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Preparation of Primary Vicinal Diamines from Amino Acid Esters and Crystal Structure of a Chiral Nickel Salen Complex

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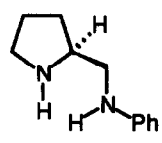
Abstract: Highly pure (*S*)-1,1-di(*p*-anisyl)-3-methyl-1,2-butane diamine (valinyl diamine), **4a**, and 1,1-di(*p*-anisyl)-1,2-propane diamine (alaninyl diamine), **4b**, were prepared from *L*-valine methyl ester hydrochloride and *L*-alanine ethyl ester hydrochloride in four steps. The X-ray crystal structure of the Ni(II)-salen type complex derived from **4a** reveals an interesting conformation around the metal center.

Chiral diamines and their derivatives have been used as ligands (chiral auxiliaries) for inducing enantioselectivity in asymmetric synthesis. To date, (*S*)-proline is the only amino acid being used in the preparation of chiral diamines.[1] Diamines **1-3** derived from proline have been intensively studied by Mukaiyama and coworkers for a variety of asymmetric synthetic methods.[2] To our knowledge, primary vicinal diamines derived from amino acids have never been synthesized. The advantage of a primary amine is the greater flexibility it affords in synthesis as well as application. We describe here a synthetic route to 1,2-diamines of the general type **4** in which the stereogenic center and R group are derived from α-amino acids.



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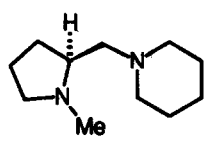

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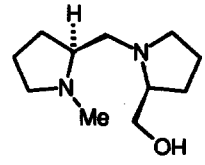

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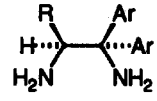
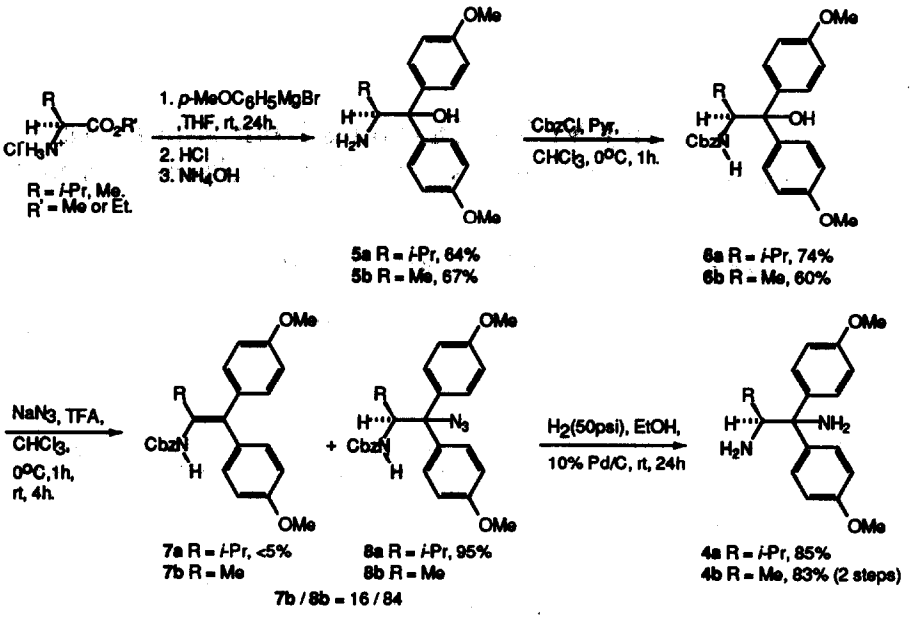


