Intramolecular Cycloaddition Reactions of ω-Unsaturated Chiral Nitrones

Jan Marcus, Johannes Brussee*, and Arne van der Gen

Leiden Institute of Chemistry, Gorlaeus Laboratories, Leiden University,
P. O. Box 9502, NL-2300 RA Leiden, The Netherlands
Fax: (internat.) + 31-71/527-4537
E-mail: Brussee@chem.leidenuniv.nl

Received May 27, 1998

Keywords: Asymmetric synthesis / Chiral induction / Cyanohydrin / Cycloaddition / Nitrone

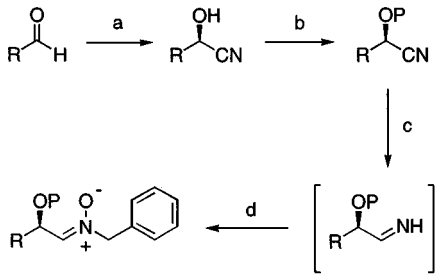
The intramolecular 1,3-dipolar cycloaddition of ω-unsaturated chiral nitrones is described. Starting materials for this reaction are *O*-protected chiral cyanohydrins, prepared by an R-oxynitrilase catalyzed asymmetric addition of hydrogen cyanide to ω-unsaturated aldehydes. Intramolecular cycloaddition, followed by reductive opening of the isoxazolidine ring, produced five- and seven-membered ring compounds with chiral hydroxy and amine functionalities of high enantiomeric purity in excellent yield.

Introduction

Over the years nitrones have become important building blocks in organic synthesis[1]. Recently, a one-pot procedure was published for the synthesis of chiral aldo and keto nitrones by way of a transimination-based reaction sequence, starting from *O*-protected chiral α-hydroxynitriles (cyanohydrins)[2] (Scheme 1). Cyanohydrins can be prepared in excellent enantiomeric purity by asymmetric addition of hydrogen cyanide to aldehydes in a reaction catalyzed by the enzyme R-oxynitrilase (E.C. 4.1.2.10), as present in almond meal[3]. A wide variety of substrates can be employed in the R-oxynitrilase catalyzed reaction, including aromatic, heterocyclic, and saturated as well as α,β-unsaturated aliphatic aldehydes[4]. The cyanohydrins thus obtained are known to possess the (*R*) configuration[5].

After protection of the hydroxy group the cyanohydrin was, by a one-pot procedure, reduced with DIBAL and then protonated with methanol to give the free imine. Transimination with benzylhydroxylamine directly produced the nitrone.

Scheme 1



Reagents: (a) HCN, oxynitrilase. − (b) Protection. − (c) 1. DIBAL 2. MeOH. − (d) *N*-Benzylhydroxylamine.

The 1,3-dipolar cycloaddition reaction between a nitrone and an alkene is a powerful method for the creation of heterocyclic structures[1a][6]. The products of these reactions are isoxazolidines: saturated, five-membered heterocycles containing an adjacent nitrogen and oxygen atom. Regio- and stereoselective nitrone cycloaddition, followed by reduction of the N−O bond, to produce both an amino and a hydroxy function, allows the synthesis of tailor-made products of possible biological interest[1a].

When both alkene and nitrone functionality are combined in one molecule, *intramolecular* 1,3-dipolar cycloaddition can occur and numerous examples of the application of this principle have been published[1a][6][7].

One way of introducing an alkene functionality into nitrones (Scheme 1) is by using an ω-unsaturated aldehyde as starting material for the cyanohydrin synthesis. To the best of our knowledge such aldehydes have not been used before in the enzyme-catalyzed reaction.

We hereby report the synthesis of ω-unsaturated chiral nitrones and their subsequent intramolecular cycloaddition reaction.

Results and Discussion

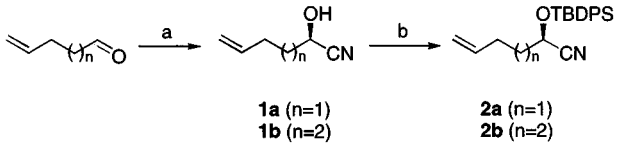
For the preparation of the ω-unsaturated chiral cyanohydrins a general procedure was used as developed in our laboratories in recent years[3]. To a buffered mixture of almond meal and an aldehyde at 5°C, a solution of hydrogen cyanide in ethyl acetate was added. The resulting mixture was then stirred for 72 hours. After work-up, cyanohydrins **1a** and **1b** were obtained, both in excellent yield. These cyanohydrins are new and interesting additions to the wide range of chiral cyanohydrins already available (Scheme 2).

