Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 4027–4034

TETRAHEDRON: *ASYMMETRY*

Diastereoselective α-iminoamine rearrangement: asymmetric synthesis of (*R*)-(−)- and (*S*)-(+)-2-benzyl-2-hydroxy-cyclohexanone †

Philippe Bisel,[a] Gerhard Lauktien,[a] Edgar Weckert[b] and August W. Frahm[a,*]

[a]*Lehrstuhl für Pharmazeutische Chemie, Pharmazeutisches Institut, Hermann-Herder-Straße 9, D-79104 Freiburg, Germany*
[b]*Institut für Kristallographie, Universität Karlsruhe (TH), Kaiserstraße 12, D-76128 Karlsruhe, Germany*

Received 30 September 1998; accepted 20 October 1998

Abstract

A convenient asymmetric synthesis of both (*R*)-(−)- and (*S*)-(+)-2-benzyl-2-hydroxycyclohexanones starting from racemic 2-benzyloxycyclohexanone and the chiral auxiliary 1-phenylethylamine is reported. The route involves a [1,3]-sigmatropic shift and a new diastereoselective α-iminoamine rearrangement of a 2-benzyl-2-iminocyclohexanamine substrate.

1. Introduction

The thermal rearrangement of α-aminoketones and to a lesser extent α-hydroxyimines was studied from a mechanistic point of view by Stevens et al.[1a–d] in the sixties. Since this type of rearrangement is believed to be involved in the biosynthesis of *Aristotelia*-type alkaloids,[2] it has gained new interest in recent years.[3] As part of a program devoted to the usefulness of the asymmetric reductive amination sequence as a tool towards the synthesis of chiral bioactive amines[4a] and α-aminoalcohols,[4b] we have recently prepared a series of racemic 2-alkoxycyclohexanones with the goal of synthesizing optically active *cis*-2-hydroxycyclohexanamines.[5] In the course of this study we have observed that 2-benzyloxycyclohexanone **3** does not lead to the expected imine but undergoes a rearrangement when submitted to the classical imine condensation conditions. Herein we wish to report on this rearrangement, on our efforts to control the diastereoselectivity of the process and on its usefulness in the first asymmetric synthesis of the acyloin **6**. Even though its racemic synthesis has been described,[6] to the best of our knowledge, an enantioselective route to **6** has yet to be devised.

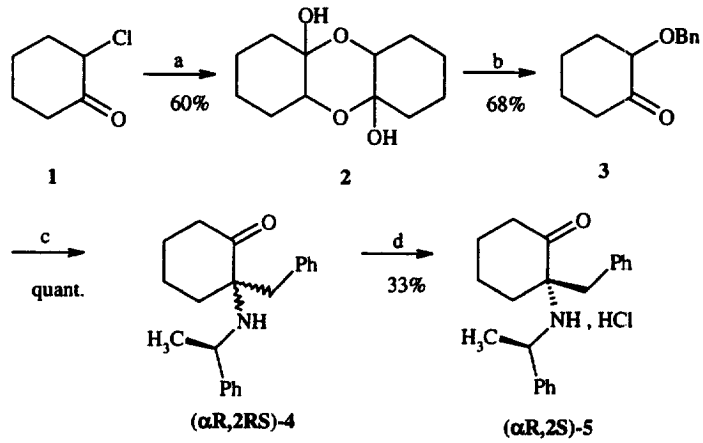
* Corresponding author. Fax: (0761) 203-6351; e-mail: awfrahm@sun2.ruf.uni-freiburg.de

† Dedicated to Prof. Dr. F. Eiden on the occasion of the 73rd anniversary of his birthday.

