11. Syntheses of Racemic Diaminosugar Derivatives Starting from 1,2-Dihydropyridines and from Nitrosobenzene

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Racemic diaminosugars were easily obtained by a regio- and stereoselective three-step synthetis. In the first step, regiospecific hetero-*Diels-Alder* cycloadditions between 1,2-dihydropyridines **1a** and **10** and nitrosobenzene led to the bicyclic compounds **2a** and **11**, respectively. *cis*-Glycol formation starting from these latter adducts, followed by hydrogenolysis of the N–O bond and by exhaustive acetylation of the OH-groups, led to the diaminolyxose **5**, the diaminomannose **14** and the diaminoallose **15**. When starting from benzyl 1,2-dihydropyridine-1-carboxylate (**1b**) and using the same reaction sequence, the racemic piperidine derivative **8** was obtained.

Racemic 4,5-Diamino-4,5-dideoxy-lyxopyranose 4. – In a preliminary paper, we described a simple three-step synthesis of the racemic diamino-dideoxy-lyxopyranose [1] which is represented in formula **4** by its α-D-enantiomer. The reaction sequence was straightforward: *i*) regiospecific *Diels-Alder* cycloaddition of dihydropyridine **1a** with

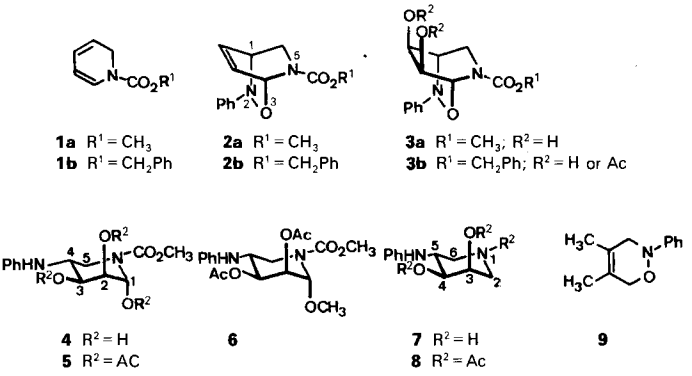
Table 1. *360-MHz ^{1}H-NMR Spectra of Diaminolyxose* **4**, *of its Triacetate* **5**, *of the Acetylated Diaminomannose* **14** *and diaminoallose* **15**[a])

	Solvents (temperature)	H–C(1)	H–C(2)	H–C(3)	H–C(4)	H_e–C(5)	H_a–C(5)	Me–C(5)	MeO	Ac	NH
4	CD_3COCD_3/D_2O (323 K)	5.72	4.05	3.92	3.69	4.18	2.88	–	3.72	–	–
5	$CDCl_3$ (330 K)	6.71	5.28	5.25	3.89	4.47	2.86	–	3.78	2.12, 2.10, 1.88	3.60
14	$CDCl_3$ (297 K)	6.75	5.24	5.28	3.76	–	3.53	1.64	3.74	2.15, 2.13, 1.78	3.50
15	CD_3COCD_3 (233 K)	6.90	5.31	5.56	4.19	–	3.90	1.55	3.68	2.15, 2.10, 1.88	5.53
	$CDCl_3$ (297 K)	6.86	5.21	5.58	3.98	–	4.10	1.49	3.74	2.16, 2.01, 1.88	4.30

		$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5e}$	$J_{4,5a}$	$J_{4,NH}$	$J_{5e,5a}$	J_{5,CH_3}
4		2.5	–	3.0	10.0	5.0	11.0	–	13.5	–
5		3.0	–	3.0	10.5	5.0	11.5	–	14.0	–
14		3.0	–	3.5	9.0	–	9.0	9.0	–	6.8
15	in (D_6)acetone	4.0	0.8	3.5	3.0	–	10.0	10.5	–	6.8
	in $CDCl_3$	3.5	0.8	5.5	6.0	–	6.5	11.0	–	7.0

[a]) Chemical shifts in δ [ppm]; coupling constants in Hz; internal standard: TMS.

Scheme 1



1a $R^1 = CH_3$
1b $R^1 = CH_2Ph$

2a $R^1 = CH_3$
2b $R^1 = CH_2Ph$

3a $R^1 = CH_3$; $R^2 = H$
3b $R^1 = CH_2Ph$; $R^2 = H$ or Ac

4 $R^2 = H$
5 $R^2 = AC$

6

7 $R^2 = H$
8 $R^2 = Ac$

9

nitrosobenzene led in high yield to the adduct **2a**[1]); *ii*) stereoselective *cis*-hydroxylation of the latter one with $KMnO_4$ gave **3a** in about 50% yield; *iii*) hydrogenolysis of the N–O bond of **3a** led to **4** in good yield. High-field ^{1}H-NMR of the ring protons of **4** *(Table 1)* permitted unambiguous determination both of the relative configuration and of the predominant conformation, as depicted in formula **4** for its α-D-enantiomer *(Scheme 1)*. This racemic aminosugar could be obtained in pure crystalline form. It was also transformed into its triacetate **5** which was easily purified and characterized. It should be noted that the *Diels-Alder* adduct **2a** although isolated in high yield is thermally instable and could not be purified by recrystallisation.

When **2a** was put into $CHCl_3$ solution together with 2,3-dimethylbutadiene under Ar at room temperature, it disappeared within 5 days and led to the known adduct **9**. For comparison, the latter was prepared from dimethylbutadiene and nitrosobenzene [3]. These results clearly show that the adduct **2a** undergoes a slow *retro-Diels-Alder* reaction in solution even at room temperature, which accounts for its instability.

cis-Hydroxylation of **2a** proceeded in moderate yield (*ca.* 45%) with $KMnO_4$ at −25°C in a neutral acetone/EtOH/H_2O solution [7]. These experimental conditions proved to be the optimal ones in our hands, the yield of glycol **3a** being lower in the presence of NaOH (standard conditions) [4]. Similar results have been obtained when using the alternative catalytic OsO_4 methodologies [5] [6]. Glycol **3a** was the only product which could be isolated from the reaction mixture; it was formed through a $KMnO_4$ or OsO_4 approach which is *anti* with respect to the N–O bridge [7] [8].

