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Synthesis of strained glycophanes from D-glucal by oxidative homocoupling of propargyl ethers

Touria Belghiti,[a] Jean-Pierre Joly,[a,*] Claude Didierjean,[b] Slimane Dahaoui[b] and Yves Chapleur[a]

[a]*Groupe SUCRES, UMR 7565 CNRS, Université Henri Poincaré-Nancy I, BP 239, F-54506 Vandœuvre, France*
[b]*LCM3B, UMR 7036 CNRS, Université Henri Poincaré-Nancy I, BP 239, F-54506 Vandœuvre, France*

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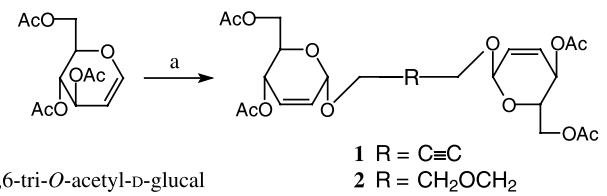
Abstract—A facile synthesis of electron-rich cage molecules based on the Ferrier allylic rearrangement of D-glucal followed by Glaser oxidative homocoupling of bridged disaccharides afforded two new 22- and 23-membered ring systems, which could be characterized by X-ray diffraction.

In this letter, we want to report some preliminary results on the synthesis of symmetric propargylic ethers en route to cage-like molecules endowed with electron-rich cavities.[1] The oxidative coupling of terminal acetylenes to the corresponding α-diacetylenes, first discovered by Carl Glaser around 1869,[2] has been widely used for the design of macrocyclic compounds,[3] synthetic receptors,[4] and catenates.[5] The first step of our strategy was based on a Ferrier rearrangement[6] of D-glucal, which afforded the glycoside dimers **1** and **2** in good yields (Scheme 1).



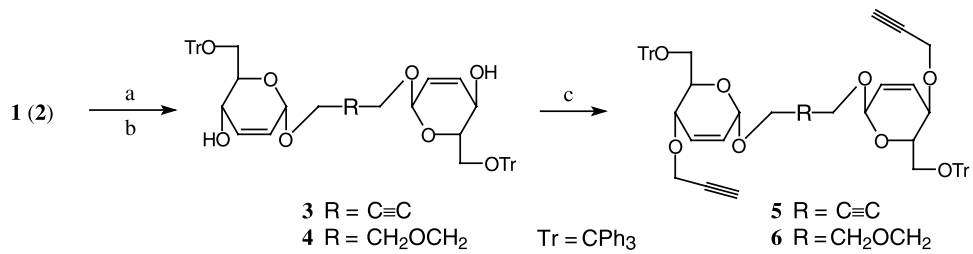
3,4,6-tri-*O*-acetyl-D-glucal

Scheme 1. *Reagents and conditions*: (a) $HOCH_2$-R-CH_2OH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 18°C; yields: **1** (86%), **2** (60%).

The boron trifluoride-catalyzed allylic rerrangements of tri-*O*-acetyl-D-glucal in dry dichloromethane at room temperature led almost exclusively to α-anomers ($J_{1-2} \leq 2$ Hz). These symmetric precursors were then deacetylated, protected as their trityl ethers (via diols **3** and **4**), and then easily transformed under phase-transfer conditions[7] into the corresponding symmetric propargylic ethers **5** and **6** (Scheme 2).

The copper-catalyzed oxidative homocoupling of bis-acetylenes **5** and **6** yielded diynes **7** and **8** via exclusive intramolecular cyclization (Scheme 3).

Under high dilution conditions, larger cyclic dimers could neither be observed by TLC nor isolated by liquid chromatography. Due to their C_2-symmetry, ^1H and ^{13}C spectra of glycophanes **7** and **8** displayed a



Scheme 2. *Reagents and conditions*: (a) MeONa, MeOH, rt; (b) TrCl, Pyr.; (c) $BrCH_2$–C≡CH, aq. NaOH, NBu_4HSO_4, C_6H_6, rt; yields: **5** (86% over three steps), **6** (73% over three steps).

