Enantioselective Synthesis of Ethyl 4,5,7,8,9-Penta-*O*-acetyl-2,6-anhydro-3-deoxy-D-*erythro*-L-*gluca*-nononate: a 2-Monodeoxygenated Derivative of '2-Keto-3-deoxy-D-*glycero*-D-*galacto*-nononic Acid'

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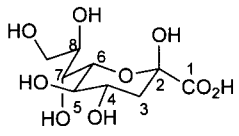
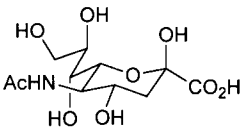
A study aimed at developing an enantioselective synthesis of the title compound **23**, a 2-monodeoxy analogue of the naturally occurring (+)-2-keto-3-deoxy-D-*glycero*-D-*galacto*-2-nononic acid (KDN), is reported. From D-mannose as starting material, the chiral 1,3-diene **10**, activated by a silyloxy substituent at C(2), was prepared in six steps (*Scheme 1*). However, the intermediates were often contaminated with varying amounts of by-products arising from overoxidation during cleavage with periodic acid. An alternative route starting from the inexpensive and readily available D-isoascorbic acid (**12**), though a little longer than the first, satisfactorily circumvented the purification problem and led to the desired dienes **17** in good yields (*scheme 2*). The [Co^{II}(*S*,*S*)-(+)-salen]-catalyzed hetero-*Diels-Alder* reactions of the aforementioned dienes with ethyl glyoxylate proceeded smoothly at room temperature, giving the dihydropyrano adducts **18** in moderate yields (*Scheme 3*). Dihydroxylation of **18a** followed by reduction of the keto function gave the desired 4,5-*trans* dihydroxy moiety of the KDN framework (*Scheme 4*, see **21**). The spectroscopic data of the penta-*O*-acetylated 2-deoxy-KDN ethyl ester **23** were consistent with those reported for the corresponding methyl ester derived from natural KDN.

Introduction. – (+)-3-Deoxy-D-*glycero*-D-*galacto*-non-2-ulosonic acid (**1**), also named '2-keto-3-deoxy-D-*glycero*-D-*galacto*-nononic acid' and normally abbreviated KDN, is a unique member of nonulosonic acids, formally derived from the most common sialic acid Neu5Ac (**2**; *N*-acetylneuraminic acid) by replacement of the N-substituent at C(5) by a hydroxy group. Since its isolation in 1986 by *Inoue* and co-workers [1], KDN and its analogues have evoked broad interest in the scientific community [2], mostly due to its novel functions. For instance, it has been shown that KDN is likely to be responsible for protection of the egg membrane from attack by bacterial sialidases [3]. More recently, the presence of elevated levels of free KDN in ovarian-tumor cells suggested [4] that it may be an oncofetal antigen and thus could be an early warning signal for the onset of disease and/or a marker for detection of recurrence of disease.

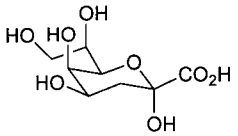
The importance of exploring the role of KDN and related compounds in normal development and malignancy highlighted by biological studies has prompted many to endeavor to prepare various analogues of KDN [5][6] (and of the structurally closely related Neu5Ac). Similar modifications, especially deoxygenation [7] at C(2) of 3-deoxy-D-*manno*-oct-2-ulosonic acid (**3**; KDO), another closely related important carbohydrate [8], also result in antibacterial agents working through novel modes of action. The observations recommend the synthesis of 2-monodeoxy analogues of KDN that possibly show a different biological-activity profile. This type of compound is easily accessible, by using the chiral [Co^{II}(salen)] **4** [9] as catalyst, in a hetero-*Diels-Alder* reaction [10][11] as the key step [11]. Reported herein is the first enantioselective total-synthesis approach to the monodeoxygenated KDN analogues.



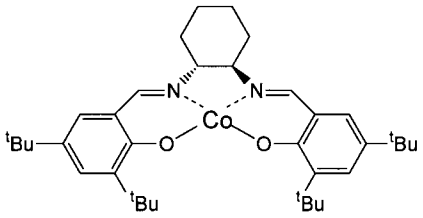
1 KDN



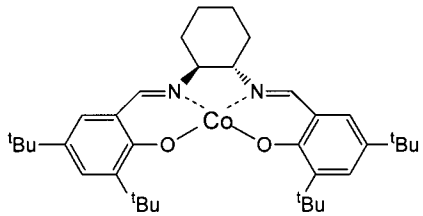
2 Neu5Ac



3 KDO



4a [Co^{II}\{(*R*,*R*)-(-)-salen\}]



4b [Co^{II}\{(*S*,*S*)-(+)-salen\}]

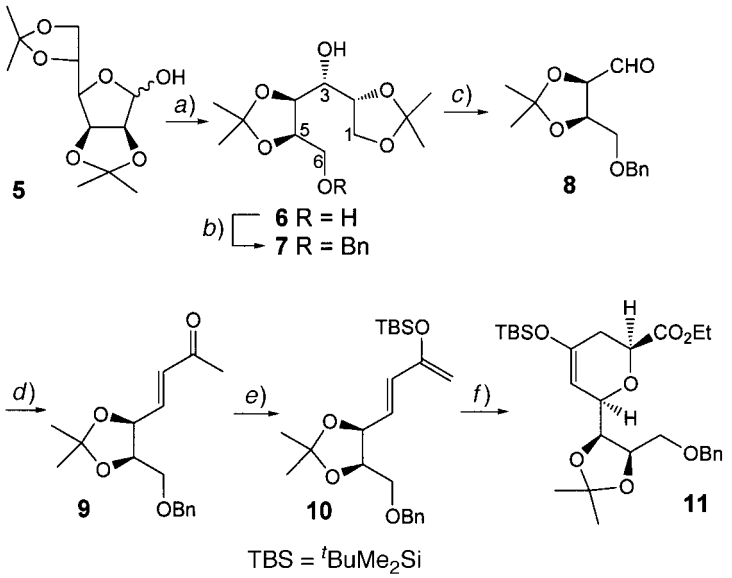
Results and Discussion. – Our previous studies [11] on the [Co^{II}(salen)]-catalyzed hetero-*Diels-Alder* reactions of ethyl glyoxylate showed that the ee of the product depends on both the catalyst and the diene, chiral dienes leading to higher enantioselectivity in the 'matched' combination. The enantiomer purity of the desired dihydropyran adduct is markedly lowered when non-chiral dienes are used. Therefore, in this work, we chose to use chiral dienes for the planned enantioselective synthesis.

