JOC*Article*

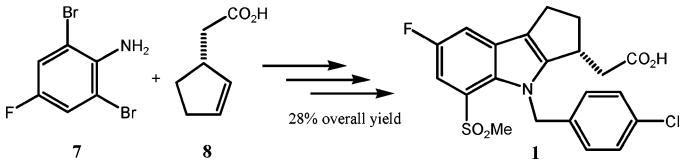
Asymmetric Synthesis of a Prostaglandin D_2 Receptor Antagonist

Kevin R. Campos,* Michel Journet, Sandra Lee, Edward J. J. Grabowski, and Richard D. Tillyer

Department of Process Research, Merck Research Laboratories, P.O. Box 2000, RY800-B267, Rahway, New Jersey 07065-0900

kevin_campos@merck.com

Received September 23, 2004

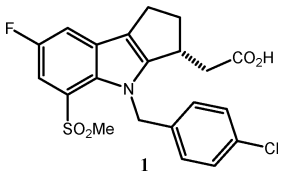


7 8 1

An asymmetric synthesis was developed for the production of a prostaglandin D_2 receptor antagonist for the treatment of allergic rhinitis. The stereogenic center was set using asymmetric allylic alkylation chemistry, and the core of the structure was constructed via Pd-catalyzed *N*-cyclization/Heck methodology. The synthesis relies on a late stage indoline oxidation which does not racemize the product.

Introduction

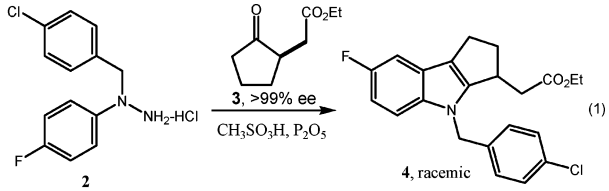
Prostaglandin D_2 (PGD_2) is the major cyclooxygenase metabolite of arachidonic acid produced by mast cells in response to antigen challenge.[1] It has been proposed that excess production of PGD_2 causes the inflammation commonly observed in allergic diseases such as allergic rhinitis, asthma, and atopic dermatitis.[2] Efforts to develop a PGD_2 receptor antagonist have identified **1** as a promising lead in the alleviation of various allergic disorders.[3] In this paper, the full details of the asymmetric synthesis of **1** are disclosed.



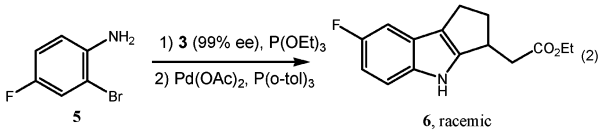
1

Results and Discussion

To determine the optimal method for the synthesis of this highly functionalized indole, several classical methods for the synthesis of indoles were attempted.[4] Fischer indole cyclization of hydrazine **2** with optically pure ketoester **3** provided the advanced intermediate **4** in good yield albeit with complete racemization of the stereogenic center (eq 1).[5] Likewise, condensation of aniline **5** with optically pure **3** followed by intramolecular Heck reaction rapidly provided the desired indole **6**, but again as a racemic mixture (eq 2).



2 4, racemic



5 6, racemic

The observed lability of the stereogenic center to racemization forced us to seek alternative methods to

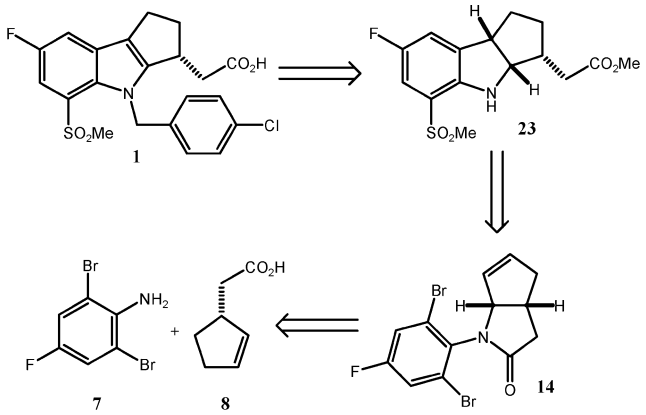
(1) Lewis, R, A.; Soter, N. A.; Diamond, P. T.; Austen, K. F.; Oates, J. A.; Roberts, L. J. *J. Immunol.* **1982**, *129*, 1627−1631.

(2) (a) Matsuoka, T.; Hirata, M.; Tanaka, H.; Takahashi, Y.; Murata, T.; Kabashima, K.; Sugimoto, Y.; Kobayashi, T.; Ushikubi, F.; Aze, Y.; Eguchi, N.; Urade, Y.; Yoshida, N.; Kimura, K.; Mizoguchi, A.; Honda, Y.; Nagai, H.; Narumiya, S.; Kato, M.; Watanabe, M.; Vogler, B.; Awen, B.; Masuda, Y.; Tooyama, Y.; Yoshikoshi, A. *Science* **2000**, *287*, 2013−2016. (b) Charlesworth, E. N.; Kagey-Sobotka, A.; Schliemer, R. P.; Norman, P. S.; Lichtenstein, L. M. *J. Immunol.* **1991**, *149*, 671−676. (c) Proud, D.; Sweet, J.; Stein, P.; Settipane, R. A.; Kagey-Sobotka, A.; Freidlander, M.; Lichtenstein, L. M. *J. Allergy Clin. Immunol.* **1990**, *85*, 896−905. (d) Murray, J. J.; Tonnel, A. B.; Brash, A. R.; Roberts, L. J.; Gosset, P.; Workman, R.; Capron, A.; Oates, J. *N. Eng. J. Med.* **1986**, *315*, 800−804.

(3) Tsuri, T.; Honma, T.; Hiramatsu, Y.; Mitsumori, S.; Inagaki, M.; Arimura, A.; Yasui, K.; Asanuma, F.; Kishino, J.; Ohtani, M. *J. Med. Chem.* **1997**, *40*, 3504−3507.

