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Synthesis of a Spirocyclic Indoline Lactone

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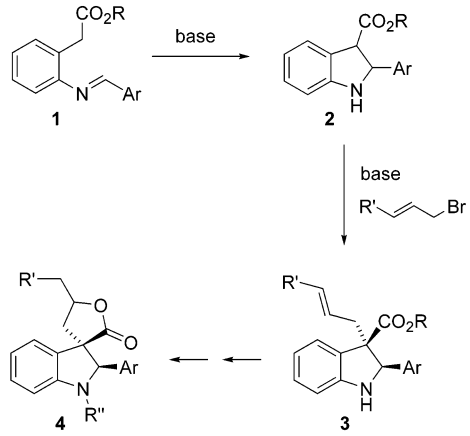
Base-promoted cyclization of *tert*-butyl [2-(benzylideneamino)phenyl]acetate (**13a**) and subsequent C3-alkylation with allyl bromide affords 3-allyl-2-phenyl-2,3-dihydro-1*H*-indole-3-carboxylic acid, *tert*-butyl ester (**15b**) in high yield as a single diastereomer. This result is contrary to prior publications that describe failed cyclization of an analogous ethyl ester (ethyl [2-(4-methoxybenzylideneamino)phenyl]acetate) under strongly basic conditions. *N*-Acylation, olefin dihydroxylation, and *tert*-butyl ester cleavage affords the spirocyclic lactone **18** as a pair of diastereomers. Isolation and characterization of individual diastereomers **18a** and **18b** are described.

Introduction

Numerous biologically active natural products contain a spirocyclic ring system and many others contain a 2,3-dihydroindole (indoline) structural component.[1] In an effort to add readily synthesized molecules with natural product features to our screening collection, we investigated synthetic routes to molecules with both indoline and spirocyclic components. The facile oxidation of indolines to indoles complicates many synthetic approaches to indolines. Thus, we chose to investigate 3,3-disubstituted indolines to block such oxidation. In particular, indolines bearing a 3,3-spirocyclic element were of interest since several synthetic approaches have previously been published.[2−5]

One approach that appeared to be conceptually attractive is shown in Scheme 1. This strategy employs base-promoted intramolecular cyclization of imines prepared from 2-aminophenylacetic acid esters such as **1**. This cyclization would potentially afford a wide variety of 2-substituted-indoline-3-carboxylates (**2**), which might be subsequently alkylated at C3 as a prelude to elaboration of spirocycles such as **4**. Considerable literature precedent is available in key papers by Speckamp et al.,[3−6] who thoroughly investigated a number of analogous reactions as shown in Scheme 2. The complete failure of **5** to undergo cyclization following treatment with a variety of solvent and base combinations advised against the approach in Scheme 1. There are two potential explanations proposed by Speckamp for the failure of **5** to cyclize:[6] (1) "unfavorable geometry for a 5-endo-trig ring closure

SCHEME 1



(anti-Baldwin process)" and (2) "incomplete carbanion formation in protic solvents". An alternative approach to cyclization,[6] utilizing a Lewis acid to promote the conversion of **10** to a mixture of **11a** and **11b**, provides evidence that unfavorable geometry for ring closure is not the primary issue. Furthermore, **6** and **8** do indeed cyclize under basic conditions and in the latter case diastereoselectivity is remarkably well controlled by variation of solvent and base. Therefore, we chose to reinvestigate the failed cyclization of **5** with the goal of finding suitable conditions for diastereoselective cyclization.

Results and Discussion

Preliminary experiments with the synthesis of the starting imine **1** revealed that the *tert*-butyl esters are typically crystalline when the imine is formed with an aromatic aldehyde. The imine methyl and ethyl esters were surprisingly difficult to crystallize and hence purification was considered an issue that could impact the success of the intramolecular cyclization. Thus the initial cyclization experiments (Scheme 3) were performed with the *tert*-butyl esters, **13a** and **13b**, which were prepared in three steps from 2-nitrophenylacetic acid, **12**.

