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Stereoselective Formation of Carbon−Carbon Bonds via S_N2-Displacement: Synthesis of Substituted Cycloalkyl[*b*]indoles

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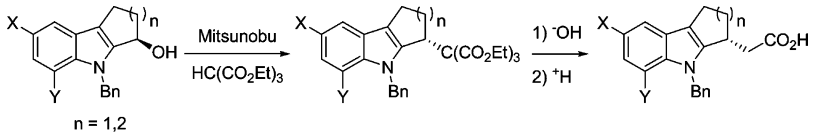
Received June 7, 2005



A general asymmetric synthesis of substituted cycloalkyl[*b*]indoles has been accomplished. The key features of this approach are (1) the utilization of a Japp−Klingemann condensation/Fischer cyclization to prepare cycloalkyl[*b*]indolones, (2) the asymmetric borane reduction of these heterocyclic ketones with (*S*)-OAB to obtain enantiomerically pure alcohols, and (3) the stereoselective S_N2-displacement of these indole alcohol substrates with a carbon nucleophile under Mitsunobu conditions to set the C_1 or C_3 tertiary carbon stereocenter. The use of trimethylphosphine (PMe_3) and bis(2,2,2-trichloroethyl) azodicarboxylate (TCEAD) was found to have an effect on the Mitsunobu dehydrative alkylation.

Introduction

Structurally, cycloalkyl[*b*]indoles containing prochiral substituents on the alkane ring represent a class of molecules not often found in the literature. Despite this relative rarity, these compounds are of interest due to the wide range of biological activity that they exhibit.[1] For example, chiral cycloalkyl[*b*]indoles similar to **1** (Figure 1) that contain an acetic acid appendage at the C_1 or C_3 position have been found to be effective antagonists of the prostaglandin D_2 receptor.[2] The interaction of this receptor with its natural substrate, prostaglandin D_2 (PGD_2), results in inflammation of the nasal vasculature and congestion.[3] This condition is commonly referred to as seasonal allergic rhinitis and affects millions of people annually.[4] Consequently, since compounds of the general structure **1**[5] can inhibit the interaction of the DP-receptor with PGD_2, they may represent a possible treatment for the general allergic response.

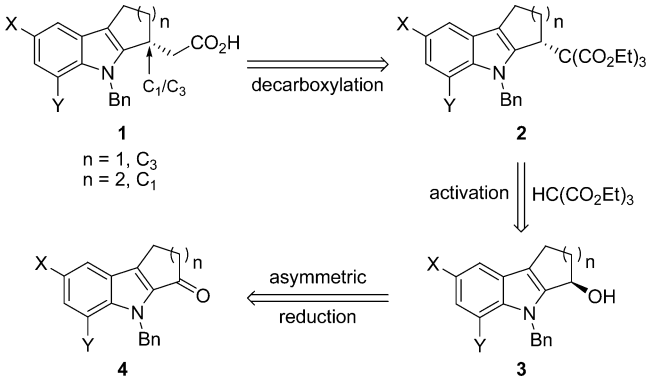


FIGURE 1. Retrosynthesis of C_1- and C_3-substituted cycloalkyl[*b*]indoles.

(1) (a) Asselin, A. A.; Humber, L. G.; Komlossy, J. *J. Med. Chem.* **1976**, *19*, 792−797. (b) Asselin, A. A.; Humber, L. G.; Dobson, T. A. U.S. Patent 4,057,599, 1977. (c) Failli, A. A.; Steffan, R. J.; Kreft, A. F.; Caggiano, T. J.; Caufield, C. E. U.S. Patent 5 830 911, 1998. (d) Kong, Y. C.; Ng, K. H.; Wat, K. H.; Wong, A.; Saxena, I. F.; Cheng, K. F.; But, P. P. H.; Chang, H. T. *Planta Med.* **1985**, *50*, 304−307. (e) Cheng, K. F.; Cheung, M, K.; Kong, Y, C. *Aust. J. Chem.* **1997**, *50*, 349−353. (f) Dionne, G.; Asselin, A. A.; Humber, L. G. U.S. Patent 4,235,903, 1098.

(2) Breyer, R. M.; Bagdassarian, C. K.; Myers, S. A.; Breyer, D. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41*, 661−690.

(3) Anonymous, *Expert Opin. Ther. Patents* **2002**, *12*, 597−599.

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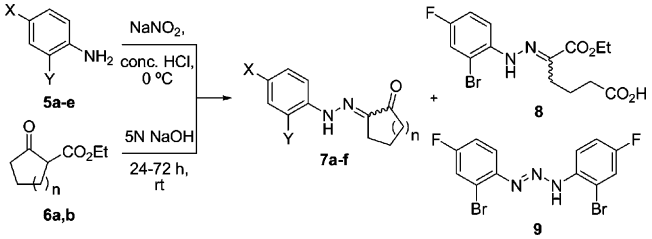
(5) (a) Guindon, Y.; Yoakim, C.; Gillard, J. W.; Girard, Y. Eur. Patent 0 300 676, 1984. (b) Labelle, M.; Sturino, C.; Roy, B. WO Patent 01/79169 A2, 2001. (c) Labelle, M.; Sturino, C.; Roy, B.; Berthelette, C.; Boyd, M.; Lachance, N.; Scheigetz, J. WO Patent 02/008186 A2, 2002. (d) Berthelette, C.; Lachance, N.; Li, L.; Sturino, C.; Zhaoyin, W. WO Patent 03/062200 A2, 2003. (e) Li, L.; Beaulieu, C.; Guay, D.; Sturino, C.; Wang, Z. WO Patent 04/103970 A1, 2004. (f) Lachance, N.; Sturino, C. WO Patent 04/111047 A2, 2004. (g) Berthelette, C.; Boyd, M. J.; Lachance, N.; Roy, B.; Sturino, C. F.; Scheigetz, J.; Zamboni, R. J. *J. Labelled Compd. Radiopharm.* **2004**, *47*, 107−113.

10.1021/jo051146p CCC: $30.25
Published on Web 09/20/2005

TABLE 1. Japp–Klingemann Condensation



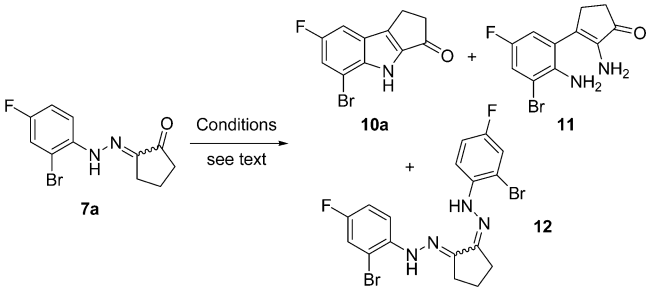
entry	aniline	X	Y	ester	*n*	product	yield, %
1	**5a**	F	Br	**6a**	1	**7a**	>95
2	**5b**	H	H	**6a**	1	**7b**	>95
3	**5b**	H	H	**6b**	2	**7c**	92
4	**5c**	F	H	**6b**	2	**7d**	>95
5	**5d**	F	F	**6b**	2	**7e**	90
6	**5e**	OMe	H	**6b**	2	**7f**	72

In these laboratories various racemic approaches to this class of heterocyclic compounds (**1**) have been formulated which rely upon chiral resolution[5,6] to obtain optically pure material. Alternatively the enantioselective synthesis of two related derivatives has also been achieved.[7] Toward the development of a more general asymmetric route to these molecules, we became interested in utilizing an S_N2-type displacement of a chiral alcohol **3** with an enolate equivalent to set the carbon stereocenter of **2**. Similar methodology has been demonstrated in a stepwise fashion for the stereoselective formation of carbon–carbon bonds in a few cases.[8] Recently, a one-pot dehydrative alkylation of a variety of chiral benzylic alcohols was developed using triethyl methanetricarboxylate (TEMT) as the nucleophile under Mitsunobu-type conditions.[9] We envisioned that this methodology would be useful for the synthesis of **2** and that the triester moiety could be converted to the acid **1** after saponification and decarboxylation. Fischer cyclization of the corresponding keto–hydrazone would provide the cycloalkyl[*b*]indolone (**4**), which after asymmetric reduction would give the chiral indole alcohol **3**. In this paper we detail the asymmetric synthesis of the general structure **1** via this approach.

Results and Discussion

Japp–Klingemann Condensation and Fischer Cyclization. Construction of the cycloalkyl[*b*]indolone core began with the preparation of a keto–hydrazone precursor using the Japp–Klingemann reaction (Table 1). In initial experiments we examined the condensation of the diazonium salt of **5a** (X = F, Y = Br) and the carboxylic acid of ethyl 2-oxocyclopentane carboxylate **6a** ($n = 1$) following a literature protocol.[10] In our hands the desired hydrazone **7a** was isolated along with the ring-opened **8** and triazene **9** impurities, which were not easily removed from the product mixture. According to Linstead and co-workers[11] the open-chain species **8** results from condensation of **6a** with the diazonium salt of **5a** followed by in situ hydrolysis. This side reaction could be avoided by careful monitoring of the ester saponification until >98% conversion or by removal of excess **6a** by extraction. The triazene adduct **9** arises from condensation of the unreacted aniline **5a** with the forming diazonium species.[12] This could be partially avoided by rapid addition of $NaNO_2$ to a cooled slurry of the HCl salt of **5a**; however, the internal reaction temperature needed to be kept below 10 °C to avoid decomposition via loss of nitrogen. An alternative solution was to remove the water-insoluble triazene by filtration of the diazonium salt solution prior to reaction with the carboxylic acid of **6a**. Using these modifications the corresponding keto–hydrazone **7a** was isolated in 95% yield as a free flowing solid after filtration and drying.[13] This same methodology was utilized for the construction of other aryl-substituted hydrazones to give products **7b–f** in good to excellent yield (72–95%) as stable crystalline solids (Table 1).[14] None of these materials required purification and could be isolated directly from the aqueous reaction mixture by simple filtration.

SCHEME 1. Fischer Cyclization of 7a



Optimization of the Fischer cyclization was carried out on **7a** under acidic conditions in order to construct the cycloalkyl[*b*]indolone core system (Scheme 1). Reaction of this substrate in the presence of excess Eaton's reagent (P_2O_5, MsOH) at room temperature gave the diamine **11**, which could not be converted to the desired product **10a**, even upon heating. When this reaction was repeated and **7a** was added to a heated solution of Eaton's reagent (60 °C), an intense exotherm (ca. 260 °C) was observed and very little product recovered (ca. <5%). Alternatively, when the reaction was repeated in acetonitrile (ACN) at 65 °C using 0.9 M H_2SO_4 in water (1.5 equiv) as the acid promoter, some of the ketone **10a** (40%) was isolated

(6) Shafiee, A.; Upadhyay, V.; Corley, E. G.; Biba, M.; Zhao, D.; Marcoux, J.-F.; Campos, K. R.; Journet, M.; King, A. O.; Larsen, R. D.; Grabowski, E. J. J.; Volante, R. P.; Tillyer, R. D. *Tetrahedron: Asymmetry*, in press.

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(8) (a) Ashwell, M. A. WO Patent 94/08983, 1994. (a) Uenishi, J.; Hamada, M. *Chem. Pharm. Bull.* **2002**, *50*, 687–700. (b) Uenishi, J.; Hamada, M. *Synthesis* **2002**, 625–630. (c) Bolshan, Y.; Chen, C.-y.; Chilenski, J. R.; Gosselin, F.; Mathre, D. J.; O'Shea, P. D.; Roy, A.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 111–114. (d) O'Shea, P. D.; Chen, C.-y.; Chen, W.; Dagneau, P.; Frey, L. F.; Grabowski, E. J. J.; Marcantonio, K. M.; Reamer, R. A.; Tan, L.; Tillyer, R. D.; Roy, A.; Wang, X.; Zhao, D. *J. Org. Chem.* **2005**, *70*, 3021–3030.

