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Total Synthesis of 1,5-Dideoxy-1,5-iminoalditols

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Abstract: *Enantiomerically pure 1,5-dideoxy-1,5-imino-D-glycero-D-allo-heptitol (**10**) has been synthesized in ca. 9% overall yield by utilizing 2,3-O-isopropylidene-D-glyceraldehyde-N-benzylimine (**1**) as a chiral source and 2-(trimethylsiloxy)furan (**2**) as a homologative reactant. The opening move was the preparation of properly protected seven-carbon butenolide **4**, followed by diastereoselective anti,cis-dihydroxylation of the lactone double bond and furanose-to-azapyranose ring expansion. This generated a piperidine intermediate **7**, the stereochemistry of which was secured by a single crystal X-ray analysis of its diacetate **9**.*

INTRODUCTION

The inhibition of glycosidases by iminoalditols, including monocyclic and bicyclic polyhydroxylated piperidine and pyrrolidine derivatives, is a general phenomenon whose mechanism and characteristics have been the subject of profound investigations.[1] As a consequence of the wide spectrum of biological

activity and promising therapeutic application associated with several of these compounds,[2] quite a number of synthetic routes to them have been exploited.[3] As part of a program directed at developing the utility of enantiomerically pure γ-substituted α,β-unsaturated γ-lactones as synthetic matrices,[4] we outline here a concise entry to polyhydroxylated piperidines, choosing 1,5-dideoxy-1,5-imino-D-*glycero*-D-*allo*-heptitol (**10**) as target for this study.

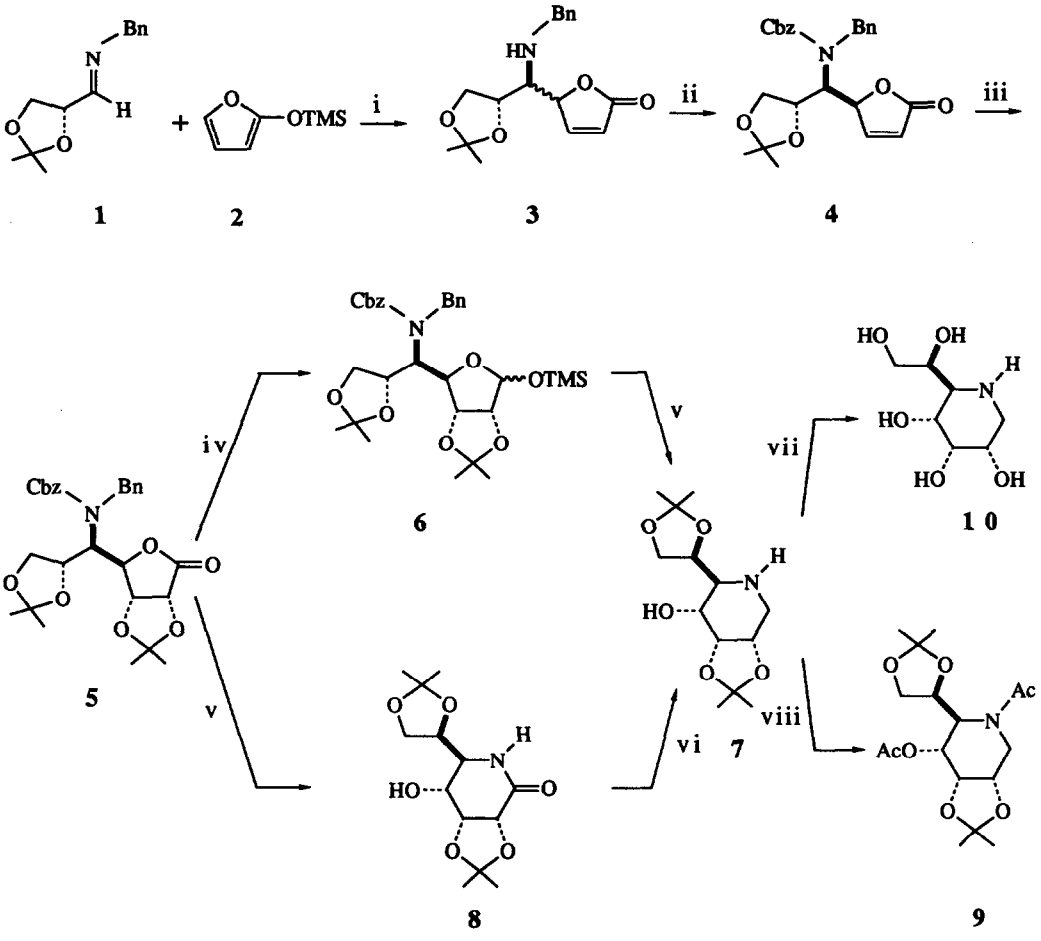
RESULTS AND DISCUSSION

***Synthesis of iminoalditol* 10.** Compound **10** containing five stereocentres, was synthesized from **1** and **2** via the reaction steps outlined in Chart I, exploiting the single chiral element in the precursor glyceraldehyde imine **1**. Our target called for D-*ribo* configurated butenolide **4** as the homochiral matrix. Four-carbon homologation of imine **1** with 2-(trimethylsiloxy)furan (**2**) in CH_2Cl_2 in the presence of BF_3 etherate resulted in formation of butenolide **3** (66%). This was isolated as a 1:1 mixture of two epimers at C-4, whose individual components could not be separated owing to rapid equilibration.[5] Mixture **3** was smoothly converted into N,N-diprotected butenolide **4** by reaction with benzyloxycarbonyl chloride under usual Schotten-Baumann conditions. Although the intermediate **3** was isolated as a mixture of isomers, the Cbz-protected butenolide **4** was isolated as the D-*ribo* stereoisomer only (68%). Presumably, the formation of **4** was controlled by thermodynamics of base-catalyzed lactone equilibration, strongly favoring, in this instance, D-*ribo* isomer.

