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Practical Asymmetric Synthesis of Aprepitant, a Potent Human NK-1 Receptor Antagonist, via a Stereoselective Lewis Acid-Catalyzed Trans Acetalization Reaction

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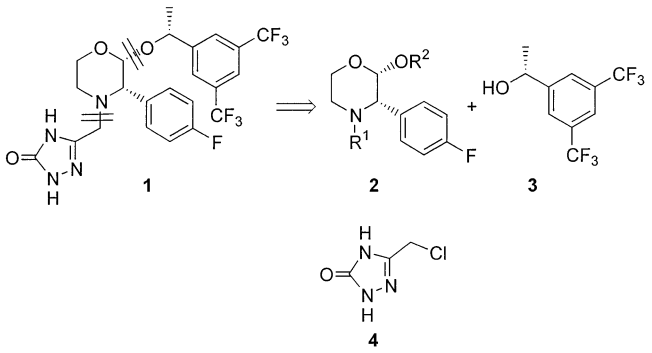
A streamlined and high-yielding synthesis of aprepitant (**1**), a potent substance P (SP) receptor antagonist, is described. The enantiopure oxazinone **16** starting material was synthesized via a novel crystallization-induced dynamic resolution process. Conversion of **16** to the penultimate intermediate *cis-sec*-amine **9** features a highly stereoselective Lewis acid-catalyzed trans acetalization of chiral alcohol **3** with trichloroacetimidate **18** followed by inversion of the adjacent chiral center on the morpholine ring. The six-step process for the synthesis of **9** was accomplished in extremely high overall yield (81%) and with only two isolations.

Introduction

Mammalian tachykinin substance P (SP) has been associated with numerous inflammatory conditions, mediation of the emetic reflex, and modulation of central nervous system (CNS) disorders.[1] Antagonists of the neurokinin-1 (NK-1) receptor to which SP preferentially binds are potential therapeutic agents for the treatment of chemotherapy-induced emesis, moderate to severe major depression, anxiety, pain, asthma, arthritis, and migraine.[1] Aprepitant (**1**) is a potent and orally active antagonist of the human neurokinin-1 (hNK-1) receptor currently in development at Merck. To support the ongoing clinical trials and eventual manufacturing, more practical and less costly syntheses were strongly desired. Very recently, an alternative synthetic approach to **1** was published.[2] We would like to disclose our new synthesis of aprepitant (**1**).

Structurally, aprepitant (**1**) features three chiral centers, two of which are on its morpholine core. A triazolinone side chain is appended to the nitrogen via a methylene spacer. An obvious and logical retrosynthetic approach to the target molecule was via a cis acetalization of the chiral alcohol **3** (Scheme 1) via the activated lactol **2**. However, this turned out to be exceedingly challenging and problematic.

SCHEME 1. Retrosynthetic Analysis



Results and Discussion

Although stereochemical control of glycosylation has been intensely investigated, a general cis glycosylation method is still lacking.[3] The synthesis of starting material oxazinone **5** (Scheme 2) has been reported previously.[4] It was reduced with DIBALH, and the resulting lactol intermediate was activated by formation of the carbamate, carbonate, phosphorodiamidite, phosphate, mesylate, and triflate (**2a**−**f**, respectively). The phosphate, mesylate, and triflate (**2d**−**f**, respectively) were

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(2) Pye, P. J.; Rossen, K.; Weissman. S. A.; Maliakal, A.; Reamer, R. A.; Ball, R.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *Chem. Euro. J.* **2002**, *8*, 1372−1376.

(3) (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212−235. (b) Kochetkov, N. K. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1994; Vol. 14, Part 1, pp 201−266.

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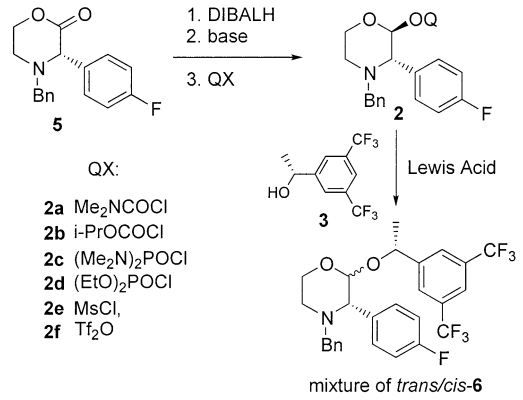
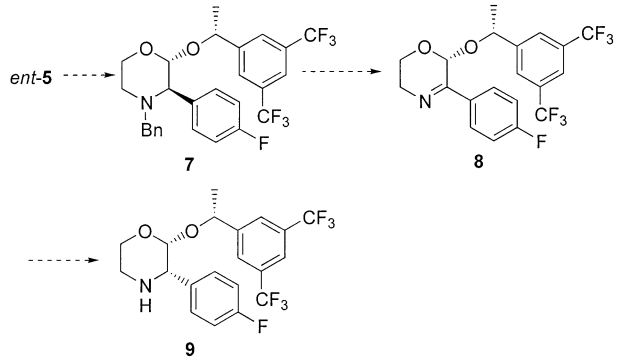
SCHEME 2. Cis Acetalization Approach