(1) Southon, I. W.; Buckingham, D. J. *Dictionary of Alkaloids*; Cordell, G. A., Saxton, J. E., Shamma, M., Eds.; Chapman and Hall; New York, 1989.
(2) Ibrahim-Ouali, M.; Sinibaldi, M.; Troin, Y.; Cuer, A.; Dauphin, G.; Gramain, J. *Heterocycles* **1995**, *41* (9), 1939−1950.
(3) Speckamp, W. N.; Veenstra, S. J.; Dijkink, J.; Fortgens, R. *J. Am. Chem. Soc.* **1981**, *103* (15), 4643−4644.
(4) Veenstra, S. J.; Speckamp, W. N. *J. Am Chem. Soc.* **1981**, *103* (15), 4645−4646.
(5) Speckamp, W. N. *Heterocycles* **1984**, *21* (1), 211−234.
(6) Dijkink, J.; Zonjee, J. N.; de Jong, B. S.; Speckamp, W. N. *Heterocycles* **1983**, *20* (7), 1255−1258.

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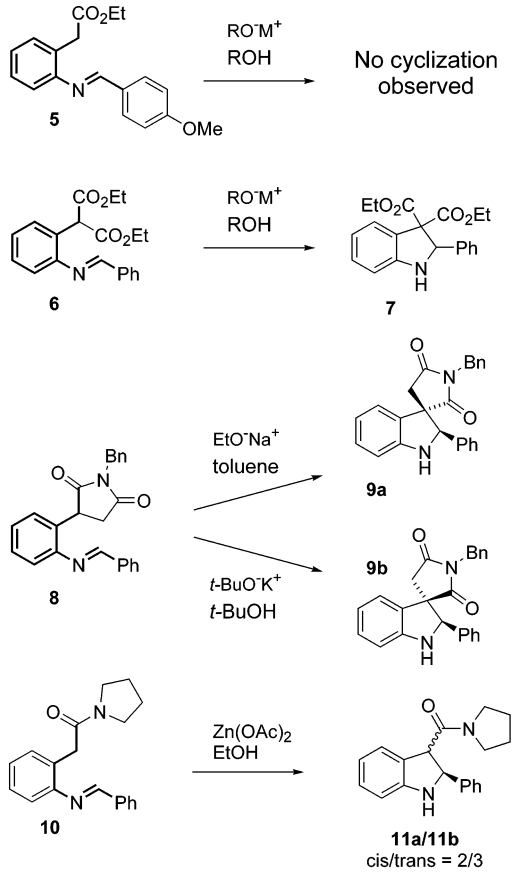
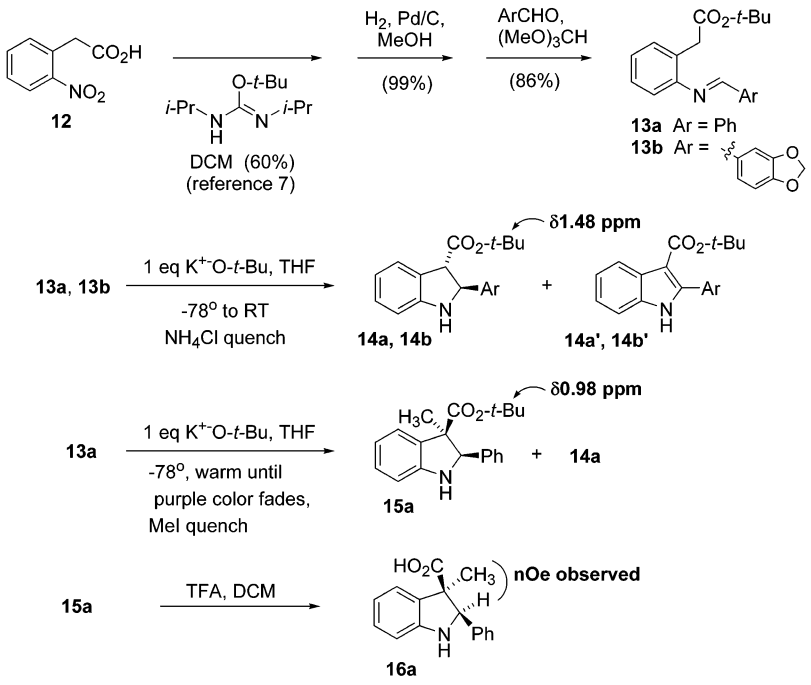
SCHEME 2



