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OPTICALLY PURE 3,4-DISUBSTITUTED AZETIDINONES FROM SUGARS

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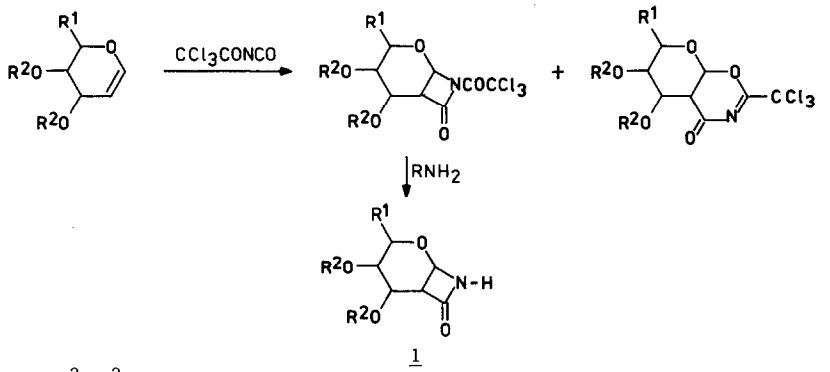
Abstract - Glycolic cleavage of the *vic*-diol grouping present in *N*-benzyl-2-carboxy-2-deoxypento and hexopyranosylaminolactams (5, 6, and 7) with sodium metaperiodate under standard conditions leads to formation of reactive dialdehydes 13 and 14 which upon standing undergo intramolecular aldol condensation to afford bicyclic β-lactams having a four-membered ring fused to the furanoid system. Reduction of dialdehydes 13 and 14 with sodium borohydride gives optically pure 3,4-disubstituted azetidinones 15, 17, 19, and 20 which can serve as starting materials for the synthesis of 1-oxabicyclic β-lactams.

We have reported a simple synthesis of 2-carboxy-2-deoxypento and hexopyranosylaminolactams 1 from the addition of trichloroacetyl isocyanate to glycals.[1,2,3] The two step, one pot, transformation consisted of cycloaddition leading to an unstable mixture of (2+2) and (4+2) cycloadducts followed by splitting of trichloroacetyl substituent from the β-lactam nitrogen atom (Scheme 1).

Scheme 1



1

R^1=H, CH_3, CH_2OR^2; R^2=Alkyl, Benzyl, Silyl

The ratio of (2+2) and (4+2)cycloadducts, a crucial determinant of reaction yield, depends on configuration of the starting glycal, substitution of its hydroxyl groups, solvent, and reaction time.

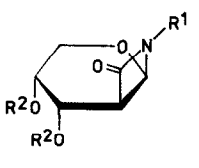
Owing to the stereospecificity of cycloaddition (isocyanate adds to a glycal molecule *anti* to the C-3 substituent) and to the variety of sugar precursors available, the reaction offers full stereocontrol of the configuration at the azetidinone carbon atoms, which is essential for biological activity of β-lactam antibiotics.[4] Compounds 1 can be used either as a base for a new family of bi-

cyclic β-lactams with potential biological activity, or as substrates for stereocontrolled synthesis of selected mono and bicyclic β-lactams having the oxygen atom at C-4 of the azetidinone ring.

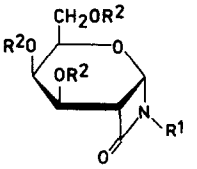
Recently we have described the synthesis of *N*-benzyl 3,4-disubstituted azetidinones *via* glycolic cleavage of the *vic*-diol grouping present in sugar β-lactams obtained from 1.[5] In the present work, we discuss all aspects of this transformation in more details.

RESULTS AND DISCUSSION

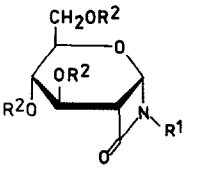
Bicyclic β-lactams 2, 3, and 4 were obtained according to the procedure leading directly to *N*- and *O*-unprotected compounds.[3]



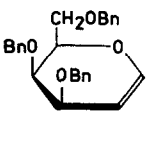
2 : R^1=R^2=H
5 : R^1=Bn, R^2=H
9 : R^1=Bn, R^2=TMS