Following our precedents for related molecules,[4] butenolide **4** was selectively hydroxylated at C-2 and C-3 by using $KMnO_4$ under solid-liquid phase-transfer conditions. There was obtained, after protection (DMP, TsOH), D-*glycero*-D-*allo*-heptono-1,4-lactone **5** as a homogeneous material (50%) with no trace of other stereoisomers. Reduction of **5** using DIBAL-H in CH_2Cl_2 at -90°C followed by silylation (TMSCl, pyridine) gave the protected lactol **6** as a mixture of anomers (57%), which was subjected to hydrogenolytic removal [$Pd(OH)_2$, methanol] of the two nitrogen substituents. This furnished piperidine **7** (80%) as a result of clean five-to-six membered ring expansion, incorporating the nitrogen at C-5.[6]

In parallel with this protocol we also examined an alternative path. Hydrogenolytic cleavage of the protective groups at C-5 nitrogen of **5** using $Pd(OH)_2$ in methanol gave the δ-lactam **8** (74%) which was then reduced to **7** in excellent yield (88%) with the $BH_3.Me_2S$ complex in CH_2Cl_2.

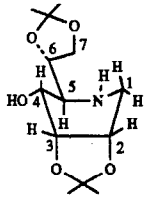
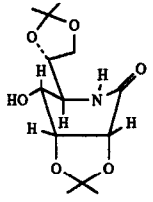
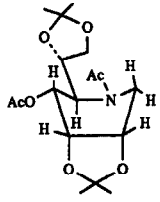
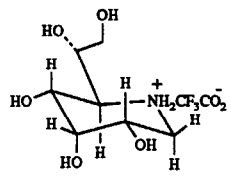
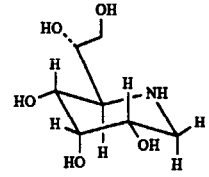
Chart I



Conditions: i, $BF_3.OEt_2$, CH_2Cl_2, -85°C; ii, Cbz-Cl, 7% aq. $NaHCO_3$, dioxane, r.t.; iii, $KMnO_4$, DCH-18-crown-6, CH_2Cl_2, r.t., then DMP, TsOH, r.t.; iv, DIBALH, CH_2Cl_2, -85°C, then TMS-Cl, pyridine, r.t.; v, H_2, $Pd(OH)_2$, MeOH, r.t.; vi, $BH_3.Me_2S$, THF, r.t.; vii, 60% aq. CF_3CO_2H, then DOWEX 1x8 (OH- form); viii, Ac_2O, DMAP, pyridine, r.t.

Assignment of the stereochemistry of the seven-carbon piperidine **7** followed from its ^1H NMR spectrum and was fully authenticated by an X-ray crystallographic study performed on its diacetate **9** (see above). Finally, the two acetonide groups in **7** were removed by aqueous trifluoroacetic acid treatment giving, after DOWEX 1x8

Table I. Characteristic ^{1}H NMR Data for Piperidine Derivatives [δ(ppm), multiplicity (J in Hz)][a]

Compd / Proton	 **7**	 **8**	 **9**	 **10**.CF_3CO_2H	 **10**
H-1$_{ax}$	2.88,dd(13.2, 5.1)		3.03,dd(14.9, 1.0)	3.07,t(12.0)	2.62,t(11.7)
H-1$_{eq}$	2.63,dd(13.2, 6.0)		2.82,dd(14.9, 1.6)	3.25,ddd(12.0, 4.8, 0.6)	2.80,dd(11.7, 4.8)
H-2	4.21,q(5.6)	4.47,d(6.6)	3.54,dt(7.8, 1.4)	4.01,ddd(12.0, 4.8, 2.1)	3.63,ddd(11.7, 4.8, 2.7)
H-3	4.48,dd(6.0, 3.6)	4.60,dd(6.6, 2.7)	4.63,dd(7.8, 2.2)	4.15,td(2.4, 0.6)	4.03,t(2.7)
H-4	3.71,dd(9.3, 3.6)	3.82,dd(9.0, 2.8)	5.54,dd(10.0, 2.5)	3.96,dd(11.1, 2.4)	3.57,dd(10.5, 2.7)
H-5	2.90,dd(9.6, 6.9)	3.84,dd(9.0, 3.1)	4.98,dd(10.0, 1.4)	3.47,dd(11.1, 3.6)	2.82,dd(10.5, 3.6)
H-6	4.23,ddd(6.9, 6.3, 3.3)	4.01,ddd(6.6, 6.0, 3.1)	4.55,ddd(8.0, 5.3, 1.4)	4.10,dt(5.1, 3.4)	3.88,dt(6.9, 3.9)
H-7a	4.13,dd(8.4, 6.3)	4.13,dd(8.4, 6.6)	3.65,dd(8.7, 7.9)	3.80,dd(10.0, 3.4)	3.70,dd(10.0, 3.6)
H-7b	3.97,dd(8.4, 3.3)	3.88,dd(8.4, 6.0)	3.85,dd(8.7, 5.4)	3.88,dd(10.0, 5.4)	3.64,dd(10.0, 7.2)

[a] At 300 MHz, 25 ± 1°C. Solvents: **7** and **8**, $CDCl_3$ (TMS=0), **9**, C_6D_6 (TMS=0); **10**.CF_3CO_2H and **10**, D_2O (DOH=4.75)

(OH^- form) chromatography and lyophilization, pure free base **10** (85%) as a white powder.

