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A Stereoselective Concise Synthesis of C_2- and *meso*-Aminodiols from (*R*)-Phenylglycinol

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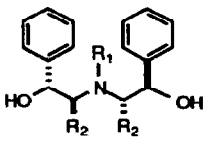
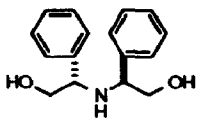
Summary : Oxazolidines derived from (R)-phenylglycinol can undergo diastereoselective vinyl- and aryl addition to give, after oxidative cleavage, meso- and C_2-diethanol amines.

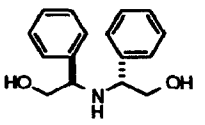
Recently, aminodiols have been employed as tridentate chiral modifiers in the asymmetric reduction of prochiral ketones.[1] These tridentate ligands offer a third binding site in the central nitrogen and provide an opportunity for C_2-symmetry. Aminodiol **1**, prepared from (*R*)-phenyloxirane and benzylamine, has been shown to be a C_2-scaffold for a *bis*-phosphinoester that serves as ligand for a catalytic Pd(0)-mediated asymmetric allylic alkylation.[2] C_2-aminodiols **2**, obtained from an optically active *O*-protected cyanohydrin,[3] have been utilized as key building blocks in the construction of chiral diaza-18-crown-6 derivatives.[4] A C_2-scaffold has also been implicated as the key structural feature responsible for the binding of inhibitors of HIV-1 protease.[5]



1 R_1 = Bn, R_2 = H
2 R_1 = H, R_2 = H, Me, Et, n-C_3H_7



S,S-**3**

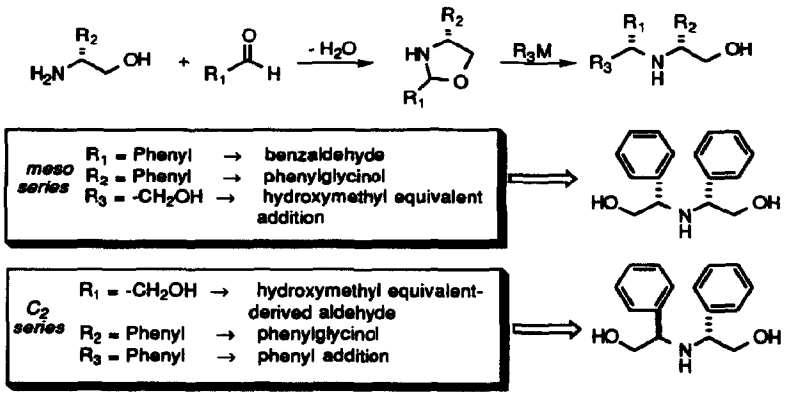


R,R-**4**

A recent report from Durst and co-workers utilized the reaction of (*R*)-pantolactone esters of α-halocarboxylic acids with optically active α-amino esters in the preparation of a new class of C_2-diethanol amines, **3**.[6] This report prompts us to describe our route to C_2-diethanol amines **4** from (*R*)-phenylglycinol.

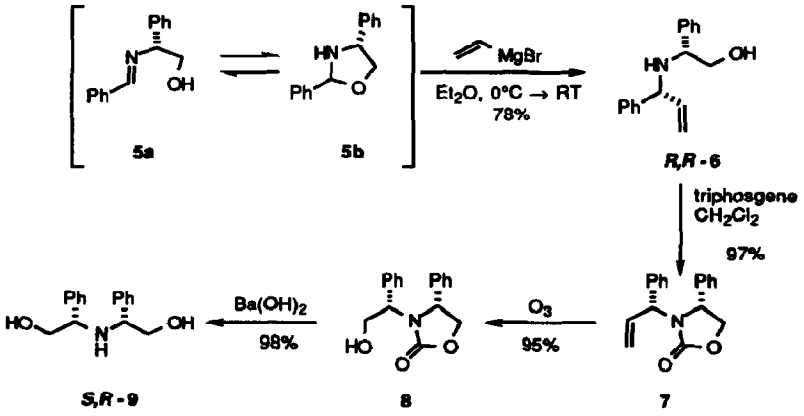
As demonstrated recently[7], oxazolidines derived from optically active amino alcohols have been shown to undergo chelation-controlled diastereoselective alkylations. We envisioned that symmetric diethanol amines derived from amino alcohols could be prepared via this methodology (Scheme 1). **Both the *meso*- and C_2-diethanol amines can be accessed by appropriate choice of aldehyde and organometallic reagent.** Addition of a hydroxymethyl equivalent (vinylmagnesium bromide)[8] to the oxazolidine derived from benzaldehyde and phenyl glycinol should lead, after ozonolytyic cleavage and reduction, to the *meso*-diethanol amine. Likewise, diastereoselective phenyl addition to the oxazolidine derived from a hydroxymethyl equivalent-containing aldehyde

(cinnamaldehyde), and phenyl glycinol would produce, after ozonolytyic cleavage and reduction, the C_2-diethanol amine.