SCHEME 3. Trans Acetalization Approach

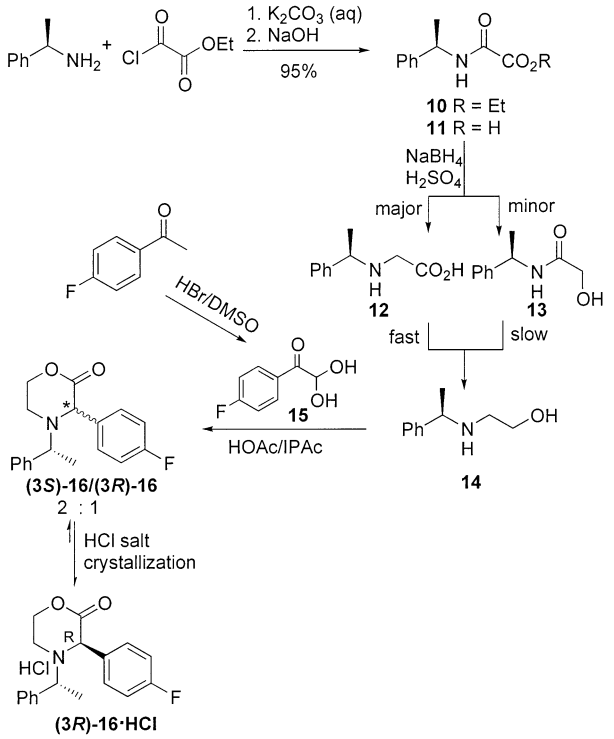


unstable for isolation and used in situ. Unfortunately, attempted cis acetalization of the chiral alcohol **3**[5] with the activated lactol **2** yielded very little of the desired isomer *cis*-**6** upon treatment with various Lewis acids. The undesired *trans*-**6** was invariably the major isomer. Elimination reaction was a major problem also. Apparently, the reaction proceeded via the stabilized carbonium intermediate to give the thermodynamically and kinetically more favored *trans*-**6**. When the lithium or potassium alkoxides of alcohol **3** were used as nucleophiles in the absence of Lewis acid, no trace of the desired product was observed.

To circumvent this inherent preference for trans acetalization, we envisioned that if one starts from *ent*-**5**, then a trans acetalization should establish the correct stereochemistry at the anomeric center to give **7** (Scheme 3). The other chiral center could then be inverted via a cis hydrogenation of the imine intermediate **8** to afford the desired *cis-sec*-amine **9**.

However, the availability of the oxazinone *ent*-**5** must be addressed first. Previously,[4] **5** was obtained via resolution with 3-bromocamphor-8-sulfonic acid (BCSA). But BCSA is expensive and limited in supply. α-Methylbenzylamine, which is very inexpensive and equally available in either enantiomeric form, appeared to be an attractive chiral auxiliary. Thus, reaction of (*R*)-(+)-α-methylbenzylamine with ethyl oxalyl chloride under Schotten−Baumann conditions gave compound **10** (Scheme 4). It could be reduced to the amino alcohol **14**[6] directly with BH_3·THF or BH_3·DMS. However, the reaction required elevated temperatures (60 °C), which raised safety issues for large-scale use. Additionally, the cost was still relatively high. Alternatively, the crude ester **10** was hydrolyzed in situ to the carboxylic acid **11**, which was then reduced at −10 °C by in situ-generated borane from $NaBH_4$ and H_2SO_4. In situ borane generation via other combinations, including $NaBH_4/I_2$, $NaBH_4/BF_3$·Et_2O, $NaBH_4$/MsOH, or $NaBH_4$/TFA gave similar results. Interestingly, two competing pathways were observed. The major one was initial reduction of the amide giving **12**, which was then smoothly reduced to the amino alcohol **14**. In the minor pathway, the carboxylic acid was reduced first affording **13**, but subsequent reduction of the amide group became exceedingly slow. Formation of a five-membered ring borane complex is postulated to interfere with the subsequent reduction. Typically, the amino alcohol **14** was obtained in 90% yield containing ∼10% **13**. The crude product was used directly since **13** does not interfere in the next step.

SCHEME 4. Synthesis of Enantiopure Oxazinone 16



The other fragment, 4-fluorophenylglyoxal hydrate **15**, was prepared from inexpensive 4-fluoroacetophenone by treatment with aqueous HBr/DMSO in ∼80% yield.[7] Simply heating a mixture of amino alcohol **14** and glyoxal **15** in the presence of acetic acid afforded oxazinone **16**.[8] However, the stereoselectivity was rather disappointing, ∼1:2 favoring the *undesired* (3*S*)-isomer. We also observed that the newly created chiral center was quite

(4) (a) Alabaster, R. J.; Gibson, A. W.; Johnson, S. A.; Edwards, J. S.; Cottrell, I. F. *Tetrahedron: Asymmetry* **1997**, *8*, 447−450.

(5) Singh, R. P.; Twamley, B.; Fabry-Asztalos, L.; Matteson, D. S.; Shreeve, J. M. *J. Org. Chem.* **2000**, *65*, 8123−8125.

(6) Amino alcohol **14** is commercially available but very expensive.

(7) Floyd, M. B.; Du, M. T.; Fabio, P. F.; Jacob, L. A.; Johnson, B. D. *J. Org. Chem.* **1985**, *50*, 5022−5027. (b) Joshi, K. C.; Pathak, V. N.; Goyal, M. K. *J. Heterocycl. Chem.* **1981**, *18*, 1651−1653.

