PREPARATION OF 2,3-DIDEOXY-2,3-EPIMINO AND 3,4-DIDEOXY-3,4-EPIMINO DERIVATIVES OF 1,6-ANHYDRO-β-D-HEXOPYRANOSES BY MITSUNOBU REACTION

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A series of new 2-, 3- and 4-benzylamino-2-, 3- and 4-deoxy derivatives of 1,6-anhydro-β-D-hexopyranoses were prepared from 1,6:2,3- and 1,6:3,4-dianhydro-β-D-hexopyranoses by treatment with benzylamine and converted into 2,3-(*N*-benzylepimino)-2,3-dideoxy- and 3,4-(*N*-benzylepimino)-3,4-dideoxy-β-D-hexopyranoses of the D-*allo*, D-*galacto* and D-*talo* configuration by Mitsunobu reaction. The structures of benzylamino and benzylimino derivatives were confirmed by ^{1}H and ^{13}C NMR spectra.

Key words: Anhydrosugars; Oxiranes; Aziridines; Epimino derivatives; Aminosugars; Carbohydrates; NMR spectroscopy.

Whereas 1,6:2,3- and 1,6:3,4-dianhydro-β-D-hexopyranoses and their derivatives are versatile starting compounds in the synthesis of sugars and non-sugar compounds[1–3], there has been only a little known on the chemistry of 1,6-anhydro-2,3-dideoxy-2,3-epimino- and 1,6-anhydro-3,4-dideoxy-3,4-epimino-β-D-hexopyranoses in the literature[2,4–8]. First epimino derivatives of hexoses, namely methyl 4,6-*O*-benzylidene-2,3-dideoxy-2,3-epimino-β-D-hexopyranoses, were synthesized[9] not earlier than in 1960. In contrast, aliphatic aziridines have been widely investigated[10,11] and used for the preparation of 2-substituted ethylamines[12–14] and amino acids[15–17].

Though the reactivity of the aziridine rings is lower than that of oxirane rings, nucleophilic reagents are effective in cleaving them to give amino compounds with *trans*-oriented nucleophiles. If necessary, the reactivity of the aziridine rings can be enhanced by protonation[18–20], by interaction with Lewis acids[21,22], and also by *N*-alkylation and *N*-acylation[18,23,24]. We assumed that the epimino derivatives of 1,6-anhydro-

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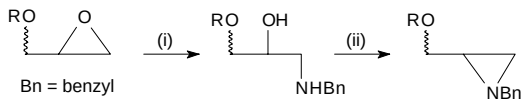
hexoses could be used as chiral synthons in a similar way as the corresponding oxirane derivatives, and hence we concentrated on their preparation.

The most frequent method used for the preparation of aziridines is the intramolecular S_N2 substitution of sulfonyloxy groups or halogen atoms by nitrogen-containing groups, such as the amino, azido, acylamino or thioureido group[4,18,25–31], and generating an amide ion under reaction conditions. In the less common Staudinger reaction[32–35], the azido group is cleaved by triphenylphosphine to give the iminophosphorane group which reacts in a similar way as described above. The Mitsunobu reaction[36–38] was used for the preparation of aliphatic aziridines from *N*-alkyl and *N*-acyl 2-amino alcohols[39–41] but in sugar chemistry, only the preparation of a phenylimino derivative of uracil from 1-(2-deoxy-2-phenylamino-β-D-arabinofuranosyl)uracil was described[42].

In this study we applied the Mitsunobu reaction for the preparation of new epimino derivatives of 1,6-anhydro-β-D-hexopyranoses from starting 1,6:2,3- and 1,6:3,4-dianhydro-β-D-hexopyranoses according to Scheme 1. We made use of benzylamine as a reactive agent for the cleavage of oxirane rings, exploiting the temporary protective function of the benzyl group.



