PERKIN 1

Tetrahydrofuran amino acids: β- and γ-azidotetrahydrofuran-carboxylic acid monomers derived from D-glucoheptonolactone as building blocks for β- and γ-oligopeptides

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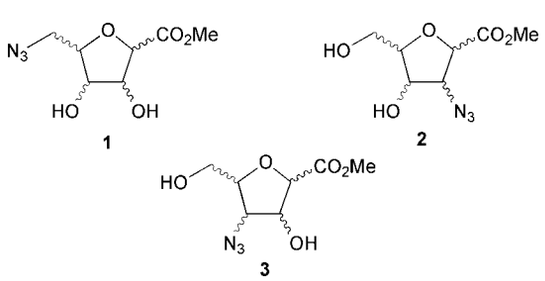
The synthesis of both a β (L-*allono*) and a γ (D-*allono*) tetrahydrofuran azido acid from a single heptono sugar lactone as monomers for peptidomimetic oligomers is described.

Introduction

Relatively short oligomers of β- and γ-amino acids, especially those of conformationally restricted systems,[1,2] have been shown to adopt ordered secondary structures. Such systems continue to provide an increased understanding of the factors which induce secondary structures, and may provide probes of the complex nature of protein folding. The biological functions of proteins and RNA, including catalysis and recognition, are critically reliant on their precise folding into well-ordered structures. Pyranose sugar amino acids, including β- and γ-amino acids, have been shown[3] to exert predictable conformational effects in peptidic systems due to the rigid conformations imposed by the all-equatorial substituents; when such systems were incorporated into cyclic hexapeptide analogues of somatostatin, the γ-amino acid served as a β-turn mimetic while the β-amino acid induced a γ-turn. The synthetic approaches[3,4] to these β- and γ-sugar amino acids, including modifications of a previously reported procedure,[5] were described. In contrast to pyranose sugar systems, the present work describes the synthesis of furanose-based sugar amino acid precursors. In these systems, the tetrahydrofuran (THF) sugar ring should again provide the β- and γ-amino acid substituents in distinct orientations necessary for the conformational properties of peptidomimetic oligomers. 5-(Azidomethyl)tetrahydrofuran-2-carboxylic acid **1** scaffolds (building blocks for δ-oligopeptides) are a family of dipeptide isosteres which show promise of providing building blocks that are predisposed towards different secondary structures, depending on the stereochemistry of the substituents around the THF ring.[6] Substitution of azide at different sites on the tetrahydrofuran ring (such as the β-azido ester **2** and the γ-azido ester **3**) should provide a set of templates which are predisposed towards induction of varied secondary structures.



Results and discussion

This paper describes the synthesis, from the readily available seven-carbon sugar lactone **8**, of β- and γ-azido THF monomers **5** and **4** which should allow the generation of oligopeptides with secondary structure. The 3-azidotetrahydrofuran-2-carboxylate **5**, a *C*-glycoside possessing L-*allonate* stereochemistry (2,5-*cis*-stereochemistry), is a building block for the synthesis of *C*-glycoside β-amino acid oligomers. Oligomers derived from **5** (with similar stereochemistry to β-L-ribofuranose) may have potential as RNA-chain mimics in which the amide bonds mimic the phosphodiester backbone of the nucleic acid. Additionally, the D-*allonate* γ-azido THF ester **4** may be considered as a *C*-glycoside with 2,5-*cis*-stereochemistry similar to the β-D-ribofuranose scaffold and has potential to generate γ-peptides likely to adopt relatively well defined secondary structures.

Both the γ-azidoTHF-2-carboxylate **4** and the β-azidoTHF-2-carboxylate **5** may be derived from azido ester **6** as a common intermediate (Scheme 1). The azido ester **6** can be formed efficiently by introduction of azide at C-4 of the THF **7** with inversion of configuration to give the D-*glycero*-D-*allo*-heptonate stereochemistry of this building block. A protected form of D-*glycero*-D-*gulo*-heptonate **7** is available in 4 steps[7] from the readily available diacetonide[8,9] of D-*glycero*-D-*gulo*-heptono-1,4-lactone **8**. The key step in the synthesis of the THF *C*-glycoside **7** involves treatment of a 2-*O*-triflate of a carbohydrate lactone with acidic methanol, conditions which result in hydrolysis of the side-chain acetonide and methanolysis of the lactone with intramolecular S_N2 displacement of the triflate at C-2 of **8** by 5-OH.[7,10] Elaboration by reductive cleavage of the side-chain C-6 and C-7 in **6** generates the γ-amino acid precursor **4**, while reduction of the ester function at C-1 of **6** followed by oxidative cleavage between C-6 and C-7 would provide access to β-amino acid building blocks from **5**. Oligomers derived from the β-azido ester **5** could be compared with those from the four diastereomeric (2,3-*cis*- and 2,3-*trans*-) 3-azidotetrahydrofuran-2-carboxylates **9**–**12** which have been prepared previously from diacetone-glucose.[11]

The objective of this work is to provide an increasingly diverse picture of the THF amino acid structures which form oligomers with a propensity to exhibit secondary structure. Different diastereomers of 5-(azidomethyl)THF-2-carboxylates **1** produce oligomers which exhibit β-turn[12] and α-helical[13] structures in solution. Likewise, α-,[14] β-[15] and γ-[16] amino-acid-

