Practical Synthesis of an Enantiomerically Pure *trans*-4,5-Disubstituted 2-Pyrrolidinone via Enzymatic Resolution. Preparation of the LTB_4 Inhibitor BIRZ-227†

Nathan K. Yee,* Laurence J. Nummy, Denis P. Byrne, Lana L. Smith, and Gregory P. Roth

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

Received August 28, 1997[⊗]

A practical synthesis of the enantiomerically pure BIRZ-227 (**1**), a LTB_4 inhibitor, has been developed. The key steps include the effective synthesis of the *trans*-diarylpyrrolidinone (±)-**8** and the enzymatic resolution of *N*-acetoxymethyl pyrrolidinone (±)-**10** by immobilized Lipase Novozym 435. Reduction of pyrrolidinone (+)-**8** with borane and subsequent coupling with chlorobenzoxazole **2** furnished BIRZ-227 in high enantiomeric purity (99% ee). The overall process described herein required no chromatographic separation and is amenable to the preparation of multikilogram quantities of the desired drug candidate in a cost-effective manner.

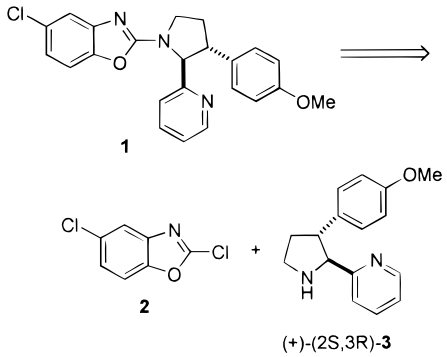
Introduction

For at least 2 decades considerable research has been centered on the discovery of compounds that inhibit the arachidonic acid cascade. One particular strategy involves the inhibition of leukotriene biosynthesis, and this area has been well-reviewed in the literature.[1] Several years ago our inflammatory disease group discovered a potent class of *cis*- and *trans*-diaryl pyrrolidines that inhibit this biosynthetic pathway, specifically the synthesis of leukotriene B_4.[2] Such compounds can be useful for the treatment of inflammatory disorders such as asthma, arthritis, inflammatory bowel disease, and psoriasis. During the preclinical evaluation of this series, a potential clinical candidate, BIRZ-227 (**1**), emerged, thus initiating the need for large quantities of enantiomerically pure material for further development.

Simple retrosynthetic analysis indicates that **1** can be split into two subunits (Scheme 1), the benzoxazole **2** and the chiral pyrrolidine **3**. In the initial synthesis,[2] 1,3-cycloaddition[3] of an azaallyl anion with 4-methoxystyrene furnished a racemic mixture of the *cis*- and *trans*-diaryl pyrrolidines which could be separated after tedious chromatography. Following reaction with a substituted chlorobenzoxazole **2**, milligram quantities were then purified using chiral HPLC to furnish material for initial biological assay. Multigram quantities of (+)-**1** were prepared through scaling up the 1,3-dipolar cycloaddition chemistry and a method of resolving racemic **3** using (−)-diacetone-2-keto-L-gulonic acid.[4]

This protocol allowed for the synthesis of essentially enantiomerically pure material but was limited for additional scale-up since several recrystallizations (five or six) were required to reach an acceptable enantiomeric excess with a modest overall yield (∼10%). In addition, the 1,3-dipolar cycloaddition step required reaction temperatures below −60 °C, which is impractical for large-scale production. These parameters initiated our decision to find an alternative synthetic route that ultimately could be demonstrated in the pilot plant. In this paper, we will detail a large-scale synthesis of the enantiomerically pure BIRZ-227 (**1**).

Scheme 1



Results and Discussion

Synthesis of Racemic Substrate. In a previous paper[5] we outlined a practical and general method for the preparation of racemic *trans*-4,5-disubstituted 2-pyrrolidinones, which was based on Michael addition of a Schiff base anion to a substituted cinnamate using phase transfer catalysis (PTC) conditions.[6] The one-pot procedure to (±)-**8** started from commercially available 2-(aminomethyl)pyridine (**4**, Scheme 2). The Schiff base **5** was

† Dedicated to Professors Robert M. Coates and Frederick E. Ziegler on the occasion of their 60th birthday.

[⊗] Abstract published in *Advance ACS Abstracts,* December 15, 1997.

(1) (a) Recent reviews: Musser, J. H.; Kreft, A. F. *J. Med. Chem.* **1992**, *35*, 2501. (b) Summers, J. B. *Drug News Perspect.* **1990**, *3*, 3517.

(2) (a) Pal, K.; Behnke, M.; Adams, J. US Patent 5594008, 1/14/97. (b) Pal, K.; Behnke, M. L.; Tong, L. *Tetrahedron Lett.* **1993**, *34*, 6205.

(3) For 1,3-cycloaddition chemistry of azaallyl anion see: Pearson, W. H.; Szura, D. P.; Postich, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 1329.

