220. Improved Nitroaldol Reactions and Reductive Routes to Vicinal Aminoalcohols

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Dedicated to Prof. *Vladimir Prelog* on the occasion of his 75th birthday

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Summary

Regioselective and flexible procedures are described for the preparation of a variety of protected vicinal nitroalcohols **1**, **3** and **5** (see *Scheme 5*), as is an efficient method for their reduction to the corresponding vicinal aminoalcohols **2**, **4** and **6**.

Vicinal aminoalcohols have broad significance in organic chemistry. Their synthetic importance can be seen in the *Tiffeneau-Demjanov* and related deaminative semipinacol rearrangements [1], and their biological relevance in the structures of adrenalin and related mediators of the sympathetic nervous system [2] [3]. All of the main synthetic routes to this functional class possess significant limitations to their use [3], particularly in terms of the attainable degree of regioselectivity. For example, the orientation of oxirane ring-opening by a N-nucleophile depends upon both the substitution pattern of the oxirane and the reaction conditions employed. The modified osmylation method of *Sharpless et al.* [4] approaches regiospecificity only in highly biased cases. Similarly, the success of the methods such as α-halogenation or α-nitrosation of ketones depends upon the degree of regioselectivity attained in the initial α-functionalization [3]. Hydride reduction of free or protected cyanohydrins [5] is of considerable utility, but only in those cases where C_1-homologation of the carbonyl substrate is desired.

An apparently attractive route to vicinal aminoalcohols requires reduction of the corresponding vicinal nitroalcohols. These latter compounds are accessible by the *Henry*- [6], or nitroaldol reaction, a regioselective method for the coupling of a carbonyl and a nitroalkane component leading to the vicinal relationship between the *O*- and *N*-substituents *(Scheme 1)*. Such a procedure has been used only infrequently, partly due to the often low yields [7] obtained (except in intramolecular cases and those reactions involving nitromethane itself), and to *retro*-

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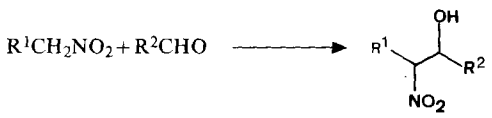
Scheme 1



(1)

aldolization frequently occurring on attempted purification. Additionally, there is a lack of a generally applicable method for the reduction of the so-formed vicinal nitroalcohols. Reduction methods which have been used include catalytic hydrogenation over *Raney*-nickel [8] and electrolytic reduction [9], neither of which is without its attendant problems. *Retro*-aldolization is often the major primary process on attempted reduction of unprotected vicinal nitroalcohols with reagents such as lithium aluminium hydride [10].

We now report in detail[3]) a sequence of nitroaldol and reduction procedures which overcomes many of the problems mentioned. This sequence is well-suited to the involvement of the higher nitroalkanes, and may encourage a much greater use of vicinal nitroalcohols as synthetic intermediates. Its utility described herein is perhaps best exemplified by the efficient preparation of 6-amino-7-tridecanol (**2a**, *Scheme 5*) a *nearly* symmetrical vicinal aminoalcohol unobtainable as a single structural isomer by any of the alternative methods outlined above.

Recently, we described in detail the efficient preparation of silyl nitronates (trialkylsilyl esters of nitronic acids (=*aci*-nitroalkanes)), and discussed their physical properties, including their structure as determined by X-ray crystallography [12][4]). In this context, we have prepared additionally the (*t*-butyl)dimethylsilyl ester of *aci*-nitro(*p*-methoxyphenyl)methane, the X-ray structure of which is included in the Experimental Part, *Figure 1*.

To summarize in brief the preparative procedure, sequential treatment of primary nitroalkanes with lithium diisopropylamide in THF, followed by quenching the resulting lithium nitronates with either chlorotrimethyl- or chloro(*t*-butyl)-dimethylsilane and non-aqueous isolation gives the corresponding silyl nitronates in distilled yields of *ca.* 70%[5]). Secondary nitroalkanes are also converted into silyl nitronates under these conditions, though in lower distilled yields of *ca.* 30–40%; these latter nitronates are somewhat less stable than those derived from primary nitroalkanes, and are accordingly best handled as their (*t*-butyl)dimethylsilyl derivatives.

