A Convenient Asymmetric Synthesis of *anti*-β-Amino Alcohols: an X-Ray Crystallographic Study of (4*R*)-2,2-Dimethyl-4-[(2*S*)-(diphenylmethyleneamino)-(1*S*)-hydroxy-3-buten-1-yl]-1,3-dioxolane

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anti-β-Diphenylmethyleneamino alcohols have been produced with high relative and absolute stereocontrol in a one-pot process; subsequent deprotection gave *anti*-β-hydroxy amines in good yield.

A multitude of methods exist for the formation of vicinal amino alcohols.[1] Yet, relatively few methods that generate the amino alcohol unit with the simultaneous construction of the interconnecting carbon–carbon bond are used in asymmetric synthesis.[2] Recently, we reported a convergent enantioselective procedure for the formation of β-hydroxy *N,N*-diphenylamines in a general one-pot process[3,4] utilising allylborane methodology.[5] The results described therein,[4] showed that *B*-[(*E*)-3-(diphenylamino)allyl]diisopinocampheylborane was a useful reagent for masked aldol chemistry. Unfortunately, there is a serious limitation with this chemistry: the product β-hydroxy *N,N*-diphenylamines could not be easily deprotected to reveal the parent β-hydroxy primary amines. Herein we report a significant methodological improvement and describe a new allylborane reagent for the stereoselective production of *anti*-β-hydroxy amines.

Deprotonation of *N*-protected allylamine systems and subsequent reaction with electrophiles have previously been examined under a variety of conditions.[6,7] Following the Würthwein and Wolf precedent,[7] 1,1-diphenyl-2-aza-1,3-pentadiene **1** was deprotonated with LDA in THF at −78 °C to give, upon reaction with (−)-*B*-chlorodiisopinocampheylborane [(−)-(Ipc)$_2$BCl], an adduct presumably the (*E*)-allylborane **2**. *In situ* reaction with cyclohexanecarboxaldehyde gave, on basic hydrogen peroxide work-up, the *anti*-β-hydroxy amine **4a** (R = *c*-C_6H_{11})† in 56% yield (Scheme 1).‡ Subsequent deprotection of the imine **4a** using methoxylammonium chloride in aqueous ethanol solution gave the corresponding amino alcohol **6a** (R = *c*-C_6H_{11})¶ in 98% yield as a pure white solid.[8] In the same way, sequential reaction of the imine **1** with LDA in THF at −78 °C, (+)-*B*-chlorodiisopinocampheylborane [(+)-(Ipc)$_2$BCl] and cyclohexanecarboxaldehyde gave the antipodal imine **5a** (R = *c*-C_6H_{11}). Subsequent deprotection furnished **7a** in 98% yield. Several other aldehydes were reacted under similar conditions to give the corresponding *anti*-β-hydroxy imines (Table 1).‡

The stereochemical integrity of the product imines requires substantiation. Examination of ^{1}H NMR and ^{13}C NMR spectra showed the relative stereochemistry of reaction to be at least 95% *anti* in all cases. Absolute stereochemical purity was determined by converting each pair of vicinal imino alcohols **4** and **5** into their corresponding (R)-(+)-Mosher esters.[9] In all cases the enantiomeric excesses were judged to be ≥90% by ^{1}H NMR except in those cases resulting from mismatched stereochemical biases between reagent and substrate (entries 8 and 9). Finally, we have rigorously established the stereochemistry of one *anti*-β-amino alcohol by carrying out an X-ray crystallographic study of **4d** (Fig. 1).§ This study unequivocally established the relative and hence the absolute stereochemistry of alcohol **4d** and, by implication, all the other amino alcohols in Table 1.

The direct conversion of aldehydes into β-amino alcohols *via* an experimentally simple one-pot procedure should be applicable to the synthesis of biologically active natural products.

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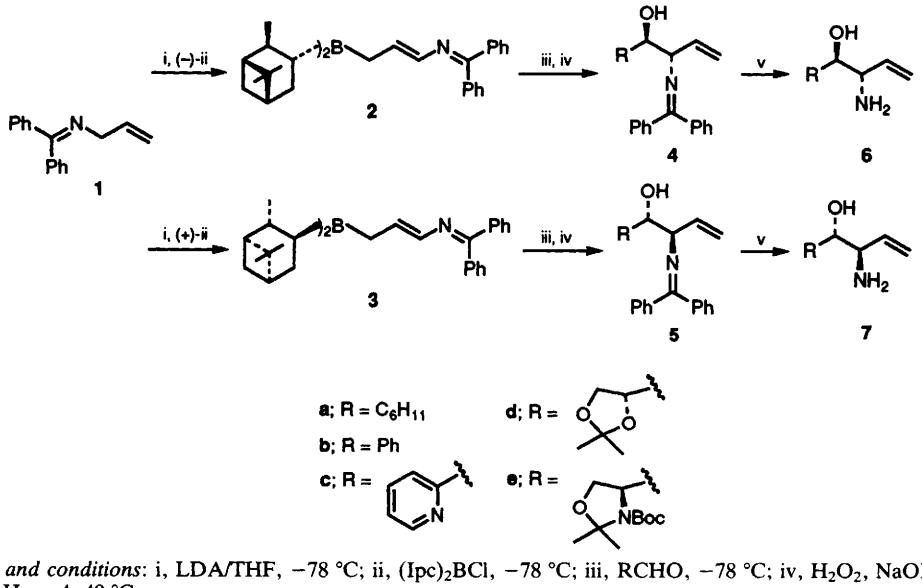
Footnotes

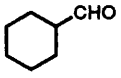
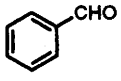
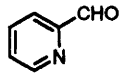
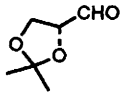
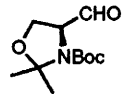
† All β-diphenylmethyleneamino alcohols were fully characterised by spectroscopic data and microanalyses or high resolution mass spectrometry.



