Organic Process Research & Development **2007**, *11*, 534–538

Development of an Asymmetric Acetate Aldol Reaction with a Trifluoromethyl Ketone

Jinhua J. Song,* Jinghua Xu, Zhulin Tan, Jonathan T. Reeves, Nelu Grinberg, Heewon Lee, Katie Kuzmich, Xuwu Feng, Nathan K. Yee, and Chris H. Senanayake

Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Old Ridgebury Road/P. O. Box 368, Ridgefield, Connecticut 06877-0368, U.S.A.

Abstract:

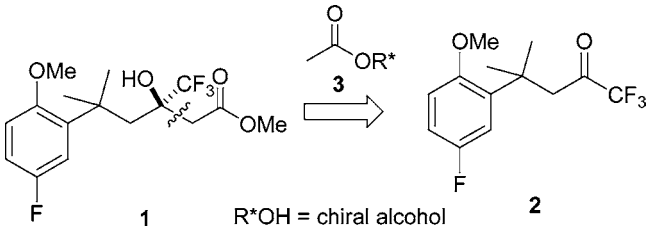
We describe the discovery and development of a chiral auxiliary-controlled asymmetric acetate aldol reaction with a trifluoromethyl ketone. Chiral acetate 3d was prepared efficiently from (1*S*,2*R*)-1-amino-2-indanol. Reaction of the lithium enolate of 3d with trifluoromethyl ketone 2 afforded aldol adducts in 95% HPLC assay yield (by weight) with a 78:22 dr. The major isomer 5 was obtained via a robust crystallization method in 45% one-crop isolated yield with a >98.7:1.3 dr. Compound 5 was subjected to transesterification to give *β*-hydroxy ester 1. The cleaved auxiliary 7 was readily recovered by a direct crystallization/filtration method. Process optimization led to better volume efficiencies, improved isolation protocols, and less consumption of organic solvents, all contributing to enhanced throughput, reduced processing labor and time, as well as reduction in chemical wastes.

Introduction

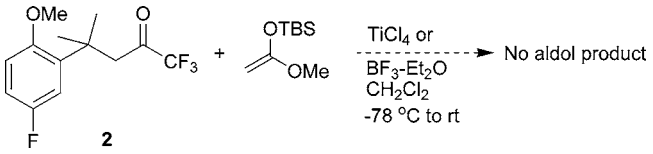
During our recent process development efforts for a drug candidate intended for treatment of various inflammatory, autoimmune, and allergic disorders,[1] we needed to establish a trifluoromethyl-substituted quaternary stereogenic center in a key intermediate (**1**) via an asymmetric acetate aldol reaction with a trifluoromethyl ketone **2**[2] as indicated in the following retrosynthetic analysis (Scheme 1).

Asymmetric acetate aldol reactions, unlike the analogous *syn*-propionate-type aldol reactions, have had a very limited application in API synthesis,[3] especially acetate aldol additions with ketones. Almost all existing asymmetric aldol methods were reported for reactions with aldehydes, and only very few asymmetric methodologies are available for ketone aldol reactions.[4] Most of these protocols lack practicality due to the high catalyst loading and/or the need to synthesize chiral ligands or chiral auxiliaries in multiple steps. Additionally, we have found that Lewis acid-catalyzed reactions between silyl ketene acetals and trifluoromethyl ketone **2** gave no desired aldol adducts (e.g., in Scheme 2). This lack of reactivity, we believe, could be attributed to the attenuated

Scheme 1



Scheme 2



Lewis basicity of the trifluoromethyl carbonyl group compared to that of regular ketones. As a consequence, the CF_3 carbonyl group could not be adequately activated towards aldol addition through binding with a Lewis acid.

In this paper, we report the discovery of a chiral auxiliary-based asymmetric acetate aldol reaction with trifluoromethyl ketone **2**, employing the simple and inexpensive *cis*-1-amino-2-indanol[5] as the chiral template. Detailed process development of this reaction and related steps, including scaleup to kilogram quantities, are presented. Emphasis is also given to discussions on our development efforts to improve the overall process throughput by maximizing volume efficiencies, minimizing the amounts and the types of organic solvents used, and developing efficient workup/isolation protocols.

