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Synthesis of bridged sugar amino acids: a new entry into conformationally locked δ- and ε-amino acids

Renate M. van Well, Marlies E. A. Meijer, Herman S. Overkleeft, Jacques H. van Boom, Gijsbert A. van der Marel* and Mark Overhand*

Gorlaeus Laboratories, Leiden Institute of Chemistry, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands

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Abstract—The synthesis of three methylene bridged sugar amino acids is described. Key transformations in the synthetic strategy are a CO-insertion on fully protected ribose, an aldol condensation with formaldehyde and an oxetane forming cyclisation step. A novel Leu-enkephalin analogue containing the δ-SAA **1** was prepared using standard solution phase peptide chemistry.

1. Introduction

Some years ago, Wengel[1a,b] and Imanishi[1c,d] independently introduced so-called locked nucleic acids (LNAs) as novel nucleotides displaying interesting properties.[1] For example, 2′–4′ LNA monomers (Fig. 1) contain a methylene bridge that connects the 2′-oxygen of ribose with the 4′-carbon, which results in a locked C3′-*endo* (north) conformation for the ribose ring.[1c,2] On the other hand, 3′–4′ LNA monomers, containing a methylene bridge that connects the 3′-oxygen of ribose with the 4′-carbon, adopt a C2′-*endo* (south) conformation.[3] Incorporation of several 2′–4′ LNA monomers in a DNA strand increases the local organisation of the phosphate backbone, and as a result improves the affinity of the LNA/DNA chimera for complementary DNA and RNA sequences.[4] The incorporation of 3′–4′ LNA monomers results in a chimera with a preference for RNA over DNA, due to destabilisation of the 3′–4′ LNA/DNA duplex.[5]

Figure 1.

Various laboratories, including our group, have used furanoid sugar amino acids (SAAs) for the introduction of conformational restriction in peptide-like oligomers.[6] Although furanoid SAAs are capable of reducing the conformational freedom in both linear and cyclic oligomers, the furan ring often exists in an equilibrium of conformations, rather than being frozen in one conformation.[6c,e] For example, we recently demonstrated that the five-membered ring in a cyclic furanoid SAA oligomer flips between a north and a south conformation.[6c] It was envisaged that the introduction of a bridging methylene function over the five-membered ring of SAAs, in analogy to the structure of 3′–4′ LNA monomers, would stabilize a south conformation of the furan ring. Consequently, incorporation of such a bridged SAA (BSAA) into peptides or SAA oligomers should result in more rigid three-dimensional structures, which might have enhanced recognition properties.

Here we present the synthesis of furanoid δ- and ε-SAAs (**1**–**3**) containing a furano-oxetane core as depicted in Figure 2. In addition, the utility of the bridged SAAs in standard peptide chemistry is demonstrated by incorporating **1** in Leu-enkephalin analogue **4**, as a replacement for the Gly-Gly dipeptide.[6d,e,7]

2. Results and discussion

Retrosynthetic analysis revealed that the three BSAAs (**1**–**3**) could be prepared starting from the commercially available acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside (**8** Scheme 1). Key steps in the synthesis are the formation of the oxetane ring (i.e. **6**→**5**), an aldol condensation with **7** for

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* Corresponding authors. Tel.: +31-715274483; fax: +31-715274307; e-mail: overhand@chem.leidenuniv.nl, g.marel@chem.leidenuniv.nl.

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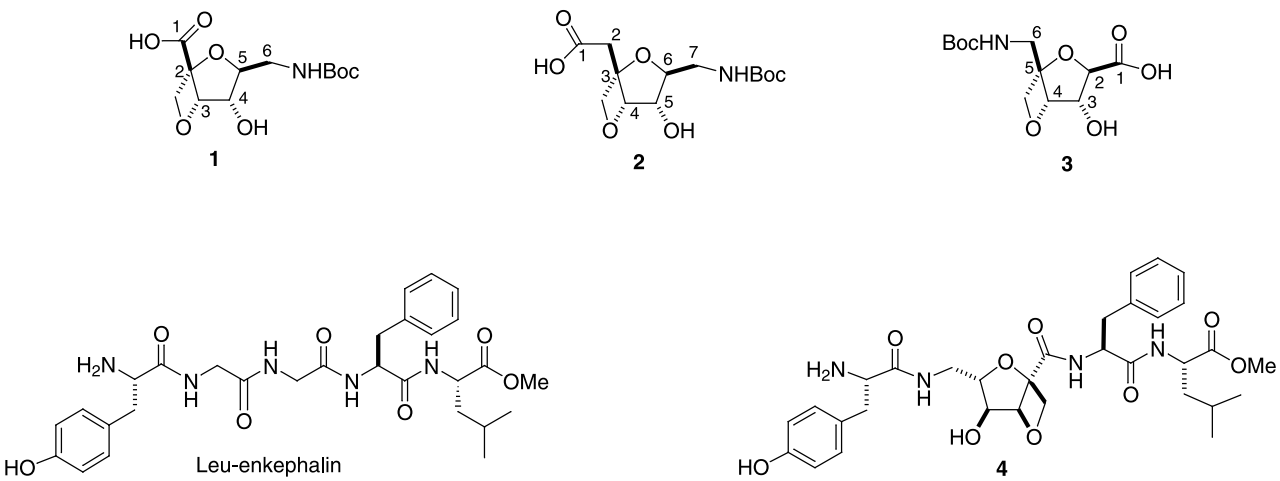
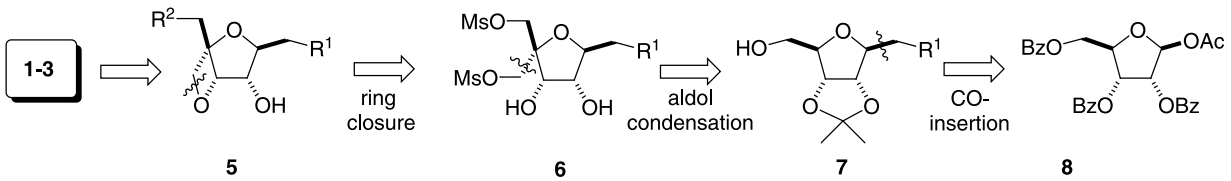


Figure 2.



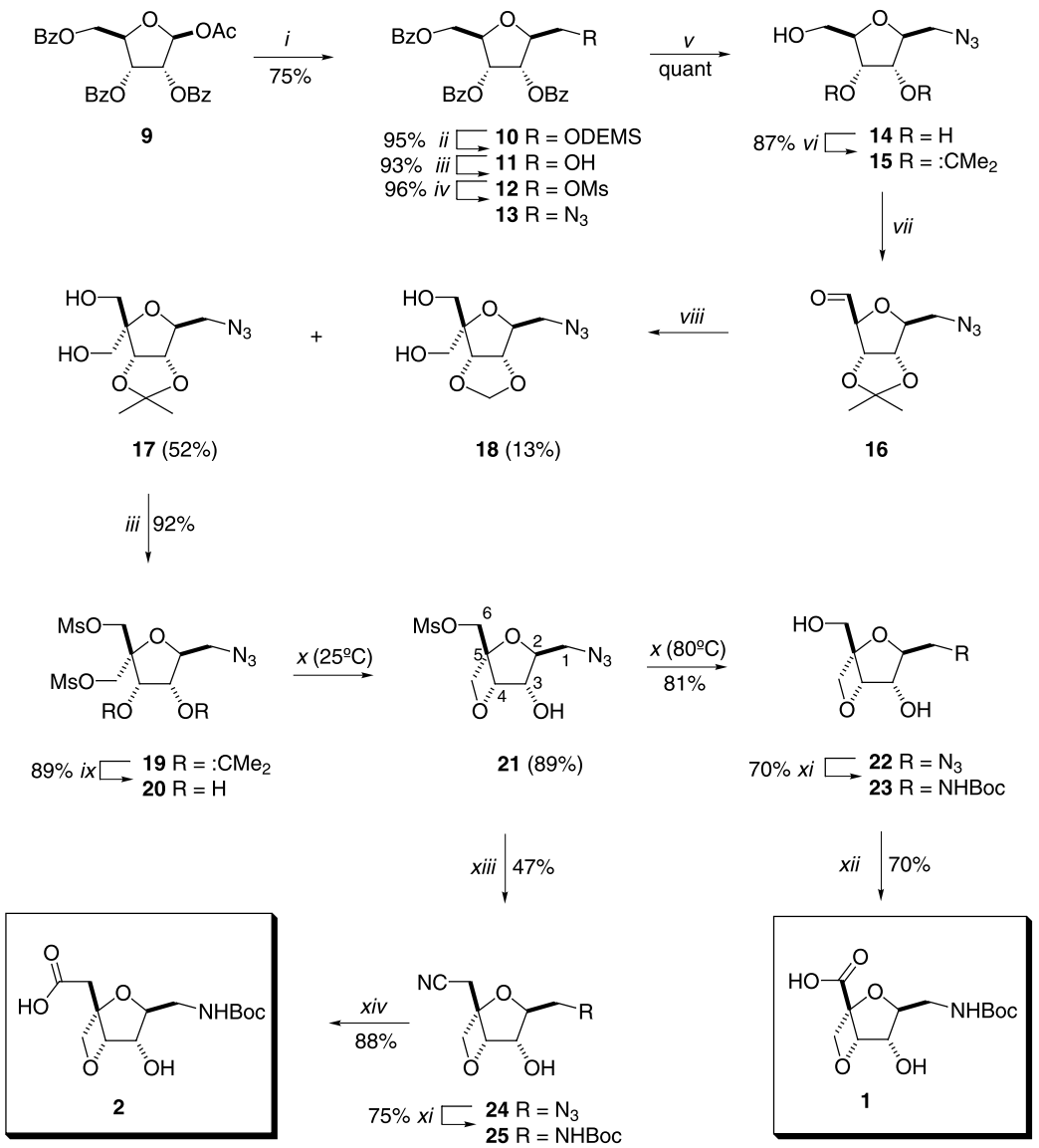
Scheme 1.

the introduction of the hydroxymethylene function, and a CO-insertion in **8**.

In Scheme 2 the synthesis of δ-BSAA **1** as well as its ε-BSAA analogue **2** is depicted. As reported in the literature,[8] carbonyl insertion in **9** using $Co_2(CO)_8$ and CO-gas in the presence of diethylmethylsilane (DEMS) gave the silyl protected allitol derivative **10**. Acidic removal of the DEMS protective group (AcOH/H_2O/THF, 3/1/6) afforded **11** in 71% over the two steps. Reaction of **11** with mesyl chloride in pyridine followed by treatment with sodium azide gave azide **13** in 89%. Removal of the benzoyl groups in **13** (KO*t*Bu in MeOH) and subsequent protection of the *cis*-diol in **14** by reaction with 2,2-dimethoxypropane and *p*TsOH in acetone yielded **15** in 87% yield. The stage was now set for the introduction of the hydroxymethylene function via an aldol condensation. To this end the primary alcohol in **15** was oxidised using the Dess–Martin reagent to provide the required aldehyde **16**.[9] According to literature precedent, treatment of the aldehyde with formaldehyde in the presence of NaOH should, after an aldol condensation directly followed by Cannizarro reduction, result in the formation of **17**.[10] However, the latter reduction proved to be very sluggish and low yielding when performed on compound **16**. After stirring for four days a yield of only 31% of **17** was obtained, together with a small amount of a slightly lower running product, which turned out to be the 3,4-*O*-methylene analogue **18**.[11] Fortunately, by modifying the reaction conditions, i.e. reduction of the initially formed β-hydroxy aldehyde by addition of $NaBH_4$ to the reaction mixture after 1 h, the desired diol **17** was obtained in 52% after a reaction time of 3 h, together with 13% of **18** and 10% of **15**.[10d] Next, the primary alcohols were converted into good leaving groups by reaction of **17** with mesyl chloride in pyridine to give **19**. Ensuing acetonide cleavage under the agency of 4 M aq. HCl afforded diol **20** in good yield. Ring closure of **20** under alkaline conditions afforded exclusively the oxetane intermediate **21**, which after prolonged stirring at elevated temperature gave **22** in 81% yield.[12] The oxetane structure in **21** was confirmed by acetylation of the remaining free hydroxyl, which resulted in a strong downfield shift for H3.[13] Furano-oxetane **22** was converted into locked δ-SAA **1** via the following two-step sequence. First, the azide in **22** was transformed into the Boc-protected amine **23** by a modified Staudinger reaction using Me_3P in the presence of 2-*t*-butoxycarbonyloxyimino-2-phenylacetonitrile (Boc-ON).[14] In the last step, TEMPO oxidation of the primary alcohol in **23** in an aqueous environment afforded **1** in 49% over the two steps.[15]

Having synthesised δ-BSAA **1** it was envisaged that intermediate **21** could also be converted into **2**, the ε-BSAA congener of **1**. To this end, the primary mesylate in derivative **21** was transformed into the cyanide **24** with sodium cyanide in DMF in a yield of 47%.[16] Subsequent reduction of the azide in **24** and protection of the resulting amine in a one-pot procedure (vide supra), followed by hydrolysis of the cyanide in **25** under basic conditions furnished BSAA **2** in 66% over the two steps.

