A Catalytic Asymmetric Synthesis of a Spirofused Azetidinone as a Cholesterol Absorption Inhibitor

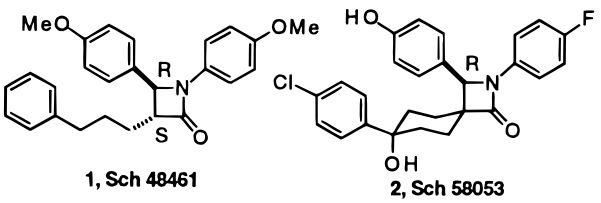
Guangzhong Wu* and Wanda Tormos

Chemical Process Research and Development, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, New Jersey 07033

Received March 10, 1997

Introduction

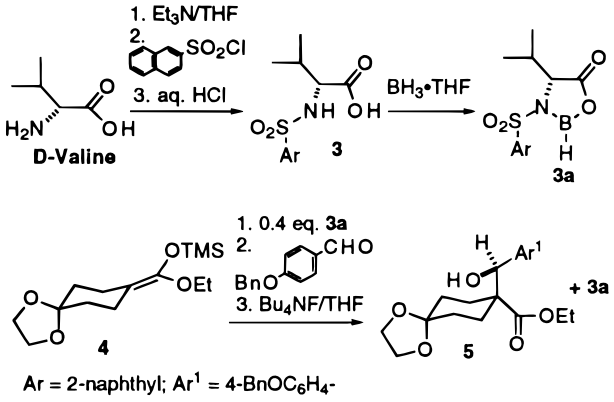
The recent discovery of potent cholesterol absorption inhibition by a class of azetidinone compounds exemplified by **1** and **2** has stimulated significant synthetic interest in developing asymmetric processes.[1−3] To date, all approaches to these type of azetidinones have employed chiral auxiliary-based chemistry.[1−4] While recycling of these auxiliaries is possible, the tedious processing and yield losses make it inefficient. Clearly, a catalytic process would be much more cost-effective. A multikilogram requirement of **2** prompted this effort, and we wish to report both a catalytic asymmetric synthesis of **2** and a novel selective hydrogenative debenzylation.



Results and Discussion

The synthetic strategy was to construct the desired chiral center *via* an aldol condensation followed by amination and cyclization.[3d] Catalysts employed for the Mukaiyama-type aldol condensation can be divided into two major categories: amino acid derivatives[4] and artificially designed chiral ligands such as the binaphthol−titanium complexes.[5] We have chosen the former type of catalyst because such ligands are readily available.

Scheme 1



After initial screening, **3a**[6] was found to give the best result and was selected for the studies. A one-step procedure was developed to afford **3** in 87% yield. Catalyst **3a** is formed *in situ* by reaction with BH_3•THF (Scheme 1).

Our initial attempts at the chiral aldol reaction afforded a poor selectivity of 55:45 (*S*:*R*). After distillation of both the solvent and the silyl enol ether **4**, the *S*:*R* ratio improved to 78:22 when 0.4 equiv of **3a** was used. During process development, we identified two more critical factors that control the enantioselectivity: (1) the best ratio of BH_3•THF to **3** is 0.9 and (2) slow addition of the aldehyde is necessary. Under the optimized conditions, the *S*:*R* ratio improved from 78:22 to 95.5:4.5.

Although this reaction required 0.4 equiv of catalyst, 87% of it was readily recovered. Thus, concentration of the organic layer resulted in **5** as a crystalline solid, enhancing the ee from 90% to 94%. Acidification of the aqueous layer, followed by extraction with *t*-BuOMe, led to the recovery of **3** in 87% yield. There was no loss of enantioselectivity after nine consecutive recycles on a kilogram scale. After recovery, the net consumption of **3** in each run was only 5 mol %.

The addition of 4-ClC_6H_4MgBr took place from both faces of the carbonyl group in ketone **6**, producing a diastereomeric mixture of **7** and **7a** with a disappointing ratio of 83:17. Moreover, there were a lot of impurities in the reaction mixture. We suspected that the complex reaction was the result of enolization which could be minimized by reverse addition. Indeed, the reaction proceeded to >98% completion when the ketone **6** was added dropwise to 1.5 equiv of the Grignard reagent. Further studies indicated that the higher the reaction temperature the better the diastereoselectivity. The best result was obtained when the reaction was carried out in toluene at 80 °C as shown in Table 1.

