Conformationally Biased Mimics of Mannopyranosylamines: Inhibitors of β-Mannosidases?

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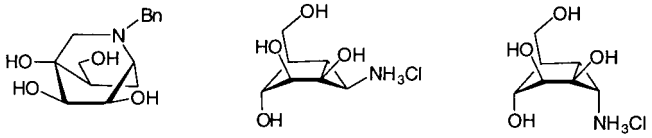
The enol ether **7** was prepared by cleavage of the N–O bond of the known isoxazolidine **3**, followed by *N*-alkylation to **4**, silylation and oxidation to the *N*-oxide **6**, and *Cope* elimination. Cu-Catalysed cyclopropanation of **7** led to the diastereoisomeric cyclopropanes **8** and **9**, which were subjected to a *Curtius* degradation. The resulting carbamates **12** and **16** were deprotected to the ammonium salts **14** and **18**, respectively. Both salts adopt a $B_{1,4}$ conformation, similarly as the ester **8**, while the isomeric ester **9** exists in a *ca.* 6:4 equilibrium of the $^4C_1$ and $B_{1,4}$ conformers. The β-mannoside mimic **14** does not inhibit snail β-mannosidase at 10 mM, but the α-mannoside mimic **18** inhibits *Jack* bean α-mannosidase ($IC_{50} = 80$ μM). These results are in keeping with the postulate that glycoside cleavage of β-D-glycopyranosides requires a conformational change in agreement with the principle of stereoelectronic control.

Introduction. – Cleavage of glycopyranosides by retaining β-glycosidases requires a conformational change of the tetrahydropyran ring to satisfy the principle of stereoelectronic control that postulates an antiperiplanar orientation of the scissile C,O bond and the double occupied nonbonding orbital of the endocyclic oxygen [1–3]. Crystal structures of three *endo*-glycosidases in complex with their substrate [4][5] or a substrate analogue [6] are in keeping with this hypothesis. Glycoside mimics possessing a skew-boat or boat-like conformation, and interacting with the catalytic acid and/or the catalytic nucleophile could, therefore, be closer to the transition state of an enzymic β-glycoside cleavage than mimics of a solvated oxycarbenium cation[1]). In keeping with this assumption are the observations that a tetrazole, mimicking the shape of an oxycarbenium cation, is only a partial transition-state analogue [7], that amino-cyclopentitols possessing a pseudo-axial amino group are strong and selective inhibitors of β-glucosidases and β-galactosidases [8][9], and that the (racemic) *manno*-configured isoquinuclidine **1** mimicking the $^{1,4}B$ conformation of a β-mannoside is a selective inhibitor ($K_i = 0.17$ μM) of snail β-mannosidase [10]. The inhibition by **1** is due to the free amine, as it is expected if the interaction of the amino group with the catalytic acid of the mannosidase contributes to binding. However, the inhibition could also be due to the interaction of the amino group of **1** with a carboxy group that does not correspond to the catalytic acid. There are three carboxy groups in the active site of a β-mannosidase from *Pyrococcus horikoshi* [11]. Two correspond to the catalytic acid and nucleophile, respectively. The third one appears to be close enough to the C(2)–OH group to interact with it, possibly facilitating a conformational change where the axial C(2)–OH group moves towards an equatorial position. This carboxy group,

[1]) A comparison of the inhibition by these two types of inhibitors is under scrutiny as it may contribute to distinguish between (relatively) early and late transition states.

rather than the catalytic acid, could interact with the amino group of **1**. Such an interaction could be independent of the conformational change of the substrate mimicked by the boat conformation of **1**, since the amino group of **1** would, in this case, mimic the HO–C(2) group rather than the glycosidic O-atom. It, therefore, appeared desirable to synthesise two structurally related mannoside analogues that cannot



1 **14** **18**

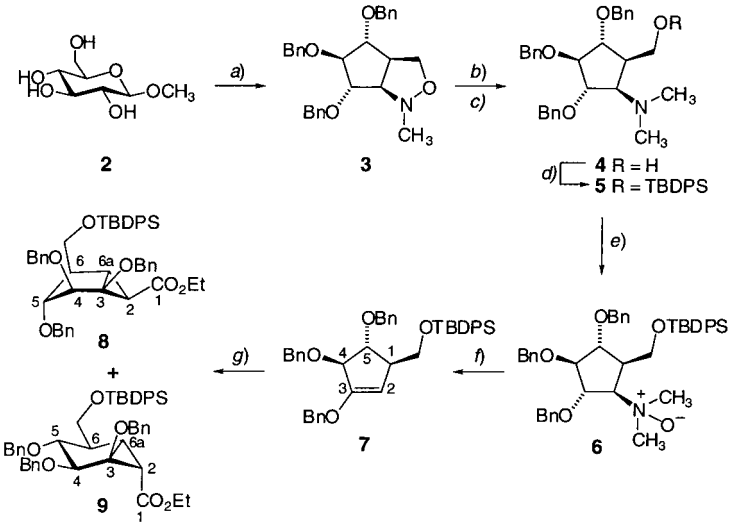
undergo the conformational change required by the principle of stereoelectronic control, but possess a basic N-atom corresponding to the glycosidic O-atom. One analogue should correspond to a β-mannoside, and the other one to the anomeric α-mannoside. The β-mannoside analogue should not inhibit β-mannosidases, if the conformatioinal change mentioned above is indeed required for the enzymic cleavage of a β-mannoside, while the α-mannoside mimic should inhibit α-mannosidases, as these do not require a similar conformational change of their substrate. We considered the bicyclic amines **14** and **18** suitable mimics satisfying these conditions, and describe their synthesis and inhibitory activity.

Results and Discussion. – The known isoxazolidine **3** (*Scheme 1*) was obtained in six steps and in an overall yield of 42% from methyl β-D-glucopyranoside [12–14]. Reductive cleavage of the N–O bond with $NaBH_4/NiCl_2$ [15], followed by reductive *N*-methylation, gave the amino alcohol **4** [16][17] that was protected to provide the *O*-silylated tertiary amine **5** in an overall yield of 69% from **3**. Oxidation with *m*-chloroperbenzoic acid (MCPBA) yielded 83% of the *N*-oxide **6** that was subjected to a *Cope* elimination [18], according to an earlier report [12]. Thus, heating neat **6** to 145° for 15 min gave the enol ether **7** (63%) besides 22% of the tertiary amine **5** (*cf.* [19]).

Cyclopropanation of the enol ether **7** with excess ethyl diazoacetate in the presence of Cu powder (0.2 equiv.) yielded 67% of a *ca.* 86 : 14 mixture of the diastereoisomeric cyclopropane carboxylates **8** and **9**, which were separated by HPLC. Hydrolysis of the ester **8** with ethanolic KOH provided the desilylated acid **10** (*Scheme 2*), which was acetylated to **11** and subsequently treated with ethyl chloroformate and NaN_3. The resulting acyl azide was subjected to a *Curtius* degradation by heating it in toluene, first in the absence, then in the presence of *t*-BuOH [20][21] to provide the *N*-Boc-protected amine **12** in an overall yield of 66% from **7**. Deacetylation of **12** to the alcohol **13**, and hydrogenolytic debenzylation of **13** in the presence of HCl at 6 bar H_2 resulted in almost quantitative yields of the cyclopropylammonium chloride **14**.

