51. Synthesis of 1,6-Dideoxynojirimycin, 1,6-Dideoxy-D-*allo*-nojirimycin, and 1,6-Dideoxy-D-*gulo*-nojirimycin *via* Asymmetric Hetero-*Diels-Alder* Reactions

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Asymmetric *Diels-Alder* reaction of sorbaldehyde *O*-methyloxime **1d** with chiral chloronitroso derivative **2** of D-mannose, followed by osmylation of the primary cycloadduct, led to diol **6a** with excellent enantioselectivity (ee > 99%; *Scheme 1*). Catalytic hydrogenolysis of **6a** gave 1,6-dideoxy-D-*allo*-nojirimycin (**7a**). Nucleophilic ring opening of cyclic sulfate **8** allowed a straightforward synthesis of 1,6-dideoxynojirimycin (**11**) and of 1,6-dideoxy-D-*gulo*-nojirimycin (**12**; *Scheme 2*).

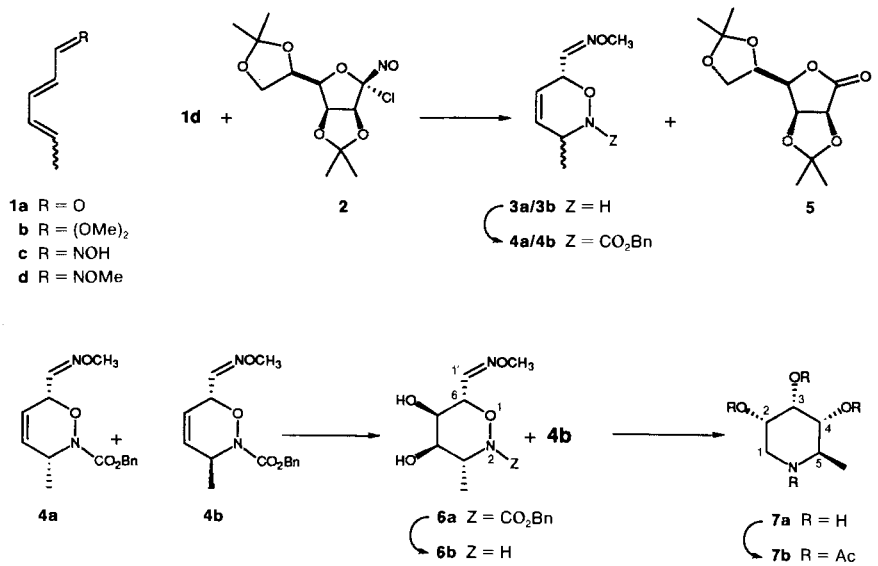
Introduction. – The 1,5,6-trideoxy-1,5-iminohexitols (ω-deoxyazasugars), which are 2-methylpiperidinetriols, are interesting compounds because of their L-fucosidase- and glycosyl-transferase inhibitory properties [1] [2]. The fucose derivative 1,5-dideoxy-1,5-imino-L-fucitol is a potent α-L-fucosidase inhibitor [4] [5]. A number of such iminoalditol derivatives have been synthesized *via* chemical transformation of naturally occurring saccharides [3] [4] [6] [7] or by biochemical synthesis using aldolases [2] [5] [8].

We describe herein the synthesis of three chiral 5-amino-1,5,6-trideoxysugars, **7a**, **11**, and **12**, belonging to the D-*allo*, D-*gluco*, and D-*gulo* series, respectively. The applied methodology has already been developed in the racemic series by hetero-*Diels-Alder* cycloaddition of sorbaldehyde (hexa-2,4-dienal) dimethyl acetal (**1b**) with acyl-nitroso dienophiles as the key step [9] [10]; osmylation of the adduct and hydrogenolysis of the N–O bond led to 5-amino-5,6-dideoxy-DL-allose and to racemic (±)-**7a** [9]. To obtain enantiomerically pure aminosugars, we used chloronitroso dienophile **2** [11]. Asymmetric hetero-*Diels-Alder* addition of **2** with acetal **1b** gave the primary cycloadduct in moderate yield only [12]; to the contrary, the *O*-methyloxime **1d** led easily to the chiral D-*allo*-aza-sugar **7a**; mono-inversion of the intermediary diol gave access to the D-glucose and to the D-gulose series. Using a similar approach, the L-*allo* compound had been prepared by *Wyatt et al.* by reaction of the cyclic sorbaldehyde-ephedrine amino-ether derivative with an acylnitroso dienophile [13]. The D-*gluco* compound **11** had been obtained by *Wong et al.* using aldolases along with some chemical reactions [1] [8]. A preliminary communication for the synthesis of **7a** from **1d** was published [14].

***Diels-Alder* Cycloadditions and Osmylations.** – D-*Allose Series*. *Kresze*, *Vasella*, and coworkers demonstrated that chiral chloronitroso dienophile **2** reacts with 1,4-disubstituted dienes, particularly with ethyl sorbate (= ethyl (*E*,*E*)-hexa-2,4-dienoate), in MeOH/$CHCl_3$ to give optically active *N*-substituted 3,6-dihydro-2*H*-oxazines with excel-

lent enantiomeric excess, along with mannonolactone **5** [11]. When we applied these conditions to sorbaldehyde **1a** or its dimethyl acetal **1b**, no corresponding cycloadducts were obtained (different conditions were required for this purpose [12]); the only product which could be identified was 3-hydroxy-6-methylpyridine. The known oxime **1c** [15] did not lead to any well defined cycloadducts either. However, the *O*-methyloxime **1d** underwent the expected cycloaddition (*Scheme 1*).

