Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 4521–4537

TETRAHEDRON: *ASYMMETRY*

Studies on the synthesis of chiral nonracemic 3,4-disubstituted azepanes, a formal synthesis of (+)- and (−)-balanol

Claus Herdeis,[a,*] Rafat M. Mohareb,[b] Reinhard B. Neder,[c] Franz Schwabenländer[c] and Joachim Telser[a]

[a]*Institut für Pharmazie und Lebensmittelchemie der Universität Würzburg, Am Hubland, 97074 Würzburg, Germany*
[b]*Faculty of Sciences, Cairo University, Giza, Egypt*
[c]*Mineralogisches Institut der Universität Würzburg, Am Hubland, 97074 Würzburg, Germany*

Received 21 October 1999; accepted 22 October 1999

Abstract

Sugar lactones were converted to 3,4-disubstituted azepanes and caprolactam derivatives by selective deoxygenation, functionalization and reductive cyclization. The cyclization proved troublesome with 6-azidolactols but led to good results with the corresponding lactones. A formal synthesis of (+)- and (−)-balanol is reported.

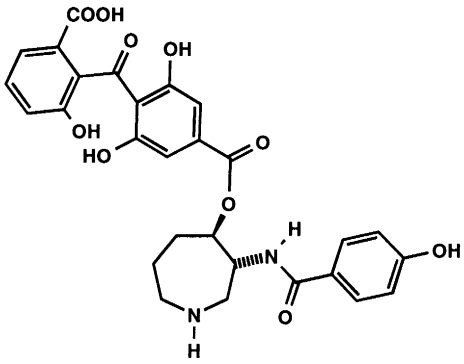
1. Introduction

Balanol **1**, a compound isolated from the fungi *Cordyceps ophioglossoides*,[1] *Verticillium balanoides*[2] and *Fusarium merismoides*[3] has recently become a popular synthetic target because of its potent inhibitory activity against proteinkinase C. Some syntheses of balanol **1** (Fig. 1) or its heterocyclic azepane core[4] have been published to date and several series of acyclic and heterocyclic analogues have been prepared and evaluated for pharmacological properties.[5] Investigations have shown that the remarkable inhibitory activity of balanol **1** is to be attributed to its binding to the ATP docking site of protein kinase.[6]

In our group, sugar lactones are frequently used as an inexpensive and versatile source of chirality for the synthesis of chiral nonracemic piperidine derivatives.[7] Therefore, we tried to extend our methodologies to the synthesis of the azepane ring system. We chose homochiral lactones with a nitrogen containing functional group at C-6 and a protected hydroxy group at C-5 as the key intermediates. Ring closure by formation of a C−N bond between the already functionalized C-1 atom and the nitrogen connected to C-6 should lead to 3,4-disubstituted heterocycles of the balanol type (see Schemes 3 and 4).

* Corresponding author. E-mail: herdeis@pharmazie.uni-wuerzburg.de

0957-4166/99/$ - see front matter
PII: S0957-4166(99)00466-8



(+)-Balanol 1

Fig. 1.

2. Results and discussion

Appropriate starting materials were obtained by the reaction sequence shown in Scheme 1. Compound **2** is readily available from L-ascorbic acid by catalytic hydrogenation[8] and subsequent treatment according to a procedure published by Chittenden and Vekemans.[9] Compound **3** is obtained from calcium-D-gluconate according to a method by Lundt.[10]

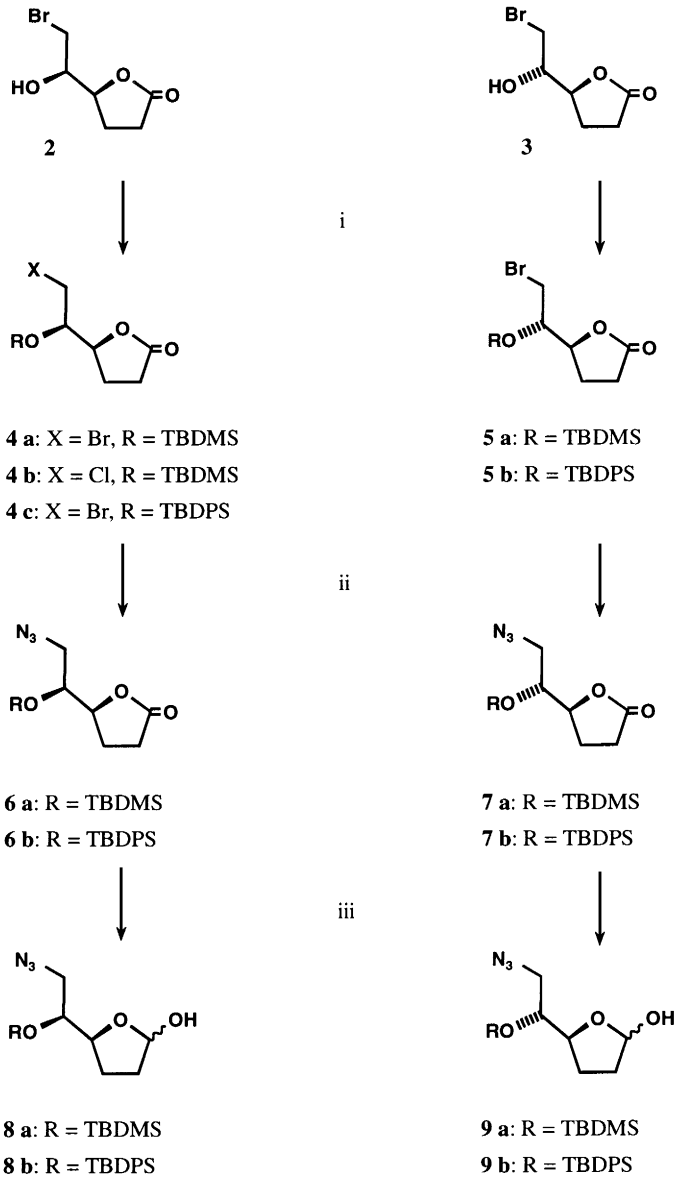
Silylation of **2** with *tert*-butyldimethylchlorosilane in DMF with an excess of imidazole gave **4a** and the chlorinated byproduct **4b** as a chromatographically inseparable mixture. Therefore the exact yield of **4a** and **4b** could not be determined. A similar chlorination reaction in the presence of *tert*-butyldimethylchlorosilane and imidazole has been described by Peyrat et al.[11] The reaction of **2** and *tert*-butyldiphenylchlorosilane under identical conditions resulted in the isolation of **4c**. Compound **3** was converted to the silyl ethers **5a** and **5b** by analogous procedures.

The azido group was introduced by nucleophilic substitution with lithium azide in DMF as a solvent to yield the azidolactones **6a**, **6b**, **7a** and **7b**. The bromolactones **4a**, **4c**, **5a** and **5b** reacted promptly but the chlorolactone **4b** required longer reaction times to obtain complete conversion.

Reduction of **6a** with diisobutyl aluminium hydride (DIBAH) in THF at –78°C gave 86% of the corresponding lactol **8a**. The product was obtained as an equilibrium mixture of anomers; ^{1}H NMR data indicated the presence of a small equilibrium concentration of open chain aldehyde. When the DIBAH reduction protocol was applied to the lactones **6b**, **7a** and **7b**, respectively, the lactols **8b**, **9a** and **9b** could be isolated. The syntheses of the four azidolactols are outlined in Scheme 1. Table 1 summarizes the isolated yields and reaction times.

We addressed the formation of azepanes from the lactols by means of a tandem Wittig–[2+3]cycloaddition reaction. This methodology has been employed successfully for the synthesis of various piperidine derivatives.[7,12] Therefore **8a** and **9a** were reacted with ethoxycarbonylmethylene-(triphenyl)-phosphorane. However, the resulting α,β-unsaturated esters **10** and **11** failed to give the expected intramolecular [2+3]cycloaddition reaction. They proved to be very stable at room temperature for months (Scheme 2). When **10** was reacted with triphenylphosphine in aqueous THF[13,14] in order to induce a Staudinger reduction–Michael addition type reaction sequence a complex mixture of products was obtained.

Since the work of Paulsen[15] it is known that 6-azidolactols undergo a reductive ring enlargement in the presence of excess hydrogen and a catalyst to yield azepanes. Paulsen found evidence for an intermediate equilibrium involving a bicyclic N,O-acetal and a cyclic imine. The latter species is reduced by hydrogen



Scheme 1. (i) RCl, imidazole, DMF, 12–24 h; (ii) LiN_3, DMF, 60°C; (iii) DIBAH, THF, −78°C, 130 min–6.5 h. Yields and reaction times are given in Table 1

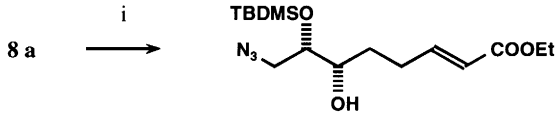
to the azepane. When **8a** was submitted to catalytic hydrogenation in methanol or ethanol using 10% Pd on charcoal the bicyclic N,O-acetal **12a** could be isolated (Scheme 3). This compound was very resistant to further hydrogenation and was converted quantitatively only after a period of seven days. Protic solvents were necessary to drive the reaction to completion but under these conditions a mixture of the regioisomers **13a** and **13b** was isolated due to migration of the silyl protecting group. The product ratio varied with the reaction time. The reaction rate could not be enhanced by changing the catalyst; identical results were obtained with 10% Pt on charcoal. We concluded that the small equilibrium concentration of the **12a** derived cyclic imine (see the literature[15]) limited the reaction rate. Efforts to reduce **12a** directly

Table 1
Synthesis of the azidolactols **8a**, **8b**, **9a** and **9b**

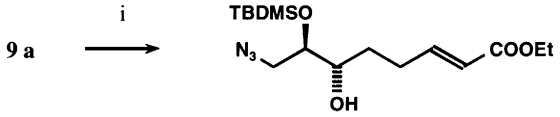
R	Silylation:			Azidation:			Reduction:		
	product	time	yield	product	time	yield	product	time	yield
TBDMS	**4a**, **b**	12 h	n.d.[a]	**6a**	26 h	74 %[b]	**8a**	2 ¼ h	86 %
TBDPS	**4c**	24 h	75 %	**6b**	20 h	91 %	**8b**	5 h	34 %
TBDMS	**5a**	24 h	95 %	**7a**	20 h	67 %	**9a**	5 h	83 %
TBDPS	**5b**	24 h	81 %	**7b**	20 h	93 %	**9b**	6 ½ h	69 %

[a] inseparable product mixture

[b] yield over 2 steps from **2**.