Hydrazinolysis of the isomeric ester **9** provided the hydrazide **15**, which was treated with $NaNO_2$ and HCl in DMF. The resulting acyl azide was degraded to the *N*-Boc-protected amine **16** similarly as described for **12** (66% from **9**). Desilylation of **16** with Bu_4NF in THF led to the alcohol **17**, which was hydrogenolytically debenzylated, similarly as described for **13**, to provide the cyclopropylammonium chloride **18** in high yield.

Scheme 1



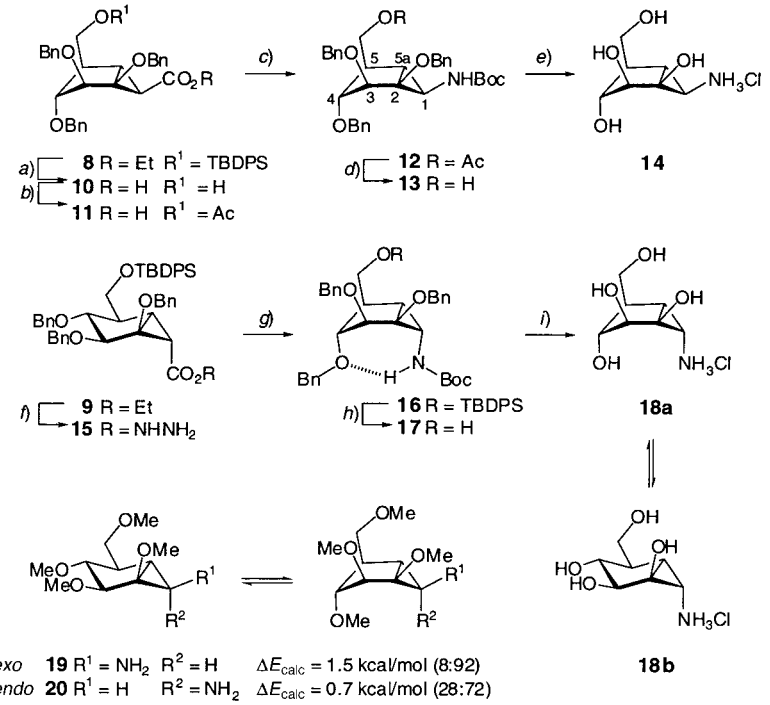
a) *Cf.* [12–14]; 42%. *b*) $NiCl_2$, $NaBH_4$, MeOH. *c*) CH_2O, AcOH, $NaBH_3CN$. *d*) (*t*-Bu)Ph_2SiCl (TBDPSCl), imidazole, DMF; 69% (from **3**). *e*) *m*-Chloroperbenzoic acid (MCPBA), CH_2Cl_2; 83%. *f*) 145°; 63%. *g*) N_2CHCO_2Et, Cu, toluene, 110°; 67%, **8**/**9** 86:14.

The enol ether **7** shows the typical enol ether IR absorption at 1650 cm^{-1}. Formation of the olefinic C=C bond is further evidenced by the H–C(2) *d* ($J = 2.3$ Hz) at 4.65 ppm and the disappearance of the H–C(OBn) *dd* at 3.81 ppm of **6**. The H–C(1) signal is shifted from 2.62 ppm in **6** to 2.78 ppm in **7**. H–C(4) of **7** resonates as a *d* ($J =$ 2.9 Hz) at 4.53 ppm. The C(2) *d* appears at 98.57 ppm and the C(3) *s* at 157.28 ppm. Formation of two cyclopropane carboxylates is confirmed by their spectroscopic data (*Table*). Particularly relevant are the IR bands and NMR signals for the EtOCO group, the appearance of a new proton signal assigned to H–C(2) at 2.63 and 2.42 ppm for **8** and **9**, respectively, and the replacement of the H–C(2) *d* of **7** by a *d* at 2.77 ppm for **8** and a *dd* at 2.12 ppm for **9**. The *J*(2,6a) values evidence the *trans* ($J \approx 3.0$ Hz) and *cis* arrangements ($J = 10.1$ Hz) for **8** and **9**, respectively [22–24]. The configuration of C(3) and C(6a) of **8** and **9** is evidenced by NOEs between H–C(2) and H–C(4) (4.8%) and between H–C(2) and H–C(6a) (3.9%) for **8** and by $J(6,6a) < 1$ Hz and $J(6,6a) = 1.5$ Hz for **8** and **9**, respectively. The chemical shift for H–C(6a) of **8**, and H–C(4) and H–C(6) of **9** is strongly influenced by the orientation of the EtOCO group[2]). The *cis*-oriented H–C(6a) of **8** is shifted downfield relative to H–C(6a) of **9** ($\Delta\delta = 0.65$ ppm). Similarly, the pseudoaxial EtOCO group causes a downfield shift for H–C(4) and H–C(6) of **9** in comparison to the corresponding signals of **8** ($\Delta\delta$(H–C(4)) = 0.71 ppm, $\Delta\delta$(H–C(6)) = 0.40 ppm).

The replacement of the EtOCO group of **8** and **9** by a (*t*-BuO)CONH (BocNH) group and the change of solvent from C_6D_6 to $CDCl_3$ lead to a downfield shift for

[2]) H–C(1) and the *cis*-oriented H–C(3) of ethyl 2,2-dimethylcyclopropanecarboxylate resonate at 1.42 and 1.03 ppm, respectively, downfield relative to the *trans*-oriented H–C(3) (0.76 ppm) [25][26].

Scheme 2



a) KOH, EtOH. *b*) Ac_2O, pyridine. *c*) 1. $ClCO_2CH_3$, Et_3N, acetone; 2. NaN_3, H_2O; 3. toluene, 110°; 4. *t*-BuOH, 110°; 66% (from **8**). *d*) K_2CO_3, MeOH; 93%. *e*) H_2, Pd/C, HCl, MeOH; quant. *f*) $NH_2NH_2 \cdot H_2O$, EtOH, 110°. *g*) 1. $NaNO_2$, HCl, DMF; 2. toluene, 110°; 3. *t*-BuOH, 110°; 66% (from **9**). *h*) Bu_4NF, THF; 94%. *i*) H_2, Pd/C, HCl, MeOH; quant.

H–C(1) of the carbamates **12** ($\delta = 3.08$ ppm) and **16** ($\delta = 3.49$ ppm), and to an upfield shift for H–C(5a) of **12** ($\delta = 1.61$ ppm) and **16** ($\delta = 1.83$ ppm). The ^{1}H-NMR spectra of the carbamates **12** and **13** are characterised by broad signals ($CDCl_3$ at 25°), due to hindered rotation about the NH–C(O) bond [27–29]), while **16** and **17** give rise to sharp signals. This difference is probably due to a NH···O–C(4) H-bond in **16** and **17** as evidenced by J(NH,1) (8.8 Hz for **16**; 9.0 Hz for **17**) and by a shift of the N–H band from 3436 cm^{-1} (**12** and **13**) to 3342 cm^{-1} for **16**, and 3344 cm^{-1} for **17**.

