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A general and efficient stereoselective synthesis of γ-azido-tetrahydrofuran carboxylic acids from glycals☆

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Dedicated to Professor Subhendu N. Ganguly on his 70th birthday

Abstract

An efficient, direct and general synthesis of enantiopure γ-azido-tetrahydrofuran carboxylic acid monomers (**5**–**8**) from commercially available glycals, suitable to design peptidomimetic oligomers with predisposed conformation, is described. The single crystal X-ray study of **8** showed that the compound crystallized in orthorhombic space group. The crystal-packing showed the presence of weak intermolecular C–H···O and aliphatic C–H···π interactions.
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1. Introduction

γ-Amino acids, both achiral and chiral, are receiving immense attention from chemical community due to their potential use in the design and synthesis of α,γ- and β,γ-hybrid peptides that fold into definite secondary structures.[1] These peptides being a new class of foldamers are creating interest among the synthetic chemists.[2] Granja et al. have showed that cyclic γ-amino acids can be a considerable promise to design new type of peptide nanotubes with hydrophobic cavities.[3] Moreover, appropriate functionalization of this kind of cyclic amino acid leads to self-assembling peptide nanotubes (SPNs) with structural and functional properties of interest for application in biology and material science.[4]

Among the various γ-peptide foldamers studied, most of the systems are based on linear amino acids with substituents at different backbone positions.[5] So, over recent years, there has been increasing interest in the development of new synthetic routes for cyclic γ-amino acids.[6] Though several reports appeared in literature for the synthesis of conformationally restricted γ-amino acids,[5,7–10,4e] very few of them dealt with the synthesis of furanoid γ-sugar amino acids (SAAs),[11–15] starting from cheaply available sugars. This class of molecules is of particular interest due to their propensity of the ring hydroxyls in the participation of intramolecular hydrogen bonding with the main chain amides.[16]

Fleet et al. have disclosed the syntheses of conformationally restricted γ-SAAs from sugar lactones.[13–15] The furanose γ-SAAs **1** and **2** (Fig. 1) synthesized from L-gulunolactone have been utilized to prepare 99-member library. Initial screening of the library indicated the biological potential of the furanose SAA scaffolds.[17] Recent studies carried out by Edwards et al. on the secondary structures of the homooligomers prepared from γ-SAAs **3** and **4**, obtained from D-ribose and L-arabinose, to ascertain the conformational preference inherent in the monomer units indicated the presence of

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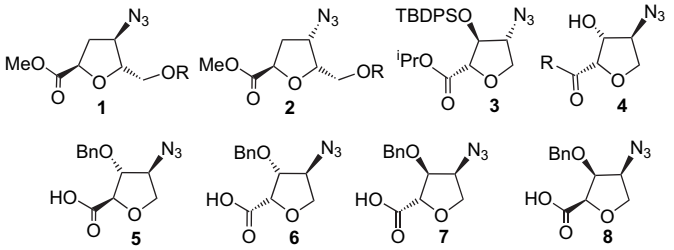
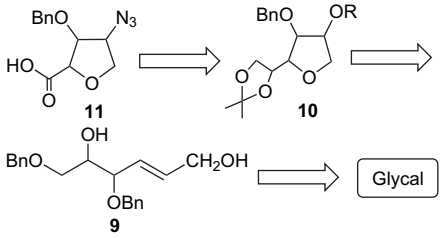


Figure 1.

hydrogen-bonded confirmations in L-ribo series.[18] Prompted by these literature reports we wish to describe a practically efficient and general strategy to synthesize γ-SAAs (**5**–**8**) with three orthogonal points of diversification suitable for rational combinatorial synthesis and spatial screening starting from commercially available glycals. The work presented herein also demonstrates the versatility of our recently synthesized enantiopure 2,3,4-trisubstituted THF domains[19] of general structure **10** (Scheme 1) towards the synthesis of compounds of biological importance.



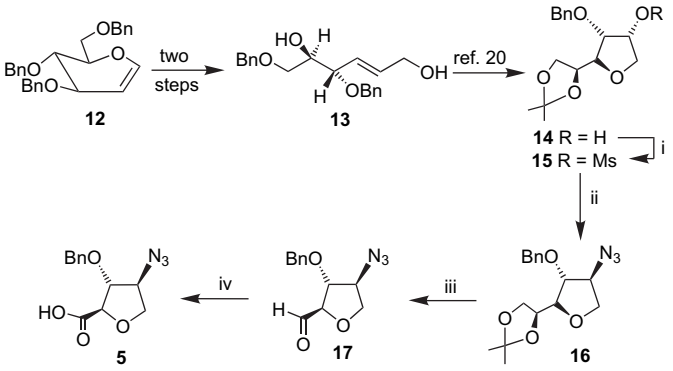
Scheme 1. General strategy followed for the synthesis of furanoid SAAs.

2. Results and discussion

The basic strategy followed for the present work is summarized in Scheme 1. The tetrahydrofuran framework of γ-SAA was obtained by the intramolecular asymmetric ring opening reaction of the acyclic precursor **9**, the concept exploited by us recently to synthesize the naturally occurring cytotoxic anhydrosphingosine, pachastrissamine (jaspine B).[20] The same approach was now extended here to synthesize the γ-SAAs of type **11** via **10**.

