Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4509–4519

TETRAHEDRON: *ASYMMETRY*

Synthesis of 4-octuloses. Part 7: Highly stereoselective synthesis of 2,3-anhydrosugar derivatives as key intermediates in the preparation of sugar β-lactams†

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Received 12 September 2000; accepted 17 October 2000

Abstract

Reaction of either **1** or **4** with (*N*,*N*-dibenzylcarbamoylmethylene)dimethylsulfurane **2** in DMSO afforded 2,3-*anhydro*-4,5-*O*-isopropylidene-D-*arabino*-pentonamide **3** or *N*,*N*-dibenzyl 2,3-*anhydro*-4,5:6,7-di-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranosonamide **5**, respectively. The configurations of **3** and **5** were determined on the basis of their spectroscopic data, in the first case, and by chemical transformation into the known 2,3-*anhydro*-4,5:6,7-di-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranose **11**. Treatment of **3** and **5** with lithium hexamethyldisilazide in THF provided the corresponding sugar β-lactams **12**, **13** and **14**, respectively.

1. Introduction

β-Lactams (azetidin-2-ones) have attracted the attention of researchers from all over the world for many years, since the discovery of the important role played by such cyclic systems in the inhibition of bacterial cell wall synthesis produced by the β-lactam antibiotics,[2] but the increase in the resistance[3] shown by microorganisms to some of the most used antimicrobial agents, have encouraged the search for new molecules bearing such a moiety that overcome this important problem.

Our group has recently reported on the highly stereoselective synthesis, starting from common hexuloses (D-fructose and L-sorbose), of several derivatives of 4-octulose,[4,5a] 2-deoxy-4-octulose[5] and 2,3-dideoxy-4-octulosononitriles[6] used as chiral intermediates in the synthesis of polyhydroxyindolizidine analogues[1,6,7] of castanospermine, a potent glycosidase inhibitor. Continuing with our efforts in preparing molecules that could show important biological activities, we

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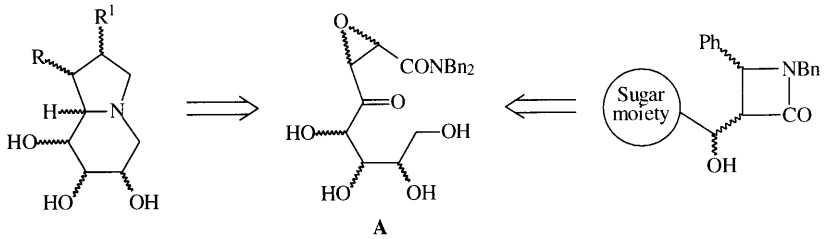
† Part VI: see Ref. 1.

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00421-3

planned the synthesis and use of 4-octulosono-α,β-epoxiamide derivatives, such as **A** shown in Scheme 1, as a key intermediate in the stereoselective synthesis of the already mentioned polyhydroxyindolizidines as well as sugar β-lactams, according to previous results.[8] We describe herein the application of this methodology to the synthesis of the latter compounds by an intramolecular cyclization of **A** (see Scheme 1) with the simultaneous transfer of the chiral information located in the sugar moiety to the target molecule.



A

Scheme 1.

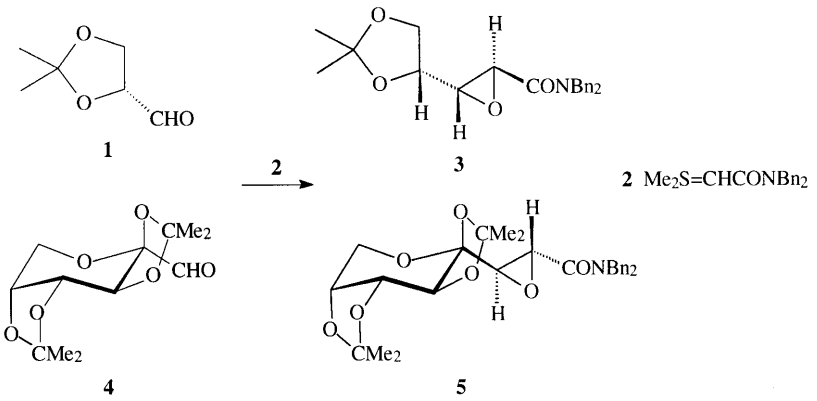
The synthesis of chiral α,β-epoxyamides in a highly stereoselective manner by reaction of *aldehydo*-sugars, such as 2,3-*O*-isopropylidene-D-glyceraldehyde, with stabilized sulfur ylides derived from *N*,*N*-dimethyl and diethylamide has been reported by López-Herrera et al.[9] Herein we have utilized this process but using (*N*,*N*-dibenzylcarbamoylmethylene)dimethyl sulfurane **2** as the sulfur ylide. More recently,[10] treatment of aldehydes with a camphor-derived chiral sulfonium ylide has been also reported. On the other hand, the use of carbohydrates as starting templates for the preparation of chiral β-lactams has been introduced by different groups, involving methods using aminosugars,[11] L-ascorbic acid,[12] D-glyceraldehyde derivatives,[13] as well as [2+2] cycloaddition reactions between enosugars and isocyanates.[14]

