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1,3-Dicarbonyl sugar derivatives from sugar nitro-olefins

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Abstract

The sugar nitro-olefins **5–9**, easily available from the *aldehydo*-sugars **1–4** and simple nitroalkanes, undergo a slow transformation, by treatment in DMF with a mixture of tetrabutylammonium hydrogensulfate (2 mol) and potassium fluoride (4 mol) at room temperature, to give the corresponding enol ethers **10–14**, in 10–71% yields, as *E/Z* mixtures, with the exception of **12**, which is configurationally homogeneous. The spectroscopic properties of the enol ethers **10–14** are in agreement with their structures. A proof of the potential usefulness of these compounds as equivalent of sugar 1,3-dicarbonyl compounds is the reaction of **12** with hydrazine hydrate, which affords the pyrazole derivative **15** (53%). The formation of **10–14** from **5–9** may be rationalised in terms of a vinylogous Nef-type reaction. Jacobson conditions, as applied to the nitroalkene **7**, led to the dimethyl acetal **16** (47%) as a *E/Z* mixture, which was transformed into the pyrazole derivative **15** in poor yield (14%). This method is therefore less convenient for **7** than the one described here, which seems to be of wider applicability in the carbohydrate field. © 1996 Elsevier Science Ltd.

Keywords: Sugar nitro-olefins; 1,3-Dicarbonyl sugar derivatives; Vinylogous Nef reaction; Pyrazole *C*-nucleosides

1. Introduction

Sugar nitro-olefins, easily available by the Fischer–Sowden procedure [1–3], are useful synthons for a diversity of functionalised sugars. These compounds, or the

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intermediate nitroaldols, have been used, for instance, as precursors of higher-carbon sugar derivatives [4,5], as dipolarophiles with diazoalkanes for the synthesis of pyrazoline and pyrazole acyclic *C*-nucleosides [6–8], and in a wide variety of transformations [9].

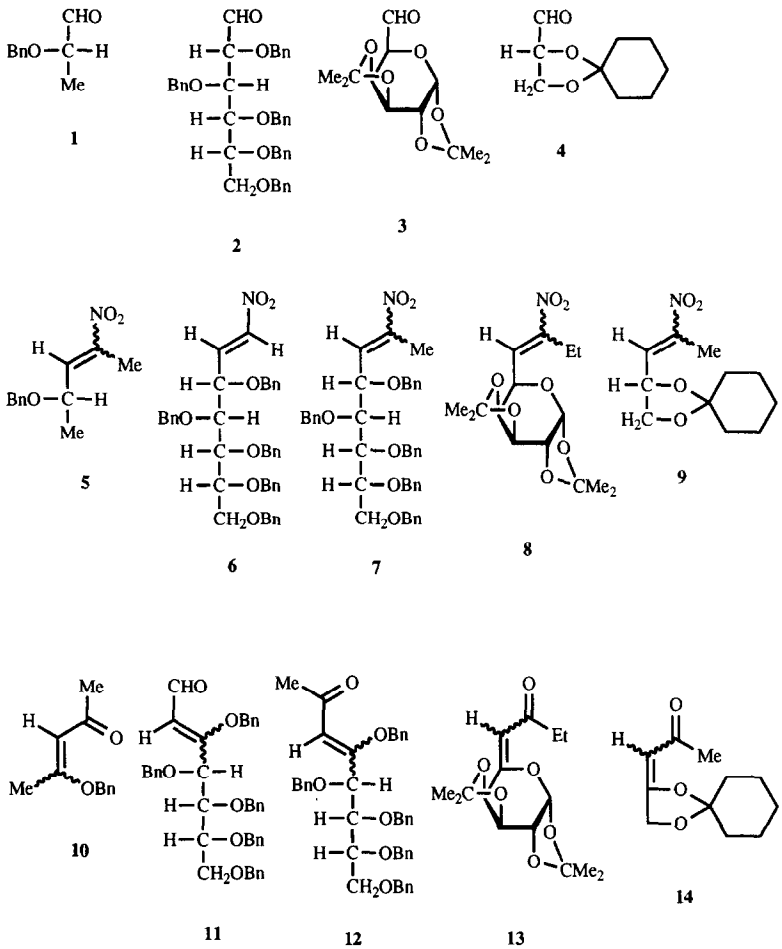
Unlike 1,3-dicarbonyl compounds substituted at the α-position by a sugar residue [10], the analogues substituted at the γ-position have rarely been described, but their utility as precursors of heterocycle derivatives may be predicted. It has recently been described [11] that sugar dialdoses can be transformed into sugar β-ketoesters, which are used as intermediates in the synthesis of heptulosurono-γ-lactones related to certain biologically active natural products.

The synthesis of aliphatic 1,3-dinitro compounds by Michael addition of primary aliphatic nitro compounds to nitro-olefins was first studied by Baer [12]. In the course of a more recent study on this reaction [13], it was observed that the addition is particularly sensitive to steric hindrance in the nitroalkene molecule; moreover, for a highly hindered nitro-olefin such as **7**, a unique reaction taking place in DMF was its slow transformation into an enol ether. Such a transformation may be of synthetic utility, since for sugar derivatives the product will contain a latent 1,3-dicarbonyl system γ-bonded to a sugar moiety. We have studied this potentiality and describe here the results obtained starting from a variety of *O*-protected sugar nitroalkenes.