Since cyanohydrins are unstable under basic or reductive conditions a protecting group at the oxygen atom was introduced to prevent decomposition and/or racemization in following steps. Silyl protecting groups are especially useful since these groups can be introduced and removed under mild conditions without loss of enantiomeric purity[8]. The protecting group of choice was *tert*-butyldiphenylsilyl

  1434−193X/98/1111−2513 $ 17.50+.50/0

(TBDPS). The TBDPS group has the additional advantage of being detectable by UV which enables the determination of the enantiomeric excess by HPLC. Cyanohydrins **1a** and **1b** were protected with TBDPSCl in the presence of imidazole affording **2a** and **2b** as pale yellow oils in good yields and with an enantiomeric excess of 97% and 95%, respectively.

Scheme 2

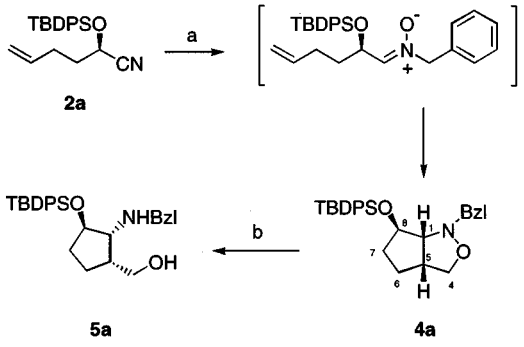


Reagents: (a) HCN, oxynitrilase, ethyl acetate. − (b) TBDPSCl, imidazole, DMF.

Preparation of the nitrones proceeded by the one-pot reduction-transimination reaction sequence. First the cyano group of the *O*-protected cyanohydrins **2a** and **2b** was reduced with DIBAL. Then dry methanol was added to liberate the free imine and destroy the excess of DIBAL. Subsequent addition of *N*-benzylhydroxylamine initiated the transimination reaction[2] (Scheme 1).

When protected cyanohydrin **2a** was used as the starting material the bicyclic cycloaddition product was obtained directly instead of the expected nitrone. The intramolecular cycloaddition reaction proceeded spontaneously to give **4a** in 92% yield and with an e.e. of 97% (Scheme 3). LeBel et al. reported that 1,3-dipolar cycloaddition of related 5-alkenyl-substituted nitrones yielded only *cis*-fused isoxazolidines[9]. Normally, diastereomeric mixtures of bicyclic compounds arise. It is known, however, that a chiral centre, especially when present at the β-position, can induce the formation of only one of the possible diastereomers[10][11]. The results showed that this was indeed the case, since **4a** was obtained as a single diastereomer.

Scheme 3

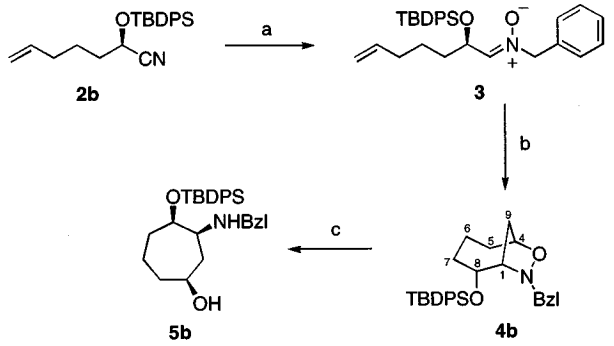


Reagents: (a) 1. DIBAL, 2. MeOH, 3. BzlNHOH. − (b) Zn, acetic acid.

Reductive opening of the isoxazolidine ring was achieved by reaction of **4a** with zinc in acetic acid[12]. As expected, the silyl protective group was stable under these conditions. Cyclopentane **5a** was formed in 99% yield, with an e.e. of 97%. The absolute configuration was determined to be (1*R*,5*S*,8*R*) by analysis of the ^{1}H-NMR and NOESY spectra of **4a**[13].