The ester **8**, the cyclopropylamines **12**, **13**, **16**, **17**, and the ammonium salts **14** and **18** adopt a boat conformation, as evidenced by $J(4,5) \approx J(5,6) \approx J(6,6a) < 1$ Hz and a long-range coupling between H–C(4) and H–C(6a) ($J(4,6a) < 1$ Hz) for **8** and $J(3,4) \approx J(4,5) \approx J(5,5a) < 1$ Hz, and a long-range coupling between H–C(3) and H–C(5a) ($J(3,5a) < 1$ Hz) for the derivates **12**–**14** and **16**–**18**[3]). Such a rigid boat conformation is a typical feature of bicyclo[3.1.0]hexane systems and has been confirmed in a few cases by X-ray crystallography and NMR analysis ([30][31] and ref. cit. therein). The

[3]) Force-field calculations (MM3*, gas phase) for the model compounds **19** and **20** evidence an equilibrium between $^4C_1$ and $B_{1,4}$ conformers (*ca.* 8:92 for **19** and 28:72 for **20**).

Table. *Selected* ^{1}*H-NMR Chemical Shifts* [ppm] *of Compounds* **8**, **9**, **12**, **13**, **14**, **16**, **17**, *and* **18**. For the sake of clarity, all compounds are numbered in the same way as **12** (see *Exper. Part*).

Compound	Solvent	H–C(1)	H–C(3)	H–C(4)	H–C(5)	H–C(5a)
8	C_6D_6	2.63	4.10	3.97	2.34	2.77
9	C_6D_6	2.42	4.81	4.42	2.74	2.12
12	CD_3OD	2.99	3.72	4.11	2.30	1.71
	$CDCl_3$	3.08	3.65	4.02	2.38	1.61
13	CD_3OD	2.96	3.80	4.11	2.16	1.73
	$CDCl_3$	3.04	3.70	4.02	2.28	1.68
16	$CDCl_3$	3.49	3.96	4.11	2.04	1.83
17	$CDCl_3$	3.61	3.97	3.97	1.97	1.88
14	CD_3OD	2.85	3.79[a])	3.84[a])	1.93	1.64
18	CD_3OD	3.04	3.99[a])	4.00[a])	1.99	1.83

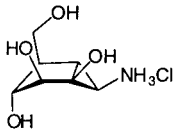
[a]) Assignment may be interchanged.

$J(4,5) = 5.3$ and $J(5,6) = 6.6$ Hz of the ester **9** evidence that this compound exists as an equilibrium of the $^5C_2$ and $B_{2,5}$ conformers. The position of the equilibrium (*ca.* 63 : 37) was deduced from the coupling constants that were calculated for the $^4C_1$ and $B_{1,4}$ conformers of the model compounds **19** and **20**[3]). The relatively high percentage of the $^5C_2$ conformer of **9** is probably due to a steric interaction between the pseudoaxial EtOCO and the BnO–C(5) substituents in the $B_{2,5}$ conformation.

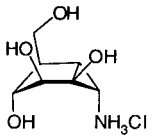
Inhibition Studies[4]). – The cyclopropylammonium chlorides **14** and **18** were tested against the β-mannosidase from snail (25°; pH 4.5) and the α-mannosidase from *Jack* beans (37°; pH 4.5).

The ammonium salt **14** does not inhibit snail β-mannosidase at a concentration of 10 mM and is a very poor inhibitor of α-mannosidase from *Jack* beans (*ca.* 30% inhibition at 12 mM). The ammonium salt **18** is a poor inhibitor of snail β-mannosidase (*ca.* 15% inhibition at 10 mM). It inhibits the α-mannosidase ($IC_{50} = 80$ μM).

The observation that the ammonium salt **14** (p*K ca.* 7) does not inhibit snail β-mannosidase is in keeping with the biased equatorial orientation of the ammonium (and the corresponding amino) group, *i.e.*, with the consequences of the principle of stereoelectronic control. The lack of inhibition could also be due to a combination of



14



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α-Mannosidase (Jack beans)	30% inhibition at [12 mM]	IC_{50} = 80 μM
β-Mannosidase (snail)	no inhibition at [10 mM]	15% inhibition at [10 mM]

[4]) Because of limited stability, the cyclopropylammonium chlorides **14** and **18** (see *Exper. Part*) were tested as crude products.

the basic properties of the cyclopropylamine (p*K ca.* 7; pH for the inhibition 4.5) and the predominant $B_{1,4}$ conformation. The inhibition by **18** of an α-mannosidase would then mean that the $B_{1,4}$ conformation is not as detrimental to the binding of **18** by the α-mannosidase as to the binding of **14** by the β-mannosidase, or that the $^4C_1$ conformer is sufficiently more favourable in **14** than in **18**. However, as indicated by the calculated energy difference (0.8 kcal/mol) between the boat and chair conformers of **19** and **20**, this factor cannot by itself explain the difference between the inhibition of the β- and α-mannosidases by **14** and **18**, respectively. The very weak inhibition of the β-mannosidase by **18**, and of the α-mannosidase by **14** may reflect an interaction of the catalytic nucleophile with the ammonium substituent. While these inhibition studies do not constitute a stringent proof for the importance of a conformational change during glycoside cleavage, as dictated by the principle of stereoelectronic control, they are in agreement with it.

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Experimental Part

General. Solvents were distilled immediately before use. TLC: *Merck* silica gel *60F-254* plates; detection by heating with mostain (400 ml of 10% H_2SO_4 soln., 20 g of $(NH_4)_6Mo_7O_{24}\cdot 6\ H_2O$, 0.4 g of $Ce(SO_4)_2$). Flash chromatography (FC): silica gel *Fluka 60* (0.04–0.063 mm). HPLC: *Merck*, with a self-packed prep. silica-gel column (250 × 20 mm, *Kromasil*-100 Å, 5-μm pore size). M.p.: uncorrected. Optical rotations: 1-dm cell. IR Spectra: KBr or 2% $CHCl_3$ soln. ^{1}H- (500 MHz, if not indicated otherwise) and ^{13}C-NMR (125 MHz, if not indicated otherwise): chemical shifts δ in ppm and coupling constants J in Hz; assignment of ^{1}H-NMR signals on the basis of DQFCOSY spectra and ^{13}C-NMR of HSQC spectra. α-Mannosidase (3.2.1.24, M-7257 from *Jack* beans), β-mannosidase (3.2.1.25, M-9400 as a suspension in acetone, from snail), and nitrophenyl α-D- and β-D-mannopyranoside were purchased from *Sigma* and used without any further purification.