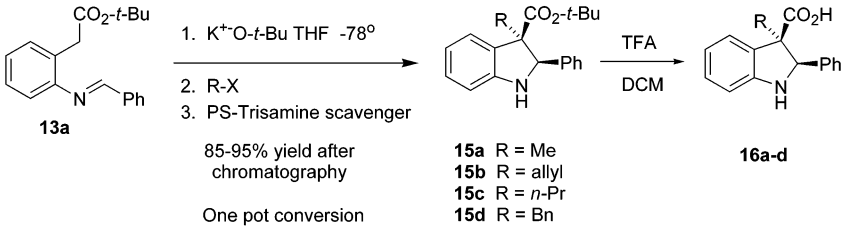
To our pleasant surprise, the first attempts to cyclize **13a** and **13b** by treatment with potassium *tert*-butoxide in THF, warming from −78 °C to room temperature, were both successful. Indolines **14a** and **14b** were the major products, found as single diastereomers. The related indoles **14a′** and **14b′** were also produced as minor byproducts, presumably by air oxidation. Furthermore, cyclization of **13a**, followed by quenching with iodomethane afforded the 3-methylated **15a**. In this reaction no *N*-methylation and no indole byproduct **14b′** were observed; however, a small amount of **14a** was isolated due to incomplete 3-methylation. Again, only one diastereomer of **15a** was produced. After removal of the *tert*-butyl ester, a 2D ROESY study showed a strong nOe between the 2-proton and the 3-methyl group of **16a**, indicating a syn relationship. A chemical shift difference between the *t*-Bu ester of **14a** (δ1.48 ppm) and **15a** (δ0.98 ppm) was observed, consistent with inversion of the 3-position upon alkylation.

In optimizing this tandem cyclization−alkylation procedure we took advantage of the intense purple color of the highly conjugated ester enolate as a colorimetric indicator. Thus 1 M KO*t*-Bu in THF was added dropwise to a −78 °C solution of **13a** in THF until the purple color persisted then 1.0 equiv more was added. The reaction was warmed gradually by removal of the cold bath until the color faded from purple to orange. The reaction flask was returned to the cold bath and excess alkyl halide was added. As the reaction mixture was allowed to warm to room temperature, the orange color faded and the potassium halide salt precipitated as a white solid, indicating completion of the reaction. The excess alkyl halide was conveniently removed with a scavenger resin.[8] A variety of alkyl halides performed well in the alkylation as is shown in Scheme 4. All gave high yields and *C*-alkylation is observed. A spot-to-spot conversion of **13a** to **15a**−**d** was observed by TLC and ^{1}H NMR spectra of the crude products are consistent with a single diastereomer in each case. The esters **15a**−**d** were converted to the corresponding acids **16a**−**d** by treatment with TFA in DCM, the latter being more crystalline and thus facilitating greater characterization. When benzyl bromide was used as the alkylating agent, the product **16d** was found to be contaminated by a small amount of 1,3-bis-benz-

