A Convenient Preparation of (1*R*,2*S*,7*S*,8*R*)-3,5-Diaza-2,7-dimethyl-1,8-diphenyloctan-1,8-diol and Its Enantiomer

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The synthesis of (1*R*,2*S*,7*S*,8*R*)-3,5-diaza-2,7-dimethyl-1,8-diphenyloctan-1,8-diol 6 and its enantiomer 7 are described utilising (−)-(1*R*,2*S*)- or (+)-(1*S*,2*R*)-norephedrine, respectively.

Key words norephedrine; polymetallated amino alcohol; homochiral base

Aminoalcohols continue to be of importance in modern synthetic chemistry, not least because of their biological properties, but also because of a wide range of synthetic applications.[1—3] Our own interest stems from our application of dilithiated aminoalcohols as chiral bases in the rearrangement of *meso*-epoxides, for example, **1** to either enantiomer of the corresponding allylic alcohol **2**/**3** using dilithiated (+)-(1*S*,2*R*)-**4** or (−)-(1*R*,2*S*)-norephedrine **5**, respectively[4—6] (Chart 1).

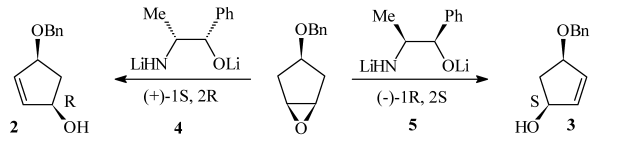


Chart 1

As part of our continuing studies in this area we wanted to prepare the "dimeric" analogues of these bases, **6** and **7**, in order to study the effects of using polymetallated bases, which are conceptually similar in nature to those utilised by Simpkins[7,8] and Alexakis[9] (Chart 2).

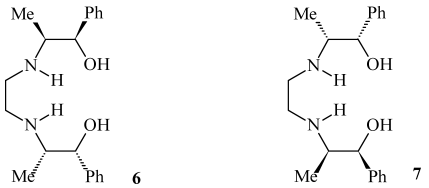


Chart 2

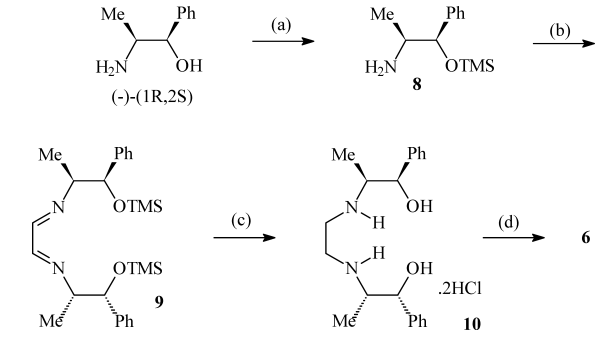
We therefore, required a simple, efficient synthesis of these compounds, which would be applicable to medium, and if necessary, large scale preparation. Prompted by reports of the synthesis of **6**,[10—12] we wish to report our method for the routine preparation of these aminoalcohols in good overall yields under mild conditions.

Thus, (−)-(1*R*,2*S*)-norephedrine was treated with trimethylsilyl chloride in THF to give the *O*-TMS ether **8** in 92% yield. This was followed by reaction with glyoxal under anhydrous conditions to afford the *bis*-imine **9**.[13] Immediate reduction of this species with sodium borohydride in methanol was accompanied by desilylation of the alcohol to give the crude amine **6**, which was purified by preparation of its *bis*-hydrochloride salt **10** ($[\alpha_D^{25}]=-12.1$ ($c=2.0$, MeOH)), in 53% overall yield (Chart 3).

The free amine **6** ($[\alpha_D^{25}]=+6.9$ ($c=0.72$, EtOH)) was obtained in 92% yield after treatment of the salt **10** with excess aqueous sodium hydroxide solution and extraction with ethyl acetate.

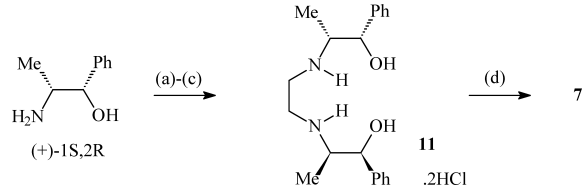
A similar reaction sequence when applied to (+)-(1*S*,2*R*)-norephedrine gave the aminoalcohol *bis*-hydrochloride **11** ($[\alpha_D^{25}]=+11.6$ ($c=2.0$, MeOH)) in 52% overall yield. The free amine **7** can again be obtained by treatment of the salt **11** with excess aqueous sodium hydroxide solution and extraction with ethyl acetate (93% yield, $[\alpha_D^{25}]=-6.3$ ($c=0.41$, EtOH)) (Chart 4).

