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Diastereoselective hydroboration of chiral enamines using an enantiomerically pure amine from an industrial waste material as the source of chirality

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Abstract

By a hydroboration/oxidation procedure *trans*-aminoalcohols with *dr* values from 74:26 to ≥95:5 were obtained. A bicyclic amine derived from the unnatural amino acid 2-azabicyclic[3.3.0]octane-3-carboxylic acid was used as the chiral precursor. The absolute configuration was clarified by X-ray structure of a descendant of the *trans*-aminoalcohols.

1. Introduction

The bifunctional nature of aminoalcohols is of special significance. On the one hand, they represent an important group of chiral auxiliaries in organic synthesis[1] and on the other hand, they have a potential biological activity.[2] Furthermore, the example vesamicol shows that the chiral environment of a receptor demands an appropriately configured aminoalcohol.[3]

Among the common methods for the stereoselective synthesis of aminoalcohols are the reduction of amino acid derivatives, e.g. amino aldehydes,[4a] amino ketones[4b] or amino ester,[4c] the amination of chiral epoxides[5] as well as the hydroboration and oxidation of enamines. For the first time the stereoselective hydroboration of enamines was performed by *B. Singaram* using chiral modified boranes[6] or enamines based on optical active ketones.[7]

2. Results and discussion

To the best of our knowledge, no chiral amine as a source of chirality has been used in the stereoselective hydroborationtion to date. Hence we would like to present our results by using a secondary, bicyclic amine derived from an industrial waste material **1**.[8] The two-step synthesis of

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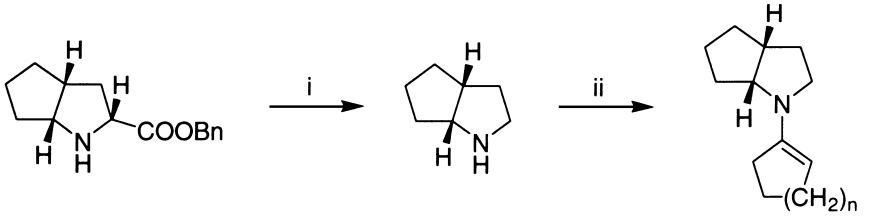
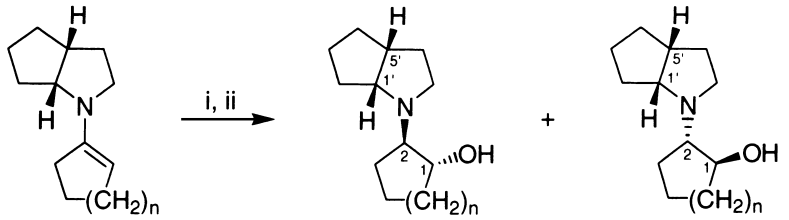
the bicyclic amine **2** starting from 1 has been already described elsewhere.[9] Amine **2** reacted with different cyclic ketones to the corresponding enamines **3–6** (Scheme 1) in good yield.



1 **2** enamines **3 - 6** (n = 1, 2, 3, 4)

Scheme 1. Reagents and conditions: (i) Ref. 9; (ii) different ketones, *p*-TSA, C_6H_6, water trap

The hydroboration of the enamines **3–6** with 1 M borane–THF solution for 2 h at 0°C followed by an oxidation with 30% hydrogen peroxide in alkaline medium afforded the aminoalcohols **7–10** (Scheme 2). The diastereomeric ratios of the crude products were determined by NMR spectroscopy. Afterwards the diastereomeric mixtures **7–9** were separated by column chromatography and purified by Kugelrohr distillation. The results are summarized in Table 1.



3 - 6 (1*R*,2*R*) **7 - 10** (1*S*,2*S*) **7 - 10**

Scheme 2. Reagents and conditions: (i) BH_3, THF, rt, 2 h then MeOH, NaOH (s), 30% H_2O_2; (ii) separation of diastereomers by column chromatography

The listed *dr* values demonstrate a clear preference for the formation of the (1*R*,2*R*)-configured aminoalcohols **7–10**. The aminoalcohol **10** was obtained with *dr* $\geq$95:5. In this case the induction of the two stereogenic centres of the amine part in combination with the special fold of the octene ring leads to a single diastereomer. While the attack on the C2′-atom of the enamine double bond and the relative *trans*-configuration of the products aminoalcohols are explained by the typical reaction mechanism of the hydroboration, the absolute configuration is predetermined by the different shieldings of the double bond sides. For enamines **3–6** the *Si*-attack on the double bond is more hindered by the bicyclic amine than an attack on the *Re*-side.