Such silyl nitronates react readily with a wide range of aliphatic and aromatic aldehydes in the presence of a catalytic quantity of fluoride ion *(Scheme 2)*. In those cases involving silyl nitronates from primary nitroalkanes, the adducts isolated are vicinal nitro-trialkylsilyloxy compounds. This parallels the results observed in the fluoride ion-catalyzed reaction between silyl enol ethers and aldehydes [14]. In a rather less efficient process, silyl nitronates derived from secondary nitroalkanes

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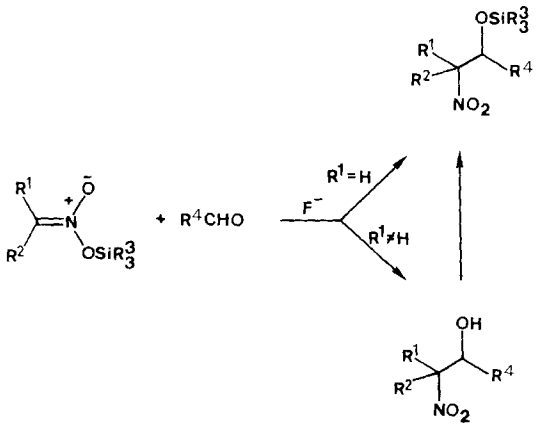
[3]) Preliminary comunication: [11].

[4]) For other routes see [13].

[5]) In large scale preparation (> 50 mmol), contact of the solutions of silyl nitronates with air must be avoided. If not, the hydrolysis products cause extensive decomposition during the final bulb-to-bulb distillations.

Scheme 2

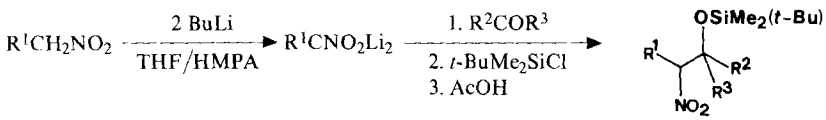


(2)

produce mixtures of free and protected vicinal nitroalcohols, which can be silylated subsequently by conventional procedures [15] [16]. No reaction occurred in the absence of the catalyst, nor did the catalyst induce any reaction between aldehydes and nitroalkanes themselves.

In continuing analogy with silyl enol ethers, neither class of silyl nitronate reacts with ketones under these reaction conditions. However, nitroalkane dianion derivatives (from primary nitroalkanes) do react efficiently with ketones [17], and the resulting intermediates can be silylated *in situ (Scheme 3)*.

Scheme 3



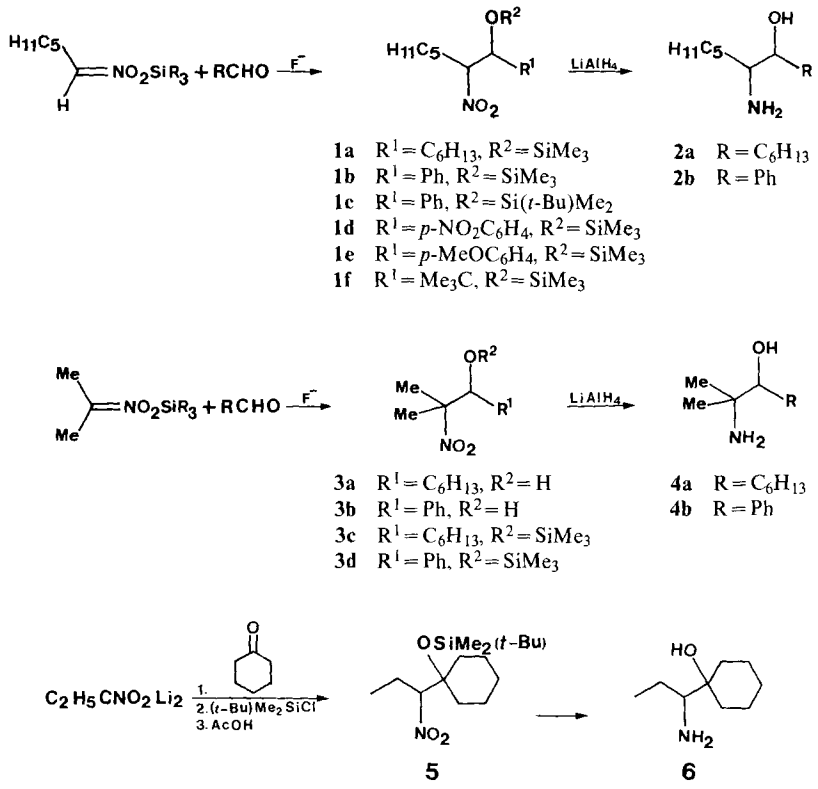
(3)