Scheme 2 shows the details of the route followed for the synthesis of γ-SAA **5**. The required allylic alcohol **13** was prepared from 3,4,6-tri-*O*-benzyl-D-glucal **12** in two steps by its Perlin hydrolysis[21] followed by Luche's reduction[22] in 57% yield. After that, the THF domain **14** was synthesized from **13** in a single step (51% yield) by our reported consecutive approach[19] under Sharpless asymmetric epoxidation conditions. The azidolysis of the crude mesylate **15** provided the azido derivative **16** with inversion of configuration in 90% yield (for two steps, from **14**). Having this in hand, the next step was to obtain γ-SAA **5**.

The deprotection of acetonide group in **16** followed by the oxidation of the resulting diol with sodium periodate in the



Scheme 2. Reagents and conditions: (i) MsCl, Et_3N, CH_2Cl_2, 0 °C→rt, 30 min; (ii) NaN_3, Bu_4NCl (cat), DMF, 120 °C, 3 h, 90% (for two steps); (iii) H_5IO_6 (1.3 equiv), EtOAc, rt, 30 min; (vi) Jones reagent, acetone, 0 °C, 10 min, 60% (for two steps).

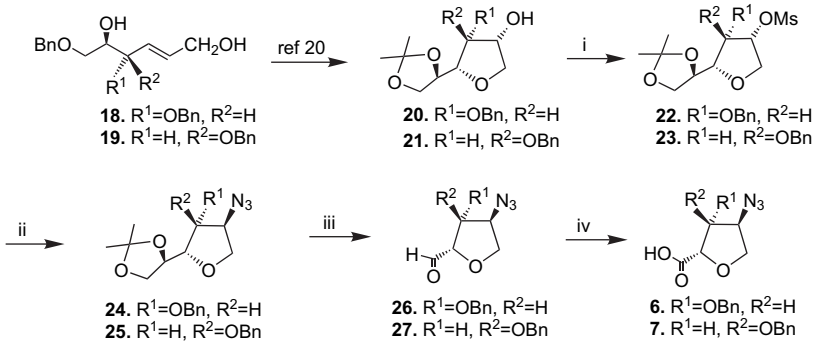
presence of catalytic amount of ruthenium chloride trihydrate[15] ended with a mixture of products which could not be separated even after repeated column chromatography. However, the desired γ-azido-tetrahydrofuran carboxylic acid **5** (γ-SAA) was obtained from **16** via the intermediate aldehyde **17**. Here, it is worth noting that the attempted oxidation of **17** by using potassium permanganate and 50% acetic acid[23] was unsatisfactory. Moreover, oxidation of this crude aldehyde (>95% pure from ^1H NMR) by the classical Jones reagent[24] provided the desired compound **5** in 60% isolated yield and 16% overall yield starting from 3,4,6-tri-*O*-benzyl-D-glucal **12**.

After devising the straightforward synthesis of γ-SAA **5**, we next focused on the syntheses of remaining three γ-SAAs (**6**–**8**) following the same method as described above. The enantiopure 2,3,4-trisubstituted THF domains **20** and **21** were synthesized from their corresponding enantiopure allylic alcohols **18** and **19**. Subsequently these THF domains were derivatized to their mesyl esters **22** and **23**.

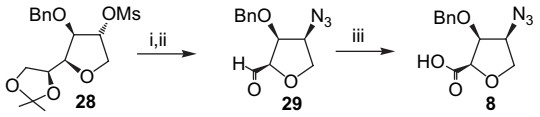
The mesyl esters **22** and **23** were smoothly converted into their azides **24** and **25** accompanied with a little amount of elimination product in less than 5% yield. Sequential hydrolysis–oxidation of the acetonide afforded the aldehydes **26** and **27** in almost quantitative yield, which on oxidation with Jones reagent afforded the SAAs **6**[12] and **7** (Scheme 3) in 10 and 16% overall yields starting from their respective glycals.

The Jones oxidation of the aldehyde **29**, an intermediate utilized by us for the synthesis of jaspine B,[20] afforded the γ-SAA **8** in 64% yield (Scheme 4). Diffraction quality crystals of compound **8** were obtained from ethyl acetate/hexane solution (1:3) by slow evaporation at room temperature. The compound crystallizes in orthorhombic unit cell with $P2_12_12_1$ space group. The single crystal X-ray structure of **8** showed (Fig. 2) that the furanose ring exists in an envelope conformation with C2 atom forming the flap (C2 atom is deviated by 0.586(7) Å from the least-squares plane formed by other four atoms C1, O1, C4 and C3).

Furthermore, the crystal-packing study of **8** revealed (Fig. 3) that it has four molecules in the unit cell. The molecule exhibits weak intermolecular C–H···O[25] and aliphatic C–H···π interactions.[26] The weak intermolecular C–H···O



Scheme 3. Reagents and conditions: (i) MsCl, Et_3N, CH_2Cl_2, 0 °C→rt, 30 min; (ii) NaN_3, Bu_4NCl (cat), DMF, 120 °C, 10 h for **24** (62% from **20**), and 3 h for **25** (90% from **21**); (iii) H_5IO_6 (1.3 equiv), EtOAc, 30 min; (iv) Jones reagent, acetone, 0 °C, 10 min, 64% for **6** from **24**, 60% for **7** from **25**.