(9) Hillier, M. C.; Desrosiers, J.-N.; Marcoux, J.-F.; Grabowski, E. J. J. *Org. Lett.* **2004**, *6*, 573–576.

(10) (a) Lions, F. *J. Proc. R. Soc. N. S. Wales* **1932**, *66*, 516–525. (b) Phillips, R. R. *Organic Reactions*; John Wiley and Sons: New York, 1959; Vol. 10, pp 143–178.

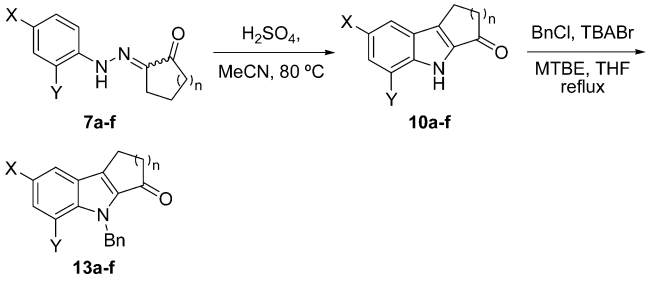
(11) See: Linstead, R. P.; Wang, A. B.-L. *J. Chem. Soc.* **1937**, 807–814 and references therein.

(12) (a) Hartman, W. W.; Dickey, J. B. *Organic Synthesis*; Wiley: New York 1948; Collect Vol. II, pp 163–265. (b) Štefane, B.; Kočevar, M.; Polanc, S. *J. Org. Chem.* **1997**, *62*, 7165–7169.

(13) The hydrazone was isolated as an inseparable mixture of isomers.

(14) The yield of the methoxy-substituted derivative **7d** was lower due to some decomposition that was observed during the reaction.

TABLE 2. Fischer Cyclization and Benzylation



substrate, **7**	*n*	X	Y	Fischer cyclization **10**, yield %	benzylation **13**, yield %
a	1	F	Br	84	84[a]
b	1	H	H	95	87
c	2	H	H	92	85
d	2	F	H	89	89
e	2	F	F	90	90
f	2	OMe	H	50	90

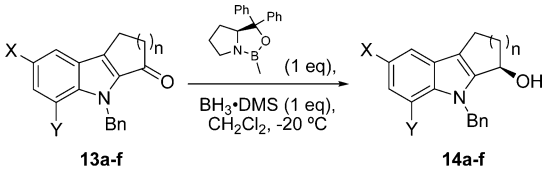
[a] Bn = *p*-chlorobenzyl.

along with a significant amount of the dimeric species **12** (30%).[15] Formation of this dimer could be avoided by heating the reaction to 80 °C to give **10a** in 70% isolated yield. When the concentration of acid was doubled (1.8 M H_2SO_4, 3 equiv), the keto−indole **10a** was produced in 84% yield after heating for 1 h at 80 °C.

These conditions were applied to the cyclization **7b−f** to provide the corresponding cycloalkyl[*b*]indolones **10b−f** in reasonable to excellent yield (Table 2). Cyclization of the difluoro keto−hydrazone **7e** gave the desired product **10e** along with some of the desfluoro compound **10d** (ca. 5%).[16] This byproduct most likely results from S_NAr-displacement of the ortho aryl fluoride during the sigmatropic rearrangement step of this reaction.[17] Only the methoxy-substituted substrate **7f** underwent Fischer cyclization in poor yield (50%) due to decomposition during the reaction. However, in all cases the products could be isolated by simple filtration and did not require further purification. Benzylation of the indole nitrogen (Table 2) was carried out under phase-transfer conditions using tetrabutylammonium bromide (TBABr) as the transfer catalyst (2 mol %).[18] The benzylated keto indole products **13a−f** were isolated in 84−90% yield after workup and recrystallization from MeOH.

Asymmetric Reduction of the Cycloalkyl[*b*]indolones. Asymmetric reduction of the cycloalkyl[*b*]indolone substrates **13a−f** was accomplished using a stoichiometric amount of (*S*)-oxazaborolidine (OAB)[19] and BH_3·DMS

TABLE 3. Asymmetric Reduction of Cycloalkyl[*b*]indolones



13	X	Y	*n*	yield, %	ee, %
a[a]	H	Br	1	98	97
b	H	H	1	90	93
c	H	H	2	91	97
d	F	H	2	96	93
e	F	F	2	96	90
f	OMe	H	2	98	95

[a] Bn = *p*-chlorobenzyl.

in methylene chloride at −20 °C to give the chiral alcohols **14a−f** in 90−98% isolated yield and 90−97% enantiomeric excess (ee) (Table 3). We were gratified to find that the optical purity of these products could be upgraded to >99% ee after a single recrystallization from EtOAc/hexanes. The use of less than stoichiometric amounts of the (*S*)-OAB catalyst gave lower yields of product and poorer enantioselectivity.[20] The workup of this reaction was of some importance as the use of methanol and acid to quench resulted in significant decomposition via methanolysis at the carbinol center.[21] This was avoided using a nonacidic workup with isopropyl alcohol as the proton source. Other methods for the asymmetric reduction of the ketone were examined, such as asymmetric hydrogenation[22] and Binal-H,[23] but these procedures were found to be inferior to the OAB method. We were able to obtain an X-ray crystal structure of **14a**, which confirms the absolute sense of stereochemistry obtained in this reaction (Figure 2).

Mitsunobu Displacement. With the requisite alcohols **14a−f** in hand, we set about examining the dehydrative alkylation of one of these intermediates under Mitsunobu conditions (Table 4). In initial trials treatment of a solution of the 5-bromo-7-fluoro-substituted cyclopent[*b*]indanol **14a**, triphenylphosphine (PPh_3, 2 equiv), and triethyl methanetricarboxylate (TEMT, 2 equiv) in THF at −78 °C with diethyl azodicarboxylate (DEAD, 2 equiv) provided product **16a** in 10% yield and 26% ee after warming to room temperature.[24] The use of a different activator, *N*,*N*,*N*′,*N*′-tetramethyldiazene-1,2-dicarboxamide (TMDD), did not improve upon this result.

(15) For similar conditions, see: (a) Fink, D. M.; Palermo, M. G.; Bores, G. M.; Huger, F. P.; Kurys, B. E.; Merriman, M. C.; Olsen, G. E.; Petko, W.; O'Malley, G. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 625−630. (b) Xing, C.; Wu, P.; Skibo, E. B. *J. Med. Chem.* **2000**, *43*, 457−466. (c) Skibo, E. B.; Xing, C.; Dorr, R. T. *J. Med. Chem.* **2001**, *44*, 3545−3562.

(16) The mono-fluoro derivative **10d** could be removed by column chromatography.

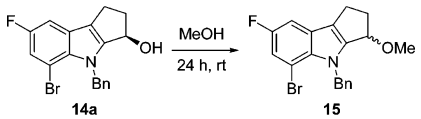
(17) (a) Brook, G. M. *J. Chem. Soc., Perkin Trans. 1* **1983**, *4*, 821−825. (b) Benke, F. D.; Brook, G. M. *J. Fluorine Chem.* **1984**, *26*, 77−86.

(18) Protection of the indole nitrogen under non-phase-transfer conditions led to poor product yield due to decomposition.

(19) (a) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880−2888. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986−2012.

(20) In general, we found these substrates to be very unreactive under catalytic OAB reducing conditions.

(21) For example, **14a** could be completely converted to racemic **15** upon standing as a solution in MeOH after 24 h.



(22) For a general review, see: Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103−151.

(23) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709−6716.

(24) Two equivalents of each reagent with respect to starting material was required for complete conversion to product for the Mitsunobu displacement reaction.

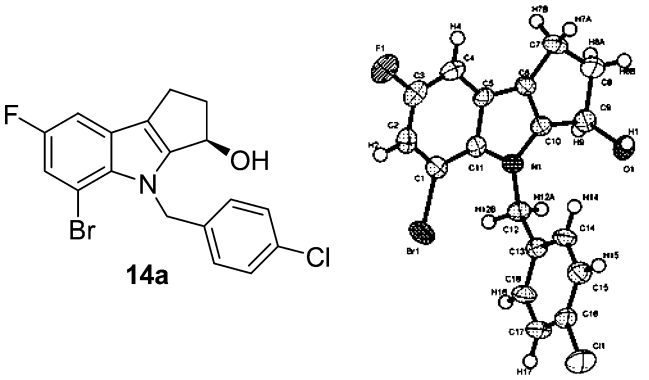
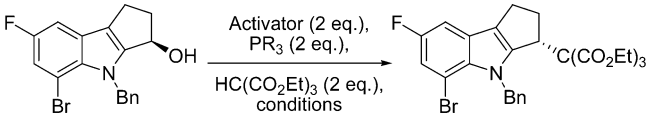


FIGURE 2. X-ray crystal structure of **14a**.

TABLE 4. Mitsunobu Displacement of 14a



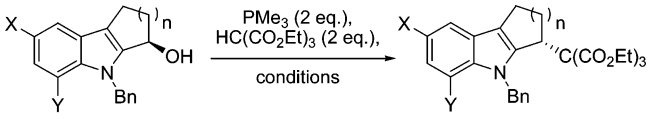
14a (99% ee) **16a**

activator	PR3	solvent	*T*, °C	yield, %	ee, %
DEAD	PPh_3	THF	−78 to room temperature	10	26
TMDD	PPh_3	THF	−78 to room temperature	18	nd
TMDD	PBu_3	THF	−78 to room temperature	45	67
DEAD	PBu_3	THF	−78 to room temperature	95	67
DEAD	PBu_3	toluene	−78 to room temperature	95	66
DEAD	PBu_3	MTBE	−78 to room temperature	81	71
DEAD	PMe_3	THF	−78 to room temperature	88	85
DEAD	PMe_3	THF	−50	90	86
DEAD	PMe_3	THF	0	92	74
DEAD	PMe_3	THF	−78[a]	95	94
TCEAD	PMe_3	THF	−78 to room temperature	nr	
TCEAD	PMe_3	toluene	0 to room temperature	84	85

[a] DEAD was added over 2.5 h; Bn = *p*-chlorobenzyl.

However, when tributylphosphine (PBu_3) was used instead of PPh_3, **16a** could be recovered in 45% yield and 67% ee. The use of DEAD as the activator resulted in a much improved 95% yield of product but no difference in optical purity (67% ee).[25] Changing solvent to either toluene or *tert*-butyl methyl ether (MTBE) did not change this outcome. A significant discovery came when a less sterically hindered phosphine, trimethylphosphine (PMe_3), was used instead of PBu_3. In this case **16a** could be isolated in good yield (88%) and an improved enantiomeric purity of 85% ee. No difference was observed when the reaction was carried out at −50 °C; however, at 0 °C significant erosion of product optical purity occurred (74% ee). On the basis of this result, the reaction was repeated at −78 °C and DEAD over 2.5 h via syringe pump.[26] The resulting solution was aged overnight at −78 °C, and the triester **16a** was isolated in 95% yield and 94% ee after workup and purification. Another commercially available activator, bis(2,2,2-trichloroethyl) azodicarboxylate (TCEAD), was also examined, but no reaction was observed in THF as solvent, even after warming to room temperature. However, when THF was replaced by toluene and the reaction was carried out at 0 °C, **16a** was formed in 84% yield and 85% ee.