Results and Discussion

We initiated our study by examining the well-known Braun's asymmetric acetate aldol reaction. Braun has reported that the lithium enolate derived from optically pure 2-acetoxy-1,1,2-triphenylethanol (**3a**, Table 1) can react with aldehydes in a stereoselective fashion, providing acetate aldols with synthetically useful diastereoselectivities.[6] However, reaction between Braun's enolate and trifluoromethyl ketone **2** gave a disappointing 64:36 stereoselectivity, which

* To whom correspondence should be addressed. E-mail: jsong@rdg.boehringer-ingelheim.com.

(1) Lee, T. W.; Proudfoot, J. R.; Thomson, D. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 654.

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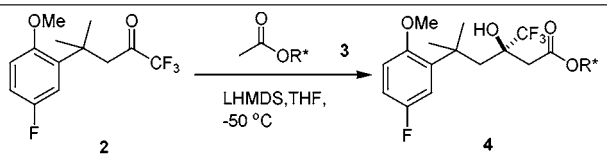
(4) (a) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233 and references therein. (b) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2951. (c) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164.

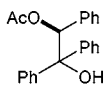
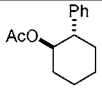
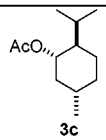
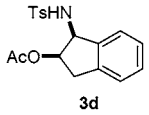
(5) Gallou, I.; Senanayake, C. H. *Chem. Rev.* **2006**, *106*, 2843.

(6) Braun, M.; Devant, R. *Tetrahedron Lett.* **1984**, *25*, 5031.

Published on Web 01/18/2007
10.1021/op060211+ CCC: $37.00

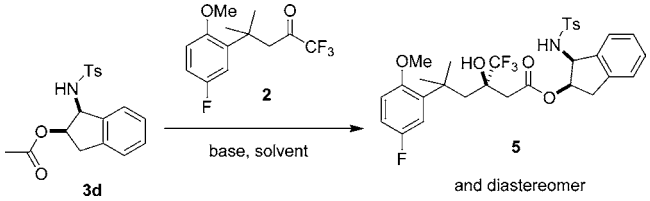
Table 1. **Acetate aldol with auxiliaries**



acetate	dr	acetate	dr
 3a	64:36*	 3b	65:35*
 3c	58:42*	 3d	**78:22**

*Absolute stereochemistry was not determined.

Table 2. **Aldol reaction**



entry	conditions	dr	conversion (%)
1	**LHMDS/THF (−50 °C)**	**78:22**	**95**
2	LHMDS/hexanes (−50 °C)	54:46	54
3	LHMDS/THF/$TiCl_4$ (−50 °C)	63:37	48
4	LHMDS/THF/$ZnCl_2$ (−50 °C)	NA	no reaction
5	LHMDS/THF/$MgBr_2$ (−50 °C)	58:42	77
6	NaHMDS/THF (−50 °C)	56:44	95
7	KHMDS/THF (−50 °C)	54:46	95
8	LHMDS/THF (−30 °C)	80:20	89
9	LHMDS/THF (0 °C)	76:24	50

is consistent with a literature example for a ketone aldol reaction using this method.[7]

We subsequently investigated the possibility of improving the stereoselectivity by using some inexpensive, readily available chiral auxiliaries. Their reactions with ketone **2** were screened, and key results are summarized in Table 1. The (1*S*,2*R*)-1-amino-2-indanol-derived chiral acetate **3d** gave improved stereoselectivity of 78:22. On the other hand, menthol acetate (**3c**) and 2-phenyl-1-cyclohexanol acetate (**3b**) gave poor selectivities.

