Synthesis of Tricyclic Indole-2-caboxylic Acids as Potent NMDA-Glycine Antagonists

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The practical synthesis of a series of tricyclic indole-2-carboxylic acids, 7-chloro-3-arylaminocarbonylmethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylic acids, as a new class of potent NMDA-glycine antagonists is described. The synthetic route to the key intermediate **12a** comprises a regioselective iodination of 4-chloro-2-nitrotoluene, modified Reissert indole synthesis, Jeffery's Heck-type reaction with allyl alcohol, Wittig−Horner−Emmons reaction, and iodination at the indole C-3 position. The key step in the route is an intramolecular cyclization of **12a** to give the tricyclic indole structure. Two methods of cyclization, (1) an intramolecular radical cyclization of **12a** and (2) a sequence of intramolecular Heck reaction of **12a** followed by a 1,4-reduction, were performed. The resulting tricyclic indole diester **13a** was selectively hydrolyzed to afford the desired tricyclic indole monocarboxylic acid **16** on a multihundred gram scale without any chromatographic purifications. Optical resolution of **16** to (−)-isomer **17** and (+)-isomer **18** was carried out, and the resulting isomers were derivatized, respectively. Evaluation of the optically active derivatives for affinity to the NMDA-glycine binding site using the radio ligand binding assay with [^{3}H]-5,7-dichlorokynurenic acid revealed that the derivatives of (−)-isomer **17** were more potent than the others and that especially substituted anilide (−)-isomer **24** (K_i = 0.8 nM) showed high affinity.

There is increasing evidence that over-excitation of the NMDA receptor plays an important role in neuronal cell death during ischemic or hypoxic conditions such as stroke.[1] Several binding sites on the NMDA receptor including glutamate, glycine, and channel blocker binding sites have been identified, and these sites offer a target for the drug treatment of not only stroke but other neurodegenerative disorders such as Alzheimer's and Hungtington's diseases.[2] However, an antagonist acting at the glycine binding site will be more promising than at other sites, since a glycine antagonist appears to have less adverse side effects.[3] Immediately after discovery of the glycine binding site, several structurally distinct antagonists of this site were identified, including quinoxalinediones such as 6,7-dichloroquinoxalinedione (**1a**), kynurenic acids such as 5,7-dichlorokynurenic acid (**2a**), and indole-2-carboxylic acids such as 4,6-dichloroindole-2-carboxylic acid (**3a**) (Figure 1).[3] These antagonists were, however, found not to penetrate the blood−brain barrier and thus did not show activities in vivo. Much effort has been devoted to identifying in vivo active glycine antagonists, and a few compounds including ACEA 1021[4] and L-701,324[5] have satisfied this criteria among a number of the compounds synthesized so far. On the basis of the quinoxalinedione structure, we have synthesized a series of tricyclic quinoxalinediones as a new class of potent NMDA-glycine antagonists,[6] both in in vitro and in vivo, including SM-18400, which showed extremely high affinity to the glycine site (K_i = 0.4 nM) and neuroprotective properties in several animal models.[7] We have also synthesized a series of tricyclic azakynurenic acids using a novel Stille-type coupling reaction.[8] These successful results led us to devise another tricyclic series based on indole-2-carboxylic acids. For the purpose of not only investigating the structure−activity relationship (SAR) but also extensive pharmacological and toxicological studies, we required a practical route leading to a large quantity of the target molecule. In this paper, we report a practical synthesis of tricyclic indole-2-carboxylic acids as a new class of potent NMDA-glycine antagonists.

(1) Review: Rothman, S. M.; Olney, J. W. *Trends Neurosci.* **1995**, *18*, 57.

(2) Reviews: (a) Lipton, S. A.; Rosenberg, P. A. *N. Engl. J. Med.* **1994**, *330*, 613. (b) Muir, K. W.; Lees, K. R. *Stroke* **1995**, *26*, 503.

(3) Reviews: (a) Carter, A. J. *Drugs Future* **1992**, *17*, 595. (b) Kemp, J. A.; Leeson, P. D. *Trends Pharmacol. Sci.* **1993**, *14*, 20. (c) Leeson, P. D.; Iversen, L. L. *J. Med. Chem.* **1994**, *37*, 4053. (d) Danysz, W.; Parsons, C. G. *Pharmacol. Rev.* **1998**, *50*, 597.

(4) For ACEA 1021, see: Lufty, K.; Weber, E. *Brain Res.* **1996**, *743*, 17.

(5) For L-701, 324, see: Bristow, L. J.; Hutson, P. H.; Kulagowski, J. J.; Leeson P. D.; Matheson, S.; Murray, F.; Rathbone, D.; Saywell, K. L.; Thorn, L.; Watt, A. P.; Tricklebank, M. D. *J. Pharmacol. Exp. Ther.* **1996**, *279*, 492.

(6) (a) Nagata, R.; Tanno, N.; Kodo, T.; Ae, N.; Yamaguchi, H.; Nishimura, T.; Antoku, F.; Tatsuno, T.; Kato, T.; Tanaka, H.; Nakamura, M.; Ogita, K.; Yoneda, Y. *J. Med. Chem.* **1994**, *37*, 3956. (b) Nagata, R.; Ae, N.; Tanno, N. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1527. (c) Nagata, R.; Kodo, T.; Yamaguchi, H.; Tanno, N. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1533. (d) Katayama, S.; Ae, N.; Nagata, R. *Tetrahedron: Asymmetry* **1998**, *9*, 4295.

(7) (a) SM-18400: (*S*)-9-chloro-5-[*p*-aminomethyl-*o*-(carboxymethoxy)phenylcarbamoylmethyl]-6,7-dihydro-1*H*,5*H*-pyrido[1,2,3-de]quinoxaline-2,3-dione hydrochloride. (b) Nagata, R.; Tanno, N.; Yamaguchi, H.; Kodo, T.; Ae, N.; Tanaka, H.; Nakamura, M.; Ogita, K.; Yoneda, Y. *Abstracts of Papers*. 210th Meeting of the American Chemical Society; Chicago, IL, August 1995; American Chemical Society: Washington, DC, 1995; Medi 150. (c) Tanaka, H.; Yasuda, H.; Kato, T.; Maruoka, Y.; Kawabe, A.; Kawashima, C.; Ohtani, K.; Nakamura, M. *J. Cereb. Blood. Flow. Metabol.* **1995**, *15*, Suppl. 1, S431. (d) Ohtani, K.; Tanaka, H.; Yasuda, H.; Maruoka, Y.; Kawabe, A.; Nakamura, M. *Brain Res.* **2000**, *871*, 311.

(8) Hume, W. E.; Nagata, R. *Synlett* **1997**, *5*, 473.

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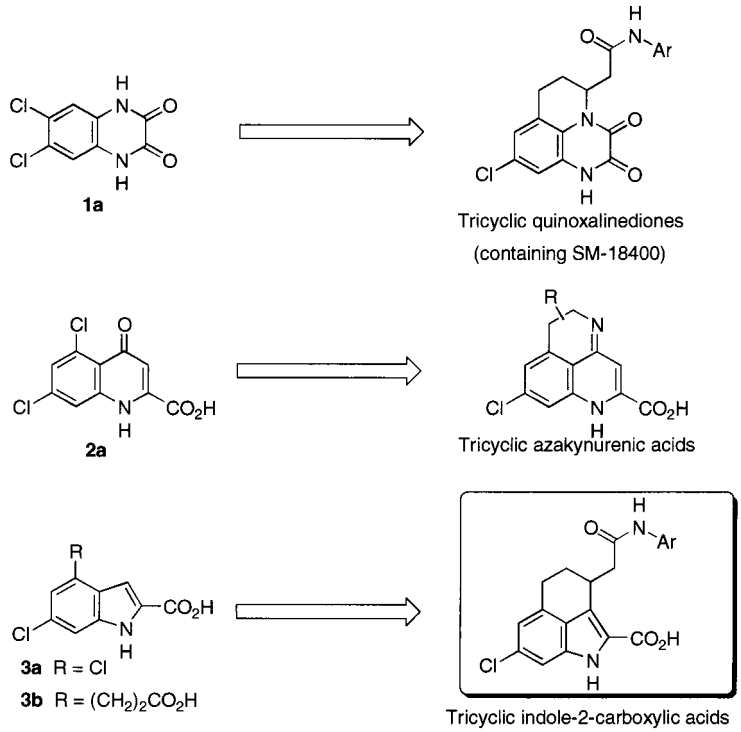
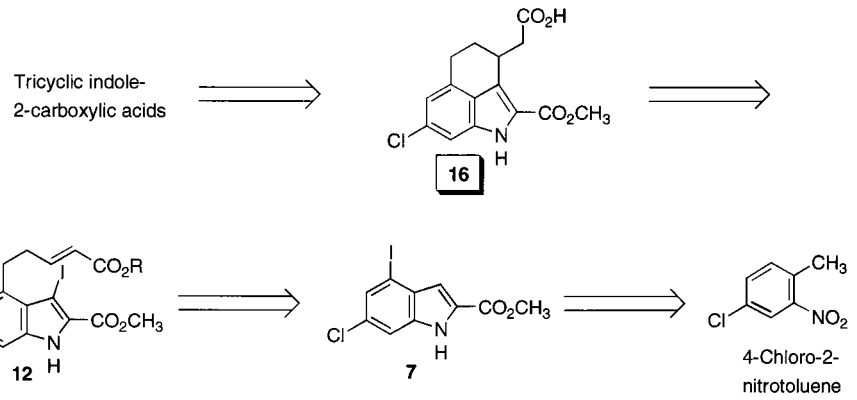


Figure 1.

