63. Syntheses of Diamino-dideoxylyxose Derivatives using Acylnitroso Dienophiles[1])

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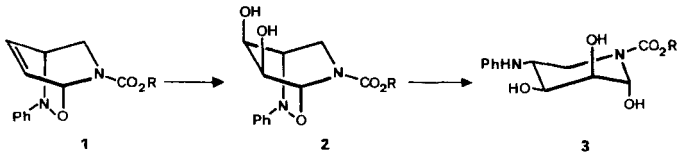
N-Acylnitroso derivatives **6** which were prepared by *in-situ* oxidation of the corresponding hydroxamic acids **5** reacted instantaneously and in high yields with dihydropyridine **4**. The *Diels-Alder* adducts **8** were formed regiospecifically with the acylnitroso dienophiles **6a–c**, whereas the dienophiles **6d–f** gave mixtures of both regioisomers **7** and **8**. These and some other results [2] were best explained by the FMO theory. The *Diels-Alder* adducts **7** and **8** gave the corresponding *'anti'-cis*-glycols when reacted with OsO_4/*N*-methylmorpholine *N*-oxide. Hydrogenolysis of the N–O bond followed by peracetylation led to the expected aminolyxose derivatives **14** and **16**. A similar sequence, using **4** and the hydroxamic-acid derivative **18** of (+)-D-mandelic acid led, with a poor asymmetric induction, to a mixture of the expected optically active aminolyxose compounds **19A/19B**.

Introduction. – In [2], we described some simple three-step syntheses of racemic diamino-sugar derivatives. During the first step, *Diels-Alder* cycloadditions between some 1,2-dihydropyridines and nitrosobenzene led regiospecifically to the bicyclic compounds **1**. These latter ones were oxidized to the *'anti'*-glycols **2** and then hydrogenolyzed to the expected racemic diamino sugars **3** *(Scheme 1)*. These syntheses permitted as a rule to obtain one racemic stereoisomer (**3**) out of the four possible ones. They seem to be of interest, since a few naturally occurring amino sugars with a piperidine ring have been isolated in recent years [3–6].

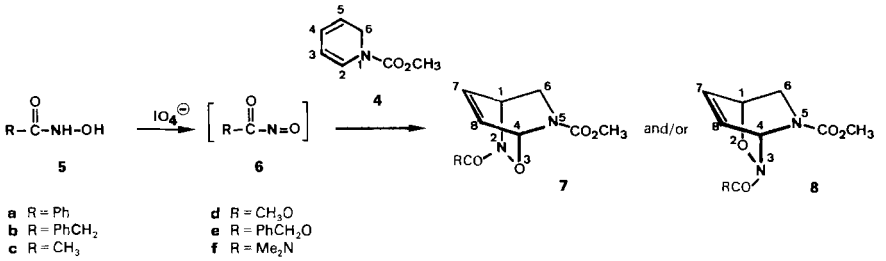
Scheme 1



The introduction of an anilino group – instead of a free primary amino group – is a major drawback of this first synthetic approach, since the Ph moiety is difficult to remove in a later step. It should be noted, however, that in a few instances, some *para*-substituted anilino derivatives could be cleaved to the corresponding free amines [7]. Our next goal was, therefore, to use acylnitroso dienophiles in order to obtain *N*-(acylamino)sugars, after hydrogenolysis of the N–O bond. Amides can be cleaved to give the corresponding

[1]) Presented at the '4th REGIO Symposium in Organic and Bioorganic Chemistry', September 26–28, 1984, at Wintzfelden, France, which was organized by the Universities of Basel, Switzerland, of Freiburg i.Br., Germany, and of Mulhouse, France. For a preliminary communication, see [1].

Scheme 2



primary amines, especially when the N-atom is part of a (benzyloxycarbonyl)amino functionality [8].

Acylnitroso dienophiles **6** are highly reactive and cannot be isolated as such. They are obtained by *in-situ* oxidation of the corresponding hydroxamic acids **5** (see *Scheme 2*), and in the presence of some diene they react instantaneously [9–11]. We shall describe here some reaction sequences analogous to the one depicted in *Scheme 1*, but using acylnitroso dienophiles **6** instead of nitrosobenzene and the diene dihydropyridine **4** [1]. Quite recently, *Dobey* and *Knaus* have described some experimental results which are identical to ours, at least as far as the cycloaddition between dihydropyridines and acylnitroso dienophiles is concerned [12]; they did not describe the total synthesis of diamino sugars.

Cycloadditions of Dihydropyridine 4 with Acylnitroso Dienophiles 6 and their Interpretation by the FMO Theory. – Slow addition of the hydroxamic acids **5a–f** to a solution of dihydropyridine **4** and of Pr_4NIO_4 at 0° in CH_2Cl_2 led in a fast reaction to the *Diels-Alder* adducts **7** and/or **8** *(Scheme 2)*. The only rate-limiting factor was the rate of dissolution of the various hydroxamic acids **5a–f**. It was pleasing to note that **4** was not oxidized under these conditions. The results collected in *Table 1* clearly indicate that the

Table 1. *Relative Yields of Cycloadducts* **7** *and* **8** *from RCO–N=O Dienophiles* **6** *and Dihydropyridine* **4**

Series	**a**	**b**	**c**	**d**	**e**	**f**	**g**
R	Ph	$PhCH_2$	CH_3	CH_3O	$PhCH_2O$	Me_2N	Ph[a]) [2]
Direct adduct[1]) **7** [%]	0	0	0	50	50	75	100
Inverse adduct[1]) **8** [%]	100	100	100	50	50	25	0

[a]) RCO is replaced by Ph.

acylnitroso dienophiles can be divided into two groups, *a)* those which lead regiospecifically to the inverse adducts[1]) **8a–c**, *i.e.* benzoyl-, phenylacetyl-, and acetylnitroso dienophiles, and *b)* those which lead to a mixture of both the direct and the inverse adducts[1]) **7d–f** and **8d–f**[2]), respectively, *i.e.* methoxycarbonyl-, benzyloxycarbonyl-, and (dimethylcarbamoyl)nitroso dienophiles. Overall yields proved to be excellent, with the exception of adduct **8c** which, for that reason, was not used any further. All these products proved

[1]) By convention, we shall name products **7** *direct adducts* and products **8** *inverse adducts*.

[2]) Nitrosobenzene led regiospecifically, but with a very small reaction rate, to the direct adducts **1** [2] (see **7g** in *Table 1*).

Table 2. *^{1}H-NMR Data* ($CDCl_3$) *of Some Direct and Inverse Adducts* 7 *and* **8**, *Respectively*. 80 MHz, 300 K; δ in ppm and J in Hz, internal standard TMS[a]).

	H–C(1)	H–C(4)	H–C(6)	H′–C(6)	H–C(7)	H–C(8)	J(1,6)	J(1,6′)	J(1,7)	J(1,8)	J(4,7)	J(4,8)	J(6,6′)	J(7,8)	Other signals
8a R = Ph	4.96	6.66	3.91	3.18	6.54	6.72	3.3	1.1	5.7	2.2	2.0	5.6	11.3	7.8	3.75 (MeO); 7–7.8 (arom. H)
8c R = CH_3	4.92	6.74	3.84	3.20	6.56	6.79	3.2	1.4	5.7	2.0	1.9	5.6	11.2	7.9	2.00 (AcN); 3.76 (MeO)
8d R = CH_3O	4.92	6.42	3.83	3.11	6.60	6.74	3.3	1.3	5.9	1.9	1.8	5.5	11.4	8.1	3.75, 3.77 (2 MeO)
8f R = Me_2N	4.72	6.22	3.81	3.07	6.54	6.78	3.4	1.2	5.9	1.8	1.7	5.4	*ca.*12	8.2	3.75 (MeO); 2.92 (Me_2N)
7d R = CH_3O	4.95	6.16	3.83	3.20	6.62	6.66	2.9	2.1	5.6	2.4	1.7	5.1	10.9	8.2	3.74, 3.76 (2 MeO)
7f R = Me_2N	4.80	6.00	3.80	3.18	6.70	6.58	2.8	2.2	5.2	2.4	2.0	4.8	10.9	8.1	3.75 (MeO); 2.92 (Me_2N)

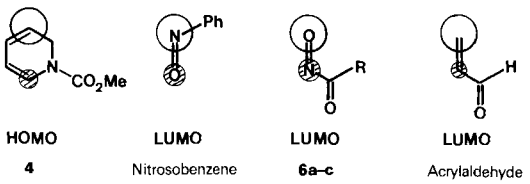
[a]) δ and J values have been calculated using the iterative ITRCAL program.

to be moderately stable entities; they were characterized by IR and ^{1}H-NMR spectra. For analytical purposes, compounds **7d**/**8d** and **7f**/**8f** were separated by column chromatography at −10°. The structures of all **7** and **8** were deduced from those of the final amino sugars *(vide infra)*.