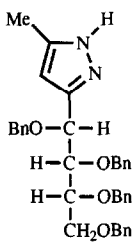
2. Results and discussion

The reaction of the *aldehydo*-sugars **1–4** with simple nitroalkanes (nitromethane, nitroethane, or 1-nitropropane) in 2-propanol, in the presence of KF, followed by treatment with DCC [14], led to the sugar nitroalkenes **5–9** in 30–75% yields as *E/Z* mixtures, with the exception of the nitromethane derivative **6**, which was obtained as pure *E* isomer ($J_{1,2}$ 13.4 Hz). In the other cases, the major diastereomer had the *E* configuration, ascertained by the δ value of the olefinic proton signal in the ^{1}H NMR spectrum [15]. One of the isomers of **8** could be recrystallised, and its *E* configuration was confirmed by X-ray analysis [16].

When the sugar nitro-olefins **5–9** were treated in DMF with a mixture of tetrabutylammonium hydrogensulfate (2 mol equiv) and potassium fluoride (4 mol equiv) at room temperature, a slow transformation into the corresponding enol ethers (**10–14**) took place. Some of the new compounds were more unstable than the others, and this fact may explain the wide range of yields (10–71%). The products were formed as *E/Z* mixtures, which could not be resolved for **10**, **11**, **13**, and **14**. In the case of **12**, the isolated product was configurationally homogeneous, but an assignment was not possible; taken into account steric factors, its configuration is probably *Z*. The spectroscopic properties of the enol ethers **10–14** are in agreement with their structures. A proof of the potential usefulness of these compounds as equivalent of sugar 1,3-dicarbonyl compounds is the reaction of **12** with hydrazine hydrate, which affords the expected pyrazole derivative **15** in 53% yield.



The transformation of the nitro-olefins **5–9** into the enol ethers **10–14** may be rationalised in terms of a vinylogous Nef-type reaction, which is possible due to the enhanced acidity of the allylic proton in these γ-alkoxy-nitroalkenes. The anion formed by action of fluoride is stabilised by delocalisation of its charge, and its evolution to the β-alkoxy-α,β-unsaturated carbonyl compound seems to involve the action of the hydrogen sulfate anion, probably following a mechanism similar to that proposed for Nef-type reactions performed in the presence of silica gel under anhydrous conditions [17]. Jacobson conditions [18] (nitronate over cold methanolic sulfuric acid) may affect some protecting groups of sugar nitroalkenes. We have applied such conditions to the *O*-benzyl nitroalkene **7**, and have obtained in 47% yield the dimethyl acetal **16** of **12** as a diastereomeric mixture, which was transformed, without further purification, into the pyrazole derivative **15**, in poor yield (14%). This method is therefore less convenient for **7** than the one described above, which seems to be of wider applicability in the carbohydrate field.



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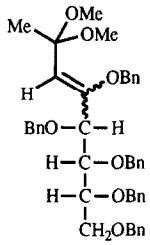

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3. Experimental

General methods.—Hexane and ether were distilled from sodium prior to use. TLC was performed on Silica Gel 60 plates (DC-Alufolien F_{254}, E. Merck, or ALUGRAM SIL G/UV_{254}, Macherey–Nagel), and detection with UV light (254 nm), iodine vapour, or by charring with H_2SO_4. Silica Gel 60 (E. Merck) was used for column chromatography and hexane–EtOAc mixtures as eluants. Solutions were concentrated under diminished pressure at $< 40°$. Melting points were determined with a Gallenkamp MFB-595 apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 MC polarimeter. IR spectra (neat or on a KBr disc) were obtained on a FTIR Bomem Michelson MB-120 spectrometer. ^{1}H NMR spectra (200, 300, and 500 MHz) were obtained for solutions in $CDCl_3$ with a Varian XL-200, a Bruker AMX-300 or a Bruker AMX-500 spectrometer. Assignments were confirmed by decoupling and homonuclear 2D COSY correlated experiments. ^{13}C NMR spectra were recorded at 50.3, 75.5, or 125.7 MHz. Proton decoupled attached proton test (APT), DEPT, and heteronuclear 2D correlated spectra were obtained in order to assist in carbon resonance assignments. EIMS spectra (70 eV) were measured with a Kratos MS-80RFA instrument, with an ionising current of 100 mA, an accelerating voltage of 4 kV, and a resolution of 10000 (10% valley definition). The FABMS spectra were recorded with the same instrument; ions were produced by a beam of xenon atoms (6–7 keV) using a matrix consisting of nitrobenzene or thioglycerol and NaI as salt; $(RbI)(CsI)_{12}Cs$ and/or $(CsI)_{37}Cs$ were used as reference.