The first route to a prospective precursor of the 2-monodeoxy-KDN is shown in *Scheme 1*. Starting from D-mannose and following a literature procedure [12], we reduced the intermediate diisopropylidene derivative **5** to the corresponding 1,4-diol **6** with $NaBH_4$ in EtOH in 97% yield. Selective protection of the primary OH group was required for the intended selective oxidative cleavage we had developed previously [13]. This was easily (93%) done by introduction of a (*tert*-butyl)dimethylsilyl group. Unfortunately, this protecting group did not survive the subsequent oxidation with H_5IO_6.

We next chose benzyl as the protecting group and tested several conditions to induce relatively good regioselectivity. Only a dibenzylated product was obtained with NaH and BnBr in DMF at temperatures ranging from $-30°$ to room temperature. Even at $-70°$, the product was still a 1:1 mixture of the mono- and dibenzyl ethers. Replacing BnBr with the less active BnCl did not improve the selectivity very much. A better result was obtained by a modified version of *Bouzide* and *Sauve*'s protocol [14], which allowed for a clean preparation of **7** in 78% yield.

The oxidative cleavage of **7** turned out to be troublesome, although H_5IO_6 had been used successfully in a number of other systems [13]; the yield of aldehyde **8** varied significantly from run to run, and the isolated product was often contaminated with (benzyloxy)acetaldehyde (resulting from overoxidation), the chromatographic behavior of the latter being extremely similar to that of **8**. After exhaustive efforts to circumvent this complication, we managed to obtain almost pure **8** in 80% yield on a 1-mmol scale with 95% methanol as solvent, $NaIO_4$ as oxidant, and a small amount of H_5IO_6 as catalyst. The good yield, unfortunately, was reduced when the reaction was

Scheme 1



a) $NaBH_4$, EtOH; 97%. *b*) BnBr, Ag_2O, Bu_4NI; 78%. *c*) H_5IO_6, Et_2O. *d*) $Ph_3P{=}CHCOMe$; 48% from **5**. *e*) ^{t}BuMe$_2$SiOTf, Et_3N; 98%. *f*) $OHCCO_2Et$, **4b** (cat.); 60%.

run on significantly larger scales. Therefore, in later preparative runs, we settled for the modest yields of the smaller-scale procedure.

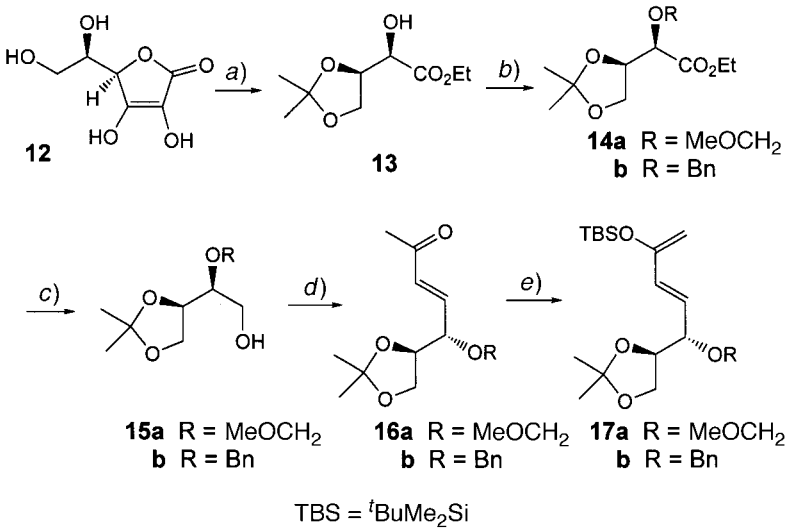
Treatment of the crude **8** with $Ph_3P{=}CHCOMe$ gave enone **9** in 48% isolated yield. But the aforementioned problem caused by (benzyloxy)acetaldehyde was still not solved. The chromatographic behavior of the enone derived from the by-product remained rather similar to that of **9**, rendering clean separation of the two enones extremely difficult. It appeared to us, at this point, that the 1,3-dioxolane ring in **7** must be hydrolyzed first to reveal the corresponding 1,2,3-triol before a clear-cut oxidative cleavage (with, *e.g.*, sodium metaperiodate under neutral conditions) might be realized. We did find some successful cases in the literature [15]. Unfortunately, none of the procedures worked satisfactorily for our system, presumably because the *cis*-relationship at C(4) and C(5) of **7** is lower in stability due to steric crowding, which made the 1,3-dioxolane much more susceptible to hydrolysis than the *trans*-isomers reported in the literature.

Converson of enone **9** to its silyl enol ether was facile. Using (*tert*-butyl)dimethylsilyl trifluoromethanesulfonate (^{t}BuMe$_2$SiOTf) [16] as the silylating agent and Et_3N as the base gave the (silyloxy)diene **10** in 98% yield. The subsequent *Diels-Alder* reaction of this diene with freshly prepared ethyl glyoxylate [17] proceeded smoothly (60% yield) in the presence of 10 mol-% of **4b** to afford the expected adduct **11**. Further modification of the double bond in the dihydropyran ring, however, was very frustrating. Under mild oxidation conditions, no reaction could be observed at all. More forcing conditions led to complicated mixtures. This difficulty, along with the separation problem mentioned above, persuaded us to turn our attention to another route described below.

D-Isoascorbic acid (**12**) is an inexpensive, readily available compound. It has been used as starting material by *Abushanab et al.* [18], who have developed a facile access to

the versatile enantiomerically pure ester **13** (*Scheme 2*). Starting from this compound, which already has two centers of chirality having the desired configuration, we only had to mask the free OH group and reduce the ester to an aldehyde before resuming the previous plan for the construction of the chiral diene. Two protecting groups, $MeOCH_2$ and Bn, were then tested in parallel in the given context. Treatment of **13** with $MeOCH_2Cl$/Pr_2EtN led to the $MeOCH_2$-protected ester **14a** in 87% yield. Similarly, BnBr/Ag_2O in the presence of Bu_4NI led to the corresponding benzyl-protected ester **14b** in 75% yield. Subsequent reduction of **14a** or **14b** with $LiAlH_4$ (*ca.* 100%) followed by *Swern* oxidation of the alcohols **15a** and **15b** afforded the needed intermediate aldehydes, which were directly treated with $Ph_3P{=}CHCOMe$ to give enones **16a** (only (*E*)-isomer) and **16b** ((*E*/*Z*)-isomers 5:1) in 84 and 82% yield (for two steps), respectively. Conversion to the 2-*O*-silyl-protected 1,3-diene-2-ol **17a** and **17b** was achieved in 98 and 97% yield, respectively, under the conditions employed for the preparation of **10**.