Scheme 1

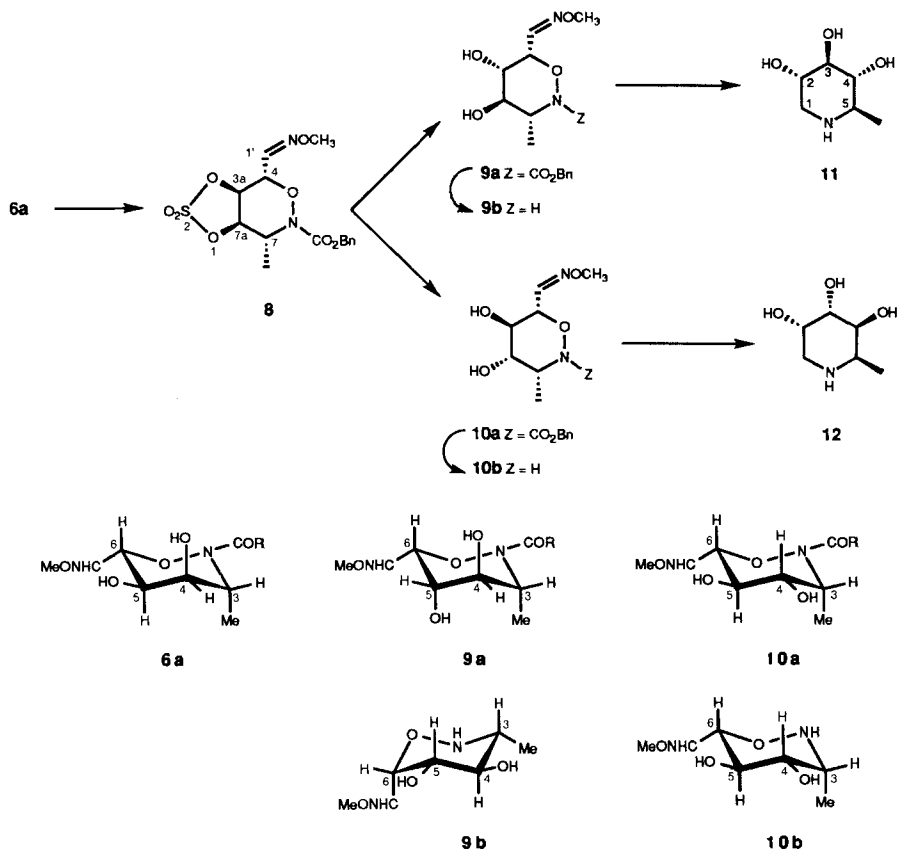


The (*Z*)/(*E*)-oxime mixture **1d** was easily prepared by condensation of sorbaldehyde **1a** with *O*-methylhydroxylamine in EtOH. As already observed in the racemic series [12], the reaction of **1d** with dienophile **2** in MeOH/$CHCl_3$ at −10° was a concerted reaction and led to a *cis*/*trans* mixture **3a**/**3b**, since diene **1d** was a 88:12 mixture of the (2*E*,4*E*)- and (2*E*,4*Z*)-isomers. Furthermore, both **3a** and **3b** were (*E*)/(*Z*)-oxime mixtures. Adducts **3a**/**3b** were separated from mannonolactone **5** by water extraction and *N*-protected (benzyl chloroformate/Na_2CO_3) at once to give **4a**/**4b**. As observed previously [9] [10], the sterically more hindered *trans*-isomer **4b** did not react in the subsequent hydroxylation with catalytic osmium tetraoxide/*N*-methylmorpholine *N*-oxide (NMO) in acetone/H_2O [16], whereas the *cis*-isomer **4a** led to diol **6a** which was easily separated by chromatography (albeit as a (*E*)/(*Z*)-oxime mixture). Hydrogenolysis over Pd/C of **6a** gave directly 1,6-dideoxy-D-*allo*-nojirimycin (= 1,5-imino-1,5,6-trideoxy-D-allitol; **7a**) which was characterized as its crystalline tetraacetate **7b**.

This straightforward five-step synthesis of *allo*-aminosugar **7a** was achieved with acceptable overall yields (32% from **1a**) and excellent enantiomeric excess (ee). Similar yields were obtained for the synthesis of racemic (±)-**7a** using acylnitroso dienophiles (*ca.* 35% from **1a** [9] [10]). The previously reported asymmetric synthesis of **7a** (by us) was achieved in 20% overall yield from **1a** [12] and for the L-enantiomer in only 10% [13].