In conclusion, we have demonstrated that the aminoalcohols **6** and **7** can be prepared in high and consistent overall yield from (−)- or (+)-norephedrine, under very mild conditions from a conveniently available dialdehyde. This methodology complements the preparative methods utilized in the work of Simpkins[7,8] and Alexakis[9] and offers the possibility for the preparation of conceptually similar bases to these *via*



(a) TMSCl, THF, 16 h; 92%. (b) $(CHO)_2$, Et_2O, 3 Å m.s., 48 h. (c) $NaBH_4$/MeOH, 30 min, then methanolic HCl; 53% overall. (d) NaOH (aq.); 92%.

Chart 3



(a) TMSCl, THF, 16 h. (b) $(CHO)_2$, Et_2O, 3 Å m.s., 48 h. (c) $NaBH_4$/MeOH, 30 min, then methanolic HCl; 52% from **5**. (d) NaOH (aq.); 93%.

Chart 4

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reaction with Grignard or organolithium reagents. We are currently investigating the application of these amines and related amines as homochiral bases and in related asymmetric processes.

Experimental

THF, diethyl ether and MeOH were dried and distilled using standard methods. Chemical ionisation (CI) mass spectra were recorded on a VG Masslab Model 12/253 spectrometer and high resolution mass spectra (HRMS) on a VG Analytical ZAB-E spectrometer at the EPSRC Mass Spectrometry Service Centre at Swansea. Proton NMR spectra were run at 250 MHz on a Bruker AC250 spectrometer. Carbon NMR spectra were run at 62.5 MHz on a Bruker AC250 spectrometer and were gate decoupled. All spectra were obtained from solutions in deuterated chloroform unless otherwise specified. Chemical shifts are reported as δ values (ppm) relative to tetramethylsilane as an internal standard.

(1*R*,2*S*,7*S*,8*R*)-3,5-Diaza-2,7-dimethyl-1.8-diphenyloctan-1,8-diol *bis*-Hydrochloride 10 L-(−)-(1*R*,2*S*)-Norephedrine (10.0 g, 66 mmol, $[\alpha_D^{25}]=-40.1$ (c=7.1, 1 N HCl)) was dissolved in THF (300 ml) and TMSCl (8.4 ml, 66 mmol) was added slowly with vigorous stirring to yield a thick white suspension. After stirring for 16 h, an aqueous solution of NaOH (16 g in 200 ml) was added to dissolve the precipitate, and the mixture extracted with diethyl ether (3×100 ml). The extracts were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give crude silyl ether **8** as an oil (13.5 g, 92%); ^{1}H-NMR: δ=7.27 (m, 5H, Ph), 4.37 (d, 1H, J=5.5 Hz, Ph-CH–NH_2), 2.99 (apparent pentet, 1H, J=6.5, 5.5 Hz, CH_3–CH–OTMS), 1.39 (s, 2H, –NH_2), 0.99 (d, 3H, J=6.5 Hz, CH_3) 0.00 ppm (s, 9H, TMS). ^{13}C-NMR: 141.98 (C, Ph), 127.86 (2×CH), 127.23 (CH), 126.87 (2×CH), 79.89 (CH), 53.16 (CH), 18.75 (CH_3), 0.00 ppm (TMS).

A solution of aqueous glyoxal (40%, 3.38 ml, 30.3 mmol) was dissolved in THF, whereupon powdered 4 Å molecular sieves (30 g) were added and the solution agitated for 1 h. After filtration under vacuum and evaporation to near dryness, the resulting glyoxal was dissolved in diethyl ether (50 ml) and added to a solution of crude silyl ether **8** (13.5 g, 60.6 mmol) in diethyl ether (25 ml). Further 4 Å molecular sieves (20 g) were added and the reaction stirred for 48 h (the reaction can be monitored by sampling if required, as the product has a diagnostic ^{1}H-NMR singlet at 7.49 ppm for the imine NH). The resulting solution was filtered under vacuum through a pad of celite, washed with diethyl ether and the solvent evaporated to give crude **9** as an oil.

