Enantioselective Synthesis of Aza Sugars from Amino Acids. 2.[1] The 3-Hydroxy-2-hydroxymethylpyrrolidines[2]

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Introduction

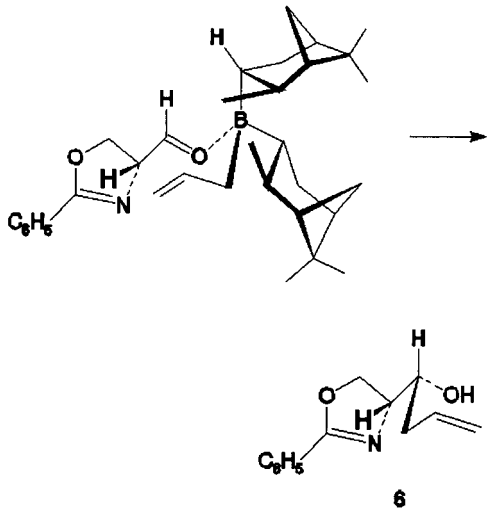
A number of polyhydroxylated pyrrolidines and piperidines (often called "aminosugars" or "azasugars") and related compounds have been found to be potent glycosidase (glycohydrolase) inhibitors.[4] Because glycoproteins mediate cell−cell recognition,[5] it is reasoned that inhibitors of glycosidases should have value in the palliation of viral infections as well as a host of other diseases in which transmission of information from one cell to another is important.

In sharp contrast to the substantial body of work on the synthesis of the eight stereoisomeric 3,4-dihydroxy-2-hydroxymethylpyrrolidines[1] (the physiologically active "azasugars" formally analogous to the ribosyl fragment of RNA), relatively little effort has been expended on the "simpler" four 3-hydroxy-2-hydroxymethylpyrrolidines (the "azaDNA" analogues). Indeed, despite some indication of physiological activity reported in the naturally occurring (2*R*,3*S*)-3-hydroxy-2-hydroxymethylpyrrolidine (**13**, vide infra) found in *Castanospermum australe* A. Cunn,[6] most of the synthetic efforts[7] resulting in the formation of these compounds have been directed toward other ends. Nonetheless, a path to these compounds, as well as to the corresponding 3,4-dihydroxy-2-hydroxymethylpyrrolidines,[1] is important since the development of methods for new types of DNA as well as RNA nucleotides in which the oxygen of the carbohydrate portion has been replaced by nitrogen or other heteroatoms may provide valuable analogues of physiologically active materials.[8]

Results and Discussion

As shown in Scheme 1, when the known,[9] readily available 4-(carbomethoxy)-2-phenyl-Δ^2-oxazolines, L-**2** and D-**2**, derived from, respectively, L- and D-serine methyl ester, **1**, were treated with an excess of DIBAL-H at low temperature, reduction of each was effected.[10] Despite the reports of others,[9] our attempts to isolate the expected aldehydes were unsuccessful. However, an alcohol quench of the reaction mixture[11] followed, in the same flask, by direct addition of either (+)- or (−)-*B*-allyldiisopinocamphenylborane [(+)- or (−)-allyl-Ipc_2, respectively] (freshly prepared from the corresponding chloroborane and allylmagnesium bromide)[12] resulted in the formation of the specific isomers **3** and **4**, i.e., (*S*,*S*)-(+)-4-hydroxy-4-(4,5-dihydro-2-phenyl-4-oxazolyl)-1-butene and (*S*,*R*)-(+)-4-hydroxy-4-(4,5-dihydro-2-phenyl-4-oxazolyl)-1-butene, respectively, from L-serine and the respective enantiomeric (+)- and (−)-allyl-Ipc_2 isomers.

The formation of the specific isomers **5** and **6**, i.e., (*R*,*S*)-(+)-4-hydroxy-4-(4,5-dihydro-2-phenyl-4-oxazolyl)-1-butene and (*R*,*R*)-(+)-4-hydroxy-4-(4,5-dihydro-2-phenyl-4-oxazolyl)-1-butene, respectively, from D-serine and the respective enantiomeric (+)- and (−)-allyl-Ipc_2 isomers is also shown in Scheme 1. The relative stereochemistry of **6** was confirmed by X-ray crystallography.[13]



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Allylation of aldehydes by this method has been reported to proceed with excellent (≥99% ee) enantio-

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(1) For the first paper in this series, see: Huang, Y.; Dalton, D. R.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 372.

(2) Presented, in part, at the 33rd Middle Atlantic Regional Meeting of the American Chemical Society, Newark, DE, May 2000; ORGN 224.

(3) To whom inquiries concerning the X-ray crystal structure should be addressed.

(4) For leading references, see: (a) Karpas, A.; Fleet, G. W. J.; Dewk, R. A.; Petrusson, S.; Mangoong, S. K.; Ramsden, J. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Nat. Acad. Sci. U.S.A.* **1988**, *85*, 9229. (b) *The Amino Sugars; the Chemistry and Biology of Compounds Containing Aminosugars;* Jeanloz, R. W., Balazs, D. A., Eds.; Academic Press: New York, 1965−1966; Vols. IA, IB, IIA, IIB.

(5) Provencher, L.; Steensma, D. H.; Wong, C.-H. *Bioorg. Med. Chem.* **1994**, *2*, 1179.

(6) Nash, R. J.; Bell, E. A.; Fleet, G. W. J.; Jones, R. H.; Williams, M. H. *J. Chem. Soc., Chem. Commun.* **1988**, 738.

(7) For recent syntheses, see, for example: Sundram, H.; Golebiowski, A.; Johnson, C. R. *Tetrahedron Lett.* **1994**, *35*, 6975. Dell'Uomo, N.; Di Giovanni, M. D.; Misiti, D.; Zappia, G.; Monache, G. D. *Tetrahedron: Assymtry* **1996**, *7*, 181 and references therein. Full structural information is not available for all of the materials reported.

(8) See, for example: Momotake, A.; Mito, J.; Yamaguchi, K.; Togo, H.; Yokoyama *J. Org. Chem.* **1998**, *63*, 7207 and references therein.

(9) (a) Tkaczuk, P.; Thornton, E. R. *J. Org. Chem.* **1981**, *46*, 4393. (b) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.

(10) Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469.