10



11

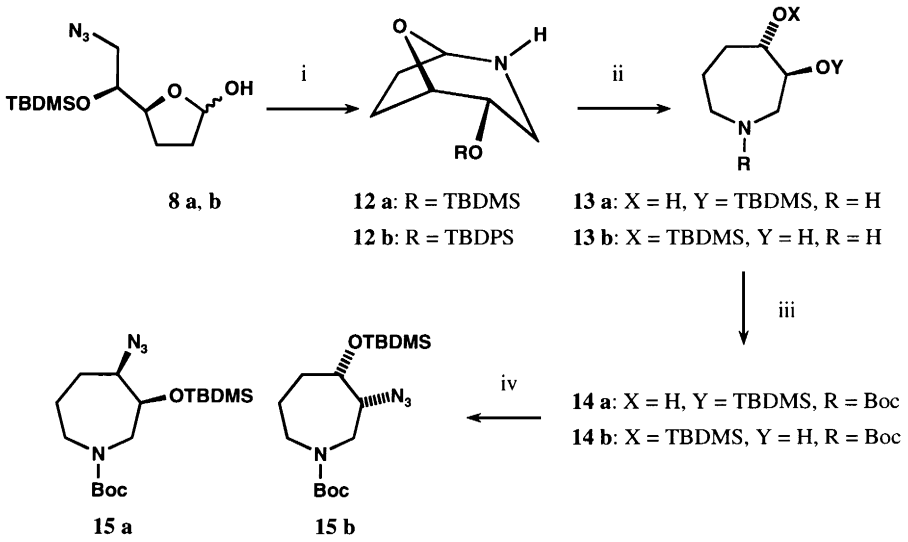
Scheme 2. (i) $Ph_3PCHCOOEt$, PhMe, rt, 48 h, 93% of **10**, 85% of **11**

with hydride transfer agents like $NaBH_4$, $LiBHEt_3$ or $LiAlH_4$ led to unsatisfying yields since extractive workup of the free amines proved to be cumbersome and inefficient.

To overcome the problem of silyl migration, the lactol **8b** with the more bulky and stable TBDPS group was hydrogenated in the presence of 10% Pd/C. In this case the bicyclic product **12b** was isolated which could not be transformed further to an azepane.

Complete hydrogenation of **8a**, therefore, was the only suitable alternative to obtain azepanes. When the regioisomers **13a** and **13b** in the mixture were converted to their *N*-Boc derivatives **14a** and **14b** immediately after the hydrogenation step, it was possible to obtain pure fractions of both isomers by column chromatography. Conversion of the free hydroxy group to the mesylate and subsequent substitution by sodium azide in DMPU resulted in the azido azepanes **15a** and **15b** in moderate yields (57% of **15a**, 37% of **15b**). These compounds can be regarded as precursors of balanol isomers with 3,4-*cis*-orientation of the substituents.

Catalytic hydrogenation of **9a** with 10% Pd/C in ethanol led to an intermediate **16a** which was detected by capillary GC (RI_p=1535). After filtration and evaporation of the solvent a colourless oil was obtained that solidified within some hours and then was insoluble in all organic solvents. It could only be dissolved in a mixture of dilute aqueous HCl and methanol. Therefore, a sample of **16a** was hydrogenated in



Scheme 3. (i) H_2, 10% Pd/C, MeOH or EtOH, 91% of **12a**, 67% of **12b**; (ii) H_2, 10% Pd/C, MeOH or EtOH, 7 days, 77% of isomeric mixture of **13a** and **13b**; (iii) Boc_2O, 2 h, rt, 55% of **14a**, 13% of **14b** for the two-step conversion starting from **8a**; (iv) (a) MsCl, Et_3N, CH_2Cl_2, −20°C, 20 min, (b) NaN_3, DMPU, 80°C, 7 days, 57% of **15a**, 34% of **15b**

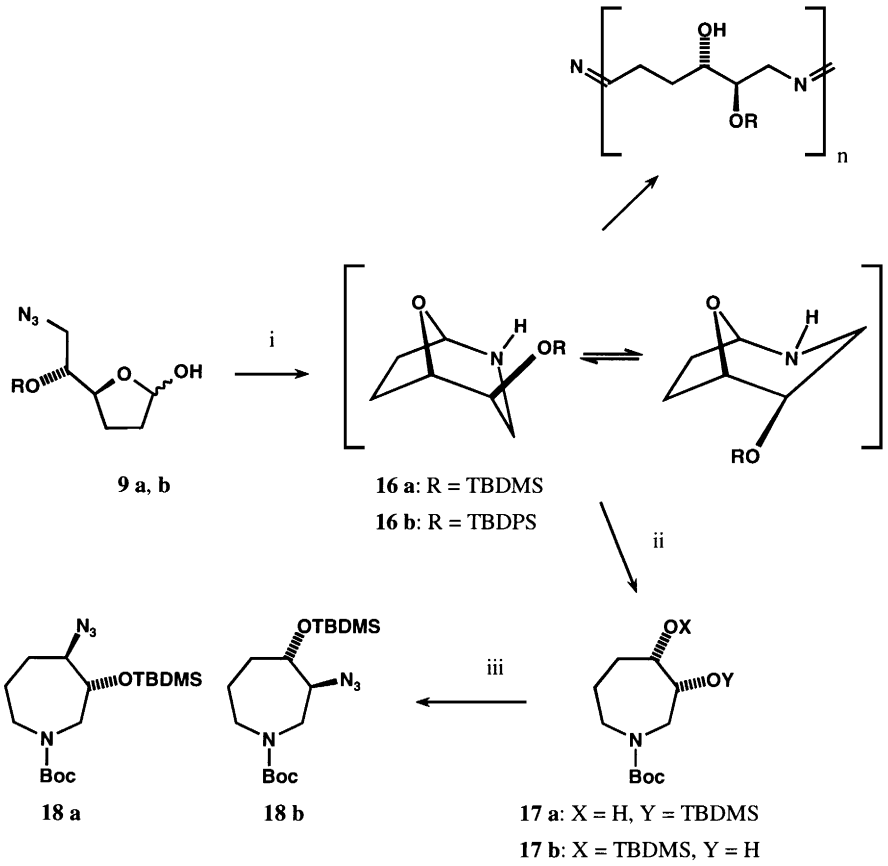
CD_3OD, the catalyst was removed by filtration and the filtrate was submitted to ^{13}C and ^{1}H NMR spectroscopy. The spectra indicated a bicyclic N,O-acetal. Attempts to trap **16a** by the addition of Boc_2O to the reaction mixture either before hydrogenation or thereafter resulted in the formation of complex product mixtures. Similar observations were made during the hydrogenation of **9b**. The resulting bicyclus **17b** solidified more slowly and allowed spectroscopic characterization.

Obviously, the bicyclic N,O-acetals of the (4*S*,5*R*)-diastereomeric series had polymerized after workup and polyimines had been formed. The appearance of a band at 1730 cm^{-1} in the IR spectrum of **17b** within some hours after isolation furnished additional evidence for this hypothesis. Since no polymerization was observed with the bicyclic N,O-acetals of the (4*S*,5*S*)-series, there must be a significant difference in their stability. Most likely, the (4*S*,5*S*)-diastereomers are more stable because the six-membered moiety in the bicyclic system may form a chair conformer with the silyloxy group in an equatorial position, whereas in the (4*S*,5*R*)-diastereomers either a boat-shaped conformer with an equatorially disposed silyloxy group is formed or the bulky substituent is forced into an axial position in a chair-like conformation (Scheme 4).

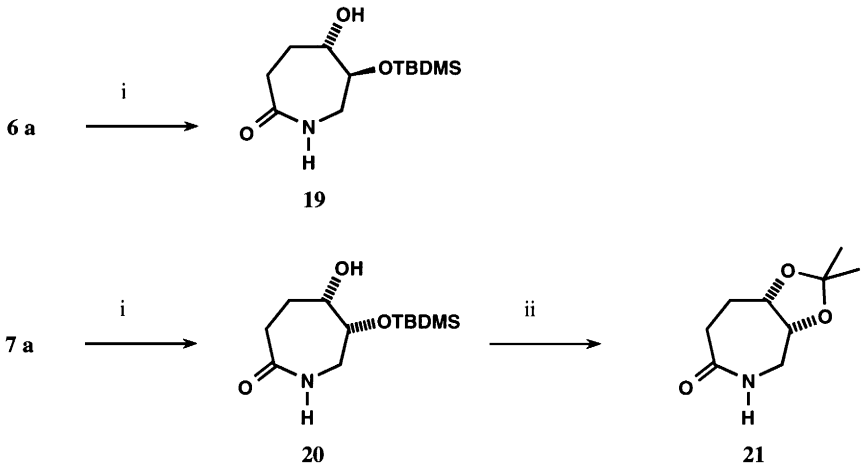
In analogy to **8a**, the complete hydrogenation of **9a** led to a mixture of regioisomeric azepanes that were converted to their *N*-Boc derivatives **17a** and **17b** to facilitate workup and purification (isomeric ratio ~1:1, determined by capillary GC). Unfortunately, this mixture was not separable by column chromatography. Conversion of **17a** and **17b** to the azido azepanes **18a** and **18b** was carried out without isolation of the intermediate mesylates in a two-step sequence. The azepanes **18a** and **18b** were isolated as a chromatographically inseparable mixture (isomeric ratio ~7:3, determined by capillary GC). In analogy to its diastereomer **12b**, the TBDPS protected bicyclus **17b** was unreactive towards further hydrogenation. This behaviour might be explained by the strong steric hindrance of the bulky TBDPS group.

Another approach to seven-membered heterocycles was the reduction of **6a** and **7a** to the corresponding aminolactones that gave the ring enlarged ε-caprolactam[16] derivatives **19** and **20** in aqueous methanol (Scheme 5). Both compounds were crystalline and could be obtained in moderate to good yields.

Since the NMR spectra of **20** exhibited broad signals due to conformational equilibria, the structure



Scheme 4. (i) H_2, 10% Pd/C, MeOH or EtOH, 2.5 h; (ii) H_2, 10% Pd/C, MeOH or EtOH, 7 days, then Boc_2O, 2 h, rt, 69% of isomeric mixture of **17a** and **17b** (1:1); (iii) (a) MsCl, Et_3N, CH_2Cl_2, −20°C, 30 min, (b) NaN_3, DMPU, 80°C, 7 days, 34% of isomeric mixture of **18a** and **18b** (7:3, determined by GC)



Scheme 5. (i) H_2, 10% Pd/C, MeOH/H_2O (9+1), 16–24 h, 65% of **19**, 85% of **20**; (ii) a.) 1 N HCl/MeOH, rt 10 min, (b) $AlCl_3$, acetone, ether, −20°C, 61% of **21**

was elucidated by 600 MHz HMQC and HMBC experiments that provided evidence for the presence of the seven-membered ring system. Furthermore, an X-ray diffraction experiment[17] revealed that, at least in the solid state, a conformation with the bulky OTBDMS group in a quasi-axial position is favoured (Fig. 2). This may be explained by the lipophilic interactions of the neighbouring silyl groups at the edge of each cell and the 'head to head' position of the more polar caprolactam rings in the middle.

