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Synthesis of Ro 25-8210 via an Enantioselective Oxazaborolidine-Catalyzed Reduction

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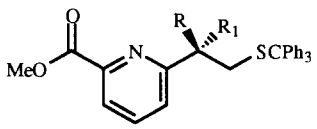
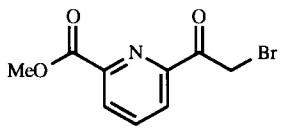
Abstract: Prochiral ketones which contain nitrogen atoms have been reduced enantioselectively with chiral oxazaborolidines in the presence of excess borane. However, the pyridine system has been shown to be a poor substrate for this asymmetric reduction. For example, catalytic reduction of 2-acetylpyridine with a chiral oxazaborolidine provided the product alcohol in only 28% ee. We wish to report the enantioselective reduction of 2-(bromoacetyl)-pyridine **1** with chiral oxazaborolidines. Good enantiomeric excess was obtained in the reductions (80% ee) and could be improved to ≥95% ee upon recrystallization. Subsequently, bromohydrin **6** was used to prepare Ro 25-8210.

Introduction

To support SAR studies in our stromelysin inhibitor project, we required a practical procedure for the preparation of enantiomers Ro 25-8210 and Ro 25-6630 in optically active form. In the past, chemists have relied on enzymatic or chemical resolution of racemic compounds to achieve such preparations. However, developments in asymmetric synthesis have allowed for commercially viable enantioselective syntheses of many important compounds. Although a number of methods have been developed for the asymmetric reduction of prochiral ketones with stoichiometric reagents[1], they suffer from a number of limitations. These limitations include their stoichiometric nature, ease of product isolation and lack of general application. Therefore, we sought a catalytic method for the enantioselective reduction of prochiral ketone **1** which could be used to prepare intermediates Ro 25-8210 and Ro 25-6630.



Ro 25-6630 R = OH, R_1 = H
Ro 25-8210 R = H, R_1 = OH

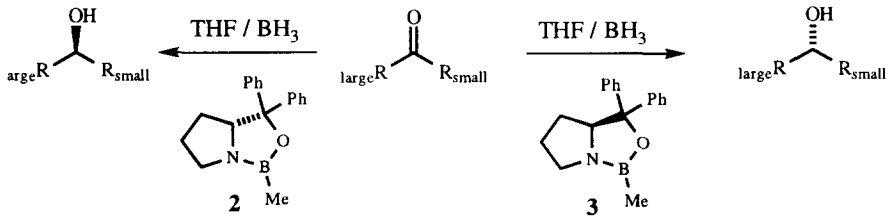


1

One of the more recent methods for the preparation of chiral secondary alcohols from prochiral ketones was reported by Corey and coworkers.[2] This procedure is especially attractive due to its catalytic nature and the high enantiomeric excess (ee) afforded with predictable absolute stereochemistry. The method employs a catalytic amount of a chiral oxazaborolidine in the presence of borane and provides the absolute stereochemistry as depicted in Scheme 1. Published examples which have successfully used this methodology include compounds which contain carbon, oxygen, halogens, sulfur and nitrogen.[3] However, Quallich and Woodall have shown that compounds containing a pyridine ring are poor substrates for this asymmetric

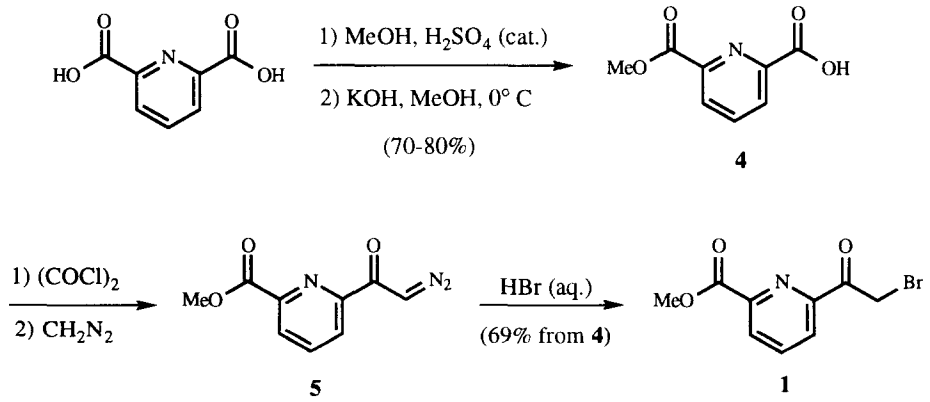
reduction.[3d] For example, catalytic reduction of 2-acetylpyridine with oxazaborolidine **2** provided the product alcohol in only 28% ee. The authors reasoned that the pyridine nitrogen was competitively coordinating with the borane and was responsible for the low enantiomeric excess observed. Coordination of borane with the pyridine nitrogen could lead to lower enantiomeric excess by activating the ketone to direct borane reduction or by intramolecular delivery of hydride to the ketone. In either case, this allows for direct borane reduction to compete with the catalyzed asymmetric reduction.