*1*L*-(1,2,4/3,5)-3,4,5-Tri*-O*-benzyl-2-(dimethylamino)-1-(hydroxymethyl)cyclopentane-3,4,5-triol* (**4**) [12]. A soln. of **3** (10.56 g, 23.7 mmol) and $NiCl_2$ (6.14 g, 47.40 mmol) in MeOH (250 ml) was treated at r.t. with 6 portions of $NaBH_4$ (5.38 g, 142.20 mmol), and stirred for 5 h (TLC: complete consumption of **3**). Solvents were evaporated. The residue was treated with aq. NH_3 soln. (200 ml) and CH_2Cl_2 (250 ml), and stirred for 2 h. The org. layer was separated, and the aq. layer was extracted with CH_2Cl_2 (3 × 50 ml). The combined org. layers were dried ($MgSO_4$) and evaporated. A soln. of the residue (9.47 g) in CH_2Cl_2 (100 ml) was treated with CH_2O (36% in H_2O, 14 ml) and AcOH (20 ml), cooled to 0°, treated with $NaBH_3CN$ (1.46 g, 23.27 mmol), stirred for 15 min at 0° and for 4 h at r.t., and neutralised with sat. aq. K_2CO_3 soln. The org. layer was separated, and the aq. layer was extracted with $CHCl_3$ (3 × 50 ml). The combined org. layers were dried ($MgSO_4$). Evaporation of the solvent gave crude **4** (10.07 g), which was used for the next reaction. R_f (AcOEt) 0.15. R_f (CH_2Cl_2/MeOH 95 : 5) 0.10.

*1*L*-(1,2,4/3,5)-3,4,5-Tri*-O*-benzyl-1-{[(*tert*-butyl)diphenylsilyloxy]methyl}-2-(dimethylamino)cyclopentane-3,4,5-triol* (**5**). A soln. of crude **4** (10.07 g, 21.81 mmol) and imidazole (3.26 g, 47.88 mmol) in DMF (60 ml) was treated with TBDPSCl (6.14 ml, 24.00 mmol), stirred at r.t. for 3 h (TLC: complete consumption of **4**), treated with aq. NH_4Cl soln. (100 ml), and extracted with hexane (3 × 50 ml). The combined org. layers were dried ($MgSO_4$). Evaporation of the solvent and FC of the residue (AcOEt/hexane 1 : 12) gave **5** (11.48 g, 69% from **3**). R_f (AcOEt) 0.57. $[\alpha]_D^{25} = +9.4$ ($c = 0.65$, $CHCl_3$). IR ($CHCl_3$): 3058*w*, 3004*m*, 2940*m*, 2885*m*, 2856*m*, 2780*w*, 1955*w*, 1876*w*, 1809*w*, 1494*m*, 1429*w*, 1386*w*, 1365*w*, 1104*w*, 1072*w*, 1007*w*, 821*w*. ^{1}H-NMR ($CDCl_3$): 1.03 (*s*, *t*-Bu); 2.05 (*s*, Me_2N); 2.46 (br. *dt*, $J \approx 11.0$, 5.8, H–C(1)); 2.76 (*dd*, $J = 8.7$, 7.0, H–C(2)); 3.72 (*t*, $J \approx 11.0$, 1 H, CH_2–C(1)); 3.85 (*dd*, $J \approx 10.7$, 4.6, 1 H, CH_2–C(1)); 3.86 (br. *dd*, $J \approx 8.2$, 3.9, H–C(3)); 4.04 (*dt*, $J = 3.5$, 1.7, H–C(4)); 4.24 (br. *s*, H–C(5)); 4.44 (*d*, $J = 11.5$, PhC*H*), 4.45 (*d*, $J = 11.6$, PhC*H*); 4.55 (*d*, $J \approx 11.8$, PhC*H*); 4.58 (*d*, $J \approx 11.2$, PhC*H*); 4.59 (*d*, $J = 11.5$, PhC*H*); 4.63 (*d*, $J = 12.2$, PhC*H*); 7.22–7.68 (*m*, 25 arom. H). ^{13}C-NMR ($CDCl_3$): 19.22 (*s*, Me_3C); 26.90 (*q*, *Me*$_3$C); 44.91 (*q*, Me_2N); 48.05 (*d*, C(1)); 60.67 (*t*, *C*H$_2$–C(1)); 69.35 (*d*, C(2)); 70.87, 71.54, 71.66 (3*t*, 3 Ph*C*H$_2$); 81.67 (*d*, C(5)); 88.20 (*d*, C(3)); 90.31 (*d*, C(4)); 127.41–129.63

(several *d*); 133.63, 133.73 (2*s*); 135.61, 135.65 (4*d*); 138.15, 138.35, 138.67 (3*s*). HR-MALDI-MS: 700.383 ($C_{45}H_{54}NO_4Si^+$, $[M+H]^+$); calc. 700.378). Anal. calc. for $C_{45}H_{53}NO_4Si$ (700.00): C 77.21, H 7.63; N 2.00; found: C 77.32, H 7.84, N 2.07.

N,N-*Dimethyl*-N-*{*IL*-(1,2,4/3,5)-3,4,5-tri*-O-*benzyl-1-{[(*tert*-butyl)diphenylsilyloxy]methyl}cyclopentane-3,4,5-triol-2-yl}amine Oxide* (**6**). A soln. of **5** (780 mg, 1.11 mmol) in CH_2Cl_2 (3 ml) was treated at 0° with MCPBA (206 mg, 1.19 mmol) and stirred at r.t. for 15 min. Evaporation, FC (basic Al_2O_3, activity I; AcOEt then CH_2Cl_2/MeOH 6:1), and drying *i.v.* gave **6** (662 mg, 83%), which was immediately used for the next reaction. R_f (AcOEt/acetone 1:1, Al_2O_3) 0.5.

IL-(1,4/5)-3,4,5-Tri-O-*benzyl-1-{[(*tert*-butyl)diphenylsilyloxy]methyl}-cyclopent-2-ene-3,4,5-triol* (**7**). Neat **6** (660 mg, 0.92 mmol) was heated at 145° for 15 min. FC (hexane/AcOEt 15:1 → 6:1) gave **7** (383 mg, 63%) and **5** (140 mg, 22%). R_f (AcOEt/cyclohexane 8:1) 0.54. $[\alpha]_D^{25} = -7.8$ ($c = 0.485$, $CHCl_3$). IR ($CHCl_3$): 3074*w*, 3021*w*, 2999*m*, 2925*m*, 2859*m*, 1954*w*, 1874*w*, 1812*w*, 1650*m*, 1587*w*, 1497*w*, 1453*m*, 1427*m*, 1389*w*, 1352*m*, 1310*w*, 1108*s*, 1021*m*, 936*w*, 842*w*. ^{1}H-NMR ($CDCl_3$): 1.06 (*s*, *t*-Bu); 2.78 (*tt*, $J \approx 6.1, 3.0$, H–C(1)); 3.63 (*dd*, $J = 10.0, 6.2$, 1 H, CH_2–C(1)); 3.66 (*dd*, $J = 10.0, 6.9$, 1 H, CH–C(1)); 3.94 (*t*, $J \approx 2.9$, H–C(5)); 4.53 (*d*, $J = 11.8$, PhC*H*); 4.53 (*d*, $J = 2.9$, H–C(4)); 4.58 (*d*, $J = 11.8$, PhC*H*); 4.62 (*d*, $J = 11.9$, PhC*H*); 4.65 (*d*, $J = 2.3$, H–C(2)); 4.75 (*d*, $J = 11.9$, PhC*H*); 4.78 (*d*, $J = 11.7$, PhC*H*); 4.82 (*d*, $J = 11.7$, PhC*H*); 7.23–7.66 (*m*, 25 arom. H). ^{13}C-NMR ($CDCl_3$): 19.31 (*s*, Me_3C); 26.92 (*q*, *Me*$_3$C); 49.02 (*d*, C(1)); 66.73 (*t*, *C*H$_2$–C(1)); 71.14, 71.45, 71.71 (3*t*, 3 PhC*H*$_2$); 84.55 (*d*, C(5)); 86.52 (*d*, C(4)); 98.57 (*d*, C(2)); 127.38–129.62 (several *d*); 133.73, 133.74 (2*s*); 133.63, 135.65 (4*d*); 136.77, 138.43, 138.62 (3*s*); 157.28 (*s*, C(3)). Anal. calc. for $C_{43}H_{46}O_4Si$ (654.91): C 78.86, H 7.08; found: C 78.78, H 7.13.