Thus representatives **1**, **3** and **5** of three, **I**–**III**, of the four possible substitution classes of vicinal aminoalcohols can be obtained readily in protected forms by one of these procedures; the single class of which representatives cannot be prepared is that of **IV** derived formally from addition of secondary nitroalkanes to ketones. It should be mentioned at this juncture that, where applicable, the silyl-protected vicinal nitroalcohols are obtained as *mixtures of diastereoisomers*, the relative proportions of which depend upon the reaction conditions.

Regardless of the particular silyl protection or of the substitution pattern, representatives of these three classes of trialkylsilyl-protected vicinal nitroalcohols

Scheme 4

Scheme 5



undergo smooth nitro-group reduction on addition to lithium aluminium hydride in refluxing ether, to afford vicinal aminoalcohols **2**, **4** and **5** in yields of 50–85% (after distillation). The silyl group is not lost prior to nitro-group reduction, since attempted reduction of the unprotected vicinal nitroalcohols using lithium aluminium hydride results in bond scission followed by reduction of the original components of the substrates [10]; for example, the adduct from benzaldehyde and 1-nitrohexane gives only benzyl alcohol and 1-aminohexane.

Any degree of diastereoisomeric excess, initially present in the protected vicinal nitroalcohol substrates, is absent in the corresponding aminoalcohols produced, which are obtained as approximately (1:1)-mixtures of diastereoisomers.

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Experimental Part

General Remarks. – All nitroaldol reactions and lithium aluminium hydride reductions were carried out in an atmosphere of Ar, employing a pre-dried two-necked round bottomed flask, one neck of which was equipped with a rubber septum. Tetrahydrofuran (THF) was freshly distilled from $LiAlH_4$ prior to

use. All introductions of liquid reagents and solvents were performed with a hypodermic syringe. Bulb-to-bulb distillations were carried out on a *Büchi GKR 50*, and distillation temp. refers to air-bath temp. ^{1}H-NMR. spectra were recorded with a *Varian EM 390* spectrometer, chemical shifts are given in ppm, coupling constants in Hz. The silyl nitronates were prepared as previously described by us [12]; for large scale preparations see also footnote 5.

Preparation of (*t*-butyl)dimethylsilyl ester of *aci*-nitro(*p*-methoxyphenyl)methane. – To a solution of 5.4 mmol lithium diisopropylamide in 15 ml THF stirred at $-78°$ under Ar were added 0.84 g (5.0 mmol) (*p*-methoxyphenyl)nitromethane[6]), and after 30 min 0.90 g (6.0 mmol) (*t*-butyl)dimethylsilyl chloride, dissolved in 2 ml THF. The temperature was allowed to rise to $+20°$ overnight, the solvent removed *in vacuo*, and the residue triturated with 25 ml pentane, filtered through *Celite* and concentrated (*cf.* [12]). The 0.61 g (43.6%) of crude silyl nitronate thus obtained were recrystallized from pentane to furnish crystals suitable for X-ray structure analysis *(Fig. 1)*. – ^{1}H-NMR. ($CDCl_3$): 7.95 and 7.05 (4 H, aryl-H); 7.1 (1 H, HC=N); 3.9 (*s*, 3 H, OCH_3); 1.05 (*s*, 9 H, $C(CH_3)_3$); 0.45 (*s*, 6 H, $Si(CH_3)_2$).