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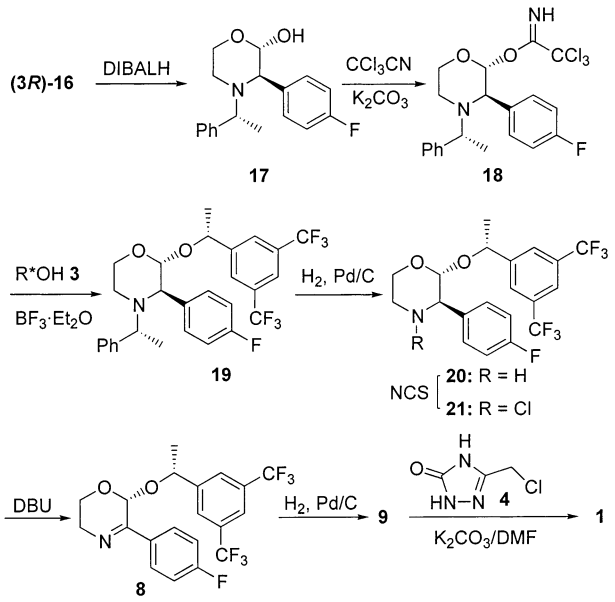
SCHEME 5. Trans Acetalization Route to *cis-sec*-Amine 9



labile under acidic conditions. This was fully explored to achieve a crystallization-driven dynamic resolution process. Since the free base **16** is an oil, crystallization of its salt with TsOH, TFA, MsOH, and HCl was screened, but only its HCl salt crystallized. Gratifyingly, when the 2/1 diastereomeric mixture of **16** was treated with HCl in *i*-PrOAc at 70 °C, the desired (3*R*)-isomer (minor) crystallized preferentially and nearly all of the other diastereomer was converted into the desired (3*R*)-isomer! A simple filtration afforded the HCl salt of oxazinone **16** in 90% yield with excellent chemical and optical purity (>98%).

Oxazinone **16** was reduced to the lactol **17** (trans/cis = 8/1) with DIBALH in a mixture of toluene and THF at −20 °C (Scheme 5). Over-reduction to the diol became significant (∼5−10%) at higher temperatures (0−5 °C). Lactol **17** was not crystalline, so it was not purified but directly activated by treatment with trichloroacetonitrile and 1.0 equiv of K_2CO_3 in toluene affording the trichloroacetimidate **18**. Since **18** is not very stable for storage, it was used directly after filtering off the K_2CO_3 and in vacuo concentration to remove the excess trichloroacetonitrile.

Among the Lewis acids and solvents examined for the acetalization, a combination of BF_3·Et_2O and toluene/THF gave the best results. Thus, treatment of **18** and the chiral alcohol **3** with a catalytic amount of BF_3·Et_2O in toluene/THF at between −30 and −20 °C afforded the trans acetalization product **19** in ∼90% overall yield (HPLC assay) from the oxazinone **16** (three steps). The *trans*/*cis* ratio was excellent (96/4) as determined by HPLC and ^{1}H NMR. Performing the reaction at −10 °C resulted in about 5% lower yield, mainly due to elimination. Compound **19** turned out to be a nicely crystalline solid, but its isolation by crystallization was hampered by its rather high solubility in most organic solvents. On the other hand, crystallization from ethanol/water proved to be very successful. After the reaction was quenched with aqueous Na_2CO_3, the organic layer was concentrated to a low volume and flushed with ethanol. Slow addition of water completed the crystallization of **19**. This isolation protocol provided complete rejection of the trichloroacetamide byproduct as well as other colored impurities with minimal loss of the product (<5%). Compound **19** was isolated in 85−87% yield with consistently high purity. The only detectable impurity was 1.5−2.5% of the cis isomer.

The chiral auxiliary on **19** was easily cleaved by Pd/C-catalyzed hydrogenolysis in the presence of a strong acid such as TsOH·H_2O, HCl, or MsOH yielding the *trans-sec*-amine **20**. Acetic acid was not very effective and resulted in incomplete conversion. Compound **20** was directly converted to the imine **8** by successive treatment with NCS and DBU in a mixture of toluene/DMF at 0 °C−rt.[9] The formation of the *N*-chloro intermediate **21** was almost instantaneous even at 0 °C, but the subsequent elimination reaction required 3 h at rt. When triethylamine was used as the base, the elimination step was much slower. The regioselectivity for the elimination was superb, and the other regioisomer was not observed. The crude solution of **8** was used directly for the hydrogenation to give the desired *cis-sec*-amine **9**. Again the stereoselectivity was excellent, and less than 1% of the trans isomer was observed. Compound **9** was isolated as its TsOH or HCl salt in 95% yield from **19**. The overall yield for the six-step process from oxazinone **16** was a remarkable 81% with an average yield of >96% per step. The key intermediate **9** has been converted into the final drug **1** by a simple alkylation with triazolinonyl chloride **4**.[10]

Conclusions

In summary, we have developed a streamlined and high-yielding synthesis of the penultimate intermediate **9** for the synthesis of aprepitant, a potent SP receptor antagonist. The key step was a highly stereoselective Lewis acid-catalyzed trans acetalization. Additionally, we have developed a new synthesis of optically pure oxazinone **16** utilizing an exceptionally efficient crystallization-driven epimerization/resolution process. This synthesis is easily scalable and cost-effective.

Experimental

Melting points were determined on an open capillary apparatus and are uncorrected. All IR spectra were recorded as thin films, and the ^{1}H NMR (250 or 400 MHz), ^{13}C NMR (62.9 or 100 MHz), and ^{19}F NMR (376.6 MHz) spectra were recorded in $CDCl_3$ unless noted. In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2, or CH_3) was determined on the basis of DEPT experiments.

