Tetrahedron: *Asymmetry* 21 (2010) 2435–2440

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Enantiospecific synthesis of the sugar amino acid (2*S*,5*S*)-5-(aminomethyl)-tetrahydrofuran-2-carboxylic acid

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ARTICLE INFO

Article history:
Received 13 August 2010
Accepted 20 August 2010
Available online 29 September 2010

ABSTRACT

An enantiospecific synthesis of the tetrahydrofuran amino acid (2*S*,5*S*)-5-(aminomethyl)-tetrahydrofuran-2-carboxylic acid **1** is reported. The sugar enone 2-(*S*)-octyl 6-*O*-acetyl-3,4-dideoxy-α-D-*glycero*-hex-3-enopyranosid-2-ulose **2a**, derived from galactose, was employed as a chiral precursor. The enone **2a** was converted by chemical manipulation of the functional groups into the 6-azido-2-*O*-tosyl-3,4,6-trideoxy-D-*erythro*-hexono-1,5-lactone **9** as key intermediate. Methanolysis of **9** induced the opening of the lactone and the attack of the hydroxyl group at C-5 to C-2 with the displacement of the tosylate. This reaction led to the formation of the tetrahydrofuran ring of methyl (2*S*,5*S*)-5-(azidomethyl)-tetrahydrofuran-2-carboxylate **10**, which was readily converted into **1**. The overall yield of the sequence was 35%, and all the intermediates and the final product have been fully characterized. In addition, the preferential conformations in solution of lactone **9** and target molecule **1** have been established.

1. Introduction

Pyranoid and furanoid amino acids are extensively used as conformationally constrained building blocks for the design of peptidomimetics and peptide scaffolds.[1,2] These amino acids are hybrid structures that carry both amino and carboxyl groups on an anhydro sugar ring; they are often referred to as sugar amino acids (SAAs) although other terms have also been used (glycosamino acids, carbopeptoids, etc.).[3] The stereochemical arrangement of the substituents of the sugar ring, the ring-size as well as the presence of additional functional groups provides monomers that lead to oligomeric libraries.[4] These building blocks, with predictable folding patterns ('foldamers'), are useful in the design and development of biologically active molecules.[5] Insertion of furanoid SAAs, known as 'turn inducers', into cyclic peptides leads to compounds stabilized by intramolecular hydrogen bonding between the stacked rings.[6,7] Thus, SAAs can be assembled rationally to create molecules with well-defined structures, which are employed to combat diseases and are used in the development of new materials.[8]

Furanoid δ-amino acids have been involved in the generation of new peptide nucleic acids, since the six-atom length of these amino acid homologs correspond to the optimal distance to mimic the ribose unit found in nucleic acids (RNA and DNA).[9] The structures of SAAs based on oxygen heterocycles with three to six-membered rings have also been recently reviewed,[3] while many surveys on their synthesis and relevant applications have been published.[1,2,4,5,8,9] In particular, 3,4-dideoxy furanoid SAAs, related to this work, have been synthesized and used as dipeptide isosteres to induce turn structures in small linear peptides. Thus, Chakraborty et al.[10] reported the synthesis of the *N*-Boc derivative of racemic *cis*-5-(aminomethyl)-tetrahydrofuran-2-carboxylic acid by the hydrogenation of 5-(aminomethyl)-furan-2-carboxylic acid prepared from D-fructose. Each component of the racemic mixture has also been synthesized in an enantiomerically pure form. The *N*-Fmoc derivate of (2*S*,5*R*)-5-(aminomethyl)-tetrahydrofuran-2-carboxylic acid was obtained from L-glutamic acid, and the corresponding (2*R*,5*S*)-enantiomer was prepared from D-glucose.[11] These SAAs have been inserted as dipeptide isosteres in place of the Tyr^{III}-Pro^{IV} segment of the receptor-binding inhibitor of the vasoactive intestinal peptide. The conformation of the resulting analogs has been studied and tested for their anticancer activities for human cancer cell lines.[12] The (2*S*,5*R*)- and (2*R*,5*S*)-tetrahydrofuran amino acids have also been employed for the synthesis of C_2 symmetric cyclic oligopeptides and their conformations have been established.[7] A third diastereoisomer with the (2*R*,5*R*)-configuration has been synthesized (but not characterized) and used in peptidomimetic studies.[13]

Herein, we report a convenient and enantiospecific synthesis of (2*S*,5*S*)-5-(aminomethyl)-tetrahydrofuran-2-carboxylic acid, the remaining fourth estereoisomer of the series.

2. Results and discussion

The retrosynthetic analysis applied to the target furanoid amino acid **1** (Scheme 1) suggests a 5-azidomethyl precursor that may be synthesized from synthon **I** via the intramolecular displacement of

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doi:10.1016/j.tetasy.2010.08.013

the 2-tosyloxy substituent by the alcohol group at C-5. Chemical manipulation of functional groups indicates that diol intermediate **II** is a convenient precursor of **I**. Subsequently, the diol **II** may be obtained by hydrogenation and carbonyl reduction from the sugar enone **2**, the product of glycosylation of 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-*lyxo*-hex-1-enitol (2-hydroxy-D-galactal peracetate, **3**).

To establish the influence of a chiral anomeric substituent on the reduction of the carbonyl group of the enone, a chiral alcohol was employed for the glycosylation of **3** (Scheme 2). Thus glycal **3**, readily prepared from D-galactose,[14] was treated with 2-(*S*)-octanol in the presence of tin(IV) chloride to afford the enone **2a** in 88% isolated yield. The anomeric configuration of **2a** was assigned as α on the basis of the NMR spectra, as already reported for analogous 2-alkoxypyran-3-one derivatives.[14–16] Catalytic hydrogenation of the double bond of **4** gave quantitatively the 2-ulose **4a**. A similar reaction sequence from **3**, using 2-propanol as a glycosylating agent, afforded the 2-keto derivative **4b** via the intermediate **2b**.[17]

The reduction of the carbonyl group of **4a** and **4b** was performed with sodium borohydride in MeOH at two different temperatures (25 °C and −18 °C). We observed that during the reduction and workup, partial O-deacetylation of the product took place. Therefore, at the end of the reduction of **4a** and **4b**, the acetoxy group was completely removed by the treatment with sodium methoxide to afford the corresponding diols **5a** and **5b**. The coupling constant values $J_{1,2}$, $J_{2,3ax}$, and $J_{2,3eq}$ from the ^{1}H NMR spectrum of **5a** were similar to those of **5b**, and confirmed the α-D-*erythro* configuration for these major products.[18] They were accompanied by variable proportions of the respective α-D-*threo* diastereoisomers, formed by the addition of the hydride from the more hindered face of the molecule that contained the axially oriented anomeric alkoxy group.