Further study on preparative scales confirmed that asymmetric aldol reaction between the lithium enolate of chiral ester **3d** and trifluoromethyl ketone **2** afforded aldol adducts in 95% HPLC assay yield (by weight) with a 78:22 dr (Table 2, entry 1). Reaction using LHMDS in hexanes was not selective (entry 2). The addition of Lewis acids such as $TiCl_4$, $ZnCl_2$, or $MgBr_2$ gave either lower selectivity or no reaction (entries 3−5). This observation was consistent with our hypothesis that binding between Lewis acids and the CF_3 carbonyl group was weakened due to the lowered Lewis basicity of the trifluoromethyl carbonyl group. Attempts to increase the diastereoselectivity by using different alkaline counterions (Na or K) were unsuccessful (entries 6−7). Finally, it was noted that the reaction needed to be run at temperatures lower than −30 °C to ensure high conversion (95%) of the ketone (entries 8−9). With critical reaction parameters established, in our subsequent studies we have extensively optimized and scaled up this asymmetric acetate aldol reaction and related steps (i.e., chiral acetate synthesis and the subsequent removal of chiral auxiliary). The details of our work are described in the following sections.

Efficient Synthesis of Chiral Acetate 3d. The literature synthesis of chiral acetate **3d** required two chemical steps from (1*S*,2*R*)-1-amino-2-indanol **6** via tosylation followed by acetylation (Table 3).[8] Selective tosylation with TsCl/TEA in THF proceeded uneventfully to give compound **7** in essentially quantitative yield. Acetylation of **7** could be achieved by treatment with $Bi(OTf)_3$ (cat.)/Ac_2O (as solvent) for 1 h or with Ac_2O/pyridine (as solvent) for 11 h.[8] On the other hand, typical acetylation conditions (amine base, AcCl, THF, or methylene chloride) that were used for synthesis of the propionate analogue of **3d**[9] gave either sluggish reactions or byproduct formation (entries 1−4). Further screening of reaction conditions revealed that the simple addition of a catalytic amount of DMAP provided the most facile and cleanest acetylation of the hydroxyl group (>95% isolated yield within 1 h at rt, entry 6). In the absence of DMAP, the reaction was not only much slower but also generated multiple byproducts.

Since both tosylation and acetylation reactions used THF as solvent, we developed this two-step sequence into the following one-pot process. This allowed us to eliminate one workup/isolation step as well as one solid drying operation, therefore tremendously reducing the processing labor and time. Thus, (1*S*,2*R*)-1-amino-2-indanol was dissolved in THF at room temperature, and TEA was added followed by TsCl. After 1 h, DMAP (cat.) and acetic anhydride were added to achieve acetylation of the hydroxyl group. The reaction was quenched with water, and after separation of layers, THF was removed by distillation. Compound **3d** was directly crystallized by addition of heptane and $NaHCO_3$ (aq) without the need for extractive workup. Then facile filtration and rinsing gave chiral acetate **3d** in 95% isolated yield (>99 area% by HPLC). The V_{max}[10] for this step was 19 L/kg, and only two organic solvents (THF and heptane) were used in this step. As a comparison, for the original stepwise procedure, two extractive isolations were required, and as a consequence the V_{max} was quite large at 40 L/kg.

Asymmetric Aldol Reaction. Chiral acetate **3d** was treated with LHMDS (1 M THF solution) at −50 to −30 °C for 1 h to generate the enolate. Ketone **2** was added

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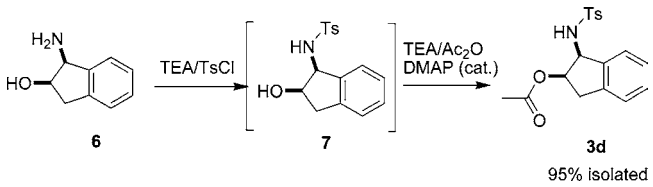
(8) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *J. Org. Chem.* **2001**, *66*, 8926.

(9) Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527.