TABLE 5. Scope of the Mitsunobu Displacement Reaction[a]



14b-f (99% ee) **16b-f**

				triester **16**	
alcohol **14**	*n*	X	Y	yield, %	ee, %
b	1	H	H	A: nr	
				B: 90	60
				C: 61	65
c	2	H	H	A: 95	50
				B: 95	67
				C: 80	75
d	2	F	H	B: 91	71
				C: 84	80
e	2	F	F	B: 90	82
				C: 91	95
f	2	OMe	H	B: 92	53
				C: 80	67

[a] Conditions: (A) DEAD, THF, −78 °C to room temperature; (B) DEAD, toluene, 0 °C to room temperature; (C) TCEAD, toluene, 0 °C to room temperature.

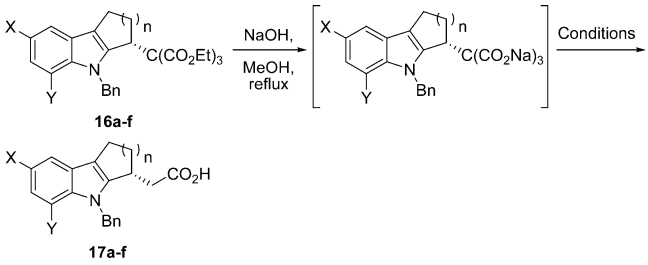
Having developed conditions for the Mitsunobu activation and S_N2-displacement of **14a**, the other indole alcohol substrates **14b**−**f** were examined (Table 5). In one case we were surprised to find that the dehydrative alkylation of the unsubstituted cyclopent[*b*]indole derivative **14b** did not proceed at −78 °C with DEAD and PMe_3 in THF even after warming to room temperature (Conditions A). When this reaction was repeated in toluene at 0 °C (Conditions B) the desired product **16b** was produced in 90% yield but with significant erosion of optical purity (60% ee). A similar result was obtained with the methoxy-substituted alcohol **14f**, which underwent displacement with significant loss of enantiomeric purity (53% ee) compared to starting material. On the other hand, when these conditions were applied to the dehydrative alkylation of **14c**−**e**, the triester products **16c**−**e** were isolated with moderate to good enantiomeric purity (67−82% ee) and in excellent yield (90−95%). When these reactions were repeated using bis(2,2,2-trichloroethyl) azodicarboxylate (TCEAD) as the activator in toluene at 0 °C (Conditions C), we were gratified to find a general improvement in the enantiomeric purity of the triester adducts thus obtained. For example, reaction of the 5,7-difluoro-substituted substrate **14e** gave **16e** in 91% yield and 95% ee using TCEAD as the activator compared to 90% yield and 82% ee using DEAD. Similar improvements were seen with all other substrates (Table 5) under these conditions.

From the results presented above it is apparent that a number of factors affect the extent of stereochemical inversion during the Mitsunobu dehydrative alkylation. First and foremost, PMe_3 is required to ensure good yield and enantiomeric purity of the displacement product. This has been observed previously[9] and may be due to an increase in the S_N2-reaction pathway leading to inversion versus nonselective S_N1-type alkylation. Clearly, the nature of the activator is also important since bis-(2,2,2-trichloroethyl) azodicarboxylate (TCEAD) results

(25) Diisopropylazodicarboxylate (DIAD) could be used instead of DEAD with little affect on the reaction outcome.

(26) The addition of DEAD is exothermic and can result in a 20 °C temperature change during uncontrolled reagent addition.

TABLE 6. Saponification and Decarboxylation of 16a−f[a]



	triester, **16**				acid, **17**		
	n	X	Y	ee, %	conditions	yield, %	ee, %
a[b]	1	F	Br	94	A	86	94
b	1	H	H	66	B	65	59
c	2	H	H	75	A	90	75
d	2	F	H	80	A	79	80
e	2	F	F	95	A	92	95
f	2	OMe	H	67	B	74	67

[a] Conditions: (A) AcOH, reflux, (B) neutralize then toluene, reflux. [b] Bn = *p*-chlorobenzyl.

in higher enantiomeric purity of product compared to the use of DEAD in most cases (e.g., **14b**−**f**). Substrate structure and electronics also have some influence on the course of this reaction. For example, the unsubstituted six-membered hydroxyl cycloalkyl[*b*]indole **14c** undergoes dehydrative alkylation under optimized conditions with some loss in enantiomeric purity (75% ee). Compare this result to the significant amount of racemization obtained during alkylation of the five-membered ring derivative **14b** (65% ee). Substrates containing electron-withdrawing groups on the aromatic portion of the indole core, such as **14a**,**d**,**e**, react with moderate to little racemization under optimized conditions. The opposite result is observed with the relatively electron-rich alcohol **14f**, which undergoes the Mitsunobu displacement to give product with significant erosion in optical purity (67% ee). Finally, the effect of reaction solvent depends on the substrate, but toluene generally ensures good yield and greater reactivity when TCEAD is used as the activator.

Saponification and Decarboxylation. The final steps in this synthetic strategy involved conversion of the triester moiety of **16a**−**f** to the corresponding acetic acid functionality via a saponification and decarboxylation sequence (Table 6). For example, the basic hydrolysis of **16a** (94% ee) was achieved by refluxing the substrate in methanol in the presence of excess NaOH to give the triscarboxylate. This intermediate was not isolated but was carried on crude to give the acid **17a** in 86% overall yield and 94% ee after refluxing in AcOH (Conditions A). We were encouraged to see that the enantiomeric purity of product had not changed compared to that of starting material. This same method was used for the saponification and decarboxylation of **16c**−**e** to give **17c**−**e** in good yield (79−92%) with no loss of enantiomeric purity. Unfortunately, the unsubstituted five-membered ring derivative **16b** was found to be acid sensitive and decomposed under the acidic decarboxylation conditions. This substrate required careful neutralization of the sodium salt intermediate followed by decarboxylation in refluxing toluene (Conditions B) to give **17b** in 65% yield and a diminished 59% ee.[27] The same procedure was utilized for the saponification and decarboxylation of **16f**, which gave **17f** in 74% overall yield and with no loss in enantiomeric purity (67% ee). In contrast, when AcOH was used during the decarboxylation step of this substrate, the product **17f** was found to have undergone significant racemization (50% ee).

In summary, an asymmetric seven-step synthesis of C_1- and C_3-substituted cycloalkyl[*b*]indoles **17a**−**f** has been developed. The key features of this approach are (1) efficient preparation of the cycloalkyl[*b*]indolones **10a**−**f** via Japp−Klingemann condensation and Fischer cyclization, (2) asymmetric reduction of these intermediates to provide the chiral alcohol substrates **14a**−**f** in excellent enantiomeric purity, and (3) stereoselective S_N2-displacement of these derivatives under Mitsunobu-type conditions with triethyl methanetricarboxylate (TEMT) as the carbon nucleophile to set the tertiary carbon stereocenter. The key to the effectiveness of the dehydrative alkylation is the use of PMe_3, which ensures both good yield and reasonable enantiomeric purity of product. Substrates containing electron-withdrawing substituents (**14a**,**d**,**e**) on the aromatic portion of the indole core underwent dehydrative alkylation to give product with less racemization compared to **14b**,**c**,**f**. The erosion of enantiomeric purity could be overcome somewhat through the use of bis(2,2,2-trichloroethyl) azodicarboxylate (TCEAD), which generally provided product in higher enantiomeric purity compared to DEAD. We are currently examining the source of this improvement and the use of this reagent in other systems.

Experimental Section

General Japp−Klingemann Procedure. *Sodium Carboxylate Preparation*. A three-neck flask was charged with ethyl 2-oxocyclopentanecarboxylate **6a** or ethyl 2-oxocyclohexanecarboxylate **6b** (1 mol), water (2 L), and 5 N NaOH (1.1 mol), and the resulting solution was stirred for 48 h at room temperature. This mixture was extracted with MTBE (2 × 400 mL) to remove any residual unreacted starting material, and the aqueous phase containing the sodium carboxylate was returned to the original three-neck flask. This solution was cooled to 0 °C, treated dropwise with concentrated HCl (1.1 mol) over 15 min, and aged at this temperature for 45 min.

Diazonium Salt Preparation. To a mixture of the aniline **5** (1 mol) in water (0.6 L) at room temperature was added concentrated HCl (3 mol), and the resulting thick white slurry was cooled to 0 °C. A solution of $NaNO_2$ (1 mol) in water (0.7 L) was added slowly over 25 min, at such a rate as not to exceed an internal temperature of 10 °C, and the reaction was aged for 30 min before filtration to remove any insoluble precipitate.

Japp−Klingemann Reaction. To the pre-prepared sodium carboxylate solution at 0 °C was added to the filtered diazonium solution dropwise over 40 min at a temperature range of 0−4 °C. The resulting thick yellow slurry was stirred to room temperature, filtered, and dried under a stream of nitrogen to give product **7**.

(1*E*/*Z*)-Cyclopentane-1,2-dione (2-Bromo-4-fluorophenyl)hydrazone (7a). 7a was isolated in 95% yield as a mixture of hydrazone isomers (4:1) from the aniline **5a** and 2-oxocyclopentanecarboxylate **6a** according to the general Japp−Klingemann procedure as a yellow solid: mp 182−187 °C; ^{1}H NMR ($CDCl_3$) δ 12.9 (s, 0.2 H, minor), 8.53 (s, 0.8 H, major),

(27) This substrate (**17f**) is extremely sensitive and rapidly decomposes in the presence of acid.

7.57−7.51 (comp, 1.2 H), 7.44 (dd, J = 5.6, 9.1 Hz, 0.8 H, major), 7.26−7.16 (comp, 1 H), 2.71 (t, J = 7.4 Hz, 1.6 H, major), 2.68 (t, J = 7.4 Hz, 0.4 H, minor), 2.47 (t, J = 7.6 Hz, 0.4 H, minor), 2.36 (t, J = 7.8 Hz, 1.6 H, major), 2.03−1.96 (comp, 2 H); ^{13}C NMR (DMSO-d_6) δ 204.0 (major), 203.0 (minor), 157.4 (d, J_{CF} = 242.4 Hz, minor), 157.1 (d, J_{CF} = 242.1 Hz, major), 145.9 (minor), 140.5 (major), 138.4 (d, J_{CF} = 2.5 Hz, minor), 137.8 (d, J_{CF} = 2.6 Hz, major), 119.7 (d, J_{CF} = 25.9 Hz, minor), 119.6 (d, J_{CF} = 25.8 Hz, major), 117.9 (d, J_{CF} = 8.1, minor), 116.3 (d, J_{CF} = 22.4 Hz, major), 116.2 (d, J_{CF} = 22.2 Hz, minor), 114.9 (d, J_{CF} = 8.2 Hz, major), 109.5 (d, J_{CF} = 10.1 Hz, minor), 107.2 (d, J_{CF} = 9.8 Hz, major), 38.5 (major), 37.9 (minor), 29.1 (major), 25.6 (minor), 19.3 (major), 17.3 (minor); IR ($CDCl_3$) ν 3332, 1713, 1560, 1516, 1458, 1184, 1047, 852 cm^{-1}; MS (ESI) calcd for $C_{11}H_{10}BrFN_2O$ + H: M + H (theory), 285.0033; M + H (found), 285.0039.