NMR and X-ray Structural Analyses. Owing to the restricted rotational behaviour of the N-Cbz linkage, the ^1H NMR spectra of the lactone intermediates **4**, **5**, and **6** showed extensive signal broadening even at high temperature; and this precluded conclusive structural analyses. Conversely, a combination of NMR methods made it possible to establish the configuration of all piperidine derivatives in this study. Gross structures were determined on the basis of ^1H and ^{13}C NMR data, including two dimensional ^1H-^1H (COSY) and ^1H-^{13}C heteronuclear (HETCOR) correlation spectra. Characteristics ^1H NMR parameters for the bicyclic intermediates **7**, **8**, and **9** and for the free base **10** and its trifluoroacetate salt are given in Table I.

For the intermediates **7**, **8**, and **9**, all having a 5-membered acetonide ring cis-fused to the C-2 and C-3 carbons of the piperidine ring, a boat-like conformation ($^{1,4}B$ form) seemed to be plausible, in solution at ambient temperature. In particular, in **7** and **9** the small coupling constants between H-2 and the methylene protons at C-1, associated with a $J_{4,5}$ of ca. 10 Hz and positive NOE's between H-1_{ax} and H-4 in a flag-pole position (ca. 3%) provided a firm support to these assignements. The stereoconfigurations of deoxyazapyranose **10** and its iminium salt ($^4C_1$ forms) was deduced based on the large coupling constants between H-1_{ax} and H-2 (J = ca. 12 Hz) and between H-4 and H-5 (J = ca. 11 Hz) and was corroborated by definite NOE's between axially disposed H-2 and H-4 (ca. 4%) and between H-1_{ax} and H-5 (ca. 6%). In addition, the presence of a W coupling constant (^4J = 0.6 Hz) between H-1_{eq} and H-3 in the salt of **10** provided a further configurational support.

Analysis by single-crystal X-ray diffraction confirmed the stereostructure of the diacetate **9**. An ORTEP plot is displayed in Figure 1 and final atomic parameters are given in Table 2. The compound possesses 2S,3S,4S,5R,6S absolute configuration corresponding to the D-*allo* nature of the azasugar. In fact, since the configuration of C(6) corresponds to the unalterated chiral atom of the starting glyceraldehyde imine, it can be deduced the absolute configuration of the other stereocenters.

The piperidine ring is in the boat conformation ($^{1,4}B$ form), probably due to the presence of a five-membered acetonide ring cis-fused to the C(2) and C(3) carbons of the six-membered ring [puckering parameters : q_2 = 0.731(5) Å, q_3 = 0.003(5) Å, Φ_2 = -128.7(4)°, Q = 0.731(5) Å, Θ_2 = 89.8(4)°].[8] In contrast, the unprotected nojirimycin[9] and simple piperidine derivatives[10] show normal chair conformations.

