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Enantiospecific synthesis of a glycoside of D-*epi*-purpurosamine

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Abstract

2-Propyl D-*epi*-purpurosaminide dihydrochloride **14** and its di-*N*-acetylated derivative **15** were synthesized by an enantiospecific sequence which involves the 2-propyl 6-*O*-acetyl-3,4-dideoxy-α-D-*erythro*-hex-3-enopyranosid-2-ulose **2** as the key precursor. The first approach through the saturated diol **4**, prepared by reduction of the enone system of **2**, was unsuccessful as the C-2 position of 2,6-di-*O*-sulfonyl derivatives **5** and **6** resisted substitution by azide. Therefore, an alternative sequence starting from the allylic alcohol **3**, also derived from **2**, was developed. In this case, the 2,6-di-*O*-tosyl derivative **9** gave the expected 2,6-diazide **10** with additional unwanted rearrangement of the double bond to the 2-propyl 4,6-diazido-2,3,4,6-tetradeoxy-α-D-*threo*-hex-2-enopyranoside **11** isomer. However, the ditriflate derivative **13**, analogous to **9**, underwent substitution to afford the diazide **10** in good yield. Upon reduction of the azide functions and saturation of the double bond of **10** by catalytic hydrogenation under acidic conditions, the dihydrochloride salt **14** was obtained as a crystalline product (43% overall yield from **3**).

1. Introduction

Sannamycin-type aminoglycoside antibiotics are a relatively simple class of pseudodisaccharides in which D-purpurosamine sugars are α-glycosidically linked to a 1,4-diaminocyclitol derivative.[1] In order to ascertain structure–activity relationships, Prinzbach and co-workers[2] prepared sets of variously protected derivatives of purpurosamine and its 2-*epi*- analogue as glycosyl donors, using a sequence based on pioneering work by Brimacombe.[3] The procedure, which starts from acrolein dimer (racemic 3,4-dihydro-2*H*-pyran-2-carbaldehyde), involves a low yielding step (nitrosochlorination, azidonitration) to introduce the amino function at C-2. Further studies[4] led to an improvement in this reaction employing an 'indirect aziridination' process; enzymatic resolution was then employed to separate the racemates which were formed.

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The resulting glycosyl donors were coupled with a convenient sannamine acceptors affording the structurally modified binuclear aminoglycosides.[5,6]

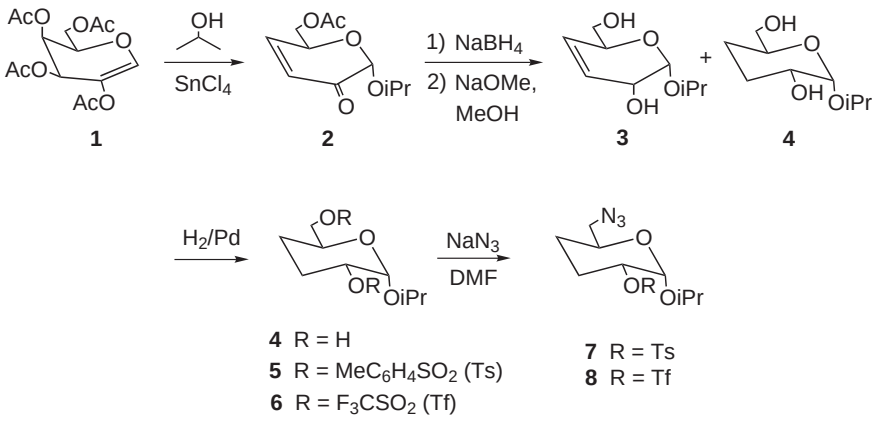
On the other hand, for the confirmation of the structure of the diaminosugar component of the antibiotics sisomicin and dihydrosisomicin, Guthrie and Williams[7,8] reported a multi-step synthesis of di-*N*-acetylated D-*epi*-purpurosamine diethyl dithioacetal. The key step was the rearrangement of an allylic 4-thiocyanate to the isomeric 2-isothiocyanate. Gero et al.[9] described a similar rearrangement of an allylic 4-azido derivative that led to methyl di-*N*-acetyl-D-*epi*-purpurosamide as an intermediate precursor of the same dithioacetal derivative.

As part of our project on the synthesis of diamino tetradeoxy sugars,[10] we wish to report here an expeditious and enantiospecific synthesis of a glycoside of D-*epi*-purpurosamine starting from 2-acetoxy-3,4,6-tri-*O*-acetyl-D-galactal **1** readily prepared from D-galactose. As far as we know, this is the first synthesis of a simple, crystalline glycoside of the free diamino sugar.