Activated Lactol 2a−c. Oxazinone **5**·BCSA salt[4] (15.2 g, 25.5 mmol) was suspended in a mixture of toluene (60 mL) and saturated aqueous $NaHCO_3$ (35 mL) until all the solid was dissolved. The organic layer was separated and washed with water (2 × 30 mL) and then brine (25 mL). The residual moisture was removed by azeotropic distillation (final volume ∼30 mL). After addition of THF (25 mL) and cooling of the mixture to −20 °C, DIBALH (1.5 M in toluene, 17.9 mL, 1.05 equiv) was added over 2 h. The mixture was stirred for 0.5 h and then cannulated into saturated aqueous Rochelle salt (potassium sodium tartrate tetrahydrate) at 0−20 °C with vigorous agitation. The mixture was stirred for 5 h at room

(9) Van, T. N.; De Kimpe, N. *Tetrahedron* **2000**, *56*, 7969−7973.
(10) Cowden, C. J.; Wilson, R. D.; Bishop, B. C.; Cottrell, I. F.; Davies, A. J.; Dolling, U.-H. *Tetrahedron Lett.* **2000**, *41*, 8661−8664.

temperature, and the organic layer was separated and washed with 1:1 water/brine. It was concentrated and dried by being flushed with toluene (final volume 25 mL). The crude product was used directly for activation:

Carbamate 2a. A solution of the crude lactol (5 mmol in 5 mL) was diluted with dry THF (15 mL) under nitrogen. After the solution was cooled to −78 °C, NaHMDS (10 mL, 0.6 M, 1.2 equiv) was added. The mixture was stirred for 20 min, and then dimethylcarbamyl chloride (0.60 mL, 6.0 mmol) was added slowly. The reaction mixture was allowed to warm to 10 °C over 3 h, and then the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was diluted with toluene, and then the organic layer was separated and washed with water and brine. It was concentrated and dried by flushing with more toluene. The product crystallized from toluene upon standing: ^{1}H NMR (250 MHz) δ 7.50−7.44 (m, 2H), 7.32−7.21 (m, 5H), 7.04 (t, J = 8.7 Hz, 2H), 5.52 (d, J = 7.7 Hz, 1H), 3.95−3.90 (m, 2H), 3.71 (d, J = 13.4 Hz, 1H), 3.33 (d, J = 7.7 Hz, 1H), 2.94 (d, J = 13.4 Hz, 1H), 2.79 (s, 6H), 2.78−2.71 (m, 1H), 2.38−2.26 (m, 1H); ^{13}C NMR (62.9 MHz) δ 162.4 [(C) d, J_{C-F} = 246 Hz], 154.2 (C═O), 138.0 (C), 133.6 [(C) d, J_{C-F} = 3.1 Hz], 130.3 [(CH) d, J_{C-F} = 7.7 Hz], 128.6 (CH), 128.3 (CH), 127.1 (CH), 115.5 [(CH) d, J_{C-F} = 21.3 Hz], 96.5 (CH), 69.5 (CH), 64.9 (CH_2), 58.7 (CH_2), 50.4 (CH_2), 36.4 (CH_3), 35.7 (CH_3).

Carbonate 2b. A procedure similar to **2a** was used except that *n*-BuLi (1.6 M in hexane) was used instead of NaHMDS as the base and *i*-PrOCOCl as the electrophile. The washed organic layer was concentrated to dryness to give **2b** as an oil: ^{1}H NMR (250 MHz) δ 7.56−7.47 (m, 2H), 7.34−7.19 (m, 5H), 7.06 (t, J = 8.7 Hz, 2H), 5.52 (d, J = 7.5 Hz, 1H), 4.73 (hep, J = 6.3 Hz, 1H), 4.03−3.79 (m, 2H), 3.71 (d, J = 13.4 Hz, 1H), 3.32 (d, J = 7.5 Hz, 1H), 2.97 (d, J = 13.4 Hz, 1H), 2.79−2.71 (m, 1H), 2.38−2.27 (m, 1H), 1.24 (d, J = 6.3 Hz, 3H), 1.13 (d, J = 6.3 Hz, 3H); ^{13}C NMR (62.9 MHz) δ 162.5 [(C−F) d, J_{C-F} = 246 Hz], 152.9 (C═O), 137.9 (C), 133.0 [(C) d, J_{C-F} = 3.0 Hz], 130.6 [(CH) d, J_{C-F} = 7.8 Hz], 128.6 (CH), 128.3 (CH), 127.2 (CH), 115.5 [(CH) d, J_{C-F} = 21.4 Hz], 98.2 (CH), 72.5 (CH), 69.0 (CH), 65.0 (CH_2), 58.5 (CH_2), 50.0 (CH_2), 21.6 (CH_3).