Scheme 1



Results and Discussion

According to the knowledge gained from our previous study on tricyclic quinoxalinediones,[6] we expected that a series of 7-chloro-3-arylaminocarbonylmethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylic acids (tricyclic indole-2-carboxylic acids) should also be potent NMDA-glycine antagonists. To synthesize tricyclic indole-2-carboxylic acid derivatives containing various aromatic moieties on the C-3 side chain and examine their pharmacological and toxicological profiles, we required a large quantity of the desired tricyclic indole **16**. As outlined in Scheme 1, we planned to synthesize **16** by an intramolecular cyclization of precursor **12**, which could be derived from **7** by installing a C_5-unit at the C-4 position. Preparation of **7** was intended to be accomplished by a regioselective iodination of the readily available 4-chloro-2-nitrotoluene followed by a Reissert indole synthesis.[9]

Our route began with regioselective iodination[10] of 4-chloro-2-nitrotoluene, which was commercially available and inexpensive. It was expected that the nitro group should contribute to the regioselectivity of the iodination at the C-6 position. Although the desired iodide **4** was formed under typical conditions such as using iodine−silver sulfate in concentrated sulfuric acid[11] (Table 1, entries 1 and 2), both the yield and the regioselectivity were poor and considerable amounts of undesired iodide **5** and diiodide were formed as byproducts. After several experiments, we found that addition of 4-chloro-2-nitrotoluene into premixed *N*-iodosuccinimide (NIS)[12] and concentrated sulfuric acid at 0 °C afforded **4** with acceptable yield and regioselectivity (Table 1, entry 3). However, NIS was too expensive to be used in a large-scale synthesis. As an alternative, treating sodium iodate with a mixture of 4-chloro-2-nitrotoluene and iodine in concentrated sulfuric acid[13] at 5−10

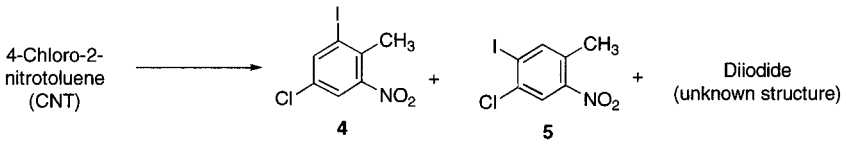
(9) Reissert, A.; Heller, H. *Chem. Ber.* **1904**, *37*, 4364.

(10) For a review of the synthesis of iodoaromatic compounds, see: Merkushev, E. B. *Synthesis* **1988**, 923.

(11) For an example of iodination using iodine−silver sulfate in concentrated sulfuric acid, see: Derbyshire, D. H., Waters, W. A. *J. Chem. Soc.* **1951**, 3694.

(12) For iodination using NIS in triflic acid, see: Olah, G. A.; Wang, Q.; Sandford, G.; Prakash, G. K. S. *J. Org. Chem.* **1993**, *58*, 3194.

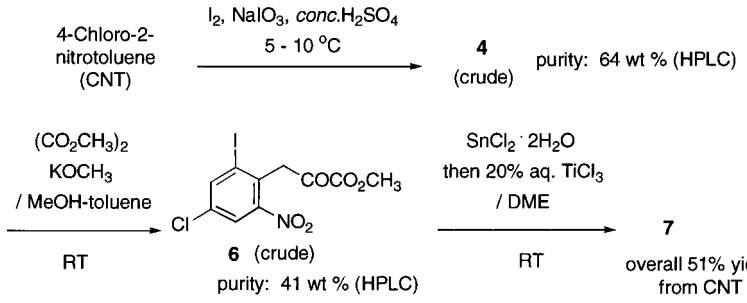
Table 1. Iodination of 4-Chloro-2-nitrotoluene



entry	reagents (molar equiv)	*T* (°C)	time (h)	yield[a] (%)	ratio[b] CNT[c]/**4**/**5**/diiodide[d]
1	I_2 (1.2), Ag_2SO_4 (1.2), H_2SO_4[e]	85	5	40	39:40:16:5
2	I_2 (1.2), Ag_2SO_4 (1.2), H_2SO_4[e]	120	3	24	0:31:26:43
3	NIS (1.8), H_2SO_4[e]	0	1	63	10:66:17:7
4	I_2 (0.4), $NaIO_3$ (0.4), H_2SO_4[e]	5−10	6	59	9:64:17:10

[a] Determined by HPLC analysis of crude products. [b] Determined by ^{1}H NMR of crude products, and values indicate the molar ratio. [c] 4-Chloro-2-nitrotoluene. [d] The structure was not determined. [e] H_2SO_4 was used as both an activator and a solvent.

Scheme 2



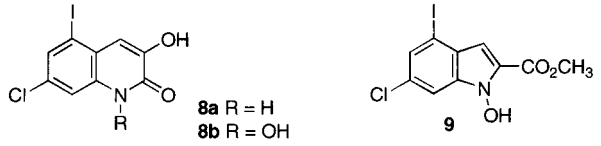


Figure 2.

°C also gave **4**, although the yield was slightly lower than that in the case of the NIS iodination (Table 1, entry 4). The crude product **4** obtained under these conditions was subjected to the next procedure without further purification (Scheme 2).

4-Iodoindole **7** was prepared from **4** in accordance with a modified Reissert procedure[9] as shown in Scheme 2. Treatment of **4** with dimethyl oxalate and potassium methoxide in a mixed solvent of toluene/methanol at ambient temperature quantitatively afforded **6**, which was used for the next step without further purification. Reductive cyclization of **6** to **7** using standard reagents such as iron powder, zinc powder, or aqueous titanium trichloride always resulted in unsatisfactory yields. The major reason for this was the accompanied formation of 3-hydroxyquinolin-2-one **8a** (Figure 2). Using zinc powder as a reducing reagent, significant deiodination was also observed. The formation of **8a** could be suppressed to less than 20% when the reduction was carried out using iron powder in a mixed solvent of toluene and acetic acid at 110 °C. An important discovery was made when tin(II) chloride dihydrate[14] was used as a reductant. Treatment of **6** with tin(II) chloride dihydrate in dimethoxyethane at room temperature did not yield **7** but *N*-hydroxyindole **9**, exclusively (Figure 2), and importantly, none of the six-membered ring product such as **8b** was detected. Quantitative conversion of **9** into the desired **7** was effected by aqueous titanium trichloride. A more useful modified Reissert indole synthesis has thus been discovered. Treatment of the crude ketoester **6** with tin(II) chloride dihydrate in DME at ambient temperature and succesive addition of aqueous titanium trichloride to the mixture produced crude **7** as a solid that was purified by a simple washing with acetonitrile to give **7** with sufficient purity (93 wt % purity, as determined by HPLC) and the overall yield from 4-chloro-2-nitrotoluene was 51%.

As shown in Scheme 3, one-step formylethylation of **7** at the C-4 position was achieved by Jeffery's Heck-type reaction using allyl alcohol.[15] More practically, cheap and readily available benzyltriethylammonium chloride was employed as a phase-transfer catalyst (PTC) instead of tetrabutylammonium chloride, which had been used in the original paper. Treatment of **7** with palladium acetate, sodium hydrogen carbonate, PTC, and allyl alcohol in DMF at 50 °C afforded aldehyde **10** in 90% yield. Wittig−Horner−Emmons reaction of **10** with ethyl diethylphosphonoacetate in THF in the presence of potassium *tert*-butoxide afforded **11a**, which underwent iodination at the C-3 position with sodium iodide-*N*-chlorosuccinimide (NCS)[16] in DMF at ambient temperature to give **12a** in 94% yield from **10**.

We next examined the intramolecular radical cyclization of **12a** to **13a**. Many successful examples in similar ω-halo-α,β-unsaturated ester systems have been re-

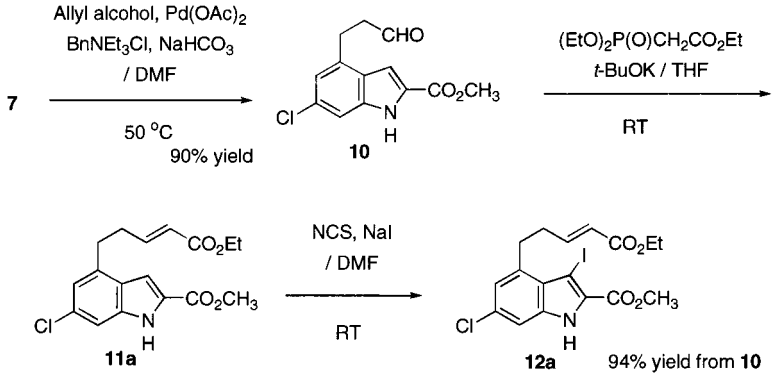
(13) For an example of iodination using a combination of iodine and sodium iodate in concentrated sulfuric acid, see: Abderhalden, E *Chem. Ber.* **1909**, *44*, 3411.

(14) For the reduction of aromatic nitro compounds with tin(II) chloride, see: Bellamy, F. D.; Ou, K. *Tetrahedron Lett.* **1984**, *25*, 839.

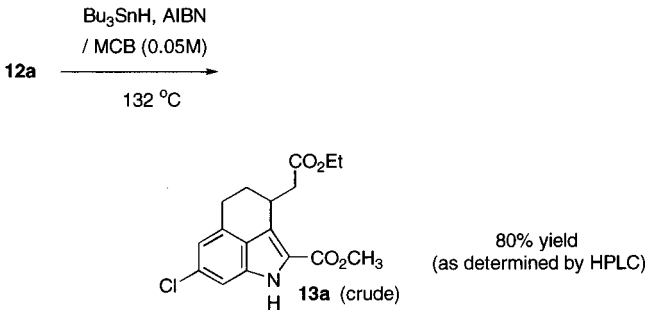
(15) For Jeffery's Heck-type reaction, see: Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287.