2. Results and discussion

The two approaches described here for the synthesis of a glycoside of D-*epi*-purpurosamine employed the sugar enone **2** as a chiral template. This compound can be readily prepared,[11] in about 90% yield, by the tin(IV) chloride-promoted glycosylation of the galactal derivative **1**. The reduction of the carbonyl function of **2** with sodium borohydride in methanol, followed by *O*-deacetylation with sodium methoxide, took place with partial saturation of the double bond to afford a 1:3.6 ratio of the saturated diol **4** and the allylic alcohol **3**. Therefore, the mixture was hydrogenated in the presence of catalytic palladium to give **4** as the main product (84% yield from **2**). The reduction of the carbonyl function of compound **2** afforded the diastereoisomer having the D-*erythro* configuration.[12] The diastereofacial selectivity may be attributed to the sterical hindrance of the anomeric substituent which blocks the α-face and induces the attack of the hydride from the opposite side. The stereocenters in **4** have the required configuration for the substitution (upon sulfonylation) of a nitrogen nucleophile, to give a precursor of *epi*-purpurosamine. Tosylation of **4**, in a 3:1 mixture of chloroform–pyridine,[13] gave the ditosylate **5** in 82% yield but the attempted substitution of both *O*-tosyl groups of **5** by sodium azide was unsuccessful. When the reaction was performed in DMF at high temperature, TLC analysis showed the formation of a main product which was less polar than the starting material. The ^{1}H NMR spectrum of this compound revealed that a tosyl group remained intact. The chemical shift of H-2 indicated that the sulfonate at this position was not substituted. Furthermore, the upfield shift of H-6,6′ with respect to the same signals in **5** was indicative that, as expected, the tosyl group at the primary C-6 position had been replaced by azide. This monosubstituted product **7** was rather stable, but when heated under reflux in DMF using concentrated solutions of sodium azide extensive decomposition occurred. Since the trifluoromethanesulfonate group (triflate) has better properties as nucleofuge, compound **4** was converted into the ditriflate **6**, which could be readily purified by column chromatography. However, the disubstitution of the sulfonyl groups of **6** by azide was unsuccessful under all the conditions studied, and again a monoazide derivative **8** was spectroscopically identified as the main product (Scheme 1).

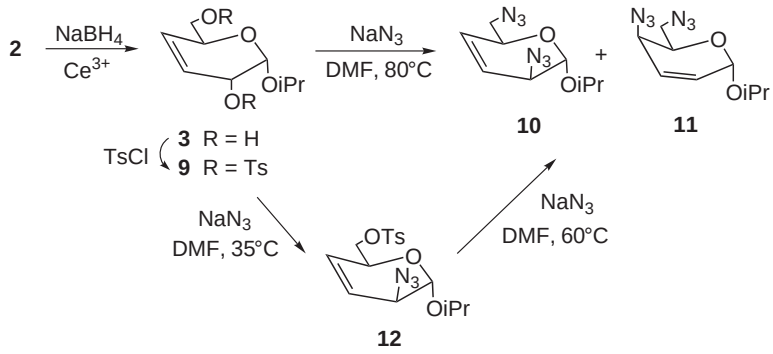
In view of these results we decided to prepare the diol **3**, by chemoselective reduction of the carbonyl group in the enone system of **2**. Such a diol could be derivatized as the corresponding disulfonate, and it should be expected that the allylic nature of the secondary sulfonate would help its nucleophilic displacement by azide. The reduction of the carbonyl group of **2** was



Scheme 1.

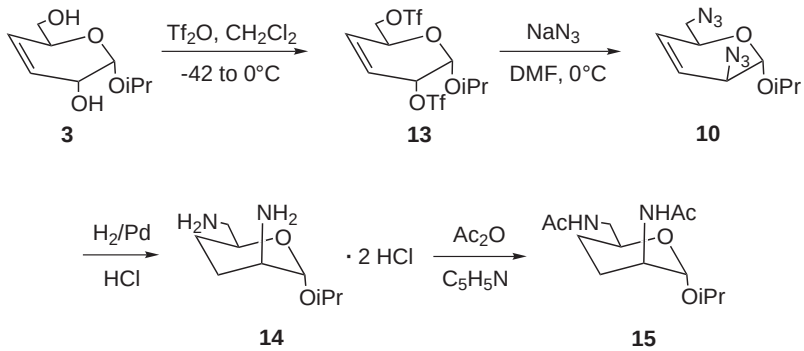
performed with sodium borohydride in the presence of cerium(III) chloride, in order to avoid the saturation of the double bond.[14] Under these conditions the diol **3** was obtained in an 81% yield. The corresponding 2,6-di-*O*-tosyl derivative **9** was then prepared in an 86% yield by the procedure applied previously in the synthesis of **5**; compound **9** was treated with sodium azide in DMF at 80°C, and the reaction mixture was monitored by TLC which indicated two main products of lower polarity than the starting material **9**. These product spots were not detectable by exposure to UV light, suggesting an absence of the tosyl groups. Column chromatography allowed the separation of the two products and their structures were determined by ^{1}H NMR spectroscopy, using 2D COSY and single frequency decoupling experiments. The least polar product was found to be the expected diazide **10**, produced by straightforward substitution of both tosyl groups. In addition to the upfield shift for the signals of H-2 and H-6,6′ in the ^{1}H NMR spectrum of **10**, the change in the $J_{1,2}$ coupling constant value from 4.1 Hz (in **9**) to <1 Hz (in **10**) indicated the change in the configuration of the C-2 stereocenter.