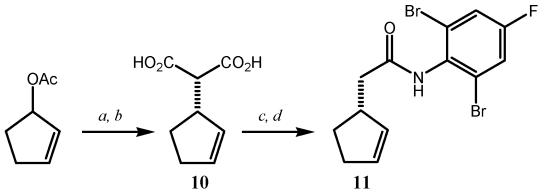
10.1021/jo048305+ CCC: $30.25
Published on Web 12/01/2004

SCHEME 1. Retrosynthetic Analysis



synthesize **1**. We envisioned that indoline **23** would be a suitable precursor to **1** that would unmask the indole functionality at a late stage (Scheme 1). We believed that **23** could be produced from bicyclic lactam **14** via intramolecular Heck reaction. We felt that **14** would be readily accessible from 2,6-dibromo-4-fluoroaniline (**7**) and (*R*)-2-cyclopentene-1-acetic acid (**8**). This strategy was attractive because the stereogenic center was introduced early in the synthesis, the design was amenable to the indole substitution pattern in **1**, and the starting materials were commercially available in bulk.

SCHEME 2. Synthesis of 11



a)[allyl-PdCl]$_2$, (*R, R*)-Trost Ligand, BSA, $CH_2(CO_2Me)_2$, KOAc, CH_2Cl_2, 0 °C, 96% ee; *b*) i) KOH, MeOH; ii) Filter; iii) HCl, 88% isolated; *c*) HOAc, 120 °C, 95%; *d*) i) $Cl(CO)_2Cl$, DMF (cat.), CH_2Cl_2; ii) **7**, 82% isolated

In accordance with literature precedent, (*R*)-2-cyclopentene-1-acetic acid (**8**) was produced via Trost asymmetric allylic alkylation of cyclopentenyl acetate with dimethyl malonate (Scheme 2).[6] Replacement of NaH/Hex_4NBr with bistrimethylsilylacetamide (BSA) as the base resulted in a more practical, reproducible procedure. The reaction was run at 0 °C with 4 mol % Pd, a 1:1 ratio of catalyst to ligand, and only 1.05 equivalents of dimethylmalonate to afford a 92% yield of the desired malonate adduct in 96% ee. We discovered that subjection of the crude allylic alkylation mixture to hydrolysis conditions (KOH/MeOH) generated a precipitate, which was determined to be ligand/Pd complex **9** by X-ray crystal structure analysis (Figure 1). Removal of **9** via filtration of the resulting slurry afforded a solution of the potassium salt of malonic acid adduct **10**, which crystallized upon acidification, extraction, and concentration (88% isolated yield, 98% LCAP, 96% ee). Decarboxylation of **10** was readily accomplished in HOAc at 120 °C to afford chiral acid **8** in 85% yield. Coupling of **8** with 2,6-dibromo-4-fluoroaniline (**7**) via the acid chloride produced amide **11**, which was isolated via recrystallization in 82% yield.

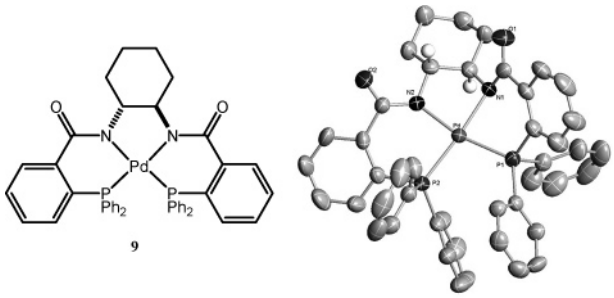
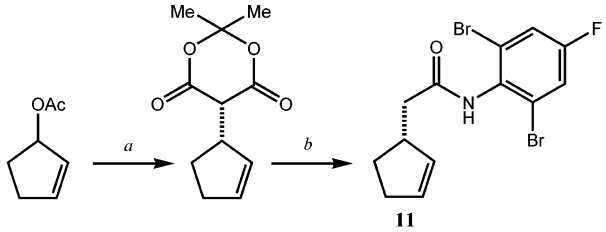


FIGURE 1. X-ray structure of ligand/Pd complex **9**.

SCHEME 3. Alternative Synthesis of 11



a)[allyl-PdCl]$_2$, (*R, R*)-Trost Ligand, BSA, Meldrum's acid, KOAc, CH_2Cl_2, 0 °C, 90% ee; *b*) **7**, toluene, reflux 90% isolated

Alternatively, Meldrum's acid could be used as the nucleophile in Trost's asymmetric allylic alkylation to afford the desired adduct in similar yield, but slightly lower enantioselectivity (90% ee). The advantage of this method lies in the ability to directly couple this intermediate with 2,6-dibromo-4-fluoroaniline in refluxing toluene in 90% isolated yield (Scheme 3). Although the process was two steps shorter, the diminished enantioselectivity in the allylic alkylation made this method less attractive.

Preliminary studies toward intramolecular *N*-cyclization to form bicyclic lactam **14** were focused on an iodolactamization/elimination sequence (Scheme 4). Subjection of **11** to conditions precedented in the literature[7] for regioselective *N*-cyclization afforded an 88:12 mixture of regioisomers favoring the desired, *N*-cyclized product **12** over the undesired O-cyclized product **13**.[8] The crude mixture of **12** and **13** was treated with DBU in toluene, which cleanly formed the elimination products **14** and **15**. The two regioisomers were readily separated by column chromatography to afford **14** in 85% yield over the two-step process.

Subjection of **14** to a variety of Heck reaction conditions[9] afforded product **16** very cleanly; however, most

(4) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045−1075 and references therein.

(5) (a) Gribble, G. W. *Contemp. Org. Synth.* **1994**, *1*, 1. (b) Hughes, D. L. *Org. Prep. Proc. Int.* **1993,** *25,* 607−632. (c) Robinson, B. *The Fischer Indole Synthesis*; Wiley-Interscience: New York, 1982.

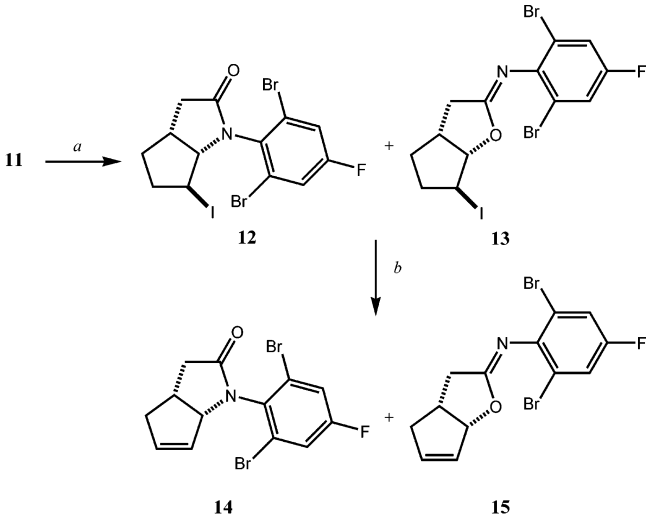
(6) (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2944. (b) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089−4090.