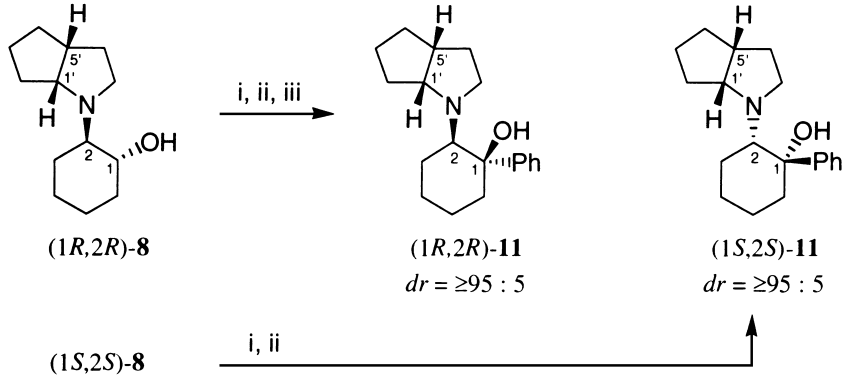
The Swern oxidation of (1*R*,2*R*)-**8** and (1*S*,2*S*)-**8** led to the formation of the corresponding amino ketones which could not be isolated in a pure form, due to the enolization of the ketone. Thus, the crude amino ketones were directly treated with phenyl lithium at –78°C in THF

Table 1
trans-Aminoalcohols **7**–**10** from hydroboration/oxidation of the enamines **3**–**6**

Entry	Enamine	n	Amino alcohol	Yield[a] (%)	*dr*[b] (%) (1*R*,2*R*) : (1*S*,2*S*)[c]
1	**3**	1	**7**	75	74 : 26
2	**4**	2	**8**	89	76 : 24
3	**5**	3	**9**	89	81 : 19
4	**6**	4	**10**	90	≥95 : 5

[a] Both diastereomers. [b] Determined by NMR spectroscopy. [c] Assignment of the configuration is based on the x-ray structure of (all-*R*)-**11**· HCl, the major diastereomer has a larger R_f-value: **7** major: R_f 0.38, minor R_f 0.32; **8** major: R_f 0.81, minor R_f 0.65; **9** major R_f 0.79, minor R_f 0.70; **10** R_f 0.80.

(Scheme 3). (1*R*,2*R*)-**11** was obtained from (1*R*,2*R*)-**8** by this two-step procedure with high diastereoselectivity, *dr* ≥95:5. Starting from (1*S*,2*S*)-**8** the *tert*-alcohol (1*S*,2*S*)-**11** was formed again with high diastereoselectivity, *dr* ≥95:5.



Scheme 3. Reagents and conditions: (i) $(COCl)_2$, DMSO, CH_2Cl_2, –60°C then Et_3N; (ii) PhLi, THF, –78°C; (iii) MeOH, $HCl_{aq.}$ then $NaOH_{aq.}$, Et_2O

After purification by column chromatography the aminoalcohol (1*R*,2*R*)-**11** was converted into its hydrochloride. By crystallisation from methanol and diethyl ether block-like crystals were obtained. In order to ascertain the absolute configuration of the new generated stereogenic centres, the X-ray structure of compound (1*R*,2*R*)-**11**·HCl was determined. The finding is illustrated in Fig. 1. Based on the known configuration of C(3) and C(7), both new stereogenic centres of the cyclohexane ring at C(13) and C(8) can be assigned the (*R*)-configuration. The Flack parameter of 0.09(17) supported the assignment of the (*R*)-configuration. The establishment of the absolute configuration allows some conclusions about the mechanism of the phenyl lithium addition. The shielding by the bicyclic amine substituent in the direction of an axial attack leads to the

predominance that the approach of the nucleophile in the equatorial direction is favoured. Furthermore a possible chelation between the ketone group and the tertiary amine by the lithium ion would also achieve a contribution for the preference of an equatorial attack.

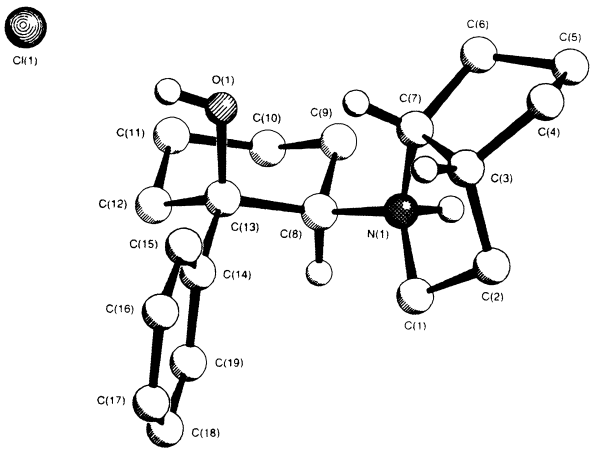


Figure 1. Crystallographic structure of (1*R*,2*R*)-**11**·HCl (the numbers of the atoms do not correspond to those used in the nomenclature)

A further conclusion that can be drawn from the crystal structure of (1*R*,2*R*)-**11**·HCl is a declaration of the stereochemical outcome of the hydroboration. Starting from the premise the hydroboration/oxidation is formal a *cis*-addition of water and is leading to *trans*-configured aminoalcohols,[10] the educt aminoalcohol **8** for the sequence to (1*R*,2*R*)-**11**·HCl must have had a (1*R*,2*R*)-configuration. Although (1*R*,2*R*)-**8** and (1*S*,2*S*)-**8** are diastereomeric species, (1*S*,2*S*)-**8** should lead to amino *tert*-alcohol (1*S*,2*S*)-**11**, because the 1,2-induction by C2-carbon should dominate over the 1,4- or 1,5-induction by C1′ and C5′, respectively.

