ (M + Na): 452.1838. Found: 452.1829.

1-(4-Methoxybenzyl)-3-(2-chloroethyl)-1*H*-indole-2-carbaldehyde (18). Purification by flash chromatography (hexane/EtOAc, 10:1) gave 0.63 g (24%) of a clear oil: ^{1}H NMR ($CDCl_3$) δ 10.25 (s, 1 H), 7.84 (d, J = 6.1 Hz, 1 H), 7.31 (m, 13 H), 5.91 (s, 2 H), 4.60 (s, 2 H), 3.86 (t, J = 7.1 Hz, 2 H), 3.52 (t, J = 6.8 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 182.0, 138.1, 131.4, 128.7, 128.6, 128.5, 128.0, 127.7, 127.7, 127.6, 127.5, 127.4, 127.3, 126.7, 126.6, 126.5, 121.5, 121.1, 120.7, 111.2, 111.0, 73.2, 70.7, 47.9, 24.8. HRMS calcd for $C_{19}H_{18}ClNO_2$ (M + H): 328.1099. Found: 328.1105.

(*S*)-(+)-*N*-((1*E*)-{1-Benzyl-3-[2-(benzyloxy)ethyl]-1*H*-indol-2-yl}methylidene)-4-methylbenzenesulfinamide (20a). In a 250 mL, oven-dried round-bottom flask equipped with a reflux condenser, magnetic stirring bar, and rubber septum under argon was placed **17a** (3.57 g, 9.66 mmol) in anhydrous CH_2Cl_2 (75 mL). To the solution were added $Ti(OEt)_4$ (22.0 g, 96.6 mmol) and *p*-toluenesulfinamide (*S*)-(+)-**19a** (1.82 g, 11.60 mmol). The solution was refluxed for 20 h, cooled to room temperature, and was slowly poured into a 1 L beaker containing ice water (200 mL) and CH_2Cl_2 (100 mL) with vigorous stirring. The resulting white solids were collected by vacuum filtration, and the organic and aqueous phases were added to a separatory funnel. The aqueous phase was extracted with CH_2Cl_2 (200 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification by flash chromatography (hexane:EtOAc, 10:1) gave 3.75 g (76%) as a light yellow oil: $[\alpha]^{20}_D$ 28.2° (*c* 2.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.19 (s, 1 H), 7.86 (d, J = 8.0 Hz, 1 H), 7.52 (d, J = 8.0 Hz, 2 H), 7.42−7.29 (m, 13 H), 7.09 (d, J = 6.2 Hz, 2 H), 6.06 (d, J = 17.2 Hz, 1 H), 5.87 (d, J = 16 Hz, 1 H), 4.65 (s, 2 H), 3.86 (m, 2 H), 3.53 (m, 2 H), 2.50 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.0, 142.6, 141.4, 140.0, 138.5, 138.3, 130.0, 129.9, 128.6, 128.5, 127.6, 127.6, 127.2, 127.1, 126.5, 126.4, 124.8, 124.8, 121.0, 120.6, 110.6, 73.1, 70.6, 48.2, 25.3, 21.6. HRMS calcd for $C_{32}H_{30}N_2O_2S$ (M + H): 507.2101. Found: 507.2076.

(S_S)-(*E*)-*N*-((1-(4-Methoxybenzyl)-3-(2-(4-methoxybenzyloxy)-ethyl)-1*H*-indol-2-yl)methylene)-4-methylbenzenesulfinamide (20b). Prepared from 1-(4-Methoxybenzyl)-3-(2-(4-methoxybenzyloxy)ethyl)-1*H*-indole-2-carbaldehyde (17b). Purification by flash chromatography (hexane/EtOAc, 10:3) gave 0.14 g (80%) of a light oil: $[\alpha]^{20}_D$ 137.8° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.01 (s, 1 H), 7.28 (m, 15 H), 6.75 (d, J = 6.9 Hz, 1 H), 5.44 (s, 2 H), 4.53 (s, 2 H), 3.86 (m, 8 H), 3.34 (t, J = 6.9 Hz, 2 H), 2.50 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.4, 159.2, 137.6, 135.5, 130.4, 130.3, 130.2, 129.8, 129.3, 129.2, 128.4, 127.6, 126.4, 126.2, 125.5, 124.4, 121.1, 121.0, 120.9, 120.3, 114.3, 113.8, 113.8, 110.8, 109.0, 72.7, 69.5, 55.3, 55.2, 48.5, 26.1, 21.5. HRMS calcd for $C_{34}H_{34}N_2O_4$ (M + H): 567.2312. Found: 567.2308.