The reductions conducted at lower temperature resulted in an increase in the diastereoselectivity in favor of the *erythro* isomers. Thus, the reduction of **4a** at −18 °C (Table 1) afforded **5a** as practically the only product [diastereomeric excess (de) >98%]; whereas a smaller de (95%) was obtained at 25 °C. Similarly, the reduction of **4b** gave diastereomeric excesses of 96% and 90% when the temperature was raised from −18 °C to 25 °C. At the same temperature, the reduction of the 2-(*S*)-octyl uloside **4a** showed higher diastereofacial selectivity than that of the 2-isopropyl analog **4b**. The increased selectivity in favor of **5a** may be attributed to the additional stereocenter located at the anomeric substituent and/or to the larger size of the octyl group compared to that of the isopropyl in **4b**. As the separation of the diastereomeric mixtures of diols by column chromatography was difficult, we selected the 2-(*S*)-octyl enulose **2a** as the starting material in view of the high selectivity achieved in the reduction of the carbonyl group at −18 °C. Thus, the overall yield of the preparative scale synthesis of diol **5a** from glycal **3**, under optimized conditions, was 83% after four steps.

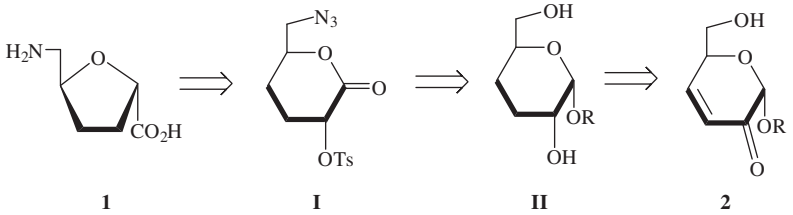
Table 1
Sodium borohydride reduction of the 2-uloses **4a** and **4b**[a]

Starting 2-ulose	Major product (α-D-*erythro*)	Temperature (°C)	Time (h)	Diastereomeric ratio[b] *erythro*:*threo*
4a	**5a**	25	1	40: 1
4a	**5a**	−18	3	>90: 1
4b	**5b**	25	1	20: 1
4b	**5b**	−18	3	50: 1

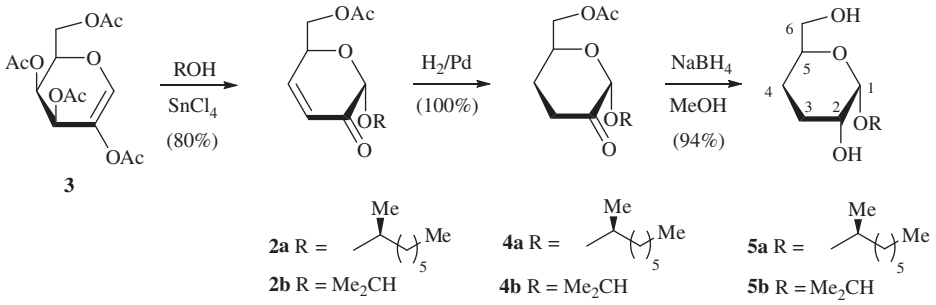
[a] Reduction followed by O-deacetylation (see Section 4).
[b] Determined by the integral of the signals of the anomeric protons from the ^{1}H NMR spectrum of the crude reaction mixture.

Tosylation of **5a** with 2.5 M equiv of *p*-tolylsulfonyl chloride (tosyl chloride) afforded the 2,6-di-*O*-tosyl derivative **6** in 88% yield (Scheme 3). Treatment of **6** with an excess of sodium azide in DMF at 125 °C for 2 h produced selective substitution of the tosylate group of the primary alcohol at C-6, whereas the tosylate at C-2 remained unreactive. The 6-azido derivative **7** was isolated in 92% yield. The ^{1}H NMR spectrum of **7** showed shielding (>0.7 ppm) of the signals of H-6 and H-6′; compared with the same signals in **6**. Also, as expected for the introduction of the azide at C-6, the ^{13}C NMR spectrum of **7** showed a strong upfield shifting of the C-6 resonance, with respect to that in **6**.

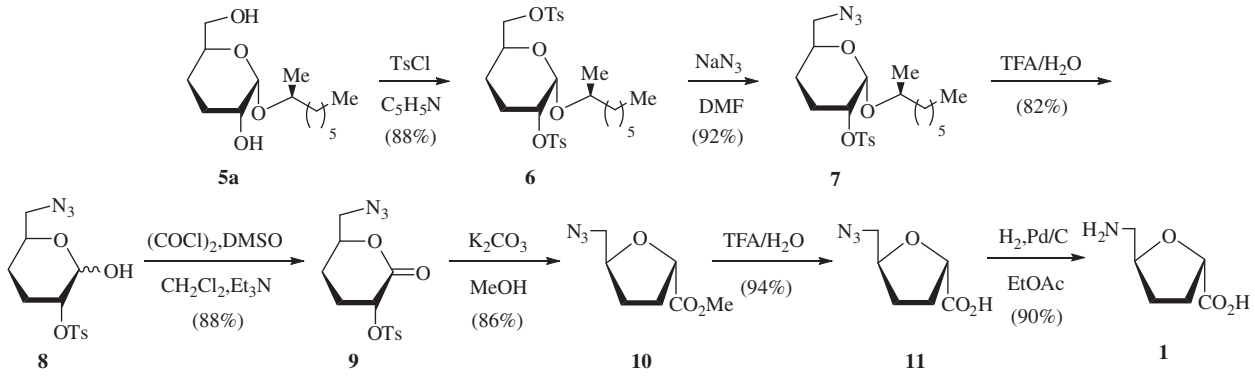
Hydrolysis of glycoside **7** with aqueous trifluoroacetic acid afforded the hexopyranose derivative **8**, as a mixture of anomers. The ^{1}H NMR spectrum of **8** showed two signals in the anomeric region at 5.20 ($J_{1,2}$ = 3.3 Hz) and 4.67 ppm ($J_{1,2}$ = 7.5 Hz) in a 6:4 ratio. The smaller coupling constant value indicated an equational–axial