3. Experimental

Melting points (uncorrected) were determined using an apparatus according to Linström. Infrared spectra were recorded using a Beckman IR 4220 spectrometer as KBr discs for solids and as films between NaCl plates for liquids. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 or a Bruker ARX 500 spectrometer. Optical rotations were measured with a Perkin–Elmer polarimeter 241 MC and mass spectra were measured with a Finnigan-MAT 212 (datasystem SS 300) spectrometer.

3.1. General procedure for the preparation of the enamines: GP 1

Refluxing under a water trap of 8.34 g (75 mmol) bicyclic amine (all-*R*)-**2**, 50 mmol ketone (4.21 g cyclopentanone, 4.91 g cyclohexanone, 5.61 g cycloheptanone, 6.31 g cyclooctanone) and a small amount of *p*-TSA in 70 ml dry benzene is continued until no further separation of water is observed. After removal of solvent and excess amine the residue is distillated in vacuo. Because of the instability, the optical rotations of the enamines were not determined.

*3.1.1. (all-*R*)-2-Cyclopent-1′-enyl-2-aza-bicyclo[3.3.0]octane (all-*R*)-**3***

GP 1: 4.21 g (50 mmol) cyclopentanone; yield: 8.17 g (92%) colourless oil, bp 120–121°C (15 mbar); IR (NaCl): ν_{max} (cm^{-1}) = 3060, 2930, 2860s (C–H); ^1H NMR ($CDCl_3$): δ (ppm) = 1.33–1.71, 1.78–2.04, 2.24–2.55, 2.58–2.72 (7H+3H+4H+1H, 4m, 2×H4, 1×H5, 2×H6, 2×H7, 2×H8, 2×H3′, 2×H4′, 2×H5′), 2.85–2.97 (1H, m, H3), 3.11–3.23 (1H, m, H3), 3.58–3.68 (1H, m, H1) and 4.10–4.17 (1H, m, H2′); ^{13}C NMR (DEPT, $CDCl_3$): δ (ppm) = 22.9, 24.7 (C7, C4′), 30.6, 31.6, 32.6, 32.9, 33.2 (C4, C6, C8, C3′, C5′), 42.9 (C5), 50.4 (C3), 65.2 (C1), 94.3 (C2′) and 149.2 (C1′); HRMS (EI): m/z = 178.1594 (MH^+; $C_{12}H_{19}N$ requires 178.1595).

*3.1.2. (all-*R*)-2-Cyclohex-1′-enyl-2-aza-bicyclo[3.3.0]octane[11] (all-*R*)-**4***

GP 1: 4.91 g (50 mmol) cyclohexanone, yield: 8.93 g (93%) colourless oil, bp 135–136°C (11 mbar); IR (NaCl): ν_{max} (cm^{-1}) = 3060, 2930, 2860 (C–H); ^1H NMR ($CDCl_3$): δ (ppm) = 1.30–1.79 (11H, m, H5, 2×H6, 2×H7, 2×H8, 2×H4′, 2H5′), 1.79–2.30 (5H, m, 1×H4, 2×H3′, 2×H6′), 2.54–2.69 (1H, m, H4), 2.78–2.90 (1H, m, H3), 3.04–3.14 (1H, m, H3), 3.62–3.75 (1H, m, H1) and 4.30–4.38 (1H, m, H2′); ^{13}C NMR (DEPT, $CDCl_3$): δ (ppm) = 23.0, 23.4, 24.6, 25.0, 27.6, 31.2, 32.7, 33.1 (C3′, C4′, C5′, C6′, C4, C6, C7, C8), 42.4 (C5), 48.5 (C3), 63.6 (C1), 95.9 (C2′) and 142.9 (C1′); HRMS (EI): m/z = 192.1750 (MH^+; $C_{13}H_{21}N$ requires 192.1752).

*3.1.3. (all-*R*)-2-Cyclohept-1′-enyl-2-aza-bicyclo[3.3.0]octane (all-*R*)-**5***

GP 1: 6.73 g (60 mmol) cycloheptanone; yield: 6.84 g (56%) colourless oil, bp 139°C (7 mbar); IR (NaCl): ν_{max} (cm^{-1}) = 3040, 2920, 2860 (C–H); ^1H NMR ($CDCl_3$): δ (ppm) = 1.29–1.84 (13H, m, 1×H5, 2×H6, 2×H7, 2×H8, 2×H4′, 2×H5′, 2×H6′), 1.87–2.02, 2.05–2.17, 2.30–2.41, 2.55–2.68 (1H+2H+2H+1H, 4m, 2×H4, 2×H3′, 2×H7′), 2.74–2.85 (1H, m, H3), 2.94–3.05 (1H, m, H3), 3.76–3.87 (1H, m, H1) and 4.44–4.57 (1H, m, H2′); ^{13}C NMR (DEPT, $CDCl_3$): δ (ppm) = 25.4, 26.4, 27.2, 28.8, 30.9, 31.0, 32.9, 32.9, 33.0 (C4, C6, C7, C8, C3′, C4′, C5′, C6′, C7′), 42.5 (C5), 48.4 (C3), 63.7 (C1), 101.4 (C2′) and 150.6 (C1′); HRMS (EI): m/z = 205.1827 (M^+; $C_{14}H_{23}N$ requires 205.1830).