Cyclopropanation of **7**. A soln. of ethyl diazoacetate (2.1 ml, 20 mmol) in dry toluene (40 ml) was added over a period of 10 h (syringe pump) to a suspension of Cu powder (51 mg, 0.8 mmol) and **7** (2.69 g, 4.10 mmol) in dry toluene (10 ml) at 110°. Evaporation and FC (CH_2Cl_2) gave a mixture **8**/**9** 86:14 (2.025 mg, 67%). The isomers were separated by prep. HPLC (CH_2Cl_2, 10 ml/min).

Ethyl 3,4,5-Tri-O-*benzyl-7*-O-*[(*tert*-butyl)diphenylsilyl]-2,6-dideoxy-2,6-methylene*-D-glycero-D-gulo-*3,6a-cycloheptonate* (**8**). R_f (CH_2Cl_2) 0.51. Prep. HPLC: t_R (CH_2Cl_2, 10 ml/min) 23 min. $[\alpha]_D^{25} = +12.1$ ($c = 0.92$, $CHCl_3$). IR ($CHCl_3$): 3055*w*, 3046*w*, 3005*w*, 2933*m*, 2861*m*, 1959*w*, 1882*w*, 1815*w*, 1718*m*, 1497*w*, 1471*w*, 1458*w*, 1426*m*, 1369*m*, 1303*w*, 1282*w*, 1190*m*, 1113*s*, 1101*s*, 1091*s*, 1026*m*, 826*w*. ^{1}H-NMR (C_6D_6): 0.93 (*t*, $J = 7.2$, *Me*CH$_2$O); 1.16 (*s*, *t*-Bu); 2.34 (*t*, $J = 8.2$, irrad. at 2.63 → NOE of 2.8%, irrad. at 2.77 → NOE of 3.2%, irrad. at 3.97 → NOE of 2.5%, irrad. at 4.10 → NOE of 0.2%, H–C(6)); 2.63 (*d*, $J = 4.0$, irrad. at 4.10 → NOE of 4.8%, irrad. at 2.34 → NOE of 3.9, irrad. at 2.77 → NOE of 1.0%, H–C(2)); 2.77 (br. *d*, $J \approx 3.0$, irrad. at 2.34 → NOE of 3.4%, irrad. at 2.63 → NOE of 1.0%, H–C(6a)); 3.85 (*dd*, $J = 10.1, 8.2$, H–C(7)); 3.88 (*dd*, $J = 10.1, 8.2$, H′–C(7)); 3.97 (*s*, irrad. at 2.34 → NOE of 2.5%, irrad. at 4.10 → NOE of 2.5%, H–C(5)); 3.98 (*dq*, $J = 10.9$, 7.2, 1 H, MeC*H*$_2$O); 4.03 (*dq*, $J = 10.9$, 7.2, 1 H, MeC*H*$_2$O); 4.10 (br. *s*, irrad. at 2.63 → NOE of 2.8%, irrad. at 3.97 → NOE of 2.5%, irrad. at 2.34 → NOE of 0.2%, H–C(4)); 4.26 (*d*, $J = 12.4$, PhC*H*); 4.32 (*d*, $J = 12.4$, PhC*H*); 4.40 (*d*, $J = 12.2$, PhC*H*); 4.44 (*d*, $J = 12.2$, PhC*H*); 4.68 (*d*, $J = 10.5$, PhC*H*); 4.74 (*d*, $J = 10.5$, PhC*H*); 7.06–7.79 (*m*, 25 arom. H). ^{13}C-NMR (C_6D_6): 14.24 (*q*, *Me*CH$_2$O); 19.51 (*s*, Me_3C); 27.18 (*q*, *Me*$_3$C); 30.74 (*d*, C(2)); 31.82 (*d*, C(6a)); 48.58 (*d*, C(6)); 60.53 (*t*, MeCH$_2$O); 65.11 (*t*, C(7)); 71.37, 72.55, 73.83 (3*t*, 3 PhCH$_2$); 75.23 (*s*, C(3)); 84.17 (*d*, C(5)); 85.57 (*d*, C(4)); 127.69–128.66 (several *d*); 133.90, 134.01 (2*s*); 136.03 (4*d*); 138.67, 138.75, 138.86 (3*s*); 168.64 (*s*, C(1)). HR-MALDI-MS: 763.342 ($C_{47}H_{52}NaO_6Si^+$, $[M+Na]^+$; calc. 763.340). Anal. calc. for $C_{47}H_{52}O_6Si$ (741.01): C 76.18, H 7.07; found: C 76.33, H 7.03.