The diaminosugar **4** was also characterized as the methyl glycoside **6** obtained from **4** in MeOH solution in the presence of trace amounts of *p*-toluenesulfonic acid, followed by treatment with Ac_2O in pyridine.

***r*-3,*c*-4-Diacetoxy-*N*-acetyl-*t*-5-(phenylamino)piperidine 8.** – Starting from nitrosobenzene and benzyl 1,2-dihydropyridine-1-carboxylate (**1b**), the regioisomer **2b** was obtained in 75% yield after recrystallisation. This adduct proved to be more stable than **2a** and was characterized both by ^{1}H- and by ^{13}C-NMR. Oxidation of **2b** with catalytic amounts of OsO_4 in the presence of *N*-methylmorpholine *N*-oxide [6] led stereospecifically and in 80% yield to the expected glycol **3b** (R^2=H) which was also characterized as its diacetate **3b** (R^2=Ac). Hydrogenation of **3b** (R^2=H) over Pd/C in a *Parr* apparatus at 50 bar led to the consumption of *three* mol-equiv. of H_2 and to the formation of the piperidine derivative **7** which was characterized as the triacetate **8**. Most likely, this

[1]) Compound **2a** has already been described by *Knaus* and coworkers [2].

Table 2. *360-MHz-^{1}H-NMR Spectrum of the Piperidine Derivative* **8** *(Rotamer* **I** *and Rotamer* **II**)[a])

	δ_I	δ_{II}	*i,j*	J_{ij} (**I**)	J_{ij} (**II**)
H_e–C(2)	3.99	4.13	2e, 2a	15.0	13.5
H_a–C(2)	3.62	3.45	2e, 3	4.5	6.0
H–C(3)	5.33	5.19	2a, 3	2.0	2.5
H–C(4)	5.05	5.11	2e, 6e	2.0	1.0
H–C(5)	3.71	3.93	3, 4	3.0	3.0
H_e–C(6)	4.66	4.00	4, 5	9.5	8.0
H_a–C(6)	2.78	3.34	5, 6e	4.5	4.0
			5, 6a	10.0	8.0
			6a, 6e	13.5	14.0

[a]) Measured at 297 K in CD_3COCD_3/D_2O; chemical shifts in δ [ppm] and coupling constants in Hz; internal standard: TMS.

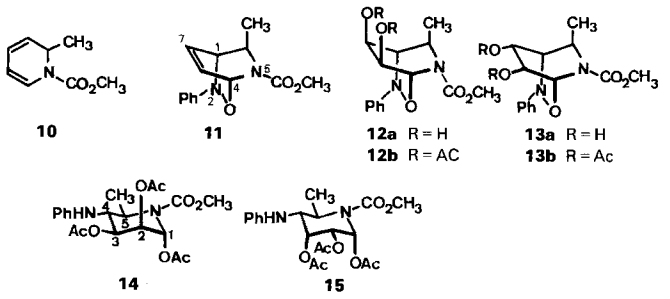
transformation proceeded stepwise: hydrogenolysis of the $PhCH_2$–O bond in **3b**, followed by decarboxylation to the corresponding N–H piperidine and then by hydrogenolysis of the N–O bond led to the free aminosugar which underwent dehydration to the corresponding imine; this latter one was quickly hydrogenated to give **7**. Similar hydrogenolyses of *N*-benzyloxycarbonyl-piperidine-like sugars, followed by dehydration and then by hydrogenation of the imine moiety, have already been described by *Paulsen* [9]. The 360-MHz-^{1}H-NMR spectrum of **8** showed that each of the two acetamido rotamers appeared with its own set of resonance peaks *(Table 2)*. Nevertheless, both rotamers occur in typical chair conformations, as depicted in formula **8** for one of the two enantiomers.

Racemic 4,5-Diamino-4,5,6-trideoxymannopyranose 14 and Racemic 4,5-Diamino-4,5,6-trideoxyallopyranose 15. – The reaction of nitrosobenzene with methyl 2-methyl-1,2-dihydropyridine-1-carboxylate (**10**) led in 75% yield to one *Diels-Alder* adduct only, which proved to be compound **11**, *i.e.* a cycloadduct in which the 5-methyl group is *anti* with respect to the N–O bridge *(Scheme 2)*. This means that the cycloaddition reaction proceeded in a highly regio- and stereospecific way and is very similar – at least as far as stereospecificity is concerned – to the results found by *Natsume* during the [4+2] cycloaddition of singlet oxygen with 2-methyl-1,2-dihydropyridines [10] [11]. Starting from similar 2-methyldihydropyridines and letting them react with maleimides, *Krow* found the same *anti*-stereospecificity for the formation of his *Diels-Alder* cycloadducts [12].

$KMnO_4$ oxidation of **11** at –25°C in neutral conditions proceeded sluggishly and led in poor overall yield (37%) to a mixture of both *cis*-glycols, namely **12a** (20%) and **13a** (17%). These compounds were also characterized as their diacetates **12b** and **13b** *(Scheme 2)*. Quite obviously, the 5-methyl group hinders the normal *anti* approach to the olefinic bond of OsO_4 or of $KMnO_4$ so that these reagents attack both sides of the olefinic double bond, a reaction course which had not been observed during OsO_4 oxidation of the cycloadducts **2a** and **2b**.

Hydrogenolysis of **12b** and of **13b** followed by peracetylation led in good yield to the racemic diaminomannose and diaminoallose **14** and **15**, respectively (highfield ^{1}H-NMR spectra, see *Table 1* and next chapter).

Scheme 2



Structures, Relative Configurations and Predominant Conformations of the Peracetylated Diaminosugars 5, 14, and 15 and of Piperidine 8. – The peracetylated diaminosugars **5**, **14**, and **15** proved to be quite suitable for high-field ^{1}H-NMR analysis which permitted to determine simultaneously the connectivity of their ring H-atoms, their relative configuration, and their major conformation. The ^{1}H-NMR data of their precursors follow from simple retrosynthetic considerations. As to the piperidine derivative **8** which may be considered to be an amino-anhydrodeoxyalditol, its NMR analysis will be discussed separately.

