93. (±)-4-Amino-4,5-dideoxyribose, (±)-4-Amino-4-deoxyerythrose, and (±)-Dihydroxyproline Derivatives from *N*-Dienyl-γ-lactams

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Hetero-*Diels-Alder* cycloaddition of acylnitroso dienophile **4** with the *N*-(butadienyl)pyrrolidinone derivatives **2a,b** led with complete regioselectivity to the oxazine adducts **5a,b** (*Scheme 1*). Sequential osmylation, protection of the ensuing glycol, and reduction of the N–O bond gave the expected hemiaminals **11a,b** which were characterized by their crystalline sulfite adducts **12a,b** (*Schemes 1* and *2*). Deprotection and saponification of the latter led to aminodeoxyerythrose and to aminodeoxyribose derivatives as an equilibrium of pyrrolidinose equivalents, *i.e.*, hemiaminals **14a,b**, imines **14'a,b**, and dimers **14''a,b**, respectively (*Scheme 3*). Hydrocyanic acid addition to **11a,b** led ultimately to the proline derivatives **16a,b** (*Scheme 2*). Compound **11b** proved to be an inhibitor of syncytium formation in AIDS-infected cells.

Introduction. – Pyrrolidinosugars, *i.e.*, 4-amino-4-deoxyaldoses, were described for the first time by *Paulsen* and coworkers in the L-xylose [1], L-lyxose [2], and D-glucose and D-galactose [3] series; more recently, in the D-arabinose, *i.e.*, nectrisine or FR 900483 [4], and in the D-ribose series [5], they were shown to be immunomodulators and glycosidase inhibitors. In their protected imino form, the D-ribose and D-threose derivatives were used for the synthesis of C-glucosides [6] and of 3,4-dihydroxyprolines [7]. Clearly these pyrrolidinoses are of interest as potential bio-active molecules and as synthetic intermediates.

Some time ago, we described the total synthesis of some racemic 4-amino-4-deoxyerythrose derivatives, the key step being hetero-*Diels-Alder* cycloadditions of acylnitroso dienophiles of type **4** with 1-(silyloxy)butadiene **1** (followed by *cis*-hydroxylation and reduction) [8]. In this case, the hetero-*Diels-Alder* cycloaddition proved to be non-regiospecific.

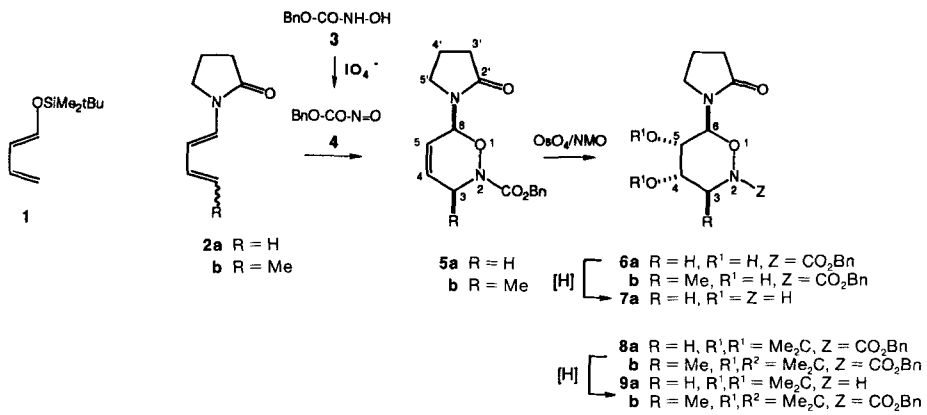
We describe herein the total synthesis of two racemic pyrrolidinose derivatives, *i.e.*, of 4-amino-4-deoxyerythrose **14a** and of 4-amino-4,5-dideoxyribose **14b**, using a similar methodology starting from the known *N*-dienylpyrrolidinones **2a** and **2b** [9], respectively. The hetero-*Diels-Alder* cycloaddition proved to be regiospecific. Acylnitroso dienophiles of type **4** are highly reactive species which cannot be isolated; they were prepared *in situ* in the presence of the diene partners by oxidation of the hydroxamic acids of type **3** with an appropriate periodate [10a, b].

We also describe the facile synthesis of the racemic dihydroxyprolines **16a** and **16b** simply by adding hydrocyanic acid to the protected pyrrolidinoses [1] [11]. Dihydroxyproline **16a** had already been synthesized, both as a racemic mixture [12] and as a chiral

entity [13], and is a potential glycosidase inhibitor: its all-*trans* (2*R*,3*R*,4*R*)-isomer was shown to be a potent inhibitor of β-D-glucuronidase [14].

Hetero-*Diels-Alder* Cycloaddition and Osmylation. – Dienyllactams **2a** and **2b** were prepared according to a known procedure by condensation of pyrrolidin-2-one to crotonaldehyde or to pentenal in toluene solution, H_2O being eliminated by azeotropic distillation [9]. Hetero-*Diels-Alder* cycloaddition was performed with these dienes at 0° in CH_2Cl_2/MeOH in the presence of hydroxamic acid **3** which was oxidized *in situ* with $(BnMe_3N)IO_4$ [10c] (*Scheme 1*). The reaction proved to be regiospecific; in both cases, only one adduct was formed, *i.e.*, **5a** and **5b**, respectively.

Scheme 1



Diene **2b** is a mixture of two geometrical diastereoisomers, *i.e.*, of the (1*E*,3*E*)- and (1*E*,3*Z*)-isomers whose ratio depends on the reaction conditions: it ranged from *ca.* 1:1 before workup to 1:3 after chromatography; in the crystalline form only the (1*E*,3*Z*)-isomer was present. Whatever the ratio of the (*E*,*E*)/(*E*,*Z*)-mixture, only *cis*-cycloadduct **5b** was formed in 50–60% yield. When the reaction was monitored by ^{1}H-NMR, a fast (albeit incomplete) (*E*,*Z*)→(*E*,*E*) isomerization was observed during the addition of some impure tetraalkylammonium periodate (*i.e.*, slightly colored by the presence of I_2) to the solution of **2b** in $CDCl_3$, the (*E*,*E*)-isomer becoming the major product. Next, hydroxamic acid **3** was added to the reaction medium: the (*E*,*E*)-diene reacted at a high rate, while the (*E*,*Z*)-isomer disappeared slowly. Once the reaction was complete, diene **2b** had totally disappeared, and cycloadduct **5b** was the only product. We could verify by ^{1}H-NMR that the (*E*,*Z*)→(*E*,*E*) isomerization does not operate, neither spontaneously, nor in the presence of hydroxamic acid **3**, nor in the presence of *pure* tetraalkylammonium periodate. On the other hand, we verified that I_2 promotes a fast (*E*,*Z*)→(*E*,*E*) isomerization, the final (*E*,*E*)/(*E*,*Z*) composition being 4:1.

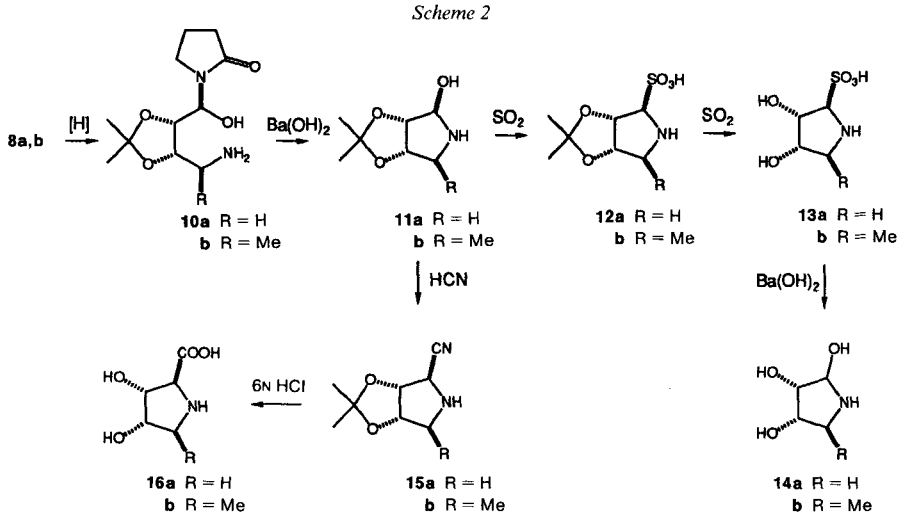
These results are best explained as follows: *cis*-cycloadduct **5b** was obtained *via* a classical (concerted) [4πs+2π] cycloaddition process of the (*E*,*E*)-isomer of **2b** with nitroso dienophile **4**. The (*E*,*Z*)-isomer, which is much less reactive toward the nitroso dienophile, isomerized gradually to the (*E*,*E*)-form *under the action of* I_2 [15], a species always present in the reaction medium, so that only *cis*-cycloadduct **5b** was formed. This

unexpected hetero-*Diels-Alder* reaction was to compare to the results obtained by *Zezza* and *Smith* for the cycloaddition of **2b** with ethyl acrylate which, according to these authors, led to a normal stereochemical outcome [9].