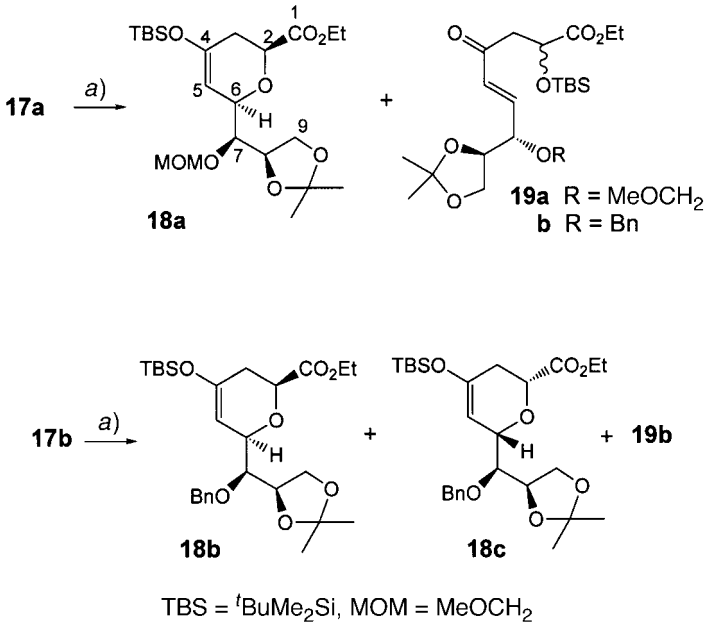
Scheme 2



a) [18]. *b*) $MeOCH_2Cl$, Pr_2EtN; or Ag_2O, Bu_4NI, BnBr; 87 (**14a**) and 75% (**14b**), resp. *c*) $LiAlH_4$; 95 (**15a**) and 100% (**15b**). *d*) *Swern* oxidation, then $MeCOCH{=}PPh_3$, THF, reflux; from **15**, 84 (**16a**) and 82% (**16b**). *e*) $^t BuMe_2SiOTf$, Et_3N; 98 (**17a**) and 97% (**17b**).

With both dienes **17a** and **17b** in hand, we set out to examine the **4b**-catalyzed hetero-*Diels-Alder* reaction, a step of critical importance to this work. An interesting difference (*Scheme 3*) was observed for the cycloaddition of ethyl glyoxylate to **17a** and **17b**. Under the same reaction conditions as used for the preparation of **11**, **17a** gave only one adduct **18a** in 56% yield, together with about half as much of the aldolization product **19a**. The benzyl-protected diene **17b**, however, behaved differently. Although the yields for the hetero-*Diels-Alder* reaction and the aldolization [19] remained essentially unchanged, the adduct consisted of two isomers **18b**/**18c** in a *ca.* 1:1 ratio. Aldolization products similar to **19** were also observed [20] in some other reactions mediated by salen-derived catalysts.

Scheme 3

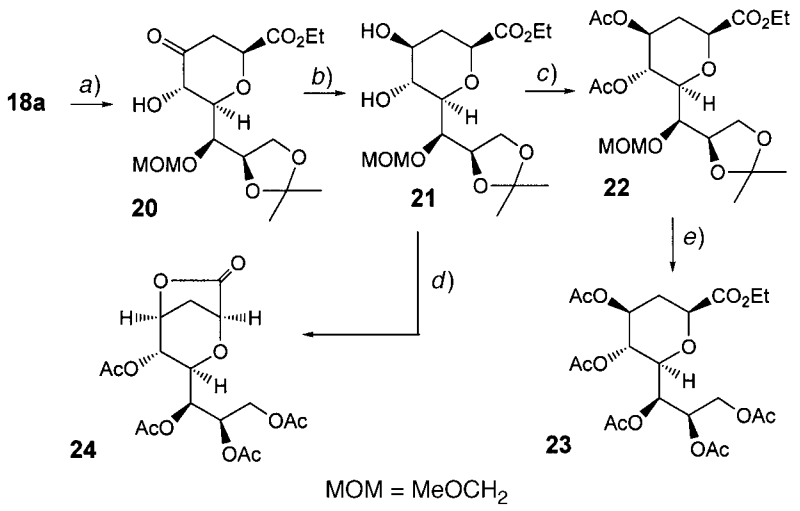


a) $OHCCO_2Et$, **4b** (cat.); from **17a**, 56.2 (**18a**) and *ca.* 27% (**19a**); from **17b**, 55.7 (**18b**/**18c** *ca.* 1:1) and *ca.* 27% (**19b**).

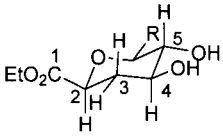
Further elaboration of **18a** into the 2-deoxy-KDN framework requires stereoselective introduction of an α-OH group at C(5) and eventual transformation of the masked carbonyl group at C(4) into a β-OH group. An apparent way to achieve this is to use the *Sharpless* asymmetric dihydroxylation [21]. However, dihydroxylation of **18a** with either 'AD-mix-α' or 'AD-mix-β' [21a] was extremely sluggish (with or without $MeSO_2NH_2$). Extending the reaction time (up to two weeks) did not lead to any improvement. Probably, the bulky substituent at C(6) blocked the access of the also bulky catalyst to the C=C bond. Fortunately, the chirality of the substrate alone was sufficient to differentiate the two π-faces of the enol ether so that the asymmetric ligand is not really necessary. Thus, at room temperature with 2.5 mol-equiv. of *N*-methylmorpholine (NMO) as cooxidant, a catalytic amount (2 mol-%) of $K_2[OsO_2(OH)_4]$ [22] smoothly converted **18a** to **20** (along with a small amount of its epimer) within 12 h (*Scheme 4*). Chromatographic purification of **20** was difficult. Therefore, in preparative runs, the crude product mixture of dihydroxylation was directly reduced with $NaBH_4$. After reduction, the isomers were easily separated by chromatography (silica gel), giving the diol **21** in 55% (from **18a**) isolated yield. The coupling constants in the ^{1}-H-NMR spectrum (assignments by COSY) of **21** are consistent with the expected structure (*Fig.*), with the pyranose ring in a chair conformation.

To confirm the identity of diol **21**, we converted it to **23**, as *Sun et al.* [5a] had reported the corresponding penta-*O*-acetylated methyl ester derived from natural KDN. We first attempted to hydrolyze both the $MeOCH_2$ and the isopropylidene acetal

Scheme 4



a) NMO, $K_2[OsO_2(OH)_4]$ acetone, H_2O. *b*) $NaBH_4$, EtOH, 0°; 55% from **18a**. *c*) Ac_2O/Py, 4-(dimethylamino)pyridine (DMAP); 94%. *d*) 1. HCl/MeOH, reflux; 2. Ac_2O/Py, DMAP. *e*) 1. $HS(CH_2)_3SH$, $BF_3 \cdot OEt_2$; 2. Ac_2O/Py, DMAP; 91% from **22**.