Pd/C-catalyzed debenzylation of compound **7** generated an unacceptable 4.7% (HPLC area normalization) of the deschloro impurity. Initially, we circumvented this problem by exchanging the benzyl group for TBDMS prior to the Grignard addition and learned that 0.6% of the deschloro impurity arose from the Grignard reagent. We thought that the dechlorination could have been taking place *via* a palladium oxidative insertion into the C−Cl bond followed by a hydrogenative reduction and speculated that addition of a Lewis acid might slow down the insertion. To our delight, the dechlorination pathway

(1) (a) Clader, J. W.; Burnett, D. A.; Caplen, M. A.; Domalski, M. S. Dugar, S.; Vaccaro, W.; Sher, R.; Browne, M. E.; Zhao, H.; Burrier, R. E.; Salisbury, B.; Davis, H. R. Jr. *J. Med. Chem*. **1996**, *39*, 3684. (b) McKittrick, B. A.; Dugar, S.; Clader, J. W.; Davis, H., Jr.; Czarniecki, M. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1947. (c) Dugar, S.; Clader, J. W.; Chan, T. M.; Davis, H., Jr. *J. Med. Chem*. **1995**, *38*, 4875.

(2) (a) Burnett, D. A.; Caplen, M. A.; Davis, H. R.; Burrier, R. E.; Clader, J. W. *J. Med. Chem*. **1994**, *37*, 1733. (b) Burnett, D. A. *Tetrahedron Lett*. **1994**, *35*. 7339. (c) Browne, M.; Burnett, D. A. Caplen, M. A.; Chen, L-y.; Clader, J. W.; Domalski, M.; Dugar, S.; Pushpavanam, P.; Sher, R.; Vaccaro, W.; Viziano, M.; Zhao, H. *Tetrahedron Lett*. **1995**, *36*, 2555.

(3) (a) Thiruvengadam, T. K.; Tann, C. H.; Lee, J.; McAllister, T.; Sudhakar, A. US Patent 5306817, 1994; *Chem. Abstr*. **1994**, *112*, 157423e. (b) Chen, L.; Zaks, A.; Chacklamanil, S.; Dugar, S. *J. Org. Chem. Soc*. **1996**, *61*, 8341. (c) For a review see: Georg, G. I. *The Organic Chemistry of β-Lactams*; VCH: New York, 1993. (d) Shirai, F.; Nakai, T. *Tetrahedron Lett*. **1988**, *29*, 6461.

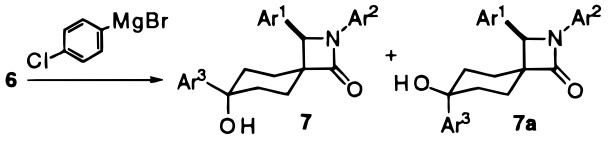
(4) (a) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett*. **1992**, *33*, 6907. (b) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc*. **1991**, *113*, 8966. (c) Parmee, E. R.; Tempkin, O.; Masamune, S. *J. Am. Chem. Soc*. **1991**, *113*, 9365. (d) Kiyooka, S.-i.; Kaneko, Y.; Kume, K.-I. *Tetrahedron Lett*. **1992**, *33*, 4927. (e) Kobayashi, S.; Horibe, M. *J. Am. Chem. Soc*. **1994**, *116*, 9805.

(5) (a) Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem*. **1995**, *60*, 2648. (b) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc*. **1994**, *116*, 8837. (c) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc*. **1989**, *111*, 1940.

(6) Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem*. **1991**, *56*, 2276.

S0022-3263(97)00436-2 CCC: $14.00

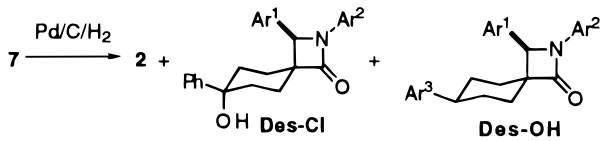
Table 1



Ar^1 = 4-$BnOC_6H_4$-; Ar^2 = 4-FC_6H_4-; Ar^3 = 4-ClC_6H_4-

entry	solvent	temp (°C)	7:7a
1	Et_2O/THF	−20	83:17
2	*t*-BuOMe/toluene	50	93:7
3	*t*-BuOMe/toluene	80	94:6