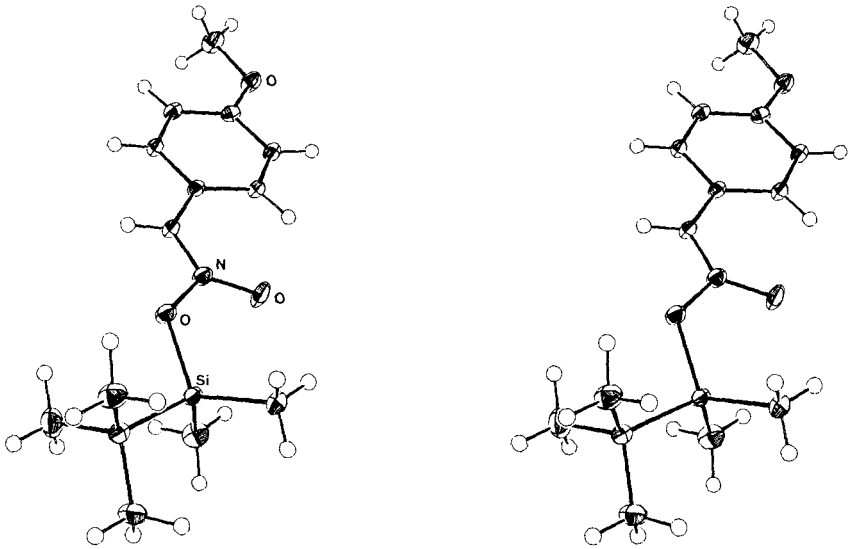

Fig. 1. *ORTEP-Drawing of* t-*butyldimethylsilyl ester of* 1-aci-*(p-methoxyphenyl)methane* [20]. (The ellipsoids of the non-hydrogen atoms include 50% of the electron density)

Silyl Nitroaldol Addition. – *General procedure.* To a solution of 160 mg (0.5 mmol, pre-dried by heating for 4 h at 90°/0.1 Torr.) of tetra(*n*-butyl)ammonium fluoride in 15 ml of THF at $-78°$ were added the aldehyde (10 mmol) followed by the silyl nitronate (11 mmol). The resulting solution was stirred at $-78°$ for 3 h, then allowed to warm up to RT. overnight. It was then poured into 200 ml of hexane, and washed with 3×20 ml of water, and dried with $MgSO_4$. Evaporation of solvent and bulb-to-bulb distillation gave the desired protected or free vicinal nitroalcohol.

6-Nitro-7-trimethylsilyloxytridecane (**1a**). Reaction of heptanal with the trimethylsilyl ester of 1-*aci*-nitrohexane gave **1a** as a colourless oil in 80% yield, b.p. 175°/0.05 Torr. – ^{1}H-NMR. ($CDCl_3$): 0.00, 0.05 (2 *s*, 9 H); 0.85 (br. *t*, 6 H); 1.25 (*m*, 18 H); 3.95 (*m*, 1 H); 4.2 (*m*, 1 H).

$C_{16}H_{35}NO_3Si$ (317.55) Calc. C 60.53 H 11.11 N 4.41% Found C 60.70 H 11.23 N 4.47%

2-Nitro-1-phenyl-1-trimethylsilyloxyheptane (**1b**). Reaction between benzaldehyde and the trimethylsilyl ester of 1-*aci*-nitrohexane gave **1b** as a colourless oil in 75% yield, b.p. 175°/0.05 Torr. – ^{1}H-NMR.

[6]) Obtained in very poor yield from *p*-methoxybenzyl bromide [18] and sodium nitrite in dimethylformamide according to ref. [19].

(CCl_4): 0.15 and 0.22 (2*s*, 9 H); 1.0 (*m*, 3 H); 1.35 (*m*, 6 H); 1.9 (br. *m*, 2 H), 4.75 (2 overlapping *t*, $J=9$, 1 H); 5.05 and 5.26 (2 *d*, $J=9$ and 6, 1 H); 7.5 (*s*, 5 H); diastereoisomeric ratio *ca.* 2:1.