*3.1.4. (all-*R*)-2-Cyclooct-1′-enyl-2-aza-bicyclo[3.3.0]octane (all-*R*)-**6***

GP 1: 7.57 g (60 mmol) cyclooctanone; yield: 10.14 g (77%) colourless oil, bp 102°C (0.01 mbar); IR (NaCl): ν_{max} (cm^{-1}) = 3030, 2910, 2840, 2800 (C–H); ^1H NMR ($CDCl_3$): δ (ppm) = 1.30–1.85 (15H, m, 1×H5, 2×H6, 2×H7, 2×H8, 2×H4′, 2×H5′, 2×H6′, 2×H7′), 1.87–2.06, 2.08–2.25, 2.30–2.50, 2.56–2.74 (1H+2H+2H+1H, 4m, 2×H4, 2×H3′, 2×H8′), 2.80–3.05 (1H, m, H3), 3.12–3.27 (1H, m, H3), 3.70–3.81 (1H, m, H1) and 4.20–4.36 (1H, m, H2′); ^{13}C NMR (DEPT, $CDCl_3$): δ (ppm) = 25.0, 26.0, 26.5, 26.7, 27.1, 28.7, 31.3, 32.1, 32.7, 33.0 (C4, C6, C7, C8, C3′, C4′, C5′, C6′, C7′, C8′), 42.6 (C5), 48.9 (C3), 63.3 (C1), 98.5 (C2′) and 145.2 (C1′), HRMS (EI): m/z = 219.1987 (M^+; $C_{15}H_{25}N$ requires 219.1987).

3.2. General procedure for the hydroboration of enamines: GP 2

Under an argon atmosphere a solution of 60 mmol borane–THF complex in 150 ml dry THF was charged into a three-necked flask. At 0°C 30 mmol of the respective enamine (5.32 g (all-*R*)-**3**, 5.74 g (all-*R*)-**4**, 6.16 g (all-*R*)-**5**, 6.58 g (all-*R*)-**6**) dissolved in 30 ml dry THF were added slowly to the borane solution. After complete addition the reaction mixture was stirred for 2 h at room temperature. For the destruction of the excess borane 10.5 ml methanol was added at 0°C. The cooling bath was removed and mixture was stirred for 30 min. After cooling to 0°C again 2.40 g

sodium hydroxide was added. The cooling bath was removed and when the temperature reached 15°C the addition of 7.5 ml 30% hydrogen peroxide was started. During the addition a temperature of 25°C was not exceeded. After complete addition the mixture was stirred for 2 h at room temperature and then filtered off. The solids were washed extensively with diethyl ether and the combined filtrates were evaporated. After adding 30 ml methanol and 3.75 ml concd hydrochloric acid the solution was stirred for 30 min and then evaporated again. The residue was dissolved in 10 ml water and alkalized with 2 M aqueous sodium hydroxide. The aqueous solution is extracted with ethyl acetate (4×50 ml) and the combined organic layers were dried over anhydrous magnesium sulphate. Evaporation of the solvent afforded the crude aminoalcohol. After determination of the diastereomeric ratio by NMR spectroscopy the diastereomeric aminoalcohols were separated by column chromatography on silica gel and purified by Kugelrohr distillation.

*3.2.1. (1*RS,*2*RS,*1′*R,*5′*R*)-2-(2′-Aza-bicyclo[3.3.0]oct-2′-yl)-cyclopentan-1-ol (1*RS,*2*RS,*1′*R,*5′*R*)-7*

GP 2: 5.32 g (30 mmol) (all-*R*)-**3**; total yield: 4.39 g (75%); *dr* 74:26 ((1*R*,2*R*,1′*R*,5′*R*)-**7**:(1*S*,2*S*,1′*R*,5′*R*)-**7**; ^{1}H NMR: m, H1); column chromatography with ethyl acetate:*n*-hexane:triethylamine, 4:5:1.

*3.2.2. Major diastereomer: (1*R,*2*R,*1′*R,*5′*R*)-7*

Yield: 3.16 g (54%) colourless oil, Kugelrohr distillation: oven temperature 140°C (0.010 mbar); R_f-value 0.69 (ethyl acetate:*n*-hexane:triethylamine 4:5:1); $[\alpha]_D^{20} = -95.0$ ($c = 1.00$ in CH_2Cl_2); IR (NaCl): ν_{max} (cm^{-1}) = 3350 (O–H) and 2950, 2860 (C–H); ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.23–2.04 (14H, m, 2×H3, 2×H4, 2×H5, 1×H4′, H5′, 2×H6′, 2×H7′, 2×H8′), 2.34–2.46, 2.46–2.59, 2.65–2.87, 3.10–3.20 (1H+1H+3 H+1H, 4m, H2, H1′, 2×H3′, 1×H4′, O*H*) and 3.98–4.08 (1H, m, H1); ^{13}C NMR (DEPT, $CDCl_3$): δ (ppm) = 20.4, 24.5, 25.4, 31.8, 32.6, 32.8, 32.9 (C3, C4, C5, C4′, C6′, C7′, C8′), 42.3 (C5′), 50.5 (C3′), 67.6, 70.9 (2C, C2, C1′) and 75.4 (C1); MS (CI, *i*-butane): m/z = 196 (MH^+, 100%), 178 (MH^+–H_20, 18%). Anal. calcd for $C_{12}H_{21}NO$ (195.3): C, 73.80; H, 10.84; N, 7.17. Found: C, 73.92; H, 10.81; N, 7.13.