(7) Arunachalam, T.; Fan, H.; Pillai, K. M. R.; Ranganathan, R. S. *J. Org. Chem.* **1995**, *60*, 4428−4438.

(8) The O-cyclized product **13** was a 2:1 mixture of *E*/*Z* imidate isomers.

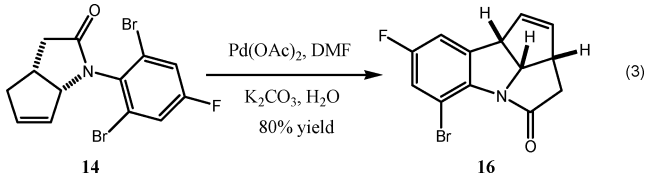
(9) (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, 2945−2964. (b) Link, J. *Org. React.* **2002**, 157. (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.

SCHEME 4. Iodolactamization/Elimination

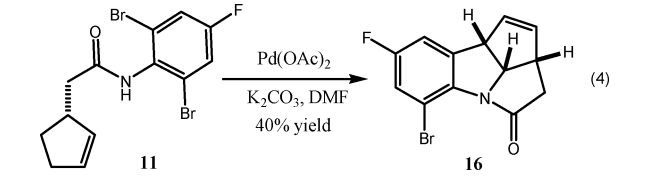


a) NIS, NaOH, MeOH/Dioxane, 88%; *b*) DBU, Toluene, reflux, 98%

conditions suffered from incomplete conversion (50% yield at best) with the remainder being starting material. Complete conversion was achieved when the reaction was performed in DMF/water in the absence of phosphine ligand, which delivered **16** in 80% isolated yield (eq 3).[10]

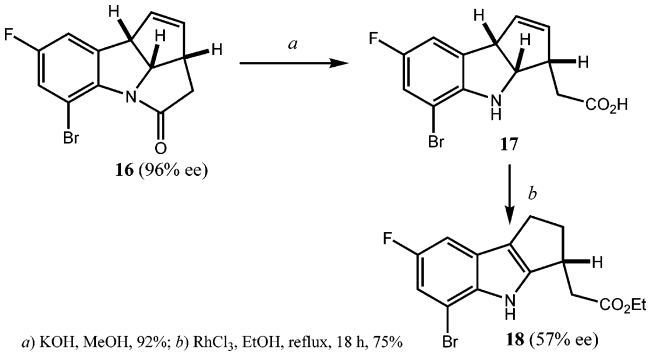


With a method for the conversion of **11** to **16** in hand (three steps), we sought to streamline this process through catalytic methods. It is precedented that intramolecular *N*-cyclizations across an olefin can be achieved using a stoichiometric amount of a Pd^{II} source.[11] We envisioned that reaction conditions should exist whereby Pd^{II} would mediate the *N*-cyclization while the byproduct of this cyclization (Pd^0) would catalyze the Heck reaction.[12] Indeed, when acyclic amide **11** was subjected to stoichiometric $Pd(OAc)_2$ and K_2CO_3 in DMF at 50 °C, the Heck adduct **16** was isolated directly in 40% yield (eq 4). Efforts to improve this process are ongoing.



The synthesis of Heck adduct **16** represented the complete synthesis of the carbon skeleton of the PGD_2 receptor antagonist **1**. In fact, we believed that the desired indole product could be obtained from **16** via isomerization of the olefin to the desired position; however, all attempts to isomerize **16** were unsuccessful, presumably due to steric constraints of the tricyclic system.[13] To reduce the strain of the tricyclic system, the lactam was hydrolyzed (KOH, MeOH, 50 °C) to cleanly afford the bicyclic amino acid intermediate **17** (Scheme 5). Subjection of **17** to isomerization conditions ($RhCl_3$, EtOH)[14] afforded the desired indole **18** in 75% yield; however, the enantiomeric excess of the product was only 57%. The remainder of the material had reverted to lactam **16**. The lactamization side reaction was a recurring problem with substrate **17** under any Lewis acidic conditions, presumably due to the nucleophilicity of the amine.

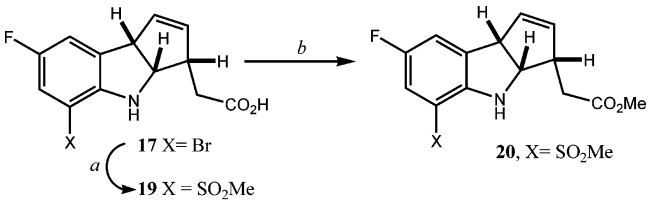
SCHEME 5. Synthesis of Bromoester 18



a) KOH, MeOH, 92%; *b*) $RhCl_3$, EtOH, reflux, 18 h, 75%

To deactivate the amine toward acylation, the sulfone moiety was introduced at this stage of the synthesis. Copper-mediated coupling of sodium sulfinate[15] with bromo acid **17**, followed by esterification afforded sulfone/ester intermediate **20** in 85% yield over the two steps (Scheme 6). This substrate did not suffer the same lactamization side reaction observed with **17**, presumably due to the attenuated nucleophilicity of the vinylogous sulfonamide.

SCHEME 6. Synthesis of Sulfone/Ester 20



a) CuI, $NaSO_2Me$, DMSO, 130 °C, 88%; *b*) H_2SO_4, MeOH, 96%

Subjection of **20** to the previously developed isomerization conditions ($RhCl_3$/EtOH) afforded clean conversion to indole **21**; however, the enantiomeric excess was only 55%, similar to that observed with **17** (Table 1).

(10) The benefits of Heck conditions performed in aqueous systems have been reported. (a) Zhao, F.; Shirai, M.; Arai, M. *J. Mol. Catal. A* **2000**, *154*, 39. (b) Demik, N. N.; Kabachnik, M. M.; Novikova, Z. S.; Beletskaya, I. P. *Russ. J. Org. Chem.* **1995**, *31*, 57. (c) Zhang, H. C.; Daves, G. D. *Organometallics* **1993**, *12*, 1499. (d) Bumagin, N. A.; More, P. G.; Beletskaya, I. P. *J. Organomet. Chem.* **1989**, *371,* 397. .