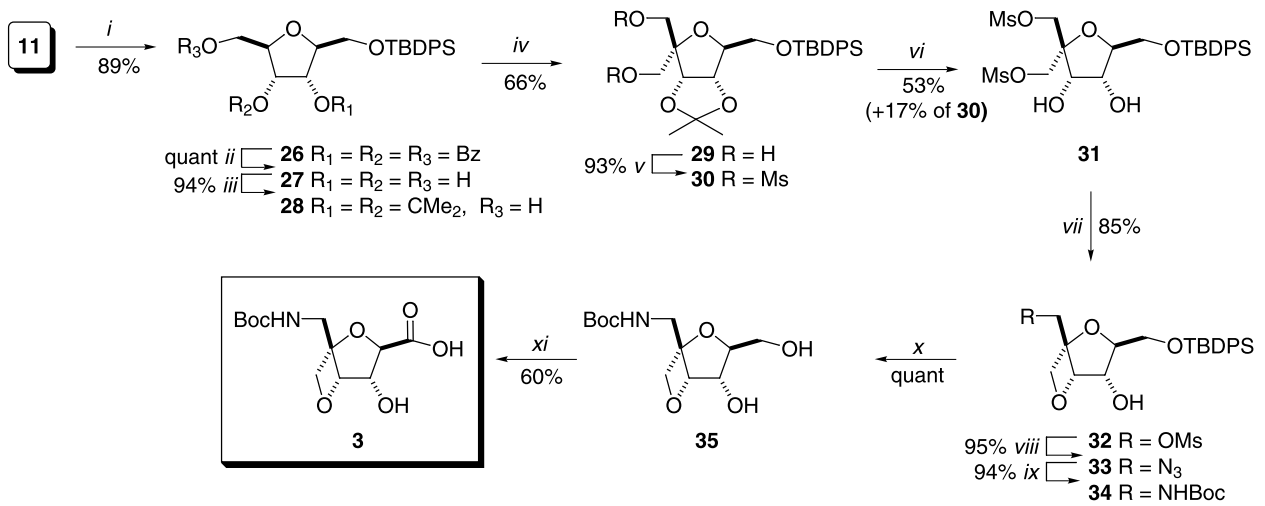
The synthesis of δ-SAA **3** was initiated by silylation of the primary alcohol in **11** using TBDPSCl in pyridine to afford **26** in 89% yield (Scheme 3). Subsequent debenzoylation and introduction of the acetonide functionality gave **28** in 94% yield over the two steps. Introduction of the hydroxymethylene group, followed by treatment of **29** with mesyl chloride in pyridine gave dimesylate **30** in 61% yield. Removal of the isopropylidene protecting group in **30**



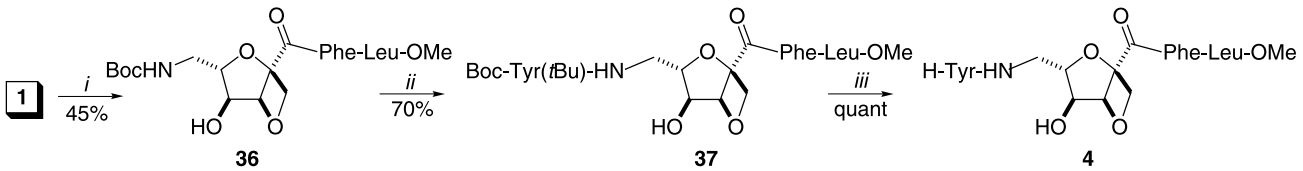
Scheme 2. *Reagents and conditions*: (i) $Co_2(CO)_8$, DEMS, CO-gas, DCM, 30°C, 16 h; (ii) AcOH/H_2O/THF (3/1/6, v/v/v), 0°C, 2 h; (iii) MsCl, pyridine, 16 h; (iv) NaN_3, DMF, 75°C, 2 h; (v) KO*t*Bu, MeOH, 2 h; (vi) 2,2 dimethoxypropane, *p*TsOH, acetone, 3 h; (vii) Dess–Martin periodinane, DCM, 0°C, 1 h; (viii) CH_2O, 2 M NaOH (aq.), dioxane, 0°C, 1 h, then $NaBH_4$, 2 h, **17**: 52%, **18**: 13%, **15**: 10%; (ix) 4 M HCl (aq.), THF, 2 h; (x) 1 M NaOH (aq.), dioxane (xi) Boc-ON, Me_3P, THF, 5 h; (xii) TEMPO, KBr, NaOCl, aq. $NaHCO_3$, aq. NaCl, H_2O, 0°C, 4 h; (xiii) NaCN, NaI, DMF, 70°C, 1.5 h; (xiv) 4 M NaOH (aq.), MeOH, 60°C, 3 h.

under the influence of 4 M aq. HCl was accompanied by the undesired cleavage of the TBDPS group. Fortunately, reaction of **30** with $FeCl_3$ in MeOH/DCM resulted in 53% of the desired product **31**, together with 17% of recovered starting material **30**.[17,18] Treatment of **31** with NaOH in dioxane exclusively led to the formation of the expected fused furano-oxetane **32** (85% yield).[19] Introduction of the azide (**32** to **33**) and subsequent conversion of **33** into the Boc-protected amine **34** as described above proceeded efficiently. Finally, desilylation of **34** with TBAF and TEMPO oxidation of the resulting primary hydroxyl in **35** provided the target BSAA **3** in 60% yield over the two steps.

Next, attention was focussed on the synthesis of Leu-enkephalin analogue **4** containing the BSAA **1**. The original Leu-enkephalin peptide H-Tyr-Gly-Gly-Phe-Leu-OMe is a selective δ-opoid receptor ligand in which the N-terminal Tyr residue and the C-terminal Phe-Leu dipeptide form the pharmacophoric groups.[20] The Gly-Gly dipeptide functions as a spacer, and has been replaced by SAAs to influence the spatial arrangement of the address and message components.[6d,e,7] The construction of Leu-enkephalin analogue **4** was performed as depicted in Scheme 4. The free carboxylate in **1** was condensed with HCl·H-Phe-Leu-OMe under the influence of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide·hydrochloride (EDC·HCl), 1-hydroxybenzotriazole (HOBt) and *N*-methylmorpholine (NMM) to give trimer **36** in 45%. Unmasking of the Boc-group in **36** (50% TFA/DCM), followed by condensation of the resulting free amine with Boc-Tyr(*t*Bu)-OH provided the protected tetramer **37** in a yield of 70%. Removal of the Boc- and *tert*-butyl protecting groups was accomplished by treatment with a 90% TFA solution in H_2O to give the target compound **4** in quantitative yield. The structure of **4** was ascertained by NMR and MS. The large values found for the $J_{4,5}$ coupling constants of the BSAA residue in



Scheme 3. *Reagents and conditions*: (i) TBDPSCl, pyridine, 16 h; (ii) KO*t*Bu, MeOH, 2 h; (iii) 2,2-dimethoxypropane, *p*TsOH, acetone, 3 h; (iv) (a) Dess–Martin periodinane, DCM, 0°C, 30 min; (b) CH_2O, 2 M NaOH, dioxane, 0°C, 1 h, then $NaBH_4$, 2 h; (v) MsCl, pyridine, 16 h; (vi) Fe_3Cl, MeOH, DCM, 1 h; (vii) 1 M NaOH, dioxane, rt, 1 h; (viii) NaN_3, DMF, 75°C, 1 h; (ix) Boc-ON, Me_3P, THF, 5 h; (x) TBAF, THF, 1 h; (xi) TEMPO, KBr, NaOCl, aq. $NaHCO_3$, aq. NaCl, H_2O, 0°C, 4 h.



Scheme 4. *Reagents and conditions*: (i) HCl·H-Phe-Leu-OMe, EDC·HCl, HOBt, NMM, 16 h; (ii) (a) 50% TFA/DCM, 5 min; (b) Boc-Tyr(*t*Bu)-OH, EDC·HCl, HOBt, NMM, 16 h; (iii) 90% TFA/H_2O, 1 h.

peptide **4** (8.8 Hz) as well as for the BSAA monomer **1** (8.3 Hz) are a strong indication that the furan ring in the BSAA residue adopts a south conformation.[21,22]

3. Conclusion

In summary, three novel bridged SAAs, i.e. the δ-BSAAs **1** and **3**, and the ε-BSAA **2**, were successfully synthesised. The key ring-closure of dimesylates **20** and **31** proceeded regioselectively to exclusively afford the four-membered ring. The δ-BSAA **1** was employed for the construction of a novel Leu-enkephalin analogue **4**. Molecular modelling studies of the BSAA monomers as well as the peptide **4** will provide information whether the methylene bridge locks the conformation of the furan ring in a specific south conformation. The BSAAs will be used for the construction of linear and cyclic homooligomers, and their ability to adopt well-defined conformations will be evaluated.

4. Experimental

4.1. General experimental

^1H and ^{13}C NMR spectra were recorded with a Jeol JNM-FX-200 (200/50.1 MHz), a Bruker WM-300 (300/75.1 MHz), a Bruker AV-400 (400/100 MHz) or a Bruker DMX-600 (600/150 MHz) spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane as internal standard. All given ^{13}C spectra are proton decoupled. Mass spectra were recorded with PE/SCIEX API 165 with electrospray interface. Infra-red spectra were recorded on a FTIR-8300 (Shimadzu) spectrometer. Column chromatography was performed on Fluka silica gel 60 (0.04–0.063 mm). TLC analysis was conducted on DC plastikfolien (Merck silica gel 60 F_{254}) with detection by UV absorption (254 nm) where applicable and by spraying with 20% H_2SO_4 in ethanol, a ninhydrin solution or ammonium molybdate (25 g/L) and ceric ammonium sulfate (10 g/L), followed by charring at ~150°C. Reactions were run at ambient temperature, unless stated otherwise. Prior to reactions that require anhydrous conditions, traces of water were removed by coevaporation with toluene, pyridine or DCE. Acetone (Acros, p.a.), DCE (Biosolve, HPLC-grade), DMF (Baker, p.a.), toluene (Biosolve, p.a.), 1,4-dioxane (Baker, p.a.), pyridine (Baker, p.a.) and DCM (Baker, p.a.) were stored over molecular sieves (4 Å). Acetonitrile (Biosolve, p.a.) and MeOH (Biosolve, p.a.) were stored over molecular sieves (3 Å). THF (Merck) and Et_2O were boiled under reflux with $LiAlH_4$ and distilled immediately prior to use. Triethylamine (Acros) was boiled under reflux for 3 h with CaH_2, distilled and stored over KOH. Diethylmethylsilane (DEMS, Acros), cobalt carbonyl ($Co_2(CO)_8$, Fluka), 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose (Aldrich), trimethylphosphine (Acros), 2-(*t*-butoxycarbonyloxyimino)-2-phenylacetonitrile (Boc-ON, Janssen chimica) were used as received.