When protected cyanohydrin **2b** was used for the formation of a nitrone, no spontaneous intramolecular cycloaddition was observed and nitrone **3** was isolated in 90% yield with an e.e. of 96% (Scheme 4). Refluxing a solution of **3** in toluene for 1 hour produced a mixture of products, which could not be separated by column chromatography. Reductive opening of the N−O bond produced a mixture of six- and seven-membered ring compounds. However, refluxing nitrone **3** in toluene in the presence of one equivalent of zinc chloride produced only one product, namely **4b** in 85% yield with an e.e. of 94%. The absolute configuration of **4b** was determined to be (1*S*,4*S*,8*R*) by analysis of the 600-MHz ^{1}H-NMR and NOESY spectra[14]. Reductive opening of the isoxazolidine ring with zinc in acetic acid afforded the seven-membered ring compound **5b** in 97% yield with an e.e. of 94%.

Scheme 4

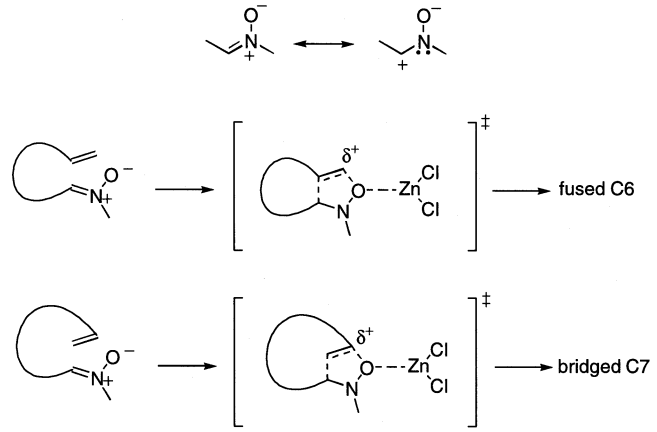


Reagents: (a) 1. DIBAL, 2. MeOH, 3. BzlNHOH. − (b) Toluene, $ZnCl_2$. − (c) Zn, acetic acid.

The fact that only the seven-membered ring product is formed in the presence of zinc chloride can be explained as follows: Nitrones are reactive 1,3-dipoles, because they contain a negatively charged oxygen atom and a positive charge that is shared by the carbon and nitrogen atoms of the C−N bond (Figure 1). When the strong Lewis acid zinc chloride binds to the oxygen atom, its negative charge will be partly neutralized, while the positive part of the dipole remains intact. In the 1,3-dipolar cycloaddition, which is a concerted, but not necessarily a synchronous process, there will be a larger tendency for the π-electrons of the alkene to form a bond with the positively charged carbon atom of the nitrone. In other words, the 1,3-dipolar cycloaddition will be non-synchronous, with carbon−carbon bond formation further advanced than carbon−oxygen bond formation. As a result, a transition state is formed in which there is a relatively well-developed positive charge on one of the carbon atoms of the alkene (Figure 1). The terminal double bond can attack the nitrone moiety via two possible routes. One will follow the bridged mode of cycloaddition and will result in the formation of a seven-membered ring. The other will follow the fused mode of cycloaddition forming the six-membered ring. The difference between the transition states will be that the bridged mode has the developing positive

charge at a secondary carbon atom whereas the fused mode has the positive charge at a primary carbon atom. As secondary carbocations are appreciably more stable than primary ones[15], this will result in a preference for the bridged transition state and therefore the formation of **4b**.

Figure 1. Difference between the fused and bridged mode of attack



Conclusion

The synthesis of five- and seven-membered ring compounds of high enantiomeric purity with hydroxy and amine substituents at chiral centres is described. The ring compounds are formed by an intramolecular cycloaddition reaction of ω-unsaturated chiral nitrones. The five-membered ring compound is formed spontaneously at room temperature with complete diastereoselectivity. The isoxazolidine ring could be quantitatively opened by reduction with zinc in acetic acid. Starting from 4-pentenal, a compound with three contiguous stereocenters was formed in 76% overall yield and with an e.e. of 97%. The seven-membered ring compound is formed after refluxing the corresponding nitrone with zinc chloride in toluene, followed by the reductive opening of the isoxazolidine ring. Starting from 5-hexenal, a seven-membered ring compound with three stereocenters was formed in 62% overall yield and with an e.e. of 94%.