2. Results and discussion

Reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde **1** with (*N*,*N*-dibenzylcarbamoylmethylene)dimethyl sulfurane **2**, prepared in situ from the corresponding sulfonium salt and $NaCH_2SOCH_3$ in anhydrous DMSO, proceeded in a highly stereocontrolled manner providing, in 67% yield, mainly *N*,*N*-dibenzyl 2,3-*anhydro*-4,5-*O*-isopropylidene-D-*arabino*-pentonamide **3**, slightly contaminated with the D-*xylo* isomer. The configurations of the two new stereogenic centers (C-2,3) in **3** were determined as follows: the chemical shifts for H-2,3 (δ 3.64 and 3.33, respectively), as well as the $J_{2,3}$ value (2 Hz), suggest a *trans* disposition for such protons. On the other hand, the $J_{3,4}$ (5.3 Hz) for **3** were relevant in order to establish the stereochemistry of **3**, since these values matched quite well (δ 3.58 and 3.20, $J_{2,3}$ 2.1, $J_{3,4}$ 5.4 Hz)[‡] with those previously reported[9a] for the *N*,*N*-dimethyl analogue, and since changing the *N*,*N*-substituents should have little significance, the configuration of **3** can be reasonably assumed (Scheme 2).

In a similar way, compound **4** reacted with **2** to afford *N*,*N*-dibenzyl 2,3-*anhydro*-4,5:6,7-di-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranosonamide **5** (see above), but in this case the configurational assignment of **5** proved to be very troublesome. Thus, in a first approach we tried to correlate compound **5** with the corresponding ester **6**, whose absolute

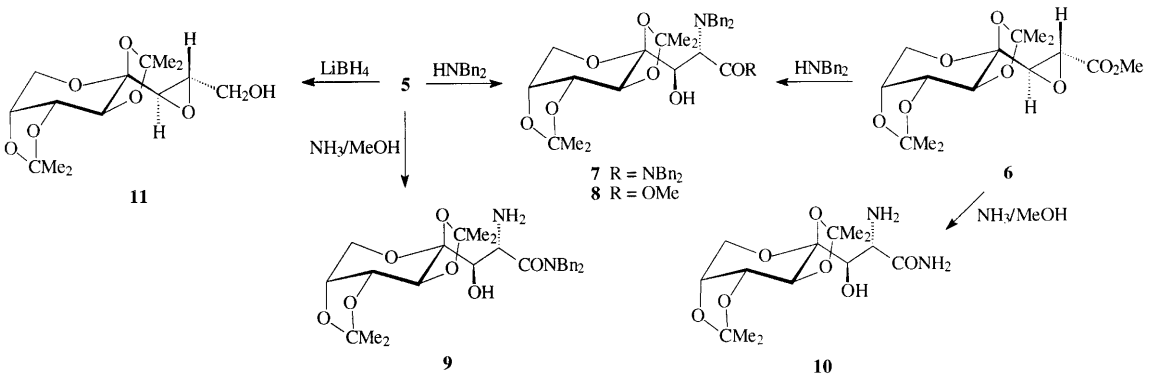
[‡] These values for the D-*xylo* isomer were δ 3.63 and 3.22, $J_{2,3}$ 2.1, $J_{3,4}$ 3.5 Hz, respectively.[9a]



Scheme 2.

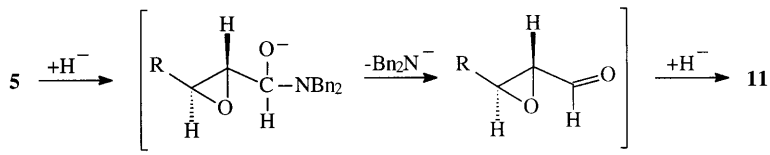
configuration is known,[5b] after transforming both compounds into the same 2-dibenzylamino-3-hydroxy derivative **7**; treatment with *N*,*N*-dibenzylamine was hoped to effect the regioselective[15] opening of the oxirane ring concomitant with a transamidation of the ester **6**, but unfortunately the latter process did not take place and instead ester **8** was obtained. Attempts to interchange functionality between **7** and **8** were unsuccessful and a new strategy had to be envisaged. Thus, compounds **5** and **6** were treated in a sealed tube with aqueous ammonia in methanol in order to promote the appropriate transformations (regioselective oxirane ring opening at C-2 and transamidation) in both molecules leading again to a common compound, namely 2-amino-2-deoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*glycero*-D-*talo*-oct-4-ulo-4,8-pyranoson amide **10**; this occurred with **6**, but transamidation of **5** again did not take place and the related *N*,*N*-dibenzyl-amide **9** was obtained. Steric factors are presumably responsible for the difficulty found in the displacement of the *N*,*N*-dibenzyl group in **5** by other nucleophiles.