(i) benzylamine, 140-150 °C;
(ii) diisopropyl azodicarboxylate, triphenylphosphine, toluene

SCHEME 1

EXPERIMENTAL

The melting points were determined with a Boëtius melting-point microapparatus and were uncorrected. The optical rotation was measured with a Bendix–Ericsson ETL-143A polarimeter at 21 °C. The ^1H and ^{13}C NMR spectra were measured with a Varian UNITY-500 apparatus (^1H at 500 MHz; ^{13}C at 125 MHz) in $CDCl_3$ or CD_3SOCD_3 solutions. The proton 2D-COSY spectra and ^1H-^{13}C 2D-HMQC spectra were used for the structural assignment of proton and carbon signals. Mass spectra were recorded on a Finnigan MAT INCOS 50 spectrometer using EI ionization (70 eV). Thin layer chromatography was performed on DC Alufolien plates (Merck) with Kieselgel 60 F_{254} with detection by spraying with 50% sulfuric acid in methanol or with a solution of anisaldehyde in sulfuric acid and heating. UV detection was also employed when appropriate. Preparative column chromatography was carried out on Kieselgel 60 (Merck, 60–230 mesh). Solutions were evaporated at a reduced pressure at temperatures below 40 °C. Triphenylphosphine was purchased from Fluka Chemie AG, diisopropyl and diethyl azodicarboxylates from Sigma–Aldrich, Czech Republic. Light petroleum was a 40–60 °C fraction. Toluene was dried by reflux with sodium, and methanol with magnesium; all solvents were distilled before use.

General Procedure for Preparation of (Benzylamino)hexopyranoses **2a**–**2e**

Dianhydro derivatives **1a**–**1e** and benzylamine were mixed and heated under argon atmosphere at 140–150 °C for a given time. After cooling to room temperature, the reaction mixture was worked up as described below for individual compounds. ^{1}H and ^{13}C NMR data for compounds **2a**–**2e** are given in Tables I and II.

1,6-Anhydro-4-*O*-benzyl-2-benzylamino-2-deoxy-β-D-glucopyranose (**2a**)

1,6:2,3-Dianhydro-4-*O*-benzyl-β-D-mannopyranose[43] **1a** (117 mg, 0.5 mmol) and benzylamine (0.6 ml, 5.4 mmol) were heated for 2 h and the reaction mixture was left at room temperature overnight. Thereafter light petroleum (about 10 ml) was added to the solidified reaction mixture, the crude product **2a** was filtered off and crystallized from ethanol. Yield 130 mg (76%), m.p. 187–188 °C, $[\alpha]_D$ –33 (*c* 0.6, chloroform). For $C_{20}H_{23}NO_4$ (341.2) calculated: 70.33% C, 6.81% H, 4.10% N; found: 70.40% C, 6.70% H, 4.06% N.

1,6-Anhydro-2-*O*-benzyl-4-benzylamino-4-deoxy-β-D-glucopyranose (**2b**)

1,6:3,4-Dianhydro-2-*O*-benzyl-β-D-galactopyranose[44] **1b** (500 mg, 2.135 mmol) and benzylamine (1.4 ml, 12.8 mmol) were heated for 2 h. The reaction mixture was worked up as described for compound **2a**. Yield 635 mg (87%), m.p. 172–173 °C, $[\alpha]_D$ –41 (*c* 1.0, chloroform). For $C_{20}H_{23}NO_4$ (341.2) calculated: 70.33% C, 6.81% H, 4.10% N; found: 70.45% C, 6.68% H, 4.11% N.

1,6-Anhydro-4-benzylamino-4-deoxy-2-*O*-(4-methylbenzenesulfonyl)-β-D-glucopyranose (**2c**)

1,6:3,4-Dianhydro-2-*O*-(4-methylbenzenesulfonyl)-β-D-galactopyranose[45] **1c** (10.48 g, 38 mmol) and benzylamine (8.7 ml, 79.6 mmol) in toluene (50 ml) were heated under reflux for 3 h. After cooling to room temperature, light petroleum (125 ml) was added, the resulting solid was separated and treated with 5% HCl (100 ml). The undissolved **1c** was recovered and the solution was adjusted to pH *ca* 9 with concentrated ammonia; the precipitated **2c** was crystallized from ethanol. Yield 8.4 g (59%), m.p. 153–154 °C, $[\alpha]_D$ –33 (*c* 0.75, chloroform). For $C_{20}H_{23}NO_6S$ (405.3) calculated: 59.21% C, 5.73% H, 3.45% N, 7.92% S; found: 58.98% C, 5.81% H, 3.58% N, 8.03% S.

1,6-Anhydro-3-benzylamino-3-deoxy-β-D-glucopyranose (**2d**)

1,6:3,4-Dianhydro-β-D-allopyranose[46] **1d** (390 mg, 2.71 mmol) and benzylamine (1.4 ml, 12.8 mmol) were heated for 70 h. After cooling to room temperature, chloroform (20 ml) was added to the reaction mixture, and the product **2d** was extracted with water (total volume 100 ml). Combined aqueous extracts were evaporated to dryness, and the residue was crystallized from an ethanol–ether–light petroleum mixture. Yield 490 mg (72%), m.p. 132–134 °C, $[\alpha]_D$ –47 (*c* 0.8, chloroform). For $C_{13}H_{17}NO_4$ (251.2) calculated: 62.11% C, 6.84% H, 5.58% N; found: 61.87% C, 7.00% H, 5.50% N.