Scheme 4. Reagents and conditions: (i) NaN_3, Bu_4NCl (cat), DMF, 120 °C, 10 h; (ii) H_5IO_6 (1.3 equiv), EtOAc, 30 min; (iii) Jones reagent, acetone, 0 °C, 10 min, 64% yield.

interaction between C1–H1 and O2–C5 (d=2.4184 Å; D=3.2215 Å; ∠C–H–O=139°; symm.: 1+x, y, z) is depicted in Figure 3. In addition, the weak intermolecular C–H···π interactions between the C6–H6B and the centroid (X) of the aromatic ring formed by atoms C7, C8, C9, C10, C11 and C12 [d(H···π)=2.91 Å; ∠C–H–π=160°, symm.: 1+x, y, z] is also shown in Figure 3. These weaker interactions would be responsible for the conformation of **8**. The confirmation of the remaining three SAAs (**5**–**7**) can be established based on the X-ray structure of **8**.

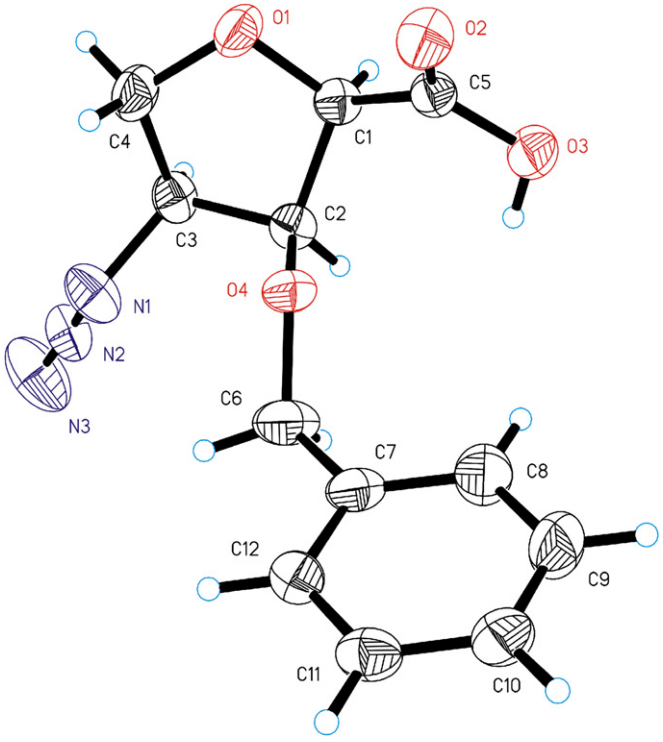


Figure 2. ORTEP plot of the SAA **8** (at 30% probability) showing the molecular conformation.

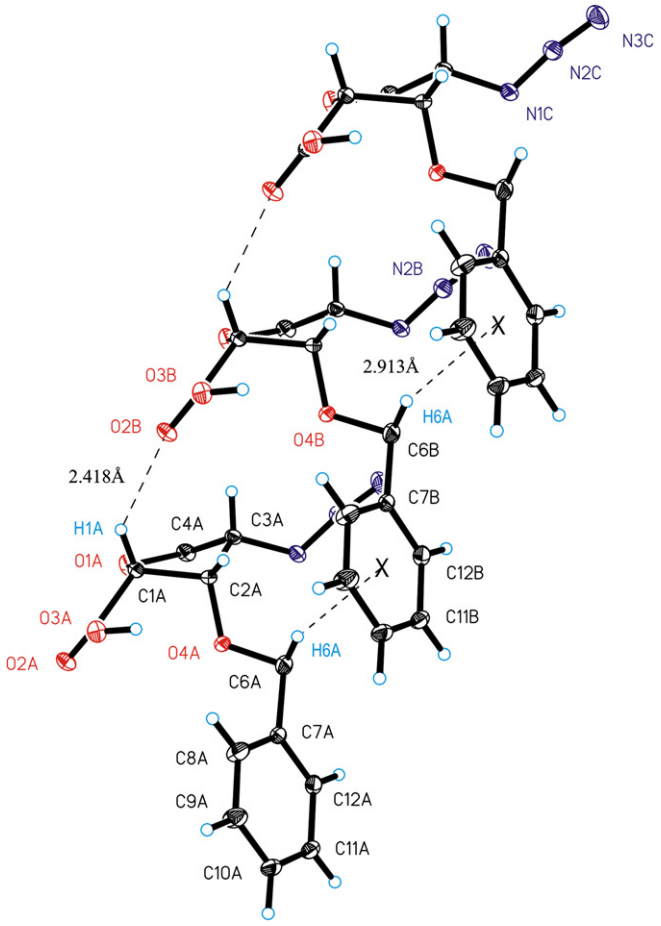


Figure 3. The partial crystal-packing of the SAA **8** showing the weak intermolecular C–H···O and C–H···π interactions. Few H-atoms have been omitted for clarity.