An attempt to open regio- and stereoselectively the 2,3-oxirane ring in **5** with $NaBH_4$ in refluxing methanol, according to the literature,[9b] was unsuccessful and decomposition of the molecule occurred, but when **5** was treated with $LiBH_4$ in THF at room temperature, only reduction of the *N*,*N*-dibenzylcarbamoyl to a hydroxymethyl group took place and the known[5b] 2,3-*anhydro*-4,5:6,7-di-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranose **11** was isolated, thus confirming the stereochemistry of the new created stereogenic centers (C-2,3) (Scheme 3).



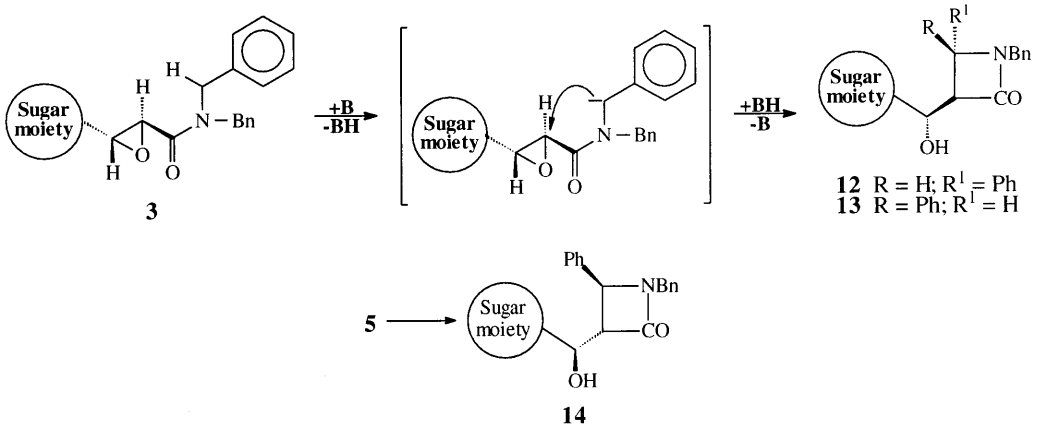
Scheme 3.

Formation of **11** could be attributed (Scheme 4) to a nucleophilic displacement of the *N*,*N*-dibenzyl by hydride to afford an intermediate aldehyde, followed by its reduction.



Scheme 4.

Finally, reaction of α,β-epoxyamides **3** and **5** with lithium hexamethyldisilazide (LHMDS) in THF at low temperature (−10°C) gave (Scheme 5) the related β-lactams **12**, **13**, in ≈1:1 ratio, and **14**. The low and high stereoselectivity, respectively, found in the intramolecular cyclizations of **3** and **5** could be rationalized in terms of steric interactions of the small and large substituent at C-3 with the phenyl group at C-4. Thus, molecular modeling calculations (AM1) on compounds **12**, **13**, and **14** and on the unisolated *cis*-isomer of the latter indicated a small (≈3 kcal/mol) difference in ground-state stability between **12** and **13**, and ≈8 kcal/mol in the case of **14** and its *cis*-isomer.



Scheme 5.

3. Experimental

3.1. General

Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300, ARX-400, and AMX-500 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin–Elmer 782 instrument and mass spectra with a Hewlett–Packard HP-5988-A and Fisons mod. Platform II and VG Autospec-Q mass spectrometers. Optical rotations were measured for solutions in $CHCl_3$ (1 dm tube) with a Jasco DIP-370 polarimeter. TLC was performed on precoated silica gel 60 F_{254} aluminum sheets and detection by charring with H_2SO_4. Column chromatography

was performed on silica gel (Merck, 7734). The noncrystalline compounds, for which elemental analyses were not obtained, were shown to be homogeneous by chromatography and characterized by NMR and HRMS.