(1*E*/*Z*)-Cyclopentane-1,2-dione Phenylhydrazone (7b). 7b was prepared in 95% yield as a mixture of hydrazone isomers (24:1) from the aniline **5b** and 2-oxocyclopentanecarboxylate **6a** according to the general Japp−Klingemann procedure as a yellow solid: mp 235−237 °C; ^{1}H NMR (DMSO-d_6) δ 12.65 (s, 0.04 H, minor), 9.89 (s, 0.96 H, major), 7.27−7.29 (comp, 4 H), 6.90−6.83 (m, 1 H), 2.62 (t, J = 7.5 Hz, 2 H), 2.41 (t, J = 7.8 Hz, 0.08 H, minor), 2.29 (t, J = 7.9 Hz, 1.92 H, major), 1.97 (t, J = 7.7 Hz, 1 H), 1.93 (t, J = 7.7 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 202.8, 144.6, 142.2, 129.5, 121.6, 114.3, 37.9, 26.3, 17.4; IR ($CDCl_3$) ν 3256, 1699, 1558, 1525, 1456, 1419, 1228, 1173 cm^{-1}; MS (ESI) calcd for $C_{11}H_{12}N_2O$: M + H (theory), 189.1022; M + H (found), 189.1020.

(1*E*/*Z*)-Cyclohexane-1,2-dione Phenylhydrazone (7c). 7c was prepared in 92% yield from the aniline **5b** and 2-oxocyclohexanecarboxylate **6b** according to the general Japp−Klingemann procedure. Spectral data matched that for the known compound.[28]

(1*E*/*Z*)-Cyclohexane-1,2-dione (4-Fluorophenyl)hydrazone (7d). 7d was prepared in 95% yield as a mixture of hydrazone isomers (10:1) from the aniline **5c** and 2-oxocyclohexanecarboxylate **6b** according to the general Japp−Klingemann procedure as a yellow solid: mp 235−237 °C; ^{1}H NMR (DMSO-d_6) δ 13.47 (s, 0.1 H, minor), 9.86 (s, 0.9 H, major), 7.31−7.27 (comp, 2 H), 7.14−7.08 (comp, 2 H), 2.60−2.54 (m, 0.2 H, minor), 2.55 (t, J = 6.2 Hz, 1.8 H, major), 2.47−2.42 (m, 0.2 H, minor), 2.40 (t, J = 6.2 Hz, 1.8 H, major), 1.90−1.70 (comp, 4 H); ^{13}C NMR (DMSO-d_6) δ 197.5 (minor), 194.6 (major), 157.7 (d, J_{CF} = 236.9 Hz), 141.4 (d, J_{CF} = 1.6 Hz), 139.1, 116.4 (minor), 116.2 (minor), 116.1, 116, 115.9, 115.8 (minor), 115.7 (major), 115.6 (minor), 40.7 (minor), 40.0 (major), 32.1 (minor), 26.8 (major), 23.5 (minor), 22.3 (major), 22.0 (minor), 21.8 (major); IR ($CDCl_3$) ν 3248, 2937, 1660, 1529, 1513, 1411, 1327, 1206, 1153, 828, 750 cm^{-1}. Anal. Calcd for $C_{12}H_{13}FN_2O$ [220.10]: C, 65.44; H, 5.95; N, 12.72. Found: C, 64.83; H, 5.92; N, 12.45.

(1*E*/*Z*)-Cyclohexane-1,2-dione (2,4-Difluorophenyl)hydrazone (7e). 7e was prepared in 90% yield as a mixture of hydrazone isomers (4:1) from the aniline **5d** and 2-oxocyclohexanecarboxylate **6b** according to the general Japp−Klingemann procedure as a yellow solid: mp 47−50 °C; ^{1}H NMR (DMSO-d_6) δ 8.52 (s, 0.8 H, major), 9.15 (s, 0.2 H, minor), 7.50 (app dt, J = 5.9, 9.2 Hz, 0.8 H, major), 7.44 (app t, J = 5.9, 9.2 Hz, 0.2 H, minor), 7.24 (ddd, J = 2.8, 8.8, 11.7 Hz, 0.8 H, major), 7.20 (ddd, J = 2.8, 8.8, 11.7 Hz, 0.2 H, minor), 7.02−6.97 (comp, 1 H), 2.60−2.55 (comp, 2 H), 2.48−2.39 (comp, 2 H), 1.85−1.65 (comp, 4 H); ^{13}C NMR (DMSO-d_6) δ 198.7 (major), 195.0 (minor), 157.3 (dd, J_{CF} = 11.4, 240.9 Hz, major), 157.2 (dd, J_{CF} = 10.9, 240.3 Hz, minor), 150.9 (dd, J_{CF} = 12.2, 139.8 Hz, minor), 149.7 (dd, J_{CF} = 12.5, 244.0 Hz, major), 142.4 (minor), 135.5 (major), 129.9 (dd, J_{CF} = 3.2, 9.6 Hz, minor), 128.6 (dd, J_{CF} = 3.2, 9.1 Hz, major), 118.2 (dd, J_{CF} = 3.5, 9.2 Hz, minor), 115.4 (dd, J_{CF} = 3.1, 9.0 Hz, major), 112.4 (dd, J_{CF} = 3.3, 22.4 Hz, major), 112.0 (dd, J_{CF} = 3.4, 22.1 Hz, minor), 104.6 (dd, J_{CF} = 22.3, 27.1 Hz, major), 104.5 (dd, J_{CF} = 22.3, 27.1 Hz, minor), 40.7 (minor), 40.0 (major), 32.2 (major), 26.7 (minor), 23.1 (major), 22.4 (minor), 22.0 (major), 21.9 (minor); IR ($CDCl_3$) ν 3084, 2943, 2869, 1639, 1721, 1439, 1287, 1190, 1137, 959, 846, 703 cm^{-1}. Anal. Calcd for $C_{12}H_{12}F_2N_2O$ [238.09]: C, 60.50; H, 5.08; N, 11.76. Found: C, 60.41; H, 4.90; N, 11.67.

(1*E*/*Z*)-Cyclohexane-1,2-dione (4-Methoxyphenyl)hydrazone (7f). 7f was prepared in 72% yield from the aniline **5e** and 2-oxocyclopentanecarboxylate **6b** according to the general Japp−Klingemann procedure. Spectral data matched that for the known compound.[28]

General Fischer Cyclization Procedure. To a three-neck round-bottom flask equipped with a mechanical stirrer, a condenser, and nitrogen inlet was charged the hydrazone **7** (10 mmol) and MeCN (25 mL). A solution of 1.8 M H_2SO_4 in water (17 mL, 30 mmol) was added in one portion, and the resulting mixture was heated under reflux (80 °C) for 5−6 h. After the reaction was judged complete by HPLC analysis, water (50 mL) was added and the resultant slurry stirred at room temperature for 1−2 h before filtration. The collected product **10** was washed with MeCN:water (1:3, 50 mL) and water (3 × 50 mL) and dried to give product.

5-Bromo-7-fluoro-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (10a). 10a was isolated in 84% yield from **7a** according to the general Fischer cyclization procedure as a solid: mp 204−206 °C; ^{1}H NMR (DMSO-d_6) δ 11.9 (s, 1 H), 7.48 (d, J = 9.0, 2 H), 2.95−2.93 (m, 2 H), 2.86−2.84 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 194.2, 156.7 (d, J_{CF} = 238.3 Hz), 145.9 (d, J_{CF} = 5.6 Hz), 141.7, 139.5, 124.1 (d, J_{CF} = 10.5 Hz), 118.1 (d, J_{CF} = 29.2 Hz), 106.2 (d, J_{CF} = 12.0 Hz), 105.9 (d, J_{CF} = 22.8 Hz), 41.0, 20.0; IR ($CDCl_3$) ν 3212, 2953, 1361, 1700, 1682, 1270, 1151, 1089 cm^{-1}. Anal. Calcd for $C_{11}H_7BrFNO$ [266.97]: C, 49.28; H, 2.63; N, 5.22. Found: C, 49.22; H, 2.30; N, 5.11.

1,4-Dihydrocyclopenta[*b*]indol-3(2*H*)-one (10b). 10b was prepared in 95% yield as a solid from **7b** via the general Fischer cyclization procedure. Spectral data matched that for the known compound.[29]

2,3,4,9-Tetrahydro-1*H*-carbazol-1-one (10c). 10c was prepared in 92% yield as a solid from **7c** via the general Fischer cyclization procedure. Spectral data matched that for the known compound.[28]

6-Fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (10d). 10d was synthesized in 89% from **7d** according to the general Fischer cyclization procedure as a solid: mp 154−158 °C; ^{1}H NMR (DMSO-d_6) δ 11.7 (s, 1 H), 7.42 (dd, J = 2.5, 9.6 Hz, 1 H), 7.39 (dd, J = 4.5, 9.0 Hz, 1 H), 7.15 (ddd, 2.5, 9.0, 9.6 Hz, 1 H), 2.89 (app t, J = 6.1 Hz, 1 H), 2.55 (dd, J = 6.1, 6.9 Hz, 1 H), 2.13 (ddd, J = 6.1, 6.1, 12.4 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 190.9, 158.3 (d, J_{CF} = 233.9 Hz), 135.0, 133.0, 128.1 (d, J_{CF} = 5.6 Hz), 125.6 (d, J_{CF} = 10.1 Hz), 115.3 (d, J_{CF} = 26.9 Hz), 114.5 (d, J_{CF} = 9.6 Hz), 105.6 (d, J_{CF} = 22.8 Hz), 38.5, 24.9, 21.1; IR ($CDCl_3$) ν 3264, 1645, 1540, 1481, 1140, 810 cm^{-1}. Anal. Calcd for $C_{12}H_{10}FNO$ [203.07]: C, 70.93; H, 4.96; N, 6.89. Found: C, 70.64; H, 4.95; N, 6.90.

6,8-Difluoro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (10e). 10e was synthesized in 90% yield from **7e** according to the general Fischer cyclization procedure as a solid: mp 224−229 °C; ^{1}H NMR ($CDCl_3$) δ 9.27 (brs, 1 H), 7.10 (dd, J = 2.1, 8.5 Hz, 1 H), 6.91 (ddd, J = 2.1, 9.3, 11.1 Hz, 1 H), 2.96 (app t, J = 6.0 Hz, 1 H), 2.69 (dd, J = 6.0, 7.0 Hz, 1 H), 2.29 (ddd, J = 6.0, 7.0, 12.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 191.0, 156.2 (dd, J_{CF} = 9.5, 236.2 Hz), 149.4 (dd, J_{CF} = 14.3, 249.9 Hz), 133.7, 128.7 (dd, J_{CF} = 2.6, 6.1 Hz), 127.9 (dd, J_{CF} = 6.9, 11.3 Hz), 123.5 (d, J_{CF} = 13.6 Hz), 101.9 (dd, J_{CF} = 4.3, 22.8 Hz), 101.5 (dd, J_{CF} = 20.6, 30.9), 38.6, 24.7, 21.2; IR ($CDCl_3$) ν 3231, 1669, 1632, 1558, 1506, 1135, 823 cm^{-1}. Anal. Calcd for $C_{12}H_9F_2NO$ [221.07]: C, 65.16; H, 4.10; N, 6.33. Found: C, 64.81; H, 4.00, N, 6.24.

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6-Methoxy-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (10f). 10f was synthesized in 50% yield as a solid from **7f** via the general Fischer cyclization procedure. Spectral data matched that for the known compound.[28]

General Benzylation Procedure. To a solution of the ketone **10** (10 mmol) in THF:MTBE (1:1, 16 mL) was added benzyl chloride (10.1 mmol), tetrabutylammonium bromide (0.2 mmol), and 3.3 N NaOH (50 mmol), and the reaction was heated to 50 °C for 22 h. The reaction was cooled to room temperature and diluted with EtOAc (20 mL) and brine (20 mL), and the layers were separated. The organic layer was concentrated in vacuo, and the crude product **13** was recrystallized from MeOH.