General procedure for preparation of per-O-substituted nitro-olefins (**5–9**).—Potassium fluoride (23 mg, 0.4 mmol) and the appropriate nitroalkane (8 mmol) were added to a stirred solution of the corresponding aldehyde (**1–4**) (4 mmol) in 2-propanol (6.5 mL) under argon at room temperature. The reaction mixture was stirred until complete transformation of **1–4** had taken place (TLC, 24 h). Rotatory evaporation of the solvent under reduced pressure left a residue which was taken up with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. The residue, dissolved in acetonitrile (20 mL), was stirred with *N,N'*-dicyclohexylcarbodiimide (1.82 g, 8.8 mmol) and CuCl (0.396 g, 4 mmol) under argon at 35 °C for 24 h. The reaction mixture was diluted with EtOAc (120 mL)

and quenched by addition of a 35% methanolic soln of oxalic acid dihydrate (3.1 mL; a change of the solution colour was observed). After filtration through Celite, the resulting solution was washed with satd aq $NaHCO_3$ (2×50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated. Purification of the residue by chromatography (hexane–EtOAc as eluant in the ratio indicated in each case) afforded pure nitro-olefins (**5–9**).

(E)- *and* (Z)-(S)-*4-Benzyloxy-2-nitropent-2-ene* (**5**).—(*S*)-2-*O*-Benzyl-lactaldehyde (**1**), prepared from methyl (*S*)-2-*O*-benzyl-lactate by the method described [19] for the racemic, reacted with nitroethane to afford **5**. Purification by preparative TLC (4:1 EtOAc–hexane) of the crude product afforded a syrupy mixture of the title diastereomers (**5**) in 70% yield (*E*/*Z* 15:1 by ^{1}H NMR); $[\alpha]_D^{23}$ −40° (*c* 0.7, $CHCl_3$), ν_{max} (film) 1649 (C = C), 1526 and 1373 (NO_2), 1098 cm^{-1} (C–O–C); FABMS: *m*/*z* 244 (100, $[M + Na]^+$); HRMS: *m*/*z* 206.0838 (Calcd for $C_{12}H_{15}NO_3$–CH_3: 206.0817); *E* isomer ^{1}H NMR (300 MHz): δ 7.38–7.26 (m, 5 H, Ph), 7.05 (dq, 1 H, $^4J_{1,3}$ 1.0, $J_{3,4}$ 8.7 Hz, H-3), 4.56 and 4.41 (each d, each 1 H, *J* 11.8 Hz, CH_2Ph), 4.27 (dq, 1 H, $J_{4,5}$ 6.5 Hz, H-4), 2.15 (d, 3 H, Me-1), and 1.38 (d, 3 H, Me-5); ^{13}C NMR (75.5 MHz): δ 147.9 (C-2), 136.5 (C-3), 137.3, 128.2, 127.6, 127.4 (6 C, Ph), 70.7 (*C*H_2Ph), 70.5 (C-4), 20.1 (C-5), and 12.6 (C-1); the *Z* isomer gave minor signals.

(E)-*3,4,5,6,7-Penta*-O-*benzyl-1,2-dideoxy-1-nitro*-D-gluco-*hept-1-enitol* (**6**).—Obtained from 2,3,4,5,6-penta-*O*-benzyl-*aldehydo*-D-glucose (**2**) [20] and nitromethane after purification by preparative TLC (4:1 hexane–EtOAc) in 30% yield; $[\alpha]_D^{20}$ +8.5° (*c* 1.0, $CHCl_3$); ν_{max} (film) 1623 (C = C), 1523 and 1350 (NO_2), 1090 (C–O–C) cm^{-1}; ^{1}H NMR (500 MHz): δ 7.36–7.21 (m, 25 H, 5 Ph), 7.17 (dd, 1 H, $J_{1,2}$ 13.4, $J_{2,3}$ 5.0 Hz, H-2), 6.80 (dd, 1 H, $J_{1,3}$ 1.6 Hz, H-1), 4.68–4.39 (m, 10 H, 5 CH_2Ph), 4.17 (dt, 1 H, $J_{2,3} \approx J_{3,4}$ 5.1 Hz, H-3), 3.90 (dd, 1 H, $J_{6,7}$ 4.9, $J_{7,7'}$ 10.1 Hz, H-7), 3.87–3.81 (m, 3 H, H-4, H-5, H-6), and 3.66 (dd, 1 H, $J_{6,7'}$ 4.5, H-7′); ^{13}C NMR (75.5 MHz): δ 140.2 (C-1), 139.4 (C-2), 138.2–127.5 (30 C, 5 Ph), 79.6, 78.4, 77.8 (C-4, C-5, C-6), 75.6 (C-3), 74.6, 73.6, 73.3, 72.4, 71.9 (5 C, 5 *C*H_2Ph), and 68.8 (C-7); FABMS: *m*/*z* 696 (100, $[M + Na]^+$); HRFABMS: *m*/*z* 758.2174 (Calcd for $[M + Rb]^+$: 758.2156); *m*/*z* 806.2064 (Calcd for $[M + Cs]^+$: 806.2093). Anal. Calcd for $C_{42}H_{43}NO_7 \cdot 0.5H_2O$: C, 73.88; H, 6.50; N, 2.05. Found: C, 73.86; H, 6.22; N, 2.22.