Experimental Section

General Methods and Materials: ^{1}H- and ^{13}C-NMR spectra were recorded with a JEOL FX-200 instrument. Samples were measured in $CDCl_3$, with Me_4Si as an internal standard for ^{1}H NMR, and $CDCl_3$ as an internal standard for ^{13}C NMR; δ in ppm, *J* in Hz. ^{1}H-NMR spectra of compounds **4a** and **5b** were recorded with a Bruker DPX-300 instrument. The ^{1}H-NMR spectrum of compound **4b** and the NOESY spectra of compounds **4a**−**b** were recorded with a Bruker DMX-600 instrument. − Enantiomeric purities were determined by HPLC using a Chiralcel OD column (250 × 4.6 mm). As eluents, mixtures of hexane (H) and isopropyl alcohol (I), which are specified in each case, were applied. A small percentage (0.2%) of diethylamine was added for **5a**. Flow = 1 ml/min, λ = 254 nm. All compounds were also prepared in racemic form to optimize the conditions for peak separation. Retention times of the first ($R_{t,1}$) and second ($R_{t,2}$) enantiomer (in min) and the chromatographic resolution (Res) are given for compounds **2a**−**b**, **3**, **4a**−**b**, and **5a**−**b**. − Optical rotations were measured using a Propol automatic polarimeter. − Melting points were measured with a Büchi melting-point apparatus and are uncorrected. − Elemental analyses were performed with a Perkin-Elmer 2400 analyzer. − 4-Pentenal was purchased from Lancaster. 5-Hexenal was prepared by a PCC oxidation of 5-hexenol. The aldehyde was purified by vacuum destillation[16]. *N*-benzylhydroxylamine was prepared by addition of NH_2OH to benzaldehyde, followed by an $NaBH_3CN$ reduction. M.p. 57°C (recrystallized from ethanol and petroleum ether 40/60).

(R)-2-Hydroxy-5-hexenenitrile (**1a**): In a round-bottom flask 3 g of defatted almond meal was swollen in 4.5 ml of a 0.025 M citrate buffer (pH = 5.4). After 15 min, a solution of 1.68 g (20 mmol) of 4-pentenal in 5 ml of ethyl acetate was added. Meanwhile 2.1 g (43 mmol) of NaCN was dissolved in 50 ml of cold water. The pH of this solution was adjusted to 5.4 by addition of acetic acid: ***CAUTION: Toxic hydrogen cyanide!*** The hydrogen cyanide solution was extracted with ethyl acetate (3 × 20 ml). The combined ethyl acetate layers were transferred into a dropping funnel that was placed on the round-bottom flask. The equipment was placed in a cold room at 5°C. After 45 min, the hydrogen cyanide solution was added dropwise. The almond meal mixture was kept stirring for the next 72 h. The reaction mixture was filtered through a funnel with a layer of silica gel and a layer of hyflo, dried ($MgSO_4$) and concentrated in vacuo. The pure cyanohydrin **1a** was obtained as a yellow oil. − Yield: 1.90 g (86%); $[\alpha]_D^{20}$ = +6.1 (*c* = 1, $CHCl_3$). − ^{1}H NMR: δ = 2.00 (m, 2 H, CH_2=CHCH_2), 2.31 (q, 2 H, *J* = 6.68, CH_2CHOH), 4.52 (t, 1 H, *J* = 6.68, C*H*OH), 5.12 (m, 2 H, CH_2=CH), 5.81 (m, 1 H, CH_2=C*H*). − ^{13}C NMR: δ = 28.41 (CH_2=CHCH), 33.79 (*C*HCHOH), 60.12 (CHOH), 116.24 (*C*H_2=CH), 119.81 (CN), 135.78 (CH_2=*C*H).

(R)-2-Hydroxy-6-heptenenitrile (**1b**): Cyanohydrin **1b** was prepared by the procedure described for **1a** starting with 5-hexenal (0.88 g, 9 mmol). Yield: 0.99 g (88%); $[\alpha]_D^{20}$ = +13.7 (*c* = 1, $CHCl_3$). − ^{1}H NMR: δ = 1.64 (m, 2 H, CH_2), 1.85 (m, 2 H, CH_2), 2.10 (m, 2 H, CH_2), 4.49 (t, 1 H, *J* = 6.68, C*H*OH), 5.03 (m, 2 H, CH_2=CH), 5.78 (m, 1 H, CH_2=C*H*). − ^{13}C NMR: δ = 23.56 (*C*H_2), 32.68 (*C*H_2), 34.25 (*C*H_2), 60.79 (*C*HOH), 115.28 (*C*H_2=CH), 119.98 (CN), 137.39 (CH_2=*C*H).