Scheme 1. Retrosynthetic analysis of the target amino acid **1**.



Scheme 2. Glycosylation and reduction of glycal **3**.



Scheme 3. Synthesis of the tetrahydrofuran amino acid **1** from the diol **5a**.

disposition for H-1 and H-2 (α anomeric configuration), whereas the larger one (7.5 Hz) is in agreement with the diaxial orientation of those protons (β configuration).

The hemiacetal (lactol) function of **8** was oxidized using Swern conditions,[19] to afford lactone **9** in 92% yield. The lactone could not be purified by column chromatography since it was highly sensitive to silica gel, undergoing hydrolysis to the corresponding hydroxy acid, thus lowering the yield considerably. However, the crude lactone **9** was pure enough to be used for the next step. Furthermore, crystals of **9** could be obtained by crystallization from a concentrated solution in EtOAc. The ^{1}H NMR spectrum of **9** showed nicely resolved signals and the coupling constants could be accurately measured. With these data in hand it was possible to estimate the conformational preference for the 1,5-lactone ring. Assuming a Karplus-type dependence of *J* values, the conformation of deoxy aldono-1,5-lactones and their derivatives was described as an equilibrium between half-chair (*H*) and boat (*B*) conformations.[20,21] Molecular mechanics calculations indicated that these two forms corresponded to the two minimum-energy conformations, with the *H* conformer being the more stable.[22] The ^{1}H NMR spectrum of **9** showed large values for $J_{2,3ax}$ (11.0 Hz), $J_{4ax,5}$ (11.4 Hz), and especially for $J_{3ax,4ax}$ (13.0 Hz) thus suggesting a strong preference of the lactone ring for the $^4H_3$ conformer. In this conformation the bulky substituents at C-2 and C-5 are equatorially (or quasi-equatorially) oriented. Horton et al.[23] reported that the half-chair conformation prevails when bulky substituents at C-2 and C-5 are *trans*-disposed, which is the case for lactone **9**. This stereochemistry is also found in D-glucono-1,5-lactone that, similar to **9**, preferentially adopts the $^4H_3$ conformation in solution[23,24] and in the crystalline state.[25] We have also studied the structure of lactone **9** through HyperChem 8.0 calculations using the semi-empirical method AM1. The geometry obtained ($^4H_3$), depicted in Figure 1, shows dihedral angles between vicinal protons associated to *J* magnitudes that are in excellent agreement with the coupling constant values measured from the ^{1}H NMR spectrum of **9**. Furthermore, for the exocyclic aminomethyl group, spectroscopic data and calculations support a large contribution to the equilibrium of the *g,g*-rotamer.

We have previously described[26,27] the formation of oxirane rings by methanolysis of derivatives that bear a sulfonyloxy substituent vicinal to the ring-oxygen atom. The hydroxyl group involved in the lactone function is released by methanolysis and promotes the intramolecular displacement of the vicinal sulfonate, with the formation of the oxirane ring. Fleet et al. have applied a similar methanolysis step to triflate derivatives of aldonolactones for the construction of oxetane,[28] tetrahydrofuran,[29] and tetrahydropyran rings.[30] The potassium carbonate-catalyzed methanolysis of lactone **9** afforded the tetrahydrofuran derivative **10** in 86% yield.

The configuration of the C-2 stereocenter in **10** was assigned as (*S*), since the nucleophilic displacement of the sulfonyloxy group

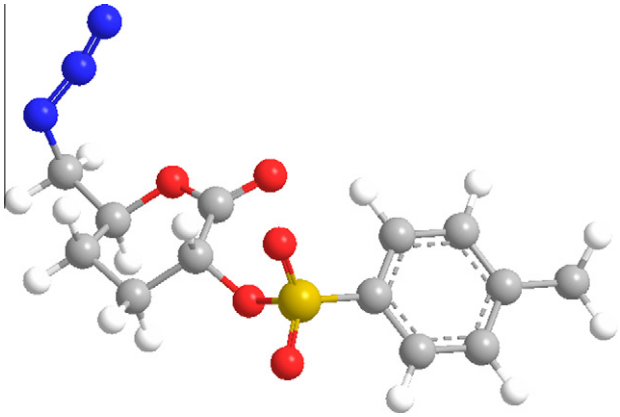


Figure 1. Calculated conformation for compound **9** (AM1 method).

usually takes place with inversion of configuration. This assignment was later confirmed by NOE experiments performed on the target molecule **1**.

Hydrolysis of the ester group of **10** with 1:1 (v/v) trifluoroacetic acid (TFA)/water afforded acid **11**, which was purified by reverse phase chromatography. Finally, target molecule **1** was obtained by catalytic hydrogenation of the azide function of **11**. The free tetrahydrofuran amino acid **1** exhibited a high degree of purity, according to the NMR spectra. However, it required an additional purification through a column filled with Dowex 50W(H^+) resin, which was eluted with water and then with 0.1 M aqueous pyridine, to afford the target molecule **1** in 90% yield. In contrast with the ^{1}H NMR spectra of **10** and **11**, the spectrum of **1** revealed a first order analysis, in spite of the highly coupled protons (H-3, H-3′, H-4 and H-4′) of the ethylene fragment of the ring. The separation of the signals facilitated the interpretation of the NOE correlations in the NOESY spectrum of **1**. The cross-peak between H-6′ and H-2 confirmed the (*S*)-configuration for C-2. The additional NOE correlation observed for H-6′ with H-4′ and the intense cross-peaks between H-2, H-3 and H-4, H-5 confirmed these assignments. Furthermore, the large $J_{5,6}$ value (8.6 Hz) indicated that H-6′ is oriented *anti* to H-5 and directed towards the tetrahydrofuran ring, which explains the cross-peaks observed.