NMR-spectral analyses permitted easily to determine the bicyclic structures of the cycloadducts **7** and **8**: in all cases, similar vicinal and allylic coupling constants between the bridgehead H-atoms H–C(1) and H–C(4) and the two olefinic H-atoms are observed (see *Table 2*). These coupling constants are very similar in magnitude to those measured with bicyclic oxazines which were obtained by cycloaddition of nitroso dienophiles with cyclohexadienes [13]. Direct and inverse cycloadducts are distinguished by the magnitude of the coupling constants $J(1,6')$, H'–C(6) being *'anti'* with respect to the N–O bridge: $J(1,6') \approx 2.2$ Hz for the direct adducts **7** and $J(1,6') \approx 1.2$ Hz for the inverse adducts **8**.

The relative rates and the regioselectivity of these *Diels-Alder* cycloadditions (see *Scheme 2*) may be rationalized in simple terms by the FMO method [14] [15]. The results may be interpreted as follows [16] *(Scheme 3): a)* In the LUMO of nitrosobenzene, the orbital coefficient of the nitroso group is *largest at the N-atom* (its electronegativity is smaller than that of the O-atom; a similar situation is to be found in any carbonyl function in which the O-atom is more electronegative than the C-atom [16]) which, for that reason, leads *only* to the *direct adduct* (see **1** or **7g** (*Table 1*)) when reacted with **4** [2]. The cycloaddition rate is small.

Scheme 3



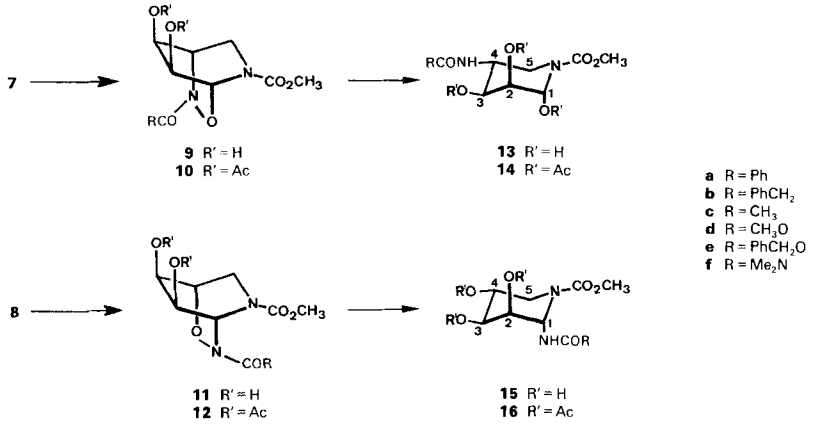
b) In the LUMO of acylnitroso dienophiles **6a–c**, the orbital coefficient of the NO group is *largest at the O-atom*, which is due to the *strong* electron-withdrawing effect of the carbonyl moiety (like in acrylaldehyde [14] [16]). For this reason, *only* the *inverse adducts* **8a–c** are obtained with **4**. The pronounced narrowing of the HOMO-diene/LUMO-dienophile energy gap leads to a very fast reaction rate.

c) In the LUMO of acylnitroso dienophiles **6d–f** – which lead to a mixture of *both* regioisomers – the orbital coefficients at the N-atom *and* at the O-atom (of the NO group) are of *similar magnitude;* this being due to a reduced electron-withdrawing effect of the corresponding carbonyl moieties (urethane and urea derivatives). As a result, regiospecific cycloadditions are no longer taking place.

These results are in good agreement with the concepts of the FMO theory as applied to orientation effects in hetero-*Diels-Alder* reactions with nitroso dienophiles [14] [16] [17].

***cis*-Hydroxylation of Cycloadducts 7 and 8.** – The crude cycloadducts **7** and **8** or mixtures **7**/**8** were oxidized to diols **9** and **11** using catalytic amounts of OsO_4 in the presence of *N*-methylmorpholine *N*-oxide in H_2O/acetone [18] *(Scheme 4)*. A few diols were crystallized and characterized (**9e**, **11d**, and **11e**). In most cases though, diols **11** or **9**/**11** were directly acetylated (→**10**, **12**), the products separated by column chromatog-

Scheme 4



raphy, and characterized (the minor isomer **12f** could not be isolated). The structure of the diacetates **10** and **12** follows from that of the amino sugars to which they lead in the next step. Structure and relative configuration of these aminopiperidine derivatives having been determined unambiguously (see below), the stereostructures of the bicyclic diacetates turned out to be straightforward: in all cases, *cis*-hydroxylation proved to be stereospecific, leading exclusively to the corresponding *'anti'*-compounds. These results are well in line with the ones we had found previously [2].

Diamino-dideoxy-α-lyxopyranose Derivatives. – Hydrogenolysis (Pd/C) of both regioisomeric-diacetate types **10** and **12** followed by acetylation led in good yields to the corresponding peracetylated amino-α-DL-lyxopyranose derivatives **14d**, **14f**, and **16a–c** *(Scheme 4)*. The latter ones were acetylated glycosylamines.

Hydrogenolysis of the crystalline glycol **11d** led to the unprotected glycosylamine **15d** which could be characterized as such and as its peracetylated derivative **16d** *(Scheme 4)*.

Catalytic hydrogenation of the bicyclic benzyloxycarbonyl-glycols **9e** and **11e** led to cleavage of the N–O and of the O–CH_2Ph bonds followed by decarboxylation to give in excellent yields to unprotected diaminolyxoses **13** (H instead of RCO) and **15** (H instead of RCO), respectively. These amino sugars proved to be rather unstable. Therefore, they were characterized as their tetraacetate derivatives **14c** and **16c**.

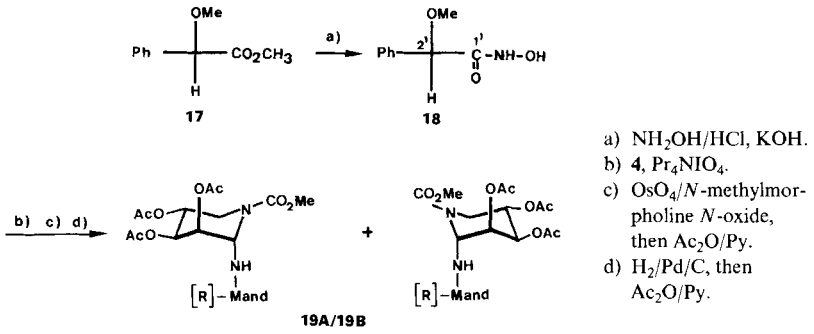
The above described syntheses represent some simple approaches to racemic aminolyxose derivatives, starting from pyridine and using a few reaction steps only. The formation of 5-aminolyxose derivatives has already been described by chemical transformations of D-arabinose [19] [20]. The advantage of these latter methodologies is that one is dealing with enantiomerically pure compounds. Their disadvantages lie in the fact that: *i)* many reaction steps are required to achieve amination in a chemo- and stereospecific way; *ii)* after the ultimate hydrolytic step, a mixture of both lyxopyranose and lyxofuranose derivatives are formed [19].

Optically Active Aminolyxoses. – Optically pure amino sugars may be obtained by resolution of their racemates, *e.g. via* the separation of diastereoisomeric salts which can easily be prepared from optically active carboxylic acids [21]. As an alternative, one may

also make use of asymmetric induction during the buildup of the amino sugars, aiming thereby at the highest possible diastereoselectivity. Such a goal could be nicely achieved by *Kresze, Vasella,* and their coworkers who made use of a *Diels-Alder* cycloaddition between some dienes and an enantiomerically pure α-chloronitroso dienophile [22].