(16) For in situ preparation of NIS using sodium iodide-*N*-chlorosuccinimide, see: (a) Vankar, Y. D.; Kumaravel, G. *Tetrahedron Lett.* **1984**, *25*, 233. For an example of bromination of indole at C-3 position using *N*-bromosuccinimide (NBS) in DMF, see: (b) Tani, M.; Ikegami, H.; Tashiro, M.; Hiura, T.; Tsukioka, H.; Kaneko, C.; Notoya, T.; Shimizu, M.; Uchida, M.; Alda, Y.; Yokoyama, Y.; Murakami, Y. *Heterocycles* **1992**, *34* (12), 2349.

Scheme 3



Scheme 4



ported.[17] Substrate **12a** was treated with tributyltin hydride in the presence of AIBN in monochlorobenzene (MCB) to give the desired cyclized product **13a** as a major product together with a considerable amount of deiodinated byproduct **11a** (e.g., **13a**/**11a** = ca. 7:3 at 100 °C, 0.2 M). To suppress the formation of **11a**, we optimized this procedure with respect to both concentration and temperature and found that both lower concentration and higher temperature were more preferable. Slow addition of tributyltin hydride was ineffective. Simply heating a 0.05 M solution of the substrate and AIBN in MCB at 132 °C gave the most satisfactory result (Scheme 4). Under these conditions, **13a** was obtained in 80% yield as determined by HPLC together with ca. 10% of **11a** and a small amount of impurity derived from the tin reagent, although almost all the impurity was removed by washing the acetonitrile solution of the crude reaction mixture with hexane. The product was then used for the next step without further purification.

Although radical cyclization could conveniently afford the desired cyclized product, use of tributyltin hydride should be avoided in a large-scale synthesis because of its toxicity. Furthermore, the high dilution conditions required were unfavorable for scaling-up. Next, we examined an intramolecular Heck reaction. The resulting α,β-unsaturated ester could be converted to the desired saturated product by an appropriate 1,4-reduction. Examples of the construction of cyclic systems using the Heck reaction have been reported.[18] Among them, we employed at first the standard conditions using palladium(II) acetate, triphenylphosphine, and triethylamine for **12a** and soon encountered two problems. Under the conditions, the reaction was sluggish, and deiodination[19] occurred significantly although a small amount of desired **14a** was formed. To overcome these problems, we intensively investigated suitable conditions using highly purified substrate and selected examples are listed in Table 2.

To the palladium(II) acetate−triphenylphosphine system in DMF, addition of both silver(I) phosphate[20] and an appropriate amount of triethylamine cooperatively improved the yield (Table 2, entries 1−4). Silver(I) phosphate afforded a better yield than other silver(I) salts such as carbonate and sulfate (Table 2, entries 4−6). Replacement of triethylamine with PTC such as tetrabutylammonium hydrogensulfate was also effective, and interestingly addition of water to the conditions significantly increased conversion of **12a** into **14a** (Table 2, entries 7, 8).[21] Moreover, tetrakis(triphenylphosphine)-palladium(0) ($Pd(PPh_3)_4$) was found to be a catalyst more suitable for our system than others.[22] In this case, the reaction proceeded smoothly with excellent yield regardless of the presence of PTC (Table 2, entries 9, 10), although anhydrous conditions resulted in the retardation of the reaction (Table 2, entry 11). It is noteworthy that water enhanced the rate of the reaction even without PTC. Heck cyclization of **12a** was performed on a large scale under the optimized conditions using $Pd(PPh_3)_4$, silver(I) phosphate, and water in DMF (e.g., Table 2, entry 10) followed by purification by washing the crude

(17) For reviews of radical cyclization, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon Press Oxford. 1986. (b) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301.

(18) For reviews of Heck cyclization, see: (a) De Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379. (b) Jeffery, T. *Adv. Met.-Org. Chem.* **1996**, *5*, 153. (c) Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, *3*(6), 447. (d) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*(22), 7371. (e) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1998; pp 231−69. (f) Brass, S.; De Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 1998; pp 99−166. (g) Link, J. T.; Overman, L. E. *CHEMTECH* **1998**, *28* (8), 19.

(19) For an example of debromination of 3-bromoindole, see: Tani, M.; Goto, M.; Shimizu, M.; Mochimaru, Y.; Amemiya, J.; Mizuno, N.; Sato, R.; Murakami, Y. *Synlett* **1996**, 931.

(20) For examples of Heck reaction using silver(I) salt effectively and examples using $AgNO_3$, see: (a) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896. (b) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130. For an example using Ag_2CO_3, see: (c) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959. For examples using Ag_3PO_4, see: (d) Madin, A.; Overman, L. E. *Tetrahedron Lett.* **1992**, *33*, 4859. (e) Sato, Y.; Honda, T.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2593.

(21) For examples of the Heck reaction in aqueous medium, see: (a) Genet, J. P.; Blart, E.; Savignac, M. *Synlett* **1992**, 715. (b) Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051.

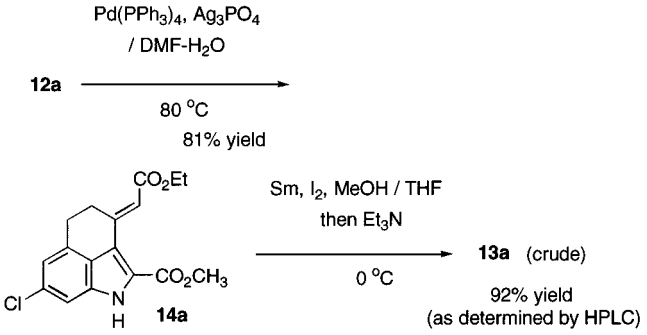
(22) For an excellent example of Heck cyclization using $Pd(PPh_3)_4$, see: McClure, K. F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 6094.

Table 2. Optimization of Conditions for Intramolecular Heck Reaction[a]

entry	catalyst[b]	additives (molar equiv)	time (h)	yield[c] (%)	ratio[d] **12a**:**14a**:**11a**
1	A	Ag_3PO_4 (2.0)	7	0	
2	A	Et_3N (3.0)	7	24	
3	A	Ag_3PO_4 (2.0), Et_3N (2.5)	7	35	39:40:21
4	A	Ag_3PO_4 (2.0), Et_3N (0.5)	7	80 (73)	10:83:7
5	A	Ag_2CO_3 (2.0), Et_3N (0.5)	7	63	17:68:15
6	A	Ag_2SO_4 (2.0), Et_3N (0.5)	7	42	41:53:6
7	A	Ag_3PO_4 (2.0), $^nBu_4NHSO_4$ (1.0)	13	70	24:73:3
8	A	Ag_3PO_4 (2.0), $^nBu_4NHSO_4$ (1.0), H_2O[e]	12	87 (82)	3:93:4
9	B	Ag_3PO_4 (0.8), $^nBu_4NHSO_4$ (0.2), H_2O[e]	6	95	1:97:2
10	B	Ag_3PO_4 (0.8), H_2O[e]	5	96 (90)	1:97:2
11	B	Ag_3PO_4 (0.8)	10	95	5:94:1

[a] Reaction conditions: 100 mg of substrate, 1.0 mL of DMF, 80 °C; other reagents and times were described in table. [b] Catalyst: (A) 4 mol % of $Pd(OAc)_2$, 0.08 equiv of Ph_3P; (B) 2 mol % of $Pd(Ph_3P)_4$. [c] Determined by HPLC analysis of crude product, and values in parentheses were isolated yields. In isolation of product, the reaction scale was 10-fold as large as that described in footote a. [d] Determined by HPLC analysis of crude product, and values were area ratio. [e] Water (0.1 mL) was added to DMF (1.0 mL).

Scheme 5



product with toluene to afford **14a** in 81% isolated yield (Scheme 5).

Unfortunately, 1,4-reduction of **14a** by hydrogenation using the typical heterogeneous catalysts such as palladium or palladium hydroxide on carbon and platinum dioxide did not proceed, even at elevated temperatures and pressures. Although the use of Wilkinson's catalyst, under 60 kg/cm^2 of hydrogen, afforded the saturated product, dechlorination was significant. Next, we investigated various electron-transfer reductions and found that the combination of samarium and iodine[23] was promising, while the use of magnesium afforded a complex mixture of products. In the literature,[23] samarium reduction of α,β-unsaturated esters was performed in alcoholic solvent such as methanol or 2-propanol. Under the conditions using methanol, however, our substrate **14a** significantly afforded the transesterified product and **14a** did not dissolve well in 2-propanol, which might have avoided the transesterification. A simple solution of the problem was to use THF as a solvent and add a small amount of methanol as a hydrogen donor. Under these conditions, the substrate was completely consumed and the desired product **13a** was formed in high yield (87%, as determined by HPLC) with concomitant formation of indoline **15a** (Figure 3, 5%). We found that **15a** could be converted into **13a** by adding some base such as triethylamine or potassium *tert*-butoxide. Under the optimum conditions with samarium, iodine, and methanol in THF at 0 °C followed by in situ treatment with triethylamine, **14a** was converted into **13a** in 92% yield (as determined by HPLC) (Scheme 5), which was used for the next step without purification. A combination of sodium borohydride and

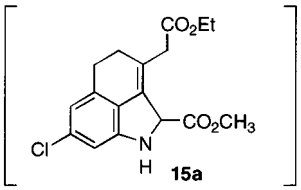
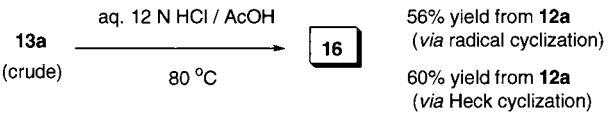


Figure 3.

Scheme 6



nickel chloride[24] in a mixed solvent of THF and methanol at 10 °C was also effective in reducing **14a** to **13a** in a practical yield (85%, as determined by HPLC).