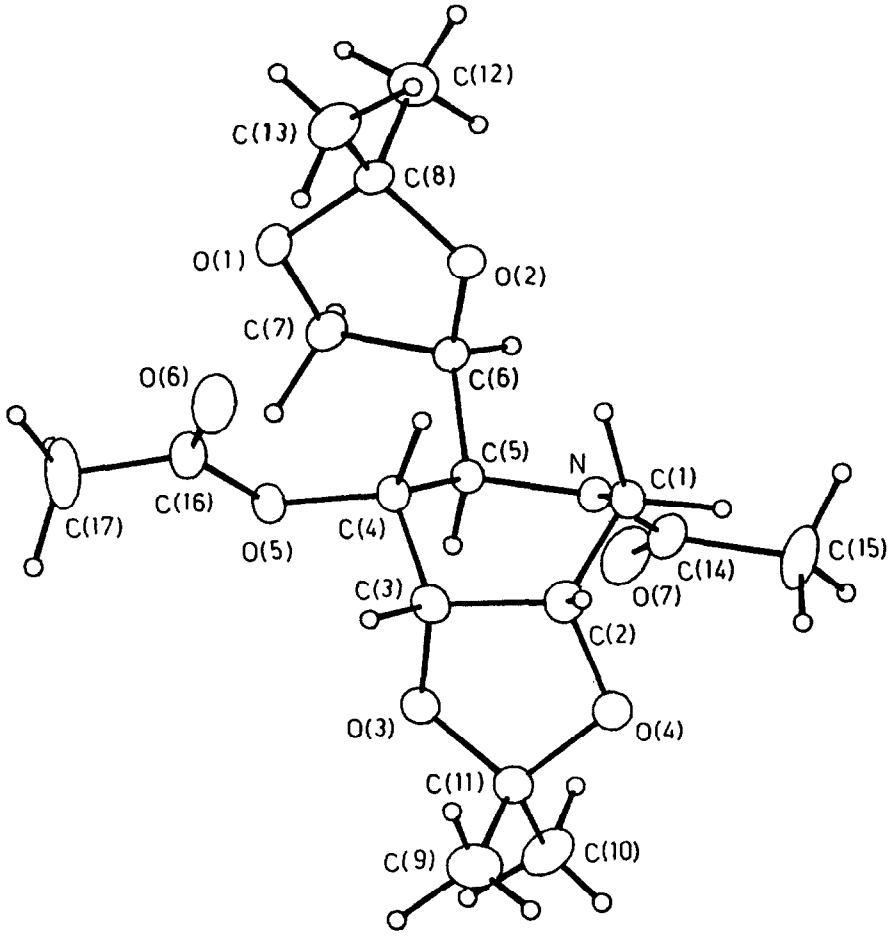


Figure 1. ORTEP view of **9** with thermal ellipsoids at 20% probability. The hydrogen atoms are drawn with an arbitrary diameter. The molecule is shown in its correct absolute configuration.

Both 6,7- and 2,3-dioxolane rings show a conformation closest to twist with a twofold axis passing through the C(6) and C(2) atoms respectively [puckering parameters are q_2 = 0.335(7) Å, φ_2 = 88.3(1.0)° and q_2 = 0.293(6) Å, φ_2 = -55.1(1.2)°

respectively].[8,11] The dihedral angles between the 6,7-dioxolane ring and the mean planes of the piperidine and of the fused 2,3-dioxolane ring are 78.9(2)° and 168.4(2)° respectively. The piperidine and the cis-fused acetonide ring are twisted about their common bond such that the torsion angles O(3)-C(3)-C(2)-O(4) and C(4)-C(3)-C(2)-C(1) are -8.8(6)° and -9.1(7)° respectively and the O(3)-C(3)-C(2)-C(1) and C(4)-C(3)-C(2)-O(4) torsion angles are 108.7(5)° and -126.6(5)°. The dihedral angle between the mean planes of the two rings is 89.9(2)°.

The two acetate substituents are in the equatorial position [torsion angles : O(5)-C(4)-C(3)-C(2) = 177.2(5)°, O(5)-C(4)-C(5)-N = -166.6(4)° and C(14)-N-C(5)-C(4) = 151.1(4)°; C(5)-N-C(14)-C(15) = -179.2(5)°. respectively]. The O-C bond distances (Table 3) in the dioxolane rings are to each other comparable (except the shorter C(11)-O(3) = 1.408(8)Å) as found from Bruce *et alii*,[12] while for the dioxolane rings fused to a furanose moiety an asymmetry in O-C bonds is observed.[13,14]

Table 2. Atomic fractional co-ordinates for compound **9**

	x/*a*	y/*b*	z/*c*
N	0.4287(0)	0.4225(0)	0.5150(0)
O(1)	0.3651(7)	0.8069(4)	0.2448(8)
O(2)	0.4418(7)	0.7002(5)	0.5593(8)
O(3)	0.0973(7)	0.2929(4)	0.1210(8)
O(4)	0.1784(7)	0.1976(4)	0.4517(9)
O(5)	0.0982(6)	0.5525(4)	0.0861(8)
O(6)	-0.0866(8)	0.6559(6)	0.2575(10)
O(7)	0.6416(7)	0.3695(5)	0.3259(11)
C(1)	0.3094(8)	0.3920(5)	0.6731(9)
C(2)	0.1399(8)	0.3181(6)	0.5330(10)
C(3)	0.0665(7)	0.3776(5)	0.3076(10)
C(4)	0.1664(7)	0.5040(5)	0.3055(9)
C(5)	0.3663(7)	0.4988(5)	0.3242(9)
C(6)	0.4818(7)	0.6270(5)	0.3670(10)
C(7)	0.4537(8)	0.7087(5)	0.1630(10)
C(8)	0.4280(10)	0.8234(6)	0.4971(11)
C(9)	0.2849(14)	0.8777(8)	0.6000(14)
C(10)	0.6071(14)	0.9026(8)	0.5659(18)
C(11)	0.1013(9)	0.1745(6)	0.2038(11)
C(12)	0.2252(14)	0.1068(7)	0.0831(15)
C(13)	-0.0914(12)	0.1052(8)	0.1633(17)
C(14)	0.5688(8)	0.3599(6)	0.4964(12)
C(15)	0.6322(10)	0.2793(8)	0.6923(17)
C(16)	-0.0297(7)	0.6270(6)	0.0864(11)
C(17)	-0.0910(11)	0.6687(10)	-0.1508(14)

Table 3. Bond distances (Å) and angles(°) for compound **9** with e.s.d.'s in parentheses.