Scheme 1



Although the results of Quallich and Woodall indicate that acetylpyridines are poor substrates for the oxazaborolidine-catalyzed reduction, we felt that the electron withdrawing nature of the methyl ester at the 6-position of bromomethyl ketone **1** would reduce the basicity of the pyridine nitrogen. This would in turn suppress formation of the borane-pyridine complex and lead to higher enantiomeric excess. In addition to reducing the basicity of the pyridine nitrogen, the methyl ester would also provide more steric bulk around the basic nitrogen which would also help suppress the formation of the borane-pyridine complex.

Scheme 2



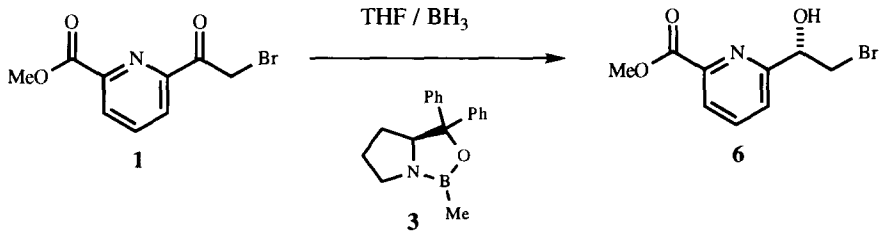
Results and Discussion

The synthesis of ketone **1** is shown in Scheme 2. Commercially available 2,6-pyridinedicarboxylic acid was converted to the dimethyl ester by a Fischer esterification with methanol in the presence of a catalytic

amount of H_2SO_4. Selective hydrolysis to the half-acid **4** was accomplished with one equivalent of KOH in methanol at 0° C for one hour followed by acidification to pH 3 with concentrated HCl.[4] This procedure, reported by Kelly and coworkers, was used to isolate the potassium salt of the half-acid. We have modified the procedure, adding the HCl work-up, so that the free acid can be isolated. The half-acid was treated with oxalyl chloride to form the acyl chloride which was then exposed to diazomethane to provide diazoketone **5**. Finally, the diazoketone was reacted with aqueous HBr[5] to afford bromomethyl ketone **1** in 60% yield from the half-acid.

With ample quantities of **1** in hand, we investigated the asymmetric reduction of this ketone with oxazaborolidine **3** under a variety of conditions. The results of this study are presented in Scheme 3. The best results were obtained using 20 mole percent of the oxazaborolidine catalyst while performing the reaction at room temperature. These findings are in concurrence with those reported by DeNinno[3a] on substrates containing a bromomethyl ketone moiety. The oxazaborolidine catalyst was prepared using a literature

Scheme 3



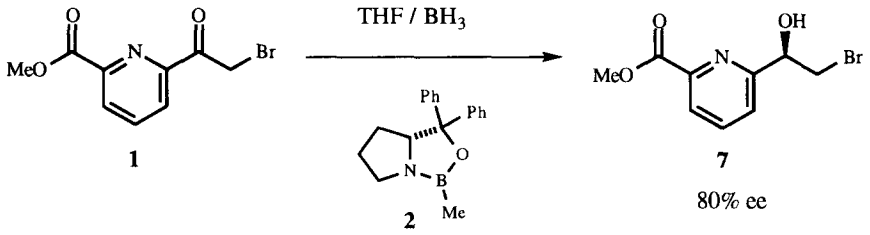
1 **3** **6**

cat. mol %	Temp.	%ee	Chem. Yield (%)
10	-20 °C	60	85
10	0 °C	66	82
10	22 °C	70	84
20	22 °C	80	86