0957-4166/98/$ - see front matter
PII: S0957-4166(98)00422-4

2. Results and discussion

Racemic 2-benzyloxycyclohexanone **3** was obtained from 2-chlorocyclohexanone **1** via the dimeric ketal **2** and consecutive refluxing with benzyl alcohol on a Dean–Stark apparatus.[7] Subsequent imine condensation with one equivalent of either (*R*)-(+)- or (*S*)-(−)-phenylethylamine (PEA) in refluxing toluene and in the presence of a catalytic amount of *p*-toluenesulfonic acid did not lead to the condensation product but gave a 1:1 diastereomeric mixture of the aminoketone **4** (Scheme 1) as established by homo- and heteronuclear 2D-NMR spectroscopy. This type of rearrangement was found earlier in our laboratories for the cyclohexane derivative[8] and has been reported on the five membered ring and on α-allyloxy cyclohexanimines by Desmaële et al.,[9] and was interpreted as a thermal non-diastereoselective [1,3]-sigmatropic shift. More recently, we have also observed an identical rearrangement on the cyclobutane ring.[4b] However, we were able to gain the diastereomerically pure (α*R*,2*R**)-**5** and (α*S*,2*S**)-**5** in 33% yield each by means of differentiating crystallization in acetone after treatment of the crude (α*R*,2*RS*)-**4** and (α*S*,2*RS*)-**4**, respectively, with HCl–ether.



Scheme 1. (a) NaOH, r.t.; (b) BnOH, HCl conc., toluene, reflux, 75 min.; (c) (*R*)-(+)- or (*S*)-(−)-PEA, *p*-TsOH, toluene, reflux, 3 h; (d) HCl:ether

Furthermore, X-ray suitable crystals of (α*R*,2*R**)-**5** could be obtained from hot isopropanol and thus, the (α*R*,2*S*) absolute configuration was established first by means of the three beam interaction method[10] which has been re-evaluated at low temperature (<120 K) by refining an enantiomorph sensitive parameter according to Flack, including all Friedel related reflections and anomalous dispersion corrections (Fig. 1).[11] Since the measured $[\alpha]_D$ values for the aminoketones obtained from (α*R*,2*RS*)-**4** and (α*S*,2*RS*)-**4**, respectively, are opposite, the (α*S*,2*R*) absolute configuration of the enantiomeric **5** could be deduced.

We reasoned that the hitherto unknown enantiomerically pure (*R*)- and (*S*)-2-benzyl-2-hydroxycyclohexanones (*R*)-**6** and (*S*)-**6** should be accessible from (α*R*,2*S*)-**5** and (α*S*,2*R*)-**5**, respectively, via a subse uent aminoketone rearrangement. Indeed, this type of rearrangement has been described along wit its stereochemical pathways,[12a–d] the suprafacial 1,2-shift proceeding with complete transfer of ste.eochemistry. Accordingly, the treatment of the corresponding free bases (α*R*,2*S*)-**4** and (α*S*,2*R*)-**4**, with a refluxing ethanol:water mixture led to (*R*)-(−)-**6** and (*S*)-(+)-**6**, respectively, in 66% yields with the chiral auxiliary being recovered (Scheme 2). The enantiomeric excess of the respective geminal substituted acyloins **6** was determined by means of derivatization of the carbonyl function to the corresponding ketals **7** with (2*R*,3*R*)-2,3-butandiol.[13] The ^1H and ^{13}C NMR

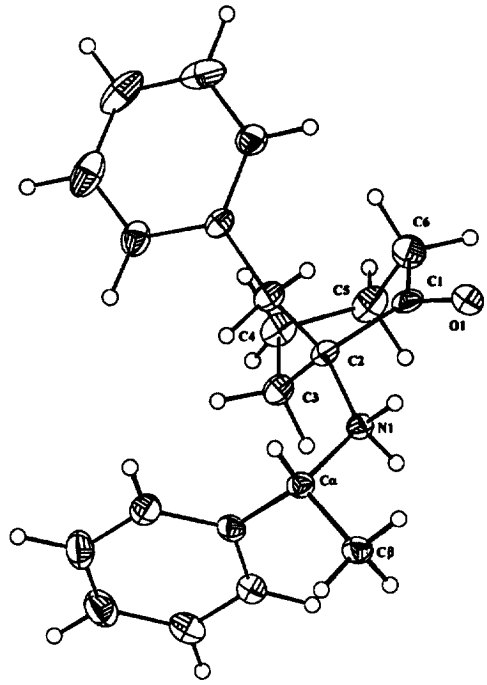
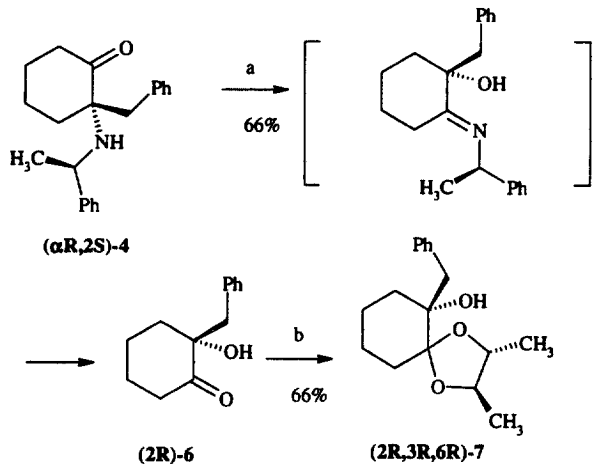