1. *Piperidine* **8**. NMR data obtained with **8** show that it occurs in the form of two rotamers – due to the restricted rotation of the *N*-acetyl group – and that the ring N-atom is flanked by two CH_2-groups *(Table 2)*. The large coupling constants between H–C(5) and Ha–C(6) and between H–C(4) and H–C(5) clearly indicate that **8** is in a chair conformation, and that the 3 protons under consideration are axial. To the contrary, H–C(3) is obviously equatorial.

2. *Structural Considerations*. Since we obtained the methyl glycoside **6** from its diaminolyxose precursor **4**, it follows that the *Diels-Alder* cycloaddition **1a**→**2a** is regiospecific as indicated in *Scheme 1*. This conclusion seems straightforward: the other regioisomer would have given a glycosamine (NHPh group attached to C(1)). The NMR data of the piperidine derivative **8**, which was obtained by hydrogenolysis/hydrogenation followed by acetylation, clearly show that the structure of its precursor must be as shown by formula **3b** (R^2=H). High-field ^{1}H-NMR data for the diaminosugar derivatives **5**, **14**, and **15** (see *Table 1*) show that the chemical shifts for H–C(1), H–C(2), and H–C(3) are as expected for secondary-alcohol and hemiacetal derivatives, whereas H–C(4) appears at higher field since it is located in α-position to the phenylamino group. These findings are corroborated by ^{13}C-NMR data for the ring C-atoms *(Table 3)*: C(1) is deshielded, whereas C(4) is shielded with respect to the chemical shifts of C(2) and C(3).

3. *Relative Configurations and Major Conformations*. The high values which are observed for $^3J_{3,4}$ and $^3J_{4,5a}$ in the ^{1}H-NMR spectra of the aminosugars **4**, **5**, and **14** *(Table 1)* clearly indicate that the piperidine rings are all in a chair conformation and that the protons under consideration are axial. Furthermore, the other $^3J_{H,H}$'s are in agreement with an equatorial H–C(2). For chemical reasons (*cis*-relationship of the C(1) and C(4) substituents, coupled with the anomeric effect), the C(1) substituent is

Table 3. *^{13}C-NMR Data of Ring C-Atoms of the Diaminosugar Derivatives* **4**, **5**, **14**, *and* **15**[a])

	Spectrum frequency [MHz]	Solvent	C(1)	C(2)	C(3)	C(4)	C(5)
4	20.1	(D_6)DMSO	78.85	70.93	69.33	50.52	41.60
5	20.1	$CDCl_3$	76.50	67.43	70.30	49.44	42.88
14	20.1	$CDCl_3$	78.64	68.07	70.67	55.96[b])	53.68[b])
15	90.5	CD_3COCD_3	77.37	67.76	68.09	54.92	50.45

[a]) Chemical shifts in δ [ppm]; internal standards: TMS.
[b]) Attributions may be interchanged.

always axially oriented. This means that we are dealing with α-anomers in the D-series, which are the enantiomers shown in *Schemes 1* and *2* in their $^4C_1$ conformations [13].

As to the diaminopyranose **15**, its ^{1}H-NMR data are also in good agreement with its being predominantly in a chair conformation as shown in *Scheme 2* for the D-enantiomer, at least when the spectrum is measured in (D_6)acetone. We notice in particular the high value for $^3J_{4,5a}$ of the two *trans*-diaxial-oriented H–C(4) and H–C(5) and the appearance of a long-distance W-coupling ($^4J_{1,3}$) between the equatorial H–C(1) and H–C(3). In $CDCl_3$ solution, the magnitude of some J's changes dramatically as shown in *Table 1*. In our opinion, this is best accounted for by assuming an intramolecular H-bond formation between PhN–*H* and *O*–C(3). Such a H-bond leads to a twisting of the chair conformation, as shown by a *Fieser-Dreiding* molecular model. $CDCl_3$ cannot prevent this intramolecular H-bonding to take place, whereas in (D_6)acetone, intermolecular H-bonding (between PhN–*H* and C=*O* of acetone) inhibits the formation of the intramolecular one.

If we compare the high-field ^{1}H-NMR spectra of the diaminolyxose **4** and of its triacetate **5** *(Table 1)*, we arrive at the conclusion that they are in the same chair-type conformation. We must, therefore, assume that the intramolecular H-bonds which occur in **4** do not lead to any distorsion of the predominant chair-type conformation.

Paulsen and *Todt* have prepared a large number of piperidine aminosugars whose ring N-atoms were acylated [14]: in all instances the C(1) substituent proved to be axial (α-anomers in the D-series). According to these authors, the anomeric effect is much stronger in the piperidine-sugar series than in the pyranose-sugar series [14] [15].

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Experimental. – *General.* Flash chromatographies [16] were carried out with silica gel (*Merck 60;* 230–400 mesh) and thin-layer chromatographies on alumina roll *(Merck 60 F_{254})*. Melting points were taken on a *Tottoli* apparatus *(Büchi)* and are not corrected. IR spectra (cm^{-1}) were determined on a *Perkin-Elmer-157-G* spectrometer. ^{1}H- and ^{13}C-NMR spectra were obtained with *Varian-T-60* (^{1}H-NMR only), *Bruker-WP-80-DS,* and *Bruker-WH-360* instruments, with Me_4Si as an internal reference (δ[ppm], J[Hz]). High resolution MS were measured on a *MAT-311* spectrometer. Microanalyses were carried out by the Service Central de Microanalyses of the *C.N.R.S.*

Methyl 2-Phenyl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylate. To a stirred suspension of nitrosobenzene (5.4 g, 50 mmol) in hexane (100 ml) was added dropwise, within 25 min at r.t. under Ar, dihydro-

pyridine **1a** (7.1 g, 50 mmol) which had been freshly purified by quick chromatography over basic alumina [17]. After a few h, the green colour of nitrosobenzene had disappeared and a light-gray precipitate had formed which was filtered off, washed with a small amount of hexane, and dried *in vacuo* at r.t. The almost colourless crystals of **2a** (10.7 g, 86%), homogeneous according to TLC, could not be recrystallized without decomposing. IR (KBr): 2960, 1710, 1590, 1480. ^{1}H-NMR ($CDCl_3$, 80 MHz): 6.91–7.37 (*m*, 5 arom. H); 6.67 (*m*, H–C(8)); 6.20 (*m*, H–C(4), H–C(7)); 4.55 (*m*, H–C(1)); 4.00 (*dd*, J = 10.5, 3.0, H–C(6)); 3.77 (*s*, CH_3O); 3.28 (*dd*, J = 10.5, 3.0, H–C(6)). MS: 246.1007 ($C_{13}H_{14}N_2O_3$, calc. 246.100434).