The other product isolated from the azide substitution reaction was the 4-azido-2-enopyranoside **11**, which resulted from an allylic rearrangement of the azido group from C-2 to C-4. This kind of rearrangement has been reported for similar allylic thiocyanates[7,8] and azides.[6,9,15] Transfer of chirality takes place during the rearrangement, and the configuration of the new stereocenter at C-4 was determined on the basis of the $J_{4,5}$ coupling constant. Its small value (2.4 Hz) indicates a *gauche* relationship for H-4 and H-5 and hence a D-*threo* configuration for the chiral centers of **11**. As allylic rearrangements are often promoted thermally, low temperature conditions for the azide substitution reaction were investigated. At lower temperature, the formation of a new product was observed. It was shown by TLC to have intermediate polarity to **9** and the diazides **10** and **11**. The product from the low temperature reaction was isolated by column chromatography and spectroscopically identified as the allylic azide **12**. Thus, its ^{1}H NMR spectrum showed a strong upfield shift for the H-2 signal, whereas the H-6,6′ signals were only slightly altered with respect to the same resonances in **9**. Interestingly, the allylic tosylate was substituted more easily than the primary tosylate. The latter required higher temperatures and when the reaction temperature was increased the formation of both diazides **10** and **11** was observed (Scheme 2).



Scheme 2.

In order to overcome the rearrangement the ditriflate derivative **13** was prepared. This was very unstable and readily decomposed at room temperature. Therefore, the crude sulfonylation product mixture was exposed directly to sodium azide in DMF at low temperature (from −42 to 0°C). Under these conditions the conversion of **13** into the desired diazide derivative **10** was almost complete in about 1 hour (Scheme 3). Compound **10** was isolated by column chromatography in 67% yield from **3**, and subjected to catalytic hydrogenation at 45 psi in methanolic hydrochloric acid solution. Simultaneous saturation of the double bond and reduction of the azide functions took place affording the glycoside of D-*epi*-purpurosamine dihydrochloride **14** in crystalline form. The ^{1}H NMR spectrum of **14** showed broad singlets for H-1 and H-2; the small $J_{1,2}$, $J_{2,3}$, and $J_{2,3'}$ values were indicative of the *S* configuration of C-2. This result was further confirmed by acetylation of compound **14** to the di-*N*-acetyl derivative **15**. In its ^{1}H NMR spectrum, the resonance of H-1 appeared as a broad singlet ($J_{1,2}$<1 Hz) in contrast with the larger value ($J_{1,2}$=3.4 Hz) found for the analogous glycoside derivative of purpurosamine C, which has opposite configuration at C-2.



Scheme 3.

In summary, the alkyl D-*epi*-purpurosaminide **14** was prepared by an operationally straightforward and enantiospecific synthesis in 43% overall yield from **3**. As the glycosidic linkage is constructed at the beginning of the sequence, and the next steps require gentle conditions, we anticipate that the procedure developed could be employed for the coupling to the conveniently protected cyclitol aglycon to obtain sannamycin-type antibiotics.

3. Experimental

3.1. General methods

Solvents were reagent grade and in most cases were dried and distilled prior to use, according to standard procedures. Melting points were determined with a Fisher–Johns apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed on 0.2 mm silica gel 60 F_{254} (Merck) aluminum supported plates. Visualization of the spots was effected by exposure to UV light or charring with a solution of 5% sulfuric acid in EtOH, containing 0.5% *p*-anisaldehyde. Column chromatography was performed with silica gel 60 (230–400 mesh, Merck). Optical rotations were measured with a Perkin–Elmer 343 polarimeter at 25°C. Nuclear magnetic resonance (NMR) were recorded on a Bruker AC 200 spectrometer (^{1}H at 200 MHz, ^{13}C at 50.3 MHz) or on a Bruker AMX-500 (^{1}H at 500 MHz) in $CDCl_3$ solutions (unless otherwise indicated) with TMS as an internal standard. Assignments were corroborated by appropriate 2D experiments.