N-C(1)	1.463(6)	N-C(5)	1.472(5)
N-C(14)	1.359(7)	O(1)-C(7)	1.429(8)
O(1)-C(8)	1.439(8)	O(2)-C(6)	1.426(8)
O(2)-C(8)	1.421(8)	O(3)-C(3)	1.440(8)
O(3)-C(11)	1.408(8)	O(4)-C(2)	1.436(8)
O(4)-C(11)	1.433(8)	O(5)-C(4)	1.442(7)
O(5)-C(16)	1.345(8)	O(6)-C(16)	1.202(9)
O(7)-C(14)	1.244(10)	C(1)-C(2)	1.500(8)
C(2)-C(3)	1.540(8)	C(3)-C(4)	1.500(8)
C(4)-C(5)	1.535(8)	C(5)-C(6)	1.540(7)
C(6)-C(7)	1.532(8)	C(8)-C(9)	1.513(13)
C(8)-C(10)	1.507(12)	C(11)-C(12)	1.517(13)
C(11)-C(13)	1.557(11)	C(14)-C(15)	1.527(12)
C(16)-C(17)	1.488(11)		
C(5)-N-C(14)	117.2(4)	C(1)-N-C(14)	123.1(4)
C(1)-N-C(5)	117.6(3)	C(7)-O(1)-C(8)	105.2(5)
C(6)-O(2)-C(8)	108.6(5)	C(3)-O(3)-C(11)	107.3(5)
C(2)-O(4)-C(11)	107.6(5)	C(4)-O(5)-C(16)	116.7(5)
N-C(1)-C(2)	109.4(4)	O(4)-C(2)-C(1)	108.5(5)
C(1)-C(2)-C(3)	111.6(5)	O(4)-C(2)-C(3)	105.2(5)
O(3)-C(3)-C(2)	103.6(5)	C(2)-C(3)-C(4)	111.5(5)
O(3)-C(3)-C(4)	109.6(5)	O(5)-C(4)-C(3)	109.1(4)
C(3)-C(4)-C(5)	112.1(5)	O(5)-C(4)-C(5)	107.6(4)
N-C(5)-C(4)	108.2(4)	C(4)-C(5)-C(6)	114.8(4)
N-C(5)-C(6)	109.9(4)	O(2)-C(6)-C(5)	109.8(5)
C(5)-C(6)-C(7)	115.9(5)	O(2)-C(6)-C(7)	104.4(5)
O(1)-C(7)-C(6)	104.3(5)	O(1)-C(8)-O(2)	104.1(5)
O(2)-C(8)-C(10)	110.6(6)	O(2)-C(8)-C(9)	110.1(6)
O(1)-C(8)-C(10)	111.0(6)	O(1)-C(8)-C(9)	106.9(6)
C(9)-C(8)-C(10)	113.6(6)	O(3)-C(11)-O(4)	105.7(5)
O(4)-C(11)-C(13)	110.0(6)	O(4)-C(11)-C(12)	108.9(6)
O(3)-C(11)-C(13)	110.1(6)	O(3)-C(11)-C(12)	107.3(6)
C(12)-C(11)-C(13)	114.5(6)	N-C(14)-O(7)	120.5(6)
O(7)-C(14)-C(15)	122.1(6)	N-C(14)-C(15)	117.3(6)
O(5)-C(16)-O(6)	123.9(6)	O(6)-C(16)-C(17)	124.6(7)
O(5)-C(16)-C(17)	111.5(6)		

Bond lenghts and angles in the piperidine ring (Table 3) are in good agreement with the values reported for similar moieties.[10] Noteworthy is the very short distance $H(1)_{ax}\cdots H(4)$ in the piperidine ring (2.05 Å) with the torsion angles C(5)-N-C(1)-H(1)= -59.5° and H(4)-C(4)-C(5)-N= 64.8°. As expected, the arrangement of H(4) and H(5) atoms is trans diaxial with a torsion angle H(4)-C(4)-C(5)-H(5) of 171.9°. The packing is mainly governed by C(3)-H(3)···O(7) (x-1,y,z) intermolecular contacts of 3.30(1) Å with the C-H···O angle of 160.4°. The short distance can be considered a C-H···O "hydrogen bond", being supported from parameters d = 0.45 Å and θ = 26°.[15] So chains of molecules run along the crystallographic *a* axis. In each chain the methyl groups of isopropylidene moieties face those of the adjacent chain with normal van der Waals contacts (Figure 2).

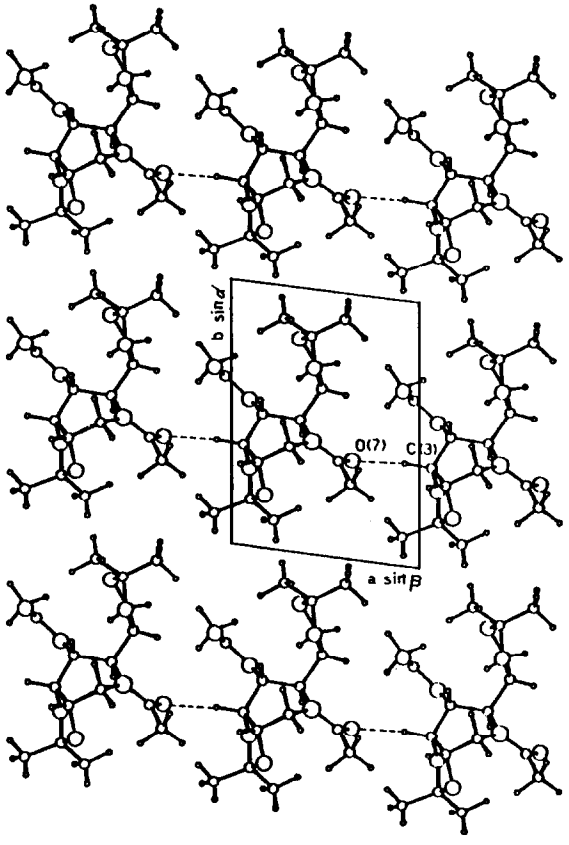


Figure 2. Molecular packing projected along [001] for compound **9**.