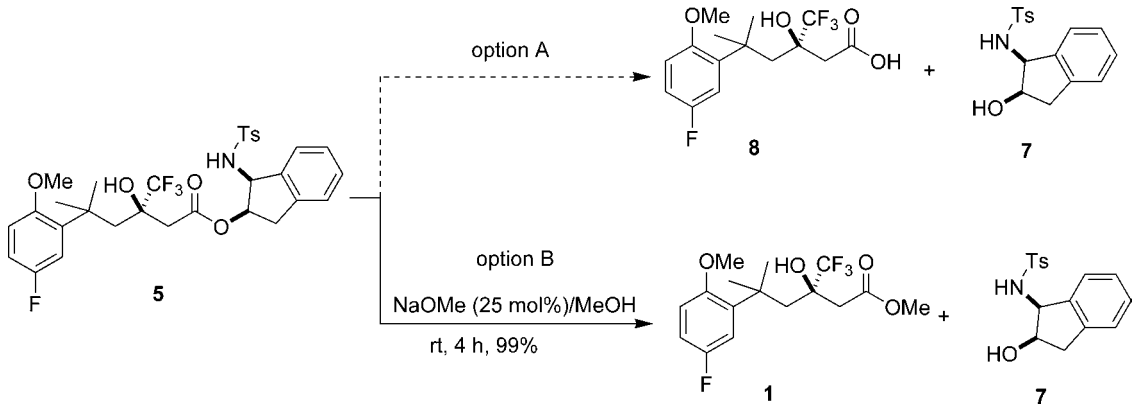
(10) V_{max} is defined as the maximum volume of the reaction mixture relative to the weight of starting material, during the entire reaction sequence (including workup and isolation). This parameter is useful in selecting reactor size and is also a useful indicator of reaction throughput.

Table 3. **Acetylation reaction**



					results (HPLC area %)		
entry	solvent	reagents	temp (°C)	time (h)	unreacted **7**	**3d**	byproduct
1	CH_2Cl_2	TEA/AcCl	0	0.5	7.4	64	8.6
2	THF	TEA/AcCl	23	16	0.6	39	multiple
3	THF	DIPEA/AcCl	0	0.5	81	7	4
4	THF	1-methyl-pyrrolidine/AcCl	23	0.2	21	54	15
5	THF	TEA/Ac_2O	23	19	85	11	multiple
6	**THF**	**TEA/Ac_2O (cat. DMAP)**	**23**	**1**		**clean, fast reaction 95% isolated yield**	

Scheme 3



as a neat liquid, maintaining the internal temperature in the range of −50 to −45 °C. After an additional 30 min at −20 °C, HCl (aq) was added, and layers were separated. HPLC analysis of the organic layer indicated a 95% assay yield (by weight) with a diastereomeric ratio of 78:22 with compound **5** as the major isomer.[11]

Isolation of the major isomer from the product mixture through crystallization proved to be challenging. Crystallization from heptane/EtOAc solvent system was not robust, and the diastereomeric ratios of isolated solids were highly dependent on crystallization time as well as the purity of starting crude product mixture. For example, if the crude mixture was filtered through silica gel, the minor isomer started to come out within 2.5 h (as monitored by HPLC). When the crude mixture was used directly, a 5−6 h window was available before the minor isomer crystallized out. Furthermore, it was found that residual THF or water were detrimental to the crystallization and needed to be controlled to very tight specifications. Overall, crystallization in this solvent system was extremely difficult to control and gave only 20% isolated yield of compound **5**. In order to identify a robust scaleable crystallization method for this reaction mixture, a number of other solvent systems were tested. We were pleased to find that MeOH/water gave satisfactory results. Crystallization from a MeOH/water mixture gave one-crop 45% yield of **5** with a >98.7:1.3 dr. Thus, the crude product solution was distilled under vacuum to remove THF and was solvent-switched to MeOH. Water was then added to crystallize the major isomer, and it was isolated in yield and purity indicated above. The V_{max} was 16 L/kg and only two organic solvents (THF and MeOH) were used in this step.