$J(2,3eq) = 1.9$ Hz; $J(4,3eq) = 4.7$ Hz; $J(4,5) = 9$ Hz;

$J(2,3ax) = J(4,3ax) = J(3eq,3ax) = 12$ Hz

21

Figure. *Configuration and conformation of* **21** *as suggested by the* ^{1}*H-NMR data*. For clarity, the structure of the substituent at C(6) is abbreviated as R.

to restore all OH groups for acetylation by treating **21** with aqueous HCl solution in MeOH at reflux. The reaction did give a product of rather high polarity, as expected. However, acetylation with Ac_2O in pyridine in the presence of a catalytic amount of 4-(dimethylamino)pyridine (DMAP) resulted in an unexpected product that contained only four instead of five Ac groups (by ^{1}H-NMR). A careful inspection of the IR, ^{1}H-NMR, and MS data revealed that this unexpected product was lactone **24**. It is noteworthy that although this undesired result forced us to adopt a longer but safer route to synthesize **23**, it did establish that OH–C(4) was *cis* to the COOH group in **21**, adding a valuable piece of evidence about the configuration of the final product.

To prevent the undesired lactone formation, the conversion to **23** was realized by first acetylating OH–C(4) (as well as OH–C(5)), followed by removal of the $MeOCH_2$ and the isopropylidene group of **22** with propane-1,3-dithiol in the presence of $BF_3 \cdot OEt_2$, and acetylation of all three newly formed OH groups with Ac_2O. The ^{1}H-NMR data (both δs and Js) of **23** (particularly those of H–C(2), H_{ax}–C(3), H_{eq}–C(3), and H–C(6)), which are well-resolved), are consistent with those [5a] reported for the corresponding methyl ester prepared form natural KDN.

Experimental Part

General. Flash column chromatography (FC): silica gel *H* (10–40 μm), eluting with petroleum ether (b.p. 60–90°) and AcOEt. $[\alpha]_D$: *Perkin-Elmer-241-MC* polarimeter. IR Spectra: *Shimadzu-IR-440* spectrometer; in cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) Spectra: *Bruker-AMX-300* or *Varian-Gemini-2000* spectrometer, δ in ppm rel. to $SiMe_4$, *J* in Hz. Mass Spectra: *HP-5989A* instrument; HR (EI) spectra, *Finnigan-MAT-8430* mass spectrometer. Microanalyses were carried out in the Microanalytical Laboratory at the Shanghai Institute of Organic Chemistry.

1-O-*Benzyl-2,3:5,6-di*-O-*isopropylidene*-D-*mannitol* (**7**). Into a soln. of 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**5**) [11] (prepared from 30.2 g, 116 mmol of D-mannose) in EtOH (150 ml), $NaBH_4$ (6.59 g, 174 mmol) was introduced in small portions with stirring and cooling (ice-water bath). The mixture was stirred at r.t. overnight. With cooling (ice-water bath) and vigorous stirring, AcOH was added to neutralize the mixture. After evaporation, the residue was dissolved in brine and extracted with AcOEt until TLC showed no product in the aq. phase. The combined org. phase was dried ($MgSO_4$) and evaporated to give the crude diol as a colorless oil (29.5 g, 97%), which was used directly in the subsequent benzylation.

To a soln. of the diol (3.65 g, 14 mmol) in AcOEt (20 ml), Ag_2O (4.84 g, 21 mmol) and Bu_4NI (1.55 g, 4.2 mmol, 30 mol-%) were added, followed by a soln. (dropwise, in the dark) of BnBr (1.8 ml, 14.9 mmol, 1.06 equiv.) in AcOEt (10 ml). The mixture was stirred at r.t. overnight. The solids were filtered off and washed with AcOEt (2×10 ml). The filtrate was washed with sat. aq. $NaHCO_3$ soln. and brine, dried ($MgSO_4$), and evaporated, and the residue was submitted to FC (petroleum ether/AcOEt 10:1): **7** (3.82 g, 78%). Colorless oil. $[\alpha]_D^{21} = -8.34$ ($c = 1.40$, $CHCl_3$). IR (film): 3500*m*, 2980*s*, 1455*m*, 1380*s*, 1210*s*, 1060*s*, 850*m*. ^{1}H-NMR: 7.41–7.21 (*m*, 5 H); 4.61 (*s*, 2 H); 4.45–4.28 (*m*, 2 H); 4.15–3.95 (*m*, 3 H); 3.82, 3.80 (2*d*, $J = 10.4$, 0.5 H each); 3.79, 3.77 (2*d*, $J = 10.4$, 0.5 H each); 3.50 (*d*, $J = 8.0$, 1 H); 2.82 (br. *s*, 1 H); 1.53 (*s*, 3 H); 1.40 (*s*, 3 H); 1.38 (*s*, 3 H); 1.35 (*s*, 3 H). EI-MS: 353 (11, $[M+1]^+$), 295 (27), 237 (11), 181 (16), 101 (25), 91 (100), 59 (13), 43 (28). Anal. calc. for $C_{19}H_{28}O_6$: C 64.76, H 8.01; found: C 64.64, H 8.05.

*(3*E*)-7*-O-*Benzyl-1,3,4-trideoxy-5,6*-O-*isopropylidene*-D-erythro-*hept*-3-*en-2-ulose* (**9**). *Procedure A:* Powdered H_5IO_6 (45 mg, 0.2 mmol) and $NaIO_4$ (856 mg, 4.0 mmol) were added to a stirred soln. of **7** (352 mg, 1.0 mmol) in MeOH/H_2O 95:5 (20 ml) at r.t. After 24 h (TLC: complete consumption of **7**), the solids were filtered off through a short pad of silica gel. The filtrate was neutralized with Na_2CO_3 and then evaporated. The residue was treated with AcOEt. After filtering off the precipitates, the filtrate was evaporated and the residue subjected to FC (AcOEt/petroleum ether 1:5): **8** (200 mg, 80%). The colorless oil was treated with $Ph_3P{=}CHCOCH_3$ (115 mg, 0.36 mmol) in THF (10 ml) at r.t. overnight. After evaporation, the residue was submitted to FC (petroleum ether/AcOEt 9:1): **9** (72 mg, 83%). Colorless oil.