(E)- *and* (Z)-*4,5,6,7,8-Penta*-O-*benzyl-1,2,3-trideoxy-2-nitro*-D-gluco-*oct-2-enitol* (**7**). —Obtained from **2** and nitroethane by the general procedure. Processing and purification by flash chromatography (gradient 20:1 to 4:1 hexane–EtOAc) of the crude product afforded a mixture of the title isomers (yield 75%) (*E*/*Z* 4:1 by ^{1}H NMR); ν_{max} (film) 1605 (C = C), 1526 and 1333 (NO_2), 1028 (C–O–C) cm^{-1}; FABMS: *m*/*z* 710 (100, $[M + Na]^+$). Anal. Calcd for $C_{43}H_{45}NO_7$: C, 75.09; H, 6.59; N, 2.04. Found: C, 75.12; H, 6.75; N, 2.11. Separation of the two stereoisomers could be achieved by preparative TLC (two irrigations with 4:1 and 9:1 hexane–EtOAc). *E* isomer: $[\alpha]_D^{20}$ +10° (*c* 0.81, $CHCl_3$); ^{1}H NMR (200 MHz): δ 7.32–7.26 (m, 25 H, 5 Ph), 7.03 (dq, 1 H, $^4J_{1,3}$ 1.0, $J_{3,4}$ 8.8 Hz, H-3), 4.69 (dd, 1 H, $J_{5,6}$ 6.3, $J_{6,7}$ 7.1 Hz, H-6), 4.46–4.51 (m, 8 H, 4 CH_2Ph), 4.28 (d, 2 H, CH_2Ph), 4.24 (dd, 1 H, $J_{4,5}$ 4.0 Hz, H-4), 4.11 (dd, 1 H, H-5), 3.90 (dd, 1 H, $J_{7,8}$ 4.8, $J_{8,8'}$ 9.5 Hz, H-8), 3.79 (m, 1 H, H-7), 3.64 (dd, 1 H, $J_{7,8'}$ 4.5 Hz, H-8′), and 1.68 (d, 3 H, Me-1); ^{13}C NMR (50.3 MHz): δ 149.0 (C-2), 133.5 (C-3), 138.4–127.1 (30 C, 5 Ph), 79.8, 79.2, 78.6, 75.4 (C-4, C-5, C-6, C-7), 75.0, 74.1, 73.3, 71.8, 71.4 (5 C, 5 *C*H_2Ph), and 12.5 (C-1); *Z* isomer: $[\alpha]_D^{20}$ +22.9° (*c* 1.1, $CHCl_3$); ^{1}H

NMR (200 MHz): δ 7.32–7.26 (m, 25 H, 5 Ph), 5.82 (dq, 1 H, $^{4}J_{1,3}$ 0.2, $J_{3,4}$ 8.0 Hz, H-3), 4.72 (dd, 1 H, $J_{4,5}$ 4.1 Hz, H-4), 4.46 (m, 1 H, H-7), 4.51–4.46 (m, 10 H, 5 CH_2Ph), 4.16 (dd, 1 H, $J_{5,6}$ 3.7, $J_{6,7}$ 7.1 Hz, H-6), 3.90 (dd, 1 H, H-5), 3.86–3.71 (m, 2 H, H-8 and H-8′), and 1.91 (d, 3 H, Me-1); ^{13}C NMR (50.3 MHz): δ 147.6 (C-2), 133.5 (C-3), 138.6–127.2 (30 C, 5 Ph), 80.3, 79.6, 79.0, 75.0 (C-4, C-5, C-6, C-7), 74.9, 74.5, 73.1, 72.0, 71.8 (5 C, 5 CH_2Ph), 69.4 (C-8), and 18.9 (C-1).

(E)- *and* (Z)-*6,7,8,9-Tetradeoxy-1,2:3,4-di-O-isopropylidene-7-nitro-α-D-galacto-non-6-enopyranose* (**8**).—Obtained from 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose (**3**) [21] and 1-nitropropane as a crystalline mixture of both stereoisomers after purification by preparative TLC (12:1 hexane–EtOAc) (yield 47%) (3:1 *E*/*Z*, by ^{1}H NMR); mp 102–107 °C; $[\alpha]_D^{25}$ −106° (*c* 1.0, CH_2Cl_2); ν_{max} (KBr) 1656 (C = C), 1524 and 1373 (NO_2), 1072 (C–O–C) cm^{-1}; HRMS: *m*/*z* 314.1240 (Calcd for $C_{15}H_{23}NO_7$–CH_3: 314.1237). Anal. Calcd for $C_{15}H_{23}NO_7$: C, 54.70; H, 7.04; N, 4.25. Found: C, 54.70; H, 7.15; N, 4.36. The less soluble *E* isomer could be isolated by recrystallisation of the mixture from EtOH and had mp 114–115 °C; $[\alpha]_D^{26}$ −116° (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz): δ 7.10 (d, 1 H, $J_{5,6}$ 7.8 Hz, H-6), 5.58 (d, 1 H, $J_{1,2}$ 5.1 Hz, H-1), 4.67 (dd, 1 H, $J_{2,3}$ 2.5, $J_{3,4}$ 7.8 Hz, H-3), 4.55 (dd, 1 H, $J_{4,5}$ 2.0 Hz, H-5), 4.39 (dd, 1 H, H-2), 4.22 (dd, 1 H, H-4), 2.70 (dq, 2 H, $J_{8,9}$ 7.4, $^{2}J_{8,8'}$ 14.9 Hz, CH_2-8), 1.57, 1.50, 1.37, 1.36 (each s, each 3 H, 2 CMe_2), and 1.18 (t, 3 H, Me-9); ^{13}C NMR (125.8 MHz): δ 155.5 (C-7), 129.6 (C-6), 109.8, 108.7 (2 *C*Me$_2$), 96.2 (C-1), 72.4 (C-4), 70.6 (C-3), 70.0 (C-2), 64.5 (C-5), 25.9, 25.7, 24.7, 24.2 (2 CMe_2), 20.7 (C-8), and 12.7 (C-9); its *E* configuration was confirmed by X-ray analysis [16]; *Z* isomer: ^{1}H NMR (500 MHz): δ 5.90 (d, 1 H, $J_{5,6}$ 7.7 Hz, H-6), 5.54 (d, 1 H, $J_{1,2}$ 5.0 Hz, H-1), 5.00 (dd, 1 H, H-5), 4.66 (dd, 1 H, $J_{2,3}$ 2.5, $J_{3,4}$ 7.8 Hz, H-3), 4.50 (dd, 1 H, $J_{4,5}$ 2.0 Hz, H-4), 4.36 (dd, 1 H, H-2), 2.63 (m, 2 H, CH_2-8), 1.52, 1.50, 1.35, 1.34 (each s, each 3 H, 2 CMe_2), and 1.17 (t, 3 H, $J_{8,9}$ 7.4 Hz, Me-9); ^{13}C NMR (125.8 MHz): δ 152.5 (C-7), 129.0 (C-6), 109.4, 109.0 (2 *C*Me$_2$), 96.3 (C-1), 72.7 (C-4), 70.8 (C-3), 70.0 (C-2), 65.5 (C-5), 25.8, 25.5, 24.8 (2 CMe_2), 20.7 (C-8), and 11.4 (C-9).