3.2. 2-Propyl 3,4-dideoxy-α-D-erythro-*hexopyranoside* **4**

A solution of 2-propyl 6-*O*-acetyl-3,4-dideoxy-α-D-*erythro*-hex-3-enopyranosid-2-ulose[11] (**2**, 146 mg, 0.64 mmol) in dry MeOH (8 mL) was cooled to 0°C and $NaBH_4$ (140 mg, 3.70 mmol) was slowly added. After 1 h of stirring at 0°C no starting material was detected by TLC. The reaction mixture was treated with a 0.5 M solution of NaOMe in MeOH (1.3 mL) and stirred at room temperature for 30 min. The solution was neutralized with Dowex 50W (H^+) resin, then filtered and concentrated. Boric acid was eliminated by successive evaporations with MeOH (3×15 mL). The resulting oil was shown by NMR to be a 3.6:1 mixture of the unsaturated **3** and saturated **4** derivatives; TLC (EtOAc): **3** and **4** had R_f 0.57 and 0.53, respectively. The oil was dissolved in EtOAc (10 mL), cooled to 0°C, and then treated with 10% Pd/C (30 mg) and hydrogen under atmospheric pressure. After 16 h TLC showed a single product had formed (R_f 0.53). The product was purified by column chromatography using a polarity gradient of toluene:EtOAc from 3:1 to 1:1. Compound **4** (102 mg, 84% from **2**) was isolated as a colorless oil; $[\alpha]_D = +129.7$ (*c* 1.0, $CHCl_3$); lit.[12] $[\alpha]_D = +128$; identical ^{1}H and ^{13}C NMR spectra to those described.[12]

3.3. 2-Propyl 3,4-dideoxy-2,6-di-O-*tosyl*-α-D-erythro-*hexopyranoside* **5**

Compound **4** (305 mg, 1.60 mmol) was dissolved in a mixture of anhydrous $CHCl_3$ (3 mL) and pyridine (1 mL, 12.4 mmol). The solution was cooled to 0°C and tosyl chloride (1.20 g, 6.29 mmol) was added. After stirring at room temperature for 16 h, TLC (3:1 toluene:EtOAc) indicated that no starting material **4** remained and a less polar product, having R_f 0.73, had formed. The mixture was diluted with CH_2Cl_2 (50 mL) and successively washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$ and water. The organic extract was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography using a polarity gradient (hexane:EtOAc from 20:1 to 5:1) affording the ditosylate **5** as an oil (652 mg, 82%); $[\alpha]_D = +63.6$ (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.78 (d, 2H, $J = 8.3$ Hz), 7.76 (d, 2H, $J = 8.3$ Hz), 7.33 (d, 4H, $J = 8.3$ Hz), 4.78 (d, 1H, $J = 3.5$ Hz), 4.33 (ddd, 1H, $J = 3.5$, 4.8, 12.0 Hz), 4.03–3.90 (m, 3H), 3.75 (septet, 1H, $J = 6.2$ Hz, C*H*Me_2), 2.45 (s, 6H), 2.03 (dddd, 1H, $J = 4.8$, ≈ 12 Hz), 1.67 (m, 2H),

1.44 (m, 1H), 1.15 (d, 3H, $J=6.2$ Hz), 1.07 (d, 3H, $J=6.2$ Hz); ^{13}C NMR δ 144.8, 129.9 (×2), 129.8 (×2), 128.0 (×2), 127.8 (×2), 94.3, 76.2, 71.4, 70.6, 65.5, 26.6, 23.4, 21.7, 21.5. Anal. calcd for $C_{23}H_{30}O_8S_2$: C, 55.40; H, 6.06. Found: C, 55.84; H, 6.56.

3.4. 2-Propyl 3,4-dideoxy-2,6-di-O-trifluoromethanesulfonyl-α-D-erythro-hexopyranoside **6**

To a solution of **4** (132 mg, 0.69 mmol) in dry CH_2Cl_2 (40 mL) was added 2,6-di-*tert*-butyl-4-methylpyridine (0.892 g, 4.34 mmol). The solution was cooled to −42°C (CH_3CN–dry ice) and trifluoromethanesulfonic anhydride (0.38 mL, 2.26 mmol) was slowly added. The mixture was stirred at 0°C for 4 h when TLC (6:1 toluene:EtOAc) showed conversion of **4** into a less polar product (R_f 0.70). The reaction mixture was poured into cold water (30 mL) and extracted twice with CH_2Cl_2 (50 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the resulting syrup purified by flash chromatography (20:1 hexane:EtOAc). Pure compound **6** was obtained as a colorless oil (230 mg, 73%); $[\alpha]_D=+73.1$ (*c* 1.3, $CHCl_3$); ^{1}H NMR δ 5.02 (d, 1H, $J=3.6$ Hz), 4.75 (ddd, 1H, $J=3.6$, 5.0, 12.0 Hz), 4.36 (d, 2H, $J=4.7$ Hz), 4.14 (dddd, 1H, $J=2.7$, 4.7, 4.7, 12.0 Hz), 3.89 (septet, 1H, $J=6.2$ Hz), 2.24 (dddd, 1H, $J=4.7$, 12.0, 12.2, 15.5 Hz), 1.98 (m, 1H), 1.78 (m, 1H), 1.56 (dddd, 1H, $J=4.3$, 11.8, 13.4, 15.5 Hz), 1.20 (d, 3H, $J=6.2$ Hz), 1.13 (d, 3H, $J=6.2$ Hz); ^{13}C NMR δ 118.5 (q, $J\approx316$ Hz), 93.9, 82.3, 76.6, 71.6, 65.3, 26.0, 23.5, 23.0, 21.4. Anal. calcd for $C_{11}H_{16}F_6O_8S_2$: C, 29.08; H, 3.55. Found: C, 29.27; H, 3.53.

