Synthesis of geminal bis(hydroxymethyl)pyrrolidine and pyrrolizidine imino sugars

Frank Schieweck and Hans-Josef Altenbach *

Bergische Universität–GH Wuppertal, Department of Chemistry, Gauss-Strasse 20, D-42119 Wuppertal, Germany

Received (in Cambridge, UK) 19th September 2000, Accepted 26th September 2001
First published as an Advance Article on the web 19th November 2001

Reductive alkylation of *N*-Boc-pyrrolecarboxylate methyl ester **1** under Birch conditions with iodomethyl pivalate and subsequent reduction of the ester moieties provided the symmetric diol **3**, a flexible building block for the synthesis of geminally disubstituted pyrrolidine imino sugars. This key intermediate was used for the first known synthesis of a 2,2-bis(hydroxymethyl)pyrrolidine imino sugar. In a similar manner a pyrrolizidine imino sugar was synthesised by oxidation of the deprotected pyrrolidine to the nitrone **10**, which was subjected to a highly diastereoselective 1,3-dipolar cycloaddition with an allylic alcohol. Reductive cleavage of the N–O bond and recyclisation yielded the polyhydroxylated pyrrolizidine **13**.

Glycoproteins occur in the blood stream and in a variety of secretions, as well as on the outer surface of cells, where they are essential for cell–cell communication, cell growth and fixation of enzymes, hormones and antibodies.[1] In the biosynthesis and processing of these glycoproteins a class of enzymes called glycosidases plays an important role by "trimming" the oligosaccharide chains.[2] Glycosidase inhibitors[3] thus have interesting biological potential and exhibit antibacterial, antiviral (including HIV),[4] antitumor[5] and antidiabetic activity.[6]

Molecules that imitate the naturally occurring substrates have proved to be highly effective glycosidase inhibitors. The polyhydroxylated pyrrolidines, piperidines, pyrrolizidines and indolizidines † are the most important class of inhibitors.[7] These monosaccharide analogues,[8] often referred to as aza- or imino sugars,[9] can be derived from the furanoid and pyranoid sugars by replacement of the oxygen in the ring by nitrogen. They can be protonated within the active site of the enzyme and thus bear resemblance to glycosyl cations, the proposed intermediates in the hydrolytic cleavage of the oligosaccharides.[10]

In our continuing work on the synthesis of sugar analogues,[11] we were interested in the development of new types of imino sugars on the basis of polyhydroxylated pyrrolidines. Examples related to structure **A** (Fig. 1) are 1,4-dideoxy-1,4-imino-D-arabinitol (R = H) and 1,4-dideoxy-1,4-imino-D-mannitol (R = CH_2OH); both are potent and specific inhibitors of α-glucosidases and α-mannosidases.[12] The 2,5-iminoglycitols of structure **B**, *e.g.* 2,5-dideoxy-2,5-imino-D-mannitol (R = CH_2-OH) and 2,5,6-trideoxy-2,5-imino-D-altritol (R = CH_3) have also been investigated in this respect and found to be highly active against various glycosidases.[12a,13]

On comparing the two structures **A** and **B** we realised that no known polyhydroxylated pyrrolidine derivatives possessed two *vicinal* side chains (**C**, Fig. 1).[14] Attracted by this observation, we focused our efforts on the development of a flexible and straightforward synthesis for this new type of 2,2-disubstituted pyrrolidine based imino sugar.

† The IUPAC name for pyrrolizidine is hexahydropyrrolizine and the IUPAC name for indolizidine is octahydroindolizine.

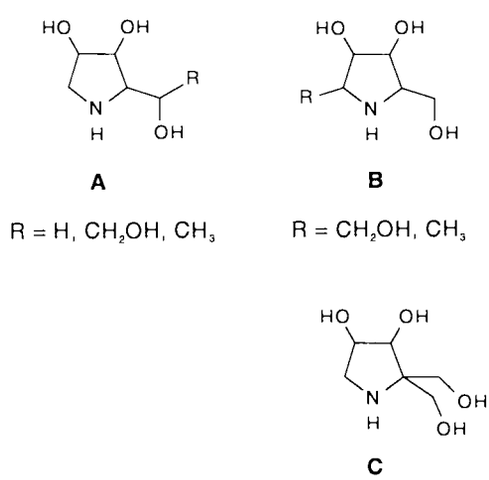
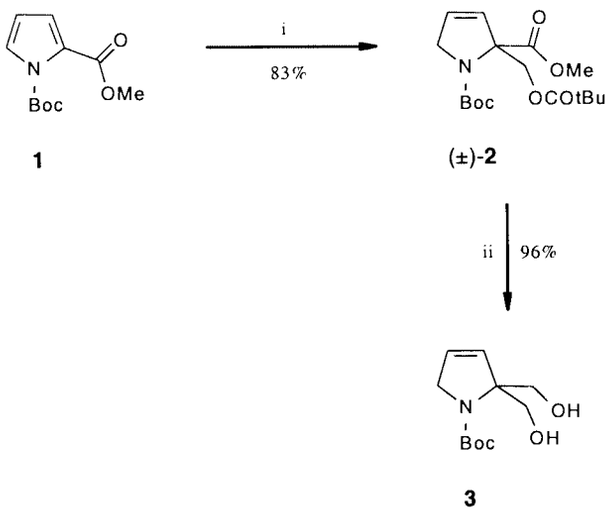


Fig. 1

Results and discussion

The synthesis started from methyl *N*-Boc-pyrrolecarboxylate **1** (Scheme 1), which can easily be prepared on a large scale from pyrrole by aromatic substitution, ester formation and subsequent protection of the amino function.[15] Having already gained some insight into the reduction of five-membered heterocycles under Birch conditions for the synthesis of sugar analogues, we wanted to use this approach to introduce the second side chain at the 2-position.[16] To accomplish the reductive alkylation of the pyrrole nucleus, a modified procedure recently developed by Donohoe *et al.* was used.[17] In iodomethyl pivalate[18] an electrophilic C_1-synthon was chosen that can easily be converted into the desired hydroxymethyl side chain. Birch reduction of the ester **1** was best accomplished with 2.2 eq. of lithium at −78 °C. After 30 min the iodomethyl pivalate was added, and the mixture was allowed to warm to room temperature. Standard work up followed by flash chromatography yielded the 2,2-disubstituted 2,5-dihydropyrrole (±)-**2** in 83% yield. The ^{1}H-NMR spectrum reveals the presence of two

DOI: 10.1039/b007607o

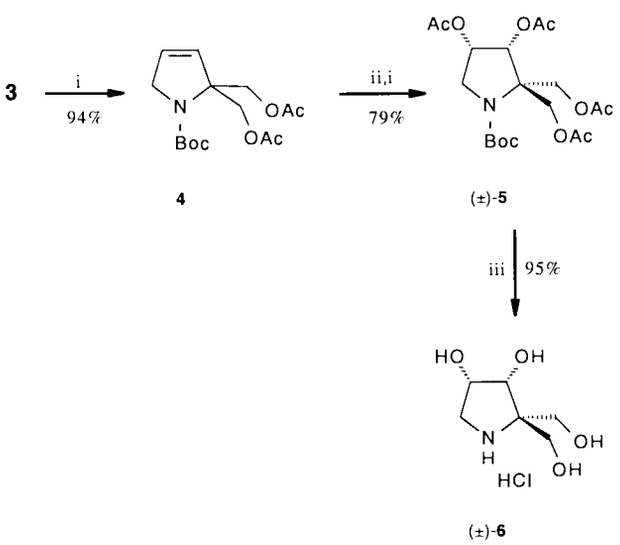


Scheme 1 *Reagents and conditions*: i, Li (2.2 eq.), NH_3–THF then ICH_2OCOBu^t–THF, −78 °C; ii, $LiBH_4$, MeOH–Et_2O, rt.

preferred amide rotamers about the C–N bond. As a result, the methylene protons of the new side chain appear as an AB-system and a pseudo singlet in a ratio of 3 : 7.