5-Bromo-4-(4-chlorobenzyl)-7-fluoro-1,4-dihydrocyclopenta[*b*]indol-3(2*H*)-one (13a). 13a was prepared in 84% yield from **10a** according to the general benzylation procedure except that *p*-chlorobenzyl chloride was used instead of benzyl chloride: mp 152−156 °C; ^{1}H NMR ($CDCl_3$) δ 7.34 (ddd, J = 2.3, 2.3, 9.0 Hz, 2 H), 7.22 (ddd, J = 2.4, 2.4, 8.5 Hz, 2 H), 6.97 (d, J = 8.5 Hz, 2 H), 5.98 (s, 2 H), 3.06−2.99 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 194.4, 157.0 (d, J_{CF} = 242.6 Hz), 144.6 (d, J_{CF} = 5.6 Hz), 141.3, 137.3, 133.1, 128.7, 127.7, 126.0 (d, J_{CF} = 9.8 Hz), 120.8 (d, J_{CF} = 28.9 Hz), 105.9 (d, J_{CF} = 22.3 Hz), 104.8 (d, J_{CF} = 11.3 Hz), 47.5, 41.4, 19.3; IR ($CDCl_3$) ν 3060, 2933, 1675, 1492, 1208, 1144 cm^{-1}. Anal. Calcd for $C_{18}H_{12}$BrClFNO [392.65]: C, 55.06; H, 3.08; N, 3.57. Found: C, 54.85; H, 2.75; N, 3.50.

4-Benzyl-1,4-dihydrocyclopenta[*b*]indole-3(2*H*)-one (13b). 13b was prepared in 87% yield from **10b** according to the general benzylation procedure as an orange solid: mp 107−110 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (ddd, J = 1.0, 1.0, 8.0 Hz, 1 H), 7.49−7.36 (m, 2 H), 7.34−7.22 (m, 5 H), 7.19 (dddd, J = 4.0, 4.0, 8.0, 8.0 Hz, 1 H), 5.54 (s, 2 H), 3.09−3.07 (m, 2 H), 3.03−3.01 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 194.5, 145.5, 144.3, 138.6, 137.5, 128.7, 127.6, 127.3, 126.9, 123.5, 121.8, 120.4, 111.8, 47.3, 41.5, 19.6; IR ($CDCl_3$) ν 3062, 2924, 1673, 1475, 1256, 1055, 744 cm^{-1}. Anal. Calcd for $C_{18}H_{15}NO$ [261.12]: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.65; H, 5.79; N, 5.36.

9-Benzyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (13c). 13c was prepared in 85% yield from **10c** according to the general benzylation procedure as a solid: mp 117−120 °C; ^{1}H NMR ($CDCl_3$) δ 7.69 (ddd, J = 1.0, 1.0, 8.0 Hz, 1 H), 7.37−7.34 (m, 2 H), 7.29−7.13 (m, 6 H), 5.85 (s, 2 H), 3.07 (app t, J = 6.1 Hz, 2 H), 2.67 (dd, J = 6.1, 7.4 Hz, 2 H), 2.26 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 191.9, 139.4, 138.4, 129.9, 129.8, 128.5, 127.1, 126.9, 126.7, 125.1, 121.3, 120.3, 110.9, 47.9, 40.0, 24.7, 21.8; IR ($CDCl_3$) ν 3060, 3030, 2940, 1656, 1612, 1461, 1181, 930, 744 cm^{-1}. Anal. Calcd for $C_{19}H_{17}NO$ [275.13]: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.59; H, 6.11; N, 5.13.

9-Benzyl-6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (13d). 13d was isolated in 89% yield from **10d** according to the general benzylation procedure as a solid: mp 97−100 °C; ^{1}H NMR ($CDCl_3$) δ 7.33−7.20 (comp, 5 H), 7.13−7.09 (comp, 3 H), 5.83 (s, 2 H), 3.01 (app t, J = 6.2 Hz, 2 H), 2.68 (app t, J = 5.8 Hz, 2 H), 2.25 (ddd, J = 6.2 Hz, 6.2 Hz, 12.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 192.0, 157.8 (dd, J_{CF} = 237.8 Hz), 138.0, 135.9, 131.0, 129.2 (d, J_{CF} = 5.8 Hz), 128.5, 127.2, 126.6, 125.1 (d, J_{CF} = 9.5 Hz), 115.8 (d, J_{CF} = 26.9 Hz), 112.0 (d, J_{CF} = 9.2 Hz), 105.5 (d, J_{CF} = 23.1 Hz), 48.0, 39.9, 24.5, 21.8; IR ($CDCl_3$) ν 2941, 1658 1489, 1457, 1161 cm^{-1}. Anal. Calcd for $C_{19}H_{16}FNO$ [293.12]: C, 77.80; H, 5.50; N, 4.77. Found: C, 77.62; H, 5.33; N, 4.77.

9-Benzyl-6,8-difluoro-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (13e). 13e was isolated in 90% yield from **10e** according to the general benzylation procedure as a solid: mp 83−85 °C; ^{1}H NMR ($CDCl_3$) δ 7.31−7.08 (comp, 6 H), 6.87 (ddd, J = 2.2, 9.2, 11.9 Hz, 1 H), 5.97 (s, 2 H), 2.97 (app t, J = 6.1 Hz, 2 H), 2.67 (dd, J = 6.1, 6.9 Hz, 2 H), 2.24 (ddd, J = 6.1, 6.1, 6.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 192.0, 156.6 (dd, J_{CF} = 9.7, 240.1 Hz), 149.9 (dd, J_{CF} = 13.5, 250.7 Hz), 138.8, 131.8, 129.9 (dd, J_{CF} = 2.0, 3.7 Hz), 128.4, 127.6 (dd, J_{CF} = 6.5, 10.6 Hz), 127.1, 126.6, 124.3 (d, J_{CF} = 8.9 Hz), 102.6 (dd, J_{CF} = 22.9, 30.4 Hz), 101.3 (dd, J_{CF} = 4.7, 22.8 Hz), 49.8, 40.1, 24.3, 21.8; IR ($CDCl_3$) ν 3064, 2946, 2361, 1262, 1044, 1074, 902, 776 cm^{-1}. Anal. Calcd for $C_{19}H_{15}F_2NO$ [311.11]: C, 73.30; H, 4.86; N, 4.50. Found: C, 73.02; H, 4.74; N, 4.50.

9-Benzyl-6-methoxy-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (13f). 13f was isolated in 90% yield from **10f** according to the general benzylation procedure as a solid: mp 120−124 °C; ^{1}H NMR ($CDCl_3$) δ 7.26−7.21 (comp, 4 H), 7.14−7.12 (comp, 2 H), 7.07−7.04 (comp, 2 H), 5.82 (s, 2 H), 3.03 (app t, J = 6.0 Hz, 2 H), 2.67 (app t, J = 6.0 Hz, 2 H), 2.25 (ddd, J = 6.2, 6.2, 12.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 191.8, 154.4, 138.4, 134.9, 130.3, 128.9, 128.4, 127.0, 126.6, 125.1, 118.5, 111.9, 101.1, 55.7, 47.9, 39.9, 24.6, 21.9; IR ($CDCl_3$) ν 2940, 2834, 1655, 1492, 1453, 1289, 1219 cm^{-1}. Anal. Calcd for $C_{20}H_{19}NO_2$ [305.37]: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.51; H, 6.07; N, 4.48.

General Asymmetric Reduction Procedure. To a solution of the ketone **13** (10 mmol) in CH_2Cl_2 (10 mL) at −20 °C was added (*S*)-oxazaborolidine (OAB) (1 M, 10 mL, 10 mmol), the solution was aged for 20 min, and 10 M BH_3·DMS was added (1 mL, 10 mmol) dropwise over 10 min. The reaction was stirred for 3.5 h at −20 °C, quenched by addition of *i*PrOH (0.6 mL), and warmed to room temperature. Solvent was removed in vacuo via rotary evaporation, and the crude product was concentrated from *i*PrOH (25 mL) three times and passed through a plug of silica gel eluting with EtOAc/hexanes (1:2). The filtrate was concentrated in vacuo, and the semipure solid product **14** was recrystallized from EtOAc/hexanes.

(3*R*)-5-Bromo-4-(4-chlorobenzyl)-7-fluoro-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-ol (14a). 14a was prepared in 98% assay yield and 97.4% ee [SFC conditions: Chiralcel OD-H, 20% MeOH in CO_2, 1.5 mL/min for 30 min, t_R = 8.4 min (*R*), 16.3 min (*S*)] from **13a** according to the general asymmetric reduction procedure. This material was recrystallized from EtOAc/hexanes to give **14a** in 93% recovery as a white solid in >99% ee according to SFC analysis: mp 123−125 °C; $[\alpha]^{23}_D$ +24.1 (c = 0.017, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.24 (ddd, J = 2.5, 2.5, 9.1 Hz, 2 H), 7.13 (ddd, J = 2.7, 2.7, 8.7 Hz, 2 H), 6.89 (ddd, J = 2.3, 2.3, 8.6 Hz, 2 H), 5.97 and 5.63 (ABq, J = 17.0 Hz, 1 H), 5.18 (brs, 1 H), 3.03−2.89 (m, 2 H), 2.76−2.68 (m, 1 H), 2.35−2.27 (m, 1 H), 1.68 (brs, 1 H); ^{13}C NMR ($CDCl_3$) δ 156.8 (d, J_{CF} = 240 Hz) 149.0, 137.8, 134.5, 132.9 128.7, 127.0, 126.5 (d, J_{CF} = 9.8 Hz), 121.3 (d, J_{CF} = 4.9 Hz), 115.5 (d, J_{CF} = 28.6 Hz), 104.4 (d, J_{CF} = 22.5 Hz), 103.4 (d, J_{CF} = 11.8 Hz) 69.9, 48.2, 45.5, 39.9, 22.1; IR ($CDCl_3$) ν 3325, 2937, 2868, 1487, 1405, 1205, 1130 cm^{-1}. Anal. Calcd for $C_{18}H_{14}$BrClFNO [394.99]: C, 54.78; H, 3.58; N, 3.55. Found: C, 54.66; H, 3.27; N, 3.43.

(3*R*)-4-Benzyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-ol (14b). 14b was prepared in 90% yield and 93% ee [SFC conditions: Chirapak AD column, 4% MeOH in CO_2 for 4 min then ramp to 40% MeOH at 2% per min, 1.5 mL/min, t_R = 15.2 min (*S*), 16.6 min (*R*)] from **13b** according to the general reduction procedure. This material was recrystallized from EtOAc/hexanes to give **14b** in 78% recovery and >99% ee according to SFC analysis as a solid: mp 170−172 °C; $[\alpha]^{23}_D$ +41.8 (0.008, CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 7.40 (ddd, J = 1.0, 1.0, 7.4 Hz, 1 H), 7.32−7.19 (comp, 6 H), 7.00 (dddd, J = 1.2, 7.1, 7.1, 22.5 Hz, 1 H), 5.43 and 5.31 (ABq, J = 16 Hz, 2 H), 5.24−5.20 (m, 1 H), 2.89 (dddd, J = 1.4, 4.2, 8.3, 14.1 Hz, 1 H), 2.85−2.77 (m, 1 H), 2.63 (ddd, J = 4.6, 8.3, 13.0 Hz, 1 H), 2.24 (ddd, J = 3.8, 7.8, 12.3 Hz, 1 H); ^{13}C NMR (DMSO-d_6) δ 147.2, 141.3, 138.8, 128.8, 127.5, 127.4, 124.0, 121.2, 119.4, 119.3, 118.8, 111.0, 68.3, 47.4, 22.5; IR ($CDCl_3$) ν 3358, 2910, 1451, 1212, 1154, 1036, 736 cm^{-1}. Anal. Calcd for $C_{18}H_{17}NO$ [263.13]: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.83; H, 6.40; N, 5.35.