(S_S)-(*E*)-*N*-((1-Benzyl-3-(2-(benzyloxy)ethyl)-1*H*-indol-2-yl)-methylene)-2-methylpropane-2-sulfinamide (20c). Prepared from *tert*-Butylsulfinamide (*S*)-(−)-19b and 1-Benzyl-3-(2-(benzyloxy)-ethyl)-1*H*-indole-2-carbaldehyde (17a). Purification by flash chromatography (hexane/EtOAc 10:2) gave 0.95 g (80%) of a yellow oil: mp 147−150 °C; $[\alpha]^{20}_D$ 35.6° (*c* 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.91 (s, 1 H), 7.79 (d, J = 8.1 Hz, 1 H), 7.36−7.18 (m, 11 H), 6.12 (d, J = 16.9 Hz, 1 H), 5.75 (d, J = 16.8 Hz, 1 H), 4.57 (s, 2 H), 3.81 (m, 2 H), 3.47 (m, 2 H), 1.097 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 152.3, 140.0, 138.7, 138.4, 130.3, 128.9, 128.6, 127.8, 127.7, 127.5, 127.3, 126.5, 126.0, 124.4, 121.2, 120.7, 110.6, 73.2, 70.9, 57.6, 48.3, 25.5, 22.5. HRMS calcd for $C_{29}H_{32}N_2O_2S$ (M + H): 473.2257. Found: 473.2232

(S_S,S)-(−)-*N*-[(1*S*)-1-{1-Benzyl-3-[2-(benzyloxy)ethyl]-1*H*-indol-2-yl}-2-(3-cyanopyridin-4-yl)ethyl]-4-methylbenzenesulfinamide (21a). In a 100 mL, three-necked oven-dried round-bottom flask equipped with a magnetic stirring bar and rubber septum under argon was placed NaHMDS (1.69 mL, 1.0 M in THF, 1.69 mmol) in THF (10 mL). The solution was cooled to −78 °C, and 4-methyl-3-cyanopyridine (**11**) (0.10 g, 0.85 mmol) in THF (1 mL) was added dropwise while keeping the internal temperature less than −76 °C. To the yellow solution was immediately added dropwise (*S*)-(+)-**20a** (0.43 g, 0.85 mmol) in dry THF (3 mL). After stirring for 2 min, the reaction mixture was quenched with saturated NH_4Cl (10 mL) at −78 °C, and the solution was warmed to room temperature. After dilution with water (10 mL), EtOAc (20 mL) was added, the organic phase was separated, and the aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography (10−40% acetone/hexanes) afforded 0.36 g (68%) of the major diastereomer as a white solid: mp 49−51 °C; $[\alpha]^{20}_D$ −44.0° (*c* 0.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1 H), 8.38 (d, J = 5.2 Hz, 1 H), 7.53 (d, J = 8 Hz, 1 H), 7.37 (d, J = 8 Hz, 2 H), 7.29−7.13 (m, 14 H), 6.71 (d, J = 7.2 Hz, 2 H), 6.60 (br s, 1 H), 5.25−5.20 (m, 1 H), 4.81−4.70 (m, 2 H), 4.26 (d, J = 12 Hz, 1 H), 4.23 (d, J = 11.6 Hz, 1 H), 3.89−3.86 (m, 1 H), 3.70 (t, J = 8 Hz, 1 H), 3.65−3.60 (m, 1 H), 3.24−3.19 (m, 3 H), 2.36 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 153.0, 152.6, 150.6, 141.8, 141.3, 138.3, 137.8, 137.3, 130.0, 129.4, 128.8, 128.4, 128.2, 127.9, 127.9, 126.2, 126.2, 125.0, 123.1, 120.1, 119.0, 116.4, 111.9, 111.8, 110.2, 73.1, 70.0, 50.3, 46.3, 41.1, 25.9, 21.3. HRMS calcd for $C_{39}H_{36}N_4O_2S$ (M + H): 625.2632. Found: 625.2659.

