4-[2′-((2,6-Dimethoxybenzoyl)amino)ethyl]-4-methoxy-2,5-cyclohexadienone (2i) (method i): **1d** (20 mg, 0.066 mmol); PIFA (34.2 mg, 0.08 mmol); MeOH (0.3 mL); 14.9 mg (68%): yellow oil; IR 3450, 1660, 1635, 1595 cm^{-1}; ^1H NMR δ 2.04 (t, 2 H, J = 7 Hz, CH_2CH_2N), 3.20 (s, 3 H, OMe), 3.56 (q, 2 H, J = 7 Hz, CH_2N), 3.80 (s, 6 H, OMe × 2), 6.05 (br s, 1 H, NH), 6.36 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.54 (d, 2 H, J = 8 Hz, Ar H), 6.85 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 7.27 (t, 1 H, J = 8 Hz, Ar H); HRMS calcd for $C_{18}H_{21}NO_5$ (M^+) 331.1420, found 331.1423.

4-Acetoxy-4-[2′-((2,6-dimethoxybenzoyl)amino)ethyl]-2,5-cyclohexadienone (2j) (method i): **1d** (30 mg, 0.12 mmol); PIFA (51.4 mg, 0.12 mmol); AcOH (0.9 mL); 20.4 mg (57%); colorless plates; mp 186–187 °C (from AcOEt); IR 3475, 1750, 1675, 1635, 1600 cm^{-1}; ^1H NMR δ 2.08 (s, 3 H, COMe), 2.16 (t, 2 H, J = 7 Hz, CH_2CH_2N), 3.55 (q, 2 H, J = 7 Hz, CH_2N), 3.80 (s, 6 H, OMe × 2), 5.79 (br s, 1 H, NH), 6.27 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.54 (d, 2 H, J = 9 Hz, Ar H), 6.95 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 7.20 (t, 1 H, J = 9 Hz, Ar H). Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.60; H, 5.90; N, 3.91.

2-(2′,6′-Dimethoxyphenyl)-1,3-oxazaspiro[5.5]undeca-7,10-dien-9-one (3d) (method ii): **1d** (50 mg, 0.17 mmol); PIFA (85.6 mg, 0.2 mmol); CF_3CH_2OH (1.6 mL); 36.8 mg (74%); colorless crystals; mp 116–118 °C (from AcOEt); IR 1670, 1630, 1600 cm^{-1}; ^1H NMR δ 2.04 (t, 2 H, J = 6 Hz, CH_2CH_2N), 3.73 (t, 2 H, J = 6 Hz, CH_2N), 3.81 (s, 6 H, OMe × 2), 6.26 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 6.54 (d, 2 H, J = 8 Hz, Ar H), 7.06 (d, 2 H, J = 10 Hz, CH=CHCO × 2), 7.26 (t, 1 H, J = 8 Hz, Ar H); HRMS calcd for $C_{17}H_{17}NO_4$ 299.1158, found 299.1174.

Oxidation of 1d by method iii: **1d** (30 mg, 0.1 mmol); PIFA (51.1 mg, 0.12 mmol), K_2CO_3 (27.6 mg, 0.2 mmol); CH_2Cl_2 (0.8 mL); **3d** (5 mg, 17%).

General Procedure for the Oxidation of *N*-Alkyl-*N*-benzoyltyramines 1e,f to Hexahydroindol-6-ones 4a,b. To a solution of *N*-alkyl-*N*-benzoyltyramine 1 (1 mmol) in CF_3CH_2OH (10 mL) was added PIFA (1.2 mmol). The mixture was stirred at room temperature for 30 min and then neutralized by addition of powered $NaHCO_3$. The mixture was concentrated in vacuo to give the residue, which was worked up as described for method i in *N*-acyltyramines 1.

Oxidation of 1e by method ii: **1e** (21.1 mg, 0.08 mmol); PIFA (43 mg, 0.1 mmol); CF_3CH_2OH (1 mL); 1-(benzoyloxy)-7-methyl-*cis*-7-azabicyclo[4.3.0]non-2-en-4-one (**4a**) (12.1 mg, 54%); hydroscopic colorless oil; IR 1715, 1685, 1600 cm^{-1}; ^1H NMR δ 2.3–2.4 (m, 1 H), 2.4–2.55 (m, 2 H), 2.34 (s, 3 H, NMe), 2.71 (dd, 1 H, J = 2, 17 Hz, 5-CH), 2.95–2.99 (m, 1 H), 3.05 (dd, 1 H, J = 5, 17 Hz, 5-CH), 3.1–3.2 (m, 1 H, 6-CH), 6.03 (d, 1 H, J = 10 Hz, 3-CH), 7.06 (dd, 1 H, J = 2, 10 Hz, 2-CH), 7.46 (t, 2 H, J = 7 Hz, Ar H), 7.59 (t, 1 H, J = 7 Hz, Ar H), 8.01 (d, 2 H, J = 8 Hz, Ar H); HRMS calcd for $C_{16}H_{17}NO_3$ 271.1206, found 271.1204. Anal. Calcd for $C_{16}H_{17}NO_3 \cdot {}^1/_{10}H_2O$: C, 70.36; H, 6.35; N, 5.13. Found: C, 70.21; H, 6.39; N, 4.77.

Oxidation of 1f by method ii: **1f** (31.7 mg, 0.12 mmol); PIFA (60.8 mg, 0.14 mmol); CF_3CH_2OH (1.5 mL); 1-(benzoyloxy)-7-ethyl-*cis*-7-azabicyclo[4.3.0]non-2-en-4-one (**4b**) (16.1 mg, 48%); colorless oil; IR 1715, 1685, 1600 cm^{-1}; ^1H NMR δ 1.07 (t, 3 H, J = 7 Hz, CH_2CH_3), 2.20–2.27 (m, 1 H), 2.32–2.40 (m, 1 H), 2.44–2.52 (m, 2 H), 2.69 (dd, 1 H, J = 3, 17 Hz, 5-CH), 2.85–2.94 (m, 1 H, 6-CH), 3.01 (dd, 1 H, J = 5, 17 Hz, 5-CH), 3.22 (q, 2 H, J = 7 Hz, CH_2CH_3), 6.03 (d, 1 H, J = 10 Hz, 3-CH), 7.08 (dd, 1 H, J = 1, 10 Hz, 2-CH), 7.45 (t, 2 H, J = 7 Hz, Ar H), 7.59 (t, 1 H, J = 7 Hz, Ar H), 8.01 (d, 2 H, J = 7 Hz, Ar H); HRMS calcd for $C_{17}H_{19}NO_3$ 285.1365, found 285.1365. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.24; H, 6.88; N, 4.52.

