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Diastereoselective Synthesis of γ-Hydroxy-β-amino Alcohols, (2S, 3S)- and (2S, 3R)-Threoninol and -Hydroxyphenylalaninol, from (R)-Glycidol via the Derived 4-Hydroxymethyloxazolidinone

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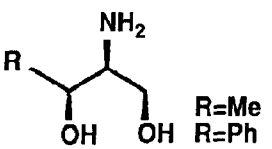
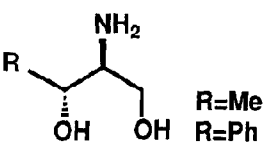
Abstract: Syntheses of enantiomerically pure (2S,3S)- and (2S,3R)-threoninol and (2S,3R)-hydroxyphenylalaninol are demonstrated starting from (R)-glycidol via (S)-4-methoxycarbonyl-2-oxazolidinone by monoalkylation of the ester followed by diastereoselective reduction.

γ-Hydroxy-β-amino alcohols are of major importance for the chiral pool[1] and as partial structures of biologically active compounds such as the sphingosines,[2] and the corresponding amino acids are found as constituents of biologically active peptides. Very recently, various methods for the synthesis of optically active γ–hydroxy-β-amino alcohols and the corresponding acids have been reported. Most of them are based on the following strategies; 1) starting from amino acids,[3] 2) use of the Sharpless asymmetric epoxidation,[4] 3) use of asymmetric aldol condensations,[5] and 4) other methods.[6] Although some of them may be applicable to the synthesis of a wide variety of β-hydroxy-α-amino acids, the development of new methods is still required. Previously, we have developed the enantiomerically pure 4-hydroxymethyloxazolidinone derivative **1** starting from R-(+)-glycidol as a chiral serinol synthon.[7] We now describe the synthesis of (2S,3S)- and (2S,3R)-N-benzylthreoninol and (2S,3S)- and (2S,3R)-N-benzyl-3-hydroxyphenylalaninol from **1** as a demonstration of a general method for the synthesis of γ-hydroxy-β-amino alcohols.





The reaction of R-(+)-glycidol, $[\alpha]_D$ +22.2 (98% ee), with benzylisocyanate in the presence of triethylamine (CH_2Cl_2 , 40-45 °C, 18h) produced the R-(+)-oxazolidinone derivative **1**, mp 74-75 °C, $[\alpha]_D$ +32.3, in 81% yield.[7] Oxidation of **1** with Jones reagent followed by esterification with diazomethane gave the methyl ester **2** in 72% yield from **1**, the corresponding aldehyde could not be isolated by various attempts at the oxidation of **1**.[8] The clean monoalkylation of the ester **2** proceeded successfully at temperatures below -100 °C, though the small amount of a di-alkylated

product was observed at -78 °C. Thus, one equivalent of methyllithium in ether was added dropwise to a partially solidified mixture of **2** in tetrahydrofuran at the temperature below -100 °C, and the reaction mixture was stirred at -78 °C for 30 minutes. The enantiomerically pure methyl ketone **3a** was obtained in 91% yield after purification on a 13 mmol scale reaction. The reaction of **2** with phenyllithium under the same conditions quantitatively afforded the enantiomerically pure phenyl ketone **3b**.[9] Highly diastereoselective reduction of **3a** and **3b** was effected with L-selectride at -78 °C in tetrahydrofuran.[10, 11] Thus, methyl ketone **3a** quantitatively afforded the alcohols **4a**[12] and its diastereomer in the ratio of 13 to 1, and **3b** gave the syn alcohol **4b**[13] in 91% yield as a sole stereoisomer. The high syn diastereoselectivity in the reduction of both **3a** and **3b** with L-selectride can be understood by considering the chelated model **5**.[14] Next, the anti isomers **7a** and **7b** were successfully synthesized by the Mitsunobu inversion of the hydroxyl group in **4a** and **4b**.[15] Thus, diethyl azodicarboxylate was slowly added dropwise to a tetrahydrofuran solution of **4a**, triphenylphosphine, and benzoic acid at room temperature to give the benzoate **6** which was successively hydrolyzed with aqueous 3% lithium hydroxide in methanol to afford the anti alcohol **7a**[16] in 78% yield from **4a**. The anti alcohol **7b**[17] was also obtained by the similar Mitsunobu procedure in 87% yield from **4b**. The obtained four kinds of secondary alcohols, **4a**, **4b**, **7a**, and **7b**, were respectively treated with 6% lithium hydroxide in ethanol at 80 °C for 12h to afford the N-benzyl derivatives of (2S,3S)-threoninol (**8a**), (2S,3R)-threoninol(D-allothreoninol) (**8b**), (2S,3S)-hydroxyphenylalaninol (**8c**), and (2S,3R)-hydroxyphenylalaninol (**8d**) in 91%, 93%, 81%, and 81% yield respectively. N-benzyl group of **8b** was removed by hydrogenolysis with palladium black in formic acid[18] to give a formic salt of the enantiomerically pure hydroxyphenylalaninol **9**, mp 111-3 °C, $[\alpha]_D$ +29.9, which was identical to an authentic sample.[19]