3 : R^1=R^2=H
6 : R^1=Bn, R^2=H
10 : R^1=H, R^2=Bn
12 : R^1=R^2=Bn



4 : R^1=R^2=H
7 : R^1=Bn, R^2=H
11 : R^1=Bn, R^2=TMS

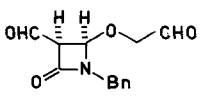


8

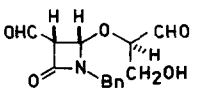
Periodate oxidation of compounds 2-4, lacking *N*-protection, under standard conditions[6] led to formation of complex mixtures of products, which were not investigated. In order to obtain more stable compounds, β-lactams 2-4 were benzylated at the nitrogen atom in a three-step procedure involving silylation of hydroxyl groups, benzylation of the nitrogen atom in boiling benzene in the presence of potassium carbonate and tetrabutylammonium bromide as a catalyst, and methanolysis of the silyl protecting groups to afford compounds 5, 6, and 7, respectively.

N-Benzyl β-lactams 5-7 can also be obtained using another sequence of reactions which was found to be particularly attractive in case of the synthesis of compound 6 (α-D-galacto configuration). Treatment of 3,4,6-tri-*O*-benzyl-D-galactal (8) with trichloroacetyl isocyanate in acetonitrile solution afforded a mixture of cycloadducts containing up to 75% of the desired (2+2)cycloadduct (Scheme 1). This result should be underlined, because in no previously performed reaction did the content of (2+2)cycloadduct exceed 50%; the amount usually varied between 30 and 40%.[1-3] Compound 10 thus obtained was benzylated at the nitrogen atom according to the procedure described for silylated compounds 2-4, and subsequently was subjected to hydrogenolysis in the presence of palladium catalyst, affording 6; no hydrogenolysis of the *N*-benzyl group was observed.

Glycolic cleavage of the *vic*-diol grouping present in 5-7 with sodium metaperiodate under standard conditions[6] led to formation of reactive dialdehydes 13 and 14, which could further undergo an intramolecular aldol condensation owing to the β-dicarbonyl fragment. Therefore, in order to achieve the desired product, control of the reaction time and pH is necessary. The progress of reaction can be stoped at the stage of 3,4-disubstituted azetidinones by the reduction of aldehyde functions to the respective hydroxymethyl groups.



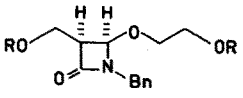
13



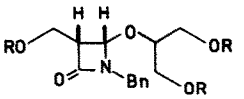
14

When periodate oxidation of 5 and 6 was performed in methanol-water solution in the presence of ammonium sulfate at -5°C, and the respective aldehydes 13 and 14 were reduced without isolation, azetidinones 15 and 17 were obtained in a good yield. The J_{34} coupling constant of 3.8 Hz for 15 and 3.7 Hz for 17 proved the *cis* configuration for both products. Oxidation of 7 under the same conditions required 2 molar equivalents of sodium metaperiodate to give 17.

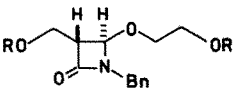
Oxidation of 5 in methanol-water solution at -5°C in the presence of sodium bicarbonate followed by sodium borohydride reduction gave a mixture of *trans* compound 19 with the 3R, 4R configuration and two bicyclic compounds 23 and 25 in a ratio of about 5:3:1 respectively, showing that epimerization at the C-3 carbon atom is faster than the following aldol condensation. Prolongation of the reaction time led after 20 h to a 1:1 mixture of bicyclic products 23 and 25 because of the reversibility of the aldol condensation. The configuration of 19 was proved on the basis of J_{34}=1.1 Hz. The configuration of 23 and 25 was assigned on the assumption that 1,3-*cis* oposition of H-1 and the *O*-acyl substituent at C-3, as well as H-3 and the β-lactam nitrogen atom present in the di-*O*-acetyl derivative 26 should cause a downfield shift in comparison with the respective chemical shifts in the alternative isomer 24. The assigned configuration is in a good agreement with our speculation on prefered conformation of furanoid β-lactams in solution (see later):



