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STEREOSELECTIVE SYNTHESIS OF THE FOUR STEREOISOMERS OF 4-(N,N-DIBENZYLAMINO)-2,2-DIMETHYL-3-HYDROXYPENTANENITRILE

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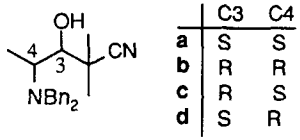
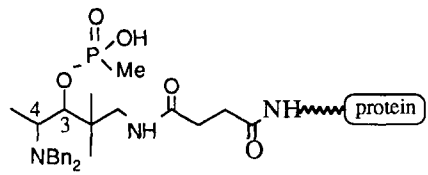
Abstract: The title compounds **1(a,b)** and **1(c,d)** were synthesized by (i) non-chelation controlled sodium borohydride reduction of their corresponding α-N,N-dibenzylaminoketones and (ii) the Aldol-type condensation of optically pure N,N-dibenzylaminoaldehydes with the lithium derivative of isobutyronitrile, respectively. Attempted inversion of configurations of these secondary alcohols using the Moriarty method yielded 4-chloro-3-N,N-dibenzylaminonitrile *via* an aziridinium ion intermediate instead of the expected inverted alcohols.

Optically active aminoalcohols are biologically important compounds[1] and are widely used as drugs[2], such as Bestatin and Amastatin[3], and show antimicrobial, anticancer and immunomodifier properties[4]. In an on-going research project based on the 'bait and switch' concept, haptens **2(a-d)** were required for the production of monoclonal catalytic antibodies[5]. In this paper we present the stereoselective synthesis of the 4-(N,N-dibenzylamino)-2,2-dimethyl-3-hydroxypentanenitriles **1(a-d)** which are the key intermediates in the preparation of **2(a-d)**.



1(a-d)

	C3	C4
a	S	S
b	R	R
c	R	S
d	S	R

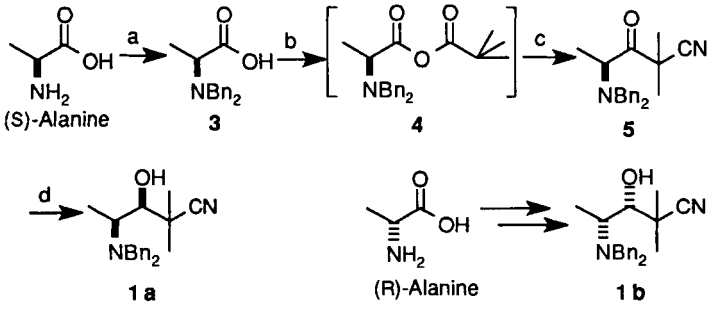


2(a-d)

* To whom correspondence should be addressed.

The (3*S*,4*S*) and (3*R*,4*R*) aminoalcohols **1(a,b)**, respectively, were synthesized from the corresponding (S)- and (*R*)-alanines. The bulky benzyl group was used for the protection of amine as well as to induce a high degree of diastereoselectivity in the sodium borohydride reduction[6] of the α-N,N-dibenzylaminoketones. Thus, N,N-dibenzyl (*S*)-alanine (**3**) was prepared by treatment of (*S*)-alanine with benzyl bromide and potassium carbonate in methanol in 70-75% yield. Compound **3** was converted to α-N,N-dibenzylaminoketone (**5**) in 92% yield *via* the mixed anhydride intermediate (**4**). Stereoselective reduction of ketone **5** with sodium borohydride in methanol/tetrahydrofuran (1:1) at -20°C gave (3*S*,4*S*)-aminoalcohol **1a** in 84% yield with 92% e.e.[7] The proton NMR of the crude product mixture of **1a** showed the presence of about 4% of the diastereomer **1c** which was removed by chromatography. The stereochemistry of this reduction reaction corresponds to *trans* addition by non-chelation control[1c], resulting almost exclusively in *threo* stereoisomer. The enantiomeric product **1b** (3*R*,4*R*) was synthesized via the same pathway starting from (*R*)-alanine[8] (Scheme 1).

Scheme 1.