* Corresponding author.

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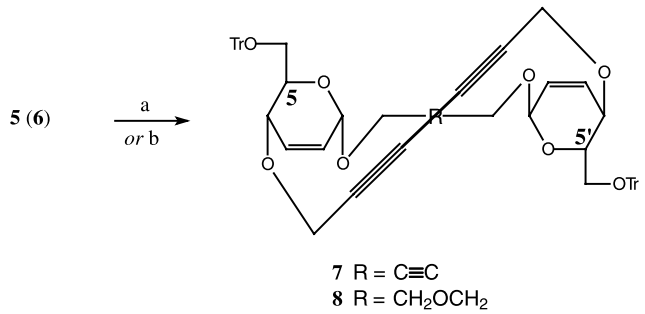

Scheme 3. *Reagents and conditions*: (a) $Cu(OAc)_2 \cdot H_2O$, MeCN/Pyr., 3:1, 50°C, 2 h, yield **7** (47%); (b) CuI, O_2, Pyr., 25°C, 3 h, yield **8** (24%).

single set of signals for both their saccharidic and half of their aglycon parts.[8]

Slow evaporation of saturated solution (CH_2Cl_2/*n*-hexane or $CHCl_3$/*n*-hexane) furnished stable monocrystals of **7** and **8** suitable for X-ray diffraction (Table 1 and Fig. 1), two asymmetric units being associated with one solvent molecule.[9]

In both cases, the electron-rich cavity is obviously of limited size; for instance, the largest distance between C-5 and C′-5 is about 6 Å in **7** and 7 Å in **8**. After deducing the van der Waals radius, the macrocycles exhibit cavity sizes of ca. 3.0×1.9 and 4.0×2.0 Å, respectively, in the solid state.

Table 1. Crystallographic data for compounds **7** and **8**

Compound	**7**	**8**
Empirical formulae	$C_{60}H_{52}O_8/CH_2Cl_2$	$C_{60}H_{56}O_9/CHCl_3$
Formula weight	901.06/84.93	921.09/119.37
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12$	$P2_12_12$
a (Å)	14.911(4)	14.989(3)
b (Å)	20.253(6)	20.479(4)
c (Å)	8.775(1)	8.955(2)
V (Å^3)	2 652.15	2 748.6
ρ	1.236	1.256

In summary, two new small cyclic monomers (**7** and **8**) were successfully synthesized and isolated in fair yields from D-glucal in only five steps. Suitable deprotected derivatives of **7** and **8** are currently under investigation for the complexation of cations as small guests.[10]

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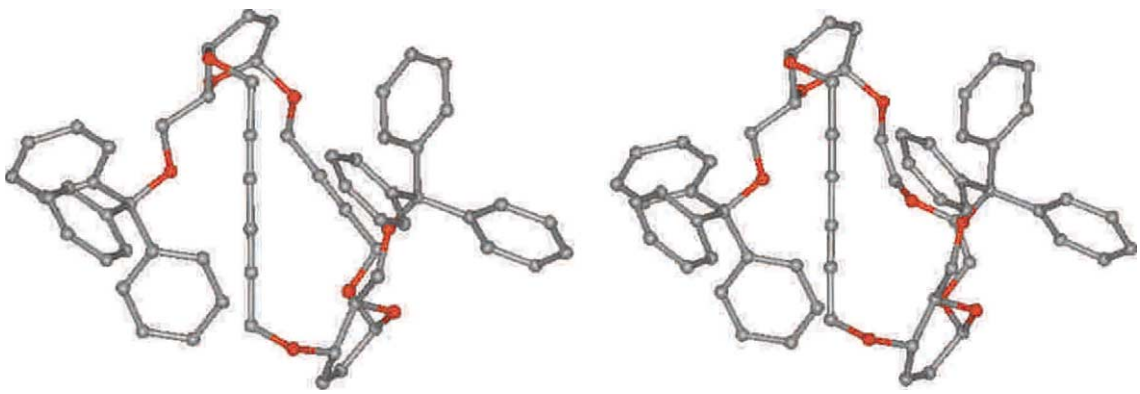

7 **8**

Figure 1. Ball-and-stick representations of the X-ray structures of **7** and **8** (solvents and hydrogen atoms are omitted for clarity).