procedure from commercially available (S)-α,α-diphenyl-2-pyrrolidinemethanol and methyl boronic acid.[3c] While 20 mole percent of the catalyst was required to achieve good ee's, we did not consider this a drawback since the catalyst precursor, (S)-α,α-diphenyl-2-pyrrolidinemethanol, could be recovered in high yield from the reaction mixture.[6] The enantiomeric excess of the reactions was determined by capillary GC analysis of the bromohydrin using a permethylated β-cyclodextrin column. Although a good enantiomeric excess was obtained in the reduction, the ee could be improved to greater than 95% upon recrystallization from methylene chloride-hexane. It is interesting to note that the initial crystals that formed in the crystallization were nearly racemic and the mother liquor contained the enantiomericly enriched material.[7] The absolute stereochemistry of bromohydrin **6** was determined by single crystal X-ray analysis[8] on a crystal grown from methylene chloride-hexane and is in agreement with the Corey model.[2a] Similarly, ketone **1** could be reduced with 20

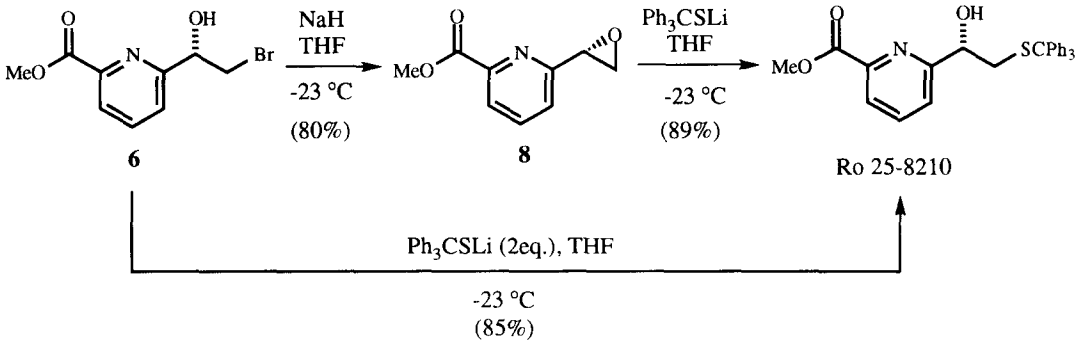
mole percent of oxazaborolidine **2** at room temperature to produce bromohydrin **7** in 80% ee (Scheme 4) and recrystallization from methylene chloride-hexane improved the ee to greater than 95%.

Scheme 4



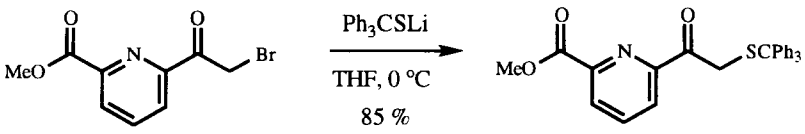
The synthesis of intermediate Ro 25-8210 was achieved via two routes (Scheme 5). Bromohydrin **6** was converted to epoxide **8** upon treatment with sodium hydride at -23 °C in THF. At this point, the crystalline epoxide could be recrystallized to further improve the enantiomeric excess. Subsequent opening of the epoxide with the lithium salt of triphenylmethyl mercaptan in THF at -23 °C provided intermediate Ro 25-8210. Alternatively, the bromohydrin could be transformed directly to Ro 25-8210 in 85% yield upon reaction with two equivalents of the lithium salt of triphenylmethyl mercaptan. Likewise, bromohydrin **7** was converted to intermediate Ro 25-6630 in one step using two equivalents of the lithium salt of triphenylmethyl mercaptan.

Scheme 5



After investigating the asymmetric reduction of bromomethyl ketone **1**, it occurred to us that we should be able to carry out the catalytic asymmetric reduction on ketone **9** (Scheme 6) and possible obtain even higher enantiomeric excess as compared to the bromohydrins. The reaction of bromomethyl ketone Ro 25-6142 with the lithium salt of triphenylmethyl mercaptan at 0 °C provided thioketone **9** in 85% yield. The oxazaborolidine catalyzed reduction of ketone **9**, using borane-THF complex as the hydride source, afforded the desired alcohol in good yield. However, we were not able to purify the alcohol. Apparently, the product

