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# Synthesis of $C_2$-Symmetric Dibenzyldiamino Diols by Double Stereoselective Grignard Addition to (*S,S*)-Tartraldehyde Dinitrone

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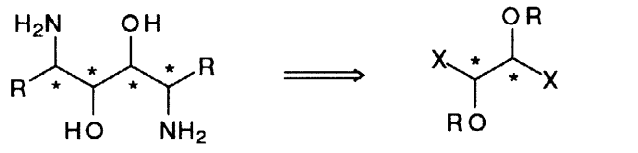
***Abstract***: A new asymmetric two-dimensional synthesis of 1,4-diamino 2,3-diols is illustrated by double addition of benzylmagnesium chloride to the bis-nitrone derived from (*R,R*)-tartraldehyde and reduction of the resulting dihydroxylamines. 

Among the numerous compounds with $C_2$-symmetry that have been prepared in recent years mainly for their potential utility in the area of asymmetric catalysis,[1] 1,4-diamino 2,3-diols **1** are receiving special attention both as $C_2$-symmetric chiral ligands[2] and core units of promising peptidic and nonpeptidic HIV protease inhibitors.[3,4] Quite logically various synthetic routes to compounds **1** have been described by simultaneous elaboration of symmetrically substituted diols[5] that in turn were prepared from readily available natural products such as L-tartaric acid, D-mannitol, D-threitol. Thus, bis-epoxides,[5a] bis-hydrazones,[5b,c] bis-aziridines,[5d] and bis-enones[5e] have been employed to introduce either the amino or the alkyl groups by suitable reactions. These complementary methods may be used for the preparation of a rich library of compounds **1**. Along the same line we would like to report here our method that employes the elaboration in two directions of a bis-nitrone **2** via double Grignard addition and reduction of the resulting bis-hydroxylamines. This two-dimensional approach[6] to $C_2$-symmetric diamino alcohols stems from our recent work concerning the installation of the amino group at a saturated carbon center by stereoselective addition of organometals to chiral nitrones.[7]




**1** **2** X = CH=N(O⁻)R

Since we focussed on the synthesis of amino diols **1** with 2*S* and 3*S* configuration, the suitable bis-nitrone **2a** was prepared starting from diethyl isopropylidene L-tartrate, reduction of the ester function with DIBAL as described,[8] and trapping the aluminum protected tartraldehyde intermediate with *N*-benzylhydroxylamine in $CH_2Cl_2$ as a solvent at 0 °C. Compound **2a** (51% yield)[9,10] was isolated by column chromatography (AcOEt-MeOH) and characterized as *Z,Z*-isomer by $^1$H NMR spectra (n.O.e between *CH*=N and *CH*$_2$Ph).[7a] Treatment of **2a** with 4 equiv of benzylmagnesium chloride in $Et_2O$-THF at -78 °C afforded a complex mixture of products

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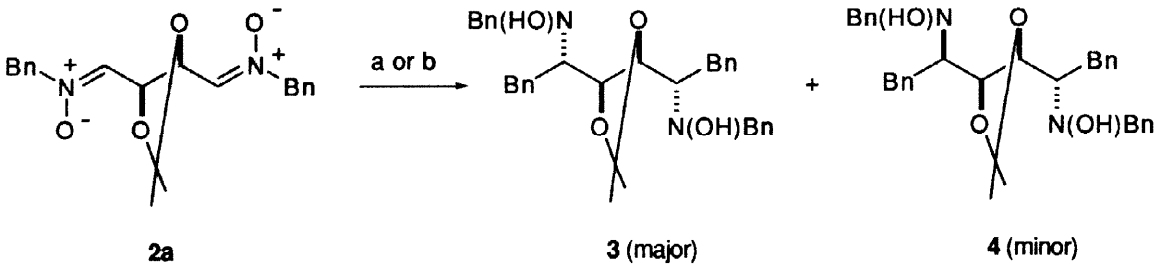
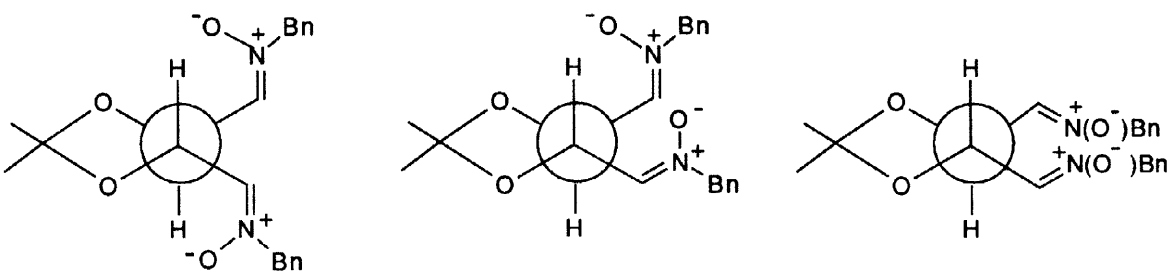
from which the bis-hydroxylamines **3** (*SSSS*-isomer) and **4** (*RSSS*-isomer) (see below for the structural assignment) were isolated in 3:2 ratio and 40% overall yield[11] (scheme 1). Higher diastereomeric ratios and yields were obtained in reactions performed in the presence of the chelate complex-inducing agents $ZnBr_2$ (2:1, 50%), $Et_2AlCl$ (4:1,45%), $CeCl_3$ (6:1, 70%).