(11) As part of another effort, a variety of alcohols were used to quench the reduction mixture (Mr. M. Kiernan). Although the reaction between the resulting aldehyde and carbomethoxymethylene triphenylphosphorane[1] was studied in that case instead of the one used here, his results, which produced a variation of the [*Z*:*E*] alkene ratio, also showed that there was no epimerization at C-4 of the oxazoline. The results here are in concert with his observations.

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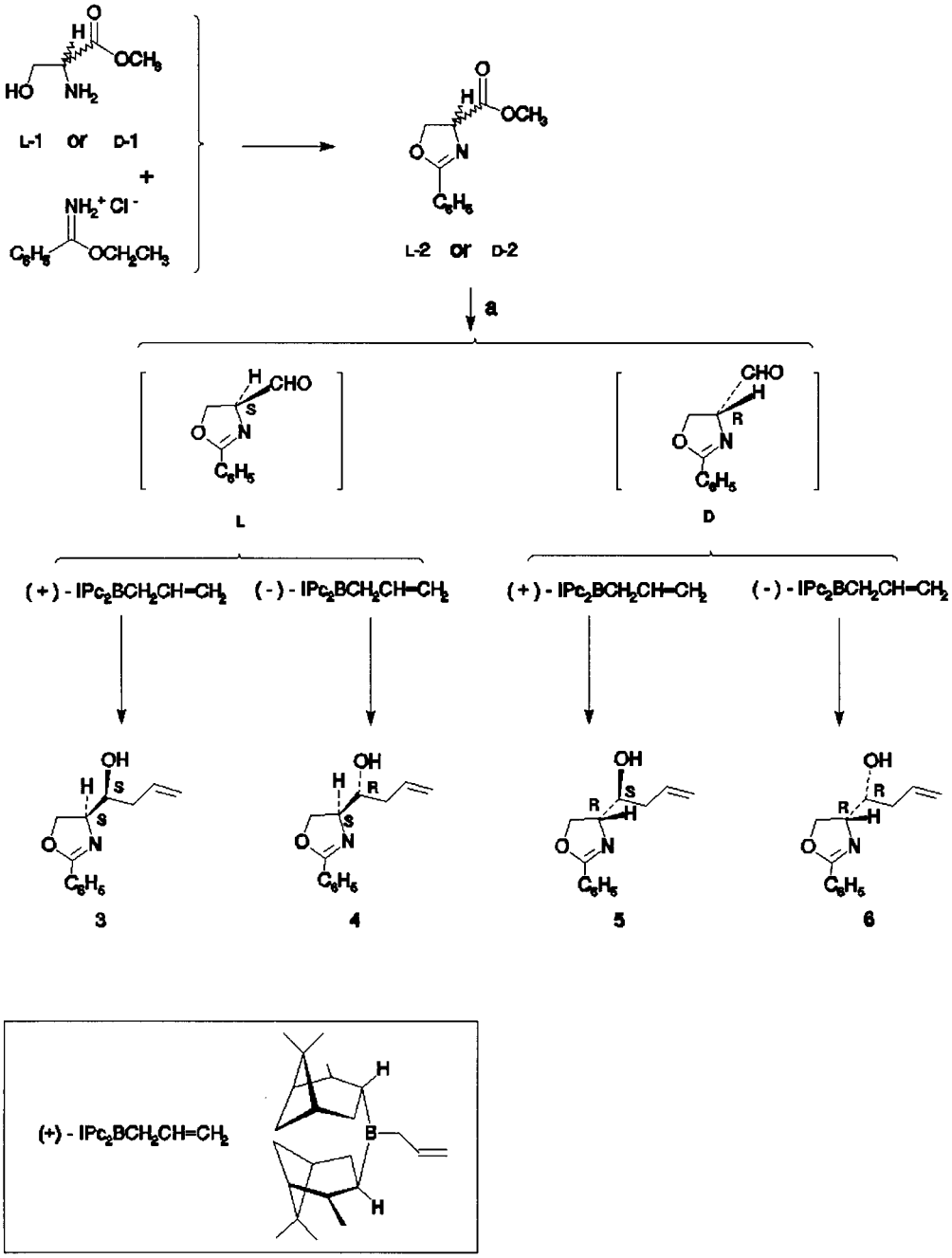
Scheme 1[a]



[a] (a) DIBAL-H, R-OH quench.

selectivity.[14] Reagent control[15] as observed under similar circumstances[16] is expected to apply, and small amounts (ca. 4−8%) of diastereomeric products from the reaction of the enantiomerically pure aldehydes with each of the allyl-Ipc_2 isomers are seen in the ^1H NMR spectra of the partially purified adducts. The minor isomer is readily removed by column chromatography. Although optical rotations for crude material were not examined, the observation of optical rotations of identical magnitudes (within experimental error) for the respective purified enantiomeric pairs (e.g., **3**/**6** or **4**/**5**) argues that they are formed in high enantiomeric excess.

The individual secondary alcohols (**3**−**6**) were converted to their corresponding acetates and the carbon−carbon double bonds oxidized with osmium tetroxide and sodium metaperiodate to produce the corresponding labile aldehydes. The latter, without isolation, were reduced to the primary alcohols **7**−**10** with sodium borohydride (Scheme 2).

As shown in Scheme 3, the individual primary alcohols (**7**−**10**) were converted to the corresponding tosylates and the oxazoline rings opened hydrolytically in dilute aque-

(12) See, for example: Goulet, M. T. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; John Wiley & Sons: New York: 1995, Vol. 1, 103 and references therein.