(11) (a) Shimada, T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, 10546−10547. (b) Danishefsky, S.; Taniyama, E. *Tetrahedron Lett.* **1983**, *24*, 15.

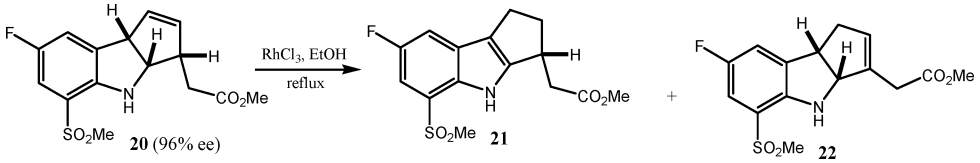
(12) For recent examples of tandem Pd-catalyzed processes, see: Pinho, P.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, 259−261 and references therein.

(13) It is quite possible that Bredt's rule applies to this system which would prohibit olefin isomerization to either "bridgehead" position. Shea, K. J. *Tetrahedron* **1980**, 1683−1715 and references therein.

(14) (a) Clive, D. L. J.; Daigneault, S. *J. Org. Chem.* **1991**, *56*, 5−5289. (b) Andrieux, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc., Perkin Trans. 1* **1977**, 359. (c) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102.

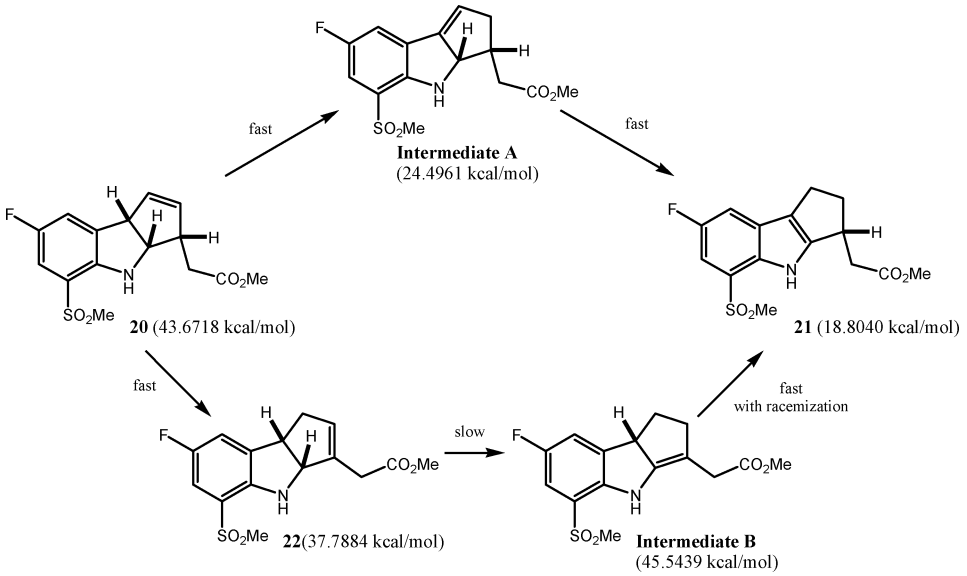
(15) (a) Baskin, J. M.; Wang, Z. *Tetrahedron Lett.* **2002**, 8479−8483. (b) Suzuki, H.; Abe, H. *Tetrahedron Lett.* **1995**, *36*, 6239−6242.

TABLE 1. Isomerization of 20 with $RhCl_3$



time (h)	**21** (% ee)/**22** (% ee)
1	50 (96):50 (96)
5	80 (65):20(96)
18	100 (55):0

SCHEME 7. Proposed Mechanism for $RhCl_3$ Isomerization of 20



When conversion and enantioselectivity were monitored over time, a new intermediate, determined by NMR to be **22**, appeared within 1 h of the start of the reaction and slowly converted to indole **21**. Additionally, the enantiomeric excess of indole product **21** after 1 h was very high (96% ee) but slowly degraded over the course of the reaction. No racemization was observed when optically pure indole **21** was subjected to the reaction conditions, so we presume that the loss of enantioselectivity was the result of conversion of intermediate **22** to **21**.

These data suggest that two reaction pathways were operating in the isomerization of **20** to **21**; one pathway that rapidly produced the indole with no racemization and another pathway that slowly produced the indole via intermediate **22** with concomitant loss of enantiomeric integrity (Scheme 7). In accord with the literature, the isomerization of **20** with $RhCl_3$ is a likely kinetic process that indiscriminately isomerizes the olefin in a "clockwise" or "counterclockwise" fashion.[14] Isomerization of the olefin in a "counterclockwise" direction affords intermediate **A**, which was not detectable, but presumably undergoes rapid isomerization to indole **21**, according to literature precedent.[16] Molecular modeling analysis of these intermediates at the PM3 level shows the following relative energy levels: **20** > intermediate **A** > **21**, which supports our proposal.

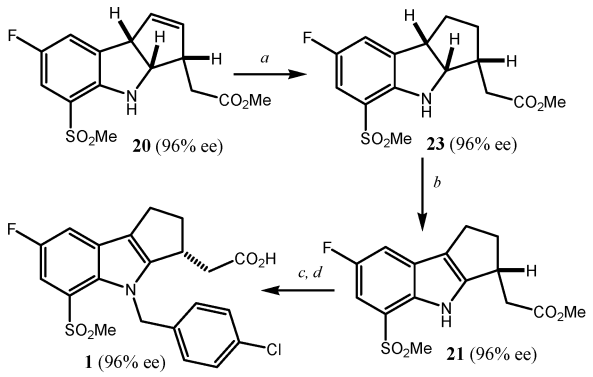
Isomerization of the olefin in the "clockwise" direction delivers intermediate **22**, which was observed in the reaction and appears to be on the pathway which results in racemization. The buildup of **22** during the reaction suggests that further isomerization in the "clockwise" direction is impaired. According to molecular modeling, intermediate **B**, the next species on the pathway of "clockwise" isomerization, is much higher in energy than **20**. This calculated activation barrier would explain the buildup of **22** during the reaction. Under the acidic reaction conditions, intermediate **B** would rapidly isomerize via protonation/deprotonation of the enamine/iminium species to the more stable indole **21**. Despite the proximal stereogenic center, the protonation sequence appears to be nonselective, resulting in the production of racemic indole **21**.

