Polish J. Chem., **75**, 683–687 (2001)

Coupling of the C6 and C6′ Positions of Sucrose by Metathesis Reaction

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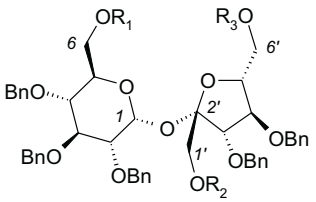
(Received December 18th, 2000)

1′,2,3,3′,4,4′-Hexa-*O*-benzylsucrose (**7**) was converted into diallyl ether **11** and subjected to metathesis reaction with the Grubbs' catalyst. The expected macrocyclic product (**12**) was obtained in a good yield as a *cis/trans* mixture of olefins, hydrogenation of which gave fully deprotected saturated compound **13**.

Key words: 1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose, metathesis reaction, sucrose macrocycles

Selective protection of the free hydroxy groups in sucrose is a big problem in transformation and utilization of this important disaccharide; only the primary ones can be easily differentiated from secondary groups by bulky ether forming reagents [1,2].

As a part of an ongoing program for conversion of sucrose into useful chiral synthons, we have elaborated a convenient synthesis of 2,3,4,3′,4′-penta-*O*-benzylsucrose (**1**, 50% overall from sucrose), in which all secondary hydroxy groups are protected as benzyl ethers, easily removable under neutral conditions [3]. We have also found, that primary functions in **1** may be rather easily distinguished, what allows the corresponding sucrose monoalcohols (**2**–**5**) to be prepared in good yields [4]. Very interesting from the synthetic point of view is the diol with the C6 and C6′ positions unprotected. In a free sucrose those positions are close to each other [5]; if this is also true for the partially protected compounds, the connection of these positions seems to be possible.

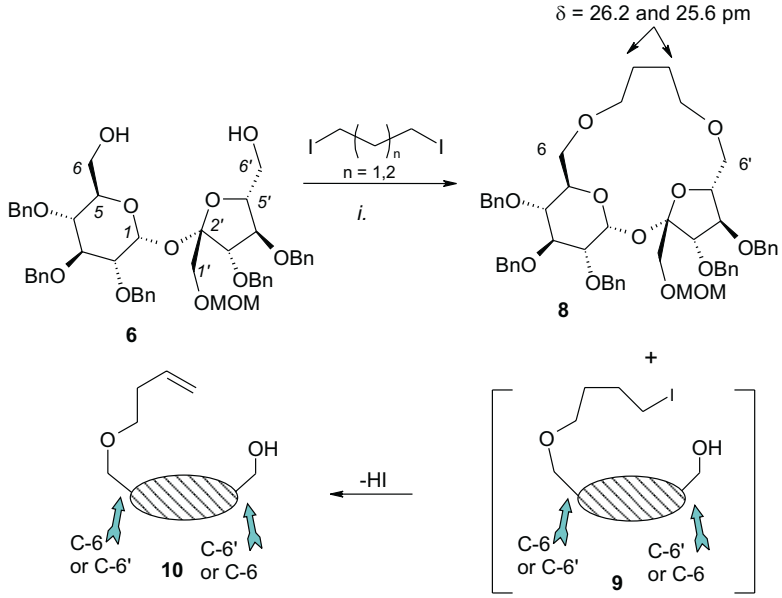


1. $R_1 = R_2 = R_3 = H$
2. $R_1 = H$, $R_2 =$ MOM $R_3 =$ TBDMS
3. $R_1 = H$, $R_2 =$ BOM, $R_3 =$ TBDPS
4. $R_1 = R_3 =$ C(O)Ar $R_2 = H$
5. $R_1 =$ TBDPS, $R_2 =$ BOM, $R_3 = H$
6. $R_1 = R_3 = H$ $R_2 =$ MOM
7. $R_1 = R_3 = H$ $R_2 =$ Bn

Recently we prepared such selectively protected sucrose derivatives – diols **6** (with the 1′-OH group protected as the MOM ether) [6] and **7** (with the benzyl protection at the C1′) [7]; their application for the synthesis of sugar macrocycles will be presented in this paper.