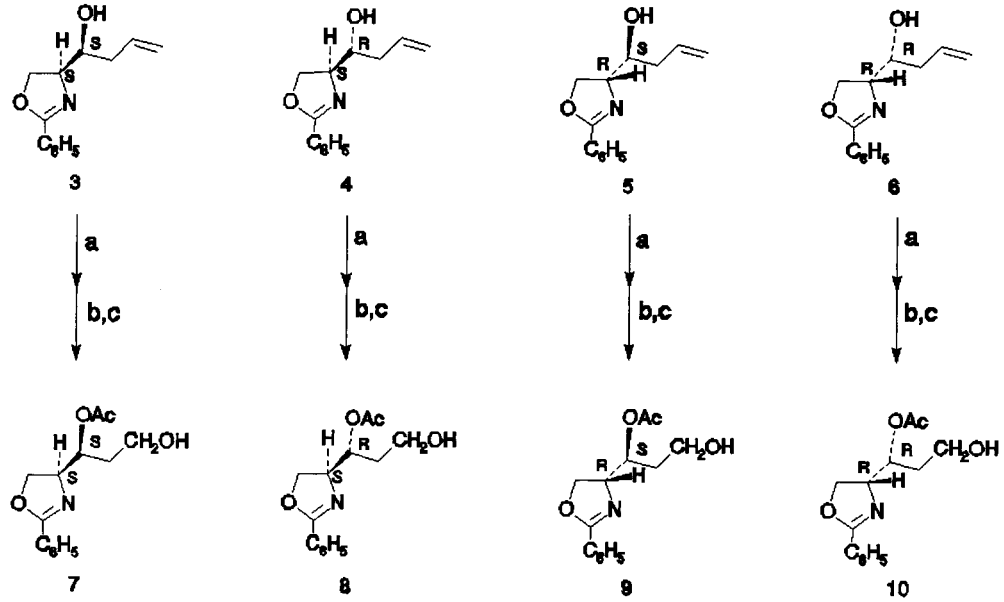
(13) An author (P.J.C.) has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. In addition, both active and static views are available at the senior author's website (http://astro.temple.edu/~dalton).

(14) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

(15) Roush, W. R. In *Houben-Weyl, Methods of Organic Chemistry*; Veralg, G. Thieme; Stuttgart, Germany: 1995; E21b, 1410ff.

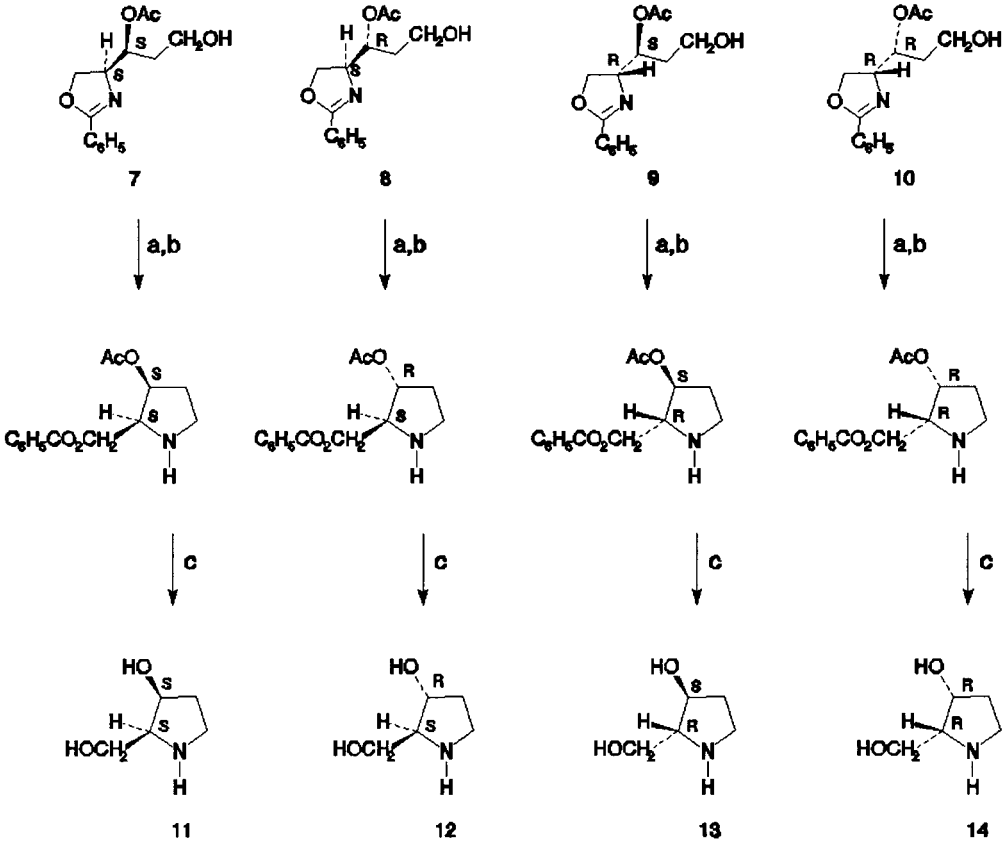
(16) We are grateful for the constructive comments of anonymous referees who brought refs 10 and 15 to our attention and suggested we reexamine our data.

Scheme 2[a]



[a] (a) Ac_2O, triethylamine; (b) OsO_4, THF, $NaIO_4$; (c) $NaBH_4$, MeOH.

Scheme 3[a]



[a] (a) Na-H, *p*-toluenesulfonyl chloride; (b) aqueous HCl; (c) aqueous NaOH.

ous HCl, whereupon recyclization to the respective pyrrolidines ensued. A final treatement with aqueous base served to hydrolyze the acetate and benzoate ester groups and produce the desired isomeric 3-hydroxy-2-hydroxymethylpyrrolidines **11**−**14**.

Conclusion

The synthesis of all four isomeric 3-hydroxy-2-hydroxymethylpyrrolidines [the isomers of (+)- and (−)-iminodeoxyribitol] from L- or D-serine methyl ester has been effected. Having begun with species of known absolute configuration, no separation of isomers is required and each can be prepared specifically.

Experimental Section

General Methods. Melting points are uncorrected. Satisfactory high-resolution mass spectrometric analyses (The Pennsylvania State University, College Park, PA or Drexel University,

Philadelphia, PA) have been obtained for all new compounds. ^{1}H (300 and 500 MHz) and ^{13}C (75 MHz) NMR spectra were obtained on GE QE-300 and Omega-500 NMR spectrometers. Chemical shifts are reported in parts per million (ppm), δ, from TMS = 0.00 ppm. NMR spectra of the deoxyazaribitol isomers **11**−**14**, along with the X-ray crystallographic data for the alkene **6**, are provided in the Supporting Information. Infrared (FT-IR) spectra were taken as neat oils (for noncrystalline materials) or as KBr pellets for crystalline samples on Mattson 4020, Nicolet 800, or Digilab FTS-40 spectrometers, and those spectra along with the ^{1}H and ^{13}C NMR spectra of the reported intermediates can be obtained from http://astro.temple.edu/~dalton or by mail from the senior author. Solvents, reactive reagents, and column materials were purchased from Acros Chemical, Fisher Scientific, and/or Aldrich Chemical Companies. Solvents were distilled under argon prior to use. Optical rotations were taken as noted in a Perkin-Elmer 341 polarimeter.