**2a** **3** (major) **4** (minor)

**Scheme 1**. Reagents and conditions: a) BnMgCl, $Et_2O$, THF, -78 °C; b) chelating agent, rt, then BnMgCl $Et_2O$, THF, -78 °C.

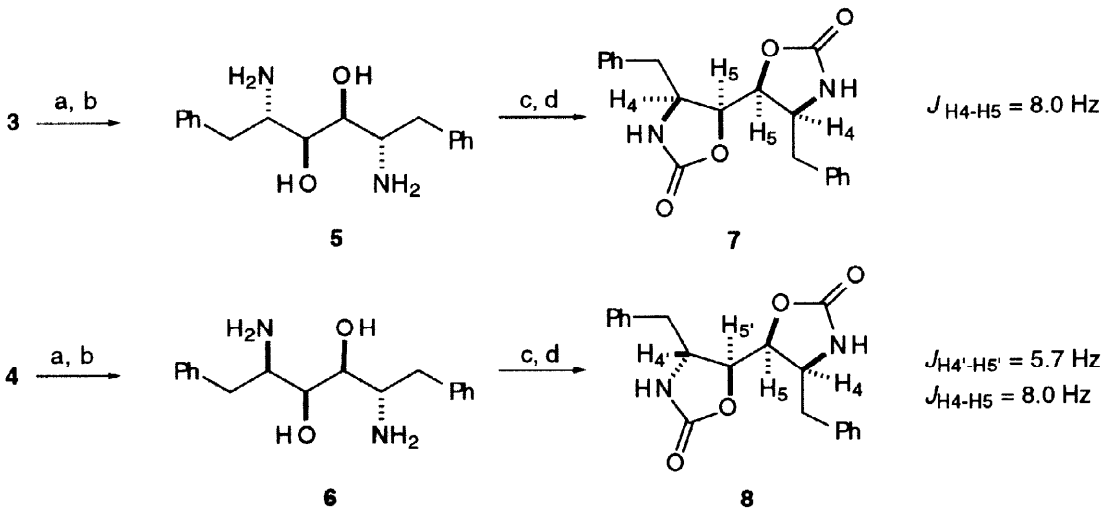
The double facial *anti*-selectivity of the Grignard addition to **2a** either in the absence or in the presence of complexing agents contrasts with the more common *syn*-addition of organometals to α-alkoxy mono-nitrones in the absence of chelating agents and the reversal *anti*-addition by the use of Lewis acids.[7] In analogy with the stereochemical models employed in double Michael addition reactions to bis-enoates,[5e,12] three ground state conformations **A-2a**, **B-2a**, and **C-2a** of the bis-nitrone **2a** can be considered. The facial *anti*-selectivity is very likely to be the consequence of the conformational preference shown by **C-2a** and addition of the nucleophile from the less hindered outside face of each nitrone group. The same conformation appears to be even more stabilized by complex inducing agents. The formation of the minor diastereomer **4** indicates that mono *syn*-addition occurs to some extent as well and therefore that also conformation **B-2a** is present. On the other hand, since double *syn*-addition to give the third possible diastereomer with *RSSR* configuration was not observed, the conformation **A-2a** appeared highly unfavoured.