Benzyl 2-Phenyl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylate (**2b**). Preparation similar to the one of **2a** starting from nitrosobenzene (5.4 g, 50 mmol) and dihydropyridine **1b** (10.7 g, 50 mmol) [18]. Adduct **2b** (12.0 g, 75%) as colourless crystals, m.p. 105.5° (MeOH). IR (KBr): 3050, 1700, 1595, 1495. ^{1}H-NMR ($CDCl_3$, 60 MHz): 6.90–7.4 (*m*, 10 arom. H); 6.7 (*m*, H–C(6)); 6.2 (*m*, H–C(4), H–C(7)); 5.2 (*s*, PhCH_2); 4.5 (*m*, H–C(1)); 4.0 (*dd*, J = 11.0, 2.5, H–C(6)); 3.3 (*dd*, J = 11.0, 2.5, H–C(6)). ^{13}C-NMR ($CDCl_3$, 20.1 MHz)[2]): 154.39 (*sm*, CO); 153.70 (*sm*, CO); 150.24 (*st*, $C_{subst.}$); 136.08 (*sm*, $C_{subst.}$); 130.20, 129.79, 128.97 (all *d*, *o*-C, *m*-C, *p*-C, C(7), C(8)); 128.38 (*dd*, *m*-C); 127.92, 127.06, 126.92 (all *d*, *o*-C, *m*-C, *p*-C, C(7), C(8)); 122.78 (*dt*, *p*-C); 117.26 (*dt*, *o*-C); 75.13, 74.77 (both *d*, J = 170, C(4)), 66.93 (*ts*, J = 147, PhCH_2); 56.32 (*d*, J = 150, C(1)); 44.57 (*ts*, J = 147, CH_2). Anal. calc. for $C_{19}H_{18}N_2O_3$ (322.35): C 70.79, H 5.63, N 8.69; found: C 70.5, H 5.6, N 9.1.

Methyl 6-Methyl-2-phenyl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylate (**11**). To a stirred solution of nitrosobenzene (8.3 g, 77 mmol) in CH_2Cl_2 (100 ml) which was kept at r.t. under Ar was added dropwise freshly purified 2-methyl-1,2-dihydropyridine **10** (11.8 g, 77 mmol) [18]. After about 20 h, the solution turned brown and was evaporated at r.t. The resulting mixture was separated by flash chromatography (cyclohexane/AcOEt 7:3) and yielded **11** as a colourless oil (15.2 g, 75%). IR (CH_2Cl_2): 2930, 1710, 1595, 1485, 1450, 1380. ^{1}H-NMR ($CDCl_3$, 80 MHz): 6.91–7.33 (*m*, 5 arom. H); 6.62 (*m*, H–C(8)); 6.10 (*m*, H–C(4), H–C(7)); 4.20–4.39 (*m*, H–C(1), H–C(6)); 3.74 (*s*, CH_3O); 1.8 (*d*, J = 6.5, CH_3–C(5)).

*4,5-Dimethyl-2-phenyl-3,6-dihydro-2*H*-1,2-oxazine* (**9**). To a solution of 2,3-dimethylbutadiene (2.25 ml, 20 mmol) in $CHCl_3$ (10 ml) was added at r.t. under Ar a solution of **2a** (500 mg, 2 mmol) in $CHCl_3$ (10 ml). After 5 days at r.t., **2a** had disappeared according to TLC. Evaporation of the solvent and separation by flash chromatography (cyclohexane/AcOEt 9:1) gave a homogeneous yellow oil which was crystallized from EtOH at −20° to yield **9** (65 mg, 17%). Oxazine **9** was synthetized independently from 2,3-dimethylbutadiene and nitrosobenzene [3], m.p. 37–38° ([3]: 39.5–40.5°). IR (KBr): 2960, 1600, 1490. ^{1}H-NMR ($CDCl_3$, 60 MHz): 6.90–7.3 (*m*, 5 arom. H); 4.3 (*m*, CH_2O); 3.6 (*m*, CH_2N); 1.6 (*m*, 2 CH_3).

7,8-Dihydroxy-2-phenyl-3-oxa-2,5-diazabicyclo[2.2.2]octane-5-carboxylate (**3a**) (*cf.* [7]). To a stirred solution of **2a** (12.3 g, 50 mmol) in EtOH (400 ml) and acetone (300 ml) at −25° was added dropwise within 2 h a solution of $KMnO_4$ (11.5 g, 75 mmol) and anh. $MgSO_4$ (11.5 g, 95 mmol) in H_2O (500 ml). The mixture was stirred for another 5 h at −25° until **2a** had disappeared according to TLC. 'Sodium metabisulfite' ($Na_2S_2O_5$; 5 g, 26 mmol) was added to the stirred mixture at r.t. After evaporation of acetone and EtOH, the remaining H_2O solution was extracted continuously for 2 days with CH_2Cl_2. The CH_2Cl_2 solution was then dried over $MgSO_4$ and evaporated. The solid residue was recrystallized from hexane/CH_2Cl_2 yielding **3a** (6.0 g); an additional amount of **3a** (600 mg) was isolated by flash chromatography (cyclohexane/AcOEt 2:8) of the residue obtained after evaporation of the mother liquors. Total amount of **3a**: 6.6 g (47%), colourless crystals, m.p. 164–164.5°. IR (KBr): 3440, 3320, 2960, 1680, 1590, 1485. IR (CCl_4): 1724, 1696. ^{1}H-NMR ($CDCl_3$, 60 MHz): 7.0–7.5 (*m*, 5 arom. H); 5.8 (*m*, H–C(4)); 4.4 (*m*, H–C(7), H–C(8)); 4.0 (*m*, H–C(1)); 3.8 (*s*, CH_3O); 3.7 (*m*, 2H–C(6)); 2.1 (*s*, 2 OH). ^{13}C-NMR (CD_3OD, 20.1 MHz): 157.77 (*s*, CO); 151.12 (*st*, $C_{subst.}$); 129.94 (*dd*, *m*-C); 123.61 (*dt*, *p*-C); 117.32 (*dt*, *o*-C); 81.29 (*d*, J = 171, C(4)); 66.54 (*d*, J = 154, C(8)); 64.44 (*d*, J = 155, C(7)); 59.52 (*dd*, J = 152, C(1)); 53.37 (*qs*, J = 152, CH_3O); 39.30 (*t*, J = 151, C(6)). Anal. calc. for $C_{13}H_{16}N_2O_5$ (280.27): C 55.71, H 5.75, N 10.00; found: C 55.8, H 5.8, N 10.0.