Phosphorodiamidite 2c. The same procedure as **2b** was used except that $ClPO(NMe_2)_2$ was used as the electrophile: ^{1}H NMR (250 MHz) δ 7.49 (dd, J = 6.6, 3.5 Hz, 2H), 7.31−7.18 (m, 5H), 7.05 (t, J = 8.7 Hz, 1H), 5.21 (t, J = 7.6 Hz, 1H), 3.95−3.82 (m, 2H), 3.65 (d, J = 13.4 Hz, 1H), 3.22 (d, J = 7.5 Hz, 1H), 2.89 (d, J = 13.4 Hz, 1H), 2.71−2.63 (m, 1H), 2.57 (d, J = 10.4 Hz, 6H), 2.35−2.23 (m, 1H), 2.17 (d, J = 10.2 Hz, 6H); ^{13}C NMR (62.9 MHz) δ 162.4 [(C−F) d, J_{C-F} = 246 Hz], 138.2 (C), 134.1 [(C) d, J_{C-F} = 3.3 Hz], 130.8 [(CH) d, J_{C-F} = 8 Hz], 128.5 (CH), 128.2 (CH), 127.0 (CH), 115.4 [(CH) d, J_{C-F} = 21.3 Hz], 98.2 [(CH) d, J_{C-P} = 4.7 Hz], 71.0 [(CH) d, J_{C-P} = 9.6 Hz], 64.9 (CH_2), 58.5 (CH_2), 50.5 (CH_2), 36.3 [(CH_3) d, J_{C-P} = 3.9 Hz], 35.8 [(CH_3) d, J_{C-P} = 3.8 Hz].

(*R*)-(+)-*N*-(2-Hydroxyethyl)-α-phenylethylamine (14). A solution of ethyl oxalyl chloride (139.2 g, 1.02 mol) in dry toluene (600 mL) was added to a mixture of (*R*)-α-methylbenzylamine (121.2 g, 1.00 mol), toluene (1.5 L), and aqueous K_2CO_3 (1.0 M, 1.0 L) at 0−10 °C over 20 min. The layers were separated, and then aqueous NaOH (1.0 M, 1.2 L) was added to the organic layer; and the mixture was heated to 40−45 °C for 30 min to hydrolyze the ester **10**. The organic layer was discarded. MTBE (2.0 L) was added to the aqueous phase. The mixture was cooled to 10 °C, acidified with aqueous 5 M H_2SO_4, and then saturated with NaCl. The organic layer was separated and washed with brine. The solution was concentrated and flushed with DME to give the crude product solution that contained 214 g of **11**. It was added slowly to a suspension of $NaBH_4$ (113 g, 3.0 mol) in dry DME (600 mL) at 0 to 8 °C. A solution of H_2SO_4 in DME was prepared by slowly adding concentrated H_2SO_4 (80 mL, 1.5 mol) to cold DME (600 mL) at <−10 °C. This H_2SO_4 solution was then added to the **11**/$NaBH_4$ mixture over 2 h at <−5 °C. The mixture was warmed to 30−35 °C and stirred for 5 h. The reaction was quenched by slowly adding aqueous H_2SO_4 (1 M, 1.2 L) at 35−45 °C. DME was removed by distillation, and the mixture was cooled to 10−15 °C. MTBE was added, and the mixture was then neutralized with 50% aqueous NaOH. The MTBE layer was separated, washed with brine, concentrated, and flushed with *i*-PrOAc (assay yield of **14**, 143 g, 89%). The ^{1}H NMR spectrum of **14** was identical to that of commercial material.[5]

4-Fluorophenyl Glyoxal Hydrate (15). Aqueous HBr (48%, 442 mL, 8.84 mole) was added to a solution of 4-fluoroacetophenone (138.1 g, 1.0 mol) in DMSO (700 mL). The mixture was heated to 55−60 °C for 10−14 h under a slow sweep of nitrogen to a bleach scrubber. The reaction mixture was cooled to ∼20 °C, diluted with water, neutralized with aqueous NaOH (5 N, 570 mL), and then further neutralized to pH > 7.5 by slowly adding $NaHCO_3$ (135 g). *i*-PrOAc (2.2 L) was added, and the mixture was filtered to remove the precipitate. The *i*-PrOAc layer was separated, and the aqueous DMSO layer was extracted with more *i*-PrOAc. The combined *i*-PrOAc extract was washed with brine and then concentrated to ∼600 mL. The precipitate was filtered off to give the crude glyoxal **15** solution in 76% yield based on HPLC assay. The ^{1}H NMR spectrum agreed with literature data.[7b]

(3*R*)-[3-(4-Fluorophenyl)]-4-[(1*R*)-1-phenylethyl]-2-morpholinone Hydrochloride (16·HCl). A mixture of crude amino alcohol solution **14** (404 mL, 115.6 g, 0.70 mol), glyoxal solution **15** (∼600 mL, 130 g, 0.76 mol) and acetic acid (126 g, 2.1 mol) was heated to reflux for 2−3 h. The water generated was removed by azeotropic distillation. The reaction mixture was diluted with *i*-PrOAc to ∼1.7 L, and then HCl gas (76.6 g, 2.1 mole) was bubbled into the solution at 40−50 °C. The mixture was heated at 70−75 °C for 6−8 h to effect the crystallization-induced epimerization/resolution of the oxazinone **16**. It was cooled to 20 °C, aged for 1 h, filtered, washed with *i*-PrOAc, and air-dried to give 211 g of **16·HCl** as a white crystalline solid, 90% yield, >98% de (by ^{1}H NMR), mp 193 °C (dec). Anal. Calcd for $C_{18}H_{19}ClFNO_2$: C, 64.38; H, 5.70; Cl, 10.56; F, 5.66; N, 4.17. Found: C, 64.76; H, 5.66; Cl, 10.66; F, 5.75; N, 4.00. The HCl salt of **16** easily epimerizes in solution; therefore, its spectra and optical rotation were taken after converting it to the free amine by stirring its suspension in toluene with aqueous $NaHCO_3$ or Na_2CO_3. Free base **16**: $[\alpha]^{22}_D$ −72.2 (c 0.88, MeOH); ^{1}H NMR (400 MHz) δ 7.58 (dd, J = 8.7, 5.4 Hz, 2H), 7.38−7.32 (m, 4H), 7.29−7.25 (m, 1H), 7.11 (t, J = 87 Hz, 2H), 4.65 (s, 1H), 4.35 (td, J = 10.5, 3.7 Hz, 1H), 4.35 (dt, J = 10.7, 3.0 Hz, 1H), 3.83 (q, J = 6.8 Hz, 1H), 2.91−2.79 (m, 2H), 1.38 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100.6 MHz) δ 169.2 (C═O), 162.4 [(C−F) d, J_{C-F} = 247.1 Hz], 141.8 (C), 133.8 [(CH) d, J_{C-F} = 3.2 Hz], 130.1 [(CH) d, J_{C-F} = 8.2 Hz], 128.20 (CH), 127.3 (CH), 127.1 (CH), 115.6 [(CH) d, J_{C-F} = 21.6 Hz], 68.4 (CH_2), 66.6 (CH), 56.5 (CH), 41.0 (CH_2), 10.4 (CH_3); ^{19}F NMR (376.6 MHz) δ −114.0; IR (cm^{-1}) 2971, 1739, 1603, 1508, 1289, 1207, 1156, 1068, 1055, 998, 823, 700.