Procedure B: Powdered H_5IO_6 (5.70 g, 25 mmol) was added to a soln. of **7** (3.52 g, 10 mmol) in Et_2O (200 ml). The mixture was stirred for 4 h, then washed with sat. Na_2CO_3 soln. and brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in THF (100 ml), treated with $Ph_3P{=}CHCOCH_3$ (3.18 g, 9.63 mmol), and stirred under reflux for 12 h. After evaporation, the residue was submitted to FC (petroleum ether/AcOEt 9:1): **9** (48%). Colorless oil. $[\alpha]_D^{21} = -19.6$ ($c = 1.00$, $CHCl_3$). IR (film): 2900*s*, 1680*s*, 1630*m*, 1450*m*, 1370*m*, 1250*m*, 1210*m*, 1080*m*. ^{1}H-NMR: 7.40–7.25 (*m*, 5 H); 6.75 (*dd*, $J = 5.5$, 15.9, 1 H); 6.35 (*d*, $J = 15.9$, 1 H); 4.82 (*t*, $J = 5.6$, 1 H); 4.52 (*d*, $J = 12$, 1 H); 4.47 (*d*, $J = 12$, 1 H); 4.50–4.44 (*m*, 1 H); 3.49 (*dd*, $J = 5.6$, 9.6, 1 H); 3.40 (*dd*, $J = 6.9$, 9.6, 1 H); 2.22 (*s*, 3 H); 1.52 (*s*, 3 H); 1.41 (*s*, 3 H). EI-MS: 291 (0.09, $[M+1]^+$), 275 (5, $[M-Me]^+$), 215 (10), 95 (12), 91 (100), 82 (29), 81 (9), 43 (36). Anal. calc. for $C_{17}H_{22}O_4$: C 70.33, H 7.64; found: C 69.77, H 7.72.

*(3*E*)-7*-O-*Benzyl-2*-O-*[(*tert-*butyl)dimethylsilyl]-1,3,4-trideoxy-5,6*-O-*isopropylidene*-D-erythro-*hept-1,3-dienitol* (**10**). To an ice-cooled soln. of **9** (600 mg, 2.07 mmol) in anh. Et_2O (50 ml) was added dropwise ^{t}BuMe$_2$SiOTf (0.58 ml, 1.2 equiv.), followed by Et_3N (0.5 ml). After stirring at 0° for 15 min, the mixture was evaporated and the residue passed through a short pad of neutral aluminium oxide: **10** (815 mg, 98%). Colorless oil. $[\alpha]_D^{20} = -19.1$ ($c = 1.32$, $CHCl_3$). IR (film): 2900*s*, 1600*m*, 1460*w*, 1380*m*, 1320*s*, 1260*s*, 1220*m*, 1030*s*. ^{1}H-NMR: 7.40–7.20 (*m*, 5 H); 6.10 (*d*, $J = 15.4$, 1 H); 5.89 (*dd*, $J = 5.4$, 15.4, 1 H); 4.75 (br. *t*, $J = 5.5$, 1 H); 4.55 (*d*, $J = 10.7$, 1 H); 4.46 (*d*, $J = 10.7$, 1 H); 4.48–4.35 (*m*, 1 H); 4.30 (br. *s*, 1 H); 4.29 (br. *s*, 1 H); 3.50–3.35 (*m*, 2 H); 1.48 (*s*, 3 H); 1.37 (*s*, 3 H); 0.91 (*s*, 9 H); 0.13 (*s*, 3 H); 0.07 (*s*, 3 H). EI-MS: 404 (3, $[M+1]^+$), 225 (11), 198 (11), 197 (17), 183 (14), 91 (100), 75 (24), 73 (31). HR-MS: 404.2379 ($C_{23}H_{36}O_4Si^+$; calc. 404.2383).

Ethyl 2,6-Anhydro-9-O-*benzyl-4*-O-*[(*tert-*butyl)dimethylsilyl]-3,5-dideoxy-7,8*-O-*isopropylidene*-D-*manno-non-4-enonate* (**11**). To a soln. of **10** (4.36 g, 10.8 mmol) in anh. CH_2Cl_2 (100 ml) stirred under N_2, **4b** (660 mg, 10 mol-% with respect to **10**) was added under stirring. After 30 min, ethyl glyoxylate (2.0 ml) was introduced, and the mixture stirred overnight. After evaporation, the residue was submitted to FC (petroleum ether/AcOEt

20:1): **11** (3.28 g, 60%). Colorless oil. $[\alpha]_D^{21} = +20.6$ ($c = 1.86$, $CHCl_3$). IR (film): 2920*s*, 1760*s*, 1740*s*, 1670*s*, 1460*m*, 1360*s*, 1250*s*, 840*s*. ^{1}H-NMR: 7.40–7.20 (*m*, 5 H); 5.01 (*s*, 1 H); 4.63 (*d*, $J = 12.3$, 1 H); 4.58 (*d*, $J = 12.3$, 1 H); 4.48–4.40 (*m*, 1 H); 4.25–4.15 (*m*, 1 H); 4.19 (*q*, $J = 7.1$, 2 H); 4.10 (*dd*, $J = 11$, 4.0, 1 H); 3.95–3.88 (*m*, 2 H); 3.69 (*dd*, $J = 8.1, 11, 1$ H); 2.40–2.30 (*m*, 1 H); 2.20 (br. *d*, $J = 17$, 1 H); 1.46 (*s*, 3 H); 1.36 (*s*, 3 H); 1.27 (*t*, $J = 7.6$, 3 H); 0.92 (*s*, 9 H); 0.16 (*s*, 3 H); 0.15 (*s*, 3 H). EI-MS: 507 (1, $[M+1]^+$), 506 (0.8, M^+), 421 (8), 340 (4), 327 (10), 287 (7), 286 (22), 285 (100).