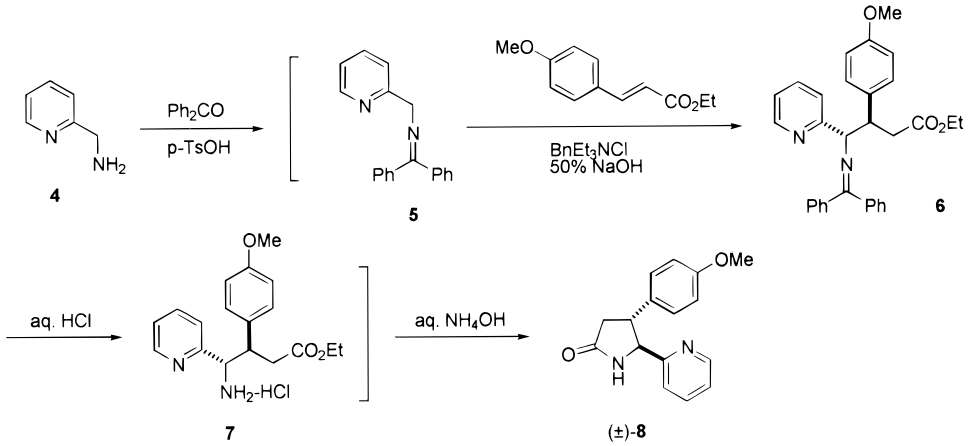
(4) Roth, G. P.; Emmanuel, M.; Tong, L. *Tetrahedron Asymmetry* **1997**, *8*, 185.

(5) Yee, N. K. *Tetrahedron Lett.* **1997**, *38*, 5091 and references therein.

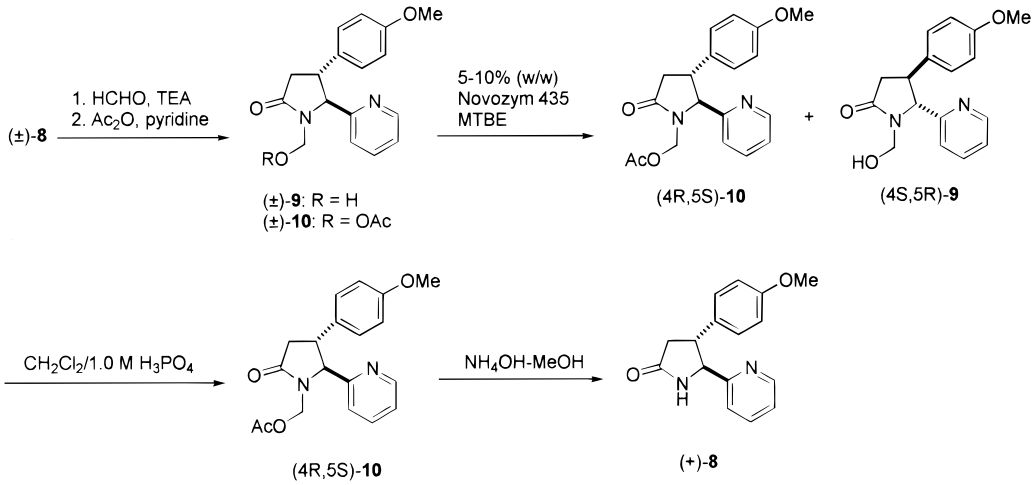
(6) For phase transfer catalysis reactions of benzylidenebenzylamine with cinnnamic acid derivatives, see: Potapov, V. M.; Gracheva, R. A.; Sivova, N. A. *Zh. Org. Khim.* **1989**, *25*, 1876. For stereoselective Michael additions of metal enolates of α-amino ester, see: (a) Tatsukawa, A.; Dan, M.; Ohbatake, M.; Kawatake, K.; Fukata, T.; Wada, E.; Kanemasa, S.; Kakei, S. *J. Org. Chem.* **1993**, 58, 4221. (b) Kanemasa, S.; Uchida, O.; Wada, E. *J. Org. Chem.* **1990**, *55*, 4411.

S0022-3263(97)01605-8 CCC: $15.00
Published on Web 01/23/1998

Scheme 2



Scheme 3



prepared from **4** and benzophenone in the presence of a catalytic amount of *p*-toluenesulfonic acid under azeotropic conditions. The PTC reaction was carried out by direct addition of ethyl 4-methoxycinnamate, 5 mol % of $BnEt_3NCl$, and 0.5 equiv of aqueous 50% NaOH to the above Schiff base at room temperature to form Michael adduct **6**.[7] Acidic hydrolysis of **6** with aqueous HCl followed by neutralizing the HCl salt of amino ester **7** with concentrated NH_4OH afforded the desired 2-pyrrolidinone (±)-**8**. On a 65 mol scale, 9.1 kg of (±)-**8** (52% yield[8] from **4**, trans:cis = 93:7) was obtained in the first crop as a crystalline solid by a single crystallization directly from the reaction mixture. The relative stereochemistry of the corresponding pyrrolidine **3**, prepared by borane reduction of **8**, was identical with that reported previously.[5]

Even though the trans:cis ratio of (±)-**8** could be enriched by recrystallization at this point, it was found the undesired cis isomer can be easily removed in the later stage of the synthesis and hence the product (±)-**8** (trans:cis = 93:7) was used directly for the next step without further purification.