3.2. N,N-*Dibenzyl-α-bromoacetamide*

To an ice-water cooled and well stirred solution of commercial dibenzylamine (Aldrich, 15 g, 76 mmol) in dichloromethane (70 mL), aqueous 40% sodium hydroxide solution (30 mL) was added and then a solution of bromoacetyl bromide (Aldrich, 6.6 mL, 76 mmol) in dichloromethane (15 mL) was added dropwise. The mixture was left to reach room temperature (1 h). The organic phase was separated and the aqueous extracted with dichloromethane (2×25 mL). The combined organic phase and extracts were washed with water and concentrated. Column chromatography (ether/hexane, 1:3→2:1) afforded the title compound (23.5 g, 97%) with data identical to those found in the literature.[16]

3.3. (N,N-*Dibenzylcarbamoylmethylene)dimethylsulfonium bromide*

A mixture of *N*,*N*-dibenzyl-α-bromoacetamide (23.4 g, 73.5 mmol) and dimethyl sulfide (20 mL) was stirred at room temperature in a sealed tube for 24 h. The reaction mixture was then diluted with ether (30 mL) and the crystalline sulfonium salt filtered off and thoroughly washed with ether to yield 25.7 g, 92%: mp: 134–135°C. NMR data (MeOH-d_4): ^{1}H, δ 7.44–7.23 (m, 10H, 2 *Ph*CH_2), 4.84 (s, 2H, CH_2CO), 5.59 (s, 4H, 2 PhC*H*$_2$), and 3.02 (s, 6H, SMe_2); ^{13}C, δ 165.50 (O=CN<), 137.24, 136.42, 130.19, 129.80, 129.35, 129.21, 128.86, and 128.41 (*Ph*CH_2), 51.91 and 49.77 (S*C*H$_2$ and Ph*C*H$_2$), and 25.83 (SMe_2). Anal. calcd for $C_{18}H_{22}BrNOS$: C, 56.84; H, 5.83; N, 3.68. Found: C, 56.43; H, 6.28; N, 3.81.

3.4. *Reaction of 2,3-*O*-isopropylidene-*D*-glyceraldehyde* ***1*** *with (*N,N*-dibenzylcarbamoylmethylene)dimethyl sulfurane* ***2***

To a stirred solution of $NaCH_2SOCH_3$ from sodium hydride (80% oil dispersion, 500 mg, 16.7 mmol) and imidazole (100 mg, 1.47 mmol) in dry DMSO (25 mL) was added (*N*,*N*-dibenzylcarbamoylmethylene)dimethylsulfonium bromide (5.76 g, 18 mmol) and the mixture kept at room temperature for 10 min. A solution of compound **1** (1.3 g, 10 mmol) in dry THF (15 mL) was added dropwise. After 1 h, the mixture was partitioned into ether/water (50 mL), the organic phase separated and the aqueous extracted with ether (3×50 mL), the combined organic phase and extracts were washed with water and concentrated to a residue that was chromatographed (ether/hexane, 1:2→1:1) to afford syrupy *N*,*N*-dibenzyl 2,3-anhydro-4,5-*O*-isopropylidene-D-*arabino*-pentonamide (**3**, 2.47 g, 67%) slightly contaminated with the D-*xylo* isomer, $[\alpha]_D^{23}$ −6, $[\alpha]_{405}^{24}$ −20 (*c* 1.4); ν_{max}^{film} 1669 (O=CN<), 1382 and 1372 (CMe_2) cm^{-1}. NMR data: ^{1}H, δ 7.40–7.12 (m, 10H, 2 *Ph*CH_2), 4.63 and 4.57 (2 d, 2H, J=14.8 Hz, PhC*H*$_2$), 4.59 (s, 2H, PhC*H*$_2$), 4.09 (dd, 1H, $J_{4,5}$=5.4, $J_{5,5'}$=7.6 Hz, H-5), 3.91 (q, 1H, H-4), 3.86 (dd, 1H, $J_{4,5'}$=5.3 Hz, H-5′), 3.64 (d, 1H, $J_{2,3}$=2 Hz, H-2), 3.33 (dd, 1H, $J_{3,4}$=5.3 Hz, H-3), 1.32 and 1.29 (2 s, 6H, CMe_2); ^{13}C, δ 167.24 (C-1), 136.48, 135.84, 129.12, 128.77, 128.58, 128.01, 127.78, and 126.74 (*Ph*CH_2), 110.13 (*C*Me_2), 74.81 (C-4), 66.87 (C-5), 58.09 (C-3), 52.05 (C-2), 49.21 and 48.56 (Ph*C*H$_2$), 26.43 and 25.10 (C*Me*$_2$). Mass spectrum (EI): m/z 368 (0.6%, M^++1), 367 (0.4, M^+), 353 (2.0, M^++1−Me), 352 (8.7, M^+−Me), 277 (1.1, M^++1−C_7H_7), 276 (6.7, M^+−C_7H_7), 267 (8.6, M^++1−$C_5H_9O_2$), 266 (37.7, M^+−$C_5H_9O_2$), 196 (85.1, Bn_2N^+), 91 (100, $C_7H_7^+$), and 43 (69.8, Ac^+).