Bis-hydroxylation of adducts **5a** and **5b** was performed with catalytic amounts of osmium tetraoxide in the presence of the co-oxidant *N*-methylmorpholine *N*-oxide (NMO) [16]. It led stereospecifically to the diols **6a** and **6b**, respectively, the osmylation occurring from the less hindered side, *i.e., anti*; these results agree with those found previously [8] [17]. Diols **6a,b** were characterized as such and as their acetonides **8a,b**.

Reduction Processes to Aminodeoxysugar Derivatives (*Scheme 2*). – The reductive cleavage of the cyclic diols was studied in the simple series (R=H). It was found that catalytic hydrogenolysis (over Pd/C) in MeOH proceeded in two steps: *i*) debenzylation and deprotection of the N-atom proceeded at high rate at room temperature and led to oxazine **7a**; *ii*) hydrogenolysis of the N–O bond occurred at 40° and led directly to the

Scheme 2



pyrrolidine-3,4-diol, as already observed in the silyloxy series [8]; nevertheless, the expected intermediate aminosugars could not be trapped. Therefore, we turned our attention to the reductive cleavage of the acetonide derivative **8a** by applying the same methodology as described above. Once again, the deprotection of the N-atom proceeded at high rate, leading to the expected oxazine **9a** which, after 1 day under the same reaction conditions, led quantitatively to the hemiaminal **10a**, *i.e.*, a simple derivative of 4-amino-4-deoxyerythrose. This compound proved to be a stable entity which was characterized as its picrate salt and as its diacetyl derivative.

Hydrogenolysis of **8b** led to the oxazine **9b** whose reduction with *Raney*-Ni gave crystalline hemiaminal **10b**. Compounds **10a** and **10b** are stable species in neutral and in acidic medium. In basic medium ($Ba(OH)_2/H_2O$), and partially by thermolysis, they lead to pyrrolidinone and to the pyrrolidinoses **11a** and **11b**, respectively. These aminosugars were easily transformed into their crystalline sulfonates (sulfite adducts) **12a** and **12b** by

the action of gaseous SO_2. Further reaction of SO_2 led to cleavage of the acetonides and to the formation of the crystalline sulfonates **13a** and **13b** which were saponified by $Ba(OH)_2$ to the aminosugars **14a** and **14b**, respectively.

These 'free' aminosugars **11a,b** and **14a,b** are tautomeric mixtures in water solution (D_2O; see *Table 1* and *Scheme 3*). The acetonide-protected aminosugars occur as a mixture of the hemiaminal **11a,b** and of the corresponding imine form **11'a,b** (formed by dehydration). The aminosugars having free OH groups occur as mixtures of three components, the hemiaminal **14a,b**, the corresponding imine form **14'a,b**, and one dimer **14''a,b** – probably *'cis-syn-cis'* for **14''a**, and *'cis-anti-cis' for* **14''b** – which is favored at high concentration or in the absence of any solvent. Dissolution of hemiaminals of type **11** or **14** does not lead immediately to the equilibrium, as observed in particular for **14a.** In all instances, an increase of temperature favors the imine forms **11'a,b** and **14'a,b**; this is particulary clear for **14a**. The acetonides **11a,b** are soluble in organic solvents and can by extracted from their aqueous solution by Et_2O, occurring thereby only in their imine forms **11'a,b** (as determined by ^{1}H-NMR in $CDCl_3$).

Scheme 3

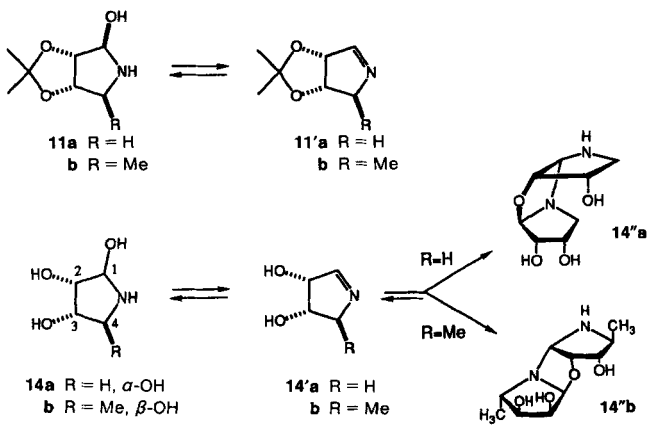


Table 1. *Proportions of Tautomeric Structures* (see *Scheme 3*) *of the Aminosugars* **11a,b** *and* **14a,b** *in Solution in* D_2O (^{1}H-NMR determination)[a])

	Temperature [K]	Imine form [%]	Hemiaminal form [%]	Dimer [%]
11a	300	40	60	–
	332	55	45	–
11b	300	80	20	–
14a	300[b])	42	25	33
	300[c])	18	71	11
	320	36	48	16
	343	*ca.* 80	*ca.* 10	*ca.* 10
14b	300	12	20	68
	320	26	23	51
	340	46	27	27

[a]) Concentrations: **14a**, 0.15M; **14b**, 0.26M; **11a,b**, *ca.* 0.2M. [b]) Immediately after solubilization. [c]) After 15 h in solution.

This type of equilibrium seems to be a general phenomenon with pyrrolidinoses and was already described qualitatively by *Paulsen* and coworkers in the L-lyxose and in the L-xylose series; these authors demonstrated in particular the structure of the corresponding dimers [1] [2]. In the D-arabinose series, a Japanese group cited the imine form only for nectrisine [4]. In the D-ribose series (4-amino-4-desoxy-D-ribose), *Witte* and *McClard* discussed the equilibrium between the various species (hemiaminal, imine, and dimer) as a function of pH [5].

Conversion to the Racemic Amino Acids 16a and 16b. – The addition of hydrocyanic acid to aminosugars in their hemiaminal form is a reaction of wide scope which was described in aqueous medium by *Böshagen et al.* for nojirimycine (5-amino-5-desoxy-D-glucose) [11] and by *Paulsen* and coworkers for L-xylopyrrolidinose [1] and for D-xylopiperidinose [18]. This type of addition was also described in anhydrous medium using Me_3SiCN as cyanating agent [7].

The addition of HCN to the acetonides **11a** and **11b** in Et_2O solution led stereospecifically to the aminonitriles **15a** and **15b** (*Scheme 2*), respectively, the approach of the CN^- anion occurring *trans* to the acetonide ring. Acid hydrolysis of the nitrile function to the carboxylate was performed with 6N HCl during 1–2 days at 80° according to *Arakawa* and *Yoshifuji* [7]. It led in good yield to the corresponding dihydroxyprolines **16a** and **16b** as the only reaction products; **16a** is a known racemic product [12]; the spectroscopic data were identical with those reported [12] [13a, c].

Structural and Conformational Analyses. – *Cycloadducts* **5a, b** *and Diols* **6a, b**. Cycloadducts **5a, b** are 3,6-dihydro-2*H*-oxazines whose conformation and relative configuration could easily be deduced from the magnitude of the vicinal and allylic coupling constants between H–C(3) and H–C(6) and the olefinic H–C(4) and H–C(5) [8] [17] [19] (see *Table 2*). *E.g.*, for adduct **5b**, the relatively large $J(3,4)$ and the rather small $J(5,6)$ indicate that H–C(3) is strictly pseudoequatorial and H–C(6) strictly pseudoaxial, the conformation being typically half-chair. This clearly points to a *cis*-topology of the substituents at C(3) and C(6).

As to the diols **6a, b**, the large magnitude of $J(5,6)$ is in good agreement with H–C(5) and H–C(6) being *trans*-diaxial in a typical chair conformation. The small magnitude of $J(4,5)$ points to an equatorial H–C(4). From these data it follows that the two OH groups are in *cis*-topology and both *trans* with respect to the pyrrolidinone moiety. In **6b**, Me–C(3) is axial and the pyrrolidinone moiety equatorial. It is worth noticing that H_a–C(3) and H_b–C(3) of **6a** (also of **8a**) have very differentiated chemical shifts; this is due to the anisotropy of the *N*-acyl moiety which deshields the equatorial H_a–C(3) (4.5 ppm) by *ca.* 1 ppm with respect to the axial H_b–C(3) (3.6 ppm) [20] (see also [8] [17]). This pronounced chemical-shift difference disappears in the *N*-non-acylated compounds **7a** and **9a** which nevertheless have the same conformation as those described above.

Linear Aminosugars **10a, b**. The medium values (5–9 Hz) of all the vicinal coupling constants between the protons of the aminosugar moiety indicate a linear rather than a cyclic structure. The existence of the NH_2 group, only present in a linear compound, is demonstrated for **10a** by the formation of a diacetyl derivative containing the amide group NHAc, whose well-defined NH signal in the ^{1}H-NMR spectrum is coupled with both neighboring H–C(4) (see *Exper. Part*).