An alternative to the isomerization of intermediate **20** was to reduce the substrate to the fully saturated indoline **23** and subsequently oxidize to the indole (Scheme 8). Reduction was accomplished with Crabtree's catalyst in THF to afford the indoline **23** in 90% yield.[17] Oxidation of the indoline with a variety of typical reagents (DDQ,[18]

(16) (a) Forbes, I. T. *Tetrahedron Lett*. **1999**, 9293−9295. (b) Tietze, L. F.; Buhr, W. *Angew. Chem., Int. Ed. Engl.* **1995**, 1366−1368. (c) Kaufman, M. D.; Greico, P. A. *J. Org. Chem.* **1994**, *59*, 7−7198. (d) Simoji, Y.; Saito, F.; Tomita, K.; Morisawa, Y. *Heterocycles* **1991**, 2389−2397.

(17) Alternatively, Wilkinson's catalyst was also found to be effective; however hydrogenation with Pd/C was found to produce isomerization products with some degradation of enantiomeric excess.

SCHEME 8. Endgame Chemistry



a) H_2, Crabtree's cat.; *b*) MnO_2, benzene, 76%; *c*) Cs_2CO_3, 4-ClBnBr; *d*) 5N NaOH, 75 °C, 90%

NBS,[19] Pd/C,[20] salcomine[21]) proved unsuccessful; however, oxidation with MnO_2 in benzene at 50 °C produced the indole **21** in 80% yield. Benzylation of **21** with 4-chlorobenzyl chloride and Cs_2CO_3 followed by hydrolysis in the same pot afforded the PGD_2 receptor antagonist **1** in 90% isolated yield.

This synthetic route provided PGD_2 receptor antagonist **1** in 12 steps and 23% overall yield (96% ee) with no loss of enantiomeric purity over the entire sequence of reactions. Key points in the synthesis are early stage introduction of the stereogenic center via Trost's asymmetric allylic alkylation, Pd-mediated cyclization/Heck reaction to afford the entire carbon skeleton in one step, and late-stage oxidation of a fully functionalized indoline to the indole. Efforts to further improve the synthesis of **1** are ongoing.

Experimental Section

2-[(1*R*)-Cyclopent-2-en-1-yl]-*N*-(2,6-dibromo-4-fluorophenyl)acetamide (11). To a solution of (*R*)-2-cyclopentene-1-acetic acid (**8**, 52.4 g, 0.415 mol) and DMF (1 mL) in CH_2Cl_2 (500 mL) at 4 °C was added oxalyl chloride (188 mL, 1.76 mol) over 45 min such that gas evolution from the reaction was controlled. Upon complete addition, the reaction mixture was aged for 30 min and then slowly warmed to rt. The reaction mixture was aged at rt for 30 min and checked for conversion (GC). The reaction mixture was concentrated by distillation to remove CH_2Cl_2 and excess oxalyl chloride. The resulting crude acid chloride was added via addition funnel to a solution of 2,6-dibromo-4-fluoroaniline (**7**, 112 g, 0.415 mol) in *N*,*N*-dimethylacetamide (500 mL) at 4 °C. The reaction mixture was aged for 4 h at which time the reaction was complete by HPLC analysis. The reaction mixture was diluted with MTBE (2 L) and washed with 1.7% $NH_4Cl_{(aq)}$ solution (1.7 L) and then with water (1.7 L). The organic layer was dried over Na_2SO_4 and concentrated. The resulting crude oil was recrystallized from 70:30 hexane/acetone to yield 101 g of **11**. A second crop of **11** (18.9 g) was recovered from the mother liquors to afford a total of 120 g, 76% isolated yield of **11**: mp = 175.6−176.4 °C; $[\alpha]^{23}_D$ −26.6 (c = 0.0086, 96% ee, CH_2Cl_2); IR (film) 3213, 3163, 3002, 2918, 2850, 1653, 1589, 1569, 1522, 1460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.36 (d, 2H, J = 7.6 Hz), 6.99 (br s, 1 H), 5.82 (m, 2H), 3.26 (m, 1H), 2.51 (dd, 1H, J = 14.4, 6.8 Hz), 2.40 (m, 3H), 2.32 (m, 1H), 1.60 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 29.7, 31.9, 42.4, 119.4, 119.7, 124.1, 124.2, 131.4, 131.6, 133.7, 159.1, 161.7, 170.6; TLC R_f = 0.25 (60% hexane, 40% EtOAc). Anal. Calcd for $C_{13}H_{12}Br_2FNO$: C, 41.41; H, 3.21; N, 3.71. Found: C, 41.42; H, 3.04; N, 3.68. Separation of enantiomers was accomplished by LC analysis with supercritical CO_2 (Chiralcel OJ, 1.5 mL/min, 200 bar, 4−40% methanol, at 2%/min, t_R = 10.2, 10.5 min).

(3a*R*,6*S*,6a*S*)-1-(2,6-Dibromo-4-fluorophenyl)-6-iodohexahydrocyclopenta[*b*]pyrrol-2(1*H*)-one (12). To a solution of amide **11** (33.4 g, 0.089 mol) in dioxane (1.8 L) were added MeOH (500 mL) and 5 M $NaOH_{(aq)}$. The mixture was stirred for 10 min, and then *N*-iodosuccinimide (54 g, 0.24 mol) was added in one portion and stirred for 3 h. The reaction was quenched with 1 M $Na_2S_2O_3$ (1 L) and extracted from the organic with MTBE (500 mL). The aqueous layer was back-extracted twice with MTBE (500 mL), and the combined organics were dried over Na_2SO_4 and concentrated. The crude reaction mixture was used directly in the next step. The assay yield of **12**, based on a purified standard of **12**, was 39.3 g (88%). A portion of the material was purified by flash chromatography (85:15 hexane/EtOAc) for characterization purposes: $[\alpha]^{23}_D$ −29.2 (c = 0.0082, CH_2Cl_2, 96% ee); IR (film) 3074, 2959, 1714, 1585, 1566, 1461 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.44 (dd, 1H, J = 7.6, 2.8 Hz), 7.42 (dd, 1H, J = 7.6, 2.8 Hz), 5.00 (dd, 1 H, J = 8.0, 2.0 Hz), 4.36 (dt, 1H, J = 4.4, 2.0 Hz), 3.14 (m, 1H), 2.91 (dd, 1H, J = 18.0, 10.8 Hz), 2.44 (m, 2H), 2.37 (dd, 1 H, J = 18.0, 4.4 Hz), 2.09 (m, 1H), 1.72 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 28.6, 33.3, 34.3, 36.7, 37.4, 75.1, 120.3, 120.5, 120.6, 120.8, 123.8, 123.9, 126.2, 160.0, 162.6, 173.8; TLC R_f = 0.25 (70% hexane, 30% EtOAc). Anal. Calcd for $C_{13}H_{11}Br_2FINO$: C, 31.05; H, 2.20; N, 2.78. Found: C, 31.19; H, 2.02; N, 2.70.