(*S*,*S*)-, (*S*,*R*)-, (*R*,*S*)-, and (*R*,*R*)-4-Hydroxy-4-(4,5-dihydro-2-phenyl-4-oxazolyl)-1-butenes (3, 4, 5, and 6). The oxazoline methyl ester **2**[1] (215 mg, 1.05 mmol) in dry toluene was cooled to −78 °C in an atmosphere of Ar, and with stirring, DIBAL-H (1.5 M, 1.3 mL. 1.9 mmol) in toluene was added slowly. The reaction mixture was stirred at −78 °C for an additional 3 h and then quenched with precooled MeOH (1 mL); after 0.5 h, the temperature was allowed to rise to −20 °C where it was held for an additional 1 h. In the meantime, under an atmosphere of Ar, one of the enantiomers of diisopinocamphenylborane chloride (DIP-chloride) (617 mg, 2.039 mmol) in dry Et_2O (5 mL) was cooled to −78 °C and, with stirring, allylmagnesium bromide in Et_2O (2.1 mL of a 1 M solution, 2.1 mmol) was added dropwise. After stirring at −78 °C for an additional 15 min, the reaction mixture was allowed to warm to room temperature and 1 h later recooled to −78 °C. Then, the aldehyde solution prepared above was transferred, via cannula, over a few minutes into the allylborane solution. Stirring was continued at −78 °C for an additional 1 h after which the reaction mixture was allowed to warm to room temperature over 1 h. When at room temperature, the reaction mixture was treated with 0.2 mL (5 mmol) of 2.5 N aqueous NaOH and 0.4 mL (3 mmol) of 30% H_2O_2. Then, with stirring, the basic solution was heated to reflux for 0.5 h before the solution was cooled to room temperature. The organic phase was separated and washed with water and brine and dried over $MgSO_4$ and the solvent removed at reduced pressure. The alkenols were purified by silica gel flash chromatography and obtained in 89−91% (purified) yields (eluting with hexane:ether [6:1]). For (*S*,*S*)-4-hydroxy-4-(4,5-dihydro-2-phenyl-4-oxazolyl)-1-butene (**3**) [from (−)-DIP-Cl], mp 94−95 °C, $[\alpha]^{20}_D$ = +91.8 (*c* = 0.101, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.94−7.96 (d, 2H); 7.45−7.48 (d, 1H); 7.37−7.42 (t, 2H); 5.89−6.03 (m, 1H); 5.12−5.21 (t, 2H); 4.39−4.45 (t, 1H); 4.29−4.35 (m, 1H); 4.20−4.27 (m, 1H); 3.63−3.69 (m, 1H); 3.54 (s, 1H); 2.37−2.42 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 165.10, 134.67, 131.50, 128.38, 128.25, 127.39, 117.54, 73.16, 70.93, 69.49, 38.35. IR (KBr, cm^{-1}) 3159.3, 3073.9, 1638.9, 1378.2, 1091.9, 687.5. HRMS calcd for [$C_{13}H_{15}NO_2$ + H] 218.1181, found [M + H]$^+$ 218.1176. The enantiomer, (*R*,*R*)-4-hydroxy-4-(4,5-dihydro-2-phenyl-4-oxazolyl)-1-butene (**6**) [from (+)-DIP-Cl], mp 95−96 °C, $[\alpha]^{20}_D$ = −91.7 (*c* = 0.101, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.96−7.99 (d, 2H); 7.49−7.451 (d, 1H); 7.40−7.45 (t, 2H); 5.90−6.04 (m, 1H); 5.15−5.23 (t, 2H); 4.44−4.50 (t, 1H); 4.32−4.438 (m, 1H); 4.23−4.31 (m, 1H); 3.66−3.72 (m, 1H); 3.31 (s, 1H); 2.39−2.44 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 161.13, 134.54, 131.54, 128.37, 128.29, 127.37, 117.70, 73.22, 70.91, 69.54, 38.42. IR (KBr, cm^{-1}) 3172.7, 3074.0, 1638.7, 1377.9, 1091.9, 687.5. HRMS calcd for [$C_{13}H_{15}NO_2$ + H] 218.1181, found [M + H]$^+$ 218.1186. The X-ray crystal structure of **6** is provided in the Supporting Information.[12] For (*S*,*R*)-4-hydroxy-4-(4,5-dihydro-2-phenyl-4-oxazolyl)-1-butene (**4**) [from (+)-DIP-Cl], $[\alpha]^{20}_D$ = +42.6 (*c* = 0.010, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.69−7.72 (d, 2H); 7.39−7.44 (t, 1H); 7.25−7.30 (t, 2H); 5.88−6.02 (m, 1H); 5.14−5.22 (m, 1H); 4.46−4.52 (t, 2H); 4.31−4.42 (m, 2H); 4.18−4.23 (m, 1H); 2.24−2.43 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 165.14, 134.61, 131.22, 128.16, 128.07, 126.93, 117.63, 70.79, 70.69, 67.35, 38.38. IR (KBr, cm^{-1}) 3223.8, 3077.4, 1633.3, 1450.1, 1360.7, 1092.3, 962.9, 694.0. HRMS calcd for [$C_{13}H_{15}NO_2$ + H] 218.1181, found [M + H]$^+$ 218.1180. The enantiomer, (*R*,*S*)-4-hydroxy-4-(4,5-dihydro-2-phenyl-4-oxazolyl)-1-butene (**5**) [from (−)-DIP-Cl], $[\alpha]^{20}_D$ = −40.9 (*c* = 0.010, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.69−7.72 (d, 2H); 7.39−7.44 (t, 1H); 7.25−7.30 (t, 2H); 5.88−6.02 (m, 1H); 5.14−5.22 (m, 1H); 4.47−4.52 (t, 2H); 4.35−4.42 (m, 2H); 4.28−4.32 (m, 1H); 4.18−4.23 (m, 1H); 2.24−2.43 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 165.15, 134.61, 131.22, 128.16, 128.07, 126.92, 117.63, 70.73, 70.69, 67.34, 38.38. IR (KBr, cm^{-1}) 3223.8, 3066.0, 1633.3, 1450.1, 1360.7, 1092.3, 962.9, 694.0. HRMS calcd for [$C_{13}H_{15}NO_2$ + H] 218.1181, found [M + H]$^+$ 218.1174.