Registry No. **1a**, 1202-66-0; **1b**, 130699-26-2; **1c**, 41859-54-5; **1d**, 130699-27-3; **1e**, 130699-28-4; **1f**, 130699-29-5; **2a**, 130699-30-8; **2b**, 130699-31-9; **2c**, 130699-32-0; **2d**, 130699-33-1; **2e**, 130699-34-2; **2f**, 130699-35-3; **2g**, 130699-36-4; **2h**, 130699-37-5; **2i**, 130699-38-6; **2j**, 130699-39-7; **3a**, 130699-40-0; **3b**, 130699-41-1; **3c**, 130699-42-2; **3d**, 130699-43-3; **4a**, 130699-44-4; **4b**, 130699-45-5; PIFA, 2712-78-9.

Supplementary Material Available: ^1H NMR spectra for compounds **2a,b,f–i** and **3a,b,d** (10 pages). Ordering information is given on any current masthead page.

Stereoselective Syntheses of Hydroxyethylene Dipeptide Isosteres

Steven A. Boyd,*[1a] Robert A. Mantei,[1a] Chi-Nung Hsiao,*[1b] and William R. Baker[1a]

Abbott Laboratories, Cardiovascular Research and Process Research, Pharmaceutical Products Division, Abbott Park, Illinois 60064

Received May 22, 1990

Hydroxyethylene dipeptide isosteres (1) play a prominent role as transition-state mimics in inhibitors of aspartic proteinases.[2] Considerable effort has been directed toward developing efficient syntheses for these molecules.[3] We desired a highly stereocontrolled and flexible method for the synthesis of hydroxyethylene dipeptide isosteres for studies in our renin inhibitors program. One avenue which has not been exploited is via deoxygenation of stereochemically defined aldol adducts.[4] In this paper, we report two methods which provide the Cha-Val hydroxyethylene dipeptide isostere **2** by this strategy.

Both of our routes make use of the versatile aldehyde **3**[5] as the P_1-containing partner in the aldol reaction. A similar aldol reaction has been reported by Thaisrivongs and co-workers for the synthesis of dihydroxyethylene isosteres.[6] In our initial route, outlined in Scheme II, the $P_{1'}$ fragment was provided by acyloxazolidinone **4**. Condensation of the boryl enolate of **4** with aldehyde **3** (8:1 mixture of 5*R*:5*S* diastereomers) led cleanly to aldol adduct **5** in good yield. With the exception of the adduct arising from the 5*S* diastereomer of **3**, no other aldol products were detected (^1H NMR, TLC). Barton–McCombie deoxygenation[7] proceeded by way of thionocarbamate **6**, which was reduced smoothly with tri-*n*-butyltin hydride to provide the diprotected isostere **7** in an overall yield of 48% for the three steps. The recently reported lithium hydroperoxide protocol for cleavage of hindered acyloxazolidinones[8] proved very efficacious for the hydrolysis of **7** to carboxylic acid **8**. The desired amide **9** then was cleanly synthesized without epimerization by first forming the *N*-hydroxybenzotriazole ester at 0 °C over 48 h, followed by addition of the amine component.[9] The free

(1) (a) Cardiovascular Research. (b) Process Research.

(2) For recent reviews, see: (a) Rich, D. H. *J. Med. Chem.* **1985**, *28*, 253. (b) Greenlee, W. J. *Pharm. Res.* **1987**, *4*, 364. (c) Kokubu, T.; Hiwada, K. *Drugs Today* **1987**, *23*, 101.

(3) For leading references, see: (a) Kaltenbronn, J. S.; Hudspeth, J. P.; Lunneyh, E. A.; Michniewicz, B. M.; Nicolaides, E. D.; Repine, J. T.; Roark, W. H.; Stier, M. A.; Tinney, F. J.; Woo, P. K. W.; Essenburg, A. D. *J. Med. Chem.* **1990**, *33*, 838. (b) Bradbury, R. H.; Revill, J. M.; Rivett, J. E.; Waterson, D. *Tetrahedron Lett.* **1989**, *30*, 3845. (c) Shiozaki, M.; Hata, T.; Furukawa, Y. *Tetrahedron Lett.* **1989**, *30*, 3669. (d) Harbeson, S. L.; Rich, D. H. *J. Med Chem.* **1989**, *32*, 1378. (e) Karlsson, J. O.; Lundblad, A.; Malm, B.; Nilsson, I.; Nitenberg, T.; Starke, I.; Sörensen, H.; Westerlund, C. *Tetrahedron Lett.* **1989**, *30*, 2653. (f) Metternich, R.; Lüdi, W. *Tetrahedron Lett.* **1988**, *29*, 3923. (k) Holladay, M. W.; Salituro, F. G.; Rich, D. H. *J. Med. Chem.* **1987**, *30*, 374 and references cited therein.

(4) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1982; Vol. 13, pp 1–115.

(5) Rosenberg, S. H.; Dellaria, J. F.; Kempf, D. J.; Hutchins, C. W.; Woods, K. W.; Maki, R. G.; de Lara, E.; Spina, K. P.; Stein, H. H.; Cohen, J.; Baker, W. R.; Plattner, J. J.; Kleinert, H. K.; Perun, T. J. *J. Med. Chem.* **1990**, *33*, 1582.

(6) Thaisrivongs, S.; Pals, D. T.; Kroll, L. T.; Turner, S. R.; Han, F.-S. *J. Med. Chem.* **1987**, *30*, 976.

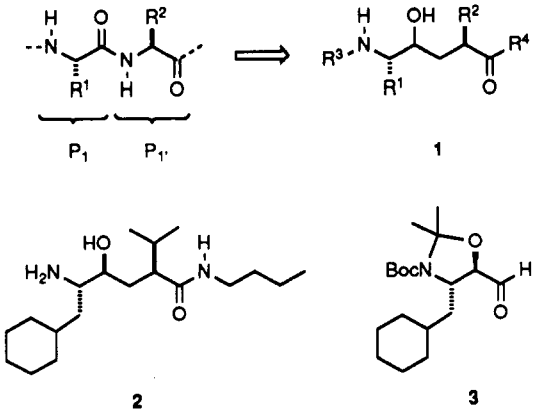
(7) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(8) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

(9) Bühlmayer, P.; Caselli, A.; Fuhrer, W.; Göschke, R.; Rasetti, V.; Rüeger, H.; Stanton, J. L.; Criscione, L.; Wood, J. M. *J. Med. Chem.* **1988**, *31*, 1839.