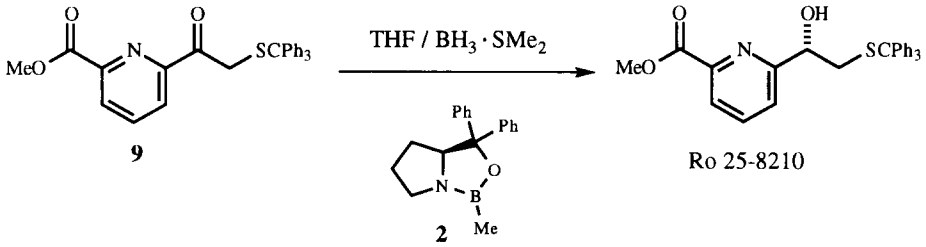
Scheme 6



Ro 25-6142 **9**

was complexed with borane and this complicated all attempts to purify it. We made several attempts to free the product of borane after the reaction was complete, using a variety of work-up conditions without success. Fortunately, we were able to circumvent the problem using borane-methyl sulfide as the hydride source in the asymmetric reduction of thioketone **9**. We performed a series of experiments to determine the optimal conditions for the reduction using oxazaborolidine catalyst **3** and these results are shown in Scheme 7. The highest enantiomeric excess (90%) was obtained when the reduction was carried out at -15 °C using 20 mole

Scheme 7



9 **2** Ro 25-8210

cat. mol %	Temp.	%ee	Chem. Yield (%)
10	22 °C	70	85
10	0 °C	74	88
10	-15 °C	81	89
20	-15 °C	90	89

percent of catalyst **3** and one equivalent of borane-methyl sulfide complex. Using less than one equivalent of the borane-methyl sulfide complex resulted in recovery of unreacted ketone. Performing the reaction at higher temperatures or with less than 20 mole percent of catalyst led to lower enantiomeric excess. The enantiomeric excess of this reduction was determined by reversed-phase HPLC analysis using a Cyclobond I RSP column. Unfortunately, recrystallization from various solvents did not significantly increase the enantiomeric excess of this compound.

In conclusion, we have demonstrated that the asymmetric oxazaborolidine-catalyzed reduction of ketones can be accomplished in good enantiomeric excess in the presence of a pyridine nitrogen with reduced basicity. Additional steric bulk around the basic nitrogen may also play a role in improving the enantiomeric excess of the reduction by hindering the formation of a borane-nitrogen complex. As mentioned previously, Ro 25-8210 and Ro 25-6630 have been used to prepare inhibitors of the matrix metalloproteinase stromelysin-1.[9] The X-ray crystal structure of one of these compounds bound to stromelysin-1 and detailed pharmacological studies of these inhibitors will be reported elsewhere.

Acknowledgments: We wish to thank Dr. Larry Courtney for providing several grams of oxazaborolidine **3** used in our initial asymmetric reductions. Also, we would like to thank Ms. A.-M. Chiu and Dr. L. Todaro for performing the X-ray analysis; Mr. J. De Gasperi and Mr. P. Riggio for performing GC and HPLC analyses.

Experimental Section

Methods and Materials. All reactions were run under an argon atmosphere, unless noted otherwise, with distilled solvents in vacuum flame-dried glassware. THF and ether were distilled from sodium/benzophenone ketyl; dimethylformamide and methylene chloride were distilled from calcium hydride. Reagent grade methanol was used without further purification. Borane-THF, borane-methyl sulfide and n-butyllithium were purchased from Aldrich Chemical Co. and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck pre-coated silica gel plates. E. Merck silica gel, particle size 0.040-0.063 mm, was used for flash column chromatography and was carried out according to the procedure of Still[10]; certified A.C.S. or HPLC grade solvents were used as eluants.

Proton NMR spectra were recorded on a Varian XL-200 or Varian Unity Plus-400 spectrometer. Chemical shifts are recorded in δ values relative to tetramethylsilane ($\delta = 0$) for proton spectra. Infrared spectra were recorded on a Bio-Rad model FTS-60A spectrophotometer. Low resolution and high resolution mass spectra were measured on a VG 70E-HF analytical or VG AutoSpec analytical spectrometer. Optical rotations were measured on a Perkin-Elmer model 241 polarimeter. Microanalyses were performed by Robertson-Microlit Laboratories (Madison, NJ).