(S_S,*S*)-(−)-*N*-[(1*S*)-2-(3-Cyanopyridin-4-yl)-1-(1-(4-methoxybenzyl)-3-{2-[(4-methoxybenzyl)oxy]ethyl}-1*H*-indol-2-yl)ethyl]-4-methylbenzenesulfinamide (21b). In a 1000 mL, three-necked oven-dried round-bottom flask equipped with a magnetic stirring bar and rubber septum under argon were placed THF (250 mL) and NaHMDS (21.2 mL, 1.0 M in THF, 21.2 mmol). The solution was cooled to −78 °C, and **11** (1.38 g, 11.7 mmol) in THF (10 mL) was added dropwise while keeping the internal temperature less than −76 °C. To the yellow solution was immediately added dropwise (*S*)-(+)-**20b** (6.0 g, 10.6 mmol) in THF (25 mL). After stirring for 5 min, the reaction mixture was quenched with aqueous NH_4Cl (200 mL) at −78 °C and the solution was warmed to room temperature. After dilution with water (100 mL), EtOAc (200 mL) was added, and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 200 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography (12.5−40% acetone:hexanes) afforded 5.9 g (81%) as a white solid: mp 55−58 °C; $[\alpha]^{20}_D$ −47.3° (*c* 1.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.55 (s, 1 H), 8.35 (d, J = 4.8 Hz, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.36 (d, J = 7.6 Hz, 2 H), 7.20 (m, 4 H), 7.12 (m, 1 H), 7.03 (d, 2 H), 6.77−6.66 (m, 5 H), 6.57 (d, J = 8.4 Hz, 2 H), 5.14 (br m, 1 H), 4.71 (br s, 2 H), 4.19 (d, J = 11.6 Hz, 1 H), 4.16 (d, J = 11.6 Hz, 1 H), 3.81 (m, 1 H), 3.77 (s, 3 H), 3.73 (s, 3 H), 3.65−3.55 (m, 2 H), 3.25−3.11 (m, 3 H), 2.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.7, 159.3, 152.9, 152.5, 150.6, 141.7, 141.4, 137.2, 135.3, 130.1, 130.0, 129.9, 127.7, 127.4, 126.2, 125.7, 125.0, 123.0, 119.9, 118.9, 116.3, 114.7, 114.1, 111.9, 111.7, 110.1, 73.1, 70.1, 55.7, 55.6, 50.5, 46.2, 41.4, 26.3, 21.7. ES HRMS calcd for $C_{41}H_{40}N_4O_4S$ (M + H): 685.2843. Found: 685.2835. Anal. Calcd for $C_{41}H_{40}N_4O_4S$: C, 71.91; H, 5.89; N, 8.18. Found: C, 71.56; H, 5.65; N, 8.04.

(1*S*,3*S*)-(−)-3-{1-Benzyl-3-[2-(benzyloxy)ethyl]-1*H*-indol-2-yl}-1-methyl-1,2,3,4-tetrahydro-2,7-naphthyridine (23a). In a 250 mL, oven-dried round-bottom flask equipped with a magnetic stirring bar and rubber septum was placed (−)-**21a** (1.0 g, 1.6 mmol) in toluene (30 mL). The solution was cooled to −18 °C, and MeLi (9.97 mL, 1.6 M in ether, 15.95 mmol) was added. After 2 h, the reaction mixture was quenched with 1 N HCl (27 mL), and stirring was continued for 1.5 h at 0 °C. At this time, saturated bicarbonate solution (50 mL) was added to neutralize the acid (pH 7.0). After dilution with water (50 mL), the solution was extracted with EtOAc (2 × 50 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated to afford a yellow solid of **22a**. Since this material was unstable to chromatography and slowly air oxidized, it was immediately taken to the reduction step.