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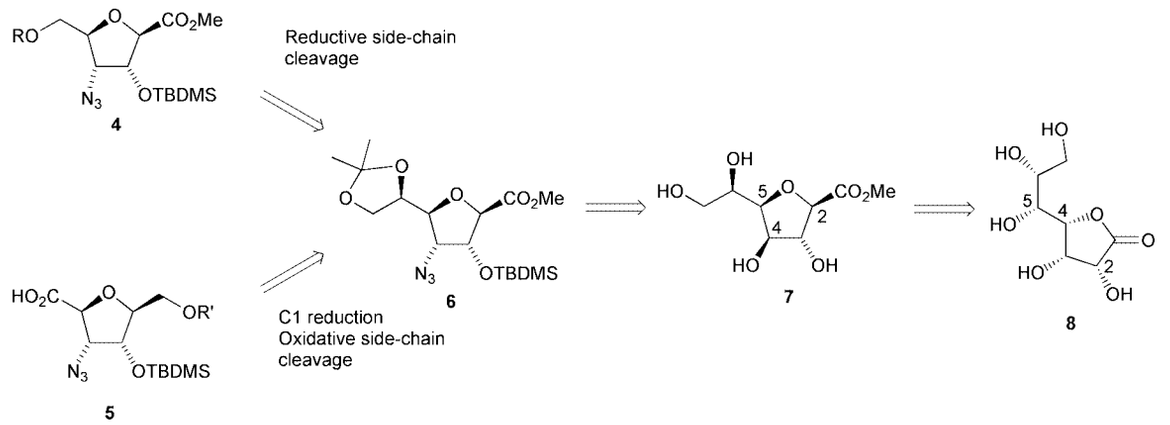
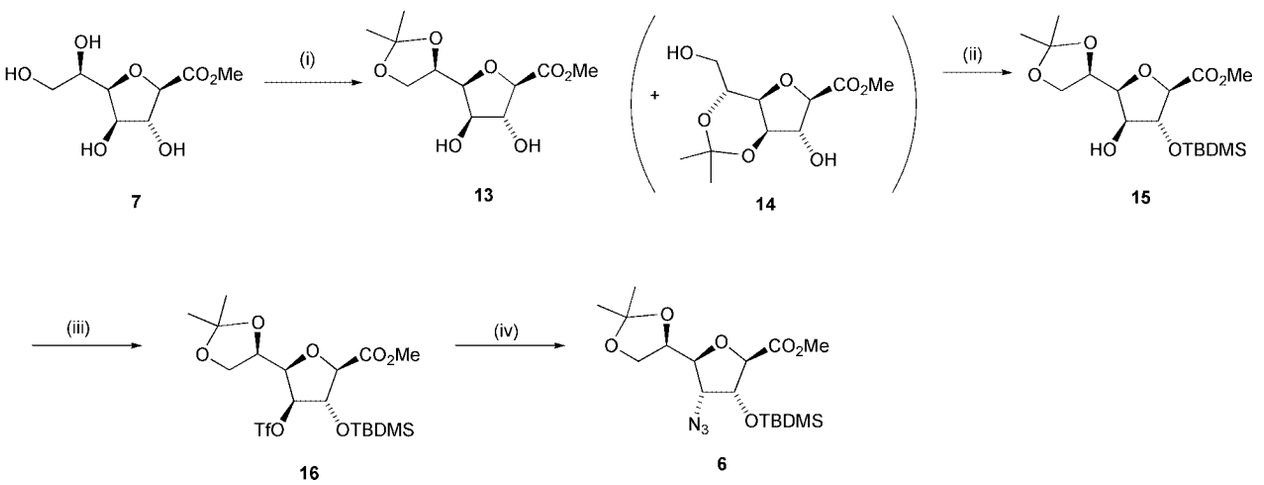
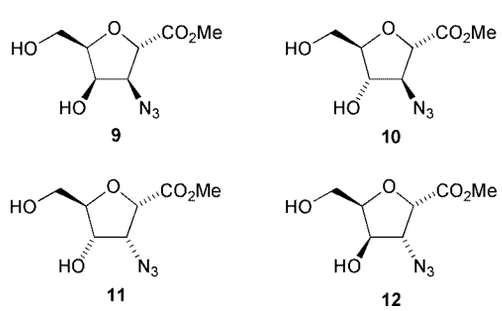


Scheme 1



Scheme 2 *Reagents and conditions* (*and yields*): (i) 2,2-DMP, CSA, acetone, RT, 16 h (61%) (ii) TBDMSCl, imidazole, DMF, −25 °C to RT, 16 h (72%) (iii) Tf_2O, py, DCM, −15 to 0 °C, 1.5 h (92%) (iv) NaN_3, DMF, RT, 1 h (71%).



containing oligomers, in addition to other scaffolds,[17] have adopted defined secondary conformations.

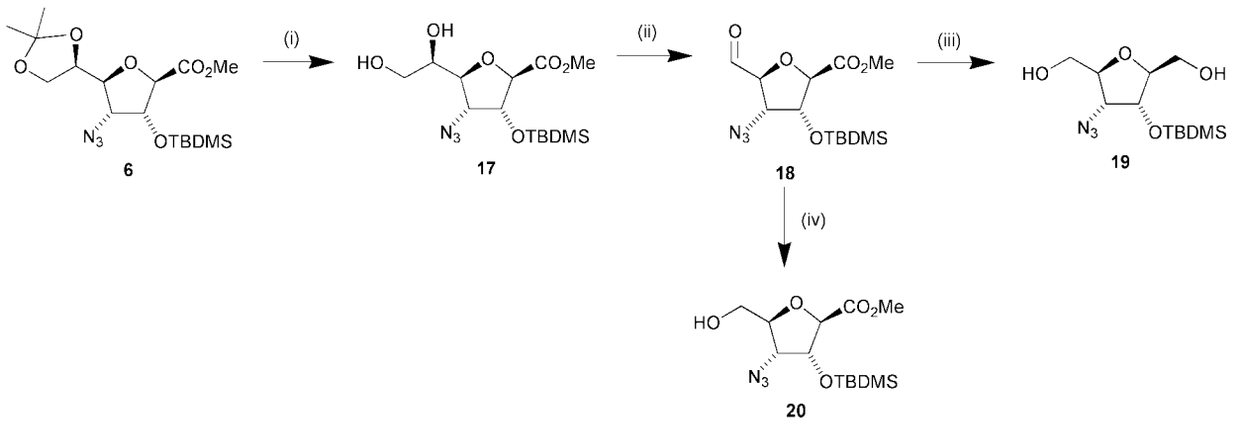
For the synthesis of the divergent intermediate **6**, it was necessary to protect all the hydroxy groups in **7** other than the C-4 OH. Treatment of the tetraol **7** with 2,2-dimethoxypropane (2,2-DMP) and (±)-camphor-10-sulfonic acid (CSA) in acetone gave the 6,7-monoacetonide **13**[18] in 61% yield (Scheme 2), together with the 4,6-acetonide **14** in 26% yield. Selective protection with *tert*-butyldimethylsilyl chloride (TBDMSCl) and imidazole in dimethylformamide (DMF) afforded **15** in 72% yield; 2D NMR experiments (COSY, HMQC, HMBC) established that the silyl ether was at C-3. Esterification of the remaining free C-4 hydroxy group with Tf_2O and pyridine (py) in dichloromethane (DCM) gave **16** in 92% yield; subsequent azide displacement of the triflate with inversion of configuration formed the key intermediate azido ester **6** in 71% yield. Divergence of the synthetic scheme at this point provided access to the β- and γ-amino acid building blocks.