The zwitterionic form of compound **1** was constructed on the GAUSSIAN 03 platform and calculations were performed using the DFT/B3LYP method that employs the 6-31G(d,p) basis set. The preliminary calculations led to the $^2T_0$ conformation for compound **1** (Fig. 2). This structure seems to be stabilized by hydrogen bonding between one of the protons of the ammonium group and the ring-oxygen atom (estimated distance H···O: 2.28 Å). Such a hydrogen bonding should restrict the rotation through the C-5–C-6 bond, resulting in a preferred *g,t*-rotamer, which is also predicted from

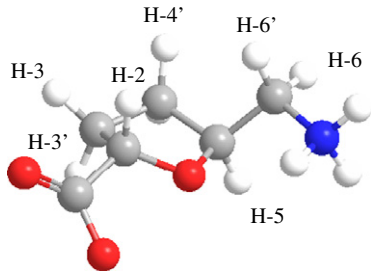


Figure 2. Stereoview of the DFT/B3LYP calculated structure of **1**.

the observed $J_{5,6}$ (3.4 Hz) and $J_{5,6'}$ (8.6 Hz) values. Furthermore, in the $^2T_0$ conformer H-2 lies out of the angle formed by the vicinal methylene protons and the values of the dihedral angles H2–C2–C3–H3 (43°) and H2–C2–C3–H3′ (163°), estimated from the calculated structure, are in agreement with those expected from the measured coupling constants ($J_{2,3} \approx J_{2,3'} = 7.5$ Hz).

3. Conclusion

The sugar amino acid (2*S*,5*S*)-5-(aminomethyl)-tetrahydrofuran-2-carboxylic acid **1** has been synthesized through an enantiospecific route in 35% overall yield, starting from per-*O*-acetyl-2-hydroxygalactal (**3**). The sequence involves two highly selective reactions: (i) the diastereoselective (de >98%) reduction of the carbonyl group of the 2-ulose **4a**, obtained by $SnCl_4$-promoted glycosylation of **3** followed by hydrogenation; and (ii) the regioselective substitution with the azide of the tosyloxy group at C-6 in the di-*O*-tosyl derivative **6**, while the one at C-2 remained intact. The key step of the synthetic route was the construction of the tetrahydrofuran ring of **1** by methanolysis of the lactone group of **9**, with intramolecular displacement of the tosylate at C-2 by HO-5. This is the first report on the synthesis of the (2*S*,5*S*) diastereoisomer of **1**, which was obtained as the free amino acid. The syntheses of the derivatives of the other three isomers of **1** have been previously described. Compound **1** may be incorporated into linear or cyclic oligopeptides as a dipeptide isostere.

4. Experimental parts

4.1. General

Solvents were reagent grade and in most cases were dried 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 digital polarimeter at 25 °C. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC 200 or on a Bruker AMX 500 instruments using tetramethylsilane as an internal standard. The spectra were assigned by the assistance of 2D-COSY and HSQC experiments. High resolution mass spectrometry (HRMS-ESI) was performed in a Bruker microTOF-Q II instrument.

4.2. Synthesis

4.2.1. 2-(*S*)-Octyl 6-*O*-acetyl-3,4-dideoxy-α-D-glycero-hex-3-enopyranosid-2-ulose 2a

A solution of glycal **3** (2.00 g, 6.06 mmol) and 2-(*S*)-octanol (1.88 mL, 12.12 mmol) in dry CH_2Cl_2 (120 mL) was cooled to −18 °C (ice-salt bath) and $SnCl_4$ (870 μL, 7.43 mmol) was added. The mixture was stirred at 0 °C for 2 h, when TLC showed complete consumption of the starting material and formation of a new spot of $R_f = 0.80$ (hexane/EtOAc 2:1). Upon dilution with CH_2Cl_2 the solution was extracted twice with saturated aqueous (satd aq) $NaHCO_3$, and then with brine. The organic extract was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (hexane/EtOAc 20:1) to afford syrupy **2a** (1.59 g, 88% yield); $[\alpha]_D = +18.5$ (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.94 (dd, 1H, $J_{4,5} = 2.0$, $J_{3,4} = 10.6$ Hz, H-4), 6.16 (dd, 1H, $J_{3,5} = 2.5$, $J_{3,4} = 10.6$ Hz, H-3), 4.96 (br s, 1H, H-1), 4.78 (m, 1H, H-5), 4.33 (dd, 1H, $J_{5,6a} = 5.6$, $J_{6a,6b} = 11.7$ Hz, H-6a), 4.25 (dd, 1H, $J_{5,6b} = 4.5$, $J_{6a,6b} = 11.7$ Hz, H-6b), 3.88 (m, 1H, $J = 6.1$ Hz, H-2′), 2.09 (s, 3H, CH_3CO), 1.65–1.25 (m, 10H, CH_2-3′ to CH_2-7′), 1.20 (d, 3H, $J = 6.1$ Hz, CH_3-1), 0.89 (t, 3H, $J = 6.1$ Hz, CH_3-8′); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 188.8 (C-2), 170.6 (MeCO), 146.8 (C-4), 126.4 (C-3), 95.6 (C-1), 74.9 (C-2′), 67.0 (C-5), 64.7 (C-6), 37.0, 31.8, 29.2, 25.7, 22.6 (C-3′ to C-7′), 20.7 (C-1′), 19.4, 14.0 (C-8′). Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.29; H, 8.91.