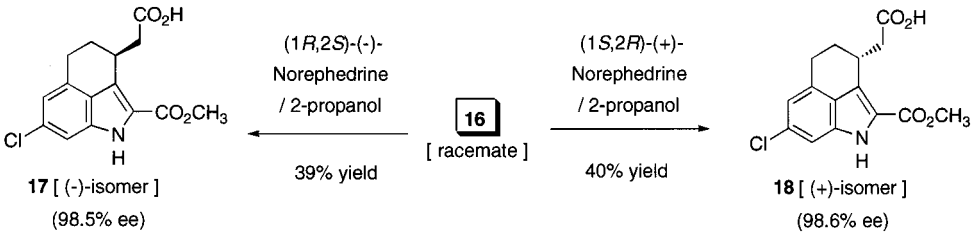
At this stage, both an ethyl and a methyl ester were present in the same molecule and it was necessary to hydrolyze selectively the ethyl ester to obtain the monocarboxylic acid **16**. Fortunately, hydrolysis of **13a** with aqueous 12 N HCl in acetic acid at 80 °C afforded **16** exclusively. As the reaction proceeded, we observed that **16** gradually precipitated out. Such precipitate formation from the reaction media might avoid further hydrolysis to the dicarboxylic acid. Crude **16** could be purified by washing with acetonitrile to sufficient purity (95 wt % purity, as determined by HPLC). Using crude **13a** obtained via radical cyclization, **16** was formed in 56% overall yield from **12a** (Scheme 6). Upon using crude **13a** obtained via the sequence of Heck cyclization and samarium reduction, the yield of **16** was slightly enhanced to 60% from **12a** (Scheme 6). It is noteworthy from the standpoint of the large-scale synthesis that any chromatographic purifications were not required through the entire sequence from 4-chloro-2-nitrotoluene to **16** whichever cyclization method was employed.

The optical resolution of racemate **16** was achieved by using (+)- and (−)-norephedrine as a resolving agent, in 2-propanol (Scheme 7). The simplified protocol of successive resolution, purification, and desalination afforded (−)-isomer **17** ($[\alpha]^{25}_D$ −105.7°, *c* 1.0, MeOH) in 39% yield using (−)-norephedrine.[25] In a similar manner, (+)-norephedrine gave (+)-isomer **18** ($[\alpha]^{25}_D$ +106.2°, *c* 1.0, MeOH) in 40% yield. The optical purity of **17** and **18** was

(23) For 1,4-reduction using samarium and iodine in alcohol, see: Yanada, R.; Bessho, K.; Yanada, K. *Synlett* **1995**, 443.

(24) For 1,4-reduction using sodium borohydride and nickel chloride, see: Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 9 (4), 817.

Scheme 7



Scheme 8

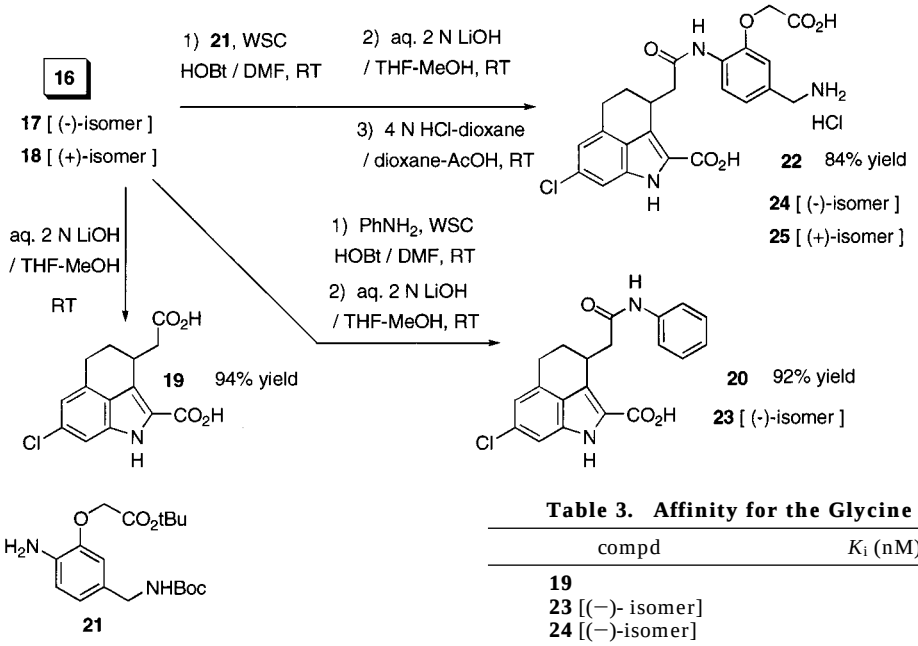


Figure 4.

determined to be 98.5% ee and 98.6% ee, respectively, by HPLC using a chiral stationary column.

Scheme 8 illustrates the synthesis of selected tricyclic indole-2-carboxylic acids which were subsequently evaluated for their biological activities. Hydrolysis of **16** with aqueous 2 N LiOH in a mixed solvent of methanol and THF provided the corresponding dicarboxylic acid **19** in 94% yield. Condensation of **16** with aniline, using a combination of 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (WSC) and 1-hydroxybenzotriazole (HOBT) in DMF, followed by saponification gave anilide **20** in 92% yield. Introduction of the anilide moiety, which is identical to that in SM-18400[7] the most potent glycine antagonist in a series of our tricyclic quinoxalinediones, to **16** by using aniline **21**[26] followed by deprotection afforded substituted anilide **22** in 84% yield. (−)-Isomers **23**, **24**, and (+)-isomer **25** were prepared starting from (−)-isomer **17** and (+)-isomer **18**, respectively, without loss of optical purity according to the procedure described for the corresponding racemic compounds as shown in Scheme 8.

Table 3. Affinity for the Glycine Binding Site[a]

compd	K_i (nM) vs [^{3}H]DCKA[b]
19	19
23 [(−)- isomer]	1.5
24 [(−)-isomer]	0.8
25 [(+)-isomer]	24
MDL29951[c] (**3b**)	13
SM-18400	0.4

[a] See ref 27. [b] DCKA: 5,7-dichlorokynurenic acid. [c] See ref 28.

The affinity of the compounds was measured by the radio ligand binding assay using [^{3}H]-5,7-dichlorokynurenic acid[27] and listed as their K_i values in Table 3. As expected, this series of tricyclic indole-2-carboxylic acids had appreciable affinity. The affinity of racemic dicarboxylic acid **19** (K_i = 19 nM) was comparable to that of MDL29951 (**3b**)[28] (K_i = 13 nM), which is a standard indole-2-carboxylic acid-based glycine antagonist. Furthermore, the affinity of anilide (−)-isomer, **23** (K_i = 1.5 nM), was much higher than that of **3b**. Remarkably, the affinity of substituted anilide (−)-isomer, **24** (K_i = 0.8 nM), was not only superior to that of **3b** but also comparable to that of SM-18400 (K_i = 0.4 nM). In contrast, the affinity of anilide (+)-isomer **25** (K_i = 24 nM) was 30-fold weaker than that of (−)-isomer **24**.

(25) The absolute configuration of (−)-isomer **17** which led to active compounds **23** and **24** was confirmed by a single X-ray crystallography to be *S*, and that was consistent with our previous results (ref 6a). The details will be published elsewhere.

(26) For the practical synthesis of SM-18400 aromatic fragment **21**, see: (a) Kodo, T.; Nishihara, T.; Nagata, R. *Abstracts of Papers*. 219th Meeting of the American Chemical Society, San Francisco, March 2000; American Chemical Society: Washington, DC, 2000; Orgn 610. For the preparation of **21** and initial synthetic routes of tricyclic indole-2-carboxylic acids, also see: (b) Nagata, R.; Tanno, N.; Ae, N. US Patent 5,496,843.

(27) For the binding assay using [^{3}H]-5,7-dichlorokynurenic acid, see: Yoneda, Y.; Suzuki, T.; Ogita, K.; Han, D. *J. Neurochem*. **1993**, *60*, 634.

(28) For MDL29951, see: Baron, B. M.; Harrison, B. L.; McDonald, I. A.; Meldrum, B. S.; Palfreyman, M. G.; Salituro, F. G.; Siegel, B. W.; Slone, A. L.; Turner, J. P.; White, H. S. *J. Pharmacol. Exp. Ther.* **1992**, *262*, 947.

Conclusion

Thus, we successfully generated a novel series of tricyclic indole-2-carboxylic acids as potent NMDA-glycine antagonists based on our tricyclic strategy by using a practical synthetic route. In particular, the anilide (−)-isomer **24** (K_i = 0.8 nM) represents a class of compounds with the highest affinity for the NMDA-glycine binding site known to date. Further modification of these molecules to improve the in vivo activities and the pharmacological evaluation are in progress.[29] The results will be published elsewhere.

Experimental Section

General Procedure. All reactions were carried out in oven-dried glassware under an atmosphere of N_2. All reagents and solvents were obtained commercially and used without purification. Melting points were uncorrected. Elemental analyses and high-resolution mass spectra were obtained from Sumitomo Analytical Center, Inc. Thin-layer chromatography and flash column chromatography were performed on silica gel glass-backed plates (5719, Merck & Co.), and silica gel 60 (230−400 or 70−230 mesh, Merck & Co.), respectively. Optical purity was determined by HPLC with chiral stationary columns (CHIRALPAK AD, Daicel; SUMICHIRAL OA-4400, OA-2500, Sumitomo Analytical Center).