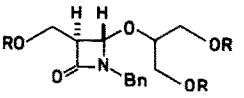
15 : R=H
16 : R=Ac



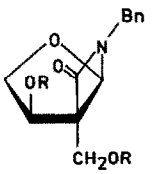
17 : R=H
18 : R=Ac



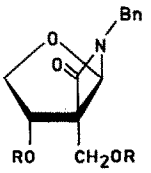
19 : R=H
20 : R=Ac



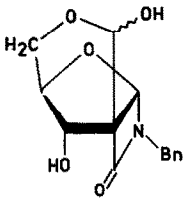
21 : R=H
22 : R=Ac



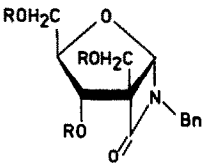
23 : R=H
24 : R=Ac



25 : R=H
26 : R=Ac

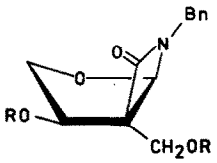


27

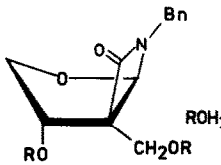


28 : R=H
29 : R=Ac

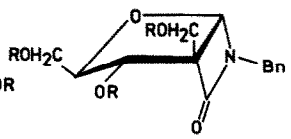
Oxidation of 6 and 7 with sodium metaperiodate followed by epimerization of C-3 with sodium bicarbonate, and subsequent reduction of the post reaction mixture afforded the desired product 21 in a low yield (30%). Prolongation of the reaction time in the presence of base led to formation of tricyclic compound 27, which could be isolated or reduced without isolation to the bicyclic β-lactam 28. In contrast to the mixture of two diastereomers 23 and 25 obtained from 5 (β-D-arabino configuration), only one product 28 was formed when 14 was allowed to undergo the intramolecular aldol condensation. The configuration of compound 28 was established by the application of the ^{1}H-n.m.r. (NOESY) which showed a crosepeak between H-3 and one of H-5 protons, indicating that it is *cis* to them. Examination of coupling constants between H-3 and H-4 protons leads to conclusion that, for all bicyclic β-lactams having a four-membered ring fused to the furanoid ring, the envelope E conformation should be assigned in which the out of plane C-4 carbon atom is located *endo* with respect to the β-lactam ring.



^{4}E



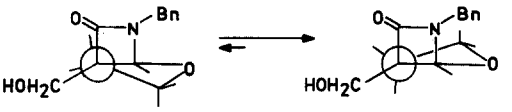
^{4}E



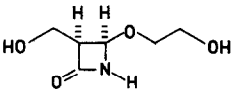
E_4

This conformation is free of synperiplanar interactions between substituents at C-2 and C-3 carbon atoms, which are present in the alternative E conformation having C-4 *exo* to the β-lactam ring (Scheme 2).

Scheme 2



The *N*-benzyl substituent can be easily removed from the β-lactam nitrogen atom by reduction with sodium in liquid ammonia. This was exemplified by the debenzylation of 15 leading to 30.



30

The presented methodology opens fully stereocontrolled access to the 1-oxa bicyclic β-lactams having desired configuration at the carbon atom connected to the nitrogen and oxygen atoms. Thus, owing to the stereospecificity of cycloaddition to D-glucal, D-galactal, L-arabinal, and D-xylal, azetidinones with the S-configuration at the C-4 carbon atom are formed, whereas from D-arabinal, L-xylal, and L-rhamnal, those of the alternative R-configuration are formed.

Finally, a new method for contraction of a six-membered pyranoid ring to a five-membered ring *via* intramolecular aldol condensation, shown herein, enables formation of a new β-lactam skeleton with unique structure and potential biological activity.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured with a Perkin-Elmer 141 spectropolarimeter. I.r. spectra were recorded with a Beckman 4240 spectrophotometer. ^{1}H-n.m.r. spectra were recorded with Bruker 300 MHz and Varian VXR 400 spectrometers. The coupling constants were measured directly from the spectra with the assumption that the first-order coupling approximation is valid. For compound 28 COSY and NOESY spectra were obtained. ^{13}C-n.m.r. spectra were recorded with Varian VXR 400 and Bruker AM 500 spectrometers. Column chromatography was performed on Merck Kieselgel 60 (230-400 mesh).

Compounds 2, 3, and 4 were obtained by the procedure described earlier.[3]