3.5. Reaction of 2,3:4,5-di-O-isopropylidene-β-D-arabino-hexos-2-ulopyranose **4** with sulfurane **2**

Reaction of **4** (1.95 g, 7.55 mmol) in dry THF (20 mL) with sulfurane **2**, prepared from (*N*,*N*-dibenzyl carbamoylmethylene)dimethylsulfonium bromide (4.20 g, 13.2 mmol), sodium hydride (80% oil dispersion, 400 mg, 13.3 mmol) and imidazole (100 mg, 1.47 mmol) in dry DMSO (15 mL) as above, gave, after column chromatography (ether/hexane, 1:3→1:1), *N*,*N*-dibenzyl 2,3-*anhydro*-4,5:6,7-di-*O*-isopropylidene-β-D-*glycero*-D-*galacto*-oct-4-ulo-4,8-pyranosonamide (**5**, 3.14 g, 84%) as a colorless solid foam: $[\alpha]_D^{27}$ +12 (*c* 1.1); ν_{max}^{film} 1664 (O=CN<), 1383 and 1373 (CMe_2) cm^{-1}. NMR data, see Tables 1 and 2. Anal. calcd for $C_{28}H_{33}NO_7$: C, 67.86; H, 6.71; N, 2.83. Found: C, 67.42; H, 6.65; N, 2.87.

3.6. Synthesis of methyl 2,3-anhydro-4,5:6,7-di-O-isopropylidene-β-D-glycero-D-galacto-oct-4-ulo-4,8-pyranosonate **6**

Reaction of **4** (4.7 g, 19.4 mmol) in dry THF (35 mL) with (methoxycarbonylmethylene)dimethylsulfurane, prepared from (methoxycarbonylmethylene)dimethyl sulfonium bromide (8.75 g, 60 mmol), sodium hydride (80% oil dispersion, 1.25 g, 42 mmol) and imidazole (200 mg, 2.94 mmol) in dry DMSO (30 mL) as above, gave, after column chromatography (ether/hexane, 1:3), **6** (4.2 g, 70%), which had the same physical and spectroscopic data as those previously reported.[5b]

3.7. N,N-Dibenzyl 2-dibenzylamino-2-deoxy-4,5:6,7-di-O-isopropylidene-β-D-glycero-D-talo-oct-4-ulo-4,8-pyranosonamide **7**

A stirred solution of **5** (70 mg, 0.14 mmol) and dibenzylamine (60 μL, 0.31 mmol) in dry methanol (2 mL) was heated in a sealed tube at 80°C for 48 h. TLC (ether/hexane, 2:3) then revealed the presence of a faster-running compound. The mixture was concentrated and the residue supported on silica gel and chromatographed (ether/hexane, 1:4) to afford **7** (85 mg, 87%) as a colorless syrup: $[\alpha]_D^{22}$ +3, $[\alpha]_{405}^{23}$ +14 (*c* 1.2); ν_{max}^{film} 3264 (OH), 1623 (O=CN<), 1382 and 1372 (CMe_2) cm^{-1}. NMR data, see Tables 1 and 2. Anal. calcd for $C_{42}H_{48}N_2O_7$: C, 72.81; H, 6.98; N, 4.04. Found: C, 72.51; H, 7.30; N, 4.21.

3.8. Methyl 2-dibenzylamino-2-deoxy-4,5:6,7-di-O-isopropylidene-β-D-glycero-D-talo-oct-4-ulo-4,8-pyranosonate **8**

A stirred solution of **6** (210 mg, 0.64 mmol) and dibenzylamine (190 mg, 0.96 mmol) in dry methanol (2 mL) was heated in a sealed tube at 60°C for 16 h. TLC (ether/hexane, 1:1) then showed the presence of a faster-running compound. The mixture was concentrated and the residue supported on silica gel and chromatographed (ether/hexane, 1:4) to afford **8** (275 mg, 82%) that crystallized on standing, mp: 127–128°C; $[\alpha]_D^{22}$ −61 (*c* 1.3); ν_{max}^{film} 3456 (OH), 1712 (CO_2Me), 1382 and 1373 (CMe_2) cm^{-1}. NMR data, see Tables 1 and 2. Anal. calcd for $C_{29}H_{37}NO_8$: C, 66.01; H, 7.07; N, 2.66. Found: C, 66.18; H, 7.21; N, 2.70.