(3*R*)-9-Benzyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-ol (14c). 14c was prepared in 91% yield and 97% ee [SFC conditions: Chiralcel OD-H column, 30% MeOH in CO_2 for 10 min, 1.5 mL/min, t_R = 6.8 (*S*), 8.5 (*R*)] from **13c** according to the general reduction procedure. This material was recrystallized from

EtOAc/hexanes to give **14c** in 65% recovery and >99% ee according to SFC analysis as a solid: mp 145−147 °C; $[\alpha]^{23}_D$ +74.9 (0.01, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.59 (d, J = 7.7 Hz, 1 H), 7.31−7.23 (comp, 1 H), 7.20 (ddd, J = 1.1, 6.9, 6.9 Hz, 1 H), 7.13 (ddd, J = 1.1, 7.9, 7.9 Hz, 1 H), 7.05 (d, J = 6.9 Hz, 2 H), 5.54 and 5.41 (ABq, J = 16.8 Hz, 2 H), 4.86−4.85 (m, 1 H), 2.94−2.89 (m, 1 H), 2.73−2.65 (m, 1 H), 2.11−1.92 (m, 4 H), 1.64 (d, J = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 138.3, 137.1, 135.4, 128.6, 127.1, 126.5, 126.1, 122.3, 119.1, 118.9, 112.5, 109.6, 61.9, 46.5, 33.1, 21.1, 18.4; IR ($CDCl_3$) ν 3343, 2929, 1454, 1206, 1151, 737 cm^{-1}. Anal. Calcd for $C_{19}H_{19}NO$ [277.15]: C, 82.28; H, 6.90; N, 5.05. Found: C, 82.06; H, 6.73; N, 4.99.

(1*R*)-9-Benzyl-6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-1-ol (14d). 14d was prepared in 96% yield and 93% ee [SFC conditions: Chiralpak AD-H column, 4% MeOH in CO_2 for 4 min then ramp to 40% MeOH at 2% per min, 1.5 mL/min, t_R = 15.7 min (*S*), 16.9 min (*R*)] from **13d** according to the general reduction procedure. This material was recrystallized from EtOAc/hexanes to give **14d** in 86% recovery and 99% ee according to SFC analysis as a solid: mp 139−142 °C; $[\alpha]^{23}_D$ +66 (0.024, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.31−7.23 (comp, 3 H), 7.21 (dd, J = 2.6, 9.5 Hz, 1 H), 7.12 (dd, J = 4.3, 8.9 Hz, 1 H), 7.04−7.01 (comp, 2 H), 6.91 (ddd, J = 2.6, 9.1, 9.1 Hz, 1 H), 5.52 and 5.38 (ABq, J = 16.9 Hz, 2 H), 4.84 (brs, 1 H), 2.83 (ddd, J = 4.4, 4.4, 16.1 Hz, 1 H), 2.67−2.60 (m, 1 H), 2.10−1.92 (comp, 4 H), 1.65 (brs, 1 H); ^{13}C NMR ($CDCl_3$) δ 157.7 (d, J_{CF} =234.6 Hz), 138.0, 137.1, 133.7, 128.7, 127.3, 126.6 (d, J_{CF} = 9.5 Hz), 126.0, 112.4 (d, J_{CF} = 4.6 Hz), 110.5 (d, J_{CF} = 25.9 Hz), 110.2 (d, J_{CF} = 9.6 Hz), 103.8 (d, J_{CF} = 22.9 Hz), 61.9, 46.7, 33.1, 21.1, 18.4; IR ($CDCl_3$) ν 3310, 2932, 1792, 1653, 1558, 1482, 1456 cm^{-1}. Anal. Calcd for $C_{19}H_{18}FNO$ [295.14]: C, 77.27; H, 6.43; N, 4.74. Found: C, 76.98; H, 6.19; N, 4.61.

(1*R*)-9-Benzyl-6,8-difluoro-2,3,4,9-tetrahydro-1*H*-carbazol-1-ol (14e). 14e was prepared in 96% yield and 90% ee [SFC conditions: Chiralcel OD-H column, 4% MeOH in CO_2 for 4 min then ramp to 40% MeOH at 2% per min, 1.5 mL/min, t_R = 13.0 min (*S*), 13.7 min (*R*)] from **13e** according to the general reduction procedure. This material was recrystallized from EtOAc/hexanes to give **14e** in 74% recovery and 99% ee according to SFC analysis as a solid: mp 130−132 °C; $[\alpha]^{23}_D$ +73 (0.009, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.31−7.19 (comp, 3 H), 7.02−6.98 (comp, 3 H), 6.70 (ddd, J = 2.3, 9.6, 12.3 Hz, 1 H), 5.60 (d, 2 H), 4.80 (brs, 1 H), 2.78 (ddd, J = 3.0, 3.0, 6.6 Hz, 1 H), 2.63−2.56 (m, 1 H), 2.07−1.89 (comp, 4 H); ^{13}C NMR ($CDCl_3$) δ 156.5 (dd, J_{CF} = 10.3, 237.0 Hz), 149.2 (dd, J_{CF} = 13.8, 246.8 Hz), 139.0, 138.4, 129.5 (dd, J_{CF} = 6.7, 10.7 Hz), 128.7, 127.3, 125.8, 121.7 (d, J_{CF} = 8.8 Hz), 113.7 (dd, J_{CF} = 3.3, 4.9 Hz), 61.6, 48.5, 33.1, 21.2, 18.2; IR ($CDCl_3$) ν 4321, 2934, 1574, 1492, 1456, 1425, 1314, 1207, 1137 cm^{-1}. Anal. Calcd for $C_{19}H_{17}F_2NO$ [313.13]: C, 72.83; H, 5.47; N, 4.47. Found: C, 72.94; H, 5.32; N, 4.55.

(1*R*)-9-Benzyl-6-methoxy-2,3,4,9-tetrahydro-1*H*-carbazol-1-ol (14f). 14f was prepared in 98% yield and 95% ee [SFC conditions: Chiralpak AS−H column, 4% MeOH in CO_2 for 4 min then ramp to 40% MeOH at 2% per min, 1.5 mL/min, t_R = 17.0 min (*S*), 18.0 min (*R*)] from **13f** according to the general reduction procedure. This material was recrystallized from EtOAc/hexanes to give **14f** in 78% recovery and >99% ee according to SFC analysis as a solid: mp 203−206 °C; $[\alpha]^{23}_D$ +82.9 (0.014, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.30−7.21 (comp, 3 H), 7.12 (d, J = 8.9 Hz, 1 H), 7.04−7.02 (comp, 3 H), 6.85 (dd, J = 2.5, 8.9 Hz, 1 H), 5.49 and 5.36 (ABq, J = 16.9 Hz, 2 H), 4.83 (brs, 1 H), 3.78 (s, 3 H), 2.86 (ddd, J = 4.0, 4.0, 7.9 Hz, 1 H), 2.69−2.61 (m, 1 H), 2.10−1.90 (comp, 4 H), 1.69 (d, J = 6.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 154.9, 138.5, 136.2, 132.5, 128.7, 127.2, 126.8, 126.1, 112.4, 112.1, 110.5, 101.0, 62.0, 55.9, 46.7, 33.2, 21.3, 18.6; IR ($CDCl_3$) ν 3420, 1652, 1558, 1484, 1455 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO_2$ [307.16]: C, 78.15; H, 6.89; N, 4.56. Found: C, 77.98; H, 6.80; N, 4.48.

Mitsunobu Displacement Procedure (Conditions A). To a solution of the alcohol **14** (1 mmol), PMe_3 (1 M in THF, 2 mL, 2 mmol), and triethyl methanetricarboxylate (2 mmol) in THF (5 mL) at −78 °C was added DEAD (2 mmol) via syringe pump over 2.5 h. The resulting yellow solution was stirred at −78 °C for 12−18 h, quenched by addition of 3.3 N NaOH (4 mmol), and warmed to room temperature. The reaction was diluted with MTBE (5 mL) and stirred at room temperature for 4 h, and the biphasic mixture was separated. The organic layer was dried ($MgSO_4$), filtered, and concentrated, and the crude residue was purified via flash chromatography eluting with EtOAc/hexanes (1:9).

Mitsunobu Displacement Procedure (Conditions C). To a solution of the alcohol **14** (1 mmol), PMe_3 (1 M in toluene, 2 mL, 2 mmol), and triethyl methanetricarboxylate (2 mmol) in toluene (5 mL) at 0 °C was added bis(2,2,2-trichloroethyl) azodicarboxylate (TCEAD, 2 mmol) as a solution in toluene (1 mL), and the resulting yellow solution was stirred for 1 h. The reaction was quenched by addition of 3.3 N NaOH (4 mmol), warmed to room temperature, diluted with MTBE (5 mL), and stirred at room temperature for 4 h. The resulting biphasic mixture was separated, the organics were dried ($MgSO_4$), filtered, and concentrated, and the crude residue was purified via flash chromatography eluting with EtOAc/hexanes (1:9).

Triethyl [(3*R*)-5-Bromo-4-(4-chlorobenzyl)-7-fluoro-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl]methanetricarboxylate (16a). 16a was prepared from 14a in 95% yield in 94% ee [SFC analysis: Chiralcel OD-H, 20% MeOH in CO_2, 1.5 mL/min for 15 min, t_R = 3.4 min (*R*), 4.2 min (*S*)] according to the Mitsunobu displacement procedure (Conditions A): $[\alpha]^{23}_D$ +51.3 (c = 0.021, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.18−1.14 (comp, 2 H), 7.05 (ddd, J = 2.4, 2.4, 2.4, 1 H), 7.03 (ddd, J = 2.4, 2.4, 2.4 Hz, 1 H), 6.69 (d, J = 8.3 Hz, 2 H), 6.00 and 5.58 (ABq, J = 17.2 Hz, 1 H), 4.28 (d, J = 8.9 Hz, 1 H), 4.17−4.03 (comp, 6 H), 2.91 (dddd, J = 8.9, 8.9, 8.9, 13.8 Hz, 1 H), 2.78 (dddd, J = 1.4, 7.6, 8.9, 8.9 Hz, 1 H), 2.65 (ddd, J = 1.4, 8.9, 8.9, 10.5 Hz), 2.56 (dd, J = 7.6, 13.8 Hz, 1 H), 1.14 (t, J = 7.2 Hz, 9 H); ^{13}C NMR ($CDCl_3$) δ 166.0, 157.0 (d, J_{CF} = 239.7 Hz), 147.8, 138.4, 135.7, 132.4, 128.4, 127.4 (d, J_{CF} = 10.0 Hz), 126.9, 124.9 (d, J_{CF} = 4.4 Hz), 115.3 (d, J_{CF} = 28.5 Hz),104.0 (d, J_{CF} = 11.6 Hz), 103.6 (d, J_{CF} = 22.5 Hz), 69.5, 62.2, 48.4, 42.9, 35.0, 22.7, 13.6; IR ($CDCl_3$) ν 2980, 2361, 1741, 1200, 1128, 1062 cm^{-1}. MS (ESI) calcd for $C_{28}H_{28}NO_6ClFBr$: M + H (theory), 608.0851; M + H (found), 608.0847.