The next step was to reduce the ester moieties of the 2,5-dihydropyrrole derivative (±)-**2**. The use of LAH in diethyl ether gave low and varying yields, presumably because the *N*-Boc protecting group is insufficiently stable toward the reducing agent. However, the use of lithium borohydride–methanol in diethyl ether turned out to be an excellent alternative.[19] By this procedure the diol **3** can be obtained in nearly quantitative yield as colourless needles.

cis-Dihydroxylation of the corresponding acetate **4** with osmium tetraoxide, followed by acetylation, yielded the tetra-acetate (±)-**5** in a total of 79% yield for the two steps (Scheme 2).

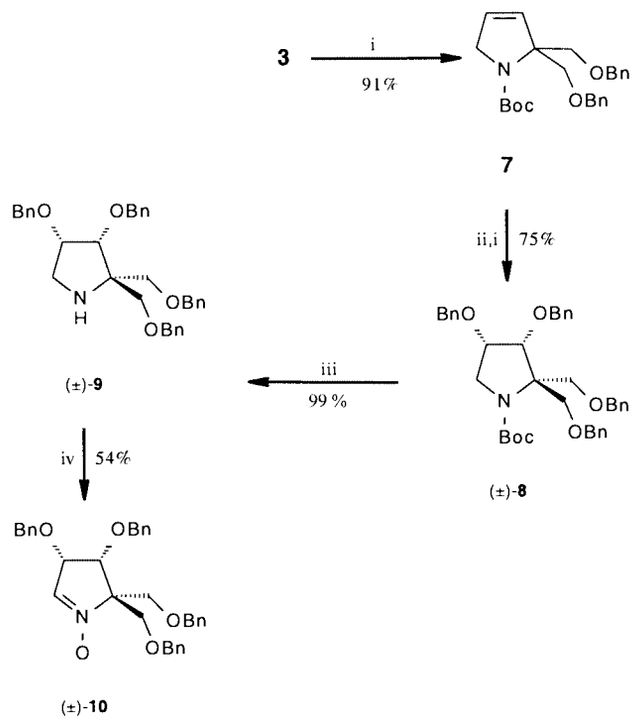


Scheme 2 *Reagents and conditions*: i, Ac_2O, pyridine, DMAP, rt; ii, OsO_4, acetone–water, NMO, rt; iii, HCl, MeOH, AcOMe, 0 °C to rt.

Finally, the synthesis of the 2,2-bis(hydroxymethyl)pyrrolidine imino sugar (±)-**6** was completed by acidic deprotection with HCl in methanol prepared *in situ* by the addition of acetyl chloride to methanol.[20] This procedure afforded the target molecule in six steps and in 56% overall yield. The spectral data of (±)-**6** were consistent with the molecular structure; especially noteworthy are the two slightly shifted AB spin systems for the methylene protons of the side chains due to the lack of symmetry compared with structures **3** and **4**.

In order to extend this concept to the synthesis of a *vicinal* bis(hydroxymethyl)pyrrolizidine, we investigated the 1,3-dipolar cycloaddition of an allylic alcohol with the corresponding cyclic nitrone derived from the symmetric diol **3**.[21] Such an approach had proved successful in various cases; the first systematic work in this field was undertaken by Tufariello's research group.[22]

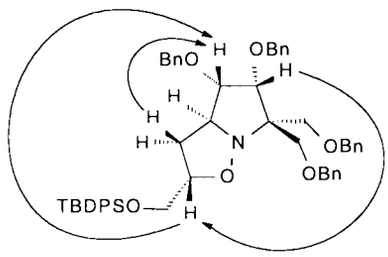
Attempts to protect the hydroxy groups with benzyl bromide by the use of sodium hydride in DMF failed because of partial intramolecular cyclisation and formation of an oxazolidinone. In the end, the reaction was best accomplished by solvent-free reaction with potassium hydroxide in the presence of a phase-transfer catalyst (Scheme 3). Thus, the dibenzyl ether **7** could be



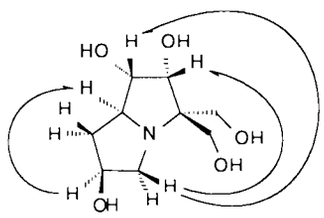
Scheme 3 *Reagents and conditions*: i, BnBr, KOH, PTC, 0 °C to rt; ii, OsO_4, acetone–water, NMO, rt; iii, HCl, MeOH, AcOMe, 0 °C to rt; iv, 2-(phenylsulfonyl)-3-phenyloxaziridine (2.1 eq.), $CHCl_3$, rt.

obtained in 91% yield. The *cis*-dihydroxylation of **7** with a catalytic amount of osmium tetraoxide yielded the diol as a thick yellowish oil that could be benzylated under the conditions described below without any further purification. Deprotection of the carbamate (±)-**8**, achieved with dry hydrogen chloride in methanol, led to the pyrrolidine hydrochloride (±)-**9·HCl**. After some experimentation we found that the best way to oxidise the amine was to use the aprotic 2-(phenylsulfonyl)-3-phenyloxaziridine (Davis' reagent).[23] With this easy-to-handle reagent the oxidation was completed within two hours, and after flash chromatography the racemic nitrone **10** was obtained in 54% yield. In the ^{1}H-NMR spectrum the methine proton of the cyclic nitrone at 7.0 ppm is separate from the aromatic protons. A peak at $m/z = 537$ was observed in the mass spectrum.