(3a*R*,6a*S*)-1-(2,6-Dibromo-4-fluorophenyl)-3,3a,4,6a-tetrahydrocyclopenta[*b*]pyrrol-2(1*H*)-one (14). To a solution of crude iodolactamization product containing **12** (39.3 g assay, 0.078 mol) in toluene (400 mL) was added DBU (36 mL, 0.234 mol), and the mixture was heated to reflux. The reaction mixture was stirred for 18 h, cooled to rt, diluted with toluene (200 mL), and washed with 1 M HCl (300 mL). The layers were separated, and the organic layer was dried over Na_2SO_4. The crude oil was purified by flash chromatography to yield **14** (28.6 g, 98%) as a solid: mp 91.5−93.0 °C; $[\alpha]^{23}_D$ −88.0 (c = 0.0084, CH_2Cl_2, 96% ee); IR (film) 3064, 2915, 2848, 1707, 1585, 1565, 1464, 1386, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.40 (dd, 1H, J = 5.2, 2.8 Hz), 7.39 (dd, 1H, J = 5.2, 2.8 Hz), 5.98 (m, 1H), 5.72 (dq, 1H, J = 5.6, 2.0 Hz), 5.04 (m, 1H), 3.20 (m, 1H), 2.85 (dd, 1H, J = 17.5, 10 Hz), 2.79 (m, 1H), 2.43 (dd, 1H, J = 17.6, 6.4 Hz), 2.38 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 33.9, 38.0, 39.2, 70.4, 120.0, 120.2, 120.5, 124.3, 125.9, 126.0, 128.7, 134.3, 162.3, 173.5. TLC R_f = 0.25 (60% hexane, 40% EtOAc). Anal. Calcd for $C_{13}H_{10}Br_2FNO$: C, 41.63; H, 2.69; N, 3.73. Found: C, 41.44; H, 2.47; N, 3.70. Separation of enantiomers was accomplished by LC analysis with supercritical CO_2 (Chiralpak AS, 1.5 mL/min, 200 bar, 4−40% methanol, at 2%/min, t_R = 9.3, 9.9 min).

(2a*S*,9b*S*,9c*S*)-6-Bromo-8-fluoro-2a,3,9b,9c-tetrahydro-4*H*-benzo[*b*]cyclopenta[*gh*]pyrrolizin-4-one (16). To a solution of amide **14** (3.64 g, 9.71 mmol) in DMF (49 mL) was added water (5.5 mL) followed by $Pd(OAc)_2$ (433 mg, mmol) and K_2CO_3 (3.4 g, mmol). The reaction mixture was heated to 100 °C and stirred for 12 h. The reaction mixture was diluted with EtOAc (150 mL) and washed with 1 M HCl (150 mL). The resulting slurry was filtered over Celite, and then the layers were separated. The organic layer was washed twice with water (50 mL) and subsequently dried over Na_2SO_4 and concentrated. The resulting crude oil was purified by flash to afford **16** (2.28 g, 80%) as a solid: mp 110.7−112.4 °C; $[\alpha]^{23}_D$ +59.6 (c = 0.0072, CH_2Cl_2, 96% ee); IR (film) 3076, 3050, 2946, 1721, 1606, 1587, 1468, 1423, 1247 cm^{-1}; ^1H NMR (400 MHz,

(18) No reaction was observed when **20** was treated with DDQ. Lee, S.; Lim, H.-J.; Cha, K.; Sulikowski, G. A. *Tetrahedron* **1997**, *53*, 16521−16532.

(19) Treatment with NBS afforded decomposition, which was the result of overoxidation of **20**. Ko, C.-W.; Chou, T. *J. Org. Chem.* **1998**, *63*, 4645−4653.

(20) No oxidation was observed using Pd/C in a variety of solvents. Pelcman, B.; Gribble, G. W. *Tetrahedron Lett.* **1990**, *31*, 2381−2384.

(21) No oxidation was observed. Inada, A.; Nakamura, Y.; Morita, Y. *Chem. Lett.* **1980**, 12.

$CDCl_3$) 7.12 (dd, 1H, J = 8.8, 2.4 Hz), 6.91 (ddd, 1H, J = 7.6, 2.4, 0.4 Hz), 5.69 (dt, 1H, J = 5.6, 1.6 Hz), 5.64 (dt, 1H, J = 5.6, 2.0 Hz), 5.25 (t, 1H, J = 6.0 Hz), 4.08 (m, 1H), 3.51 (m, 1H), 3.12 (dd, 1H, J = 16.0, 7.6 Hz), 2.44 (d, 1H, J = 16.0 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) 39.7, 44.2, 54.3, 72.2, 110.9, 111.1, 111.6, 118.7, 118.9, 130.3, 133.3, 133.9, 137.4, 140.5, 140.6, 159.0, 161.5, 175.8; TLC R_f = 0.25 (65% hexane, 35% EtOAc). Anal. Calcd for $C_{13}H_9BrFNO$: C, 53.09; H, 3.08; N, 4.76. Found: C, 54.06; H, 2.85; N, 4.77.