*3.2.3. Minor diastereomer: (1*S,*2*S,*1′*R,*5′*R*)-7*

Yield: 1.23 g (21%) colourless oil, Kugelrohr distillation: oven temperature 140°C (0.019 mbar); R_f-value 0.46 (ethyl acetate:*n*-hexane:triethylamine, 4:5:1); $[\alpha]_D^{20} = +12.1$ ($c = 1.00$, CH_2Cl_2); ν_{max} (film)/cm^{-1} 3340 (O–H) and 2930, 2850 (C–H); ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.38–2.01 (14H, m, 2×H3, 2×H4, 2×H5, 1×H4′, H5′, 2×H6′, 2×H7′, 2×H8′), 2.37–2.78 (4H, m, 2×H3′, 1×H4′, O*H*), 2.96–3.16 (2H, m, H2, H1′) and 4.07–4.18 (1H, m, H1); ^{13}C NMR (DEPT, $CDCl_3$): δ (ppm) = 21.3, 25.0 (C4, C7′), 29.3, 31.8, 32.6, 34.0, 34.1 (C3, C5, C4′, C6′, C8′), 42.9 (C5′), 54.0 (C3′), 67.8, 73.1 (C2, C1′) and 76.1 (C1); MS (CI, *i*-butane): m/z = 196 (MH^+, 100%), 178 (MH^+–H_20, 20%). Anal. calcd for $C_{12}H_{21}NO$ (195.3): C, 73.80; H, 10.84; N, 7.17. Found: C, 73.86; H, 10.79; N, 7.16.

*3.2.4. (1*RS,*2*RS,*1′*R,*5′*R*)-2-(2′-Aza-bicyclo[3.3.0]oct-2′-yl)-cyclohexan-1-ol (1*RS,*2*RS,*1′*R,*5′*R*)-8*

GP 2: 5.74 g (30 mmol) (all-*R*)-**4**; total yield: 5.61 g (89%); *dr* 76:24 ((1*R*,2*R*,1′*R*,5′*R*)-**8**:(1*S*,2*S*,1′*R*,5′*R*)-**8**; ^{13}C NMR: C1); column chromatography with *n*-hexane:triethylamine 9:1.

*3.2.5. Major diastereomer: (1*R*,2*R*,1′*R*,5′*R*)-**8***

Yield: 4.27 g (68%) colourless oil, Kugelrohr distillation: oven temperature = 140°C (0.008 mbar); R_f-value 0.81 (*n*-hexane:triethylamine 9:1); $[\alpha]_D^{20} = -95.1$ ($c = 1.00$, CH_2Cl_2); IR (NaCl): ν_{max} (cm^{-1}) = 3440 (O–H) and 2960, 2930, 2860 (C–H); ^1H NMR ($CDCl_3$): δ (ppm) = 1.12–1.85, 1.90–2.02, 2.05–2.17, 2.25–2.54 (14H+1H+1H+3H, 5m, 2×H3, 2×H4, 2×H5, 2×H6, 2×H3′, 2×H4′, H5′, 2×H6′, 2×H7′, 2×H8′), 2.67–2.77, 3.10–3.20, 3.24–3.33 (1H+1H+1H, 3m, H1, H2, H1′) and 3.92 (1H, s, O*H*); ^{13}C NMR (DEPT, $CDCl_3$): δ (ppm) = 21.6, 23.5, 24.2, 25.5, 32.5, 32.7, 33.1, 33.2 (C3, C4, C5, C6, C4′, C6′, C7′, C8′), 41.4 (C5′), 45.4 (C3′), 63.7, 64.6 (C2, C1′) and 70.0 (C1); MS (CI, *i*-butane): m/z = 210 (MH^+, 100%). Anal. calcd for $C_{13}H_{23}NO$ (209.3): C, 74.59; H, 11.07; N, 6.69. Found: C, 74.52; H, 11.04; N, 6.63.

*3.2.6. Minor diastereomer: (1*S*,2*S*,1′*R*,5′*R*)-**8***

Yield: 1.34 g (21%) colourless oil, Kugelrohr distillation: oven temperature = 140°C (0.008 mbar); R_f-value 0.65 (*n*-hexane:triethylamine 9:1); $[\alpha]_D^{20} = +45.4$ ($c = 1.00$, CH_2Cl_2); IR (NaCl): ν_{max} (cm^{-1}) = 3450 (O–H) and 2910, 2840, 2790 (C–H); ^1H NMR ($CDCl_3$): δ (ppm) = 1.13–1.94, 2.05–2.16, 2.35–2.60, 2.69–2.84 (15H+1H+2H+2H, 4m, 2×H3, 2×H4, 2×H5, 2×H6, 2×H3′, 2×H4′, 1×H5′, 2×H6′, 2×H7′, 2×H8′, H2 or H1′), 3.23–3.37 (2H, m, H1, H2 or H1′) and 4.03 (1H, br s, O*H*); ^{13}C NMR (DEPT, $CDCl_3$): δ (ppm) = 22.5, 24.3, 25.0, 25.7, 31.9, 32.6, 33.6, 34.4 (C3, C4, C5, C6, C4′, C6′, C7′, C8′), 43.5 (C5′), 53.7 (C3′), 61.1, 66.2 (C2, C1′) and 71.2 (C1); MS (CI, *i*-butane): m/z = 210 (MH^+, 100%). Anal. calcd for $C_{13}H_{23}NO$ (209.3): C, 74.59; H, 11.07; N, 6.69. Found: C, 74.68; H, 10.99; N, 6.61.