Ethyl 3,4-5-Tri-O-*benzyl-7*-O-*[(*tert*-butyl)diphenylsilyl]-2,6-dideoxy-2,6-methylene*-D-glycero-D-ido-*3,6a-cycloheptonate* (**9**). R_f (CH_2Cl_2) 0.56. Prep. HPLC: t_R (CH_2Cl_2, 10 ml/min) 18 min. $[\alpha]_D^{25} = +16.2$ ($c = 0.575$, $CHCl_3$). IR ($CHCl_3$): 3067*w*, 3011*m*, 2923*m*, 2862*m*, 1959*w*, 1887*w*, 1815*w*, 1717*s*, 1492*w*, 1477*s*, 1456*m*, 1426*m*, 1374*w*, 1364*m*, 1303*w*, 1215*m*, 1169*m*, 1113*s*, 1093*m*, 1026*m*, 918*w*, 820*m*. ^{1}H-NMR (C_6D_6): 0.96 (*t*, $J = 7.1$, *Me*CH$_2$O); 1.14 (*s*, *t*-Bu); 2.12 (*dd*, $J = 10.1, 1.5$, irrad. at 2.42 → NOE of 7.3%, irrad. at 2.74 → NOE of 2.2%, H–C(6a)); 2.42 (*d*, $J = 10.1$, irrad. at 2.12 → NOE of 8.9%, H–C(2)); 2.74 (*dtd*, $J \approx 6.7, 5.3, 1.6$, irrad, at 2.12 → NOE of 2.3%, irrad. at 4.42 → NOE of 2.2%, H–C(6)); 3.86 (*dd*, $J = 10.3, 5.1$, H–C(7)); 3.91 (*dd*, $J = 10.6, 5.3$, H′–C(7)); 3.92 (*dq*, $J = 10.9$, 7.2, 1 H, MeC*H*$_2$O); 3.96 (*dq*, $J = 10.9$, 7.2, 1 H, MeC*H*$_2$O); 4.42 (*dd*, $J = 6.6$, 5.4, irrad. at 2.74 → NOE of 1.9%, H–C(5)); 4.53 (*d*, $J = 11.5$, PhC*H*); 4.59 (*d*, $J = 12.0$, PhC*H*); 4.66 (*d*, $J = 11.6$, PhC*H*); 4.72 (*d*, $J = 12.1$, PhC*H*); 4.81 (*d*, $J = 12.0$, PhC*H*); 4.81 (*d*, $J = 5.3$, irrad. at 4.42 → NOE of 2.2%, irrad. at 2.74 → NOE of 1.9%, H–C(4)); 5.05 (*d*, $J = 11.6$, PhC*H*); 7.03–7.76 (*m*, 25 arom. H). ^{13}C-NMR (C_6D_6): 14.24 (*q*, *Me*CH$_2$O); 19.56 (*s*, Me_3C); 27.17 (*q*, *Me*$_3$C); 30.99 (*d*, C(6a)); 33.83 (*d*, C(2)); 42.14 (*d*, C(6)); 60.34 (*t*, MeCH$_2$O); 64.67 (*t*, C(7)); 71.93 (*s*, C(3)); 72.05, 72.87, 73.11 (3*t*, 3 PhCH$_2$); 83.10 (*d*, C(4)); 89.06 (*d*, C(5)); 127.49–128.49 (several *d*); 133.88, 133.99 (2*s*); 136.06 (4*d*); 138.98, 139.06, 139.46 (3*s*); 168.80 (*s*, C(1)). HR-

MALDI-MS: 763.344 ($C_{47}H_{52}NaO_6Si^+$, $[M+Na]^+$; calc. 763.340). Anal. calc. for $C_{47}H_{52}O_6Si$ (741.01): C 76.18, H 7.07; found: C 75.94, H 6.86.

3,4,5-Tri-O-*benzyl-2,6-dideoxy-2,6-methylene*-D-glycero-D-gulo-*3,6a-cycloheptonic Acid* (**10**). A soln. of **8** (1.027 g, 1.38 mmol) in EtOH (40 ml) and 1N aq. KOH soln. (20 ml) was heated at 100° for 15 h (TLC: complete consumption of **7**), neutralised with 2.5N aq. HCl soln., and extracted with Et_2O (3 × 30 ml). The combined org. layers were dried ($MgSO_4$). Evaporation of the solvents gave crude **10** (865 mg), which was used for the next reaction. R_f (AcOEt/cyclohexane 1:1) 0.29.

7-O-*Acetyl-3,4,5-tri*-O-*benzyl-2,6-dideoxy-2,6-methylene*-D-glycero-D-gulo-*3,6a-cycloheptonic Acid* (**11**). A soln. of crude **10** (865 mg, *ca.* 1.82 mmol) in Ac_2O (345 µl, 3.64 mmol) and pyridine (10 ml) was kept at r.t. for 4 h (TLC: complete consumption of **10**), treated with aq. NH_4Cl soln. (10 ml), and extracted with CH_2Cl_2 (3 × 20 ml). The combined org. layers were dried ($MgSO_4$). Evaporation of the solvents gave crude **11** (963 mg), which was used for the next reaction. R_f (AcOEt/cyclohexane 1:1) 0.49.

6-O-*Acetyl-2,3,4-tri*-O-*benzyl*-N-*[(*tert-*butoxy)carbonyl]-5a-carba-2,5a-cyclo-β*-D-*glucopyranosylamine* (**12**). A soln. of crude **11** (787 mg, 1.52 mmol) in dry acetone (9 ml) was cooled to 0°, treated with Et_3N (276 µl, 1.98 mmol) and ethyl chloroformate (164 µl, 2.13 mmol), stirred for 1 h at 0°, treated with a soln. of NaN_3 (158 mg, 2.44 mmol) in H_2O (3.5 ml), and stirred for 30 min at 0° and for 2 h at 23°. Acetone was removed *i.v.* at 23°. The residue was treated with H_2O (10 ml) and extracted with Et_2O (2 × 20 ml). The combined org. phases were washed with H_2O (10 ml), dried ($MgSO_4$), freed of solvents at 23°, and dried *i.v.* at 23° for 12 h to give crude acyl azide (805 mg) as a colourless oil, sufficiently clean for the following reaction.

A soln. of the acyl azide (805) in dry toluene (4 ml) was kept at 100° for 1.5 h (TLC: complete consumption of the azide), treated with dry *t*-BuOH (15 ml), and kept for 24 h at 100°. Evaporation of the solvents and FC of the residue (AcOEt/cyclohexane 1:8 → 1:4) gave **12** (555 mg, 66% from **7**). R_f (AcOEt/cyclohexane 1:2) 0.41. $[\alpha]_D^{25} = -12.4$ ($c = 0.42$, $CHCl_3$). IR ($CHCl_3$): 3436*w*, 3067*w*, 3005*w*, 2974*m*, 2933*w*, 2872*w*, 1959*w*, 1877*w*, 1815*w*, 1733*s*, 1708*s*, 1497*m*, 1451*m*, 1426*m*, 1390*m*, 1364*m*, 1251*s*, 1220*s*, 1164*s*, 1077*m*, 1041*m*, 913*w*, 861*w*. ^{1}H-NMR (CD_3OD): 1.37 (*s*, *t*-Bu); 1.71 (br. *d*, $J \approx 2.2$, H–C(5a)); 1.98 (*s*, AcO); 2.30 (br. *t*, $J \approx 8.0$, H–C(5)); 2.99 (*d*, $J =$ 2.4, H–C(1)); 3.72 (br. *s*, irrad. at 1.71 → *s*, H–C(3)); 4.09 (*dd*, $J = 10.9$, 8.1, H–C(6)); 4.11 (*s*, H–C(4)); 4.16 (*dd*, $J = 10.9$, 7.7, H′–C(6)); 4.46 (*s*, PhCH_2); 4.50 (*d*, $J = 11.2$, PhC*H*); 4.51 (*d*, $J = 12.1$, PhC*H*); 4.55 (*d*, $J = 12.2$, PhC*H*); 4.70 (*d*, $J = 11.2$, PhC*H*); 7.22–7.37 (*m*, 15 arom. H). ^{13}C-NMR (CD_3OD): 20.88 (*q*, Me); 28.75 (*q*, *Me*$_3$C); 31.09 (*d*, C(5a)); 36.27 (*d*, C(1)); 45.70 (*d*, C(5)); 66.21 (*t*, C(6)); 72.13 (*t*, Ph*C*H$_2$); 72.80 (*s*, Me$_3$*C*); 73.13, 73.68 (2*t*, 2 Ph*C*H$_2$); 80.49 (*s*, C(2)); 84.42 (*d*, C(3)); 84.70 (*d*, C(4)); 128.63–129.50 (several *d*); 139.36, 139.44, 139.66 (3*s*); 159.02 (*s*, ^{t}BuC=O); 172.68 (*s*, C=O). HR-MALDI-MS: 610.278 ($C_{35}H_{41}NaNO_7^+$, $[M+Na]^+$; calc. 610.278). Anal. calc. for $C_{35}H_{41}NO_7$ (587.71): C 71.53, H 7.03, N 2.38; found: C 71.29, H 6.90, N 2.41.