$C_{16}H_{27}NO_3Si$ (309.48) Calc. C 62.09 H 8.79 N 4.53% Found C 62.19 H 8.92 N 4.52%

1-(t-Butyl)dimethylsilyloxy-2-nitro-1-phenylheptane (**1c**). Reaction of benzaldehyde with the (*t*-butyl)dimethylsilyl ester of 1-*aci*-nitrohexane gave **1c** in 83% yield as a colourless oil, b.p. 200°/0.1 Torr. – ^{1}H-NMR. (CCl_4): 0.05 and 0.3, 0.12 and 0.36 (4 *s*, 6 H); 1.11 and 1.12 (2 *s*, 9 H); 1.1 (*m*, 3 H); 1.5 (*m*, 6 H); 2.1 (br. *m*, 2 H); 4.8 (2 overlapping *t*, $J=9$, 1 H); 5.15 and 5.4 (2 *d*, $J=9$ and 6, 1 H); 7.75 (*s*, 5 H); diastereoisomeric ratio *ca.* 5:3.

$C_{19}H_{33}NO_3Si$ (351.57) Calc. C 64.92 H 9.56 N 3.92% Found C 64.91 H 9.53 N 3.98%

2-Nitro-1-(p-nitrophenyl)-1-trimethylsilyloxyheptane (**1d**). Reaction of *p*-nitrobenzaldehyde with the trimethylsilyl ester of 1-*aci*-nitrohexane gave **1d** in 91% yield as a colourless oil, b.p. 200°/0.1 Torr. – ^{1}H-NMR. (CCl_4): 0.2 and 0.25 (2 *s*, 9 H); 1.1 (*m*, 3 H); 1.45 (*m*, 6 H); 2.0 (br. *m*, 2 H); 4.65 (2 superimposed *t*, $J=10$, 1 H); 5.23 and 5.35 (2 *d*, $J=9$ and 6, 1 H); 7.75 and 8.45 (two superimposed *ABq*, $J_{AB}=9$, 4 H), diastereoisomeric ratio *ca.* 2:1.

$C_{16}H_{26}N_2O_5Si$ (354.48) Calc. C 54.21 H 7.39 N 7.90% Found C 54.12 H 7.39 N 7.82%

1-(p-Methoxyphenyl)-2-nitro-1-trimethylsilyloxyheptane (**1e**). Reaction between *p*-anisaldehyde and the trimethylsilyl ester of 1-*aci*-nitrohexane gave **1e** as a colourless oil in 70% yield, b.p. 190°/0.05 Torr. – ^{1}H-NMR. ($CDCl_3$): 0.1 and 0.2 (2 *s*, 9 H); 1.1 (br. *m*, 3 H); 1.4 (*m*, 6 H); 1.9 (*m*, 2 H); 3.95 and 4.02 (2 *s*, 3 H); 4.55 (2 superimposed *t*, $J=7$, 1 H); 4.95 and 5.15 (2 *d*, $J=9$ and 6, 1 H); 7–8 (*m*, 4 H); diastereoisomeric ratio *ca.* 2:1.

$C_{17}H_{29}NO_4Si$ (339.51) Calc. C 60.14 H 8.61 N 4.13% Found C 61.45 H 8.67 N 4.32%

2,2-Dimethyl-4-nitro-3-trimethylsilyloxynonane (**1f**). Reaction of 2,2-dimethylpropanal with the trimethylsilyl ester of 1-*aci*-nitrohexane gave **1f** as a colourless oil in 57% yield, b.p. 175°/0.1 Torr. – ^{1}H-NMR. ($CDCl_3$): 0.15 (*s*, 9 H); 0.9 (br. *s*, 12 H); 1.3 (*m*, 6 H); 1.8 (br. *m*, 2 H); 3.70 and 3.71 (2 *s*, 1 H); 4.4 and 4.5 (2 *t*, $J=2$, 1 H); diastereoisomeric ratio *ca.* 1:1.