Benzyl 7,8-Dihydroxy-2-phenyl-3-oxa-2,5-diazabicyclo[2.2.2]octane-5-carboxylate (**3b**; R^2=H). To a solution of *N*-methylmorpholine *N*-oxide monohydrate (4.45 g, 33 mmol) in H_2O (100 ml) and acetone (150 ml) was added a solution of **2b** (10 g, 31 mmol) in acetone (250 ml). To this stirred mixture cooled to 0° was added dropwise a solution of OsO_4 (152 mg, 0.6 mmol) in *t*-BuOH (31 ml) whereby the mixture turned brown. After 1 h at 0° and 23 h at r.t., **2b** had disappeared according to TLC. Excess of oxidation agents was destroyed by addition of Na_2SO_3 (4 g). Then, the mixture was diluted at r.t. with acetone (200 ml). After filtration and removal of the solid material, the solution was evaporated. The resulting brown residue was dissolved in CH_2Cl_2

[2]) Mixture of two rotamers (urethane moiety).

(900 ml), washed twice with 2N H_2SO_4, with H_2O, $NaHCO_3$ soln. and some brine, dried with $MgSO_4$ and the solvent evaporated to give 10 g of a slightly brown product. This residue was treated with decolourising charcoal and then recrystallized from $CHCl_3$/petroleum ether: **3b** (R^2=H; 8.8 g, 80%) as colourless crystals, m.p. 161.5°. IR (KBr): 3440, 3300, 1675, 1600, 1495. IR (CCl_4): 1722, 1677. ^{1}H-NMR ($CDCl_3/D_2O$, 80 MHz): 6.99–7.37 (*m*, 10 arom. H); 5.75 (*d*, *J* = 3.0, H–C(4)); 5.14 (*s*, PhCH_2); 4.40 (*m*, H–C(7), H–C(8)); 3.94 (*m*, H–C(1)); 3.67 (*m*, 2H–C(6)). Anal. calc. for $C_{19}H_{20}N_2O_5$ (356.37): C 64.03, H 5.66, N 7.86; found: C 64.5, H 5.7, N 7.6.

Benzyl 7,8-Diacetoxy-2-phenyl-3-oxa-2,5-diazabicyclo[2.2.2]octane-5-carboxylate (**3b**, R^2=Ac). A solution of **3a** (R^2=H; 1.84 g, 5.2 mmol) in pyridine (4.1 g, 50 mmol) and Ac_2O (2.1 g, 20 mmol) was left to stand at r.t. overnight. After evaporation of the liquids, the residue was dissolved in CH_2Cl_2, washed with 1N HCl, H_2O, $NaHCO_3$ soln., and brine, and dried over $MgSO_4$. After evaporation of the solvent, the resulting solid material was dissolved in EtOH and the solution evaporated. This procedure was repeated 3 times (removal of Ac_2O). Colourless crystals of **3b** (R=Ac; 2.04 g, 90%), m.p. 141° (EtOH). IR (KBr): 1740, 1710, 1595, 1490. IR (CCl_4): 1723 (urethane). ^{1}H-NMR ($CDCl_3$, 80 MHz): 7.00–7.35 (*m*, 10 arom. H); 5.90 (*m*, H–C(4)); 5.38 (*m*, H–C(7), H–C(8)); 5.14 (*m*, PhCH_2); 4.07 (*m*, H–C(4)); 3.70 (*m*, 2H–C(5)); 2.09 (*s*, 2 Ac). Anal. calc. for $C_{23}H_{24}N_2O_7$ (440.44): C 62.72, H 5.49, N 6.36; found: C 62.8, H 5.6, N 6.3.

Methyl 7,8-Dihydroxy-6-methyl-2-phenyl-3-oxa-2,5-diazabicyclo[2.2.2]octane-5-carboxylates (**12a** and **13a**; R=H). To a stirred solution of **11** (4.6 g, 17.7 mmol) in EtOH (250 ml) at −25° was added dropwise within 1 h a solution of $KMnO_4$ (4.2 g, 26.6 mmol) and anh. $MgSO_4$ (3.2 g, 26.6 mmol) in H_2O (200 ml). After 7 h at −25°, a small amount of $KMnO_4$ (0.8 g, 5 mmol) was added and the mixture left overnight at −25°. 'Sodium metabisulfite' (2.5 g, 13 mmol) was added and the stirred mixture left to warm up to r.t. After evaporation of EtOH the aq. soln. was extracted continuously for 2 days with CH_2Cl_2, the CH_2Cl_2 solution dried over $MgSO_4$, and evaporated. The residue was separated by flash chromatography (cyclohexane/AcOEt 3:7) leading to **12a** (890 mg, 17%) and **13a** (1.04 g, 20%) in that order. *Glycol* **12a**: Colourless oil, homogeneous according to TLC. IR ($CHCl_3$): 3400, 1705, 1595, 1490. IR (CCl_4): 1727, 1688. ^{1}H-NMR ($CDCl_3$, 60 MHz): 6.9–7.4 (*m*, 5 arom. H); 5.8 (*m*, H–C(4)); 4.4 (*m*, H–C(7), H–C(8)); 3.7–4.1 (*m*, H–C(1), H–C(6)); 3.7 (*s*, CH_3O); 2.1 (*s*, OH); 1.5 (*d*, *J* = 6.5, CH_3). ^{13}C-NMR ($CDCl_3$, 20.1 MHz): 156.94 (*sm*, CO); 148.92 (*st*, $C_{subst.}$), 128.79 (*dd*, *m*-C); 122.46 (*dt*, *p*-C); 115.90 (*dt*, *o*-C); 78.78 (*ds*, *J* = 170, C(4)); 65.02 (*dm*, *J* = 154, C(8)); 64.43 (*dm*, *J* = 154, C(7)); 61.42 (*dm*, *J* = 149, C(1)); 52.68 (*qs*, *J* = 149, CH_3O); 48.30 (*dm*, *J* = 146, C(6)); 17.38 (*q*, *J* = 129, CH_3). MS 294.1206 ($C_{14}H_{18}N_2O_5$, calc. 294.121560).