Removal of Chiral Auxiliary by Transesterification. Cleavage of the chiral auxiliary from aldol product **5** deserves some careful considerations. On large scales, the development of a nonchromatographic method for separating the cleaved auxiliary from the desired product is of great importance. There are two possible ways to cleave the auxiliary from aldol product **5** (options A and B, Scheme 3). For example, aldol adduct **5** can be saponified to give the free β-hydroxy acid **8** and *N*-tosyl-*cis*-1-amino-2-indanol **7** (option A). However, both **8** and **7** are acidic compounds, and it might not be easy to separate them without resorting to column chromatography. On the other hand, if aldol product **5** is subjected to transesterification to give a neutral compound β-hydroxy ester **1** and an acidic compound **7**, we might be able to separate them by acid/base extraction (option B). Following this thought, we have treated compound **5** with MeOH/0.25 equiv of NaOMe for 4 h at rt to obtain a mixture

(11) The absolute stereochemistry of the major diastereomer (**5**) was confirmed by conversion of **5** to final drug substance and comparison with an authentic sample by chiral HPLC and optical rotation.

containing β-hydroxy methyl ester **1** and alcohol **7**. The reaction mixture was then diluted with MTBE and extracted with NaOH (1 M aq) to remove *N*-tosyl-*cis*-1-amino-2-indanol **7** as its sodium salt. However, due to the low solubility of the sodium salt of compound **7** in aqueous NaOH, at least 10 extractions were required to completely remove it from the organic layer. Additionally, neutralization and more back extractions had to be carried out to recover the auxiliary from the aqueous NaOH layer. Consequently, this operation was labor-intensive, and the V_{max} for this whole reaction sequence was also relatively high (22 L/kg).

To improve the throughput, we have designed a highly efficient recovery protocol where the cleaved chiral auxiliary **7** was directly crystallized during workup. After the reaction, the pH was adjusted to 7. Heptane was added followed by gradual addition of water to crystallize compound **7** from the mixture. At this point, the reactor content was a three-phase mixture consisting of the heptane phase with product **1**, the aqueous/MeOH phase with water soluble materials, and the solid phase which was the chiral auxiliary (**7**). Filtration of this mixture gave compound **7** in 93% yield which could be directly reused after drying. The recycling of chiral auxiliary not only reduced raw material costs but also cut down the amount of waste for disposal.

The heptane phase was distilled to provide the desired product (**1**) as a concentrated heptane solution. By using this direct crystallization method, the processing labor and time were significantly reduced. The V_{max} for this step was dramatically improved from 22 L/kg to 7.8 L/kg, and only two organic solvents (MeOH and heptane) were required in this step. The yield of compound **1** was consistently 99% on multikilogram scales (99 area % purity, 98.7:1.3 er).

Conclusion

In summary, we have reported a chiral auxiliary-controlled asymmetric acetate aldol reaction with a trifluoromethyl ketone. Chiral acetate **3d** was prepared efficiently from (1*S*,2*R*)-1-amino-2-indanol, which is readily available in bulk. Reaction of the lithium enolate of **3d** with trifluoromethyl ketone **2** afforded aldol adducts in 95% HPLC assay yield (by weight) with a 78:22 dr. The major isomer (**5**) was isolated via a robust crystallization method in 45% one-crop yield with a >98.7:1.3 dr. A one-pot synthesis of the chiral acetate **3d** as well as a simple procedure for the cleavage and recovery of chiral auxiliary was also reported. Optimization of these steps led to better volume efficiencies (low V_{max}), improved isolation protocols, and less consumption of organic solvents, all contributing to enhanced throughput, reduced processing labor and time, and reduction in chemical wastes.

Experimental Section

General Procedures. All reactions were performed under nitrogen with mechanical stirring. All commercial reagents were used as received. HPLC analyses were performed on Agilent 1100 using Tosohass super-ODS column, 4.6 mm × 10 cm, particle size 2 μm, at wavelength 220 nm, at 25 °C. Mobile phases are A: water with 0.05% TFA, B: MeCN with 0.05% TFA. Gradient conditions are 90% A to 10% A in 15 min, hold 5 min, back to 90% A followed by a 3-min postrun.