4.1.1. 2,5-Anhydro-3,4,6-tri-*O*-benzoyl-1-*O*-diethylmethylsilyl-D-allitol (10). After flushing a 100 mL flask with CO-gas, $Co_2(CO)_8$ (0.341 g, 1 mmol) was added

followed by diethylmethylsilane (9.11 mL, 62.5 mmol). To this mixture, a solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribose (**9**, 12.6 g, 25 mmol) in DCM (30 mL) was added slowly. The reaction mixture was stirred for 16 h under an atmosphere of CO at 30°C. The solution was directly applied to a silica gel column, and elution with EtOAc/light petroleum (0/1→3/7, v/v) gave **10** in 75% (10.8 g) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 7.98–7.80, 7.45–7.17 (2×m, 15H, H_{arom} Bz), 5.57 (m, 2H, H3, H4), 4.60–4.27 (m, 4H, H2, H5, 2×H6), 3.77 (d, 2H, 2×H1, *J*=3.6 Hz), 1.61 (t, 6H, 2×CH_3CSi, *J*=7.3 Hz), 0.84 (q, 4H, 2×CH_2Si, *J*=8.0 Hz), 0.08 (s, 3H, CH_3Si). ^{13}C NMR ($CDCl_3$): δ 165.7, 165.1, 164.9 (3×C(O) Bz), 132.9, 132.6, 129.3, 127.9 (CH_{arom} Bz), 128.7 (C_q Bz), 83.0, 77.5, 72.8 (C2, C3, C4, C5), 64.4 (C6), 62.4 (C1), 6.14 (CH_3CH_2Si), 5.7 (CH_2Si), −5.0 (CH_3Si).

4.1.2. 2,5-Anhydro-3,4,6-tri-*O*-benzoyl-D-allitol (11). Compound **10** (10.8 g, 18.8 mmol) was dissolved in a mixture of AcOH/H_2O/THF (100 mL, 3/1/6, v/v/v). After stirring for 2 h, the solution was concentrated and the resulting oil dissolved in EtOAc (100 mL), washed with H_2O (1×75 mL), sat. aq. $NaHCO_3$ (2×75 mL), brine (1×75 mL), dried ($MgSO_4$) and concentrated. The crude product was subjected to silica gel column chromatography (EtOAc/light petroleum, 1/9→4/6, v/v) to give title compound **11** in 95% (8.5 g) as a colourless syrup. ^{1}H NMR ($CDCl_3$): δ 8.11–7.93 (m, 6H, 6×H_{arom} Bz), 7.58–7.26 (m, 9H, 9×H_{arom} Bz), 5.69 (m, 2H, H3, H4), 4.69–4.60 (m, 3H, H2, H5, H6a), 4.39 (m, 1H, H6b), 3.97 (dd, 1H, H1a, $J_{1a,2}$=1.8 Hz, $J_{1a,1b}$=12.4 Hz), 3.82 (dd, 1H, H1b, $J_{1b,2}$=2.6 Hz, $J_{1a,1b}$=12.4 Hz), 2.37 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 165.9, 165.1, 164.9 (3×C(O) Bz), 132.9, 132.7, 129.2, 127.9 (CH_{arom} Bz), 128.8, 128.7 (C_q Bz), 82.4, 79.2, 72.6, 71.9 (C2, C3, C4, C5), 64.0 (C6), 61.4 (C1).

4.1.3. 2,5-Anhydro-3,4,6-tri-*O*-benzoyl-1-*O*-mesyl-D-allitol (12). Compound **11** (5.6 g, 11.7 mmol) was dissolved in pyridine (50 mL), methanesulfonyl chloride (1.09 mL, 14.0 mmol) was added and the reaction mixture was stirred for 16 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (100 mL). The organic phase was washed with H_2O (50 mL), sat. aq. $NaHCO_3$ (3×50 mL) and brine (50 mL), dried $MgSO_4$ and concentrated. The crude product was applied to a silica gel column and eluted with EtOAc/light petroleum (1/9→4/6, v/v) to afford compound **12** in 93% (6.04 g) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 8.11–7.92 (m, 6H, 6×H_{arom} Bz), 7.59–7.32 (m, 9H, 9×H_{arom} Bz), 5.63 (m, 2H, H3, H4), 4.78–4.13 (m, 6H, 2×H1, H2, H5, 2×H6), 2.99 (s, 3H, CH_3 Ms). ^{13}C NMR ($CDCl_3$): δ 165.5, 164.8, 164.7 (3×C(O) Bz), 133.0, 132.7, 129.2, 127.9 (CH_{arom} Bz), 128.5, 128.4, 121.1 (3×C_q Bz), 79.3, 79.1, 71.9, 71.2 (C2, C3, C4, C5), 67.9 (C1), 63.3 (C6), 36.6 (CH_3 Ms). ESI-MS: *m*/*z* 577.4 $[M+Na]^+$, 1131.3 $[2M+Na]^+$.

4.1.4. 2,5-Anhydro-1-azido-3,4,6-tri-*O*-benzoyl-1-deoxy-D-allitol (13). Compound **12** (6.04 g, 10.9 mmol) was dissolved in DMF (50 mL), sodium azide (2.13 g, 32.7 mmol) was added and the resulting mixture was stirred at 75°C for 1.5 h. The reaction mixture was allowed to cool to room temperature and subsequently diluted with H_2O (50 mL). Extraction with EtOAc (3×100 mL), drying ($MgSO_4$) of the combined organic phases and concentration gave crude **13**. After purification by column cromatography (eluent: EtOAc/light petroleum, 1/9→4/6, v/v) the product **13** was obtained in 96% (5.24 g) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 8.11–7.92 (m, 6H, 6×H_{arom} Bz), 7.52–7.26 (m, 9H, 9×H_{arom} Bz), 5.68 (q, 1H, H4, *J*=5.8 Hz), 5.63 (q, 1H, H3, *J*=5.8 Hz), 4.79–4.41 (m, 4H, H2, H5, 2×H6), 3.74 (dd, 1H, H1a, $J_{1a,2}$=2.9 Hz, $J_{1a,1b}$=13.2 Hz), 3.54 (dd, 1H, H1b, $J_{1b,2}$=4.4 Hz, $J_{1a,1b}$=13.5 Hz). ^{13}C NMR ($CDCl_3$): δ 165.6, 164.9, 164.8 (3×C(O) Bz), 132.9, 132.6, 129.2, 127.9 (CH_{arom} Bz), 128.5 (C_q Bz), 80.4, 79.5, 72.3, 71.9 (C2, C3, C4, C5), 63.6 (C6), 51.2 (C1). ESI-MS: *m*/*z* 524.5 $[M+Na]^+$, 1025.3 $[2M+Na]^+$.

4.1.5. 2,5-Anhydro-1-azido-1-deoxy-3,4-*O*-isopropylidene-D-allitol (15). Compound **13** (5.24 g, 10.45 mmol) was coevaporated with toluene (3×30 mL) and dissolved in MeOH (50 mL). KO*t*Bu (0.12 g, 1.05 mmol) was added and the resulting mixture was stirred for 2 h. The solution was neutralized with DOWEX-H^+ (50W×4), the ion exchange resin was removed by filtration, and the filtrate concentrated. The crude product was dissolved in acetone (50 mL) and 2,2-dimethoxypropane (1.94 mL, 15.7 mmol) and *p*TsOH (cat) were added. After stirring the resulting mixture for 3 h, the solution was neutralized with sat. aq. $NaHCO_3$ and concentrated. The residue was taken up in EtOAc (100 mL) and washed with H_2O (1×50 mL), $NaHCO_3$ (3×50 mL), brine (1×50 mL), dried ($MgSO_4$) and concentrated. Purification by silica gel column chromatography (eluent: EtOAc/light petroleum, 1/9→2/1, v/v) afforded **15** in 87% (2.08 g) as a colourless syrup. ^{1}H NMR ($CDCl_3$): δ 4.70 (dd, 1H, H4, $J_{4,5}$=4.0 Hz, $J_{3,4}$=6.6 Hz), 4.57 (dd, 1H, H3, $J_{2,3}$=4.8 Hz, $J_{3,4}$=6.6 Hz), 4.14–4.08 (m, 2H, H2, H5), 3.91–3.66 (m, 2H, 2×H6), 3.65 (dd, 1H, H1a, $J_{1a,2}$=3.3 Hz, $J_{1a,1b}$=12.8 Hz), 3.43 (dd, 1H, H1b, $J_{1b,2}$=4.4 Hz, $J_{1a,1b}$=13.2 Hz), 1.54, 1.35 (2×s, 6H, 2×CH_3 isoprop). ^{13}C NMR ($CDCl_3$): δ 114.3 (C_q isoprop), 84.7, 82.9, 81.6, 81.3 (C2, C3, C4, C5), 62.5 (C6), 52.1 (C1), 27.1, 25.1 (2×CH_3 isoprop). ESI-MS: *m*/*z* 252.1 $[M+Na]^+$.

4.1.6. 2,5-Anhydro-1-azido-1-deoxy-5-*C*-hydroxymethyl-3,4-*O*-isopropylidene-D-allitol (17). Compound **15** (0.79 g, 3.8 mmol) was dissolved in DCM (20 mL) and the solution was cooled to 0°C and Dess–Martin reagent (1.93 g, 4.56 mmol) was added under an Ar atmosphere. After stirring for 30 min the reaction mixture had turned milky white and the reaction was finished. Sat. aq. $Na_2S_2O_3$ (20 mL), sat. aq. $NaHCO_3$ (20 mL) and EtOAc (40 mL) were added and the reaction mixture was stirred vigorously untill both phases were clear. The layers were seperated and the organic phase was washed with H_2O (3×30 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated. The crude aldehyde **16** together with CH_2O (0.85 mL, 35% solution in H_2O) were dissolved in dioxane (10 mL). The resulting mixture was cooled to 0°C and NaOH aq. (3.8 mL, 2N in H_2O) was added. After 1 h, $NaBH_4$ (0.73 g, 22.8 mmol) was added and the reaction mixture was stirred for another 2 h. The solution was neutralized with AcOH and concentrated, the residue was dissolved in EtOAc and washed with H_2O (1× mL), $NaHCO_3$ (3× mL), brine (1× mL), dried ($MgSO_4$) and concentrated. Purification was accomplished by silica gel column chormatography (eluent: EtOAc/light petroleum, 1/9→1/1, v/v) to give pure title compound **17**

in 52% (0.51 g) as a colourless oil together with 13% of a slightly lower running fraction identified as the methylene analog **18** and 10% of **15**, both colourless oils. **17**: ^{1}H NMR ($CDCl_3$): δ 4.82 (d, 1H, H4, $J_{3,4}$=6.6 Hz), 4.68 (dd, 1H, H3, $J_{2,3}$=5.5 Hz, $J_{3,4}$=6.6 Hz), 4.18–4.07 (m, 1H, H2), 3.87–3.66 (m, 4H, 2×H6, 2×H7), 3.65 (dd, 1H, H1a, $J_{1a,2}$=3.7 Hz, $J_{1a,1b}$=13.2 Hz), 3.47 (dd, 1H, H1b, $J_{1b,2}$=4.0 Hz, $J_{1a,1b}$=12.8 Hz), 2.60 (bs, 2H, 2×OH), 1.56, 1.36 (2×s, 6H, 2×CH_3 isoprop). ^{13}C NMR ($CDCl_3$): δ 114.6 (C_q isoprop), 86.7 (C5), 83.3, 82.5, 82.0 (C2, C3, C4), 65.4, 62.8 (C6, C7), 52.4 (C1), 26.8, 24.9 (2×CH_3 isoprop). ESI-MS: *m*/*z* 282.3 $[M+Na]^+$, 541.5 $[2M+Na]^+$. **18**: ^{1}H NMR ($CDCl_3$): δ 5.15 (d, 1H, CHa methylene, *J*=21.2 Hz), 4.71 (m, 2H, H3, H4), 4.12 (m, 1H, H2), 3.73 (m, 6H, 2×H6, 2×H7, H1a, CHb methylene), 3.53 (dd, 1H, H1b, $J_{1b,2}$=4.0 Hz, $J_{1a,1b}$=12.8 Hz), 2.39 (bs, 2H, 2×OH). ^{13}C NMR ($CDCl_3$): δ 97.1 (CH_2 methylene), 87.4 (C5), 83.3, 82.0, 80.5 (C2, C3, C4), 65.5, 62.8 (C6, C7), 52.5 (C1). ESI-MS: *m*/*z* 254.1 $[M+Na]^+$.