Enzymatic Resolution and Separation of the Resolved Mixture. As mentioned earlier, chemical resolution of (±)-**3** with (−)-diacetone-2-keto-L-gulonic acid proved to be inefficient in terms of operation and cost. At this point in our development of the process, we explored the possibility of using enzymatic methods to resolve a derivative of (±)-**8**. Lipase-catalyzed enantioselective hydrolysis of racemic *N*-acyloxymethyl-2-azetidinones was previously reported.[9] Limited reports have appeared on an analogous resolution of 2-pyrrolidinone derivatives.[10] Therefore, we investigated this enzymatic resolution strategy for (±)-**10** (Scheme 3).

The synthesis of racemic *N*-acyloxymethylated 2-pyrrolidinone (±)-**10** is straightforward. Hydroxymethylation (37% CH_2O in H_2O, TEA, THF)[11] of (±)-**8** followed by acylation (Ac_2O, pyridine) gave the desired substrate (±)-**10** in 96% yield. Our initial enzymatic resolution of (±)-**10** was conducted according to the literature procedure,[9a] except that immobilized Novozym 435[12] was used (0.2 M in $(i\text{-}Pr)_2O-H_2O$, 50 wt % Novozym 435, rt).

(7) Michael adduct **6** can be isolated and characterized see ref 5.

(8) The actual yield of (±)-**8** was estimated to be ~70% by flash column chromatography, see ref 5.

(9) (a) Nagai, H.; Shiozawa, T.; Achiwa, K.; Terao, Y. *Chem. Pharm. Bull.* **1993**, *41*, 1933; **1992**, *40*, 2227. (b) Csomos, P.; Kanerva, L. T.; Bernath, G.; Fulop, F. *Tetrahedron Asymmetry* **1996**, *7*, 1789. (c) Oumoch, S.; Rousseau, G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2841.

(10) (a) Nakano, H.; Iwasa, K.; Okuyama, Y.; Hongo, H. *Tetrahedron Asymmetry* **1996**, *7*, 2381. (b) Jouglet, B.; Rousseau, G. *Tetrahedron Lett.* **1993**, *34*, 2307.

(11) Patthy, A.; Vezer, C. *J. Heterocycl. Chem.* **1989**, *26*, 133.

(12) Novozym 435 was purchased from Novo Nordisk Co.

(13) (a) The percent ee reported in the text refers only to the trans-isomer. (b) Chiral HPLC column, Daicel Chiralpak AS (4.6 mm × 25 cm); mobile phase, 25% (v/v) absolute ethanol in hexane, isocratic, 1.0 mL/min; ambient temperature. Retention times: (4*S*,5*R*)-**9**, 11.65 min; (4*R*,5*S*)-**9**, 13.09 min; (4*S*,5*R*)-**10**, 19.65 min; (4*R*,5*S*)-**10**, 24.58 min; (+)/(−)-**8**, 32.15 min.

The progress of the reaction and the enantiomeric excess of **9** and **10** were monitored by a chiral HPLC method.[13] When completed, the desired (4*R*,5*S*)-**10** was obtained in 32% yield (97% ee) after flash chromatography. Lipase PS-30[14] was also tested and succeeded in resolution of **10**, but the isolation of product was problematic due to the fact that the enzyme was not immobilized. Therefore, the commercially available and inexpensive immobilized Novozym 435 was preferred in the process development.

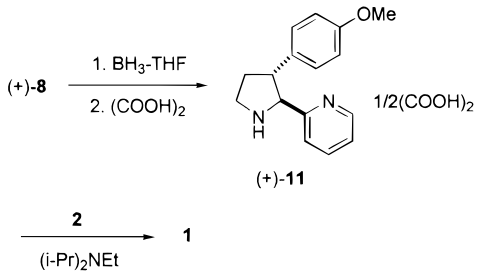
To achieve a process suitable for larger scale in terms of safety, throughput, and cost, we screened a variety of reaction parameters focusing on solvent, concentration, enzyme load, and reaction temperature. The optimized conditions (10−200 g scale) are realized as follows: Substrate (±)-**10** was dissolved in methyl *tert*-butyl ether (MTBE) at a 1.0 M concentration, and it was observed that the use of 5 wt % of Novozym 435 and 3 equiv of water were sufficient to achieve 62% conversion at 40 °C after 4 days. The enantiomeric enrichment of (4*R*,5*S*)-**10** was determined to be 97% ee while (4*S*,5*R*)-**9** was 57% ee. The desired (4*R*,5*S*)-**10** was obtained in 35% yield by flash chromatography. No attempt was made to recycle the enzyme.