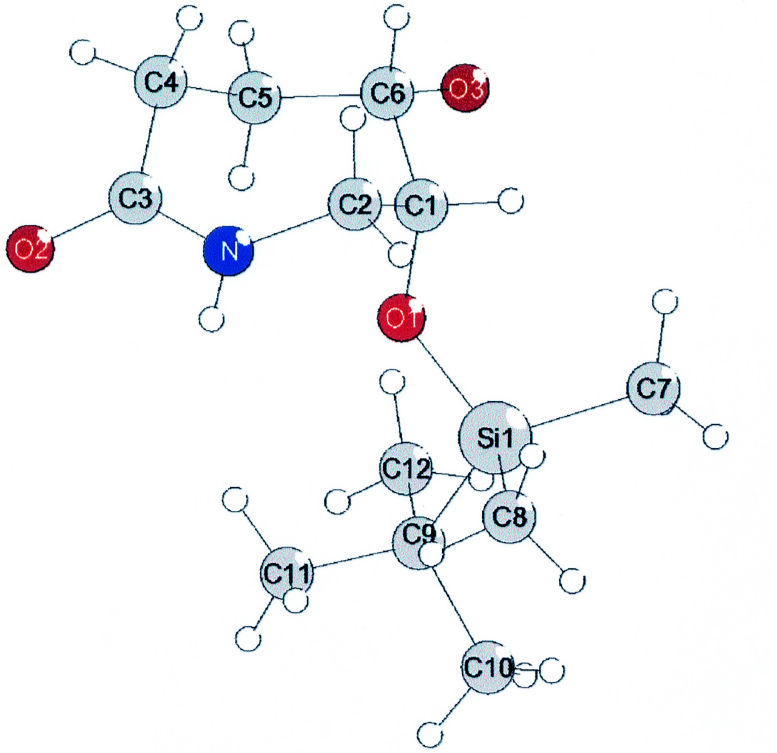


Fig. 2. Crystal structure of the lactam **20**

It proved cumbersome to reduce the lactams **19** and **20** with $BH_3 \cdot SMe_2$ or with $BH_3 \cdot THF$ because the resulting borane–amine complexes were more stable towards hydrolysis than the silyl protecting group. The selective protection of the amide group in the presence of the hydroxy group with Boc_2O and a base caused severe problems, so that this problem could not be overcome. Therefore, we decided to exchange the silyl group in **20** by an isopropylidene moiety. The TBDMS group was then cleaved by 1 M HCl. Since ring contraction occurred under acidic conditions in the free diol, it was immediately exposed to $AlCl_3$ and acetone in ether.[18] Thus, the bicyclic compound **21** was obtained in 61% yield which is a known precursor of (+)- and (−)-balanol.[4g,n,p]

3. Experimental

General procedures: ^{1}H-, HH COSY and ^{13}C-NMR: Bruker AC 200; HMBC and HMQC: Bruker AC 600. Chemical shifts are given referring to the solvent as internal standard. IR spectra: Perkin–Elmer 681. Gas chromatography: Carlo Erba HRGC 5160 Mega Series, Macherey + Nagel Optima 5 column (25 m×0.2 mm ID, 0.1 μm film thickness), helium at 27 cm/s. Retention indices (RI_p) were determined

according to the method of Van den Dool and Kratz[19] referring to a standard of *n*-paraffins C_8–C_{22}. Zone temperatures: inj. 250°C, det. 290°C, oven 60//5/290/20. TLC: Merck silica gel 60 F_{254} plates. Optical rotation: Perkin–Elmer 241. Melting points are uncorrected. Column chromatography: silica gel 60 (0.063–0.2 mm). Petroleum ether (PE) with a boiling range of 30–50°C was used. All reactions were carried out under nitrogen. THF and ether were distilled from potassium sodium couple; acetone from calcium chloride; DMF, dichloromethane and triethylamine from calcium hydride.

3.1. *Silylation of the lactones **2** and **3***

General procedure for the silylation: **2** or **3** and imidazole are dissolved in DMF (abs). The silylating agent is added and the mixture is stirred at ambient temperature for 12 or 24 h. Water is then added followed by extraction with four portions of ether. The combined organic layers are washed with water, dried over Na_2SO_4 and evaporated. The residue is purified by column chromatography and dried at 0.01 mbar for two days.

3.1.1. *6-Bromo-5-*tert*-butyldimethylsilyloxy-2,3,6-trideoxy-*L-threo*-hexono-1,4-lactone **4a** and 5-*tert*-butyldimethylsilyloxy-6-chloro-2,3,6-trideoxy-*L-threo*-hexono-1,4-lactone **4b***

Starting materials: 8.00 g (38.45 mmol) of **2**, 5.76 g (84.60 mmol, 2.2 equivalents) of imidazole, 10.43 g (69.22 mmol, 1.8 equivalents) of *tert*-butyldimethylchlorosilane in 50 ml of DMF; reaction time: 12 h; yield: not determined, the colourless oil contains 11.12 g of an inseparable mixture of the two halogenated silylation products **4a** and **4b** which may be used without further workup; RI_p=1848[a], RI_p=1765[b]; IR (neat): ν (cm^{-1})=1775 (C=O), 1465, 1455, 1250; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm)=−0.54, −0.52 (s, 6H, Si(C*H*$_3$)$_2$), 0.81 (s, 9H, SiC(C*H*$_3$)$_3$), 1.95–2.41 (2H, m, 3-H), 2.44–2.58 (2H, m, 2-H), 3.18–3.58 (2H, m, 6-H), 3.73–3.82 (1H, m, 5-H), 4.68–4.88 (1H, m, 4-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=−4.8, −4.5 (CH_3, Si(*C*H$_3$)$_2$), 17.8, 18.0 (Si*C*(CH$_3$)$_3$), 23.4 (CH_2, C-3[b]), 23.5 (CH_2, C-3[a]), 25.6 (CH_3, SiC(*C*H$_3$)$_3$), 28.1 (CH_2, C-2), 31.5 (CH_2, C-6[a]), 43.4 (CH_2, C-6[b]), 74.1 (CH, C-5[a]), 74.4 (CH, C-5[b]), 78.3 (CH, C-4[b]), 78.6 (CH, C-4[a]), 176.8 (C-1).

3.1.2. *6-Bromo-5-*tert*-butylphenylylsilyloxy-2,3,6-trideoxy-*L-threo*-hexono-1,4-lactone **4c***

Starting materials: 2.51 g (12.00 mmol) of **2**, 2.45 g (36.0 mmol, 3 equivalents) of imidazole and 4.29 g (15.60 mmol, 1.3 equivalents) of *tert*-butyldiphenylchlorosilane in 10 ml of DMF; reaction time: 24 h; purification: column chromatography (Et_2O/PE 1+1, R_f=0.38); yield: 4.03 g (9.01 mmol, 75%) as colourless crystals; mp=76°C; $[\alpha]_D^{20}$=+36.7 (c=2.0, *t*BuOMe); IR (neat): ν (cm^{-1})=3090, 2990, 2860, 1775 (C=O), 1590 (C=C), 1430, 1110; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm)=1.07 (9H, s, SiC(C*H*$_3$)$_3$), 2.03–2.33 (2H, m, 3-H), 2.42–2.73 (2H, m, 2-H), 3.17 (1H, dd, $J_{5,6A}$=3.7, J_{AB}=10.1 Hz, 6-H_A), 3.45 (1H, dd, $J_{5,6B}$=9.0, J_{AB}=10.1 Hz, 6-H_B), 3.85 (1H, ddd, $J_{4,5}$=2.6, $J_{5,6A}$=3.7, $J_{5,6B}$=9.0 Hz, 5-H), 4.92 (1H, ddd, $J_{4,5}$=2.6, $J_{3,4}$=6.1, $J_{3,4}$=8.1 Hz, 4-H), 7.36–7.49 (6H, m, arom.-H), 7.66–7.73 (4H, m, arom.-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=19.3 (Si*C*(CH$_3$)$_3$), 23.2 (CH_2, C-3), 26.8 (CH_3, SiC(*C*H$_3$)$_3$), 28.3 (CH_2, C-2), 31.7 (CH_2, C-6), 74.4 (CH, C-5), 78.9 (CH, C-4), 127.8 (CH), 128.0 (CH), 130.1 (CH), 130.3 (CH), 132.0, 133.0, 135.6 (CH), 176.7 (C-1); $C_{22}H_{27}BrO_3Si$ (447.45); calcd: C 59.06, H 6.08; found: C 59.31, H 6.33.

3.1.3. *6-Bromo-5-*tert*-butyldimethylsilyloxy-2,3,6-trideoxy-*D-erythro*-hexono-1,4-lactone **5a***

Starting materials: 22.51 g (107.7 mmol) of **3**, 16.14 g (237 mmol, 2.2 equivalents) of imidazole, 29.23 g (193.9 mmol, 1.8 equivalents) of *tert*-butyldimethylchlorosilane in 100 ml of DMF; reaction time: 24 h; purification: column chromatography (Et_2O/PE 2+1, R_f=0.54); yield: 32.93 g (102 mmol,

95%) as a colourless oil. RI_p=1829; $[\alpha]_D^{20}$=+0.4 (c=2.3, *t*BuOMe); IR (neat): ν (cm^{-1})=3000, 2940, 1800 (C=O), 1485, 1275, 1200; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm)=0.09 (6H, s, Si(CH_3)$_2$), 0.88 (9H, s, SiC(CH_3)$_3$), 2.14–2.26 (2H, m, 3-H), 2.48–2.57 (2H, m, 2-H), 3.24 (1H, dd, $J_{5,6A}$=7.8, J_{AB}=10.7 Hz, 6-H_A), 3.38 (1H, dd, $J_{5,6B}$=4.4, J_{AB}=10.7 Hz, 6-H_B), 4.10 (1H, ddd, $J_{4,5}$=3.5, $J_{5,6B}$=4.4, $J_{5,6A}$=7.8 Hz, 5-H), 4.80 (1H, dt, $J_{4,5}$=3.5, $J_{3,4}$=7.0 Hz, 4-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=−4.8 (CH_3, Si(CH_3)$_2$), 18.0 (SiC(CH_3)$_3$), 21.0 (CH_2, C-3), 25.6 (CH_3, SiC(CH_3)$_3$), 28.4 (CH_2, C-2), 31.8 (CH_2, C-6), 72.1 (CH, C-5), 79.9 (CH, C-4), 176.8 (C-1); $C_{12}H_{23}BrO_3Si$ (323.31); calcd: C 44.58, H 7.17; found: C 44.43, H 7.23.

*3.1.4. 6-Bromo-5-*tert*-butyldiphenylsilyloxy-2,3,6-trideoxy-*D*-erythro-hexono-1,4-lactone **5b***

Starting materials: 2.51 g (12.00 mmol) of **3**, 2.45 g (36.0 mmol, 3 equivalents) of imidazole and 4.29 g (15.60 mmol, 1.3 equivalents) of *tert*-butyldiphenylchlorosilane in 10 ml of DMF; reaction time: 24 h; purification: column chromatography (Et_2O/PE 1+1, R_f=0.45; yield: 4.35 g (9.72 mmol, 81%) as colourless crystals; mp=121°C; $[\alpha]_D^{20}$=+13.2 (c=1.3, *t*BuOMe); IR (KBr): ν (cm^{-1})=3060, 3080, 2870, 2780, 1785 (C=O), 1590 (C=C), 1430; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm)=1.08 (9H, s, SiC(CH_3)$_3$), 2.14–2.29 (2H, m, 3-H), 2.43–2.53 (2H, m, 2-H), 3.18 (1H, dd, $J_{5,6A}$=6.7, J_{AB}=10.8 Hz, 6-H_A), 3.28 (1H, dd, $J_{5,6B}$=3.5, J_{AB}=10.8 Hz, 6-H_B), 4.02 (1H, ddd, $J_{5,6B}$=3.5, $J_{4,5}$=4.7, $J_{5,6A}$=6.7 Hz, 5-H), 4.80 (1H, dt, $J_{4,5}$=4.7, $J_{3,4}$=7.1 Hz, 4-H), 7.37–7.48 (6H, m, arom.-H), 7.66–7.72 (4H, m, arom.-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=19.3 (SiC(CH_3)$_3$), 22.1 (CH_2, C-3), 26.9 (CH_3, SiC(CH_3)$_3$), 28.3 (CH_2, C-2), 32.8 (CH_2, C-6), 72.2 (CH, C-5), 79.9 (CH, C-4), 127.9 (CH), 128.0 (CH), 130.2 (CH), 130.3 (CH), 132.1, 133.2, 135.8 (CH), 135.9 (CH), 176.5 (C-1); $C_{22}H_{27}BrO_3Si$ (447.50); calcd: C 59.06, H 6.08; found: C 58.75, H 6.06.