Glycol **13a**: Colourless crystals (from EtOH), m.p. 154.5°. IR (KBr): 3340, 1710, 1600, 1490. IR (CCl_4): 1726. ^{1}H-NMR ($CDCl_3/D_2O$, 60 MHz): 6.9–7.3 (*m*, 5 arom. H); 5.6 (*s*, H–C(4)); 4.1–4.4 (*m*, H–C(7), H–C(8)); 3.7–4.0 (*m*, H–C(1), H–C(6)); 3.7 (*s*, CH_3O); 1.0 (*d*, *J* = 6.0, CH_3). ^{13}C-NMR (20.1 MHz, $CDCl_3$): 155.34 (*sm*, CO); 149.29 (*st*, $C_{subst.}$); 129.02 (*dd*, *m*-C); 122.73 (*dt*, *p*-C); 116.26 (*dt*, *o*-C); 81.87 (*dm*, *J* = 171, C(4)); 65.61 (*d*, *J* = 152, C(8)); 63.38 (*dm*, *J* = 148, C(1)); 62.52 (*dm*, *J* = 156, C(7)); 52.77 (*qs*, *J* = 149, CH_3O); 46.62 (*dm*, *J* = 142, C(6)); 16.65 (*qs*, *J* = 129, CH_3). Anal. calc. for $C_{14}H_{18}N_2O_5$ (294.30): C 57.13, H 6.17, N 9.52; found: C 57.2, H 6.1, N 9.6.

Diacetyl Derivative **12b**. Acetylation of **12a** (2.45 g, 8.33 mmol) as above for **3b**. After flash chromatography (cyclohexane/AcOEt 6:4) and recrystallisation from EtOH/hexane (2.3 g, 73%), m.p. 117°. IR (KBr): 1740, 1710, 1590, 1490. IR (CCl_4): 1726 (CO, urethane). ^{1}H-NMR ($CDCl_3$, 60 MHz): 6.8–7.4 (*m*, 5 arom. H); 6.0 (*m*, H–C(4)); 5.4 (*m*, H–C(7), H–C(8)); 3.9–4.2 (*m*, H–C(1), H–C(6)); 3.7 (*s*, CH_3O); 2.1 (*s*, 2 AcO); 1.4 (*d*, *J* = 6.5, CH_3). Anal. calc. for $C_{18}H_{22}N_2O_7$ (378.37): C 57.13, H 5.86, N 7.40; found: C 57.5, H 5.8, N 7.5.

Diacetyl Derivative **13b**. Acetylation of **13a** (1.95 g, 6.63 mmol) as above for **3b** gave **13b** (2.3 g, 92%) as colourless crystals, m.p. 140.5° (AcOEt/petroleum ether). IR (KBr): 1755, 1735, 1710, 1590, 1485. IR (CCl_4): 1728 (CO, urethane). ^{1}H-NMR ($CDCl_3$, 80 MHz): 6.97–7.39 (*m*, 5 arom. H); 5.84 (*m*, H–C(4)); 5.60 (*dd*, *J* = 9.0, 2.75; H–C(7)); 5.06 (*dd*, *J* = 9.0, 1.75; H–C(8)); 4.10 (*m*, H–C(1), H–C(6)); 3.72 (*s*, CH_3O); 2.18 (*s*, AcO); 2.08 (*s*, AcO); 1.32 (*d*, *J* = 6.4, CH_3). Anal. calc. for $C_{18}H_{22}N_2O_7$ (378.37): C 57.13, H 5.86, N 7.40; found: C 57.0, H 5.8, N 7.8.

*4,5-Dideoxy-5-(methoxycarbonyl)amino-4-(phenylamino)-αβ-*DL*-lyxopyranose* (**4**). A stirred solution of **3a** (545 mg, 1.9 mmol) in EtOH (20 ml) was placed under H_2 at r.t. in the presence of 10% Pd/C (60 mg). After 5 h, **3a** had disappeared according to TLC, the mixture was filtered over *Celite* and the resulting soln. evaporated. The colourless and viscous residue was crystallized from THF/petroleum ether yielding **4** (382 mg, 71%), m.p. 147.5–148.5°. IR (KBr): 3400–3320, 1635, 1600, 1495. ^{1}H-NMR: see *Table 1*. ^{13}C-NMR ((D$_6$)DMSO, 20.1 MHz): see also *Table 3;* 155.69 (*s*, CO); 148.73 (*st*, $C_{subst.}$); 129.05 (*dd*; *m*-C); 115.89 (*dt*, *p*-C); 112.33 (*dm*, *o*-C); 78.85 (*d*, *J* = 163, C(1)); 70.93 (*d*, *J* = 150, C(2)), 69.33 (*dm*, *J* = 141, C(3)); 52.39 (*qs*, *J* = 147, CH_3O); 50.52 (*dm*, *J* = 140, C(4)); 41.60 (*tm*, *J* = 141, C(5)). MS: 282.1212 ($C_{13}H_{18}N_2O_5$, calc. 282.1216).