(2*S*,3*R*)-3-(4-Fluorophenyl)-4-[(1*R*)-1-phenylethyl]-2-morpholinol (17). A mixture of the oxazinone **16**·HCl (10.0 g 29.7 mmol), toluene (40 mL), and saturated aqueous $NaHCO_3$ (35 mL) was stirred until all the solid was dissolved. The organic layer was separated and washed with water and then brine. The residual moisture was removed by azeotropic distillation. After addition of THF (25 mL) and cooling of the mixture to −20 °C, DIBAL-H (1.5 M in toluene, 20.8 mL, 1.05 equiv) was added over 2 h. The mixture was stirred for 0.5 h and then cannulated into saturated aqueous Rochelle salt (25 mL) at 0−20 °C with vigorous agitation. The mixture was stirred for 2−5 h at rt, and the organic layer was separated and washed with 1/1 water/brine, flushed with toluene, and used directly for the next step. Lactol **17** was not crystalline. Removing all of the solvent gave a gel. Further drying in a vacuum oven at 80 °C and then cooling to rt afforded an amorphous solid. $[\alpha]^{22}_D$ +67.1 (c 0.76, MeOH); ^{1}H NMR (400 MHz) δ 7.53 (dd, J = 8.6, 5.5 Hz, 2H), 7.39 (d, J = 7.8 Hz, 2H), 7.33 (dd, J = 7.8, 7.3 Hz, 2H), 7.27−7.13 (m, 1H), 7.10

(dd, J = 8.9, 8.6 Hz, 2H), 4.73 (d, J = 6.9 Hz, 1H), 3.94−3.85 (m, 1H), 3.78 (q, J = 6.9 Hz, 1H), 3.72 (td, J = 11.2, 2.4 Hz, 1H), 3.47 (d, J = 7.1 Hz, 1H), 3.41 (br, 1H), 2.56 (td, J = 11.5, 3.3 Hz, 1H), 2.34 (dt, J = 11.8, 2.0 Hz, 1H), 1.25 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz) δ 162.4 [(C−F) d, J_{C-F} = 246.4 Hz], 143.0 (C), 134.3 [(C) d, J_{C-F} = 3.1 Hz], 130.3 [(CH) d, J_{C-F} = 7.9 Hz], 128.0 (CH), 127.4 (CH), 126.6 (CH), 115.5 [(CH) d, J_{C-F} = 21.1 Hz], 98.1 (CH), 69.0 (CH), 64.7 (CH_2), 54.6 (CH), 42.7 (CH_2), 8.5 (CH_3); ^{19}F NMR (376.6 MHz) δ −114.5; IR (cm^{-1}) 3381 (br), 2969, 2827, 1603, 1509, 1221, 1152, 1107, 698, 549. Anal. Calcd for $C_{18}H_{20}FNO_2$: C, 71.74; H, 6.69; F, 6.30; N, 4.65. Found: C, 71.71; H, 6.70; F, 6.46; N, 4.65.

Trichloroacetimidate 18. A mixture of crude lactol solution **17** (38 mL), K_2CO_3 (4.12 g, 1.0 equiv), and CCl_3CN (4.47 mL, 1.5 equiv) was stirred at rt for 5 h (∼95% conversion by ^{1}H NMR). The K_2CO_3 was filtered off and rinsed with toluene. The filtrate was concentrated under vacuum to give the crude **18**: ^{1}H NMR (400 MHz) δ 8.40 (s, 1H), 7.58−7.52 (m, 2H), 7.42−7.22 (m, 6H), 7.08−7.00 (m, 2H), 5.85 (d, J = 7.4 Hz, 1H), 4.04−3.98 (m, 1H), 3.91−3.80 (m, 3H), 2.67 (dt, J = 11.4, 3.4 Hz, 1H), 2.41 (dt, J = 11.4, 2.5 Hz, 1 H), 1.27 (d, J = 6.9 Hz, 3H).