2,3,4-Tri-O-*benzyl*-N-*[(*tert-*butoxy)carbonyl]-5a-carba-2,5a-cyclo-β*-D-*glucopyranosylamine* (**13**). A soln. of **12** (121 mg, 0.21 mmol) and K_2CO_3 (80 mg, 0.57 mmol) in MeOH (1.5 ml) was stirred at r.t. for 45 min (TLC: complete consumption of **12**), treated with aq. NH_4Cl soln. (5 ml), and extracted with Et_2O (3 × 10 ml). The combined org. layers were dried ($MgSO_4$). Evaporation of the solvents and FC (AcOEt/hexane 1:2) gave **13** (104 mg, 93%). R_f (AcOEt/cyclohexane 1:2) 0.15. $[\alpha]_D^{25} = -19.7$ ($c = 0.655$, $CHCl_3$). IR ($CHCl_3$): 3605*w*, 3436*m*, 3013*w*, 2998*m*, 2978*m*, 2920*m*, 2875*m*, 1955*w*, 1876*w*, 1809*w*, 1708*s*, 1601*w*, 1495*m*, 1450*m*, 1394*m*, 1362*m*, 1306*w*, 1164*m*, 1078*m*, 1026*m*, 908*w*, 863*w*. ^{1}H-NMR (CD_3OD): 1.38 (*s*, *t*-Bu); 1.73 (br. *d*, irrad. at 3.80 → *d*, $J \approx 2.2$, H–C(5a)); 2.16 (*t*, $J \approx 8.0$, H–C(5)); 2.96 (*d*, $J = 2.4$, H–C(1)); 3.58 (*dd*, $J = 10.7$, 8.5, H–C(6)); 3.65 (*dd*, $J =$ 10.7, 7.6, H′–C(6)); 3.80 (br. *s*, irrad. at 1.73 → *s*, H–C(3)); 4.11 (*s*, H–C(4)); 4.49 (*s*, PhCH_2); 4.49 (*d*, $J = 11.1$, PhC*H*); 4.50 (*d*, $J = 11.8$, PhC*H*); 4.59 (*d*, $J = 11.8$, PhC*H*); 4.68 (*d*, $J = 11.1$, PhC*H*); 7.23–7.34 (*m*, 15 arom. H). ^{13}C-NMR (CD_3OD): 28.75 (*q*, *Me*$_3$C); 31.30 (*d*, C(5a)); 36.32 (*d*, C(1)); 49.32 (*d*, C(5)); 64.16 (*t*, C(6)); 72.14 (*t*, Ph*C*H$_2$); 72.77 (*s*, Me$_3$*C*); 72.90, 73.58 (2*t*, 2 Ph*C*H$_2$); 80.41 (*s*, C(2)); 84.54 (*d*, C(3)); 84.93 (*d*, C(4)); 128.29–129.45 (several *d*); 139.49, 139.62, 139.69 (3*s*); 159.07 (*s*, C=O). HR-MALDI-MS: calc. for $C_{33}H_{39}NaNO_6^+$ 568.269; found: 568.268 ($[M+Na]^+$). Anal. calc. for $C_{33}H_{39}NO_6$ (545.67): C 72.64, H 7.20, N 2.57; found: C 72.62, H 7.38, N 2.60.

5a-Carba-2,5a-cyclo-β-D-*glucopyranosylammonium Chloride* (**14**). Hydrogenation of **13** (66 mg, 0.12 mmol) in MeOH (5 ml) and conc. HCl (0.7 ml) in the presence of 10% Pd/C (57 mg) at 6 bar for 24 h, filtration through *Celite*, washing of the residue with MeOH (5 ml), and evaporation of the combined filtrates gave crude **14** (25.9 mg, quant.). Colourless unstable solid (dec. after *ca.* 12 h). ^{1}H-NMR (300 MHz, CD_3OD): 1.64 (br. *s*, irrad. at 2.85 → *s*, H–C(5a)); 1.93 (*t*, irrad. at 3.66 → *s*, $J \approx 6.0$, H–C(5)); 2.85 (br. *s*, irrad. at 1.64 → *s*, H–C(1)); 3.62 (*dd*, $J \approx 10.6$, 6.5, irrad. at 1.93 → *d*, $J = 10.6$, H–C(6)); 3.68 (*dd*, $J \approx 10.9$, 5.9, irrad. at 1.93 → *d*, $J = 10.6$, H′–C(6)); 3.79, 3.84 (2*s*, H–C(3), H–C(4)). ^{13}C-NMR (75 MHz, CD_3OD): 30.94, 33.26 (2*d*, C(1), C(5a)); 51.02 (*d*, C(5)); 64.14 (*t*, C(6)); 66.00 (*s*, C(2)); 79.00, 80.61 (2*d*, C(3), C(4)). ESI-MS: 176 ($[M+Na]^+$).

3,4,5-Tri-O-*benzyl*-7-O-*[(*tert-*butyl)diphenylsilyl]*-*2,6-dideoxy-2,6-methylene-3,6a-cyclo*-D-glycero-D-ido-*heptonohydrazide* (**15**). A mixture of **9** (170 mg, 0.23 mmol) and $NH_2NH_2 \cdot H_2O$ (4 ml) in EtOH (5 ml) was heated at 110° for 6 h (TLC: complete consumption of **9**). Solvents were evaporated and co-evaporated with toluene (3 × 3 ml) to give crude **15** (171 mg), which was used for the next reaction.

2,3,4-Tri-O-*benzyl*-N-*[(*tert-*butoxy)carbonyl]*-*6*-O-*[(*tert-*butyldiphenylsilyl]*-*5a-carba-2,5a-cyclo*-α-D-*glucopyranosylamine* (**16**). A soln. of crude **15** (171 mg, *ca.* 0.23 mmol) in DMF (4 ml) was treated at −10° with 3N HCl (1 ml) and, after 5 min, with $NaNO_2$ (18 mg, 0.26 mmol). The mixture was stirred for 15 min, treated with H_2O (5 ml), and extracted with Et_2O (3 × 10 ml). The combined org. phases were dried ($MgSO_4$). Solvents were evaporated at 23°. Drying of the residue *i.v.* at 23° for 12 h gave crude acyl azide (805 mg) as a colourless oil, sufficiently clean for the following reaction step.