1,6-Anhydro-2-*O*-benzyl-3-benzylamino-3-deoxy-β-D-mannopyranose (**2e**)

1,6:3,4-Dianhydro-2-*O*-benzyl-β-D-altropyranose[47] **1e** (300 mg, 1.28 mmol) and benzylamine (0.7 ml, 6.4 mmol) were heated for 70 h. After cooling to room temperature, the reaction mixture was evaporated under reduced pressure at 90 °C to give a light yellow syrup which did not crystallize. Analysis of its NMR spectra proved small contamination with traces of benzylamine, but the product is sufficiently pure to be used for further reactions. Yield 219 mg (50%). For $C_{20}H_{23}NO_4$ (341.2) found mass spectrum: *m/z* 341 (M^+).

TABLE I
Proton NMR data of benzylamino derivatives **2a**–**2e** in $CDCl_3$ (C) and/or in CD_3SOCD_3 (S)

Compound	Solvent	Chemical shifts, ppm/Signal multiplicity											
		H-1	H-2	H-3	H-4	H-5	H-6*en*	H-6*ex*	$NCH_2C_6H_5$		$OCH_2C_6H_5$		C_6H_5
2a[a]	C	5.56 t	2.65 m	3.99 um	3.47 m	4.61 m	4.08 dd	3.73 dd	3.81 d	3.92 d	4.66 d	4.68 d	7.22–7.37 m
2b[b]	C	5.48 t	3.33 m	3.95 m	2.64 m	4.62 m	4.05 dd	3.72 dd	3.86 d	3.90 d	4.62 d	4.68 d	7.23–7.35 m
2d	C	5.45 bt	3.53 q	2.80 m	3.70 m	4.53 m	4.27 dd	3.75 dd	3.83 d	3.88 d	–		7.24–7.35 m
2d[c]	S	5.17 t	3.22 ddd	2.49 m	3.38 ddd	4.35 dq	3.94 dd	3.50 dd	3.77 bs		–		7.21–7.32 m
2d[d] (+HCl)	S	5.18 s	3.66 d	2.69 tt	3.83 bd	4.40 dm	3.71 dd	3.58 dd	4.30 dt	4.34 dt	–		7.41–7.59 m
2e	C	5.40 bt	3.62 dd	3.10 m	3.74 t	4.45 dm	4.69 dd	3.72 dd	3.69 d	3.81 d	4.41 d	4.47 d	7.23–7.35 m
2e[e]	S	5.31 b	3.60 dd	2.93 dq	3.66 dt	4.35 dm	4.42 bd	3.46 dd	3.57 bd	3.77 bd	4.41 s		7.22–7.36 m
2e (+DCl)	S	5.57 d	3.82 dd	3.06 dd	4.00 d	4.35 bd	4.03 bd	3.59 dd	4.12 s		4.41 d	4.49 d	7.19–7.44 m

		Coupling constants, Hz											
		1,2	2,3	3,4	4,5	5,6*en*	5,6*ex*	6*en*,6*ex*	1,3	2,4	3,5	N–CH_2	O–CH_2
2a[f]	C	1.9	1.8	1.4	2.3	0.8	5.3	7.6	1.8	1.7	1.6	13.1	12.3
2b[g]	C	1.75	2.55	1.6	2.75	0.8	5.2	7.3	1.5	1.25	1.5	13.3	11.8
2d[g]	C	2.0	1.8	1.8	2.1	0.85	5.4	7.4	1.5	1.6	1.7	13.3	–
2d[h]	S	1.6	3.3	3.3	1.7	1.1	5.6	7.0	0.8	<1	1.1		–
2d[i] (+HCl)	S	≈0	7.6	7.6	<0.5	1.3	5.5	7.6				13.5	–
2e[j]	C	1.9	6.4	1.9	2.2	1.0	5.7	6.8	1.3		1.9	13.4	12.1
2e[k]	S	1.7	6.4	1.6	2.0	<1	5.7	6.5	1.3		1.4	13.0	
2e (+DCl)	S	3.2	6.3	4.5	<1	<1	5.7	8.2					11.5