D-*Glucose and* D-*Gulose Series*. To enter the D-glucose and D-gulose series from the preceding D-allose one, a single and specific configurational inversion was required. For that purpose, we used the *Sharpless* method, *i.e.*, formation of a cyclic sulfate followed by a nucleophilic ring opening [17]. Thus, reaction of **6a** with thionyl chloride in pyridine and oxidation of the cyclic sulfites with $Ru^{VIII}/NaIO_4$ led to cyclic sulfate **8** (74%). Nucleophilic ring opening with ammonium benzoate in DMF followed by acid hydrolysis of the sulfate monoester and by saponification of the benzoate ester led in 53% overall yield to a 85:15 mixture of *trans*-diols **9a** and **10a**. The preferred formation of **9a** resulting from

Scheme 2



inversion at C(3a) of **8** can easily be rationalized by stereoelectronic requirements: axial nucleophilic attack at C(3a) of **8** is obviously preferred over an equatorial one at C(7a). Separation of the diols was performed by flash chromatography after reductive *N*-deprotection (hydrogenolysis over Pd/C at room temperature) to **9b**/**10b**, yielding **9b** as a crystalline compound and **10b** as an oil. Hydrogenolysis at 55° of the major product **9b** led directly to enantiomerically pure piperidinetriol **11**, *i.e.*, to 1,6-dideoxynojirimycin,

and hydrogenolysis of the minor compound **10b** gave 1,6-dideoxy-D-*gulo*-nojirimycin (**12**). The 1,6-dideoxynojirimycin (**11**) was obtained in 6% overall yields from **1a**.

Absolute Configurations. – *Kresze*, *Vasella*, and coworkers have already demonstrated that hetero-*Diels-Alder* cycloaddition of ethyl (*E*,*E*)-hexa-2,4-dienoate with chiral dienophile **2** gave the (3*R*,6*R*)-cycloadduct with ee > 95% [11b]. Since we use a similar diene and the same chiral dienophile **2**, we can conclude that the major cycloadduct **3a** has also the (3*R*,6*R*)-configuration. Consequently, the target molecules **7a**, **11**, and **12** appear to be D-piperidinose derivatives. This point was confirmed for compounds **7a** and **11** by comparison with reported data [8c] [13] (see below). The ee values were measured using HPLC (*Chiralpack AD* and *Chiralcel OD*) by comparison of the major chiral diol **6a** with the racemic (±)-**6a**: ee > 99% for **6a**. Racemic (±)-**6a** was prepared by reaction of **1d** with the acylnitroso derivative BnOCONO [10] (→ (±)-**4a**/(±)-**4b**) followed by osmylation and chromatographic separation.

Structural Analyses. – All oximes described above were mixtures of a major (*E*)- and a minor (*Z*)-oxime, with the exception of **10a** ((*E*)-oxime only). The NMR data ($CDCl_3$) of each pair of (*E*)- and (*Z*)-*O*-methyloximes are quite similar (the signals of H–C(1′) at the C=N bond appears at *ca.* 7.5 ppm for the (*E*)-oximes and at *ca.* 6.7–7.0 ppm for the (*Z*)-oximes; see *Table 1*).

The conformation of the *N*-acylated diols **6a**, **9a**, and **10a** could be determined as a consequence of the severe steric interaction between the *N*-acyl substituent and the vicinal Me–C(3) group. To minimize the above cited steric interaction [18], this latter group appears to be strictly axial. Chiral diol **6a** is analogous to the racemic diol we had synthesized from sorbaldehyde dimethyl acetal using a similar methodology (MeON=CH moiety replaced by $(MeO)_2CH$) [10]. *J* Values and, therefore, conformation and relative configuration are closely related (see **6a** in *Scheme 2*); *e.g.*, H–C(5) and H–C(6) are both axial (large *J*(5,6) values). As to diol **9a**, all ^3J values are small, and since H–C(5) is now equatorial, a W-type long-range coupling ^4J(3,5) appears. Diol **10a** shows some large ^3J, *i.e.*, *J*(4,5) and *J*(5,6) indicating that H–C(4), H–C(5), and H–C(6) are axial. Thus, the configurations at C(5) in **9a** and C(4) in **10a** are inverted with respect to the ones of **6a** (see *Scheme 2*).

N-Deprotection of **9a** led to **9b** which has a different conformation (in D_2O), Me–C(3) being now equatorial and H–C(3), H–C(4), and H–C(5) being axial (large *J*(3,4) and *J*(4,5) values). This effect is not general; **6b** appears to be in a conformational equilibrium and **10b** seems to be in the same conformation as *N*-acylated **10a**.

Stereostructures of aminodeoxypiperidinose sugar derivatives **7a**, **11**, and **12** follow from those of their oxazanediol precursors. Since the ring N-atom is no longer acylated, the vicinal Me–C(3) substituent is equatorial and dictates the conformation of the piperidine ring. ^{1}H-NMR Data of these compounds are characterized by large *J*(1a,2) values which correspond to the axial H–C(2) (*Table 2*). All substituents of the glucose derivative **11** are equatorial, the corresponding vicinal H,H-coupling constants being large. The L-enantiomer of 1,6-dideoxy-D-*allo*-nojirimycin (**7a**) has already been described [13]. The ^{1}H-NMR data of the latter are very similar to those of **7a** and the $[\alpha]_D$ values of the corresponding tetraacetyl derivatives are opposite. ^{1}H- and ^{13}C-NMR Data and $[\alpha]_D$ of 1,6-dideoxynojirimycin (**11**) are known [8c] and parallel those of the compound synthesized by us.