(E)- *and* (Z)-*4,5-O-Cyclohexylidene-1,2,3-trideoxy-2-nitro-D-glycero-pent-2-enitol* (**9**).—Obtained from 2,3-*O*-cyclohexylidene-D-glyceraldehyde (**4**) [22] and nitroethane after purification by flash chromatography (gradient 19:1 to 6:1 hexane–EtOAc) as a syrupy mixture of the title stereoisomers (yield 50%) (*E*/*Z* 14:1 by ^{1}H NMR); $[\alpha]_D^{21}$ +8.7° (*c* 1.0, $CHCl_3$); ν_{max} (film): 1530 and 1355 (NO_2), 1098 (C–O–C) cm^{-1}; HRMS: *m*/*z* 227.1161 (Calcd for $C_{11}H_{17}NO_4$: 227.1575); *E* isomer: ^{1}H NMR (300 MHz): δ 7.03 (dq, 1 H, $^{4}J_{1,3}$ 1.0, $J_{3,4}$ 8.1 Hz, H-3), 4.79 (dt, 1 H, $J_{4,5} \approx J_{4,5'}$ 6.7 Hz, H-4), 4.20, 3.75 (each dd, each 1 H, $^{2}J_{5,5'}$ 8.4, $J_{4,5}$ 6.3, $J_{4,5'}$ 6.7 Hz, H-5, H-5′), 2.24 (dd, 3 H, $^{5}J_{1,4}$ 0.4 Hz, Me-1), and 1.65–1.40 (m, 10 H, C_6H_{10}); ^{13}C NMR (75.5 MHz): δ 149.3 (C-2), 132.6 (C-3), 111.2 (C-6), 71.4 (C-4), 68.2 (C-5), 36.0, 35.0 (C-7, C-11), 24.8 (C-9), 23.7 (C-8, C-10), and 12.9 (C-1); *Z* isomer: ^{1}H NMR: δ 6.16 (dq, 1 H, $^{4}J_{1,3}$ 1.1, $J_{3,4}$ 6.2 Hz, H-3), 5.20 (dt, 1 H, $J_{4,5} \approx J_{4,5'}$ 6.8 Hz, H-4), 4.43, 3.73 (each dd, each 1 H, $^{2}J_{5,5'}$ 8.5, $J_{4,5}$ 6.4, $J_{4,5'}$ 7.0 Hz, H-5, H-5′), 2.21 (t, 1 H, $^{4}J_{1,3} \approx {}^{5}J_{1,4}$ 1.1 Hz, H-1), and 1.65–1.40 (m, 10 H, C_6H_{10}).

General procedure for preparation of enol ethers (**10–14**).—To a suspension of tetrabutylammonium hydrogensulfate (0.685 g, 2 mmol) in DMF (7 mL), potassium fluoride (0.232 g, 4 mmol) was added. The mixture was stirred under argon for 30 min

at room temperature; then a solution of the appropriate nitroalkene (**5–9**) (1 mmol) in DMF (3 mL) was dropped in during ca. 15 min. The reaction mixture was stirred until TLC (9:1 or 6:1 hexane–EtOAc) indicated an almost complete transformation of the starting compound into the more slowly migrating enol ether (4–7 days). The solvent was evaporated under reduced pressure, and the residue was taken up in water (240 mL) and extracted with CH_2Cl_2 (2 × 240 mL). The combined organic layers were washed with brine (240 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by chromatography (hexane–EtOAc as eluant in the ratio stated below) afforded pure enol ethers (**10–14**).