**A-2a** **B-2a** **C-2a**

The elaboration of the bis-hydroxylamines **3** and **4** to the corresponding diamino diols **5** and **6** (72 and 75% overall yields) was carried out in two steps,[7b] i.e. reduction of N(OH)Bn to $NH_2$ by low pressure hydrogenolysis over $Pd(OH)_2$ and deacetonation by acid treatment in dioxane (Scheme 2). The $C_2$-symmetric diamino diol **5** and the pseudo symmetric diastereoisomer **6** showed NMR spectra fully consistent with their structures.[13,14] Unequivocal evidence of the structure of these compounds was obtained from selected coupling

constants in the $^1H$ NMR spectra of the corresponding bis-oxazolidinones **7** and **8**. These structural data indirectly proved the configuration at the two newly formed stereocenters in their progenitor bis-hydroxylamines **3** and **4**.




**Scheme 2.** Reagents and conditions: a) $H_2$, $Pd(OH)_2$-C, AcOH, EtOH, 3 atm, 18 h; b) HCl in dioxane 4.8 M 18 h, then NaOH 3 M (73% for the two steps); c) $(Boc)_2O$, dioxane; d) NaH, THF, reflux.

In summary, the readily available bis-nitrone **2a** derived from L-tartraldehyde appears to be an interesting intermediate for a two-dimensional synthesis of chiral diamino diols via Grignard addition. Of the two stereoisomers (*S,S,S,S*)- **5** and (*R,S,S,S*)-**6** that have been prepared, the former has been previously reported.[3b] Quite deceptively, the third possible stereoisomer with (*R,S,S,R*)-configuration that serves as a core unit of cyclic ureas employed as HIV protease inhibitors,[4] was not obtained in the present work. A study on the scope and limitations of this approach is now underway in our laboratory.

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## References and Notes

1. Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

2. Konradi, A. W., Pedersen, S. F. *J. Org. Chem.* **1992**, *57*, 28 and references therein.

3. For peptide-type inhibitors, see : (a) Kempf, D. J.; Norbeck, D. W.; Codacovi, L. M.; Wang, X. C.; Kohlbrenner, W. E.; Wideburg, N. E.; Paul, D. A.; Knigge, M. F.; Vasavanonda, S.; Craig-Kennard, A.; Saldivar, A.; Rosenbrook Jr., W.; Clement, J. J.; Plattner, J. J.; Erickson, J. *J. Med. Chem.* **1990**, *33*, 2687; (b) Kempf, D. J.; Sowin, T. J.; Doherty, E. M.; Hannick, S. M.; Codavoci, L.; Henry, R. F.; Green, B. E.; Spanton, S. G.; Norbeck, D. W. *J. Org. Chem.* **1992**, *57*, 5692.

4. For nonpeptide cyclic ureas, see : (a) Lam, P. Y. S.; Jadhav, P. K.; Eyermann, C. J.; Hodge, C. N.; Ru, Y.; Bacheler, L. T.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Wong, Y. N.; Chang, C.-H.; Weber, P. C.; Jackson, D. A.; Sharpe, T. R.; Erickson-Viitanen, S. *Science* **1994**, *263*, 380; (b) Hultén, J.; Bonham, N. M.; Nillroth, U.; Hansson, T.; Zuccarello, G.; Bouzide, A.; Åqvist, J.; Classon, B.; Danielson, U. H.; Karlén, A.; Kvarnström, I.; Samuelsson, B.; Hallberg, A. *J. Med. Chem.* **1997**, *40*, 885.

5. (a) Ghosh, A. K., McKee, S. P., Thompson, W. J. *Tetrahedron Lett.* **1991**, *32*, 5729. (b) Baker, W. R.; Condon, S. L. *J. Org. Chem.* **1993**, *58*, 3277. (c) Rossano, L. T.; Lo, Y. S.; Anzalone, L.; Lee, Y.-C.; Meloni, D. J.; Moore, J. R.; Gale, T. M.; Arnett, J. F. *Tetrahedron Lett.* **1995**, *36*, 4967. (d) Kang, S. H.; Ryu, D. H. *Chem. Commun.* **1996**, 355. (e) Schreiner, E. P.; Pruckner, A. *J. Org. Chem.* **1997**, *62*, 5380.