Preparation of half-acid 4. A solution of 2,6-pyridinedicarboxylic acid (316 g, 1.89 mol), 4.00 ml of concentrated H_2SO_4, and 1.5 liters of methanol was heated to 70 °C for two days. The reaction mixture was cooled to room temperature then neutralized with a solution of saturated $NaHCO_3$. The methanol was removed *in vacuo* and the residue was dissolved in chloroform. The organic phase was washed with H_2O, washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude dimethyl ester (303 g, 83%) was used in the next step without further purification.

To a solution of the dimethyl ester (75.0 g, 380 mmol) in 2.5 liters of methanol at 0 °C was added KOH pellets (24.6 g, 380 mmol) and the resulting solution was stirred for 2h at 0 °C. The reaction mixture was warmed to room temperature and the methanol was removed *in vacuo*. Ethyl acetate was added to the residue and the potassium salt was collected by filtration. The potassium salt was dissolved in water and acidified (pH 3) with concentrated HCl. The aqueous solution was extracted (4 x 500 ml) with $CHCl_3$. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Recrystallization of the crude carboxylic acid from 2-propanol provided **4** (59.0 g, 85%) as a white solid: mp. 148-150 °C; IR ($CHCl_3$) 3330

(br), 3028, 2956, 1774, 1731, 1493, 1364, 1277, 1225, 1164, 1127, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.04 (s, 3 H), 8.14 (t, *J* = 7.8 Hz, 1 H), 8.37 (d, *J* = 6.8 Hz, 1H), 8.42 (d, *J* = 7.8 Hz, 1H); high resolution mass spectrum *m/z* 182.0456 [$(M+H)^+$; Calcd for $C_8H_8NO_4$: 182.0453].

Preparation of diazoketone 5. To a suspension of **4** (20.0 g, 0.110 mole), DMF (1 ml, cat.) and 200 ml of THF at 0 °C was added dropwise oxalyl chloride (14.7 g, 0.116 mole). The resultant solution was stirred at 0 °C for 1.5 h then warmed to room temperature. The THF was removed *in vacuo* to afford the crude acyl chloride (22.0 g). The crude acyl chloride was used in the next step without further purification.

A solution of the crude acyl chloride (22.0 g, 0.110 mole) in $CHCl_3$ (150 ml) was added dropwise to a solution of diazomethane (generated from 40.0 g of 1-methyl-3-nitro-1-nitrosoguanidine, 0.280 mole) in ether (600 ml) at 0 °C. The resultant solution was stirred for 30 min. at 0 °C then warmed to room temperature. Nitrogen gas was bubbled through the reaction mixture for 1h to remove excess diazomethane and then the reaction mixture was concentrated *in vacuo* to afford crude **5** (22 g) as a brown solid. An analytical sample was prepared by recrystallization of 0.5 g of this material from methanol: IR ($CHCl_3$) 3126, 3021, 2112 (diazo stretching), 1726, 1631, 1438, 1366, 1140 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 3 H), 5.21 (s, 0.1 H), 6.88 (s, 0.9 H), 8.02 (t, *J* = 7.8 Hz, 1 H), 8.27 (d, *J* = 7.8 Hz, 2H).

Preparation of bromomethyl ketone 1. Diazoketone **5** (22 g, crude) was added to a round bottom flask (250 ml) and cooled to 0 °C. Hydrogen bromide (48% aqueous solution) was added dropwise to the reaction flask until all of the diazoketone had dissolved (~80 ml). The resultant solution was stirred for 30 min. at 0 °C and then allowed to warm to room temperature. The reaction mixture was made basic by slow addition of saturated $NaHCO_3$ solution and the resultant aqueous solution was extracted with ethyl acetate (4 x 200 ml). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, using hexane-ethyl acetate (9:1 then 5:1), provided **5** (19.6 g, 69% from **4**) as a light brown solid: mp. 79-81 °C; IR ($CHCl_3$) 3028, 3016, 2955, 1722, 1707, 1437, 1328, 1295, 1251, 1158, 1139, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.04 (s, 3 H), 4.97 (s, 2H), 8.04 (t, *J* = 7.8 Hz, 1 H), 8.26 (dd, *J* = 1.1 and 7.8 Hz, 1H), 8.32 (dd, *J* = 1.1 and 7.8 Hz, 1H); mass spectrum *m/z* 257 (M+). Anal. Calcd for $C_9H_8NO_3Br$: C, 41.88; H, 3.12; N, 5.43; Br, 30.96. Found: C, 42.01; H, 3.04; N, 5.47; Br, 30.69.