Aminosugars and Cyanohydrins. These five-membered rings (pyrrolidines) are known to have rather flexible conformations. Their vicinal *cis*- and *trans*-coupling constants cannot easily be differentiated since J_{cis} varies from 4 to 7 Hz and J_{trans} from 0 to 9 Hz [21]. Therefore, the configuration at C(1) is difficult to ascertain (*Table 3*). Nevertheless, should an anomeric effect exist, *e.g.* in furanoses, a single rule seems to be valid, *i.e.*, $J_{trans}(1,2)$ *ca.* 0–2 Hz and $J_{cis}(1,2) = 4$–5 Hz [21]. From the observed small $J(1,2)$ values, it follows that pyrrolidinoses **11a, b** and **14b** and cyanohydrins **15a, b** occur as *trans*-isomers (β-anomers for aminosugars), whereas aminoerythrose **14a** appears as the *cis*-isomer (α-anomer) ($J_{cis}(1,2) = 5.8$ Hz). This latter conclusion is confirmed by the observed shielding of H–C(1) and H–C(2) with respect to the corresponding H-atoms of **14b** whose H–C(1) (resp. H–C(2)) is deshielded by the neighboring OH–C(2) (resp. OH–C(1)) in *cis*-position.

The dimerization in the ribose series led to dimer **14″b** whose ^{1}H-NMR data pertaining to the anomeric H-atoms of both pyrrolidine moieties are similar to those reported for a dimer belonging to the L-lyxose series [1].

Table 2. *^{1}H-NMR Data* ($CDCl_3$) *of Oxazines* **5**–**9**. 250 MHz, 300 K; δ in ppm, J in Hz, int. standard $SiMe_4$[a]).

	H_a–C(3)	H_b–C(3)[b])	H–C(4)	H–C(5)	H–C(6)	PhCH_2[c])	J(3a,3b)[b])	J(3a,4)	J(3b,4)	J(4,5)	J(5,6)
5a[d])[e])	4.14	4.14	6.13	5.70	6.13	5.16, 5.28	n.d.	3.2		10.2	2.5
b[f])	4.55	1.35	6.07	5.57	6.27	5.18, 5.28	6.7	4.6	–	10.4	1.6
6a	4.30	3.40	4.15	3.95	5.49	5.15, 5.23	14.4	2.6	1.4	3.0	10.0
b[g])	4.52	1.31	4.01	4.37	5.18	5.18, 5.22	7.2	2.0	–	3.2	9.6
7a	3.32	3.16	4.12	3.75	5.34	–	14.5	1.6	2.7	3.2	9.6
8a[d])[h])	4.42	3.68	4.38	4.52	5.34	5.19, 5.26	14.8	2.1	3.2	5.1	8.4
b[h])	4.70	1.37	4.16	4.60	5.34	5.18, 5.29	7.2	1.3	–	4.9	8.8
9a[h])[i])	*ca.* 3.5	*ca.* 3.5	4.35	4.25	5.24	–	n.d.	2.4		5.0	8.7
b[h])[i])	3.27	1.21	4.08	4.24	5.25	–	7.1	3.6	–	5.1	6.6

[a]) Pyrrolidinone moiety: 2.30–2.47 (*m*, 2 H–C(3′)); 1.87–2.07 (*m*, 2 H–C(4′)); 3.37–3.63 (*m*, 2 H–C(5′)); arom. protons: 7.3–7.5.

[b]) For **5b**, **6b**, **8b**, and **9b**, Me–C(3) instead of H_b–C(3), and J(3a,Me) instead of J(3a, 3b).

[c]) $J(CH_2) = 12.3$.

[d]) J values in C_6D_6.

[e]) $J(3,5) = 2.2$, $J(3,6) = 2.5$, $J(4,6) = 1.8$.

[f]) $J(3,5) = 1.6$, $J(3,6) = 2.4$, $J(4,6) = 2.0$.

[g]) 330 K; δ(OH–C(4)): 2.61, δ(OH–C(5)): 3.81; J(4,OH–C(4)) = 1.8, J(5,OH–C(5)) = 6.2.

[h]) Me signals of the acetonide moiety: **8a**: 1.35, 1.40; **8b**: 1.33, 1.38; **9a**: 1.40, 1.59; **9b**: 1.31, 1.50.

[i]) NH at 5.44.

Table 3. *^{1}H-NMR Data of Aminosugars* **14a,b** *and Derivatives* **11a,b**, **12a,b**, **13a,b**, *and* **15a,b** *in D_2O.* δ in ppm, J in Hz, int. ref. (D_4)-TSP or δ(DOH) = 4.76 ppm.

	H–C(1)	H–C(2)	H–C(3)	H_a–C(4)	H_b–C(4)[a]	J(1,2)	J(2,3)	J(3,4a)	J(3,4b)	J(4a,4b)[a]
11a[d])	4.82	4.57	4.89	3.14	3.03	0	5.6	4.2	0	12.6
11'a[b])[d])	7.68	5.29	4.93	4.01	4.01	0	5.7	2.6	2.6	–
11b[d])	4.90	4.62	4.53	3.33	1.20	1.8	6.2	2.0	–	7.0
11'b[c])[d])	7.62	5.39	4.58	4.27	1.20	0	5.5	0	–	7.3
12a[d])	4.62	5.23	5.15	3.70	3.55	1.3	5.6	4.4	0.5	13.1
12b[d])	4.54	5.17	4.74	3.88	1.44	4.3	5.8	3.1	–	7.2
13a	4.41	4.60	4.47	3.55	3.45	7.1	4.1	3.6	2.2	12.6
13b	4.39	4.58	4.04	3.67	1.42	4.6	4.8	6.7	–	6.8
14a	3.13	3.92	4.28	3.44	2.45	5.8	6.8	7.0	4.6	10.3
14'a[b])	7.65	4.72	4.28	3.84	3.84	0.8	5.4	3.3	3.3	–
14''a	4.70	4.45	4.10	3.08	2.58	4.8	5.0	6.7	9.2	10.6
	4.88	4.18	4.33	3.17	2.99	1.6	4.8	4.2	5.5	11.3
14b	4.06	4.35	3.71	3.20	1.21	2.6	5.4	8.2	–	6.4
14'b[c])	7.63	4.83	3.95	4.06	1.20	0.6	5.4	1.8	–	7.0
14''b	4.72	4.62	3.53	2.94	1.18	4.9	4.9	9.4	–	6.2
	5.05	4.18	3.70	2.94	1.22	4.1	5.2	8.2	–	6.2
15a[d])[e])	4.06	4.85	4.81	3.25	3.00	0	5.4	0	3.3	13.4
15b[d])[e])[f])	3.99	4.97	4.50	3.47	1.27	1.8	5.6	1.3	–	7.3

[a]) For the 4-methyl derivates Me–C(4) instead of H_b–C(4) and J(4a,Me–C(4)) instead of J(4a,4b).
[b]) J(1,4a) = J(1,4b) = 2.5, J(2,4a) = J(2,4b) = 1.0.
[c]) J(1,4a) = 1.7, J(2,4a) = 1.1.
[d]) Acetonide signals: **11a**: 1.36, 1.48; **11'a**: 1.40, 1.41; **11b**: 1.36, 1.51; **11'b**: 1.41; **12a**: 1.39, 1.54; **12b**: 1.56, 1.40; **15a**: 1.45, 1.32; **15b**: 1.47, 1.31.
[e]) For convenience, **15a,b** are numbered like **11**–**14**; for systematic names, see *Exper. Part.*
[f]) In $CDCl_3$, ref. $SiMe_4$; δ(NH) = 2.56; J(1,NH) = 5.8, J(4,NH) = 4.0.

It follows that **14''b** is likely to occur in the '*cis-anti-cis*'-topology postulated for this lyxose dimer. On the contrary, for the dimer **14''a**, one J(1,2) is small; a simple explanation is that this dimer appears in the '*cis-syn-cis*'-topology (*Scheme 3*).

In the sulfite adducts **12a**, **b**, and **13a**, **b**, the anomeric effect (of SO_3H) is known to be weak or even inverse, and the SO_3H group appears in its equatorial configuration [22] [23]. As a consequence, the J(1,2) values vary widely. The *trans*-configuration was demonstrated for **13b** by nuclear *Overhauser* effects (NOE, H–C(1) and H–C(4) being *cis* to each other: irradiation of Me–C(4) led to a NOE of 6% for H–C(2) and of 11% for H–C(3); and irradiation of H–C(4) to a NOE of 6% for H–C(1).) The configuration of the other sulfite adducts is β-DL also since J(1,2) is small for **12a** and since **12b** and **13a** are directly related to the preceding ones.