3.2. Introduction of the azido group

General procedure for the introduction of the azido group: The silylated bromolactone (**4** or **5**) is dissolved in dry DMF. LiN_3 is added. The mixture is stirred at 60°C until complete conversion has occurred. The reaction is monitored by GC. If necessary, another portion of about 1.4 equivalents of lithium azide is added after some hours. Then water is added and the mixture is extracted with ether. The combined organic extracts are dried over Na_2SO_4 and purified by column chromatography.

*3.2.1. 6-Azido-5-*tert*-butyldimethylsilyloxy-2,3,6-trideoxy-*L*-threo-hexono-1,4-lactone **6a***

Starting materials: 11.12 g of a mixture of **4a** and **4b**, 2×2.64 g (54 mmol) of lithium azide in 50 ml of DMF; reaction time: 26 h; column chromatography: EtOAc/PE 1+2 (R_f=0.45); yield: 8.13 g (28.48 mmol, 74% over two steps from compound **2**) of **6a** as a colourless oil; RI_p=1860; $[\alpha]_D^{20}$=+30.17 (c=1.1, MeOH); IR (neat): ν (cm^{-1})=2100 (N_3), 1780 (C=O), 1120; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 0.07 (6H, s, Si(CH_3)$_2$), 0.85 (9H, s, SiC(CH_3)$_3$), 1.97–2.37 (2H, m, 3-H), 2.45–2.52 (2H, m, 2-H), 3.24 (1H, dd, $J_{5,6A}$=5.4, J_{AB}=12.4 Hz, 6-H_A), 3.45 (1H, dd, $J_{5,6B}$=6.2, J_{AB}=12.4 Hz), 3.72 (1H, ddd, $J_{4,5}$=3.8, $J_{5,6A}$=5.4, $J_{5,6B}$=6.2 Hz, 5-H), 4.56 (1H, ddd, $J_{4,5}$=3.8, $J_{3A,4}$=6.2, $J_{3B,4}$=6.6 Hz, 4-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=−4.9, −4.8 (CH_3, Si(CH_3)$_2$), 17.8 (SiC(CH_3)$_3$), 23.3 (CH_2, C-3), 25.5 (CH_3, SiC(CH_3)$_3$), 28.1 (CH_2, C-2), 52.8 (CH_2, C-6), 72.9 (CH, C-5), 79.7 (CH, C-4), 176.6 (C-1); $C_{12}H_{23}N_3O_3Si$ (285.47); calcd: C 50.49, H 8.12, N 14.72; found: C 50.43, H 8.00, N 14.64.

*3.2.2. 6-Azido-5-*tert*-butyldiphenylsilyloxy-2,3,6-trideoxy-*L*-threo-hexono-1,4-lactone **6b***

Starting materials: 3.49 g (7.80 mmol) of **4c**, 527 mg (10.76 mmol, 1.4 equivalents) of LiN_3 in 10 ml of DMF; reaction time: 20 h; column chromatography: Et_2O/PE 1+1 (R_f=0.0.28); yield: 2.90 g (7.08

mmol, 91%) as a colourless oil; $[\alpha]_D^{20}$=+39.8 (c=0.8, *t*BuOMe); IR (neat): ν (cm^{-1})=3090, 2950, 2880, 2110 (N_3), 1775 (C=O), 1590 (C=C), 1430, 1110; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm)=1.07 (9H, s, SiC(C*H*$_3$)$_3$), 2.09–2.23 (2H, m, 3-H), 2.39–2.62 (2H, m, 2-H), 3.19 (1H, dd, $J_{5,6A}$=4.6, J_{AB}=12.3 Hz, 6-H_A), 3.44 (1H, dd, $J_{5,6B}$=7.4, J_{AB}=12.3 Hz, 6-H_B), 3.77 (1H, ddd, $J_{4,5}$=3.3, $J_{5,6A}$=4.6, $J_{5,6B}$=7.4 Hz, 5-H), 4.61 (1H, ddd, $J_{4,5}$=3.3, $J_{3,4}$=6.8, $J_{3,4}$=7.6 Hz, 4-H), 7.34–7.43 (6H, m, arom.-H), 7.66–7.73 (4H, m, arom.-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ (ppm)=19.4 (Si*C*(CH$_3$)$_3$), 23.1 (CH_2, C-3), 26.8 (CH_3, SiC(*C*H$_3$)$_3$), 28.3 (CH_2, C-2), 52.3 (CH_2, C-6), 73.1 (CH, C-5), 79.3 (CH, C-4), 127.9 (CH), 128.0 (CH), 130.1 (CH), 130.2 (CH), 132.2, 133.0, 135.7 (CH), 135.8 (CH), 176.7 (C-1); $C_{22}H_{27}N_3O_3Si$ (409.56); calcd: C 64.52, H 6.64, N 10.26; found: C 64.33, H 6.83, N 9.89.

*3.2.3. 6-Azido-5-*tert*-butyldimethylsilyloxy-2,3,6-trideoxy-*D*-erythro-hexono-1,4-lactone **7a***

Starting materials: 19.35 g (59.85 mmol) of **5a**, 4.11 g (84 mmol, 1.4 equivalents) of LiN_3 in 50 ml of DMF; reaction time: 20 h; column chromatography: Et_2O/PE 2+1 (R_f=0.40); yield: 10.39 g (39.89 mmol, 67%) as a colourless oil; RI_p=1864; $[\alpha]_D^{20}$=+5.6 (c=0.9, *t*BuOMe); IR (neat): ν (cm^{-1})=2970, 2890, 2100 (N_3), 1800 (C=O), 1480, 1280, 1190; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm)=0.09, 0.13 (6H, 2s, Si(C*H*$_3$)$_2$), 0.88 (9H, s, SiC(C*H*$_3$)$_3$), 2.16–2.35 (2H, m, 3-H), 2.48–2.56 (2H, m, 2-H), 3.26 (1H, dd, $J_{5,6A}$=5.0, J_{AB}=12.8 Hz, 6-H_A), 3.39 (1H, dd, $J_{5,6B}$=5.2, J_{AB}=12.8 Hz, 6-H_B), 4.00 (1H, ddd, $J_{4,5}$=3.9, $J_{5,6A}$=5.0, $J_{5,6B}$=5.2 Hz, 5-H), 4.52 (1H, dt, $J_{4,5}$=3.9, $J_{3,4}$=7.2 Hz, 4-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ (ppm)=−4.8, −4.7 (CH_3, Si(*C*H$_3$)$_2$), 17.9 (Si*C*(CH$_3$)$_3$), 21.9 (CH_2, C-3), 25.6 (CH_3, SiC(*C*H$_3$)$_3$), 28.4 (CH_2, C-2), 53.5 (CH_2, C-6), 71.7 (CH, C-5), 80.1 (CH, C-4), 176.6 (C-1); $C_{12}H_{23}N_3O_3Si$ (285.42); calcd: C 50.50, H 8.12, N 14.72; found: C 50.34, H 7.83, N 14.96.

*3.2.4. 6-Azido-5-*tert*-butyldiphenylsilyloxy-2,3,6-trideoxy-*D*-erythro-hexono-1,4-lactone **7b***

Starting materials: 4.13 g (9.23 mmol) of **5b**, 625 mg (12.75 mmol, 1.4 equivalents) of LiN_3 in 10 ml of DMF; reaction time: 20 h; column chromatography: Et_2O/PE 1+1 (R_f=0.33); yield: 3.50 g (8.42 mmol, 93%) as a colourless oil; $[\alpha]_D^{20}$=+7.9 (c=2.3, *t*BuOMe); IR (neat): ν (cm^{-1})=3090, 2950, 2870, 2120 (N_3), 1775 (C=O), 1590 (C=C), 1110; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm)=1.09 (9H, s, SiC(C*H*$_3$)$_3$), 2.15–2.28 (2H, m, 3-H), 2.42–2.53 (2H, m, 2-H), 3.21 (1H, dd, $J_{5,6A}$=4.5, J_{AB}=13.0 Hz, 6-H_A), 3.30 (1H, dd, $J_{5,6B}$=4.5, J_{AB}=13.0 Hz, 6-H_B), 3.97 (1H, td, $J_{5,6}$=4.5, $J_{4,5}$=4.7 Hz, 5-H), 4.59 (dt, $J_{4,5}$=4.7, $J_{3,4}$=7.2 Hz, 4-H), 7.38–7.48 (6H, m, arom.-H), 7.69–7.75 (4H, m, arom.-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=19.2 (Si*C*(CH$_3$)$_3$), 22.5 (CH_2, C-3), 26.8 (CH_3, SiC(*C*H$_3$)$_3$), 28.1 (CH_2, C-2), 52.7 (CH_2, C-6), 72.2 (CH, C-5), 79.8 (CH, C-4), 127.8 (CH), 128.8 (CH), 130.1 (CH), 130.2 (CH), 131.9, 133.0, 135.7 (CH), 136.2 (CH), 176.7 (C-1); $C_{22}H_{27}N_3O_3Si$ (409.56); calcd: C 64.52, H 6.64, N 10.26; found: C 64.43, H 6.39, N 9.80.

3.3. Reduction of lactones to lactols with DIBAH

General procedure for the reduction with DIBAH: The azidolactones **6a**, **6b**, **7a**, or **7b** are dissolved in THF (abs), cooled to –78°C and a solution of DIBAH is added. The mixture is kept at –78°C. The reaction is monitored by capillary GC (for the compounds **8a** and **9a**) or by IR spectroscopy (for **8b** and **9b**). Reaction times are variable and depend strongly on the quality of DIBAH. If the reaction is not complete after 40 minutes, another portion of DIBAH is added and the mixture is stirred at –78°C until no more starting material can be detected. Then water is added very carefully at –78 to −60°C, the mixture is warmed to room temperature, acidified with 2 M HCl and extracted with five portions of dichloromethane. The combined organic extracts are washed twice with satd $NaHCO_3$, dried over

Na_2SO_4 and the solvent is distilled. The residue is purified by filtration over silica gel or by column chromatography.

3.3.1. 6-Azido-5-tert-*butyldiphenylsilyloxy-2,3,6-trideoxy*-D-threo-*hexofuranose* ***8a***

Starting materials: 8.13 g (28.48 mmol) of **6a**, 38 ml (38 mmol, 1.33 equivalents)+20 ml (20 mmol, 0.70 equivalents) of DIBAH (1 M in hexane) in 40 ml of THF; reaction time: 130 min; purification: filtration over silica gel (Et_2O); yield: 7.03 g (24.47 mmol, 86%) as a colourless oil; RI_p=1764; IR (neat): ν (cm^{-1})=3400 (OH), 2100 (N_3), 1255, 1110; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm)=0.12 (6H, s, Si(C*H*$_3$)$_2$), 0.90 (9H, s, SiC(C*H*$_3$)$_3$), 1.69–2.06 (4H, m, 2-H, 3-H), 3.10–3.41 (2H, m, 6-H), 3.49–3.58 (1H, m), 3.66–3.77 (1H, m), 4.17–4.28 (1H, m, 4-H), 5.37–5.52 (1H, m, O*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=−4.7, −4.8 (CH_3, Si(*C*H$_3$)$_2$), 18.0 (Si*C*(CH$_3$)$_3$) 23.9, 25.7 (CH_2, C-3), 25.7 (CH_3, SiC(*C*H$_3$)$_3$), 33.3, 34.4 (CH_2, C-2), 53.6, 53.9 (CH_2, C-6), 73.1, 73.2 (CH, C-5), 78.9, 80.4 (CH, C-4), 98.4, 98.7 (CH, C-1); $C_{12}H_{25}N_3O_3Si$ (287.44); calcd: C 50.14, H 8.77, N 14.62; found: C 50.10, H 8.81, N 15.06.