1,5-Anhydro-3,4,6-tri-*O*-benzyl-2-deoxy-D-lyxohex-1-enitol (tri-*O*-benzyl-D-galactal, 8). The crude tri-*O*-acetyl-D-galactal obtained from 60 g of D-galactose according to the known procedure was deacetylated with sodium methoxide in methanol. Subsequently solvent was evaporated, and the crude syrup was dissolved in DMSO (500 ml); 110 g of pulverized KOH was added followed by benzyl bromide (170 g) added dropwise at a temperature below 30°C. The reaction mixture was stirred overnight, poured into ice-water, and extracted with ethyl ether. The extract was dried, evaporated and purified on a silica gel column to give 53 g (38%) of crystalline 8; m.p. 52-53°C; $[\alpha]_D$ -38.0° (c 1, CH_2Cl_2); ^{1}H-n.m.r. ($CDCl_3$): 3.64(dd, 1H, J_{56}=5.1, $J_{66'}$=10.1 Hz, H-6), 3.78 (dd, 1H, $J_{56'}$=7.2 Hz, H-6'), 3.84 (ddd, 1H, J_{24}=1.4, J_{34}=4.0, J_{45}=2.6 Hz, H-4), 4.18 (m, 2H, H-3,5), 4.85 (ddd, 1H, J_{12}= 6.3, J_{23}=2.9 Hz, H-2), 6.36 (dd, 1H, J_{13}=1.7 Hz, H-1). Anal. Calcd for $C_{27}H_{28}O_4$: C, 77.86; H, 6.87. Found: C, 77.9; H, 7.0.

General procedure for *N*-benzylation of β-lactams 2, 3, and 4. To a solution of 5 mmol of β-lactam in pyridine (15 ml), chlorotrimethylsilane (3 ml) was added dropwise. After 1h, the mixture was poured into ice-water and extracted with hexane. The extract was washed, dried, evaporated, and dissolved in benzene (50 ml). To the benzene solution were added K_2CO_3 pulverized (10 g), tetrabutylammonium bromide (0.1 g), and benzyl chloride (3 ml). The mixture was stirred under reflux for 2 h, at which time the silylated β-lactam had disappeared (tlc). The reaction mixture was than filtered, evaporated, and extracted with hexane. The hexane solution was evaporated: the residue was dissolved in methanol (50 ml), and Dowex 50 Wx8 resin (0.5 g) was added. After shaking for 15 min, the resin was filtered off and the methanol evaporated. The crystalline residue was washed with hexane to remove benzyl chloride. *N*-Benzyl β-lactams 5, 6, and 7 were obtained in 70% yield.

N-Benzyl-2-carboxy-2-deoxy-α-D-arabinopentopyranosylaminolactam (5). Compound 5 was obtained according to the procedure described above. Spectral and analytical data of 5 were reported previously.[5] A sample of 9 obtained after evaporation of hexane solution (see above) was purified on a silica gel column (flash chromatography); syrup; $[\alpha]_D$ -65.5°C (c 1.5, CH_2Cl_2); i.r. ($CHCl_3$): 1750 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): 3.23(t, 1H, J_{12}=J_{23}=4.3 Hz, H-2), 3.48 (dd, 1H, J_{45}=3.8, $J_{55'}$=11.0 Hz, H-5), 3.66 (dd, 1H, $J_{45'}$=6.4 Hz, H-5'), 3.81 (ddd, 1H, J_{34}=2.9 Hz, H-4), 4.09 (dd, 1H, H-3), 4.26, 4.42 (2d, 2H, J=14.8 Hz, CH_2Ph), 5.14 (d, 1H, H-1). Anal. Calcd for $C_{19}H_{31}NO_4Si_2$: C, 57.98; H, 7.94; N, 3.56. Found: C, 57.8; H, 8.1; N, 3.3.

N-Benzyl-2-carboxy-2-deoxy-α-D-galactohexopyranosylaminolactam (6). Compound 6 was obtained according to the procedure described above. Spectral and analytical data of 6 were reported previously.[5]

N-Benzyl-2-carboxy-2-deoxy-α-D-glucohexopyranosylaminolactam (7). Compound 7 was obtained according to the procedure described above; m.p. 143-144°C; $[\alpha]_D$ +112.3°C (*c* 1, MeOH); i.r. (KBr): 1760 cm^{-1}; ^{1}H-n.m.r. (D_2O): 3.44(m, 1H, J_{12}=4.2 Hz, H-2), 3.45(m, 1H, H-5), 3.55 (t, 1H, J_{34}=7.0, J_{45}= 7.7 Hz, H-4), 3.57 (dd, 1H, J_{56}=2.7, $J_{66'}$=12.3 Hz, H-6), 3.68 (dd, 1H, $J_{56'}$=5.1 Hz, H-6), 4.06 (dd, 1H, J_{23}=3.1 Hz, H-3), 5.49 (d, 1H, H-1). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.20; H, 6.13; N, 5.01. Found: C, 60.2; H, 6.3; N, 4.8. A sample of 11 obtained after evaporation of hexane solution (see above) was purified on a silica gel column (flash chromatography); syrup; $[\alpha]_D$ +79.8° (*c* 1.2, CH_2Cl_2); i.r. ($CHCl_3$): 1750 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): 3.16 (dd, 1H, J_{12}=4.4, J_{23}=3.0 Hz, H-2), 3.35 (m, 1H, J_{45}=8.1, J_{56}=3.2, $J_{56'}$=4.7 Hz, H-5), 3.48 (dd, 1H, $J_{66'}$=11.1 Hz, H-6), 3.58 (dd, 1H, J_{34}=7.1 Hz, H-4), 3.63 (dd, 1H, H-6'), 4.04 (dd, 1H, H-3), 4.46, 4.33 (2d, 2H, J=14.1 Hz, CH_2Ph), 5.21 (d, 1H, H-1). Anal. Calcd for $C_{23}H_{41}NO_5Si_3$: C, 55.71; H, 8.33; N, 2.82. Found: C, 56.1; H, 8.5; N, 2.8.