AIDS-Inhibition Assays. – Some of the compounds synthesized herein were submitted to anti-HIV assays (see *Exper. Part* and *Table 4*). The aminodeoxyribose **11b** proved

Table 4. *Anti-HIV Activities and Cytotoxicities as Determined for Compounds* **7a**, **11b**, *and* **13a,b** (in μM)

	Syncytia inhibition	EC_{50}[a])	TC_{50}[b])
7a	> 10000	> 10000	> 10000
11b	> 100	20	100
13a	> 2000	400	4000
13b	> 2000	400	4000
AZT	> 0.4	0.016	> 1000

[a]) Concentration which reduces the virus yield by 50% in infected cells.
[b]) Concentration which reduces cell growth by 50%.

to be somewhat more active than castanospermine [24], but less active than AZT. Nevertheless, **11b** showed a relatively pronounced cytotoxicity.

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Experimental Part

1. *General. Raney*-Ni (slurry in H_2O), 5% Pd/C catalyst, 2,2-dimethoxypropane, pent-2-enal, *N*-methylmorpholine-*N*-oxide (NMO), OsO_4, *tert*-butyl hydroperoxide, SO_2 gas, pyrrolidin-2-one, and toluene-4-sulfonic acid (TsOH) were purchased from *Fluka*, crotonaldehyde from *Merck*, and NaCN and $Ba(OH)_2 \cdot 8\ H_2O$ from *Prolabo*. Usual solvents were freshly distilled, CH_2Cl_2 was kept over Na_2CO_3. Flash chromatography (FC): silica gel (*Merck 60*, 230–400 mesh). TLC: Al-roll silica gel (*Merck 60*, F_{254}). M.p.: *Kofler* hot-bench or *Büchi-SMP-20* apparatus; corrected. IR Spectra (ν in cm^{-1}): *Perkin-Elmer 157 G* or *Nicolet 205*. ^1H- and ^{13}C-NMR Spectra: *Bruker AC-F250*, using double-irradiation techniques; $SiMe_4$ or sodium (trimethylsilyl)(D_4)propanoate ((D_4)-TSP) in D_2O (^1H-NMR), and $CDCl_3$, C_6D_6, CD_3OD, or (in D_2O) CH_3OH or dioxane ($\delta(CDCl_3)$ 77.0, $\delta(C_6D_6)$ 128.0, $\delta(CD_3OD)$ 49.0, in D_2O $\delta(CH_3OH)$ 50.3, δ(dioxane) 67.6 with respect to $SiMe_4$; ^{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*, F–69390 Vernaison.

2. *Dienylpyrrolidinones.* N-*(Buta-1,3-dienyl)pyrrolidin-2-one* (**2a**). According to [9] with some modifications: A soln. of pyrrolidin-2-one (20 g, 18 ml, 0.234 mol), TsOH (20–100 mg), and crotonaldehyde (19.6 ml, 0.24 mol, 1 equiv.) in toluene (100 ml) was refluxed and the H_2O removed in a *Dean-Stark* trap. After 1 h and again after 1.5 h, crotonaldehyde (9.8 ml (0.5 equiv.) and 4.9 ml (0.25 equiv.)) was added. After 2 h, the cooled soln. was washed with aq. 1M Na_2CO_3, H_2O, and brine (3 × 20 ml). The aq. phases were extracted with Et_2O (2 × 50 ml) and the org. phases dried ($MgSO_4$) and evaporated. FC (Et_2O) gave **2a** (18.0 g, 56%) as a yellow resin which crystallized at 0°. Yellow crystals. M.p. 58° ((i-Pr)$_2$O) ([9]: 58–59°). IR (KBr): 1695, 1645, 1430, 1395, 1300. ^1H-NMR ($CDCl_3$): 2.13 (*q*, J = 8, 2 H–C(4)); 2.51 (*t*, J = 8, 2 H–C(3)); 3.56 (*t*, J = 7, 2 H–C(5)); 4.99 (*d*, H_a–C(4′)); 5.14 (*d*, H_b–C(4′)); 5.63 (*dd*, H–C(2′)); 6.35 (*dt*, H–C(3′)); 7.11 (*d*, H–C(1′)); $J(1',2')$ = 14.3, $J(1',3')$ = $J(1',4'a)$ = $J(1',4'b)$ = 0.8, $J(2',3')$ = 10.4, $J(2',4'a)$ = $J(2',4'b)$ = 0.8, $J(3',4'a)$ = 10.3, $J(3',4'b)$ = 16.9, $J(4'a,4'b)$ = 1.7.

N-*(Penta-1,3-dienyl)pyrrolidin-2-one* (**2b**). A soln. of pyrrolidin-2-one (8.0 ml, 0.1 mol), TsOH (23 mg) and pent-2-enal [25] (5.2 ml, 53 mmol) in toluene (67 ml) was refluxed for 3 h as above. The cooled soln. was washed with aq. 1M Na_2CO_3 and H_2O (2 × 20 ml) and the aq. soln. extracted with Et_2O (2 × 50 ml): The org. solns. were dried ($MgSO_4$) and evaporated: **2b** (7.2 g, 90%) (*E,E*)/(*E,Z*) 1:1. Purification by FC (Et_2O) gave **2b** (4.97 g, 62%), (*E,E*)/(*E,Z*) 1:3 ([9]: 81:19 mixture), crystallizing at 0° as the (*E,Z*)-isomer. Yellow resin (isomer mixture) or yellow crystals. M.p. 70° (toluene/cyclohexane). ^1H-NMR ($CDCl_3$): 2.11 (*m*, 2 H–C(4)); 2.51 (*m*, 2 H–C(3)); 3.60 (*m*, 2 H–C(5)); (*E,Z*)-isomer: 7.07 (H–C(1′)); 5.81 (H–C(2′)); 6.02 (H–C(3′)); 5.43 (H–C(4′)); 1.73 (Me–C(4′)); $J(1',2')$ = 14.0, $J(1',4')$ = 0.9, $J(2',3')$ = 11.0, $J(2',4')$ = 0.9, $J(3',4')$ = 10.8, $J(3',Me)$ = 1.7, $J(4',Me)$ = 7.2; (*E,E*)-isomer: 6.96 (H–C(1′)); 5.58 (H–C(2′)); 6.03 (H–C(3′)); 5.60 (H–C(4′)); 1.74 (Me–C(4′)); $J(1',2')$ = 14.4, $J(1',4')$ = 0.6, $J(2',3')$ = 10.4, $J(2',4')$ = 0.6, $J(3',4')$ = 15.1, $J(3',Me)$ = 1.7, $J(4',Me)$ = 6.6. ^{13}C-NMR: identical to [9].

3. Diels-Alder *Addition. General Procedure.* To a soln. of diene **2** (10 mmol) in 10 ml of solvent containing ($BnMe_3N$)IO_4 [10c] (1.37 g, 4 mmol) in an ice bath was added within 0.5 h portionwise hydroxamic acid **3** [8] (2.0 g, 12 mmol, 1.2 equiv.). After 1 h at 0°, AcOEt (50 ml) was added to the red soln. and the org. phase washed with 1M aq. Na_2CO_3 (10 ml; and enough Na_2SO_3 to suppress color) and brine (3 × 10 ml). The aq. phases were extracted with AcOEt and the combined org. soln. dried ($MgSO_4$) and evaporated to give crude adducts **5**.

*(±)-Benzyl 3,6-Dihydro-6-(2′-oxopyrrolidin-1′-yl)-2*H*-1,2-oxazine-2-carboxylate* (**5a**). *General Procedure* with **2a** (13.55 g, 99 mmol), ($BnMe_3N$)IO_4 (13.55 g, 39.5 mmol) in CH_2Cl_2 (48 ml)/MeOH (48 ml), and **3** (19.8 g, 119 mmol, 1.2 equiv.). Crude product was washed with Et_2O and recrystallized: **5a** (12.5 g, 42%). FC of the mother liquor gave a second crop (1.5 g, 5%). Cream-colored crystals. M.p. 90° (AcOEt/Et_2O). IR (KBr): 2965, 1785, 1455, 1435, 1405, 1360, 1280, 1270, 1220, 1210, 1090, 1010, 700. ^1H-NMR: *Table 2*. ^{13}C-NMR ($CDCl_3$): 175.5 (C(2′)); 154.9 (NCO_2); 135.9, 128.4, 128.1, 128.0 (arom. C); 127.5, 123.5 (C(4), C(5)); 77.7 (C(6)); 67.5 (Ph*C*H_2); 44.2 (C(3)); 44.1 (C(5′)); 30.8 (C(3′)); 18.2 (C(4′)). Anal. calc. for $C_{16}H_{18}N_2O_4$ (302.33): C 63.56, H 6.00, N 9.27; found: C 63.4, H 5.9, N 9.3.