Trans Acetalization to 19. Crude **18** (29.8 mmol) was slowly added to a solution of chiral alcohol **3** (7.69 g, 29.8 mmol) and BF_3·Et_2O (0.51 g, 12 mol %) in dry THF (70 mL) at <−20 °C. The mixture was stirred for 1 h, and then the reaction was quenched with a mixture of 10% Na_2CO_3/brine (6/24 mL). The organic layer was separated and concentrated and the solvent switched to EtOH (final volume ∼80 mL). Water (20 mL) was added slowly over 2 h at 50 °C, and the mixture was cooled to rt and stirred for 2 h. The product was filtered and washed with 3/1 EtOH/water. The wet cake was used directly for the next step or air-dried to give 14.3 g of the product **19**, 85% yield from **16**: mp 109−110.5 °C; $[\alpha]^{22}_D$ +97.4 (*c* 0.89, MeOH); ^{1}H NMR (400 MHz) δ 7.70 (s, 1H), 7.40−7.17 (m, 9H), 7.03−6.97 (m, 2H), 4.94 (q, J = 6.6 Hz, 1H), 4.22 (d, J = 7.3 Hz, 1H), 3.90 (ddd, J = 11.2, 3.1, 1.5 Hz, 1H), 3.74 (q, J = 6.9 Hz, 1H), 3.60 (td, J = 11.4, 2.4 Hz, 1H), 3.57 (d, J = 7.3 Hz, 1H), 2.59 (td, J = 11.6, 3.2 Hz, 1H), 2.30 (dt, J = 11.6, 1.8 Hz, 1H), 1.40 (d, J = 6.6 Hz, 3H), 1.22 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100.6 MHz) δ 162.4 [(C) d, J_{C-F} = 246.9 Hz], 145.4 (C), 142.9 (C), 133.8 [(C) d, J_{C-F} = 3.3 Hz], 131.5 [(C) q, J_{C-F} = 33.3 Hz], 130.0 [(CH) d, J_{C-F} = 7.9 Hz], 128.0 (CH), 127.5 (CH), 126.6 (CH) 126.2 [(CH) d, J_{C-F} = 2.9 Hz], 123.1 [(CF_3) q, J_{C-F} = 272.8 Hz], 121.5 [(CH) m, J_{C-F} = 3.7 Hz], 115.5 [(CH) d, J_{C-F} = 21.4 Hz], 101.6 (CH), 73.9 (CH), 67.5 (CH), 64.8 (CH_2), 54.4 (CH), 42.7 (CH_2), 24.3 (CH_3), 7.9 (CH_3); ^{19}F NMR (376.6 MHz) δ −63.1 (CF_3), −114.4; IR (cm^{-1}) 2973, 1606, 1510, 1375, 1279, 1176, 1132, 898, 838, 698, 682, 503. Anal. Calcd for $C_{28}H_{26}F_7NO_2$: C, 62.11; H, 4.84; F, 24.56, N, 2.59. Found: C, 62.00; H, 4.47; F, 24.61; N, 2.43.

***trans-sec*-Amine 20.** A solution of **19** (14.3 g, 25.3 mmol) and TsOH·H_2O (4.94 g, 1.02 equiv) in 1/1 toluene/EtOH (70 mL) was hydrogenated at 30 °C and 40 psi for 3 h in the presence of 5% Pd/C (0.7 g). The catalyst was filtered off and then rinsed with 1/1 toluene/EtOH. The filtrate was washed with 5% Na_2CO_3 and water and then used directly for the next step. Alternatively, the HCl salt was isolated by carrying out the reaction in MeOH (200 mL) in the presence of 2.50 mL of concentrated HCl (1.0 equiv). The filtrate was concentrated and the solvent switched to methyl ethyl ketone. Heptane was added until the ratio of MEK/heptane was ∼2/1 to crystallize the HCl salt of **20** in 94% yield: mp 241 °C (dec); $[\alpha]^{22}_D$ +60.4 (*c* 0.97, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11−10 (br, 2H), 7.88 (s, 1H), 7.63 (dd, J = 8.8, 5.3 Hz, 2H), 7.43 (s, 2H), 7.13 (t, J = 8.8 Hz, 2H), 5.15 (q, J = 6.5 Hz, 1H), 4.86 (d, J = 8.3 Hz, 1H), 4.25 (d, J = 8.3 Hz, 1H), 4.24−4.11 (m, 2H), 3.23−3.15 (m, 2H), 1.33 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 163.0 [(C−F) d, J_{C-F} = 246.5 Hz], 146.2 (C), 131.4 [(CH) d, J_{C-F} = 8.4 Hz], 130.6 [(C) q, J_{C-F} = 32.8 Hz], 129.4 [(CH) d, J_{C-F} = 2.8 Hz], 126.8 (CH), 123.5 [(CF_3) q, J_{C-F} = 272.2 Hz], 121.7 (CH), 115.8 [(CH) d, J_{C-F} = 21.7 Hz], 98.6 (CH), 74.6 (CH), 61.4 (CH_2), 60.6 (CH), 43.2 (CH_2), 24.6 (CH_3); ^{19}F NMR (376.6 MHz, DMSO-d_6) δ −61.7 (CF_3), −112.8; IR (cm^{-1}) 2882, 2705, 2609, 2452, 1518, 1279, 1176, 1134, 1078, 841, 683. Anal. Calcd for $C_{20}H_{19}ClF_7NO_2$: C, 50.70; H, 4.04; Cl, 7.48; F, 28.07, N, 2.96. Found: C, 50.54; H, 3.72; Cl, 7.74; F, 27.97; N, 2.86.