8. *Spectroscopic data for* **7**: White crystals, mp (Tottoli) 206–207°C (*n*-hexane/CH_2Cl_2); R_f (SiO_2, EtOAc/*n*-hexane, 1:1) 0.7; $[\alpha]_D$ +101.3 (*c* 1.0, $CHCl_3$); IR *v* 2958, 2360 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 3.5 (d, 2H, J_{gem} 16.7, 2×OC*H*H), 3.54 (dd, 2H, J_{gem} 9.7, J_{5-6} 7.9, 2×H-6), 3.75 (dd, 2H, $J_{5-6'} \leq 2$, 2×H-6′), 3.78 (d, 2H, 2×OC*H*H), 3.9 (d, 2H, J_{gem} 13.4, 2×OCH*H*), 4.11 (dd, 2H, J_{3-4} 1.7, $J_{2-4} \leq 2$, $J_{4-5} \sim 8$, 2×H-4), 4.63 (d, 2H, J_{1-2} 2.6, 2×H-1), 5.04 (d, 2H, 2×OCH*H*), 5.23 (bt, 2H, 2×H-5), 5.36 (dd, 2H, J_{2-3} 10.2, 2×H-3), 5.69 (ddd, 2×H-2), 7.09 (t, 6H, Ar), 7.32 (t, 12H, Ar), 7.77 (bd, 12H, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 52.0 (O*C*H_2–C≡C on C-1), 55.0 (O*C*H_2–C≡C), 63.0 (C-6), 67.5 (C-5), 70.0 (OCH_2–C≡*C*), 72.0 (C-4), 76.0 (OCH_2–*C*≡C), 82.0 (OCH_2–*C*≡C on C-1), 86.0 (CPh_3), 92.0 (C-1), 126.7 (C-4 Ar), 127.7 (C-2), 128.8 (C-2, -6 Ar), 130.5 (C-3, -5 Ar), 131.0 (C-3), 144.0 (C-1 Ar); ES-MS: *m*/*z* 918 (55%) $[M+H_2O]^+$.

Spectroscopic data for ***8***: White crystals, mp (Tottoli) 185–186°C (*n*-hexane/$CHCl_3$); R_f (SiO_2, EtOAc/*n*-hexane, 1:1) 0.5; $[\alpha]_D$ −1.6 (*c* 1.7, $CHCl_3$); IR *v* 3063, 2922, 1727 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.3 (dd, 2H, J_{gem} 10, J_{5-6} 5, 2×H-6), 3.43 (d, 2H, $J_{5-6'}$ 3, 2×H-6′), 3.75 (m, 2H, 2×H-5), 3.88–4.05 (m, 8H, 2×OCH_2CH_2), 4.27 (dd, 4H, 2×OCH_2C≡C), 4.75 (m, 2H, 2×H-4), 5.1 (bs, 2H, 2×H-1), 5.84 (d, 2H, J_{2-3} 10, 2×H-2), 6.1 (m, 2H, 2×H-3), 7.21 (t, 6H, Ar), 7.32 (t, 12H, Ar), 7.52 (bd, 12H, Ar); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 52.7 (OCH_2), 63.4 (C-6), 67.7 (C-5), 68.6 (C-7), 70.1 (C≡*C*–C), 71.6 (CH_2–*C*≡C and OCH_2), 74.4 (C-4), 86.2 (CPh_3), 94.4 (C-1), 126.7 (C-4 Ar), 127.7 (C-2), 128.9 (C-2, -6 Ar), 130.5 (C-3, -5 Ar), 130.8 (C-3), 144.2 (C-1 Ar); MALDI-MS (2,5-dihydroxybenzoic acid matrix): *m*/*z* 959.5 (100%) $[M+K]^+$.

9. X-Ray data for glycophanes **7** and **8** have been deposited at the Cambridge Crystallographic Data Centre as supplementary material.

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