0022-3263/91/1956-0438$02.50/0

Scheme I



amine **2** was liberated by simultaneous deprotection of the Boc and acetonide under acidic conditions.[6,10] The physical and spectral characteristics of **2** produced by this method were in excellent agreement with those previously reported.[9]

A related approach using the recently reported 4(*R*)-(methoxycarbonyl)-1,3-thiazolidine-2-thione (**10**) as chiral auxiliary for the aldol reaction was also carried out (Scheme III).[11] This auxiliary, derived from L-cysteine methyl ester in one step, was acylated with isovaleryl chloride under mild conditions to provide the optically pure (*R*)-3-isovaleryl-4-(methoxycarbonyl)-1,3-thiazolidine-2-thione (**11**) in 80% yield. Treatment of **11** with dibutylboryl triflate in dichloromethane followed by slow addition of diisopropylethylamine strictly at 0 °C effected the formation of the corresponding boryl enolate **12**, which condensed with aldehyde **3** to give the aldol product **13** in 73% yield. The chiral auxiliary was easily removed by direct aminolysis of **13** with butylamine in acetonitrile at room temperature to provide the butylamide **14** in 78% yield after purification. The chiral auxiliary **10** was also recovered in 89% yield without detectable loss of optical purity. Sequential treatment of **14** with carbon disulfide, methyl iodide, and sodium hydride led smoothly to the formation of xanthate **15**. Subsequent reduction of **15** by tri-*n*-butyltin hydride in refluxing toluene gave **9** (74% yield over both steps) with all physical and spectral characteristics identical with those of the sample prepared by the previous route.

In summary, we have developed two useful methods for preparing hydroxyethylene dipeptide isosteres. The unambigous stereochemical outcome of the asymmetric aldol reaction provides the desired $P_{1'}$ side chain chirality, and the P_1 chirality ultimately derives from the amino acid precursor for aldehyde **3**. These methods should find utility in preparations of related peptide isosteres.

Experimental Section

3-(3(*R*)-(3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4(*S*)-(cyclohexylmethyl)-5(*R*)-oxazolidinyl)-3-hydroxy-2(*R*)-isopropyl-1-oxopropyl)-4(*R*)-methyl-5(*S*)-phenyl-2-oxazolidinone (5). Dibutylboryl trifluoromethanesulfonate[12] (17.8 mL, 19.5 g, 71.2 mmol) was added dropwise over 15 min to a solution of acyloxazolidinone **4** (16.9 g, 64.7 mmol) in 62 mL of CH_2Cl_2, cooled to −78 °C, under an argon atmosphere. The resultant mixture was allowed to warm by removal of the cooling bath for 3 min, during which time the reaction mixture became a homogeneous yellow solution. The solution was recooled to −78 °C, and then diisopropylethylamine (13.6 mL, 10.1 g, 78.3 mmol) was added dropwise over 20 min. After stirring 0.5 h at −78 °C, the dry ice–acetone bath was replaced by an ice–water bath, and the reaction was stirred at 0 °C for an additional 1 h. The resultant boryl enolate solution was then cooled again to −78 °C, and a solution of aldehyde **3**[5] (16.2 g, 49.8 mmol, dried by azeotropic distillation of a toluene solution followed by drying at 50 °C under 0.03 mmHg) in 30 mL of CH_2Cl_2 was added dropwise over 20 min. The resulting solution was stirred for 1 h at −78 °C, the cooling bath was removed, and the reaction was stirred an additional 1 h, at which time TLC (1.5% MeOH–CH_2Cl_2) indicated complete consumption of aldehyde **3**. The reaction was quenched at 0 °C by addition of a mixture containing 43 mL of pH 7 aqueous phosphate buffer and 86 mL of methanol. This was then followed by careful dropwise addition of a solution of 30% hydrogen peroxide (43 mL) in 86 mL of methanol, maintaining the internal temperature below 10 °C. The resultant mixture was vigorously stirred at 0 °C for 1 h, and then it was partitioned between CH_2Cl_2 (350 mL) and pH 7 phosphate buffer (100 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 200 mL), and then the combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 50.3 g of a viscous oil. Purification by flash chromatography (0.5% MeOH–CH_2Cl_2) provided 18.3 g (63%)[13] of aldol **5** as a white foam: mp 97 °C; R_f 0.41 (1.5% MeOH–CH_2Cl_2); $[\alpha]_D$ +16.9° (*c* 1.01, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.91 (d, *J* = 6.6 Hz, 3 H), 1.06 (d, *J* = 6.6 Hz, 3 H), 1.1 (d, *J* = 7 Hz, 3 H), 1.48 (s, 9 H), 0.9–1.9 (several br m, 12 H total), 2.12 (br d, *J* = 9.2 Hz, 1 H), 2.3 (m, 1 H), 3.81 (dd, *J* = 2.5, 5.0 Hz, 1 H), 3.94 (td, *J* = 2.9, 8.6 Hz, 1 H), 4.04 (br m, 1 H), 4.22 (dd, *J* = 5.5, 8.5 Hz, 1 H), 4.84 (dq, *J* = 6.6, 7 Hz, 1 H), 5.61 (d, *J* = 7 Hz, 1 H), 7.31–7.45 (m, 5 H); IR ($CDCl_3$) 3550, 2970, 2920, 2850, 1780, 1685, 1390, 1365, 1340, 1190, 1120 cm^{-1}; high-resolution MS calcd for $(M + H)^+$ of $C_{33}H_{51}N_2O_7$ *m/e* 587.3698, found *m/e* 587.3696. Anal. Calcd for $C_{33}H_{50}N_2O_7$: C, 67.55; H, 8.59; N, 4.77. Found: C, 67.41; H, 8.61; N, 4.77.