Cycloaddition of (±)-**10** and allyl *tert*-butyldiphenylsilyl ether in refluxing toluene led to the highly diastereoselective formation of two cycloadducts in a ratio of 11 : 1 and in a combined yield of 58%. The major isomer was assigned structure (±)-**11** on the basis of detailed NMR experiments, in particular by its NOESY spectrum, in which an NOE signal was observed between 2-H and 4-H/5-H as well as between 3β-H and 4-H/5-H (Fig. 2). This outcome corresponds to the addition to the more sterically accessible face of (±)-**10** *via* an *exo*-transition state that is well documented for the cycloaddition of cyclic nitrones.[24]

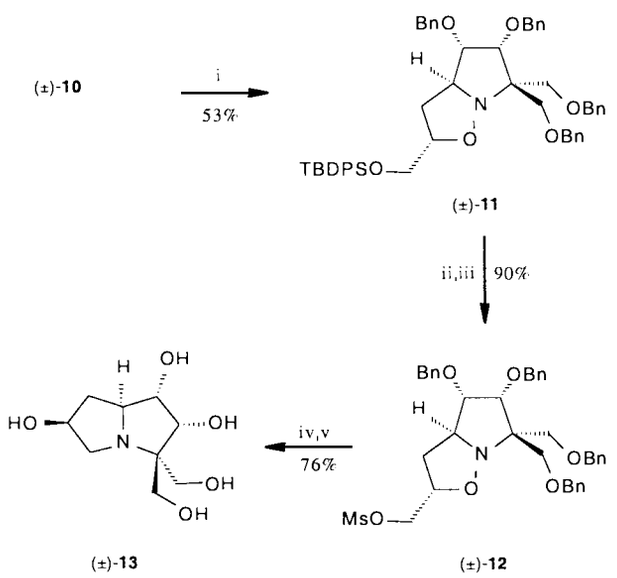


(±)-**11**



(±)-**13**

Fig. 2



Scheme 4 *Reagents and conditions*: i, CH_2=$CHCH_2OTBDPS$, toluene, reflux; ii, TBAF, THF, rt; iii, MsCl, NEt_3, CH_2Cl_2; iv, Pd/C, H_2, MeOH; v, Dowex 50W-X8.

Desilylation of the major cycloadduct (±)-**11** with tetrabutylammonium fluoride in THF at room temperature gave the corresponding alcohol, which was converted into the mesylate (±)-**12** in excellent yield (Scheme 4). Hydrogenolysis of the isoxazolidine with palladium on charcoal resulted in the reduction of the N–O bond together with the removal of all benzyl groups and was accompanied by intramolecular recyclisation to the pyrrolizidine (±)-**13** as its methanesulfonate. Application to a Dowex 50W-X8 column (H^+ form), washing with water and elution with 1 M ammonia produced the free pyrrolizidine base (±)-**13** as a colourless solid. All spectral data were consistent with the molecular structure, and the stereochemistry was further established by a NOESY spectrum, in which a significant NOE was present between 5β-H and 1-H/2-H and between 6-H and 7a-H (Fig. 2).

In conclusion, starting from methyl *N*-Boc-pyrrolecarboxylate we have developed a general synthesis of the hitherto unknown polyhydroxylated *vicinal* bis(hydroxymethyl)pyrrolidines and pyrrolizidines. The symmetric diol **3**, which was accessible by reductive alkylation of pyrrole with iodomethyl pivalate, proved to be a valuable and flexible building block for our synthetic strategy. Further functionalisation and the development of an enantiopure derivative of **3** is currently under investigation in our laboratories.

Experimental

General details

IR spectra were taken with a Perkin-Elmer 1420 Ratio Recording spectrometer as KBr disks or neat oils, as appropriate. The ^{1}H- and ^{13}C-NMR spectra were obtained on a Bruker ARX 400 spectrometer. *J*-values are given in Hz. ψ stands for pseudo. Mass spectra were obtained on a Varian MAT 311A operating in the electron impact mode (70 eV). Elemental analyses were performed on a Perkin-Elmer Mikroelementar Analysator 240B. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. GC studies were performed with a Shimadzu GC-14A equipped with a SE-52-CB-0.25 column (25 m). HPLC was performed on a Shimadzu 6A with a Shimadzu UV-Detector SPD-6A (220 nm) on a Merck Hibar RT column with heptane–propan-2-ol 95 : 5. Merck silica gel plates (60 F_{254}) were used for the thin-layer chromatography, and spots were visualised with UV light (254 nm) and/or phosphomolybdic acid in methanol. Flash chromatography was performed on Merck silica gel (F 60) with a pressure of 0.2–0.6 bar. All solvents were purified by the following standard literature methods and stored under argon: diethyl ether was dried over LAH, methanol over magnesia and THF over potassium. Cyclohexane, *tert*-butyl methyl ether, ethyl acetate and acetyl chloride were distilled before use. All reactions were run in flame-dried glassware under an argon atmosphere unless otherwise stated.

N-(*tert*-Butoxycarbonyl)-2-methoxycarbonyl-2-(2,2-dimethylpropionyloxymethyl)-2,5-dihydropyrrole 2

A solution of *N*-Boc-pyrrolecarboxylate methyl ester **1** (6.50 g, 28.7 mmol) in THF (50 cm^3) was added rapidly to a well stirred mixture of liquid ammonia (700 cm^3), THF (250 cm^3) and lithium (439 mg, 63.2 mmol) at −78 °C. After 30 min, a solution of iodomethyl pivalate (8.34 g, 1.2 eq.) in THF (20 cm^3) was added over a period of 10 min. After another 90 min, NH_4Cl (excess) was added. The mixture was slowly warmed to room temperature, and THF was removed under reduced pressure. Saturated $NaHCO_3$ solution was added and the product extracted with dichloromethane (3 × 350 cm^3), washed with brine (100 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (eluting with cyclohexane–*tert*-butyl methyl ether 17 : 3) afforded the dihydropyrrole **2** (8.13 g, 83%) as a colourless oil (Found: C, 59.87; H, 8.02; N, 3.83. Calc. for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10%); ν_{max}(film)/cm^{-1} 3085, 2955, 2849, 1728, 1697 and 1385; δ_H (400 MHz, $CDCl_3$) 6.01 (1 H × 0.7, dt, *J* 6.1 and 2.0, CH_2-C*H*), 5.93 (1 H × 0.3, dt, *J* 6.3 and 1.9, CH_2-C*H*), 5.53 (1 H, dt, *J* 6.1 and 2.3, CH=C*H*), 4.76 (1 H × 0.3, J_{AB} 11.5, CH_2O), 4.65 (1 H × 0.3, J_{AB} 11.5, CH_2N), 4.60 (1 H × 0.7, ψs, CH_2O), 4.35 (1 H × 0.7, dt, *J* 15.8 and 2.0, CH_2N), 4.27 (1 H × 0.3, dt, *J* 15.4 and 2.2, CH_2N), 4.14 (1 H × 0.7, dt, *J* 15.8 and 2.0, CH_2N), 4.09 (1 H × 0.3, dt, *J* 15.3 and 2.0, CH_2N), 3.70 (3 H, s, OCH_3), 1.44 (9 H × 0.3, s, OCMe_3), 1.40 (9 H × 0.7, s, OCMe_3) and 1.12 (9 H, s, COCMe_3); δ_C (100 MHz, $CDCl_3$) 177.7, 177.6, 170.5, 170.1, 153.1, 152.7, 129.3, 129.2, 127.5, 80.7, 80.1, 74.8, 74.1, 63.2, 62.2, 54.7, 54.6, 52.3, 52.2, 38.7, 38.6, 28.3, 28.1, 27.0 and 27.0; *m*/*z* (70 eV) 341 (M$^+$, 4%), 282 (14), 182 (18), 126 (36), 80 (50), 57 (100) and 41 (27).