4.2.2. 2-(*S*)-Octyl 3,4-dideoxy-α-D-erythro-hexopyranoside 5a

Compound **2a** (1.59 g, 5.33 mmol) dissolved in EtOAc (120 mL) and 10% Pd/C (160 mg) was subjected to catalytic hydrogenation at 45 psi (3 atm) for 3 h. The product showed similar chromatographic behavior as the starting material, although it was not UV reactive. Crude compound **4a** (1.60 g, quantitative) was pure enough to be used in the next step. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.68 (br s, 1H, H-1), 4.40 (dddd, 1H, $J_{4eq,5} = 1.3$, $J_{5,6a} = 3.7$, $J_{5,6b} = 6.2$, $J_{4ax,5} = 11.6$ Hz, H-5), 4.10 (dd, 1H, $J_{5,6a} = 3.7$, $J_{6a,6b} = 11.7$ Hz, H-6a), 4.06 (dd, 1H, $J_{5,6b} = 6.2$, $J_{6a,6b} = 11.7$ Hz, H-6b), 3.78 (m, 1H, $J = 6.1$ Hz, H-2′), 2.75 (ddd, 1H, $J_{3ax,4eq} = 6.6$, $J_{3ax,4eq} = 13.2$, $J_{3ax,3eq} = 14.9$ Hz, H-3ax), 2.37 (dddd, 1H, $J_{1,3eq} = 0.8$, $J_{3eq,4eq} = 2.5$, $J_{3eq,4ax} = 4.5$, $J_{3ax,3eq} = 14.9$ Hz, H-3eq), 2.03 (s, 3H, CH_3CO), 2.00 (m, 1H, H-4eq), 1.87 (dddd, 1H, $J_{3eq,4ax} = 4.8$, $J_{4ax,5} = 11.6$, $J_{3ax,4ax} = 13.2$, $J_{4ax,4eq} = 13.4$ Hz, H-4ax), 1.58–1.20 (m, 10H, CH_2-3′ to CH_2-7′), 1.08 (d, 3H, $J = 6.1$ Hz, CH_3-1′), 0.83 (t, 3H, $J = 6.1$ Hz, CH_3-8′); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 202.3 (C-2), 170.7 (MeCO), 97.2 (C-1), 74.0 (C-2′), 66.5 (C-6), 65.8 (C-5), 37.1, 34.8, 31.8, 29.3, 29.1, 25.8, 22.6 (C-3, C-4, C-3′ to C-7′), 20.8 (CH_3CO), 19.2 (CH_3-1′), 14.1 (CH_3-8′).

A solution of the crude 2-(*S*)-octyl 6-*O*-acetyl-3,4-dideoxy-α-D-*erythro*-hexopyranoside-2-ulose **4a** obtained (1.30 g, 4.33 mmol) in MeOH (100 mL) was cooled at −18 °C and $NaBH_4$ (189 mg, 5 mmol) was added. After 3 h analysis of the reaction mixture by TLC, two products of $R_f = 0.67$ and 0.27 were seen (hexane/EtOAc, 1:1). A solution of 0.05 M NaMeO in MeOH (55 mL) was added, and the reaction was continued for 1 h, when TLC showed the disappearance of the spot of $R_f = 0.67$. The solution was adjusted to pH 5 by the addition of Dowex 50W(H^+) resin, and then filtered and concentrated. The ^{1}H NMR spectrum of the crude mixture showed a large proportion of the *erythro* isomer **5a** (de >98%). Column chromatography (hexane/EtOAc 85:15) of the residue led to **5a** (1.06 g, 94%); $[\alpha]_D = +113.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.91 (d, 1H, $J_{1,2} = 3.8$ Hz, H-1), 3.84 (m, 1H, H-5), 3.81 (m, 1H, $J = 6.1$ Hz, H-2′), 3.61 (dd, 1H, $J_{5,6a} = 3.3$, $J_{6a,6b} = 11.4$ Hz, H-6a), 3.59 (ddd, 1H, $J_{1,2} = 3.8$, $J_{2,3eq} = 5.0$, $J_{2,3ax} = 11.8$, Hz, H-2), 3.50 (dd, 1H, $J_{5,6b} = 6.5$, $J_{6a,6b} = 11.4$ Hz, H-6b), 1.90 (dddd, 1H, $J_{3eq,4ax} = 3.7$, $J_{3eq,4eq} = 4.4$, $J_{2,3eq} = 5.0$, $J_{3eq,3ax} = 12.0$ Hz, H-3eq), 1.82 (br s, 2H, HO), 1.69 (dddd, 1H, $J_{3ax,4eq} = 4.1$, $J_{2,3ax} = 11.8$, $J_{3ax,3eq} = 12.0$, $J_{3ax,4ax} = 13.3$ Hz, H-3ax), 1.63–1.58 (m, 1H, H-4 eq), 1.48 (dddd, 1H, $J_{3eq,4ax} = 3.7$, $J_{4ax,5} = 11.7$, $J_{4ax,4eq} = J_{3ax,4ax} = 13.1$ Hz, H-4ax), 1.36–1.22 (m, 10H, CH_2-3′ to CH_2-7′), 1.15 (d, 3H, $J = 6.1$ Hz, CH_3-1′), 0.89 (3H, $J = 6.1$ Hz, CH_3-8′); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 95.4 (C-1), 74.6, 72.3, 69.0 (C-2, C-5, C-2′), 65.5 (C-6), 37.4, 31.8, 29.3, 27.2, 26.0, 25.8, 22.7 (C-3, C-4, C-3′ to C-7′), 19.3, 14.1 (CH_3-1′, CH_3-8′). Anal. Calcd for $C_{14}H_{28}O_4$: C, 64.58; H, 10.84. Found: C, 64.36; H, 11.09.