Synthesis of the γ-azidoTHF-2-carboxylate involved reductive cleavage between C 6 and C 7 of the side-chain diol in **6** (Scheme 3). Acetonide deprotection of **6** using 80% aq. acetic acid gave **17** in 98% yield. Periodate cleavage of the diol **17** was followed by immediate hydride reduction of the aldehyde **18**. However, reduction with sodium borohydride in aq. ethanol gave diol **19** (in 59% over 3 steps from **6**) obtained from concomitant reduction of the ester; only a trace of the required ester **20** was isolated. Although esters are not usually reduced by sodium borohydride, the ester carbonyl group in **18** is activated by the presence of the α oxygen of the THF ring. Reduction of **18** with sodium cyanoborohydride in acetic acid caused regioselective reduction of the aldehyde in **18** to afford the ester **20** in an overall yield of 76% from **6** in 3 steps.

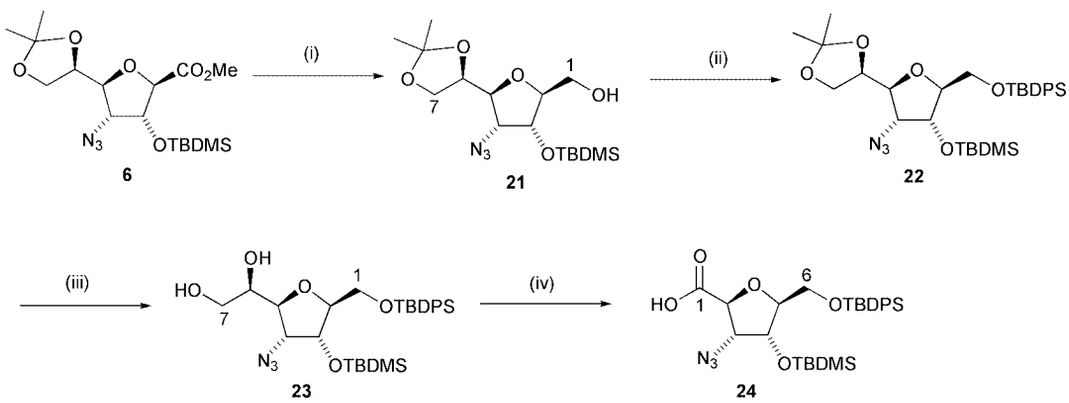
For access to the β-azidoTHF-2-carboxylate from the azido ester **6**, the ester functionality was reduced by sodium borohydride in aq. ethanol to yield the primary alcohol **21** in 64% yield (Scheme 4). Protection of the primary hydroxy group as the *tert*-butyldiphenylsilyl (TBDPS) ether to give **22** (73% yield) was followed by selective deprotection of the 6,7-acetonide by aq. acetic acid to afford the diol **23** in 65% yield. Oxidation of the diol moiety in **23** with sodium periodate in the presence of catalytic ruthenium(III) chloride[19] resulted in the formation of the target 3-azidotetrahydrofuran-2-carboxylate **24** in 62% yield.

Conclusions

This paper describes a viable synthetic route to the 3-azido- and 4-azido-tetrahydrofuran-2-carboxylates **20** and **24** from a readily available seven-carbon sugar lactone as building blocks for the generation of β- and γ-oligopeptides. These materials provide further examples of an increasingly diverse library of THF amino acid building blocks for the generation of



Scheme 3 *Reagents and conditions* (*and yields*): (i) 80% AcOH (aq.), RT, 16 h; (ii) H_5IO_6, THF, RT, 5 min; (iii) $NaBH_4$, aq. EtOH, RT, 15 min [59% (3 steps)]; (iv) $NaBH_3CN$, AcOH, 10 min, RT [76% (3 steps)].



Scheme 4 *Reagents and conditions* (*and yields*): (i) $NaBH_4$, aq. EtOH, RT, 3 h (64%) (ii) TBDPSCl, imidazole, DMF, −30 °C to RT, 16 h (73%) (iii) 80% AcOH (aq.), RT, 36 h (65%) (iv) $NaIO_4$, $RuCl_3{\cdot}H_2O$, CCl_4–CH_3CN–water, RT, 5 h (62%).

THF-based peptidomimetic oligomers and for the incorporation of such units into libraries. Comparison of the structures of the oligomers derived from these monomers with those derived from other THF systems should eventually provide a set of monomers for the design of foldamers[17b] with predictable conformations, or for the incorporation of peptide mimetics with a predisposition for the generation of designed secondary structures.

Experimental

^{1}H NMR (δ_H) spectra were recorded on a Bruker DPX 400 spectrometer (at 400 MHz), Bruker DPX 200 or Varian Gemini 200 (200 MHz), Bruker AMX 500 or AM 500 (500 MHz) spectrometer at ambient probe temperatures (≈298 K). Coupling constants (J) were measured in Hz and are averaged. ^{13}C NMR (δ_C) spectra were recorded on a Bruker DPX 200 (at 50 MHz), Bruker DPX 400 spectrometer (at 100 MHz) or Bruker AMX 500 or AM500 (125 MHz) spectrometer; multiplicities were assigned using a DEPT sequence. All chemical shifts are quoted on the δ-scale using residual solvent as internal standard. IR spectra were recorded on a Perkin-Elmer 1750 IR FT spectrophotometer. Mass spectra were recorded on VG Micromass 20–250, ZAB 1F, Micromass Platform 1 or Trio-1 GCMS (DB-5 column) spectrometers using chemical ionisation (CI, NH_3), atmospheric pressure chemical ionisation (APCI) or electrospray techniques (ES) as stated. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. $[a]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}. Concentrations are given in g/100 ml. Mps were recorded on a Kofler block and are uncorrected. Microanalyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, Oxford. TLC was carried out on plastic or aluminium sheets coated with $60F_{254}$ silica or glass plates coated with silica blend 41. Plates were developed using a spray of 0.2% w/v cerium(IV) sulfate and 5% ammonium molybdate in 2 M sulfuric acid. Flash chromatography was carried out using Sorbsil C60 40/60 silica. Solvents and commercially available reagents were dried and purified before use according to standard procedures. A solution of KH_2PO_4 (85 g) and NaOH (14.5 g) in distilled water (950 ml) was used as a pH 7 buffer solution. The tetrahydrofuran ester **7** was prepared from the heptonolactone **8** as previously described.[7]

Methyl 2,5-anhydro-6,7-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptonate[18] 13 and methyl 2,5-anhydro-4,6-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptonate 14

