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Note

Synthesis and spontaneous dimerization of the tri-*O*-benzyl derivative of ''2-keto-1-*C*-methylene-D-glucopyranose'' (2,6-anhydro-4,5,7-tri-*O*-benzyl-1-deoxy-D-*arabino*-hept-1-en-3-ulose)

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In the context of our synthetic studies on methylene-bridged disaccharide analogues (*C*-disaccharides [1,2]), we considered that the coupling of ''2-keto-1-*C*-methylene hexopyranose'' derivatives such as **1** with glycosyl halides or halogeno sugars by way of a free-radical chain mechanism might provide a novel approach to ''linear'' [(1→1)- or (1→6)-linked] as well as ''branched-chain'' *C*-disaccharides. The Bu_3SnH-mediated reaction of halogeno sugars with radical acceptors (e.g., acrylonitrile) is an efficient carbon–carbon bond-forming process which has been developed by Giese and co-workers [3,4] using glycosyl bromides as the source of radicals and 2-*C*-methylene aldonolactones as acceptors [5,6] (including the regioisomer of **1** in which the positions of the carbonyl and methylene groups are interchanged [6]). This process has led to (1→2)-linked *C*-disaccharides such as *C*-kojibiose [6]. As it already contains the *C*-glycosidic linkage and might be able to react with sugar derivatives bearing a group susceptible of homolysis at any position, compound **1** would constitute a general precursor of *C*-disaccharides. Compound **1** was found, however, to undergo spontaneous dimerization upon generation from its precursor and could not be submitted to radical coupling processes. We describe in this note our attempts to prepare **1** and the characteristics of its dimer.

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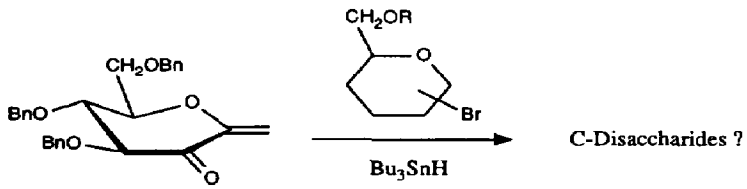
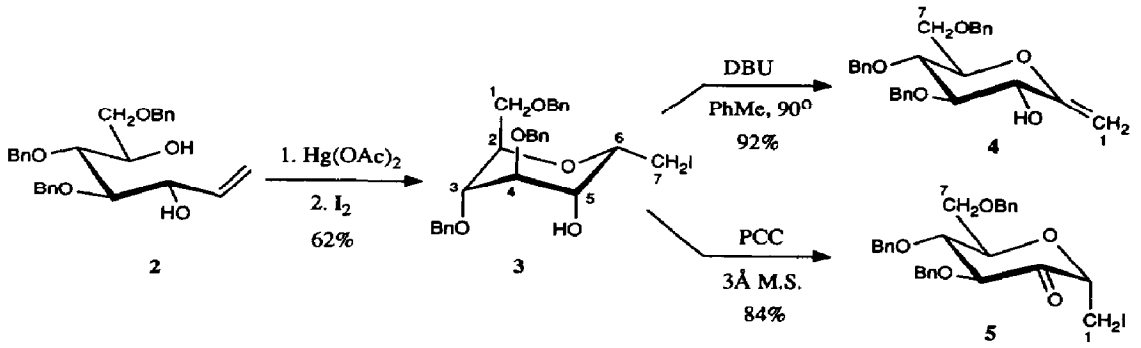
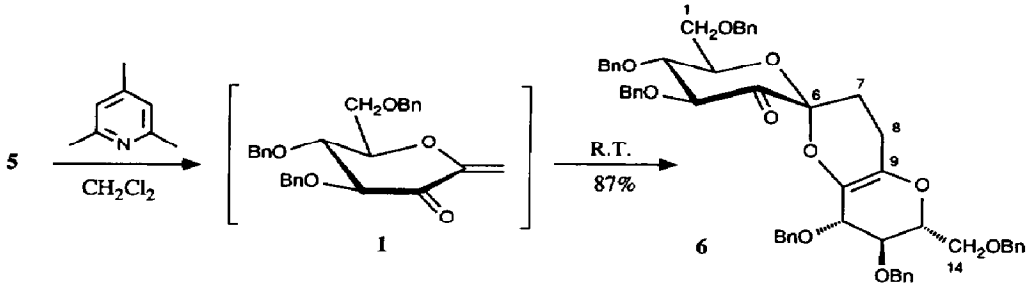