*N-[(1S,2R)-2-(Acetyloxy)-2,3-dihydro-1H-inden-1-yl]-4-methyl-benzenesulfonamide (**3d**).* Into the reactor under N2 and agitation that was set at ~100 rpm were charged 33.2 g (0.22 mol, 1.0 equiv) of (1*S*,2*R*)-1-amino-2-indanol (**6**) and 150 mL (133.4 g) of THF (KF < 500 ppm water); 92.6 mL (67.2 g, 0.66 mol, 3.0 equiv) of triethylamine was added. The suspension was cooled to 10 °C. Under nitrogen, tosyl chloride solution in THF was prepared using 42.32 g (0.22 mol, 1.0 equiv) of tosyl chloride and 100 mL (88.9 g) of THF. The TsCl solution was added into the reactor at such a rate that the internal temperature was maintained between 20 to 25 °C. The transfer line was rinsed with 10 mL (8.9 g) of THF into the reaction mixture. The suspension was stirred at about 22 °C for about 0.5 h, when an HPLC sample was taken to confirm reaction completion. The suspension was cooled to 10 °C. DMAP (1.36 g, 0.011 mol, 0.05 equiv) dissolved in 15 mL (13.3 g) of THF was added. The transfer line was rinsed with 2 mL (1.8 g) of THF into the reaction mixture. Then into the reaction mixture was slowly added 25.2 mL (27.3 g, 0.26 mol, 1.2 equiv) of acetic anhydride so that the internal temperature was maintained between 20 and 25 °C. The transfer line was rinsed with 8 mL (7.1 g) of THF into the reaction mixture. The suspension was stirred at about 22 °C for 30 min when an HPLC sample was taken to monitor reaction completion. The reaction mixture was cooled to 10 °C, and 160 mL of water was added slowly so that the internal temperature did not exceed 25 °C. The jacket temperature was set to 22 °C and the mixture was agitated at 22−25 °C for 15 min and the layers were cut. The organic layer was distilled under vacuum to remove about 170 mL of solvents. The distillation should be stopped when the weight ratio of THF/product is ~1.1:1 (by GC and HPLC). The mixture was diluted with 240 mL (164.2 g) of heptane over 20 min. The slurry was cooled to ~22 °C over 30 min; 5% $NaHCO_3$ aq solution (60 mL) was added. The stirring was continued for 15 min. The slurry was filtered, and the cake was rinsed with 40 mL of water and 40 mL (27.4 g) of heptane. The product was dried under vacuum at 60 °C for at least 4 h until the solids contained <5% heptane and <500 ppm water by weight to give 73 g (95% yield) of **3d**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, J = 8.4 Hz, 2H), 7.34−7.17 (m, 6H), 5.11−4.96 (m, 3H), 3.08 (dd, J = 17.2, 5.2 Hz, 1H), 2.90 (d, J = 17.2 Hz, 1H), 2.45 (s, 3H), 1.91 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 143.8, 139.9, 138.7, 138.0, 129.9, 128.6, 127.3, 126.9, 125.0, 124.3, 74.8, 59.5, 37.4, 21.6, 20.9. Mp 130.1 °C. IR (cm^{-1}): 1745, 1343, 1240, 1161. $[\alpha]^{25}_{365}$ −74.8 (*c* 1.0, MeOH). Anal. Calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.69; H, 5.57; N, 4.08.

*1,1,1-Trifluoro-4-(5-fluoro-2-methoxyphenyl)-4-methyl-pentan-2-one (**2**).* Synthesis of this compound was described previously. See refs 1 and 2. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.04 (dd, J = 10.8, 3.2 Hz, 1H), 6.88 (m, 1H). 6.76 (dd, J = 8.8, 4.4 Hz, 1H), 3.78 (s, 3H), 3.36 (s, 2H), 1.46 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.4, 190.1, 189.8, 189.4,

158.2, 155.9, 153.5, 136.1, 119.7, 116.8, 114.9, 114.6, 113.9, 113.4, 113.1, 111.8, 111.7, 111.0, 55.2, 46.0, 36.5, 28.3. IR (cm^{-1}): 1764, 1498, 1282, 1204, 1151, 1131, 1031. Anal. Calcd for $C_{13}H_{14}F_4O_2$: C, 56.12; H, 5.07. Found: C, 56.25; H, 5.03.