4-Benzyloxy-3-penten-2-one (**10**).—Obtained from **5** (*E*/*Z* mixture) as a very unstable oil after purification by preparative TLC (9:1 hexane–EtOAc) (reaction time 7 days; yield 10%); ^{1}H NMR (500 MHz): δ 7.41–7.32 (m, 5 H, Ph), 5.60 (s, 1 H, H-3), 4.86 (s, 2 H, CH_2Ph), 2.35 (s, 3 H, Me-1), and 2.18 (s, 3 H, Me-5) (these values agree with lit. data [23]); ^{13}C NMR (125.7 MHz): δ 189.9 (C = O), 166.0 (C-4), 128.6, 128.3, 127.5 (6 C, Ph), 100.3 (C-3), 70.0 (*C*H_2Ph), 31.8 (C-1), and 22.6 (C-5).

(Z)- *and* (E)-*3,4,5,6,7-Penta*-O-*benzyl-2-deoxy*-D-arabino-*hept-2-enose* (**11**).—Obtained from **6** (reaction time 4 days) after purification by preparative TLC (4:1 hexane–EtOAc), as a syrupy 2:1 mixture (by ^{1}H NMR) of the title stereoisomers (yield 20%); $[\alpha]_D^{20}$ −30° (*c* 0.4, $CHCl_3$); ν_{max} (film) 2855 (=CH), 1682 (C = O), 1667 (C = C), and 1028 (C–O–C) cm^{-1}; FABMS: *m*/*z* 665 (100, [M + Na]$^+$); HRFABMS: *m*/*z* Calcd for [M + Cs]$^+$: 775.2035, found: 775.2019; major isomer ^{1}H NMR (300 MHz): δ 9.98 (d, 1 H, $J_{1,2}$ 7.5 Hz, H-1), 7.36–7.14 (m, 25 H, 5 Ph), 5.47 (d, 1 H, H-2), 4.74–4.25 (m, 6 H, 3 CH_2Ph-4, -5, -6), 4.72, 4.64 (each d, each 1 H, $^2J_{H,H'}$ 11.8 Hz, CH_2Ph-3), 4.47 (d, 1 H $J_{4,5}$ 3.5 Hz, H-4), 4.04 (d, 2 H, $^2J_{H,H'}$ 11.5 Hz, CH_2Ph-7), and 3.84–3.62 (m, 4 H, H-5, H-6, H-7, H-7′); ^{13}C NMR (75.5 MHz): δ 191.7 (C = O), 164.8 (C-3), 138.2–126.9 (30 C, 5 Ph), 108.5 (C-2), 79.2, 78.4, 77.9 (C-4, C-5, C-6), 75.0, 73.3, 72.1, 71.9, 70.6 (5 *C*H_2Ph), and 65.3 (C-7); minor isomer ^{1}H NMR (300 MHz): δ 10.3 (d, 1 H, $J_{1,2}$ 8.1 Hz, H-1), 7.36–7.14 (m, 25 H, 5 Ph), 5.81 (d, 1 H, H-2), 5.15, 4.94 (each d, each 1 H, $^2J_{H,H'}$ 12.2 Hz, CH_2Ph-3), 4.74–4.25 (m, 6 H, 3 CH_2Ph-4, -5, -6), 4.35 (d, 1 H, $J_{4,5}$ 2.8 Hz, H-4), 4.29 (d, 2 H, $^2J_{H,H'}$ 10.8 Hz, CH_2Ph-7), 3.93 (dd, 1 H, $J_{5,6}$ 7.8 Hz, H-5), and 3.84–3.62 (m, 3 H, H-6, H-7, H-7′).

(E)- *or* (Z)-*4,5,6,7,8-Penta*-O-*benzyl-1,3-dideoxy*-D-arabino-*oct-3-en-2-ulose* (**12**).—Obtained from **7** (*E*/*Z* mixture) as a syrup after purification by preparative TLC (4:1 hexane–EtOAc) (reaction time 6 days; yield 40%); $[\alpha]_D^{20}$ +25° (*c* 0.83, $CHCl_3$); ν_{max} (film) 1678 (C = O) and 1028 (C–O–C) cm^{-1}; ^{1}H NMR (300 MHz): δ 7.30–7.16 (m, 30 H, Ph), 5.88 (s, 1 H, H-3), 5.31, 4.91 (each d, each 1 H, $^2J_{H,H'}$ 12.4 Hz, CH_2Ph-4), 4.26 (d, 1 H, $J_{5,6}$ 2.6 Hz, H-5), 4.54–4.47 (m, 6 H, CH_2Ph-5, -6, -7), 4.15, 4.14 (each d, each 1 H, $^2J_{H,H'}$ 11.5 Hz, CH_2Ph-8), 3.89 (dd, 1 H, $J_{6,7}$ 5.2 Hz, H-6), 3.77–3.71 (m, 1 H, H-7), 3.64–3.60 (m, 2 H, H-8 and H-8′), and 2.18 (s, 3 H, Me-1); ^{13}C NMR (75.5 MHz): δ 196.7 (C = O), 165.1 (C-4), 138.4–127.4 (30 C, 5 Ph), 108.0 (C-3), 78.8, 78.2, 77.8 (C-5, C-6, C-7), 74.8, 73.6, 73.3, 72.1, 71.7 (5 *C*H_2Ph), 68.5 (C-8), and 31.6 (C-1); FABMS: *m*/*z* 679 (100, [M + Na]$^+$); HRMS: *m*/*z* 656.3073 (Calcd for $C_{43}H_{44}O_6$: 656.3126).