[(3*S*,3a*S*,8b*S*)-5-Bromo-7-fluoro-3,3a,4,8b-tetrahydrocyclopenta[*b*]indol-3-yl]acetic Acid (17). To a solution of amide **16** (1.73 g, 5.88 mmol) in MeOH (19 mL) was added 3 M $KOH_{(aq)}$ (8.5 mL), and the mixture was heated to 50 °C overnight. The next day, the solution was cooled to room temperature, concentrated, and then diluted with MTBE (100 mL). The resulting solution was quenched with 3 M HCl (30 mL) and diluted with water (50 mL). The layers were separated, and the organic solution was washed once with water (50 mL). The organic layer was dried over Na_2SO_4 and concentrated to yield **17** as a solid which was suitable for further reaction (1.77 g, 92%). A small sample was purified by flash chromatography for characterization purposes: mp 172.4−173.5 °C; $[\alpha]^{23}_D$ −102.0 (c = 0.0049, CH_2Cl_2, 96% ee); IR (film) 3383, 3056, 1696, 1588, 1479, 1211 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 6.93 (ddd, 1H, J = 8.4, 2.4, 0.4 Hz), 6.82 (ddd, 1H, J = 7.6, 2.4, 0.8 Hz), 5.69 (m, 1H), 4.79 (dd, 1H, J = 8.0, 6.4 Hz), 4.49 (m, 1H), 3.31 (m, 1H), 2.81 (dd, 1H, J = 16.0, 10.4 Hz), 2.69 (dd, 1H, J = 16.0, 4.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) 34.5, 46.5, 56.0, 63.7, 110.3, 110.6, 116.4, 116.6, 130.6, 131.6, 131.7, 133.1, 178.4; TLC R_f = 0.25 (50% hexane, 50% EtOAc). Anal. Calcd for $C_{13}H_{11}BrFNO_2$: C, 50.02; H, 3.55; N, 4.49. Found: C, 49.69; H, 3.33; N, 4.15. Separation of enantiomers was accomplished by LC analysis with supercritical CO_2 (Chiralpak AD 1.5 mL/min, 200 bar, 4−40% (25 mM ^{i}BuNH$_2$ in MeOH), t_R = 13.5, 13.8 min).

[(3*S*,3a*S*,8b*S*)-7-Fluoro-5-(methylsulfonyl)-3,3a,4,8b-tetrahydrocyclopenta[*b*]indol-3-yl]acetic Acid (19). To a solution of bromo acid **17** (1.61 g, 5.16 mmol) in DMSO (120 mL) were added CuI (3.91 g, 20.6 mmol), 5 M NaOH (1.2 mL), and then $NaSO_2Me$ (2.10 g, 20.6 mmol). The reaction mixture was evacuated and purged three times and then heated to 120 °C. The reaction mixture was stirred at 120 °C overnight, cooled to rt, diluted with EtOAc (250 mL) and water (250 mL), and quenched with 3 N HCl (8 mL). The resulting mixture was filtered over Celite, and then the layers were separated. The organic layer was washed twice with water (100 mL), dried over Na_2SO_4, and concentrated. The crude product was assayed by HPLC for **19** based on a purified standard of **19** (1.42 g, 88%). The crude material was used directly in the next reaction; however, a small sample was purified for characterization purposes: mp 173.5−175.2 °C; $[\alpha]^{23}_D$ −54.5 (c = 0.0051, THF, 96% ee); IR (film) 3399, 3015, 2952, 1701, 1476, 1434, 1293, 1133 cm^{-1}; ^{1}H NMR (400 MHz, THF-d8) 7.14 (dd, 1H, J = 8.0, 2.0 Hz), 7.06 (dd, 1H, J = 8.8, 2.4 Hz), 5.77 (m, 1H), 5.71 (m, 2H), 4.84 (m, 1H), 4.45 (d, 1H, J = 8.4 Hz), 3.30 (q, 1H, J = 7.2 Hz), 2.92 (s, 3H), 2.52 (m, 2H); ^{13}C NMR (400 MHz, THF-d8) 34.5, 41.4, 47.0, 53.7, 64.3, 110.8, 111.1, 116.7, 117.0, 117.6, 129.7, 134.0, 135.7, 135.8, 145.9, 153.4, 155.7, 175.0; TLC R_f = 0.25 (95% CH_2Cl_2, 5% MeOH). Anal. Calcd for $C_{14}H_{14}FNO_4S$: C, 54.01; H, 4.53; N, 4.50. Found: C, 53.94; H, 4.33; N, 4.37. Separation of enantiomers was accomplished by LC analysis with supercritical CO_2 (Chiralcel OBH, 1.5 mL/min, 200 bar, 4−40% methanol, at 2%/min, t_R = 11.9, 14.4 min).

Methyl [(3*S*,3a*S*,8b*S*)-7-Fluoro-5-(methylsulfonyl)-3,3a,4,8b-tetrahydrocyclopenta[*b*]indol-3-yl]acetate (20). To a solution of acid **19** (1.42 g assay, 4.57 mmol) in MeOH (20 mL) was added concd H_2SO_4 (15 drops), and the mixture was heated to 50 °C. The reaction mixture was stirred for 2 h, cooled to rt, and concentrated. The crude reaction mixture was diluted with EtOAc (50 mL), washed with 1 M $NaHCO_3$ (50 mL), and then washed twice with water (50 mL × 2). The organic layer was dried over Na_2SO_4 and concentrated. The crude product was assayed by HPLC for **20** using a sample purified by recrstallization from 70:30 hexane/EtOAc (1.42 g, 96%). The crude material was used directly in the next reaction; however, a small sample was purified by recrystallization (70:30 hexane/EtOAc) for characterization purposes: mp 118.0−119.4 °C; $[\alpha]^{23}_D$ −55.2 (c = 0.0075, CH_2Cl_2, 96% ee); IR (film) 3403, 2909, 2844, 1731, 1476, 1295 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.12 (dd, 1H, J = 8.4, 2.0 Hz), 7.04 (d, 1H, J = 7.6 Hz), 5.70 (m, 2H), 5.53 (br s, 1 H), 4.85 (m, 1H), 4.45 (d, 1H, J = 8.4 Hz), 3.76 (s, 3H), 3.36 (m, 1H), 2.99 (s, 3H), 2.60 (dd, 1H, J = 16.0, 5.6 Hz), 2.53 (dd, 1H, J = 16.0, 10.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) 35.0, 42.5, 46.7, 51.9, 53.8, 64.2, 111.4, 111.7, 117.5, 117.8, 130.1, 133.9, 135.3, 145.8, 173.2; TLC R_f = 0.30 (70% hexane, 30% EtOAc). Anal. Calcd for $C_{15}H_{16}FNO_4S$: C, 55.37; H, 4.96; N, 4.31. Found: C, 55.63; H, 4.75; N, 4.25. Separation of enantiomers was accomplished by HPLC analysis (Chiralcel AD, 1.0 mL/min, 90% hexane, 10% 2-propanol, t_R = 12.4, 13.2 min).