Figure 1. X-Ray structure of (α*R*,2*S*)-**5**

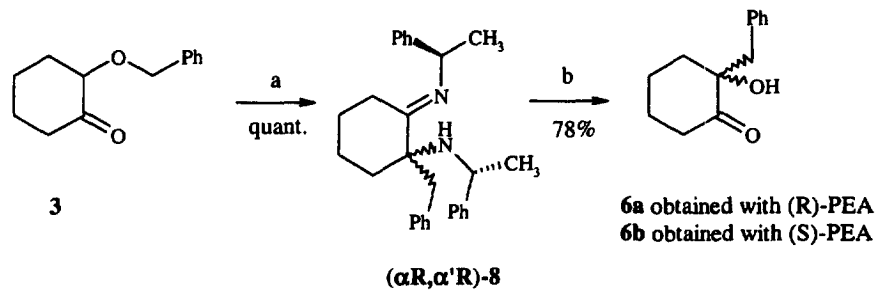
spectra of these ketals exhibited only one set of signal groups each accounting for a single diastereomer and thus, an enantiomeric excess of >99% was deduced.



Scheme 2. (a) EtOH:H_2O (3:1) reflux, 24 h; (b) (2*R*,3*R*)-2,3-butandiol (2 equiv.), toluene, *p*-TsOH, reflux

Besides offering a first convenient asymmetric synthesis of the enantiomerically pure (*R*)-(−)- and (*S*)-(+)-**6**, respectively, the above findings represented an analytical tool for further studying the key rearrangement in our route, the major issue being whether the stereochemistry can be controlled or not. Among a series of experiments we have found that the treatment of racemic 2-benzyloxycyclohexanone **3** with two equivalents of (*R*)-(+)- or (*S*)-(−)-PEA gave rise to a non-equimolar mixture of two

diastereomeric imines **8** (Scheme 3). Indeed, out of the four theoretically feasible NMR spectroscopically differing stereoisomers, only two sets of signals could be observed in the crude ^{13}C NMR spectra of ($\alpha R,\alpha' R$)-**8** and ($\alpha S,\alpha' S$)-**8**, respectively, the ratios of which were readily determined by comparing the intensities of corresponding C-atom signals. After 4 days in refluxing toluene, a thermodynamic equilibrium was attained with a product ratio of 78:22. Since the Z-isomers at the C=N double bond are unlikely because of steric hindrance, we assume that the two imines must be epimers at the quaternary C-2 position. In order to confirm the diastereoselectivity (de 56%) and to establish the absolute configuration at the C-2 carbon of the major and the minor components, we submitted the crude imine mixtures **8** to hydrolysis under the same conditions as described previously for the aminoketones **4**. Theoretically, since the hydrolysis process is completely stereoselective,[12a] the expected crude enantiomeric acyloin mixtures **6a** and **6b**, obtained from ($\alpha R,\alpha' R$)-**8** and ($\alpha S,\alpha' S$)-**8**, respectively, should be optically active and should reflect the diastereomeric excesses of the parent imine mixtures **8** (Scheme 3). The $[\alpha]_D$ values of +55.0 and −56.2 measured for **6a** and **6b**, respectively, can be compared to the ones measured for the enantiomerically pure acyloins. They indicate ee values of 50.5% and 51.2% for **6a** and **6b**, respectively. One recrystallization in cyclohexane gave the acyloins **6a** and **6b** with enantiomeric excesses of 96.8% and 96.7%



Scheme 3. (a) (*R*)-(+)- or (*S*)-(−)-PEA (2 equiv.), toluene, *p*-TsOH, reflux, 4 days; (b) EtOH:H_2O (3:1) reflux, 24 h