(R)-2-[(tert-Butyldiphenylsilyl)oxy]-5-hexenenitrile (**2a**): In a dry round-bottom flask 2.04 g (30 mmol) of imidazole was dissolved in 75 ml of dry dimethylformamide. The flask was cooled to 5°C in an ice bath and 4.7 ml (18 mmol) of TBDPSCl was added. The solution was stirred for 10 min after which time 1.67 g (15 mmol) of **1a** was added. The solution was allowed to warm to room temperature and was stirred overnight. The reaction mixture was poured into H_2O (175 ml) and extracted with diethyl ether (3 × 75 ml). The combined organic layers were washed with water (4 × 50 ml), saturated brine (1 × 50 ml), and dried ($MgSO_4$). The solvents were evaporated in vacuo. The protected cyanohydrin **2a** was obtained as a yellow oil. Yield: 5.02 g (96%); $[\alpha]_D^{20}$ = +16.3 (*c* = 1, $CHCl_3$); e.e. 97% (HPLC eluent H/I = 99.75:0.25); $R_{t,1}$ = 5.30 (*R*), $R_{t,2}$ = 7.35 (*S*), Res = 2.9. − ^{1}H NMR: δ = 1.10 (s, 9 H, *Me*$_3$C), 1.84 (m, 2 H, CH_2), 2.21 (m, 2 H, CH_2), 4.35 (t, 1 H, *J* = 6.2, C*H*OSi), 4.97 (m, 2 H, CH_2=CH), 5.63 (m, 1 H, CH_2=C*H*), 7.42−7.68 (m, 10 H, H-arom). − ^{13}C NMR: δ = 19.08 (Me$_3$*C*), 26.52 (*Me*$_3$C), 28.21 (CH_2=CH*C*H), 35.03 (*C*HCHOSi), 62.19 (CHOSi), 115.87 (*C*H_2=CH), 119.71 (CN), 131.56 (C_{ipso}), 127.45, 127.83, 129.30, 129.90, 130.24, 134.68, 135.14 (C-arom), 135.53 (CH_2=*C*H).

(R)-2-[(tert-Butyldiphenylsilyl)oxy]-6-heptenenitrile (**2b**): Protected cyanohydrin **2b** was prepared by the procedure described for **2a** starting with **1b** (0.99 g, 8 mmol). Yield: 2.73 g (95%); $[\alpha]_D^{20}$ = +18.5 (*c* = 1, $CHCl_3$); e.e. 95% (HPLC eluent H/I = 99.75:0.25); $R_{t,1}$ = 5.47 (*R*), $R_{t,2}$ = 7.85 (*S*), Res = 3.0. – ^{1}H NMR: δ = 1.09 (s, 9 H, Me_3C), 1.57 (m, 2 H, CH_2), 1.73 (m, 2 H, CH_2), 2.05 (m, 2 H, CH_2), 4.34 (t, 1 H, *J* = 6.2, C*H*OSi), 4.97 (m, 2 H, CH_2=CH), 5.69 (m, 1 H, CH_2=C*H*), 7.43–7.67 (m, 10 H, H-arom). – ^{13}C NMR: δ = 18.90 (Me_3*C*), 23.01 (*C*H_2), 26.43 (*Me*$_3$C), 32.44 (*C*H_2), 35.04 (*C*H_2), 62.43 (*C*HOSi), 114.99 (*C*H_2=CH), 118.99 (CN), 131.72 (C_{ipso}), 127.34, 127.63, 129.68, 130.03, 134.96, 135.20 (C-arom), 135.34 (CH_2=*C*H).