Methyl [(3*R*,3a*S*,8b*S*)-7-Fluoro-5-(methylsulfonyl)-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-3-yl]acetate (23). To a solution of **20** (937 mg assay, 2.88 mmol) in THF (10 mL) was added Crabtree's catalyst (220 mg, 10 mol %), and then the mixture was evacuated and purged with H_2 five times. The reaction mixture was stirred overnight, concentrated to dryness, and purified by flash chromatography (70:30 hexane/EtOAc to 60:40 hexane/EtOAc) to yield **23** as a solid (890 mg, 95%): mp 95.3−96.4 °C; $[\alpha]^{23}_D$ −59.8 (c = 0.0101, CH_2Cl_2, 96% ee); IR (film) 3408, 2951, 2848, 1733, 1479, 1298, 1133 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.10 (dd, 1H, J = 8.4, 2.4 Hz), 6.95 (dd, 1H, J = 8.0, 2.0 Hz), 5.40 (s, 1H), 4.53 (sept, 1H, J = 3.2 Hz), 3.89 (t, 1H, J = 8.8 Hz), 3.72 (s, 3H), 3.01 (s, 3H), 2.53 (dd, 1H, J = 15.6, 8.8 Hz), 2.47 (dd, 1H, J = 15.6, 4.4 Hz), 2.30 (dsept, 1H, J = 6.0, 2.8 Hz), 2.04 (dsept, 1H, J = 6.4, 2.8 Hz), 1.79 (m, 2H), 1.22 (dq, 1H, J = 12.4, 6.8 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) 29.9, 33.9, 34.4, 42.4, 42.6, 46.2, 51.7, 65.8, 111.2, 111.4, 116.1, 117.9, 118.2, 138.9, 139.0, 146.9, 153.7, 156.1, 173.2; TLC R_f = 0.25 (60% hexane, 40% EtOAc). Anal. Calcd for $C_{15}H_{18}FNO_4S$: C, 55.03; H, 5.54; N, 4.28. Found: C, 54.99; H, 5.42; N, 4.23. Separation of enantiomers was accomplished by HPLC analysis (Chiralcel AD, 1.0 mL/min, 90% hexane, 10% 2-propanol, t_R = 11.7, 12.2 min).

Methyl [(3*R*)-7-Fluoro-5-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl]acetate (21). To a solution of **23** (738 mg assay, 2.24 mmol) in benzene (10 mL) was added MnO_2 (4.9 g, 0.056 mol), then the mixture was heated to 50 °C overnight. The next day, the reaction mixture was cooled to rt, filtered over Celite, and then washed with EtOAc. The resulting solution was concentrated to dryness, and the product was purified by flash chromatography (50:50 hexane/EtOAc) to yield **21** as a solid (582 mg, 80%): mp 141.2−143.4 °C; $[\alpha]^{23}_D$ −96.2 (c = 0.0073, CH_2Cl_2, 96% ee); IR (film) 3414, 2953, 2849, 1718, 1575, 1476, 1305, 1129 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 9.79 (br s, 1 H), 7.36 (m, 2H), 3.79 (s, 3H), 3.62 (m, 1H), 3.14 (s, 3H), 2.95−2.72 (m, 4H), 2.57 (dd, 1H, J = 16.8, 10.8 Hz), 2.17 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 23.1, 35.2, 35.7, 39.1, 44.7, 52.0, 108.1, 108.4, 110.2, 110.5, 119.7, 121.9, 122.0, 126.8, 126.9, 133.2, 150.0, 155.1, 157.4, 173.4; TLC R_f = 0.25 (50% hexane, 50% EtOAc). Anal. Calcd for $C_{15}H_{16}FNO_4S$: C, 55.37; H, 4.96; N, 4.31. Found: C, 55.37; H, 4.76; N, 4.25. Separation of enantiomers was accomplished by HPLC analysis (Chiralcel AD, 1.0 mL/min, 90% hexane, 10% 2-propanol, t_R = 10.7, 12.5 min).

[(3*R*)-4-(4-Chlorobenzyl)-7-fluoro-5-(methylsulfonyl)-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl]acetic Acid (1). To a solution of **21** (500 mg assay, 1.54 mmol) in DMAc (5 mL) at rt were added Cs_2CO_3 (1.5 g, 4.61 mmol) and 4-chlorobenzyl bromide (379 mg, 1.85 mmol). The reaction mixture was stirred for 3 h, 5 N NaOH (1.23 mL) was added to the reaction mixture, and the mixture was heated to 50 °C for 2 h. The reaction mixture was cooled to 0 °C, and 5 N HCl (3.0 mL) was added slowly, keeping the temperature below 15 °C. The reaction mixture was diluted with water (5 mL) and

extracted with isopropyl acetate (10 mL). The organic layer was dried over Na_2SO_4 and concentrated to dryness. The product was purified by flash chromatography (50:50 hexane/EtOAc) to yield **1** as a solid (604 mg, 90%): mp 175 °C; $[\alpha]^{23}_D$ −29.3 (c = 1, MeOH, 99.8% ee); ^{1}H NMR (400 MHz, $CDCl_3$) 7.65 (dd, 1H, J = 9.2, 2.4 Hz), 7.42 (dd, 1H, J = 8.0, 2.8 Hz), 7.23 (m, 2H), 6.67 (m, 2H), 6.14 (d, 1H, J = 17.6 Hz), 5.65 (d, 1H, J = 17.6 Hz), 3.47 (m, 1H), 2.95 (m, 1H), 2.82 (m, 2H), 2.71 (s, 3H), 2.61 (dd, 1H, J = 16.0, 2.0 Hz), 2.45 (dd, 1H, J = 16.0, 10.4 Hz), 2.31 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 22.8, 35.4, 35.8, 38.4, 44.4, 50.1, 110.7, 111.0, 112.6, 112.9, 121.4, 125.9, 126.6, 129.2, 132.5, 133.4, 137.3, 151.8, 154.6, 157.1, 177.0. Anal. Calcd for $C_{21}H_{19}ClFNO_4S$: C, 57.86; H, 4.39; N, 3.21. Found: C, 57.81; H, 4.33; N, 3.24. Separation of enantiomers was accomplished by HPLC analysis (Chiralcel OJR, 1.5 mL/min, 99.9% MeOH, 0.1% trifluoroacetic acid, t_R 2.5, 3.3 min).

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048305+