As a first approach to the synthesis of optically active amino sugars, we report now the use of an acylnitroso dienophile which was synthesized from (−)-D-mandelic acid by treatment of its dimethylated derivative **17** [23] with hydroxylamine in a basic medium [24] *(Scheme 5)*. The hydroxamic acid **18** was then reacted with **4**, and the products (separable by chromatography at 5°; both of inverse type ($J(1,6') \approx 1$ Hz)) were converted as described above to the two expected, diastereoisomeric, optically active aminolyxose derivatives **19A** and **19B** (6:4 mixture). The piperidine moiety of **19A** is enantiomeric to the one of **19B**; unfortunately, it is not possible to assign the absolute configurations.

Scheme 5



a) NH_2OH/HCl, KOH.
b) **4**, Pr_4NIO_4.
c) OsO_4/*N*-methylmorpholine *N*-oxide, then Ac_2O/Py.
d) H_2/Pd/C, then Ac_2O/Py.

The $[4\pi + 2\pi]$ cycloaddition step leads in good yield, but with a poor diastereoisomeric excess only, to the expected adducts.

Structural and Conformational Analyses of the Acetylated Amino Sugars. – *General Aspects.* Structural and conformational assignments could be made unambiguously, using high-field ^{1}H-NMR for the amino sugars **14c**, **14d**, and **14f** derived from direct adducts and **16a–d**, **19A**, and **19B** (*Tables 3* and *4*). ^{13}C-NMR spectra were taken for the *N*-acetylated compounds **14c** and **16c** and for **14f** *(Table 5)*. At low temperature (−40°) and in some cases even at r.t., ^{1}H-NMR signals appear as a series of two sets, which are due to hindered rotation around the N–CO_2CH_3 bond of the carbamate moiety (→rotamers **I** and **II**)[3]). Therefore, all spectra were measured at 323 K (+50°), *i.e.* above

[3]) Protons H_a–C(5) and H_e–C(5) appear as two sets of bands (corresponding to rotamers **I** and **II**) which are markedly differentiated ($\Delta\delta$ = 40–160 Hz) in the series derived from the inverse cycloadducts *(Table 4)*. A similar situation appears with H–C(1) and H–C(2) ($\Delta\delta$ = 40–50 Hz) in the series derived from the direct cycloadducts *(Table 3)*. Their signals coalesce at *ca.* 298 K. It follows that $\Delta G^{\neq} \approx 14$ kcal/mol, a value which is similar to the ones reported for carbamates (13–16 kcal/mol) [25]. On the contrary, the presence of the two carbamate rotamers **I** and **II** does not have any effect upon H–C(3) in neither case. This clearly indicates that *i)* H–C(3) is far away from *N*–C(5) and that *ii)* the *N*-substituted amide function does not have a similar effect when compared to the one of the carbamate moiety; it is known that amides prefer to be in a *trans* conformation, even if the substituent at the N-atom is bulky; this is the case here [25].

Table 3. *^{1}H-NMR Spectra* ($CDCl_3$) *of Amino Sugars* **14c**[a]), **14d**, *and* **14f** *Derived from the Direct Cycloadducts* **7e**[a]), **7d**, *and* **7f**, *Respectively.* δ in ppm and J in Hz, internal standard TMS.

	Frequency	Temperature	H–C(1)	H–C(2)	H–C(3)	H–C(4)	H_e–C(5)	H_a–C(5)	NH	J(NH,4)	J(1,2)	J(2,3)	J(3,4)	J(4,5e)	J(4,5a)	J(5e,5a)	Other spectral data
14c	400 MHz	323 K	6.70	5.28	5.18	*ca.*4.40	*ca.*4.40	2.85	5.61	*ca.*7.5	3.0	3.0	11.0	[b])	[b])	[b])	2.11, 2.09, 2.05 (3 AcO); 1.95 (AcN); 3.75 (OMe)
14c I	400 MHz	233 K	6.79	5.34	5.23	*ca.*4.43	*ca.*4.43	2.90	6.06								
II			6.68	5.24	5.23	*ca.*4.43	*ca.*4.43	2.86	5.92								
14d	300 MHz	300 K	6.70	5.28	5.16	4.13	4.39	2.90	4.85	–	2.8	3.2	11.0	5.5	11.4	13.0	2.06, 2.11, 2.13 (3 AcO); 3.69, 3.77 (2 MeO)
14f	400 MHz	323 K	6.72	5.28	5.18	4.29	4.45	2.82	4.70	7.2	2.8	3.2	11.2	5.5	11.2	13.0	J(1,5e) = 1.2; 2.10, 2.09, 2.05 (3 AcO); 2.86 (Me_2N); 3.75 (MeO)
14f I	400 MHz	233 K	6.79	5.35	5.23	4.26	4.46	2.84	5.03								
II			6.69	5.22	5.23	4.34	4.46	2.84	4.87								

[a]) Amino sugar **14c** is derived from **7e** (see text).

[b]) Not determined.

Table 4. *^{1}H-NMR Spectra* ($CDCl_3$) *of Amino Sugars* **16a–d**, *and* **19A** *and* **19B** *Derived from the Inverse Cycloadducts.* δ in ppm and J in Hz; internal standard TMS.

	Frequency	Temperature	H–C(1)	H–C(2)	H–C(3)	H–C(4)	H_e–C(5)	H_a–C(5)	NH	J(NH,1)	J(1,2)	J(2,3)	J(3,4)	J(4,5e)	J(4,5a)	J(5a,5e)	Other spectral data
16a	400 MHz	323 K	6.13	5.54	5.35	5.10	4.19	3.44	7.04	7.2	5.5	3.2	7.7	4.5	7.7	14.0	3.76 (MeO); 2.08, 2.07, 2.06 (3 AcO); 7.78 (H_o); 7.47 (H_m); 7.52 (H_p)
16b	400 MHz	323 K	5.91	5.33	5.03	5.05	4.15	3.00	6.23	7.5	4.8	2.5	*ca.*8	4.5	8.2	13.5	3.70 (MeO); 2.01, 2.01, 2.00 (3 AcO); 3.58 (CH_2); 7.25 (H_o); 7.36 (H_m); 7.29 (H_p)
16b I	400 MHz	233 K	6.10	5.34	*ca.*5.13	*ca.*5.13	4.41	2.78									
II			5.98	5.37	*ca.*5.13	5.00	4.06	3.19									
16c[a])	400 MHz	323 K	6.01	5.36	5.26	5.10	4.28	3.13	6.48	7.5	3.7	2.8	8.7	5.2	9.2	13.5	3.74 (MeO); 2.08, 2.04, 2.02 (3 AcO); 2.01 (AcN)
16c I	400 MHz	233 K	6.17	5.34	5.31	5.18	4.48	2.97	7.64								
II			6.17	5.38	5.31	5.10	4.27	3.17	7.48								
16d	300 MHz	300 K	5.90	5.36	5.28	5.14	4.35	3.06	5.92	*ca.*7	3.0	2.8	9.3	5.5	10.0	13.5	3.71, 3.77 (2 MeO); 2.04, 2.06, 2.11 (3 AcO)
19A	400 MHz	323 K	5.97	5.46	5.23	5.13	4.32	3.02	7.25	7.2	4.0	3.2	8.7	5.5	9.7	13.7	3.67 (CO_2Me); 4.63 (H–C(2′)); 7.32 (Ph); 3.40 (MeO); 2.07, 2.06, 2.03 (3 AcO)
19B	400 MHz	323 K	5.96	5.35	5.25	5.10	4.27	3.23	7.47	7.8	4.8	3.2	8.2	5.2	9.2	14.0	3.75 (CO_2Me); 4.62 (H–C(2′)); 7.35 (Ph); 3.35 (MeO); 2.06, 2.02, 1.95 (3 AcO)

[a]) Amino sugar **16c** is derived from **8e** (see text).

Table 5. *^{13}C-NMR Spectra ($CDCl_3$) of Some Amino Sugars* **14** *and* **16**. δ in ppm and J in Hz, internal standard TMS.