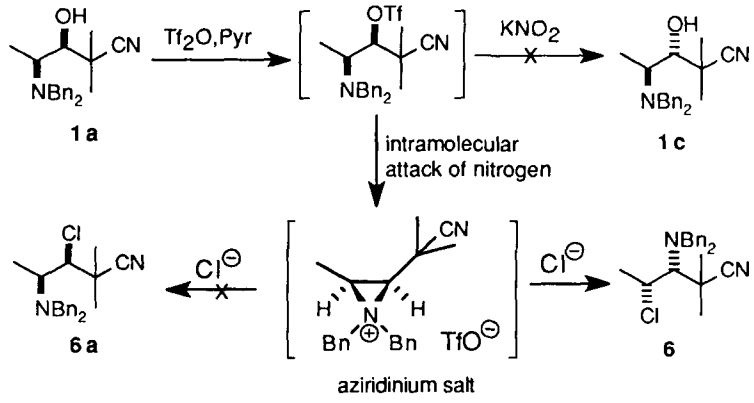


(a) $PhCH_2Br$, K_2CO_3, MeOH, rt, 24hr. (b) Me_3CCOCl, Et_3N, THF, -78°C, 1hr. (c) $LiC(Me_2)CN$, THF, -78°C, 1hr. (d) $NaBH_4$, MeOH-THF, -20°C, 1hr.

Next we turned our attention to inversion of the secondary alcohol functions in **1a** and **1b**. We have reported previously that the Mitsunobu method failed in the inversion of configuration in neopentyl-type secondary alcohol systems, but the

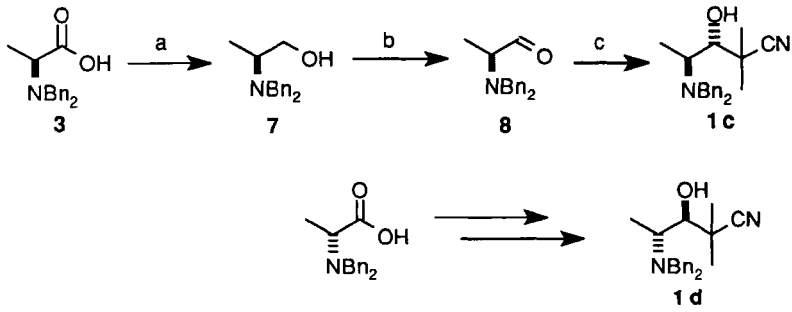
Moriarty method (i, Tf_2O, py; ii, KNO_2, DMF, 18-crown-6) worked very well in such systems[9]. However, when the latter method was applied to N,N-dibenzylaminoalcohol **1a**, 4-chloro-3-dibenzylaminonitrile (**6**) was obtained instead of an expected inverted aminoalcohol **1c**. The chloro compound **6** was probably formed *via* aziridinium ion intermediate[10] during aqueous work-up with 2N HCl (Scheme 2). The chloro compound **6a** was not observed presumably due to steric hindrance. Recently a similar observation has been reported in the Mitsunobu inversion reaction with an aminoalcohol system[11].

Scheme 2.



In order to obtain the *erythro* stereoisomers **1(c,d)**, which possess the alternative configuration of secondary alcohol at C3 relative to **1a** and **1b**, an Aldol-type condensation reaction[1(b)] was used. N,N-Dibenzylalanine **3** was reduced to N,N-dibenzyl alaninol (**7**) by lithium aluminum hydride in ether at 0°C and subsequently converted to the corresponding aldehyde (**8**) by Swern oxidation yielding 80% overall. The N,N-dibenzylaminoaldehyde **8** was used immediately in the next step without further purification to avoid possible racemization[12]. Condensation of **8** with the lithium derivative of isobutyronitrile (prepared *in situ* from isobutyronitrile and LDA in THF at -78°C) afforded N,N-dibenzylaminoalcohol (**1c**) in 85% yield with more than 98% e.e. and 4% of the diastereoisomer **1a** was also isolated by column chromatography (Scheme 3). The other isomer **1d** was synthesized in the same manner starting from (*R*)-alanine.

Scheme 3.