In conclusion, all sterecisomers of threoninol and hydroxyphenylalaninol can be obtained, since enantiomerically pure S-(-)-glycidol along with R-(+)-isomer is available based on a biological resolution of epichlorohydrin.[20] The procedure mentioned here is a general method for the synthesis of γ-hydroxy-β–aminoalcohols and -amino acids.[3c, 3d, 4a]

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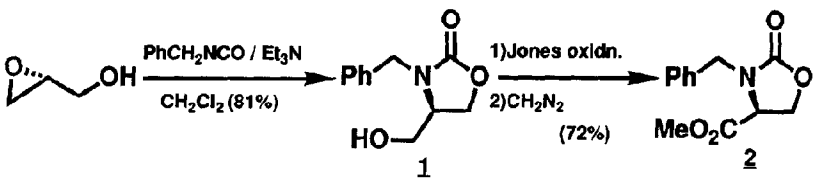
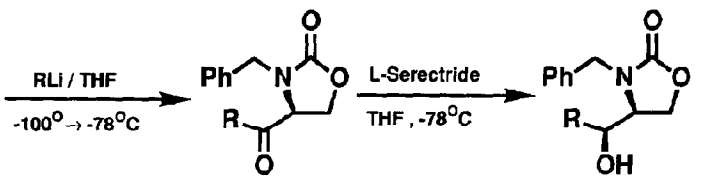
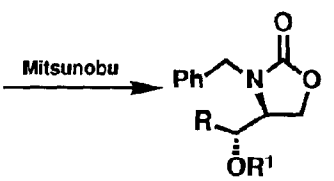


1 2

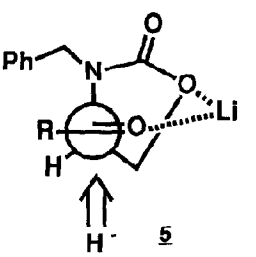


3a R=Me(91%)
3b R=Ph(quant.)

4a R=Me(93%)
4b R=Ph(91%)



6 R=Me, R^1=COPh
7a R=Me, R^1=H(78%)
7b R=Ph, R^1=H(87%)



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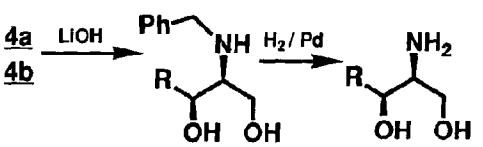
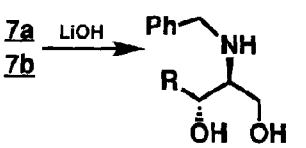