*(±)-Benzyl 3,6-Dihydro-*r*-3-methyl-*c*-6-(2'-oxopyrrolidin-1'-yl)-2*H*-1,2-oxazine-2-carboxylate* (**5b**). *General Procedure* with **2b** (4.44 g, 29.2 mmol), $(BnMe_3N)IO_4$ (4.03 g, 10.7 mmol), and **3** (5.89 g, 35.2 mmol, 1.2 equiv.) in MeOH (15 ml)/CH_2Cl_2 (15 ml). The crude product (9.84 g) was purified by FC (AcOEt, 180 g of SiO_2): pure **5b** (5.82 g, 63%). Yellowish resin. ^{1}H-NMR: *Table 2*. ^{13}C-NMR ($CDCl_3$): 175.7 (C(2')); 154.7 (NCO_2); 135.9, 128.4, 128.0, 127.9 (arom. C); 133.4 (C(4)); 123.7 (C(5)); 77.9 (C(6)); 67.6 (Ph*C*H_2); 49.8 (C(3)); 42.4 (C(5')); 31.0 (C(3')); 17.9, 17.7 (C(4'), *Me*–C(3)). Too unstable for analysis.

4. *Cyclic Diols. General Procedure for* cis-*Hydroxylation* [8] [16]. The catalyst was prepared according to [26] from OsO_4 (1 g) and 1 ml of 70% *t*-BuOOH in *t*-BuOH (200 ml). To a stirred soln. of **5** (10 mmol) and *N*-methylmorpholine *N*-oxide (NMO; 2.0 g, 15 mmol, 1.5 equiv.) in acetone (10 ml) and H_2O (5 ml) was added dropwise a soln. of OsO_4 (3 ml). The soln. was kept 17–24 h at 40° until completion of the reaction. AcOEt (50 ml) was added, the org. phase washed with brine (3 × 10 ml), the aq. phase extracted with AcOEt, and the combined org. soln. dried ($MgSO_4$) and evaporated.

(±)-Benzyl r-*4*,c-*5-Dihydroxy*-t-*6-(2'-oxopyrrolidin-1'-yl)-1,2-oxazane-2-carboxylate* (**6a**). *General Procedure* with **5a** (12.45 g, 41.2 mmol), NMO (8.36 g, 62 mmol), acetone (38 ml), H_2O (21 ml), and OsO_4 soln. (12.5 ml; 17 h at 40°). The diol crystallized and was washed with i-PrOH: pure **6a** (12.22 g, 88%). Colorless crystals. M.p. 154° (EtOH). IR (KBr): 3440, 3310, 2930, 1705, 1675, 1412, 1345, 1335, 1285, 1275, 1215, 1090, 1000, 985, 752, 692. ^{1}H-NMR: *Table 2*. Anal. calc. for $C_{16}H_{20}N_2O_6$ (336.34): C 57.13, H 5.99, N 8.33; found: C 57.2, H 6.1, N 8.3.

(±)-Benzyl t-*4*,t-*5-Dihydroxy*-r-*3-methyl*-c-*6-(2'-oxopyrrolidin-1'-yl)-1,2-oxazane-2-carboxylate* (**6b**). *General Procedure* with **5b** (21.3 g, 67.4 mmol). NMO (18.19 g, 135 mmol), acetone (60 ml), H_2O (30 ml) and OsO_4 soln. (25 ml): **6b** (19.25 g, 81%). Oil. Characterized as its acetonide **8b**. ^{1}H-NMR: *Table 2*.

*(±)-*r-*4*,c-*5-Dihydroxy*-t-*6-(2'-oxopyrrolidin-1-yl)-1,2-oxazane* (**7a**). A stirred soln. of **6a** (0.64 g, 1.9 mmol) in MeOH (6.4 ml) was hydrogenated over 5% Pd/C (77 mg) for 3 h at r.t. After centrifugation, the solvent was evaporated. The resulting crystals were washed with i-PrOH: pure **7a** (0.377 g, 98%). Colorless crystals. M.p. 190° (MeOH). ^{1}H-NMR: *Table 2*. ^{13}C-NMR (D_2O, ref. MeOH): 182.4 (C(2')); 81.8 (C(6)); 68.0, 67.9 (C(4), C(5)); 54.2 (C(3)); 45.0 (C(5')); 32.8 (C(3')); 19.3 (C(4')). Anal. calc. for $C_8H_{14}N_2O_4$ (202.21): C 47.52, H 6.98, N 13.86; found: C 47.2, H 7.3, N 13.8.

5. *Acetonides. General Procedure*. To a stirred soln. of diol **6** (10 mmol) in 2,2-dimethoxypropane (10 ml) and acetone (50 ml) was added *Amberlyst-15* (H^+ form; 200 mg). After completion of the reaction, the soln. was filtered and evaporated. The product crystallized and was washed with iPrOH.

(±)-Benzyl r-*4*,c-*5-(Isopropylidenedioxy)*-t-*6-(2'-oxopyrrolidin-1'-yl)-1,2-oxazane-2-carboxylate* (**8a**). *General Procedure* with **6a** (11.15 g, 33.0 mmol), dimethoxypropane (36 ml), acetone (170 ml), and *Amberlyst-15* (0.7 g; 1.5 h at 35°): pure **8a** (12.3 g, 98%). Colorless crystals. M.p. 143° (i-PrOH). IR (KBr): 2980, 1728, 1698, 1418, 1285, 1237, 1218, 1160, 1105, 1070, 970. ^{1}H-NMR: *Table 2*. ^{13}C-NMR ($CDCl_3$): 176.1 (C(2')); 155.6 (NCO_2); 135.8, 128.4, 128.4, 128.2 (arom. C); 110.5 (Me_2C); 82.2 (C(6)); 71.3, 70.4 (C(4), C(5)); 68.0 (Ph*C*H_2); 46.2 (C(3)); 44.0 (C(5')); 31.1 (C(3')); 27.7, 26.2 (2 Me); 18.1 (C(4')). Anal. calc. for $C_{19}H_{24}N_2O_6$ (376.40): C 60.62, H 6.43, N 7.44; found: C 60.4, H 6.5, N 7.4.

(±)-Benzyl t-*4*,t-*5-(Isopropylidenedioxy)*-r-*3-methyl*-c-*6-(2'-oxopyrrolidin-1'-yl)-1,2-oxazane-2-carboxylate* (**8b**). *General Procedure* with **6b** (2.80 g, 8 mmol), dimethoxypropane (8.4 ml), acetone (42 ml), and *Amberlyst-15* (1.168 g; 3.5 h at 35°): pure **8a** (2.15 g, 69%). Colorless crystals. M.p. 131.5° (i-PrOH). IR (KBr): 3400, 2985, 1710, 1695, 1428, 1395, 1323, 1287, 1220, 1110, 1088, 1068, 1030, 995, 732. ^{1}H-NMR: *Table 2*. ^{13}C-NMR ($CDCl_3$): 176.1 (C(2')); 155.4 (NCO_2); 135.9, 128.4, 128.4, 128.1 (arom. C); 110.3 (Me_2C); 82.1 (C(6)); 76.1 (C(4)); 69.0 (C(5)); 67.9 (Ph*C*H_2); 51.2 (C(3)); 43.8 (C(5')); 31.2 (C(3')); 26.3, 27.8 (*Me*$_2$C); 18.1 (C(4')); 16.0 (Me–C(3)). Anal. calc. for $C_{20}H_{26}N_2O_6$ (390.42): C 61.32, H 6.71, N 7.18; found: C 60.9, H 6.7, N 7.3.

*(±)-*r-*4*,c-*5-(Isopropylidenedioxy)*-t-*6-(2'-oxopyrrolidin-1'-yl)-1,2-oxazane* (**9a**). A stirred suspension of **8a** (3.00 g, 7.97 mmol) in EtOH (30 ml) and MeOH (15 ml) was hydrogenated over 5% Pd/C (177 mg) for 4 h at r.t. (TLC (AcOEt) monitoring). Centrifugation and evaporation gave crystals which were washed with $(i\text{-}Pr)_2O$: **9a** (1.715 g, 89%). Colorless crystals. M.p. 145° ($(i\text{-}Pr)_2O$/AcOEt 1:1). IR (KBr): 3275, 2980, 2900, 1685, 1675, 1422, 1370, 1270, 1248, 1220, 1075, 1062, 1020, 1002, 890, 850. ^{1}H-NMR: *Table 2*. ^{13}C-NMR ($CDCl_3$): 176.4 (C(2')); 110.1 (Me_2C); 82.4 (C(6)); 71.5, 70.6 (C(4), C(5)); 49.2 (C(3)); 42.9 (C(5')); 31.0 (C(3')); 27.9, 26.4 (*Me*$_2$C); 18.1 (C(4')). Anal. calc. for $C_{11}H_{18}N_2O_4$ (242.27): C 54.53, H 7.49, N 11.56; found: C 54.7, H 7.7, N 11.3.