Table 4. *400-MHz-^{1}H-NMR Spectrum of the Ring Protons of* **6** *(2 Rotamers), Measured at 253 K in $CDCl_3$*

	δ_I (ppm)	δ_{II} (ppm)	i, j	$J_{i,j}$ [Hz]
H–C(1)	5.44	*ca.* 5.30	1, 2	3.0
H–C(2)	*ca.* 5.30	5.21	2, 3	3.0
H–C(3)	*ca.* 5.30	5.30	3, 4	10.0
H–C(4)	*ca.* 3.80	*ca.* 3.80	4, 5e	5.0
H_e–C(5)	4.48	4.31	5e, 5a	13.0
H_a–C(5)	2.81	2.75	4, 5a	12.0
			1, 5e	1.0

*1,2,3-Tri-*O*-acetyl-4,5-dideoxy-5-(methoxycarbonyl)amino-4-(phenylamino)-αβ-*DL*-lyxopyranose* (**5**). Acetylation of **4** (290 mg, 1 mmol) as above for **3b** gave **5** as colourless crystals (325 mg, 79%), m.p. 163.5–164.5° (EtOH). IR (KBr): 3350, 1760, 1740, 1735, 1710, 1600, 1500. ^{1}H-NMR: see *Table 1.* ^{13}C-NMR ($CDCl_3$, 20.1 MHz): see also *Table 3;* 170.65 (*sqd*, CH_3CO); 169.05 (*sqd*, CH_3CO); 168.01 (*sqd*, CH_3CO); 154.89 (*s*, NCO_2CH_3); 146.46 (*st*, $C_{subst.}$); 129.02 (*dd*, *m*-C); 117.81 (*dt*, *p*-C); 112.89 (*dt*, *o*-C); 76.50 (*dd*, J = 170, C(1)); 70.30 (*dm*, J = 147, C(3)); 67.43 (*ds*, J = 157, C(2)); 53.09 (*qs*, J = 148, CH_3O); 49.44 (*dm*, J = 140, C(4)); 42.88 (*tm*, J = 144, C(5)); 20.16 (*qs*, J = 131, 3 CH_3CO). Anal. calc. for $C_{19}H_{24}N_2O_8$ (408.40): C 55.87, H 5.92, N 6.86; found: C 55.5, H 5.9, N 7.0.

*Methyl 2,3-Di-*O*-acetyl-4,5-dideoxy-5-(methoxycarbonyl)amino-4-(phenylamino)-αβ-*DL*-lyxopyranoside* (**6**). A solution of **4** (420 mg, 1.5 mmol) and trace amounts of TsOH in anh. MeOH (30 ml) was left to stand at r.t. under Ar in the dark. After 3 days, the solution turned dark-red and the starting material had disappeared according to TLC. Some pyridine was added, and the MeOH was evaporated. Some additional pyridine (4 ml) and Ac_2O (1.8 g, 15.5 mmol) were added and the mixture was left to stand at r.t. for 20 h. After evaporation, the viscous residue was dissolved in CH_2Cl_2, washed with H_2O and brine, dried over $MgSO_4$, and the solvent evaporated. The residue was taken up in EtOH and again evaporated; this was repeated 3 times (removal of Ac_2O). Flash chromatography of the residue (cyclohexane/AcOEt 6:4) led to **6** (325 mg; 57%), m.p. 168–169° (EtOH). IR (KBr): 3360, 1740, 1700, 1600, 1500. ^{1}H-NMR: see *Table 4.* Anal. calc. for $C_{18}H_{24}N_2O_7$ (380.39): C 56.83, H 6.36, N 7.37; found: C 56.8, H 6.7, N 7.4.

r-*3*,c-*4-Diacetoxy-*N*-acetyl-5-(phenylamino)piperidine* (**8**). To a stirred solution of **3b** (1.0 g, 2.8 mmol) in THF (25 ml) and EtOH (25 ml) was added 10% Pd/C (100 mg). The suspension was placed under H_2 (50 bar) at r.t. in a *Parr* apparatus overnight. After filtration of the mixture over *Celite*, the solution was evaporated, the residue dissolved in pyridine (4 ml), Ac_2O (1 ml) added, and the mixture left to stand overnight at r.t. After addition of some toluene, the solution was evaporated; this was reproduced twice, with EtOH instead of toluene (removal of Ac_2O). The residue was purified by flash chromatography (cyclohexane/AcOEt 2:8) giving **8** (712 mg, 76%) which was recrystallised from EtOH/petroleum ether, m.p. 156.5°. IR (KBr): 3340, 1745, 1650, 1230. ^{1}H-NMR: see *Table 2.* ^{13}C-NMR ($CDCl_3$, 20.1 MHz; mixture of 2 rotamers **I** and **II**): 170.65 (*s*, CO); 170.01 (*s*, CO); 169.83 (*s*, CO); 169.60 (*s*, CO); 146.51 (*st*, $C_{subst.}$ **I**); 146.23 (*st*, $C_{subst.}$ **II**); 129.15 (*dd*, *m*-C); 117.99 (*dt*, *p*-C **II**); 117.81 (*dt*, *p*-C **I**); 112.98 (*d*, *o*-C); 72.22 (*d*, J = 147, C(3) **I**); 71.85 (*d*, J = 147, C(3) **II**); 67.62 (*d*, J = 153, C(2) **I**); 66.80 (*d*, J = 153, C(2) **II**); 50.49 (*d*, J = 141, C(4) **II**); 50.26 (*d*, J = 141, C(4) **I**); 48.21 (*t*, J = 141, C(5) **II**); 47.39 (*t*, J = 141, C(5) **I**); 44.25 (*t*, J = 142, C(1) **I**); 42.20 (*t*, J = 142, C(1) **II**); 20.88 (*q*, $COCH_3$ **II**); 20.47 (*q*, $COCH_3$ **I**). Anal. calc. for $C_{17}H_{22}N_2O_5$ (334.36): C 61.06, H 6.63, N 8.38; found: C 61.3, H 6.7, N 8.7.