2-Iodo-4-chloro-6-nitrotoluene (4). To an ice-cooled mixture of 4-chloro-2-nitrotoluene (343 g, 2.00 mol), iodine (204 g, 0.800 mol), and concentrated sulfuric acid (1.96 kg, 20.0 mol) was added portionwise sodium iodate (158 g, 0.800 mol) while the temperature was maintained below 10 °C. The mixture was then stirred at 5−10 °C for 6 h. The reaction mixture was poured slowly into 1:1 ice/water (2 L) with stirring while cooling in an ice bath, and the mixture was extracted with toluene (2.5 L). The organic layer was treated with aqueous 10% sodium thiosulfate solution (1 L × 2), washed with water (1 L × 2) and aqueous 1 N NaOH (1 L × 2) successively, dried over sodium sulfate, and concentrated to give crude **4** (548 g) as a yellow oil. This crude product was used in the following reaction without further purification. The purity of crude **4** at this stage was 62 wt % determined by HPLC. HPLC conditions: column, SUMIPAX ODS A-212; mobile phase, acetonitrile/0.1% aqueous H_3PO_4 (60:40); flow rate, 1.0 mL/min; UV detection, 254 nm; t_R for 4-chloro-2-nitrotoluene, 10.5 min; 3-iodo-4-chloro-6-nitrotoluene **5**, 17.8 min; 2-iodo-4-chloro-6-nitrotoluene **4**, 20.7 min; diiodide, 30.7 min. The crude product can be further purified by silica gel column chromatography with hexane to give the analytically pure sample as a white solid: mp 42−44 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.56 (s, 3H), 7.74 (d, 1H, J = 2.0 Hz), 8.06 (d, 1H, J = 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.48, 103.47, 124.04, 132.76, 133.63, 142.33, 149.86; HRMS (EI) (m/z) calcd for $C_7H_5NO_2ClI$ 296.9053, found 296.9064. Anal. ($C_7H_5NO_2ClI$): C, H, N.

5: ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.54 (s, 3H), 7.89 (s, 1H), 8.04 (s, 1H).

Diiodide: ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.40 (s, 3H), 8.00 (s, 1H).

Methyl (2-Iodo-4-chloro-6-nitrophenyl)pyruvate (6). Toluene (700 mL) and dimethyl oxalate (795 g, 6.73 mol) were added to a solution of potassium methoxide (470 g, 6.70 mol) in methanol (1.4 L). The mixture was stirred at room temperature for 20 min, and a solution of crude **4** (500 g) obtained above in toluene (700 mL) was added dropwise. The resulting mixture was stirred at room temperature for 4 h. The reaction mixture, being occasionally diluted with methanol (total 600 mL), was poured slowly into aqueous 5 N HCl (1.5 L) with stirring while cooling in an ice bath. After ethyl acetate (2.5 L) and water (1.5 L) were added, the organic layer was separated and the aqueous layer was extracted with 2:1 ethyl acetate/toluene (750 mL). The organic layers were combined and concentrated to give crude **6** (935 g) as a brown oil. This product was used in the following reaction without further purification. The purity of crude **6** was 41 wt % determined by HPLC. HPLC conditions: column, SUMIPAX ODS A-212; mobile phase, acetonitrile/0.1% aqueous H_3PO_4 (60:40); flow rate, 1.0 mL/min; UV detection, 254 nm; t_R for **6**, 10.1 min; **4**, 20.7 min. A pure sample of **6** was obtained as a white solid after purification by silica gel column chromatography with 20:1 hexane/ethyl acetate: mp 101−103 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.95 (s, 3H), 4.70 (s, 2H), 8.01 (d, 1H, J = 2.0 Hz), 8.15 (d, 1H, J = 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.28, 53.42, 104.71, 125.32, 130.51, 134.99, 143.57, 149.18, 160.18, 187.25; HRMS (EI) (m/z) calcd for $C_{10}H_7NO_5ClI$ 382.9057, found 382.9017. Anal. ($C_{10}H_7NO_5ClI$): C, H, N.

Methyl 4-Iodo-6-chloroindole-2-carboxylate (7). A solution of crude **6** (880 g) obtained above in dimethoxyethane (1.65 L) was added dropwise to a solution of $SnCl_2 \cdot 2H_2O$ (1.16 kg, 5.15 mol) in dimethoxyethane (1.65 L) at room temperature while the temperature was maintained below 30 °C. The mixture was stirred for 1 h at room temperature. 20% Aqueous $TiCl_3$ solution (2.65 kg, 3.43 mol) was then added dropwise to the mixture under cooling with an ice bath while the temperature was kept below 10 °C. The resulting mixture was stirred at 0−10 °C for a further 1 h. Aqueous 6 N HCl (5.6 L) and 2:1 ethyl acetate/toluene (9.6 L) were added to the reaction mixture. The organic layer was separated, washed with aqueous 1 N HCl (5.6 L), and concentrated to give the crude product (632 g). This product was suspended in acetonitrile (6.3 L), heated at reflux for 30 min, and then allowed to cool to room temperature. The precipitate produced was collected by filtration, washed with ice-cooled acetonitrile (600 mL × 2), and dried in vacuo to give **7** (295 g, 51% overall yield from 4-chloro-2-nitrotoluene) as a white solid. The purity of **7** was 93 wt % determined by HPLC. HPLC conditions: column, SUMIPAX ODS A-212; mobile phase, acetonitrile/0.1% aqueous H_3PO_4 (55:45); flow rate, 1.0 mL/min; UV detection, 254 nm; t_R for **6**, 13.7 min; intermediate **9**, 19.1 min; **7**, 27.8 min. Compound **7** could be further purified by recrystallization from acetone/water to give the analytically pure sample as a white solid: mp 216−218 °C; ^{1}H NMR (270 MHz, DMSO-d_6) δ 3.89 (s, 3H), 6.91 (s, 1H), 7.48 (m, 1H), 7.56 (d, 1H, J = 2.0 Hz), 12.5 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 52.15, 89.80, 110.24, 112.18, 128.46, 129.02, 129.40, 130.07, 135.84, 161.07; HRMS (EI) (m/z) calcd for $C_{10}H_7NO_2ClI$ 334.9209, found 334.9185. Anal. ($C_{10}H_7NO_2ClI$): C, H, N.

8a: ^{1}H NMR (270 MHz, DMSO-d_6) δ 7.12 (s, 1H), 7.31 (d, 1H, J = 1.8 Hz), 7.71 (d, 1H, J = 1.8 Hz), 10.21 (s, 1H), 12.20 (bs, 1H); HRMS (FAB) (m/z) calcd for $C_9H_6NO_2ClI$ (MH^+) 321.9131, found 321.9117.

9: ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.02 (s, 3H), 6.90 (d, 1H, J = 0.7 Hz), 7.53−7.55 (m, 2H); LC-MS (ESI) (m/e) calcd for $C_{10}H_7NO_3ClI$ (MH^+) 351.9, found 352.1.

Methyl 4-(2-Formylethyl)-6-chloroindole-2-carboxylate (10). To a solution of **7** (280 g, 835 mmol) in DMF (1.4 L) were added sodium hydrogen carbonate (140 g, 1.67 mol), benzyltriethylammonium chloride (190 g, 835 mmol), palladium(II) acetate (3.74 g, 16.7 mmol), and allyl alcohol (97.0 g, 1.67 mol). The mixture was stirred at 50 °C for 4 h and then allowed to cool to room temperature. A solution of sodium thiosulfate pentahydrate (8.32 g, 33.5 mmol) in water (58 mL) was added, and the resulting mixture was stirred vigorously at room temperature for 20 min. Activated charcoal (14 g) was added and the mixture stirred for 15 min. The mixture was filtered, and the solid collected on the filter was washed with DMF (180 mL). Water (4.8 L) was added slowly to the combined filtrate under cooling with an ice bath while the temperature was maintained below 10 °C. The mixture was allowed to warm to room temperature and stirred for 30 min. The precipitate produced was collected by filtration and washed with water (960 mL × 2) and dried in vacuo to give **10** (200 g, 90% yield) as a white solid. The purity of **10** was 83 wt % determined by HPLC. HPLC conditions: column, SUMIPAX ODS A-212; mobile phase, acetonitrile/0.1% aqueous TFA

(29) Katayama, S.; Ae, N.; Tanaka, H.; Nagata, R. *Abstracts of Papers*. 220th Meeting of the American Chemical Society, Washington, DC, August 2000; American Chemical Society: Washington, DC, 2000; Medi 215.

(60:40); flow rate, 1.0 mL/min; UV detection, 254 nm; t_R for **10**, 6.2 min; **7**, 17.8 min. Compound **10** could be further purified by recrystallization from toluene/ethyl acetate to give the analytically pure sample as a white solid: mp 167−169 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.90 (t, 2H, J = 7.4 Hz), 3.20 (t, 2H, J = 7.4 Hz), 3.96 (s, 3H), 6.96 (d, 1H, J = 1.7 Hz), 7.22 (d, 1H, J = 1.7 Hz), 7.29 (d, 1H, J = 1.3 Hz), 9.06 (bs, 1H), 9.86 (t, 1H, J = 1.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.76, 43.30, 51.86, 106.44, 110.00, 119.69, 125.02, 127.54, 129.31, 136.61, 137.50, 161.46, 202.50; Anal. ($C_{13}H_{12}NO_3Cl\cdot{}^1/_8H_2O$): C, H, N.