	Frequency	Temperature	C(1)	C(2)	C(3)	C(4)	C(5)	CO_2Me	Other spectral data
14c[a])	20.1 MHz	300 K	76.5 (J = 170)	66.7 (J = 158)	68.8 ($J \approx 150$)	45.3 ($J \approx 147$)	42.2 ($J \approx 146$)	154.8 53.1 (J = 148)	170.7; 170.2; 169.2; 168.0; 20.20; 20.20; 20.20 (J = 131); 22.7 (J = 129, AcNH)
14f Major rotamer	100.6 MHz	233 K	76.2	66.7	69.1	47.8	43.4	155.1 53.6	172.8; 169.7; 168.4; 35.9 (Me_2N); 21.2; 21.0; 20.9; 157.2 (CO)
Minor rotamer	100.6 MHz	233 K	76.2	67.1	69.0	47.3	43.4	155.0 53.4	172.5; –; 168.6; 35.9 (Me_2N); 21.1; 21.0; 20.9; 157.0 (CO)
16c[a])	20.1 MHz	300 K	60.3 (J = 156.5)	68.8[b]) (J = 158)	69.3 (J = 150)	66.7[c]) (J = 158)	41.4 (J = 144)	155.6 53.2 (J = 148.5)	170.2; 170.1; 169.7; 169.5; 20.5; 20.5; 20.5 (J = 131); 22.7 (J = 129, AcNH)

[a]) Amino sugars **14c** and **16c** are derived from **7e** and **8e**, resp. (see text).

[b]) Or C(4).

[c]) Or C(2).

the temperature of coalescence at which only one set of bands was observed. Chemical shifts and coupling constants are to be compared with those of some known aminolyxose derivatives [2] [20].

Structural Assignments. The aminolyxoses derived from the direct adducts can easily be distinguished from the other ones. The differences $\Delta\delta$ of the chemical shifts of *H*–C(1)/C(1) or *H*–C(4)/C(4) and H–C(2)/C(2) and H–C(3)/C(3) are much larger in the series **14** (from direct adducts) than in the series **16** and **19** (from inverse adducts). In these latter compounds, the 3 AcO groups are at C(2), C(3), and C(4), and H–C(2), H–C(3), and H–C(4) have roughly the same chemical shift. An amido group at C(4) (series **14**) leads to a pronounced shielding of C(4) and H–C(4) which appear with chemical shifts similar to the ones of C(5) and H–C(5), respectively. Not surprisingly, the opposite holds for C(1) and H–C(1). Furthermore, we notice a relatively large coupling constant (*ca.* 7 Hz) between N–H (of the *N*-substituted amide group) and the vicinal H-atom, *i.e.* with H–C(4) in the series **14** and with H–C(1) in the series **16** and **19**.

Conformational Analyses. In the series **14** (from direct adducts), two large coupling constants ($J(3,4) \approx 11.0$ Hz, $J(4,5a) \approx 11.3$ Hz) clearly indicate that the piperidine rings appear in a single $^4C_1$(D) chair conformation, as indicated by formula **14** for one set of enantiomers: H–C(3), H–C(4), and the most shielded H–C(5) are axial. It follows that H–C(2) and the least shielded H–C(5) are equatorial. Chemical considerations force H–C(1) and H–C(4) to be *cis*-oriented to one another: H–C(4) being axial, H–C(1) must be equatorial. This can be clearly demonstrated for compound **14f** in which a long-range *W* coupling constant appears between H–C(1) and H–C(5e).

In the series **16** and **19A**/**19B** (from inverse adducts), $J(3,4)$ and $J(4,5a)$ (7.7–10.0 Hz) are somewhat smaller than in the series **14**; simultaneously, the $J(1,2)$ are larger. This is best explained by the existence of a conformational equilibrium between the two possible chair conformers[4]). In these equilibria, the dominant conformations $^4C_1$(D) are still the ones depicted in formula **16** for one set of enantiomers. Assuming that the aminolyxoses **14** derived from the direct series are totally in the chair conformation $^4C_1$(D) (see formula **14** and also [20]), assuming, furthermore, that the peracetylated derivative of α-D-lyxopyranosylamine is entirely in the other chair conformation $^1C_4$(D) [27], one may determine the relative amounts of the *minor chair conformations* by comparing the coupling constants between the *trans* protons $J(1,2)$, $J(3,4)$, and $J(4,5a)$: **16a**, 40%; **16b**, 35%; **16c**, 26%; **16d**, 15%; **19A**, 25%; **19B**, 30%.

Anomeric Effect. N-Acylated amino-sugar derivatives with an OH or OAc substituent at C(1) have been shown by *Paulsen* and coworkers to occur in their chair conformations with *axial anomeric* substituents only, this anomeric effect being estimated in terms of energy gain at more than 3 kcal/mol [20]. We observed the same behaviour in series **14**. Although this very strong anomeric effect (no β-DL-anomers could be detected by NMR) had not been interpreted so far, we believe that it can be explained by the FMO theory. Modern sugar chemists admit that the anomeric effect in carbohydrates results from an

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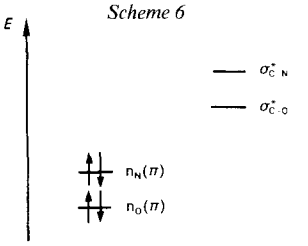
[4]) One of the referees suggested that the difference in magnitude of the coupling constants of the series **16** (when compared to series **14**) could be due to a distorted chair conformation for **16** as a consequence of the steric repulsion of the bulky NHCOR group which is axial. Such a distortion cannot be entirely ruled out. Nevertheless, a pronounced conformational distortion would lead to a decrease of the $J(1,2)$ value [26] and to some modifications of $J(2,3)$ and $J(4,5e)$, which we do not observe.

Scheme 6



interaction between the p orbital of the endocyclic O-atom, and the antibonding σ^* MO of the C(1)–X substituent. This interaction is most pronounced when the X substituent is axially oriented [16] [28] [29]. Replacing the endocyclic O-atom by the less electronegative N-atom [30] or replacing C(1)–O by C(1)–N leads to an energy increase to the $n_N(\pi)$ and of the σ^*_{C-N} levels, respectively, without leading to any appreciable modification of the molecular geometry and of the overlapping of the orbitals *(Scheme 6)* [16] [28]. On the other hand, replacement of O by N leads to an energy gap which is smaller between the $n_N(\pi)$ and σ^*_{C-O} levels than between the $n_O(\pi)$ and σ^*_{C-O} levels of the better known pyranose derivatives [16] [31][5]). As a consequence of this energy-gap narrowing, the $n_N(\pi),\sigma^*_{C-O}$ interaction is increased leading thereby to a strong anomeric effect. A similar result has been observed with the naturally occurring nojirimycine, a piperidinose [28].

Let us consider now pyranoses bearing a N-atom at C(1) which have been encountered with tetra- and pentaacetylated α- and β-D-lyxopyranosylamines. *Paulsen* who studied these latter ones [27] found that their C(1) substituents are either entirely or predominantly equatorial, a result which once more is best explained by *Scheme 6*. In these lyxosylamines, the energy of the σ^*_{C-N} MO is increased. The correlation diagram clearly shows then that there is a strong interaction between the $n_N(\pi)$ bonding orbital of the exocyclic N-atom and the antibonding σ^*_{C-O} MO of the endocyclic O-atom, a situation which leads to the so-called *'exo'*-anomeric effect [29] [33]. This correlation takes place whether the C(1) substituent is axial or equatorial. As a consequence, the classical anomeric effect is strongly diminished, so that the C(1) substituent becomes predominantly or exclusively equatorial.

Finally, we have to focus our attention to the diaminolyxoses **16** and **19** in which the $n_N(\pi),\sigma^*_{C-N}$ interactions (the energy levels of these two orbitals are heightened) are less pronounced than in the examples discussed above. Experimentally it was shown *(vide supra)* that these diamino sugars give rise to an equilibrium between the two chair conformations $^4C_1$(D) and $^1C_4$(D). The first one is the major conformer which bears an axial anomeric substituent. The observed anomeric effect is similar to the one which has been determined with the peracetylated α-D-lyxopyranosylamine [27] [32].

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[5]) In the lyxopyranose series, the α-anomer is the dominant one [26b], as well as the conformation in which the anomeric substituent is axial [32].

Experimental Part

General. Flash chromatography (FC) [34]: silica gel (*Merck 60;* 230–400 mesh). TLC: alumina roll (*Merck 60* F_{254}). M.p.: *Kofler* hot bench or *Büchi SMP 20* apparatus; corrected. IR spectra (cm^{-1}): *Perkin-Elmer 157-G.* ^1H- and ^{13}C-NMR spectra: *Varian T-60, SC-300, Bruker WP-80-DS, W-200, WH-360,* and *WM-400* using double-ir-radiation techniques; TMS (^1H-NMR) and $CDCl_3$ (δ ($CDCl_3$) = 77.00 with respect to TMS; ^{13}C-NMR) as internal references; δ in ppm and J in Hz. High-resolution (HR) MS were measured on a *MAT-311* spectrometer at the University of Rennes. Microanalyses were carried out by the Service Central de Microanalyses of the CNRS.