Preparation of ketone 9. To a solution of triphenylmethyl mercaptan (20.8 g, 75.3 mmol) in THF (250 ml) at 0 °C was added n-butyllithium (47.1 ml, 1.6M in hexane, 75.3 mmol) dropwise. The resultant suspension was stirred for 30 min. at 0 °C. A THF (25 ml) solution of bromide **1** (19.4 g, 75.3 mmol) was added dropwise to the reaction mixture at 0 °C. The resultant solution was allowed to slowly warm to room temperature and stirred for 1h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (50 ml) and the resultant heterogeneous mixture diluted with ethyl acetate (350 ml). The aqueous layer was separated and extracted with ethyl acetate (3 x 150 ml). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was passed through a short column of silica gel, using hexane-ethyl acetate (3:1), and then recrystallized from hexane-ethyl acetate (5:1) to provide ketone **9** (29.0 g, 85%) as a light brown solid. mp. 119-121 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 2 H), 4.00 (s, 3H), 7.19 (t, *J* = 6.7 Hz, 3 H), 7.26 (t, *J* = 8.0 Hz, 6H), 7.45 (d, J = 8.0 Hz, 6H), 7.93 (t, J = 7.7 Hz, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 8.22 (d, *J* = 7.7 Hz, 1H); high resolution mass spectrum *m/z* 454.1474

[$(M+H)^+$; Calcd for $C_{28}H_{24}NO_3S$: 454.1477]. Anal. Calcd for $C_{28}H_{23}NO_3S$: C, 74.15; H, 5.11; N, 3.09; S, 7.07. Found: C, 73.98; H, 5.07; N, 3.05; S, 7.00.

Asymmetric Reduction of Bromomethyl Ketone 1: Preparation of bromohydrin (S)-(+)-6. To a solution of bromomethyl ketone **1** (3.00 g, 11.6 mmol), (S)-oxazaborolidine[3c] **3** (644 mg, 2.32 mmol) and THF (15 ml) was added borane-THF (7.00 ml, 1M in THF, 7.00 mmol) dropwise. The resultant solution was stirred at room temperature for 30 min. and then cooled to 0 °C. The reaction was quenched by cautious addition of methanol (20 ml). After complete addition of methanol, the reaction mixture was warmed to room temperature and stirred for 4h. The resultant solution was concentrated *in vacuo*, the residue diluted with methanol (200 ml), and concentrated again to remove any remaining volatile boron species. Purification by flash column chromatography, using hexane-ethyl acetate (2:1), provided (+)-**6** (2.6 g, 86%) in 80% enantiomeric excess as a white powder. Recrystallization from hexane-methylene chloride afforded (+)-**6** (2.0 g) in ≥ 95% ee. mp. 95-100 °C; $[\alpha]_D^{22}$ +28.1° (c 1.08, $CHCl_3$); IR ($CHCl_3$) 3400, 3026, 3017, 2956, 1727, 1591, 1439, 1321, 1297, 1242, 1226, 1197, 1161, 1141, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (dd, *J* = 6.2 and 10.3 Hz, 1H), 3.83 (dd, *J* = 4.7 and 10.3 Hz, 1H), 3.90 (br s, 1H), 4.00 (s, 3H), 5.08-5.13 (br m, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.90 (t, *J* = 7.7 Hz, 1 H), 8.08 (d, *J* = 7.7 Hz, 1H); mass spectrum *m/z* 259 (M+). Anal. Calcd for $C_9H_{10}NO_3Br$: C, 41.56; H, 3.88; N, 5.39. Found: C, 41.72; H, 3.75; N, 5.31.

Continued elution with ethyl acetate-methanol (9:1 then 7:1) afforded the (S)-diphenylprolinol (465 mg).