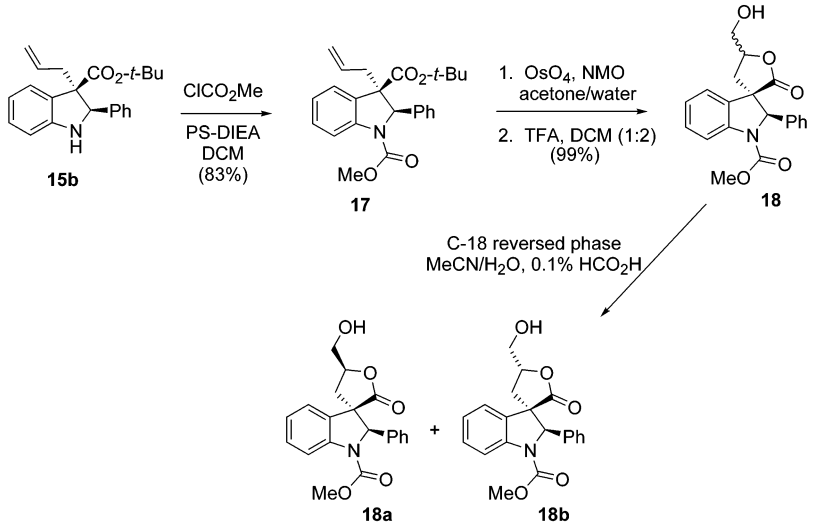
SCHEME 3



SCHEME 4



SCHEME 5



ylated product, which is observed in the ^{1}H NMR and mass spectra. Unlike the cyclization of **13a** to **14a**, indole contaminant **14a** was not observed in the conversion of **13a** to **15a**−**d**. Quenching with an alkylating agent appears to block this oxidative side reaction.

The remaining three steps of the synthesis are shown in Scheme 5. Acylation of **15b** with methyl chloroformate, using polymer-supported Hunig's base, afforded **17**. Catalytic dihydroxylation of the allyl group with OsO_4-NMO and removal of the *tert*-butyl ester with trifluoroacetic acid in dichloromethane afforded the spirocyclic lactone **18** as a 1:1 mixture of diastereomers. The overall yield of the 7-step process for preparation of **18** from **12** was 40%. The diastereomeric products were separated by preparative reversed-phase chromatography, affording the faster eluting diastereomer **18a** and the slower eluting diastereomer **18b**. 2D ROESY spectra were found to be consistent with the relative stereochemistry as shown for **18a** and **18b**.

Conclusions

The results presented herein correct a long-standing fallacy in preexisting literature. In contrast with previously published results describing the lack of base-promoted cyclization with **5**, our investigations show that the KO*t*-Bu-promoted cyclization of analogous *tert*-butyl ester-imines such as **13a** and **13b** is indeed a feasible route to 2,3-disubstituted indolines such as **14a** and **14b**. Furthermore, cyclization and tandem 3-alkylation offers an efficient and diastereospecific method for the conversion of **13a** to 2,3,3-trisubsituted indolines such as **15a**−**d**. It is convenient to determine the correct amount of base required and follow the progress of the cyclization reaction by observing the appearance and disappearance of the intensely purple enolate of **13a**. Indoline **15b** is subsequently converted by routine synthetic transformations to the diastereomeric spirocyclic lactones **18a** and **18b** in high yield.

Experimental Section

The following solvent and reagent abbreviations are employed in the experimental methods: dichloromethane (DCM), *N*,*N*-diisopropycarbodiimide (DIC), *N*,*N*′-diisopropylurea (DIU), *N*-methylmorpholine-*N*-oxide (NMO), tetrahydrofuran (THF), and trifluroacetic acid (TFA).

[2-(Benzylideneamino)phenyl]acetic Acid *tert*-Butyl Ester (13a). Step A: 2-*tert*-Butyl-1,3-diisopropylisourea.[7] A mixture of DIC (6.3 g, 50 mmol) and anhydrous *t*-BuOH (4.3 g, 58 mmol) was treated with CuCl (50 mg, 0.5 mmol) and stirred 24 h at room temperature. Polyvinylpyridine (1 g) and DCM (25 mL) were added and the resulting slurry was stirred for 15 min before filtering and evaporation of DCM at reduced pressure to afford crude 2-*tert*-butyl-1,3-diisopropylisourea (8.4 g, 84%) as a colorless liquid that was used without further purification in Step B below. ^{1}H NMR ($CDCl_3$) δ 1.04 (d, 6H), 1.08(d, 6H), 1.46 (s, 9H), 3.13 (m, 1H), 3.67 (m, 3H), 3.73 (m, 1H).

Step B: (2-Nitrophenyl)acetic Acid, *tert*-Butyl Ester. A solution of the isourea from above (3.0 g, 15 mmol) and (2-nitrophenyl)acetic acid (1.81 g, 10 mmol) in DCM (50 mL) were stirred overnight at room temperature. Hexanes (50 mL) were added, stirring for 15 min before filtering to remove precipitated DIU. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel, eluting with

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(8) Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119* (21), 4882−4886.

hexanes/EtOAc (90:10) to afford (2-nitrophenyl)acetic acid *tert*-butyl ester (1.42 g, 60%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 3.94 (s, 2H), 7.34 (d, 1H), 7.45 (t, 1H), 7.58 (t, 1H), 8.09 (d, 1H).[9] This procedure was repeated and the combined products used in Step C below.