In the larger scale batch, 10.5 kg of crude (±)-**10** was equally divided in three portions and the enzymatic resolution was carried out in three 22 L flasks separately using the above procedure (1.0 M in MTBE, 5 wt % Novozym 435, 3 equiv of H_2O, 40 °C). After 5 days, HPLC analysis indicated that the reaction proceeded to 41% conversion and the optical purity of **10** was 49% ee. An additional 5 wt % Novozym 435 was added and the reaction continued for another 5 days. At this point, the reaction proceeded to 60% conversion [97.5% ee for (4*R*,5*S*)-**10** and 56.6% ee for (4*S*,5*R*)-**9**]. The reaction mixture was simply filtered through a pad of Celite and concentrated to afford the crude mixture (4*R*,5*S*)-**10**/(4*S*,5*R*)-**9** as a thick oil. The desired (4*R*,5*S*)-**10** (2.6 kg, 36% yield, 97.5% ee) was isolated by silica gel chromatography. The slower hydrolysis rate observed in these batches can be attributed to the insufficient agitation by the mechanical stirrer in the 22 L round-bottomed flask.

Separation of the enzymatically resolved (4*R*,5*S*)-**10**/(4*S*,5*R*)-**9** mixture by column chromatography was not desirable for large-scale production and an alternative to such an operation is required. After the attempts to separate the mixture through crystallization failed, we investigated another approach taking advantage of the different physical and chemical properties that (4*R*,5*S*)-**10** and (4*S*,5*R*)-**9** exhibit. It was found that treatment of a solution of the (4*R*,5*S*)-**10**/(4*S*,5*R*)-**9** mixture in methylene chloride with 1.0 M H_3PO_4 resulted in the hydrolysis of (4*S*,5*R*)-**9** to the corresponding pyrrolidinone (4*S*,5*R*)-**8,** and the (4*R*,5*S*)-**10** remained intact under these conditions. Furthermore, the salt form of (4*S*,5*R*)-**8** was extracted into the aqueous layer, and the (4*R*,5*S*)-**10** remained in the organic layer. Pure (4*R*,5*S*)-**10** (>98% purity) was obtained in 35% yield (97.5% ee) by concentrating the organic layer. Apparently the solubility difference between the salt forms of (4*R*,5*S*)-**10**/(4*S*,5*R*)-**8** in organic/aqueous layers accounts for their separation.

Hydrolysis of (4*R*,5*S*)-**10** proceeded smoothly in a 1:1 mixture of concentrated NH_4OH and MeOH at 45 °C. After evaporation of MeOH, (+)-**8** was crystallized directly from the aqueous layer and collected by filtration to give pure material in 98% yield (trans:cis = 97:3 by ^1H NMR).

Scheme 4



Synthesis of BIRZ-227. Borane reduction (BH_3−THF, reflux) of (+)-**8** to pyrrolidine was carried out according to standard protocol[15] (Scheme 4). The crude pyrrolidine (2*S*,3*R*)-**3** was treated with 0.5 equiv of oxalic acid and its (2*S*,3*R*)-pyrrolidine oxalate salt (+)-**11** was isolated in 79% yield as a crystalline solid. At this point, the undesired cis isomer of **11** was determined to be present only at a level of 0.43% by HPLC.[16] Attempted reduction of (+)-**8** by other reagents such as $LiAlH_4$ or Red-Al failed since the pyridine ring in (+)-**8** was also reduced. Condensation of free base of (2*S*,3*R*)-**11** with 2,5-dichlorobenzoxazole (**2**, EtN(i-Pr)$_2$, THF) gave BIRZ-227 (**1**) in 84% yield (99% ee by chiral HPLC[17]) as crystalline solids.

Conclusion

We have developed an effective synthesis of enantiomerically pure BIRZ-227 (**1**) via an enzymatic resolution method. The simple one-pot synthesis of racemic (±)-**8**, which involves the Schiff base formation, the PTC Michael addition, hydrolysis, and cyclization, was efficient. A novel enzymatic resolution of its derivative (±)-**10** and the following nonchromatographic separation of the resolved mixture were devised and demonstrated on a large scale. The chemical process described herein should allow preparation of large quantities of the leukotriene biosynthesis inhibitor **1**.

Experimental Section

General Methods. All melting points are uncorrected. The ^1H and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, respectively. The elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ. Solvents, starting materials, and reagents were used as purchased without further purification. Novozym 435 was purchased from Novo Nordisk Co.