CONCLUSION

Homochiral γ-substituted butenolides are clearly valuable synthetic intermediates for the synthesis of complex monosaccharide structures. Here, homogeneous butenolide **4** allowed preparation of substantial amount of a novel azasugar, namely the seven-carbon homologue of 1-deoxyallonojirimycin **10**. Starting with simple precursors **1** and **2**, employing six clean and selective reactions, pure free base **10** was synthesized in a gratifying 9% overall yield. The synthetic result described here augurs well for future studies directed toward exploiting this butenolide approach en route to other biologically important sugar structures.

EXPERIMENTAL

2,3-*O*-Isopropylidene-D-glyceraldehyde *N*-Benzylimine (1). This material was prepared by reacting 2,3-*O*-isopropylidene-D-glyceraldehyde with benzylamine (1.0 equiv) in anhydrous diethyl ether at 0°C in the presence of anhydrous $MgSO_4$. After filtration and removal of the solvent, imine **1** was obtained (quantitative) as a viscous oil, which was used as such in the next reactions.

2-(Trimethylsiloxy)furan (2). This material was prepared on a multigram scale from commercial 2-furaldehyde, via 2(5H)furanone, according to literature protocols.[16,17]

5-(*N*-Benzylamino)-6,7-*O*-isopropylidene-2,3,5-trideoxy-D-*ribo*- and D-*arabino*-hept-2-enono-1,4-lactones (3). 2,3-*O*-Isopropylidene-D-glyceraldehyde N-benzylimine **1** (5.0 g, 22.8 mmol) and TMSOF (4.9 mL, 29.6 mmol) were dissolved in dry CH_2Cl_2 (100 mL) under argon, and the mixture was cooled to -85° C. With stirring, BF_3 etherate (2.8 mL, 22.8 mmol) cooled to the same temperature was added via cannula over 5 min., and the solution was allowed to stir for 6 h. A saturated aqueous $NaHCO_3$ solution was added at -85° C and, after ambient temperature was reached, the mixture was extracted with CH_2Cl_2 (3x20 mL) and the organic layer washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica (40:60 hexane/ethyl acetate) to afford 4.6 g (66%) of **3** as a mixture of isomers. A further chromatographic separation allowed the less moving stereoisomer to be obtained in a pure state: $[\alpha]_D$ -32.6° (*c* 1.0, $CHCl_3$); mp. 153-155°C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (dd, J = 5.7, 1.2, 1H, H-3), 7.69 and

7.42 (m, 5H, CH_2Ph), 6.30 (dd, J = 5.7, 1.8, 1H, H-2), 5.64 (m, 1H, H-4), 4.53 (bq, J = 6.0, 1H, H-6), 4.0-4.4 (m, 4H, H_2-7 and CH_2Ph), 3.55 (bt, J = 5.0, 1H, H-5), 1.60 (bs, 1H, NH), 1.45 and 1.29 (2s, each 3H, Me). Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.45; H, 6.87; N, 4.83.

5-(*N*-Benzyl-*N*-benzoxycarbonylamino)-6,7-*O*-isopropylidene-2,3,5-trideoxy-D-*ribo*-hept-2-enono-1,4-lactone (4). To a solution of **3** (4.3 g, 14.1 mmol) in dioxane (172 mL) a 7% aqueous $NaHCO_3$ solution (49 mL) and benzylchloroformate (2.0 mL, 14.1 mmol) were added under stirring at 0°C. The suspension was stirred for 3 h at room temperature, quenched with water (500 mL) and extracted with CH_2Cl_2 (3x200 mL). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography over silica gel (60:40 hexane/ethyl acetate) afforded 4.2 g (68%) of **4**: a glass; $[\alpha]_D$ -100.83° (*c* 4.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (bd, J = 5.7, 1H, H-3), 7.1-7.4 (m, 10H, 2xCH_2Ph), 5.87 (bd, J = 5.7, 1H, H-2), 5.47 (m, 1H, H-4), 4.6-5.2 (m, 7H, H-6, H_2-7, and 2xCH_2Ph), 3.69 (bt, J = 7.2, H-5), 1.25 and 1.23 (2bs, each 3H, Me). Anal. Calcd. for $C_{25}H_{27}NO_6$: C, 68.64; H, 6.22; N, 3.20. Found: C, 68.50; H, 6.35; N, 3.42.

5-(*N*-benzyl-*N*-benzoxycarbonylamino)-2,3;5,6-di-*O*-isopropylidene-5-deoxy-D-*glycero*-D-*allo*-heptono-1,4-lactone (5). To a solution of **4** (3.9 g, 8.9 mmol) in CH_2Cl_2 (120 mL), dicyclohexano-18-crown-6-ether (0.8 g, 2.1 mmol) and powdered $KMnO_4$ (4.9 g, 31 mmol) were added at -10° C under stirring. The mixture was stirred at ambient temperature for 4 h, then solid sodium sulfite (6 g) and water (80 mL) were added and the brown slurry filtered over a celite pad. The filtrates were extracted with CH_2Cl_2 (3x30 mL) and the combined extracts dried ($MgSO_4$) and evaporated to dryness. Flash chromatography over silica gel (20:80 hexane/ethyl acetate) afforded 2.5 g (59%) of a diol intermediate which was dissolved in 30 mL of dimethoxypropane and treated with 340 mg (1.8 mmol) of *p*-toluensulfonic acid. The solution was stirred at room temperature for 5 h. The reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (3x20 mL) and dried over $MgSO_4$. The organic layer was evaporated and the residue was chromatographed on silica gel (70:30 hexane/ethyl acetate) to afford 2.3 g (84%) of **5** as a glass: $[\alpha]_D$ +11.5° (*c* 3.24, $CHCl_3$); ^{1}H NMR (300 MHz, C_6D_6, 65° C) δ 7.0-7.20 (m, 10H, 2xCH_2Ph), 4.2-5.1 (m, 9H), 3.60 (dd, J = 7.1, 6.3, 1H), 3.45 (m, 1H), 1.34, 1.18, 1.11, 0.99 (4s, each 3H, Me). Anal. Calcd. for $C_{28}H_{33}NO_8$: C, 65.74; H, 6.50; N, 2.74. Found: C, 65.59; H, 6.35; N, 2.94.