4.1.7. 2,5-Anhydro-1-azido-1-deoxy-3,4-*O*-isopropylidene-6-*O*-mesyl-5-*C*-mesyloxymethyl-D-allitol (19). Compound **17** (0.12 g, 0.46 mmol) was dissolved in pyridine (4 mL), methanesulfonyl chloride (0.08 mL, 1.02 mmol) was added and the reaction mixture was stirred for 16 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (20 mL). The organic phase was washed with H_2O (10 mL), sat. aq. $NaHCO_3$ (3×10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated. The crude product was applied to a silica gel column and eluted with EtOAc/light petroleum (1/9→1/1, v/v) to afford compound **19** in 92% (0.18 g) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 4.79 (d, 1H, H4, $J_{3,4}$=6.6 Hz), 4.70 (dd, 1H, H3, $J_{2,3}$=4.4 Hz, $J_{3,4}$=6.7 Hz), 4.47–4.16 (m, 5H, H2, 2×H6, 2×H7), 3.56 (dd, 1H, H1a, $J_{1a,2}$=3.7 Hz, $J_{1a,1b}$=13.2 Hz), 3.42 (dd, 1H, H1b, $J_{1b,2}$=5.1 Hz, $J_{1a,1b}$=13.2 Hz), 3.10 (s, 6H, 2×CH_3 Ms), 1.54, 1.34 (2×s, 6H, 2×CH_3 isoprop). ^{13}C NMR ($CDCl_3$): δ 115.2 (C_q isoprop), 82.9 (C5), 82.8, 81.9 (C2, C3, C4), 68.4 67.2 (C6, C7), 52.1 (C1), 37.6, 37.4 (2×CH_3 Ms), 26.5, 24.8 (2×CH_3 isoprop). ESI-MS: *m*/*z* 438.1 $[M+Na]^+$, 853.4 $[2M+Na]^+$.

4.1.8. 2,5-Anhydro-1-azido-1-deoxy-6-*O*-mesyl-5-*C*-mesyloxymethyl-D-allitol (20). Compound **19** (0.99 g, 2.38 mmol) was dissolved in a mixture of 4 M aq. HCl/THF (20 mL, 1/1, v/v) and the resulting solution was stirred for 2 h. After neutralization with sat. aq. $NaHCO_3$ the reaction mixture was extracted with EtOAc (3×30 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (2×50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel column chromatography (eluent: EtOAc/light petroleum, 2/8→8/2, v/v) to afford **20** in 89% (0.82 g) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 4.47 (d, 2H, 2×H6, *J*=1.7 Hz), 4.31 (d, 1H, H7a, $J_{7a,7b}$=10.4 Hz), 4.21 (d, 1H, H4, $J_{3,4}$=5.4 Hz), 4.18 (d, 1H, H7b, $J_{7a,7b}$=10.4 Hz), 4.12 (m, 1H, H3), 4.03 (m, 1H, H2), 3.63 (dd, 1H, H1a, $J_{1a,2}$=2.0 Hz, $J_{1a,1b}$=13.5 Hz), 3.35 (dd, 1H, H1b, $J_{1b,2}$=3.0 Hz, $J_{1a,1b}$=13.5 Hz), 3.11 (s, 6H, 2×CH_3 Ms), 2.88 (bs, 2H, 2×OH). ^{13}C NMR ($CDCl_3$): δ 83.1 (C5), 81.1, 72.4, 71.2 (C2, C3, C4), 68.7, 68.1 (C6, C7), 51.5 (C1), 37.2 (2×CH_3 Ms). ESI-MS: *m*/*z* 398.0 $[M+Na]^+$, 773.1 $[2M+Na]^+$.

4.1.9. 2,5-Anhydro-1-azido-1-deoxy-4-*O*,5-*C*-methylene-D-allitol (22). Compound **20** (0.17 g, 0.46 mmol) was dissolved in dioxane (4.6 mL) and NaOH (4.6 mL, 1 M in H_2O) was added. After stirring for 1 h, TLC analysis showed complete conversion of the starting material in a slightly lower running product. The reaction mixture was heated to 85°C and stirred for another 96 h, the solvent was removed under reduced pressure and traces of H_2O were removed from the residue by coevaporation with toluene (3×5 mL). Purification was accomplished by silica gel column chromatography (eluent: EtOAc/light petroleum, 2/8→8/2, v/v) to furnish **22** in 81% (0.074 g) as a colourless oil. ^{1}H NMR (MeOD): δ 4.94 (d, 1H, H4, $J_{3,4}$=4.8 Hz), 4.82 (d, 3H, 2×H6, H7, $J_{7a,7b}$=7.7 Hz), 4.46 (d, 1H, H7b, $J_{7a,7b}$=7.7 Hz), 2.30 (ddd, 1H, H2, $J_{1a,2}$=2.4 Hz, $J_{1b,2}$=5.8 Hz, $J_{2,3}$=8.2 Hz), 3.79 (dd, 1H, H3, $J_{2,3}$=8.2 Hz, $J_{3,4}$=4.8 Hz), 3.75 (dd, 1H, H1a, *J*=2.4 Hz), 3.44 (dd, 1H, H1b, $J_{1b,2}$=5.8 Hz, $J_{1,1'}$=13.5 Hz). ^{13}C NMR (MeOD): δ 88.2, 81.8, 74.0 (C2, C3, C4), 87.1 (C5), 78.7 (C7), 62.6 (C6), 52.6 (C1). ESI-MS: *m*/*z* 224.0 $[M+Na]^+$.

4.1.10. 2,5-Anhydro-1-*tert*-butoxycarbonylamino-1-deoxy-4-*O*,5-*C*-methylene-D-allitol (23). Compound **22** (0.074 g, 0.37 mmol) was dissolved in THF (2 mL), the solution was placed under an argon atmosphere and Me_3P (0.45 mL, 1 M in toluene) was added. The reaction mixture was stirred for 1 h and subsequently cooled to −20°C. A solution of Boc-ON (0.11 g, 0.45 mmol) in toluene (0.5 mL) was slowly added and the resulting mixture was stirred for 5 h. The solvent was removed in vacuo and the residue was applied to a silica gel column, which was eluted with EtOAc/light petroleum (8/2→1/0) followed by MeOH/EtOAc (0/1→1/9, v/v) to give **23** in 70% (0.075 g) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 5.41 (bs, 1H, HN), 5.00 (d, 1H, H4, $J_{3,4}$=4.4 Hz), 4.73 (d, 1H, H7a, $J_{7a,7b}$=8.0 Hz), 4.49 (d, 1H, H7b, $J_{7a,7b}$=8.0 Hz), 4.18 (m, 1H, H2), 3.80–3.72 (m, 3H, H3, 2×H6), 3.53–3.43 (m, 2H, 2×H1), 1.45 (s, 9H, *t*Bu Boc). ^{13}C NMR ($CDCl_3$): δ 156.5 (C(O) Boc), 86.9, 80.4, 72.9 (C2, C3, C4), 84.0 (C5), 79.2 (C_q Boc), 77.5 (C7), 61.8 (C6), 41.1 (C1), 28.0 (*t*Bu Boc). ESI-MS: *m*/*z* 276.1 $[M+H]^+$, 298.2 $[M+Na]^+$, 573.5 $[2M+Na]^+$, 848.3 $[3M+Na]^+$.

4.1.11. 2,5-Anhydro-6-*tert*-butoxycarbonylamino-6-deoxy-2-*C*,3-*O*-methylene-L-*allo*-hexonic acid (1). Compound **23** (0.29 g, 1.04 mmol), TEMPO (3 mg, 0.0016 mmol) and KBr (0.012 g, 0.11 mmol) were dissolved in H_2O (5 mL) containing sat. aq. $NaHCO_3$ (2.5 mL). The reaction mixture was cooled to 0°C, and a solution of NaOCl (2 mL, 13% in H_2O), sat. aq. $NaHCO_3$ (1.25 mL) and brine (2.5 mL) was added dropwise over a period of 15 min. Stirring was continued for another 4 h at 0°C, then the reaction mixture was neutralized with 4 M aq. HCl and concentrated. The residue was dissolved in THF, mixed with silica gel and evaporated to dryness uder reduced pressure. The silica gel containing absorbed product was applied to a silica gel column and purification using EtOAc/MeOH/H_2O/Et_3N (50/45/5/3, v/v/v/v) afforded **1** in 70% (0.21 g) as a colourless syrup. ν_{max} (neat): 3294.2, 1685.7, 1558.4, 1411.8, 1164.9 cm^{-1}. ^{1}H NMR, COSY, HMQC (MeOD): δ 5.15 (d, 1H, H7a, $J_{7a,7b}$=7.3 Hz), 5.04 (d, 1H, H3, $J_{3,4}$=4.4 Hz), 4.49 (d, 1H, H7b, $J_{7a,7b}$=7.3 Hz), 4.18 (ddd, 1H, H5, *J*=4.0 Hz, *J*=4.4 Hz, $J_{4,5}$=8.8 Hz), 3.68

(dd, 1H, H4, $J_{4,5}$=8.8 Hz, $J_{3,4}$=4.4), 3.48 (m, 1H, H6a), 3.31 (m, 1H, H6b), 1.44 (s, 9H, *t*Bu Boc). ^{13}C NMR (MeOD): δ 174.9 (C1), 159.2 (C(O) Boc), 89.9 (C3), 86.1 (C2), 82.8 (C5), 80.9 (C_q Boc), 80.3 (C7), 72.7 (C4), 41.5 (C6), 28.7 (*t*Bu Boc). ESI-MS: *m/z* 312.1 $[M+Na]^+$.

4.1.12. 2,5-Anhydro-1-azido-1-deoxy-6-*O*-mesyl-4-*O*,5-*C*-methylene-D-allitol (21). Compound **20** (0.12 g, 0.33 mmol) was dissolved in dioxane (3.3 mL) and 1 M aq. NaOH (3.3 mL) was added. After stirring for 1 h, TLC analysis showed complete conversion of the starting material in a slightly lower running product. The reaction mixture was neutralized with AcOH, concentrated and traces of H_2O were removed from the residue by coevaporation with toluene (3×5 mL). Purification was done by silica gel column chromatography (eluent: EtOAc/light petroleum, 2/8→8/2, v/v) to furnish compound **21** in 89% (0.082 g) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 5.06 (d, 1H, H4, $J_{3,4}$=4.8 Hz), 4.86 (d, 1H, H7a, $J_{7a,7b}$=8.3 Hz), 4.56 (d, 1H, H7b, $J_{7a,7b}$=8.3 Hz), 4.48 (d, 1H, H6a, $J_{6a,6b}$=11.5 Hz), 4.40 (d, 1H, H6b, $J_{6a,6b}$=11.4 Hz), 4.25 (ddd, 1H, H2, $J_{1a,2}$=2.8 Hz, $J_{1b,2}$=5.2 Hz, $J_{2,3}$=8.0 Hz), 3.98 (dd, 1H, H3, $J_{2,3}$=8.0 Hz, $J_{3,4}$=4.8 Hz), 3.79 (dd, 1H, H1a, $J_{1a,2}$=2.7 Hz, $J_{1a,1b}$=13.5 Hz), 3.48 (dd, 1H, H1b, $J_{1b,2}$=5.2 Hz, $J_{1a,1b}$=13.5 Hz), 3.15 (bs, 1H, OH), 3.08 (s, 3H, CH_3 Ms). ^{13}C NMR ($CDCl_3$): δ 86.1, 81.6, 72.1 (C2, C3, C4), 82.5 (C5), 77.3 (C7), 67.7 (C6), 50.8 (C1), 37.4 (CH_3 Ms). ESI-MS: *m/z* 280.2 $[M+H]^+$, 302.0 $[M+Na]^+$, 581.2 $[2M+Na]^+$.