1

As it offers two possible approaches to **1** (by dehydrohalogenation, followed by oxidation, or by the reverse sequence), compound **3**, which we used previously in our *C*-disaccharide work [2], was selected as the starting material for our synthesis of **1**. This *C*-glycosyl compound is readily available in high yield from 2,3,5-tri-*O*-benzyl-D-arabinofuranose by way of two highly stereoselective processes described by Nicotra and co-workers [7], namely addition of divinyl zinc which leads to the D-*gluco*-1-heptenitol **2**, followed by the $Hg(OAc)_2$-promoted cyclization of **2**. Treatment, in situ, of the resulting organomercurial compound with iodine gave **3** in 60% overall yield from 2,3,5-tri-*O*-benzyl-D-arabinofuranose. As shown by its ^1H NMR parameters, compound **3** does not adopt the usual $^4C_1$ conformation: the small vicinal coupling constants between ring-protons and the existence of $^4J_{H,H}$ couplings indicate that the alternate $^1C_4$ conformation is the preponderant form in the conformational equilibrium of **3**.



Dehydrohalogenation of **3** using DBU afforded the expected enol ether **4** in high yield (92%). All attempts to oxidize the allylic alcohol function in **4** were unsuccessful, leading either to the recovery or to the degradation of the starting material. The alternative oxidation–elimination approach to **1** was then investigated. Oxidation of **3** using PCC gave the corresponding 2-keto derivative **5** in good yield (84%); compound **5** thus obtained was contaminated by ~15% of a byproduct, later found to be identical to the dimer of **1**. With the expectation of generating **1**, compound **5** was treated with *s*-collidine in CH_2Cl_2 at room temperature. After 30 min, the reaction was complete, with a single product being formed (87% isolated yield). As described below, this product was identified as the dimer of **1**, compound **6**, resulting from a formal [4+2] cycloaddition with the enone function of one of the two units acting as heterodiene (enone cyclodimerization [8]). Remarkably, compound **1** was never observed and thus must dimerize spontaneously as soon as it is formed.



The dimeric structure of **6** was readily established from its mass spectrum and from its ^1H and ^{13}C NMR spectra which exhibit the signals of two nonequivalent pyranoid residues. Further evidence for the proposed structure was provided by the values of the $J_{H,H}$ coupling constants (Fig. 1), and in particular by the existence of $^5J_{H,H}$ couplings across the C_9–C_{10} double bond between H-8A,8B and H-11.

The anomeric configuration of the 2-ketopyranose unit in **6** (i.e., the configuration at C-6) was established on the basis of NOE experiments (360 MHz instrument, in $CDCl_3$), whereby irradiation of H-2 promoted the expected, significant enhancement of its syn-diaxial neighbor H-4 (8%) and only a negligible effect on H-7eq ($\sim$1%); irradiation of H-7eq had no effect on the signals of H-2 and H-4. These observations are consistent with the α configuration at C-6 (protons at C-7 remote from H-2 and H-4). In the β anomer of **6** (structure **7**), the C-7 methylene group would be axial, and H-7eq would be located in close proximity to H-2 and H-4. In the most favorable conformation of (debenzylated) **7** (MMX), the proton H-2 is found to be actually closer to H-7eq (2.2 Å) than it is to its syn-diaxial neighbor H-4 (2.7 Å), and thus an important NOE effect would be expected between these two protons. Both kinetic and thermodynamic factors actually favor the α anomer **6** over **7**: the *endo*-transition state leading to **7** is more crowded than that leading to **6** (because of interactions between the substituents of the two pyranoid units), and the α anomer is

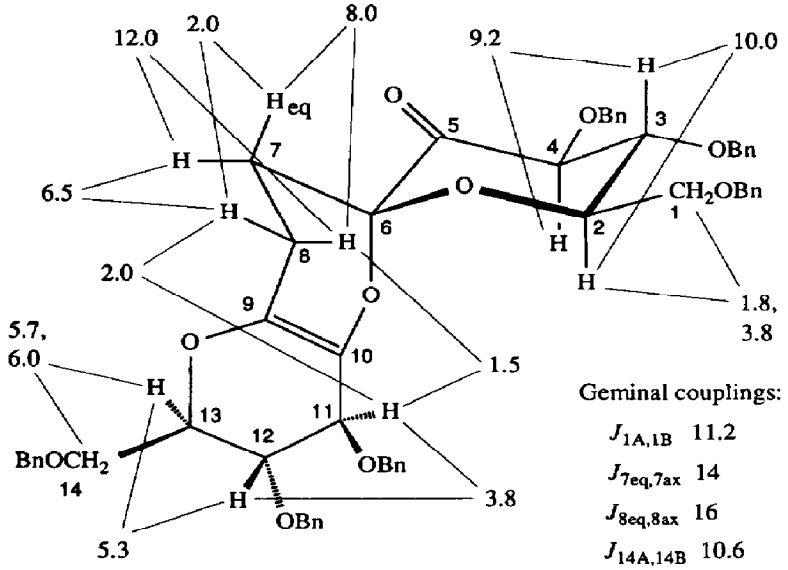
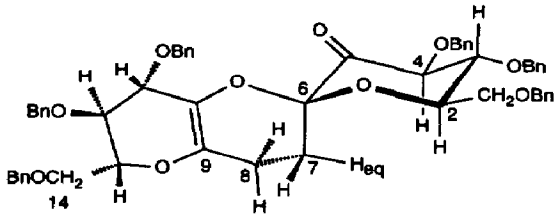