Starting Materials. 1,2-Dihydropyridine (**4**), benzohydroxamic acid (**5a**; R = C_6H_5), and *C*-benzyloxycarbohydroxamic acid (**5e**; R = $C_6H_5CH_2O$) were prepared according to [35], [24], and [36], resp. Acetohydroxamic acid (**5c**; R = CH_3) and (–)-D-mandelic acid (**17**) were purchased from *Aldrich* and tetrapropylammonium periodate from *Fluka*.

Hydroxamic Acids. – They were prepared according to [37] with some modifications.

Phenylacetohydroxamic Acid (**5b**; R = $C_6H_5CH_2$). To a stirred soln. of $NH_2OH \cdot HCl$ (4.9 g, 70.5 mmol) and K_2CO_3 (9.7 g, 70.0 mmol) in 30 ml of Et_2O and 0.5 ml of H_2O at 0° was added dropwise phenylacetyl chloride (10.0 g, 64.7 mmol). This soln. was left at 0° for 7 h and then at r.t. overnight. The solid phase was washed several times with hot AcOEt. After evaporation of the solvents, the oily crystals were washed with Et_2O: colourless crystals (8.05 g, 82%), m.p. 150–152° ([38]: 145°).

C-Methoxycarbohydroxamic Acid (**5d**; R = CH_3O). To a stirred soln. of $NH_2OH \cdot HCl$ (17.8 g, 0.4 mol) and of K_2CO_3 (44.4 g, 0.3 mol) in 120 ml of Et_2O and 2 ml of H_2O was added dropwise methyl chloroformate (23.1 g, 0.244 mol) at 0°. This soln. was left to stand at 0° for 30 min and then at r.t. overnight. The solid was filtered off and washed several times with Et_2O. After evaporation of the solvents, the oily residue was crystallized in Et_2O: colourless hygroscopic crystals (13.8 g, 62%), m.p. 50° ([37]: 50–51°).

N,N-*Dimethylcarbamohydroxamic Acid* (**5f**; R = NMe_2) [39]. To a stirred soln. of $NH_2OH \cdot HCl$ (6.5 g, 0.09 mol) and of K_2CO_3 (11.5 g, 0.083 mol) in 50 ml of AcOEt and 1 ml of H_2O was added at 0° *N,N*-dimethylcarbamoyl chloride (8 g, 0.075 mol). This soln. was left at r.t. overnight. The solid phase was washed several times with boiling AcOEt. After evaporation of the solvents, the oily residue was recrystallized (AcOEt/EtOH 95:5): a colourless compound (4.5 g, 58%), m.p. 111–112° ([40]: 107–109°).

(–)-D-2-Methoxy-2-phenylacetohydroxamic Acid (**18**). Methyl (–)-D-*O*-methylmandelate (**17**) was prepared according to [23] and transformed into **18** according to [24]: To a stirred soln. of KOH (13.7 g, 0.24 mol) in 34 ml of MeOH kept under Ar was added dropwise at 0° a soln. of $NH_2OH \cdot HCl$ (11.4 g, 0.16 mol) in 80 ml of MeOH and then **17** (14.7 g, 0.08 mol). KCl which precipitated was filtered off and the remaining soln. stirred at r.t. for 24 h. The solvent was partly evaporated, some H_2O (125 ml) added, and the soln. treated with conc. HCl to pH 6. The precipitate was filtered off and the remaining soln. extracted with AcOEt (3 × 150 ml). The org. phase was dried ($MgSO_4$) and evaporated. The solid residue was recrystallized (acetone/benzene): colourless **18** (9.4 g, 63%). M.p. 137–139°. $[\alpha]_D^{23} = -63°$ (*c* = 0.66, acetone). ^1H-NMR ($CDCl_3$, 10% (D_6)DMSO): 7.37 (*m*, 5 arom. H); 4.63 (*s*, H–C(2)); 3.37 (*s*, 3 H, MeO); 3.17 (acidic H). Anal. calc. for $C_9H_{11}NO_3$ (181.19): C 59.66, H 6.12, N 7.73; found: C 59.9, H 6.0, N 7.7.

Bicyclic Oxazines. *General Procedure.* To a stirred soln. of dihydropyridine **4** (2 g, 14.4 mmol) and of Pr_4NIO_4 (1.64 g, 4.4 mmol) in 30 ml of CH_2Cl_2 at 0° containing *ca.* 20 beads of 4-Å molecular sieves was added a hydroxamic acid (14–16 mmol; see above; monitoring by TLC). After 1 h, the mixture was diluted with 100 ml of AcOEt, washed with 1N Na_2CO_3 (15 ml) containing a few ml of sat. aq. Na_2SO_3 soln., and finally washed several times with brine, all aq. phases being extracted again with AcOEt. The combined org. solns. were dried ($MgSO_4$) and evaporated. The crude residues were used as such for the following reaction step.

Methyl 3-Benzoyl-2-oxa-3,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylate (**8a**). From **4** (2.0 g, 14.4 mmol) and **5a** (R = C_6H_5; 1.91 g, 13.9 mmol), **8a** (3.9 g, 99%) was obtained without any further purification due to its low stability. IR (CH_2Cl_2): 1710, 1650, 1440, 1330. ^1H-NMR: *Table 2.*

Methyl 3-Phenylacetyl-2-oxa-3,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylate (**8b**). From **4** (1 g, 7.2 mmol), and **5b** (R = $C_6H_5CH_2$; 1.19 g, 8.7 mmol), **8b** (1.9 g, 92%) was obtained as a crude product. IR ($CHCl_3$): 3000, 2960, 1705, 1660, 1450, 1375, 1335, 1125, 1112. ^1H-NMR ($CDCl_3$, 80 MHz): 7.25 (*s*, 5 arom. H); 6.3–6.7 (*m*, H–C(4), H–C(7), H–C(8)); 4.84 (*m*, H–C(1)); 3.73 (*dd*, *J* = 11.5, 3.3, H–C(6)); 3.72 (*s*, MeO); 3.62 (*s*, $PhCH_2$); 3.13 (*dd*, *J* = 11.5, 1.4, H'–C(6)).

Methyl 3-Acetyl-2-oxa-3,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylate (**8c**). From **4** (1 g, 7.2 mmol), and **5c** (R = CH_3; 0.59 g, 8 mmol), **8c** (1 g, 67%) was obtained as a crude compound. IR ($CHCl_3$): 3000, 2960, 1705, 1660, 1610, 1450, 1376, 1333, 1260, 1125, 1112, 910. ^1H-NMR: *Table 2.*

Dimethyl 3-Oxa-2,5-diazabicyclo[2.2.2]oct-7-ene-2,5-dicarboxylate (**7d**) *and Dimethyl 2-Oxa-3,5-diazabicyclo[2.2.2]oct-7-ene-3,5-dicarboxylate* (**8d**). From **4** (5.7 g, 41 mmol) and **5d** (R = CH_3O; 4.9 g, 53.9 mmol), a crude mixture (7.3 g, 78%) was obtained. Regioisomers were separated at −10° by column chromatography with Et_2O. **7d:** IR (CH_2Cl_2): 1720, 1460, 1400, 1345. ^{1}H-NMR: *Table 2*.

8d: IR (CH_2Cl_2): 1730, 1720, 1460, 1410, 1345. ^{1}H-NMR: *Table 2*. MS: 149 (100), 148 (92), 124 (45), 84 (50), 59 (36). HR-MS: 228.0754 ($C_9H_{12}N_2O_5$, calc. 228.0746).

Methyl 2-Benzyloxycarbonyl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylate (**7e**) *and Methyl 3-Benzyloxycarbonyl-2-oxa-3,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylate* (**8e**). From **4** (6 g, 43.2 mmol) and **5e** (R = $C_6H_5CH_2O$; 7.92 g, 47.4 mmol), a crude mixture (13.5 g, 100%) was obtained containing **7e**/**8e** 1:1; they were not separated. ^{1}H-NMR ($CDCl_3$, 60 MHz): 7.3 (*s*, 5 arom. H); 6.2–6.8 (*m*, H–C(4), H–C(7), H–C(8)); 5.1 (*s*, PhCH_2); 4.9 (*m*, H–C(1)); 3.8 (*dd*, H–C(6)); 3.68 (*s*, CH_3O); 3.13 (*dd*, *J* = 11, 2, H′–C(6)); 3.03 (*dd*, *J* = 11, 1, H′–C(6)).