(*S*,*S*)-, (*S*,*R*)-, (*R*,*S*)-, and (*R*,*R*)-4-Hydroxy-4-(4,5-dihydro-2-phenyl-4-oxazolyl)-1-butene Acetates (3-OAc, 4-OAc, 5-OAc, and 6-OAc). A hydroxyalkene (2.9 g, 13.4 mmol) was dissolved in methylene chloride (100 mL), and triethylamine (26.7 mmol, 3.73 mL) and acetic anhydride (26.7 mmol, 2.5 mL) were sequentially added at room temperature. After permitting the reaction mixture to stir overnight, it was quenched with water, and the organic phase was separated, washed with water and brine, and dried over magnesium sulfate. The solvent was removed at reduced pressure and the residue purified by flash chromatography on silica gel. The esters (93−96% yield) were eluted with hexanes−ether (6:4). For (*S*,*S*)-4-hydroxy-4-(4,5-dihydro-2-phenyl-4-oxazolyl)-1-butene acetate (**3**-OAc), $[\alpha]^{20}_D$ = +33.4 (*c* = 0.011, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.89−7.92 (d, 2H); 7.27−7.40 (m, 3H); 5.67−5.80 (m, 3H); 4.99−5.10 (m, 1H); 4.38−4.45 (m, 1H); 4.25−4.32 (t, 1H); 4.09−4.14 (t, 1H); 2.39−2.45 (m, 2H); 1.93 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.45, 164.65, 133.49, 131.34, 128.27, 128.19, 127.48, 117.88, 73.35, 68.69, 68.26, 35.12, 20.83. IR (neat oil, cm^{-1}) 3076.3, 2897.5, 1738.3, 1650.1, 1369.8, 1237.1, 1026.3, 698.5. HRMS calcd for [$C_{15}H_{17}NO_3$ + H] 260.1287, found [M + H]$^+$ 260.1294. The enantiomer, (*R*,*R*)-4-hydroxy-4-(4,5-dihydro-2-phenyl-4-oxazolyl)-1-butene acetate (**6-OAc**), $[\alpha]^{20}_D$ = −33.2 (*c* = 0.011, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.85−7.88 (d, 2H); 7.25−7.36 (m, 3H); 5.62−5.76 (m, 3H); 4.95−5.06 (m, 1H); 4.34−4.41 (m, 1H); 4.22−4.28 (t, 1H); 4.05−4.10 (t, 1H); 2.35−2.41 (m, 2H); 1.89 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.42, 164.62, 133.44, 131.30, 128.24, 128.15, 127.44, 117.85, 73.31, 68.65, 68.21, 35.07, 20.80. IR (neat oil, cm^{-1}) 3076.3, 2897.5, 1738.3, 1651.7, 1369.8, 1237.5, 1026.3, 698.7. HRMS calcd for [$C_{15}H_{17}NO_3$ + H] 260.1287, found [M + H]$^+$ 260.1239. For (*S*,*R*)-4-hydroxy-4-(4,5-dihydro-2-phenyl-4-oxazol-yl)-1-butene acetate (**4-OAc**), $[\alpha]^{20}_D$ = +59.6 (*c* = 0.015, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.87−7.89 (m, 2H); 7.29−7.42 (m, 3H); 5.67−5.83 (m, 1H); 5.01−5.09 (m, 3H); 4.22−4.38 (m, 3H); 2.35−2.45 (m, 2H); 1.92 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.19, 164.88, 133.12, 131.41, 128.23, 127.32, 118.05, 74.26, 68.99, 68.81, 35.87, 20.87. IR (neat oil, cm^{-1}) 1739.8, 1648.8, 1371.8, 1234.9. HRMS calcd for [$C_{15}H_{17}NO_3$ + H] 260.1287, found [M + H]$^+$ 260.1294. The enantiomer, (*R*,*S*)-4-hydroxy-4-(4,5-dihydro-2-phenyl-4-oxazolyl)-1-butene acetate (**5-OAc**), $[\alpha]^{20}_D$ = −58.1 (*c* = 0.019, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.87−7.89 (m, 2H); 7.30−7.43 (m, 3H); 5.68−5.81 (m, 1H); 5.01−5.09 (m, 3H); 4.21−4.41 (m, 3H); 2.33−2.49 (m, 2H); 1.92 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.17, 164.85, 133.13, 131.41, 128.22, 127.32, 118.04, 74.25, 68.98, 68.80, 35.84, 20.85. IR (neat oil, cm^{-1}) 1740.1, 1648.9, 1371.5, 1235.3. HRMS calcd for [$C_{15}H_{17}NO_3$ + H] 260.1287, found [M + H]$^+$ 260.1287.

(*S*,*S*)-, (*S*,*R*)-, (*R*,*S*)-, and (*R*,*R*)-3-(4,5-Dihydro-2-phenyl-4-oxazolyl)-3-acetoxy-1-propanols (7, 8, 9, and 10). An acetoxyalkene (2.0 g, 7.7 mmol) was dissolved in dry THF (30 mL) and water (10 mL), and osmium tetroxide (31.6 mg, 0.124 mmol) was added. The reaction mixture was stirred at room temperature for 5 min, and then sodium periodate (a total of 3.24 g, 15.4 mmol) was added in portions over 0.5 h while the temperature of the reaction mixture was maintained at room temperature. The slurry was stirred for an additional 1.5 h and quenched in water (10 mL). The reaction mixture was extracted with chloroform (3 × 25 mL), and the organic phases were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent at reduced pressure, the residue was dissolved in methanol and cooled to 0 °C. Then, with cooling and stirring, sodium borohydride (300 mg, 7.93 mmol) was added in portions over 1 h. Stirring was continued for an additional 0.5 h, and the solution was neutralized by dropwise addition of aqueous 1 N HCl. The solvents were removed at reduced pressure, and the residue was purified by flash chromatography on silica gel (eluting with acetone/hexane; 3:1) to produce the desired primary alcohols (58−62% yield). For (*S*,*S*)-3-(4,5-dihydro-2-phenyl-4-oxazolyl)-3-acetoxy-1-propanol (**7**) $[\alpha]^{20}_D$ = +50.0 (*c* = 0.004, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.87−7.90 (m, 2H); 7.42−7.47 (m, 1H); 7.33−7.38 (m, 2H); 4.40−4.44 (m, 2H); 4.19−