3. Conclusions

In this paper we disclosed a general, easy to scale up and straightforward synthetic route to obtain enantiopure γ-SAA monomers (**5**–**8**) in seven steps and 10–16% overall yields

starting from easily available glycal derived enantiopure 2,3,4-trisubstituted THF domains. The X-ray crystal of one of the γ-SAAs (**8**) exhibits weak intermolecular C−H···O and aliphatic C−H···π interactions. Such information is of great significance for the design of compounds with predisposed conformation, e.g., peptidomimetics and nanomaterials.[18] These chirally diverse γ-SAAs can enable secondary structural study such as helices, β-turns, etc. Additionally, these γ-SAAs can also act as convenient stereodiverse library scaffolds.

4. Experimental

4.1. General

CH_2Cl_2 was dried over anhydrous calcium chloride overnight and distilled over phosphorous pentoxide. Ethyl acetate was distilled and dried over molecular sieves overnight, Ti(O−*i*-Pr)$_4$, (+)-diethyltartrate, (−)-diethyltartrate, 6.0 M solution of *t*-BuOOH in nonane were purchased from Aldrich chemical co. All the products were characterized by ^{1}H, ^{13}C, IR, ESI-MS, EI-HRMS and DART-HRMS. TLC was performed using 2.5×5 cm plates coated with a 0.25 mm thickness of silica gel (60F-254), and visualization was accomplished with $CeSO_4$. The ^{1}H and ^{13}C NMR were recorded with Bruker DRX 300 spectrometers for solution in $CDCl_3$. Chemical shifts were given in parts per million downfield from internal standard Me_4Si. Carbon atom types (CH, CH_2, CH_3) were determined by DEPT pulse sequence. Yields refer to pure compounds after chromatography unless and otherwise mentioned. IR spectra were recorded on Perkin−Elmer 881 and FTIR-8210 PC Shimadzu spectrophotometers. Mass spectra were recorded on a JEOL JMS-600H high-resolution spectrometer using EI mode at 70 eV, and Accutof DART JMS-T100LC. Optical rotations were determined on an Autopol III polarimeter using a 1 dm cell, $CHCl_3$ as the solvent; concentrations mentioned are in g/100 mL.

4.2. Preparation of Jones reagent

CrO_3 (25 g) was dissolved in 25 mL H_2SO_4 (concd). The solution prepared was added slowly to 75 mL H_2O, precooled at 0 °C. The resulting solution was stirred for 5 min.

4.3. Representative procedure for mesylation

To a magnetically stirred solution of alcohol **14** (147 mg, 0.50 mmol) in dry CH_2Cl_2 cooled to 0 °C (10 mL), Et_3N (0.14 mL, 1.0 mmol) was added. After 5 min of stirring, a solution of methanesulphonylchloride (0.04 mL, 0.60 mmol) in dry CH_2Cl_2 (3 mL) was added dropwise and the reaction mixture was allowed to warm up to room temperature. After 30 min of stirring, the reaction was quenched by saturated solution of $NaHCO_3$. The organic phase was washed with water and brine, extracted with CH_2Cl_2 (3×10 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude mesylate **15** (190 mg) obtained was directly used in the next step without further purification.

4.3.1. Compound **15** (2S,3S,4R,5R)-1,2-isopropylidine-3,6-anhydro-4-O-benzyl-5-O-methanesulfonyl-D-glucitol

Purification of a small amount of crude product by column chromatography for data generation afforded pure mesylate **15** as a syrup. $[\alpha]_D^{28}$ −74.0 (*c* 0.27, $CHCl_3$), column chromatography (9/41 ethyl acetate/hexane v/v); R_f=0.43 (1/1 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H, C(CH_3)$_2$), 1.45 (s, 3H, C(CH_3)$_2$), 3.03 (s, 3H, SO_2CH_3), 3.86 (dd, *J*=6.1, 8.5 Hz, 1H, H-1a), 3.96−4.13 (m, 4H, H-3, H-1b, H-6), 4.15−4.26 (m, 2H, H-2, H-4), 4.63 (d, *J*=11.1 Hz, 1H, CH_2Ph), 4.76 (d, *J*=11.1 Hz, 1H, CH_2Ph), 5.33 (dd, *J*=3.8, 4.4 Hz, 1H, H-5), 7.33−7.42 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.4 (C(*C*H$_3$)$_2$), 26.9 (C(*C*H$_3$)$_2$), 39.4 (SO_2CH_3), 66.2 (C-1), 71.0 (C-6), 73.5 (*C*H$_2$Ph), 75.9 (C-2), 78.0 (C-5), 78.6 (C-4), 81.2 (C-3), 110.3 (*C*(CH$_3$)$_2$), 128.7 (ArC), 128.9 (ArC), 129.1 (ArC), 137.5 (ArqC); IR (neat, cm^{-1}): 3032 (=C−H str), 2936 (C−H str), 1597, 1458, 1358 (C=C str), 1259, 1175, 1077 (C−O str). Mass (ESI-MS): *m/z* 373 (M^++1); EI-HRMS: calcd for $C_{17}H_{24}O_7S_1$ (M^+) 372.1243, measured 372.1246.