The same reduction of **5a** conducted at 25 °C, afforded a mixture of **6a** and its α-D-*threo* isomer (Table 1). Anomeric signals for 2-(*S*)-octyl 3,4-dideoxy-α-D-*threo*-hexopyranoside: $\delta_{H\text{-}1}$ = 4.81 ppm, $\delta_{C\text{-}1}$ = 96.5 ppm.

4.2.3. 2-Propyl 3,4-dideoxy-α-D-erythro-hexopyranoside 5b

The reduction of the keto compound **4b**[15] with $NaBH_4$ was performed at −18 °C and 25 °C as described above for **4a**. After O-deacetylation the crude product was analyzed by NMR which showed the presence of **5b** and its α-D-*threo* isomer (Table 1). Anomeric signals for 2-propyl 3,4-dideoxy-α-D-*threo*-hexopyranoside: $\delta_{H\text{-}1}$ = 4.79 ppm, $\delta_{C\text{-}1}$ = 97.4 ppm.

4.2.4. 2-(*S*)-Octyl 2,6-di-*O*-tosyl-3,4-dideoxy-α-D-*erythro*-hexopyranoside 6

Diol **5b** (1.00 g, 3.84 mmol) and tosyl chloride (1.82 g, 9.60 mmol) were dissolved in pyridine (50 mL) and the reaction mixture was stirred at room temperature for 20 h. Next, MeOH was added at 0 °C and the solvent was evaporated in vacuo. Purification by column chromatography (hexane/EtOAc, 9:1) afforded the ditosylate **6** (1.92 g, 88%, R_f = 0.60 hexane/EtOAc 2:1); $[\alpha]_D$ = +68.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76, 7.78 (2d, 4H, *J* = 8.0 Hz, H-aromatic), 7.33 (2d, 4H, *J* = 8.0 Hz, H-aromatic), 4.78 (d, 1H, *J* = 3.5 Hz, H-1), 4.33 (ddd, 1H, $J_{1,2}$ = 3.5, $J_{2,3eq}$ = 4.8, $J_{2,3ax}$ = 12.4 Hz, H-2), 3.99 (m, 1H, H-5), 3.96 (dd, 1H, $J_{5,6a}$ = 5.2, $J_{6a,6b}$ = 10.1 Hz, H-6a), 3.91 (dd, 1H, $J_{5,6a}$ = 3.8, $J_{6a,6b}$ = 10.1 Hz, H-6b), 3.60 (m, 1H, *J* = 6.1 Hz, H-2′), 2.02 (ddd, 1H, $J_{3ax,4eq}$ = 4.0, $J_{2,3ax}$ = $J_{3ax,3eq}$ = $J_{3ax,4ax}$ = 12.4 Hz, H-3ax), 1.72–1.62 (m, 2H, H-3eq, H-4ax), 1.54 (m, 1H, H-4b), 1.55–1.22 (m, 10H, CH_2-3′ to CH_2-7′), 1.03 (d, 3H, *J* = 6.1 Hz, CH_3-1′), 0.88 (t, 3H, *J* = 6.1 Hz, CH_3-8′); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 144.9, 129.9 (×2), 127.9, 127.8 (C-aromatic), 93.5 (C-1), 76.2 (C-2), 73.5 (C-2′), 71.2 (C-5), 65.6 (C-6), 37.0, 31.8, 29.3, 26.5, 25.8, 23.4, 22.6 (C-3, C-4, C-3′ to C-7′), 21.6 (2 × CH_3Ar), 19.0, 14.1 (CH_3-1′, CH_3-8′). Anal. Calcd for $C_{28}H_{40}O_8S_2$: C, 59.13; H, 7.09; S, 11.28. Found: C, 59.09; H, 7.19; S, 11.13.

4.2.5. 2-(*S*)-Octyl 6-azido-2-*O*-tosyl-3,4,6-trideoxy-α-D-erythro-hexopyranoside 7

Compound **6** (1.78 g, 3.13 mmol) was dissolved in DMF (30 mL) and NaN_3 (427 mg, 6.57 mmol) was added. The reaction mixture was stirred at 125 °C for 2 h, when TLC showed complete consumption of the starting material and formation of a less polar product (R_f = 0.75, hexane/EtOAc 2:1). The mixture was filtered and the solvent evaporated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 96:4) to give **7** (1.27 g, 92%); $[\alpha]_D$ = +77.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (d, 2H, *J* = 8.2 Hz, H-aromatic), 7.34 (d, 2H, *J* = 8.2 Hz, H-aromatic), 4.85 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1), 4.41 (ddd, 1H, $J_{1,2}$ = 3.3, $J_{2,3eq}$ = 4.8, $J_{2,3ax}$ = 12.3 Hz, H-2), 3.98 (dddd, 1H, $J_{4eq,5} \approx J_{5,6b}$ = 3.6, $J_{4ax,5}$ = 9.6, $J_{5,6a}$ = 7.0 Hz, H-5), 3.71 (m, *J* = 6.1 Hz, H-2′), 3.21 (dd, 1H, $J_{5,6a}$ = 7.0, $J_{6a,6b}$ = 13.0 Hz, H-6a), 3.12 (dd, 1H, $J_{5,6b}$ = 3.6, $J_{6a,6b}$ = 13.0 Hz, H-6b), 2.44 (s, 3H, CH_3Ar), 2.07 (dddd, 1H, $J_{3ax,4eq}$ = 4.3, $J_{2,3ax} \approx J_{3ax,4ax} \approx J_{3ax,3eq}$ = 12.3 Hz, H-3ax), 1.74 (dddd, 1H, $J_{3eq,4ax}$ = $J_{3eq,4eq}$ = 3.8, $J_{2,3eq}$ = 4.8, $J_{3ax,3eq}$ = 12.3 Hz, H-3eq), 1.68–1.57 (m, 2H, H-4ax, H-4eq), 1.51–1.23 (m, 10H, CH_2-3′ to CH_2-7′), 1.07 (d, 3H, *J* = 6.1 Hz, CH_3-1′), 0.88 (t, 3H, *J* = 6.1 Hz, CH_3-8′); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 144.8, 134.0, 129.9, 127.7 (C-aromatic), 93.5 (C-1), 76.5 (C-2), 73.6 (CHO), 67.4 (C-5), 54.4 (C-6), 37.1, 31.8, 29.3, 27.8, 25.8, 23.6, 22.6 (C-3, C-4, C-3′ to C-7′), 21.6 (CH_3Ar), 19.1, 14.1 (2 × CH_3). Anal. Calcd for $C_{21}H_{33}N_3O_5S$: C, 57.38; H, 7.57; N, 9.56. Found: C, 57.49; H, 7.77; N, 9.61.