Table 1
^{1}H NMR data for compounds **5** and **7–10**

Compound	^{1}H Chemical shifts (δ) with multiplicities and coupling constants (Hz)									
	H-2	H-3	H-5	H-6	H-7	H-8a	H-8e	$PhCH_2$	$PhCH_2$	CMe_2
5	3.94d $J_{2,3}=2$	3.45d	4.33d $J_{5,6}=2.6$	4.61dd $J_{6,7}=7.9$	4.21bdd	3.81dd $J_{7,8a}=1.9$ $J_{8a,8e}=13$	3.68d	7.40–7.15m	4.71d & 4.37d $J=14.7$ 4.60d & 4.46d $J=16.5$	1.46s, 1.44s 1.35s, 1.30s
7[a]	4.21s	4.46d $J_{3,OH}=9.1$	4.85d $J_{5,6}=2.6$	4.70dd $J_{6,7}=7.9$	4.25dd	3.83dd $J_{7,8a}=1.7$ $J_{8a,8e}=12.8$	3.50d	7.35–6.91m	5.18d & 3.67d $J=14.8$ 4.16d & 3.64d $J=13.6$ 4.01d & 3.59d $J=17.3$	1.57s, 1.47s 1.38s
8[b]	4.02bs	4.14dd $J_{2,3}=0.8$ $J_{3,OH}=10.5$	4.66d $J_{5,6}=2.7$	4.62dd $J_{6,7}=7.8$	4.18dd	3.73dd $J_{7,8a}=1.4$ $J_{8a,8e}=12.9$	3.54d	7.37–7.19m	4.00d & 3.73d $J=14.6$	1.58s, 1.40s 1.37s, 1.34s
9[c]	3.78bd $J_{2,NH}=9.6$	4.62s	4.24d $J_{5,6}=2.4$	4.60dd $J_{6,7}=7.6$	4.19dd	3.85dd $J_{7,8a}=1.9$ $J_{8a,8e}=12.7$	3.60d	7.30m	4.94d & 4.16d $J=14.7$ 4.79d & 4.37d $J=16.2$	1.41s, 1.39s 1.31s
10[d]	3.61bs	3.80bd $J_{2,3}=3.8$	4.69d $J_{5,6}=2.8$	4.59dd $J_{6,7}=7.9$	4.20dd	3.88dd $J_{7,8a}=1.8$ $J_{8a,8e}=12.9$	3.69d	–	–	1.50s, 1.47s 1.42s, 1.32s

[a] OH-3 at δ 7.83.
[b] OH-3 and OMe at δ 4.92 and 3.74, respectively.
[c] NH_2 and OH at δ 5.43 and 1.80, respectively.
[d] NH_2 and OH at δ 7.26s, 5.96 and 2.00, respectively.

Table 2
^{13}C NMR data for compounds **5** and **7**–**10**

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	CMe$_2$	CMe_2	CH$_2$Ph
5	167.21	50.88	57.91	100.76	70.11	70.77	71.97	61.52	109.40 109.27	26.35, 26.05 24.85, 24.26	49.16, 47.79
7	174.76	50.91	69.23	104.77	69.61	70.65	71.01	61.07	108.78 108.74	26.67, 26.46 25.76, 23.97	54.82, 48.99 47.48
8[a]	173.73	57.16	73.37	103.82	69.67	70.95	70.43	61.61	109.01 108.74	26.56, 26.15 25.52, 24.27	55.68
9	177.22	47.08	77.64	103.69	70.25	70.34	70.84	61.15	109.07 108.95	26.56, 25.99 25.54, 23.93	49.82, 48.19
10	178.63	55.22	74.42	104.63	70.04	70.29	70.77	61.26	109.07 108.99	26.63, 25.96 25.66, 24.02	–

[a] OMe at 51.64 ppm.