The stereochemical issues of the iminoamine rearrangement with respect to the absolute configuration at C-2 have been elucidated by means of analogy conclusions. Indeed, as stressed earlier, the aminoketone ($\alpha R,2S$)-**4** (Scheme 2) yielded the acyloin **6** with a negative $[\alpha]_D$ value. Therefore the major component of the diastereomeric imine mixture **8** which leads to the acyloin with a negative $[\alpha]_D$ value must be *S*-configured at C-2. The experimental data show that the treatment of benzyloxycyclohexanone **3** with two equivalents of (*S*)-(−)-PEA and subsequent hydrolysis afforded the acyloin **6** with the negative $[\alpha]_D$ value with the inverse counting for **3** treated with (*R*)-(+)-PEA. Conclusively, the major enantiomers of the **6a** and **6b** mixtures are (*S*)-(+)-**6** and (*R*)-(−)-**6**, respectively. Thus, the like induction[14] at C-2 of the imine could be established.

Since the thermal [1,3]-sigmatropic shift is not diastereoselective, our observations suggest that the stereoselectivity has to occur during the α-iminoamine rearrangement. The stereochemical outcome was rationalized assuming that the migrating benzyl moiety has to be placed in an axial position to attain a certain degree of coplanarity with the developing electron deficient orbital at the imine carbon[4d] and that the sterically demanding phenyl group of the phenyl ethyl imino moiety has to occupy a pseudo-equatorial orientation. Accordingly, the observed ratio of 78:22 for ($\alpha R,\alpha' R$)-**8**, for example, arises from the favored *re*-face attack of the migrating group at the (*S*)-configured C-2 epimer in comparison to the *si*-face attack at the (*R*)-configured C-2 epimer. Indeed, if the attack is hindered by an α-proton in the first case, it is blocked by an α-methyl group in the latter (Fig. 2) with the inverse counting for ($\alpha S,\alpha' S$)-**8**.

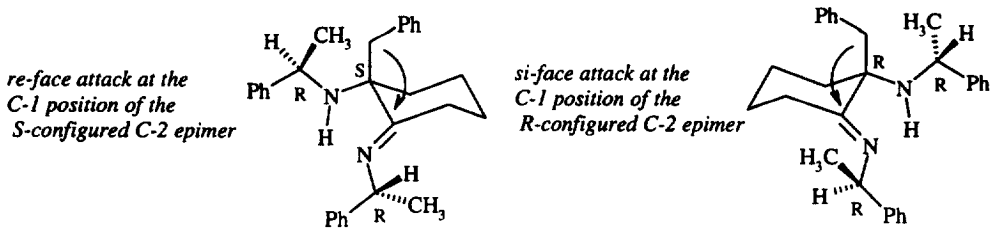


Figure 2. Diastereoselective iminoamine rearrangement exemplified on the (α*R*,α′*R*)-**8** diastereomeric imine mixture

The sequential treatment of the benzyloxycyclohexanone **3** with one equivalent of (R)-PEA for 4 h, in refluxing toluene in the presence of *p*-toluenesulfonic acid followed by one equivalent of the enantiomeric (*S*)-PEA under the same conditions afforded the crude iminoamine as an expected 1:1 mixture of diastereomers. The absolute stereochemistry of the phenylethylimino moiety is responsible for the stereochemical pathway of the rearrangement and the process consists of a formal 'iminoamine–aminoimine' equilibrium. Thus, the (α*S*,α′*R*)-iminoamine rearranges to the (α*R*,α′*S*)-iminoamine with the absolute stereochemistry of the key phenylethylimino group being either *R*- or *S*-configured to 50% each. This mismatching situation finally leads to a 1:1 diastereomeric iminoamine mixture. In summary, according to Izumi's[14] nomenclature, the reaction proceeds with diastereoface differentiation and 'like'-induction at C-2.