4.2.6. 6-Azido-2-*O*-tosyl-3,4,6-trideoxy-α,β-D-erythro-hexopyranose 8

Compound **7** (673 mg, 1.53 mmol) was suspended in a mixture of TFA (5 mL) and water (1.40 mL) and externally heated at 90 °C for 6 h. TLC showed a single spot of R_f = 0.55 (hexane/EtOAc 2:1). After evaporation of the solvent under reduced pressure, and further purification by column chromatography, compound **8** was isolated (410 mg, 82%); $[\alpha]_D$ = +14.0 (*c* 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.82, 7.35 (2d, 4H, H-aromatic), 5.20 (d, 0.6H, $J_{1,2}$ = 3.3 Hz, H-1α), 4.67 (d, 0. 4H, $J_{1,2}$ = 7.5 Hz, H-1β), 4.45 (dd, 0.6H, $J_{1,2}$ = 3.3, $J_{2,3ax}$ = 4.9, $J_{2,3ax}$ = 12.0 Hz, H-2α), 4.23–4.05 (m, 1H, H-2β, H-5α), 3.67 (m, 0. 4H, H-5β), 3.42–3.19 (m, 2H, H-6α/β, H-6′α/β), 2.45 (s, 3H, $ArCH_3$), 2.29–1.37 (m, 4H, H-3α/β, H-3′α/β, H-4α/β, H-4′α/β); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 130.0, 129.8, 128.8, 127.8 (C-aromatic), 95.9 (C-1β), 90.1 (C-1α), 79.2, 76.8, 74.8, 66.9 (C-2α/β, C-5α/β), 54.3, 54.0 (C-6α/β), 28.5, 27.4, 22.8, 21.7 (C-3 α/β, C-4 α/β). Anal. Calcd for $C_{13}H_{17}N_3O_5S$: C, 47.70; H, 5.23; N, 12.84. Found: C, 47.90; H, 5.46; N, 13.03.

4.2.7. 6-Azido-2-*O*-tosyl-3,4,6-trideoxy-D-erythro-hexono-1,5-lactone 9

A solution of oxalyl chloride (1.03 mL, 12.22 mmol) in dry CH_2Cl_2 (13 mL) was prepared in a round-bottomed flask, under an Ar atmosphere, and it was cooled to −78 °C (dry ice/acetone bath). A solution of DMSO (1.73 mL, 24.44 mmol) dissolved in CH_2Cl_2 (2 mL) was added dropwise over a period of 15 min. After stirring the mixture for 10 min, a solution of compound **8** (2.00 g, 6.11 mmol) in dry CH_2Cl_2 (6 mL) was added dropwise and stirring maintained for 1 h. Triethylamine (3 mL) was added and, after 15 min, water (20 mL) was added. The mixture was allowed to reach room temperature and extracted with 5% aq HCl. The organic layer was concentrated to afford **9** (1.67 g, 88%) as a white solid (R_f = 0.70, hexane/EtOAc 1:1). The lactone did not resist purification by column chromatography, but the crude product was pure enough to be used in the following step. Recrystallization from a minimum amount of EtOAc afforded an analytical sample. Mp 77 °C; $[\alpha]_D$ = +9.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (d, 2H, *J* = 8.2 Hz, H-aromatic), 7.36 (d, 2H, *J* = 8.2 Hz, H-aromatic), 4.91 (dd, 1H, $J_{2,3eq}$ = 6.1, $J_{2,3ax}$ = 11.0 Hz, H-2), 4.53 (dddd, 1H, $J_{5,6}$ = 4.1, $J_{4eq,5}$ = 4.3, $J_{5,6'}$ = 4.8, $J_{4ax,5}$ = 11.4 Hz, H-5), 3.52 (dd, 1H, $J_{5,6}$ = 4.1, $J_{6,6'}$ = 14.2 Hz, H-6), 3.42 (dd, 1H, $J_{5,6'}$ = 4.8, $J_{6,6'}$ = 14.2 Hz, H-6′), 2.48 (m, 1H, H-3eq), 2.44 (s, 3H, CH_3Ar), 2.20 (dddd, 1H, $J_{3ax,4eq}$ = 4.3, $J_{2,3ax}$ = 11.0, $J_{3ax,3eq}$ = $J_{3ax,4ax}$ = 13.0 Hz, H-3ax), 2.03 (dddd, 1H, $J_{3ax,4eq}$ = $J_{3eq,4eq}$ = $J_{4eq,5}$ = 4.3, $J_{4ax,4eq}$ = 14.6 Hz, H-4eq), 1.94 (dddd, 1H, $J_{3eq,4ax}$ = 4.3, $J_{4ax,5}$ = 11.4, $J_{3ax,4ax}$ = 13.0, $J_{4ax,4eq}$ = 14.6 Hz, H-4ax); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 165.0 (C-1), 145.4, 132.8, 129.8, 128.2 (C-aromatic), 79.2 (C-5), 73.4 (C-2), 53.9 (C-6), 27.2 (C-3), 24.4 (C-4), 21.7 (CH_3Ar). Anal. Calcd for $C_{13}H_{15}O_5SN_3$: C, 47.99; H, 4.65; S, 9.86; N, 12.92. Found: C, 48.20; H, 4.60; S, 9.95; N, 12.83.