*3.2.7. (1*RS*,2*RS*,1′*R*,5′*R*)-2-(2′-Aza-bicyclo[3.3.0]oct-2′-yl)-cycloheptan-1-ol (1*RS*,2*RS*,1′*R*,5′*R*)-**9***

GP 2: 6.16 g (30 mmol) (all-*R*)-**5**; total yield: 5.96 g (89%); *dr* 81:19 ((1*R*,2*R*,1′*R*,5′*R*)-**9**:(1*S*,2*S*,1′*R*,5′*R*)-**9**; ^{13}C NMR: C1); column chromatography with (*n*-hexane:triethylamine, 9:1). It was not possible to obtain the minor diastereomer in pure form by column chromatography (minor diastereomer: R_f-value 0.70, *n*-hexane:triethylamine, 9:1; mixed fraction: 2.37 g, 35%).

*3.2.8. Major diastereomer: (1*R*,2*R*,1′*R*,5′*R*)-**9***

Yield: 3.59 g (54%) colourless oil, Kugelrohr distillation: oven temperature = 140°C (0.008 mbar); R_f-value 0.79 (*n*-hexane:triethylamine, 9:1); $[\alpha]_D^{20} = -51.4$ ($c = 0.99$, CH_2Cl_2); IR (NaCl): ν_{max} (cm^{-1}) = 3370 (O–H) and 2930, 2860 (C–H); ^1H NMR ($CDCl_3$): δ (ppm) = 1.16–1.81, 1.89–2.11, 2.22–2.52 (16H+2H+3H, 3m, 2×H3, 2×H4, 2×H5, 2×H6, 2×H7, 2×H3′, 2×H4′, H5′, 2×H6′, 2×H7′, 2×H8′), 2.66–2.76, 3.08–3.17 (1H+1H, 2m, H2, H1′), 3.25–3.37 (1H, m, H1) and 4.40 (1H, br s, O*H*); ^{13}C NMR (DEPT, $CDCl_3$): δ (ppm) = 21.8, 21.9, 23.5, 24.4, 26.9, 32.2, 32.5, 33.2, 33.2 (C3, C4, C5, C6, C7, C4′, C6′, C7′, C8′), 41.3 (C5′), 45.0 (C3′), 64.7, 64.9 (2C, C2, C1′) and 72.2 (C1); MS (CI, *i*-butane): m/z = 224 (MH^+, 100%). Anal. calcd for $C_{14}H_{25}NO$ (223.4): C, 75.28; H, 11.28; N, 6.27. Found: C, 75.34; H, 11.37; N, 6.26.

*3.2.9. (1*R*,2*R*,1′*R*,5′*R*)-2-(2′-Aza-bicyclo[3.3.0]oct-2′-yl)-cyclooctan-1-ol (1*R*,2*R*,1′*R*,5′*R*)-**10***

GP 2: 6.58 g (30 mmol) (all-*R*)-**6**; *dr* = ≥95:5 ((1*R*,2*R*,1′*R*,5′*R*)-**10**:(1*S*,2*S*,1′*R*,5′*R*)-**10**; NMR); column chromatography with (*n*-hexane:triethylamine, 9:1, R_f-value 0.80), Kugelrohr distillation: oven temperature = 140°C (0.009 mbar); yield: 6.42 g (90%) colourless oil; $[\alpha]_D^{20} = -41.3$ ($c = 1.00$, CH_2Cl_2); IR (NaCl): ν_{max} (cm^{-1}) = 3370 (O–H) and 2920, 2850 (C–H); δ_H (300 MHz, $CDCl_3$) 1.18–2.02 (20H, m, 2×H3, 2×H4, 2×H5, 2×H6, 2×H7, 2×H8, 2×H4′, 2×H6′, 2×H7′, 2×H8′), 2.19–2.80 (4H, m, H1′, 2×H3′, H′5), 3.03–3.19 (1H, m, H2), 3.32–3.48 (1H, m, H1) and 4.72 (1H,

br s, O*H*); ^{13}C NMR (DEPT, $CDCl_3$): δ (ppm) = 22.2 (2×), 23.6, 25.0, 27.0, 27.3, 30.9, 32.1, 32.3, 33.2 (C3, C4, C5, C6, C7, C8, C4′, C6′, C7′, C8′), 41.3 (C5′), 44.8 (C3′) and 61.8, 64.6, 71.2 (C1, C2, C1′); MS (CI, *i*-butane): m/z = 238 (MH^+, 100%). Anal. calcd for $C_{15}H_{27}NO$ (237.4): C, 75.90; H, 11.46; N, 5.90. Found: C, 75.79; H, 11.38; N, 5.87.