RESULTS AND DISCUSSION

To test how long should be the chain, which is able to connect both positions, we performed the model reaction, the Williamson's coupling of 1′-*O*-MOM-2,3,4,3′,4′-penta-*O*-benzyl-sucrose [6] (**6**) with 1,3-di-iodopropane and 1,4-di-iodobutane. The C_3 bridge was too short, but a C_4 unit was long enough to connect the C-6,6′-positions and the desired macrocycle **8** was obtained. The yield was, however, low and the product was contaminated with both monosubstituted (at C-6 or C-6′) olefinic derivatives **10** (resulting from elimination of the primary products **9**; Scheme 1).

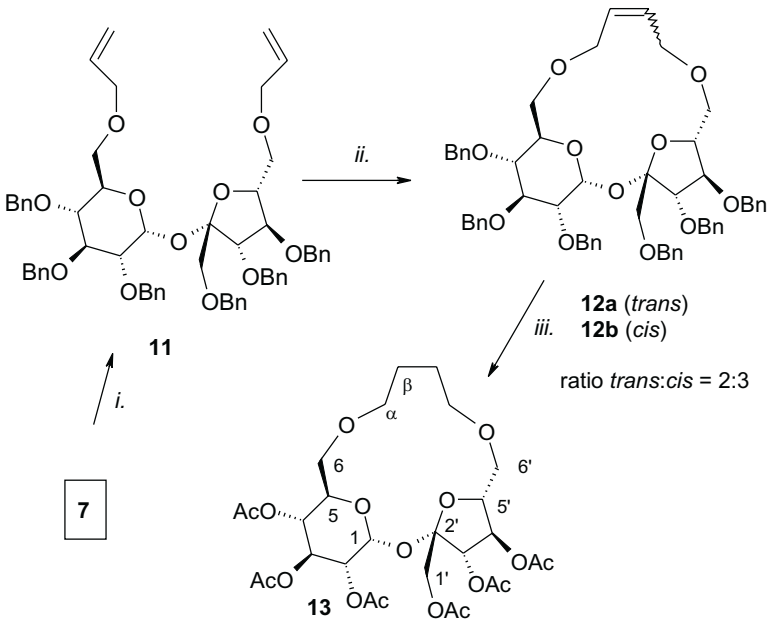


Scheme 1. *i*. NaH, THF, $ICH_2(CH_2)_nCH_2I$.

This result opened the possibility of connection the C6 and C6′ positions using the metathesis reaction. Although this process is known for a long time, its application to synthetic organic chemistry was noted only recently in the last decade [7].

Diol **7** [8] was converted into diallyl ether **11**, which was subjected to the metathesis conditions. Reaction of **11** in methylene chloride at room temperature in the presence of the Grubbs' catalyst [9] afforded both olefins: **12a** (*trans*) and **12b** (*cis*) in the ratio 2:3 in 78% overall yield. These compounds could be separated into pure isomers. The ^{1}H NMR spectra of the olefinic products were very complicated (even at 500 MHz), but allowed to assign the *trans* configuration to **12a** ($J_{olef.}$ = 16.1 Hz) and *cis*- to **12b** ($J_{olef.}$ = 12.1 Hz).

Reduction of the newly formed double bond with simultaneous deprotection of the sucrose backbone was conveniently performed under hydrogenation conditions; the free sucrose, in which the C6 and C6' positions were connected *via* a C4-bridge (Scheme 2), was obtained in a reasonable yield.



Scheme 2. *i*. NaH, DMF, AllBr; *ii*. Grubb's cat., CH_2Cl_2, rt, 2 days; *iii*. H_2/Pd, then Ac_2O, Py.