1-*O*-Trimethylsilyl-5-(*N*-benzyl-*N*-benzoxycarbonylamino)-2,3;6,7-di-*O*-isopropylidene-D-*glycero*-D-*allo*-heptofuranose (6). To a stirred solution of **5** (2.3 g, 4.5 mmol) in 50 mL of anhydrous CH_2Cl_2 a 1M solution of DIBAL in CH_2Cl_2 (13 mL) was slowly added via cannula at -85° C. After the reaction was stirred at this temperature for 3 h, methanol (1.0 mL) and then solid sodium-potassium tartrate (1.9 g) and water (20 mL) were added and the mixture was stirred at room temperature for 4 h. The mixture was extracted with CH_2Cl_2 (3x20 mL), dried over $MgSO_4$ and evaporated. The residue was flash chromatographed over silica gel (70:30 hexane/ethyl acetate) to afford 1.5 g of a lactol intermediate (65%) that was dissolved in pyridine (10 mL). TMSCl (0.7 mL, 5.8 mmol) was added and the mixture was stirred at ambient temperature for 3 h. Water (15 mL) was added and the mixture extracted with CH_2Cl_2 (3x15 mL). The organic extracts, washed with water and dried over $MgSO_4$, were concentrated in vacuo to give a residue which was subjected to flash chromatography over silica gel eluting with a hexane/ethyl acetate 70:30 solvent mixture. Protected lactol **6** was obtained as a mixture of anomers: 1.5 g (88%); colorless oil; $[\alpha]_D$ +15.5° (*c* 2.28; $CHCl_3$); ^1H NMR (300 MHz, C_6D_6, 65°C) δ 7.0-7.2 (m, 10H, 2xCH_2Ph), 5.54 (s, 0.37H, H-1β), 5.45 (d, J = 2.4, 0.63H, H-1α), 3.4-5.2 (m, 11H), 1.50, 1.43, 1.38, 1.36, 1.26, 1.23, 1.17, 1.13 (8s, overall 12H, Me), 0.13 (m, 9H, $SiMe_3$). Anal. Calcd. for $C_{31}H_{43}NO_8Si$: C, 63.56; H, 7.40; N, 2.39. Found: C, 63.74; H, 7.25; N, 2.20.

2,3;6,7-Di-*O*-isopropylidene-D-*glycero*-D-*allo*-heptono-δ-lactam (8). To a solution of **5** (500 mg, 0.98 mmol) in methanol (30 mL), $Pd(OH)_2/C$ (20%) (50 mg) was added, and the mixture subjected to hydrogenation for 2 h. Filtration, evaporation of the solvent and flash chromatography over silica gel (90:10 ethyl acetate/methanol) afforded 210 mg (74%) of lactam **8**: a glass; $[\alpha]_D$ +52.0° (*c* 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) see Table 1, in addition: δ 6.48 (s, 1H, NH), 3.27 (bs, 1H, OH), 1.50, 1.48, 1.43, 1.37 (4s, each 3H, Me); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.34, 111.01, 109.72, 74.85, 73.28, 66.97, 64.73, 60.34, 53.13, 26.51, 26.25, 24.86, 24.51. Anal. Calcd. for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.50; H, 7.47; N, 4.98.

2,3;6,7-Di-*O*-isopropylidene-1,5-dideoxy-1,5-imino-D-*glycero*-D-*allo*-heptitol (7). Protected lactol **6** was dissolved in methanol (100 mL), $Pd(OH)_2/C$ (20%) (150 mg) was added, and the mixture subjected to hydrogenation

for 8 h. Filtration and evaporation of the solvent afforded 550 mg (80%) of **7** as a white solid: mp 108-112° C (sealed capillary); $[\alpha]_D$ +7.3° (*c* 1.37, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) see Table 1, in addition: δ 4.30 (bs, 2H, NH and OH), 1.53, 1.45, 1.37, 1.35 (4s, each 3H, Me); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 109.60, 109.20, 78.13, 74.59, 73.46, 69.85, 66.68, 56.31, 45.51, 27.41, 26.46, 25.33, 25.04. Anal. Calcd. for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.25; H, 8.30; N, 5.32.

Alternatively, iminoheptitol **7** was obtained as follows: to a solution of lactam **8** (200 mg, 0.70 mmol) in anhydrous THF (7 mL) a solution of $BH_3.Me_2S$ (0.21 mL, 2.10 mmol) was added dropwise at room temperature under stirring. After the mixture was allowed to react under argon for 1 h at room temperature methanol (4 mL) was added and the mixture concentrated in vacuo to give a residue which was chromatographed over silica gel eluting with an hexane/ethyl acetate 30:70 solvent mixture. Pure heptitol **7** was obtained (170 mg, 88%) with physical and spectral characteristics identical to those reported in the previous preparation.