3.3. General procedure for the preparation of amino ketones by the method of Swern followed by an addition of phenyl lithium: GP 3

According to the procedure of D. Swern[12] 1.52 g (12 mmol) oxalyl chloride was dissolved in 30 ml dry methylene chloride under an argon atmosphere. At –70°C a solution of 1.72 g (22 mmol) abs. DMSO in 15 ml dry methylene chloride is added dropwise. During the addition a temperature of –60°C was not exceeded. After complete addition the reaction mixture was stirred for 30 min at –70°C. Afterwards a solution of 10 mmol aminoalcohol (2.09 g (all-*R*)-**8** and (1*S*,2*S*,1′*R*,5′*R*)-**8**, respectively) dissolved in 25 ml dry methylene chloride was added slowly. After complete addition the reaction mixture was stirred for 2 h at –60°C. Then 5.06 g (50 mmol) triethylamine was added (T < –60°C) and the reaction mixture was allowed to warm to room temperature. Water (40 ml) was added and the phases were separated. The organic layer was washed with water (2×30 ml), dried over magnesium sulphate and evaporated at room temperature. Because an epimerization was ascertained during the purification by column chromatography on silica gel the crude amino ketone was used without isolation.

Concerning this, the crude product was dissolved in 25 ml dry THF and added slowly to a solution 22.22 ml (40 mmol) phenyl lithium (1.8 M, cyclohexane:diethyl ether, 7:3) in 40 ml abs. THF. After complete addition the reaction mixture was stirred 3 h at –78°C, allowed to warm to room temperature and stirred for 16 h. Hydrolysis occurred with saturated ammonium chloride solution. The aqueous solution was extracted with methylene chloride (3×15 ml). The combined layers were dried over anhydrous magnesium sulphate. After evaporation of the solvent the diastereomeric ratio was determined by NMR spectroscopy. The crude product was purified by column chromatography.

*3.3.1. (1*S*,2*S*,1′*R*,5′*R*)-2-(2′-Aza-bicyclo[3.3.0]oct-2′-yl)-1-phenyl-cyclohexan-1-ol (1*S*,2*S*,1′*R*,5′*R*)-**11**

GP 3: 2.09 g (10 mmol) (1*S*,2*S*,1′*R*,5′*R*)-**8**; *dr* ≥95:5 (^{1}H NMR), column chromatography with ethyl acetate:*n*-hexane:triethylamine 1:8.5:0.5, R_f-value 0.74; yield: 1.06 g (37%) light-yellow oil; $[\alpha]_D^{20}$ = +17.9 (*c* = 1.01, CH_2Cl_2); IR (NaCl): ν_{max} (cm^{-1}) = 3300 (O–H) and 3040, 3020, 2930, 2860, 2820 (C–H); ^{1}H NMR ($CDCl_3$): δ (ppm) = 0.98–198 (16H, m, 2×H3, 2×H4, 2×H5, 2×H6, 2×H4′, 2×H6′, 2×H7′, 2×H8′), 2.03–2.32 (3H, m, 2×H3′, 1×H5′), 2.92–3.04 (1H, m, H1′), 3.04 (1H, dd, *J* 4.6 and 11.8, H2), 3.98 (1H, br s, O*H*) and 7.13–7.24, 7.24–7.35, 7.45–7.55 (1H+2H+2H, 3m, arom. H); ^{13}C NMR (DEPT, $CDCl_3$): δ (ppm) = 21.6, 24.8, 25.6, 28.3, 31.7, 33.0, 34.0, 40.4 (C3, C4, C5, C6, C4′, C6′, C7′, C8′), 41.5 (C5′), 53.2 (C3′), 65.2, 66.3 (C2, C1′), 73.8 (C1), 124.9, 125.8, 127.7 (5C, arom. C) and 150.9 (q. arom. C); MS (CI, *i*-butane): m/z = 286 (MH^+, 100%). Anal. calcd for $C_{19}H_{27}NO$ (285.4): C, 79.95; H, 9.53; N, 4.91. Found: C, 79.83; H, 9.48; N, 4.82.

*3.3.2. (all-*R*)-2-(2′-Aza-bicyclo[3.3.0]oct-2′-yl)-1-phenyl-cyclohexan-1-ol hydrochloride (all-*R*)-**11**·HCl*

GP 3: 2.09 g (10 mmol) (all-*R*)-**8**; *dr* ≥95:5 (^{1}H NMR); after purification by column chromatography with ethyl acetate:*n*-hexane:triethylamine, 1.5:8:0.5, R_f-value 0.70, the aminoalcohol