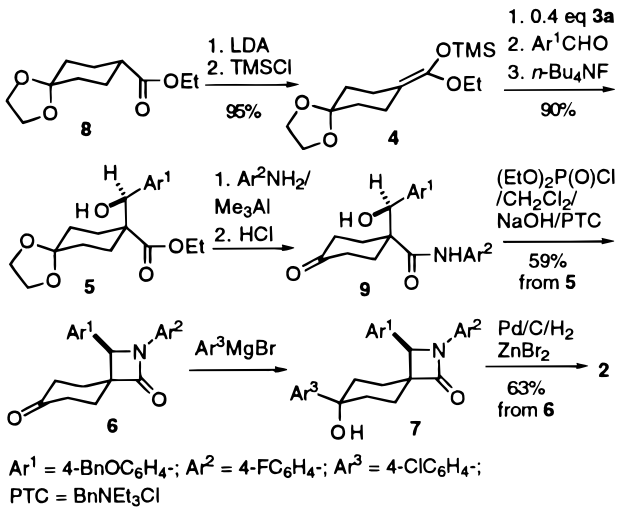
Table 2



Ar^1 = 4-HOC_6H_4-; Ar^2 = 4-FC_6H_4-; Ar^3 = 4-ClC_6H_4-

entry	$ZnBr_2$	HOAc	Des-Cl, %	Des-OH, %
1	0	0	4.7	2.6
2	0	2 drops	7.1	3.3
3	0.6 equiv	0	0.6	2.0

Scheme 2



Ar^1 = 4-$BnOC_6H_4$-; Ar^2 = 4-FC_6H_4-; Ar^3 = 4-ClC_6H_4-;
PTC = $BnNEt_3Cl$

is completely blocked when $ZnBr_2$ is used. For comparison, organic acids such as HOAc do not prevent the dechlorination as shown in entry 2 of Table 2. In addition, $ZnBr_2$ does not increase the des-OH impurity. To the best of our knowledge, this is a novel selective debenzylation.[7]

With the development delineated above, we were able to complete the catalytic enantio- and diastereoselective synthesis of **2** as shown in Scheme 2. Thus, enolization of ester **8** with LDA, followed by trapping with TMSCl, gave silyl enol ether **4** in 94% yield. A catalytic chiral aldol reaction followed by *n*-Bu_4NF deprotection afforded the hydroxy ester **5** in 95% ee. Amination of **5** was achieved in high yield with 4-$FC_6H_4NH_2$ by using Me_3Al.[8] Conversion of the hydroxy function into a leaving group with $(EtO)_2P(O)Cl$,[3] followed by NaOH-promoted cyclization in the presence of a catalytic amount of $BnNEt_3Cl$, generated the β-lactam ring in 59% overall yield. Addition of 4-ClC_6H_4MgBr to ketone **6** in toluene followed by the novel selective debenzylation produced **2** in 99.5% chemical purity and 99.5% ee. This process was scaled up smoothly and produced 1.5 kg of **2**.

In summary, we have invented a catalytic enantio- and diastereoselective synthesis of **2** which has proven robust enough for large scale use. We have also discovered a novel selective debenzylation mediated by $ZnBr_2$.

Experimental Section

All reactions were carried out under nitrogen. ^1H and ^{13}C NMR spectra (300 or 400 MHz) were recorded in $CDCl_3$ and referred to TMS unless otherwise noted. All starting materials were purchased commercially, and 4-$BnOC_6H_4CHO$ was recrystallized from toluene.

8-Carbethoxy-1,3-dioxaspiro[1.4]decane (8). A mixture of 307.5 g (1.968 mol) of ethyl 4-oxocyclohexanecarboxylate, 131.7 mL (2.362 mol) of ethylene glycol, and 3.74 g (19.68 mmol) of 4-$MeC_6H_4SO_3H$ in a 2-L flask was heated at reflux. Water produced was removed *via* azeotropic distillation. When the reaction slowed, 75 mL of toluene was added and the distillation was continued for about 4 h. The cooled reaction mixture was added slowly to 450 mL of ice cold saturated $NaHCO_3$ solution and extracted three times with 300 mL of EtOAc. The combined extract was washed with brine, dried with $MgSO_4$, and concentrated. The residue was distilled at 115−125 °C/0.3 mmHg to give 319.0 g (81%) of **8**. HRMS 215.1283 ($M^+ + H$), calcd for $C_{11}H_{19}O_4$ 215.1292. ^1H NMR δ 4.13 (q, J = 7.0 Hz, 2H), 3.96 (s, 4H), 2.4−2.3 (m, 1H), 2.0−1.9 (m, 2H), 1.9−1.75 (m, 4H), 1.65−1.5 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H); IR (neat) 2940 (s), 2840 (s),1730 (s) cm^{-1}.