6. Maier, M. in *Organic Synthesis Highlights II* , Waldmann, H. Ed.; VCH: Weinheim, **1995**, pp 203-222.

7. (a) Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino, P.; Tejero, T.; Bertolasi, V. *Chem. Eur. J.* **1995**, *1*, 505. (b) Dondoni, A.; Perrone, D. *Tetrahedron Lett.* **1997**, 38, 499. (c) For a review, see : Dondoni, A.; Perrone, D. *Aldrichimica Acta* **1997**, *30*, 35.

8. Krief, A.; Dumont, W.; Pasau, P.; Lecomte, Ph. *Tetrahedron* **1989**, *45*, 3039.

9. All new compounds reported in this and the following Scheme gave consistent $^{1}H$ and $^{13}C$ NMR spectra and satisfactory elemental analyses (C, H, and N). MALDI-TOF MS analyses were performed using α-cyano-4-hydroxycinnamic acid as matrix. Some data are reported for selected compounds.

10. **2a**: mp 105-106 °C; $[\alpha]_D$ +79.0 (*c* 0.4, $CHCl_3$); $^{1}H$ NMR (300 MHz, $CDCl_3$) δ: 1.40 (s, 6 H), 4.90 (s, 4 H), 5.02-5.10 (m, 2 H), 6.86-6.94 (m, 2 H), 7.36-7.46 (m, 10 H);$^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 26.3, 69.3, 73.3, 110.6, 128.9, 129.0, 129.4, 132.0, 135.4; MALDI-TOF MS (0.6 μJ): 369 ($M + H^+$), 391 ($M + Na^+$), 407 ($M + K^+$).

11. An overall yield of 60% was obtained by the use of dimethylpropylene urea (DMPU) as additive.

12. Saito, S.; Narahara, O.; Ishikawa, T.; Asahara, M.; Moriwake, T.; Gawronski, J.; Kazmierczak, F. *J. Org. Chem.* **1993**, *58*, 6292.

13. (1*S*,2*S*,3*S*,4*S*)-**5**: mp 183-185 °C; $[\alpha]_D$ - 31.7 (*c* 0.4, $CHCl_3$); $^{1}H$ NMR (300 MHz, $CDCl_3$) δ: 2.64 (dd, 2 H, *J* = 10.6, 13.4 Hz), 2.85 (dd, 2 H, *J* = 3.5, 13.4 Hz), 3.60 (ddd, 2 H, *J* = 2.8, 3.5, 10.6 Hz), 3.92 (d, 2 H, *J* = 2.8 Hz), 7.15-7.42 (m, 10 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 38.5, 56.8, 72.8, 126.7, 128.7, 129.0, 138.5; MALDI-TOF MS (1.0 μJ): 301 ($M + H^+$), 323 ($M + Na^+$).

14. (1*R*,2*S*,3*S*,4*S*)-**6**: mp 114-115 °C; $[\alpha]_D$ - 45.7 (*c* 0.7, $CHCl_3$); $^{1}H$ NMR (300 MHz, $CDCl_3$) δ: 2.60 (dd, 1 H, *J* = 10.3, 13.3 Hz), 2.72 (dd, 1 H, *J* = 3.9, 11.5 Hz), 2.80 (dd, 1 H, *J* = 4.2, 13.3 Hz), 2.94 (dd, 1 H, *J* = 5.4, 11.5 Hz), 2.95-3.01 (m, 1 H), 3.52 (ddd, 1 H, *J* = 3.6, 4.2, 10.3 Hz), 3.60 (dd, 1 H, *J* = 1.2, 3.6 Hz), 3.96 (s, 1 H), 7.10-7.36 (m, 10 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 38.6, 43.3, 56.7, 57.5, 71.0, 76.2, 126.4, 126.6, 128.6, 128.7, 129.0, 129.3, 138.6, 138.8; MALDI-TOF MS (0.9 μJ): 301 ($M + H^+$), 323 ($M + Na^+$).