Methyl 2-Dimethylcarbamoyl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylate (**7f**) *and Methyl 3-Dimethylcarbamoyl-2-oxa-3,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylate* (**8f**). From **4** (2.68 g, 19.3 mmol) and **5f** (R = NMe_2; 2.19 g, 21.2 mmol), a crude mixture (4.0 g, 86%) was obtained containing **7f** (75%) and **8f** (25%); they were separated at −10° by column chromatography with Et_2O. **7f:** IR ($CHCl_3$): 3005, 2960, 1692, 1680, 1492, 1450, 1397. ^{1}H-NMR: *Table 2*.

8f: IR ($CHCl_3$): 3000, 2960, 1700, 1660, 1490, 1450, 1387. ^{1}H-NMR: *Table 2*.

(1S,4R,2′R)- and (1R,4S,2′R)-Methyl 3-(2′-Methoxy-2′-phenylacetyl)-2-oxa-3,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylate[6]. From **4** (4 g, 28.8 mmol) and **18** (5.72 g, 31.6 mmol), a crude mixture (yield 80%) was isolated and separated by FC at +5° (AcOEt/cyclohexane 7:3) leading to a major stereoisomer[6] (2.8 g, 31%), a minor stereoisomer[6] (1.9 g, 21%), and a mixture of both (1.7 g, 19%). *Major stereoisomer:* ^{1}H-NMR ($CDCl_3$, 60 MHz): 7.35 (*m*, 5 arom. H); 6.7 (*m*, H–C(4)); 6.4–6.0 (*m*, H–C(7), H–C(8)); 5.0 (*s*, H–C(2′)); 4.73 (*m*, H–C(1)); 3.7 (*m*, H–C(6)); 3.73 (*s*, CO_2Me); 3.39 (*s*, MeO); 3.03 (*dd*, *J* = 12, 1, H′–C(6)).

Minor stereoisomer: ^{1}H-NMR ($CDCl_3$, 60 MHz): 7.35 (*m*, 5 arom. H); 6.4–6.7 (*m*, H–C(4), H–C(7), H–C(8)); 4.97 (*s*, H–C(2′)); 4.8 (*m*, H–C(1)); 3.8 (*m*, H–C(6)); 3.67 (*s*, CO_2Me); 3.37 (*s*, MeO); 2.97 (*dd*, *J* = 12, 1, H′–C(6)).

Bicyclic Diols and the Corresponding Diacetates. – *General Procedure.* The catalyst was prepared according to [41]: OsO_4 (1 g) and 1 ml of 70% *t*-BuOOH were dissolved in 200 ml of *t*-BuOH. The general procedure for the *cis*-glycolisation was performed according to [18]: to a stirred soln. of oxazines (**8** or **7**/**8**, 10 mmol) in 50 ml of acetone and 30 ml of H_2O at 0°, were added *N*-methylmorpholine *N*-oxide hydrate (1.50 g, 11 mmol) and the catalyst soln. (10 ml). After 1 h at 0°, the mixture was kept at r.t. overnight, treated with a few ml of a sat. aq. Na_2SO_3 soln. and then diluted with 30 ml of acetone. The solid residue was filtered off, the org. solvents were removed, and the remaining aq. soln. was neutralized with conc. HCl and then extracted several times with AcOEt. The org. soln. was washed with 2N Na_2CO_3 and brine, dried ($MgSO_4$), and evaporated. The crude diols were acetylated at r.t. overnight using 4 equiv. of Ac_2O (4.08 g, 40 mmol) in 8 ml (0.1 mol) of pyridine. The crude mixture was evaporated, dissolved in AcOEt, washed with aq. NaCl soln. containing 10% conc. HCl soln., and then with 2N Na_2CO_3. The aq. washing portions were extracted with AcOEt and the combined org. solns. dried ($MgSO_4$) and evaporated. The resulting diacetates were then separated and purified by FC.

Methyl 7,8-Diacetoxy-3-benzoyl-2-oxa-3,5-diazabicyclo[2.2.2]octane-5-carboxylate (**12a**). From crude **8a** (4.03 g, 14.7 mmol), the corresponding diol and then **12a** (0.7 g, 19% overall yield) were obtained; colourless crystals. M.p. 159–160° (Et_2O/MeOH). IR (CH_2Cl_2): 1750, 1710, 1670, 1450, 1370, 1240. ^{1}H-NMR ($CDCl_3$, 80 MHz): 7.70 (*m*, 2 arom. H); 7.40 (*m*, 3 arom. H); 6.23 (*s*, H–C(4)); 5.41 (*m*, H–C(7), H–C(8)); 4.48 (*t*, H–C(1)); 3.65–3.85 (*m*, 2 H–C(6)); 3.70 (*s*, MeOH); 2.06 (*s*, AcO); 2.09 (*s*, AcO). Anal. calc. for $C_{18}H_{20}N_2O_8$ (392.36): C 55.10, H 5.17, N 7.14; found: C 55.3, H 5.1, N 7.1.

Methyl 7,8-Diacetoxy-3-phenylacetyl-2-oxa-3,5-diazabicyclo[2.2.2]octane-5-carboxylate (**12b**). Crude **8b** (1.9 g, 6.6 mmol) gave the corresponding diol and then **12b** (0.81 g, 30% overall yield); colourless crystals. M.p. 101–102° (i-Pr_2O/acetone 10:1). IR (CH_2Cl_2): 1750, 1710, 1450, 1370, 1230. ^{1}H-NMR ($CDCl_3$, 80 MHz): 7.26 (*s*, 5 arom. H); 6.29 (*s*, H–C(4)); 5.22 (*m*, H–C(7), H–C(8)); 4.42 (*m*, H–C(1)); 3.74 (*s*, PhCH_2); 3,71 (*s*, CH_3O); 3.70 (*m*, H–C(6)); 3.34 (*dd*, *J* = 12.5, 2, H–C(6)); 2.05 (*s*, AcO); 2.03 (*s*, AcO). Anal. calc. for $C_{19}H_{22}N_2O_8$ (406.38): C 56.15, H 5.46, N 6.89; found: C 56.4, H 5.4, N 6.9.

Dimethyl 7,8-Dihydroxy-2-oxa-3,5-diazabicyclo[2.2.2]octane-3,5-dicarboxylate (**11d**), *its 7,8-Diacetoxy Derivative* **12d**, *and Dimethyl 7,8-Diacetoxy-3-oxa-2,5-diazabicyclo[2.2.2]octane-2,5-dicarboxylate* (**10d**). The *General*

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[6]) We do not know which configuration the major isomer has.

Procedure was slightly modified: the mixture **7d/8d** (4.0 g, 17.5 mmol) gave **9d/11d** of which **11d** (1.0 g, 22%) crystallized out of an Et_2O soln. containing 1% MeOH. The mother liquors were acetylated and **10d** (0.72 g, 12%) and **12d** (0.25 g, 4%) separated by FC (AcOEt). **11d:** M.p. 142°–143° (Et_2O/MeOH 9:1), colourless crystals. IR (KBr): 3480, 1750, 1690, 1465, 1405, 1300, 1070. Anal. calc. for $C_9H_{14}N_2O_7$ (262.22): C 41.22, H 5.38, N 10.69; found: C 41.1, H 5.4, N 10.5.

12d: Colourless resin. IR (CH_2Cl_2): 1750, 1720, 1450, 1380, 1240, 1080. ^{1}H-NMR ($CDCl_3$, 200 MHz; 2 rotamers): 5.99, 6.09 (2*s*, H–C(4)); 5.33 (*m*, H–C(7), H–C(8)); 4.50 (*s*, H–C(1)); 3.7–3.9 (*m*, 2 H–C(6)); 3.84 (*s*, CO_2Me–C(3)); 3.76, 3.78 (2*s*, CO_2Me–C(5)); 2.11 (*s*, AcO); 2.07 (*s*, AcO). MS: 346 (7), 304 (9), 287 (34), 213 (19), 154 (94), 59 (25), 43 (100). HR-MS: 346.1003 ($C_{13}H_{18}N_2O_9$, calc. 346.1012).