8-[Ethoxy(trimethylsiloxy)methylidene]-1,3-dioxaspiro[1.5]decane (4). To 23.3 mL (166 mmol) of *i*-Pr_2NH and 130 mL of THF in a dry 1-L three-necked flask equipped with a mechanical stirrer was added dropwise at −20 °C 104 mL (166 mmol) of 1.6 M *n*-BuLi/hexane. After 30 min at −20 °C, a solution of 29.6 g (138 mmol) **8** in 30 mL of THF was added, and the resulting mixture was stirred at −20 °C for 1 h. To the above enolate at −20 °C was added dropwise 26.3 mL (207 mmol) of TMSCl. The resulting mixture was stirred at −20 °C for 30 min and allowed to warm to rt for 1 h. After removal of THF, the residue was transferred into a smaller flask *via* a Schlenk filter and distilled at 87−92 °C/0.3 mmHg to give 38.9 g (94%) of **4**. HRMS 285.1512 ($M^+ - 1$), calcd for $C_{14}H_{27}O_4$ 285.1522. ^1H NMR δ 3.89 (s, 4H), 3.71 (q, J = 7.0 Hz, 2H),2.25−2.20 (m, 2H), 2.19−2.10 (m, 2H), 1.48−1.40 (m, 4H), 1.15 (t, J = 7.0 Hz, 3H), 0.13 (s, 9H).

(1*S*)-8-[4-(Benzyloxy)phenyl]-1-(hydroxymethyl)-1-carbethoxy-1,3-dioxaspiro[1.5]decane (5). To 1.23 g (4.0 mmol) of **3** in 5 mL of at 5 °C was added dropwise 4.0 mL (4.0 mmol) of 1.0 M BH_3·THF. The resulting mixture was stirred at 5 °C for 10 min and cooled to −78 °C. To the reaction mixture were added sequentially 3.15 g (11.0 mmol) of silyl enol ether **4** and a solution of 2.12 g (10.0 mmol) 4-$BnOC_6H_4CHO$ in 4 mL EtCN over 2 h using a syringe pump. After stirring at −78 °C for 1 h, the reaction was poured into 50 mL of ice cold saturated $NaHCO_3$ and extracted three times with 50 mL of EtOAc. The combined extract was washed four times with $NaHCO_3$ and concentrated to a small volume. To the residue was added 7 mL (7.0 mmol) of 1.0 M *n*-Bu_4NF in THF. After stirring at rt for 1 h, the mixture was extracted with toluene. The combined extract was washed, dried over $MgSO_4$, and concentrated. The precipitate was filtered and dried at 55 °C to give 3.85 g (90%) of **5** with a 91% ee. $[\alpha]^{22.6}_D = +10.7°$ (*c* 0.52, EtOH). Mp 83−85 °C. HRMS 449.1940 ($M^+ + Na$), calcd for $C_{25}H_{30}O_6Na$ 449.1942. ^1H NMR δ 7.40−7.25 (m, 5H), 7.07 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H),4.99 (s, 2H), 4.61 (s, 1H), 4.15−4.0 (m, 2H), 3.85 (s, 4H), 2.91 (bs, 1H), 2.3−2.2 (m, 1H), 2.0−1.9 (m, 1H), 1.7−1.4 (m, 6H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR δ 175.2, 158.7, 137.2, 1330., 128.9, 128.5, 127.8, 114.5, 108.7, 79.6, 70.3, 64.6, 61.2, 52.3, 32.3, 32.2, 29.2, 27.8, 14.4. IR (KBr, Nujol) 3480 (m), 2920 (s), 1720 (m) cm^{-1}. Anal. Calcd for $C_{25}H_{30}O_6$: C, 70.39, H, 7.09. Found: C, 70.07, H, 7.14.