Table 1. *^{1}H-NMR Data* ($CDCl_3$) *of Oxazanes* **6a, b, 8, 9a, b,** *and* **10a, b**. 250 MHz, 300 K, δ in ppm, J in Hz. Internal standard $SiMe_4$.

		H–C(3)	H–C(4)	H–C(5)	H–C(6)	H–C(1′)[a]	Me	CH_2[b]	MeO	J(3,Me)	J(3,4)	J(4,5)	J(5,6)	J(6,1′)[a]
6a	(*E*)[c][d]	4.54	3.88	4.08	4.63	7.44	1.32	5.19, 5.22	3.88	7.1	2.3	3.2	9.6	4.0
	(*Z*)[c][e]	4.53	3.84	3.84	5.16	6.75	1.31	5.18, 5.23	3.91	7.3	2.4	3.0	10.0	5.8
6b	(*E*)[f]	3.23	3.73	4.01	4.38	7.44	1.24	–	3.87	6.9	4.9	3.3	7.0	4.0
	(*Z*)[f]	3.22	3.49	3.98	4.90	7.03	1.18	–	3.90	6.7	6.5	3.3	5.3	4.9
8[g])	(*E*)	4.85	5.00	5.41	4.86	7.46	1.41	5.25	3.92	7.4	1.6	4.7	9.5	4.3
9a	(*E*)[h]	4.29	3.88	3.96	4.76	7.50	1.49	5.21, 5.22	3.90	7.3	1.8	3.1	1.5	4.3
	(*Z*)[h]	4.28	3.79	4.13	5.28	6.76	1.48	5.22	3.88	7.3	1.9	3.1	2.0	4.3
9b	(*E*)[i]	3.05	3.47	3.90	4.72	7.81	1.14	–	3.91	6.6	8.9	9.1	6.1	5.9
	(*Z*)[i]	3.03	3.47	3.90	5.20	7.21	1.15	–	3.91	6.6	8.6	[k])	5.9	6.1
10a	(*E*)	4.56	3.79	3.96	4.19	7.44	1.29	5.20	3.90	7.0	5.8	9.1	9.4	4.0
10b	(*E*)	3.41	3.75	3.75	4.02	7.43	1.24	–	3.88	6.9	*ca.* 4	*ca.* 8	*ca.* 8	5.1

[a]) For convenience, H–C(1′) is used for C*H*=NOMe of all studied compounds. [b]) Benzyl group. Ar–H at 7.37 ppm. [c]) At 333 K. [d]) OH–C(5): 2.91; OH–C(4): 2.45; J(5,OH–C(5)) = 4.0. [e]) OH–C(5): 3.22; OH–C(4): 2.56; J in C_6D_6. [f]) At 329 K. [g]) For convenience, **8** is numbered like **6a**; systematic numbering in *Scheme 2*. [h]) J(3,5) = 1.1 Hz. [i]) In D_2O. [k]) Not determined.

Table 2. *^{1}H-NMR Data* (D_2O) *of Aminodeoxysugars* **7a, 11,** *and* **12**. 250 MHz, 300 K, δ in ppm, J in Hz. Internal standard (D_4)TSP.

	H_a–C(1)	H_e–C(1)	H–C(2)	H–C(3)	H–C(4)	H–C(5)	Me	J(1a,1e)	J(1a,2)	J(1e,2)	J(2,3)	J(3,4)	J(4,5)	J(5,6)	J(1,3)
7a	2.69	2.78	3.71	4.06	3.23	2.73	1.12	12.2	11.0	5.3	2.8	2.7	10.0	6.4	1.0
11	2.48	3.09	3.52	3.29	3.03	2.54	1.16	12.3	10.9	5.1	9.1	9.1	9.6	6.3	
12	3.02	3.15	4.12	4.03	3.91	3.46	1.26	12.7	10.0	4.8	3.1	4.6	2.3	6.9	1.0

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Experimental Part

General. Hexa-2,4-dienal was obtained from *Lancaster*, ammonium benzoate from *Prolabo*, $RuCl_3 \cdot 3\ H_2O$ from *Aldrich*, and *O*-methylhydroxylamine·HCl, sodium periodate, 5% Pd/C catalyst, *N*-methylmorpholine-*N*-oxide (NMO), OsO_4, benzyl chloroformate, and tetrapropylammonium periodate $(Pr_4N)IO_4$ from *Fluka*. *Amberlyst-15* (H^+) was a gift from *Rohm & Haas*. $SOCl_2$ and Et_3N were distilled. 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: AI-roll silica gel (*Merck 60*, F_{254}). M.p.: *Kofler* hot bench or *Büchi-SMP-20* apparatus; corrected. $[\alpha]_D$ Values: *Schmidt-Haensch-Polartronic-Universal* polarimeter; at 20°. IR Spectra (cm^{-1}): *Perkin-Elmer 157 G* and *590 B*. ^1H- and ^{13}C-NMR Spectra: *Bruker AC-F250*, using double-irradiation techniques; $SiMe_4$ or natrium trimethylsilyl(D_4)-propionate ((D_4)TSP) in D_2O (^1H-NMR) and $CDCl_3$, CD_3OD or (in D_2O) CH_2OH or dioxane (^{13}C-NMR; $\delta(CDCl_3)$ 77.0, $\delta(CD_3OD)$ 49.0, in D_2O δ (CH_3OH) 50,0, δ(dioxane) 67.4 rel. to $SiMe_4$) as internal standards; δ in ppm and J in Hz. High resolution (HR) MS: *MAT-311* spectrometer; in m/z (%); measured at the University of Rennes. Microanalyses were carried out by the 'Service Central de Microanalyses' of the CNRS, F–69390 Vernaison.