Step C: (2-Aminophenyl)acetic Acid, *tert*-Butyl Ester. A solution of (2-nitrophenyl)acetic acid, *tert*-butyl ester (3 g, 12.6 mmol) in a mixture of EtOH (50 mL) and THF (50 mL) was treated with 5% Pd/C (0.3 g) and placed under H_2 atmosphere (45 psi) for 4 h. The resulting mixture was filtered through Celite and evaporated to afford a brown liquid. Flash chromatograpy on silica gel, eluting with hexane/EtOAc (90:10), afforded (2-aminophenyl)acetic acid *tert*-butyl ester as a yellow oil (2.6 g, 99%). ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 3.45 (s, 2H), 4.06 (br, 2H), 6.74 (m, 2H), 7.06 (m, 2H).[9]

Step D: [2-(Benzylideneamino)phenyl]acetic Acid, *tert*-Butyl Ester (13). A mixture of (2-aminophenyl)acetic acid, *tert*-butyl ester (0.99 g, 4.8 mmol), benzaldehyde (0.53 g, 5.0 mmol), and trimethyl orthoformate (4 mL) was stirred at room temperature for 24 h. The mixture was concentrated on a rotary evaporator then further concentrated under high vacuum (0.2 mmHg) at room temperature until it became a wet crystalline mass. Recrystallization from hexanes gave **13** as off-white crystals (1.22 g, 86%). ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 9H), 3.74 (s, 2H), 7.01 (d, 1H), 7.19 (t, 1H), 7.28 (m, 3H), 7.47 (m, 3H), 7.90 (m, 2H), 8.40 (s, 1H). Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.55; H, 7.30; N, 4.48.

Compound **13b** was also prepared by the above method. See the Supporting Information for the ^{1}H NMR spectrum.

2-Phenyl-2,3-dihydro-1*H*-indole-3-carboxylic Acid, *tert*-Butyl Ester (14a). A septum-sealed flask containing a solution of imine **13** (75 mg, 0.25 mmol) in dry THF (5 mL) was evacuated and pressurized with N_2 five times. The flask was then chilled on a dry ice/acetone bath. A solution of 1 M KO*t*-Bu in THF (0.25 mL, 0.25 mmol) was added by syringe. The cold bath was removed and the resulting purple solution was allowed to warm gradually. After a few minutes the solution faded to orange. After 20 min, the reaction was quenched with saturated aqueous NH_4Cl (0.5 mL). The reaction mixture was diluted with a mixture of EtOAc (10 mL) and hexanes (10 mL). The organic layer was separated, dried over $MgSO_4$, and evaporated. The residue was purified by flash chromatography on silica gel, eluting with hexane/EtOAc (97:3) to give **14a** as a colorless film (60 mg) that crystallized on standing. Trituration with cold pentane afforded a colorless solid (28 mg, 37%). TLC (silica gel, hexanes−EtOAc, 90:10, I_2 stain) R_f 0.6. ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 3.98 (d, 1H), 4.19 (br d, 1H), 5.33 (d of d, 1H), 6.69 (d, 1H), 6.76 (t, 1H), 7.14 (t, 1H), 7.22−7.38 (m, 4H), 7.47 (d, 2H). MS (APCI+) 296 (m + 1). IR (KBr; cm^{-1}) 1707 (C=O), 3336 (NH). Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 76.84; H, 7.26; N, 4.67.

A highly UV-active, minor byproduct (**14a′**, 4 mg, 5%) eluted after the desired product. TLC (silica gel, hexanes−EtOAc, 90:10, I_2 stain) R_f 0.25. ^{1}H NMR lacks H(2) and H(3) seen at δ 3.98 and 5.33 ppm. MS (APCI+) 294 (m + 1).

Compound **14b** was also prepared by the above method. See the Supporting Information for the ^{1}H NMR spectrum.