*Ethyl 3,4-*O*-Isopropylidene-2-*O*-(methoxymethyl)-*D*-erythronate* (**14a**). $MeOCH_2Cl$ (1.6 ml, *ca.* 20 mmol) was added to a soln. of **13** (1.00 g, 4.9 mmol) in dry CH_2Cl_2 (15 ml) stirred at 0°. The mixture was stirred at 0° for 15 min before $^i Pr_2NEt$ (4.0 ml, ca. 24 mmol) was introduced. After another hour at 0°, stirring was continued at r.t. for 2 days. The mixture was then diluted with Et_2O (50 ml), the org. phase washed with aq. sat. NH_4Cl soln., aq. sat. $NaHCO_3$ soln., and brine, dried ($MgSO_4$), and evaporated, and the residue submitted to FC (petroleum ether/AcOEt 10:1): **14a** (1.05 g, 87%). Colorless oil. $[\alpha]_D^{20} = +5.28$ ($c = 1.35$, $CHCl_3$). IR (film): 2980*s*, 1750*s*, 1445*m*, 1370*s*, 1250*s*. ^{1}H-NMR: 4.71 (*s*, 2 H); 4.36 (*q*, $J = 5.8$, 1 H); 4.23 (br. *q*, $J = 7.0$, 2 H); 4.13 (*d*, $J = 5.7$, 1 H); 4.04 (*d*, $J = 6.6$, 2 H); 3.39 (*s*, 3 H); 1.43 (*s*, 3 H); 1.35 (*s*, 3 H); 1.30 (*t*, $J = 7.2$, 3 H). EI-MS: 249 (0.3, $[M+1]$), 233 (14, $[M-Me]^+$), 159 (18), 101 (37), 45 (100), 43 (49). Anal. calc. for $C_{11}H_{20}O_6$: C 53.22, H 8.12; found: C 53.21, H 8.25.

*3,4-*O*-Isopropylidene-2-*O*-(methoxymethyl)-*D*-erythitol* (**15a**). Under stirring and cooling (ice-water bath), a soln. of **14a** (13.9 g, 56.1 mmol) in anh. THF (30 ml) was added dropwise to a suspension of powdered $LiAlH_4$ (2.77 g, 73.0 mmol) in anh. THF (100 ml). Stirring was continued at r.t. for 2 h and then under reflux for another 2 h. The excess $LiAlH_4$ was carefully decomposed (ice-bath cooling) by gradual addition of H_2O (3.0 ml), followed by 15% NaOH soln. (3.0 ml) and more H_2O (10 ml). The mixture was filtered with suction and the filter cake washed with warm AcOEt (3×100 ml). The combined filtrate and washings were dried ($MgSO_4$) and evaporated: crude **15a** (11.0 g, 95%) as a colorless liquid which was used directly without further purification in the subsequent step in prep. runs. An anal. sample of **15a** was obtained by FC (petroleum ether/AcOEt 4:1). $[\alpha]_D^{20} = -32.1$ ($c = 1.32$, $CHCl_3$). IR (film): 3500*m*, 2950*m*, 1378*m*, 1216*s*, 1160*s*, 920*m*. ^{1}H-NMR: 4.74 (*d*, $J = 6.9$, 1 H); 4.70 (*d*, $J = 6.9$, 1 H); 4.14–4.04 (*m*, 2 H); 3.94–3.85 (*m*, 1 H); 3.82 (*dd*, $J = 2.8, 11.5$, 1 H); 3.63 (*dd*, $J = 5.8, 11.8$, 1 H); 3.58 (*dt*, $J = 2.7, 3.4$, 1 H); 3.42 (*s*, 3 H); 2.30 (br. *s*, OH); 1.41 (*s*, 3 H); 1.34 (*s*, 3 H). EI-MS: 207 (0.2, $[M+1]^+$), 191 (6, $[M-Me]^+$), 159 (20), 101 (82), 73 (18), 59 (23), 45 (100), 43 (63), 41 (14). Anal. calc. for $C_9H_{18}O_5$: C 52.42, H 8.80; found: C 52.09, H 9.13.

*(3*E*)-1,3,4-Trideoxy-6,7-*O*-isopropylidene-5-*O*-(methoxymethyl)-*D*-erythro-hept-3-en-2-ulose* (**16a**). With cooling (−78°) and stirring, a soln. of DMSO (6.0 ml, 84.5 mmol) in anh. CH_2Cl_2 (20 ml) was added dropwise to a soln. of oxalyl chloride (3.5 ml, 38.5 mmol) in anh. CH_2Cl_2 (100 ml). The mixture was stirred at −78° for 30 min, before a soln. of **15a** (7.00 g, 34.0 mmol) in anh. CH_2Cl_2 (20 ml) was introduced. Stirring was continued at −78° for another 2 h. Et_3N (18.7 ml, 134 mmol) was added and the mixture stirred at −78° for 30 min and then allowed to warm to r.t. Brine (50 ml) was added, the aq. phase extracted with CH_2Cl_2 (50 ml), and the combined org. phase washed with aq. sat. NH_4Cl soln. and brine, dried ($MgSO_4$), and evaporated: intermediate aldehyde. This yellowish oil was directly dissolved in THF (100 ml) and treated with $Ph_3P{=}CHCOCH_3$ (13.0 g, 40.8 mmol, 1.2 equiv.). The mixture was heated under reflux for 8 h and then evaporated. FC (petroleum ether/AcOEt 10:1) gave **16a** (7.00 g, 84% from **15a**). Colorless oil. $[\alpha]_D^{20} = +35.2$ ($c = 1.10$, $CHCl_3$). IR (film): 2952*s*, 1680*s*, 1638*m*, 1378*s*, 1260*s*, 1216*s*, 1160*s*, 920*m*. ^{1}H-NMR: 6.68 (*dd*, $J = 16.2$, 5.8, 1 H); 6.27 (*dd*, $J = 16.2$, 1.1, 1 H); 4.65 (*d*, $J = 6.9$, 1 H); 4.62 (*d*, $J = 6.9$, 1 H); 4.21 (*dt*, $J = 1.1, 6.0$, 1 H); 4.13 (*q*, $J = 5.6$, 1 H); 4.04 (*dd*, $J = 6.0, 8.2$, 1 H); 3.87 (*dd*, $J = 6.0, 8.3$, 1 H); 3.37 (*s*, 3 H); 2.28 (*s*, 3 H); 1.41 (*s*, 3 H); 1.33 (*s*, 3 H). EI-MS: 245 (0.4, $[M+1]^+$), 229 (12, $[M-Me]^+$), 144 (34), 125 (23), 101 (75), 73 (16), 45 (97), 43 (100), 41 (18). Anal. calc. for $C_{12}H_{20}O_5$: C 59.01, H 8.25; found: C 58.95, H 8.38.