4.1.13. 2,5-Anhydro-1-azido-6-*C*-cyano-1,6-dideoxy-4-*O*,5-*C*-methylene-D-allitol (24). Compound **21** (0.13 g, 0.44 mmol) was dissolved in DMF (3 mL), NaCN (0.07 g, 1.32 mmol) was added and the resulting mixture was stirred at 75°C for 1.5 h. The reaction mixture was allowed to cool to room temperature, and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography (eluent: EtOAc/light petroleum, 1/1→1/0, v/v) to give compound **24** in 47% (0.043 g) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 5.05 (d, 1H, H4, $J_{3,4}$=4.8 Hz), 4.83 (d, 1H, H7a, $J_{7a,7b}$=8.4 Hz), 4.61 (d, 1H, H7b, $J_{7a,7b}$=8.4 Hz), 4.26 (ddd, 1H, H2, $J_{1a,2}$=2.9 Hz, $J_{1b,2}$=5.5 Hz, $J_{2,3}$=8.4 Hz), 4.01 (dd, 1H, H3, $J_{2,3}$=8.4 Hz, $J_{3,4}$=4.8 Hz), 3.78 (dd, 1H, H1a, $J_{1a,2}$=2.9 Hz, $J_{1a,1b}$=13.5 Hz), 3.49 (dd, 1H, H1b, $J_{1b,2}$=5.5 Hz, $J_{1a,1b}$=13.5 Hz), 2.91 (s, 2H, 2×H6), 2.45 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 115.2 (CN), 87.4, 82.2, 72.4 (C2, C3, C4), 81.0 (C5), 79.2 (C7), 50.9 (C1), 23.4 (C6). ESI-MS: *m/z* 233.1 $[M+Na]^+$, 249.2 $[M+K]^+$, 443.3 $[2M+Na]^+$, 459.1 $[2M+K]^+$.

4.1.14. 2,5-Anhydro-1-*tert*-butoxycarbonylamino-6-*C*-cyano-1,6-dideoxy-4-*O*,5-*C*-methylene-D-allitol (25). Compound **24** (0.040 g, 0.19 mmol) was dissolved in THF (2 mL) and Me_3P (0.21 mL of a 1 M solution in toluene) was added. After 1 h, TLC analysis revealed that the starting material was completely transformed into a lower running product. The reaction mixture was cooled to −20°C and a solution of Boc-ON (0.052 g, 0.21 mmol) in toluene (0.5 mL) was added slowly. After stirring for 5 h, the solvent was removed and the residue was redissolved in THF (2 mL), mixed with silica gel and evaporated to dryness uder reduced pressure. The silica gel containing absorbed product was applied to a silica gel column and purification (eluent: EtOAc/light petroleum, 9/1→1/0, followed by MeOH/EtOAc, 0/1→1/20, v/v) afforded the title compound **25** in 75% (0.040 g) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 5.04 (d, 1H, H4, $J_{3,4}$=4.8 Hz), 4.78 (d, 1H, H7a, $J_{7a,7b}$=8.0 Hz), 4.60 (d, 1H, H7b, $J_{7a,7b}$=8.4 Hz), 4.22 (m, 1H, H2), 3.82 (dd, 1H, H3, $J_{2,3}$=8.4 Hz, $J_{3,4}$=4.8 Hz), 3.56 (m, 2H, 2×H1), 3.00 (s, 2H, 2×H6), 1.46 (s, 9H, *t*Bu Boc). ^{13}C NMR ($CDCl_3$): δ 156.5 (C(O) Boc), 115.4 (CN), 87.9, 81.6, 72.9 (C2, C3, C4), 80.5 (C5), 79.9 (C_q Boc), 79.2 (C7), 41.0 (C1), 28.3 (*t*Bu Boc), 23.4 (C6). ESI-MS: *m/z* 307.2 $[M+Na]^+$, 591.4 $[2M+Na]^+$.

4.1.15. 3,6-Anhydro-7-*tert*-butoxycarbonylamino-2,7-dideoxy-3-*C*,4-*O*-methylene-L-*allo*-heptonic acid (2). Compound **25** (0.017 g, 0.06 mmol) was dissolved in a mixture of dioxane/4 M aq. NaOH (2 mL, 1/1, v/v). The reaction mixture was stirred at 60°C for 4 h, after which TLC analysis indicated the conversion of the starting material into a lower running product. The solvent was removed in vacuo and traces of H_2O were removed from the residue by coevaporation with toluene (3×2 mL). Purification was accomplished by silica gel column chromatography (eluent: EtOAc/MeOH/H_2O/Et_3N, 50/45/5/3, v/v/v/v) giving compound **2** as a colourless syrup in 88% (0.016 g). ^{1}H NMR, COSY, HMQC (400 MHz, $CDCl_3$): δ 4.92 (bs, 1H, HN), 4.61 (d, 1H, H8a, $J_{8a,8b}$=10.7 Hz), 4.31 (d, 1H, H8b, $J_{8a,8b}$=10.7 Hz), 4.14 (d, 1H, H4, $J_{4,5}$=4.9 Hz), 3.97 (m, 1H, H5), 3.93 (m, 1H, H6), 3.40 (ddd, 1H, H7a, *J*=3.8 Hz, *J*=7.0 Hz, $J_{7a,7b}$=14.9 Hz), 3.33 (ddd, 1H, H7b, *J*=3.9 Hz, *J*=5.6 Hz, $J_{7a,7b}$=14.9 Hz), 2.71 (d, 1H, H2a, $J_{2a,2b}$=17.5 Hz), 2.55 (d, 1H, H2b, $J_{2a,2b}$=17.5 Hz), 1.44 (s, 9H, *t*Bu Boc). ^{13}C NMR (400 MHz, $CDCl_3$): δ 178.0 (C(O) acid), 158.6 (C(O) Boc), 81.7 (C2), 74.6 (C4), 73.7 (C7), 72.2 (C3), 41.5 (C6), 39.7 (C1), 28.3 (*t*Bu Boc). ESI-MS: *m/z* 304.1 $[M+H]^+$, 326.0 $[M+Na]^+$, 342.1 $[M+K]^+$, 629.4 $[2M+Na]^+$.

4.1.16. 2,5-Anhydro-3,4,6-tri-*O*-benzoyl-1-*O*-*tert*-butyldiphenylsilyl-D-allitol (26). Compound **11** (7.56 g, 16.1 mmol) was dissolved in pyridine (150 mL), TBDPSCl (4.63 mL, 17.68 mmol) was added and the resulting mixture stirred for 16 h. TLC analysis revealed complete conversion of the starting material in a higher running product. MeOH (1 mL) was added and the solvent was removed under reduced pressure. The residue was taken up in EtOAc (150 mL), washed with sat. aq. $NaHCO_3$ (2×100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated. Purification was effected by silica gel column chromatography (eluent: EtOAc/light petroleum, 0/1→3/7, v/v) to give **26** in 89% (11.25 g) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 8.11–7.92 (m, 6H, 6×H_{arom} Bz), 7.81–7.66 (m, 4H, H_{arom} TBDPS), 7.56–7.29 (m, 15H, 9×H_{arom} Bz, 6×H_{arom} TBDPS), 5.88 (dd, 1H, H3, $J_{2,3}$=4.4 Hz, $J_{3,4}$=5.5 Hz), 5.73 (t, 1H, H4, $J_{3,4}$=$J_{4,5}$=5.5 Hz), 4.74–4.49 (m, 3H, H5, 2×H6), 4.41 (q, 1H, H2, $J_{1a,2}$=$J_{1b,2}$=$J_{2,3}$=3.7 Hz), 3.94 (d, 2H, 2×H1, *J*=3.3 Hz), 1.10 (s, 9H, *t*Bu TBDPS). ^{13}C NMR ($CDCl_3$): δ 165.8, 165.1, 164.9 (3×C(O) Bz), 135.4, 133.0, 132.7, 129.4, 128.0, 127.5 (CH_{arom} Bz, TBDPS), 132.6, 129.1, 128.9 (C_q Bz, TBDPS), 82.8, 78.6, 72.7, 72.5 (C2, C3, C4, C5), 64.5, 63.4 (C1, C6), 26.5 (*t*Bu TBDPS), 18.9 (C_q *t*Bu TBDPS). ESI-MS: *m/z* 737.5 $[M+Na]^+$.

4.1.17. 2,5-Anhydro-1-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-isopropylidene-D-allitol (28). Compound **26** (11.25 g, 15.75 mmol) was converted into compound **28** as described for the azide analog **15**. Purification of the crude product by column chromatography (eluent: EtOAc/light petroleum 1/0→1/1, v/v) afforded **28** as a pale yellow oil in 94% (6.58 g). ^{1}H NMR ($CDCl_3$): δ 7.70–7.65 (m, 4H, H_{arom} TBDPS), 7.40 (m, 6H, H_{arom} TBDPS), 4.80 (dd, 1H, H4, $J_{3,4}$=6.2 Hz, $J_{4,5}$=4.4 Hz), 4.70 (dd, 1H, H3, $J_{2,3}$=3,3 Hz, $J_{3,4}$=6.6 Hz), 4.17 (q, 1H, H2, $J_{1a,2}$=$J_{1b,2}$=$J_{2,3}$=3.3 Hz), 4.05 (dt, 1H, H5, $J_{4,5}$=4.4 Hz, $J_{5,6a}$=$J_{5,6b}$=2.9 Hz), 3.90 (dd, 1H, H1a, $J_{1a,2}$=2.9 Hz, $J_{1a,1b}$=11.3 Hz), 3.79 (dd, 1H, H6a, $J_{5,6a}$=2.9 Hz, $J_{6a,6b}$=8.8 Hz), 3.69 (dd, 1H, H6b, $J_{5,6b}$=2.9 Hz), 3.65 (dd, 1H, H1b, $J_{1b,2}$=3.3 Hz, $J_{1a,1b}$=12.1 Hz), 2.50 (bs, 1H, OH), 1.53, 1.36 (2×s, 6H, 2×CH_3 isoprop), 1.08 (s, 9H, *t*Bu TBDPS). ^{13}C NMR ($CDCl_3$): δ 135.2, 135.1, 129.5, 127.4 (CH_{arom} TBDPS), 132.5 (C_q TBDPS), 113.1 (C_q isoprop), 84.6, 84.3, 81.7, 81.1 (C2, C3, C4, C5), 63.9, 62.8 (C1, C6), 27.1, 25.1 (2×CH_3 isoprop), 26.4 (*t*Bu TBDPS), 18, 7 (C_q *t*Bu TBDPS). ESI-MS: *m*/*z* 465.1 $[M+Na]^+$.