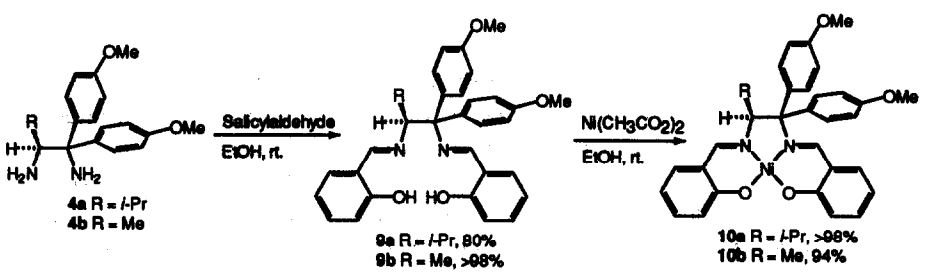
4a R = *i*-Pr
4b R = Me

Two diamines were initially prepared: **4a**, derived from *L*-valine, and **4b**, derived from *L*-alanine. Diamine **4a** was synthesized in the following fashion. *L*-Valine methyl ester hydrochloride was added to an excess (4.5 equiv.) of *p*-methoxyphenylmagnesium bromide at room temperature to yield the desired amino alcohol **5a** (64%). Protection of the amine with of benzyl chloroformate (CbzCl, 1.2 equiv.) was achieved in 74% yield. Substitution of the hydroxyl group with azide was performed with sodium azide (5.5 equiv.) and trifluoroacetic acid (TFA, 2.6 equiv.) in chloroform and gave the substituted product **8a** in 95% yield.[3] Deprotection and reduction with 10% Pd/C at 50 psi H_2 for 24 h yielded (*S*)-1,1-di(*p*-anisyl)-3-methyl-1,2-butane diamine (valinyl diamine) **4a** (85%). A small amount of dehydrated product **7a** was formed in the substitution of the hydroxy group by the azido group. Although the dehydrated product can be separated by column chromatography, it was not essential to do so. After hydrogenation the desired diamine could isolated by recrystallization from diethyl ether. Analysis by chiral HPLC[4] indicated that the diamine was enantiomerically pure (>99%).

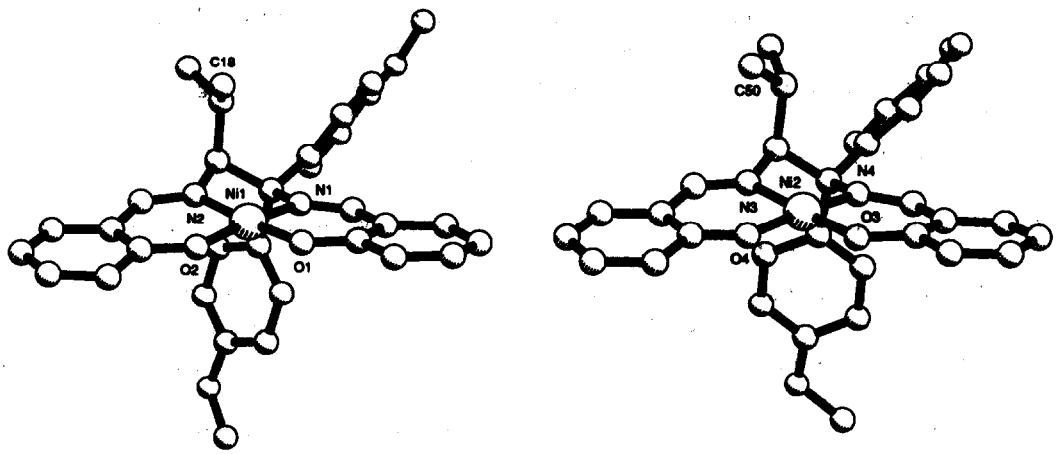


Following the same procedure as stated above and starting from *L*-alanine ethyl ester hydrochloride the desired amino alcohol **5b** was prepared in 67% yield. Protection of the amine with CbzCl was achieved in 60% yield. The yield of the dehydrated product **7b** formed from the substitution reaction was higher (~15%) than in the valine series (<5%), but it could not be separated by simple column chromatography. Hydrogenation of this mixture provided 1,1-di(*p*-anisyl)-1,2-propane diamine (alaninyl diamine) **4b** which was then purified by column chromatography giving an 83% yield (from **6b**).[5]

Initial studies of the new diamines focussed upon their incorporation into chiral metal complexes. Accordingly, the diamines were condensed with salicylaldehyde (2.2 equiv) in ethanol at room temperature to afford chiral salens **9a** and **9b**. Complexation with $Ni(CH_3CO_2)_2$ (1.3 equiv) gave reddish brown solids after evaporation of the ethanol. The Ni(II)-complexes could be recrystallized from methanol/diethyl ether. A burgundy diamond-shaped single crystal of the Ni-valinyl salen complex **10a** was submitted for X-ray crystallographic analysis.[6]