3. Experimental

3.1. General procedures

Solvents were purified according to standard procedures. Melting points are uncorrected. The given yields are for isolated products. Column chromatography was performed on Merck silica gel (70–230 mesh ASTM). Infrared spectra were recorded on a Perkin–Elmer IR 298 spectrometer. NMR spectra were obtained on a Varian XL 300 spectrometer at 300 MHz (^{1}H) and 75.4 MHz (^{13}C), respectively. Chemical shifts are reported as δ values from TMS as internal standard. Optical rotation values were obtained with a Perkin–Elmer 214 polarimeter. Elemental analyses were carried out on a Perkin–Elmer DIA-CHN RS at the Analytical Laboratory, Institute for Organic Chemistry and Biochemistry, Bonn.

3.2. Dodecahydrodibenzo-1,4-dioxan-4a,9a-diol 2

140 g of sodium hydroxide (28.5%) were added within 3 h to 132.6 g (1.0 mol) of 2-chlorocyclohexanone **1**, whereby the reaction temperature was kept below 0°C. After this, the mixture was stirred for 12 h at room temperature when it showed a neutral reaction. The product was filtered off, freed of chloride with demineralized water, washed with EtOH (3×25 ml) and Et_2O (3×25 ml) and finally dried in vacuo, yielding 68.5 g (60%, 0.3 mol) of **2**: mp 123–128°C [lit.[15]: 132.5°C]; ^{13}C NMR (CD_3OD): δ 23.5 (t), 25.5 (t), 29.0 (t), 36.6 (t), 74.1 (d), 96.4 (s).

3.3. 2-Benzyloxycyclohexanone 3

A solution of 22.8 g (0.1 mol) of **2** and 32.4 g (0.3 mol) of benzylalcohol in 40 ml of toluene and 10 ml of conc. hydrochloric acid was refluxed for 75 min on a Dean–Stark apparatus. The reaction was stopped,

toluene was evaporated and the oily residue was distilled in vacuo affording 28.0 g (68%, 0.14 mol) of the ketone **3**: bp_1 136–138°C [lit.[7]: $bp_{0.5}$ 110–112°C]; IR (film): 1720 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.65 (m, 1H, 4-H), 1.70 (m, 1H, 5-H), 1.75 (m, 1H, 3-H), 1.95 (m, 2H, 4-H, 5-H), 2.20 (m, 1H, 3-H), 2.25 (m, 1H, 6-H), 2.52 (m, 1H, 6-H), 3.87 (ddd, *J*=10.0, 5.5, 1.5 Hz, 1H, 2-H_{ax}), 4.47 (d, *J*=10.0 Hz, 1H, H-benzyl), 4.75 (d, *J*=10.0 Hz, 1H, H-benzyl), 7.32 (m, 5H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 22.7 (t), 27.2 (t), 34.1 (t), 40.2 (t), 71.2 (t), 81.3 (d), 127.6 (d), 127.7 (d), 128.3 (d), 137.9 (s), 209.6 (s).

3.4. (αR,2S)- and (αS,2R)-2-Benzyl-2-[N-(1-phenylethyl)amino]cyclohexanone hydrochloride ((αR,2S)-5 and (αS,2R)-5)

A solution of 10.2 g (0.05 mol) of **3** and 6.2 g (0.05 mol) of (*R*)-(+)- and (*S*)-(−)-PEA, respectively, in 50 ml of toluene containing a catalytic amount of *p*-TsOH was refluxed for 3.5 h on a Dean–Stark apparatus. The solvent was removed in vacuo and the residue was treated with HCl–ether. The solvent was removed again and the residue taken up in 50 ml acetone. The colorless crystals were filtered off and recrystallized from isopropanol to give 5.5 g (0.016 mol) of (α*R*,2*S*)-**5** and (α*S*,2*R*)-**5**, respectively: mp 191–194°C; IR (KBr): 1710 cm^{-1} (C=O); $[\alpha]_D^{30}$ +111.6 and −111.3 (c=0.3, ethanol), respectively; ^1H NMR (CD_3OD): δ 1.58 (m, 1H, H-5_{ax}), 1.68 (d, *J*=7 Hz, 1H, H-β′), 1.79 (m, 2H, H-4), 1.95 (m, 1H, H-5_{eq}), 1.98 (ddd, *J*=12.5, 12.5, 5.5 Hz, 1H, H-3_{ax}), 2.18 (ddd, *J*=12.5, 5.0, 3.0 Hz, 1H, H-3_{eq}), 2.37 (ddd, *J*=15.5, 4.0, 4.0 Hz, 1H, H-6_{eq}), 2.66 (ddd, *J*=15.5, 13.0, 6.0 Hz, 1H, H-6_{ax}), 3.44 (d, *J*=15.0 Hz, 1H, H-benzyl), 3.66 (d, *J*=15.0 Hz, 1H, H-benzyl), 4.69 (q, *J*=7 Hz, 1H, H-α′), 7.2–7.5 (m, 10H, H-arom). Anal. calcd for $C_{21}H_{26}NOCl$: C 73.30, H 7.62, N 4.10. Found: C 73.0, H 7.74, N 3.80 and C 73.40, H 7.79, N 4.20, respectively.