Fig. 1. The proposed dimeric structure of **6** and its $J_{H,H}$ coupling constants.

more stable for both steric (equatorial C_6–C_7 bond) and electronic reasons (axial C_6–O bond).



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The spontaneous dimerization of **1** is surprising as simple α-alkoxyenones such as 3-methoxy-3-butene-2-one (**8**) are much less reactive towards dienes than the corresponding unsubstituted enones [9–11]. For example, the cycloaddition of **8** with cyclopentadiene requires very high temperatures, and the yield is modest [10,11]. This decreased reactivity is consistent with the rise of the HOMO and the LUMO levels of the enone promoted by the addition of the α-alkoxy substituent [12]; the HOMO level is affected, however, much more significantly than the LUMO level, thus reducing the energy gap between these levels and making the α-alkoxyenones more likely to undergo cyclodimerization (by way of a "neutral" Diels–Alder reaction [13]) than simple enones [8]. Nevertheless, spontaneous dimerization of α-alkoxyenones has been rarely observed. While compounds such as **8** are rather unstable in pure form at room temperature or below [10,14,15], they appear to degrade primarily by polymerization; an exception is 3-trimethylsilyloxy-3-buten-2-one which cyclodimerizes to the corresponding dihydropyran on prolonged standing at room temperature (or in 4 h at 100°C) [16]. This compound is however sufficiently stable to participate in a cycloaddition with cyclopentadiene (at 160°C for 48 h). Compound **1** is thus unusually sensitive to dimerization, and a number of factors must contribute to this behavior: steric effects due to the pyranoid residue and its substituents which may preclude polymerization, inductive effects of the alkoxy substituents which alter the reactivity of the enone, etc. Furthermore, the possibility of a nonconcerted mechanism, by way of a zwitterionic intermediate, cannot be excluded. Further work is needed to elucidate the origin of the remarkable reactivity of **1**.

Compound **6** is interesting in that it contains a continuous, C_{14}-chain and thus constitutes a derivative of a tetradecodiulose. Further elaboration of **6** should lead to ethylene-bridged disaccharide analogues, a novel class of pseudodisaccharides.

1. Experimental

General methods.—See Ref [17]. The ^1H and ^{13}C NMR spectra were recorded, respectively, at 360 and at 90 MHz on a Bruker AM 360 spectrometer. Chromatographic separations were achieved by flash chromatography using Silica Gel 60 (230-400 mesh) and one of the following solvent systems (v/v): *A*, 8:1; *B*, 5:1; *C*, 3:1 hexanes–EtOAc.

*2,6-Anhydro-1,3,4-tri-O-benzyl-7-deoxy-7-iodo-*D-glycero-L-gulo-*heptitol* (**3**).—To a solution of 4,5,7-tri-*O*-benzyl-1,2-dideoxy-D-*gluco*-1-heptenitol (**2**) [7] (2.35 g, 5.23