Asymmetric Reduction of Bromomethyl Ketone 1: Preparation of bromohydrin (S)-(-)-7. To a solution of bromomethyl ketone **1** (3.00 g, 11.6 mmol), (R)-oxazaborolidine[3c] **2** (644 mg, 2.32 mmol) and THF (15 ml) was added borane-THF (7.00 ml, 1M in THF, 7.00 mmol) dropwise. The resultant solution was stirred at room temperature for 30 min. and then cooled to 0 °C. The reaction was quenched by careful addition of methanol (20 ml). After complete addition of methanol, the reaction mixture was warmed to room temperature and stirred for 4h. The resultant solution was concentrated *in vacuo*, the residue diluted with methanol (200 ml), and concentrated again to remove any remaining volatile boron species. Purification by flash column chromatography, using hexane-ethyl acetate (2:1), provided (-)-**7** (2.5 g, 83%) in 80% enantiomeric excess as a white powder. Recrystallization from hexane-methylene chloride afforded (-)-**7** (1.9 g) in ≥ 95% ee: $[\alpha]_D^{22}$ -28.9° (c 1.10, $CHCl_3$).

Continued elution with ethyl acetate-methanol (9:1 then 7:1) afforded the (R)-diphenylprolinol (440 mg).

Determination of Enantiomeric Purity for the Bromohydrins. A racemic sample of the bromohydrin (the bromomethyl ketone was reduced with $NaBH_4$ to provide the bromohydrin as a racemate) was used to determine the optimal parameters for the separation of the enantiomers. The enantiomeric purity of the bromohydrins, **6** and **7**, was determined by analytical gas chromatography (GC) using a permethylated β-cyclodextrin column [25 m x 0.32 mm column; hydrogen carrier gas; isothermal temp. = 150 °C; flow = 24.6 cm/sec; solvent = CH_2Cl_2; concentration = 0.6%, volume = 5.0 mL]. Retention times (t_R) and integrals were obtained from a Hewlett-Packard 3396A integrator. GC analysis: (R)-(-)-**7** t_R = 80.6 min., (S)-(+)-**6** t_R = 83.2 min.

Preparation of epoxide (S)-(+)-8. To a suspension of 95% NaH (91 mg, 3.8 mmol) in THF (20 ml) at -23 °C was added dropwise a THF (8 ml) solution of bromohydrin (S)-(+)-**6** (1.0 g, 3.8 mmol). After the

addition was complete, the resultant solution was stirred at - 23 °C for 15 min. and then allowed to warm to 22 °C. The reaction mixture was quenched with sat. NH_4Cl solution (5 ml) and diluted with ethyl acetate (100 ml). The aqueous layer was separated and back extracted with ethyl acetate (2 x 50 ml). The combined organic layer was washed with sat. brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, using hexane-ethyl acetate (4:1), afforded (S)-(+)-**8** (545 mg, 80%) as a white solid in ≥ 95% ee. mp. 56-57 °C; $[\alpha]_D^{22}$ +43.7° (c 1.07, $CHCl_3$); IR ($CHCl_3$) 3027, 1728, 1596, 1463, 1443, 1314, 1297, 1241, 1232, 1196, 1138, 996, 973, 900, 860, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.84 (dd, *J* = 2.4 and 5.5 Hz, 1H), 3.22 (t, *J* = 5.5 Hz, 1H), 4.03 (s, 3H), 4.20 (dd, J = 2.4 and 5.5 Hz, 1H), 7.39 (d, *J* = 7.3 Hz, 1H), 7.85 (t, *J* = 7.9 Hz, 1 H), 8.08 (d, *J* = 6.9 Hz, 1H); mass spectrum *m/z* 179 (M+). Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.58; H, 5.06; N, 7.56.