[a] δ(OH) 2.64 b; [b] δ(OH) 2.40 b, δ(NH) 1.92 b; [c] δ(2-OH) 4.80 d, δ(4-OH) 4.86 d, δ(NH) 2.03 b; [d] $\delta(NH_2^+)$ 9.61 um and 9.49 um; [e] δ(OH) 5.02 d; [f] $J(1,4) = 0.6$, $J(2,5) = 0.6$ Hz; [g] $J(1,4) = 0.5$ Hz; [h] $J(OH,2) = 7.2$ Hz, $J(OH,4) = 6.9$ Hz; [i] $J(NH_2,CH_2) = 5.5$ Hz, $J(NH_2,3) = 5.2$ Hz; [j] $J(1,5) < 0.5$ Hz, $J(1,6en) < 0.5$ Hz, $J(1,6ex) < 0.5$ Hz; [k] $J(OH,4) = 5.2$ Hz.

TABLE II
Carbon-13 chemical shifts of benzylamino derivatives **2a**–**2e** in $CDCl_3$ (C) and/or in CD_3SOCD_3 (S)

Compound	Solvent	C-1	C-2	C-3	C-4	C-5	C-6	N**CH**$_2$C$_6$H$_5$	O**CH**$_2$C$_6$H$_5$	C$_6$H$_5$
2a	C	102.96	59.90	68.28	74.43	78.56	65.68	51.24	71.64	140.13, 137.82, 128.56(2), 128.43(2), 127.14(2), 127.92, 127.72(2), 127.03
2b	C	100.91	75.14	68.93	59.20	77.23	66.70	50.82	72.08	138.96, 137.53, 128.55(2), 128.45(2), 128.10(2), 127.84(2), 128.00, 127.05
2d	C	102.18	70.05	62.38	70.34	77.00	65.39	52.84	–	141.29, 128.26(2), 128.20(2), 126.67
2d	S	102.91	70.73	62.76	71.38	77.35	65.46	51.73	–	141.29, 128.26(2), 128.20(2), 126.67
2d (+HCl)	S	103.98	70.37	62.50	71.01	78.15	66.77	49.43	–	132.01, 130.61(2), 128.99, 128.70(2)
2e	C	100.48	73.26	59.49	70.57	76.90	65.42	53.65	71.06	140.38, 137.48, 128.48(2), 128.37(2), 128.26(2), 127.69(2), 127.95, 126.98
2e	S	99.66	73.77	59.38	69.49	76.84	64.86	53.03	70.04	138.26, 133.78, 128.48(2), 128.40(2),128.36(2), 127.79(3), 126.91
2e (+DCl)	S	98.25	71.36	57.63	69.29	77.89	66.86	51.52	72.17	138.09, 131.82, 131.36(2), 129.48(2), 129.94, 129.13(2), 128.93(2), 128.72

2-Amino-1,6-anhydro-4-*O*-benzyl-β-D-glucopyranose (**2f**)

To a well-stirred solution of compound **2a** (340 mg, 1 mmol) and triphenylphosphine (293 mg, 1.12 mmol) in chloroform (10 ml, acidified with gaseous HCl to pH *ca* 1), diethyl azodicarboxylate (0.2 ml, 1.27 mmol) was added dropwise at room temperature during 1 h, and the reaction mixture was allowed to stand for 24 h. The 5% KOH solution (25 ml) and chloroform (20 ml) were added and the reaction mixture was stirred for 3 days at room temperature in order to hydrolyse the present hydrazodicarboxylate. Then the organic layer was separated and extracted with diluted HCl (50 ml, 5%), aqeous extract neutralized with concentrated ammonia and reextracted with chloroform (5 × 15 ml). The chloroform solution was dried ($CaCl_2$) and evaporated. Resulting oil was crystallized from an ethanol–chloroform mixture to yield 176 mg (70%) of **2f**, m.p. 148–152 °C, $[\alpha]_D$ –47 (*c* 1.0, chloroform) (ref.[6] gives m.p. 151–152 °C, $[\alpha]_D$ –46). ^1H and ^{13}C NMR data were the same as described in ref.[6].