Typical Tandem Cyclization−Alkylation Procedure: 3-Methyl-2-phenyl-2,3-dihydro-1*H*-indole-3-carboxylic Acid (16a). Step A: 3-Methyl-2-phenyl-2,3-dihydro-1*H*-indole-3-carboxylic Acid, *tert*-Butyl Ester (15a). A septum-sealed flask containing a solution of imine **13** (118 mg, 0.4 mmol) in dry THF (8 mL) was evacuated and pressurized with N_2 five times. The flask was then chilled on a dry ice/acetone bath. KO*t*-Bu (1 M) in THF was added dropwise until a purple color persisted then 1.0 equiv more (0.4 mL) was added. The cold bath was removed and the flask warmed gradually by ambient air until the color faded to orange (~7 min). The flask was returned to the cold bath for 2 min, iodomethane (125 μL, 2.0 mmol) was added, and the reaction was allowed to warm to room temperature over 2 h. Trisamine resin (0.5 g, 1.68 mmol) and DCM (5 mL) were added, stirring at room temperature overnight. The resulting mixture was diluted with hexanes (30 mL) and filtered through a pad of Celite, rinsing solids with hexanes−EtOAc (1:1). Evaporation of solvent afforded a yellow oil. Flash chromatography on silica gel, eluting with hexane−$CHCl_3$ (50:50 to 40:60), provided purified **15a** as a pale yellow gum upon evaporation. Drying to constant weight at 0.25 mmHg, room temperature, afforded 118 mg (95.5% yield). ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 9H), 1.72 (s, 3H), 4.03 (br, 1H), 4.67 (s, 1H), 6.72 (d, 1H), 6.79 (t, 1H), 7.14 (t, 1H), 7.19 (d, 1H), 7.26 (m, 3H), 7.34 (m, 2H). MS (APCI+) 310 (m + 1). Crystallization of **15a** was not achieved. Therefore, further characterization is provided by removal of the *tert*-butyl ester, affording **16a** as described below.

Step B: 3-Methyl-2-phenyl-2,3-dihydro-1*H*-indole-3-carboxylic Acid (16a). A solution of **15a** (102 mg, 0.33 mmol) in DCM (6 mL) was treated with TFA (3 mL) and stirred for 22 h at room temperature. The resulting solution was concentrated at reduced pressure then dissolved in $CHCl_3$ (10 mL) and evaporated three times to remove excess TFA. Flash chromatography on silica gel, eluting with $CHCl_3$−MeOH (98.5:1.5), gave **16a** as a gum upon evaporation of solvent. This gum was dissolved in DCM, concentrated to a syrup, and diluted dropwise with pentane to effect crystallization, 56 mg (67%). ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 3H), 4.84 (s, 1H), 6.79 (d, 1H), 6.84 (t, 1H), 7.11 (d, 1H), 7.17 (t, 1H), 7.28 (m, 3H), 7.41 (m, 2H). MS (APCI+) 254 (m + 1). IR (KBr; cm^{-1}) 1698 (C=O), 3356 (NH). Calcd for $C_{16}H_{15}NO_2 \cdot 0.15H_2O$: C, 75.07; H, 6.02; N, 5.47. Found: C, 75.26; H, 5.93; N, 5.45.

3-Allyl-2-phenyl-2,3-dihydro-1*H*-indole-3-carboxylic Acid (16b). Allyl bromide was substituted for iodomethane in the typical procedure above. ^{1}H NMR ($CDCl_3$) δ 2.78 and 2.97 (ABX, 2H), 4.85 (s, 1H), 5.16 (m, 2H), 5.73 (m,1H), 6.75 (d, 1H), 6.82 (t, 1H), 7.18 (m, 2H), 7.17 (t, 1H), 7.25 (m, 3H), 7.30 (m, 2H). MS (APCI+) 280 (m + 1). IR (KBr; cm^{-1}) 1719 (C=O), 3372 (NH). Calcd for $C_{18}H_{17}NO_2 \cdot 0.15H_2O$: C, 76.65; H, 6.18; N, 4.97. Found: C, 76.69; H, 5.79; N, 4.80.