(7) (a) Rylander, P. N. *Catalytic Hydrogenation in Organic Syntheses*; Academic Press: New York, 1979. (b) Augustine, R. L. *Catalytic Hydrogenation*; Marcel Dekker: New York, 1965. (c) A manuscript on $ZnBr_2$-mediated selective hydrogenation is in preparation.

(8) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.

***N*-(2-Naphthalenesulfonyl)-D-valine (3)**. To a mixture of 400.0 g (3.414 mol) of D-valine, 3 L of water, 380 mL of THF, and 1190 mL (8.572 mol) of TEA in a 12-L three-necked flask with a mechanical stirrer was added dropwise at 5−10 °C a solution of 774 g (3.414 mol) of 2-naphthalenesulfonyl chloride in 800 mL of THF. The mixture was allowed to warm to rt and stirred for 2 h. After evaporation of THF, the reaction was poured into 4 L of 3 N HCl and extracted with *t*-BuOMe. Concentration of the solvent gave 910.0 g (87%) of **3** as a white solid. Mp 170−172 °C, (lit.[6] 170−172 °C), whose spectra data were identical to those reported.[6]

(1*S*)-4-[4-(Benzyloxy)phenyl]-4-(hydroxymethyl)-4-[[(4-fluorophenyl)amino]carbonyl]cyclohexan-1-one (9). To a dry 2-L three-necked flask with a mechanical stirrer were added 41.3 mL (436 mmol) of 4-$FC_6H_4NH_2$, 120 mL of CH_2Cl_2, and 218 mL (436 mmol) of 2.0 M Me_3Al in toluene. After agitating at rt for 30 min, a solution of 46.7 g (109 mmol) of **5** in 110 mL of CH_2Cl_2 was added dropwise, and the resulting mixture was heated at 50−55 °C for 2 d. The cooled reaction mixture was added dropwise to a solution of 700 mL of 3 N HCl and 400 mL of toluene. The mixture was extracted two times with 400 mL of EtOAc and washed with 300 mL of 3 N HCl. After concentration of the solvent, the residue was dissolved in 250 mL of THF, followed by addition of 300 mL of 3 N HCl, and the mixture was stirred at rt for 3 d. After removal of THF, the crude product was filtered and slurried with saturated $NaHCO_3$ to give 40.9 g of **9**. Recrystallization from EtOAc/hexane gave an analytical sample. Mp 173−175 °C. HRMS 448.1924 ($M^+ + H$), calcd for $C_{27}H_{27}FNO_4$ 448.1920. ^{1}H NMR δ 8.88 (s, 1H), 7.48 (dd, J = 8.9, 4.8 Hz, 2H), 7.40−7.30 (m, 5H), 7.13 (d, J = 8.6 Hz, 2H), 7.04 (t, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 5.00 (s, 2H), 4.56 (s, 1H), 3.16 (bs, 1H), 2.85−2.75 (m, 1H), 2.75−2.65 (m, 1H), 2.45−2.32 (m, 2H), 2.27 (dm, J = 15.8 Hz, 1H), 2.15−2.05 (m, 1H), 1.93 (td, J = 13.4, 5.3 Hz, 1H), 1.55 (td, J = 13.4, 5.3 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 210.6, 171.5, 159.7, 157.4, 156.5, 137.0, 135.1, 133.7, 128.2, 128.2, 127.7, 127.5, 122.5, 122.4, 115.1, 114.8, 113.6, 76.2, 69.0, 51.4, 37.7, 37.6, 29.5, 29.1. IR (KBr, Nujol) 3280 (m), 2920 (m), 1700 (s), 1640 (s) cm^{-1}.