(a) $LiAlH_4$, Et_2O, 0°C, 1hr. (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C, 1hr. (c) $LiC(Me_2)CN$, THF, -78°C, 2hr.

The synthesis of the bifunctional amino-phosphonic haptens **2(a-d)** will be published in a future communication.

Experimental:

Melting points were determined using a Thomas Unimelt capillary tube melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300 at 300MHz for ^{1}HNMR and at 75MHz for ^{13}CNMR. IR spectra were recorded on a FTIR spectrometer. Mass spectra were obtained with a Finnigan MAT-90 mass spectrometer. All reagents were purchased from Aldrich Chemical Co. and used without further purification. THF was distillled from sodium / benzophenone immediately prior to use. All reactions were performed in oven-dried apparatus and under an argon atmosphere. Crude products were purified by flash chromatography with the use of E. Merk grade silica gel (230-400 mesh). Intermediates **3,7,8** were known compounds and prepared according to literature procedures[2]. Preparations of **1b** and **1d** were operationally the same as those of **1a** and **1c** and therefore not presented here. Specific rotation $[\alpha]_D$ (c0.04-0.05, $CHCl_3$): **1a**, +15.3°; **1b**, -14.9°; **1c**, +12.0°; **1d**, -11.4°.

4-(S)-(N,N-Dibenzylamino)-2,2-dimethyl-3-oxopentanenitrile (5). To a stirred solution of (S)-N,N-dibenzylalanine (5.0g, 18.59mmol) in dry THF (200mL) at -78°C was added triethylamine (3.88mL, 27.88mmol) dropwise, and the mixture was stirred for 30min. Then a solution of trimethylacetyl chloride

(2.37mL, 19.14mmol) in dry THF (50mL) was added dropwise at -78°C and stirred for 1hr, and thus formed mixed anhydride solution was used in the next step without isolation.

To a solution of isobutyronitrile (5.13g, 74.35mmol) in dry THF (100mL) at -78°C was added a THF solution of LDA (1.5M, 14.87mL, 22.31mmol), and the mixture was stirred for 40min. This solution was then transferred to the above mixed anhydride solution using a double-ended needle and stirred at -78°C for 1hr. The mixture was warmed up slowly to above -30°C and then quenched with saturated NaCl solution. The organic phase was separated, washed with saturated NaCl solution (2X100mL), dried ($MgSO_4$), and concentrated in vacuo to give a light brown liquid. This crude product was purified by column chromatography to yield **5** (5.45g, 92%, colorless liquid). ^{1}HNMR ($CDCl_3$) δ 1.27 (d, J=7.0Hz, 3H), 1.39 (s, 3H), 1.43 (s, 3H), 3.72 (d, J=14.1Hz, 2H), 3.83 (d, J=14.1Hz, 2H), 4.16 (q, J=7.0Hz, 1H), 7.23-7.36 (m, 10H); ^{13}CNMR ($CDCl_3$) δ 205.24, 138.77, 128.88, 128.34, 127.18, 122.05, 59.40, 53.98, 42.48, 24.74, 24.63, 11.30. IR(neat): 2235(CN), 1720(C=O) cm^{-1}. MS(CI) m/z 321 (M^+,100%), 319, 243, 224. Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.72; H, 7.55; N, 8.74. Found: C, 78.74; H, 7.60; N, 8.79%.