The tetrahydrofuran ester **7**[7] (4.36 g, 19.6 mmol) was stirred in acetone (90 mL) containing 2,2-dimethoxypropane (2.45 g, 23.6 mmol). DL-Camphor-10-sulfonic acid (0.23 g, 0.98 mmol) was added and the mixture was stirred for 16 h at room temperature. TLC (ethyl acetate–MeOH 9:1) showed no starting material (R_f 0.2) and a major product (R_f 0.6) and a minor product (R_f 0.5). Sodium bicarbonate (0.4 g) was added and stirring was continued until the solution was pH 6. The mixture was filtered through Celite, the filter was washed with acetone, and the solvent was removed *in vacuo*. Repeated flash chromatography (ethyl acetate–hexane 2:1 followed by DCM–MeOH 19:1, then 9:1) yielded the side-chain acetonide **13** (3.13 g, 61%), mp 98–100 °C (lit.,[18] 87–89 °C) $[a]_D^{22}$ −45.0 (*c* 1.00 in $CHCl_3$) [lit.,[18] −41.6 (*c* 1.00 in $CHCl_3$)] [HRMS *m*/*z* (CI+) Found: 263.1135 (M + H$^+$). $C_{11}H_{19}O_7$ requires *m*/*z*, 263.1131] (Found: C, 50.29; H, 6.91. Calc. for $C_{11}H_{18}O_7$: C, 50.38; H, 6.92%); ν_{max} (thin film) 3700–3100 (OH), 1734 (C=O) cm^{-1}; δ_H (CD_3CN; 400 MHz) 1.35 (3H, s, CH_3C), 1.41 (3H, s, CH_3C), 3.24 (1H, d, *J* 4.6, 4-OH), 3.68 (1H, d, *J* 4.1, 3-OH), 3.72 (3H, s, CH_3O), 4.01 (1H, ddd, *J* 4.6, 3.4, 1.2, H-4), 4.06–4.11 (3H, m, H-5, H_2-7), 4.30 (1H, d, *J* 1.2, H-2), 4.33 (1H, a-dt, *J* ≈ 4.0, 1.2, H-3), 4.37 (1H, a-q, *J* 6.3, H-6); δ_C (CD_3CN; 125 MHz) 25.0 (q, *C*H$_3$C), 26.4

(q, *C*H$_3$C), 51.9 (d, CH$_3$O), 67.0 (t, C-7), 73.6 (d, C-6), 76.2 (d, C-4), 81.2 (d, C-3), 83.5 (d, C-5), 84.0 (d, C-2), 108.8 (s, O–C–O), 171.6 (s, C-1); *m*/*z* (APCI+) 285 (M + Na$^+$, 100%), 263 (M + H$^+$, 80), 205 (90).

Further elution afforded *the 4,6-O-isopropylidene ester* **14** (1.34 g, 26%), mp 117–119 °C; $[a]_D^{22}$ −9.4 (*c* 1.09 in acetone) [HRMS *m*/*z* (CI+) Found: 263.1133 (M + H$^+$). $C_{11}H_{19}O_7$ requires *m*/*z*, 263.1131] (Found: C, 50.38; H, 6.94. $C_{11}H_{18}O_7$ requires C, 50.38; H, 6.92%); ν_{max} (thin film) 3700–3100 (OH), 1734 (C=O) cm^{-1}; δ_H (CD$_3$CN; 500 MHz) 1.25 (3H, s, CH$_3$C), 1.31 (3H, s, CH$_3$C), 3.05 (1H, a-t, *J* 6.0, 7-OH), 3.57 (1H, ddd, *J* 11.9, 6.6, 6.0, H-7), 3.70 (3H, s, OCH$_3$), 3.72 (1H, ddd, *J* 11.9, 6.0, 2.9, H′-7), 3.86 (1H, d, *J* 4.7, 3-OH), 3.88 (1H, ddd, *J* 7.9, 6.6, 2.9, H-6), 4.10 (1H, dd, *J* 4.3, 0.5, H-4), 4.20 (1H, dd, *J* 7.9, 4.3, H-5), 4.42–4.44 (2H, m, H-2, -3); δ_C (CD$_3$CN; 50 MHz) 23.6 (q, *C*H$_3$C), 23.9 (q, *C*H$_3$C), 52.0 (q, CH$_3$O), 63.3 (t, C-7), 72.6 (d, C-6), 76.7 (d, C-4), 79.0 (d, C-3), 80.3 (d, C-5), 84.6 (d, C-2), 100.6 (s, O–C–O), 171.4 (s, C-1); *m*/*z* (APCI+) 285 (M + Na$^+$, 100%), 263 (M + H$^+$, 35), 205 (60).

Methyl 2,5-anhydro-3-*O*-(*tert*-butyldimethylsilyl)-6,7-*O*-isopropylidene-D-*glycero*-D-*gulo*-heptonate 15

The acetonide **13** (2.30 g, 8.8 mmol) was dissolved in dry DMF (2.3 mL). Imidazole (0.72 g, 10.5 mmol) was added and the mixture was cooled to −25 °C. *tert*-Butyldimethylsilyl chloride (1.46 g, 9.7 mmol) was added and the mixture was stirred at room temperature overnight. TLC (ethyl acetate–hexane 1 : 1) showed a major product at R_f 0.5 and only a small amount of residual starting material (R_f 0.2). Ethanol (3 drops) was added and the solvent was removed under reduced pressure. The residue obtained was co-evaporated with toluene and then dissolved in ethyl acetate (80 mL); the solution was washed with pH 7 buffer solution (50 mL), dried (MgSO$_4$), and concentrated. Flash chromatography purification (ethyl acetate–hexane 1 : 3) afforded *the silyl ether* **15** (2.39 g, 72%) as a colourless oil, $[a]_D^{22}$ −28.6 (*c* 1.09 in acetone) (Found: C, 54.13; H, 8.46. $C_{17}H_{32}O_7Si$ requires C, 54.23; H, 8.57%); ν_{max} (thin film) 3200–3600 (O–H), 1738 (C=O) cm^{-1}; δ_H (CD$_3$CN; 400 MHz) 0.16 [6H, s, Si(CH$_3$)$_2$], 0.93 [9H, s, SiC(CH$_3$)$_3$], 1.32 (3H, s, CCH$_3$), 1.38 (3H, s, CCH$_3$), 3.33 (1H, d, *J* 4.4, 4-OH), 3.69 (3H, s, OCH$_3$), 3.94 (1H, ddd, *J* 4.4, 3.2, 1.1, H-4), 4.05–4.08 (3H, m, H-5, H$_2$-7), 4.28 (1H, d, *J* 0.6, H-2), 4.34 (1H, a-dt, *J* 6.7, 6.3, H-6), 4.41 (1H, br s, H-3); δ_C (CD$_3$CN; 100.6 MHz) −5.4 (q, CH$_3$Si), −5.3 (q, CH$_3$Si), 18.0 [s, Si*C*(CH$_3$)$_3$], 25.0 (q, *C*H$_3$C), 25.5 [q, SiC(*C*H$_3$)$_3$], 26.5 (q, *C*H$_3$C), 51.9 (q, CH$_3$O), 66.9 (t, C-7), 73.5 (d, C-6), 76.3 (d, C-4), 82.4 (d, C-3), 83.4 (d, C-5), 84.6 (d, C-2), 108.7 (s, O–C–O), 171.4 (s, C-1); *m*/*z* (APCI+) 399 (M + Na$^+$, 90%), 377 (M + H$^+$, 15), 319 (100), 169 (80).