***trans*-4-(4-Methoxyphenyl)-5-(2-pyridyl)-2-pyrrolidinone (8).** In a 50 gallon reactor, a solution of 2-(aminomethyl)pyridine (**4**, 7.05 kg, 65.1 mol), benzophenone (11.85 kg, 65.0 mol), and *p*-TsOH monohydrate (124 g, 0.65 mol) in toluene (65 L) was heated at reflux. Azeotropic distillation of the reaction mixture was carried out by continuous addition/distillation of toluene (~50 L) for 24 h. The reaction mixture was cooled to rt and ethyl 4-methoxycinnamate (13.50 kg, 65.5

(14) Lipase PS-30 was purchased from Amano Co.

(15) Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153.

(16) HPLC column, Novapak C18 (3.9 mm × 15 cm); mobile phase, MeCN/MeOH/aqueous phosphate, pH = 2.0 (20:50:30); flow rate, 1.0 mL/min.

(17) Chiral HPLC column, chiralcel OD (4.6 mm × 25 cm); mobil phase, 5% ethanol in hexane; flow rate, 1.0 mL/min; ambient temperature. Retention times: (+)−(2*S*,3*R*)-**1** (BIRZ-227), 12.39 min; (−)-(2*R*,3*S*)-**1**, 14.05 min.

mol), $BnEt_3NCl$ (744 g, 3.3 mol), and 50% (w/w) NaOH (2.65 kg, 33.1 mol) were added. The resulting mixture was stirred at rt for 19 h. TLC analysis indicated the reaction was completed. Hydrochloric acid (12 M, 19.5 L, 234 mol) and water (15 L) were added at rt. The two-phase mixture was stirred at rt for 20 h, and the layers were separated. The organic layer was washed with water (2 × 10 L). The combined aqueous layers were washed with toluene (2 × 25 L), mixed with toluene (87 L), and basified with concentrated NH_4OH (15 M, 19.2 L, 288 mol) at rt. This two-phase mixture was stirred at rt for 18 h. The layers were separated, and the aqueous layer was extracted with toluene (2 × 10 L). The combined organic layers were washed with water (2 × 16.5 L) and concentrated under house vacuum (jacket temperature, 65 °C). After ~90 L of toluene was distilled, the mixture was cooled to rt and stirred for 14 h. The crystalline solids were collected by filtration and washed with toluene (12 L) to give product **8** (9.1 kg, 52%) as crystalline solids (^{1}H NMR indicated that its purity was >98% and trans:cis = 93:7): mp 118−119 °C; IR (KBr) 3190, 1695, 1511, 1250 cm^{-1}. *trans*-**8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 4.6 Hz, 1H), 7.64 (dt, J = 7.7 and 1.7 Hz, 1H), 7.22−7.25 (br s, 1H), 7.19 (m, 1H), 7.17−7.15 (m, 3H), 6.86 (dd, J = 6.8 and 1.8 Hz, 2H), 4.81 (d, J = 6.6 Hz, 1H), 3.79 (s, 3H), 3.62 (q, J = 6.7 Hz, 1H), 2.86, 2.60 (ABq of d, J_{gem} = 17.0 Hz, J_{vic} = 9.0 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.5, 160, 159.1, 150, 137.3, 133.6, 128.9, 123.3, 121.3, 114.6, 67.1, 55.6, 48.2, 39.1. *cis*-**8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 4.2 Hz, 1H), 7.40 (t, J = 1.7 Hz, 1H), 7.17 (br.s, 1H), 7.01 (dd, J = 6.8 and 4.6 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 6.76, 6.57 (ABq of d, J = 6.7 and 1.8 Hz, 4H), 5.13 (d, J = 7.6 Hz, 1H), 4.08 (q, J = 7.9 Hz, 1H), 3.67 (s, 3H), 2.82, 2.74 (ABq of d, J_{gem} = 16.7 Hz, J_{vic} = 7.7 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 179.3, 158.6, 158.4, 149.2, 136.5, 130.7, 129.2, 122.7, 121.8, 113.7, 64.3, 55.5, 45.5, 36.7. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.51; H, 5.97; N, 10.42.