3.3.2. 6-Azido-5-tert-*butyldiphenylsilyloxy-2,3,6-trideoxy*-D-threo-*hexofuranose* ***8b***

Starting materials: 2.83 g (6.91 mmol) of **6b**, 9.0 ml (9.0 mmol, 1.3 equivalents)+3×4.1 ml (4.1 mmol, 0.6 equivalents) of DIBAH (1 M in CH_2Cl_2) in 20 ml of THF; reaction time: ca. 5 h; purification: column chromatography (Et_2O/PE 1+1, R_f=0.43); yield: 980 mg (2.38 mmol, 34%) as a colourless oil; IR (neat): ν (cm^{-1})=3420 (OH), 3090, 2950, 2100 (N_3), 1590 (C=C), 1430; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm)=1.10 (9H, s, SiC(C*H*$_3$)$_3$), 1.69–2.05 (4H, m, 2-H, 3-H), 3.08–3.59 (2H, m, 6-H), 3.69–3.83 (1H, m, 5-H), 4.20–4.31 (1H, m, 4-H), 5.24–5.48 (1H, m, 1-H), 7.26–7.48 (6H, m, arom.-H), 7.69–7.79 (4H, m, arom.-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=19.4 (Si*C*(CH$_3$)$_3$), 24.1, 24.6 (CH_2, C-3), 33.0, 34.2 (CH_2, C-2), 53.1, 53.4 (CH_2, C-6), 75.2, 75.5 (CH, C-5), 78.5, 80.5 (CH, C-4), 98.1, 98.7 (CH, C-1), 127.7 (CH), 129.8 (CH), 129.9 (CH), 133.0, 133.7, 135.9 (CH), 135.1 (CH); $C_{22}H_{29}N_3O_3Si$ (411.58); calcd: C 64.20, H 7.10, N 10.21; found: C 64.34, H 6.85, N 9.32.

3.3.3. 6-Azido-5-tert-*butyldimethylsilyloxy-2,3,6-trideoxy*-D-erythro-*hexofuranose* ***9a***

Starting materials: 9.34 g (32.70 mmol) of **7a**, 42.5 ml (42.5 mmol, 1.3 equivalents)+19.6 ml (19.6 mmol, 0.6 equivalents) of DIBAH (1 M in hexane); reaction time: 5 h; purification: column chromatography (Et_2O/PE 2+1, R_f=0.48); yield: 7.85 g (27.29 mmol, 83%) as a colourless oil; RI_p=1766; IR (neat): ν (cm^{-1})=3370 (OH), 2900, 2830, 2100 (N_3), 1440, 1235; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm)=0.05, 0.08, 0.10 (6H, s, Si(C*H*$_3$)$_2$), 0.88 (9H, s, SiC(C*H*$_3$)$_3$), 1.77–2.23 (4H, m, 2-H, 3-H), 3.13–3.52 (2H, m, 6-H), 3.69–3.76 (1H, m, 5-H), 3.99–4.23 (1H, m, 4-H), 5.43–5.51 (1H, m, 1-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=−4.7, −4.6, −4.3 (CH_3, Si(*C*H$_3$)$_2$), 17.9 (Si*C*(CH$_3$)$_3$), 24.4, 26.5 (CH_2, C-3), 25.7 (CH_3, SiC(*C*H$_3$)$_3$), 32.7, 33.4 (CH_2, C-2), 54.5, 54.6 (CH_2, C-6), 73.0, 75.0 (CH, C-5), 79.0, 80.5 (CH, C-4), 98.4, 98.5 (CH, C-1); $C_{12}H_{35}N_3O_3Si$ (287.44); calcd: C 50.14, H 8.77, N 14.62; found: C 49.94, H 8.73, N 14.46.

3.3.4. 6-Azido-5-tert-*butyldiphenylsilyloxy-2,3,6-trideoxy*-D-erythro-*hexofuranose* ***9b***

Starting materials: 3.42 g (8.36 mmol) of **7b**, 10.9 ml (10.9 mmol, 1.3 equivalents)+3×5.0 (5.0 mmol, 0.6 equivalents) of DIBAH (1 M in CH_2Cl_2) in 20 ml of THF; reaction time: 6.5 h; purification: column chromatography (Et_2O/PE 1+1, R_f=0.41); yield: 2.36 g (5.73 mmol, 69%) as a colourless oil; IR (neat): ν (cm^{-1})=3400 (OH), 3090, 2950, 2110 (N_3), 1596 (C=C), 1430; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm)=1.09 (9H, s, SiC(C*H*$_3$)$_3$), 1.71–2.09 (4H, m, 2-H, 3-H), 2.86–3.39 (2H, m, 6-H), 3.67–3.81 (1H, m, 5-H), 4.11–4.33 (1H, m, 4-H), 5.40–5.43 (1H, m, 1-H), 7.26–7.46 (6H, m, arom.-H), 7.66–7.76 (4H,

m, arom.-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=19.3 (Si*C*$(CH_3)_3$), 24.9, 26.9 (CH_2, C-3), 26.9 (CH_3, SiC(*C*$H_3)_3$), 32.5, 33.4 (CH_2, C-2), 53.8, 54.0 (CH_2, C-6), 73.4, 75.1 (CH, C-5), 78.9, 80.6 (CH, C-4), 98.4, 98.5 (CH, C-1), 127.7 (CH), 127.8 (CH), 129.8 (CH), 133.0, 133.2, 133.4, 135.8 (CH), 135.9 (CH); $C_{22}H_{29}N_3O_3Si$ (411.58); calcd: C 64.20, H 7.10, N 10.21; found: C 64.15, H 6.98, N 9.40.

*3.4. Ethyl (6*S*,7*S*)-8-azido-7-*tert*-butyldimethylsilyloxy-6-hydroxy-oct-2-enoate* ***10***

A mixture of 240 mg (0.83 mmol) of **8a** and 291 mg (0.83 mmol, 1 equivalent) of triphenylcarbethoxymethylenphosphorane in 5 ml of toluene is stirred at ambient temperature for 48 h. Then the solvent is distilled in vacuo at room temperature and the residue is purified by column chromatography (EtOAc/PE 1+2). 276 mg (0.77 mmol, 93%) of **10** are isolated as a colourless oil (R_f=0.48); $[\alpha]_D^{20}$=−20.6 (c=1.2, MeOH); IR (neat): ν (cm^{-1})=2100 (N_3), 1720 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm)=0.07 (6H, s, Si(C*H*$_3)_2$), 0.91 (9H, s, SiC(C*H*$_3)_3$), 1.25 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.51–1.65 (2H, m, 5-H), 2.17–2.48 (2H, m, 4-H), 3.24 (1H, dd, $J_{7,8A}$=5.4, J_{AB}=12.3 Hz, 8-H_A), 3.46 (1H, dd, $J_{7,8B}$=5.5, J_{AB}=12.3 Hz, 8-H_B), 3.54–3.64 (2H, m, 6-H, 7-H), 4.16 (2H, q, J=7.1, OCH_2CH_3), 5.83 (1H, dt, $J_{2,4}$=1.5, $J_{2,3}$=15.6 Hz, 2-H), 6.95 (1H, dt, $J_{3,4}$=7.0, $J_{2,3}$=15.6 Hz, 3-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=−4.8 (CH_3, Si(*C*$H_3)_2$), 14.2 (CH_3, OCH_2CH_3), 18.0 (Si*C*$(CH_3)_3$), 25.7 (CH_3, SiC(*C*$H_3)_3$), 28.6 (CH_2, C-5), 32.1 (CH_2, C-4), 53.7 (CH_2, OCH_2CH_3), 60.1 (CH_2, C-8), 71.1 (CH, C-7), 73.9 (CH, C-6), 121.8 (CH, C-2), 148.2 (CH, C-3), 166.5 (C-1); $C_{16}H_{31}N_3O_4Si$ (357.53); calcd: C 53.75, H 8.74, N 11.75; found: C 53.48, H 8.54, N 15.06.

*3.5. Ethyl (6*S*,7*R*)-8-azido-7-*tert*-butyldimethylsilyloxy-6-hydroxy-oct-2-enoate* ***11***

The compound is synthesized according to the procedure described for **10** starting from 230 mg (0.80 mmol) of **9a** and 279 mg (0.80 mmol, 1 equivalent) of triphenylcarbethoxymethylenphosphorane in 5 ml of toluene; column chromatography: Et_2O/PE 2+1 (R_f=0.53), yield: 243 mg (0.68 mmol, 85%) as a colourless oil; RI_p=1864; $[\alpha]_D^{20}$=−1.4 (c=1.0, *t*BuOMe); IR (neat): ν (cm^{-1})=3450 (OH), 2890, 2820, 2080 (N_3), 1700 (C=O), 1630 (C=C), 1230; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm)=0.09, 0.13 (6H, s, Si(C*H*$_3)_2$), 0.90 (9H, s, SiC(C*H*$_3)_3$), 1.26 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.41–1.69 (2H, m, 5-H), 2.16–2.51 (2H, m, 4-H), 3.20–3.39 (2H, m, 8-H), 3.54–3.76 (2H, m, 6-H, 7-H), 4.16 (2H, q, J=7.1, OCH_2CH_3), 5.82 (1H, dt, $J_{2,4}$=1.5, $J_{2,3}$=15.6 Hz, 2-H), 6.95 (1H, dt, $J_{3,4}$=7.0, $J_{2,3}$=15.6 Hz, 3-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=−4.9, −4.6 (CH_3, Si(*C*$H_3)_2$), 14.2 (CH_3, OCH_2CH_3), 17.9 (Si*C*$(CH_3)_3$), 25.7 (CH_3, SiC(*C*$H_3)_3$), 28.7 (CH_2, C-5), 30.6 (CH_2, C-4), 52.8 (CH_2, OCH_2CH_3), 60.2 (CH_2, C-8), 72.5 (CH, C-7), 74.5 (CH, C-6), 121.8 (CH, C-2), 148.1 (CH, C-3), 166.5 (C-1); $C_{16}H_{31}N_3O_3Si$ (357.53); calcd: C 53.75, H 8.74, N 11.75; found: C 53.84, H 8.64, N 10.75.

*3.6. (1*R*,4*S*,5*S*)-4-*tert*-Butyldimethylsilyloxy-2-aza-8-oxabicyclo[3,2,1]octane* ***12a***

8a (1.40 g, 4.87 mmol) is dissolved in 60 ml of ethanol and hydrogenated at 30 bar in the presence of 200 mg 10% Pd/C over 2.5 h at ambient temperature. The catalyst is then removed by filtration, the solvent is distilled and the residue is purified by column chromatography (EtOAc/MeOH 9+1, R_f=0.37); yield: 1.08 g (4.44 mmol, 91%) as a colourless oil; RI_p=1546; $[\alpha]_D^{20}$=−12.8 (c=0.89, Et_2O); IR (neat): ν (cm^{-1})=2100 (N_3), 1720 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$) COSY: δ (ppm)=0.06 (6H, s, Si(C*H*$_3)_2$), 0.88 (9H, s, SiC(C*H*$_3)_3$), 1.61–2.13 (4H, m, 6-H, 7-H), 2.64 (1H, dd, $J_{3A,4}$=10.0, J_{AB}=14.1 Hz, 3-H_A), 2.89 (1H, dd, $J_{3B,4}$=6.0, J_{AB}=14.1 Hz, 3-H_B), 3.60–3.73 (1H, m, 4-H), 4.18 (1H, ddd, J=1.2, J=4.2, J=5.4 Hz, 5-H), 4.93 (1H, d, $J_{1,7}$=5.8 Hz, 1-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=−4.7 (CH_3,

Si(CH_3)$_2$), 18.0 (SiC(CH_3)$_3$), 22.8 (CH_2, C-6), 25.7 (CH_3, SiC(CH_3)$_3$), 28.1 (CH_2, C-7), 44.5 (CH_2, C-3), 66.5 (CH, C-4), 78.1 (CH, C-5), 85.9 (CH, C-1); $C_{12}H_{25}NO_2Si$ (243.42); calcd: C 59.21, H 10.35, N 5.75; found: C 59.02, H 10.09, N 5.92.