3.9. N,N-*Dibenzyl 2-amino-2-deoxy-4,5:6,7-di*-O-*isopropylidene-β-D*-glycero-*D*-talo-*oct-4-ulo-4,8-pyranosonamide* **9**

A stirred solution of **5** (2.1 g, 4.24 mmol) and aqueous 30% ammonia solution (15 mL) in methanol (15 mL) was heated in a sealed tube at 100°C, for 3 h. TLC (ether/triethylamine, 10:0.1) then revealed the presence of a slower-running compound. The mixture was concentrated and the residue supported on silica gel and chromatographed (ether/methanol/triethylamine, 15:1:0.1) to afford **9** (1.95 g, 90%) as a colorless syrup: $[\alpha]_D^{27}$ −22 (*c* 1); ν_{max}^{film} 3382 (OH, NH_2), 1623 (O=CN<), 1382 and 1373 cm^{-1} (CMe_2). NMR data, see Tables 1 and 2. Anal. calcd for $C_{42}H_{48}N_2O_7$: C, 72.81; H, 6.98; N, 4.04. Found: C, 72.51; H, 7.30; N, 4.21. Mass spectrum (LSIMS): *m*/*z*: 535.24202 (M^++Na) for $C_{42}H_{48}N_2NaO_7$ 535.24226 (deviation −0.4 ppm).

3.10. *2-Amino-2-deoxy-4,5:6,7-di*-O-*isopropylidene-β-D*-glycero-*D*-talo-*oct-4-ulo-4,8-pyranosonamide* **10**

A stirred solution of **6** (200 mg, 0.6 mmol) and aqueous 30% ammonia solution (5 mL) in methanol (5 mL) was heated in a sealed tube at 100°C for 3 h. TLC (ether/methanol/triethylamine, 10:2:0.1) then showed the presence of a slower-running compound. The mixture was concentrated and the residue supported on silica gel and chromatographed (ether/methanol/triethylamine, 10:1:0.2) to afford crystalline **10** (95 mg, 47%): mp: 159–160°C; $[\alpha]_D^{22}$ −23 (*c* 0.8); ν_{max}^{KBr} 3436 and 3312 (OH and NH_2), 1675 (O=CN<), 1384 and 1372 (CMe_2) cm^{-1}. NMR data, see Tables 1 and 2. Anal. calcd for $C_{14}H_{24}N_2O_7$: C, 50.59; H, 7.28; N, 8.43. Found: C, 50.29; H, 7.14; N, 8.20.

3.11. *2,3-Anhydro-4,5:6,7-di*-O-*isopropylidene-β-D*-glycero-*D*-galacto-*oct-4-ulo-4,8-pyranose* **11**

To a stirred solution of **5** (130 mg, 0.26 mmol) in dry THF (8 mL) lithium borohydride (100 mg) was added portionwise. After 3 days, TLC (ether/hexane, 2:1) then showed a slower-running compound. The mixture was diluted with methanol, neutralized with acetic acid, and finally concentrated. The residue was partitioned into dichloromethane/water, the organic phase separated and concentrated. Column chromatography (ether/hexane, 1:2) gave **11** (50 mg, 73%), which showed the same physical and spectroscopic data as those previously reported.[5b]

3.12. *(3*R,*4*R*)-1-Benzyl-3-(2′,3′*-O-*isopropylidene-D*-erythro-*propanetriol-1′-yl)-4-phenylazetidin-2-one* **12** *and its (3*R,*4*S*)-isomer* **13**

To a stirred and cooled (−10°C) solution of **3** (1.6 g, 4.35 mmol) in dry THF (30 mL) was added dropwise an M solution of LHMDS in the same solvent (4 mL), and the mixture was allowed to reach room temperature. After 2 h, TLC (ether) then revealed the presence of two slower-running compounds. The mixture was neutralized with acetic acid, concentrated and the residue dissolved in ether, washed with brine, then concentrated. Column chromatography (ether/hexane, 1:1→2:1) afforded first crystalline **12** (320 mg): mp: 119–120°C; $[\alpha]_D^{23}$ +7, $[\alpha]_{405}^{25}$ +27 (*c* 1); ν_{max}^{KBr} 3456 (OH), 1733 (O=CN<), 1380 and 1370 (CMe_2) cm^{-1}. NMR data: ^1H, δ

7.40–7.15 (m, 10H, *Ph* and *Ph*CH_2), 4.85 and 3.79 (2d, 2H, $J=15$ Hz, PhCH_2), 4.41 (d, 1H, $J_{3,4}=1.9$ Hz, H-4), 4.07–4.03 (m, 3H, H-2′,3′a,3′b), 3.93–3.90 (m, 1H, H-1′), 3.21 (dd, 1H, $J_{1',3}=6.2$ Hz, H-3), 1.35 and 1.30 (2s, 6H, CMe_2); ^{13}C, δ 168.13 (C-2), 137.19, 135.35, 129.00, 128.81, 128.59, 128.39, 127.79, and 126.78 (*Ph*CH_2), 109.43 (*C*Me_2), 77.70 (C-2′), 70.96 (C-1′), 66.55 (C-3′), 62.78 (C-3), 57.12 (C-4), 44.63 (Ph*C*H_2), 26.73 and 25.22 (C*Me*$_2$). Anal. calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.42; H, 6.85; N, 4.04.