Scheme 1

To demonstrate this protocol, oxazolidine **5**[9], prepared from benzaldehyde and (*R*)-phenyl glycinol underwent chelation controlled vinyl addition upon treatment with vinylmagnesium bromide (3 equiv.) to give **6** in a diastereoselectivity of 11:1 by ^{1}H NMR (Scheme 2).[10]

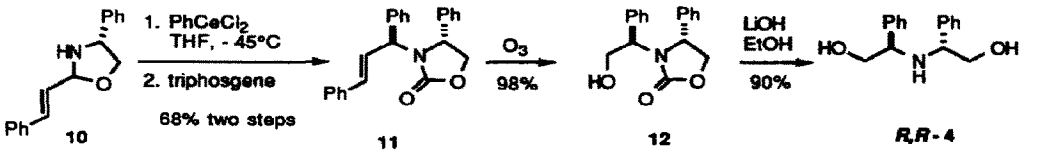


Scheme 2

Transformation of the amino alcohol to the oxazolidinone **7** using triphosgene (0.4 equiv.)[11] followed by ozonolysis afforded hydroxy-oxazolidinone **8** after reductive workup with $NaBH_4$. Hydrolysis of the oxazolidinone with barium hydroxide[12] gave the *meso*-diethanol amine **9** in

good yield.[13] The stereochemistry of **8** was confirmed by single crystal x-ray determination which supports chelation controlled addition to **5**.

The C_2-symmetric aminodiol **4** was prepared as follows: oxazolidine **10**, prepared from *trans*-cinnamaldehyde and (*R*)-phenyl glycinol[14] underwent complete diastereoselective phenyl addition on treatment with phenylcerium dichloride (Scheme 3).[15]



Scheme 3

Formation of the oxazolidinone **11** (triphosgene, CH_2Cl_2) was once again followed by ozonolysis and reductive workup ($NaBH_4$) to give hydroxy-oxazolidinone **12** in near quantitative yield.[16] Finally, hydrolysis of the latter with ethanolic lithium hydroxide then furnished C_2-diethanol amine **4** in good yield.[17]

In conclusion we have described an expedient, high yielding routes to the (*R*)-phenyl glycinol-derived *meso*- and C_2-diethanol amines. The present route to aminodiols **9** and **4** can be run on multigram scale. The synthetic application of these type of tridentate ligands is currently under investigation.

Acknowledgment. This work was supported by a grant from the National Science Foundation. We thank Professor Tony Durst for providing spectral data for comparison of our material with that of (*S,S*)-**3** prepared in his laboratory. The x-ray structure of **8** was performed by S. Miller of the x-ray laboratory in this department.

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8 To our knowledge addition of sp^2 nucleophilic organometallic species to chiral hydroxy-aldimines (oxazolidines) has not been reported.

9 It was found that these oxazolidines of phenyl glycinol exist predominately in solution as their hydoxy-imine tautomers as demonstrated by the appropriate resonances in their ^1H and ^{13}C spectra.

10 All new compounds displayed spectroscopic data consistent with their structural assignments.

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13 Purified by flash chromatography on Amicon silica gel using 50% EtOAc/hexanes → EtOAc and isolated as a colorless crystalline solid (mp = 106 -107 °C). ^1H-NMR ($CDCl_3$) δ : 7.22 (m, 5H), 3.84 (dd, J = 4.72 and 6.63 Hz, 1H), 3.78 (dd, J = 4.72 and 10.90 Hz, 1H), 3.64 (dd, J = 6.63 and 10.90 Hz), 2.66 (br s, 1.5H). ^{13}C-NMR ($CDCl_3$) δ : 140.9 (s), 128.6 (d), 127.6 (d), 127.2 (d), 66.0 (t), 61.8 (d). Anal. Calcd. for $C_{16}H_{19}NO_2$:C, 74.68; H, 7.44; N, 5.44. Found : C, 74.59; H, 7.40; N, 5.39. $[\alpha]^{25}_D = 0°$.

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16 Purified by flash chromatography on Amicon silica gel using 25 → 50% EtOAc/hexanes.

17 Crude (*R,R*)-4, purified by flash chromatography on Amicon silica gel using 50% EtOAc/hexanes → EtOAc was isolated as a foam. HCl salt white powder (Mp > 250 °C d). ^1H-NMR ($CDCl_3$) δ : 7.27 (m, 5H), 3.60 (m, 3H), 2.55 (br s, 1.5 H). ^{13}C-NMR ($CDCl_3$) δ : 139.9 (s), 128.7 (d), 127.7 (d), 127.4 (d), 67.2 (t), 61.0 (d). Anal. Calcd. for $C_{16}H_{20}ClNO_2$: C, 65.41; H, 6.86; N, 4.76. Found : C, 65.22; H, 6.91; N, 4.68. $[\alpha]^{25}_D$ = 193.4 ° (c 1.4, CH_2Cl_2). Lit.[6] $[\alpha]^{25}_D = 133°$ (*S,S* enantiomer). Chiral HPLC analysis showed (*R,R*) as a single peak on Chiralcel OD column (rt = 42.16 min., 96:4 IPA/hexanes @ flow rate of 1 mL/min). Verification of ee was acomplished by comparison with baseline-separated racemic-4.

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