This oil was immediately dissolved in dry methanol (50 ml), cooled (0 °C) and $NaBH_4$ (3.5 g, 90.7 mmol, 3 eq) added slowly with vigorous stirring over 30 min. After warming to room temperature the reaction was stirred for 16 h, whereupon the solvent was removed under reduced pressure and the resulting semi-solid triturated with chloroform (2×50 ml) and the triturates filtered and evaporated to give the crude amine **6** (9.65 g). The amine was redissolved in methanolic HCl (prepared by addition of acetyl chloride (7.4 ml, 0.1 mol), to cooled (0 °C), dry methanol (100 ml)); after 30 min the resulting suspension was heated to reflux for 5 min and then cooled in ice/water. Filtration of the resulting precipitate and washing with diethyl ether, gave the *bis*-hydrochloride **10** (4.96 g); evaporation to half the original volume and cooling (−20 °C) of the mother liquor, gave a further crop of **10** (2.02 g, 53% overall yield).

mp 273 °C. $[\alpha_D^{25}]=-12.1$ (c=2.0, MeOH). ^{1}H-NMR (CD_3OD): δ=7.58 (m, 10H, 2×Ph), 5.29 (d, 2H, J=2.7 Hz, 2×Ph-CH), 3.49 (m, 6H, 2×CH_2–NH, 2×CH–OH), 1.12 (d, 6H, J=6.75 Hz, 2×CH_3). ^{13}C-NMR (CD_3OD): δ=141.7 (2×C, Ph), 129.9 (4×CH, Ph), 129.3 (2×CH, Ph), 127.3 (4×CH, Ph), 71.9 (2×CH, CH–OH), 61.5 (2×CH, CH–NH), 42.8 (2×CH_2, –CH_2–NH), 10.1 (2×CH_3). MS(CI): m/z=329 (100% $[M+H]^+$). HR-MS(CI): $C_{20}H_{29}O_2N_2$ ($[M+H]^+$) requires 329.2229, found 329.2226.

(1*R*,2*S*,7*S*,8*R*)-3,5-Diaza-2,7-dimethyl-1,8-diphenyloctan-1,8-diol 6 *bis*-Hydrochloride **10** (1 g, 2.49 mmol) was dissolved in aqueous sodium hydroxide (2 M, 5 ml) and stirred for 10 min. Extraction with ethyl acetate (2×25 ml) followed by drying ($MgSO_4$), filtration and evaporation gave the free amine **6** as a white solid (0.75 g, 92%).

mp 116 °C (lit,[10—12] 116 °C). $[\alpha_D^{25}]=+6.9$ (c=0.72, EtOH). ^{1}H-NMR ($CDCl_3$): δ=7.25 (m, 10H, 2×Ph), 4.69 (d, 2H, J=3.8 Hz, 2×Ph-CH–NH), 3.20 (br s, 4H, 2×NH/OH), 2.5—2.9 (m, 6H, 2×CH_2–NH, 2×CH–OH), 0.82 (d, 6H, J=6.5 Hz, 2×CH_3). ^{13}C-NMR ($CDCl_3$): δ=141.7 (2×C, Ph), 128.1 (4×CH, Ph), 127.1 (2×CH, Ph), 126.2 (4×CH, Ph), 73.8 (2×CH, CH–OH), 58.6 (2×CH, CH–NH), 46.6 (2×CH_2, CH_2–NH), 14.3 (2×CH_3). MS(CI): m/z=329 (90% $[M+H]^+$). HR-MS(CI): $C_{20}H_{29}O_2N_2$ ($[M+H]^+$) requires 329.2229, found 329.2228. Microanalysis; $C_{20}H_{29}O_2N_2$ requires: C=73.14, H=8.59, N=8.53; found: C=72.72, H=8.52, N=8.49.

(1*S*,2*R*,7*R*,8*S*)-3,5-Diaza-2,7-dimethyl-1,8-diphenyloctan-1,8-diol *bis*-Hydrochloride 11 D-(+)-(1*R*,2*S*)-Norephedrine (10.0 g, 66 mmol, $[\alpha_D^{25}]=+38$ (c=7.0, 1 N HCl)) was converted to **11** (6.90 g, 52% overall yield) under identical conditions to those described for **10** and displayed identical analytical data with the exception of the optical rotation. mp=275 °C. $[\alpha_D^{25}]=+11.6$ (c=2.0, MeOH).

(1*S*,2*R*,7*R*,8*S*)-3,5-Diaza-2,7-dimethyl-1,8-diphenyloctan-1,8-diol 7 In a similar fashion to that described for the preparation of **6**, *bis*-hydrochloride **11** (1 g, 2.49 mmol) was dissolved in aqueous sodium hydroxide (2 M, 5 ml) and stirred for 10 min. Extraction with ethyl acetate (2×25 ml) followed by drying ($MgSO_4$) filtration and evaporation gave the free amine **7** as a white solid (0.76 g, 93%). This material displayed identical analytical data to **6** with the exception of the optical rotation. mp 116 °C. $[\alpha_D^{25}]=-6.3$ (c=0.41, EtOH). Microanalysis; $C_{20}H_{29}O_2N_2$ requires: C=73.14, H=8.59, N=8.53; found: C=72.76, H=8.56, N=8.54.

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References and Notes

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