*(3*E*)-2-*O*-[(*tert*-Butyl)dimethylsilyl]-1,3,4-trideoxy-6,7-*O*-isopropylidene-5-*O*-(methoxymethyl)-*D*-erythro-hepta-1,3-dienitol* (**17a**). As described for **10**: **17a** (98%). Yellow oil. $[\alpha]_D^{20} = +71.5$ ($c = 1.21$, $CHCl_3$). IR (film): 2900*s*, 1600*s*, 1459*m*, 1317*s*, 1158*s*, 963*m*. ^{1}H-NMR: 6.18 (*d*, $J = 15.4$, 1 H); 5.94 (*dd*, $J = 15.4$, 6.9, 1 H); 4.76 (*d*, $J = 6.9$, 1 H); 4.65 (*d*, $J = 6.9$, 1 H); 4.41 (br. *s*, 1 H); 4.40 (br. *s*, 1 H); 4.29 (br. *t*, $J = 5.8$, 1 H); 4.22 (br. *q*, $J = 5.0$, 1 H); 4.16 (*d*, $J = 5.5, 8.2$, 1 H); 3.95 (*dd*, $J = 5.1, 8.4$, 1 H); 3.45 (*s*, 3 H); 1.49 (*s*, 3 H); 1.47 (*s*, 3 H); 0.98 (*s*, 9 H); 0.24 (*s*, 3 H); 0.16 (*s*, 3 H). EI-MS: 358 (8, M^+), 343 (0.8, $[M-Me]^+$), 101 (100), 83 (9), 75 (17), 73 (47), 45 (54), 43 (42), 41 (10). HR-MS: 358.2185 ($C_{18}H_{34}O_5Si^+$; calc. 358.2175).

*Ethyl 2,6-Anhydro-4-*O*-[(*tert*-butyl)dimethylsilyl]-3,5-dideoxy-8,9-O-isopropylidene-7-*O*-(methoxymethyl)-*D*-manno-non-4-enonate* (**18a**). As described for **11**: **18a** (56%). Colorless oil. $[\alpha]_D^{20} = +38.3$ ($c = 2.13$, $CHCl_3$). IR (film): 2900*s*, 1765*s*, 1676*s*, 1460*m*, 1260*s*, 920*s*. ^{1}H-NMR: 4.92 (br. *s*, 1 H); 4.79 (br. *s*, 2 H); 4.42 (br. *s*, 1 H); 4.25–4.00 (*m*, 5 H); 4.07 (*dd*, $J = 5.0, 6.0$, 1 H); 3.90 (*m*, 1 H); 3.40 (*s*, 3 H); 2.40–2.25 (*m*, 1 H); 2.20 (br. *d*, $J = 16$, 1 H); 1.40 (*s*, 3 H); 1.34 (*s*, 3 H); 1.27 (*t*, $J = 7.1$, 3 H); 0.92 (*s*, 9 H); 0.17 (*s*, 3 H); 0.16 (*s*, 3 H). EI-MS: 460

(0.4, M^+), 287 (8), 285 (100), 211 (6), 73 (25), 59 (3), 45 (20), 43 (9), 41 (3). HR-MS: 445.2296 ($C_{21}H_{37}O_8Si^+$, $[M-Me]^+$; calc. 445.2258).

*Ethyl 2,6-Anhydro-3-deoxy-8,9-*O*-isopropylidene-7-*O*-(methoxymethyl)-*D*-glycero-*D*-talo-non-4-ulosonate* (**20**). To a soln. of **18a** (1.10 g, 2.39 mmol) in acetone/H_2O 4:1 (25 ml) stirred at r.t., $K_2[OsO_2(OH)_4]$ (18 mg, 2 mol-%) and NMO (810 mg, 6 mmol) were added. Stirring was continued overnight. When TLC showed full consumption of the starting material, $NaHSO_3$ (500 mg) was added, and the mixture was stirred for another hour before the solids were filtered off. The filtrate was evaporated to give a colorless syrup (623 mg, 74%) consisting of **20** and an isomer (presumably a 5-epimer) in a ratio of *ca.* 4:1. In prep. runs, this mixture was used directly in the subsequent reduction with $NaBH_4$. For characterization, a small anal. sample of **20** was obtained by FC (AcOEt/petroleum ether 1:2): $[\alpha]_D^{20} = +42.0$ ($c = 0.91$, $CHCl_3$). IR (film): 3450*m*, 2950*m*, 1750*s*, 1725*s*, 1370*m*, 1208*s*, 1160*s*. ^{1}H-NMR: 5.03 (*s*, OH); 4.90 (*d*, $J = 6.6$, 1 H); 4.76 (*d*, $J = 6.6$, 1 H); 4.47 (*q*, $J = 6.7$, 2 H); 4.42 (br. *d*, $J = 11.3$, 1 H); 4.25 (*q*, $J = 7.1$, 2 H); 4.22 (*dd*, $J = 15$, 3.3, 1 H); 4.15 (*dd*, $J = 6.3$, 8.5, 1 H); 4.09 (br. *d*, $J = 7.4$, 1 H); 4.03 (*dd*, $J = 6.0$, 8.8, 1 H); 3.73 (*dd*, $J = 10.2$, 0.9, 1 H); 3.42 (*s*, 3 H); 2.88 (*dd*, $J = 14$, 3.4, 1 H); 2.81 (br. *dd*, $J = 14$, 15, 1 H); 1.43 (*s*, 3 H); 1.36 (*s*, 3 H); 1.31 (*t*, $J = 7.1$, 3 H). EI-MS: 362 (0.6, M^+), 347 (2, $[M-Me]^+$), 331 (15), 273 (49), 101 (98), 73 (23), 45 (100), 43 (48), 41 (11). HR-MS: 347.1318 ($C_{15}H_{23}O_9^+$, $[M-Me]^+$; calc. 347.1342).

*Ethyl 2,6-Anhydro-3-deoxy-8,9-*O*-isopropylidene-7-*O*-(methoxymethyl)-*D*-erythro-*L*-gluco-nononate* (**21**). To an ice-cooled soln. of **20** (290 mg, 0.80 mmol) in EtOH (20 ml), $NaBH_4$ (32 mg, 1.05 equiv.) was added. After stirring for 1 h, the basic mixture was neutralized with 5% HCl soln. and then evaporated. FC (petroleum ether/AcOEt 1:2) afforded **21** (274 mg, 94%). Colorless syrup. $[\alpha]_D^{20} = +21.0$ ($c = 1.09$, $CHCl_3$). IR (film): 3500*s*, 2950*s*, 1750*s*, 1380*m*, 920*w*. ^{1}H-NMR: 4.80 (*s*, MeOCH_2); 4.42 (*m*, H–C(8)); 4.20 (*q*, $J = 7.1$, MeCH_2O); 4.15–4.07 (*m*, H–C(7), H–C(9)); 4.06–3.97 (*m*, H–C(2), H–C(9)); 3.72 (*ddd*, $J = 12.9$, 8.3, 4.9, H–C(4)); 3.48 (*t*, $J = 9.0$, H–C(5)); 3.42 (*s*, *Me*OCH$_2$); 3.40–3.36 (*m*, H–C(6)); 3.14 (v. br. *s*, 2 OH); 2.30 (*ddd*, $J = 12$, 4.7, 1.9, H_α–C(3)); 1.65 (*q*, $J = 12$, H_β–C(3)); 1.42 (*s*, 3 H, Me_2C); 1.36 (*s*, 3 H, Me_2C); 1.28 (*t*, $J = 7.1$, *Me*CH$_2$O). EI-MS: 364 (0.2, M^+), 349 (10, $[M-Me]^+$), 275 (14), 101 (76), 73 (27), 59 (10), 45 (100), 43 (52), 41 (13). HR-MS: 349.1521 ($C_{15}H_{25}O_9^+$, $[M-Me]^+$; calc. 349.1499).