mmol) in anhydr THF (100 mL) was added $Hg(OAc)_2$ (2.52 g, 7.9 mmol). The mixture was stirred for 72 h under N_2 in the dark at room temperature, then cooled to 0°C. A solution of I_2 (6.6 g, 26.2 mmol) in THF (100 mL) was added and the mixture was stirred for 15 h at room temperature. The volume of the solution was then reduced to ~20 mL by evaporation under reduced pressure. Ether (200 mL) was added and the solution was washed successively with 5 M aq $Na_2S_2O_3$ (10×70 mL), satd aq $NaHCO_3$ (70 mL) and water (70 mL), dried (Na_2SO_4), and concentrated. The residue was submitted to flash chromatography (solvent *A*) which afforded pure **3** (1.90 g, 62%) as a syrup; $[\alpha]_D^{25}$ +26.6° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$; overlapping signals resolved by 1D-TOCSY experiments): δ 3.11 (d, 1 H, $J_{5,OH}$ 9.2 Hz, 5-OH), 3.28 (dd, 1 H, $J_{6,7A}$ 8.8, $J_{7A,7B}$ 10.5 Hz, H-7A), 3.39 (dd, 1 H, $J_{6,7B}$ 5.8 Hz, H-7B), 3.62 (t, 1 H, $J_{2,3}$ 4.0, $J_{3,4}$ 4.5, $J_{3,5}$ 0.9 Hz, H-3), 3.72 (dd, 1 H, $J_{1A,2}$ 5.8, $J_{1A,1B}$ 10.3 Hz, H-1A), 3.74 (occluded t, 1 H, $J_{2,4}$ 0.7, $J_{4,5}$ 5.0 Hz, H-4), 3.83 (occl. ddd, 1 H, $J_{5,6}$ 2.5 Hz, H-5), 3.83 (dd, 1 H, $J_{1B,2}$ 6.0 Hz, H-1 B), 4.01 (ddd, 1 H, H-6), 4.10 (br dt, 1 H, H-2), 4.50–4.61 (m, 6 H, 3 OCH_2Ph), 7.4–7.7 (m, 15 H, 3 Ph); ^{13}C NMR ($CDCl_3$; assignments verified by ^1H-^{13}C correlations): δ 3.71 (C-7), 67.64 (C-1), 68.32 (C-5), 71.76 (C-6), 72.46, 72.96, 73.19 (OCH_2Ph), 73.96 (C-3), 74.03 (C-2), 76.46 (C-4), 127.5–128.4 (Ar-CH's), 137.04, 137.51, 137.92 (Ar-C's). Anal. Calcd for $C_{28}H_{31}IO_5$: C, 58.54; H, 5.44; I, 22.09. Found: C, 58.40; H, 5.41; I, 22.18.

2,6-Anhydro-4,5,7-tri-O-*benzyl-1-deoxy*-D-gluco-*1-heptenitol* (**4**).—A solution of **3** (810 mg, 1.41 mmol) and DBU (1 mL) in toluene (10 mL) was heated at 90°C for 2 h. The cooled mixture was diluted with EtOAc (20 mL), and the solution was washed with water (10 mL), dried (Na_2SO_4), and concentrated. The residue was submitted to flash chromatography (solvent *B*, then *C*) which afforded crystalline **4** (540 mg, 86%); mp 105.5–106.5°C; $[\alpha]_D^{22}$ +6.4° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.38 (d, 1 H, $J_{3,OH}$ 4.1 Hz, 3-OH), 3.50 (t, 1 H, $J_{3,4}$ 8.9, $J_{4,5}$ 8.7 Hz, H-4), 3.60 (td, 1 H, $J_{5,6}$ 9.5, $J_{6,7}$ 2.9 Hz, H-6), 3.77 (d, 2 H, 2 H-7), 3.82 (dd, 1 H, H-5), 4.105 (dd, 1 H, $J_{1A,3} \cong J_{1B,3} = 1.9$ Hz, H-3), 4.70 (narrow dd, 1 H, $J_{1A,1B}$ 1.0 Hz, H-1A), 4.73 (narrow dd, 1 H, H-1B), 4.54 (d, 1 H, J_{AB} 12.1 Hz) and 4.66 (d, 1 H), 4.57 (d, 1 H, J_{AB} 10.9 Hz) and 4.81 (d, 1 H), 4.79 (d, 1 H, J_{AB} 11.4 Hz) and 4.915 (d, 1 H) (3 OCH_AH_BPh), 7.16–7.37 (m, 15 H, 3 Ph); ^{13}C NMR ($CDCl_3$): δ 68.57 (C-7), 73.59, 74.67, 75.00 (3 OCH_2Ph), 71.07, 77.39, 79.62, 85.49, 93.96 (C-1), 127.69–128.59 (Ar-CH's), 137.89, 137.93, 138.32 (Ar-C's), 158.31 (C-2). Anal. Calcd for $C_{28}H_{30}O_5$: C, 75.31; H, 6.77. Found: C, 75.22; H, 6.81.