Hexa-2,4-dienal O-*Methyloxime* (**1d**). To a stirred soln. of $NH_2OMe \cdot HCl$ (1.95 g, 23.4 mmol, 1.5 equiv.) in aq. 1N $NaHCO_3$ (24 ml) and EtOH (20 ml), hexa-2,4-dienal (**1a**; 1.72 ml, 15.6 mmol) was added under Ar. After 1 h at r.t., the mixture was extracted with Et_2O, the org. soln. washed with H_2O, dried ($MgSO_4$), and evaporated to give **1d** (1.4 g, 72%; (*NE*,2*E*,4*E*)/(*NZ*,2*E*,4*E*)/(*NE*,2*E*,4*Z*)/(*NZ*,2*E*,4*Z*) 63:23:10:4). Purification by distillation gave **1d** as yellowish resin or crystals. B.p. 63°/17 Torr. M.p. 13–14°. IR (CCl_4): 2950, 2810, 1640, 1610, 1045, 990, 900, 860. ^1H-NMR ($CDCl_3$): 7.78, 7.70, 7.09, 7.01 (4*d*, H–C(1) of (*NE*,2*E*,4*Z*), (*NE*,2*E*,4*E*), (*NZ*,2*E*,4*Z*), (*NZ*,2*E*,4*E*)); 6.8–5.7 (*m*, 4 H); 3.92, 3.91, 3.88, 3.87 (4*s*, MeO of (*NZ*,2*E*,4*Z*), (*NZ*,2*E*,4*E*), (*NE*,2*E*,4*Z*), (*NE*,2*E*,4*E*)); 1.82 (*m*, Me(6)). No satisfactory elemental analysis.

*(3*R,6R*)/(3*S,6R*)-3,6-Dihydro-3-methyl-2*H*-1,2-oxazine-6-carbaldehyde* O-*Methyloxime* (**3a**/**3b**). To a soln. of **2** (3.82 g, 12.4 mmol, 1.1 equiv.) in $CHCl_3$ (38 ml) at −20°, **1d** (1.41 g, 11.3 mmol) in EtOH (15 ml) was added. The green soln. was stirred for 1 d at 0°, then 1.5 h at r.t. Et_2O (50 ml) was added and the mixture extracted with 1N HCl (5 × 10 ml). The combined aq. solns. were neutralized with 1N $NaHCO_3$ and extracted several times with $CHCl_3$. The org. phase was dried ($MgSO_4$) and evaporated: 1.46 g (83%) of **3a**/**3b** 85:15 ((*NE*)/(*NZ*) 2:1 to 3:1).

*Benzyl (3*R,6R*)/(3*S,6R*)-3,6-Dihydro-6-[(methoxyimino)methyl]-3-methyl-2*H*-1,2-oxazine-2-carboxylate* (**4a**/**4b**). To a stirred suspension of crude **3a**/**3b** (1.46 g, 9.4 mmol) in 1N Na_2CO_3 (15 ml), benzyl chloroformate (2.6 ml, 18.5 mmol) was added. After 6 h at r.t., the soln. was extracted with CH_2Cl_2 and the org. phase dried ($MgSO_4$) and evaporated to give crude **4a**/**4b** (3.63 g).

*Benzyl (3*R,4R,5R,6,S*)-*t*-4,*t*-5-Dihydroxy-*c*-6-[(methoxyimino)methyl]-*r*-3-methyl-1,2-oxazane-2-carboxylate* (**6a**). To a stirred soln. of crude **4a**/**4b** (3.63 g) in acetone (25 ml) and H_2O (10 ml) were added NMO (1.90 g, 14 mmol, 1.5 equiv.) and 5% OsO_4 soln. in *t*-BuOH (9.3 ml) [16] [19]. After 4 days at 40°, some Na_2SO_3 was added, the acetone evaporated, brine (10 ml) added, and the soln. extracted with AcOEt (3 × 50 ml). The combined org. soln. was dried ($MgSO_4$) and evaporated and the crude **4b**/**6a** chromatographed (silica gel (120 g), AcOEt): **4b** (0.43 g, 16%) and **6a** (2.25 g, 75%).

4b: Impure yellowish resin ((1′*E*)/(1′*Z*) 2:1). ^1H-NMR ($CDCl_3$): 7.49 (*d*, *J* = 5.6, H–C(1′) (*E*)); 6.92 (*d*, *J* = 4.2, H–C(1′) (*Z*)); 5.9 (*m*, H–C(4), H–C(5)); 5.37 (*t*, *J* = 5, H–C(6) (*Z*)); 5.2 (*m*, CH_2); 4.88 (*t*, *J* = 5, H–C(6) (*E*)); 4.50 (*quint.*, *J* = 7, H–C(3) (*E*)); 4.43 (*m*, H–C(3) (*Z*)); 3.86, 3.84 (2*d*, MeO); 1.31, 1.30 (2*d*, *J* = 6.7, Me–C(3)).