In a separate 100 mL, oven-dried round-bottom flask equipped with a magnetic stirring bar and rubber septum were placed anhydrous MeOH (25 mL), crude imine (*S*)-**22a** (0.70 g, 1.44

mmol), and $NaBH_4$ (0.11 g, 2.88 mmol) at −78 °C. After 2 h, the reaction mixture was quenched with aqueous NH_4Cl (30 mL), and EtOAc (75 mL) was added. At this time, the solution was extracted with EtOAc (2 × 50 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography (hexanes:acetone, 70:30) afforded 0.32 g (46%) over two steps of a yellow solid: mp 55−58 °C; $[\alpha]^{20}_D$ −47.3° (*c* 1.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.44 (s, 1 H), 8.31 (d, J = 4.8 Hz, 1 H), 7.65 (m, 1 H), 7.29−7.24 (m, 8 H), 7.18−7.15 (m, 3 H), 6.93 (d, J = 6.4 Hz, 2 H), 6.78 (d, J = 5.0 Hz, 1 H), 5.92 (d, J = 17.2 Hz, 1 H), 5.59 (d, J = 17.2 Hz, 1 H), 4.51 (m, 2 H), 4.06 (q, J = 6 Hz, 1 H), 3.78 (t, J = 6.8 Hz, 2 H), 3.60 (t, J = 6.8 Hz, 2 H), 3.20−3.13 (dd, J = 11.6, 17.2 Hz, 1 H), 2.69−2.64 (dd, J = 3.4, 17.0 Hz, 1 H), 1.34 (d, J = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 147.6, 147.2, 144.1, 139.1, 138.8, 137.7, 137.5, 135.9, 129.1, 128.7, 128.1, 128.0, 127.4, 126.1, 123.9, 122.4, 119.8, 119.0, 110.7, 110.4, 73.6, 71.4, 52.0, 51.2, 48.3, 35.6, 25.7, 22.0. ES HRMS calcd for $C_{33}H_{33}N_3O$ (M + H): 488.2697. Found: 488.2716.

(1*S*,3*S*)-(−)-3-(1-(4-Methoxybenzyl)-3-{2-[(4-methoxybenzyl)-oxy]ethyl}-1*H*-indol-2-yl)-1-methyl-1,2,3,4-tetrahydro-2,7-naphthyridine (23b). In a 500 mL, oven-dried three-necked round-bottom flask equipped with a magnetic stirring bar and rubber septa was placed **21b** (2.47 g, 3.60 mmol) in ether (100 mL). The solution was cooled to −18 °C (salt water ice bath), and MeLi (22.5 mL, 1.6 M in ether, 36.0 mmol) was added dropwise. Upon addition of MeLi, the solution became heterogeneous and turned yellow. After 1 h, the reaction mixture was quenched with 1 N HCl (72 mL), stirring was continued for 1.5 h at 0 °C, and saturated bicarbonate solution (200 mL) was added. At this time, the solution was extracted with EtOAc (2 × 200 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated to give crude imine (*S*)-**22b**.

In a separate 100 mL, oven-dried round-bottom flask equipped with a magnetic stirring bar and rubber septa were placed crude imine (*S*)-**22b** (0.92 g, 1.69 mmol) and sodium borohydride (0.128 g, 3.37 mmol) in anhydrous MeOH (25 mL) at −78 °C. After stirring for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (30 mL), and EtOAc (75 mL) was added. The solution was extracted with EtOAc (2 × 50 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Flash chromatography (CH_2Cl_2/MeOH, 98:2) afforded 0.60 g (65%) and an orange solid: mp 66−70 °C; $[\alpha]^{20}_D$ −43.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.41 (s, 1 H), 8.27 (d, J = 5.1 Hz, 1 H), 7.59 (m, 1 H), 7.17−7.09 (m, 5 H), 6.85−6.75 (m, 7 H), 5.80 (d, J = 17.1 Hz, 1 H), 5.47 (d, J = 17.4 Hz, 1 H), 4.50−4.45 (dd, J = 3.6, 11.4 Hz, 1 H), 4.40 (m, 2 H), 4.03 (q, J = 6.9 Hz, 1 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 3.71 (t, J = 6.6 Hz, 2 H), 3.20 (t, J = 6.6 Hz, 2 H), 3.13 (m, 1 H), 2.63 (dd J = 3.6, 16.9 Hz, 1 H), 1.90 (br s, 1 H), 1.33 (d, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.5, 159.0, 147.6, 147.2, 144.2, 137.6, 137.5, 136.0, 131.1, 130.9, 129.7, 128.2, 127.2, 123.9, 122.4, 119.7, 119.0, 114.4, 114.1, 110.7, 110.4, 73.2, 71.1, 55.6, 55.6, 52.0, 51.2, 47.7, 35.6, 25.7, 22.1. ES HRMS calcd for $C_{35}H_{37}N_3O_3$ (M + H): 548.2913. Found: 548.2901.