Triethyl [(3*R*)-4-Benzyl-1,2,3,4-tetrahydrocyclopenta-[*b*]indol-3-yl]methanetricarboxylate (16b). 16b was prepared from **14b** in 61% yield and 65% ee [SFC conditions: Chiralpak AS−H column, 4% MeOH in CO_2 for 4 min then ramp to 40% MeOH at 2% per min, 1.5 mL/min, t_R = 17.0 min (*S*), 18.0 min (*R*)] according to the Mitsunobu displacement procedure (Conditions C): ^1H NMR ($CDCl_3$) δ 7.45−7.42 (m, 1 H), 7.27−7.18 (comp, 3 H), 7.08−7.01 (comp, 5 H), 5.45 and 5.37 (ABq, J = 16.9 Hz, 2 H), 4.41 (ddd, J = 1.8, 1.8, 8.9 Hz, 1 H), 4.09−3.97 (comp, 6 H), 3.02−2.93 (m, 1 H), 2.85 (dddd, J = 1.9, 7.6, 7.6, 14.5 Hz, 1 H), 2.72 (ddd, J = 1.7, 9.3, 14.2 Hz, 1 H), 2.62 (dddd, J = 1.9, 1.9, 7.6, 13.6 Hz, 1 H); 1.09 (t, J = 7.2 Hz, 9 H); ^{13}C NMR ($CDCl_3$) δ 166.3, 142.8, 142.6, 138.7, 128.3, 126.6, 126.1, 124.0, 123.3, 121.3, 119.2, 118.8, 111.0, 69.8, 62.0, 48.2, 42.9, 35.2, 22.8, 13.6; IR ($CDCl_3$) ν 2981, 1744, 1456, 1223, 1065, 740 cm^{-1}. Anal. Calcd for $C_{28}H_{31}NO_6$ [477.22]: C, 70.42; H, 6.54; N, 2.93. Found: C, 70.64; H, 6.62; N, 2.86.

Triethyl [(1*R*)-9-Benzyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl]methanetricarboxylate (16c). 16c was prepared from **14c** in 80% yield and 75% ee [SFC analysis: Chiralcel OD-H column, 4% MeOH in CO_2 for 4 min then ramp to 40% MeOH at 2% per min, 1.5 mL/min, t_R = 9.2 min (*S*), 10.3 min (*R*)] according to the Mitsunobu displacement procedure (Conditions C): ^1H NMR ($CDCl_3$) δ 7.47 (d, J = 7.4 Hz, 1 H), 7.23−7.14 (comp, 4 H), 7.09 (ddd, J = 1.3, 6.9, 6.9 Hz, 1 H), 7.04 (ddd, J = 1.3, 7.8, 7.8 Hz, 1 H), 6.87 (d, J = 6.9 Hz, 2 H), 5.79 and 5.28 (ABq, J = 17.2 Hz, 1 H), 4.29 (brs, 1 H), 4.07−3.92 (comp, 6 H), 2.85 (ddd, J = 1.4, 9.0, 16.4 Hz, 1 H), 2.76 (ddd, J = 7.7, 10.0, 17.3 Hz, 1 H), 2.43−2.32 (m, 1 H), 2.14

(app dq, J = 3.4, 14.2 Hz, 1 H), 1.89−1.80 (comp, 2 H), 1.09 (t, J = 7.2 Hz, 9 H); ^{13}C NMR ($CDCl_3$) δ 166.0, 139.2, 137.5, 134.1, 128.3, 127.2, 126.6, 125.8. 121.8, 118.7, 118.2, 113.1, 109.7, 69.3, 61.8, 46.3, 34.9, 28.5, 20.0, 17.1, 13.5; IR ($CDCl_3$) ν 2981, 1745, 1652, 1558, 1456, 1243, 1070 cm^{-1}. MS (ESI) calcd for $C_{29}H_{33}NO_6$: M + H (theory), 492.2386; M + H (found), 492.2385.

Triethyl [(1*R*)-9-Benzyl-6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl]methanetricarboxylate (16d). 16d was prepared from **14d** in 84% yield and 80% ee [SFC analysis: Chiralpak IA-H column, 4% MeOH in CO_2 for 4 min then ramp to 40% MeOH at 2% per min, 1.5 mL/min, t_R = 7.7 min (*S*), 8.0 min (*R*)] according to the Mitsunobu displacement procedure (Conditions C): ^{1}H NMR ($CDCl_3$) δ 7.27−7.16 (comp, 3 H), 7.11 (d, J = 2.5, 9.3 Hz, 1 H), 7.04 (dd, J = 4.2, 8.9 Hz, 1 H), 6.86 (d, J = 6.7 Hz, 2 H), 6.81 (dd, J = 2.5, 9.3 Hz, 1 H), 5.83 and 5.24 (ABq, J = 17.2 Hz, 2 H), 4.30 (m, 1 H), 4.08−3.94 (comp, 6 H), 2.80 (app dd, J = 7.4, 15.7 Hz, 1 H), 2.72 (ddd, J = 7.6, 9.7, 17.4 Hz, 1 H), 2.44−2.32 (m, 1 H), 2.16 (app dq, J = 3.1, 14.1 Hz, 1 H), 1.88 (ddd, J = 3.7, 3.9, 8.1 Hz, 1 H), 1.83 (ddd, J = 3.7, 3.7, 7.7 Hz, 1 H), 1.10 (t, J = 7.2 Hz, 9 H); ^{13}C NMR ($CDCl_3$) δ 166.0, 157.5 (d, J_{CF} = 234.0 Hz), 138.9, 136.0, 134.0, 128.4, 127.5 (d, J_{CF} = 9.5 Hz), 126.7, 125.8, 113.1 (d, J_{CF} = 4.6 Hz), 110.4 (d, J_{CF} = 9.6 Hz), 109.9 (d, J_{CF} = 26.1 Hz), 103.1 (d, J_{CF} = 22.8 Hz), 69.2, 61.9, 46.6, 34.9, 28.3, 19.9, 17.1, 13.6; IR ($CDCl_3$) ν 2982, 1785, 1746, 1652, 1458, 1244, 1071 cm^{-1}. MS (ESI) calcd for $C_{29}H_{32}FNO_6$: M + H (theory), 509.2292; M + H (found), 510.2287.

Triethyl [(1*R*)-9-Benzyl-6,8-difluoro-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl]methanetricarboxylate (16e). 16e was prepared from **14e** in 91% yield and 95% ee [SFC analysis: Chiralpak IA-H column, 4% MeOH in CO_2 for 4 min then ramp to 40% MeOH at 2% per min, 1.5 mL/min, t_R = 5.8 min (*S*), 6.2 min (*R*)] according to the Mitsunobu displacement procedure (Conditions C): ^{1}H NMR ($CDCl_3$) δ 7.23−7.14 (comp, 3 H), 6.89 (dd, J = 2.3, 8.7 Hz, 1 H), 6.79 (d, J = 7.0 Hz, 2 H), 6.60 (ddd, J = 2.2, 9.4, 12.1 Hz, 1 H), 5.87 and 5.45 (ABq, J = 17.1 Hz, 2 H), 4.29 (m, 1 H), 4.11−3.97 (comp, 6 H), 2.75 (ddd, J = 1.3, 7.7, 16.6 Hz, 1 H), 2.67 (ddd, J = 7.6, 10.3, 17.5 Hz, 1 H), 2.35−2.24 (m, 1 H), 2.21−2.17 (m, 1 H), 1.87−1.78 (comp, 2 H), 1.13 (t, J = 7.0 Hz, 9 H); ^{13}C NMR ($CDCl_3$) δ 165.9, 156.5 (dd, J_{CF} =10.3, 236.8 Hz), 149.0 (dd, J_{CF} = 13.8, 247.4 Hz), 130.3 (dd, J_{CF} = 6.8, 10.6 Hz), 128.4, 126.7, 125.4, 121.9 (d, J_{CF} = 8.1 Hz), 114.9 (d, J_{CF} = 3.6 Hz), 99.0 (dd, J_{CF} = 3.9, 22.6 Hz), 97.8 (dd, J_{CF} = 23.1, 29.9 Hz), 69.0, 61.9, 48.2, 34.6, 28.1, 20.0, 16.9, 13.5; IR ($CDCl_3$) ν 2982, 1786, 1746, 1636, 1585, 1494, 1246, 1072 cm^{-1}. MS (ESI) calcd for $C_{29}H_{31}F_2NO_6$: M + H (theory), 528.2198; M + H (found), 528.2196.

Triethyl [(1*R*)-9-Benzyl-6-methoxy-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl]methanetricarboxylate (16f). 16f was prepared from **14f** in 80% yield and 67% ee [SFC analysis: Chiralpak IA-H column, 4% MeOH in CO_2 for 4 min then ramp to 40% MeOH at 2% per min, 1.5 mL/min, t_R = 10.6 min (*S*), 11.0 min (*R*)] according to the Mitsunobu displacement procedure (Conditions C): ^{1}H NMR ($CDCl_3$) δ 7.23−7.14 (comp, 3 H), 7.03 (d, J = 8.9 Hz, 1 H), 6.92 (d, J = 2.4 Hz, 1 H), 6.86 (d, J = 7.1 Hz, 2 H), 6.75 (dd, J = 2.4, 8.8 Hz, 1 H), 5.77 and 5.23 (ABq, J = 17.2 Hz, 2 H), 4.28 (m, 1 H), 4.07−3.93 (comp, 6 H), 3.84 (s, 3 H), 2.81 (app dd, J = 7.5, 16.1 Hz, 1 H), 2.72 (ddd, J = 7.6, 9.9, 17.4 Hz, 1 H), 2.43−2.32 (m, 1 H), 2.14 (app dq, J = 3.1, 14.1 Hz, 1 H), 1.85 (comp, 2 H), 1.10 (t, J = 7.2 Hz, 9 H); ^{13}C NMR ($CDCl_3$) δ 166.2, 153.7, 139.5, 135.0, 133.0, 128.5, 127.6, 126.7, 126.0, 112.9, 111.8, 110.7, 100.4, 69.5, 61.9, 55.8, 46.6, 35.2, 28.6, 20.2, 17.3, 13.7; IR ($CDCl_3$) ν 2982, 1785, 1746, 1500, 1485, 1456, 1243, 1154, 1070 cm^{-1}. MS (ESI) calcd for $C_{30}H_{35}NO_7$: M + Na (theory), 544.2306; M + Na (found), 544.2303.

General Saponification Procedure. The triester **16** (1 mmol) was taken up in MeOH (3 mL) and treated with 3.3 N NaOH (5−10 mmol), and the reaction was heated to reflux for 24 h. When all of the starting material had converted to the trisacid intermediate according to HPLC analysis, the reaction was cooled to room temperature and solvent was concentrated in vacuo.

Acidic Decarboxylation Procedure (Conditions A). The crude product from the saponification reaction (1 mmol) was dissolved in AcOH (2 mL) and heated to reflux for 24 h. Solvent was removed in vacuo, and the residual product was purified by silica gel chromatography eluting with EtOAc:hexanes (1:3) to give the acid **17**.

Nonacidic Decarboxylation Procedure (Conditions B). The crude saponification product (1 mmol) was taken up in H_2O (4 mL), neutralized by addition of 3 N HCl (5−10 mmol), and extracted with EtOAc (2 × 2 mL). The combined organics were dried ($MgSO_4$), solvent was removed in vacuo, and the crude residue was diluted in toluene (2 mL). This solution was heated to reflux for 2−4 h and cooled to room temperature, and solvent was removed via rotary evaporation. The crude acid product **17** was purified via column chromatography eluting with EtOAc:hexanes (1:3).