3.5. (αR,α′R,2RS)- and (αS,α′S,2RS)-N-(1-Phenylethyl)-1-benzyl-2-[N-(1-phenylethyl)amino]cyclohexanamine ((αR,α′R)-8 and (αS,α′S)-8)

A solution of 2 g (9.8 mmol) of **3** with 2.50 g (20.58 mmol) of (*R*)-(+)- and (*S*)-(−)-PEA, in toluene is refluxed for 4 days on a Dean–Stark apparatus in presence of a catalytic amount of *p*-TsOH. After cooling, the PEA/*p*-toluenesulfonate salt was filtered off and the solvent evaporated in vacuo. The crude residue was used without any further purification.

3.6. (2R)-(−)- and (2S)-(+)-2-Benzyl-2-hydroxycyclohexanone ((2R)-(−)-6 and (2S)-(+)-6)

3.6.1. Method A

The hydrochloride (688 mg, 2 mmol) of (α*R*,2*S*)-**5** and (α*S*,2*R*)-**5**, respectively, was suspended in 20 ml of a 5% $NaHCO_3$ solution and extracted 3 times with 20 ml ether. The solvent was removed in vacuo, the residue taken up in ethanol:water (3:1) and refluxed for 24 h. The solvent was evaporated and the residue purified by means of flash chromatography with ethyl acetate. The product was recrystallized from cyclohexane to afford (2*R*)-(−)-**6** and (2*S*)-(+)-**6** (270 mg, 66%), respectively: mp 84–85°C; $[\alpha]_D^{30}$ −109.7 (c=1.0, $CHCl_3$) and +109.0 (c=1.3, $CHCl_3$), respectively. Anal. calcd for $C_{13}H_{16}O_2$: C 76.40, H 7.90; Found: C 76.30, H 7.89 and C 76.30, H 8.14, respectively.

3.6.2. Method B

A solution of the crude (α*R*,α′*R*)-**8** and (α*S*,α′*S*)-**8** (2 g, 4.87 mmol), respectively, in ethanol:water (3:1) was refluxed for 24 h, the solvent removed in vacuo and the residue purified by flash chromatography with ethyl acetate to yield **6a** and **6b**, respectively (780 mg, 78%): mp 83°C and 82°C, respectively;

$[\alpha]_D^{30}$ +55.0 and −56.2, respectively. A single recrystallization from cyclohexane yielded (2*S*)-(+)-**6** and (2*R*)-(−)-**6** (435 mg, 56%), respectively: $[\alpha]_D^{30}$ +105.4 (c=1.0, $CHCl_3$) and −106.2 (c=1.0, $CHCl_3$), respectively.

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (m, 2H, H-5_{ax}, H-3_{eq}), 1.87 (m, 2H, H-4), 2.2 (m, 2H, H-5_{eq}, H-3_{ax}), 2.54 (m, 1H, H-6_{eq}), 2.70 (ddd, *J*=13.5, 13.5, 6.5 Hz, 1H, H-6_{ax}), 2.97 (d, J_{ab}=13.5 Hz, 1H, H-benzyl), 3.14 (d, J_{ab}=13.5 Hz, 1H, H-benzyl), 3.9 (s, 1H, OH), 7.25 (m, 5H, H-arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.7 (t), 27.3 (t), 38.5 (t), 40.3 (t), 43.2 (t), 79.2 (s), 126.9 (d), 128.1 (d), 130.0 (d), 135.3 (s), 213.1 (s).