(R)-(Z)-N-{2-[(tert-Butyldiphenylsilyl)oxy]-6-heptenylidene}-benzylamine N-Oxide (**3**): The reaction was carried out under dry nitrogen. In a three-necked flask, 1.82 g (5 mmol) of **2b** was dissolved in 50 ml of dry diethyl ether. At −70°C 7.5 ml (7.5 mmol) of 1 M DIBAL in cyclohexane was added to the stirred solution. The cooling bath was removed and the mixture was allowed to warm to −10°C. After cooling to −90°C, 3 ml of dry methanol was added, immediately followed by 0.62 g (5 mmol) of *N*-benzylhydroxylamine. The mixture was stirred at room temp. for 4 h, poured into H_2O (85 ml) and extracted with diethyl ether (3 × 150 ml). The combined organic layers were washed with saturated brine (1 × 85 ml), and dried ($MgSO_4$). The solvents were evaporated in vacuo. The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 75:25). Yield: 2.12 g (90%); $[\alpha]_D^{20}$ −27.3 (*c* = 1, $CHCl_3$);); e.e. 96% (HPLC eluent H/I = 99:1); $R_{t,1}$ = 24.74 (*S*), $R_{t,2}$ = 27.86 (*R*), Res = 1.2. M.p. = 79°C. – ^{1}H NMR: δ = 1.03 (s, 9 H, Me_3C), 1.49 (m, 2 H, CH_2), 1.69 (m, 2 H, CH_2), 1.99 (m, 2 H, CH_2), 4.56 (q, 2 H, *J* = 5.14, CH_2Ph), 4.99 (m, 3 H, CH_2=CH + C*H*C=N$^+$), 5.73 (m, 1 H, CH_2=C*H*), 6.49 (d, 1 H, *J* = 5.65, C*H*=N$^+$), 7.11–7.60 (m, 15 H, H-arom). – ^{13}C NMR: δ = 18.96 (Me_3*C*), 23.79 (*C*H_2), 26.66 (*Me*$_3$C), 32.95 (*C*H_2), 33.25 (*C*H_2), 68.55 (*C*HOSi), 68.78 (*C*H_2Ph), 114.32 (*C*H_2=CH), 127.40, 128.54, 129.03, 129.53 (C-arom), 132.15, 133.62 (C_{ipso}), 135.37 (CH_2=*C*H), 141.44 (C=N$^+$). – $C_{30}H_{37}NO_2Si$ (471.71): calcd. C 76.39, H 7.91; found C 76.02, H 8.11.

(1R,5S,8R)-8-[(tert-Butyldiphenylsilyl)oxy]-3-oxo-2-azobicyclo-[3.3.0]-octane (**4a**): Isoxazolidine **4a** was prepared by the procedure described for **3** starting with **2a** (1.75 g, 5 mmol). The crude product was purified by column chromatography (petroleum ether/ethyl acetate = 95:5). Yield: 2.10 g (92%); $[\alpha]_D^{20}$ = +50.1 (*c* = 1, $CHCl_3$);); e.e. 97% (HPLC eluent H/I = 99.75:0.25); $R_{t,1}$ = 10.39 (*R*), $R_{t,2}$ = 18.97 (*S*), Res = 3.3. – ^{1}H NMR: δ = 1.05 (s, 9 H, Me_3CSi), 1.47 (m, 1 H, 6-H), 1.66 (m, 1 H, 7-H), 1.80 (m, 1 H, 7-H), 2.12 (m, 1 H, 6-H), 3.14 (m, 1 H, 5-H), 3.22 (m, 1 H, 1-H), 3.24 (d, 1 H, *J* = 13.8, CH_2Ph), 3.33 (dd, 1 H, *J* = 8.6 and *J* = 4.9, 4-H), 3.57 (d, 1 H, *J* = 13.8, CH_2Ph), 4.03 (t, 1 H, *J* = 8.6, 4-H), 4.13 (m, 1 H, 8-H), 7.20–7.67 (m, 15 H, H-arom). – ^{13}C NMR: δ = 19.07 (Me_3*C*), 26.89 (*Me*$_3$C), 28.79 (C-6), 33.08 (C-7), 46.25 (C-5), 60.71 (*C*H_2Ph), 72.39 (C-4), 78.14 (C-8), 79.19 (C-1), 126.93, 127.57, 128.07, 128.60, 129.44, 129.59, 134.73, 135.66, 135.75 (C-arom), 134.09 (Si-C_{ipso}), 137.65 (CH_2C_{ipso}). – $C_{29}H_{35}NO_2Si$ (457.69): calcd. C 76.10, H 7.71; found C 76.29, H 7.97.