[(3*R*)-5-Bromo-4-(4-chlorobenzyl)-7-fluoro-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl]acetic Acid (17a). 17a was isolated from the triester **16a** using the general saponification and acidic decarboxylation (Conditions A) procedures in 86% yield and 94% ee [SFC analysis: Chiralcel OD-H column, 20% MeOH in CO_2, 1.5 mL/min for 15 min, t_R = 7.3 min (*S*), 10.4 min (*R*)] as a yellow solid: mp 188−191 °C; $[\alpha]^{23}_D$ +51.3 (c = 0.0207, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.27−2.32 (comp, 2 H), 7.10−7.06 (comp, 2 H), 6.81 (d, J = 8.2 Hz, 2 H), 5.72 and 5.64 (ABq, J = 17.5 Hz, 2 H), 3.54 (brs, 1 H), 2.95−2.75 (comp, 3 H), 2.56 (dd, J = 3.7, 16.0 Hz, 1 H), 2.39 (dd, J = 10.2, 16.0 Hz, 1 H), 2.29−2.25 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 177.4, 158.1, 156.9 (d, J_{CF} = 241.5), 150.2, 137.5, 134.1, 133.0, 128.9, 127.0 (d, J_{CF} = 10.1 Hz), 126.7, 119.9 (d, J_{CF} = 4.4 Hz), 114.6 (d, J_{CF} = 30.2 Hz), 103.6 (20.1 Hz), 103.2 (d, J_{CF} = 10 Hz), 48.5, 38.7, 35.6, 35.0, 22.8; IR ($CDCl_3$) 2936, 2361, 1700, 1472, 1406, 1199, 1131 cm^{-1}. Anal. Calcd for $C_{20}H_{16}BrClFNO_2$ [435.00]: C, 55.01; H, 3.69; N, 3.21. Found: C, 55.20; H, 3.66; N, 3.24.

[(3*R*)-4-Benzyl-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl]acetic Acid (17b). 17b was isolated from the triester **16b** using the general saponification and neutral decarboxylation (Conditions B) procedures in 65% yield and 59% ee [SFC analysis: Chiralcel OD-H column, 4% MeOH in CO_2 for 4 min then ramp to 40% MeOH at 2% per min, t_R = 15.7 min (*S*), 16.5 min (*R*)] as an oil: $[\alpha]^{23}_D$ +7.1 (0.016, CH_2Cl_2); ^{1}H NMR (MeOD-d^3) δ 7.43−7.38 (m, 1 H), 7.24−7.12 (comp, 4 H), 7.03−6.97 (comp, 4 H), 5.33 and 5.24 (ABq, 16.8 Hz, 2 H), 3.51 (m, 1 H), 2.91−1.82 (m, 1 H), 2.80−7.07 (comp, 2 H), 2.57 (dd, J = 4.0, 15.5 Hz, 1 H), 2.28 (dd, J = 10.0, 15.5 Hz, 1 H), 2.27−1.18 (m, 1 H); ^{13}C NMR (MeOD-d^3) δ 174,5, 146.4, 141.7, 138.3, 128.2, 126.8, 126.7, 125.8, 124.2, 120.2, 118.7, 118.3, 118.2, 109.6, 47.1, 38.7, 35.6, 35.0, 22.3; IR (MeOH) ν 3024, 2934, 2855, 1704, 1452, 1345, 1206, 1153, 737 cm^{-1}. MS (ESI) calcd for $C_{20}H_{19}NO_2$: M + H (theory), 306.1489; M + H (found), 306.1483.

[(1*R*)-9-Benzyl-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl]acetic Acid (17c). 17c was isolated from the triester **16c** using the general saponification and acidic decarboxylation (Conditions A) procedures in 90% yield and 75% ee [SFC analysis: Chiralcel OD-H column, 4% MeOH in CO_2 for 4 min then ramp to 40% MeOH at 2% per min, 1.5 mL/min for 15 min, t_R = 12.5 min (*R*), 13.4 min (*S*)] as an oil: $[\alpha]^{23}_D$ −19.7 (c = 0.015, MeOH); ^{1}H NMR (MeOD-d^3) δ 7.44−7.40 (m, 1 H), 7.23−7.13 (comp, 4 H), 7.04 (app dt, J = 1.3, 7.0 Hz, 1 H), 6.99 (app dt, J = 1.1, 7.1 Hz, 1 H), 6.91−6.89 (comp, 2 H), 5.36 and 5.27 (ABq, J = 17.2 Hz, 2 H), 3.37 (m, 1 H), 2.84−2.80 (m, 1 H), 2.67−2.59 (m, 1 H), 2.51−2.40 (m, 1 H), 1.95−1.82 (comp, 4 H); ^{13}C NMR (MeOD-d^3) δ 174.3, 138.4, 137.2, 136.6, 128.1, 127.2, 126.7, 125.5, 120.8, 118.5, 117.4, 109.9, 109.0, 45.5, 28.3, 27.5, 20.4, 17.8; IR (MeOH) ν 3029, 2931, 1705, 1465, 1301, 739 cm^{-1}. MS (ESI) calcd for $C_{21}H_{21}NO_2$: M + H (theory), 320.1645; M + H (found), 320.1643.

[(1*R*)-9-Benzyl-6-fluoro-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl]acetic Acid (17d). 17d was isolated from the triester **16d** using the general saponification and acidic decarboxylation (Conditions A) procedures in 79% yield and 80% ee [SFC analysis: Chiralcel OD-H column, 4% MeOH in CO_2 for 4 min then ramp to 40% MeOH at 2% per min, 1.5 mL/min for 15 min, t_R = 14.4 min (*S*), 14.8 min (*R*)] as an oil: $[\alpha]^{23}_D$ −25.6 (*c* = 0.008, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.32−7.22 (comp, 3 H), 7.16 (dd, *J* = 2.5, 9.4 Hz, 1 H), 7.03 (dd, *J* = 4.3, 8.9 Hz, 1 H), 6.99−6.94 (comp, 2 H), 6.85 (app dt, *J* = 2.5, 11.6 Hz, 1 H), 5.33 and 5.27 (ABq, *J* = 17.2 Hz, 2 H), 3.45−3.42 (m, 1 H), 2.82 (dd, *J* = 4.6, 15.3 Hz, 1 H), 2.96−2.60 (m, 1 H), 2.56 (dd, *J* = 10.2, 16.0 Hz, 1 H), 2.50 (dd, *J* = 3.5, 16.0 Hz, 1 H), 1.99−1.80 (comp, 4 H); ^{13}C NMR ($CDCl_3$) δ 177.5, 158.8 (d, J_{CF} = 234.5 Hz), 138.2, 137.5, 133.5, 128.8, 127.5, 127.4, 125.8, 110.7 (d, J_{CF} = 4.3 Hz), 110.0 (d, J_{CF} = 9.6 Hz), 109.4 (d, J_{CF} = 25.9 Hz), 103.2 (d, J_{CF} = 23.2 Hz), 46.4, 38.3, 28.3, 27.7, 20.8, 18.0; IR ($CDCl_3$) ν 2932, 1706, 1624, 1480, 1452, 1293, 1141, 792 cm^{-1}. MS (ESI) calcd for $C_{21}H_{20}FNO_2$: M + H (theory), 338.1551; M + H (found), 338.1544.

[(1*R*)-9-Benzyl-6,8-difluoro-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl]acetic Acid (17e). 17e was isolated from the triester **16e** using the general saponification and acidic decarboxylation (Conditions A) procedures in 92% yield and 95% ee [SFC analysis: Chiralcel OD-H column, 4% MeOH in CO_2 for 4 min then ramp to 40% MeOH at 2% per min, 1.5 mL/min for 15 min, t_R = 13.3 min (*S*), 13.7 min (*R*)] as an oil: $[\alpha]^{23}_D$ −45.7 (0.024, CH_2Cl_2); ^{1}H NMR (MeOD-d^3) δ 7.31−7.21 (comp, 3 H), 6.98−6.91 (comp, 3 H), 5.49 and 5.40 (ABq, *J* = 17.0 Hz, 2 H), 3.45−3.25 (m, 1 H), 2.78 (dd, *J* = 4.4, 15.0 Hz, 1 H), 2.67−2.50 (comp, 3 H), 2.00−1.79 (comp, 4 H); ^{13}C NMR ($CDCl_3$) δ 177.9, 156.6 (dd, J_{CF} = 10.1, 237.0 Hz), 148.9 (dd, J_{CF} = 14.1, 246.7 Hz), 139.5, 138.5, 130.2 (dd, J_{CF} = 6.7, 10.9 Hz), 128.7, 127.3, 125.5, 121.3 (d, J_{CF} = 8.8 Hz), 112.0 (dd, J_{CF} = 1.6, 5.6 Hz), 99.1 (dd, J_{CF} = 3.9, 22.9 Hz), 97.4 (dd, J_{CF} = 22.7, 29.8 Hz), 48.1, 38.3, 28.1, 27.6, 20.8, 17.7; IR ($CDCl_3$) ν 3031, 2936, 1707, 1641, 1587, 1491, 1454, 1316, 1135, 909, 732 cm^{-1}. MS (ESI) calcd for $C_{21}H_{19}F_2NO_2$: M + H (theory), 356.1457; M + H (found), 356.1451.

[(1*R*)-9-Benzyl-6-methoxy-2,3,4,9-tetrahydro-1*H*-carbazol-1-yl]acetic Acid (17f). 17f was isolated from the triester **16f** using the general saponification and neutral decarboxylation (Conditions B) procedures in 74% yield and 67% ee [SFC analysis: Chiralcel OD-H column, 4% MeOH in CO_2 for 4 min then ramp to 40% MeOH at 2% per min, t_R = 15.9 min (*S*), 16.4 min (*R*)] as an oil: $[\alpha]^{23}_D$ −20 (0.004, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.29−7.21 (comp, 3 H), 7.03 (d, *J* = 8.8 Hz, 1 H), 6.99 (d, *J* = 2.5 Hz, 1 H), 6.99−6.97 (comp, 2 H), 6.79 (dd, *J* = 2.5, 8.5 Hz, 1 H), 7.32 and 5.26 (ABq, *J* = 17.1 Hz, 2 H), 3.87 (s, 3 H), 3.44−3.42 (m, 1 H), 2.84 (dd, *J* = 4.5, 15.3 Hz, 1 H), 2.71−2.64 (m, 1 H), 2.56 (dd, *J* = 9.9, 16.0 Hz, 1 H), 2.49 (dd, *J* = 3.9, 16.0 Hz, 1 H), 1.99−1.80 (comp, 4 H); ^{13}C NMR ($CDCl_3$) δ 177.8, 153.9, 137.9, 137.1, 132.2, 128.7, 127.4, 127.2, 125.8, 111.2, 110.3, 100.5, 55.9, 46.3, 38.5, 28.3, 27.8, 20.9, 18.1, 14.1; IR ($CDCl_3$) ν 2933, 1701, 1653, 1559, 1482, 1456, 1159, 732 cm^{-1}. MS (ESI) calcd for $C_{22}H_{23}NO_3$: M + H (theory), 350.1751; M + H (found), 350.1750.

Acknowledgment. We thank Mirlinda Biba for the development of chiral assays and Dr. Kevin Campos for useful discussions.

Supporting Information Available: Copies of the ^{1}H NMR spectra for of all compounds described in the Experimental Section including **11**, **12**, and **15** and X-ray crystallographic data for **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051146P