3.5. 2-Propyl 6-azido-2-O-tosyl-3,4,6-trideoxy-α-D-erythro-hexopyranoside **7**

To a solution of **5** (389 mg, 0.78 mmol) in dry DMF (3.2 mL) was added sodium azide (101 mg, 1.55 mmol). The mixture was stirred at 60°C for 16 h, and then at 125°C for 2 h. TLC (6:1 toluene:EtOAc) showed complete conversion of **5** into a less polar product (R_f 0.54, UV active spot). The reaction mixture was diluted with water (20 mL) and extracted twice with ether (50 mL). The ethereal extract was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (20:1 hexane:EtOAc) affording **7** as a viscous oil (231 mg, 80%); $[\alpha]_D=+80.0$ (*c* 0.8, $CHCl_3$); ^{1}H NMR δ 7.79 (d, 2H, $J=8.3$ Hz), 7.34 (d, 2H, $J=8.3$ Hz), 4.84 (d, 1H, $J=3.5$ Hz), 4.41 (dddd, 1H, $J=3.5$, 4.8, 12.0 Hz), 4.00 (m, 1H), 3.85 (septet, 1H, $J=6.2$ Hz), 3.22 (dd, 1H, $J=6.6$, 12.9 Hz), 3.12 (dd, 1H, $J=4.0$, 12.9 Hz), 2.45 (s, 3H), 2.07 (dddd, 1H, $J=4.5$, ≈12.2 Hz), 1.78–1.60 (m, 2H), 1.46 (dddd, 1H, $J\approx4.2$, 11.5, 13.3 Hz), 1.23 (d, 3H, $J=6.2$ Hz), 1.15 (d, 3H, $J=6.2$ Hz); ^{13}C NMR δ 145.0, 134.2, 133.0, 129.8 (×2), 127.7 (×2), 94.2, 76.4, 70.6, 67.1, 54.4, 27.8, 23.5, 23.1, 21.6, 21.5. Anal. calcd for $C_{16}H_{23}N_3O_5S$: C, 52.02; H, 6.27. Found: C, 52.01; H, 6.21.

3.6. 2-Propyl 6-azido-2-O-trifluoromethanesulfonyl-3,4,6-trideoxy-α-D-erythro-hexopyranoside **8**

The crude **6** product mixture obtained by sulfonylation of **4** (130 mg, 0.68 mmol) was dissolved in DMF (3 mL) previously cooled to −18°C. At this temperature sodium azide (200 mg, 3.08 mmol) was slowly added. The mixture was stirred at −10°C for 1 h, when TLC showed complete consumption of the starting material. The product was extracted and chromatographed as indicated for **7**, affording compound **8** (72 mg, 30% from **4**); ^{1}H NMR δ 5.09 (d, 1H, $J=4.5$ Hz), 4.84 (ddd, 1H, $J=4.5$, 5.0, 12.0 Hz), 4.07 (m, 1H), 4.01 (septet, 1H, $J=6.2$ Hz), 3.28 (dd, 1H, $J=6.5$, 13.0 Hz), 3.19 (dd, 1H, $J=4.1$, 13.0 Hz), 2.29 (ddd, $J=4.6$, ≈12.2 Hz), 2.02 (m, 1H), 1.86–1.51 (m, 2H), 1.30 (d, 3H, $J=6.2$ Hz), 1.21 (d, 3H, $J=6.2$ Hz); ^{13}C NMR δ 93.8, 83.1, 71.2, 67.3, 54.3, 27.8, 23.8, 23.2, 21.5.

Compound **8** was rather unstable and the attempted substitution of the triflate group at C-2 by azide by increasing the temperature resulted in complete decomposition.