was dissolved in 20 ml methanol and 20 ml 2 M hydrochloric acid and stirred for 15 min. The reaction mixture was evaporated, dissolved in 20 ml methanol and evaporated again. The residue was crystallised with ethanol and diethyl ether and yielded colourless crystals 1.32 g (41%), mp 221°C (decomposition); $[\alpha]_D^{20} = -48.6$ ($c = 1.00$, methanol); IR (KBr): ν_{max} (cm^{-1}) = 3330 (O–H), 3030, 3010, 2930, 2860 (C–H) and 2550 (N–HCl); ^1H NMR ($CDCl_3$): δ (ppm) = conformeric ratio 67:33; 1.04–2.90 (19H, m, 2×H3, 2×H4, 2×H5, 2×H6, 2×H3′, 2×H4′, 1×H5′, 2×H6′, 2×H7′, 2×H8′), 3.45–3.66, 4.23–4.37 (1H+1H, 2m, H2, H1′, major conformer), 3.70–3.85, 4.00–4.10 (1H+1H, 2m, H2, H1′, minor conformer), 5.35 (1H, s, O*H*, minor conformer), 5.50 (1H, s, O*H*, major conformer), 7.20–7.74 (5H, m, arom. H), 9.70 (1H, br s, *tert-N-H*Cl, minor conformer) and 11.00 (1H, br s, *tert*-N-*H*Cl, major conformer); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = major conformer: 20.4, 24.9, 25.0, 26.2, 26.7, 30.0, 33.3, 38.5 (C3, C4, C5, C6, C4′, C6′, C7′, C8′), 43.7 (C5), 51.6 (C3′), 67.5, 67.9 (C2, C1′), 74.8 (C1), 124.5, 127.2, 128.7 (5C, arom. C), 147.4 (q. arom. C); minor conformer: 20.5, 24.2, 25.2, 26.0, 29.2, 30.8, 30.9, 42.6 (C3, C4, C5, C6, C4′, C6′, C7′, C8′), 43.4 (C5′), 54.7 (C3′), 70.3, 72.3 (C2, C1′), 75.3 (C1), 125.5, 127.4, 145.6 (5C, arom. C) and 145.5 (q. arom. C); MS (CI, *i*-butane): m/z = 286 (MH^+–HCl, 100%) and 268 ($MH^{\oplus}$–HCl–H_2O, 25%). Anal. calcd for $C_{19}H_{28}ClNO$ (321.9): C, 70.90; H, 8.77; N, 4.35. Found: C, 70.94; H, 8.74; N, 4.33.

3.3.3. (*all*-R)-2-(2′-Aza-bicyclo[3.3.0]oct-2′-yl)-1-phenyl-cyclohexan-1-ol (*all*-R)-**11**

The hydrochloride (all-*R*)-**11**·HCl was dissolved in 10 ml 2 M sodium hydroxide solution. After the addition of 15 ml diethyl ether the reaction mixture was stirred for 15 min. The layers were separated and the aqueous layer was extracted with diethyl ether (3×15 ml). The combined organic layers were dried over anhydrous magnesium sulphate. Evaporation of the solvent yielded a light-yellow oil (0.73 g, 91%); R_f-value 0.70 (ethyl acetate:*n*-hexane:triethylamine 1.5:8:0.5); $[\alpha]_D^{20} = -49.8$ ($c = 0.46$, CH_2Cl_2); IR (NaCl): ν_{max} (cm^{-1}) = 3410 (O–H), 3080, 3050, 3020, 2940, 2860, 2810 (C–H); ^1H NMR ($CDCl_3$): δ (ppm) = 0.95–1.92 (16H, m, 2×H3, 2×H4, 2×H5, 2×H6, 2×H4′, 2×H6′, 2×H7′, 2×H8′), 2.20–2.36, 2.44–2.54 (2H+1H, 2m, 2×H3′, 1×H5′), 2.86 (1H, dd, *J* 4.1 and 11.0, H2), 2.97 (1H, br s, O*H*), 3.14–3.22 (1H, m, H1′), 7.12–7.50 (5H, m, arom. H); ^{13}C NMR (DEPT, $CDCl_3$): δ (ppm) = 21.8, 24.1, 24.2, 25.6, 30.6, 32.6, 33.3 (C3, C4, C5, C4′, C6′, C7′, C8′), 40.5 (C5′), 40.9, (C6), 49.2 (C3′), 64.0, 66.9 (C2, C1′), 76.1 (C1), 125.0, 125.9, 127.5 (5C, arom. C), 149.7 (q. arom. C); MS (CI, *i*-butane): m/z = 286 (MH^+, 100%). Anal. calcd for $C_{19}H_{27}NO$ (285.4): C, 79.95; H, 9.53; N, 4.91. Found: C, 79.86; H, 9.59; N, 4.87.

3.4. X-Ray crystal structure determinations of (*all*-R)-**11**·HCl

Single crystals of (all-*R*)-**11**·HCl were obtained from a solution in ethanol and diethyl ether. Diffraction data were recorded on a Siemens STOE STADI4 4-circle-diffractometer. The intensities were collected at 293 K with ω–2θ scan technique using graphite-monochromated Mo-Kα radiation. The standard reflections measured three times every 45 min showed no systematic variation throughout the data collections. Reflections were corrected for Lorentz and polarization effects. From a total of 2020 unique measurements those 1703 with $I > 2\sigma(I)$ were retained for the analysis. The crystal structure was solved by direct methods using SHELXTL program package. All non-hydrogen atoms were refined anisotropically by the full-matrix least-square method. In the final cycles of the refinement based on 188 variable parameters the hydrogens were included at calculated positions according to the riding model. Pertinent crystallographic data for (all-*R*)-**11**·HCl: orthorhombic, $P2_12_12_1$, $a = 872.10(10)$, $b = 1192.90(10)$, $c = 1719.6(2)$ pm,

$\alpha=\beta=\gamma=90^{\circ}$, $V=1788.9\times10^{6}(3)$ pm^3, $Z=4$, $D_{calc}=1.195$ mg/m^3, μ(Mo-K)$=0.216$ mm^{-1}, $R_{final}=0.0479$, $R_w=0.1194$, goodness-of-fit $=1.144$.

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