General Procedure for Preparation of Epiminohexopyranoses **3a**–**3e**

Compound **2a**–**2e** (1 mmol) was mixed with a solution of triphenylphosphine (1.1–1.15 mmol) in toluene (10 ml). Diisopropyl azodicarboxylate (1.1–1.15 mmol) in toluene (5 ml) was added dropwise within 1 h with stirring and cooling at 0–5 °C in an ice-water bath. The reaction was monitored by TLC with toluene–acetone 5 : 1 (for dibenzyl derivatives) or with ethyl acetate (for monobenzyl derivatives), in these systems the R_F of epimines are in the range 0.4–0.5. When the reaction ceased (total reaction time was 2 h for **3a**–**3c** and 2–3 days for **3d**–**3e**), the solvent was removed *in vacuo* and the resulting oil was chromatographed on silica gel (25 g, Merck 60–230 mesh, TLC solvent mixture). The combined fractions containing a mixture of epimine and diisopropyl hydrazodicarboxylate were concentrated and the residue was hydrolyzed with 5% NaOH in aqueous ethanol at 45 °C for 24 h and extracted several times with dichloromethane (100 ml). After drying (Na_2SO_4) and evaporation of the solvent, the residue was crystallized from an ethanol–ether–light petroleum mixture. ^1H and ^{13}C NMR data for compounds **3a**–**3e** are given in Tables III and IV.

1,6-Anhydro-4-*O*-benzyl-2,3-(*N*-benzylepimino)-2,3-dideoxy-β-D-allopyranose (**3a**)

The epimine **3a** was prepared according to general procedure from **2a**. Yield 75%, m.p. 85–88 °C, $[\alpha]_D$ +113 (*c* 0.88, chloroform). For $C_{20}H_{21}NO_3$ (323.2) calculated: 74.25% C, 6.60% H, 4.33% N; found: 74.05% C, 6.59% H, 4.38% N.

1,6-Anhydro-2-*O*-benzyl-3,4-(*N*-benzylepimino)-3,4-dideoxy-β-D-allopyranose (**3b**)

The epimine **3b** was prepared according to general procedure from **2b**. Yield 73%, m.p. 94–96 °C, $[\alpha]_D$ –137 (*c* 0.79, chloroform). For $C_{20}H_{21}NO_3$ (323.2) calculated: 74.25% C, 6.60% H, 4.33% N; found: 74.18% C, 6.56% H, 4.36% N.

1,6-Anhydro-3,4-(*N*-benzylepimino)-3,4-dideoxy-2-*O*-(4-methylbenzenesulfonyl)-β-D-allopyranose (**3c**)

The epimine **3c** was prepared according to general procedure from **2c**. Yield 37%, m.p. 123–124 °C, $[\alpha]_D$ –68 (*c* 0.84, chloroform). For $C_{20}H_{21}NO_5S$ (387.3) calculated: 61.96% C, 5.47% H, 3.61% N, 8.28% S; found: 62.24% C, 5.32% H, 3.72% N, 8.10% S.

TABLE III
Proton NMR data of benzylepimines **3a**–**3e** in $CDCl_3$

Compound	Chemical shifts, ppm/Signal multiplicity											
	H-1	H-2	H-3	H-4	H-5	H-6*en*	H-6*ex*	N**CH**$_2$C$_6$H$_5$		O**CH**$_2$C$_6$H$_5$		C$_6$H$_5$
3a	5.63 bs	1.82 dd	1.96 dt	3.38 dd	4.42 dm	3.59 dd	3.84 dd	3.38 d	3.69 d	4.30 d	4.44 d	7.23–7.45 m
3b	5.27 dt	3.40 dd	1.87 ddd	1.76 dd	4.71 dm	3.81 d	3.66 dd	3.44 d	3.66 d	4.34 d	4.44 d	7.23–7.45 m
3c[a]	5.20 m	4.38 dd	1.97 dt	1.79 dd	4.67 bdd	3.81 d	3.65 dd	3.35 d	3.60 d	–		7.22–7.37 m
3d[b]	5.20 t	3.74 bd	1.80 dd	2.25 t	4.72 bdd	4.02 d	3.42 dd	3.10 d	3.87 d	–		7.26–7.35 m
3e	5.27 bd	3.57 dd	1.87 ddd	2.32 dd	4.66 dd	4.10 d	3.44 dd	3.06 d	3.74 d	4.59 d	4.65 d	7.24–7.41 m
	Coupling constants, Hz											
	1,2	2,3	3,4	4,5	5,6*en*	5,6*ex*	6*en*,6*ex*	1,3	N–CH$_2$	O–CH$_2$		
3a[c]	1.1	6.3	6.0	0.9	2.3	6.9	7.8	<0.5	13.1	12.4		
3b	0.85	5.7	6.5	1.3	≈0	4.3	6.9	1.6	13.3	12.3		
3c	0.9	6.1	6.2	1.3	≈0	4.3	7.1	1.65	13.6	–		
3d[d]	1.1	<0.5	6.6	6.1	<0.5	4.6	6.0	1.5	13.3	–		
3e	3.7	5.0	6.9	5.9	≈0	4.5	6.0	0.9	13.2	12.6		