3-(3(*R*)-(3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4(*S*)-(cyclohexylmethyl)-5(*R*)-oxazolidinyl)-3-((1-imidazolylthionyl)oxy)-2(*R*)-isopropyl-1-oxopropyl)-4(*R*)-methyl-5(*S*)-phenyl-2-oxazolidinone (6). Aldol product **5** (7.29 g, 12.4 mmol) and 1,1′-(thiocarbonyl)diimidazole (4.43 g, 24.8 mmol) were refluxed in 78 mL of 1,2-dichloroethane under a nitrogen atmosphere for 48 h. TLC analysis indicated the presence of unreacted **5**. An additional portion of 1,1′-thiocarbonyldiimidazole (1.11 g, 6.2 mmol) was added, and reflux was continued for an additional 18 h. The solution was decanted from a dark viscous residue, and the residue was triturated with warm CH_2Cl_2. The combined solutions were concentrated under reduced pressure, and the residue purified by flash chromatography (2.5% MeOH–CH_2Cl_2) to afford 7.04 g (84%) of thionocarbamate **6** as a pale yellow foam: mp 102–7 °C; R_f 0.39 (25% EtOAc–hexane); $[\alpha]_D$ +35.8° (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.93 (d, *J* = 6.6 Hz, 3 H), 1.04 (d, *J* = 7 Hz, 3 H), 1.08 (d, *J* = 7.7 Hz, 3 H), 1.5 (br s, 9 H), 0.9–1.9 (several br m, 13 H total), 2.05 (m, 1 H), 4.13 (br m, 1 H), 4.23 (dd, *J* = 1.7, 3.3 Hz, 1 H), 4.81 (m, 1 H), 4.94 (m, 1 H), 5.70 (d, *J* = 7.5 Hz, 1 H), 6.33 (dd, *J* = 3, 9.5 Hz, 1 H), 7.06 (br s, 1 H), 7.3–7.5 (m, 5 H), 7.61 (t, *J* = 1.5 Hz, 1 H), 8.40 (br s, 1 H); IR ($CDCl_3$) 2960, 2920, 2825, 1780, 1690, 1455, 1390, 1365, 1340, 1280, 1220, 1195 cm^{-1}; high-resolution MS calcd for $(M + H)^+$ of $C_{37}H_{53}N_4O_7S$ *m/e* 697.3635, found *m/e* 697.3629. Anal. Calcd for $C_{37}H_{52}N_4O_7S$: C, 63.77; H, 7.52; N, 8.04. Found: C, 63.58; H, 7.44; N, 7.94.

3-(3-(3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4(*S*)-(cyclohexylmethyl)-5(*S*)-oxazolidinyl)-2(*R*)-isopropyl-1-oxopropyl)-4(*R*)-methyl-5(*S*)-phenyl-2-oxazolidinone (7). A solution of **6** (17.8 g, 25.5 mmol) in 760 mL of dry toluene was degassed with argon for 30 min and then warmed to reflux (under argon). An argon-degassed solution of tri-*n*-butyltin hydride (13.7 ml, 14.8 g, 51.1 mmol) in 75 mL of dry toluene was added dropwise over 45 min. After an additional 2 h of reflux, the reaction was cooled, concentrated under reduced pressure, and purified by flash chromatography (elution with hexanes initially, to remove tin-

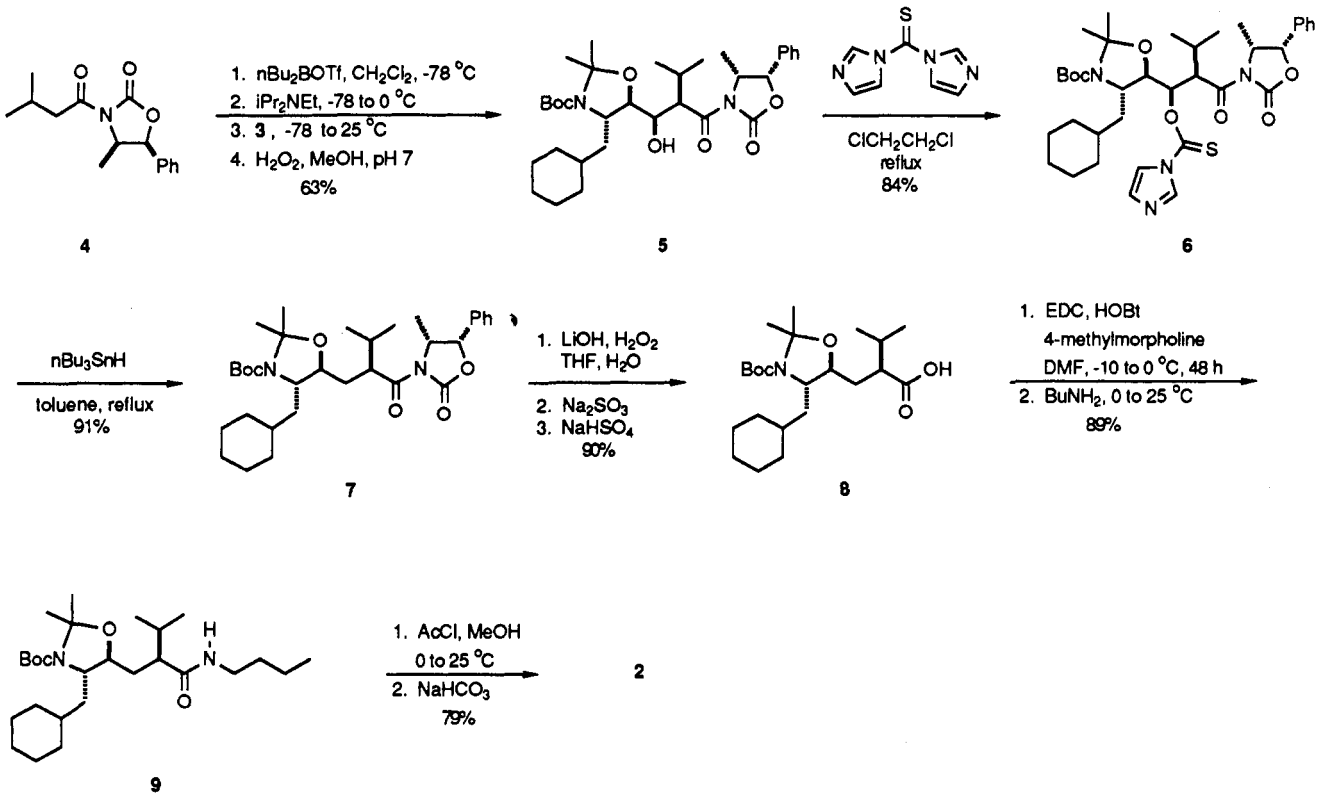
(10) This deprotection was also accomplished under milder conditions: (a) 1:1 (v:v) TFA–CH_2Cl_2/0 °C/3 h; (b) 3:1 THF–H_2O/25 °C/18 h; (c) Na_2CO_3.

(11) Hsiao, C.-N.; Liu, L.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 2201.