3,4,6-Tri-*O*-benzyl-2-carboxy-2-deoxy-α-D-galactohexopyranosylaminolactam (10). Galactal 8 (6.24 g, 15 mmol) was dissolved in dry acetonitrile (20 ml) and trichloroacetyl isocynate (3.6 ml, 30 mmol) was added dropwise at 16°C. The mixture was left for 2 h at 16°C to complete the cycloaddition, the time of reaction being determined by conducting a pilot experiment in a ^{1}H-n.m.r. tube.[23] Subsequently, the mixture was cooled to -30°C, benzylamine (5.6 ml, 48 mmol) in acetonitrile (5 ml) was added, and the temperature was allowed to rise to room temperature. The solvent was then evaporated, and the residue was treated with hexane. The crystalline precipitate was removed by filtration and washed with hexane. The filtrate and washings were combined and evaporated. The oily residue was purified on a column of silica gel by flash chromatography to give 10 (4.5 g, 65%); m.p. 71.5-72.5°C; $[\alpha]_D$ +16.8° (*c* 1, CH_2Cl_2); ^{1}H-n.m.r. ($CDCl_3$): 3.38 (ddd, 1H, J_{12}=4.6, J_{23}=5.9 Hz, H-2), 3.44 (dd, 1H, J_{56}=6.6, $J_{66'}$=9.4 Hz, H-6), 3.53 (dd, 1H, $J_{56'}$=6.1 Hz, H-6'), 3.83 (dd, 1H, J_{34}=3.0, J_{45}=0.9 Hz, H-4), 3.87 (dt, 1H, H-5), 3.89 (dd, 1H, H-3), 5.53 (d, 1H, H-1). Anal. Calcd for $C_{28}H_{29}NO_5$: C, 73.18; H, 6.39; N, 3.05. Found: C, 73.5; H, 6.6; N, 3.1.

N-Benzyl-3,4,6-tri-*O*-benzyl-2-carboxy-2-deoxy-α-D-galactohexopyranosylaminolactam (12). β-Lactam 10 (0.46 g, 1 mmol) in toluene (10 ml) was treated with benzyl chloride (0.3 ml, 4.3 mmol), K_2CO_3 (1 g) and tetrabutylammonium bromide (0.05 g). The mixture was stirred under reflux for 3 h, filtered, and evaporated. The residue was purified on a silica gel column to give 12 (0.28 g, 51%); m.p. 89-91°C; $[\alpha]_D$ +21.5° (*c* 1, CH_2Cl_2); ^{1}H-n.m.r. ($CDCl_3$): 3.35 (bt, 1H, J_{12}=4.5, J_{23}=5.7 Hz, H-2), 3.40 (dd, 1H, J_{56}=5.6, $J_{66'}$=9.2 Hz, H-6), 3.47 (dd, 1H, $J_{56'}$=7.4 Hz, H-6'), 3.64 (dd, 1H, H-5), 3.82-3.87 (m, 2H, H-3,4), 5.29 (d, 1H, H-1). Anal. Calcd for $C_{35}H_{35}NO_5$: C, 76.47; H, 6.42; N, 2.55. Found: C, 76.5; H, 6.3; N, 2.8.

N-Benzyl-2-carboxy-2-deoxy-α-D-galactohexopyranosylaminolactam (6). Compound 12 (0.2 g, 0.36 mmol) in methanol-ethyl acetate (4:1 v/v; 10 ml) was shaken at room temperature in the presence of 10% Pd/C under hydrogen (3 atm) for 4 h. Subsequently solvents were evaporated to afford 6 (0.096 g, 96%).