[a] Ts: δ(CH_3) 2.43 bs, δ(C_6H_4) 7.29 m, 2 H and 7.71 m, 2 H; [b] δ(OH) 1.89 d, [c] J(1,4) < 0.5 Hz, J(1,5) < 0.5 Hz, J(3,5) = 1.3 Hz; [d] J(OH,2) = 10.0 Hz.

TABLE IV
Carbon-13 chemical shifts of benzylepimines **3a**–**3e** in $CDCl_3$

Compound	C-1	C-2	C-3	C-4	C-5	C-6	$NCH_2C_6H_5$	$OCH_2C_6H_5$	C_6H_5
3a	97.90	37.95	35.08	72.92	75.16	65.62	63.54	69.84	137.90(2), 128.69(2), 128.31(2), 128.26(2), 127.62(2), 127.54, 127.34
3b	100.74	70.13	34.94	38.12	72.09	66.26	63.58	70.44	138.14, 138.01, 128.58(2), 128.31(2), 128.26(2), 127.72(2), 127.56, 127.27
3c[a]	99.65	72.72	34.17	37.43	69.65	66.26	62.45	–	137.47, 128.38(4), 127.34
3d	100.64	66.00	38.46	39.88	71.94	66.04	63.69	–	138.25, 128.40(2), 128.08(2), 127.29
3e	97.30	72.06	36.68	43.51	72.99	65.54	64.06	70.97	138.35, 138.20, 128.41(2), 128.38(2), 128.33(2), 127.99(2), 127.77, 127.22

[a] Ts: $\delta(CH_3)$ 21.61; $\delta(C_6H_4)$ 144.87, 133.64, 129.81(2), 127.98(2).

1,6-Anhydro-3,4-(*N*-benzylepimino)-3,4-dideoxy-β-D-galactopyranose (**3d**)

The epimine **3d** was prepared according to general procedure from **2d**. Yield 67%, m.p. 103.5–104.5 °C, $[\alpha]_D$ –55 (*c* 0.72, chloroform). For $C_{13}H_{15}NO_3$ (233.2) calculated: 66.90% C, 6.50% H, 6.00% N; found: 66.50% C, 6.57% H, 5.80% N.

1,6-Anhydro-2-*O*-benzyl-3,4-(*N*-benzylepimino)-3,4-dideoxy-β-D-talopyranose (**3e**)

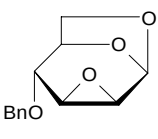
The epimine **3e** was prepared according to general procedure from **2e**. Yield 76%, syrup, $[\alpha]_D$ +15 (*c* 0.9, chloroform). For $C_{20}H_{21}NO_3$ (323.2) found mass spectrum: *m/z* 323 (M^+).

1,6-Anhydro-2,3-dideoxy-2,3-epimino-β-D-allopyranose (**4**)

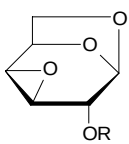
A well-stirred solution of benzylepimine **3a** (122 mg, 0.4 mmol) and about 20 mg of 10% Pd on charcoal (Fluka) in dry methanol (15 ml) was hydrogenated under atmospheric pressure at room temperature. The reaction course was monitored by TLC using propan-2-ol–chloroform–concentrated ammonia–water system (10 : 10 : 1 : 1). After disappearing of the starting epimine (≈ 5 h), the catalyst was filtered off with suction and the solution was evaporated to dryness. Yield 45 mg (78%) of **4**, syrup, $[\alpha]_D$ +92 (*c* 0.65, chloroform). Physical constants and ^1H and ^{13}C NMR data are in agreement with those of the authentic sample[48].