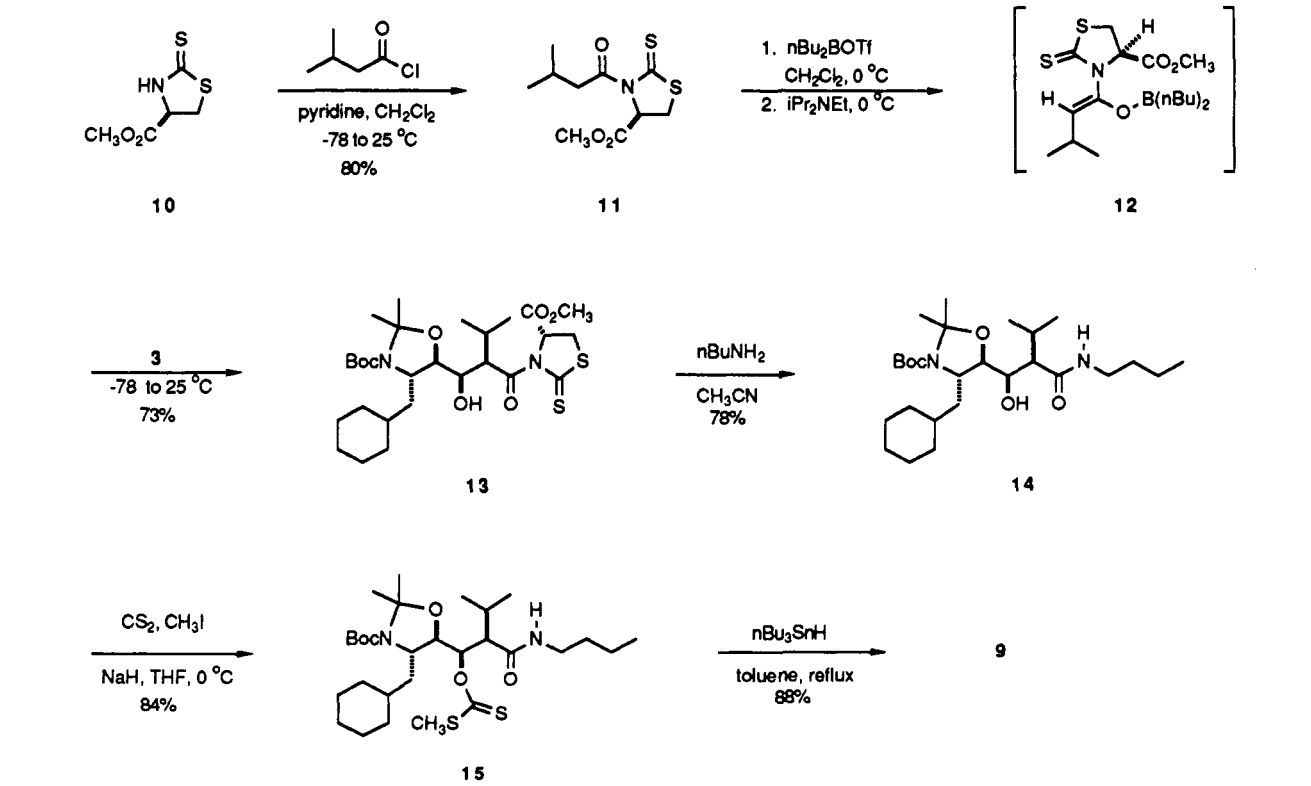
(12) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

(13) The yield is not corrected for the percentage of 5*S* aldehyde present in the starting material.

Scheme II



Scheme III



containing compounds, then with 5% EtOAc–hexane) to afford 13.3 g (91%) of **7** as a white foam: mp 68–75 °C; R_f 0.54 (25% EtOAc–hexane); $[\alpha]_D$ +8.0° (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.90 (d, J = 6.6 Hz, 3 H), 0.92 (d, J = 7 Hz, 3 H), 0.9–1.1 (br m, 3 H), 1.06 (d, J = 7 Hz, 3 H), 1.15–1.35 (br m, 3 H), 1.51 (s, 9 H), 1.57–2.14 (several br m, 16 H total), 3.6–3.8 (br m, 1 H), 3.97 (m, 1 H), 4.85 (dq, J = 7, 7 Hz, 1 H), 5.68 (d, J = 7 Hz 1 H), 7.3–7.46 (m, 5 H); IR ($CDCl_3$) 2960, 2925, 2845, 1780, 1690, 1450, 1390, 1365, 1320, 1235, 1185, 1160 cm^{-1}; MS *m/e* 571 ($(M + H)^+$). Anal. Calcd for $C_{33}H_{50}N_2O_6$: C, 69.44; H, 8.83; N, 4.91. Found: C, 69.31; H, 8.82; N, 4.89.

2(*S*)-((3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4(*S*)-(cyclohexylmethyl)-5(*S*)-oxazolidinyl)methyl)-3-methylbutanoic Acid (8). The procedure of Evans et al.[8] was employed. Acyloxazolidinone **7** (6.10 g, 10.7 mmol) was dissolved in 115 mL of THF and 38 mL of H_2O. The resulting solution was cooled

to 0 °C and treated dropwise with a solution of lithium hydroxide monohydrate (0.91 g, 21.8 mmol) in 8.4 mL of 30% aqueous H_2O_2. The resulting cloudy mixture was stirred at room temperature for 20 h, recooled to 0 °C, and quenched with 69 mL of 1.5 M aqueous Na_2SO_3 (added dropwise to maintain internal temperature <10 °C). After the addition was completed, the mixture was stirred an additional 1 h and concentrated in vacuo. The resultant aqueous mixture was cooled in an ice bath and acidified to pH 2 with 1 M aqueous $NaHSO_4$. The aqueous mixture was extracted with CH_2Cl_2 (3 × 150 mL), and the combined organic phases were washed with brine (250 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The glassy residue was purified by flash chromatography (15% EtOAc–0.5% HOAc–hexane) to provide 3.53 g (90%) of carboxylic acid **8** as a viscous colorless oil: R_f 0.26 (HOAc–EtOAc–hexane, 1:40:159); $[\alpha]_D$ −6.1° (*c* 1.04, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.96 (d, *J* = 7 Hz, 3 H), 1.00 (d, *J* = 7 Hz, 3 H), 1.1–1.3 (br m, 5 H), 1.48 (s, 9 H), 1.5–1.9 (several br m, 15 H total), 1.94–2.06 (m, 1 H), 2.66 (m, 1 H), 3.55–3.85 (br m, 1 H), 3.90 (m, 1 H); IR ($CDCl_3$) 3500, 3400–2300 (br), 2965, 2925, 2850, 1740, 1700, 1690, 1450, 1390, 1375, 1365, 1255, 1175, 1100, 1085 cm^{-1}; MS *m/e* 412 ($(M + H)^+$). Anal. Calcd for $C_{23}H_{41}NO_5 \cdot 0.25H_2O$: C, 66.39; H, 10.05; N, 3.37. Found: C, 66.46; H, 9.84; N, 3.36.