4.29 (m, 1H); 3.65−3.67 (m, 1H); 3.53−3.61 (m, 1H); 2.01 (s, 3H); 1.83−1.89 (m 2H). ^{13}C NMR ($CDCl_3$) δ 171.13, 165.31, 131.55, 128.26, 127.20, 71.21, 70.28, 69.39, 61.32, 32.78, 20.90. IR (KBr, cm^{-1}) 3163.4, 1726.2, 1635.5, 1380.3, 1254.8. HRMS calcd for [$C_{14}H_{17}NO_4$ + H] 264.1236, found [M + H]$^+$ 264.1227. The enantiomer, (*R*,*R*)-3-(4,5-dihydro-2-phenyl-4-oxazolyl)-3-acetoxy-1-propanol (**10**) $[\alpha]^{20}_D$ = −53.2 (*c* = 0.007, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.85−7.87 (m, 2H); 7.39−7.44 (m, 1H); 7.30−7.35 (m, 2H); 4.34−4.41 (m, 2H); 4.19−4.25 (m, 1H); 3.63−3.66 (m, 1H); 3.53−3.61 (m, 1H); 1.98 (s, 3H); 1.83−1.89 (m 2H). ^{13}C NMR ($CDCl_3$) δ 171.10, 165.26, 131.52, 128.26, 128.22, 127.21, 71.22, 70.19, 69.35, 61.34, 32.71, 20.88. IR (KBr, cm^{-1}) 3161.4, 1726.2, 1639.7, 1380.4, 1255.4. HRMS calcd for [$C_{14}H_{17}NO_4$ + H] 264.1236, found [M + H]$^+$ 264.1238. For (*S*,*R*)-3-(4,5-dihydro-2-phenyl-4-oxazolyl)-3-acetoxy-1-propanol (**8**) $[\alpha]^{20}_D$ = +29.6 (*c* = 0.005, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.74−7.76 (m, 2H); 7.39−7.44 (m, 1H); 7.27−7.32 (t, 2H); 4.39−4.46 (m, 1H); 4.23−4.36 (m, 2H); 4.06−4.09 (m, 1H); 2.05 (s, 3H); 1.81−1.86 (m 2H); 1.66−1 76 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 171.21, 165.32, 131.43, 128.17, 126.87, 71.20, 68.58, 67.74, 61.53, 32.59, 20.93. IR (KBr, cm^{-1}) 3226.0, 2916.5, 1723.7, 1637.6, 1374.4, 1248.0, 1031.6 HRMS calcd for [$C_{14}H_{17}NO_4$ + H] 264.1236, found [M + H]$^+$ 264.1238. The enantiomer, (*R*,*S*)-3-(4,5-dihydro-2-phenyl-4-oxazolyl)-3-acetoxy-1-propanol (**9**) $[\alpha]^{20}_D$ = −28.5 (*c* = 0.006, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.66−7.69 (m, 2H); 7.34−7.39 (m, 1H); 7.21−7.27 (t, 2H); 4.32−4.44 (m, 1H); 4.22−4.29 (m, 2H); 4.03−4.10 (m, 1H); 2.02 (s, 3H); 1.77−1.86 (m 2H); 1.64−1 74 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 171.14, 165.22, 131.32, 128.10, 126.83, 71.23, 68.40, 67.59, 61.55, 32.59, 20.88. IR (KBr, cm^{-1}) 3224.6, 2911.9, 1722.6, 1637.6, 1374.4, 1249.9, 1062. HRMS calcd for [$C_{14}H_{17}NO_4$ + H] 264.1236, found [M + H]$^+$ 264.1227.