Methyl 4-(4-Ethoxycarbonyl-3-butenyl)-6-chloroindole-2-carboxylate (11a). To a suspension of potassium *tert*-butoxide (87.8 g, 792 mmol) in THF (1.1 L) was added dropwise triethyl phosphonoacetate (176 g, 792 mmol), and the mixture was stirred for 30 min at room temperature. A solution of **10** (189 g, 713 mmol) in THF (1.9 L) was added dropwise followed by stirring for 1.5 h at room temperature. Water (2.0 L) was added, and the resulting mixture was extracted with 1:1 ethyl acetate/toluene (4.0 L). The organic layer was washed with water (2.0 L × 2) and concentrated in vacuo to give **11a** (237 g, 99% yield) as a white solid. The purity of **11a** was 83 wt % determined by HPLC. HPLC conditions: column, SUMIPAX ODS A-212; mobile phase, acetonitrile/0.1% aqueous H_3PO_4 (66:33); flow rate, 1.0 mL/min; UV detection, 254 nm; t_R for **10**, 5.9 min; **11a**, 10.8 min. Compound **11a** could be further purified by recrystallization from toluene to give the analytically pure sample as a white solid: mp 134−137 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.29 (t, 3H, J = 7.2 Hz), 2.63 (m, 2H), 3.02 (m, 2H), 3.96 (s, 3H), 4.19 (q, 2H, J = 7.2 Hz), 5.87 (d, 1H, J = 15.8 Hz), 6.95 (d, 1H, J = 1.65 Hz), 7.02 (dt, 1H, J = 15.8, 6.9 Hz), 7.21 (t, 1H, J = 1.0 Hz), 7.29 (s, 1H), 9.02 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.09, 30.59, 32.12, 51.81, 59.68, 106.57, 109.99, 119.68, 121.44, 125.17, 127.52, 129.32, 136.73, 137.55, 148.47, 161.49, 165.61. Anal. ($C_{17}H_{18}NO_4Cl$): C, H, N.

Methyl3-Iodo-4-(4-ethoxycarbonyl-3-butenyl)-6-chloroindole-2-carboxylate (12a). To DMF (880 mL) with stirring in a water bath was added portionwise sodium iodide (118 g, 785 mmol), a solution of *N*-chlorosuccinimide (105 g, 785 mmol) in DMF (880 mL) was added slowly, and the mixture was stirred at room temperature for 1 h. A solution of **11a** (220 g, 655 mmol) obtained above in DMF (880 mL) was added slowly followed by stirring at room temperature for 2 h. To the reaction mixture were added dropwise aqueous 10% sodium thiosulfate solution (1.3 L) and water (4.9 L), and the resulting mixture was stirred at room temperature for 2 h. The precipitate produced was collected by filtration, washed with water (1 L × 3), and dried in vacuo to give **12a** (286 g, 95% yield) as a white solid. The purity of **12a** was 87 wt % determined by HPLC. HPLC conditions: column, SUMIPAX ODS A-212; mobile phase, acetonitrile/0.1% aqueous H_3PO_4 (66:33); flow rate, 1.0 mL/min; UV detection, 254 nm; t_R for **12a**, 17.6 min; **11a**, 11.0 min. Compound **12a** could be further purified by recrystallization from toluene to give the analytically pure sample as a white solid: mp 188−190 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.31 (t, 3H, J = 7.2 Hz), 2.61 (m, 2H), 3.44 (m, 2H), 3.99 (s, 3H), 4.21 (q, 2H, J = 7.2 Hz), 5.94 (d, 1H, J = 15.8 Hz), 6.94 (d, 1H, J = 1.7 Hz), 7.10 (dt, 1H, J = 15.8, 6.9 Hz), 7.32 (d, 1H, J = 1.7 Hz), 9.35 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.14, 29.19, 34.33, 51.92, 59.76, 61.56, 110.83, 121.47, 122.10, 124.57, 127.72, 129.42, 137.58, 137.91, 147.91, 160.55, 165.61; HRMS (EI) (m/z) calcd for $C_{17}H_{17}NO_4ClI$ 460.9890, found 460.9880. Anal. ($C_{17}H_{17}NO_4ClI$): C, H, N.

Radical Cyclization of 12a. Methyl 7-Chloro-3-ethoxycarbonylmethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylate (13a). To a solution of **12a** (160 g, 347 mmol) in monochlorobenzene (6.4 L), heated at reflux was added dropwise a solution of tributyltin hydride (121 g, 415 mmol) and azobisisobutyronitrile (14.2 g, 86.6 mmol) in monochlorobenzene (710 mL). The mixture was heated at reflux for 1 h. The reaction mixture was allowed to cool to room temperature, and the solvent was removed in vacuo. Acetonitrile (1 L), hexane (1 L), and activated charcoal (16 g) were added to the residue, and the mixture was stirred rapidly at room temperature for 30 min and filtered. The acetonitrile layer was separated, and the hexane layer was extracted with acetonitrile (360 mL). The combined acetonitrile layers were washed with hexane (1 L × 3) and concentrated in vacuo to give crude **13a** (111 g). This product was used in the following reaction without further purification. The purity of **13a** was 73 wt % determined by HPLC. HPLC conditions: column, SUMIPAX ODS A-212; mobile phase, acetonitrile/H_2O (66:33); flow rate, 1.0 mL/min; UV detection, 254 nm; t_R for **11a**, 11.4 min; **13a**, 13.2 min; **12a**, 17.7 min. Compound **13a** could be further purified by recrystallization from hexane/toluene to give the analytically pure sample as a white solid: mp 127−129 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.28 (t, 3H, J = 7.3 Hz), 2.01 (m, 1H), 2.17 (m, 1H), 2.48 (dd, 1H, J = 14.9, 10.5 Hz), 2.73 (dd, 1H, J = 14.9, 4.0 Hz), 2.82 (m, 1H), 3.00 (m, 1H), 3.92 (m, 1H), 3.95 (s, 3H), 4.18 (q, 2H, J = 7.3 Hz), 6.88 (s, 1H), 7.17 (s, 1H), 8.70 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.07, 22.18, 27.68, 28.92, 38.04, 51.61, 59.87, 108.97, 116.76, 121.44, 123.22, 124.39, 130.43, 134.64, 134.77, 161.59, 171.54. Anal. ($C_{17}H_{18}NO_4Cl$): C, H, N.

Methyl 7-Chloro-3-carboxymethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylate (16). Crude **13a** (110 g) obtained above was dissolved in acetic acid (660 mL) at 80 °C. Aqueous 12 N HCl (220 mL) was added, and the mixture was stirred at 80 °C for 3.5 h and then cooled to room temperature. Water (1.2 L) was added, and the mixture was extracted with 1:3 THF/ethyl acetate (4.8 L). The organic layer was washed with water (1.2 L × 2), treated with activated charcoal (6.5 g), filtered, and concentrated in vacuo to give crude product (108 g). This product was suspended in acetonitrile (500 mL), heated at reflux for 1 h, and allowed to cool to room temperature. The precipitated crystals were collected by filtration, washed with acetonitrile (60 mL × 3), and dried in vacuo to give **16** (59.5 g, 56% yield from **12a**) as white crystals. The purity of **16** was 95 wt % determined by HPLC. HPLC conditions: column, SUMIPAX ODS A-212; mobile phase, acetonitrile/0.1% aqueous H_3PO_4 (66:33); flow rate, 1.0 mL/min; UV detection, 254 nm; t_R for **16**, 4.95 min; **13a**, 13.0 min. Compound **16** could be recrystallized from 2-propanol: mp 235 °C dec; ^{1}H NMR (270 MHz, DMSO-d_6) δ 1.88 (m, 1H), 2.11 (md, 1H, J = 12.5 Hz), 2.37 (dd, 1H, J = 15.2, 10.6 Hz), 2.56 (dd, 1H, J = 15.2, 4.3 Hz), 2.80 (md, 1H, J = 17.2 Hz), 2.94 (mt, 1H, J = 13.9 Hz), 3.77 (m, 1H), 3.88 (s, 3H), 6.84 (s, 1H), 7.17 (s, 1H), 11.60 (s, 1H), 12.17 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.20, 27.57, 28.77, 38.10, 51.57, 108.93, 116.69, 121.35, 123.58, 124.45, 130.42, 134.65, 134.85, 161.65, 173.20. Anal. ($C_{15}H_{14}NO_4Cl\cdot{}^1/_{10}H_2O$): C, H, N.

Intramolecular Heck Reaction of 12a. Methyl 7-Chloro-3-ethoxycarbonylmethylidene-1,3,4,5-tetrahydrobenz-[*cd*]indole-2-carboxylate (14a). To a solution of **12a** (240 g, 520 mmol) and tetrakis(triphenylphosphine)palladium(0) (12.0 g, 10.4 mmol) in DMF (2.4 L) were added silver(I) phosphate (174 g, 416 mmol) and water (480 mL) at room temperature, and the mixture was stirred at 90 °C for 4 h and then allowed to cool to room temperature. The reaction mixture was treated with activated charcoal (12 g) at room temperature for 15 min and filtered. The solid collected on the filter was washed with 1:1 ethyl acetate/toluene (1 L × 2). To the combined filtrates were added water (2 L) and 1:1 ethyl acetate/toluene (2 L). The organic layer was separated, washed with water (1.2 L × 2), treated with activated charcoal (12 g), dried over magnesium sulfate, and concentrated in vacuo to give the crude product (187 g). The product was triturated in toluene (380 mL), filtered, washed with toluene (19 mL × 2), and dried in vacuo to give **14a** (140 g, 81% yield) as a yellow solid. The purity of **14a** was 88 wt % determined by HPLC. HPLC conditions: column, SUMIPAX ODS A-212; mobile phase, acetonitrile/H_2O (60:40); flow rate, 1.0 mL/min; UV detection, 254 nm; t_R for **14a**, 19.6 min; **12a**, 22.1 min. Compound **14a** could be further purified by recrystallization from hexane/*tert*-butyl methyl ether to give the analytically pure sample as a pale yellow solid: mp 180−181 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.34 (t, 3H, J = 7.2 Hz), 3.06 (t, 2H, J = 6.5 Hz), 3.48 (t, 2H, J = 6.5 Hz), 3.99 (s, 3H), 4.24 (q, 2H, J = 7.2 Hz), 6.96 (d, 1H, J = 1.3 Hz), 7.20 (d, 1H, J = 1.3 Hz),

7.26 (s, 1H), 9.01 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.07, 30.58, 32.10, 51.79, 59.66, 106.54, 109.97, 119.66, 121.42, 125.15, 127.50, 129.30, 136.71, 137.53, 148.44, 161.47, 165.59; HRMS (EI) (*m*/*z*) calcd for $C_{17}H_{16}NO_4Cl$ 333.0768, found 333.0770. Anal. ($C_{17}H_{16}NO_4Cl$): C, H, N.