***N*-Butyl-2(*S*)-((3-(*tert*-butyloxycarbonyl)-2,2-dimethyl-4(*S*)-(cyclohexylmethyl)-5(*S*)-oxazolidinyl)methyl)-3-methylbutanamide (9).** The procedure of Bühlmayer et al.[9] was adapted. A solution of acid **8** (6.50 g, 15.8 mmol), 1-hydroxybenzotriazole (3.18 g, 20.8 mmol, monohydrate), and 4-methylmorpholine (2.61 mL, 2.40 g, 23.7 mmol) in 180 mL of DMF was cooled to −15 °C (under N_2). *N*-Ethyl-*N'*-(dimethylamino)-ethylcarbodiimide hydrochloride (4.55 g, 23.7 mmol) was added as a solid, and then the mixture was stirred for 2 h at −15 °C. The vessel was sealed and allowed to react at 0 °C (in a refrigerator) for 48 h, at which time TLC indicated complete conversion of acid **8** to active ester (R_f 0.49, EtOAc–hexane, 1:3). Butylamine (1.50 g, 20.5 mmol) was added to the ice-cooled active ester solution, and the stirred reaction solution was allowed to warm slowly to ambient temperature. After the mixture was stirred for 18 h, the volatiles were removed under reduced pressure, and the residue was partitioned between 300 mL of saturated aqueous $NaHCO_3$ and 300 mL of CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (2 × 250 mL), and then the combined organic phases were washed sequentially with 0.2 M aqueous $NaHSO_4$ (250 mL) and brine (250 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to produce 7.46 g of yellow oil. Flash chromatography (10% EtOAc–hexane) provided 6.56 g (89%) of amide **9** as a white foam: R_f 0.45 (25% EtOAc–hexane); $[\alpha]_D$ −13.1° (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.92 (d, *J* = 6.6 Hz, 3 H), 0.92 (t, *J* = 7 Hz, 3 H), 0.93 (d, *J* = 5.9 Hz, 3 H), 1.48 (s, 9 H), 1.58 (br s, 3 H), 0.8–1.7 (several br m, approximately 29 H total), 1.73–1.84 (m, 3 H), 1.87 (m, 1 H), 2.0 (m, 1 H), 3.27 (t, *J* = 7 Hz, 1 H), 3.29 (t, *J* = 7 Hz, 1 H), 3.5–3.8 (v br m, 1 H), 3.75 (m, 1 H), 5.63 (br t, *J* = 6 Hz, 1 H); MS *m/e* 467 ($(M + H)^+$). Anal. Calcd for $C_{27}H_{50}N_2O_4 \cdot 0.5H_2O$: C, 68.17; H, 10.81; N, 5.89. Found: C, 67.81; H, 10.56; N, 5.71.

(2*S*,4*S*,5*S*)-*N*-Butyl-5-amino-6-cyclohexyl-4-hydroxy-2-(2-methylethyl)hexanamide (2).[10] The procedure of Thaisrivongs et al.[6] was followed. To an ice-cooled solution of protected amino alcohol **9** (6.49 g, 13.9 mmol) in 130 mL of dry methanol under argon was added acetyl chloride (8.40 mL, 9.27 g, 118 mmol) over 10 min. The resulting solution was stirred at 0 °C for 2 h and then at room temperature for 36 h. Analysis by TLC indicated complete consumption of **9**. The reaction solution was degassed with nitrogen and then was made basic by careful addition of solid sodium bicarbonate (10 g, 119 mmol). After dilution with CH_2Cl_2 (175 mL), the mixture was filtered through Celite, using 3 × 100 mL of CH_2Cl_2 to wash the filtercake. The combined filtrate was concentrated under reduced pressure to give a viscous oil, which was crystallized from hot hexanes to provide 2.99 g (66%) of amino alcohol **2** as a white crystalline solid, mp 88–89 °C (lit.[9] mp 91–92 °C). The mother liquor was concentrated and purified by flash chromatography (30% aqueous NH_4OH–MeOH–CH_2Cl_2, 1:10:189) to yield an additional 0.60 g (13%) of **2**: R_f 0.21 (30% aqueous NH_4OH–MeOH–CH_2Cl_2, 1:20:179); $[\alpha]_D$ −25.5° (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.7–1.7 (several br m, 18 H), 0.92 (t, *J* = 7.2 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 1.87 (m, 1 H), 2.09 (ddd, *J* = 2.9, 8.5, 11.4 Hz, 1 H), 2.57 (ddd, *J* = 3.3, 5.5, 10 Hz, 1 H), 3.07 (ddd, *J* = 2.6, 5.9, 11 Hz, 1 H), 3.22 (m, 1 H), 3.30 (m, 1 H), 5.7 (br t, *J* = 6 Hz, 1 H); MS *m/e* 327 ($(M + H)^+$). Anal. Calcd for $C_{19}H_{38}N_2O_2$: C, 69.9; H, 11.7; N, 8.6. Found: C, 69.5, H, 11.5; N, 8.5.

(*R*)-3-(3-Methylbutanoyl)-4-(methoxycarbonyl)-1,3-thiazolidine-2-thione (11). To a solution of **10**[11] (4.91 g, 27.7 mmol) in 70 mL of CH_2Cl_2 at −78 °C under nitrogen was added 3.5 mL (43.3 mmol) of pyridine. After the reaction mixture was stirred for 5 min, a solution of isovaleryl chloride (5.41 mL, 44.4 mmol) in 10 mL of CH_2Cl_2 was added dropwise. The mixture was stirred at −78 °C for 1 h, allowed to warm to room temperature over 30 min, and then stirred overnight. TLC analysis indicated the total disappearance of **10**. Additional CH_2Cl_2 (250 mL) was added, and the reaction mixture was washed sequentially with water, 5% aqueous citric acid, and again with water, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The oily yellow residue was chromatographed on silica gel (20% EtOAc–hexane) to provide 5.78 g (80%) of **11** as a light yellow oil which solidified upon standing: mp 41–42 °C; R_f 0.30 (20% EtOAc–hexane); $[\alpha]_D$ −121.4° (*c* 1.92, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.96 (d, *J* = 6 Hz, 3 H), 1.00 (d, *J* = 6 Hz, 3 H), 2.23 (heptet, *J* = 6 Hz, 1 H), 3.06 (dd, *J* = 6, 15 Hz, 1 H), 3.28 (dd, *J* = 6, 15 Hz, 1 H), 3.38 (dd, *J* = 3, 9 Hz, 1 H), 3.68 (dd, *J* = 9, 9 Hz, 1 H), 3.82 (s, 3 H), 5.66 (dd, *J* = 3, 9 Hz, 1 H); IR ($CHCl_3$) 1750, 1700, 1220, 1160, 1040 cm^{-1}; MS *m/e* 261 (M^+). Anal. Calcd for $C_{10}H_{15}NO_3S_2$: C, 45.96; H, 5.74; N, 5.36; S, 24.51. Found: C, 45.57; H, 5.84; N, 5.31; S, 24.44.