*3.7. 2-Propyl 3,4-dideoxy-α-D-*erythro*-hex-3-enopyranoside* ***3***

To a solution of **2** (315 mg, 1.38 mmol) in dry MeOH (17 mL) was added cerium(III) chloride heptahydrate (514 mg, 1.38 mmol). The solution was cooled to 0°C and $NaBH_4$ (209 mg, 5.52 mmol) was added. The mixture was stirred for 1 h at 0°C and then treated with a 0.5 M solution of sodium methoxide in MeOH (12 mL) at room temperature for 30 min, when TLC (EtOAc) showed a main spot having R_f 0.57. The solid formed was filtered, and the filtrate treated with Dowex 50W (H^+) resin. The work up was the same as was described in the preparation of compound **4**. Upon purification by column chromatography (toluene:EtOAc from 3:1 to 1:1) the unsaturated diol **3** was obtained as a viscous oil (211 mg, 81%); $[\alpha]_D = +34.6$ (*c* 1.0, $CHCl_3$); ^1H NMR δ 5.78 (bd, 1H, $J = 10.7$ Hz), 5.67 (d, 1H, $J = 10.7$ Hz), 5.09 (d, 1H, $J = 4.1$ Hz), 4.20 (m, 2H), 4.00 (septet, 1H, $J = 6.2$ Hz), 3.70 (dd, 1H, $J = 3.4$, 11.4 Hz), 3.57 (dd, 1H, $J = 5.9$, 11.4 Hz), 2.16 (bs, 2H, interchanges with D_2O), 1.25 (d, 3H, $J = 6.2$ Hz), 1.20 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR δ 129.0, 126.4, 95.3, 70.7, 69.2, 65.0, 64.0, 23.3, 21.9. Anal. calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.05; H, 8.63.

*3.8. 2-Propyl 3,4-dideoxy-2,6-di-*O*-tosyl-α-D-*erythro*-hex-3-enopyranoside* ***9***

Tosylation of **3** (302 mg, 1.60 mmol) under the conditions described for the preparation of **5** afforded the ditosyl derivative **9** (687 mg, 86%) as a crystalline product; mp 69–69.5°C; $[\alpha]_D = +11.4$ (*c* 0.8, $CHCl_3$); ^1H NMR δ 7.78 (d, 2H, $J = 8.2$ Hz), 7.76 (d, 2H, $J = 8.2$ Hz), 7.34 (d, 4H, $J = 8.2$ Hz), 5.71 (dt, 1H, $J = 1.9$, 10.6 Hz), 5.55 (bd, 1H, $J = 10.6$ Hz), 5.02 (d, 1H, $J = 4.1$ Hz), 4.89 (ddd, $J = 1.9$, 4.1, 5.5 Hz), 4.34 (m, 1H), 4.06 (dd, 1H, $J = 3.6$, 10.6 Hz), 4.01 (dd, 1H, $J = 5.5$, 10.6 Hz), 3.82 (septet, 1H, $J = 6.2$ Hz), 2.44 (s, 6H), 1.16 (d, 3H, $J = 6.2$ Hz), 1.12 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR δ 145.1, 133.7, 133.0, 130.0 (×2), 129.9 (×2), 128.0 (×2), 127.8 (×2), 124.3, 93.6, 71.5, 70.6, 66.5, 23.2, 21.6. Anal. calcd for $C_{23}H_{28}O_8S_2$: C, 55.63; H, 5.68. Found: C, 55.01; H, 5.92.

*3.9. 2-Propyl 2,6-diazido-2,3,4,6-tetradeoxy-α-D-*threo*-hex-3-enopyranoside* ***10*** *and 2-propyl 4,6-diazido-2,3,4,6-tetradeoxy-α-D-*threo*-hex-2-enopyranoside* ***11***

To a solution of **9** (1.30 g, 2.62 mmol) in dry DMF (10 mL) was added sodium azide (1.49 g, 22.9 mmol). The mixture was heated to 80°C and stirred at this temperature for 3 h. TLC (6:1 toluene:EtOAc) showed two main product spots having R_f 0.66 and 0.63, which were not fluorescent to the UV light. The reaction mixture was diluted with ethyl ether (100 mL) and washed with water (2×50 mL). The organic extract was dried ($MgSO_4$) and concentrated. The residue was subjected to column chromatography using mixtures of increasing polarity of hexane:EtOAc (from 70:1 to 40:1). The fractions from the column which had R_f 0.66 were concentrated to afford **10** as an oil (0.32 g, 51%); $[\alpha]_D = +396.5$ (*c* 1.2, $CHCl_3$); ^1H NMR δ 6.01 (dd, 1H, $J = 1.1$, 10.5 Hz), 5.82 (dddd, 1H, $J = 1.1$, 2.0, 5.0, 10.5 Hz), 5.00 (s, 1H), 4.32 (m, 1H), 3.93 (septet, 1H, $J = 6.2$ Hz), 3.35 (dd, 1H, $J = 7.1$, 12.7 Hz), 3.27 (m, 1H), 3.24 (dd, 1H, $J = 4.6$, 12.7 Hz), 1.17 (d, 3H, $J = 6.2$ Hz), 1.12 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR δ 131.2, 120.9, 96.9, 70.3, 67.8, 55.3, 54.4, 23.2, 21.6. Anal. calcd for $C_9H_{14}N_6O_2$: C, 45.37; H, 5.92. Found: C, 45.64; H, 5.82.