Continued elution (ethyl acetate–hexane 3 : 1) afforded recovered starting material **13** (0.36 g, 16%).

Methyl 2,5-anhydro-3-*O*-(*tert*-butyldimethylsilyl)-6,7-*O*-isopropylidene-4-*O*-trifluoromethylsulfonyl-D-*glycero*-D-*gulo*-heptonate 16

Dry pyridine (1.14 mL, 1.11 g, 14.1 mmol) was added to a solution of the silyl ether **15** (2.30 g, 6.1 mmol) in dry DCM (25 mL). Upon cooling of this solution to −15 °C, trifluoromethanesulfonic anhydride (1.34 mL, 2.24 g, 8.0 mmol) was added dropwise *via* syringe. Stirring was continued for 1 h between −15 and 0 °C. TLC (ethyl acetate–hexane 1 : 1) revealed a single product (R_f 0.8) together with residual starting material (R_f 0.5). Additional pyridine (0.8 mL) was added and the mixture was re-cooled to −15 °C before further trifluoromethanesulfonic anhydride (1.0 mL) was added *via* syringe. Upon stirring of the mixture for 30 min at 0 °C, TLC analysis revealed the reaction to be complete. Water (10 mL) was added and the mixture was applied directly to a flash chromatography column (ethyl acetate–hexane 1 : 9) to give *the triflate* **16** (2.87 g, 92%) as an unstable material which was used directly in the next reaction.

Methyl 2,5-anhydro-4-azido-3-*O*-(*tert*-butyldimethylsilyl)-4-deoxy-6,7-*O*-isopropylidene-D-*glycero*-D-*allo*-heptonate 6

The triflate **16** (0.138 g, 0.27 mmol) was dissolved in dry DMF (3 mL) and sodium azide (0.019 g, 0.29 mmol) was added. The mixture was stirred at room temperature for 1 h, when TLC (ethyl acetate–hexane 1 : 4) showed very little starting material (R_f 0.6) and the presence of product (R_f 0.5). Water (80 mL) was added and the mixture was extracted with ethyl acetate (5 × 50 mL). The combined extracts were dried over MgSO$_4$ and concentrated. Residual DMF was removed by *in vacuo* co-evaporation with toluene. Flash chromatography (ethyl acetate–hexane 1 : 8) afforded the protected azide **6** (0.77 g, 71%) as a colourless oil, $[a]_D^{25}$ −27.6 (*c* 0.32 in CHCl$_3$) [HRMS *m*/*z* (CI+) Found: 402.2075 (M + H$^+$). $C_{17}H_{32}N_3O_6Si$ requires *m*/*z*, 402.2060] (Found: C, 50.70; H, 7.69; N, 9.94. $C_{17}H_{31}N_3O_6Si$ requires C, 50.85; H, 7.78; N, 10.47%); ν_{max} (thin film) 2108 (N$_3$), 1752 (C=O) cm^{-1}; δ_H (CD$_3$CN; 400 MHz) 0.28 (3H, s, SiCH$_3$), 0.31 (3H, s, SiCH$_3$), 1.08 [9H, s, SiC(CH$_3$)$_3$], 1.46 (3H, s, CCH$_3$), 1.54 (3H, s, CCH$_3$), 3.84 (3H, s, OCH$_3$), 3.87 (1H, m, H-4), 4.04 (1H, dd, *J* 8.5, 5.2, H-7), 4.06 (1H, m, H-5), 4.25 (1H, dd, *J* 8.6, 6.5, H′-7), 4.31 (1H, a-dt, *J* ≈ 6.6, 5.2, H-6), 4.42 (1H, d, *J* 4.1, H-2), 4.70 (1H, dd, *J* 4.8. 4.1, H-3); δ_C (CD$_3$CN; 100.6 MHz) −5.6 (q, SiCH$_3$), −5.3 (q, SiCH$_3$), 18.1 [s, Si*C*(CH$_3$)$_3$], 24.8 (q, *C*H$_3$C), 25.4 [q, SiC(*C*H$_3$)$_3$], 26.2 (q, *C*H$_3$C), 52.2 (q, CH$_3$O), 64.2 (d, C-4), 67.1 (t, C-7), 76.5 (d, C-6), 77.2 (d, C-3), 82.1 (d, C-5), 82.9 (d, C-2), 109.8 (s, O–C–O), 171.0 (s, C-1); *m*/*z* (APCI+) 402 (M + H$^+$, 20%), 374 (M + H$^+$ − N$_2$, 100).

Methyl 2,5-anhydro-4-azido-3-*O*-(*tert*-butyldimethylsilyl)-4-deoxy-D-*glycero*-D-*allo*-heptonate 17