*(±)-*t-*4*,t-*5-(Isopropylidenedioxy)*-r-*3-methyl*-c-*6-(2'-oxopyrrolidin-1'-yl)oxazane* (**9b**). A stirred suspension of **8b** (1.784 g, 4.57 mmol) in MeOH (27 ml) was hydrogenated over 5% Pd/C (109 mg) for 1.5 h at r.t. The standard workup gave **9b** (1.152 g, 98%). Colorless crystals. M.p. 149° (AcOEt/$(i\text{-}Pr)_2O$ 1:1). IR (KBr): 3240, 2985, 2975, 2930, 2880, 1689, 1415, 1380, 1285, 1270, 1215, 1060, 990, 840. ^{1}H-NMR: *Table 2*. ^{13}C-NMR ($CDCl_3$): 176.3 (C(2')); 109.6 (Me_2C); 82.1 (C(6)); 76.2 (C(4)); 70.4 (C(5)); 53.9 (C(3)); 44.4 (C(5')); 31.2 (C(3')); 28.0, 26.5 (*Me*$_2$C);

18.3 (C(4')); 16.6 (*Me*–C(3)). Anal. calc. for $C_{12}H_{20}N_2O_4$ (256.30): C 56.23, H 7.87, N 10.93; found: C 55.4, H 7.9, N 10.8.

*4-Amino-1,4-dideoxy-2,3-*O*-isopropylidene-1-(2'-oxopyrrolidin-1'-yl)-*DL*-ribose* (**10a**). a) *From* **9a**: A stirred suspension of **9a** (0.27 g, 1.11 mmol) in MeOH (3 ml) was hydrogenated over 5% Pd/C (34 mg) overnight at r.t. After centrifugation, evaporation at r.t. gave pure **10a** (0.27 g, quant.).

b) *From* **8a**: A stirred suspension of **8a** (0.82 g, 2.24 mmol) in MeOH (8 ml) was hydrogenated over 5% Pd/C (49 mg and another 55 mg after 7 h) for 24 h at r.t.: **10a** (0.56 g, quant.). Colorless oil. ^{1}H-NMR (C_6D_6): 5.94 (*d*, H–C(1)); 4.12 (*dd*, H–C(2)); 3.90 (*m*, H–C(3)); 3.46, 3.27 (2*m*, 2 H–C(5')); 2.80 (*m*, H_a–C(4)); 2.66 (*m*, H_b–C(4)); 2.08 (*t*, 2 H–C(3')); 1.38 (*m*, 2 H–C(4')); 1.56, 1.47 (2*s*, Me_2C); $J(1,2) = 9.4$, $J(2,3) = 5.7$, $J(3,4a) = 8.4$, $J(3,4b) = 4.8$, $J(4a,4b) = 12.7$. ^{13}C-NMR ($CDCl_3$): 176.0, 108.7, 77.7, 75.9, 72.2, 41.8, 40.7, 31.6, 27.7, 25.5, 18.0.

Picrate of **10a**: A soln. of **10a** (60 mg, 0.25 mmol) in CH_2Cl_2 (0.2 ml) was added to a soln. of picric acid (54 mg, 0.24 mmol) in EtOH (0.1 ml). Some crystals appeared by scratching, Et_2O (0.5 ml) was added and the picrate isolated as yellow crystals. M.p. 134–139°. Anal. calc. for $C_{11}H_{20}N_2O_4 \cdot C_6H_3N_3O_7$ (473.29): C 43.13, H 4.88, N 14.80; found: C 42.8, H 4.8, N 14.4.

Diacetate of **10a**: A mixture of **10a** (60 mg, 0.25 mmol), Ac_2O (50 µl), and pyridine (0.2 ml) was left to react for 2 h. MeOH (0.2 ml) was added, and the solvents were evaporated. The diacetate was crystallized and washed with $(i\text{-}Pr)_2O$ to give colorless crystals (34 mg, 42%). M.p. 142° (toluene). IR (KBr): 3420, 3280, 3090, 1750, 1680, 1650, 1590, 1442, 1372, 1210, 1070, 1020. ^{1}H-NMR (C_6D_6): 6.72 (*d*, H–C(1)); 5.23 (br. *s*, NH); 4.20 (*m*, H–C(3)); 4.01 (*dd*, H–C(2)); 3.85 (*m*, H_a–C(4)); 3.14, 2.93 (2*m*, 2 H–C(5')); 2.96 (*m*, H_b–C(4)); 1.95 (*t*, 2 H–C(3')); 1.29 (*m*, 2 H–C(4')); 1.69, 1.50 (2*s*, 2 AcO); 1.52, 1.16 (2*s*, 2 Me_2C); $J(1,2) = 9.2$; $J(2,3) = 5.6$; $J(3,4a) = 3.2$; $J(3,4b) = 8.7$; $J(4a,4b) = 13.7$; $J(NH,4a) = 7.3$; $J(NH,4b) = 4.6$. Anal. calc. for $C_{15}H_{24}N_2O_6$ (328.36): C 54.86, H 7.37, N 8.53; found: C 55.0, H 7.5, N 8.4.

*4-Amino-1,4,5-trideoxy-2,3-*O*-isopropylidene-1-(2'-oxopyrrolidin-1'-yl)-*DL*-ribose* (**10b**). A soln. of **9b** (1.01 g, 4 mmol) in MeOH (18 ml) was hydrogenated over *Raney*-Ni (2.0 g wet) overnight at r.t. After centrifugation, evaporation gave **10a** (0.98 g, 96%). Colorless crystals. M.p. 135° (AcOEt). IR (KBr): 3330, 2905, 1669, 1610, 1436, 1370, 1290, 1265, 1225, 1090, 1072, 980, 853. ^{1}H-NMR ($CDCl_3$): 5.60 (*d*, H–C(1)); 4.17 (*dd*, H–C(2)); 3.86 (*m*, H–C(3)); 3.61, 3.44 (2*m*, 2 H–C(5')); 3.27 (*m*, H–C(4)); 2.42 (*t*, $J = 7$, 2 H–C(3')); 2.04 (*m*, 2 H–C(4')); 1.38, 1.32 (2*s*, Me_2C); 1.31 (*d*, Me–C(4)); $J(1,2) = 9.4$, $J(2,3) = 5.4$, $J(3,4) = 9.3$, $J(4,Me\text{–}C(4)) = 6.3$. ^{13}C-NMR ($CDCl_3$): 175.7 (C(2')); 108.7 (Me_2C); 81.8 (C(6)); 76.6 (C(4)); 72.5 (C(5)); 46.1 (C(3)); 41.7 (C(5')); 31.6 (C(3')); 27.7, 25.7 (Me_2C); 23.2 (C(4')); 18.1 (*Me*–C(4)). Anal. calc. for $C_{12}H_{22}N_2O_4$ (258.31): C 55.79, H 8.58, N 10.85; found: C 55.7, H 8.7, N 10.8.

6. *4-Amino-4-deoxyerythrose, 4-Amino-4,5-dideoxyribose, and Their Derivatives. 4-Amino-4-deoxy-2,3-*O*-isopropylidene-*DL*-erythrofuranose* (**11a**). To a stirred soln. of **10a** (0.56 g, 2.18 mmol; from 0.82 g of **8a**) in H_2O (5 ml) was added $Ba(OH)_2 \cdot 8\ H_2O$ (0.69 g, 2.18 mmol). After 15 min at r.t., aq. 1N H_2SO_4 (4.3 ml) was added, $BaSO_4$ eliminated by centrifugation, the aq. soln. extracted with Et_2O (5 × 20 ml), and the org. phase washed with brine and carefully evaporated: **11a** (0.13 g, 42%). Colorless resin: mixture **11a**/**11'a**. ^{1}H-NMR: *Table 3*. MS: 423 (37, $M_3^{+\cdot}$), 267 (16), 253 (15), 142 (100, MH^+), 126 (78), 84 (57), 59 (18). HR-MS: 423.2361 ($C_{21}H_{33}N_3O_6^+$, trimer of **11'a**; calc. 423.2369).

*4-Amino-4,5-dideoxy-2,3-*O*-isopropylidene-*DL*-ribofuranose* (**11b**). To a stirred soln. of **10b** (2.0 g, 7.8 mmol) in H_2O (25 ml) was added $Ba(OH)_2 \cdot 8\ H_2O$ (2.46 g, 7.8 mmol, 1 equiv.). After 30 min, the centrifugated aq. soln. was extracted with Et_2O (5 × 20 ml) and the org. phase washed with brine and carefully evaporated: **11b** (0.90 g, 75%). Colorless resin: mixture **11b**/**11'b**. ^{1}H-NMR: *Table 3*. ^{1}H-NMR ($CDCl_3$) of **11'b**: 7.51 (*d*, $J = 1.6$, H–C(1)); 5.11 (*d*, $J = 5.7$, H–C(2)); 4.31 (*m*, H–C(3), H–C(4)); 1.38, 1.35 (2*s*, Me_2C); 1.21 (*d*, $J = 7.4$, Me–C(4)). ^{13}C-NMR ($CDCl_3$) of **11'b**: 164.1 (C(1)); 111.7 (Me_2C); 86.3, 86.3 (C(2), C(3)); 73.6 (C(4)); 27.0, 25.7 (Me_2C); 19.3 (*Me*–C(4)).