The crystal structure indicated that the complex had a square planar orientation.[7] Each asymmetric unit contained two unique molecules of **10a** whose structures are shown below (H atoms are omitted for clarity).[8] The *i*-propyl group and one of the *p*-methoxyphenyl groups are in axial positions on the five-membered ring. Interestingly, one methyl of the *i*-propyl group is in an anisotropic shielding position of the imine bond[9] and could also be further shielded by the induced local diamagnetic shielding of the Ni valence electrons. However, the ^{1}H NMR signal for one of the methyl protons (on C18 and C50) shows a very downfield-shifted absorption at 2.07 ppm, overlapping with the methine proton of the *i*-propyl group, and suggesting that the Ni atom deshielding effect caused by electronic repulsion is much stronger than the sum of the two shielding effects.



Scheme. X-ray crystal structures of two unique molecules of the Ni-valinyl salen complex **10a**.

In this four-step procedure, we have successfully prepared primary vicinal diamines from commercially available amino acid esters. The first application of these diamines will focus on their Mn(III)-salen complexes as asymmetric catalysts.[10] This is currently under investigation.

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1. Mukaiyama, T. *Tetrahedron* **1981**, *37*, 4111-4119.
2. Examples are: (a) Mukaiyama, T.; Sakito, Y.; Asami, M. *Chem. Lett.* **1978**, 1253-1256. (b) Mukaiyama, T.; Soai, K.; Sato , T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455-1460. (c) Stevens, R. W.; Mukaiyama, T. *Chem. Lett.* **1983**, 1799-1802. (d) Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 297-300. (d) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247-4252. (e) See also ref. 1.

3. Substitution of the hydroxyl group could not be achieved when PhMgBr was used. The *p*-methoxy group presumably stabilizes the S_N1 intermediate for the substitution reaction.
4. Analysis was by Chiralcel® OD column (J. T. Baker) with *i*-PrOH:hexane=9:1 (v:v) as eluent at a flow rate of 0.5 mL/min. A racemic mixture of the valinyl diamine was prepared by the same procedure and used for comparison.
5. All compounds synthesized have satisfactory physical data including 1D and 2D NMR (300 MHz), MS, IR and microanalysis.
6. *Crystal Data*: $C_{33}H_{32}N_2O_4Ni$, FW = 579.32; hexagonal, space group $P6_1$ (No. 169), a = 11.652(3), b = 11.652(3), c = 73.404(9) Å, V = 8630 $Å^3$, Z = 12, Dc = 1.337 g/cm^3. X-ray intensity data were collected on an Enraf-Nonius CAD-4 diffractometer employing graphite-monochromated Cu-K_α radiation (λ = 1.54178 Å) with ω-2θ ($0<2\theta<120°$) scan technique. A total of 1969 unique reflections were measured and were used during structure refinement. Refinement converged to R = 0.065 and R_w = 0.060. Selected bond distances (Å): Ni(1)-O(1) 1.83(1), Ni(1)-O(2) 1.83(1), Ni(1)-N(1) 1.83(1), Ni(1)-N(2) 1.83(1), Ni(2)-O(3) 1.84(1), Ni(2)-O(4) 1.85(1), Ni(2)-N(3) 1.85(1), Ni(2)-N(4) 1.87(1).
7. Ni(1) and Ni(2) atoms are in the mean plane of two oxygen and two nitrogen atoms with a deviation of 0.0068 and 0.1659 Å respectively.
8. The major structural differences between the two unique molecules containing Ni(1) and Ni(2) are (*i*) methyl groups of the anisole within the same molecule were pointed in the same or in opposite directions, (*ii*) the orientation of the *i*-Pr groups differ by ~35° and (*iii*) the orientation of the phenyl groups in the axial position differ by ~43°.
9. Intramolecular atom distances (Å): C(18)···Ni(1) 3.341, C(18)-H(18)···Ni(1) 2.634, C(18)···N(2) 2.797, C(18)-H(18)···N(2) 2.624, C(50)···Ni(2) 3.594, C(50)-H(45)···Ni(2) 2.926, C(50)···N(3) 2.784 C(50)-H(45)···N(3) 2.527.
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