Scheme 1 *Reagents and conditions*: i, LDA/THF, −78 °C; ii, (Ipc)$_2$BCl, −78 °C; iii, RCHO, −78 °C; iv, H_2O_2, NaOH, 20 °C; v, $MeONH_3^+Cl^-$, 80% EtOH, pH *ca.* 4, 40 °C

‡ The preparation of imine **5a** is representative: to a solution of diisopropylamine (0.51 g, 5.0 mmol) in dry THF (30 mL) at −78 °C was added Bu^{n}Li in hexane (2.5 mol dm^{-3}, 2.0 ml). The solution was kept at −78 °C for 20 min. 1,1-diphenyl-2-azapenta-1,3-diene (1.11 g, 5.0 mmol) in dry THF (5 mL) was added to the anionic solution and stirring continued at −78 °C for 3 h. The resulting dark red solution was treated with (+)-*B*-chlorodiisopinocampheylborane (1.60 g, 5.0 mmol) in dry THF (5 mL) and maintained at −78 °C for 2 h. To this solution was added cyclohexanecarboxaldehyde (0.45 g, 4.0 mmol) in dry THF (1 mL). The reaction mixture was maintained at −78 °C for 3 h and was allowed to warm up to 0 °C after which aqueous NaOH (2.5 mol dm^{-3}, 2 mL) and 30% H_2O_2 (2 mL) were added. The reaction mixture was stirred at room temperature for 12 h, diluted with ether (40 mL) and the organic phase separated. This was dried ($MgSO_4$), concentrated *in vacuo*, and the residue was purified by flash chromatography (silica gel, 4:1 hexane/EtOAc) to yield imine **5a** (0.81 g, 61%).

Table 1

Entry	Aldehyde	Product (%)	D.s.[a]	% E.e.[b]
1		**4a** (56)	≥95 : 5	91
2		**5a** (61)	≥95 : 5	93
3		**4b** (53)	≥95 : 5	93
4		**5b** (52)	≥95 : 5	90
5		**4c** (49)	≥95 : 5	91
6		**5c** (51)	≥95 : 5	90
7		**4d** (43)	≥95 : 5	—
8		**4d** (30), **5d** (11)	2.7 : 1	—
9		**4e** (17), **5e** (21)	1 : 1.2	—
10		**5e** (40)	≥95 : 5	—

[a] D.s. = diastereoselectivity. [b] E.e. = enantiomeric excess.

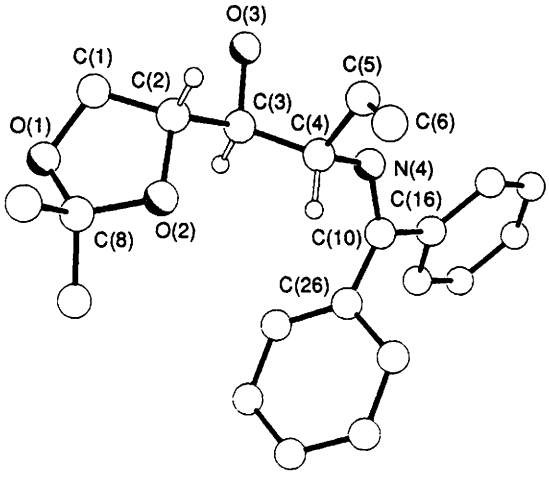


Fig. 1 The molecular structure of **4d** showing the absolute stereochemistry

¶ Deprotection of **5a**:[8] methoxylammonium chloride in an 80% aqueous ethanol solution (0.5 mol dm^{-3}, 10 ml) (pH = 4) was heated to 40 °C. Imine **5a** (66 mg, 0.2 mmol) in chloroform (1 ml) was added to the alcohol solution and the mixture stirred for 5 min. The mixture was concentrated *in vacuo* and the resulting residue diluted with H_2O (2 ml). The aqueous solution was extracted with diethyl ether (2 × 10 ml), separated and basified with aqueous NaOH (2.5 mol dm^{-3}, 10 ml). Extraction with ethyl acetate (3 × 10 ml), drying (K_2CO_3) and concentration *in vacuo* gave **7a** (33 mg, 98%).

§ *Crystal data* for **4d**: $C_{22}H_{25}NO_3$, monoclinic, space group *P*2, a = 13.386(12), b = 8.938(4), c = 18.147(12) Å, β = 110.76(2), U = 2030 Å^3, Z = 4 (two crystallographically independent molecules), M = 351.4, D_c = 1.150 g cm^{-3}, μ(Cu–Kα) = 6.1 cm^{-1}. The crystals suffer from severe lamella twining and full data sets were collected for three different partially twined fragments. Data were measured on a Siemens P4/PC diffractometer with graphite monochromated (Cu–Kα) radiation using ω-scans. The structure was solved by direct methods and refined anisotropically using the best of the three data sets. The phenyl rings were refined as idealised rigid bodies and the hydrogen atoms were added in calculated positions and allowed to ride on their parent atoms. Refinement converged to give R = 0.109, R_w = 0.106 for 1771 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\sigma \leq 120°$]; the high R factor is due to the crystal twinning and partial disorder. The relative stereochemistries of the C(2), C(3) & C(4) centres are however definitive. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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