N-(*tert*-Butoxycarbonyl)-2,2-bis(hydroxymethyl)-2,5-dihydropyrrole 3

A solution of the 2,5-dihydropyrrole **2** (1.00 g, 2.93 mmol) in 8 cm^3 diethyl ether was added to a mixture of $LiBH_4$ (127 mg, 5.83 mmol) and methanol (235 μL) in diethyl ether (7 cm^3) at

room temperature. After disappearance of the diester (monitored by TLC) water was added, and the product was extracted with diethyl ether (5 × 40 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (eluting with cyclohexane–*tert*-butyl methyl ether 1 : 3) afforded the diol **3** (645 mg, 96%) as a colourless solid (Found: C, 57.49; H, 8.14; N, 6.18. Calc. for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11%); ν_{max}(film)/cm^{-1} 3370, 2941, 2858, 1665, 1625, 1394, 1165 and 1045; δ_H (400 MHz, $CDCl_3$) 5.83 (1 H, dt, *J* 6.6 and 2.0, CH_2-C*H*), 5.62 (1 H, dt, *J* 6.6 and 2.0, CH=C*H*), 4.12 (2 H, *ψ*s, CH_2N), 3.90 (2 H, J_{AB} 11.7, CH_2OH), 3.82 (2 H, J_{AB} 11.7, CH_2OH), and 1.48 (9 H, s, COCMe_3); δ_C (100 MHz, $CDCl_3$) 155.9, 130.3, 126.7, 80.7, 75.1, 64.6, 55.5 and 28.3; *m*/*z* (70 eV) 198 ($M^+ - CH_2OH$, 36%), 181 (8), 156 (14), 142 (51), 125 (18), 98 (59), 80 (25), 68 (74) and 57 (100).

2,2-Bis(acetoxymethyl)-*N*-(*tert*-butoxycarbonyl)-2,5-dihydropyrrole 4

The diol **3** (600 mg, 2.62 mmol) was dissolved in pyridine (4.0 cm^3) and acetic anhydride (2.0 cm^3) and stirred for 24 h at room temperature. The mixture was diluted with diethyl ether (25 cm^3), washed sequentially with aqueous HCl (2 M; 2 × 25 cm^3), saturated $NaHCO_3$ (25 cm^3) and brine (20 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (eluting with cyclohexane–*tert*-butyl methyl ether 5 : 2) provided the diacetate **4** (772 mg, 94%) as a colourless liquid (Found: C, 57.38; H, 7.37; N, 4.36. Calc. for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47%); ν_{max}(film)/cm^{-1} 2960, 2858, 1745, 1690, 1630, 1375, 1220, 1165, 1105, 1045 and 735; δ_H (400 MHz, $CDCl_3$) 5.93 (1 H × 0.55, d, *J* 6.6, CH_2-C*H*), 5.85 (1 H × 0.45, d, *J* 6.6, CH_2-C*H*), 5.59 (1 H, d, *J* 6.1, CH=C*H*), 4.55 (1 H, J_{AB} 11.0, CH_2OAc), 4.49 (1 H, J_{AB} 11.0, CH_2OAc), 4.39 (1 H, J_{AB} 10.9, CH_2OAc), 4.36 (1 H, J_{AB} 10.9, CH_2OAc), 4.18 (2 H × 0.5, *ψ*t, *J* 2.0, CH_2N), 4.11 (2 H × 0.5, *ψ*t, *J* 2.0, CH_2N), 2.03 (6 H × 0.5, s, COCH_3), 2.02 (6 H × 0.5, s, COCH_3), 1.50 (9 H × 0.55, s, COCMe_3) and 1.47 (9 H × 0.45, s, COCMe_3); δ_C (100 MHz, $CDCl_3$) 170.4, 170.4, 153.3, 153.2, 129.2, 127.1, 126.9, 80.9, 79.8, 71.5, 70.4, 64.5, 63.7, 55.4, 55.2, 28.4 and 20.7; *m*/*z* (70 eV) 313 (M^+, 2%), 256 (3), 240 (39), 212 (3), 198 (14), 184 (19), 156 (9), 140 (35), 96 (7), 80 (13) and 57 (100).

3,4-Diacetoxy-2,2-bis(acetoxymethyl)-*N*-(*tert*-butoxycarbonyl)-pyrrolidine (±)-5

The diacetate **4** (705 mg, 2.25 mmol) and NMO (580 mg, 4.95 mmol) were dissolved in acetone (6.0 cm^3), and a solution of OsO_4 in water (5.5 cm^3, 2 mg cm^{-3}) was added. The mixture was kept for 12 days at room temperature, and after the reaction was completed (monitored by TLC) a saturated solution of $Na_2S_2O_3$ was added, and the solvent was completely removed under reduced pressure. Pyridine (3.5 cm^3) and acetic anhydride (1.7 cm^3) were added and stirred overnight at room temperature. The mixture was diluted with diethyl ether (20 cm^3), washed sequentially with HCl (2 M; 2 × 20 cm^3), saturated $NaHCO_3$ (20 cm^3) and brine (15 cm^3), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Flash chromatography (eluting with cyclohexane–ethyl acetate 8 : 2) provided the tetraacetate (±)-**5** (767 mg, 79%) as a colourless oil (Found: C, 52.90; H, 6.79; N, 3.37. Calc. for $C_{19}H_{29}NO_{10}$: C, 52.89; H, 6.77; N, 3.25%); ν_{max}(CCl_4)/cm^{-1} 2965, 1742, 1695, 1360 and 1214; δ_H (400 MHz, $CDCl_3$) 5.48–5.42 (2 H, m, C*H*(OAc)-C*H*(OAc)), 4.78 (1 H × 0.5, J_{AB} 11.2, CH_2OAc), 4.64 (1 H, m, CH_2OAc), 4.49 (3 H × 0.5, m, CH_2OAc), 4.31 (1 H × 0.5, J_{AB} 11.2, CH_2(OAc)), 4.16 (1 H × 0.5, d, *J* 11.2, CH_2(OAc)), 3.75 (1 H, m, CH_2N), 3.54 (1 H × 0.5, d, *J* 10.5, CH_2N), 3.44 (1 H × 0.5, d, *J* 10.7, CH_2N), 2.07, 2.05, 2.03, 2.00 (3 H × 4, s, 4 × COCH_3), 1.45 (9 H × 0.5, s, COCMe_3) and 1.43 (9 H × 0.5, s, COCMe_3); δ_C (100 MHz, $CDCl_3$) 169.9, 169.8, 169.2, 153.0, 81.7, 80.6, 74.2, 73.5, 68.4, 67.9, 64.8, 63.9, 63.2, 62.8, 62.3, 52.6, 49.8, 28.2, 20.7, 20.6, 20.5 and 20.3; *m*/*z* (70 eV) 371 ($M^+ - CH_3CO_2H$, 14%), 358 (56), 302 (6), 271 (82), 258 (97), 96 (100), 57 (100) and 43 (87).