1-Acetoxymethyl-*trans*-4-(4-methoxyphenyl)-5-(2-pyridyl)-2-pyrrolidinone (10). A mixture of **8** (8.90 kg, 33.2 mol), triethylamine (4.76 kg, 47.0 mol), and aqueous formaldehyde (37% in H_2O, 3.41 kg, 42.0 mol) in THF (26 L) was stirred at rt for 4 days, at which point the HPLC analysis[12] indicated that the reaction was completed. The reaction mixture was concentrated to remove all volatiles. The residue was treated with toluene (36 L) and the resulting suspension was filtered to give ~190 g of a crystalline solid, which was identified by ^{1}H NMR to be mainly the cis hydroxymethylated pyrrolidinone **9** (trans:cis = 7:93). The filtrate was concentrated to dryness and the residue was used directly for the next step. An analytical sample was obtained by chromatography. *trans*-**9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 4.2 Hz, 1H), 7.66 (dt, J = 7.7 and 1.8 Hz, 1H), 7.26 (t, J = 8.8 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 7.10, 6.83 (ABq, J = 8.7 Hz, 4H), 5.09 (d, J = 10.8 Hz, 1H), 4.96 (d, J = 6.8 Hz, 1H), 4.30 (d, J = 10.8 Hz, 1H), 3.77 (s, 3H), 3.54 (q, J = 8.1 Hz, 1H), 2.99, 2.66 (ABq of d, J_{gem} = 17.1, J_{vic} = 9.1 and 8.5 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.8, 159.1, 158.4, 150.3, 137.5, 133.2, 128.6, 123.7, 123.3, 114.6, 70.4, 65.7, 55.6, 45.7, 39.4. *cis*-**9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, J = 4.2 Hz, 1H), 7.41 (dt, J = 7.7 and 1.7 Hz, 1H), 7.05 (dd, J = 7.3 and 5.4 Hz, 1H), 6.75 (d, J = 6.8 Hz, 1H), 6.75, 6.60 (ABq, J = 6.8 Hz, 4H), 5.22 (d, J = 8.0 Hz, 1H), 5.12 (d, J = 10.6 Hz, 1H), 4.55 (d, J = 10.6 Hz, 1H), 4.02 (q, J = 8.9 Hz, 1H), 3.70 (s, 3H), 3.02, 2.72 (ABq of d, J_{gem} = 16 Hz, J_{vic} = 10.3 and 8.4 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.7, 158.7, 157.2, 149.4, 136.4, 129.8, 129.3, 123.3, 122.9, 113.8, 67.7, 66.9, 55.5, 43.8, 36.2; HRMS *m*/*z* calcd for $C_{17}H_{19}N_2O_3(MH)^+$ 299.1395, found 299.1396.

The above residue was mixed with pyridine (7.95 kg, 100.6 mol) and acetic anhydride (9.00 kg, 88.2 mol) at rt. The reaction mixture was stirred at rt for 22 h and then quenched with water (1.2 L). The mixture was concentrated to dryness and the residue was dissolved in toluene (40 L). This solution was washed with water (6 × 10 L), at which point the aqueous layer was pH = 5, and concentrated to dryness. The residue was redissolved in MTBE (30 L) and then concentrated to give the crude product (±)-**10** (13.63 kg, 96% yield from **8** based on 21% (w/w) content of MTBE in the crude product). An analytical sample was obtained by chromatography: mp 66−68 °C; IR (KBr) 2832, 1739, 1699, 1514, 1399 cm^{-1}. *trans*-**10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 4.4 Hz, 1H), 7.66 (dt, J = 7.6 and 1.8 Hz, 1H), 7.26 (dd, J = 8.0 and 4.0 Hz, 1H), 7.12 (d, J = 7.7 Hz, 1H), 7.09, 6.84 (ABq, J = 8.7 Hz, 4H), 5.61 (d, J = 10.6 Hz, 1H), 4.83 (d, J = 10.6 Hz, 1H), 4.79 (d, J = 6.3 Hz, 1H), 3.79 (s, 3H), 3.61 (q, J = 7.7 Hz, 1H), 3.06, 2.68 (ABq of d, J_{gem} = 17.3 Hz, J_{vic} = 7.1 and 7.9 Hz, 2H), 1.98 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.9, 171.0, 159.1, 158.1, 150.7, 137.2, 133.4, 128.4, 123.7, 123.3, 114.6, 70.7, 65.9, 55.6, 45.4, 38.5, 21.0. *cis*-**10**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 4.2 Hz, 1H), 7.38 (dt, J = 7.6 and 1.6 Hz, 1H), 7.06 (dd, J = 8.0 and 4.3 Hz, 1H), 6.75, 6.61 (ABq, J = 8.6 Hz, 4H), 6.69 (d, J = 7.8 Hz, 1H), 5.61 (d, J = 10.6 Hz, 1H), 5.10 (d, J = 8.1 Hz, 1H), 4.95 (d, J = 10.6 Hz, 1H), 4.02 (m, 1H), 3.70 (s, 3H), 3.13, 2.68 (ABq of d, J_{gem} = 16.6 Hz, J_{vic} = 12.0 and 8.3 Hz, 2H), 1.99 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 177.0, 171.3, 158.8, 156.9, 149.7, 136.2, 129.3, 123.6, 123.0, 113.8, 68.1, 66.7, 55.5, 43.7, 35.0, 21.1; HRMS *m*/*z* calcd for $C_{19}H_{21}N_2O_4(MH)^+$ 341.1501, found 341.1501. See (+)-**10** for elemental analysis.