2-{2-[(1*S*,3*S*)-1-Methyl-1,2,3,4-tetrahydro-2,7-naphthyridin-3-yl]-1*H*-indol-3-yl}ethanol (24). In a 50 mL, oven-dried round-bottom flask equipped with a magnetic stirring bar and rubber septa was placed **23b** (0.28 g, 0.51 mmol), and cold TFA (9 mL) was added followed by anisole (0.28 mL, 2.53 mmol). After 0.5 h, the green solution was slowly poured into ice cold saturated sodium bicarbonate solution (50 mL), and EtOAc (50 mL) was added. The solution was extracted with EtOAc (2 × 50 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography (MeOH:$CHCl_3$, 2−8%) afforded 0.99 g (64%) of a white powder: mp 203−205 °C; $[\alpha]^{20}_D$ −13.0° (*c* 1.0, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 8.66 (s, 1 H), 8.47 (d, J = 5.1 Hz, 1 H), 7.69 (d, J = 7.8 Hz, 1 H), 7.51 (d, J = 8.1 Hz, 1 H), 7.41 (d, J = 5.4 Hz, 1 H), 7.27 (t, J = 6.9 Hz, 1 H), 7.09 (t, J = 6.9 Hz, 1 H), 4.63 (dd, J = 3.0, 11.7 Hz, 1 H), 4.58−4.52 (q, J = 6.3 Hz, 1 H), 3.96 (t, J = 6.6 Hz, 2 H), 3.54 (m, 1 H), 3.23−3.14 (m, 3 H), 1.75 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (CD_3OD) δ 146.2, 146.0, 145.4, 136.2, 136.0, 135.6, 127.9, 124.1, 121.3, 118.5, 117.9, 110.7, 109.0, 62.1, 51.2, 49.4, 34.3, 27.3, 19.8. ES HRMS calcd for $C_{19}H_{21}N_3O$ (M + H): 308.1758. Found: 308.1729.

(−)-Normalindine (9). In an oven-dried 11 dram vial equipped with a magnetic stirring bar and rubber septum was added **24** (0.02 g, 0.065 mmol) in a 1:1 CH_2Cl_2/DMF (2 mL) mixture. Mesyl chloride (5 L, 0.065 mmol) and DMAP (0.002 g, 0.02 mmol) were added, and the reaction mixture was stirred at 0 °C for 1.5 h. At this time, water (5 mL) and EtOAc (5 mL) were added, and the solution was extracted with EtOAc (5 × 5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography (MeOH:CH_2Cl_2, 4%) afforded 0.010 g (90%) of a light yellow solid: mp 120−124 °C [lit.[2f] 131−136 °C]; $[\alpha]^{20}_D$ −204.0° (*c* 0.4, $CHCl_3$) [lit.[2f] $[\alpha]^{20}_D$ −210° (*c* 0.1, $CHCl_3$)]; ^{1}H NMR ($CHCl_3$) δ 8.52 (s, 1 H), 8.37 (d, J = 5.1 Hz, 1 H), 7.94 (br s, 1 H), 7.52 (d, J = 7.2 Hz, 1 H), 7.33 (d, J = 7.5 Hz, 1 H), 7.20−7.07 (m, 3 H), 3.82 (m, 2 H), 3.60 (ddd, J = 1.8, 5.3, 11.4 Hz, 1 H), 3.09−2.94 (m, 3 H), 2.84 (m, 1 H), 2.58 (td, J = 3.7, 11.4 Hz, 1 H), 1.64 (d, J = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 148.7, 146.6, 142.6, 136.5, 136.0, 134.3, 127.1, 123.1, 121.8, 119.6, 118.4, 110.9, 109.2, 57.3, 55.1, 48.8, 34.8, 22.4, 22.1. ES HRMS calcd for $C_{19}H_{19}N_3$ (M + H): 290.1652. Found: 290.1656.

Acknowledgment. This work was supported by a grant from the National Institutes of Health (GM51982), Merck through a fellowship to J.Y.M., and support in part to S.S.S. by the Howard Hughes Medicinal Institute Grant to the Undergraduate Biological Sciences Education Program at Temple University. Mass spectra were provided by Charles Ross and Joan Murphy at Merck.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds and (−)-**9**. This material is available free of charge via the Internet http://pubs.acs.org.

JO061443+