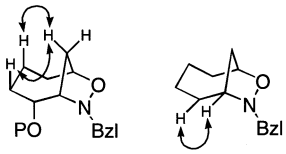
(1S,4S,8R)-8-[(tert-Butyldiphenylsilyl)oxy]-3-oxo-2-azobicyclo[4.2.1]nonane (**4b**): Nitrone **3** (1.88 g, 4 mmol) and $ZnCl_2$ (0.54 g, 4 mmol) were dissolved in 50 ml of toluene. The reaction mixture was stirred and heated for 30 min under reflux. After cooling, the mixture was washed with water (2 × 20 ml) and saturated brine (1 × 10 ml), and dried ($MgSO_4$). The toluene was evaporated. The crude product was purified by column chromatography (silica gel, eluent: petroleum ether 40/60/ethyl acetate = 90:10). Yield: 1.60 g (85%); $[\alpha]_D^{20}$ = +12.8 (*c* = 0.25, $CHCl_3$);); e.e. 94% (HPLC eluent H/I = 99.75:0.25); $R_{t,1}$ = 11.05 (*R*), $R_{t,2}$ = 21.93 (*S*), Res = 1.2. – ^{1}H NMR: δ = 1.02 (s, 9 H, Me_3C), 1.45 (m, 1 H, 6-H), 1.53 (m, 2 H, 5-H + 7-H), 1.64 (m, 1 H, 5′-H), 1.78 (m, 1 H, 7′-H), 1.94 (m, 1 H, 6′-H), 2.19 (dt, 1 H, *J* = 8.1 *J* = 12.8, 9-H), 2.43 (d, 1 H, *J* = 12.8, 9′-H), 3.20 (dd, 1 H, *J* = 4.2 *J* = 7.5, 1-H), 3.56 (d, 1 H, *J* = 12.8, CH_2Ph), 3.90 (d, 1 H, *J* = 12.7, CH_2Ph), 3.92 (m, 1 H, 8-H), 4.63 (dt, 1 H, *J* = 1.9 *J* = 9.5, 4-H), 7.17–7.72 (m, 15 H, H-arom). – ^{13}C NMR: δ = 16.51 (C-6), 19.24 (Me_3*C*), 26.97 (*Me*$_3$C), 28.43 (C-9), 30.49 (C-7), 32.82 (C-5), 62.72 (*C*H_2Ph), 66.96 (C-1), 71.91 (C-8), 77.73 (C-4), 127.12, 127.49, 128.27, 128.94, 129.52, 135.55, 135.61 (C-arom), 134.09, 137.43 (C_{ipso}). – $C_{30}H_{37}NO_2Si$ (471.71): calcd. C 76.39, H 7.91; found C 76.67, H 8.23.

(1R,2R,3S)-2-Benzylamino-1-[(tert-butyldiphenylsilyl)oxy]-3-hydroxymethylcyclopentane (**5a**): A solution of **4a** (1.05 g, 2.3 mmol) in 15 ml of glacial acetic acid was added dropwise to a stirred suspension of zinc dust (0.60 g, 9.2 mmol) in aqueous acetic acid (30%, 60 ml). The reaction mixture was stirred overnight at 65°C. Then aqueous K_2CO_3 (30%, 300 ml) was slowly added. After extraction with dichloromethane (3 × 100 ml), the organic layers were washed with water (1 × 50 ml) and dried ($MgSO_4$). The solvent was evaporated in vacuo. Yield: 1.04 g (99%); $[\alpha]_D^{20}$ = +9.5 (*c* = 1, $CHCl_3$);); e.e. 97% (HPLC eluent H/I = 99:1 + 0.2% Et_2N); $R_{t,1}$ = 15.21 (*R*), $R_{t,2}$ = 23.51 (*S*), Res = 3.0. – ^{1}H NMR: δ = 1.06 (s, 9 H, Me_3C), 1.34 (m, 2 H, CH_2CH), 1.72 (m, 2 H, CH_2), 2.39 (m, 1 H, C*H*CH_2OH), 3.11 (t, 1 H, *J* = 6.45, C*H*NH), 3.59 (m, 4 H, CH_2OH + CH_2Ph), 4.11 (q, 1 H, *J* = 6.45, C*H*OTBDPS), 7.10–7.67 (m, 15 H, H-arom). – ^{13}C NMR: δ = 19.11 (Me_3*C*), 23.30 (*C*H_2), 26.96 (*Me*$_3$C), 31.62 (*C*H_2), 38.81 (*C*H), 53.32 (*C*H_2Ph), 64.71 (*C*H_2OH), 69.03 (*C*HOTBDPS), 77.91 (*C*HNH), 127.10, 127.63, 127.76, 128.04, 128.42, 129.76, 129.85, 135.74 (C-arom), 133.92 (Si-C_{ipso}), 139.37 (CH_2C_{ipso}). – $C_{29}H_{37}NO_2Si$ (459.70): calcd. C 75.77, H 8.11; found C 76.08, H 8.51.