5-Fluoro-β-hydroxy-2-methoxy-δ,δ-dimethyl-β-trifluoromethyl-benzenepentanoic Acid (1S,2R)-2,3-Dihydro-1-[[(4-methylphenyl)sulfonyl]amino]-1H-inden-2-yl Ester (***5***). Acetate **3d** (1.365 kg, 3.95 mol, 1.0 equiv) and THF (2.64 L, 2.35 kg, KF <500 ppm water) were charged into the reactor under nitrogen. The resulting solution was cooled to −50 to −55 °C. LHMDS (1 M in THF, 9.09 L, 2.3 equiv) was added at a rate that the internal temperature gradually warmed to and maintained at −30 °C. The reaction mixture was stirred for ∼30 min at −30 °C and cooled back to −50 °C. Then ketone **2** (1.05 kg, 3.75 mol, 0.95 equiv) was added slowly at a rate that the internal *T* was between −50 to −45 °C. The reaction mixture was stirred for 30 min at −50 °C and warmed to −20 °C over 30 min and maintained at −20 °C for 30 min. An HPLC sample was taken (diluted with HCl/CH_3CN) for reaction monitoring. (The product should be ∼90 area% by HPLC.) HCl aq solution (5 M, 3.52 L) was added to neutralize the reaction mixture. The internal *T* gradually warmed to −20 °C at the end of the addition. The mixture was further warmed to ∼20 °C over ∼15 min with the aid of the jacket heating (jacket *T* was about 35 °C**)** and stirred for 10 min. The pH was 7 (small amounts of HCl or $NaHCO_3$ might be needed to fine-tune the pH to 7). The layers were separated. The organic layer was evaporated under reduced pressure to the minimum stirrable volume. Methanol (6 L) was added and distilled to the stirrable minimum volume. Another portion of methanol (3 L) was added to bring the mixture to a clear solution. GC was used to check the residual THF (specification: <1% relative to product). Then KF and GC were used to check the residual methanol and H_2O content. Methanol was added to reach a total of 6.4 L, followed by H_2O (1 L in total after adjustment of the residual water). Seed [20 g, suspended in 10 mL of 6/1(v/v) MeOH/H_2O] was added to the mixture. The mixture was aged for 14 h at rt, H_2O (300 mL) was added slowly (about 2 h), and the mixture was stirred at ∼9 °C for 1 h. The mixture was filtered, and the cake was washed with mixed solvent of cold (∼10 °C) MeOH/H_2O (6/1, v/v, 5 L). The desired isomer **5** was obtained as a white solid after drying under vacuum at 60 °C for 5 h (1.09 kg, 45% yield, >98.5 area % by HPLC, >98.7:1.3 dr). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, J = 7.8 Hz, 2H), 7.28−7.14 (m, 6H), 7.09 (dd, J = 10.4, 3.2 Hz, 1H), 6.94 (m, 1H), 6.85 (dd, J = 8.8, 4.8 Hz, 1H), 5.01−4.87 (m, 3H), 4.70 (m, 1H), 3.84 (s, 3H), 3.00 (dd, J = 17.6, 5.2 Hz, 1H), 2.77 (d, J = 17.6 Hz, 1H), 2.66 (d, J = 15.2 Hz, 1H), 2.44 (s, 3H), 2.18(d, J =15.6 Hz, 1H), 2.03 (d, J = 15.2 Hz, 1H), 1.97 (d, J = 15.2 Hz, 1H), 1.55 (s, 3H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 158.2, 155. 9, 154.3, 144.2, 139.4, 138.3, 137.7, 137.5, 137.4, 130.1, 129.9, 128.8, 127.4, 126.8, 125.1, 124.3, 115.0, 114.8, 113.6, 113.4, 112.7, 112.6, 76.0, 75.7, 75.5, 75.2, 59.4, 55.6, 40.8, 37.4, 37.0, 35.6, 31.3, 29.6, 21.5. IR (cm^{-1}): 1718, 1162, 1031, 668. Anal. Calcd for $C_{31}H_{33}F_4NO_6S$: C, 59.70; H, 5.33; N, 2.25. Found: C, 59.75; H, 5.24; N, 2.23. Mp 110.0 °C. $[\alpha]^{25}_{365}$ −71.0 (*c* 1.0, MeOH).