Concentration of the next fractions from the column afforded **11** as an oil (0.19 g, 30%); $[\alpha]_D = -379.9$ (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 6.07 (dd, 1H, $J = 2.5$, 10.0 Hz, H-2), 5.98 (dd, 1H, $J = 5.1$, 10.0 Hz, H-3), 5.10 (d, 1H, $J = 2.5$ Hz, H-1), 4.20 (ddd, 1H, $J = 2.4$, 4.9, 8.0 Hz, H-5), 3.99 (septet, 1H, $J = 6.2$ Hz, C*H*Me$_2$), 3.55 (dd, 1H, $J = 8.0$, 12.8 Hz, H-6), 3.26 (dd, 1H, $J = 4.9$, 12.8 Hz, H-6′), 3.22 (dd, 1H, $J = 2.4$, 5.1 Hz, H-4), 1.19 (d, 3H, $J = 6.2$ Hz, CH_3), 1.13 (d, 3H, $J = 6.2$ Hz, CH_3); ^{13}C NMR δ 131.6, 123.6, 92.1, 70.2, 69.4, 52.8, 52.0, 23.4, 21.6. Anal. calcd for $C_9H_{14}N_6O_2$: C, 45.37; H, 5.92. Found: C, 45.63; H, 6.03.

*3.10. 2-Propyl 2-azido-6-*O*-tosyl-2,3,4-trideoxy-α-D-*threo*-hex-3-enopyranoside* **12**

A solution of **9** (230 mg, 0.46 mmol) and sodium azide (71 mg, 1.09 mmol) in dry DMF (2 mL) was heated at 35°C. TLC (6:1 toluene:EtOAc) showed gradual conversion of **9** into a less polar product having R_f 0.56. A 1 mL aliquot of the mixture was taken, diluted with water and extracted with ethyl ether. The extract was dried ($MgSO_4$) and concentrated to afford a viscous oil, which was the product with R_f 0.56, and starting material (R_f 0.45). The former was isolated by column chromatography (hexane:EtOAc 30:1) and spectroscopically identified as **12**; ^{1}H NMR δ 7.82 (d, 2H, $J = 8.2$ Hz), 7.35 (d, 2H, $J = 8.2$ Hz), 5.86 (dddd, $J = 1.0$, 2.1, 5.0, 10.3 Hz), 4.96 (s, 1H), 4.44 (m, 1H), 4.12 (dd, 1H, $J = 6.1$, 10.4 Hz), 4.08 (dd, 1H, $J = 5.5$, 10.4 Hz), 3.91 (septet, 1H, $J = 6.2$ Hz), 3.30 (m, 1H), 2.46 (s, 3H), 1.19 (d, 3H, $J = 6.2$ Hz), 1.16 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR δ 144.8, 134.0, 132.8, 129.8 (×2), 129.6, 128.0 (×2), 121.5, 96.7, 70.8, 70.3, 66.5, 55.2, 23.1, 21.5.

The original mixture was then heated at 60°C for 1.5 h when TLC revealed the formation of the spot of R_f 0.56 together with those corresponding to the diazides **10** and **11**. The mixture was processed as described above and the resulting crude product was monitored by ^{1}H NMR spectroscopy showing the signals characteristic of compounds **10**, **11** and **12**.

*3.11. 2-Propyl 3,4-dideoxy-2,6-di-*O*-trifluoromethanesulfonyl-α-D-*erythro*-hex-3-enopyranoside* ***13*** *and its conversion into* ***10***

To a solution of compound **3** (198 mg, 1.05 mmol) in anhydrous CH_2Cl_2 (60 mL) was added 2,6-di-*tert*-butyl-4-methylpyridine (1.15 g, 5.6 mmol) and the mixture was cooled at about −42°C (CH_3CN–dry ice). Trifluoromethanesulfonic anhydride (0.66 mL, 3.92 mmol) was added to the solution, which was allowed to warm slowly until 0°C. After 30 min TLC (6:1 toluene:EtOAc) showed complete conversion of **3** into a faster moving product having R_f 0.56. The mixture was concentrated at 0°C and the residue dissolved in DMF (20 mL) previously cooled at −42°C, and at this temperature sodium azide (860 mg, 13.23 mmol) was added. The temperature was slowly increased until 0°C, and in about 1 h, TLC showed that the intermediate ditriflate **13** was completely converted into a major product having identical polarity to **10**. The reaction mixture was diluted with cold water (20 mL) and extracted with ethyl ether (3×50 mL), dried ($MgSO_4$) and chromatographed to give **10** (168 mg, 67% from **3**); which showed the same physical and spectroscopic properties as the product previously synthesized from **9**.