4.4. Representative procedure for azidation

To a magnetically stirred solution of crude mesylate **15** (190 mg, 0.51 mmol) in DMF (15 mL) were added excess NaN_3 (100 mg, 1.50 mmol) and Bu_4NCl (catalytic, ≤0.01 g), and the reaction mixture was stirred at 120 °C for 3 h. DMF was removed under reduced pressure. The residue was washed with H_2O and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic phase was dried (anhydrous Na_2SO_4), and evaporated to yield **16** (143 mg) as a syrup.

4.4.1. Compound **16** (2S,3S,4R,5S)-1,2-O-isopropylidine-3,6-anhydro-4-O-benzyl-5-azido-5-deoxy-D-glucitol

Yield 90% for two steps from **14**. $[\alpha]_D^{28}$ +38.3 (*c* 0.23, $CHCl_3$), column chromatography (1/49 ethyl acetate/hexane v/v); R_f=0.66 (3/7 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 3H, C(CH_3)$_2$), 1.47 (s, 3H, C(CH_3)$_2$), 3.85 (dd, *J*=2.5, 6.8 Hz, 1H, H-3), 3.90−4.05 (m, 4H, H-1, H-6a, H-5), 4.09−4.19 (m, 3H, H-4, H-2, H-6b), 4.61 (d, *J*=11.7 Hz, 1H, CH_2Ph), 4.66 (d, *J*=11.7 Hz, 1H, CH_2Ph), 7.33−7.39 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7 (C(*C*H$_3$)$_2$), 27.2 (C(*C*H$_3$)$_2$), 66.5 (C-5), 67.6 (C-6), 71.5 (C-1), 72.6 (*C*H$_2$Ph), 75.8 (C-2), 85.4 (C-4), 85.9 (C-3), 110.2 (*C*(CH$_3$)$_2$), 128.5 (ArC), 128.6 (ArC), 129.1 (ArC), 137.8 (ArqC); IR (neat, cm^{-1}): 3033 (=C−H str), 2934 (C−H str), 2102 (−N_3 str), 1637, 1456, 1373 (C=C str), 1250, 1153, 1071 (C−O str). Mass (ESI-MS): *m/z* 292 (M^++1−N_2); DART-HRMS: calcd for $C_{16}H_{22}N_3O_4$ (M^++1) 320.16103, measured 320.16265, mass difference 1.62 mmu.

4.5. Representative procedure for the synthesis of aldehyde

A solution of azide acetonide **16** (143 mg, 0.45 mmol) and periodic acid (122 mg, 0.53 mmol) in 15 mL of dry ethyl acetate was allowed to stir at room temperature for 30 min. The reaction was quenched with saturated solution of $NaHCO_3$

and extracted with ethyl acetate (3×15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford 115 mg of crude aldehyde **17** (>95% pure from ^{1}H NMR) as a colourless syrup which was immediately used for next step.

4.5.1. Compound *17*

R_f=0.32 (3/7 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.96–4.09 (m, 3H, H-4, H-5), 4.15–4.19 (m, 1H, H-3), 4.35 (br s, 1H, H-2), 4.57 (d, *J*=11.6 Hz, 1H, C*H*$_2$Ph), 4.67 (d, *J*=11.6 Hz, 1H, C*H*$_2$Ph), 7.32–7.40 (m, 5H, ArH), 9.63 (s, 1H, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 64.9 (C-4), 72.1 (C-5), 72.8 (*C*H$_2$Ph), 85.8 (C-3), 88.1 (C-2), 128.5 (ArC), 128.8 (ArC), 129.2 (ArC), 137.2 (ArqC), 201.7 (*C*HO); IR (neat, cm^{-1}): 3444 (O–H str), 2926 (=C–H str), 2104 (–N_3 str), 1735 (C=O str), 1635, 1545, 1457 (C=C str), 1316, 1258, 1084 (C–O str). Mass (ESI-MS): *m/z* 248 (M^++1); EI-HRMS: calcd for $C_{12}H_{12}NO_3$ (M^+–1–N_2) 218.0817, measured 218.0799.

4.6. Representative procedure for oxidation by Jones reagent

To a solution of aldehyde **17** (115 mg, 0.47 mmol) in acetone (5 mL) at 0 °C freshly prepared Jones reagent (0.50 mL, 0.61 mmol) was added dropwise. After the reaction was stirred for 10 min methanol was added to destroy the excess Jones reagent. The solvent was removed under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (3×5 mL), and the combined organic extract was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Purification of the residue obtained by a short column of silica gel furnished the pure SAA **5** (70 mg) as a syrup.