3-(3(*R*)-(3-(*tert*-Butyloxycarbonyl)-2,2-dimethyl-4(*S*)-(cyclohexylmethyl)-5(*R*)-oxazolidinyl)-3-hydroxy-2(*R*)-isopropyl-1-oxopropyl)-4(*R*)-(methoxycarbonyl)-1,3-thiazolidine-2-thione (13). To a stirred solution of **11** (450 mg, 1.72 mmol) in 25 mL of CH_2Cl_2 at 0 °C (internal temperature) under nitrogen was added dibutylboryl trifluoromethanesulfonate (2.0 mmol, 2.0 mL of an 1.0 M solution in CH_2Cl_2, Aldrich). After the mixture was stirred for 5 min at 0 °C, diisopropylethylamine (0.4 mL, 2.30 mmol) was added dropwise. The internal temperature was carefully maintained at 0 °C during the process. The resulting light yellow solution was stirred at 0 °C for another 30 min and then cooled to −78 °C, and a solution of aldehyde **3** (500 mg, 1.53 mmol) in 5 mL of CH_2Cl_2 was added by syringe. The reaction mixture was stirred for 30 min at −78 °C and then allowed to warm to room temperature over 20 min. After the mixture was stirred for another 5 h, no starting aldehyde could be detected by TLC. The reaction was quenched with pH 7 phosphate buffer (50 mL), and the resulting mixture was stirred vigorously at 0 °C for 3 min. The yellow organic solution was separated, concentrated, and filtered through a silica gel column with EtOAc as the eluant to remove the boric acid byproduct. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel (20% EtOAc–hexane) to isolate 652 mg (73%)[13] of **13** as a light yellow glassy solid: mp 54–57 °C; R_f 0.22 (20% EtOAc–hexane); $[\alpha]_D$ −102.0° (*c* 3.25, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.85–1.85 (m, 13 H), 1.14 (d, *J* = 6 Hz, 3 H), 1.16 (d, *J* = 6 Hz, 3 H), 1.45 (s, 3 H), 1.62 (s, 3 H), 1.75 (s, 9 H), 2.17 (br d, *J* = 6 Hz, 1 H), 2.28 (heptet, *J* = 6 Hz, 1 H), 3.38 (dd, *J* = 3, 12 Hz, 1 H), 3.58 (dd, *J* = 9, 12 Hz, 1 H), 3.75 (br t, *J* = 4.5 Hz, 1 H), 3.84 (s, 3 H), 3.94 (dd, *J* = 3, 6 Hz, 1 H), 3.98 (ddd, *J* = 3, 6, 7.5 Hz, 1 H), 5.11 (dd, *J* = 6, 7.5 Hz, 1 H), 5.70 (dd, *J* = 3, 9 Hz, 1 H); IR ($CHCl_3$) 3560, 1740, 1690, 1400, 1170 cm^{-1}; MS *m/e* 587 (M^+). Anal. Calcd for $C_{28}H_{46}N_2O_7S_2$: C, 57.33; H, 7.85; S, 10.92. Found: C, 57.53; H, 8.07; S, 10.45.

***N*-Butyl-2(*S*)-((3-(*tert*-butyloxycarbonyl)-2,2-dimethyl-4(*S*)-(cyclohexylmethyl)-5(*S*)-oxazolidinyl)-(*R*)-hydroxymethyl)-3-methylbutanamide (14).** To a solution of **13** (600 mg, 1.02 mmol) in 25 mL of acetonitrile at room temperature was added 5 mL (50.6 mmol) of butylamine, and the reaction mixture was stirred for 1 h. TLC analysis indicated the complete absence of **13**. The reaction mixture was concentrated under reduced pressure, and the oily residue was chromatographed on silica gel (EtOAc–hexane, 1:8) to isolate 384 mg (78%) of **14** as a colorless oil: R_f 0.63 (EtOAc–hexane, 1:2); $[\alpha]_D$ +12.3° (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.85–1.75 (m, 17 H), 0.93 (t, *J* = 7.5 Hz, 3 H), 1.03 (d, *J* = 6 Hz, 3 H), 1.05 (d, *J* = 6 Hz, 3 H), 1.47 (s, 9 H), 1.59 (s, 3 H), 1.62 (s, 3 H), 1.75–1.85 (m, 1 H), 3.14–3.26 (m, 1 H), 3.25–3.40 (m, 1 H), 3.80–3.90 (m, 2 H), 3.90–4.00 (m, 1 H), 5.74

(m, 1 H); IR ($CHCl_3$) 3360, 1700, 1650, 1400, 1360, 1180, 1090 cm^{-1}; MS *m/e* 483 ($(M + H)^+$).

***N*-Butyl-2(*S*)-((3-(*tert*-butyloxycarbonyl)-2,2-dimethyl-4(*S*)-(cyclohexylmethyl)-5(*S*)-oxazolidinyl)-(*R*)-(((methylthio)thionyl)oxy)methyl)-3-methylbutanamide (15).** To a solution of **14** (109 mg, 0.23 mmol) in 25 mL of tetrahydrofuran at 0 °C was added carbon disulfide (1 mL, 16.6 mmol) and iodomethane (1 mL, 16.0 mmol). After the mixture was stirred for 5 min at 0 °C, sodium hydride (16 mg, 0.40 mmol, 60% in oil) was added. The resulting mixture was stirred for another 20 min, carefully poured into ice (~10 g), and extracted with EtOAc. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to an oily residue, which was column chromatographed on silica gel (10% EtOAc–hexane) to provide 108 mg (84%) of **15** as a light yellow solid: mp 135–136 °C; R_f 0.45 (20% EtOAc–hexane); $[\alpha]_D$ +43.5° (*c* 1.27, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.75–1.95 (m, 18 H), 0.94 (t, J = 7.5 Hz, 3 H), 1.02 (br d, J = 6 Hz, 6 H), 1.43 (s, 9 H), 1.50 (s, 3 H), 1.72 (s, 3 H), 2.58 (s, 3 H), 2.69 (dd, J = 6, 7.5 Hz, 1 H), 3.29 (dt, J = 6, 6 Hz, 2 H), 4.06 (m, 1 H), 4.18 (m, 1 H), 5.62 (br t, J = 6 Hz, 1 H), 6.28 (dd, J = 3, 7.5 Hz, 1 H); IR ($CHCl_3$) 1690, 1660, 1400, 1200, 1060 cm^{-1}; MS *m/e* 573 ($(M + H)^+$). Anal. Calcd for $C_{29}H_{52}N_2O_5S_2$: C, 60.82; H, 9.08; N, 4.90; S, 11.18. Found: C, 60.41; H, 9.29; N, 4.96; S, 10.90.