3,4-Dihydroxy-2,2-bis(hydroxymethyl)pyrrolidine hydrochloride (±)-6

The tetraacetate (±)-**5** (320 mg, 0.742 mmol) was dissolved in methanol (4.0 cm^3) and added to a solution of HCl in methanol–methyl acetate (freshly prepared by addition of AcCl (5.2 cm^3) to methanol (14.4 cm^3) at 0 °C); the mixture was allowed to warm to room temperature and stirred for a further 30 min. After removal of the volatiles *in vacuo* the pyrrolidine (±)-**6** (141 mg, 95%) was isolated as a colourless solid. δ_H (400 MHz, D_2O) 4.66 (O*H*), 4.48 (1 H, dt, *J* 4.3 and 4.1, CH_2-C*H*(OH)), 4.31 (1 H, d, *J* 4.6, CH_2-CH(OH)-C*H*(OH)), 3.96 (1 H, J_{AB} 12.5, CH_2OH), 3.83 (1 H, J_{AB} 12.2, CH_2OH), 3.77 (1 H, J_{AB} 12.5, CH_2OH), 3.74 (1 H, J_{AB} 12.2, CH_2OH), 3.45 (1 H, J_{AB} 12.7 and J_{AX} 4.6, CH_2N) and 3.36 (1 H, J_{AB} 12.7 and J_{BX} 3.0, CH_2N); δ_C (100 MHz, D_2O) 74.8, 72.8, 72.1, 62.7, 61.1 and 51.1; *m*/*z* (70 eV) 163 (M^+, 2%), 133 (41), 115 (17) and 36 (100) (Found: *m*/*z* 164.0916 (M^+ + H). $C_6H_{14}O_4N$ requires 164.0923).

2,2-Bis(benzyloxymethyl)-*N*-(*tert*-butoxycarbonyl)-2,5-dihydropyrrole 7

A mixture of the diol **3** (3.00 g, 13.1 mmol) and Aliquat-336 phase-transfer-catalyst (540 mg) was stirred well, and potassium hydroxide was added (218 mg, 0.3 eq.) with cooling at 0 °C in an ice bath. First benzyl bromide (3.4 cm^3, 2.2 eq.) was added dropwise and then again potassium hydroxide (1.96 g, 2.7 eq.) in small portions. The resulting mixture was slowly warmed up and stirred for 12 h at room temperature, and then stirred for 24 h at 50 °C. After the disappearance of the diol (monitored by TLC), methanol (16 cm^3) and ethyl acetate (8 cm^3) were added at room temperature and stirred for 4 h. The slurry was filtered through a pad of silica gel, washed with ethyl acetate and the filtrate concentrated under reduced pressure. Flash chromatography (eluting with cyclohexane–ethyl acetate 9 : 1) afforded the benzyl ether **7** (4.88 g, 91%) as a colourless oil. ν_{max}(film)/cm^{-1} 3080, 3060, 3020, 3005, 2960, 2910, 2850, 1690, 1635, 1540, 1450, 1385, 1360, 1325, 1250, 1170 and 730; δ_H (400 MHz, $CDCl_3$) 7.39–7.27 (10 H, m, *Ar*), 5.94–5.86 (2 H, m, *olefin*), 4.50 (1 H, J_{AB} 11.5, CH_2Ph), 4.49 (2 H, *ψ*s, CH_2Ph), 4.49 (1 H, J_{AB} 11.5, CH_2Ph), 4.20 (2 H × 0.5, *ψ*s, CH_2N), 4.14 (2 H × 0.5, *ψ*s, CH_2N), 3.94 (2 H × 0.5, J_{AB} 9.3, CH_2-Cq), 3.80 (2 H × 0.5, J_{AB} 9.3, CH_2-Cq), 3.71 (2 H × 0.5, J_{AB} 9.4, CH_2-Cq), 3.69 (2 H × 0.5, J_{AB} 9.4, CH_2-Cq), 1.49 (9 H × 0.5, s, ^{t}*Bu*) and 1.40 (9 H × 0.5, s, ^{t}*Bu*); δ_C (100 MHz, $CDCl_3$) 153.7, 153.5, 138.6, 138.3, 131.3, 131.2, 128.6, 128.4, 127.8, 127.7, 127.4, 127.3, 125.4, 125.4, 79.8, 79.1, 73.6, 73.4, 73.1, 72.1, 71.9, 71.1, 55.5, 28.5 and 28.4; *m*/*z* (70 eV) 409 (M^+, 4%), 288 (42), 188 (77), 158 (50), 91 (99) and 57 (100) (Found: *m*/*z* 410.2365 (M^+ + H). $C_{25}H_{32}O_4N$ requires 410.2331).

3,4-Bis(benzyloxy)-2,2-bis(benzyloxymethyl)-*N*-(*tert*-butoxycarbonyl)pyrrolidine (±)-8

The dibenzyl ether **7** (3.81 g, 9.30 mmol) and NMO (4.37 g, 32.3 mmol) were dissolved in acetone (30 cm^3), and a solution of osmium tetraoxide in water (48 cm^3, 2 mg cm^{-3}) was added at room temperature. The mixture was stirred for 2 days; after the disappearance of the olefin (monitored by TLC) a saturated solution of $Na_2S_2O_3$ was added and stirred for 30 min. The organic solvent was removed, and the product was extracted with diethyl ether (3 × 100 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Without any further purification the diol (*ca.* 3.7 g) was again benzylated according to the procedure described above. Flash chromatography (eluting with cyclohexane–ethyl

acetate 9 : 1) provided the tetrabenzyl ether (±)-**8** (4.66 g, 75%) as a colourless oil. ν_{max}(film)/cm^{-1} 3025, 2960, 2920, 2860, 1690, 1605, 1585, 1494, 1450, 1385, 1365, 1165, 1100, 1050, 735 and 695; δ_H (400 MHz, $CDCl_3$) 7.35–7.21 (20 H, m, *Ar*), 4.82–3.25 (14 H, m, CH_2Ar, Cq-CH_2, CH_2N), 1.48 (9 H × 0.55, s, ^{t}*Bu*) and 1.48 (9 H × 0.45, s, ^{t}*Bu*); δ_C (100 MHz, $CDCl_3$) 154.1, 153.9, 138.3, 138.1, 137.8, 137.1, 128.4, 128.3, 128.3, 128.2, 127.8, 127.8, 127.7, 127.5, 127.4, 127.3, 127.3, 126.8, 80.6, 79.8, 79.3, 73.7, 73.7, 73.3, 73.2, 71.9, 71.3, 70.4, 69.4, 68.2, 67.0, 66.8, 66.4, 66.2, 66.1, 65.8, 65.5, 65.0, 55.0, 28.4 and 28.3; *m*/*z* (70 eV) 623 (M^+, 2%), 502 (5), 476 (1), 432 (2), 403 (34), 312 (3), 220 (2), 181 (6), 91 (100) and 57 (72) (Found: *m*/*z* 624.3344 (M^+ + H). $C_{39}H_{46}O_6N$ requires 624.3325).