***N*-5-*O*-Diacetyl-2,3;6,7-di-*O*-isopropylidene-1,5-dideoxy-1,5-imino-D-*glycero*-D-*allo*-heptitol (9).** To a solution of **7** (150 mg, 0.55 mmol) in dry pyridine (300 mL) Ac_2O (155 mL, 1.65 mmol) and a catalytic amount of DMAP were added under argon. The mixture was stirred for 4 h at room temperature, quenched with water, extracted with CH_2Cl_2 (3x5 mL), and dried over $MgSO_4$. Concentration of the solution gave compound **9** as a white solid which was crystallizated from dichloromethane-hexane: yield 140 mg (71%); colorless crystals; mp 225-227° C; $[\alpha]_D$ -38.62° (*c* 0.87, $CHCl_3$); ^1H NMR (300 MHz, C_6D_6) see Table 1, in addition: δ 1.86 and 1.67 (2s, each 3H, 2x$COCH_3$), 1.46, 1.28, 1.07, 0.98 (4s, each 3H, 4xMe); ^{13}C NMR (75.4 MHz, C_6D_6) δ 170.53 and 170.43 (2s, *C*OMe) 110.30 and 110.09 (2s, O*C*Me_2O), 78.32 (d, *J* = 153.1, C-6), 74.25 (d, *J* = 157.7, C-2), 73.62 (d, *J* = 155.5, C-3), 68.09 (d, *J* = 148.5, C-4), 67.03 (t, *J* = 150.4, C-7), 52.11 (d, *J* = 143.3, C-5), 46.12 (t, *J* = 141.1, C-1), 26.40 and 26.27 (2q, *J* = 133.8, CO*Me*), 26.40 and 26.27 (2q, *J* = 133.8, Me), 24.65, 24.63, 21.20 (3q, *J* = 127.3, Me), 22.20 (q, *J* = 129.2, Me). Anal. Calcd. for $C_{17}H_{27}NO_7$: C, 57.13; H, 7.61; N, 3.92. Found: C, 57.03; H, 7.82; N, 4.10.

1,5-Dideoxy-1,5-imino-D-*glycero*-D-*allo*-heptitol (10). Compound **7** (550 mg, 2.0 mmol) was dissolved in 10 mL of 60% aqueous trifluoroacetic acid at room temperature and the solution allowed to stir for 2 h. Evaporation of the solvent gave essentially pure **10** as its trifluoroacetate salt: yield 583 mg (95%); a

glass; $[\alpha]_D$ +22.79° (*c* 0.26, H_2O); ^1H NMR (300 MHz, D_2O) see Table 1; ^{13}C NMR (75.4. MHz, D_2O) 72.9 (C-3), 71.0 (C-6), 68.0 (C-4), 66.9 (C-2), 64.9 (C-7), 58.3 (C-5), 44.6 (C-1). This material was dissolved in distilled water (5 mL) and passed through a column charged with 200 mg of DOWEX 1x8 (OH- form) resin. Evaporation of the water and liophilization afforded pure free base **10**: yield 330 mg (90%); white powder; $[\alpha]_D$ +6.0° (*c* 0.5, H_2O); ^1H NMR (300 MHz, D_2O) see Table 1; ^{13}C NMR (75.4, D_2O) δ 74.58, 73.19, 70.74, 69.65, 64.40, 57.18, 45.53. Anal. Calcd. for $C_7H_{15}NO_5$: C, 43.52; H, 7.83; N, 7.25. Found: C, 43.62; H, 7.68; N, 7.45.

X-ray Crystallography. Crystals of **9** were obtained from hexane-diethyl ether at room temperature. Crystal data are : $C_{17}H_{24}NO_7$, M= 354.38, triclinic space group P*1* No.1 (from systematic absences and structure analysis); cell dimensions : a = 7.737(3), b = 10.840(3), c = 5.822(2)Å, α =94.63(2), β = 101.89(3), γ= 96.31(2)°; V= 472.2(3)Å^3; Z = 1; D_c = 1.246 g·cm^{-3}, F(000)=189, Cu-Kα radiation, λ=1.54178Å, μ=7.76 cm^{-1}.

A selected crystal (0.06x0.13x0.48 mm^3) was sealed and the intensity data for 1800 reflections (2θ<140°) were collected at room temperature in the ω-2θ step-scanning mode on a Siemens AED three-circle diffractometer under the control of a General Automation Jumbo 220 Computer. No correction for absorption was applied because of the size of the crystal used. The structure was solved by direct methods using SIR program[18] and refined by full-matrix least-squares to a final R= 0.048 and Rw = 0.058 (w = $1/[\sigma^2(F_o)+0.009005F_o^2]$) for 1494 reflections with $I \geq 3\sigma(I)$ using the SHELX-76 program. All hydrogen atoms were located from a difference synthesis, except those bonded to methyl carbons which were geometrically generated. The parameters of all hydrogen atoms were not refined (for thermal parameters was assumed the value U_{iso}=0.05 Å^2). No peaks >0.09 and <-0.12 eÅ^{-3} were found in the last ΔF map. Scattering factors for C, H, N and O were taken from ref.19. All calculations were performed on a Gould 6040 Powernode Computer of the Centro di Studio per la Strutturistica Diffrattometrica del CNR (Parma , Italy) using the PARST,[20] ORTEP,[21] and PLUTO[22] programs.[23]

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