The coupling of sucrose "ends" *via* ring closing metathesis reaction is possible. Deprotection of the sucrose backbone in such products can be done conveniently by simple hydrogenation, although under these conditions the double bond is reduced.

EXPERIMENTAL

General. ^1H and ^{13}C NMR spectra were recorded with a Bruker AM 500 MHz spectrometer for solutions in $CDCl_3$ (internal Me_4Si). Most of the resonances were assigned by the ^1H-^1H and ^1H-^{13}C correlations and DEPT 135° experiments. Mass spectra (LSIMS; *m*-nitrobenzyl alcohol was used as a matrix to which sodium acetate was added or ESI) were recorded with an AMD-604 or PE SCIEX API 365. Optical rotations were measured with a Digital Jasco polarimeter DIP-360 for solutions in $CHCl_3$ (c = 1) at room temperature. Column chromatography was performed on silica gel (Merck, 70–230 or 230–400 mesh). HPLC separations were done on Shimadzu LC-8A liquid chromatograph equipped with a Shimadzu SPD-6A UV detector and Nucleosil 100-7 column (from Machery-Nagel), using hexanes – ethyl acetate, 4:1 as eluent. For chromatography purposes a fraction of mineral oil with boiling point in range of 70–90°C was used as a mixture of hexanes. All solutions were dried over anhydrous sodium sulfate. For numbering of atoms see Schemes 1 and 2.

2,3,3′,4,4′-Penta-*O*-benzyl-1′-*O*-methoxymethylene-6,6′-*O*-tetramethylenesucrose (8). To a stirred solution of diol **6** (250 mg, 0.3 mmol) in such amount of dry THF to achieve concentration ~0.01 M/L (30 mL), sodium hydride (60% dispersion in mineral oil; 50 mg, 1.2 mmol) was added followed by catalytic amounts of imidazole (~5 mg). The mixture was stirred under argon atmosphere at room temperature for 30 min and then di-*n*-butyl iodide (95 mg, 1.2 equiv., 0.36 mmol) was added and the mixture was stirred for another 2 h. Excess of hydride was decomposed by careful addition of water and the product(s) were extracted with ethyl acetate (3×15 mL). The organic layer was washed with brine, water, dried and concentrated leaving the crude product, which was homogeneous on TLC in a number of solvents. How-

ever, this product contained – besides the desired macrocycle – significant amounts of the olefinic product(s) **10** (δ_C 135.8 and 116.3 ppm CH=CH_2 grouping) resulting from elimination of HI from the monosubstituted derivatives **9**. In order to differentiate these compounds, the crude mixture was acetylated (Ac_2O, py) and the products: **8** and **10-Ac** [acetylated alcohol(s) **10**; both regioisomers were seen in the ^{13}C NMR spectrum: δ 116.4 and 116.3 $OCH_2CH_2CH=\underline{C}H_2$] were separated by column chromatography using hexanes – ethyl acetate, 8:1 to 3:1. Yield, 187 mg (21%). *m/z*: 914 [M($C_{53}H_{62}O_{12}$) + Na]. ^1H NMR δ: 5.38 (d, 1H, $J_{1,2}$ = 3.4 Hz, H1), 4.38 (d, 1H, $J_{3',4'}$ = 7.3 Hz, H3′), 4.31 (m, 1H, H5), 4.24 (dd, $J_{4'5'}$ = 7.4 Hz, H4′), 4.05 (m, 1H, H5′), 4.04 (dd, 1H, $J_{2,3}$ = 9.7, $J_{3,4}$ = 9.0 Hz, H3), 3.75 and 3.34 (AB of both H6, $J_{6,6}$ = 10.3, $J_{5,6}$ = 8.2 and 9.2), 3.70 and 3.58 (AB of both H1′, $J_{1',1'}$ = 11.3 Hz), 3.50 (dd, 1H, H2), 3.28 (s, 3H, OCH_3), 3.19 (dd, 1H, $J_{4,5}$ = 10.1 Hz, H4). ^{13}C NMR δ: 138.76, 138.66, 138.65, 138.20, 138.00 (5×quat. OBn), 103.7 (C2′), 95.6 ($O\underline{C}H_2OCH_3$), 90.1 (C1), 84.1 (C4′), 83.8 (C3′), 81.9 (C3), 80.0 (C2), 79.7 (C4 and C5′), 75.5, 74.8, 73.7, 72.8, 72.0, 71.3, 71.0, 70.7, 70.3, 68.6 (10 secondary C-atoms: 5×OBn, $O\underline{C}H_2CH_2CH_2\underline{C}H_2O$, C1′, C6, C6′), 70.8 (C5), 55.4 (OMe), 26.1, 25.6 ($OCH_2\underline{C}H_2\underline{C}H_2CH_2O$).