(3S, 4R) *N*-Benzyl-3-hydroxymethyl-4-(hydroxyethoxy)-azetidinone-2 (15). To a solution of 5 (1.0 g, 4 mmol) in methanol-water (1:1 v/v; 60 ml), ammonium sulfate (1.6 g) dissloved in water (10 ml) was added. The mixture was cooled to -5°C and sodium metaperiodate (0.9 g, 4.2 mmol) in water (10 ml) was added. The stirring and cooling were maintained for 15 min. Subsequently sodium borohydride (0.3 g) in water (5 ml) was added. The precipitate of sodium iodate was removed by filtration, methanol was evaporated, and ammonium sulfate (5 g) was added. The solution was extracted with ethyl acetate (6x10 ml). The extract was dried, evaporated, and purified on a silica gel column to give 15 (0.82 g, 82%); syrup; $[\alpha]_D$ +52.4°C (*c* 1.7 $CHCl_3$); i.r. ($CHCl_3$): 3400, 1755 cm^{-1}; ^{1}H-n.m.r. (CD_3CN): 4.95 (d, 1H, J_{34}=3.8 Hz, H-4). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.3; H, 6.7; N, 5.4. Compound 15 was characterized on the basic of analytical and spectral data of its diacetate 16 which were reported previously.[5]

N-Benzyl-2-carboxy-2-deoxy-2-hydroxymethyl-α-L-erythro and β-D-threotetrofuranosyaminolactam and(3R, 4R) *N*-benzyl-3-hydroxymethyl-4-(hydroxyethoxy)-azetidinone-2 (23, 25, and 19). To a solution of 5 (0.75 g, 3 mmol) in methanol (20 ml) and water (15 ml), saturated aqueous sodium hydrogencarbonate (15 ml) was added. The mixture was cooled to -5°C; sodium metaperiodate (0.673 g, 5.15 mmol) in water (7 ml) was added, and the temperature was allowed to rise to 16°C. After 30 min, sodium borohydride (0.23 g) was added, and after another 5 min, ammonium sulfate (5 g) was added. The mixture was concentrated to 30 ml and extracted with ethyl acetate (6x20 ml). The extract was dried, evaporated, and separated on a silica gel column (ethyl ether-methanol 9:1) to give the following fractions:

23 (0.19 g, 25%); m.p. 175-176°C; $[\alpha]_D$ -68.0° (*c* 1, MeOH); ^{1}H-n.m.r. (DMSO-d_6): 3.60 (m, 2H, H-4, CH_AH_BOH), 3.94 (d, 1H, J_{AB}=11.6 Hz, CH_AH_BOH), 4.12 (m, 2H, H-3,4'), 4.30, 4.52 (2d, 2H, J=15.7, CH_2Ph), 5.36 (s, 1H, H-1). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 62.6; H, 6.1; N, 5.6. ^{1}H-n.m.r. data of diacetate 24 (Ref. 5) ($CDCl_3$): 3.85 (t, 1H, J_{34}=8.6, $J_{4'}$=9.6 Hz, H-4), 4.43 (dd, 1H, $J_{34'}$=7.3 Hz, H-4'), 4.13, 4.69 (2d, 2H, J=15.2 Hz, CH_2Ph), 4.34, 4.56 (2d, 2H, J=12.2 Hz, CH_2OAc), 5.04 (dd, 1H, H-3), 5.25 (s, 1H, H-1).

25 (0.65 g, 8.7%); m.p. 89-91°C; $[\alpha]_D$ -51.5° (*c* 1, MeOH); ^{1}H-n.m.r. (DMSO-d_6): 3.83, 3.89 (2d, 2H, J=11.8 Hz, CH_2OH), 3.93 (dd, 1H, J_{34}=2.9, $J_{4'}$=11.0 Hz, H-4), 3.99 (d, 1H, H-4'), 4.20, 4.38 (2d, 2H, J=15.8 Hz, CH_2Ph), 4.22 (bs, 1H, H-3), 5.53 (s, 1H, H-1). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.06; N, 5.62. Found: C, 61.9; H, 6.2; N, 5.5. ^{1}H-n.m.r. data of diacetate 26 (ref. 5) ($CDCl_3$): 4.06, 4.64 (2d, 2H, J=15.2 Hz, CH_2Ph), 4.16 (m, 2H, H-4,4'), 4.41, 4.48 (2d, 2H, J=11.8 Hz, CH_2OAc), 5.44 (m, 2H, H-1,3).