4.6.1. Compound *5*

Yield 60% for two steps from **16**. $[\alpha]_D^{28}$ +34.3 (*c* 0.07, $CHCl_3$), column chromatography (9/1 chloroform/hexane v/v); R_f=0.37 (9/1 chloroform/methanol, two drops acetic acid); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.03–4.10 (m, 3H, H-4, H-5a, –O*H*), 4.29 (br s, 1H, H-3), 4.49 (br s, 1H, H-5b), 4.58–4.75 (m, 3H, H-2, C*H*$_2$Ph), 7.34 (br s, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 65.6 (C-4), 72.1 (C-5), 72.8 (*C*H$_2$Ph), 83.0 (C-3), 86.8 (C-2), 128.5 (ArC), 128.7 (ArC), 129.1 (ArC), 137.5 (ArqC), 174.4 (*C*OOH); IR (neat, cm^{-1}): 3448 (O–H str), 2927 (=C–H str), 2114 (–N_3 str), 1720 (C=O str), 1681, 1459, 1356 (C=C str), 1271, 1206, 1082 (C–O str). Mass (ESI-MS): *m/z* 236 (M^++1–N_2); EI-HRMS: calcd for $C_{12}H_{12}O_4N_1$ (M^+–1–N_2) 234.0766, measured 234.0765.

4.6.2. Compound *22* (2R,3R,4R,5R)-1,2-O-isopropylidine-3,6-anhydro-4-O-benzyl-5-O-methanesulfonyl-D-glucitol

$[\alpha]_D^{28}$ –15.3 (*c* 0.13, $CHCl_3$); R_f=0.51 (2/3 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (s, 3H, C(C*H*$_3$)$_2$), 1.43 (s, 3H, C(C*H*$_3$)$_2$), 2.99 (s, 3H, SO_2CH_3), 3.95–4.05 (m, 4H, H-1, H-3, H-6a), 4.07–4.15 (m, 1H, H-6b), 4.30 (t, *J*=4.8 Hz, 1H, H-4), 4.37 (dd, *J*=6.2, 12.9 Hz, 1H, H-2), 4.75 (s, 2H, C*H*$_2$Ph), 5.18 (dd, *J*=5.8, 10.7 Hz, 1H, H-5), 7.31–7.42 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9 (C(*C*H$_3$)$_2$), 27.3 (C(*C*H$_3$)$_2$), 38.9 (SO_2CH_3), 67.1 (C-1), 69.6 (C-6), 74.1 (C-2), 74.6 (*C*H$_2$Ph), 78.0 (C-5), 78.3 (C-4), 80.9 (C-3), 109.6 (*C*(CH$_3$)$_2$), 128.5 (ArC), 128.6 (ArC), 129.0 (ArC), 138.2 (ArqC); IR (neat, cm^{-1}): 3433 (O–H str), 2817 (C–H str), 1593, 1460, 1352 (C=C str), 1259, 1177, 1047 (C–O str). Mass (ESI-MS): *m/z* 373 (M^++1); EI-HRMS: calcd for $C_{17}H_{24}O_7S_1$ (M^+) 372.1243, measured 372.1242.

4.6.3. Compound *24* (2R,3R,4R,5S)-1,2-O-isopropylidine-3,6-anhydro-4-O-benzyl-5-azido-5-deoxy-D-glucitol

Yield 62% for two steps from **20**. $[\alpha]_D^{28}$ +26.2 (*c* 0.08, $CHCl_3$), column chromatography (3/97, ethyl acetate/hexane v/v); R_f=0.68 (2/3 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (s, 3H, C(C*H*$_3$)$_2$), 1.47 (s, 3H, C(C*H*$_3$)$_2$), 3.80 (dd, *J*=2.0, 9.9 Hz, 1H, H-3), 3.97–4.06 (m, 4H, H-1, H-5, H-6a), 4.09–4.17 (m, 2H, H-4, H-2), 4.37 (q, *J*=6.3 Hz, 1H, H-6b), 4.68 (s, 2H, C*H*$_2$Ph), 7.33–7.39 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9 (C(*C*H$_3$)$_2$), 27.2 (C(*C*H$_3$)$_2$), 65.6 (C-5), 67.6 (C-6), 71.2 (C-1), 73.3 (*C*H$_2$Ph), 73.7 (C-2), 82.1 (C-4), 83.0 (C-3), 109.5 (*C*(CH$_3$)$_2$), 128.3 (ArC), 128.6 (ArC), 129.1 (ArC), 137.9 (ArqC); IR (neat, cm^{-1}): 3033 (=C–H str), 2987, 2936 (C–H str), 2103 (–N_3 str), 1606, 1457, 1374 (C=C str), 1255, 1156, 1069 (C–O str). Mass (ESI-MS): *m/z* 292 (M^++1–N_2); DART-HRMS: calcd for $C_{16}H_{22}N_3O_4$ (M^++1) 320.16103, measured 320.16210, mass difference 1.07 mmu.

4.6.4. Compound *26*

R_f=0.55 (4/6 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.99–4.09 (m, 2H, H-4, H-5a), 4.29–4.35 (m, 2H, H-3, H-5b), 4.41 (dd, *J*=1.7, 5.0 Hz, 1H, H-2), 4.53–4.62 (m, 2H, C*H*$_2$Ph), 7.32–7.37 (m, 5H, ArH), 9.64 (d, *J*=2.3 Hz, 1H, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 65.1 (C-4), 72.2 (C-5), 73.6 (*C*H$_2$Ph), 85.0 (C-3), 85.1 (C-2), 128.5 (ArC), 128.9 (ArC), 129.3 (ArC), 136.9 (ArqC), 200.5 (*C*HO); IR (neat, cm^{-1}): 3445, 2926 (C–H str), 2106 (–N_3 str), 1737 (C=O str), 1636, 1544, 1459 (C=C str), 1260, 1084 (C–O str). Mass (ESI-MS): *m/z* 248 (M^++1).