3,4-Bis(benzyloxy)-2,2-bis(benzyloxymethyl)pyrrolidine hydrochloride (±)-9·HCl

The tetrabenzyl ether (±)-**8** (780 mg, 1.25 mmol) was dissolved in methanol (2.0 cm^3) and added to a solution of HCl in methanol–methyl acetate (freshly prepared by addition of AcCl (5.5 cm^3) to methanol (18 cm^3) at 0 °C), and the mixture was allowed to warm to room temperature and stirred for a further 60 min. The volatiles were removed *in vacuo* to afford the pyrrolidine hydrochloride (±)-**9·HCl** (693 mg, 99%) as a colourless solid. δ_H (400 MHz, d_4-MeOH) 7.37–7.19 (20 H, m, *Ar*), 4.71 (1 H, J_{AB} 11.4, CH_2Ar), 4.61–4.53 (3 H, m, CH_2Ar), 4.60 (1 H, J_{AB} 11.4, CH_2Ar), 4.41 (1 H, d, *J* 11.5, CH_2Ar), 4.31–4.37 (4 H, m, CH_2Ar, C*H*(OBn)), 3.99 (1 H, J_{AB} 10.7, CH_2-Cq), 3.86 (1 H, J_{AB} 9.9, CH_2-Cq), 3.59 (1 H, J_{AB} 10.7, CH_2-Cq), 3.51 (1 H, d, *J* 12.2, CH_2N), 3.45 (1 H, J_{AB} 9.9, CH_2-Cq) and 3.19 (1 H, dd, *J* 12.2 and 3.2, CH_2N); δ_C (100 MHz, D_2O) 138.9, 138.8, 138.7, 138.5, 129.5, 129.5, 129.4, 129.2, 129.2, 129.1, 129.0, 128.9, 80.7, 76.9, 74.7, 74.6, 73.3, 70.1, 69.6, 69.0 and 48.8; *m*/*z* (70 eV) 523 (M^+, 1%), 432 (9), 416 (2), 402 (100), 312 (8), 181 (14) and 91 (67).

3,4-Bis(benzyloxy)-2,2-bis(benzyloxymethyl)-3,4-dihydro-2*H*-pyrrole 1-oxide (±)-10

The pyrrolidine hydrochloride (±)-**9·HCl** (535 mg, 0.955 mmol) was dissolved in methanol (10 cm^3) and water (10 cm^3) and adjusted to pH 8 with 1 M ammonia. The solvent was completely removed under reduced pressure and the residue redissolved in methanol (3 cm^3), filtered and concentrated to dryness. The remaining amine was then dissolved in chloroform (7 cm^3), and 2-(phenylsulfonyl)-3-phenyloxaziridine (524 mg, 2.1 eq.) was added at room temperature. The mixture was stirred for 2 h, filtered and concentrated under reduced pressure. Flash chromatography (eluting with cyclohexane–ethyl acetate 65 : 35) provided the pure nitrone (±)-**10** (280 mg, 54%) as a colourless syrup. ν_{max}(film)/cm^{-1} 3058, 3020, 2915, 2855, 1715, 1565, 1492, 1445, 1090, 730 and 694; δ_H (400 MHz, $CDCl_3$) 7.36–7.23 (20 H, m, *Ar*), 7.00 (1 H, ψs, C*H*N), 4.72–4.42 (10 H, m, CH_2Ar, C*H*(OBn)), 4.18 (1 H, J_{AB} 10.5, CH_2-Cq), 4.04 (1 H, J_{AB} 10.1, CH_2-Cq), 3.93 (1 H, J_{AB} 10.1, CH_2-Cq) and 3.80 (1 H, J_{AB} 10.5, CH_2-Cq); δ_C (100 MHz, $CDCl_3$) 137.0, 136.8, 136.7, 127.5, 127.4, 127.4, 127.3, 126.9, 126.9, 126.8, 126.7, 126.6, 126.5, 80.0, 74.6, 73.9, 72.7, 72.5, 72.4, 71.4, 68.0 and 67.0; *m*/*z* (70 eV) 537 (M^+, 0.6%), 520 (4), 446 (3), 430 (5), 416 (9), 338 (9), 181 (30), 105 (77) and 91 (100) (Found: *m*/*z* 538.2569 (M^+ + H). $C_{34}H_{36}O_5N$ requires 538.2593).

4,5-Bis(benzyloxy)-6,6-bis(benzyloxymethyl)-2-(*tert*-butyldiphenylsilyloxymethyl)hexahydropyrrolo[1,2-*b*]isoxazole (±)-11

The nitrone (±)-**10** (420 mg, 0.781 mmol) and allyl *tert*-butyldiphenylsilyl ether (370 mg, 1.6 eq.) were dissolved in toluene (21 cm^3) and heated at reflux for 18 h. After the reaction was completed (monitored by TLC) the solvent was removed under reduced pressure and the residual oil purified by flash chromatography (eluting with cyclohexane–ethyl acetate 95 : 5). The *exo*-cycloadduct (±)-**11** (345 mg, 53%) was eluted first as a colourless oil, and in a second fraction the *endo*-product was obtained (33 mg, 5%). ν_{max}(film)/cm^{-1} 3060, 3030, 2930, 2855, 1500, 1452, 1460, 1110, 745 and 695; δ_H (400 MHz, $CDCl_3$) 7.65 (4 H, ψd, *J* 7.1, Si*Ph*), 7.41–7.24 (26 H, m, *Ar*), 4.70 (1 H, d, *J* 11.2, CH_2Ar), 4.62–4.45 (7 H, m, CH_2Ar), 4.30 (1 H, d, *J* 5.1, Cq-C*H*(OBn)), 4.11 (1 H, ψquint., *J* 6.4, CH_2-C*H*O), 3.97 (1 H, dd, *J* 5.9 and 5.3, Cq-CH(OBn)-C*H*(OBn)), 3.94–3.86 (4 H, m, Cq-CH_2, C*H*N), 3.73 (1 H, J_{AB} 10.4 and J_{AX} 5.9, CH_2OTBDPS), 3.61 (1 H, m, Cq-CH_2), 3.58 (1 H, J_{AB} 10.4 and J_{BX} 5.3, CH_2OTBDPS), 2.11 (1 H, m, CH_2-CHN) and 1.97 (1 H, ddd, *J* 12.3, 6.2 and 2.4, CH_2-CHN); δ_C (100 MHz, $CDCl_3$) 138.7, 138.2, 135.6, 133.6, 133.4, 129.6, 128.3, 128.1, 127.8, 127.6, 127.5, 127.3, 127.2, 82.5, 81.4, 78.9, 74.9, 73.8, 73.4, 73.3, 72.4, 71.2, 69.4, 67.3, 65.4, 36.3, 26.8 and 19.2; *m*/*z* (70 eV) 772 (M^+ − 62, 2%), 740 (2), 711 (23), 637 (2), 564 (4), 520 (5), 444 (11), 414 (6), 336 (10), 296 (9), 241 (68), 199 (75), 163 (85) and 91 (100) (Found: *m*/*z* 834.4178 (M^+ + H). $C_{53}H_{60}O_6NSi$ requires 834.4190).