1,4-Reduction of 14a. Methyl 7-Chloro-3-ethyoxycarbonylmethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylate (13a). To a mixture of **14a** (135 g, 405 mmol), methanol (54.1 mL, 1.33 mol), and metallic samarium (134 g, 890 mmol) in THF (1.0 L) was added slowly a solution of iodine (103 g, 405 mmol) in THF (350 mL) at 0−5 °C, and the mixture was stirred for 2 h at the same temperature. Triethylamine (113 mL, 809 mmol) was added, and the resulting mixture was allowed to warm to room temperature and stirred for 3 h. After the reaction mixture was cooled to 0 °C again, aqueous 1 N HCl (2.4 L) was added slowly while the temperature was maintained below 5 °C. Ethyl acetate (2.4 L) was then added, and the mixture was stirred vigorously at room temperature for 30 min. The organic layer was separated, washed with aqueous 1 N HCl (1.2 L × 2), aqueous 10% sodium thiosulfate solution (1.2 L × 2), and brine (800 mL) successively, treated with activated charcoal (6.7 g), dried over magnesium sulfate, and concentrated in vacuo to give crude **13a** (132 g). This product was used in the following reaction without further purification. The purity of **13a** was 83 wt % determined by HPLC. HPLC conditions: column, SUMIPAX ODS A-212; mobile phase, acetonitrile/H_2O (60:40); flow rate, 1.0 mL/min; UV detection, 254 nm; t_R for indoline **15a**, 11.2 min; **13a**, 15.7 min; **14a**, 19.9 min. The physical data of **13a** was described above.

15a: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26 (t, 3H, J = 7.3 Hz), 2.44−2.54 (m, 2H), 2.92−2.68 (m, 2H), 3.32 (s, 2H), 3.75 (s, 3H), 4.18 (q, 2H, J = 7.3 Hz), 5.02 (s, 1H), 6.55 (m, 2H); GC−EIMS *m*/*z* 335 (M^+).

Methyl 7-Chloro-3-carboxymethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylate (16). A procedure similar to that described in synthesis of **16** from crude **13a** obtained via radical cyclization was carried out with crude **13a** (130 g) obtained above (via Heck reaction) to give the title compound (91.2 g, 60% yield from **12a**). The purity of **16** was 95 wt % determined by HPLC. The physical data of **16** were described above.

Methyl (−)-7-Chloro-3-carboxymethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylate (17). Compound **16** (126 g, 409 mmol) was dissolved in boiling 2-propanol (6.3 L), and a solution of (1*R*,2*S*)-(−)-norephedrine (61.8 g, 409 mmol) in 2-propanol (1.2 L) was added. The mixture was stirred at reflux for 10 min, cooled gradually to 50 °C, followed by maintenance of the temperature at 50 °C for 5 h, and then allowed to cool to room temperature and stirred for 20 h. The crystals precipitated were collected by filtration, washed with ice-cooled 2-propanol (300 mL × 2), and dried in vacuo to give (1*R*,2*S*)-(−)-norephedrine salt of **17** (88.8 g, 79.7% ee). A suspension of the above crystals in 2-propanol (1.78 L) was stirred at reflux for 4 h. The mixture was then cooled gradually to room temperature and stirred for 20 h. The crystals precipitated were collected by filtration, washed with ice-cooled 2-propanol (180 mL × 2), and dried in vacuo to give the (1*R*,2*S*)-(−)-norephedrine salt of **17** (75.8 g, 98.6% ee), which was dissolved in a mixture of aqueous 1 N HCl (600 mL), ethyl acetate (1.8 L), and THF (600 mL). The organic layer was separated, washed with water (600 mL × 2), treated with activated charcoal (3.8 g), dried over magnesium sulfate, and concentrated in vacuo to give the solid material (51 g), which was suspended in acetonitrile (250 mL), filtered, washed with acetonitrile (12 mL × 2), and dried in vacuo to give **17** (49.5 g, 98.5% ee, 39% yield from **16**) as white crystals. Chiral HPLC conditions: column, CHIRALPAK AD; mobile phase, 0.1% AcOH in EtOH/hexane (60:40); flow rate, 0.5 mL/min; UV detection, 254 nm; t_R for (−)-isomer **17**, 9.2 min; (+)-isomer **18**, 13.1 min. Both **17** and **18** could be recrystallized from 2-propanol: mp 200−201 °C; $[\alpha]^{25}_D$ = −105.7° (*c* 1.05, MeOH); The spectral properties of the title compound were identical with those of the racemate.

Methyl (+)-7-Chloro-3-carboxymethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylate (18). A procedure similar to that described in synthesis of **17** was carried out with **16** (60.0 g, 195 mmol) using (1*S*,2*R*)-(+)-norephedrine instead of (1*R*,2*S*)-(−)-norephedrine to give the title compound (23.8 g, 98.6% ee, 40% yield from **16**): mp 200−201 °C; $[\alpha]^{25}_D$ = +106.2° (*c* 1.00, MeOH). The spectral properties of the title compound were identical with those of the racemate.

7-Chloro-3-carboxymethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylic Acid (19). To a solution of **16** (1.00 g, 3.25 mmol) in 1:1 THF/methanol (20 mL) was added aqueous 2 N LiOH (10 mL, 20 mmol) The mixture was stirred at room temperature for 20 h, acidified with aqueous 1 N HCl, and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over magnesium sulfate, and concentrated. The residual solid was rinsed with 1:1 hexane/2-propanol, collected by filtration, and dried in vacuo to give **19** (900 mg, 94% yield) as a white solid: mp 245−247 °C dec; ^{1}H NMR (270 MHz, DMSO-d_6) δ 1.87 (m, 1H), 2.08 (md, 1H, J = 12.2 Hz), 2.35 (dd, 1H, J = 15.5, 11.5 Hz), 2.64 (dd, 1H, J = 15.3, 3.0 Hz), 2.78 (md, 1H, J = 15.8 Hz), 2.93 (mt, 1H, J = 12.7 Hz), 3.76 (m, 1H), 6.83 (s, 1H), 7.14 (s, 1H), 11.45 (s, 1H), 12.58 (bs, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.28, 27.34, 28.66, 37.98, 108.90, 116.53, 122.54, 122.94, 124.72, 130.06, 134.46, 134.83, 162.82, 173.29. Anal. ($C_{14}H_{12}NO_4Cl\cdot{}^1/_8H_2O$): C, H, N.

7-Chloro-3-phenylaminocarbonylmethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylic acid (20). Methyl 7-Chloro-3-phenylaminocarbonylmethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylate. To a solution of **16** (1.00 g, 3.25 mmol) and aniline (333 mg, 3.58 mmol) in DMF (15 mL) were added 1-hydroxybenzotriazole (483 mg, 3.58 mmol) and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (685 mg, 3.58 mmol) at 0 °C. The mixture was stirred at room temperature for 20 h, acidified with aqueous 5% $KHSO_4$, and extracted with 1:1 toluene/ethyl acetate. The organic layer was washed successively with aqueous 5% $KHSO_4$, water, aqueous 5% $NaHCO_3$, and brine, dried over magnesium sulfate, and concentrated. The residual solid was rinsed with 2-propanol, collected by filtration, and dried in vacuo to give the title compound (1.20 g, 96% yield) as an amorphous solid: ^{1}H NMR (270 MHz, DMSO-d_6) δ 1.88 (m, 1H), 2.08 (md, 1H, J = 13.2 Hz), 2.53 (m, 1H), 2.61 (dd, 1H, J = 14.1, 5.1 Hz), 2.80 (md, 1H, J = 16.5 Hz), 3.05 (mt, 1H, J = 13.2 Hz), 3.77 (s, 3H), 3.90 (m, 1H), 6.86 (s, 1H), 7.03 (t, 1H, J = 7.3 Hz), 7.19 (s, 1H), 7.29 (t, 2H, J = 7.9 Hz), 7.61 (d, 2H, J = 8.1 Hz), 9.85 (s, 1H), 11.59 (s, 1H), 11.70 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.33, 27.75, 29.19, 40.83, 51.59, 108.94, 116.66, 119.12 (2C), 121.37, 123.07, 123.90, 124.53, 128.64 (2C), 130.39, 134.78, 134.98, 139.23, 161.74, 169.68; HRMS (FAB) (*m*/*z*) calcd for $C_{21}H_{20}N_2O_3Cl$ (MH^+) 383.1162, found 383.1153.

7-Chloro-3-phenylaminocarbonylmethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylic Acid (20). To a solution of methyl 7-chloro-3-phenylaminocarbonylmethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylate (1.20 g, 3.13 mmol) in 2:1 THF/methanol (45 mL) was added aqueous 2 N LiOH (15 mL, 30 mmol). The mixture was stirred at room temperature for 24 h, acidified with aqueous 1 N HCl, and extracted with 1:1 THF/ethyl acetate. The organic layer was washed successively with water and brine, dried over magnesium sulfate, and concentrated. The residual solid was rinsed with 1:1 hexane/2-propanol, collected by filtration, and dried in vacuo to give **20** (1.10 g, 95% yield) as a white solid: mp 268 °C dec; ^{1}H NMR (270 MHz, DMSO-d_6) δ 1.85 (m, 1H), 2.06 (md, 1H, J = 12.2 Hz), 2.50 (m, 1H), 2.68 (dd, 1H, J = 14.2, 4.3 Hz), 2.79 (md, 1H, J = 16.8 Hz), 3.06 (mt, 1H, J = 12.6 Hz), 3.89 (m, 1H), 6.85 (s, 1H), 7.03 (t, 1H, J = 7.3 Hz), 7.16 (s, 1H), 7.30 (t, 2H, J = 7.3 Hz), 7.60 (d, 2H, J = 7.3 Hz), 9.86 (s, 1H), 11.44 (s, 1H), 12.92 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.37, 27.26, 28.90, 40.42, 108.88, 116.44, 119.21 (2C), 122.42, 123.11, 123.36, 124.75, 128.69 (2C), 130.02, 134.53, 134.90, 139.19, 162.83, 169.72. Anal. ($C_{20}H_{17}N_2O_3Cl\cdot{}^1/_4H_2O$): C, H, N.