19 (0.28 g, 38%), syrup; $[\alpha]_D$ +25.3° (*c* 0.5, CH_2Cl_2); i.r. (film): 3400, 1750 cm^{-1}; ^{1}H-n.m.r. ($CDCl_3$): 3.25 (bt, 1H, H-3), 3.4-3.6 (m, 4H, CH_2CH_2OH), 3.83 (dd, 1H, J_{3A}=5.6, J_{AB}=11.9 Hz, CH_AH_BOH), 3.87 (dd, 1H, J_{3B}=4.4 Hz, CH_AH_BOH), 4.23, 4.60 (2d, 2H, J=15.4 Hz, CH_2Ph), 4.92 (d, 1H, J_{34}=1.1 Hz, H-4). Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.3; H, 6.9; N, 5.3. The analytical and spectral data of diacetate 20 were reported previously.[5]

N-Benzyl-2-carboxy-2-deoxy-2-hydroxymethyl-α-L-erythro and β-D-threotetrofuranosylaminolactam (23 and 25). To a solution of 5 (0.25 g, 1 mmol) in methanol (7 ml) and water (5 ml), saturated aqueous sodium hydrogen carbonate (5 ml) was added. The mixture was cooled to -5°C, and sodium metaperiodate (0.235 g, 1.1 mmol) in water (2 ml) was added. Subsequently, the temperature was allowed to rise to 18°C, and the mixture was left for 18 h. Sodium borohydride (0.076 g, 2 mmol) was then added; sodium iodate was filtered off; ammonium sulfate (2 g) was added, and methanol evaporated. The mixture was extracted, the extract was dried, evaporated, and separated on a silica gel column to give 23 (0.1 g, 40%) and 25 (0.11 g, 45%).

(3R, 4S) *N*-Benzyl-3-hydroxymethyl-4-(1',3'-dihydroxyizopropoxy)-azetidinone-2 (17). Compound 17 was obtained from 6 in 78% yield according to the procedure described for 15; m.p. 76-78°C; $[\alpha]_D$ -33.0° (c 1, MeOH); i.r. ($CHCl_3$): 3400, 1760 cm^{-1}; ^{1}H-n.m.r. (DMSO-d_6): 3.3-3.6 [m, 6H, H-3, $CH(CH_2OH)_2$], 3.71 (dd, 1H, J_{3A}=4.1, J_{AB}=11.5 Hz, CH_AH_BOH), 3.86 (dd, 1H, J_{3B}=9.0 Hz, CH_AH_BOH), 4.31, 4.53 (2d, 2H, J=15.5 Hz, CH_2Ph), 5.23 (d, 1H, J =3.7 Hz, H-4). Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.5; H, 6.9; N, 4.7. Analytical and spetral data of triacetate 18 were reported previously. [5]

Compound 17 can be obtained from 7 in 88% yield according to the procedure described for 15, but 2 molar equivalents of sodium metaperiodate must be used.

(3S, 4S) *N*-Benzyl-3-hydroxymethyl-4-(1',3'-dihydroxyizopropoxy)-azetidinone-2. (21). A solution of compounds 6 (0.28 g, 1 mmol) in methanol (2 ml) and water (4 ml) was cooled to -5°C and treated with sodium metaperiodate (0.24 g, 1.12 mmol) in water (2 ml). After 15 min, saturated aqueous sodium hydrogencarbonate (4 ml) was added, and the mixture was left at 0°C for an additional 15 min. Subsequently, sodium borohydride (0.1 g) was added, and after 10 min, ammonium sulfate (4 g) was added. Methanol was evaporated, and the mixture was extracted with ethyl acetate. The extract was dried and evaporated. The crude mixture (0.26 g) was purified on a silica gel column to give 21 (0.081 g, 29%); syrup; $[\alpha]_D$ -45.3° (c 0.6, MeOH). Triacetate 22; $[\alpha]_D$ -30.0° (c 1, CH_2Cl_2); ^{1}H-n.m.r. ($CDCl_3$): 3.32 (m, 1H, H-3), 3.76 (m, 1H, H-2'), 4.00, 4.19 (2dd, 2H, H_A,H_B-1',1'), 4.06, 4.10 (2dd, 2H, H-$3'_A$,$3'_B$), 4.28 (dd, 1H, J_{3A}=5.4, J_{AB}=12.1 Hz, CH_AH_BOAc), 4.42 (dd, 1H, J_{3A}=1.1 Hz, H-4). Anal. Calcd for $C_{20}H_{25}NO_8$: C, 58.96; H, 6.18; N, 3.43. Found: C, 58.4; H, 6.4; N, 3.7.