(*βR)-5-Fluoro-β-hydroxy-2-methoxy-δ,δ-dimethyl-β-trifluoromethyl-benzenepentanoic Acid Methyl Ester* (***1***). Aldol adduct **5** (3.3 kg, 5.29 mol, 1.0 equiv) was charged into a glass reactor. Methanol (7.05 L) was added to form a clear solution. NaOMe (25 w/w% in MeOH, 0.3 L, 0.25 equiv) was added, and the reaction mixture was stirred at ∼22 °C for ∼4 h. HCl aq solution (2 M, 0.66 L) was added to neutralize the reaction mixture to pH = 7. The reaction mixture was transferred to a 50-L reactor equipped with an agitator. Heptane (7.14 L) was added, and then water (7.14 L) was added slowly over 0.5 h. The mixture was agitated vigorously for 30 min and filtered. The two layers of the filtrate were separated. The cake was rinsed with heptane (3.57 L × 2) and was combined with the organic layer. The solids **(**compound **7**) were dried in the oven under vacuum and reused for future synthesis (1.49 kg, 93% yield). The combined organic layer was washed with NaOH aq solution (1 M, 2.64 L) and with NH_4Cl aq solution (10%, 2.64 L) consecutively. The organic layer was concentrated under vacuum to give product **1** as a concentrated solution in heptane (1.84 kg by HPLC wt % assay, 99% yield, 99 area % by HPLC at 220 nm, 98.7:1.3 er). This solution can be used directly in subsequent synthetic steps. An analytical sample of **1** was obtained by completely removing solvents under high vacuum. The chiral purity of this compound was determined by using the following chiral HPLC method after being hydrolyzed to the corresponding hydroxy acid: Chiralcel OJ 4.6 mm × 250 mm; isocratic 99:5 hexanes/IPA with 0.1% TFA; flow rate: 0.5 mL/min; temp: 20 °C; injection volume: 5 μL; UV: 220 nm; retention times: 11.8 and 16.7 min (desired enantiomer). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.05 (dd, J = 11.8, 3.2 Hz, 1H), 6.90 (m, 1H), 6.79 (dd, J = 8.8, 4.8 Hz, 1H), 4.93 (s, 1H), 3.83 (s, 3H), 3.63 (s, 3H), 2.85 (d, J = 15.2 Hz, 1H), 2.22 (d, J = 15.6 Hz, 1H), 2.09 (d, J = 15.6 Hz, 1H), 1.98 (d, J = 15.2 Hz, 1H), 1.56 (s, 3H), 1.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 158.3, 155.9, 154.2, 137.5, 130.1, 127.3, 124.4, 121.5, 115.1, 114.9, 113.4, 113.2, 112.2, 112.1, 76.0, 75.7, 75.4, 75.2, 55.3, 52.2, 40.6, 37.5, 35.1, 31.4, 29.2. IR (cm^{-1}): 1718, 1494, 1231, 1177, 1104, 1031, 741. Anal. Calcd for $C_{16}H_{20}F_4O_4$: C, 54.54; H, 5.72. Found: C 54.57; H 5.68. Mp 41.5 °C. $[\alpha]^{25}_{365}$ +35.6 (*c* 1.1, MeOH).

Supporting Information Available

Copies of ^{1}H NMR spectra of compounds **1**, **2**, **3d**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review October 13, 2006.

OP060211+