(Z)- *and* (E)-*6,8,9-Trideoxy-1,2:3,4-di*-O-*isopropylidene-β*-L-arabino-*non-5-eno-pyranos-7-ulose* (**13**).—Obtained from **8** (*E*/*Z* mixture) as a syrup after purification by

preparative TLC (9:1 hexane–EtOAc) (reaction time 7 days; yield 71% of *E/Z* mixture); $[\alpha]_D^{25}$ −85° (*c* 1, CH_2Cl_2); ν_{max} (film) 1688 (C = O), 1661 (C = C), and 1061 (C–O–C) cm^{-1}; ^1H NMR (300 MHz): δ 5.84 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1), 5.58 (s, H-6, minor component), 5.56 (s, H-6, major component), 4.67 (dd, 1 H, $J_{2,3}$ 2.0 Hz, H-3), 4.51 (dd, 1 H, $J_{3,4}$ 6.8 Hz, H-4), 4.34 (dd, 1 H, H-2), 2.87 (q, 2 H, $J_{8,9}$ 7.2 Hz, CH_2-8), 1.52, 1.45, 1.42, 1.41 (each s, each 3 H, 2 CMe_2), and 1.10 (t, 3 H, Me-9); ^{13}C NMR (75.5 MHz): δ 201.9 (C = O, minor component), 200.6 (C = O, major component), 157.2 (C-5, minor component), 156.4 (C-5, major component), 110.2 and 110.4 (2 CMe_2), 98.0 (C-1), 74.0 (C-6), 73.5 (C-2), 72.5 (C-4), 70.8 (C-3), 36.4 (C-8), 27.0, 26.4, 25.3, 24.6 (2 CMe_2), and 7.70 (C-9); HRMS: *m/z* 298.1428 (Calcd for $C_{15}H_{22}O_6$: 298.1416).

(Z)- *and* (E)-*4,5-O-Cyclohexylidene-1,3-dideoxy-pent-3-en-2-ulose* (**14**).—Obtained from **9** (*E/Z* mixture) as an unstable oil after purification by preparative TLC (6:1 hexane–EtOAc) [reaction time 4 days, yield 10% of 3:1 mixture (by ^1H NMR) of stereoisomers]; ν_{max} (film) 1687 (C = O), 1660 (C = C), and 1086 (C–O–C) cm^{-1}; FABMS: *m/z* 219 (100, $[M + Na]^+$); HRMS: *m/z* 196.1101 (Calcd for $C_{11}H_{16}O_3$: 196.1099); major isomer ^1H NMR (300 MHz): δ 5.05 (br s, 1 H, H-3), 4.66 (s, 2 H, H-5, H-5′), 2.36 (s, 3 H, Me-1), and 1.72–1.56 (m, 10 H, C_6H_{10}); ^{13}C NMR (75.5 MHz): δ 197.7 (C = O), 162.9 (C-4), 117.7 (C-6), 98.4 (C-3), 68.3 (C-5), 30.6 (C-1), 34.5 (C-7 and C-11), 24.6 (C-9), and 23.5 (C-8, C-10); minor isomer ^1H NMR (300 MHz): δ 5.70 (br s, 1 H, H-3), 4.72 (s, 2 H, H-5, H-5′), 2.11 (s, 3 H, Me-1), and 1.85–1.72 (m, 10 H, C_6H_{10}).

*Reaction of 4,5,6,7,8-Penta-O-benzyl-1,3-dideoxy-*D-arabino-*oct-3-en-2-ulose* (**12**) with hydrazine. Preparation of 3(5)-methyl-5(3)-(1,2,3,4-tetra-O-benzyl-D-arabino-*tetritol-1-yl)pyrazole* (**15**).—A solution of the benzyl enol ether **12** (96 mg, 0.15 mmol) in EtOH (4 mL) was treated with hydrazine hydrate (0.29 mL, 6 mmol). The solution was kept under argon at room temperature, until complete transformation of **12** had taken place (TLC, 2:1 hexane–EtOAc) (30 h). Evaporation of the solvent and purification of the residue by preparative TLC (2:1 hexane–EtOAc) afforded pure **15** (45 mg, 53%). $[\alpha]_D^{20}$ −30° (*c* 0.5, $CHCl_3$); ν_{max} (film) 3450–3150 (NH), 1605 (phenyl), 1582 (pyrazole C = N), 1530 and 1453 (C = C and C = N aromatic), 1090 (C–O–C), 737 and 700 (= CH) cm^{-1}; ^1H NMR (300 MHz): δ 7.20–7.41 (m, 20 H, Ph), 6.50 (br s, 1 H, NH), 6.05 (s, 1 H, H-4), 4.85 (d, 1 H, $J_{1',2'}$ 4.2 Hz, H-1′), 4.22–4.59 (m, 8 H, 4 CH_2Ph), 3.87 (dd, 1 H, $J_{2',3'}$ 6.4 Hz, H-2′), 3.66–3.82 (m, 3 H, H-3′, H-4′, and H-4″), and 2.29 (s, 3 H, Me-5); ^{13}C NMR (75.5 MHz): δ 145.5, 138.0 (C-3 and C-5), 137.8–127.5 (24 C, 4 Ph), 104.0 (C-4), 81.5 (C-1′), 77.9, 74.2 (C-2′ and C-3′), 75.0, 73.3, 72.1, and 71.3 (4 CH_2Ph), 68.8 (C-4′), and 12.7 (Me-5); EIMS: *m/z* 471 (2, $M^{+\cdot}$ − Bn), 363 (5, 471 − BnOH), 108 (45, BnOH), 91 (100, tropylium$^+$), and 77 (45, Ph^+); FABMS: *m/z* 585 ($[M + Na]^+$), 563 ($[M + H]^+$). HRMS: *m/z* 563.2879 (Calcd for $C_{36}H_{38}N_2O_4$ + H: 563.2909). Anal. Calcd for $C_{36}H_{38}N_2O_4$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.26; H, 6.78; N, 4.18.