Preparation of alcohol (S)-(-)-Ro 25-8210 from epoxide 8. To a solution of triphenylmethyl mercaptan (4.12 g, 14.9 mmol) in THF (30 ml) was added dropwise a 1.6 M hexane solution of n-butyllithium (9.00 ml, 14.4 mmol) at 0 °C. The mixture was stirred for 20 min. at 0 °C and the resultant suspension was transferred to an addition funnel. To a solution of **8** (2.42 g, 13.5 mmol) in THF at -23 °C was added dropwise a suspension of the lithium salt of the mercaptan in THF. After the addition was complete, the resultant solution was stirred at - 23 °C for 10 min. and then allowed to warm to 22 °C over a period of 1 h. The reaction mixture was quenched with sat. NH_4Cl solution (10 ml) and diluted with ethyl acetate (100 ml). The aqueous layer was separated and back extracted with ethyl acetate (2 x 50 ml). The combined organic layer was washed with sat. brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, using hexane-ethyl acetate (3:1 then 2:1), afforded (S)-(-)-**Ro 25-8210** (5.49 g, 89%) as a white powder. mp. 141-143 °C; $[\alpha]_D^{22}$ -40.4° (c 1.11, $CHCl_3$); IR ($CHCl_3$) 3400, 3025, 3015, 2980, 2940, 1725, 1593, 1490, 1443, 1320, 1290, 1245, 1161, 1141, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.70 (d, *J* = 6.2 Hz, 2H), 3.82 (d, *J* = 5.8 Hz, 1H), 3.98 (s, 3H), 4.47-4.54 (m, 1H), 7.18-7.29 (m, 9H), 7.40-7.45 (m, 7H), 7.44 (t, *J* = 7.8 Hz, 1 H), 7.99 (d, *J* = 7.8 Hz, 1H); high resolution mass spectrum *m/z* 456.1668 [$(M+H)^+$; Calcd for $C_{28}H_{26}NO_3S$: 456.1634]. Anal. Calcd for $C_{28}H_{25}NO_3S$: C, 73.82; H, 5.53; N, 3.07; S, 7.04. Found: C, 73.76; H, 5.46; N, 3.05; S, 6.88.

Preparation of (S)-(-)-Ro 25-8210 from bromohydrin 6. To a solution of triphenylmethyl mercaptan (531 mg, 1.92 mmol) in THF (5 ml) was added dropwise a 1.6 M hexane solution of n-butyllithium (1.06 ml, 1.69 mmol) at 0 °C. The mixture was stirred for 20 min. at 0 °C and the resultant suspension was transferred to an addition funnel. To a solution of **6** (200 mg, 0.770 mmol) in THF at -23 °C was added dropwise a suspension of the lithium salt in THF. After the addition was complete, the resultant solution was stirred at - 23 °C for 10 min. and then allowed to warm to 22 °C over a period of 1 h. The reaction mixture was quenched with sat. NH_4Cl solution (10 ml) and diluted with ethyl acetate (100 ml). The aqueous layer was separated and back extracted with ethyl acetate (2 x 50 ml). The combined organic layer was washed with sat. brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography, using hexane-ethyl acetate (3:1 then 2:1), afforded (S)-(-)-**Ro 25-8210** (298 mg, 85%) as a white powder.

Asymmetric reduction of ketone 9. Preparation of (S)-(-)-Ro 25-8210. To a solution of ketone **9** (0.38 g, 0.84 mmol), (S)-oxazaborolidine[3c] **3** (46.0 mg, 0.17 mmol) and THF (4 ml) at -23 °C was added dropwise borane-$S(CH_3)_2$ (0.42 ml, 2M in THF, 0.84 mmol). The resultant solution was stirred at -23 °C for 3.5 hours and then warmed to 0 °C. The reaction was quenched by careful addition of methanol (5 ml). After

complete addition of methanol, the reaction mixture was warmed to room temperature and stirred overnight. The resultant solution was concentrated *in vacuo*, the residue diluted with methanol (50 ml), and concentrated again to remove any remaining volatile boron species. Purification by flash column chromatography, using hexane-ethyl acetate (3:1), provided (-)-**Ro 25-8210** (340 mg, 89%) in 90% enantiomeric excess as a white powder: $[\alpha]_D^{22}$ -34.6° (c 1.20, $CHCl_3$).

The enantiomeric purity of (-)-**Ro 25-8210** was determined by reversed-phase HPLC using a Cyclobond I RSP column (25 cm x 4.6 mm with 5 mm media). The chiral phase is a composite formed by reaction of β-cyclodextrin with racemic propylene oxide. Operating conditions: an isocratic mobile phase consisting of 40% methanol and 60% buffer (pH 4) [0.1% triethylamine in water adjusted with glacial acetic acid], flow = 0.5 ml/min. and uv detection at 220 nM. HPLC analysis: (-)-**Ro 25-8210** t_R = 40.2 min., (+)-**Ro 25-6630** t_R = 44.3 min.

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7) For a recent example in which a racemate is removed through crystallization, see: Imperiali, B. and Fisher, S. L. *J. Org. Chem.* **1992**, *57*, 757.

8) The absolute configuration of bromohydrin **6** is based on the anomalous scattering of the bromine atom and was established by refining both enantiomers. The final weighted R values were 0.0680 for the S configuration and 0.0746 for its antipode. Thus, by Hamilton's test, the S configuration is absolute.

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