N-Benzyl-2-carboxy-2-deoxy-2-hydroxymethyl-α-D-ribopentofuranosylaminolactam (28). To a solution of 6 (0.28 g, 1 mmol) in methanol (2 ml) and water (4 ml), saturated aqueous sodium hydrogencarbonate (2 ml) and sodium metaperiodate (0.25 g, 1.2 mmol) in water (2 ml) were added. The mixture was left at room temperature for 3 days. Subsequently, sodium borohydride (0.1 g) was added. The mixture was saturated with ammonium sulfate and extracted with ethyl acetate. The extract was dried and evaporated to afford 28 (0.24 g, 86%); m.p. 148-149°C; $[\alpha]_D$ +75.0° (c 1, MeOH); ^{1}H-n.m.r. (D_2O): 3.66 (dd, 1H, J_{45}=4.5, $J_{5'5''}$=12.9 Hz, H-5), 3.77 (dd, 1H, $J_{45''}$=2.4 Hz, H-5'), 3.79, 4.03 (2d, 2H, J=12.3 Hz, CH_2OH), 3.85 (ddd, 1H, H-4), 3.97 (d, 1H, J_{34}=8.6 Hz, H-3), 4.43, 4.50 (2d, 2H, J=15.3Hz, CH_2Ph), 5.45 (s, 1H, H-1); ^{13}C-n.m.r. (D_2O): 4.22 (CH_2Ph), 58.37 (CH_2OH), 60.21 (C-5), 70.70 (C-3), 71.67 (C-2), 82.58 (C-4), 88.28 (C-1), 128.89, 129.16, 129.81, 136.20 (Ph), 169.20 (C=O) assignments proved by HETCOR spectrum. Anal. Calcd for $C_{14}H_{18}NO_5$: C, 60.20; H, 6.13; N, 5.01. Found C, 60.2; H, 6.0; N, 4.8.

Aldol condensation product 27 can be isolated from the reaction mixture before sodium borohydride is added (82%); m.p. 110-115°C. Reduction of 27 with sodium borohydride in methanol-water (1:1 v/v followed by extraction with ethyl acetate affords 28 (73%).

Acetate 29; syrup; $[\alpha]_D$ +80.6° (c 1, CH_2Cl_2); ^{1}H-n.m.r. ($CDCl_3$): 4.06 (dd, 1H, J_{45}=4.3, $J_{5'5''}$= 12.2 Hz, H-5), 4.10, 4.61 (2d, 2H, J=15.3 Hz, CH_2Ph), 4.2-4.4 (m, 2H, H-4,5'), 4.31, 4.49 (2d, 2H, J=12.2 Hz, CH_2OAc), 4.91 (d, 1H, J_{34}=7.9 Hz, H-3), 5.21 (s, 1H, H-1). Anal. Calcd for $C_{20}H_{23}NO_8$: C, 59.25; H, 5.72; N, 3.45. Found: C, 59.7; H, 5.9; N, 3.6.

(3S, 4R) 4-(Hydroxyethoxy)-3-hydroxymethoxyazetidinone-2 (30). To a solution of compound 15 (4.0 g, 16 mmol) in liquid ammonia (50 ml), sodium was added in portions until a dark blue color was firmly established. Subsequently, ammonium chloride (2 g) was added, and ammonia was evaporated. The residue was extracted with methanol, the extract was evaporated and purified on a silica gel using ethyl acetate-methanol (4:1 v/v) as an eluant to afford 30 (2.0 g, 78%); m.p. 83-85°C; $[\alpha]_D$ +42.7° (c 1, MeOH); ^{1}H-n.m.r. (D_2O): 3.63 (dt, 1H, J_{34}=4.0, J_{3A}=3.9, J_{3B}=7.3 Hz, H-3), 3.7-3.9 (m, 4H, CH_2CH_2OH), 3,95 (dd, 1H, J_{AB}=12.1 Hz, CH_AH_BOH), 4.02 (dd, 1H, CH_AH_BOH), 5.33 (d, 1H, H-4); ^{13}C-n.m.r. (D_2O): 57.78 (C-3), 58.36 (C-2'), 62.41 (CH_AH_BOH), 72.30 (C-1'), 82.66 (C-4), 173.40 (C=O). Anal. Calcd for $C_6H_{11}NO_4$: C, 44.72; H, 6.88; N, 8.69. Found: C, 44.5; H, 6.8; N, 8.7.

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