*4-Amino-4-deoxy-*DL*-erythrofuranose* (**14a**). To a stirred soln. of **13a** (0.25 g, 1.35 mmol) in H_2O (5 ml) was added $Ba(OH)_2 \cdot 8\ H_2O$ (0.43 g, 1.35 mmol, 1 equiv.). After 20 min, precipitated $BaSO_3$ was separated and washed with MeOH (baryte can be exactly precipitated with 1N H_2SO_4), the solns. were evaporated to give **14a**, *i.e.*, **14a**/**14'a**/**14"a** (0.12 g, 88%). Yellowish resin. ^{1}H-NMR: *Table 3*. ^{13}C-NMR (D_2O) of **14a**: 87.5, 74.0, 69.4, 55.2; other peaks: 100.5, 87.7, 81.4, 74.6, 71.8, 68.3, 60.2, 51.6, 51.4.

*4-Amino-4,5-dideoxy-*DL*-ribofuranose* (**14b**). By the same procedure, **14b** was prepared from **13b** or directly from **10b**. To a soln. of **10b** (0.274 g, 1.06 mmol) in H_2O (5 ml) was added $Ba(OH)_2 \cdot 8\ H_2O$ (0.336 g, 1.06 mmol, 1 equiv.) and stirred for 20 min at r.t. Baryte in excess was eliminated and the soln. stirred under SO_2 atmosphere in a glass vessel overnight at 35°, then evaporated. The white solid ($BaSO_3$ + **13b**) was washed with MeOH (to eliminate the pyrrolidinone) and dissolved in H_2O (5 ml), and baryte (0.336 g) was added. The suspension was

stirred for 20 min and filtered and the soln. evaporated (excess of baryte can be exactly precipitated with 1N H_2SO_4) to give **14b**, *i.e.*, **14b**/**14'b**/**14''b** (96 mg, 79%). Yellowish resin. ^{1}H-NMR: *Table 3*. ^{13}C-NMR (D_2O): **14b** and **14''b**: 98.3, 81.3, 81.2, 80.0, 78.9, 77.6, 77.0, 73.7, 71.3, 63.0, 57.2, 56.9, 18.6, 18.1, 17.1; **14'b**: 169.2, 77.7, 75.3, 74.2, 18.0.

7. *Sulfite Adducts. 4-Amino-1,4-dideoxy-2,3-*O*-isopropylidene-*DL*-erythrofuranose-1-sulfonic Acid* (**12a**). Direct action of SO_2: A soln. of **10a** (0.578 g, 2.37 mmol) in Et_2O (5 ml) was stirred under SO_2 in a glass vessel at –20°. Some white crystals appeared immediately. After 1 h, MeOH (1 ml) was added and **12a** (0.265 g, 50%) isolated by filtration. White crystals. M.p. *ca.* 180° (subl.; EtOH). IR (KBr): 3430, 3080, 1645, 1615, 1448, 1388, 1377, 1275, 1255, 1225, 1165, 1070, 1055, 1035, 1010. ^{1}H-NMR: *Table 3*. ^{13}C-NMR (CD_3OD): 113.7 (Me_2C); 82.2 (C(2)); 80.0 (C(3)); 77.9 (C(1)); 52.6 (C(4)); 29.1, 24.0 (Me_2C). Anal. calc. for $C_7H_{13}NO_5S$ (223.24): C 37.66, H 5.88, N 6.27, S 14.36; found: C 37.9, H 5.8, N 6.5, S 14.0.

*4-Amino-1,4,5-trideoxy-2,3-*O*-isopropylidene-*DL*-ribofuranose-1-sulfonic Acid* (**12b**). An Et_2O soln. of **11b** was prepared from **10b** (0.40 g, 1.55 mmol) with $Ba(OH)_2 \cdot 8\ H_2O$ (0.49 g, 1.55 mmol) in H_2O (5 ml) by extraction with Et_2O (5 × 10 ml). After concentration to 5–10 ml, the Et_2O soln. was stirred at 0° under SO_2 in a glass vessel. White crystals appeared immediately and were isolated by filtration: **12b** (0.306 g, 77%). M.p. 135° (subl.; EtOH/H_2O). IR (KBr): 3610, 3540, 2945, 2775, 2700, 2515, 1603, 1428, 1385, 1372, 1250, 1220, 1180, 1068, 1040, 850, 605. ^{1}H-NMR: *Table 3*. ^{13}C-NMR (CD_3OD): 115.0 (Me_2C); 86.0 (C(3)); 82.6 (C(2)); 78.2 (C(1)); 62.9 (C(4)); 27.3, 25.1 (Me_2C); 16.2 (*Me*–C(4)). Anal. calc. for $C_8H_{15}NO_5S \cdot H_2O$ (255.27): C 37.49, H 6.68, N 5.46, S 12.51; found: C 37.7, H 6.7, N 5.7, S 12.6.

*4-Amino-1,4-dideoxy-*DL*-erythrofuranose-1-sulfonic Acid* (**13a**). A soln. of **12a** (1.0 g, 4.48 mmol) in H_2O (10 ml) was stirred overnight at 50° under SO_2. At 0°, cold MeOH (20 ml) was added and the precipitate isolated: **13a** (0.52 g, 63%). Evaporation of the solvents gave a second crop of **13a** (0.14 g, 17%). White crystals. M.p. 170° (dec.; MeOH/H_2O). IR (KBr): 3510, 2980, 2770, 1710, 1590, 1428, 1300, 1205, 1175, 1128, 1000, 942, 813, 550. ^{1}H-NMR: *Table 3*. ^{13}C-NMR (D_2O): 74.3 (C(2)); 73.7 (C(3)); 70.8 (C(1)); 51.2 (C(4)). Anal. calc. for $C_4H_9NO_5S$ (183.13): C 26.23, H 4.95, N 7.65, S 17.51; found: C 26.1, H 5.1, N 7.6, S 17.5.

*4-Amino-1,4,5-trideoxy-*DL*-ribofuranose-1-sulfonic Acid* (**13b**). A soln. of **12b** (0.1 g, 0.39 mmol) in H_2O (3 ml) was stirred overnight at 35° under SO_2. After evaporation of H_2O, the residue was recrystallized in EtOH/H_2O to give anal. pure **13b** (30 mg, 40%). White crystals. M.p. > 160° (dec.; EtOH/H_2O). IR (KBr): 3460, 3000, 2960, 2780, 1600, 1240, 1222, 1185, 1045, 823, 610. ^{1}H-NMR: *Table 3*. ^{13}C-NMR (D_2O): 75.9, 75.8 (C(2), C(3)); 72.4 (C(1)); 60.2 (C(4)); 15.3 (*Me*–C(4)). Anal. calc. for $C_5H_{11}NO_5S$ (197.21): C 30.45, H 5.62, N 7.10, S 16.26; found: C 30.2, H 5.7, N 7.1, S 15.8.

8. *Cyano Derivatives. General Procedure.* To a HCN soln. in Et_2O (prepared from NaCN (0.3 g, 6 mmol, 6 equiv.) and a soln. of 2.1N HCl in Et_2O (2.2 ml, 4.5 equiv.) in Et_2O (1.5 ml) and H_2O (0.3 ml)) was added **11** (1 mmol) in Et_2O (1.5 ml). The soln. was stirred for 2 h at r.t. and then filtered and evaporated: pure **15**.

*2,5-Imino-2,5-dideoxy-3,4-*O*-isopropylidene-*DL*-ribo-pentononitrile* (**15a**). *General Procedure* with **11a** (94 mg, 0.67 mmol), HCl soln. in Et_2O (1.44 ml), and NaCN (0.2 g, 4 mmol): **15a** (0.11 g, 98%). Yellowish resin. IR ($CHCl_3$): 2254 (CN). ^{1}H-NMR: *Table 3*. ^{13}C-NMR ($CDCl_3$): 117.9 (CN); 112.0 (Me_2C); 84.5 (C(3)); 82.7 (C(4)); 56.0 (C(2)); 52.5 (C(3)); 25.8, 24.0 (Me_2C). MS: 168 (6), 153 (31), 126 (78), 110 (40), 93 (54), 84 (35), 82 (40), 81 (40), 68 (13), 59 (34), 55 (63), 43 (100). HR-MS: 168.0895 ($C_8H_{12}N_2O_2$, calc. 168.0899).