Methanesulfonic acid 4,5-bis(benzyloxy)-6,6-bis(benzyloxymethyl)hexahydropyrrolo[1,2-*b*]isoxazol-2-ylmethyl ester (±)-12

To a solution of (±)-**11** (296 mg, 0.355 mmol) in anhydrous THF (6.0 cm^3) was added tetrabutylammonium fluoride (112 mg, 1.0 eq.) and the mixture was stirred for 60 min at room temperature. The solvent was removed under reduced pressure; water (6 cm^3) was added to the residue and the mixture was extracted with diethyl ether (3 × 8 cm^3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated to dryness. The crude alcohol was directly converted into the mesylate by dissolving the residue in anhydrous CH_2Cl_2 (5.5 cm^3) at 0 °C followed by addition of anhydrous triethylamine (0.062 cm^3, 1.2 eq.) and dropwise methanesulfonic acid chloride (0.029 cm^3, 1.15 eq.) dissolved in anhydrous CH_2Cl_2 (0.30 cm^3). The mixture was allowed to warm to room temperature and was stirred for 120 min. After the reaction was completed (monitored by TLC) water (12 cm^3) was added and extracted with CH_2Cl_2 (3 × 8 cm^3). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (eluting with cyclohexane–ethyl acetate 7 : 3) to yield (±)-**12** (214 mg, 97%) as a colourless oil (Found: C, 67.36; H, 6.36; N, 2.00; S, 4.92. Calc. for $C_{38}H_{43}NO_8S$: C, 67.73; H, 6.43; N, 2.08; S, 4.76%); ν_{max}(film)/cm^{-1} 3075, 3035, 2935, 2870, 1495, 1450, 1355, 1170, 1090, 985, 960, 825, 735 and 695; δ_H (400 MHz, $CDCl_3$) 7.33–7.24 (20 H, m, *Ar*), 4.67 (1 H, J_{AB} 11.7, CH_2Ar), 4.59 (1 H, J_{AB} 12.0, CH_2Ar), 4.58 (1 H, J_{AB} 11.7, CH_2Ar), 4.53 (1 H, J_{AB} 12.0, CH_2Ar), 4.50 (2 H, ψs, CH_2Ar), 4.46 (1 H, J_{AB} 12.0, CH_2Ar), 4.42 (1 H, J_{AB} 12.0, CH_2Ar), 4.27 (1 H, d, *J* 4.6, Cq-C*H*(OBn)), 4.23 (1 H, dddd, *J* 6.7, 6.7, 6.7 and 3.2, C*H*-CH_2OMs), 4.16 (1 H, J_{AB} 10.9, J_{AX} 6.7, CH_2OMs), 4.16 (1 H, J_{AB} 10.9 and J_{BX} 3.0, CH_2OMs), 3.92 (2 H, m, C*H*N-C*H*(OBn)), 3.83 (2 H, ψs, Cq-CH_2), 3.82 (1 H, J_{AB} 9.9, Cq-CH_2), 3.58 (1 H, J_{AB} 9.9, Cq-CH_2), 2.92 (3 H, s, O*Ms*), 2.07 (1 H, m, CHN-CH_2) and 1.99 (1 H, ddd, *J* 12.2, 6.9 and 2.3, CHN-CH_2); δ_C (100 MHz, $CDCl_3$) 138.5, 138.4, 138.0, 137.9, 128.4, 128.2, 127.8, 127.7, 127.6, 127.5, 127.4, 82.3, 81.3, 75.6, 74.9, 73.9, 73.6, 73.5, 72.5, 71.0, 70.1, 69.3, 67.2, 37.4 and 35.1; *m*/*z* (70 eV) 582 (M^+ − Bn, 0.4%), 578 (M^+ − OMs, 2), 559 (2), 458 (63), 380 (7), 360 (7), 352 (2), 333 (3), 290 (3), 105 (87), 91 (84), 77 (100) and 51 (99).

rac-(1*S*,2*R*,6*S*)-3,3-Bis(hydroxymethyl)hexahydropyrrolizine-1,2,6-triol (±)-13

To a solution of the isoxazole (±)-**12** (136 mg, 0.202 mmol) in anhydrous methanol (15 cm^3) 135 mg palladium on charcoal (10%, Fluka) was added at room temperature. The resultant suspension was stirred under hydrogen (*ca.* 0.1 bar) for 3 days. After Pd/C was filtered off, the filtrate was concentrated. The residue was dissolved in a small amount of water and added

onto a column filled with Dowex 50W-X8 (H^+ form). After washing with water (2 × 25 cm^3) and propan-2-ol (15 cm^3) the imino sugar was eluted with 1 M aqueous ammonia, and the eluent was lyophilised to yield (±)-**13** (34 mg, 76%) as a colourless solid. δ_H (400 MHz, D_2O) 4.66 (O*H*), 4.33 (1 H, ψqi, *J* 6.4, C*H*(OH)-CH_2N), 4.16–4.11 (2 H, m, C*H*(OH)-C*H*(OH)-Cq), 3.80 (2 H, ψs, CH_2OH), 3.73 (1 H, J_{AB} 11.2, CH_2OH), 3.61 (1 H, J_{AB} 11.2, CH_2OH), 3.45 (1 H, q, *J* 7.1, C*H*N), 3.00 (1 H, J_{AB} 10.2, J_{AX} 5.6, CH_2N), 2.87 (1 H, J_{AB} 10.2, J_{BX} 7.1, CH_2N), 2.32 (1 H, ψqi, *J* 6.7, CH_2-CHN) and 1.64 (1 H, ddd, *J* 13.2, 6.6 and 6.9, CH_2-CHN); δ_C (100 MHz, D_2O) 78.4, 77.8, 74.0, 72.2, 69.0, 64.5, 63.5, 55.3 and 39.1; *m*/*z* (70 eV) 219 (M^+, 4%), 202 (4), 189 (100), 159 (10), 142 (14), 129 (12), 96 (32), 86 (91) and 79 (30) (Found: *m*/*z* 218.0955 ($M^+ - H$). $C_9H_{16}O_5N$ requires 218.1028).

Acknowledgements

This work was supported by a scholarship from the state Nordrhein-Westfalen for F. S. The authors also wish to thank Bayer AG, Wuppertal, for the high-resolution mass spectra.