(*S*,*S*)-, (*S*,*R*)-, (*R*,*S*)-, and (*R*,*R*)-3-(4,5-Dihydro-2-phenyl-4-oxazolyl)-3-acetoxy-1-propyl Tosylates (7-OTs, 8-OTs, 9-OTs, and 10-OTs). A primary alcohol (1.0 g, 3.8 mmol) was dissolved in dry THF (10 mL), and a solution of toluenesulfonyl chloride (876.6 mg, 4.59 mmol) in the same solvent (10 mL) was also prepared. The two solutions were then added simultaneously to a suspension of sodium hydride (729.6 mg, 30.4 mmol) in dry THF (30 mL) with stirring. The resulting mixture was heated to 40 °C for 5 h and allowed to cool, and water was added to destroy the excess sodium hydride. The reaction mixture was extracted with ethyl acetate (3 × 25 mL), and the combined organic layers were washed with brine and dried over magnesium sulfate. The solvent was removed at reduced pressure, and the tosylates were purified (58−62% yield) by silica gel flash column chromatography (eluting with hexanes−ethyl acetate (1:1). For (*S*,*S*)-3-(4,5-dihydro-2-phenyl-4-oxazolyl)-3-acetoxy-1-propyl tosylate (**7-OTs**) $[\alpha]^{20}_D$ = +15.2 (*c* = 0.009, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.86−7.88 (d, *J* = 7.5 Hz, 2H); 7.78−7.81 (d, *J* = 7.8 Hz, 2H); 7.45−7.49 (t, *J* = 7.2 Hz, 1H); 7.36−7.41 (t, *J* = 7.5 Hz, 2H); 7.29−7.32 (d, *J* = 7.8 Hz, 2H); 4.91−4.97 (m, 1H); 4.65−4.71 (m, 1H); 4.35−4.49 (m, 2H); 4.04−4.13 (m, 1H); 3.81−3.91 (m, 1H); 2.42 (s, 3H); 1.95 (s, 3H); 1.90−1.95 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 170.55, 165.63, 145.03, 133.37, 131.71, 129.82, 128.31, 127.78, 127.09, 78.89, 68.13, 59.98, 28.57, 21.59, 20.73. IR (KBr, cm^{-1}) 2968.3, 1740.2, 1647.3, 1365.68, 1242.4, 1176.2. HRMS calcd for [$C_{21}H_{23}NSO_6$ + H] 418.1324: Found [M + H]$^+$ 418.1319. The enantiomer, (*R*,*R*)-3-(4,5-dihydro-2-phenyl-4-oxazolyl)-3-acetoxy-1-propyl tosylate (**10-OTs**) $[\alpha]^{20}_D$ = −16.1 (*c* = 0.011, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.85−7.88 (d, *J* = 7.5 Hz, 2H); 7.76−7.79 (d, *J* = 7.8 Hz, 2H); 7.44−7.49 (t, *J* = 7.2 Hz, 1H); 7.35−7.39 (t, *J* = 7.5 Hz, 2H); 7.28−7.31 (d, *J* = 7.8 Hz, 2H); 4.90−4.96 (m, 1H); 4.64−4.71 (m, 1H); 4.35−4.49 (m, 2H); 4.04−4.11 (m, 1H); 3.82−3.90 (m, 1H); 2.40 (s, 3H); 1.95 (s, 3H); 1.90−1.95 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 170.55, 165.63, 145.06, 133.44, 131.78, 129.83, 128.32, 128.36, 127.76, 112.86, 78.91, 68.22, 68.04, 59.97, 28.63, 21.58, 20.73. IR (KBr, cm^{-1}) 2963.3, 1740.7, 1648.9, 1366.4, 1243.6, 1175.9. HRMS calcd for [$C_{21}H_{23}NSO_6$ + H] 418.1324, found [M + H]$^+$ 418.1316. For (*S*,*R*)-3-(4,5-dihydro-2-phenyl-4-oxazolyl)-3-acetoxy-1-propyl tosylate (**8-OTs**) $[\alpha]^{20}_D$ = +32.7 (*c* = 0.009, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.73−7.76 (d, *J* = 9.0 Hz, 2H); 7.65−7.68 (d, *J* = 9.0 Hz, 2H); 7.43−7.49 (m, 1H); 7.32−7.37 (m, 2H); 7.10−7.08 (d, *J* = 8.1 Hz, 2H); 4.85−4.91 (m, 1H); 4.30−4.45 (m, 3H); 4.08−4.20 (m, 1H); 2.29 (s, 3H), 2.05−2.13 (m, 2H); 2.02 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.66, 165.35, 149.55, 144.58, 133.70, 135.90, 133.70, 131.54, 129.60, 128.32, 128.11, 127.51, 126.94, 80.90, 69.29, 68.61, 59.98, 31.43, 29.59, 21.54, 20.81. IR (KBr, cm^{-1}) 2965.33, 1739.9, 1646.9, 1363.0, 1176.0. HRMS calcd for [$C_{21}H_{23}NSO_6$ + H] 418.1324, found [M + H]$^+$ 418.1319. The enantiomer, (*R*,*S*)-3-(4,5-dihydro-2-phenyl-4-oxazolyl)-3-acetoxy-1-propyl tosylate (**9-OTs**) $[\alpha]^{20}_D$ = −30.6 (*c* = 0.01, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.72−7.75 (d, *J* = 9.0 Hz, 2H); 7.64−7.67 (d, *J* = 9.0 Hz, 2H); 7.42−7.47 (m, 1H); 7.31−7.36 (m, 2H); 7.07−7.09 (d, *J* = 8.1 Hz, 2H); 4.85−4.91 (m, 1H); 4.29−4.47 (m, 3H); 4.07−4.21 (m, 1H); 2.27 (s, 3H), 2.04−2.12 (m, 2H); 2.01 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 170.65, 165.33, 149.57, 144.58, 133.69, 131.54, 129.59, 128.32, 127.50, 126.92, 80.91, 69.28, 68.58, 59.98, 31.41, 21.53, 20.81. IR (KBr, cm^{-1}) 2966.23, 1740.2, 1652.6, 1362.9, 1176.0. HRMS calcd for [$C_{21}H_{23}NSO_6$ + H] 418.1324, found [M + H]$^+$ 418.1322.

(*S*,*S*)-, (*S*,*R*)-, (*R*,*S*)-, and (*R*,*R*)-3-Hydroxy-2-hydroxymethylpyrrolidine Acetoxy Benzoates [11 (-OAc, -OBz), 12 (-OAc, -OBz), 13 (-OAc, -OBz) and 14 (-OAc, -OBz)]. A tosylate (823 mg, 1.98 mmol) was dissolved in methanol (30 mL), water (2 mL), and aqueous hydrochloric acid (1 M, 2.98 mL). The resulting solution was stirred at room temperature overnight and then neutralized by addition of solid sodium bicarbonate. The solvent was removed at reduced pressure and the residue purified by silica gel flash column chromatography [eluting with hexane−ethyl acetate (3:7)] to yield the respective acetoxybenzoates (68−72% yield). For (*S*,*S*)-3-acetoxy-2-hydroxymethylpyrrolidine benzoate (**11**, **-OAc**, **-OBz**) $[\alpha]^{20}_D$ = −26.8 (*c* = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.04−8.07 (m, 2H); 7.54−7.57 (m, 1H); 7.41−7.46 (m, 2H); 4.34 (dd, *J* = 6.9 Hz, 12.0 Hz, 2H); 4.24 (m, 2H); 2.54 (q, *J* = 6.0 Hz, 1H), 2.28 (q, *J* = 6.0 Hz, 1H), 2.06 (s, 3H); 1.67−1.88 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 170.99, 166.44, 133.02, 129.89, 129.59, 128.33, 64.59, 62.75, 31.98, 31.52, 28.33, 20.92. IR (neat oil, cm^{-1}) 3318.3, 1737.2, 1721.7, 1273.7, 1112.6. HRMS calcd for [$C_{14}H_{17}NO_4$ + H] 264.1236, found [M + H]$^+$ 264.1239. The enantiomer, (*R*,*R*)-3-acetoxy-2-hydroxymethylpyrrolidine benzoate (**14**, **-OAc**, **-OBz**) $[\alpha]^{20}_D$ = +25.1 (*c* = 1.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.05−8.08 (m, 2H); 7.55−7.63 (m, 1H); 7.44−7.49 (m, 2H); 4.35 (dd, *J* = 6.9 Hz, 12.0 Hz, 2H); 4.26 (m, 2H); 2.54 (q, *J* = 6.0 Hz, 1H), 2.27 (q, *J* = 6.0 Hz, 1H), 2.07 (s, 3H); 1.67−1.88 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 170.99, 166.44, 133.63, 133.02, 129.04, 128.61, 128.33, 62.80, 60.55, 53.82, 28.63, 28.32, 20.89. IR (neat oil, cm^{-1}) 3318.1, 1737.2, 1720.7, 1273.6, 1247.9. HRMS calcd for [$C_{14}H_{17}NO_4$ + H] 264.1236, found [M + H]$^+$ 264.1224. For (*S*,*R*)-3-acetoxy-2-hydroxymethylpyrrolidine benzoate (**12**, **-OAc**, **-OBz**) $[\alpha]^{20}_D$ = −35.9 (*c* = 1.1 $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.03−8.06 (m, 2H); 7.55−7.59 (m, 1H); 7.42−7.47 (m, 2H); 4.47 (dd, *J* = 4.8 Hz, 12.0 Hz, 1H); 4.15−4.25 (m, 3H); 2.17−2.21 (m, 1H); 2.04 (s, 3H); 2.01−2.06 (m, 1H); 1.73−1.86 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 170.97, 166.49, 133.10, 129.60, 128.35, 67.11, 62.49, 34.93, 32.78, 20.85. IR (neat oil, cm^{-1}) 3296.5, 2927.8, 1717.3, 1451.6, 1273.4, 1111.9. HRMS calcd for [$C_{14}H_{17}NO_4$ + H] 264.1236, found [M + H]$^+$ 264.1239. The enantiomer, (*R*,*S*)-3-acetoxy-2-hydroxymethylpyrrolidine benzoate (**13**, **−OAc**, **−OBz**) $[\alpha]^{20}_D$ = +37.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.01−8.04 (m, 2H); 7.53−7.58 (m, 1H); 7.40−7.45 (m, 2H); 4.44 (dd, *J* = 4.8 Hz, 12.0 Hz, 1H); 4.13−4.25 (m, 3H); 2.17−2.21 (m, 1H); 2.02 (s, 3H); 2.01−2.06 (m, 1H); 1.69−1.86 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 170.96, 166.46, 133.55, 133.09, 129.58, 128.54, 128.34, 67.13, 65.18, 62.49, 58.85, 56.29, 34.92, 33.86, 32.76, 20.83. IR (neat oil, cm^{-1}) 3296.4, 2957.3, 1732.3, 1451.6, 1271.0, 1112.0. HRMS calcd for [$C_{14}H_{17}NO_4$ + H] 264.1236, found [M + H]$^+$ 264.1239.