A soln. of the crude acyl azide (172 mg) in dry toluene (3 ml) was kept at 100° for 1.5 h (TLC: complete consumption of the azide), treated with dry *t*-BuOH (10 ml), and kept for 24 h at 100°. Evaporation of the solvents and FC (AcOEt/cyclohexane 1:8 → 1:5) gave **16** (119 mg, 66% from **9**). R_f (AcOEt/cyclohexane 1:3) 0.57. $[\alpha]_D^{25} = -12.6$ ($c = 0.52$, $CHCl_3$). IR ($CHCl_3$): 3342*m*, 3045*w*, 3011*m*, 2975*m*, 2928*m*, 2867*m*, 1955*w*, 1872*w*, 1817*w*, 1711*s*, 1525*m*, 1496*m*, 1449*m*, 1392*m*, 1361*m*, 1230*m*, 1156*m*, 1081*m*, 1026*m*, 910*w*, 831*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.07 (*s*, *t*-Bu); 1.41 (*s*, *t*-Bu); 1.83 (br. *d*, $J \approx 9.1$, H−C(5a)); 2.04 (br. *t*, $J \approx 8.0$, H−C(5)); 3.49 (br. *t*, $J \approx 8.2$, H−C(1)); 3.76 (*t*, $J \approx 10.0$, H−C(6)); 3.80 (*dd*, $J = 10.0, 6.3$, H′−C(6)); 3.96 (br. *s*, H−C(3)); 4.11 (br. *s*, H−C(4)); 4.41 (*d*, $J = 11.3$, PhC*H*); 4.49 (*d*, $J = 11.3$, PhC*H*); 4.54 (*d*, $J = 11.6$, PhC*H*); 4.56 (*s*, PhCH_2); 4.71 (*d*, $J = 11.6$, PhC*H*); 5.86 (br. *d*, $J \approx 8.8$, NH); 7.22–7.73 (*m*, 25 arom. H). ^{13}C-NMR (100 MHz, $CDCl_3$): 19.29 (*s*, Me_3*C*Si); 26.91 (*q*, *Me*$_3$CSi); 29.71 (*q*, *Me*$_3$CO); 30.82 (*d*, C(5a)); 38.95 (*d*, C(1)); 44.51 (*d*, C(5)); 65.22 (*t*, C(6)); 70.96 (*s*, Me_3*C*O); 71.90, 72.58, 72.93 (3*t*, 3 Ph*C*H_2); 79.84 (*s*, C(2)); 83.36 (*d*, C(4)); 88.12 (*d*, C(3)); 127.75–129.43 (several *d*); 133.86, 133.92 (2*s*); 135.57 (4*d*); 137.86, 138.01, 138.13 (3*s*); 157.21 (C=O). HR-MALDI-MS: 806.390 ($C_{49}H_{57}NaNO_6Si^+$, $[M+Na]^+$; calc. 806.390). Anal. calc. for $C_{49}H_{57}NO_6Si$ (784.07): C 75.06, H 7.33, N 1.79; found: C 75.12, H 7.31, N 1.83.

2,3,4-Tri-O-*benzyl*-N-*[(*tert-*butoxy)carbonyl]*-*5a-carba-2,5a-cyclo*-α-D-*glucopyranosylamine* (**17**). A soln. of **16** (24 mg, 0.03 mmol) in THF (1.6 ml) was treated with TBAF · 3 H_2O (15 mg, 0.046 mmol), stirred at r.t. for 1.5 h (TLC: complete consumption of **16**), treated with aq. NaCl soln. (3 ml), and extracted with Et_2O (3 × 3 ml). The combined org. phases were dried ($MgSO_4$) and taken to dryness. FC (AcOEt/cyclohexane 1:3) gave **17** (15.7 mg, 94%). R_f (AcOEt/cyclohexane 1:1) 0.57. $[\alpha]_D^{25} = -6.7$ ($c = 0.40$, $CHCl_3$). IR ($CHCl_3$): 3608*w*, 3344*m*, 3066*w*, 3008*m*, 2982*m*, 2930*m*, 2874*m*, 1956*w*, 1872*w*, 1817*w*, 1706*s*, 1540*m*, 1497*m*, 1454*m*, 1392*m*, 1368*m*, 1231*m*, 1165*m*, 1073*m*, 1028*m*, 910*w*. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.41 (*s*, *t*-Bu); 1.88 (br. *d*, $J = 9.5$, H−C(5a)); 1.97 (br. *t*, $J \approx 5.4$, H−C(5)); 3.61 (br. *t*, $J \approx 7.9$, H−C(1)); 3.67–3.80 (*m*, 2 H−C(6)); 3.97 (br. *s*, H−C(3), H−C(4)); 4.46 (*d*, $J = 12.0$, PhC*H*); 4.53 (*d*, $J = 12.0$, PhC*H*); 4.54 (*d*, $J = 11.2$, PhC*H*); 4.58 (*s*, PhCH_2); 4.76 (*d*, $J = 11.2$, PhC*H*); 5.87 (br. *d*, $J \approx 9.0$, NH)); 7.22–7.36 (*m*, 15 arom. H). ^{13}C-NMR (75 MHz, $CDCl_3$)); 27.96 (*q*, *Me*$_3$C); 30.56 (*d*, C(5a)); 38.72 (*d*, C(1)); 43.93 (*d*, C(5)); 64.40 (*t*, C(6)); 70.81 (*s*, Me_3*C*); 71.33, 71.68, 71.87 (3*t*, 3 Ph*C*H_2); 79.88 (*s*, C(2)); 82.41 (*d*, C(4)); 88.15 (*s*, C(3)); 127.17–128.09 (several *d*); 136.92, 137.42, 137.71 (3*s*); 156.02 (C=O). HR-MALDI-MS: 568.268 ($C_{33}H_{39}NaNO_6^+$, $[M+Na]^+$; calc. 568.269). Anal. calc. for $C_{33}H_{39}NO_6$ (545.67): C 72.64, H 7.20, N 2.57; found: C 72.58, H 7.16, N 2.52.

5a-Carba-2,5a-cyclo-α-D-*glucopyranosylammonium Chloride* (**18**). Hydrogenation of **17** (9 mg, 0.016 mmol) in MeOH (1 ml) and conc. HCl (0.1 ml) in the presence of 10% Pd/C (4 mg) at 6 bar for 23 h, filtration through *Celite*, washing of the residue with MeOH (3 ml), and evaporation of the combined filtrates gave crude **18** (3.5 mg, quant.). Colourless unstable solid (dec. after *ca.* 8 h). ^{1}H-NMR (300 MHz, CD_3OD): 1.83 (*d*, $J = 8.7$, irrad. at 3.04 → *s*, H−C(5a)); 1.99 (*t*, $J \approx 6.3$, irrad. at 3.71 → *s*, H−C(5)); 3.04 (*d*, $J = 8.7$, irrad. at 1.83 → *s*, H−C(1)); 3.71 (*d*, $J = 6.2$, irrad. at 1.99 → *s*, 2 H−C(6)); 3.99, 4.00 (2*s*, H−C(3), H−C(4)). ^{13}C-NMR (75 MHz, CD_3OD): 30.91, 33.20 (2*d*, C(1), C(5a)); 50.98 (*d*, C(5)); 64.06 (*t*, C(6)); 65.93 (*s*, C(2)); 78.89, 80.47 (2*d*, C(3), C(4)). ESI-MS: 176 ($[M+Na]^+$).

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