6a: Yellowish resin ((1′*E*)/(1′*Z*) 74:26). $[\alpha]_D^{20} = -41$ (*c* = 1, $CHCl_3$). IR ($CHCl_3$): 3500, 2950, 1710, 1410, 1310, 1140, 1090, 1050. ^1H-NMR: *Table 1*. Anal. calc. for $C_{15}H_{20}N_2O_6$ (324.33): C 55.55, H 6.22, N 8.64; found: C 55.4, H 6.4, N 8.3.

Racemic (±)-**6a**. According to [20]: To a stirred soln. of **1d** (0.2 g, 1.6 mmol) in CH_2Cl_2 (2 ml) at 0° containing some 4 Å molecular sieves, $(Pr_4N)IO_4$ (0.17 g, 0.5 mmol) and portionwise benzyl *N*-hydroxycarbamate [20] (0.266 g, 1.6 mmol) were added. After 1 h, Et_2O was added, the org. soln. washed with 1N Na_2CO_3 (containing some $NaHSO_3$ for reduction of I_2) and twice with H_2O, the aq. soln. re-extracted with Et_2O, and the combined org. phase

dried ($MgSO_4$) and evaporated. The crude adduct mixture (0.44 g) was osmylated as described for **6a** in acetone (4 ml) and H_2O (1.5 ml) with aq. NMO (0.6 ml, 3.1 mmol, 2 equiv.) and 5% OsO_4 soln. (0.8 ml, and another 0.8 ml after 8 h). After 1 day at 45°, chromatographic purification of the crude product gave impure (±)-**4b** (20 mg, 5%; not further analyzed) and (±)-**6a** (0.27 g, 52%) as yellowish oil. Anal. calc. for $C_{15}H_{20}N_2O_6$ (324.33): C 55.55, H 6.22, N 8.64; found: C 55.3, H 6.4, N 8.5.

HPLC Determination of ee Value of **6a**. Two different HPLC columns were used. On a *Chiralpak AD* column (hexane/i-PrOH 95:5, detection at 240 nm), (±)-**6a** showed an (*R*)/*S* ratio of 3603:3525 and t_R 43.0 (3*S*,6*R*,1′*E*/*Z*), 59.4 (3*R*,6*S*,1′*E*), and 63.1 min (3*R*,6*S*,1′*Z*); for purified **6a**, t_R was 59.8 min and no (3*S*,6*R*) enantiomer was detected (< 0.5%). On a *Chiralcel OD* column (hexane/i-PrOH 95:5, detection at 240 nm), (±)-**6a** showed an (*R*)/(*S*) ratio of 7242:7203 and t_R 62.4 (3*RS*,6*SR*,1′*Z*), 73.0 (3*S*,6*R*,1′*E*), and 85.4 min (3*R*,6*S*,1′*E*); for chiral **6a**, t_R was 63.6 (3*R*,6*S*,1′*Z*) and 86.4 min (3*R*,6*S*,1′*E*) and no (3*S*,6*R*) enantiomer was detected (< 0.5%).

*1,5-Imino-1,5,6-trideoxy-*D*-allitol* (= *1,6-Dideoxy-*D*-allo-nojirimycin*; **7a**) [9]. A soln. of **6a** (245 mg, 0.75 mmol) in H_2O (2.5 ml) was hydrogenolyzed over 5% Pd/C (20 mg, after 8 h another 20 mg) at 50° for 1 d. After elimination of the catalyst by centrifugation, the soln. was mixed with *Amberlyst-15* (H^+; 5 ml) and H_2O (10 ml) and stirred for 1.5 h. The resin was washed with H_2O and extracted by stirring in 1N NH_4OH for 1 h and the aq. soln. evaporated: **7a** (79 mg, 72%). Brownish resin. ^{1}H-NMR: *Table 2*; data similar to those of the L-isomer [13]. ^{13}C-NMR: 75.3 (C(4)); 72.7 (C(3)); 69.8 (C(2)); 50.1 (C(5)); 45.1 (C(1)); 18.2 (Me(6)).

*(3*R*,4*R*,5*R*,6*S*)-*t*-4,*t*-5-Dihydroxy-*r*-3-methyl-1,2-oxazane-*c*-6-carbaldehyde* O-*Methyloxime* (**6b**). Hydrogenolysis of **6a** in EtOH at r.t. for 1 h gave **6b** quantitatively. ^{1}H-NMR: *Table 1*.

*2,3,4-Tri-*O*-acetyl-1,5-(acetylimino)-1,5,6-trideoxy-*D*-allitol* (**7b**). At 30°, **7a** (0.16 g, 1.1 mmol) was stirred for 2 d in pyridine (2 ml) and Ac_2O (1 ml, 10 equiv.). MeOH was added and the soln. evaporated. Purification by FC (AcOEt) gave **7b** (0.12 g, 35%). Colorless crystals. M.p. 120° (i-Pr_2O; [13]: 119–120° for L-isomer). $[\alpha]_D^{16} = +7$ ($c = 1$, $CHCl_3$; [13]: $[\alpha]_D^{20} = -4$ ($c = 0.23$, $CHCl_3$) for L-isomer). IR (KBr): 1745, 1730, 1650, 1440, 1373, 1250, 1228, 1070, 1055. ^{1}H-NMR ($C_2D_2Cl_4$, 380 K; similar data is in [13]): 1.35 (*d*, $J = 7.3$, Me–C(5)); 2.04, 2.10, 2.11, 2.11 (4*s*, 4 Ac); 3.27 (*d*, $J = 15.2$, H_{eq}–C(1)); 4.40 (*d*, $J = 15.2$, H_{ax}–C(1)); 4.74 (*q*, $J = 7.3$, H–C(5)); 5.10 (*dd*, $J = 2.4$, 4.6, H–C(4)); 5.21 (*m*, H–C(2), H–C(3)). Anal. calc. for $C_{14}H_{21}NO_7$ (315.32): C 53.32, H 6.71, N 4.44; found: C 53.1, H 6.7, N 4.3.