Enzymatic Resolution of (±)-10, (4*R*,5*S*)-1-Acetoxymethyl-4-(4-methoxyphenyl)-5-(2-pyridyl)-2-pyrrolidinone [(+)-10]. The enzymatic resolution of the above crude product (±)-**10** (13.63 kg) was carried out in three separate 22 L flasks by equally dividing the substrate. The reaction conditions were all identical in these three batches (A−C).

Batch A: A suspension of the crude product (±)-**10** (4.54 kg, 10.55 mol), water (561 g, 31.17 mol), and Novozym 435 (188 g, 5 wt % based on the substrate) in MTBE (11 L) was stirred at 40 °C. The reaction was monitored by HPLC (Chiralpak AS).[13] After 5 days, it was observed that the reaction proceeded at 41% conversion and the optical purity of (+)-**10** was 49% ee. At this point, additional 5 wt % Novozym 435 (188 g) was added and the reaction continued for another 5 days. The HPLC analysis indicated that the optical purity of (+)-**10** was 97.5% ee (60% conversion). The reaction mixture was cooled to rt and filtered through a pad of Celite. The cake was washed with MTBE (5 × 1 L). The combined filtrates were concentrated to dryness to give the crude product (+)-**10**/(−)-**9** (3.60 kg) as a thick oil. The crude product (+)-**10**/(−)-**9** (3.60 kg) was purified by flash chromatography on silica gel (15 kg) eluted with EtOAc−hexane (4:1) to give pure (+)-**10** (1.28 kg, 36% yield, 97.5% ee) as crystalline solids. In the batch B, 1.30 kg (36%) of (+)-**10** was obtained in the same manner: mp 76−78 °C; $[\alpha]^{25}_D$ = +156.7° (c = 1.0, $CHCl_3$); ^{1}H and ^{13}C NMR spectra were identical with (±)-**10** as described above. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.14; H, 5.94; N, 8.16

The nonchromatographic separation of (+)-**10**/(−)-**9** was performed as follows. A solution of the enzymatically resolved crude product (+)-**10**/(−)-**9** [19.5 g, 58.8 mmol, prepared from 20.0 g of (±)-**10**] in methylene chloride (100 mL) was washed with 1.0 M H_3PO_4 (5 × 60 mL), at which point the HPLC analysis indicated there was no (−)-**9** present in the organic layer. The organic layer was dried ($MgSO_4$) and concentrated to give 7.06 g (35%) of (+)-**10** as crystalline solids. The optical purity (97.5% ee) and chemical purity (>98%) were determined by a chiral HPLC method.[13]

(4*R*,5*S*)-4-(4-Methoxyphenyl)-5-(2-pyridyl)-2-pyrrolidinone [(+)-9]. A solution of (+)-**10** (1.28 kg, 3.76 mol) in MeOH (3.4 L) was treated with concentrated NH_4OH (3.4 L) at rt. The reaction mixture was heated to 45 °C and stirred at 45 °C for 6 h. The HPLC analysis indicated that the reaction was complete. The reaction mixture was evaporated to remove most of MeOH, and the crystalline solids were precipitated during this period. The solids were collected by filtration and the cake was washed with water (1 L). This product was dried in an oven at rt overnight to afford 840 g (98%) of (+)-**8** as crystalline solids (its purity was determined to be >99% by HPLC and the trans:cis ratio = 98:2 by ^{1}H NMR): mp 144−146 °C; $[\alpha]^{25}_D$ = +151.5° (c = 1.01, $CHCl_3$); ^{1}H and ^{13}C NMR spectra were identical with (±)-**8** as described above.

(2*S*,3*R*)-2-(2-Pyridyl)-3-(4-methyoxyphenyl)pyrrolidine Hemioxalate (11). In a 22 L flask, 2-pyrrolidinone (+)-**8** (731 g, 2.73 mol) was added to a BH_3−THF solution (1.0 M, 9.4 L, 9.4 mol) at rt over 2 h. Gases evolved during this period and the internal temperature arose to 42 °C at the end. The reaction mixture was heated at reflux overnight (16 h). The mixture was then cooled to rt, quenched with MeOH (850 mL), and concentrated to dryness by rotavap. The resulting residue was dissolved in MeOH (2 L) and evaporated; such treatment was repeated twice. The residue was dissolved in MeOH (6 L) and treated with a solution of HCl (462 g, 12.6 mol) in MeOH (3 L). The mixture was heated at reflux for 2 h and then evaporated to dryness. The residue was redissolved in MeOH (2 L) and evaporated; such treatment was repeated twice. The residue was dissolved in aqueous 2.4 N HCl (5 L) and the aqueous layer was washed with toluene (3 × 3 L). The aqueous layer was mixed with toluene (3.5 L) and basified with 50% NaOH (∼1.4 kg) until pH = 13 (internal temperature was kept below rt by cooling). The layers were separated, and the aqueous layer was extracted with toluene (2 × 3 L). The combined organic layers were filtered and concentrated to dryness to yield crude pyrrolidine (633 g) as an oil. ^{1}H NMR analysis indicated this crude product contained 4.5 wt % of toluene and trans:cis = 97:3.