4.1.18. 2,5-Anhydro-1-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-isopropylidene-5-*C*-hydroxy methyl-D-allitol (29). Compound **28** (1.91 g, 4.33 mmol) was oxidized and treated with CH_2O, followed by $NaBH_4$ as described for compound **17**. Purification of the crude mixture by column chromatography (eluent: EtOAc/light petroleum 1/0→1/1, v/v) afforded the title compound **29** in 66% (1.14 g) as colourless oil, together with 9% of starting material (0.16 g). ^{1}H NMR ($CDCl_3$): δ 7.69–7.64 (m, 4H, H_{arom} TBDPS), 7.45–7.36 (m, 6H, H_{arom} TBDPS), 4.94 (dd, 1H, H3, $J_{2,3}$=5.1 Hz, $J_{3,4}$=6.6 Hz), 4.84 (d, 1H, H4, $J_{3,4}$=6.2 Hz), 4.08 (m, 1H, H2), 3.90 (dd, 1H, H1a, $J_{1a,2}$=2.9 Hz, $J_{1a,1b}$=11.7 Hz), 3.81–3.67 (m, 5H, H1b, 2×H6, 2×H7), 2.84, 2.36 (2×bs, 2H, 2×OH), 1.54, 1.37 (2×s, 6H, 2×CH_3 isoprop), 1.07 (s, 9H, *t*Bu TBDPS). ^{13}C NMR ($CDCl_3$): δ 135.4, 135.3, 129.7, 129.7, 127.6 (CH_{arom} TBDPS), 132.5, 132.4 (2×C_q TBDPS), 113.5 (C_q isoprop), 86.4 (C5), 84.3, 83.6, 81.3 (C2, C3, C4), 65.5, 63.9, 62.8 (C1, C6, C7), 26.6 (*t*Bu TBDPS), 18, 9 (C_q *t*Bu TBDPS). ESI-MS: *m*/*z* 495.5 $[M+Na]^+$.

4.1.19. 2,5-Anhydro-1-*O*-*tert*-butyldiphenylsilyl-3,4-*O*-isopropylidene-5-*C*-mesyloxy methyl-6-*O*-mesyl-D-allitol (30). Compound **29** (1.14 g, 2.51 mmol) was mesylated as described for compound **19** and subsequent purification by column chromatography (eluent: EtOAc/light petroleum 1/0→4/6, v/v) to give the title compound **30** in 93% (1.47 g) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 7.67–7.62 (m, 4H, H_{arom} TBDPS), 7.42 (m, 6H, H_{arom} TBDPS), 4.82 (dd, 1H, H3, $J_{2,3}$=3.7 Hz, $J_{3,4}$=6.2 Hz), 4.74 (d, 1H, H4, $J_{3,4}$=6.6 Hz), 4.41–4.07 (m, 3H, H2, 2×H6), 3.80 (dd, 1H, H1a, $J_{1a,2}$=3.7 Hz, $J_{1a,1b}$=11.3 Hz), 3.72 (dd, 1H, H1b, $J_{1b,2}$=4.0 Hz, $J_{1a,1b}$=11.3 Hz), 3.06, 2.95 (2×s, 6H, 2×CH_3 Ms), 1.53, 1.33 (2×s, 6H, 2×CH_3 isoprop), 1.07 (s, 9H, *t*Bu TBDPS). ^{13}C NMR ($CDCl_3$): δ 135.4, 129.8, 127.7 (CH_{arom} TBDPS), 132.6 (C_q TBDPS), 114.4 (C_q isoprop), 98.2 (C5), 84.4, 83.0, 81.7, (C2, C3, C4), 67.9, 64.0, 60.1 (C1, C6, C7), 37.4, 37.1 (2×CH_3 Ms), 26.9 (*t*Bu TBDPS), 26.7, 24.6 (2×CH_3 isoprop), 19.0 (C_q TBDPS). ESI-MS: *m*/*z* 651.3 $[M+Na]^+$.

4.1.20. 2,5-Anhydro-1-*O*-*tert*-butyldiphenylsilyl-5-*C*-mesyloxymethyl-6-*O*-mesyl-D-allitol (31). Compound **30** (1.47 g, 2.34 mmol) was dissolved in DCM (15 mL), $FeCl_3$ (2.21 g, 8.19 mmol) and MeOH (0.19 mL, 4.68 mmol) were added and the resulting mixture was stirred for 1.5 h. After addition of sat. aq. $NaHCO_3$ (10 mL), the solution was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel column chromatography (eluent: EtOAc/light petroleum, 2/8→8/2, v/v) to afford **31** as a pale yellow oil in 53% (0.73 g) together with 17% (0.25 g) of starting material. ^{1}H NMR ($CDCl_3$): δ 7.66 (m, 4H, H_{arom} TBDPS), 7.40 (m, H_{arom} TBDPS), 4.51 (s, 2H, 2×H6), 4.32 (m, 2H, H2, H4), 4.15 (d, 1H, H7a, $J_{7a,7b}$=6.9 Hz), 4.08 (d, 1H, H7b, $J_{7a,7b}$=7.0 Hz), 4.02 (m, 1H, H3), 3.85 (dd, 1H, H1a, J_{1a2}=3.7 Hz, $J_{1a,1b}$=11.3 Hz), 3.76 (dd, 1H, H1b, $J_{1b,2}$=3.7 Hz, $J_{1a,1b}$=11.3 Hz), 3.06, 2.95 (2×s, 6H, 2×CH_3 Ms), 1.07 (s, 9H, *t*Bu TBDPS). ^{13}C NMR ($CDCl_3$): δ 135.3, 129.7, 127.6 (CH_{arom} TBDPS), 132.8, 132.7 (2×C_q TBDPS), 83.0, 73.2, 70.9 (C2, C3, C4), 82.5 (C5), 68.8, 68.3, 63.4 (C1, C6, C7), 37.1, 36.9 (2×CH_3 Ms), 26.6 (*t*Bu TBDPS), 19.0 (C_q TBDPS). ESI-MS: *m*/*z* 611.3 $[M+Na]^+$.

4.1.21. 2,5-Anhydro-1-*O*-*tert*-butyldiphenylsilyl-6-*O*-mesyl-4-*O*,5-*C*-methylene-D-allitol (32). Compound **31** (2.06 g, 3.5 mmol) was converted into compound **32** as previously described for the azide analogue **21**. The crude product was purified by column chromatography (eluent: EtOAc/light petroleum, 1/9→6/4, v/v) to give **32** in 85% (1.46 g) as a colourless syrup. ^{1}H NMR ($CDCl_3$): δ 7.69 (m, 4H, H_{arom} TBDPS), 7.39 (m, H_{arom} TBDPS), 5.02 (d, 1H, H4, $J_{3,4}$=4.7 Hz), 4.82 (d, 1H, H7a, $J_{7a,7b}$=8.2 Hz), 4.53 (d, 1H, H7b, $J_{7a,7b}$=8.2 Hz), 4.43 (d, 1H, H6a, $J_{6a,6b}$=11.3 Hz), 4.38 (d, 1H, H6b, $J_{6a,6b}$=11.3 Hz), 4.17 (ddd, 1H, H2, $J_{1a,2}$=2.5 Hz, $J_{1b,2}$=4.0 Hz, $J_{2,3}$=8.0 Hz), 4.09 (m, 1H, H3), 4.06 (dd, 1H, H1a, $J_{1a,2}$=2.4 Hz, $J_{1a,1b}$=11.6 Hz), 3.95 (dd, 1H, H1b, $J_{1b,2}$=4.2 Hz, $J_{1a,1b}$=11.6 Hz), 2.93 (s, 3H, CH_3 Ms), 1.07 (s, 9H, *t*Bu TBDPS). ^{13}C NMR ($CDCl_3$): δ 135.0, 129.3, 127.3 (CH_{arom} TBDPS), 132.7, 132.6 (2×C_q TBDPS), 86.0, 82.8, 70.8 (C2, C3, C4), 81.6 (C5), 77.0 (C7), 67.6, 62.2 (C1, C6), 36.9 (CH_3 Ms), 26.3 (*t*Bu TBDPS), 18.8 (C_q TBDPS). ESI-MS: *m*/*z* 515.3 $[M+Na]^+$, 531.2 $[M+K]^+$.

4.1.22. 2,5-Anhydro-6-azido-1-*O*-*tert*-butyldiphenylsilyl-6-deoxy-4-*O*,5-*C*-methylene-D-allitol (33). Compound **32** (0.40 g, 0.81 mmol) was dissolved in DMF (3 mL), NaN_3 (0.16 g, 2.43 mmol) was added and the reaction mixture was stirred for 2 h. H_2O (3 mL) was added, and the resulting mixture was extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine (5 mL), dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (eluent: EtOAc/light petroleum, 1/9→1/1, v/v) to give **33** in 95% (0.34 g) as a colourless syrup. ^{1}H NMR ($CDCl_3$): δ 7.70 (m, 4H, H_{arom} TBDPS), 7.39 (m, H_{arom} TBDPS), 4.95 (d, 1H, H4, $J_{3,4}$=4.4 Hz), 4.76 (d, 1H, H7a, $J_{7a,7b}$=8.0 Hz), 4.55 (d, 1H, H7b, $J_{7a,7b}$=8.0 Hz), 4.15 (m, 2H, H2, H3), 4.05 (dd, 1H, H1a, $J_{1a,2}$=2.9 Hz, $J_{1a,1b}$=11.3 Hz), 3.95 (dd, 1H, H1b, $J_{1b,2}$=4.0 Hz, $J_{1a,1b}$=11.3 Hz), 3.60 (d, 1H, H6a, $J_{6a,6b}$=13.2 Hz), 3.51 (d, 1H, H6b, $J_{6a,6b}$=13.2 Hz), 1.07 (s, 9H, *t*Bu TBDPS). ^{13}C NMR ($CDCl_3$): δ 135.4, 129.6, 127.5 (CH_{arom} TBDPS), 133.0 (C_q TBDPS), 87.1, 83.2, 71.5 (C2, C3, C4), 83.5 (C5), 78.3 (C7), 62.7 (C1), 52.4 (C6),

26.6 (*t*Bu TBDPS), 19.1 (C_q TBDPS). ESI-MS: *m/z* 462.2 $[M+Na]^+$, 901.5 $[2M+Na]^+$.

4.1.23. 2,5-Anhydro-6-*tert*-butoxycarbonylamino-1-*O*-*tert*-butyldiphenylsilyl-6-deoxy-4-*O*,5-*C*-methylene-D-allitol (34). Compound **33** (0.34 g, 0.77 mmol) was transformed into the Boc-protected analogue **34** as described for compound **23**. Purification of the crude product was accomplished by column chromatography (eluent: EtOAc/light petroleum, 1/9→1/1, v/v) to give **34** in 94% (0.36 g) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 7.70 (m, 4H, H_{arom} TBDPS), 7.40 (m, H_{arom} TBDPS), 4.94 (d, 1H, H4, $J_{3,4}$=3.7 Hz), 4.73 (d, 1H, H7a, $J_{7a,7b}$=7.7 Hz), 4.64 (bs, 1H, HN), 4.48 (d, 1H, H7b, $J_{7a,7b}$=7.7 Hz), 4.07 (m, 3H, H2, H3, H1a), 3.92 (dd, 1H, H1b, $J_{1b,2}$=3.7 Hz, $J_{1a,1b}$=11.7 Hz), 3.69 (dd, 1H, H6a, $J_{6a,NH}$=8.0 Hz, $J_{6a,6b}$=14.0 Hz), 3.32 (dd, 1H, H6b, $J_{6b,NH}$=4.8 Hz, $J_{6a,6b}$=13.9 Hz), 1.42 (s, 9H, *t*Bu Boc), 1.07 (s, 9H, *t*Bu TBDPS). ^{13}C NMR ($CDCl_3$): δ 155.9 (C(O) Boc), 135.4, 129.6, 127.5 (CH_{arom} TBDPS), 133.0 (C_q TBDPS), 87.3, 82.6, 71.3 (C2, C3, C4), 83.5 (C5), 79.4 (Cq Boc), 78.6 (C7), 62.4 (C1), 42.6 (C6), 28.6 (*t*Bu Boc), 26.7 (*t*Bu TBDPS), 19.1 (C_q TBDPS). ESI-MS: *m/z* 536.2 $[M+Na]^+$, 1049.6 $[2M+Na]^+$.