Reaction of diol 6 with diiodopropane. This reaction was performed analogously as that with diiodobutane; no macrocyclic compound was obtained; all crude product underwent acetylation.

6,6′-Di-*O*-allyl-1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose (11). A solution of diol **7** (908 mg, 1.0 mmol) in DMF (10 mL) was added slowly to a slurry of NaH (50% dispersion in mineral oil; 150 mg, 3.0 mmol) in DMF (15 mL) containing catalytic amounts of imidazole (~10 mg). The mixture was stirred with exclusion of moisture for 30 min., allyl bromide (0.43 mL, 4.8 mmol) was added dropwise and the mixture was stirred for another 30 min. The excess of hydride was decomposed carefully with water, the mixture was partitioned between water and ether, the organic phase was separated, washed with water, dried and concentrated and the product isolated by column chromatography using hexanes – ethyl acetate, 4:1. Yield, 720 mg (75%). *m/z*: 985 [M($C_{60}H_{66}O_{11}$) + Na]. $[\alpha]_D$ = +29.9°. ^{13}C NMR δ: 138.8, 138.6, 138.2, 138.13, 138.09, 137.8 (6×C, quaternary signals of Bn), 134.6 (2×), 117.1, 116.8 (both allyl groups), 104.5 (C-2′), 90.0 (C-1), 83.9, 82.5, 81.8, 79.69, 79.59, 77.5 (6×CH), 75.4, 74.8, 73.4, 72.9, 72.4, 72.3, 72,1 (double intensity), 71.4, 71.0 (10×CH_2 6×$\underline{C}H_2$Ph, C-6′, 2×$O\underline{C}H_2CH=CH_2$), 70.4 (CH), 68.3 (CH_2) ppm. 29.7.

Metathesis reaction of 11. Compound **11** (500 mg, 0.52 mmol) was dissolved in dry methylene chloride and stirred at room temperature with the Grubbs' catalyst (50 mg) under an argon atmosphere. After 2 days the conversion of **11** into the less polar products was complete and the mixture of olefins **12** (390 mg, 0.41 mmol, 78%) were isolated by column chromatography using hexanes – ethyl acetate, 5:1 to 3:1. The isomers were separated into pure individuals by preparative HPLC (*trans/cis* ratio according to HPLC = 2:3).

1′,2,3,3′,4,4′-Hexa-*O*-benzyl-6,6′-*O*-[1,4-but-2(*E*)-ene] *(trans*-12a); ^1H NMR δ (*inter alia*): 5.70–5.58 (m, 2H, both olefinic protons, $J_{olef.}$ 16.1 Hz), 5.37 (d, 1H, $J_{1,2}$ 3.9 Hz, H-1); ^{13}C NMR δ: 138.6, 138.4, 138.2, 138.1, 138.0, 137.9 (6×quat. benzyl), 133.4 and 131.9 (both olefinic C), 104.2 (C-2′), 89.4 (C-1), 83.8, 83.5, 82.4, 79.6, 78.8, 78.1, 70.6 (7×CH), 75.4, 74.8, 73.6, 73.2, 72.35, 72.32, 71.6, 70.3, 70.2, 68.9, 63.9 (11×CH_2) ppm. *m/z*: 957 [$C_{58}H_{62}O_{11}$ = (M + Na^+)].