The azide **6** (0.100 g, 0.25 mmol) was dissolved in a mixture of acetic acid and water (8 mL : 2 mL) and the solution was stirred at room temperature overnight. TLC (ethyl acetate–hexane 1 : 1) showed complete conversion of starting material (R_f 0.8) to a single product (R_f 0.2). The reaction mixture was concentrated *in vacuo* with toluene co-evaporation to give the diol **17** (0.88 g, 98%), which was used without further purification in the following reactions. A sample was purified by flash chromatography (ethyl acetate–hexane 1 : 1) to give *the diol* **17** as a colourless oil, $[a]_D^{22}$ −27.6 (*c* 0.71 in MeOH) (Found: C, 46.47; H, 7.65, N, 11.28. $C_{14}H_{27}N_3O_6Si$ requires C, 46.52; H, 7.53, N, 11.62%); ν_{max} (thin film) 3200–3600 (OH), 2107 (N$_3$), 1744 (C=O) cm^{-1}; δ_H (CD$_3$CN; 400 MHz) 0.18 (3H, s, SiCH$_3$), 0.19 (3H, s, SiCH$_3$), 0.97 [9H, s, SiC(CH$_3$)$_3$], 3.58 (1H, dd, *J* 11.3, 6.1, H-7), 3.62 (1H, dd, *J* 11.3, 5.1, H′-7), 3.75 (3H, s, CH$_3$), 3.82 (1H, dd, *J* 6.9, 5.2, H-4), 3.83 (1H, a-dt, *J* 6.9, 5.2, H-6), 4.09 (1H, dd, *J* 6.8, 5.2, H-5), 4.35 (1H, d, *J* 3.4, H-2), 4.60 (1H, dd, *J* 4.9, 3.4, H-3); δ_C (CD$_3$CN; 50 MHz) −4.9 (q, SiCH$_3$), −4.6 (q, SiCH$_3$), 18.8 [s, Si*C*(CH$_3$)$_3$], 26.1 [q, SiC(*C*H$_3$)$_3$], 53.2 (q, OCH$_3$), 62.6 (d, C-4 or -6), 63.6 (t, C-7), 72.7 (d, C-6 or -4), 78.3 (d, C-3), 82.8 (d, C-5), 83.4 (d, C-2), 173.0 (C-1); *m*/*z* (APCI+) 334 (M + H$^+$ − N$_2$, 100%), 302 (40), 142 (85).

Methyl 2,5-anhydro-4-azido-3-*O*-(*tert*-butyldimethylsilyl)-4-deoxy-D-allonate 20

The diol **17** (0.088 g, 0.24 mmol) was dissolved in dry THF (1.0 mL) and periodic acid (0.061 g, 0.27 mmol) was added. After stirring of the mixture for 5 min at room temperature, TLC (ethyl acetate–hexane 1 : 1) suggested complete consumption of starting material (R_f 0.2) and conversion to a new product (R_f 0.5). The reaction mixture was filtered through Celite, with washing of the filter with THF, and the combined filtrate and washings were concentrated *in vacuo*. The residue was dissolved in acetic acid (0.6 mL) and sodium cyanoborohydride (0.015 g, 0.24 mmol) was added. The mixture was stirred at room

temperature for 10 min, when TLC (ethyl acetate–hexane 1:1) showed complete conversion to product (R_f 0.6). Water (4 drops) was added and the mixture was concentrated *in vacuo*. The resulting residue was re-dissolved in ethyl acetate and pre-adsorbed onto silica. Flash chromatography (ethyl acetate–hexane 1:1) gave *the ester* **20** [0.063 g, 78% (76% overall from **6**)] as a colourless oil, $[\alpha]_D^{25}$ −20.1 (*c* 0.77 in $CHCl_3$) [HRMS *m*/*z* (CI+) Found: 349.1912 (M + NH_4^+). $C_{13}H_{29}N_4O_5Si$ requires *m*/*z*, 349.1907] (Found: C, 47.45; H, 7.92; N, 12.19. $C_{13}H_{25}N_3O_5Si$ requires C, 47.11; H, 7.60; N, 12.68%); ν_{max} (thin film) 3200–3600 (OH), 2107 (N_3), 1743 (C=O) cm^{-1}; δ_H ($CDCl_3$; 500 MHz) 0.21 (3H, s, $SiCH_3$), 0.23 (3H, s, $SiCH_3$), 0.99 [9H, s, $SiC(CH_3)_3$], 3.69 (1H, br d, *J* 12.6, H-6), 3.81 (1H, dd, *J* 8.0, 4.6, H-4), 3.83 (3H, s, OCH_3), 4.06 (1H, dd, *J* 12.6, 2.4, H′-6), 4.30 (1H, a-dt, *J* 8.0, 2.0, H-5), 4.46 (1H, d, *J* 2.2, H-2), 4.55 (1H, dd, *J* 4.6, 2.1, H-3); δ_C ($CDCl_3$; 125.6 MHz) −5.2 (q, $SiCH_3$), −5.0 (q, $SiCH_3$), 18.0 [s, $SiC(CH_3)_3$], 25.6 [q, $SiC(CH_3)_3$], 52.7 (q, OCH_3), 60.2 (d, C-4), 61.0 (t, C-6), 77.4 (d, C-3), 81.6 (d, C-5), 83.0 (d, C-2), 172.3 (s, C-1); *m*/*z* (APCI+) 332 (M + H^+, 10%), 304 (M + H^+ − N_2, 100).

2,5-Anhydro-4-azido-3-*O*-(*tert*-butyldimethylsilyl)-4-deoxy-D-allitol 19

The diol **17** (0.034 g, 0.10 mmol) was dissolved in dry THF (0.4 mL) and periodic acid (0.026 g, 0.11 mmol) was added. After stirring of the mixture for 10 min at room temperature, TLC (ethyl acetate–hexane 1:1) suggested complete conversion of starting material (R_f 0.2) to product (R_f 0.5). The reaction mixture was filtered through Celite, with washing of the filter with THF, and the combined filtrate and washings were concentrated *in vacuo*. The resulting residue was dissolved in a 9:1 mixture of ethanol and water (0.8 mL), and treated with sodium borohydride (0.008 g, 0.10 mmol). After 15 min at room temperature a major product (R_f 0.2) was observed by TLC (ethyl acetate–hexane 1:1) together with a minor product (R_f 0.6). The reaction mixture was quenched with excess ammonium chloride, concentrated, and partitioned between brine and DCM. The combined organic phases were dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (ethyl acetate–hexane 1:20, then 1:4, then 1:1) yielded the ester **20** (0.001 g, 3%) and 2,5-anhydro-4-azido-3-*O*-(*tert*-butyldimethylsilyl)-4-deoxy-D-allitol **19** (0.017 g, 59% overall from **6**) as a colourless oil, $[\alpha]_D^{24}$ +15.1 (*c* 0.31 in $CHCl_3$) [HRMS *m*/*z* (CI+) Found: 276.1636 (M + H^+ − N_2). $C_{12}H_{26}NO_4Si$ requires *m*/*z*, 276.1631]; ν_{max} (thin film) 3200–3600 (OH), 2104 (N_3) cm^{-1}; δ_H ($CDCl_3$; 400 MHz) 0.14 (3H, s, $SiCH_3$), 0.17 (3H, s, $SiCH_3$), 0.94 [9H, s, $SiC(CH_3)_3$], 3.63 (1H, dd, *J* 12.0, 2.8, H-1), 3.69 (1H, dd, *J* 12.1, 2.7, H-6), 3.74 (1H, a-t, *J* 5.9, H-4), 3.87 (1H, dd, *J* 12.0, 2.6, H′-1), 3.90–3.95 (2H, m, H-2, H′-6), 4.07 (1H, a-dt, *J* 5.9, 2.6, H-5), 4.41 [1H, a-t (br), *J* ≈ 5.1, H-3]; δ_C ($CDCl_3$; 100.6 MHz) −5.0 (q, $SiCH_3$), −4.8 (q, $SiCH_3$), 18.0 [s, $SiC(CH_3)_3$], 25.7 [q, $SiC(CH_3)_3$], 61.9, 62.3 (2 × t, C-1, -6), 62.3 (d, C-4), 73.8, 81.1, 85.0 (3 × d, C-2, -3, -5); *m*/*z* (APCI+) 276 (M + H^+ − N_2, 50%), 228 (50), 122 (100).