RESULTS AND DISCUSSION

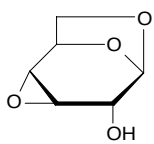
Free or substituted 1,6:2,3- and 1,6:3,4-dianhydro-β-D-hexopyranoses **1a**–**1e** were heated with neat benzylamine or with a solution of benzylamine in boiling toluene at 140–150 °C to give *N*-benzylamino derivatives **2a**–**2e**. The oxirane ring cleavage pro-



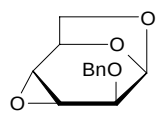
1a



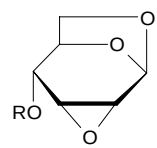
1b, R = Bn
1c, R = Ts



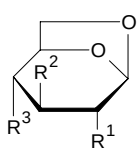
1d



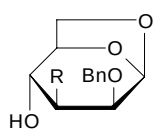
1e



1f, R = Bn
1g, R = H



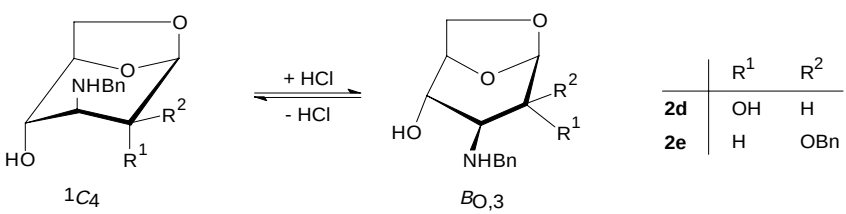
	R^1	R^2	R^3
2a	NHBn	OH	OBn
2b	OBn	OH	NHBn
2c	OTs	OH	NHBn
2d	OH	NHBn	OH
2f	NH_2	OH	OBn



2e, R = NHBn

ceeded diaxially with high regioselectivity, in good yields and without formation of by-products. Dianhydrides **1a**–**1c** with the oxirane ring *endo*-oriented toward the 1,6-anhydro bridge react more rapidly than those **1d**–**1f** with *exo*-orientation. Thus, the steric hindrance caused by presence of the 1,6-anhydro bridge might play an important role in controlling the reaction rate. The failure of the reaction in the case of dianhydride **1f**, which gradually decomposed on prolonged heating, could be explained by analogous reactions of dianhydrides **1f** and **1g** with sodium hydroxide[2] and with potassium *tert*-butoxide[43], respectively.

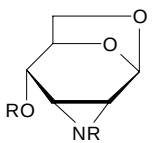
The structure of amino derivatives **2a**–**2e** was determined from ^{1}H and ^{13}C NMR spectra (Tables I and II). All non-protonated benzylamines **2a**–**2d** adopt the chair conformation $^1C_4$ in chloroform solution as indicated by low values of coupling constants J(2,3) and J(3,4) (J(2,3) = 1.8–2.6 Hz and J(3,4) = 1.4–1.8 Hz) and characteristic long-range couplings J(1,3), J(2,4) and J(3,5) (see Table I). The increase of coupling constants J(2,3) and J(3,4) of benzylamine **2d** in CD_3SOCD_3 (from 1.8 to 3.3 Hz) indicates certain population of the boat form $B_{O,3}$, which becomes the predominant conformer of protonated **2d** in CD_3SOCD_3 as follows from large values J(2,3) = J(3,4) = 7.6 Hz and the absence of long-range couplings J(1,3), J(2,4) and J(3,5) (see Table I). A comparison with reference J-values of **2d** observed in $CDCl_3$ (chair-form) and of protonated **2d** (boat-form) gives for **2d** in CD_3SOCD_3 *ca* 25% of the boat-form. This corresponds with the known behaviour of 3-amino-1,6-anhydro-3-deoxy-β-D-glucopyranose and its *N*-methyl derivatives[49,50]. A significant increase in population of the boat form on protonation was deduced for benzylamine **2e** of D-*manno* configuration from coupling constants J(1,2), J(3,4) and J(4,5). While the values J(3,4) = 1.9 Hz and J(4,5) = 2.2 Hz observed in $CDCl_3$ solution of **2e** are very similar to those of **2d** in the same solvent and clearly indicate chair conformation $^1C_4$ in $CDCl_3$ (and also in CD_3SOCD_3), then the changed values (J(3,4) = 4.5 Hz and J(4,5) < 1 Hz) observed for the protonated form of **2e** in CD_3SOCD_3 indicate a conformational equilibrium with a significant population of the boat conformation (the ratio $^1C_4$: $B_{O,3}$ ≈ 54 : 46 was calculated from J(3,4) values). These conformational changes (Scheme 2) induced by protonation of the benzylamino group may be explained by effective solvation of the corresponding ammonium salts and consequent unfavourable steric interaction with the 1,6-anhydro bond.