*3.12. 2-Propyl 2,6-diamino-2,3,4,6-tetradeoxy-α-D-*threo*-hexopyranoside dihydrochloride (2-propyl D-*epi*-purpurosaminide dihydrochloride)* ***14***

Compound **10** (68 mg, 0.29 mmol) dissolved in MeOH (5 mL) containing conc. HCl (0.15

mL) was hydrogenated at 45 psi in the presence of 10% Pd on carbon (20 mg). After 2 h TLC revealed complete consumption of the starting **10**; the catalyst was removed by filtration and ethyl ether was slowly added to induce crystallization of the hydrochloride salt, which precipitated as a white solid. Compound **14** (48 mg, 64%) gave mp >230°C; $[\alpha]_D = +102.4$ (*c* 0.8, MeOH); ^{1}H NMR (DMSO-d_6) δ 8.62 (bs, 3H, NH_3-2), 8.26 (bs, 3H, NH_3-6), 5.04 (s, 1H, H-1), 4.00 (m, 1H, H-5), 3.94 (septet, 1H, $J = 6.1$ Hz, CHMe$_2$), 3.03 (bs, 1H, H-2), 2.90 (m, 2H, H-6,6′), 1.98–1.74 (m, 3H), 1.48 (m, 1H), 1.18 (d, 3H, $J = 6.1$ Hz, CH_3), 1.09 (d, 3H, $J = 6.1$ Hz, CH_3); ^{1}H NMR (D_2O) δ 5.08 (s, 1H, H-1), 4.20 (m, 1H, H-5), 4.06 (septet, 1H, $J = 6.2$ Hz, CHMe$_2$), 3.38 (bs, 1H, H-2), 3.22–3.00 (m, 2H, H-6,6′), 2.26 (m, 1H), 1.92 (m, 1H), 1.75–1.59 (m, 2H), 1.26 (d, 3H, $J = 6.2$ Hz, CH_3), 1.20 (d, 3H, $J = 6.2$ Hz, CH_3); ^{13}C NMR (DEPT) δ 92.8 (C-1), 68.2 (*C*HMe$_2$), 64.6 (C-5), 46.8 (C-2), 42.3 (C-6), 23.0, 20.9 (C-3,4), 20.6, 19.8 (*C*H$_3$). Anal. calcd for $C_9H_{22}Cl_2N_2O_2$: C, 41.39; H, 8.49; N, 10.73. Found: C, 41.63; H, 8.40; N, 10.68.

3.13. 2-Propyl 2,6-N,N-*diacetamido*-2,3,4,6-tetradeoxy-α-D-threo-*hexopyranoside* ***15***

Compound **14** (50 mg, 0.19 mmol) was dissolved in dry pyridine (1 mL) and to the solution, cooled at 0°C, was added acetic anhydride (1 mL) under argon. The mixture was stirred at 0°C for 1 h, and then at room temperature for an additional 5 h, when TLC (4:1 EtOAc:MeOH) showed complete conversion of **14** into a product which had R_f 0.43. To the reaction mixture, cooled at 0°C, was added MeOH (8 mL) and the resultant solution was stirred at room temperature for 1 h, and then concentrated. The residue was dissolved in toluene (10 mL) and concentrated in vacuum, in order to remove the excess of pyridine (this process was repeated four times). The resulting oil was purified by column chromatography (from EtOAc to 10:1 EtOAc:MeOH). Compound **15** (38 mg, 73%) was obtained as a crystalline product; mp 31°C; $[\alpha]_D = +100.4$ (*c* 1.0, MeOH); ^{1}H NMR δ 6.16 (d, 1H, $J = 8.3$, NH), 6.03 (bt, 1H, NH), 4.65 (s, 1H, H-1), 3.89 (m, 2H, H-2,5), 3.84 (septet, 1H, $J = 6.2$ Hz, CHMe$_2$), 3.46 (ddd, 1H, $J = 3.7$, 6.9, 13.6 Hz, H-6), 3.05 (ddd, 1H, $J = 4.9$, 7.9, 13.6 Hz, H-6′), 2.00 (m, 1H), 1.97 (s, 3H), 1.94 (s, 3H), 1.59 (m, 1H), 1.42 (m, 2H), 1.17 (d, 3H, $J = 6.2$ Hz), 1.11 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR (DEPT) δ 170.0, 169.4 (*C*O), 96.7 (C-1), 69.4, 67.3 (C-5, *C*HMe$_2$), 46.2 (C-2), 43.8 (C-6), 23.4, 23.2, 23.1, 21.7 (*C*H$_3$), 23.3, 22.3 (C-3,4). Anal. calcd for $C_{13}H_{24}N_2O_4$: C, 57.33; H, 8.88; N, 10.29. Found: C, 56.93; H, 8.79; N, 10.26.

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