$C_{14}H_{31}NO_3Si$ (289.49) Calc. C 58.08 H 10.79 N 4.84% Found C 58.18 H 10.86 N 4.86%

2-Methyl-2-nitro-3-nonanol (**3a**). Reaction of heptanal with the (*t*-butyl)dimethylsilyl ester of 2-*aci*-nitropropane gave **3a** as a colourless oil in 30% yield, b.p. 135°/0.1 Torr. – ^{1}H-NMR. (CCl_4): 0.9 (br. *t*, 3 H); 1.3 (*m*, 10 H); 1.48 (*s*, 3 H); 1.5 (*s*, 3 H); 2.68 (*d*, $J=5$, 1 H, disappears on addition of D_2O); 3.9 (*m*, 1 H).

$C_{10}H_{21}NO_3$ (203.28) Calc. C 59.08 H 10.41 N 6.89% Found C 59.53 H 10.51 N 6.75%

2-Methyl-2-nitro-3-trimethylsilyloxynonane (**3c**). To a solution of 1.17 g (5.7 mmol) of **3a** in 5 ml of DMF were added 1 g (14.7 mmol) of imidazole and 0.9 ml (7.1 mmol) of chlorotrimethylsilane. The reaction mixture was stirred for 24 h at RT. in an atmosphere of Ar. It was then partitioned between 100 ml of pentane and 100 ml of water, and the layers were separated. The aqueous layer was extracted once more with 100 ml of pentane, the pentane extracts were combined, washed with two 100 ml portions of water, and dried with $MgSO_4$. Evaporation of solvent and distillation gave 1.32 g (84.2%) of pure **3c**, b.p. 85°/0.04 Torr. – ^{1}H-NMR. (CCl_4): 0.01 (*s*, 9 H); 0.9 (br. *t*, 3 H); 1.3 (br. *s*, 10 H); 1.45 (*s*, 3 H); 1.47 (*s*, 3 H); 4.15 (br. *t*, 1 H).

$C_{13}H_{29}NO_3Si$ (275.47) Calc. C 56.68 H 10.61 N 5.08% Found C 57.01 H 9.99 N 5.15%

2-Methyl-2-nitro-1-phenyl-1-propanol (**3b**). Reaction between benzaldehyde and the (*t*-butyl)dimethylsilyl ester of 2-*aci*-nitropropane gave **3b** as a colourless oil in 25% yield, b.p. 135°/0.1 Torr. – ^{1}H-NMR. (CCl_4): 1.35 (*s*, 3 H); 1.5 (*s*, 3 H); 3.05 (br. *s*, 1 H, disappears on addition of D_2O); 5.15 (*s*, 1 H); 7.3 (*s*, 5 H). This product was not further characterized, but directly *O*-silylated as described in the following procedure. When different F^--catalysts [21] [22] are used, the *O*-silylated derivative of **3b** can be present in the reaction mixture to a large extent.

2-Methyl-2-nitro-1-phenyl-1-trimethylsilyoxypropane (**3d**). To a stirred solution of 300 mg (1.54 mmol) of **3b** in 0.5 ml (excess) of hexamethyldisilazane was added dropwise a solution of 0.5 ml

(excess) of chlorotrimethylsilane in 5 ml of pentane. The resulting mixture was heated under reflux for 4 h. It was then cooled, diluted with 20 ml of pentane, and filtered. Evaporation and bulb-to-bulb distillation gave 340 mg (83%) of **3d** as a colourless oil, b.p. 100°/0.05 Torr. This product was reduced to the aminoalcohol **4b** as described below.

Reduction of 1,2-Nitro-trialkylsilyloxy compounds to vicinal aminoalcohols. – *General procedure.* To a stirred slurry of $LiAlH_4$ (20 mmol) and 20 ml ether was added dropwise, *via* a hypodermic syringe, the protected nitroalcohol (5 mmol) at such a rate as to maintain gentle reflux. The mixture was heated under reflux for 5 further h. It was then cooled to 0°, and treated with sat. aq. Na_2SO_4-solution until all solids had become granular. The clear supernatant solution was decanted, and the residual slurry extracted with 4×50 ml of ethyl acetate. The combined organic extracts were washed with 20 ml of water, 20 ml of sat. NaCl-solution, and dried with $MgSO_4$. Evaporation of solvent and bulb-to-bulb distillation gave the desired vicinal aminoalcohol.