4.6.5. Compound *6*

Yield 64% for two steps from **24**. $[\alpha]_D^{28}$ +35.0 (*c* 0.3, $CHCl_3$), column chromatography (9/1 chloroform/hexane v/v); R_f=0.59 (9/1 chloroform/methanol, two drops acetic acid); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.94–4.02 (m, 2H, H-4, H-5a), 4.26–4.33 (m, 2H, H-5b, H-3), 4.57–4.69 (m, 3H, H-2, C*H*$_2$Ph), 7.31–7.38 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 65.1 (C-4), 72.2 (C-5), 74.0 (*C*H$_2$Ph), 80.5 (C-3), 83.5 (C-2), 128.6 (ArC), 128.9 (ArC), 129.2 (ArC), 137.0 (ArqC), 173.1 (*C*OOH); IR (neat, cm^{-1}): 3449 (O–H str), 2934 (=C–H str), 2105 (–N_3 str), 1720 (C=O str), 1629, 1421, 1345 (C=C str), 1311, 1261, 1063 (C–O str). Mass (ESI-MS): *m/z* 286 (M^++23); EI-HRMS: calcd for $C_{12}H_{12}N_1O_4$ (M^+–1–N_2) 234.0766, measured 234.0766.

*4.6.6. Compound **23** (2R,3R,4S,5R)-1,2-O-isopropylidine-3,6-anhydro-4-O-benzyl-5-O-methanesulfonyl-D-galactitol*

$[\alpha]_D^{28}$ +7.2 (*c* 0.11, $CHCl_3$), crystallization in ethyl acetate/hexane, mp 101–102 °C; R_f=0.64 (2/3 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H, C(CH_3)$_2$), 1.44 (s, 3H, C(CH_3)$_2$), 3.02 (s, 3H, SO_2CH_3), 3.85–3.94 (m, 2H, H-1a, H-3), 4.02–4.17 (m, 4H, H-1b, H-2, H-6), 4.30 (d, *J*=3.0 Hz, 1H, H-4), 4.67 (d, *J*=12.1 Hz, 1H, CH_2Ph), 4.72 (d, *J*=12.1 Hz, 1H, CH_2Ph), 5.15 (d, *J*=3.5 Hz, 1H, H-5), 7.32–7.39 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.6 (C(CH_3)$_2$), 27.2 (C(CH_3)$_2$), 39.2 (SO_2CH_3), 67.4 (C-1), 72.3 (C-6), 72.7 (CH_2Ph), 75.6 (C-2), 83.4 (C-5), 84.6 (C-4), 85.8 (C-3), 110.2 (C(CH$_3$)$_2$), 128.5 (ArC), 128.6 (ArC), 129.0 (ArC), 137.7 (ArqC); IR (KBr, cm^{-1}): 3468 (O–H str), 2992 (=C–H str), 2938 (C–H str), 1633, 1455, 1356 (C=C str), 1245, 1147, 1058 (C–O str). Mass (ESI-MS): *m/z* 373 (M^++1); EI-HRMS: calcd for $C_{17}H_{24}O_7S_1$ (M^+) 372.1243, measured 372.1245.

*4.6.7. Compound **25** (2R,3R,4S,5S)-1,2-O-isopropylidine-3,6-anhydro-4-O-benzyl-5-azido-5-deoxy-D-galactitol*

Yield 90% for two steps from **21**. $[\alpha]_D^{28}$ +71.5 (*c* 0.13, $CHCl_3$), column chromatography (1/24 ethyl acetate/hexane v/v); R_f=0.37 (1/4 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 3H, C(CH_3)$_2$), 1.41 (s, 3H, C(CH_3)$_2$), 3.79–3.95 (m, 4H, H-1a, H-3, H-5, H-6a), 3.99–4.05 (m, 2H, H-1b, H-6b), 4.08–4.18 (m, 2H, H-2, H-4), 4.63 (d, *J*=11.6 Hz, 1H, CH_2Ph), 4.72 (d, *J*=11.6 Hz, 1H, CH_2Ph), 7.32–7.42 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5 (C(CH_3)$_2$), 27.0 (C(CH_3)$_2$), 61.4 (C-5), 66.7 (C-1), 70.3 (C-6), 73.3 (CH_2Ph), 76.2 (C-2), 80.5 (C-4), 83.2 (C-3), 110.3 (C(CH$_3$)$_2$), 128.6 (ArC), 128.7 (ArC), 129.0 (ArC), 137.8 (ArqC); IR (neat, cm^{-1}): 3449 (O–H str), 3032 (=C–H str), 2929 (C–H str), 2106 (–N_3 str), 1602, 1457, 1375 (C=C str), 1262, 1214, 1071 (C–O str). Mass (ESI-MS): *m/z* 292 (M^++1–N_2); DART-HRMS: calcd for $C_{16}H_{22}N_3O_4$ (M^++1) 320.16103, measured 320.16033, mass difference 0.70 mmu.