(*S*,*S*)-, (*S*,*R*)-, (*R*,*S*)-, and (*R*,*R*)-3-Hydroxy-2-hydroxymethylpyrrolidines (11, 12, 13 and 14). A solution of sodium hydroxide (106 mg, 2.65 mmol) in methanol (14.7 mL) was added to each of the individually purified benzoates (100 mg, 0.379 mmol). The reaction mixture was stirred for 1 h at room temperature and the solvent removed at reduced pressure. The residue was triturated with methylene chloride and the methylene chloride extract purified by silica gel column chromatography, eluting with a 10:5:1 mixture of methanol:methylene chloride:ammonium hydroxide to yield the free bases directly (68−72% yield). For (*S*,*S*)-3-hydroxy-2-hydroxymethylpyrrolidine **(11)** $[\alpha]^{20}_D$ = 24.7 (*c* = 1.4, CH_3OH). ^{1}H NMR (CD_3OD) δ 3.66−3.78 (m, 3H); 3.47−3.54 (dd, *J* = 6.9 Hz, 11.7 Hz, 1H); 2.24−2.35 (m, 2H); 1.67−1.73 (q, *J* = 6.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 61.08, 58.87, 35.75, 31.68, 29.97. IR (neat oil, cm^{-1}) 3344.9, 1734.4, 1600.7, 1558.6, 1436.8, 1053.2. HRMS calcd for [$C_5H_{11}NO_2$ + Na] 140.0687, found [M + Na]$^+$ 140.0686. The enanti-

omer, (*R*,*R*)-3-hydroxy-2-hydroxymethylpyrrolidine **(14)** $[\alpha]^{20}_D = -23.7$ ($c = 1.5$, $CHCl_3$). ^{1}H NMR (CD_3OD) δ 3.66−3.76 (m, 3H); 3.48−3.54 (dd, $J = 6.9$ Hz, 11.7 Hz, 1H); 2.22−2.31 (m, 2H); 1.65−1.71 (q, $J = 6.0$ Hz, 2H). ^{13}C NMR (CD_3OD) δ 61.28, 59.80, 34.77, 31.63, 30.57. IR (neat oil, cm^{-1}) 3295.0, 1732.8, 1596.2, 1548.5, 1411.5, 1057.2. HRMS calcd for [$C_5H_{11}NO_2$ + Na] 140.0687, found [M + Na]$^+$ 140.0686. For (*S*,*R*)-3-hydroxy-2-hydroxymethylpyrrolidine **(12)** $[\alpha]^{20}_D = -43.4$ ($c = 1.5$, CH_3OH). ^{1}H NMR (CD_3OD) δ 3.63−3.76 (m, 2H); 3.63 (dd, $J = 4.5$ Hz, 12.0 H, 1H); 3.58 (dd, $J = 5.1$ Hz, 11.7 Hz, 1H); 1.93−1.99 (m, 2H); 1.62−1.74 (m, 2H). ^{13}C NMR (CD_3OD) δ 63.09, 60.39, 39.11, 36.43, 32.68. IR (neat oil, cm^{-1}) 3415.02, 1599.9, 1561.3, 1451.5. HRMS calcd for [$C_5H_{11}NO_2$ + H] 118.0868, found [M + H]$^+$ 118.0869. The enantiomer, (*R*,*S*)-3-hydroxy-2-hydroxymethylpyrrolidine **(13)** $[\alpha]^{20}_D = +45.3$ ($c = 1.3$, CH_3OH). ^{1}H NMR (CD_3OD) δ 3.68−3.74 (m, 2H); 3.65 (dd, $J = 4.5$ Hz, 12.0 H, 1H); 3.55 (dd, $J = 5.1$ Hz, 11.7 Hz, 1H); 1.97−2.03 (m, 2H); 1.62−1.74 (m, 2H). ^{13}C NMR (CD_3OD) δ 62.39, 59.54, 37.81, 35.26, 31.99. IR (neat oil, cm^{-1}) 3415.47, 1599.2, 1560.1, 1452.4. HRMS calcd for [$C_5H_{11}NO_2$ + H] 118.0868, found [M + H]$^+$ 118.0866.

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Supporting Information Available: The X-ray crystal structure data for the hydroxyoxazoline **6**, ^{1}H NMR spectra for all of the compounds reported, and ^{13}C NMR spectra for the isomers **11** and **12** (which are similar to those of **14** and **13**, respectively). This material is available free of charge via the Internet at http://pubs.acs.org.

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