*4-(S)-(N,N-Dibenzylamino)-2,2-dimethyl-3-(S)-hydroxypentanenitrile (**1a**).* To a stirred solution of **5** (3.6g, 11.25mmol) in MeOH (36mL) and THF (36mL) at -20°C was added solid $NaBH_4$ (0.86g, 22.50mmol) portionwise. The mixture was stirred at -20°C for 40min, and then neutralized with 2N HCl to pH 6-7. The organic solvents were removed in vacuo and water (100mL) was added to the residue. The resulting mixture was extracted with ethyl acetate (3X30mL), and the combined extracts were washed with saturated NaCl solution (1X30mL), dried ($MgSO_4$), and concentrated to give a solid which was subject to column chromatography to yield the needle-like crystalline product **1a** (2.89g, 84%). mp: 67-68°C. ^{1}HNMR ($CDCl_3$) δ 0.92 (s, 3H), 1.31 (d, J=6.9Hz, 3H), 1.37 (s, 3H), 2.84 (m, 1H), 3.34 (d, J=13.2Hz, 2H), 3.45 (d, J=9.0Hz, 1H), 3.82 (d, J=13.2Hz, 2H), 5.42 (s, 1H), 7.26-7.35 (m, 10H); ^{13}CNMR ($CDCl_3$) δ 137.96, 129.07, 128.55, 127.47, 124.60, 74.55, 54.36, 53.17, 34.80, 25.70, 19.65, 10.55. IR: 3261 (br, OH), 2234 (CN) cm^{-1}. MS(CI) m/z 323 (M^+, 100%), 254, 245, 224. Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.09; H, 8.21; N, 8.89%.

*4-(S)-(N,N-Dibenzylamino)-2,2-dimethyl-3-(R)-hydroxypentanenitrile (**1c**).* To a solution of isobutyronitrile (3.65g, 52.87mmol) in dry THF (80mL) at -78°C was added dropwise a 1.5M LDA-THF solution (35.3mL, 52.87mmol) and stirred at that temperature for 40min. This solution was then transferred into a precooled (-78°C) solution of (S)-N,N-dibenzylalaninal **8** (8.93g, 35.25mmol) in dry THF (180mL) using a double-ended needle. The mixture was stirred at -78°C for 1hr, warmed up to 0°C, and quenched with saturated NaCl solution (80mL). The organic phase was separated, washed with saturated NaCl solution (2X80mL), dried ($MgSO_4$), and concentrated to give a light yellow solid. The crude product was purified by column chromatography to give **1c** (9.97g, 88%). mp: 113-114°C. ^{1}HNMR ($CDCl_3$) δ 1.04 (s, 3H), 1.24 (d, J=6.9Hz, 3H), 1.27 (s, 3H), 2.20 (br s, 1H), 3.04 (dq, J=1.8, 6.9Hz, 1H), 3.60 (d, J=14.1Hz, 2H), 3.69 (d, J=1.8Hz, 1H), 3.77 (d, J=14.1Hz, 2H), 7.22-7.39 (m, 10 H); ^{13}CNMR ($CDCl_3$) δ 139.76, 128.61, 128.20, 126.94, 123.88, 78.72, 54.24, 53.11, 37.97, 24.50, 22.51, 8.39. IR: 3432 (OH), 2238(CN) cm^{-1}. MS(CI) m/z 323 (M^+, 100%), 254, 245, 233, 224, 215, 161, 134, 107. Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.15; H, 8.21; N, 8.77%.

*4-(R)-Chloro-3-(R)-(N,N-dibenzylamino)-2,2-dimethylpentanenitrile (**6**).* Trifluoromethanesulfonic anhydride (0.21mL, 1.24mmol) was added at 0°C to a solution of **1a** (200mg, 0.62mmol) and pyridine (0.10mL, 1.24mmol) in dry CH_2Cl_2 (4mL). The mixture was stirred at 0°C for 1hr. Water (10mL) was then added, the organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2X5mL). Combined organics was washed with 2N HCl (2X5mL), saturated $NaHCO_3$ solution (2X5mL), and saturated NaCl solution (2X5mL), dried ($MgSO_4$), and concentrated to give a brown oily residue. Purification by column chromatography gave **6** (70mg) as a colorless semisolid. The starting material **1a** (95mg) was also recovered. ^{1}HNMR ($CDCl_3$) δ 1.32 (s,3H), 1.43 (s, 3H), 1.83 (d, J=6.9Hz, 3H), 2.90 (d, J=2.7Hz, 1H), 3.82 (d, J=13.2Hz, 2H), 4.29 (s, 2H), 4.62 (dq, J=6.9, 2.7Hz, 1H), 7.25-7.34 (m, 10H). IR: 2229(CN), 1600, 1495, 1454, 1388, 742, 700 cm^{-1}. MS(CI) m/z 341 (M^+, 100%), 305, 277, 272, 263, 251, 238, 215, 182, 146.

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