1′,2,3,3′,4,4′-Hexa-*O*-benzyl-6,6′-*O*-[1,4-but-2(*Z*)-ene] (*cis*-12a); ^1H NMR δ (*inter alia*): 5.90–5.77 (m, 2H, both olefinic protons, $J_{olef.}$ 12.1 Hz), 5.50 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1); ^{13}C NMR δ: 138.5 (2×), 138.2, 138.1, 138.0, 137.9 (6×quat. benzyl), 134.2 and 131.8 (both olefinic C), 104.6 (C-2′), 90.6 (C-1), 83.6, 83.4, 81.8, 80.3, 80.0, 79.3, 71.8 (7×CH), 75.5, 74.9, 73.6, 73.2, 72.6, 72.1, 70.9 (2×), 68.9, 66.8, 66.0 (11×CH_2) ppm. *m/z*: 957 [$C_{58}H_{62}O_{11}$ = (M + Na^+)].

1′,2,3,3′,4,4′-Hexa-*O*-acetyl-6,6′-*O*-tetramethylenesucrose (13). A mixture of *trans-cis* olefins (**12a/b**, 380 mg, 0.40 mmol) was dissolved in ethyl acetate (3 mL), ethanol (10 mL) and water (0.25 mL). Catalytic amounts of 10% Pd/C (40 mg) were added, and the mixture was stirred under hydrogen atmosphere for 2 days. Solvents were removed in vacuum and the residue suspended in pyridine (8 mL) to which acetic anhydride (2 mL) was added followed by dimethylamino-pyridine (*ca* 10 mg). After 2 h at room temperature, the mixture was concentrated and the product isolated by column chromatography (hexane – ethyl acetate, 1: to 1:2) to afford **13** as white amorphous solid (98 mg, 0.15 mmol, 37%). HRMS: *m/z* 671.2172 [calcd. for $C_{28}H_{40}O_{17}Na$ (M + Na): 671.2158]; $[\alpha]_D$ 42.1°. ^1H NMR δ: 5.57 (~t, 1H, $J_{2',3'}$ = $J_{3',4'}$ 6.4 Hz, H-4′), 5.53 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 5.43 (dd, 1H, $J_{2,3}$ 10.3, $J_{3,4}$ 9.7 Hz, H-3), 4.86 (dd, 1H, $J_{4,5}$ 10.2 Hz, H-4), 4.85 (dd, 1H, H-2), 4.34 (m, 1H, H-5), 4.16 (m, 1H, H-5′), 4.15–4.03 (AB quartet of both H1′, J_{AB} 12.0 Hz), 3.89 (dd, 1H, $J_{5'6'}$ 6.2, $J_{6'6'}$ 10.0 Hz, one of H-6′), 3.64 (dd, 1H, $J_{5'6'}$ 6.7 Hz, second H-6′), 3.56 (m, 3H, 3×Hα), 3.46 (m, 3H, 1×Hα + both H-6), 2.22, 2.103, 2.099, 2.093, 2.08, 2.06, 2.00 (6×s, 6×OAc), 1.70 (m, 4H, 4×Hβ). ^{13}C NMR δ: 170.18, 170.14, 170.06, 169.95, 169.88, and 169.70

(6×*C*OCH$_3$), 103.1 (C-2′), 89.5 (C-1), 79.5 (C-5′), 76.5 (C-3′), 75.7 (C-4′), 71.3 and 70.7 (both Cα), 70.5 (C-2), 70.3 (C-6), 69.95 (C-4), 69.91 (C-6′), 69.7 (C-3), 69.4 (C-5), 63.1 (C-1′), 26.4 and 25.1 (both Cβ), 20.83, 20.66, 20.60, 20.58, 20.54, 20.53 (6×CO*C*H$_3$).

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