3.7. (2R,3R,6R)- and (2R,3R,6S)-1,4-Dioxa-6-benzyl-6-hydroxy-2,3-dimethyl-spiro[4,5]-decan ((6R)-7 and (6S)-7)

A solution of 102 mg (0.5 mmol) (−)-(2*R*)-**6** and (+)-(2*S*)-**6**, respectively, and 90 mg (1 mmol) (2*R*,3*R*)-2,3-butandiol in 7 ml toluene was refluxed for 14 h in the presence of a catalytic amount of *p*-TsOH. The solvent was removed and the residue chromatographed with cyclohexane:ethyl acetate (9:1) to give 119 mg (0.033 mmol, 66%) of (6*R*)-**7** and (6*S*)-**7**, respectively: mp 86°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (d, *J*=6.0 Hz, 3H, CH_3), 1.30 (d, *J*=6.0 Hz, 3H, CH_3), 1.3–2.0 (m, 8H, -CH_2-), 1.78 (s, 1H, OH), 2.89 (s, 2H, H-benzyl), 3.66 (dq, *J*=8.5, 6.0 Hz, 1H, H-2), 3.79 (dq, *J*=8.5, 6.0 Hz, 1H, H-3), 7.25 (m, 5H, H-arom); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.1 (q), 17.7 (q), 20.3 (t), 22.9 (t), 32.8 (t), 33.4 (t), 39.3 (t), 75.2 (d), 77.9 (d), 79.8 (d), 109.9 (s), 125.4 (d), 127.8 (d), 130.8 (d), 137.2 (s) and, 16.2 (q), 17.7 (q), 20.3 (t), 23.1 (t), 32.4 (t), 32.8 (t), 40.4 (t), 75.3 (d), 78.4 (d), 79.6 (d), 110.1 (s), 126.0 (d), 127.8 (d), 130.9 (d), 137.4 (s), respectively.

3.8. X-Ray structure of (αR,2S)-5

$C_{21}H_{25}ON \cdot HCl$, Mr=343.90, transparent crystal of size 0.25×0.4×0.6 mm^3, orthorhombic, space group P2,2,2 (No. 19 of IT[16]). Lattice parameters are *a*=8.535 (2) Å, *b*=11.628 (3) Å, *c*=18.018 (5) Å and *V*=1788.2 (8) Å^3 (determined from 13 211 reflections, 3°<θ<27°), *Z*=4, d_{calc}=1.277 g cm^{-3} and μ_x (MoKα radiation, λ=0.7107 Å)=2.18 cm^{-1}. Intensity data were collected with an image plate detector system (MarResearch) using MoKα radiation and a graphite monochromator at T=150 K. Data collection was carried out in the range $-9 \le h \le 9$, $-14 \le k \le 14$, $-22 \le l \le 22$ with $(\sin\theta/\lambda)_{max}$=0.639. The total number of reflections measured is 13 497, from which 3270 are unique (R_{merged}=1.91%, completeness: 94%). Data were integrated, reduced and scaled using XDS.[17] 3187 reflections have $I(h)>3\sigma(I(h))$ and were retained for further analysis. The structure was solved by Direct Methods.[18] All non-hydrogen atoms were refined anisotropically using full-matrix least-squares[19] based on |F| with weights $1/(\sigma(|F|)^2+0.1)$. H-1 to H-3 were refined isotropically. The positions of all other H atoms were calculated with a C–H distance of 0.97 Å and a hydrogen displacement parameter of 1.1 times that of the corresponding C atoms. The shifts $(\Delta/\sigma)_{max}$ of the final least-square cycle were smaller than 0.01. *R*-values were *R*w=0.037 and *R*=0.028 for refined parameters. Goodness of the fit is 1.51. The final difference Fourier is featureless ($\Delta\rho_{min}$=−0.33, $\Delta\rho_{max}$=0.44 c/Å). The absolute configuration was determined by refining an enantiomorph sensitive parameter (χ=0.02 (4)) according to Flack,[20] including all Friedel related reflections. Anomalous dispersion corrections were taken from IT Vol. IV, Table 2.3.1.[16] The Cl ion is weakly bound by a hydrogen bridge N1–H1...Cl1–N1, the N1–Cl1 distance is 3.118 (1) Å and the bond angle at the H atom is 171 (2)°.

Under consideration of the measurements errors, all distances and angles are within the expected values.[21]

Acknowledgements

Financial support from The Fonds der Chemischen Industrie, Frankfurt a.M., Germany, is gratefully acknowledged.