*1,2,3-Tri-*O*-acetyl-4,5,6-trideoxy-5-(methoxycarbonyl)amino-4-(phenylamino)-αβ-*DL*-mannopyranose* (**14**). To a stirred soln. of **12b** (380 mg, 1 mmol) in THF (20 ml) was added 5% Pd/C (60 mg). The suspension was placed under H_2 at r.t. for 20 h. The suspension was filtered over *Celite*, and pyridine (3 ml) and Ac_2O (1 g; 10 mmol) were added to the resulting soln. After about 20 h at r.t., the solution was evaporated, the residue dissolved in a few ml of CH_2Cl_2, washed with 2N HCl, some H_2O, aq. $NaHCO_3$ soln., brine, dried over $MgSO_4$, and the solvent evaporated. The solid residue was taken up in EtOH and evaporated; this was repeated 3 times (removal of Ac_2O). The resulting **14** was recrystallised from EtOH/petroleum ether (330 mg, 78%), m.p. 134.5–135°. IR (KBr): 3350, 1765, 1745, 1735, 1715, 1600, 1530, 1495. ^{1}H-NMR: see *Table 1.* ^{13}C-NMR ($CDCl_3$, 20.1 MHz): see also *Table 3;* 170.47 (*sqd*, CH_3CO); 169.14 (*sqd*, CH_3CO); 168.28 (*sqd*, CH_3CO); 155.89 (*sm*, NCO_2CH_3); 147.37 (*st*, $C_{subst.}$); 129.06 (*dd*, *m*-C); 117.86 (*dt*, *p*-C); 113.12 (*dt*, *o*-C); 78.64 (*ds*, J = 170, C(1)); 70.67 (*d*, J = 150, C(3)); 68.07 (*dd*, J = 156, C(2)); 55.96 (*dm*, J = 142, C(4) or C(5)); 53.68 (*dm*, J = 142, C(5) or C(4)); 52.68 (*qs*, J = 148, CH_3O); 20.43 (*qs*, J = 131, CH_3CO); 20.34 (*qs*, J = 131, CH_3CO); 20.20 (*qs*,

J = 131, CH_3CO); 17.42 (*qs*, J = 130, CH_3). Anal. calc. for $C_{20}H_{26}N_2O_8$ (422.42): C 56.86, H 6.20, N 6.63; found: C 57.1, H 6.1, N 6.5.

1,2,3-Tri-O-acetyl-4,5,6-trideoxy-5-(methoxycarbonyl)amino-4-(phenylamino)-αβ-DL-allopyranose (**15**). Prepared as above for **14**. Starting from **13b** (380 mg; 1 mmol), **15** (270 mg, 64%) was obtained as colourless crystals, m.p. 161.5° (CH_2Cl_2/petroleum ether). IR (KBr): 3370, 1765, 1750, 1720, 1600, 1525, 1495. ^{1}H-NMR: see *Table 1*. ^{13}C-NMR ((D_6)aceton, 90.5 MHz): see also *Table 3;* 170.41 (*sm*, CH_3CO); 169.71 (*sm*, CH_3CO); 169.63 (*sm*, CH_3CO); 156.28 (*sm*, NCO_2CH_3); 148.33 (*sm*, $C_{subst.}$); 129.88 (*dd*, *m*-C); 117.98 (*dt*, *p*-C); 114.14 (*dt*, *o*-C); 77.37 (*dd*, J = 167, C(1)); 68.09 (*dm*, J = 155.0, C(3)); 67.75 (*dt*, J = 144.5, C(2)); 54.92 (*dt*, J = 138.5, C(4)); 53.16 (*qs*, J = 147.0, CH_3O); 50.45 (*ddq*, J = 142.5, C(5)); 20.82 (*qs*, J = 128, CH_3CO); 20.72 (*qs*, J = 128, CH_3CO); 20.45 (*qs*, J = 129, CH_3CO); 18.05 (*qt*, J = 128.4, C(6)). Anal. calc. for $C_{20}H_{26}N_2O_8$ (422.42): C 57.86, H 6.20, N 6.63; found: C 57.2, H 6.4, N 6.8.

REFERENCES

[1] J. Streith, G. Augelmann, H. Fritz, H. Strub, *Tetrahedron Lett.* **1982,** *23,* 1909.
[2] E.E. Knaus, K. Avasthi, C.S. Giam, *Can. J. Chem.* **1980,** *58,* 2447.
[3] Yu. A. Arbuzov, N.L. Fedyukina, V.V. Shavyrina, R.I. Shepeleva, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk* **1952,** 566; *Chem. Abstr.* **1953,** *47,* 4342f.
[4] K.B. Wiberg, K.A. Saegebarth, *J. Am. Chem. Soc.* **1957,** *79,* 2822.
[5] K. Akashi, R.E. Palermo, K.B. Sharpless, *J. Org. Chem.* **1978,** *43,* 2063.
[6] V. Van Rheenen, R.C. Kelly, D.Y. Cha, *Tetrahedron Lett.* **1976,** 1973; V. Van Rheenen, D.Y. Cha, W.M. Hartley, *Org. Synth.* **1978,** *58,* 44.
[7] G. Kresze, P. Heidegger, A. Asbergs, *Justus Liebigs Ann. Chem.* **1970,** *738,* 113.
[8] C.H. Kuo, N.L. Wendler, *Tetrahedron Lett.* **1984,** *25,* 2291.
[9] H. Paulsen, Y. Hagauchi, V. Sinnwell, *Chem. Ber.* **1980,** *113,* 2601.
[10] M. Natsume, M. Wada, M. Ogawa, *Chem. Pharm. Bull. Jpn.* **1978,** *26,* 3364.
[11] M. Natsume, M. Ogawa, *Heterocycles* **1980,** *14,* 169; *ibid.* **1980,** *14,* 615; *ibid.* **1981,** *16,* 973.
[12] G.R. Krow, J.T. Carey, D.E. Zacharias, E.E. Knaus, *J. Org. Chem.* **1982,** *47,* 1989.
[13] J. Stoddart, in 'Stereochemistry of Carbohydrates', Wiley-Interscience, New York, 1971; IUPAC-IUB, *Pure Appl. Chem.* **1981,** *53,* 1901.
[14] H. Paulsen, K. Todt, *Adv. Carbohydr. Chem.* **1968,** *23,* 115.
[15] H. Paulsen, F. Leupold, *Chem. Ber.* **1969,** *102,* 2804.
[16] W.C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978,** *43,* 2923.
[17] F.W. Fowler, *J. Org. Chem.* **1972,** *37,* 1321.
[18] R.J. Sundberg, J.D. Bloom, *J. Org. Chem.* **1981,** *46,* 4836.