Imine 8. To a mixture of crude **20** (∼70 mL of solution, 25.3 mmol), DMF (20 mL), and K_2CO_3 (0.70 g, 0.20 equiv) was added NCS (3.88 g, 29.1 mmol, 1.15 equiv) in portions at 0 °C. After the mixture was stirred for 0.5 h, DBU (4.81 g, 31.6 mmol, 1.25 equiv) was added (exothermic). The mixture was allowed to warm to rt and stirred for 3 h. Water (40 mL) was added, and the organic layer was separated and washed with water. The solution of crude imine **8** was used for the hydrogenation step directly. An analytical sample of **8** was obtained by crystallization from a 10:1 heptane/toluene mixture: mp 105−106.5 °C; $[\alpha]^{22}_D$ +13.1 (*c* 0.96, MeOH); ^{1}H NMR (400 MHz) δ 7.87 (s, 1H), 7.76 (s, 2H), 7.46−7.41 (dd, J = 8.9, 5.4 Hz, 2H), 6.97 (dd, J = 8.9, 8.6 Hz, 2H), 5.12 (q, J = 6.6 Hz, 1 H), 5.10 (s, 1H), 4.11−4.04 (m, 1H), 3.91−3.88 (m, 2H), 3.83−3.78 (m, 1H), 1.55 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100.6 MHz) δ 164.0 [(C−F) d, J_{C-F} = 250.5 Hz], 161.5 (C═N), 144.8 (C), 132.6 [(C) d, J_{C-F} = 3.2 Hz], 132.0 [(C) q, J_{C-F} = 33.4 Hz], 128.4 [(CH) d, J_{C-F} = 8.6 Hz], 127.1 (CH), 123.2 [(CF_3) q, J_{C-F} = 272.9 Hz], 122.1 [(CH) m, J_{C-F} = 3.8 Hz], 115.3 [(CH) d, J_{C-F} = 21.8 Hz], 88.4 (CH), 73.1 (CH), 55.9 (CH_2), 47.9 (CH_2), 23.9 (CH_3); ^{19}F NMR (376.6 MHz) δ −63.3 (CF_3), −110.8; IR (cm^{-1}) 2985, 1640, 1594, 1507, 1373, 1289, 1279, 1120, 1067, 927, 897, 847, 707, 683. Anal. Calcd for $C_{20}H_{16}F_7NO_2$: C, 55.18; H, 3.70; F, 30.55; N, 3.22. Found: C, 55.07; H, 3.46; F, 30.46; N, 3.18.

***cis-sec*-Amine 9·HCl.** To the crude solution of imine **8** were added EtOH (25 mL) and 5% Pd/C (0.50 g). The mixture was hydrogenated under 40 psi of H_2 at rt for 2 h. The catalyst was filtered off and rinsed with toluene. TsOH·H_2O (4.55 g, 1.0 equiv) was added to the filtrate, and the mixture was azeotropically distilled to ∼60 mL under a slight vacuum at 60−80 °C. The mixture was slowly cooled to 20 °C, and then heptane (20 mL) was added. The product was collected by filtration and dried at 40 °C to give 15.3 g of the tosylate salt of the *cis-sec*-amine **9**. HPLC indicated ∼94% purity and ∼4−5% residue toluene. The overall isolated yield of **9** from the acetalization product **19** was 94% corrected for purity. Alternatively, the HCl salt was isolated by using 1.0 equiv of concentrated HCl instead of TsOH, and then the solvent was switched to MEK. Adding 0.5 volume of heptane completed the crystallization. **9·HCl**: mp 246 °C (dec); $[\alpha]^{22}_D$ +78.3 (*c* 0.78, MeOH); ^{1}H NMR (400 MHz) δ 10.89 (br d, J = 9 Hz, 1H), 10.48 (br d, J = 10 Hz, 1H), 7.67 (s, 1H), 7.57 (dd, J = 8.7, 5.0 Hz, 2H), 7.23 (s, 2H), 7.06 (dd, J = 8.5, 8.5 Hz, 2H), 4.94 (q, J = 6.6 Hz, 1H), 4.55−4.49 (m, 2H), 4.24 (d, J = 11.5 Hz, 1H), 3.84 (dd, J = 12.5, 3.4 Hz, 1H), 3.48 (d, J = 12.2 Hz, 1H), 3.30−3.20 (m, 1H), 0.93 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100.6 MHz) δ 163.4 [(C−F) d, J_{C-F} = 250.5 Hz], 144.2 (C), 131.9 [(C) q, J_{C-F} = 33.6 Hz], 130.0 [(CH) d, J_{C-F} = 8.3 Hz], 127.3 [(C) d, J_{C-F} = 3.2 Hz], 126.2 (CH), 122.9 [(CF_3) q, J_{C-F} = 272.8 Hz], 121.9 (CH), 116.1 [(CH) d, J_{C-F} = 22.0 Hz], 93.0 (CH), 73.0 (CH), 60.7 (CH), 55.2 (CH_2), 44.0 (CH_2), 24.2 (CH_3); ^{19}F NMR (376.6 MHz) δ −63.2 (CF_3), −111.3; IR (cm^{-1}) 3600−3100 (brd), 2919, 1610, 1518, 1442, 1280, 1180, 1128, 1026, 1007, 900, 838, 708, 682. Anal. Calcd for $C_{20}H_{19}ClF_7NO_2$: C, 50.70; H, 4.04; Cl, 7.48; F, 28.07; N, 2.96. Found: C, 50.73; H, 3.60; Cl, 7.78; F, 28.11; N, 2.88.

Supporting Information Available: ^{1}H and ^{13}C NMR and IR spectra for all new compounds and ^{19}F NMR for most new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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