In their ^{1}H-NMR. spectra, the aminoalcohols exhibited their exchangeable protons as a three-proton singlet at 2–3 ppm. For analytical purposes, the crystalline salts formed on reaction of the aminoalcohols with anhydrous oxalic acid in ether were favoured.

6-Amino-7-tridecanol (**2a**). Reduction of **1a** as described afforded **2a** in 84% yield as a low-melting solid, b.p. 150°/0.1 Torr. – ^{1}H-NMR. ($CDCl_3$): 0.9 (br. *t*, 6 H); 1.27 (br. *s*, 18 H); 2.62 (br. *s*, 4 H); 3.3 (*m*, 1 H). This aminoalcohol was analyzed as its (1:1)-salt with anhydrous oxalic acid, m.p. 150.4–151.4 (pentane/methanol).

$C_{13}H_{29}NO \cdot (CO_2H)_2$ (305.42) Calc. C 58.99 H 10.23 N 4.59% Found C 59.00 H 10.29 N 4.55%

2-Amino-1-phenyl-1-heptanol (**2b**). Following the general procedure, reduction of **1b** gave **2b** in 64% yield as a colourless oil, b.p. 175°/0.03 Torr. – ^{1}H-NMR. (CCl_4): 0.85 (br. *t*, 3 H); 1.2 (br. *s*, 8 H); 2.15 (br. *s*, 3 H); 2.75 (*m*, 1 H); 4.13 and 4.4 (2 *d*, $J = 6$ and 4, 1 H); 7.2 (*s*, 5 H); diastereoisomeric ratio *ca.* 1:1. This aminoalcohol was analyzed as its (1:1)-salt with anhydrous oxalic acid, m.p. 192–193° (ethanol).

$C_{13}H_{21}NO \cdot (CO_2H)_2$ (297.35) Calc. C 60.59 H 7.80 N 4.71% Found C 60.46 H 7.85 N 4.69%

2-Amino-2-methyl-3-nonanol (**4a**). Reduction of **3a** by the above procedure gave **4a** in 55% yield as a colourless oil, b.p. 85°/0.005 Torr. – ^{1}H-NMR. (CCl_4): 0.9 (br. *t*, 3 H); 1.0 (*s*, 3 H); 1.1 (*s*, 3 H); 1.3 (br. *s*, 10 H); 2.1 (br. *s*, 3 H); 3.1 (*m*, 1 H). This compound was analyzed as its (2:1)- salt with anhydrous oxalic acid, m.p. 263.6–264.6°.

$(C_{10}H_{23}NO)_2 \cdot (CO_2H)_2$ (436.64) Calc. C 60.52 H 11.08 N 6.41% Found C 60.31 H 10.95 N 6.33%

2-Amino-2-methyl-1-phenyl-1-propanol (**4b**). Reduction of **3b** as described gave crude **4b** in 66% yield, purity > 90%, as a colourless oil. – ^{1}H-NMR. (CCl_4): 0.83 (*s*, 3 H); 0.95 (*s*, 3 H); 2.75 (br. *s*, 3 H); 4.17 (*s*, 1 H); 7.15 (*s*, 5 H). This compound was analyzed as its (2:1)-salt with anhydrous oxalic acid, m.p. 279–281° (methanol/ether).

$(C_{10}H_{15}NO)_2 \cdot (CO_2H)_2$ (420.51) Calc. C 62.84 H 7.67 N 6.66% Found C 62.40 H 7.71 N 6.53%

1-(1-Aminopropyl)cyclohexanol (**6**). Reduction of **5** [17b] as described afforded **6** in 76% yield as a colourless oil. b.p. 100°/0.05 Torr.

$C_9H_{19}NO$ (157.25) Calc. C 68.74 H 12.18 N 8.91% Found C 68.58 H 12.16 N 8.69%

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