(3*R*)-2-(4-Fluorophenyl)-3-[4-(benzyloxy)phenyl]-2-azaspiro[3.5]nonane-1,7-dione (6.) To a mixture of 39.3 g of crude **9**, 4 g of $BnNEt_3Cl$, and 1.0 L of CH_2Cl_2 in a 2-L three-necked flask with a mechanical stirrer were added slowly 232 g of 50% NaOH and 19 mL (132 mmol) of $(EtO)_2P(O)Cl$ over 20 min. The resulting mixture was stirred at rt for 2 h, added slowly to 2 L of ice cold 3 N HCl, and extracted three times with 500 mL of EtOAc. The combined extract was washed with brine, dried over $MgSO_4$, and concentrated. Addition of 200 mL of Et_2O to the residue precipitated 23.4 g (59% over two steps) of **6**. $[\alpha]^{22.6}_D$ = +41.6° (*c* 0.54, EtOH). Mp 127−129 °C. HRMS 430.1818 ($M^+ + H$), calcd for $C_{27}H_{25}FNO_3$ 430.1805. ^{1}H NMR δ 7.34−7.17 (m, 7H), 7.09 (d, J = 8.6 Hz, 2H), 6.90−6.96 (m, 4H), 4.95 (s, 2H), 4.80 (s, 1H), 2.80−2.75 (m, 1H), 2.5−2.45 (m, 3H), 2.25−2.15 (m, 1H), 1.95−1.80 (m, 2H), 1.52−1.42 (m, 1H). ^{13}C NMR δ 209.7, 169.5, 160.5, 159.4, 158.1, 136.7, 133.96, 133.94 128.9, 128.4, 128.1, 127.8, 126.5, 119.0, 118.9, 116.3, 116.1, 115.6, 70.4, 65.2, 58.3, 38.7, 37.9, 32.9, 28.2. IR (KBr, Nujol) 2920 (s), 1735 (m), 1720(m) cm^{-1}.

(3*R*)-7-(4-Chlorophenyl)-2-(4-fluorophenyl)-3-[4-(benzyloxy)phenyl]-2-azaspiro[3.5]nonan-1-one (7). To 1750 mL of 1.0 M 4-ClC_6H_4MgBr/*t*-BuOMe in a dry 12-L three-necked flask with a mechanical stirrer was added at 48−52 °C a solution of 500 g (1.164 mol) of **6** in 2 L of toluene over 1 h. After agitating for 30 min, the reaction was cooled to rt and added slowly to 6 L of ice cold 3 N HCl. The mixture was extracted three times with 3 L of EtOAc. The combined extract was washed with 3 L of 3 N HCl and brine, dried over $MgSO_4$, and concentrated to give 567.0 g of crude **7** as a mixture of two diastereomers (94:6). HRMS 541.1820 (M^+), calcd for $C_{33}H_{29}ClFNO_3$ 541.1816. **7.** ^{1}H NMR δ 7.50−7.20 (m, 8H), 7.00 (d, J = 8.6 Hz, 2H), 6.93 (t, J = 8.6 Hz, 2H), 5.04 (s, 2H), 4.86 (s, 1H), 2.60−2.50 (m, 1H), 2.16 (td, J = 13.8, 4.3 Hz, 1H), 2.05−1.90 (m, 3H), 1.63 (dm, J = 13.8 Hz, 1H), 1.32 (dm, J = 14.3 Hz, 1H), 1.10 (td, J = 13,8, 4.3 Hz, 1H). ^{13}C NMR δ 171.2, 160.4, 159.3, 158.0, 147.4, 133.0, 128.9, 128.7, 128.5, 128.4, 127.9, 127.3, 126.2, 119.0, 118.9, 117.0, 116.2, 116.0, 115.5, 71.8, 70.4, 66.5, 59.3, 35.9, 33.7, 28.3, 22.2; IR (KBr, Nujol) 3410 (w), 2920 (s), 1730 (m) cm^{-1}. **7a.** ^{1}H NMR δ 7.47 (dd, J = 6.8, 1.9 Hz, 2H), 7.44−7.21 (m, 9H), 7.15 (d, J = 8.5 Hz, 2H), 6.96 (d, J = 8.9 Hz, 2H), 7.00−6.95 (m, 2H),2.53 (td, J = 13.4, 4.0 Hz, 1 H), 2.42 (td, J =13.4, 4.3 Hz, 1 H), 2.36 (td, J = 13.1, 3.7 Hz, 1 H), 2.16 (dm, J = 13.4, 1 H), 1.81 (dm, J =14.0 Hz, 1 H), 1.67−1.49 (m, 3 H), 1.39 (td, J = 13.4, 4.0 Hz, 1 H). ^{13}C NMR δ 170.8, 160.5, 158.8, 157.3, 147.1, 136.7, 134.1, 134.1, 132.7, 128.6, 128.4, 128.1, 127.9, 127.5, 126.7, 126.0, 118.6, 118.5, 116.0, 115.7, 115.0, 72.5, 70.1, 65.3, 58.4, 36.0, 35.9, 29.2, 24.8. IR (KBr, Nujol) 3450 (w), 2920 (s), 2820 (s), 1730 (m) cm^{-1}.