Preparation of 9 by Reduction of 15. To a refluxing solution of tri-*n*-butyltin hydride (800 mg, 2.96 mmol) in toluene (30 mL) under nitrogen was added a solution of **15** (189 mg, 0.33 mmol) in toluene (2 mL). Reflux was continued for another 10 min, at which time TLC analysis indicated the total disappearance of **15**. The reaction mixture was cooled and concentrated under reduced pressure, and the resulting oily residue was chromatographed on silica gel (10% EtOAc–hexane) to provide 135 mg (88%) of **9**: $[\alpha]_D$ −13.6° (*c* 1.36, $CHCl_3$); ^1H NMR and MS match those from the sample prepared by the first route.

Acknowledgment. We would like to express their gratitude to Messrs. William Arnold and Hormoz Mazdiyasni for the preparation of aldehyde **3** and to Professor David A. Evans for sharing a preprint of the lithium hydroperoxide hydrolysis procedure.

Registry No. **2**, 105852-64-0; **3**, 117997-58-7; **4**, 107599-99-5; **5**, 112190-42-8; **6**, 129921-91-1; **7**, 129921-92-2; **8**, 129921-93-3; **9**, 129921-94-4; **10**, 80963-80-0; **11**, 129921-95-5; **13**, 129921-96-6; **14**, 129921-97-7; **15**, 129921-98-8; Me_2CHCH_2COCl, 108-12-3.

A Catalytic Enantioselective Synthesis of Denopamine, a Useful Drug for Congestive Heart Failure

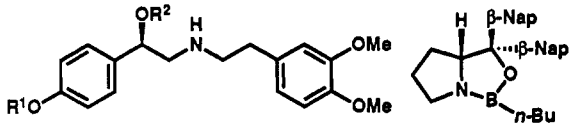
E. J. Corey* and John O. Link

Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138

Received April 16, 1990

Recent advances in drug specificity and duration of action have produced β-blockers and agonists that are highly effective in the treatment of cardiovascular disease, cardiac failure, asthma, and glaucoma. Notwithstanding these advances, many β-adrenoreceptor active drugs are sold as racemates[1] despite a clear preference for the use of enantiomerically pure drugs since the biological activity generally resides in a single enantiomer. A catalytic enantioselective method applicable to the synthesis of key arylethanolamine β-adrenoreceptor active drugs is desirable.

A good candidate for enantioselective synthesis is denopamine (**1**), a new selective β_2-agonist important for the treatment of congestive heart failure without promotion of increased myocardial oxygen consumption or heart rate.[2]



1 R^1=R^2=H (*R* form) **2**
8 R^1=TBS R^2=TES

Previous approaches to (*R*)-(−)-denopamine have included optical resolution[3a] or the use of chiral precursors ending with low overall yield[3c] or with significant racemization.[3b] Described here is a practical route to enantiomerically pure (*R*)-(−)-denopamine or its enantiomer in >60% overall yield that does not involve chromatography. This route demonstrates the applicability of the recently described CBS[4b] enantioselective catalytic reduction process to the synthesis of enantiomerically pure members of the therapeutically significant arylethanolamine drug class.

Reaction of 2-chloro-1-(4-hydroxyphenyl)ethanone (**3**)[5] with *tert*-butylchlorodimethylsilane (TBSCl) and imidazole in dimethylformamide (DMF) afforded ketone **4** in 96% yield. Ketone **4** was reduced by borane (0.6 equiv) in the

3 R^1=H
4 R^1=TBS

5 R^2=H R^3=Cl
6 R^2=H R^3=I
7 R^2=TES R^3=I

presence of (*R*)-oxazaborolidine·**2**[4e] as catalyst at 23 °C in tetrahydrofuran (THF) to give, after addition of methanolic hydrogen chloride and filtration, secondary alcohol **5** in 96% yield and 97% enantiomeric excess (ee%) and recovered 2-(di-β-naphthylhydroxymethyl)pyrrolidine as the crystalline hydrochloride salt. Chloro alcohol **5** was converted to iodide **6** (92%) by refluxing in acetone saturated with sodium iodide, which was then protected with ethyltrichlorosilane (TESCl) in DMF with imidazole to produce iodide **7** in 94% yield. Protected amino alcohol **8** was formed in 92% yield by reaction of iodide **7** with 2-(3,4-dimethoxyphenyl)ethylamine and triethylamine in THF at 100 °C in a sealed tube. Deprotection of amine **8** in methanol with potassium fluoride and hydrogen chloride afforded, after extractive isolation and recrystallization, optically pure denopamine (**1**) in 83% yield.

The practicality and effectiveness of this synthetic route can be evaluated from the detailed experimental procedure

(1) Lunts, L. H. C.; Main, B. G.; Tucker, H. In *Medicinal Chemistry, The Role of Organic Chemistry in Drug Research*; Roberts, S. M., Price, B. J., Ed.; Academic Press: New York, 1985; pp 49–92. The biological activity of arylethanolamine β-blockers and agonists is generally dependent on absolute stereochemistry, as exemplified by (*R*)-(−)-denopamine, which is the active form.

(2) (a) Bristow, M. R.; Hershberger, R. E.; Port, J. D.; Minobe, W.; Rasmussen, R. *Mol. Pharmacol.* **1989**, *35*, 295. (b) Yokoyama, H.; Yanagisawa, T.; Taira, N. *J. Cardiovasc. Pharmacol.* **1988**, *12*, 323.

(3) (a) Ikezaki, M.; Umino, N.; Gaino, M.; Aoe, K.; Iwakuma, T.; Ohishi, T. *Yakugaku Zasshi* **1986**, *106*, 80. (b) Noguchi, K.; Irie, K. Jpn. Patent 79 70,233, 1979; *Chem. Abstr.* **1979**, *91*, 630. (c) Noguchi, K.; Irie, K. Jpn. Patent 79 70,231, 1979; *Ibid.* **1979**, *91*, 630.

(4) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *Ibid.* **1987**, *109*, 7925. (c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861. (d) Corey, E. J. *Proceedings of the 31st National Organic Symposium*; American Chemical Society: Washington, DC, 1989; p 1. (e) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275. (f) Waldrop, M. M. *Science* **1989**, *245*, 354. (g) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611.

(5) Kajigaeshi, S.; Kakinami, T.; Moriwaki, M.; Fujisaki, S.; Maeno, K.; Okamoto, T. *Synthesis* **1988**, *7*, 545.

0022-3263/91/1956-0442$02.50/0