2-Phenyl-3-propyl-2,3-dihydro-1*H*-indole-3-carboxylic Acid, Hydrochloride (16c). 1-Iodopropane was substituted for iodomethane in the general procedure given above. The product was converted to a hydrochloride salt with ethereal hydrogen chloride. ^{1}H NMR (DMSO-d_6) δ 0.80 (t, 3H), 1.08 (m, 1H), 1.33 (m, 1H), 1.79 (t, 1H), 2.02 (t, 1H), 4.58 (d, 1H), 6.60 (m, 2H), 6.97−7.17 (complex, 7H). MS (APCI+) 282 (m + 1). IR (KBr; cm^{-1}) 1742 (C=O). Calcd for $C_{18}H_{19}NO_2 \cdot$ HCl: C, 68.03; H, 6.34; N, 4.41. Found: C, 67.95; H, 6.46; N, 4.35.

3-Benzyl-2-phenyl-2,3-dihydro-1*H*-indole-3-carboxylic Acid (16d). Benzyl bromide was substituted for iodomethane in the typical procedure above. ^{1}H NMR ($CDCl_3$) δ 3.18 (d, 1H), 3.63 (d, 1H), 4.75 (s, 1H), 6.53 (d, 1H), 6.65 (t, 1H), 6.70 (d, 1H), 6.84 (d, 2H), 7.15−7.28 (complex, 9H). MS (APCI+) 330 (m + 1). IR (KBr; cm^{-1}) 1692,1708 (C=O), 3386 (NH). Contains ~4% 1,3-dibenzyl-2-phenyl-2,3-dihydro-1*H*-indole-3-carboxylic acid by ^{1}H NMR δ 3.21 (d, 0.04H), 3.55 (d, 0.04H), 3.81 (d, 0.04H), 4.35 (d, 0.4H), 4.63 (s, 0.04H) and MS 420 (m + 1).

5-(Hydroxymethyl)-2-oxo-2′-phenyl-4,5-dihydrospiro-[furan-3,3′-indole]-1′(2′*H*)carboxylic Acid, Methyl Ester (18). Step A: 3-Allyl-2-phenyl-2,3-dihydro-ndole-1,3-dicarboxylic Acid, 3-*tert*-Butyl Ester, 1-Methyl Ester (17). A solution of **15b** (201 mg, 0.60 mmol) in DCM (2.5 mL) was added to PS-DIEA (0.5 g, 1.83 mmol). The resulting slurry was treated with methyl chloroformate (51 μL, 0.66 mmol). The reaction was stirred gently in a capped flask. After 3 h the addition of methyl chloroformate was repeated. After another 3 h PS-trisamine (150 mg, 0.5 mmol) was added, stirring 1 h further before resins were filtered and rinsed several times with DCM. The combined filtrate and washings were evaporated and the residual gum was triturated with *t*-BuOMe. The

(9) NMR spectra are consistent with: Flitsch, W.; Russkamp, P. *Liebigs Ann. Chem.* **1985**, *1985* (7), 1398−1412.

resulting slurry was evaporated to give **17** as an off-white solid (195 mg, 82.7%). ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 9H), 1.57 (s,3H), 2.59 (m, 1H), 2.88 (m, 1H), 3.62 (br s, 3H), 5.02 (m, 3H), 5.59 (m, 1H), 7.0−7.6 (complex, 9H). MS (APCI+) 393 (m − *t*Bu + 1). This material was used directly in Step B below without further purification.

Step B: 3-(2,3-Dihydroxypropyl)-2-phenyl-2,3-dihydroindole-1,3-dicarboxylic Acid, 1-Methyl Ester. A solution of **17** (115 mg, 0.29 mmol) in a mixture of acetone (4 mL) and H_2O (1 mL) was treated with OsO_4 (0.075 M in *t*-BuOH, 125 μL, 9 μmol) and NMO (68 mg, 0.58 mmol). The reaction was stirred 5 h at room temperature then concentrated at reduced pressure. The residue was treated with 10% aqueous $NaHSO_3$ (6 mL) and EtOAc (25 mL), stirring vigorously for 5 min. The organic layer was separated, washed successively with 1 N HCl, water, and brine, dried over $MgSO_4$, and evaporated. The residue was dissolved in $CHCl_3$ and evaporated again, drying under vacuum to constant weight to afford the crude glycol. ^{1}H NMR is complex due to the presence of two diastereomers (see the Supporting Information). MS (APCI+) 372 (m + 1), 354 (m − H_2O + 1).