The above crude product was dissolved in 2-propanol (2 L) and evaporated; such treatment was repeated again. The residue was dissolved in 2-propanol (2.4 L) and the solution was stirred and heated to 60 °C as a solution of oxalic acid dihydrate (152 g, 1.2 mol) in 2-propanol (915 mL) and water (34 mL) was added. The mixture was heated at reflux for 15 min, and cooled to rt overnight (13 h). The crystalline product was collected by filtration, and the cake was rinsed with 2-propanol (2 × 1 L) and dried under vacuum to afford pyrrolidine hemioxalate salt (+)-**11** (652 g, 79% yield, trans:cis = 99.6:0.4): mp 184−185.5 °C; $[\alpha]^{25}_D$ = +135.31° (*c* = 1.0, MeOH); IR (KBr) 1595, 1514, 1311, 1251 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (d, *J* = 4.4 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.32 (dd, *J* = 7.1 and 5.1 Hz, 1H), 7.13, 6.82 (ABq, *J* = 8.5 Hz, 4H), 7.03 (d, *J* = 7.8 Hz, 1H), 4.50 (d, *J* = 10.2 Hz, 1H), 3.67 (s, 3H), 3.35 (m, 3H), 2.34 (m, 1H), 2.09 (m, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 166.3, 158.8, 158.2, 149.9, 137.7, 133.0, 129.4, 124.0, 123.4, 114.7, 69.6, 55.8, 51.9, 46.0, 35.2. Anal. Calcd for $C_{17}H_{19}N_2O_3$: C, 68.21; H, 6.40; N, 9.36. Found: C, 68.15; H, 6.38; N, 9.32.

2-[1-(2*S*,3*R*)-2-(2-Pyridyl)-3-(4-methyoxyphenyl)pyrrolidinyl]-5-chlorobenzoxazole (1, BIRZ-227). Pyrrolidine salt (+)-**11** (652 g, 2.18 mol) was dissolved in water (5.5 L) and mixed with toluene (5.5 L). The mixture was stirred at 0 °C as a 50% NaOH solution was added until pH = 13. The layers were separated, and the aqueous layer was extracted with toluene (2 × 2.5 L). The organic layers were combined, washed with water (3 × 1 L), and concentrated to dryness. The residue was dissolved in toluene (2 L) and evaporated. Such treatment was repeated again. ^{1}H NMR analysis indicated that the crude pyrrolidine (723 g, trans:cis = 99.6:0.4) contained 22 wt % of toluene. Chiral HPLC analysis showed its optical purity was 97% ee.

A solution of 2,5-dichlorobenzoxazole (**2**, 374 g, 1.99 mol) in THF (4.8 L) was stirred at rt as a solution of the above crude pyrrolidine (723 g, 2.22 mol) in THF (4.8 L) and also diisopropylethylamine (541 g, 4.18 mol) were added. The reaction mixture was stirred at rt for 2 h and TLC analysis indicated that the reaction was complete. The mixture was evaporated to dryness. The residue was redissolved in EtOAc (2.4 L) and then evaporated; such treatment was repeated again. The residue was diluted with EtOAc (2.4 L) and extracted with water (1.2 L). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 1.2 L). The combined organic layers were washed with water (2 × 1.2 L) and concentrated to dryness. A single crystallization of the residue in cyclohexane (2 L) afforded the desired product **1** (739 g, 84% yield, 99% ee): mp 90−92 °C; $[\alpha]^{25}_D$ = +46.97°; IR (KBr) 2833, 1641, 1512, 1246 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.2 Hz, 1H), 7.62 (dt, *J* = 7.6 and 1.8 Hz, 1H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.21−7.13 (m, 4H), 7.04 (d, *J* = 8.4 Hz, 1H), 6.92 (dd, *J* = 8.5 and 2.0 Hz, 1H), 6.86 (dd, *J* = 7.1 and 1.8 Hz, 2H), 5.19 (d, *J* = 5.2 Hz, 1H), 4.13 (m, 2H), 3.40 (s, 3H), 3.71 (q, *J* = 6.3 Hz, 1H), 2.52 (m, 1H), 2.22 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.8, 160.7, 158.9, 150.1, 148.0, 145.1, 136.9, 133.7, 129.5, 128.4, 122.8, 121.8, 120.4, 116.8, 114.5, 109.6, 70.8, 55.6, 52.3, 48.9, 32.5. Anal. Calcd for $C_{23}H_{20}ClN_3O_2$: C, 68.06; H, 4.97; N, 10.35. Found: C, 67.95; H, 4.96; N, 10.42.

JO971605P