Eluted second (530 mg) was a mixture of **12** and **13**, in a 2:3 ratio. Finally pure **13** (320 mg) was obtained as a colorless solid: mp: 170–171°C; $[\alpha]_D^{26}$ −59, $[\alpha]_{405}^{26}$ −163 (*c* 0.8); ν_{max}^{KBr} 3413 (OH), 1744 (O=CN<), 1387 and 1372 (CMe_2) cm^{-1}. NMR data: ^{1}H, δ 7.41–7.14 (m, 10H, *Ph* and *Ph*CH_2), 4.95 and 3.95 (2 d, 2H, $J=15$ Hz, PhCH_2), 4.60 (d, 1H, $J_{3,4}=5.7$ Hz, H-4), 3.99–3.95 (m, 2H, 3′a,3′b), 3.85 (m, 1H, H-2′), 3.69 (dd, 1H, $J_{1',3}=3.8$ Hz, H-3), 3.50 (dd, 1H, $J_{1',2'}=5.4$ Hz, H-1′), 1.26 and 1.23 (2s, 6H, CMe_2); ^{13}C, δ 167.45 (C-2), 135.36, 135.15, 128.94, 128.85, 128.68, 128.56, 127.86, and 127.42 (*Ph*CH_2), 109.30 (*C*Me_2), 77.35 (C-2′), 68.02 (C-1′), 65.97 (C-3′), 57.63 and 57.04 (C-3,4), 44.84 (Ph*C*H_2), 26.44 and 25.25 (C*Me*$_2$). Anal. calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.89; H, 7.15; N, 3.90.

*3.13. (3*S*,4*S*)-1-Benzyl-3-(2′,3′:4′,5′-di-*O*-isopropylidene-β-D-*manno*-hex-2′-ulo-2′,6′-pyranos-1′-yl)-4-phenylazetidin-2-one* ***14***

To a stirred and cooled (−10°C) solution of **5** (305 mg, 0.6 mmol) in dry THF (10 mL) was added dropwise an M solution of LHMDS in the same solvent (2 mL), and the mixture was allowed to reach room temperature. After 1 h, TLC (ether/hexane, 3:1) then revealed the presence of a slower-running compound. Work-up of the mixture as above, gave, after column chromatography (ether/hexane, 1:1) crystalline **14** (255 mg, 84%): mp: 135–136°C; $[\alpha]_D^{21}$ −19 (*c* 1); ν_{max}^{KBr} 3406 (OH), 1748 (O=CN<), 1382 and 1373 (CMe_2) cm^{-1}. NMR data: ^{1}H, δ 7.35–7.05 (m, 10H, *Ph* and *Ph*CH_2), 4.87 and 3.71 (2d, 2H, $J=14.9$ Hz, PhCH_2), 4.62 (d, 1H, $J_{3',4'}=2.7$ Hz, H-3′), 4.58 (dd, 1H, $J_{4',5'}=7.8$ Hz, H-4′), 4.31 (d, 1H, $J_{3,4}=1.8$ Hz, H-4), 4.17 (dd, 1H, H-5′), 4.03 (dd, 1H, $J_{1',3}=8.6$, $J_{1',OH}=5.5$ Hz, H-1′), 3.74 (dd, 1H, $J_{5',6'a}=1.7$ Hz, H-6′a), 3.57 (d, 1H, $J_{6'a,6'e}=12.9$ Hz, H-6′e), 3.38 (dd, 1H, H-3), 3.00 (d, 1H, OH-1′), 1.42, 1.39, 1.31, and 1.24 (4s, 12H, 2CMe_2); ^{13}C, δ 168.94 (C-2), 137.47, 135.42, 128.83, 128.77, 128.70, 128.43, 128.22, 127.67, and 127.04 (*Ph* and *Ph*CH_2), 109.27 and 108.97 (2*C*Me_2), 103.63 (C-2′), 71.99 (C-1′), 70.97 (C-5′), 70.22 (C-4′), 70.04 (C-3′), 61.10 (C-6′), 60.46 (C-3), 58.84 (C-4), 44.38 (Ph*C*H_2), 26.67, 25.87, 25.59 and 23.97 (2C*Me*$_2$). Anal. calcd for $C_{28}H_{33}NO_7$: C, 67.86; H, 6.71; N, 2.83. Found C, 67.59; H, 7.02; N, 3.09.

Acknowledgements

This work was supported by Ministerio de Educación y Cultura (Spain) (Project PB98-1357) and by a grant (A. J. Mota) from the University of Granada (Spain).

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