*Benzyl (3a*S*,4*S*,7*R*,7a*R*)-3a,6,7,7a-Tetrahydro-4-[(methoxyimino)methyl]-7-methyl-4*H*-1,3,2-dioxathiolo-[4,5-*d*][1,2]oxazine-6-carboxylate 2,2-Dioxide* (**8**) [17]. To a stirred soln. of **6a** (334 mg, 1.03 mmol) in CH_2Cl_2 (3.3 ml) and Et_3N (0.58 ml, 4.1 mmol) at 0°, a soln. of $SOCl_2$ (0.11 ml, 1.5 mmol) in CH_2Cl_2 (0.3 ml) was slowly added. After 10 min, Et_2O (10 ml) was added and the org. soln. washed with H_2O, dried ($MgSO_4$), and evaporated. To the crude oil in $CHCl_3$/MeCN/H_2O 3:3:5 (11 ml) at 0°, $NaIO_4$ (0.4 g, 1.9 mmol, 1.9 equiv.) and $RuCl_3 \cdot 3\,H_2O$ (24 mg, 0.1 equiv.) were added under stirring. After 2 h, the same treatment as above gave **8** (283 mg, 74%). Yellowish oil ((1′*E*)/(1′*Z*) 91:9). $[\alpha]_D^{20} = -59$ ($c = 1$, $CHCl_3$). IR ($CHCl_3$): 2950, 1725, 1400, 1290, 1125, 1080, 1010. ^{1}H-NMR: *Table 1*. Anal. calc. for $C_{15}H_{18}N_2O_8S$ (386.31): C 46.63, H 4.69, N 7.25, S 8.30; found: C 46.3, H 4.5, N 6.8, S 8.0.

*(3*R*,4*R*,5*S*,6*S*)-*t*-4,*c*-5-Dihydroxy-*r*-3-methyl-1,2-oxazane-*c*-6-carbaldehyde* O-*Methyloxime* (**9b**) *and (3*R*,4*S*,5*R*,6*S*)-*c*-4,*t*-5-Dihydroxy-*r*-3-methyl-1,2-oxazan-*c*-6-carbaldehyde* O-*Methyloxime* (**10b**). To a soln. of **8** (1.60 g, 4.13 mmol) in DMF (16 ml) was added ammonium benzoate (1.15 g, 2 equiv.). The soln. was stirred at 90° for 1 d and then evaporated to give a brownish oil (3.8 g). This crude sulfate was stirred in a soln. of dioxane (20 ml) with H_2SO_4 (60 µl) and H_2O (20 µl) at r.t. After 2 h, Na_2CO_3 (1 g) was added and the soln. evaporated. The crude benzoate was dissolved in MeOH (20 ml), and Na_2CO_3 (1 g) was added. The soln. was stirred 5 days at 50°, then filtered, and evaporated. FC (AcOEt/cyclohexane 7:3, silica gel (80 g)) gave purified **9a**/**10a** 85:15 (0.71 g, 53%). ^{1}H-NMR: *Table 1*.

A soln. of **9a**/**10a** (0.71 g, 2.19 mmol) in EtOH (7 ml) was hydrogenolyzed over Pd/C (43 mg) at r.t. for 2 h. After centrifugation, the soln. was evaporated, and FC (AcOEt, silica gel (40 g)) gave **9b** (239 mg, 58%) and **10b** (46 mg, 11%).

9b: Colorless crystals. M.p. 144–145° (AcOEt). $[\alpha]_D^{20} = -127$ ($c = 1$, MeOH). IR (KBr): 3480, 3190, 3050, 2930, 2895, 2700, 1455, 1330, 1175, 1050, 1000, 910, 878, 828. ^{1}H-NMR: *Table 1*. Anal. calc. for $C_7H_{14}N_2O_4$ (190.20): C 44.20, H 7.42, N 14.74; found: C 44.5, H 7.8, N 14.4.

10b: Colorless resin. Only characterized by ^{1}H-NMR: *Table 1*.