4.1.24. 2,5-Anhydro-6-*tert*-butoxycarbonylamino-6-deoxy-4-*O*,5-*C*-methylene-D-allitol (35). Compound **34** (0.36 g, 0.68 mmol) and TBAF·3H_2O (0.24 g, 0.76 mmol) were dissolved in THF (2 mL). The reaction mixture was stirred for 1 h, after which TLC analysis revealed complete conversion of the starting material in a lower running compound. The solvent was removed under reduced pressure and the resulting crude oil was purified by silica gel column chromatography (eluent: EtOAc/light petroleum, 3/7→8/2, v/v) to yield **35** quantitatively (0.20 g) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 5.12 (bs, 1H, HN), 4.97 (d, 1H, H4, $J_{3,4}$=4.8 Hz), 4.76 (d, 1H, H7a, $J_{7a,7b}$=7.7 Hz), 4.51 (d, 1H, H7b, $J_{7a,7b}$=8.0 Hz), 4.14 (ddd, 1H, H2, $J_{1a,2}$=2.6 Hz, $J_{1b,2}$=4.0 Hz, $J_{2,3}$=8.4 Hz), 4.03 (dd, 1H, H1a, $J_{1,2}$=2.7 Hz, $J_{1a,1b}$=12.4 Hz), 3.96 (m, 1H, H3), 3.81 (dd, 1H, H1b, $J_{1b,2}$=4.0 Hz, $J_{1a,1b}$=12.4 Hz), 3.63 (dd, 1H, H6a, $J_{6a,NH}$=7.3 Hz, $J_{6a,6b}$=14.6 Hz), 3.36 (dd, 1H, H6b, $J_{6b,NH}$=5.1 Hz, $J_{6a,6b}$=14.6 Hz), 2.87 (bs, 1H, OH), 1.44 (s, 9H, *t*Bu Boc). ^{13}C NMR ($CDCl_3$): δ 156.5 (C(O) Boc), 87.5, 81.8, 70.9 (C2, C3, C4), 83.9 (C5), 81.8 (Cq Boc), 78.4 (C7), 60.4 (C1), 42.2 (C6), 27.9 (*t*Bu Boc). ESI-MS: *m/z* 276.1 $[M+H]^+$, 298.2 $[M+Na]^+$.

4.1.25. 2,5-Anhydro-6-*tert*-butoxycarbonylamino-6-deoxy-4-*O*,5-*C*-methylene-D-*allo*-hexonic acid (3). Oxidation of compound **35** (0.20 g, 0.68 mmol) was performed as described for compound **1** to afford **3** as a colourless oil in 60% (0.123 g) after purifucation by column chromatography (eluent: EtOAc/MeOH/H_2O/Et_3N, 50/45/5/3, v/v/v/v). ν_{max} (neat): 3256.5, 1697.7, 1577.7, 1421.7, 1165.7 cm^{-1}. ^{1}H NMR, COSY, HMQC (400 MHz, MeOD): δ 4.94 (d, 1H, H4, $J_{3,4}$=4.2 Hz), 4.74 (d, 1H, H7a, $J_{7a,7b}$=7.9 Hz), 4.51 (d, 1H, H2, $J_{2,3}$=8.8 Hz), 4.49 (d, 1H, H7b, $J_{7a,7b}$=7.7 Hz), 3.86 (dd, 1H, H3, $J_{2,3}$=8.9 Hz, $J_{3,4}$=4.2 Hz), 3.55 (d, 1H, H6a, $J_{6a,6b}$=15.0 Hz), 3.42 (d, 1H, H6b, $J_{6a,6b}$=15.0 Hz), 1.42 (s, 9H, *t*Bu Boc). ^{13}C NMR (MeOD): δ 177.8 (C1), 159.1 (C(O) Boc), 88.8 (C4), 86.2 (C5), 81.3 (C2), 80.6 (Cq Boc), 79.7 (C7), 75.6 (C3), 43.2 (C6), 28.8 (*t*Bu Boc). ESI-MS: *m/z* 304.1 $[M+H]^+$, 325.8 $[M+Na]^+$, 629.7 $[2M+Na]^+$.

4.1.26. Boc-BSAA1-Phe-Leu-OMe (36). A solution of Boc-Phe-Leu-OMe (0.055 g, 0.14 mmol) in DCM/TFA (2 mL, 1/1, v/v) was stirred for 5 min. toluene was added and the reaction mixture subsequently concentrated. Traces of acid were removed from the residue by coevaporation with toluene (3×2 mL) and the residue was dissolved in DMF (1 mL). BSAA **1** (0.038 g, 0.13 mmol) was added and the resulting mixture was cooled to 0°C. HOBt (0.019 g, 0.14 mmol) and EDC·HCl (0.027 g, 0.14 mmol) were added and the reaction mixture was neutralized with NMM. After stirring for 16 h the reaction mixture was concentrated and the residue redissolved in EtOAc (5 mL). The organic phase was washed with H_2O (3 mL), aq. $NaHCO_3$ (2×3 mL), H_2O (3 mL), $KHSO_4$ (2×3 mL) and brine (3 mL), dried ($MgSO_4$) and concentrated. Purification by silica gel column chromatography (eluent: EtOAc/light petroleum, 1/1→1/0, v/v) afforded **36** as an amorphous white solid in 45% (0.033 g), mp 147–149°C. ^{1}H NMR ($CDCl_3$): δ 7.30 (m, 6H, 5×H_{arom} Phe, HN-Phe), 6.51 (d, 1H, HN-Leu, *J*=7.6 Hz), 5.20 (d, 1H, H7a, $J_{7a,7b}$=7.5 Hz), 5.15 (t, 1H, HN-LSA1, *J*=6.2 Hz), 4.80 (d, 1H, H4, $J_{3,4}$=4.6 Hz), 4.72 (m, 1H, Hα-Phe), 4.52 (m, 1H, Hα-Leu), 4.38 (d, 1H, H7b, $J_{7a,7b}$=7.5 Hz), 4.21 (m, 1H, H2), 3.73 (s, 3H, OMe), 3.57 (dd, 1H, H3, *J*=3.5 Hz, *J*=5.9 Hz), 3.53 (m, 1H, H1a), 3.52 (m, 1H, H1b), 3.18 (dd, 1H, Hβa-Phe, $J_{\alpha,\beta a}$=6.2 Hz, $J_{\beta a,\beta b}$=14.0 Hz), 3.00 (dd, 1H, Hβb-Phe, $J_{\alpha,\beta b}$=8.4 Hz, $J_{\beta a,\beta b}$=13.9 Hz), 1.62–1.46 (m, 3H, 2×Hβ-Leu, Hγ-Leu), 1.44 (s, 9H, *t*Bu Boc), 0.89 (d, 3H, Hδ-Leu, *J*=3.5 Hz), 0.88 (d, 3H, Hδ-Leu, *J*=3.4 Hz). ^{13}C NMR ($CDCl_3$): δ 172.8, 170.3, 167.0 (3×C(O), Leu, Phe, SAA-C1), 156.5 (C(O) Boc), 136.4 (Cq Phe), 129.4, 128.5, 127.1 (CH_{arom} Phe), 87.6 (C4), 83.8 (C5), 82.9 (C2), 80.0 (Cq Boc), 77.6 (C7), 72.8 (C3), 53.9 (Cα-Phe), 52.3 (OMe), 51.0 (Cα-Leu), 41.8 (C6), 41.3 (Cβ-Leu), 37.8 (Cβ-Phe), 28.4 (*t*Bu Boc), 24.8 (Cγ-Leu), 22.6, 21.9 (2×Cδ-Leu). ESI-MS: *m/z* 564.4 $[M+H]^+$, 586.2 $[M+Na]^+$, 1149.6 $[2M+Na]^+$.

4.1.27. Boc-Tyr(*t*Bu)-BSAA1-Phe-Leu-OMe (37). Compound **36** (0.033 g, 0.06 mmol) was dissolved in TFA/DCM (1 mL, 1/1, v/v) and the resulting mixture was stirred for 5 min, toluene was added and the reaction mixture subsequently concentrated. Traces of acid were removed from the residue by coevaporation with toluene (3×2 mL) and the residue was dissolved in DMF (1 mL), Boc-Tyr-(*t*Bu)-OH (0.022 g, 0.065 mmol) was added and the reaction mixture was cooled to 0°C. HOBt (0,01 g, 0.065 mmol) and EDC·HCl (0.012 g, 0.065 mmol) were added and the reaction mixture was neutralized with NMM. After 16 h the solvent was removed under reduced pressure and the residue was taken up in EtOAc (5 mL) and washed with H_2O (3 mL), sat. aq. $NaHCO_3$ (2×3 mL), H_2O (3 mL), 1 M aq. $KHSO_4$ (2×3 mL) and brine (3 mL), the organic phase was dried ($MgSO_4$) and concentrated. The crude product was applied to a silica gel column and eluted with EtOAc/light petroleum (1/1→1/0, v/v) to give the title compound **37** in 70% (0.033 g) as a white solid, mp 141–143°C. ^{1}H NMR ($CDCl_3$): δ 7.29–7.19 (m, 7H, 5×H_{arom} Phe, HN-Phe, HN-SAA), 7.17 (d, 2H, 2×H_{arom} Tyr, *J*=8.2 Hz), 6.88 (d, 3H, 2×H_{arom} Tyr, HNLeu, *J*=8.4 Hz), 5.30 (d, 1H, HN-Tyr, *J*=7.2 Hz), 5.15 (m, 2H, Hα-Phe,

H7a), 4.60 (m, 1H, Hα-Tyr), 4.46 (q, 1H, Hα Leu, J=6.8 Hz), 4.20 (m, 1H, H4), 4.00 (m, 1H, H7b), 3.67 (s, 3H, OMe), 3.60 (dd, 1H, H1a, J=6.6 Hz, J=12.6 Hz), 3.22–3.16 (m, 2H, H3, Hβa-Phe), 3.05–2.88 (m, 4H, 2×Hβ-Tyr, Hβb-Phe, H1b), 1.62–1.48 (m, 3H, 2×Hβ-Leu, Hγ-Leu), 1.44, 1.31 (2×s, 18H, *tert*-Bu Boc, *tert*-Bu), 0.99 (d, 3H, Hδ-Leu, $J_{\gamma,\delta}$=5.4 Hz), 0.94 (d, 3H, Hδ-Leu, $J_{\gamma,\delta}$=5.9 Hz). ^{13}C NMR ($CDCl_3$): δ 173.0, 172.4, 171.5, 167.4 (4×C(O), Tyr, SAA, Phe, Leu), 156.0 (C(O) Boc), 154.3 (Cζ-Tyr), 137.4, 131.6 (Cγ-Tyr, Cγ-Phe), 130.0, 124.1 (CH_{arom} Tyr), 129.4, 128.3, 126.8 (CH_{arom} Phe), 87.8 (C4), 83.6 (C5), 82.6 (C2), 80.12 (Cq Boc), 78.4 (C7), 73.0 (C3), 56.1 (Cα-Tyr), 54.4 (Cα-Phe), 52.1 (OMe), 51.5 (Cα-Leu), 40.9 (C1, Cβ-Leu), 38.6 (Cβ-Phe), 38.2 (Cβ-Tyr), 29.7 (Cq *tert*-Bu), 28.8, 28.4 (*tert*-Bu Boc, *tert*-Bu), 24.8 (Cγ-Leu), 22.5, 22.2 (2×Cδ-Leu). ESI-MS: *m/z* 783.5 $[M+H]^+$, 805.6 $[M+Na]^+$.