3.7. (1R,4S,5S)-4-tert-Butyldiphenylsilyloxy-2-aza-8-oxabicyclo[3,2,1]octane **12b**

8b (505 mg, 1.23 mmol) is reacted according to the method described for **12a** using 30 mg of 10% Pd/C in 12 ml of ethanol; reaction time: 34 h at 50 bar; column chromatography: EtOAc/MeOH 9+1 (R_f=0.51); yield: 298 mg (0.81 mmol, 67%) as a colourless oil; $[\alpha]_D^{20}$=+4.6 (c=1.0, MeOH); IR (neat): ν (cm^{-1})=3340 (NH), 3080, 2960, 1595 (C=C), 1475; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm)=1.07 (9H, s, SiC(CH_3)$_3$), 1.80–2.34 (4H, m, 6-H, 7-H), 2.75–2.80 (2H, m, 3-H), 3.73 (1H, ddd, J=3.8, J=7.2, J=8.4 Hz, 4-H), 4.15–4.21 (1H, m, 5-H), 4.87 (1H, d, J=5.3 Hz, 1-H), 7.33–7.48 (6H, m, arom.-H), 7.62–7.67 (4H, m, arom.-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=19.1 (SiC(CH_3)$_3$), 23.0 (CH_2, C-6), 26.9 (CH_3, SiC(CH_3)$_3$), 28.1 (CH_2, C-7), 44.3 (CH_2, C-3), 67.0 (CH, C-4), 77.6 (CH, C-5), 85.9 (CH, C-1), 127.6 (CH), 129.8 (CH), 133.8, 133.9, 136.6 (CH); $C_{22}H_{29}NO_2Si$ (367.57); calcd: C 71.99, H 7.95, N 3.81; found: C 71.66, H 7.90, N 3.66.

3.8. (3S,4S)-3-tert-Butyldimethylsilyloxy-4-hydroxyazepane **13a** and (3S,4S)-4-tert-butyldimethylsilyloxy-3-hydroxyazepane **13b**

8a (520 mg, 1.81 mmol) is hydrogenated at room temperature in the presence of 120 mg of 10% Pd/C in 20 ml of methanol at a pressure of 50 bar. After 7 days the catalyst is removed by filtration, the solvent is distilled and the residue is submitted to Kugelrohr distillation (oven temperature: 100–250°C, 0.05 mbar); yield: 340 mg (1.39 mmol, 77%) of a mixture of **13a** and **13b** as colourless crystals; RI_p=1610[b], RI_p=1621[a]; mp=85°C; IR (KBr): ν (cm^{-1})=3300 (OH, NH), 1480, 1270; ^{1}H NMR (200 MHz, CD_3OD): δ (ppm)=0.21 (6H, s, Si(CH_3)$_2$), 1.07 (9H, s, SiC(CH_3)$_3$), 1.63–2.12 (4H, m, 5-H, 6-H), 2.70–3.06 (4H, m, 2-H, 7-H), 3.68–3.97 (2H, m, 3-H, 4-H); ^{13}C NMR (50.3 MHz, CD_3OD) DEPT: δ (ppm)=−4.7, −4.6, −4.4 (CH_3, Si(CH_3)$_2$), 18.9 (SiC(CH_3)$_3$), 22.5, 23.0 (CH_2, C-6), 26.4 (CH_3, SiC(CH_3)$_3$), 29.8, 30.0 (CH_2, C-5), 47.9, 48.6, 48.9 (CH_2, C-2 and C-7), 74.7, 75.2, 73.3, 77.0 (CH, C-3, C-4); $C_{12}H_{27}NO_2Si$ (245.44); calcd: C 58.72, H 11.09, N 5.74; found: C 58.78, H 10.71, N 5.61.

3.9. (3S,4S)-3-tert-Butyldimethylsilyloxy-1-tert-butoxycarbonyl-4-hydroxyazepane **14a** and (3S,4S)-4-tert-butyldimethylsilyloxy-1-tert-butoxycarbonyl-3-hydroxyazepane **14b**

12a (2.19 g, 8.98 mmol) is dissolved in 50 ml of ethanol p.a. and hydrogenated over 7 days in the presence of 200 mg of 10% Pd/C at room temperature. The catalyst is removed by filtration, 2.38 g (10.88 mmol, 1.2 equivalents) of di-*tert*-butyldicarboxylate are added and the mixture is stirred for 2 h until the evolution of gas ceases. The solvent is distilled and the residue is purified by column chromatography (Et_2O/PE 1+1). 1.71 g (4.95 mmol, 55%) of **14a** are obtained as a colourless oil (R_f=0.34); 399 mg (1.15 mmol, 13%) of **14b** are obtained as a colourless oil (R_f=0.48).

14a: RI_p=1975; $[\alpha]_D^{20}$=−6.4 (c=1, *t*BuOMe); IR (neat): ν (cm^{-1})=3500 (OH), 2950, 2900, 1700 (C=O), 1430, 1180; ^{1}H NMR (200 MHz, [D_6]DMSO, 353 K): δ (ppm)=0.18 (6H, s, Si(CH_3)$_2$), 0.98 (9H, s, SiC(CH_3)$_3$), 1.58 (9H, s, CO_2C(CH_3)$_3$), 1.59–1.93 (4H, m, 5-H, 6-H), 3.10–3.21 (2H, m, 7-H), 3.48–3.55 (2H, m, 2-H), 3.59–3.69 (2H, m, 3-H, 4-H), 4.22 (1H, d, J=4.4 Hz, OH); ^{13}C NMR (50.3 MHz, [D_6]DMSO, 353 K): δ (ppm)=−4.6, −4.4 (CH_3, Si(CH_3)$_2$), 17.9 (SiC(CH_3)$_3$), 21.4 (CH_2, C-6), 26.0 (CH_3, SiC(CH_3)$_3$), 28.4 (CH_3, CO_2C(CH_3)$_3$), 30.2 (CH_2, C-5), 46.3 (CH_2, C-7), 47.6 (CH_2, C-

2), 74.5 (CH), 75.2 (CH), 78.5 ($CO_2C(CH_3)_3$), 154.9 ($CO_2C(CH_3)_3$); $C_{17}H_{35}NO_4Si$ (345.56); calcd: C 59.05, H 10.21, N 4.05; found: C 58.74, H 9.92, N 3.84.

14b: RI_p=1982; $[\alpha]_D^{20}$=−16.4 (c=1.0, *t*BuOMe); IR (neat): ν (cm^{-1})=3450 (OH), 2960, 2860, 1680 (C=O), 1420, 1255; ^{1}H NMR (200 MHz, [D_6]DMSO, 353 K): δ (ppm)=0.15 (6H, s, $Si(CH_3)_2$), 0.98 (9H, s, $SiC(CH_3)_3$), 1.50 (9H, s, $CO_2C(CH_3)_3$), 1.62–1.92 (4H, m, 5-H, 6-H), 3.18–3.30, 3.45–3.64 (4H, m, 2-H, 7-H), 3.71–3.78 (1H, m, 4-H), 4.30–4.31 (1H, m, 3-H); ^{13}C NMR (50.3 MHz, [D_6]DMSO, 353 K) DEPT: δ (ppm)=−5.9, −5.7 (CH_3, $Si(CH_3)_2$), 17.0 ($SiC(CH_3)_3$), 20.4 (CH_2, C-6), 24.7 (CH_3, $SiC(CH_3)_3$), 27.1 (CH_3, $CO_2C(CH_3)_3$), 28.7 (CH_2, C-5), 45.2, 46.9 (CH_2, C-2 and C-7), 72.3, 74.4 (CH, C-3 and C-4), 77.3 ($CO_2C(CH_3)_3$), 158.5 ($CO_2C(CH_3)_3$); $C_{17}H_{35}NO_4Si$ (345.56); calcd: C 59.05, H 10.21, N 4.05; found: C 58.97, H 9.84, N 4.13.

*3.10. (3*S*,4*R*)-4-Azido-3-*tert*-butyldimethylsilyloxy-1-*tert*-butoxycarbonylazepane* ***15a***

14a (1.0 g, 2.89 mmol) and 1.2 ml (8.67 mmol, 3 equivalents) of triethylamine in 20 ml of dichloromethane are cooled to –20°C. Mesyl chloride (270 μl, 3.47 mmol, 1.2 equivalents) is slowly added. The mixture is stirred for 20 min at −20°C, then it is warmed to room temperature. Water is added followed by extraction with 3 portions of ether. The combined organic extracts are dried (Na_2SO_4), the solvent is distilled and the residue is purified by column chromatography (Et_2O, R_f=0.65). The resulting pale yellow oil (1.06 g, 2.50 mmol) is dissolved in 5 ml of DMPU and 813 mg (12.50 mmol, 5 equivalents) of NaN_3 are added. The mixture is heated to 80°C for 7 days under intense magnetic stirring. Then water is added, the mixture is extracted with two portions of ether, the combined organic extracts are dried over Na_2SO_4 and the solvent is distilled. The residue is purified by column chromatography (Et_2O/PE 1+4, R_f=0.38). Yield: 525 mg (1.42 mmol, 57%) as a colourless oil; RI_p=2084; $[\alpha]_D^{20}$=−24 (c=1.0, *t*BuOMe); IR (neat): ν (cm^{-1})=2950, 2880, 2100 (N_3), 1695 (C=O), 1420, 1260; ^{1}H NMR (200 MHz, [D_6]DMSO, 353 K): δ (ppm)=0.22 (6H, s, $Si(CH_3)_2$), 0.99 (9H, s, $SiC(CH_3)_3$), 1.58 (9H, s, $CO_2C(CH_3)_3$), 1.60–2.07 (4H, m, 5-H, 6-H), 3.10–3.34 (2H, m, 7-H), 3.58–3.74 (2H, m, 2-H), 3.83–3.87 (1H, m, 4-H), 4.03–4.11 (1H, m, 3-H); ^{13}C NMR (50.3 MHz, [D_6]DMSO, 353 K): δ (ppm)=−4.9, −4.7 ($Si(CH_3)_2$), 17.7 ($SiC(CH_3)_3$), 22.2 (C-6), 25.8 (C-5, $SiC(CH_3)_3$), 46.2, 48.0 (C-2, C-7), 65.1 (C-4), 73.5 (C-3), 79.0 ($CO_2C(CH_3)_3$), 154.7 ($CO_2C(CH_3)_3$); $C_{17}H_{34}N_4O_3Si$ (370.57); calcd: C 55.10, H 9.25, N 15.12; found: C 55.32, H 9.00, N 14.84.