*1,5-Imino-1,5,6-trideoxy-*D*-glucitol* (= *1,6-Dideoxynojirimycin*; **11**). As described for **7a**, with **9b** (0.10 g, 0.5 mmol), H_2O (1 ml), and 5% Pd/C (6 mg; 6 mg after 8 h): **11** (47 mg, 61%). Colorless resin. $[\alpha]_D^{20} = +13$ ($c = 1$, H_2O); $[\alpha]_D^{20} = +11$ ($c = 1$, MeOH); [8c]: $[\alpha]_D^{20} = +12$ ($c = 2.5$, H_2O). ^{1}H-NMR: *Table 2*. ^{13}C-NMR: 79.3 (C(3)); 77.7 (C(4)); 72.3 (C(2)); 56.2 (C(5)); 50.0 (C(1)); 18.2 (Me(6)); similar data as in [8c]. MS: 147 (3), 130 (8), 129 (13), 112 (10), 73 (11), 69 (11), 58 (23), 57 (100), 56 (50), 44 (84). HR-MS: 147.0886 ($C_6H_{13}NO_3^+$; calc. 147.08954).

*1,5-Imino-1,5,6-trideoxy-*D*-gulitol* (= *1,6-Dideoxy-*D*-gulo-nojirimycin*; **12**). As described for **7a**, with **10b** (31 mg, 0.16 mmol), H_2O (0.3 ml), and 5% Pd/C (2 mg; 2 mg after 8 h): **12** (17 mg, 71%). Colorless resin. $[\alpha]_D = -3$ ($c = 1$, H_2O). ^{1}H-NMR: *Table 2*. ^{13}C-NMR (D_2O): 73.3 (C(4)); 71.7 (C(3)); 67.2 (C(2)); 49.3 (C(5)); 45.2 (C(1)); 16.0 (Me–C(5)). MS: 147 (4), 130 (4), 129 (4), 112 (9), 73 (7), 69 (5), 57 (65), 56 (32), 44 (100). HR-MS: 147.0902 ($C_6H_{13}NO_3^+$; calc. 147.08954).

REFERENCES

[1] Ch.-H. Wong, T. Kajimoto, K.K.-C.Liu, L. Chen, PCT Int. Appl. WO. 92 21657 (*CA*: **1993,** *118,* 192187); Ch.-H. Wong, Y. Ichikawa, G.J. Shen, PCT Int. Appl. WO. 92 16640 (*CA*: **1993,** *118,* 186950).

[2] D.P. Dumas, T. Kajimoto, K.K.-C. Liu, Ch.-H. Wong, D.B. Berkowitz, S.J. Danishefsky, *Bioorg. Med. Chem. Lett* **1992,** *2,* 33.

[3] G.W.J. Fleet, A.N. Shaw, St.V. Evans, L.E. Fellows, *J. Chem. Soc., Chem. Commun.* **1985,** 841.

[4] S. Washiyama, A. Kamiya, S. Esaki, A. Tanaka, N. Sugiyama, Sh. Kamiya, *Biosci. Biotechnol. Biochem.* **1993,** *57,* 847.

[5] P. Zhou, H.M. Salleh, Ph.C.M. Chan, G. Lajoie, J.F. Honek, P.T.Ch. Nambiar, O.P. Ward, *Carbohydr. Res.* **1993,** *239,* 155.

[6] H. Paulsen, M. Matzke, *Liebigs Ann. Chem.* **1988,** 1121.

[7] G.W.J. Fleet, S. Petursson, A.L. Campbell, R.A. Mueller, J.R. Behling, K.A. Babiak, J.S. Ng, M.G. Scaros, *J. Chem. Soc., Perkin Trans. 1* **1989,** 665; Sh. Takahashi, H. Kuzuhara, *Chem. Lett.* **1992,** 21.

[8] a) T. Kajimoto, L. Chen, K.K.-C. Liu, Ch.-H. Wong, *J. Am. Chem. Soc.* **1991,** *113,* 6678; b) K.K.-C. Liu, T. Kajimoto, L. Chen, Z. Zhong, Y. Ichikawa, Ch.-H. Wong, *J. Org. Chem.* **1991,** *56,* 6280; c) T. Kajimoto, K.K.-C. Liu, R.L. Pederson, Z. Zhong, Y. Ichikawa, J.A. Porco, Ch.-H. Wong, *J. Am. Chem. Soc.* **1991,** *113,* 6187 (some incorrect ^{1}H-NMR data for 1,6-dideoxynojirimycin).

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

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

[11] a) H. Felber, G. Kresze, R. Prewo, A. Vasella, *Helv. Chim. Acta* **1986,** *69,* 1137; corrigendum: H. Braun, R. Charles, G. Kresze, M. Sabuni, J. Winkler, *Liebigs Ann. Chem.* **1987,** 1129; b) H. Braun, H. Felber, G. Kresze, Fr.P. Schmidtchen, R. Prewo, A. Vasella, *ibid.* **1993,** 261.

[12] A. Defoin, H. Sarazin, J. Streith, *Synlett.* **1995,** *34,* 1187.

[13] A. Hussain, P.B. Wyatt, *Tetrahedron* **1993,** *49,* 2123.

[14] A. Defoin, H. Sarazin, Ch. Strehler, J. Streith, *Tetrahedron Lett.* **1994,** *35,* 5653.

[15] R. Kuhn, M. Hoffer, *Chem. Ber.* **1931,** *64,* 1977.

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

[17] a) Y. Gao, K.B. Sharpless, *J. Am. Chem. Soc.* **1988,** *110,* 7538; b) B.M. Kim, K.B. Sharpless, *Tetrahedron Lett.* **1989,** *30,* 655.

[18] H. Paulsen, Kl. Todt, H. Ripperger, *Chem. Ber.* **1968,** *101,* 3365.

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

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