2,5-Anhydro-4-azido-3-*O*-(*tert*-butyldimethylsilyl)-4-deoxy-6,7-*O*-isopropylidene-D-*glycero*-D-*allo*-heptitol 21

The protected azide **6** (0.156 g, 0.39 mmol) was dissolved in a 9:1 mixture of ethanol and water (4 mL), and sodium borohydride (0.030 g, 0.78 mmol) was added. After 3 h at room temperature a major product (R_f 0.4) was observed by TLC (ethyl acetate–hexane 1:1) with no starting material (R_f 0.8) remaining. The reaction mixture was quenched with excess solid ammonium chloride (0.053 g, 1 mmol), concentrated, and partitioned between brine and DCM. The combined organic phases were dried ($MgSO_4$), and concentrated *in vacuo*. Flash chromatography (ethyl acetate–hexane 1:3) afforded *the alcohol* **21** (0.093 g, 64%) as a colourless oil, $[\alpha]_D^{22}$ −10.8 (*c* 1.04 in MeOH) (Found: C, 51.26; H, 8.36; N, 10.82. $C_{16}H_{31}N_3O_5Si$ requires C, 51.45; H, 8.37; N, 11.25%); ν_{max} (thin film) 3200–3600 (OH), 2107 (N_3) cm^{-1}; δ_H (CD_3OD; 500 MHz) 0.18 (3H, s, $SiCH_3$), 0.20 (3H, s, $SiCH_3$), 0.98 [9H, s, $SiC(CH_3)_3$], 1.36 (3H, s, CCH_3), 1.45 (3H, s, CCH_3), 3.54 (1H, dd, *J* 12.1, 4.4, H-1), 3.67 (1H, dd, *J* 12.1, 3.4, H′-1), 3.71 (1H, a-t, *J* ≈ 5.5, H-4), 3.82 [1H, a-q (br), *J* ≈ 4.4, H-2], 3.85 (1H, dd, *J* 5.7, 5.5, H-5), 3.91 (1H, dd, *J* 7.7, 4.3, H-7), 4.09–4.16 (2H, m, H-6, H′-7), 4.36 (1H, a-t, *J* ≈ 5.4, H-3); δ_C (CD_3OD; 125 MHz) −4.9 (q, $SiCH_3$), −4.5 (q, $SiCH_3$), 18.9 [s, $SiC(CH_3)_3$], 25.3 (q, CCH_3), 26.3 [q, $SiC(CH_3)_3$], 26.9 (q, CCH_3), 62.4 (t, C-1), 65.5 (d, C-4), 68.0 (t, C-7), 75.0 (d, C-3), 77.8 (d, C-6), 82.7 (d, C-5), 86.2 (d, C-2), 110.9 (s, O–C–O); *m*/*z* (APCI+) 346 (M + H^+ − N_2, 100%).

2,5-Anhydro-4-azido-3-*O*-(*tert*-butyldimethylsilyl)-1-*O*-(*tert*-butyldiphenylsilyl)-4-deoxy-6,7-*O*-isopropylidene-D-*glycero*-D-*allo*-heptitol 22

The heptitol **21** (0.093 g, 0.25 mmol) was dissolved in dry DMF (100 μL). Imidazole (0.023 g, 0.35 mmol) was added and the mixture was cooled to −30 °C. *tert*-Butyldiphenylsilyl chloride (0.082 g, 0.30 mmol) was added and the mixture was stirred at room temperature overnight. TLC (ethyl acetate–hexane 1:3) showed a major product at R_f 0.7. Ethanol (3 drops) was added and the solvent was removed under reduced pressure. The residue obtained was co-evaporated with toluene and then dissolved in ethyl acetate (20 mL); the solution was washed with pH 7 buffer solution (10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography purification (ethyl acetate–hexane 1:24) gave *the silyl ether* **22** (0.111 g, 73%) as a colourless oil, $[\alpha]_D^{22}$ −23.7 (*c* 1.35 in acetone) (Found: C, 62.77; H, 7.98; N, 6.73. $C_{32}H_{49}N_3O_5Si_2$ requires C, 62.81; H, 8.07; N, 6.87%); ν_{max} (thin film) 2103 (N_3) cm^{-1}; δ_H (C_6D_6; 400 MHz) 0.06 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.95 [9H, s, $SiC(CH_3)_3$], 1.12 [9H, s, $SiC(CH_3)_3$], 1.24 (3H, s, CCH_3), 1.42 (3H, s, CCH_3), 3.62 (1H, dd, *J* 11.7, 3.2, H-1), 3.76 (1H, dd, *J* 11.7, 3.3, H′-1), 3.82 (1H, ddd, *J* 5.4, 2.5, 2.5, H-4), 3.92–3.98 (3H, m, H-2, H_2-7), 4.02–4.08 (2H, m, H-5, -6), 4.50 (1H, a-t, *J* 5.4, H-3), 7.20–7.25 (6H, m, ArH), 7.72–7.79 (4H, m, ArH); δ_C ($CDCl_3$; 100.6 MHz) −4.6 (q, $SiCH_3$), −4.2 (q, $SiCH_3$), 18.6 [s, $SiC(CH_3)_3$], 19.6 [s, $SiC(CH_3)_3$], 25.5 (q, CCH_3), 26.2 [q, $SiC(CH_3)_3$], 27.0 (q, CCH_3), 27.3 [q, $SiC(CH_3)_3$], 63.3 (t, C-1), 65.1 (d, C-4), 67.8 (t, C-7), 73.9 (d, C-3), 77.3 (d, C-5 or -6), 82.2 (d, C-5 or -6), 84.9 (d, C-2), 110.2 (s, O–C–O), 128.4 (d, Ar CH), 128.4 (d, Ar CH), 130.4 (d, Ar CH), 130.5 (d, Ar CH), 133.6 (s, Ar CC), 133.8 (s, Ar CC), 136.3 (d, Ar CH), 136.3 (d, Ar CH); *m*/*z* (APCI+) 584 (M + H^+ − N_2, 100%).