(1R,2S,4S)-2-Benzylamino-1-[(tert-butyldiphenylsilyl)oxy]-cycloheptan-4-ol (**5b**): Product **5b** was prepared by the procedure described for **5a** starting with **4b** (1.41 g, 3 mmol). Yield: 1.37 g (97%); $[\alpha]_D^{20}$ = +2.4 (*c* = 0.25, $CHCl_3$);); e.e. 94% (HPLC eluent H/I = 95:5); $R_{t,1}$ = 9.13 (*R*), $R_{t,2}$ = 12.89 (*S*), Res = 3.0. – ^{1}H NMR: δ = 1.02 (s, 9 H, Me_3C), 1.32-2.62 (8 H, CH_2), 2.91 (dt, 1 H, *J* = 28 *J* = 6.6, C*H*NHBn), 3.48 (d, 1 H, *J* = 12.7, CH_2Ph), 3.79 (1 H, d, *J* = 12.7, CH_2Ph), 3.79 (m, 1 H, C*H*OTBDPS), 4.03 (m, 1 H, C*H*OH), 7.13–7.64 (m, 15 H, H-arom). – ^{13}C NMR: δ = 18.18 (*C*H_2), 19.12 (Me_3*C*), 26.87 (*Me*$_3$C), 33.74, 34.73, 37.54 (*C*H_2), 51.57 (*C*H_2Ph), 62.56 (*C*HNH), 70.27 (*C*HOTBDPS), 77.41 (*C*H_2OH), 126.80, 127.40, 127.57, 128.06, 128.21, 129.50, 129.61, 135.61 (C-arom), 133.49 (Si-C_{ipso}), 139.59 (CH_2C_{ipso}). – $C_{30}H_{39}NO_2Si$ (473.73): calcd. C 76.06, H 8.30; found C 76.18, H 8.42.

[1] [1a] M. Frederickson, *Tetrahedron* **1997**, *53*, 403–425. – [1b] A. Dondoni, D. Perrone, *Tetrahedron Lett.* **1997**, *38*, 499–502. – [1c] P. Merino, A. Lanaspa, F. L. Merchan, T. Tejero, *Tetrahedron: Asymmetry* **1998**, *9*, 629–646. – [1d] P. Merino, E. Castillo, S. Franco, F. L. Merchan, T. Tejero, *J. Org. Chem.* **1998**, *63*, 2371–2374.
[2] E. Hulsbos, J. Marcus, J. Brussee, A. van der Gen, *Tetrahedron: Asymmetry* **1997**, *8*, 1061–1067.
[3] P. Zandbergen, J. van der Linden, J. Brussee, A. van der Gen, *Synth. Commun.* **1991**, *21*, 1387–1391.
[4] [4a] C. G. Kruse in *Chirality in Industry* (Eds.: A. N. Collins, G. N. Sheldrake, J. Crosby), John Wiley & Sons Ltd., **1992**, p.

279−299. – [4b] F. Effenberger, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1555−1564; *Angew. Chem.* **1994**, *106*, 1609−1619.
[5] Provided that the hydroxy substituent has priority over substituent R.
[6] K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863-909.
[7] H. G. Aurich, M. Boutahar, H. Köster, K.-D. Möbus, L. Ruiz, *Chem. Ber.* **1990**, *123*, 1999−2014.
[8] J. Brussee, W. T. Loos, C. G. Kruse, A. van der Gen, *Tetrahedron* **1990**, *46*, 979−986.
[9] N. A. LeBel, M. E. Post, J. J. Whang, *J. Am. Chem. Soc.* **1964**, *86*, 3759.
[10] R. Annunziata, M. Cinquini, F. Cozzi, L. Raimondi, *Gazz. Chim. Ital.* **1989**, *119*, 253.
[11] B. Bernet, A. Vasella, *Helv. Chim. Acta* **1979**, *62*, 2411.
[12] H. G. Aurich, F. Biesemeier, *Synthesis* **1995**, 1171−1178
[13] NOE interaction between protons at C1 and C5, no interaction observed between protons at C1 and C8.
[14] NOE interactions between the different protons of compound **4b**. For the sake of clarity only the relevant atoms are presented.



[15] A. Streitwieser, C. Heathcock, *Introduction to Organic Chemistry*, 1st ed., Collier Macmillan International Editions, London, **1976**, p. 149−150.
[16] Care has to be taken that all chromium is removed from the aldehyde. It was observed that traces of chromium have a negative effect on the e.e. of the cyanohydrin.

[98239]