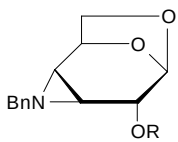
	R^1	R^2
2d	OH	H
2e	H	OBn

SCHEME 2

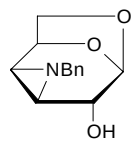
Compounds **2a**–**2d** described above were converted into epimines **3a**–**3d** by treatment with triphenylphosphine and diisopropyl azodicarboxylate in dry toluene at reduced temperature; the yields in dry ether or tetrahydrofuran were only a few per cent lower. Inert atmosphere[37,38] can be avoided and does not influence the yields. The reaction time at the optimum temperature of 0–5 °C was strongly dependent on the structure of the starting amino compound. Diisopropyl azodicarboxylate was chosen as a more convenient reagent than diethyl azodicarboxylate because it made possible to perform the reaction at 0 °C and thus to minimize the formation of by-products. However, some *N*-debenzylation (up to 5%) of starting compound during the cyclization was observed. In the case of compound **2a**, when chloroform was used as solvent instead of toluene, the free amine **2f** was isolated from the reaction mixture in 70% yield. Probably, this results from the change of the acidity of the reaction mixture. Another experiment, in which amine **2a** was treated with diisopropyl azodicarboxylate–triphenylphosphine mixture (in the presence of HCl, pH *ca* 1), gave the same yield of amine **2f**. Thus, the presence of HCl in the reaction mixture might play the key role.



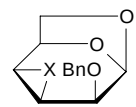
3a, R = Bn
4, R = H



3b, R = Bn
3c, R = Ts



3d



3e, X = NBn

The course of the Mitsunobu reaction was not negatively affected by the presence of an additional free or substituted hydroxyl group in the starting amines **2**. Epimines **3a**–**3e** were easily obtained from compound **2d** (free OH group) as well as from compounds **2a**, **2b**, **2e** (*O*-benzyl group) and **2c** (*O*-tosyl group). Axial hydroxyl group activated by diisopropyl azodicarboxylate–triphenylphosphine adduct exhibited good leaving capability, nevertheless with the reactivity decreasing in the order C(4)–OH > C(3)–OH > C(2)–OH. Therefore, as expected, epimine **3d** was formed from **2d** with high regioselectivity due to a higher reactivity of the OH group at C(4) than that at C(2) (*cf.* a similar reactivity of tosyl groups at C(4) and C(2), refs[45,51]). A rather unexpected, relatively high reactivity of the OH group at C(3) indicates that the potentially unfavourable steric interaction between the 1,6-anhydro bond and the diisopropyl azodicarboxylate–triphenylphosphine adduct does not play a dominant role. A free amino group exhibited a markedly lower reactivity than a benzylamino group as we could show in the reaction of free amine **2f** under the conditions used for the preparation of epimines. Tetrahydrofuran was used as a solvent instead of toluene; unreacted amine **2f** was isolated as a sole product.

As usual with Mitsunobu reaction, it is difficult to separate the reaction product(s) from triphenylphosphine oxide and/or diisopropyl hydrazodicarboxylate. In our case,

the reaction mixture was first chromatographed on silica gel to separate a mixture of epimine and hydrazodicarboxylate. Then, after hydrolysis of hydrazodicarboxylate by sodium hydroxide in aqueous ethanol, the epimine was extracted with dichloromethane.

The structure of epimines was determined from ^{1}H and ^{13}C NMR spectra (Tables III and IV) and by comparison with the data for 1,6:2,3- and 1,6:3,4-dianhydro-β-D-hexopyranoses[3]. The 2,3-epimines adopt a half-chair conformation ^5H_O whereas the 3,4-epimines adopt the ^1H_O conformation, similar to the corresponding 2,3- and 3,4-epoxides[1,3]. The coupling constant values of aziridine ring protons are $J(2,3)$ = 6.3 Hz for 2,3-epimine **3a** and $J(3,4)$ = 6.2–6.9 Hz for 3,4-epimines **3b**–**3e**, the chemical shifts of corresponding hydrogens H-2, H-3 and H-3, H-4, respectively, appear in the narrow range δ 1.80–2.33. Epimine carbon atoms of **3b**–**3e** give characteristic signals in the upfield region of ^{13}C NMR spectra (δ ≈ 34–44).

The free epimine **4** was obtained with a good yield (78%) after hydrogenolysis of *N*-benzyl epimine **3a** on Pd on charcoal under the conditions described in ref.[4].

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