2,6-Anhydro-4,5,7-tri-O-*benzyl-1-deoxy-1-iodo*-D-manno-*hept-3-ulose* (**5**).—A solution of **3** (200 mg, 0.35 mmol) in anhyd CH_2Cl_2 (1 mL) was added to a mixture of PCC (350 mg, 1.6 mmol) and powdered 3A molecular sieves (1.5 g) in CH_2Cl_2 (8 mL). The mixture was stirred for 3 h at room temperature, and ether (20 mL) was then added. The solids and the salts were removed by filtration through a short column of silica gel. Concentration of the filtrate afforded **5** (167 mg, ~84%) contaminated by ~15% of dimer **6**; compound **5** could not be separated from **6** by flash chromatography (solvent *A*; yield of mixture: 120 mg, ~60%). Compound **5**: ^1H NMR ($CDCl_3$): δ 3.32 (dd, 1 H, $J_{1A,2}$ 4.3, $J_{1A,1B}$ 10.7 Hz, H-1A), 3.41 (dd, 1 H, $J_{1B,2}$ 6.0 Hz, H-1B), 3.54 (dd, 1 H, $J_{6,7A}$ 3.7, $J_{7A,7B}$ 10.7 Hz, H-7A), 3.70 (dd, 1 H, $J_{6,7B}$ 2.5 Hz, H-7B), 4.01 (dd, 1 H, $J_{4,5}$ 9.4, $J_{5,6}$ 7.0 Hz, H-5), 4.08 (ddd, 1 H, H-6), 4.36 (br dd, 1 H, H-2), 4.55 (dd, 1 H, $J_{2,4}$ 0.7 Hz, H-4), 4.36 (d, 1 H, J_{AB} 12.0 Hz) and 4.47 (d, 1 H), 4.52 (d, 1 H, J_{AB} 11.4 Hz) and 4.85 (d, 1 H), 4.67 (d, 1 H, J_{AB} 11.5 Hz) and 5.00 (d, 1 H) (3 OCH_AH_BPh), 7.2–7.45 (m, 15 H, 3 Ph).

*6,10; 9,13-Dianhydro-1,3,4,11,12,14-hexa-*O*-benzyl-9,10-didehydro-7,8-dideoxy-*D-erythro-*α*-L-gulo-*tetradeco-5,6-diulo-2,6-pyranose* (**6**).——To a solution of **5** (100 mg, containing ~15% **6**) in CH_2Cl_2 (5 mL) was added *s*-collidine (excess); the solution rapidly turned yellow. After 20 min at room temperature, CH_2Cl_2 (20 mL) was added; the solution was washed with water (3×10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (solvent *B*) of the residue afforded homogeneous **6** (65 mg, 84%) as a syrup; $[\alpha]_D^{22}$ +2.1° (*c* 1.1, $CHCl_3$); IR: ν 1751 cm^{-1} (C=O); ^1H NMR ($CDCl_3$; $J_{H,H}$ given in Fig. 1): δ 2.04 (distorted ddd, 1 H, H-7eq), 2.09 (distorted ddd, 1 H, H-7ax), 2.21 (ddt, 1 H, H-8eq), 2.41 (dddd, 1 H, H-8ax), 3.575 (dd, 1 H, H-1A), 3.65 (dd, 1 H, H-14A), 3.70 (dd, 1 H, H-14B), 3.71 (dd, 1 H, H-1B), 3.875 (dd, 1 H, H-12), 3.99 (t, 1 H, H-3), 4.00 (br m, 1 H, H-11), 4.32 (br q, 1 H, H-13), 4.35 (ddd, 1 H, H-2), 4.72 (d, 1 H, H-4), 4.435 (narrow AB, 2 H), 4.46 (s, 2 H), 4.41 and 4.55 (2d, 2 H), 4.56 and 4.94 (2d, 2 H), 4.575 and 4.95 (2d, 2 H), 4.605 and 4.67 (2d, 2 H) (6 OCH_AH_BPh), 7.05–7.5 (m, 30 H, 6 Ph); ^{13}C NMR ($CDCl_3$): δ 19.68, 24.34 (C-7,8), 67.89, 68.17 (C-1, 14), 72.53, 72.78, 73.02, 73.27 (2C), 74.93 (6 OCH_2Ph), 71.43, 73.68, 74.27, 75.82, 80.58, 84.09, 96.45 (C-6), 126.48, 135.29 (C-9,10), 127.49–128.44 (Ar-CH's), 137.57, 137.74 (2C), 138.04, 138.11, 138.29 (6 Ar-C's), 197.76 (C-5); CIMS: *m/z* 906 (100%, $[M+NH_4]^+$). HRFABMS: calcd for $C_{56}H_{56}O_{10}$: 888.3873; found: 888.3836.

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