4.1.28. Tyr-BSAA1-Phe-Leu-OMe (4). Compound **37** (0.033 g, 0.042 mmol) was dissolved in a mixture of TFA/H_2O (1 mL, 9/1, v/v) and the reaction mixture was stirred for 1 h and subsequently concentrated. Traces of H_2O and acid were removed from the residue by coevaporation with toluene and the residue was applied to a silica gel column. Elution with DCM→MeOH/DCM (1/9, v/v) afforded compound **4** quantitatively (0.026 g) as a colourless syrup. ν_{max} (neat): 3394.4, 3274.9, 2958.6, 2920.0, 1735.8, 1662.5, 1515.9, 1442.7, 1207.4, 1137.9, 1029.9, 840.9, 821.6, 702.0 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.31 (d, 2H, Hδ-Phe, J=7.3 Hz), 7.26 (t, 2H, Hε-Phe, J=7.4 Hz), 7.19 (t, 1H, Hζ-Phe, J=7.3 Hz), 7.09 (d, 2H, 2×H_{arom} Tyr, J=8.4 Hz), 6.67 (d, 2H, 2×H_{arom} Tyr, J=8.5 Hz), 5.09 (d, 1H, H7a, $J_{7a,7b}$=7.2 Hz), 4.85 (dd, 1H, Hα-Phe, $J_{\alpha,\beta a}$=5.1 Hz, $J_{\alpha,\beta b}$=9.4 Hz), 4.62 (d, 1H, H4, $J_{3,4}$=4.5 Hz), 4.57 (t, 1H, Hα-Leu, $J_{\alpha,\beta}$=7.7 Hz), 4.25 (dt, 1H, H2, J=2.7 Hz, J=8.3 Hz), 4.20 (d, 1H, H7b, $J_{7a,7b}$=7.2 Hz), 3.81 (dd, 1H, H1a, $J_{1a,2}$=9.5 Hz, $J_{1a,1b}$=14.0 Hz), 3.76 (t, 1H, Hα-Tyr, $J_{\alpha,\beta}$=5.4 Hz), 3.63 (s, 3H, OMe), 3.59 (dd, 1H, H3, $J_{2,3}$=8.0 Hz, $J_{3,4}$=4.5 Hz), 3.44 (dd, 1H, H1b, $J_{1b,2}$=2.6 Hz, $J_{1a,1b}$=14.5 Hz), 3.26 (dd, 1H, Hβa-Phe, $J_{\alpha,\beta a}$=5.1 Hz, $J_{\beta a,\beta b}$=13.8 Hz), 3.07 (dd, 1H, Hβb-Phe, $J_{\alpha,\beta b}$=9.5 Hz, $J_{\beta a,\beta b}$=13.7 Hz), 2.95 (d, 2H, 2×Hβ-Tyr, $J_{\alpha,\beta}$=5.4 Hz), 1.59 (m, 1H, Hγ-Leu), 1.55 (m, 2H, Hβ-Leu), 0.81 (d, 3H, Hδ-Leu, $J_{\gamma,\delta}$=6.5 Hz), 0.80 (d, 3H, Hδ-Leu, $J_{\delta,\gamma}$=6.5 Hz). ^{13}C NMR ($CDCl_3$): δ 176.9, 173.3, 171.8, 167.6 (4×C(O), Tyr, LSA1, Phe, Leu), 156.9 (Cζ-Tyr), 138.5 (Cγ-Phe), 131.7, 115.7 (CH_{arom} Tyr), 130.5, 128.9, 127.3 (CH_{arom} Phe), 89.3 (C4), 84.9 (C5), 83.2 (C2), 77.5 (C7), 75.2 (C3), 60.1 (Cα-Tyr), 54.9 (Cα-Phe), 52.4 (OMe), 51.5 (Cα-Leu), 43.4 (C1), 41.4 (Cβ-Leu), 38.8 (Cβ-Phe), 36.9 (Cβ-Tyr), 25.3 (Cγ-Leu), 23.1, 21.9 (2×Cδ-Leu). ESI-MS: *m/z* 627.5 $[M+H]^+$, 649.4 $[M+Na]^+$.

4.1.29. 2,5-Anhydro-3-*O*-acetyl-1-azido-1-deoxy-6-*O*-mesyl-4-*O*,5-*C*-methylene-D-allitol (38). Compound **21** (0.028 g, 0.1 mmol) was dissolved in pyridine (1 mL) and Ac_2O (0.019 mL, 0.2 mmol) was added. The reaction mixture was stirred for 3 h, and then concentrated under reduced pressure. The residue was taken up in EtOAc (5 mL), washed with sat. aq. $NaHCO_3$ (2×3 mL), brine (3 mL), dried ($MgSO_4$) and concentrated. Purification was effected by silica gel column chromatography (eluent: EtOAc/light petroleum, 0/1→7/3, v/v) to give **38** in 90% (0.029 g) as a colourless oil. ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ 5.31 (d, 1H, H4, $J_{3,4}$=4.4 Hz), 4.82 (d, 1H, H7a, $J_{7a,7b}$=8.2 Hz), 4.80 (dd, 1H, H3, $J_{2,3}$=8.6 Hz, $J_{3,4}$=4.4 Hz), 4.63 (m, 1H, H2), 4.58 (d, 1H, H7b, $J_{7a,7b}$=8.2 Hz), 4.48 (d, 1H, H6a, $J_{6a,6b}$=11.4 Hz), 4.41 (d, 1H, H6b, $J_{6a,6b}$=11.4 Hz), 3.77 (dd, 1H, H1a, $J_{1a,2}$=2.7 Hz, $J_{1a,1b}$=13.6 Hz), 3.44 (dd, 1H, H1b, $J_{1b,2}$=4.8 Hz, $J_{1a,1b}$=13.6 Hz), 3.08 (s, 3H, Ms), 2.13 (s, 3H, CH_3 Ac). ESI-MS: *m/z* 322.1 $[M+H]^+$, 344.0 $[M+Na]^+$, 665.2 $[2M+Na]^+$.

4.1.30. 2,5-Anhydro-3-*O*-acetyl-1-*O*-*tert*-butyldiphenylsilyl-6-*O*-mesyl-4-*O*,5-*C*-methylene-D-allitol (39). Compound **32** (0.059 g, 0.1 mmol) was dissolved in pyridine (1 mL) and Ac_2O (0.019 mL, 0.2 mmol) was added. The reaction mixture was stirred for 3 h, and then concentrated under reduced pressure. The residue was taken up in EtOAc (5 mL), washed with sat. aq. $NaHCO_3$ (2×3 mL), brine (3 mL), dried ($MgSO_4$) and concentrated. Purification was affected by silica gel column chromatography (eluent: EtOAc/light petroleum, 0/1→7/3, v/v) to give **39** in 88% (0.053 g) as a colourless oil. ^{1}H NMR, COSY (300 MHz, $CDCl_3$): δ 7.66 (m, 4H, H_{arom} TBDPS), 7.39 (m, 6H, H_{arom} TBDPS), 5.29 (d, 1H, H4, $J_{3,4}$=4.4 Hz), 4.92 (dd, 1H, H3, $J_{3,4}$=4.4 Hz, $J_{2,3}$=8.4 Hz), 4.79 (d, 1H, H7a, $J_{7a,7b}$=8.1 Hz), 4.57 (d, 1H, H7b, $J_{7a,7b}$=8.2 Hz), 4.53 (m, 1H, H2), 4.42 (2H, 2×H6), 4.03 (dd, 1H, H1a, $J_{1a,2}$=2.3 Hz, $J_{1a,1b}$=11.8 Hz), 3.88 (dd, 1H, H1b, $J_{1b,2}$=3.7 Hz, $J_{1a,1b}$=11.6 Hz), 2.96 (s, 3H, OMs), 2.07 (s, 3H, CH_3 Ac), 1.06 (s, 9H, *tert*-Bu TBDPS). ESI-MS: *m/z* 557.2 $[M+Na]^+$, 1091.3 $[2M+Na]^+$.

4.1.31. Tricyclic compound (41). Compound **21** (0.50 g, 1.78 mmol) was dissolved in THF (10 mL), and Me_3P (2.14 mL of a 1 M solution in toluene) was added. After 1 h, TLC analysis revealed that the starting material was completely transformed into a lower running product. The reaction mixture was cooled to −20°C and a solution of Boc-ON (0.52 g, 2.14 mmol) in toluene (0.5 mL) was added slowly. After stirring for 5 h, the solvent was removed and the residue was redissolved in THF (10 mL), mixed with silica gel and evaporated to dryness under reduced pressure. The silica gel containing absorbed product was applied to a silica gel column and purification (eluent: EtOAc/light petroleum, 9/1→1/0, followed by MeOH/EtOAc, 0/1→1/20, v/v) afforded 11% of **40** (0.07 g) together with 60% of **41** (0.17 g), both colourless oils. **40**: ^{13}C NMR ($CDCl_3$): δ 86.5, 81.2, 72.7 (C2, C3, C4), 82.1 (C5), 79.6 (C_q Boc), 77.1 (C7), 67.7 (C6), 40.9 (C1), 37.6 (CH_3 Ms), 28.2 (*t*Bu Boc). **41**: ^{13}C NMR ($CDCl_3$): δ 86.8, 81.7, 72.5 (C2, C3, C4), 85.3 (C5), 77.6 (C7), 62.4 (C6), 51.0 (C1).

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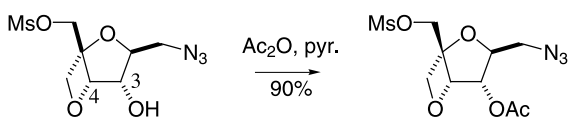
11. The formation of a side product in which the isopropylidene is replaced by a methylene group was also observed by Moffat et al. when they performed an aldol/Cannizaro reaction on N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine-5′-aldehyde (see Ref. 10d).
12. The same selectivity for the formation of a 4-membered ring over the thermodynamically more stable 5-membered ring was observed by Imanishi et al.[1d] in the ring closure of 4′-(*p*-toluenesulfonyl)oxymethyluridine. They ascribed this selectivity for the formation of a 4-membered ring to the predominant *S*-puckering of the ribose ring, which locates the 3′-OH in close proximity to the 4′-carbon center.
13. The chemical shift of H4 shifted from 5.06 ppm (**21**) to 5.31 ppm (**38**), while the chemical shift of H3 shifted from 3.98 ppm (**21**) to 4.80 ppm (**38**) (see Section 4)



21 **38**

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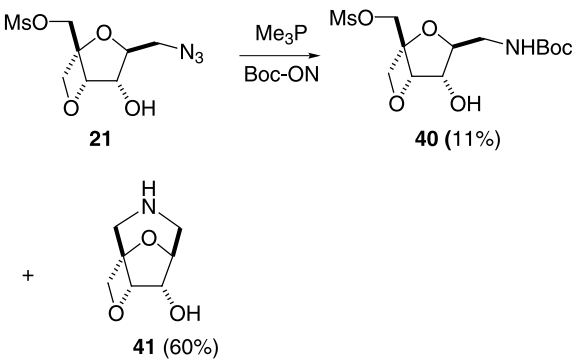
16. When attempts were made to react the azide **21** with Me_3P and Boc-ON prior to the substitution of the mesyl with NaCN the major product that was isolated did not correspond to the desired Boc-protected amine adduct **40**, but appeared to be the tricyclic compound **41**. Apparently the intermolecular attack of the intermediate iminophosphorane on the mesyl protected primary hydroxyl proceeds faster than the intramolecular reaction with Boc-ON



21 **40** (11%)

41 (60%)

17. Prolonged treatment of **30** with $FeCl_3$ also resulted in partial cleavage of the TBDPS group.
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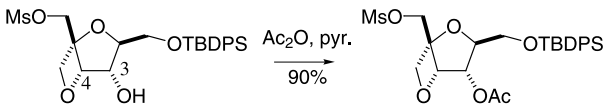
19. The chemical shift of H4 shifted from 5.02 ppm (**32**) to 5.29 ppm (**39**), while the chemical shift of H3 shifted from 3.09 ppm (**32**) to 4.92 ppm (**39**) (see Section 4)



32 **39**

20. (a) Portoghese, P. S.; Sultana, M.; Takemori, A. E. *J. Med. Chem.* **1990**, *33*, 1714. (b) Portoghese, P. S. *J. Med. Chem.* **1992**, *35*, 1927.

21. Altona, C.; Sudaralingam, M. *J. Am. Chem. Soc.* **1973**, *95*, 2333.

22. The ^{1}H NMR spectrum of BSAA **3** and the precursors (**24** and **25**) of BSAA **2**, also displayed a large value for $J_{5,6}$ and $J_{2,3}$ (8.8 Hz) respectively. Unfortunately, the $J_{2,3}$ coupling constant of BSAA **2** could not be determined due to signal overlap.