(−)-7-Chloro-3-phenylaminocarbonylmethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylic Acid (23). The

title compound was prepared starting with **17** as described for **20**. The optical purity of the product was determined by chiral HPLC to be 98.6% ee. Chiral HPLC conditions: column, SUMICHIRAL OA-4400; mobile phase, hexane/2-propanol/MeOH/TFA (75:15:10:0.2); flow rate, 1.0 mL/min; UV detection, 254 nm; t_R for (−)-isomer **23**, 13.9 min; (+)-isomer, 11.1 min: mp 268−270 °C dec; $[\alpha]^{25}_D = -112.4°$ (*c* 0.53, DMF). The spectral properties of the title compound were identical with those of the racemate.

7-Chloro-3-(4-aminomethyl-2-(carboxymethoxy)phenyl)-aminocarbonylmethyl-1,3,4,5-tetrahydrobenz[*cd*]-indole-2-carboxylic Acid Hydrochloride (22). Methyl 7-Chloro-3-(4-*tert*-butoxycarbonylaminomethyl-2-(*tert*-butoxycarbonylmethoxy)phenyl)aminocarbonylmethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylate. To a solution of **16** (1.00 g, 3.25 mmol) and 4-*tert*-butoxycarbonylaminomethyl-2-*tert*-butoxymethoxyaniline **21** (1.20 g, 3.41 mmol) in DMF (7 mL) were added 1-hydroxybenzotriazole (597 mg, 3.90 mmol) and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (748 mg, 3.90 mmol) at 0 °C. The mixture was stirred at room temperature for 22 h, acidified with aqueous 5% $KHSO_4$, and extracted with 1:1 toluene/ethyl acetate. The organic layer was washed successively with aqueous 5% $KHSO_4$, water, aqueous 5% $NaHCO_3$, and brine, dried over magnesium sulfate, and concentrated. The residue was purified by silica gel column chromatography with 2:1 hexane/ethyl acetate to give the title compound (1.83 g, 88% yield) as an amorphous solid: ^{1}H NMR (270 MHz, DMSO-d_6) δ 1.39 (s, 9H), 1.42 (s, 9H), 1.86 (m, 1H), 2.12 (md, 1H, J = 12.7 Hz), 2.63−2.71 (m, 2H), 2.79 (md, 1H, J = 16.9 Hz), 3.08 (mt, 1H, J = 13.6 Hz), 3.79 (s, 3H), 3.88 (m, 1H), 4.06 (d, 2H, J = 5.5 Hz), 4.65 (s, 2H), 6.80−6.85 (m, 3H), 7.17 (s, 1H), 7.30 (t, 1H, J = 5.5 Hz), 7.93 (d, 1H, J = 7.9 Hz), 9.04 (s, 1H), 11.58 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.34, 27.64 (4C), 28.21 (3C), 29.36, 40.56, 43.18, 51.57, 66.15, 77.74, 81.64, 108.89, 111.46, 116.62, 119.63, 121.35, 121.87, 123.98, 124.57, 126.49, 130.36, 134.74, 135.16, 136.19, 148.13, 155.73, 161.75, 167.90, 169.70; HRMS (FAB) (*m*/*z*) calcd for $C_{33}H_{41}N_3O_8Cl$ (MH^+) 642.2582, found 642.2585.

7-Chloro-3-(4-*tert*-butoxycarbonylaminomethyl-2-(carboxymethoxy)phenyl)aminocarbonylmethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylic Acid. To a solution of methyl 7-chloro-3-(4-*tert*-butoxycarbonylaminomethyl-2-(*tert*-butoxycarbonylmethoxy)phenyl)aminocarbonylmethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylate (1.28 g, 2.00 mmol) in 1:1 THF/methanol (20 mL) was added aqueous 2 N LiOH (6 mL, 12 mmol) The mixture was stirred at room temperature for 24 h, acidified with aqueous 5% $KHSO_4$, and extracted with ethyl acetate. The organic layer was washed successively with water and brine, dried over magnesium sulfate, and concentrated. The residual solid was rinsed with diethyl ether, collected by filtration, and dried in vacuo to give the title compound (1.10 g, 97% yield) as an amorphous solid: ^{1}H NMR (270 MHz, DMSO-d_6) δ 1.39 (s, 9H), 1.83 (m, 1H), 2.08 (md, 1H, J = 11.7 Hz), 2.58−2.66 (m, 2H), 2.78 (md, 1H, J = 17.4 Hz), 3.08 (mt, 1H, J = 13.2 Hz), 3.87 (m, 1H), 4.05 (d, 2H, J = 6.0 Hz), 4.67 (s, 2H), 6.82 (d, 1H, J = 7.9 Hz), 6.84 (s, 2H), 7.14 (s, 1H), 7.34 (t, 1H, J = 6.0 Hz), 7.89 (d, 1H, J = 7.9 Hz), 9.15 (s, 1H), 11.44 (s, 1H), 13.04 (bs, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.40, 27.16, 28.26 (3C), 29.15, 40.34, 43.19, 65.99, 77.82, 108.81, 111.93, 116.42, 119.68, 122.05, 122.43, 123.40, 124.79, 126.58, 130.01, 134.51, 135.08, 136.36, 148.41, 155.78, 162.85, 169.74, 170.41; HRMS (FAB) (*m*/*z*) calcd for $C_{28}H_{31}N_3O_8Cl$ (MH^+) 572.1800, found 572.1807.

7-Chloro-3-(4-aminomethyl-2-(carboxymethoxy)phenyl)-aminocarbonylmethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylic Acid Hydrochloride (22). To a solution of methyl 7-chloro-3-(4-*tert*-butoxycarbonylaminomethyl-2-(carboxymethoxy)phenyl)aminocarbonylmethyl-1,3,4,5-tetrahydrobenz[*cd*]indole-2-carboxylic acid (950 mg, 1.66 mmol) in a mixture of 1,4-dioxane (8 mL) and acetic acid (16 mL) was added 4 N HCl in 1,4-dioxane (8 mL). The mixture was stirred at room temperature for 24 h and concentrated. The residual solid was rinsed with 1:1 diethyl ether/dichloromethane, collected by filtration, and dried in vacuo to give **22** (830 mg, 98% yield) as a white solid: mp 232−236 °C dec; ^{1}H NMR (270 MHz, DMSO-d_6) δ 1.85 (m, 1H), 2.08 (m, 1H), 2.69 (m, 2H), 2.78 (m, 1H), 3.09 (m, 1H), 3.90−3.95 (m, 3H), 4.74 (s, 2H), 6.84 (s, 1H), 7.06 (d, 1H, J = 8.3 Hz), 7.16 (s, 1H), 7.20 (s, 1H), 8.04 (d, 1H, J = 8.3 Hz), 8.30 (bs, 3H), 9.24 (s, 1H), 11.45 (s, 1H), 13.05 (bs, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.39, 27.15, 29.16, 40.39, 42.04, 66.13, 108.84, 114.06, 116.41, 121.75, 121.87, 122.51, 123.24, 124.77, 128.16, 129.76, 129.96, 134.47, 135.02, 148.18, 162.86, 170.00, 170.21. Anal. ($C_{23}H_{23}N_3O_6Cl_2 \cdot H_2O$): C, H, N.

(−)-7-Chloro-3-(4-aminomethyl-2-(carboxymethoxy)-phenyl)aminocarbonylmethyl-1,3,4,5-tetrahydrobenz-[*cd*]indole-2-carboxylic Acid Hydrochloride (24). The title compound was prepared starting with **17** as described for **22**. The optical purity of the product was determined by chiral HPLC to be > 99% ee. Chiral HPLC conditions: column, SUMICHIRAL OA-2500; mobile phase, acetonitrile/5 mM aqueous 1-heptanesulfonic acid, sodium salt (adjusted to pH 2.5 with H_3PO_4) (27:73); flow rate, 1.0 mL/min; UV detection, 240 nm; t_R for (−)-isomer **24**, 25.0 min; (+)-isomer **25**, 28.7 min: mp 195−200 °C, dec; $[\alpha]^{25}_D = -44.1°$ (*c* 0.23, MeOH). The spectral properties of the title compound were identical with those of the racemate.

(+)-7-Chloro-3-(4-aminomethyl-2-(carboxymethoxy)-phenyl)aminocarbonylmethyl-1,3,4,5-tetrahydrobenz-[*cd*]indole-2-carboxylic Acid Hydrochloride (25). The title compound was prepared starting with **18** as described for **22**. The optical purity of the product was determined by chiral HPLC to be > 99% ee. Chiral HPLC conditions were the same as described for **24**: mp 195−200 °C dec; $[\alpha]^{25}_D = +44.0°$ (*c* 0.24, MeOH). The spectral properties of the title compound were identical with those of the racemate.

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Supporting Information Available: Elemental analytical data for products **4**−**7**, **10**, **11a**−**14a**, **16**, **19**, **20**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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