References

1 H. Paulsen, *Angew. Chem.*, 1990, **102**, 851.
2 (*a*) J. Montreuil, J. F. Vliegenthart and H. Schachter, *Glycoproteins*, Elsevier, New York, 1995; (*b*) L. Warren, *Bound Carbohydrates in Nature*, Cambridge University Press, Cambridge, 1994; (*c*) C.-H. Wong, R. L. Halcomb, Y. Ichikawa and T. Kajimoto, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 521.
3 For reviews see (*a*) A. D. Elbein, *Am. Rev. Biochem.*, 1987, **56**, 497; (*b*) A. D. Elbein, *FASEB J.*, 1991, **5**, 3055; (*c*) B. Winchester and G. W. J. Fleet, *Glycobiology*, 1992, **2**, 199; (*d*) E. Truscheidt, W. Frommer, B. Junge, L. Muller, D. D. Schmidt and W. Wingender, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 744; (*e*) B. Winchester and G. W. J. Fleet, *J. Carbohydr. Chem.*, 2000, **19**, 471.
4 (*a*) R. A. Gruters, J. J. Neefjes, M. Tersmette, R. E. Y. de Goede, A. Tulp, H. G. Huisman, F. Miedema and H. L. Ploegh, *Nature*, 1987, **330**, 74; (*b*) G. W. J. Fleet, A. Karpas, R. A. Dwek, L. E. Fellows, A. S. Tyms, S. Petursson, S. K. Namgoong, N. G. Ramsden, P. W. Smith, J. C. Son, F. Wilson, D. R. Witty, G. S. Jacob and T. W. Rademacher, *FEBS Lett.*, 1988, **237**, 128; (*c*) L. Ratner, *AIDS Res. Hum. Retroviruses*, 1992, **8**, 8210.
5 (*a*) M. A. Spearman, J. M. Ballon, J. M. Gerrard, A. H. Greenberg and J. A. Wright, *Cancer Lett. (Shannon, Irel.)*, 1991, **60**, 185; (*b*) P. E. Goss, M. A. Baker, J. Carver and J. W. Dennis, *Clin. Cancer Res.*, 1995, **1**, 935; (*c*) J.-L. D. Klein, J. D. Roberts, M. D. George, J. Kurtzberg, P. Breton, J.-C. Chermann and K. Olden, *Br. J. Cancer*, 1999, **30**, 37; (*d*) K. Olden and P. Breton, *Pharmacol. Ther.*, 1990, **50**, 285; (*e*) R. Pili, J. Chang, R. A. Partis, R. A. Mueller, F. J. Chrest and A. Passaniti, *Cancer Res.*, 1995, **55**, 2920; (*f*) P. E. Goss, C. L. Peid, D. Bailey and J. W. Dennis, *Clin. Cancer Res.*, 1997, **3**, 1077.
6 (*a*) B. Junge, F.-R. Heiker, J. Kurz, L. Müller, D. D. Schmidt and C. Wünsche, *Carbohydr. Res.*, 1984, **128**, 235; (*b*) K. M. Robinson, E. W. Heineke and M. E. Begovic, *J. Nutr.*, 1990, **120**, 105; (*c*) P. B. Anzeveno, L. J. Creemer, J. K. Daniel, C.-H. R. King and P. S. Liu, *J. Org. Chem.*, 1989, **54**, 2539.
7 H. Häusler, R. P. Kawakami, E. Mlaker, W. B. Severn, T. M. Wrodnigg and A. E. Stütz, *J. Carbohydr. Chem.*, 2000, **19**, 435.
8 P. Sears and C.-H. Wong, *Angew. Chem.*, 1999, **111**, 2446.
9 According to IUPAC/IUBMB, cyclic sugar derivatives in which the ring oxygen has been replaced by NH have the class name "imino sugar". *Pure Appl. Chem.*, 1996, **68**, 1919.
10 (*a*) B. Ganem, *Acc. Chem. Res.*, 1996, **29**, 340; (*b*) S. G. Withers, *Pure Appl. Chem.*, 1995, **67**, 1673; (*c*) M. Ichikawa, *Bioorg. Med. Chem.*, 1995, **3**, 161.
11 (*a*) H.-J. Altenbach and G. Blanda, *Tetrahedron: Asymmetry*, 1998, **9**, 1519; (*b*) H.-J. Altenbach, D. J. Brauer and G. F. Merhof, *Tetrahedron*, 1997, **53**, 6019; (*c*) H.-J. Altenbach and G. F. Merhof, *Tetrahedron: Asymmetry*, 1996, **7**, 3087; (*d*) H.-J. Altenbach and K. Himmeldirk, *Tetrahedron: Asymmetry*, 1995, **6**, 1077.
12 (*a*) N. Asano, K. Oseki, H. Kizu and K. Matsui, *J. Med. Chem.*, 1994, **37**, 3701 and references cited therein; (*b*) G. W. J. Fleet, S. J. Nicholas, P. W. Smith, S. V. Evans, L. E. Fellows and R. J. Nash, *Tetrahedron Lett.*, 1985, **26**, 3127.
13 A. Defoin, T. Sifferlen, J. Streith, I. Dosbaâ and M.-J. Foglietti, *Tetrahedron: Asymmetry*, 1997, **8**, 363.
14 To the best of our knowledge, based on a literature search of the Beilstein chemical database and a CAS online structure search, these systems represent a formerly unknown class of pyrrolidine alkaloids. Similar structures known in the literature are the 2,2-disubstituted γ-lactams and saturated 2,2-bis(hydroxymethyl)pyrrolidine derivatives, for example (*a*) R. Kuciak and W. Sas, *Tetrahedron Lett.*, 1994, **35**, 8647; (*b*) Y. Kishida and A. Terada, *Chem. Pharm. Bull.*, 1969, **17**, 2417; (*c*) M. Koszytkowska-Stawinska, W. Sas and A. Sowinska, *J. Chem. Res. (S)*, 1998, 298; (*d*) T. Sheradsky and L. Yusupova, *Tetrahedron Lett.*, 1995, **36**, 7701; (*e*) S. Toii, H. Okumoto and A. Genba, *Chem. Lett.*, 1996, 747.
15 (*a*) J. W. Harbuck and H. Rapoport, *J. Org. Chem.*, 1972, **37**, 3618; (*b*) T. J. Donohoe and P. M. Guyo, *J. Org. Chem.*, 1996, **61**, 7664.
16 (*a*) H.-J. Altenbach, D. J. Brauer and G. F. Merhof, *Tetrahedron: Asymmetry*, 1996, **7**, 2493; (*b*) F. Schieweck and H.-J. Altenbach, *Tetrahedron: Asymmetry*, 1998, **9**, 403.
17 T. J. Donohoe, P. M. Guyo, R. L. Beddoes and M. Helliwell, *J. Chem. Soc., Perkin Trans. 1*, 1998, 667.
18 N. Bodor, K. B. Sloan, J. J. Kaminski, C. Shih and S. J. Pogany, *J. Org. Chem.*, 1983, **48**, 5280.
19 K. Soai and A. Okawa, *J. Org. Chem.*, 1986, **51**, 4000.
20 A. Nudelman, Y. Bechor, E. Falb, B. Fischer, B. A. Wexler and A. Nudelman, *Synth. Commun.*, 1998, **28**, 471.
21 G. Broggini and G. Zecchi, *Synthesis*, 1999, 905.
22 (*a*) J. J. Tufariello and J. P. Tette, *J. Chem. Soc., Chem. Commun.*, 1971, 469; (*b*) J. J. Tufariello and G. E. Lee, *J. Am. Chem. Soc.*, 1980, **102**, 373; (*c*) J. J. Tufariello and K. Winzenberg, *Tetrahedron Lett.*, 1986, **27**, 1645.
23 (*a*) F. A. Davis, J. M. Billmers, D. J. Gosciniak, J. C. Towson and R. D. Bach, *J. Org. Chem.*, 1986, **51**, 4240 and literature cited therein; (*b*) W. W. Zajac, Jr., T. R. Walters and M. G. Darcy, *J. Org. Chem.*, 1988, **53**, 5856.
24 (*a*) J. J. Tufariello and J. M. Puglis, *Tetrahedron Lett.*, 1986, **27**, 1265; (*b*) S. A. Ali, J. H. Khan, M. I. M. Wazer and H. P. Perzanowski, *Tetrahedron*, 1989, **45**, 5979 for 2,2-disubstituted nitrones; (*c*) H. G. Aurich, G. Frenzen and M. G. Rohr, *Tetrahedron*, 1994, **50**, 7417; (*d*) G. R. Delpierre and M. Lamchen, *J. Chem. Soc.*, 1963, 4693.