*2,5-Imino-2,5,6-trideoxy-3,4-*O*-isopropylidene-*DL*-allo-hexononitrile* (**15b**). *General Procedure* with **11b** (0.148 g, 0.95 mmol), HCl soln. in Et_2O (2.04 ml), and NaCN (0.28 g, 5.7 mmol; 6 h at r.t.): **15b** (0.133 g, 77%). IR ($CHCl_3$): 2254 (CN). ^{1}H-NMR: *Table 3*. ^{13}C-NMR ($CDCl_3$): 120.1 (CN); 112.8 (Me_2C); 86.7 (C(4)); 85.2 (C(3)); 61.0 (C(5)); 54.8 (C(2)); 26.5, 24.4 (Me_2C); 18.7 (*Me*–C(4)). MS: 182 (5), 167 (13), 124 (35), 107 (24), 101 (11), 95 (18), 91 (16), 82 (100), 69 (37), 55 (26). HR-MS: 182.1055 ($C_9H_{14}N_2O_2^+$; calc. 182.1055).

9. *Amino Acids. General Procedure.* Nitrile **15** (1 mmol) was hydrolyzed in 6N HCl (1.5 ml) at 50°. The black soln. was neutralized with 2.5N NaOH and evaporated and the residue chromatographed ($CHCl_3$/MeOH/conc. NH_3 soln. 2:6:2).

*(2*RS*,3*SR*,4*RS*)-3,4-Dihydroxyproline. General Procedure* with **15a** (0.11 g, 0.65 mmol; overnight): **16a** (80 mg, 83%). Brown crystals. M.p. > 219° (H_2O/i-PrOH) ([12]: 241–242° (dec.)). IR (KBr): 3345, 3117, 2690, 2560, 2410, 1635, 1590, 1408, 1370, 1330, 1295, 1137, 1098, 1060; in good agreement with [12]. ^{1}H-NMR: 4.23 (*m*, H–C(3), H–C(4)); 3.86 (*d*, *J* = 5, H–C(2)); 3.42 (*dd*, *J* = 12, 5, H_a–C(5)); 3.18 (*dd*, *J* = 12, 4, H_b–C(5)). ^{13}C-NMR (D_2O): 171.3, 74.0, 69.8, 64.2, 48.2; ^{1}H- and ^{13}C-NMR in good agreement with [13a] [13b] for the (2*R*,3*S*,4*R*)- and (2*S*,3*R*,4*S*)-isomers.

*(2*RS*,3*SR*,4*RS*,5*RS*)-3,4-Dihydroxy-4-methylproline* (**16b**). *General Procedure* with **15b** (0.12 g, 0.65 mmol; 27 h). The collected crystals were recrystallized in H_2O/i-PrOH: pure **16b** (78 mg, 74%). Cream-colored crystals.

M.p. 115–116° (dec.). IR (KBr): 3307, 3060, 1620, 1569, 1440, 1405, 1384, 1325, 1281, 1140, 1070, 1040, 880, 665. ^{1}H-NMR (D_2O): 4.45 (*dd*, H–C(3)); 4.07 (*d*, H–C(2)); 3.94 (*dd*, H–C(4)); 3.69 (*q*, H–C(5)); 1.49 (*d*, Me–C(5)); $J(2,3) = 2.4$, $J(3,4) = 4.1$, $J(4,5) = 8.4$, $J(5,Me) = 6.7$. ^{13}C-NMR (D_2O): 172.4 (CO_2H); 76.1 (C(4)); 74.3 (C(3)); 66.8 (C(2)); 58.0 (C(5)); 15.8 (*Me*–C(5)). HR-MS: 125.0473 ($C_6H_7NO_2^+$, $[M - 2\,H_2O]^+$; calc. 125.0477).

10. *AIDS-Inhibition Assays.* The tests were made on aminosugars in C8166 cells infected with HIV-1 MN. Thus, $4 \cdot 10^4$ cells were mixed with 5-fold dilutions of compounds prior to addition of virus (10, 50% cell culture infectious dose). Inhibition of infection was assessed by examining reduction of syncytia formation and by measuring virus yield after 5–6 days of incubation at 37°. Cell viability of infected and uninfected cells was determined by the XTT-formazan assay [27].

Virus yield was titrated on C8166 cells by doubling dilutions of the freshly collected supernatant from infected cells after 5–6 days of incubation.

REFERENCES

[1] H. Paulsen, K. Propp, J. Brüning, *Chem. Ber.* **1969,** *102,* 469.

[2] H. Paulsen, J. Brüning, K. Heyns, *Chem. Ber.* **1970,** *103,* 1621.

[3] H. Paulsen, K. Steinert, K. Heyns, *Chem. Ber.* **1970,** *103,* 1599.

[4] T. Shibata, O. Nakayama, Y. Tsurumi, M. Okuhara, H. Terano, M. Kohsaka, *J. Antibiot.* **1988,** *41,* 296; H. Kayakiri, K. Nakamura, Sh. Takase, H. Setoi, I. Uchida, H. Terano, M. Hashimoto, T. Tada, Sh. Koda, *Chem. Pharm. Bull.* **1991,** *39,* 2807; H. Kayakiri, Sh. Takase, H. Setoi, I. Uchida, H. Terano, M. Hashimoto, *Tetrahedron Lett.* **1988,** *29,* 1725.

[5] J. F. Witte, R. W. McClard, *Tetrahedron Lett.* **1991,** *32,* 3927.

[6] B. A. Horenstein, R. F. Zabinski, V. L. Schramm, *Tetrahedron Lett.* **1993,** *34,* 7213.

[7] Y. Arakawa, Sh. Yoshifuji, *Chem. Pharm. Bull.* **1991,** *39,* 2219.

[8] A. Defoin, J. Pires, J. Streith, *Helv. Chim. Acta* **1991,** *74,* 1653.

[9] Ch. A. Zezza, M. B. Smith, *J. Org. Chem.* **1988,** *53,* 1161.

[10] a) G. W. Kirby, J. G. Sweeny, *J. Chem. Soc., Chem. Commun.* **1973,** 704; b) G. E. Keck, R. R. Webb, J. B. Yates, *Tetrahedron* **1981,** *37,* 4007; c) H.-Sh. Dang, A. G. Davies, *J. Chem. Soc., Perkin Trans. 2* **1991,** 721.

[11] H. Böshagen, W. Geiger, B. Junge, *Angew. Chem.* **1981,** *93,* 800.

[12] C. B. Hudson, A. V. Robertson, W. R. J. Simpson, *Aust. J. Chem.* **1968,** *21,* 769.

[13] a) P. D. Baird, J. C. Dho, G. W. J. Fleet, J. M. Peach, K. Prout, P. W. Smith, *J. Chem. Soc., Perkin Trans. 1* **1987,** 1785; b) G. W. J. Fleet, J. Ch. Son, *Tetrahedron* **1988,** *44,* 2637; c) N. Ikota, *Chem. Pharm. Bull.* **1993,** *41,* 1717.

[14] C. J. Rule, B. A. Wurzburg, B. Ganem, *Tetrahedron Lett.* **1985,** 26, 5379.

[15] W. Kirmse, in 'Houben-Weyl, Methoden der organischen Chemie', 4th edn., G. T. Thieme Verlag, Stuttgart, 1972, Vol. 5/1b, p. 670.

[16] V. Van Rheenen, R. C. Kelly, D. Y. Cha, *Tetrahedron Lett.* **1976,** *17,* 1973.

[17] A. Defoin, H. Fritz, G. Geffroy, J. Streith, *Helv. Chim. Acta* **1988,** *71,* 1642.

[18] H. Paulsen, F. Leupold, K. Todt, *Liebigs Ann. Chem.* **1966,** *692,* 200.

[19] J. Firl, *Chem. Ber.* **1969,** *102,* 2169.

[20] H. Paulsen, K. Todt, *Chem. Ber.* **1967,** *100,* 3385.

[21] J. D. Stevens, H. G. Fletcher, Jr., *J. Org. Chem.* **1968,** *33,* 1799.

[22] Y. Kodama, T. Tsuruoka, T. Niwa, Sh. Inouye, *J. Antibiot.* **1985,** *38,* 116.

[23] A. Defoin, H. Sarazin, J. Streith, *Tetrahedron Lett.* **1993,** *34,* 4327.

[24] B. D. Walker, M. Kowalski, W. Ch. Goh, K. Kozarsky, M. Krieger, C. Rosen, L. Rohrschneider, W. A. Haseltine, J. Sodroski, *Proc. Natl. Acad. Sci. U.S.A.* **1987,** *84,* 8120.

[25] O. Bayer, in 'Houben-Weyl, Methoden der organischen Chemie', 4th edn., G. T. Thieme Verlag, Stuttgart, 1954, Vol. 7/1b, p. 118.

[26] K. Akashi, R. E. Palermo, K. B. Sharpless, *J. Org. Chem.* **1978,** *43,* 2063.

[27] O. S. Weislow, R. Kiser, D. L. Fine, J. Bader, R. H. Shoemaker, M. R. Boyd, *J. Natl. Cancer Inst.* **1989,** *81,* 577.