*Ethyl 4,5-*O*-Diacetyl-2,6-anhydro-3-deoxy-8,9-*O*-isopropylidene-7-*O*-(methoxymethyl)-*D*-erythro-*L*-gluco-nononate* (**22**). A soln. of **21** (560 mg, 1.54 mmol) and DMAP (50 mg) in pyridine (5 ml) and Ac_2O (3 ml) was stirred at r.t. for 24 h before being partitioned between H_2O and AcOEt. The crude product obtained from the org. phase was purified by FC (petroleum ether/AcOEt 4:1): **22** (650 mg, 94%). Colorless syrup. $[\alpha]_D^{27} = +21.1$ ($c = 1.01$, $CHCl_3$). IR (film): 2960*s*, 1755*s*, 1440*m*, 1365*s*, 1230*s*, 1150*s*. ^{1}H-NMR: 5.10–4.94 (*m*, 2 H); 4.76 (*d*, $J = 6.6$, 1 H); 4.73 (*d*, $J = 6.6$, 1 H); 4.26–4.01 (*m*, 5 H); 3.96 (*dd*, $J = 7.1$, 8.5, 1 H); 3.88–3.83 (*m*, 1 H); 3.76–3.71 (*m*, 1 H); 3.37 (*s*, 3 H); 2.41 (*ddd*, $J = 2.2$, 4.7, 11.3, 1 H); 2.05 (*s*, 3 H); 2.01 (*s*, 3 H); 1.75 (*dd*, $J = 3.4$, 11.3, 1 H); 1.38 (*s*, 3 H); 1.34 (*s*, 3 H); 1.27 (*t*, $J = 7.1$, 3 H). EI-MS: 433 (7, $[M-Me]^+$), 183 (18), 171 (11), 101 (88), 73 (18), 72 (9.7), 45 (94), 43 (100). HR-MS: 433.1734 ($C_{19}H_{29}O_{11}^+$, $[M-Me]^+$; calc. 433.1710).

*Ethyl 4,5,7,8,9-Penta-*O*-acetyl-2,6-anhydro-3-deoxy-*D*-erythro-*L*-gluco-nononate* (**23**). A soln. of **22** (70 mg, 0.16 mmol), propane-1,3-dithiol (40 µl, 0.40 mmol), and a cat. amount of $BF_3 \cdot Et_2O$ in dry CH_2Cl_2 (2 ml) was stirred at r.t. overnight. After evaporation, the residue was dissolved in pyridine (2 ml) and treated with Ac_2O (1 ml) in the presence of a cat. amount of DMAP. After stirring for 24 h, the mixture was poured into cold H_2O and extracted with AcOEt. The crude residue recovered from the org. phase was submitted to FC (petroleum ether/AcOEt 2:1): **23** (70 mg, 91%). Colorless syrup. $[\alpha]_D^{27} = +19.1$ ($c = 1.50$, MeOH). IR (film): 2950*m*, 1745*s*, 1430*m*, 1360*s*, 1200*s*, 1030*s*, 940*w*. ^{1}H-NMR: 5.34–5.26 (*m*, H–C(7), H–C(8)); 5.10–4.92 (*m*, H–C(4), H–C(5)); 4.53 (*dd*, $J = 2.5$, 13.7, H–C(9)); 4.25–4.14 (*m*, H–C(9), MeCH_2O); 4.04 (*dd*, $J = 2.2$, 12.1, H–C(2)); 3.63 (*dd*, $J = 1.5$, 9.8, H–C(6)); 2.41 (*ddd*, $J = 2.2$, 5.0, 12.9, H_{eq}–C(3)); 2.07, 2.06, 2.05, 2.01, 2.00 (5*s*, each 3 H); 1.76 (br. *q*, $J = 12.6$, H_{ax}–C(3)); 1.25 (*t*, $J = 7.1$, *Me*CH$_2$O). EI-MS: 491 (0.3, $[M+1]^+$), 432 (8), 431 (35), 417 (8), 268 (10), 213 (11), 195 (8), 43 (100). HR-MS: 472.1537 ($C_{21}H_{28}O_{12}^+$, $[M-H_2O]^+$; calc. 472.1581).

*5,7,8,9-Tetra-*O*-acetyl-2,6-anhydro-deoxy-*D*-erythro-*L*-gluco-nonono-1,4-lactone* (**24**). A mixture of **21** (91 mg, 0.25 mmol), MeOH (10 ml), conc. HCl soln. (10 drops), and H_2O (2 ml) was heated under reflux for 12 h. After neutralization with dil. NaOH soln., the mixture was evaporated and the residue treated with Ac_2O/py in the presence of DMAP to give, after chromatographic purification, **24** (*ca.* 80 mg). Colorless syrup. $[\alpha]_D^{20} = +62.6$ ($c = 0.99$, $CHCl_3$). IR (film): 2900*m*, 1745*s*, 1730*s*, 1660*m*, 1360*m*, 1210*s*, 1020*s*, 800*m*. ^{1}H-NMR: 5.24 (*ddd*, $J = 2.4$, 4.9, 7.3, 1 H); 5.02 (br. *d*, $J = 2.4$, 1 H); 4.71 (br. *s*, 1 H); 4.64 (*dd*, $J = 2.4$, 12.2, 1 H); 4.59 (*d*, $J = 7.9$, 1 H); 4.44 (br. *d*, $J = 4.3$, 1 H); 4.21 (*dd*, $J = 4.9$, 12.2, 1 H); 4.05 (br. *s*, 1 H); 2.14 (*s*, 3 H); 2.10 (*s*, 3 H); 2.07 (*s*, 3 H); 2.04 (*s*, 3 H). EI-MS: 403 (2, $[M+1]^+$), 167 (8), 166 (12), 109 (17), 85 (8), 81 (8), 67 (34), 43 (100). HR-MS: 402.1417 ($C_{17}H_{22}O_{11}^+$; calc. 402.1462).

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