2,5-Anhydro-4-azido-3-*O*-(*tert*-butyldimethylsilyl)-1-*O*-(*tert*-butyldiphenylsilyl)-4-deoxy-D-*glycero*-D-*allo*-heptitol 23

The silyl acetonide **22** (0.087 g, 0.14 mmol) was dissolved in a mixture of acetic acid and water (8 mL:2 mL) and the solution was stirred at room temperature for 36 h. TLC (ethyl acetate–hexane 1:3) showed a small amount of residual starting material (R_f 0.7) to a single product (R_f 0.2). The reaction mixture was concentrated *in vacuo* with toluene co-evaporation and the residue was purified by flash chromatography (ethyl acetate–hexane 1:3) to give *the diol* **23** (0.53 g, 65%) as a colourless oil, $[\alpha]_D^{22}$ −18.3 (*c* 0.80 in MeOH) (Found: C, 61.25; H, 7.51; N, 6.97. $C_{29}H_{45}N_3O_5Si$ requires C, 60.91; H, 7.93; N, 7.35%); ν_{max} (thin film) 3200–3600 (OH), 2105 (N_3) cm^{-1}; δ_H (C_6D_6; 400 MHz) 0.03 (3H, s, $SiCH_3$), 0.13 (3H, s, $SiCH_3$), 0.94 [9H, s, $SiC(CH_3)_3$], 1.14 [9H, s, $SiC(CH_3)_3$], 2.57 (1H, br d, *J* 3.3, 6-OH), 3.42–3.55 (2H, m, H_2-7), 3.58 (1H, dd, *J* 11.7, 3.1, H-1), 3.67–3.73 (1H, m, H-6), 3.79 (1H, dd, *J* 11.7, 3.2, H′-1), 3.85–3.94 (3H, m, H-2, -4, 7-OH), 4.04 (1H, a-t, *J* 5.3, H-5), 4.46 (1H, a-t, *J* 5.5, H-3), 7.20–7.26 (6H, m, ArH), 7.72–7.78 (4H, m, ArH); δ_C (C_6D_6; 63 MHz) −4.9 (q, $SiCH_3$), −4.6 (q, $SiCH_3$), 19.3 [s, $SiC(CH_3)_3$], 20.5 [s, $SiC(CH_3)_3$], 25.9 [q, $SiC(CH_3)_3$], 27.1 [q, $SiC(CH_3)_3$], 63.3 (2 × t, 1 × d, C-1, -7, -2 or -4), 72.7 (d, C-6), 73.9 (d, C-3), 82.0 (d, C-5), 84.4 (d, C-4 or -2), 130.2,

130.3, 136.0, 136.0 [4 × d, 4 × Ar CH (some Ar CH obscured by C_6D_6)], 133.2, 133.3 (2 × s, 2 × Ar CC); *m*/*z* (APCI+) 594 ($M + Na^+$, 5%), 544 ($M + H^+ - N_2$, 80), 466 (100).

2,5-Anhydro-3-azido-4-*O*-(*tert*-butyldimethylsilyl)-6-*O*-(*tert*-butyldiphenylsilyl)-3-deoxy-L-allonic acid 24

The diol **23** (0.033 g, 0.58 mmol) was stirred vigorously in a mixture of CCl_4–CH_3CN–water (2:2:3) (0.4 mL) to which sodium periodate (0.052 g, 0.24 mmol) was added. Ruthenium trichloride hydrate (<1 mg) was then immediately added. Upon stirring of the mixture for 5 h at room temperature, TLC (ethyl acetate–hexane 1:1) showed no residual starting material (R_f 0.6) and a major product (R_f 0.7). The reaction mixture was diluted with ethyl acetate and filtered through Celite, with washing of the filter with ethyl acetate. Upon concentration *in vacuo* the residue obtained was purified by flash chromatography (ethyl acetate–hexane 1:10, then 1:3) to give the acid **24** an oil (0.020 g, 62%) [HRMS *m*/*z* (CI+) Found: 528.2620 ($M + H^+ - N_2$). $C_{28}H_{42}NO_5Si$ requires *m*/*z*, 528.2602]; $[a]_D^{22}$ +4.16 (*c* 0.77 in $CHCl_3$); ν_{max} (thin film) 3500–2500 (OH), 2110 (N_3), 1733 (C=O) cm^{-1}; δ_H ($CDCl_3$; 500 MHz) −0.01 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.84 [9H, s, $SiC(CH_3)_3$], 1.10 [9H, s, $SiC(CH_3)_3$], 3.59 (1H, dd, *J* 11.6, 1.2, H-6), 4.00 (1H, ddd, *J* 11.6, 3.1, 0.8, H′-6), 4.03 (1H, ddd, *J* 7.5, 3.1, 1.2, H-5), 4.11 (1H, dd, *J* 4.7, 2.4, H-3), 4.44 [1H, dd (br), *J* 7.5, 4.7, H-4], 4.52 (1H, d, *J* 2.4, H-2), 7.40–7.52 (6H, m, ArH), 7.64–7.70 (4H, m, ArH); δ_C ($CDCl_3$; 125 MHz) −4.7 and −4.3 (q, $SiCH_3$), −4.1 (q, $SiCH_3$), 18.3 [s, $SiC(CH_3)_3$], 19.4 [s, $SiC(CH_3)_3$], 26.0 [q, $SiC(CH_3)_3$], 27.4 [q, $SiC(CH_3)_3$], 61.7 (t, C-6), 66.5 (d, C-3), 71.9 (d, C-4), 79.9 (d, C-2), 83.6 (d, C-5), 128.4 (d, Ar CH), 128.5 (d, Ar CH), 130.6 (d, Ar CH), 130.8 (d, Ar CH), 132.1 (s, Ar CC), 132.2 (s, Ar CC), 135.9 (d, Ar CH), 136.2 (d, Ar CH); *m*/*z* [CI (NH_3)] 528 ($M + H^+ - N_2$, 100%), 484 (55), 352 (90); *m*/*z* (APCI−) 554 ($M - H^-$, 100%), 255 (30).

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