(Z)- *and* (E)-*4,5,6,7,8-Penta-*O*-benzyl-1,3-dideoxy-*D-arabino-*oct-3-en-2-ulose dimethyl acetal* (**16**).—A solution of **7** (0.43 g, 0.62 mmol) in 0.5 M methanolic sodium methoxide (4 mL, 2 mmol) was stirred at room temperature until TLC (9:1 hexane–EtOAc) showed almost complete transformation of **7** (5 h), then added dropwise to a

cold (−30 °C) solution of H_2SO_4 (4 mL) in MeOH (15 mL). The mixture was poured into CH_2Cl_2 (100 mL) and washed with ice–water (2 × 50 mL) and M NaOH (50 mL). The organic layer was dried (K_2CO_3) and concentrated under reduced pressure. Purification of the crude residue (0.36 g) by preparative TLC (7:1 hexane–EtOAc) afforded 0.205 g (47%) of **16** as a syrupy 2:1 mixture (by ^{1}H NMR) of the title isomers; $[\alpha]_D^{20}$ +3.5° (*c* 2, CH_2Cl_2); ν_{max} (film) 1645, 1609 (C = C), and 1092, 1028 (C–O–C) cm^{-1}; major isomer ^{1}H NMR (300 MHz): δ 7.33–7.21 (m, 25 H, Ph), 4.74, 4.70 (each d, each 1 H, $^2J_{H,H'}$ 11.4 Hz, CH_2Ph-4), 4.63–4.43 (m, 8 H, CH_2Ph-5, -6, -7, -8), 4.55 (s, 1 H, H-3), 4.03 (d, 1 H, $J_{5,6}$ 4.1 Hz, H-5), 3.90–3.60 (m, 4 H, H-6, H-7, H-8, H-8′), 3.39, 3.19 (each s, each 3 H, 2 OMe), and 1.26 (s, 3 H, Me-1); ^{13}C NMR (75.5 MHz): δ 162.1 (C-4), 138.8–127.1 (30 C, 5 Ph), 134.3 (C-2), 105.0 (C-3), 79.6, 79.5, 79.4 (C-5, C-6, C-7), 75.0, 74.3, 73.8, 73.2, 71.8 (5 CH_2Ph), 69.9 (C-8), 55.3, 54.1 (2 OMe), and 29.5 (C-1); minor isomer ^{1}H NMR (300 MHz): δ 7.33–7.21 (m, 25 H, 5 Ph), 4.85, 4.78 (each d, each 1 H, $^2J_{H,H'}$ 11.5 Hz, CH_2Ph-4), 4.63–4.43 (m, 8 H, CH_2Ph-5, -6, -7, -8), 4.53 (s, 1 H, H-3), 4.06 (d, 1 H, $J_{5,6}$ 4.0 Hz, H-5), 3.90–3.54 (m, 4 H, H-6, H-7, H-8, H-8′), 3.41, 3.36 (each s, each 3 H, 2 OMe), and 1.43 (s, 3 H, Me-1); ^{13}C NMR (75.5 MHz): δ 171.7 (C-4), 138.8–127.1 (30 C, 5 Ph), 135.6 (C-2), 104.9 (C-3), 78.9, 78.5 (3 C, C-5, C-6, C-7), 74.1, 73.3, 73.2, 73.1, 72.3 (5 CH_2Ph), 69.8 (C-8), 55.4, 55.3 (2 OMe), and 30.2 (C-1).

Transformation of **16** *into* **15**.—The crude product **16** (0.175 g, 0.25 mmol) was treated with 9:1 trifluoroacetic acid–water (1.75 mL) for 75 min. The mixture was poured into ice–water (100 mL) and the resulting syrup was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were washed with satd aq $NaHCO_3$ (2 × 90 mL) and water (100 mL), dried ($MgSO_4$), and concentrated to give a syrup (0.153 g), whose ^{1}H NMR spectrum showed no signal for OMe. A solution of this syrup in EtOH (5 mL) was treated with hydrazine hydrate (0.45 mL, 9 mmol) under argon for 30 h at room temperature. Evaporation of the solvent and purification of the residue by preparative TLC (2:1 hexane–EtOAc) afforded pure **15** (18 mg, 14%), identical to the product obtained from **12** (see above).

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