Step C: 5-(Hydroxymethyl)-2-oxo-2′-phenyl-4,5-dihydrospiro[furan-3,3′-indole]-1′(2′*H*)-carboxylic Acid, Methyl Ester (18, 18a, 18b). The crude glycol from Step B above (0.29 mmol) was dissolved in DCM (2 mL) and treated with TFA (1 mL). The resulting solution was stirred at room temperature for 4 h, diluted with DCM (10 mL), and evaporated. The residue was dissolved in DCM (10 mL) and evaporated twice to afford a brown gum. Filtration through a pad of silica gel, eluting with $CHCl_3$−MeOH (99:1), removed a trace of TLC baseline material from the major product. Evaporation gave **18** as a colorless foam that was dried to constant weight under vacuum (103 mg, 100% from **17**). TLC (silica gel, $CHCl_3$−MeOH, 99:2, I_2 stain) shows a single spot, R_f 0.3. ^{1}H NMR ($CDCl_3$) δ 1.88 (t, 0.5H), 1.91 (t, 0.5H), 2.45 (d of d, 0.5H), 2.64 (d of d, 0.5H), 2.68 (d of d, 0.5H), 2.82 (d of d, 0.5H), 3.6−3.8 (m + br, 4H), 4.04 (m, 1H), 4.74 (m, 0.5H), 4.84 (m. 0.5H), 5.43 (s, 0.5H), 5.59 (s, 0.5H), 7.11 (m, 2.5H), 7.15 (m, 0.5H), 7.29 (m, 4H), 7.39 (m, 1H), 7.87 (br s, 1H). MS (APCI+) 354 (m + 1). Analytical HPLC shows two diastereomers of equal amounts: Stationary phase Xterra 150 × 4.6 mm, C_{18}. Mobile phase MeCN−H_2O buffered with 0.1% HCO_2H, linear gradient 30% to 50% MeCN over 20 min, flow 1.0 mL/min. **18a** retention time 8.83 min. **18b** retention time 9.78 min. They were separated by preparative HPLC: Stationary phase Xterra 150 × 30 mm, C_{18}. Mobile phase MeCN−H_2O buffered with 0.1% HCO_2H, linear gradient 30% to 50% MeCN over 20 min, flow 35 mL/min. For **18a**: ^{1}H NMR ($CDCl_3$) δ 1.88 (br t, 1H), 2.45 (d of d, 1H), 2.68 (d of d, 1H), 3.72 (br s, 3H), 4.02 (d, 1H), 4.84 (m, 1H), 5.43 (s, 1H), 7.11 (m, 3H), 7.29 (m, 4H), 7.39 (m,1H), 7.87 (br s, 1H). HRMS: calcd 354.1341; found (ESI MeCN/H_2O) 354.1340 (m + 1). Calcd for $C_{20}H_{19}NO_5 \cdot 0.5H_2O$: C, 66.19; H, 5.57; N, 3.86. Found: C, 65.81; H, 5.29; N, 3.76. For **18b**: ^{1}H NMR ($CDCl_3$) δ 1.91 (t, 01H), 2.64 (d of d, 1H), 2.82 (d of d, 1H), 3.69 (br s, 3H), 3.78 (m, 1H), 4.04 (m, 1H), 4.74 (m, 1H), 5.59 (s, 1H), 7.11 (m, 2H), 7.15 (m, 2H), 7.27 (m, 4H), 7.37 (m,1H), 7.87 (br s, 1H). HRMS: calcd 354.1341; found (ESI MeCN/H_2O) 354.1339 (m + 1). Calcd for $C_{20}H_{19}NO_5 \cdot H_2O$: C, 64.65; H, 5.70; N, 3.77. Found: C, 64.27; H, 5.24; N, 3.71.

Supporting Information Available: ^{1}H NMR spectra for compounds **13a**,**b**, **14a**,**b**, **16a**−**d**, **17** and related glycol, **18**, and **18a**,**b**; HPLC traces for the separation of **18a** and **18b**; and 2D ROESY spectra for compounds **16a**, **18a**, and **18b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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