10d: Colourless resin. IR (CH_2Cl_2): 1760, 1720, 1450, 1240, 1220, 1070. ^{1}H-NMR ($CDCl_3$, 200 MHz; 2 rotamers): 5.85, 5.78 (2*d*, J = 2.5, H–C(4)); 5.31 (*m*, H–C(7), H–C(8)); 4.54 (*s*, H–C(1)); 3.7–3.9 (*m*, 2 H–C(6)); 3.84 (*s*, CO_2Me–C(2)); 3.76, 3.79 (2*s*, CO_2Me–C(5)); 2.06 (*s*, AcO); 2.12 (*s*, AcO). MS: 304 (11), 213 (22), 171 (22), 154 (100), 59 (13). HR-MS: 304.0909 ($C_{11}H_{16}N_2O_8$, $M^{+\cdot} - CH_2CO_2$, calc. 304.0907).

Methyl 2-Benzyloxycarbonyl-7,8-dihydroxy-3-oxa-2,5-diazabicyclo[2.2.2]octane-5-carboxylate (**9e**), *its 7,8-Diacetoxy Derivative* **10e**, *Methyl 3-Benzyloxycarbonyl-7,8-dihydroxy-2-oxa-3,5-diazabicyclo[2.2.2]octane-5-carboxylate* (**11e**) *and its 7,8-Diacetoxy Derivative* **12e**. The *General Procedure* was somewhat modified: crude **7e/8e** (13.5 g, 43.2 mmol) gave the corresponding diols as a mixture (7.95 g, 55%) after FC (AcOEt/cyclohexane 7:3). From a AcOEt soln. of this mixture, **9e** (1.7 g, 12%) crystallized out. Prep. column chromatography on reversed-phase silica (H_2O/MeOH 6:4) permitted to separate **9e** and **11e**. On the other hand, the mother liquid (mixture) led, after acetylation and a double FC (AcOEt/cyclohexane 6:4), to **10e** (14%) and **12e** (24%). **9e:** Colourless crystals. M.p. 111–112° (AcOEt). IR (KBr): 3400, 2910, 1730, 1680, 1630, 1450, 1400, 1280, 1060. ^{1}H-NMR ($CDCl_3$, 60 MHz): 7.32 (*s*, 5 arom. H); 5.63 (*s*, H–C(4)); 5.16 (*s*, PhCH_2O); 3.66 (CH_3O); other H-atoms not clearly visible. Anal. calc. for $C_{15}H_{18}N_2O_7$ (388.31): C 53.25, H 5.36, N 8.28; found: C 53.1, H 5.4, N 8.3.

11e: Colourless resin. IR (CH_2Cl_2): 3380, 2960, 1720, 1450, 1390, 1290, 1060. ^{1}H-NMR ($CDCl_3$, 60 MHz): 7.32 (*s*, 5 arom. H); 5.85 (*s*, H–C(4)); 5.20 (*s*, PhCH_2O); 3.61 (*s*, CH_3O); other H-atoms not clearly visible.

10e: Colourless resin. IR (CH_2Cl_2): 1750, 1720, 1450, 1400, 1220. ^{1}H-NMR ($CDCl_3$, 60 MHz): 7.33 (*s*, 5 arom. H); 5.78 (*s*, H–C(4)); 5.30 (*m*, H–C(7), H–C(8)); 5.22 (*s*, PhCH_2O); 4.48 (*m*, H–C(1)); 3.72 (*s*, CH_3O, 2 H–C(6)); 2.10 (*s*, AcO); 2.03 (*s*, AcO). MS: 380 (9), 320 (9), 229 (11), 213 (19), 197 (11), 171 (13), 155 (23), 91 (100). HR-MS: 380.1204 ($C_{17}H_{20}N_2O_8$, $M^{+\cdot} - CH_2CO$, calc. 380.1220).

12e: Colourless resin, IR (CH_2Cl_2): 1750, 1710, 1450, 1400, 1375, 1230. ^{1}H-NMR ($CDCl_3$, 60 MHz; 2 rotamers): 7.35 (*s*, 5 arom. H); 6.07, 5.97 (2*s*, H–C(4)); 5.32 (*m*, H–C(7), H–C(8)); 5.20 (*m*, PhCH_2); 4.47 (*s*, H–C(1)); 3.5–3.9 (*m*, CH_3O, 2 H–C(6)); 2.08 (*s*, AcO); 2.05 (*s*, AcO). MS: 319 (21), 154 (12), 91 (100). HR-MS: 422.1334 ($C_{19}H_{22}N_2O_9$, calc. 422.1325).

Methyl 7,8-Diacetoxy-2-dimethylcarmoyl-3-oxa-2,5-diazabicyclo[2.2.2]octane-5-carboxylate (**10f**). From **7f/8f** (4.0 g, 16.6 mmol) one obtained, after FC (AcOEt/cyclohexane 7:3), only **10f** (1.51 g, 29%) as a colourless oil. IR (CH_2Cl_2): 1750, 1710, 1670, 1450, 1390, 1370, 1240. ^{1}H-NMR ($CDCl_3$, 80 MHz): 5.68 (*s*, H–C(4)); 5.33 (*m*, H–C(7), H–C(8)); 4.26 (*s*, H–C(1)); 4.00 (*dd*, J = 11, 2, H–C(6)); 3.75 (*s*, CH_3O); 3.67 (*dd*, J = 11, 2, H–C(6)); 2.94 (*s*, Me_2N); 2.11 (*s*, AcO); 2.04 (*s*, AcO). MS: 299 (10), 213 (17), 197 (40), 171 (18), 155 (50), 72 (100), 43 (33). HR-MS: 359.1325 ($C_{14}H_{21}N_3O_8$, calc. 359.1329).

(1R,4R,7R,8R,2′R)- and (1S,4S,7S,8S,2′R)-Methyl 7,8-Diacetoxy-3-(2′-methoxy-2′-phenylacetyl)-2-oxa-3,5-diazabicyclo[2.2.2]octane-5-carboxylates. a) From the major optically active cycloadduct (4 g, 12.6 mmol, see above), the corresponding diacetate (1.2 g, 22%) was obtained *via* the crude diol (3.3 g) and purified by FC (AcOEt/cyclohexane 6:4): colourless resin. IR (CH_2Cl_2): 1750, 1710, 1450, 1370, 1230, 1110. $[\alpha]_D^{20} = +16.2°$ (c = 2.5, acetone). ^{1}H-NMR ($CDCl_3$, 60 MHz): 7.32 (*s*, 5 arom. H); 6.30 (*s*, H–C(4)); 5.14 (*s*, H–C(2′)); 4.95 (*m*, H–C(7), H–C(8)); 4.43 (*m*, H–C(1)); 3.77 (*s*, CO_2CH_3); 3.70 (*m*, 2 H–C(6)); 3.39 (*s*, CH_3O); 2.04 (*s*, AcO); 2.03 (*s*, AcO). MS: 255 (1), 214 (2), 197 (2), 171 (3), 154 (3), 121 (100), 105 (6), 92 (10), 91 (16), 72 (10). HR-MS: 255.0608 ($C_{10}H_{11}N_2O_6$, $M^{+\cdot} - CH_3CO_2H - PhCHOCH_3$, calc. 255.0617), 121.0649 (C_8H_9O, Ph–CHOCH$_3$, calc. 121.0653).

b) From the minor optically active cycloadduct (1 g, 3.14 mmol; see above) the corresponding diacetate (0.31 g, 23%) was obtained *via* the crude diol (0.8 g) and purified by FC (AcOEt/cyclohexane 6:4): colourless resin. IR (CH_2Cl_2): 1750, 1720, 1450, 1370, 1230, 1110. $[\alpha]_D^{20} = -128.5°$ (c = 1.25, acetone). ^{1}H-NMR ($CDCl_3$, 60 MHz): 7.32 (*s*, 5 arom. H); 6.27 (*s*, H–C(4)); 5.06 (*s*, H–C(2′)); 5.26 (*m*, H–C(7), H–C(8)); 4.23 (*s*, H–C(1)); 3.69 (*s*, CO_2CH_3); 3.5–3.6 (*m*, 2 H–C(6)); 3.40 (*s*, CH_3O); 2.04 (*s*, AcO); 2.04 (*s*, AcO). MS: 255 (1), 214 (2), 154 (5), 121 (100), 105 (5), 91 (6), 77 (7). HR-MS: 315.0817 ($C_{12}H_{15}N_2O_8$, $M^{+\cdot}$ – PhCHOCH$_3$, calc. 315.0828).