(3*R*)-7-(4-Chlorophenyl)-2-(4-fluorophenyl)-3-(4-hydroxyphenyl)-2-azaspiro[3.5]nonan-1-one (2). To a 2-L Pyrex pressure bottle were added 35.0 g of 10% Pd/C, 350.0 g (ca. 645 mmol) of crude **7**, and 87.0 g (387 mmol) of $ZnBr_2$. The bottle was sealed, evacuated, and purged with nitrogen three times. To the sealed bottle was added through a cannula 1100 mL of EtOH. The mixture was hydrogenated at 50 psi for 16 h, filtered through a pad of Celite, and concentrated. The residue was dissolved in 1 L of EtOAc, poured slowly into 1 L of ice cold saturated $NaHCO_3$, extracted two times with 300 mL of EtOAc. The combined extract was washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated. Addition of 1 L of CH_2Cl_2 precipitated 178.0 g (63% over two steps) of **2**. Mp 235−236 °C. $[\alpha]^{25}_D$ = +50.9° (*c* 0.42, MeOH). ^{1}H NMR (DMSO-d_6) δ 9.57 (s, 1H), 7.40−7.15 (m, 10H), 6.80 (d, J = 8.5 Hz, 2H), 5.14 (s, 1H), 5.04 (s, 1H), 2.30 (td, J = 12.8, 3.5 Hz, 1H), 2.05 (td, J = 13.6 Hz, 3.5 Hz, 1H), 1.96 (td, J = 13.6, 3.9 Hz, 1H), 1.87 (dm, J = 13.6 Hz, 1H), 1.72 (dm, J = 13.6 Hz, 1H), 1.48 (dm, J = 13.6 Hz, 1H), 1.13 (dm, J = 12.8 Hz, 1H), 0.84 (td, J = 13.6, 3.5 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 170.6, 158.1 (d, J = 240 Hz), 157.4, 149.4, 134.1 (d, J = 2.3 Hz), 130.9, 130.0, 126.6, 125.4, 118.6 (d, J = 8.0 Hz), 116.0 (d, J = 23 Hz),115.6, 70.2, 64.9, 58.5, 34.8, 33.4, 27.5, 21.7. IR (KBr, Nujol) 3420 (m), 3180 (m), 2920 (s) 1730 (s) cm^{-1}. Anal. Calcd for $C_{26}H_{23}ClFNO_3$: C, 69.10; H, 5.13; N, 3.10; Cl, 7.86; F, 4.21. Found: C, 69.16; H, 5.42; N, 3.19; Cl, 7.75; F, 4.30. Chiral HPLC: 99.5% ee. **Deschloro.** Mp 216−218 °C. HRMS 417.1743 (M^+), calcd for $C_{26}H_{24}FNO_3$ 417.1740. ^{1}H NMR δ 7.34−7.18 (m, 9H), 69.3−6.86 (m, 4H), 6.76 (bs, 1H), 4.84 (s, 1H), 2.56−2.49 (m, 1H), 2.17−1.88 (m, 4H), 1.60−1.56 (m, 1H), 1.29−1.11 (m, 2H). ^{13}C NMR (DMSO-d_6) δ 170.7, 159.3, 157.4, 156.9, 150.4, 134.12, 134.10, 128.0, 126.3, 125.4, 124.5, 118.7, 118.6, 116.1, 115.9, 115.6, 70.4, 65.0, 58.6, 35.0, 33.4, 27.6, 21.7. IR (KBr, Nujol) 3350, 2920, 1725 cm^{-1}.

Acknowledgment. We thank the staff of Physical-Analytical Department for assays. We also thank D. Schumacher, Bruce Shutts, Michael Mitchell, G. Love, J. Yang, B. Wang, A. Miller, and D. Moloney for their support and help.

Supporting Information Available: ^{1}H NMR, ^{13}C NMR, and IR spectra for **4**, **5**, **6**, **7**, **7a**, **8**, **9**, and **2**. Also chiral HPLC chromatograms for **5**, **6**, **9**, and **2** (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

JO9704366