*3.11. (3*R*,4*S*)-3-Azido-4-*tert*-butyldimethylsilyloxy-1-*tert*-butoxycarbonylazepane* ***15b***

14b (212 mg, 0.61 mmol) is treated with 260 μl (185 mg, 1.83 mmol, 3 equivalents) of triethylamine and 60 μl (84 mg, 0.73 mmol, 1.2 equivalents) of mesyl chloride in 6 ml of dichloromethane. The resulting mesylate (242 mg, 0.57 mmol) is reacted with 186 mg (2.86 mmol, 5 equivalents) of NaN_3 in 1 ml of DMPU as described above; column chromatography: Et_2O/PE 1+4 (R_f=0.47); yield: 79 mg (0.21 mmol, 34%) as a colourless oil; RI_p=2089; $[\alpha]_D^{20}$=+50.4 (c=0.9, *t*BuOMe); IR (neat): ν (cm^{-1})=2940, 2100 (N_3), 1700 (C=O), 1410, 1255; ^{1}H NMR (200 MHz, [D_6]DMSO, 343 K) DEPT: δ (ppm)=−5.4, −5.2 (CH_3, $Si(CH_3)_2$), 17.4 ($SiC(CH_3)_3$), 21.0 (CH_2, C-6), 28.1 (CH_3, $CO_2C(CH_3)_3$), 29.9 (CH_2, C-5), 44.5, 46.1 (C-2 and C-7), 64.2 (CH, C-3), 72.0 (CH, C-4), 78.6 ($CO_2C(CH_3)_3$), 154.3 ($CO_2C(CH_3)_3$); ^{13}C NMR (50.3 MHz, [D_6]DMSO, 343 K) DEPT: δ (ppm)=−5.4, −5.2 (CH_3, $Si(CH_3)_2$), 17.4 ($SiC(CH_3)_3$), 21.0 (CH_2, C-6), 28.1 (CH_3, $CO_2C(CH_3)_3$), 29.9 (CH_2, C-5), 44.5, 46.1 (CH_2, C-2, C-7), 64.2 (CH, C-3), 72.0 (CH, C-4), 78.6 ($CO_2C(CH_3)_3$), 154.3 ($CO_2C(CH_3)_3$); $C_{17}H_{34}N_4O_3Si$ (370.57); calcd: C 55.10, H 9.25, N 15.12; found: C 55.08, H 8.93, N 15.23.

*3.12. (3*R,*4*S*)-3-*tert*-Butyldimethylsilyloxy-1-*tert*-butoxycarbonyl-4-hydroxyazepane **17a** and (3*R,*4*S*)-4-*tert*-butyldimethylsilyloxy-1-*tert*-butoxycarbonyl-3-hydroxyazepane **17b***

9a is hydrogenated and derivatized according to the procedure described for **14a** and **14b**. Starting materials: 2.42 g (8.43 mmol) of **9a**, 200 mg 10% Pd/C in 50 ml ethanol, then 2.21 g (10.12 mmol, 1.2 equivalents) of di-*tert*-butyldicarboxylate; column chromatography: Et_2O/PE 1+1 (R_f=0.41–0.48); yield: 2.00 g (5.79 mmol, 69%) of a mixture of **17a** and **17b** (1:1, determined by GC) as a colourless oil; RI_p=1957, RI_p=2001; IR (neat): ν (cm^{-1})=3480 (OH), 2940, 1700 (C=O), 1470, 1410; ^{1}H NMR (200 MHz, [D_6]DMSO, 353 K): δ (ppm)=0.16, 0.18, 0.19 (6H, s, Si(CH_3)$_2$), 1.00 (9H, s, SiC(CH_3)$_3$), 1.56 (9H, s, CO_2C(CH_3)$_3$), 1.60–1.98 (4H, m, 5-H, 6-H), 3.08–3.30 (2H, m, 7-H), 3.53–3.67 (2H, m, 2-H), 3.70–4.17 (2H, m, 3-H, 4-H); ^{13}C NMR (50.3 MHz, [D_6]DMSO, 353 K); δ (ppm)=−5.4, −5.3, −5.1 (Si(*C*H_3)$_2$), 17.3, 17.4 (Si*C*(CH_3)$_3$), 21.3 (C-6), 25.4 (SiC(*C*H_3)$_3$), 27.8 (CO_2C(*C*H_3)$_3$), 28.2, 28.6 (C-5), 45.8, 47.7 (C-2, C-7), 71.1, 71.7, 73.4, 73.6 (C-3, C-4), 77.8, 78.0 (CO_2*C*(CH_3)$_3$), 154.2 (*C*O_2C(CH_3)$_3$); $C_{17}H_{35}NO_4Si$ (345.56); calcd: C 59.05, H 10.21, N 4.05; found: C 58.87, H 9.99, N 4.12.

*3.13. (3*S,*4*S*)-3-Azido-4-*tert*-butyldimethylsilyloxy-1-*tert*-butoxycarbonylazepane **18a** and (3*R,*4*R*)-4-azido-3-*tert*-butyldimethylsilyloxy-1-*tert*-butoxycarbonylazepane **18b***

According to the procedure described for **15a**, a mixture of the compounds **17a** and **17b** is reacted. Starting materials: mesylation: 1.08 g (3.12 mmol) of **17a** and **17b**, 1.30 ml (9.36 mmol, 3 equivalents) of triethylamine, 290 μl (3.74 mmol, 1.2 equivalents) of mesyl chloride in 30 ml of CH_2Cl_2, the reaction time of the mesylation is 40 min at –20°C, yield of mesylation: 1.11 g (ca. 2.63 mmol) of crude product; azidation: 855 mg (13.15 mmol, 5 equivalents) of NaN_3 in 5 ml of DMPU; column chromatography: Et_2O/PE 1+4 (R_f=0.38); yield: 398 mg (1.07 mmol, 34%) as an inseparable mixture (7:3, capillary GC) of **18a** and **18b** as a colourless oil; RI_p=2078, RI_p=2066; IR (neat): ν (cm^{-1})=2920, 2095 (N_3), 1695 (C=O), 1410; ^{1}H NMR (200 MHz, [D_6]DMSO, 343 K): δ (ppm)=0.18, 0.20, 0.24 (6H, s, Si(CH_3)$_2$), 0.99 (9H, s, SiC(CH_3)$_3$), 1.60 (9H, s, CO_2C(CH_3)$_3$), 1.62–2.01 (4H, m, 5-H, 6-H), 2.99–3.56 (4H, m, 2-H, 7-H), 3.71–3.83 (2H, m, 3-H, 4-H); ^{13}C NMR (50.3 MHz, [D_6]DMSO, 343 K): δ (ppm)=−5.3, −5.1, −5.0 (Si(*C*H_3)$_2$), 17.2 (Si*C*(CH_3)$_3$), 20.9, 22.0 (C-6), 25.3 (SiC(*C*H_3)$_3$), 26.7, 27.7 (CO_2C(*C*H_3)$_3$), 31.2, 44.6, 45.1, 45.5, 48.3, 66.8, 68.1, 73.4, 74.3, 78.6 (CO_2*C*(CH_3)$_3$), 155.0 (*C*O_2C(CH_3)$_3$); $C_{17}H_{34}N_4O_3Si$ (370.57); calcd: C 55.10, H 9.25, N 15.12; found: C 55.40, H 8.95, N 14.70.

*3.14. (5*S,*6*S*)-6-*tert*-Butyldimethylsilyloxy-5-hydroxyazepane-2-one **19***

6a (10.35 g, 36.56 mmol) is hydrogenated in 200 ml of MeOH/H_2O (9+1) in the presence of 500 mg 10% Pd/C for 24 h at 50 bar at ambient temperature. The catalyst is removed by filtration, the solvent is distilled and the residue is filtered over a layer of silica gel. The solvent is removed and the residue is recrystallized from acetone/EtOAc. Yield: 6.16 g (23.72 mmol, 65%) as colourless crystals; mp=154°C; RI_P=1971; $[\alpha]_D^{20}$=+33.5 (c=1.0, MeOH); IR (KBr): ν (cm^{-1})=3300 (OH), 3100 (NH), 1650 (C=O), 1250, 1130; ^{1}H NMR (200 MHz, [D_6]acetone) COSY: δ (ppm)=0.10 (6H, s, Si(CH_3)$_2$), 0.90 (9H, s, SiC(CH_3)$_3$), 1.58–1.70 (1H, m, 4-H_A), 1.90–1.96 (1H, m, 4-H_B), 2.07–2.20 (1H, m, 3-H_A), 2.51–2.63 (1H, m, 3-H_B), 3.01–3.15 (1H, m, 7-H_A), 3.41–3.48 (1H, m, 7-H_B), 3.51–3.60 (1H, m, 6-H), 3.64–3.73 (1H, m, 5-H), 4.01 (1H, d, J=3.8 Hz, O-*H*), 6.51 (1H, s, N-*H*); ^{13}C NMR (50.3 MHz, [D_6]acetone) DEPT: δ (ppm)=−4.7 (CH_3, Si(*C*H_3)$_2$), 18.9 (Si*C*(CH_3)$_3$), 26.3 (CH_3, SiC(*C*H_3)$_3$), 27.3 (CH_2), 29.6 (CH_2), 42.2 (CH_2, C-7), 71.2 (CH, C-6), 73.4 (CH, C-5), 181.0 (C-2); $C_{12}H_{25}NO_3Si$ (259.42); calcd: C 55.56, H 9.71, N 5.40; found: C 55.35, H 9.46, N 5.36.

3.15. (5S 6R)-6-tert-Butyldimethylsilyloxy-5-hydroxyazepane-2-one **20**

7a (6.00 g, 21.02 mmol) is hydrogenated in 120 ml MeOH/H_2O (9+1) in the presence of 200 mg 10% Pd/C for 16 h at 50 bar at room temperature. The catalyst is removed by filtration, the solvent is distilled and 5.45 g (21.00 mmol, 99%) of crude product are obtained as colourless crystals. The product is further purified by column chromatography (EtOAc/MeOH 9+1); yield: 4.64 g (17.88 mmol, 85%) of colourless crystals. Recrystallization from *tert*-butylmethyl ether:petroleum ether 30:50 gives crystals for crystallographic purposes; mp=139°C; RI_p=1951; $[\alpha]_D^{20}$=+4.7 (c=1.5, EtOAc); IR (KBr): ν=3400 (O–H), 1710 (C=O), 1485, 1280, 1090 cm^{-1}; ^1H NMR (600 MHz, [D_6]acetone): δ (ppm)=0.12 (6H, s, $Si(CH_3)_2$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.70–1.75 (1H, m, 4-H_A), 1.89–1.94 (1H, m, 4-H_B), 2.0–2.1 (1H, m, 3-H_A), 2.67–2.71 (1H, m, 3-H_B), 2.83–2.94 (1H, m, 7-H_A), 3.52–3.58 (1H, m, 7-H_B), 3.78 (1H, td, J=2.1, J=9.2 Hz, 6-H), 3.85–3.88 (1H, m, 5-H), 6.67 (1H, br s, 1-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=−4.9, −4.8 (CH_3, $Si(CH_3)_2$), 17.9 ($SiC(CH_3)_3$), 25.6 (CH_3, $SiC(CH_3)_3$), 27.0 (CH_2, C-4), 28.6 (CH_2, C-3), 41.8 (CH_2, C-7), 71.2 (CH, C-6), 72.5 (CH, C-5), 178.6 (C-2); $C_{12}H_{25}NO_3Si$ (259.42); the assignment of ^1H- and ^{13}C-NMR signals is verified by 600 MHz HMBC and HMQC; calcd: C 55.56, H 9.71, N 5.40; found: C 55.31, H 9.45, N 5.30.