Amino Sugars. – *General Procedure.* i) *Hydrogenolysis.* A stirred soln. of the bicyclic diol or acetate (1 mmol) in 10 ml of abs. EtOH containing 100 mg of 5% Pd/C was kept under H_2 (1 atm) at r.t. overnight. The mixture was then filtered over *Celite*, the latter one washed with EtOH, and the combined org. solns. were evaporated. ii) *Acetylation.* For each OH or NH_2 group to be acetylated were used 2 equiv. of Ac_2O and 5 equiv. of pyridine. The stirred mixture was kept overnight at r.t. under Ar and worked up as described above.

*2,3,4-Tri-*O*-acetyl-*N^1*-benzoyl-5-deoxy-5-methoxycarbonylamino-*α*-*DL*-lyxopyranosylamine* (**16a**). From **12a** (0.191 g, 0.49 mmol), **16a** (0.157 g, 74%) was obtained as colourless crystals. M.p. 179–181° (Et_2O/MeOH 95:5). IR (KBr): 3400, 1750, 1720, 1640, 1530, 1440, 1370, 1230, 1060. ^{1}H-NMR: *Table 4.* Anal. calc. for $C_{20}H_{24}N_2O_9$ (436.41): C 55.04, H 5.54, N 6.42; found: C 54.7, H 5.4, N 6.4.

*2,3,4-Tri-*O*-acetyl-5-deoxy-5-methoxycarbonylamino-*N^1*-phenylacetyl-*α*-*DL*-lyxopyranosylamine* (**16b**). From **12b** (0.370 g, 0.91 mmol; hydrogenolysis: 55° for 17 h), **16b** was obtained as colourless crystals (94%). M.p. 90–91° (benzene). IR (KBr): 3300, 3020, 1750, 1720, 1660, 1540, 1440, 1370, 1220, 1050. ^{1}H-NMR: *Table 4.* Anal. calc. for $C_{21}H_{26}N_2O_9$ (450.43): C 55.99, H 5.82, N 6.22; found: C 56.2, H 5.8, N 6.0.

*5-Deoxy-*N*-methoxycarbonyl-5-methoxycarbonylamino-*α*-*DL*-lyxopyranosylamin* (**15d**) *and its 2,3,4-Tri-*O*-acetyl Derivative* **16d**. From **11d** (0.5 g, 1.91 mmol), **15d** (0.4 g, 79%) was obtained as colourless crystals. Triol **15d** (0.2 g, 0.76 mmol) gave **16d** (0.24 g, 81%) as a colourless resin. **15d:** M.p. 172° (Et_2O/acetone 95:5). IR (KBr): 3360, 1735, 1675, 1550, 1470, 1250. ^{1}H-NMR (CD_3OD, 60 MHz): 5.8 (*m*, H–C(1)); 4.73 (br. *s*, OH); 3.7–4.1 (*m*, H–C(2), H–C(3), H–C(4), 1 H–C(5)); 3.73 (*s*, CO_2CH_3); 3.63 (*s*, CO_2CH_3); 2.73 (*m*, H–C(5)). Anal. calc. for $C_9H_{16}N_2O_7$ (264.23): C 40.91, H 6.10, N 10.60; found: C 41.1, H 6.2, N 10.4.

16d: Resin. IR (KBr): 3360, 2980, 1750, 1530, 1445, 1370, 1220, 1050. ^{1}H-NMR: *Table 4.* MS: 271 (49), 229 (69), 211 (47), 196 (38), 161 (28), 154 (100), 126 (22). HR-MS: 347.1087 ($C_{13}H_{19}N_2O_9$, $M^{+\cdot} - COCH_3$, calc. 347.1090).

*1,2,3,-Tri-*O*-acetyl-4,5-dideoxy-4,5-bis(methoxycarbonylamino)-*α*-*DL*-lyxopyranose* (**14d**). From **10d** (0.5 g, 1.44 mmol), **14d** (0.450 g, 80%) was obtained as colourless crystals. M.p. 194–196° (EtOH). IR (KBr): 3260, 1750, 1690, 1570, 1460, 1380, 1230. ^{1}H-NMR: *Table 3.* Anal. calc. for $C_{15}H_{22}N_2O_{10}$ (390.34): C 46.15, H 5.68, N 7.18; found: C 46.2, H 5.8, N 7.0

*1,2,3,-Tri-*O*-acetyl-4-acetylamino-4,5-dideoxy-5-methoxycarbonylamino-*α*-*DL*-lyxopyranose* (**14c**). From **9e** (1.2 g, 3.55 mmol), **14c** (1.15 g, 86%) was obtained as colourless crystals. M.p. 192–194° (AcOEt). IR (KBr): 3200, 3060, 1750, 1720, 1640, 1570, 1450, 1370, 1220. ^{1}H-NMR: *Table 3.* ^{13}C-NMR: *Table 5.* Anal. calc. for $C_{15}H_{22}N_2O_9$ (374.34): C 48.12, H 5.92, N 7.48; found: C 48.1, H 5.8, N 7.5

*1-*N*,2-*O*,3-*O*,4-*O*-Tetraacetyl-5-deoxy-5-methoxycarbonylamino-*α*-*DL*-lyxopyranosylamine* (**16c**). From **12e** (0.478 g, 1.13 mmol), **16c** (0.356 g, 84%) was obtained as colourless crystals. M.p. 179–180° (EtOH/MeOH 95:5). IR (KBr): 3280, 1750, 1710, 1665, 1550, 1450, 1375, 1230. ^{1}H-NMR: *Table 4.* ^{13}C-NMR: *Table 5.* Anal. calc. for $C_{15}H_{22}N_2O_9$ (374.34): C 48.12, H 5.92, N 7.48; found: C 48.1, H 5.9, N 7.5.

*1,2,3-Tri-*O*-acetyl-4,5-dideoxy-4-dimethylcarbamoylamino-5-methoxycarbonylamino-*α*-*DL*-lyxopyranose* (**14f**). From **10f** (0.6 g, 1.67 mmol), **14f** (0.610 g, 91%) was obtained as colourless crystals. M.p. 192–193.5° (i-PrOH). IR (KBr): 3240, 2940, 1750, 1720, 1630, 1530, 1450, 1370, 1220. ^{1}H-NMR: *Table 3.* Anal. calc. for $C_{16}H_{25}N_3O_9$ (403.38): C 47.64, H 6.25, N 10.42; found: C 47.9, H 6.2, N 10.3.

*2,3,4-Tri-*O*-acetyl-5-deoxy-5-methoxycarbonylamino-*N^1*-((2′*R*)-2′-methoxy-2′-phenylacetyl)-*α*-*D*-lyxopyranosylamine* (**19A**) *and 2,3,4-Tri-*O*-acetyl-5-deoxy-5-methoxycarbonylamino-((2′*R*)-2′-methoxy-2′-phenylacetyl)-*α*-*L*-lyxopyranosylamine* (**19B**)[6]). The hydrogenolysis of the bicyclic major oxazine (1.0 g, 2.29 mmol; see above) was performed at 60° for 2.5 d and of the minor oxazine (1.4 g, 3.97 mmol) at 55° for 5 d. After acetylation and column chromatography (AcOEt/cyclohexane 6:4), the major lyxopyranosylamine (0.850 g, 78%) was obtained as colourless crystals, the minor one as a colourless oil (1.13 g, 60%). *Major stereoisomer:* M.p. 140° (i-Pr_2O/acetone 95:5). IR (KBr): 3260, 2940, 1740, 1710, 1640, 1520, 1440, 1370, 1220, 1100, 1050. $[\alpha]_D^{20} = -2.6°$ (*c* = 1.03, acetone). ^{1}H-NMR: *Table 4.* Anal. calc. for $C_{22}H_{28}N_2O_{10}$ (480.46): C 54.99, H 5.87, N 5.83; found: C 55.0, H 5.8, N 5.9.

Minor stereoisomer: IR (CH_2Cl_2): 3400, 1750, 1710, 1500, 1440, 1370, 1220, 1100, 1060. $[\alpha]_D^{20} = -43°$ (*c* = 0.41, acetone). ^{1}H-NMR: *Table 4.* HR-MS: 316.1058 ($C_{13}H_{18}NO_8$, $M^{+\cdot}$ – NHCOCHOMePh, calc. 316.1032).

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