8a R=Me
8b R=Ph

9 R=Ph



8c R=Me
8d R=Ph

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7. Katsumura,S.; Kondo,A.; Han,Q. *Chem. Lett.*, **1991**, 1245. R-(+)-glycidol gives R-(+)-3-benzyl-4-hydroxymethyl-2-oxazolidinone (1). The absolute structure drawn in the previous paper must be revised.
8. The Swern oxidation gave unstable products which decomposed to the unidentified products. Other oxidations, for example, PCC, PDC, tetrapropylammonium perruthenate, or sulfur trioxide pyridine complex, gave the similar unsatisfactory results.
9. The enantiomerical purities of **3a** and **3b** were determined by high performance liquid chromatography using chiral column (CHIRALCEL OD supplied by Daisel Co. Ltd, eluted with n-haxane : *iso*-propanol = 85:15, 0.7ml / min.).
10. Reduction of **3a** with sodium borohydride in alcohol showed no significant diastereoselectivity.
11. The diastereoselectivity of the reduction was determined by ^{1}H NMR analysis of the crude products at 400 MHz in $CDCl_3$ solution. Stereochemistry of the major isomer **4a** was confirmed by the comparison with the compound which was derived from (2S, 3R)-N-*t*-butoxycarbonyl-O-benzylthreonine.
12. **4a**: mp 76.5-77.2 °C; $[\alpha]_D$ +34.6(c=0.91, $CHCl_3$, 23.2 °C); ^{1}H NMR($CDCl_3$) δ= 1.13(3H,d,J=6.4 Hz), 2.04(1H,d,J=4.4Hz), 3.63(1H, m), 3.97(1H,m), 4.13(1H,dd,J=5.5Hz,J=9.1 Hz), 4.23(1H, t,J=9.0Hz), 4.33(1H,d,J=15.1Hz), 4.77(1H,d,J=15.1Hz), 7.33(5H,m); ^{13}CNMR($CDCl_3$) δ=17.80, 47.53, 58.73, 63.66, 68.08, 127.94, 128.15, 128.82, 136.21, 159.00; IR(Nujol) 3450, 1730 cm^{-1}.
13. **4b**: mp 134.9-136.0 °C; $[\alpha]_D$ +72.1(c=0.96, $CHCl_3$, 23.1 °C); ^{1}H NMR($CDCl_3$) δ= 2.12(1H,d, J= 3.6 Hz), 3.91(3H,m), 4.45(1H,d,J=14.9Hz), 4.76(1H,m), 4.88(1H,d,J=14.7Hz), 7.26-7.38(5H,m); ^{13}C NMR ($CDCl_3$) δ=47.79, 59.00, 64.20, 76.78, 126.56, 127.77, 128.45, 128.67, 128.92, 128.99, 136.58, 139.41, 159.02; IR(Nujol) 3340, 1740 cm^{-1}.
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16. **7a**: mp 85.8-86.6 °C; $[\alpha]_D$ +19.2(c=1.00, $CHCl_3$, 22.7 °C); ^{1}H NMR($CDCl_3$) δ= 1.06(3H,d,J=6.5 Hz), 1.67(1H,J=3.1Hz), 3.60(1H,m), 3.98(1H,m), 4.20-4.33(2H,m), 4.38(1H,d,J=15.2Hz), 4.63(1H,d,J=15.2Hz); ^{13}C NMR ($CDCl_3$) δ=17.53, 46.43, 59.61, 62.08, 63.55, 128.00, 128.06, 128.98, 136.10, 159.25; IR(Nujol) 3450, 1720 cm^{-1}.
17. **7b:** mp 116.5-117.4 °C; $[\alpha]_D$ +17.2(c=0.92, $CHCl_3$, 24.6 °C); ^{1}H NMR($CDCl_3$) δ= 2.10 (1H, d, J=3.0 Hz), 3.82(1H,m), 3.97(1H,t,J=8.9Hz), 4.17(1H,d,J=15.1Hz), 4.35(1H,dd,J=9.0,J=5.8Hz), 4.74(1H, d,J=15.1Hz), 4.91(1H,m), 7.22-7.38(10H,m); ^{13}CNMR($CDCl_3$) δ=46.42, 59.90, 62.61, 69.69, 125. 69, 128.02, 128.12, 128.15, 128.64, 128.96, 135.83, 138.90, 159.29 ; IR(Nujor) 3400, 1745 cm^{-1}.
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