4.2.8. Methyl (2*S*,5*S*)-5-(azidomethyl)-tetrahydrofuran-2-carboxylate 10

A solution of **9** (200 mg, 0.61 mmol) in MeOH (12 mL) was stirred with potassium carbonate (84 mg, 0.61 mmol) at 20 °C. After 1 h, TLC (hexane/EtOAc 1:1) showed total conversion of the starting material into a less polar product (R_f = 0.73). The reaction mixture was neutralized with Dowex 50W(H^+), filtered and was concentrated. The residue was subjected to flash chromatography (hexane/EtOAc 9:1) to afford **10** as a syrup (106 mg, 86%); $[\alpha]_D$ = −8.8 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.63 (dd, 1H, *J* = 5.3, 8.0 Hz, H-2), 4.43 (dddd, 1H, *J* = 4.1, 4.6, 7.0, 7.0 Hz, H-5), 3.78 (s, 3H, CH_3O), 3.52 (dd, 1H, *J* = 4.1, 12.9 Hz, H-6), 3.26 (dd, 1H, *J* = 4.7, 12.9 Hz, H-6′), 2.37 (m, 1H, H-3), 2.09 (m, 2H, H-3′, H-4), 1.84 (m, 1H, H-4′); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 173.4 (C-1), 79.0 (C-5), 77.3 (C-2), 54.1 (C-6), 52.1 (CH_3O), 30.2 (C-3), 27.9 (C-4). HRMS-ESI: Calcd for ($C_7H_{11}N_3O_3 + H^+$) = 186.0873. Found = 186.0877. Calcd for ($C_7H_{11}N_3O_3 + Na^+$) = 208.0697. Found = 208.0697.

4.2.9. (2*S*,5*S*)-5-(Azidomethyl)-tetrahydrofuran-2-carboxylic acid 11

A mixture of **10** (70 mg, 0.38 mmol) and 1:1 TFA/H_2O (4 mL) was stirred at room temperature for 14 h, when TLC (hexane/EtOAc 1:1) revealed the presence of a single product (R_f = 0.25). The solvent was evaporated in vacuo and the residue, dissolved in water (2 mL), was purified by reverse phase chromatography (Amprep Amersham TM C-18), equilibrated with water and eluted with a gradient of MeOH/water, to give **11** as a pure oil (60 mg, 94%); $[\alpha]_D = -5.0$ (*c* 0.7, H_2O); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.57 (dd, *J* = 6.1, 7.9 Hz, H-2), 4.31 (dddd, 1H, *J* = 3.4, 6.2, 6.8 Hz, H-5), 3.47 (dd, 1H, *J* = 3.4, 13.3 Hz, H-6), 3.26 (dd, 1H, *J* = 6.2, 13.3 Hz, H-6′), 2.36 (m, 1H, H-3), 2.01 (m, 2H, H-3′, H-4), 1.73 (m, 1H, H-4′); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 177.2 (C-1), 79.6 (C-5), 76.8 (C-2), 53.7 (C-6), 29.9 (C-3), 27.5 (C-4). HRMS-ESI: Calcd for ($C_6H_9N_3O_3 + Na^+$) = 194.0536. Found = 194.0536.

4.2.10. (2*S*,5*S*)-5-(Aminomethyl)-tetrahydrofuran-2-carboxylic acid 1

Compound **11** (60 mg 0.35 mmol) dissolved in EtOAc (10 mL) was hydrogenated at 45 psi in the presence of 10% Pd/C (10 mg). After 3 h, TLC (hexane/EtOAc 1:1) revealed complete consumption of the starting material. The catalyst was removed by filtration, the residue was washed with water and the combined liquids were concentrated to afford crude **1**. This product was dissolved in water and loaded onto a Dowex 50W(H^+) column which was rinsed with water and eluted with 0.1 M pyridine to give pure **1** as an oil (46 mg, 90%); R_f = 0.2 (MeCN/EtOH/H_2O/AcOH, 13:4:2:1) positive to the ninhydrin test; $[\alpha]_D$ = +20.4 (*c* 1.0, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 4.34 (t, 1H, $J_{2,3} \approx J_{2,3'}$ = 7.5 Hz, H-2), 4.29 (dddd, 1H, $J_{4,5}$ = 6.8, $J_{4',5}$ = 8.0, $J_{5,6}$ = 3.4, $J_{5,6'}$ = 8.6 Hz, H-5), 3.09 (dd, 1H, $J_{5,6}$ = 3.4, $J_{6,6'}$ = 13.2 Hz, H-6), 2.93 (dd, 1H, $J_{5,6'}$ = 8.6, $J_{6,6'}$ = 13.2 Hz, H-6′), 2.27 (dddd, 1H, $J_{2,3}$ = 7.5, $J_{3,4}$ = 5.2, $J_{3,4'}$ = 8.0, $J_{3,3'}$ = 12.8 Hz, H-3), 2.04 (dddd, 1H, $J_{3,4}$ = 5.2, $J_{3',4}$ = 8.0, $J_{4,5}$ = 6.8, $J_{4,4'}$ = 12.8 Hz, H-4), 1.87 (ddd, 1H, $J_{2,3'}$ = 7.5, $J_{3',4} = J_{3',4'}$ = 8.0, $J_{3,3'}$ = 12.8 Hz, H-3′), 1.61 (ddd, 1H, $J_{3,4'} = J_{3',4'} = J_{4',5}$ = 8.0, $J_{4,4'}$ = 12.8 Hz, H-4′); ^{13}C NMR (125.7 MHz, D_2O) δ: 180.8 (C-1), 78.7 (C-2), 75.8 (C-5), 42.7 (C-6), 30.1 (C-3), 28.1 (C-4). HRMS-ESI: Calcd for ($C_6H_{11}NO_3 + H^+$) = 146.0812. Found = 146.0816.

Acknowledgments

Support of this work by the National Agency for Promotion of Science and Technology (ANPCyT, Project PICT 2007-00291), the National Research Council of República Argentina (CONICET, Project PIP N° 0064), and the University of Buenos Aires (Project UBACyT N° 227) is gratefully acknowledged. The authors are research members of CONICET.

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