3.16. (5S,6R)-5,6-O-Isopropylidene-azepane-2-one **21**

20 (260 mg, 1.00 mmol) is dissolved in 4.2 ml of methanol (abs). 1.0 ml of 5.2 M methanolic HCl is added and the mixture is stirred at ambient temperature for 10 min. Then the solvent and the HCl are distilled at room temperature under vacuum (0.05 mbar) into a cooling trap. The residue is taken up in 2 ml of dry acetone and the solution is cooled to –20°C. A solution of 266 mg (2.00 mmol, 2 equivalents) of water-free $AlCl_3$ in 4.0 ml of ether (abs) is freshly prepared at –20°C. This solution is carefully added to the solution of the substrate in acetone. The resulting mixture is first stirred over 15 min at –20°C, then for 30 min at 0°C and finally at room temperature for 2.25 h. During this time a colourless precipitate is formed and the colour of the reaction mixture changes to yellow. After this, the mixture is once more cooled to –20°C and 3 ml of concd $NaHCO_3$ are added. The mixture is warmed to room temperature, diluted with water until the precipitate is dissolved and is then extracted with 3 portions of dichloromethane.The combined organic extracts are dried over Na_2SO_4 and the solvent is distilled. The residue crystallizes spontaneously and requires no further purification. Yield: 113 mg (0.61 mmol, 61%) as colourless crystals: mp=87°C (lit.[4p]: mp=85–86°C); RI_P=1614; $[\alpha]_D^{20}$=+43 (c=1.3, $CHCl_3$); lit. [4p]: $[\alpha]_D^{20}$=+46.1 (c=0.98, $CHCl_3$); IR (KBr): ν (cm^{-1})=3220 (NH), 2950, 1670 (C=O), 1220, 1095; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm)=1.35 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.95–2.32 (3H, m, 3-H_A, 4-H), 2.78–2.92 (1H, m, 3-H_B), 3.03 (1H, ddd, $J_{6,7A}$=4.1, $J_{1,7A}$=7.0, J_{AB}=14.7 Hz, 7-H_A), 3.44 (1H, ddd, $J_{1,7B}$=5.0, $J_{6,7B}$=10.5, J_{AB}=14.7 Hz, 7-H_B), 4.47 (1H, ddd, $J_{6,7A}$=4.1, $J_{5,6}$=4.6, $J_{5,7B}$=10.5 Hz, 6-H), 4.35 (1H, dd, $J_{5,6}$=4.6, $J_{4,5}$=8.7 Hz, 5-H), 6.28 (1H, br s, 1-H); ^{13}C NMR (50.3 MHz, $CDCl_3$) DEPT: δ (ppm)=24.0 (CH_2, C-2), 25.7 (CH_3, OCH_3), 28.2 (CH_3, OCH_3), 29.5 (CH_2, C-3), 42.0 (CH_2, C-7), 74.6 (CH), 74.9 (CH), 108.0 ($O_2C(CH_3)_2$), 177.4 (C-2); $C_9H_{15}NO_3$ (185.22); calcd: C 58.36, H 8.16, N 7.56; found: C 58.09, H 8.07, N 7.33.

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft (He 1513/5-1, He 1513/5-2) and the Fonds der Chemischen Industrie for their financial support and the Humboldt-Gesellschaft for funding Professor R. M. Mohareb. We express our gratitude to Mrs. A. Betz for the preparation of starting materials.

References

1. (a) König, W. A.; Sinnwell, V.; Witt, W. A.; Kneifel, H. *Chem. Ber.* **1980**, *113*, 2221–2226. (b) Müller, A.; Takyar, D. K.; Witt, S.; König, W. A. *Liebigs Ann. Chem.* **1993**, 651–655.
2. (a) Kulanthaivel, P.; Hallock, Y. F.; Boros, C.; Hamilton, S. M.; Janzen, W. P.; Ballas, L. M.; Loomis, D. R.; Jiang, J. B. *J. Am. Chem. Soc.* **1993**, *115*, 6452–6453. (b) Boros, C.; Hamilton, S. M.; Katz, B.; Kulanthaivel, P. *J. Antibiot.* **1994**, *47*, 1010–1016.
3. Ohshima, S.; Yanagisawa, M.; Katoh, A.; Fujii, T.; Sano, T.; Matsukama, S.; Furumai, T.; Fujiu, M.; Watanabe, K.; Yokose, K.; Arisawa, M.; Okuda, T. *J. Antibiot.* **1994**, *47*, 639–647.
4. (a) Hughes, P. F.; Smith, S. H.; Olson, J. T. *J. Org. Chem.* **1994**, *59*, 5799–5802. (b) Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1994**, *59*, 5147–5148. (c) Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *J. Am. Chem. Soc.* **1994**, *116*, 8402–8403. (d) Nicolaou, K. C.; Bunnage, M. E.; Koide, K. *Chem. Eur. J.* **1995**, *1*, 454–466. (e) Adams, C. P.; Fairway, S. M.; Hardy, C. J.; Hibbs, D. E.; Hursthouse, M. B.; Morley, A. D.; Sharp, B. W.; Vicker, N.; Warner, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2355–2362. (f) Hu, H.; Jagdmann Jr., G. E.; Hughes, P. F.; Nichols, J. B. *Tetrahedron Lett.* **1995**, *36*, 3659–3662. (g) Tanner, D.; Almario, A.; Högberg, T. *Tetrahedron* **1995**, *51*, 6061–6070. (h) Lampe, J. W.; Hughes, P. F.; Biggers, C. K.; Smith, S. H.; Hu, H. *J. Org. Chem.* **1996**, *61*, 4572–4581. (i) Tuch, A.; Sanière, M.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron: Asymmetry* **1996**, *7*, 2901–2909. (j) Naito, T.; Torieda, M.; Tajiri, K.; Ninomiya, I.; Kiguchi, T. *Chem. Pharm. Bull.* **1996**, *44*, 624–626. (k) Tanner, D.; Tedenborg, L.; Almario, A.; Pettersson, I.; Csöregh, I.; Kelly, N. M.; Andersson, P. G.; Högberg, T. *Tetrahedron* **1997**, *53*, 4857–4868. (l) Morie, T.; Kato, S. *Heterocycles* **1998**, *48*, 427–431. (m) Barbier, P.; Stadlwieser, J. *Chimia* **1996**, *50*, 530–532. (n) Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V. *Synlett* **1996**, 29–30. (o) Wu, M. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1997**, *38*, 1693–1696. (p) Albertini, E.; Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Zanirato, V. *Tetrahedron* **1997**, *53*, 17177–17194. (q) Tanner, D.; Tedenborg, L.; Almario, A.; Pettersson, I.; Csöregh, I.; Kelly, N. M.; Andersson, P. G.; Högberg, T. *Tetrahedron* **1997**, *53*, 4857–4868. (r) Morie, T.; Kato, S. *Heterocycles* **1998**, *48*, 427–431. (s) Miyabe, H.; Torieda, M.; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397–4407.
5. (a) Hollinshead, S. P.; Nichols, J. B.; Wilson, J. W. *J. Org. Chem.* **1994**, *59*, 6703–6709. (b) Heerding, J. M.; Lampe, J. W.; Darges, J. W.; Stamper, M. L. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1839–1842. (c) Jagdmann Jr., G. E.; Defauw, J. M.; Lai, Y.-S.; Crane, H. M.; Hall, S. E.; Buben, J. A.; Hu, H.; Gosnell, P. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2015–2020. (d) Crane, H. M.; Menaldino, D. S.; Jagdmann Jr., G. E.; Darges, J. W.; Buben, J. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2133–2138. (e) Lai, Y.-S.; Stamper, M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2147–2150. (f) Mendoza, J. S.; Jagdmann Jr., G. E.; Gosnell, P. A. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2211–2216. (g) Hu, H.; Hollinshead, S. P.; Hall, S. E.; Kalter, K.; Ballas, L. M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 973–978. (h) Jagdmann Jr., G. E.; Defauw, J. M.; Lampe, J. W.; Darges, J. W.; Kalter, K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1759–1764. (i) Defauw, J. M.; Murphy, M. M.; Jagdmann Jr., G. E.; Hu, H.; Lampe, J. W.; Hollinshead, S. P.; Mitchell, T. J.; Crane, H. M.; Heerding, J. M.; Mendoza, J. S.; Davis, J. E.; Darges, J. W.; Hubbard, F. R.; Hall, S. E. *J. Med. Chem.* **1996**, *39*, 5215–5227. (j) Nielsen, J.; Lyngsø, L. O. *Tetrahedron Lett.* **1996**, *46*, 8439–8442. (k) Lai, Y.-S.; Mendoza, J. S.; Jagdmann Jr., G. E.; Menaldino, D. S.; Biggers, C. K.; Heerding, J. M.; Wilson, J. W.; Hall, S. E.; Jiang, J. B.; Janzen, W. P.; Ballas, L. M. *J. Med. Chem.* **1997**, *40*, 226–235.
6. Narayana, N.; Diller, T. C.; Koide, K.; Bunnage, M. E.; Nicolaou, K. C.; Brunton, L. L.; Xuong, N.-H.; Ten Eyck, L. F.; Taylor, S. S. *Biochemistry* **1999**, *38*, 2367–2376.
7. (a) Herdeis, C.; Schiffer, T. *Tetrahedron* **1996**, *52*, 14745–14756. (b) Herdeis, C.; Schiffer, T. *Synthesis* **1997**, 1405–1410. (c) Herdeis, C.; Telser, J. *Eur. J. Org. Chem.* **1999**, 1407–1414.
8. Andrews, G. C.; Crawford, T. C.; Bacon, B. E. *J. Org. Chem.* **1981**, *46*, 2976–2977.
9. Vekemans, J. A. J. M.; Dapperens, C. W. M.; Claessen, R.; Koten, A. M. J.; Godefroi, E. F.; Chittenden, G. J. F. *J. Org. Chem.* **1990**, *55*, 5336–5344.
10. Bock, K.; Lundt, I.; Pedersen, C. *Carbohydr. Res.* **1979**, *68*, 313–319.
11. Peyrat, J.-F.; Figadère, B.; Cavé, A. *Synth. Commun.* **1996**, *26*, 4563–4567.
12. Krülle, T. M.; de la Fuente, C.; Pickering, L.; Aplin, R. T.; Tsitsanou, K. E.; Zographos, S. E.; Oikonomakos, N. G.; Nash, R. J.; Griffiths, R. C.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1997**, *8*, 3807–3820.
13. Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635–646.
14. Nagarajan, S.; Ganem, B. *J. Org. Chem.* **1987**, *52*, 5044–5046.
15. (a) Paulsen, H.; Todt, K. *Chem. Ber.* **1967**, *100*, 512–520. (b) Morís-Varas, F.; Qian, X.-H.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 7647–7652.
16. Long, D. D.; Stetz, R. J. E.; Nash, R. J.; Marquess, D. G.; Lloyd, J. D.; Winters, A. L.; Asano, N.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 901–908.
17. Herdeis, C.; Neder, R.; Schwabenländer, F.; Telser, J., unpublished results.
18. Lal, B.; Gidwani, R. M.; Rupp, R. H. *Synthesis* **1989**, 711–713.
19. Van Den Dool, H.; Kratz, P. D. *J. Chromatogr.* **1963**, *11*, 463–471.