*4.6.8. Compound **27***

R_f=0.20 (2/3 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85–3.89 (m, 1H, H-4), 4.02–4.05 (m, 2H, H-5), 4.22–4.26 (m, 1H, H-3), 4.37 (dd, *J*=1.1, 5.7 Hz, 1H, H-2), 4.66–4.77 (m, 2H, CH_2Ph), 7.33–7.39 (m, 5H, ArH), 9.66 (s, 1H, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 61.5 (C-4), 71.6 (C-5), 73.5 (CH_2Ph), 80.5 (C-3), 86.1 (C-2), 128.6 (ArC), 128.9 (ArC), 129.2 (ArC), 137.1 (ArqC), 200.7 (*C*HO); IR (neat, cm^{-1}): 2931 (C–H str), 2108 (–N_3 str), 1635, 1459, 1384 (C=C str), 1273, 1076 (C–O str). Mass (ESI-AQTOF): *m/z* 265 (M+NH_4^+), 247 (M^+); ESI-HRMS: calcd for $C_{12}H_{17}N_4O_3$ (M+NH_4^+) 265.13006, measured 265.13203, mass difference 1.96 mmu.

*4.6.9. Compound **7***

Yield 60% for two steps from **25**. $[\alpha]_D^{28}$ +45.1 (*c* 0.41, $CHCl_3$), column chromatography (9/1 chloroform/hexane v/v); R_f=0.43 (9/1 chloroform/methanol, two drops acetic acid); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.91–4.19 (m, 3H, H-5, H-4), 4.37 (br s, 1H, H-3), 4.58 (d, *J*=3.8 Hz, 1H, H-2), 4.75 (d, *J*=12.1 Hz, 1H, CH_2Ph), 4.81 (d, *J*=12.1 Hz, 1H, CH_2Ph), 7.33–7.48 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 61.2 (C-4), 71.3 (C-5), 73.4 (CH_2Ph), 80.9 (C-3), 82.7 (C-2), 128.5 (ArC), 128.7 (ArC), 129.1 (ArC), 137.3 (ArqC), 176.0 (*C*OOH); IR (neat, cm^{-1}): 3433 (O–H str), 3034 (=C–H str), 2927 (C–H str), 2108 (–N_3 str), 1741 (C=O str), 1653, 1457, 1352 (C=C str), 1269, 1203, 1095 (C–O str). Mass (ESI-MS): *m/z* 236 (M^++1–N_2); EI-HRMS: calcd for $C_{12}H_{12}N_1O_4$ (M^+–1–N_2) 234.0766, measured 234.0769.

*4.6.10. Compound **8***

Yield 64%, crystallization in ethyl acetate/hexane, mp 121–123 °C. $[\alpha]_D^{28}$ +61.7 (*c* 0.06, $CHCl_3$); R_f=0.44 (9/1 chloroform/methanol, two drops acetic acid); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (dd, *J*=4.7, 6.9 Hz, 1H, H-4), 4.10 (d, *J*=7.1 Hz, 2H, H-5), 4.45 (t, *J*=4.9 Hz, 1H, H-3), 4.63 (d, *J*=5.3 Hz, 1H, H-2), 4.75 (s, 2H, CH_2Ph), 7.25–7.35 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 61.4 (C-4), 69.9 (C-5), 75.0 (CH_2Ph), 80.0 (2C, C-2, C-3), 128.6 (ArC), 128.7 (ArC), 128.9 (ArC), 137.0 (ArqC), 171.5 (*C*OOH); IR (KBr, cm^{-1}): 3485 (O–H str), 3040 (=C–H str), 2938 (C–H str), 2105 (–N_3 str), 1734 (C=O str), 1609, 1494, 1456 (C=C str), 1103, 1091 (C–O str). Mass (ESI-MS): *m/z* 264 (M^++1); EI-HRMS: calcd for $C_{12}H_{14}N_3O_4$ (M^++1) 264.0984, measured 264.0980.

*4.7. Crystal data for **8***

$C_{12}H_{13}N_3O_4$, *M*=263.25, orthorhombic, $P2_12_12_1$, *a*=5.375 (1), *b*=9.309 (1), *c*=25.382 (3) Å, *V*=1270.0(3) Å^3, *T*=293 (2) K, *Z*=4, D_c=1.377 g cm^{-3}, μ=0.105 mm^{-1}, $F_{(000)}$=552, λ (Mo Kα)=0.71073 Å, reddish block, crystal size 0.250×0.125×0.050 mm, 1917 reflections measured (R_{int}=0.0201), 1706 unique, *R*1=0.0441 for 903, $F_o>4\sigma$ (F_o) and 0.1131 for all 1706 data, *S*=0.965 for all data and 174 parameters. Unit cell determinations and intensity data collection (2θ=49.43°) were performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix-least-squares methods on F^2. Programs: *XSCANS* [(Siemens Analytical X-ray Instruments Inc.: Madison, Wisconsin, USA 1996) were used for data collection and data processing], *SHELXTL-NT* [(Bruker AXS Inc.: Madison, Wisconsin, USA 1997) was used for structure determination, refinements and molecular graphics]. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK (CCDC deposit no. 659847).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.12.032.

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