References

1. (a) Stevens, C. L.; Elliot, B.; Winch, B. L. *J. Am. Chem. Soc.* **1963**, *85*, 1464. (b) Stevens, C. L.; Hanson, H. T.; Taylor, K. G. *J. Am. Chem. Soc.* **1966**, *88*, 2769. (c) Stevens, C. L.; Ash, A. B.; Thuillier, A.; Amin, J. H.; Balys, A.; Dennis, W. E.; Dickerson, J. P. Glinsky, R. P.; Hanson, H. T.; Pillai, M. D.; Stoddard, J. W. *J. Org. Chem.* **1966**, *31*, 2593. (d) Stevens, C. L.; Klundt, I. L.; Munk, M. E.; Pillai, M. D. *J. Org. Chem.* **1965**, *30*, 2967.
2. Kyburz, R.; Schöpp, E.; Bick, I. R. C.; Hesse, M. *Helv. Chim. Acta* **1981**, *64*, 2555.
3. Compain, P.; Gore, J.; Vatele, J. M. *Tetrahedron* **1996**, *52*, 6647.
4. (a) Landsiedl-Maier, D.; Frahm, A. W. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 59. (b) Bisel, P.; Breitling, E.; Frahm, A. W. *Eur. J. Org. Chem.* **1998**, 729.
5. Lauktien, G.; Volk, F.-J.; Frahm, A. W. *Tetrahedron: Asymmetry* **1997**, *8*, 3457.
6. Wakamatsu, T.; Fukui, M.; Ban, Y. *Synthesis* **1976**, 341.
7. Kossolapoff, G. M. *CA* **1964**, *61*, 1770g.
8. Lauktien, G. PhD Thesis, University of Bonn, 1990.
9. Desmaële, D.; Champion, N. *Tetrahedron Lett.* **1992**, *33*, 4447.
10. Platzbecher, R.; Will, G.; Hümmer, K.; Weckert, E.; Lauktien, G.; Frahm, A. W. *Acta Cryst.* **1993**, *C49*, 307.
11. The full X-ray data will be deposited at the Cambridge Crystallographic Data Centre.
12. (a) Stevens, C. L.; Pillai, P. M.; Munk, M. E.; Taylor, K. G. *Mech. Mol. Migr.* **1971**, *3*, 291. (b) Mizumo, H.; Terashima, S.; Yamada, S. *Chem. Pharm. Bull.* **1971**, *2*, 227. (c) Compain, P.; Gore, J.; Vatele, J. M. *Tetrahedron Lett.* **1995**, *36*, 4059. (d) Compain, P.; Gore, J.; Vatele, J. M. *Tetrahedron Lett.* **1995**, *36*, 4063.
13. Tamura, Y.; Annoura, H.; Kondo, H.; Fuji, M.; Yoshida, T.; Fujioko, H. *Chem. Pharm. Bull.* **1987**, *35*, 2305.
14. Izumi, Y.; Tai, A. *Stereodifferentiation Reactions*; Academic Press: New York, London, 1977.
15. Dürbeck, H. W.; Frischhorn, C.; Hilpert, K. *Tetrahedron* **1971**, *27*, 2927.
16. *International Tables for X-Ray Crystallography*; Kynoch Press: Birmingham, England, 1979 (present distributor: Kluwer Academic, Dordrecht, Holland).
17. Kabsch, W. *J. Appl. Crystallogr.* **1993**, *26*, 795.
18. Burla, M. C.; Camalli, M.; Caserano, G.; Giacovazzo, C.; Polidori, G.; Spagna, R.; Viterbo, D. J. *J. Appl. Crystallogr.* **1988**, *22*, 239.
19. Watkin, D. J.; Carruther, J. R.; Betteridge, P. W. *Program CRYSTALS, User Guide*; Chemical Crystallography Laboratory, University of Oxford, Oxford, 1985.
20. Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876.
21. Allen, F. H.; Kennard, O.; Watson, D. J.; Bramnen, L.; Orpen, A. G.; Taylor, R. *International Tables for X-Ray Crystallography*, Volume C; Wilson, A. J. C., Ed.; Kluwer Academic Publishers: London, 1992; Vol. C.