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Synthesis of an α-C-Galactoside of a Carbasugar: A New Class of Disaccharide Mimics.

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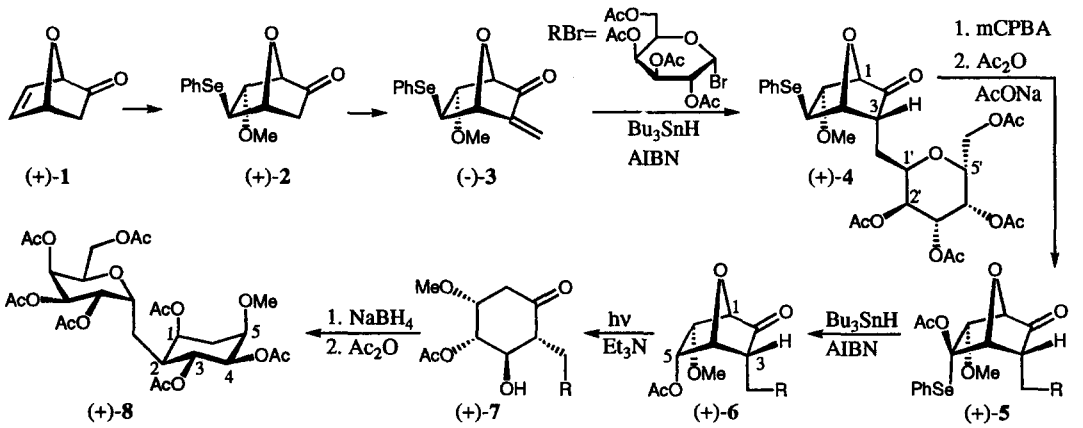
Abstract: (+)-(1*S*,2*S*,3*R*,4*R*,5*R*)-2-[(2',3',4',6'-tetra-O-acetyl-α-D-galactopyranosyl)methyl]-5-methoxycyclohexa-1,3,4-triyl triacetate was derived from D-galactose and (1*R*,4*R*)-7-oxabicyclo[2.2.1]-hept-5-en-2-one.

Several antibiotics and compounds of biological interest incorporate glycosides of cyclohexanepolyols.[1] Some cyclohexanepolyols have been called pseudo-sugars[2] or carba-sugars.[3] The replacements of the interglycosidic oxygen atom in a glycoside by a methylene moiety generate the corresponding deoxy-(glycosylmethyl) analogue which may imitate the physical[4] and biological properties of the O-glycoside but should be inert towards acidic and enzymatic hydrolysis. We report here the synthesis of an α-C-galactoside of a cyclohexanetetrol derivative which can be seen as an α-C-galactoside of a carbapentopyranose, a new class of disaccharide mimics.[5]



The "naked sugar" (+)-**1**[6] reacted with PhSeCl in MeOH to give (+)-**2**.[7] Treatment of the lithium enolate of (+)-**2** (LiHMDS, THF, -60°C) with the Eschenmoser's salt (CH_2=NMe_2I) afforded enone (-)-**3** (75%). Radical glycosidation of (-)-**3** with acetobromogalactose[4b] gave the 3-*endo*-(α-D-galactopyranosyl)methyl derivative (+)-**4** (74%). Oxidation of selenide (+)-**4** with mCPBA (one equivalent, -78°C, THF), followed by treatment with Ac_2O/AcONa led to a seleno-Pummerer rearrangement[8] with formation of (+)-**5** (82%). Deselenation of (+)-**5** with Bu_3SnH (AIBN, PhH, 80°C) gave (+)-**6** (97%). As for reaction (-)-**3** → (+)-**4**, quenching of the intermediate bicyclic radical was *exo* face selective.[9] Irradiation of (+)-**6** in isopropanol in the presence of 5 equivalents of Et_3N (254 nm, quartz vessel, 20°C)[10] led to a mixture from which (+)-**7** was isolated in 28% yield, together with 67% of unreacted (+)-**6**. Reduction of ketone (+)-**7** with $NaBH_4$/MeOH,

followed by esterification with Ac_2O/pyridine/DMAP (20°C, 14 h) provided (+)-**8** (46%), the ^{1}H-NMR characteristics (COSY-DQF, NOESY) of which were consistent with the conformation shown.[11]

Compound (+)-**7** is the polyacetate of the dicarba-analogue of O-α-D-galactopyranosyl-(1→4)-α-L--(methyl xylopyranurono-5,1-lactone) and (+)-**8** can be seen as polyacetate of the dicarba-analogue of O-α-D--galactopyranosyl-(1→2)-α-D-(xylopentodialdo-1,5-pyranose-6-α-methyl acetal) or of O-α-D-galactopyranosyl-(1→2)-α-L-(methyl xylopentodialdo-1,5-pyranoside). We plan to apply the method disclosed here to the synthesis of other C-glycosides[9] of cyclohexanepolyols and aminocyclohexanepolyols.[12]

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[1] See e.g.: Higton, A. A.; Roberts, A. D. "Dictionary of Antibiotics and Related Substances", Bycroft, B. W. Ed.; Chapman & Hall, London, 1988; Suami, T. in "Carbohydrates-Synthetic Methods and Applications in Medicinal Chemistry", Ogura, H.; Hasegawa, A.; Suami, T. Eds., Kodansha Ltd. & VCH, Tokyo, 1992; Bach, G.; Breiding-Mack, S.; Grabley, S.; Hammann, P.; Hütter, K.; Thiericke, R.; Uhr, H.; Wink, J.; Zeeck, A. *Liebigs Ann. Chem.* **1993**, 241.

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[4] See e.g. the C-disaccharide conformations: a) Kishi, Y. *Pure Appl. Chem.* **1993**, *65*, 771; Wei, A.; Kishi, Y. *J. Org. Chem.* **1994**, *59*, 88; b) Ferritto, R.; Vogel, P. *Tetrahedron: Asymmetry* **1994**, *5*, 2077.

[5] For other sugar mimics, see e.g.: Johnson, C. R.; Miller, M. W.; Golebiowski, A.; Sundram, H.; Ksebati, M. B. *Tetrahedron Lett.* **1994**, *35*, 8991 and ref. cited therein.

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[10] Cossy, J.; Adinou, P.; Bellosta, V.; Furet, N.; Baranne-Lafont, J.; Sparfel, D.; Souchaud, C. *Tetrahedron Lett.* **1991**, *32*, 1315.

[11] Data of (-)-**3**: oil, $[\alpha]_D^{25}$ = -0.9 (c=2, $CHCl_3$); (+)-**4**: oil, $[\alpha]_D^{25}$ = 51 (c=2, $CHCl_3$); (+)-**5**: oil, $[\alpha]_D^{25}$ = 24 (c=1, $CHCl_3$); (+)-**6**: oil, $[\alpha]_D^{25}$ = 41 (c=1.2, $CHCl_3$), ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 5.39 (t, ^3J = 3.0, H-C(4')), 5.23 (dd, ^3J = 7.7, 3.8, H-C(2')), 5.19 (dd, ^3J = 7.7, 3.0, H-C(3')), 5.10 (dd, ^3J = 7.8, 4.9, H-C(5)), 4.91 (t, ^3J = 4.9, H-C(4)), 4.60 (d, ^3J = 5.6, H-C(1)), 4.38 (m, H-C(1'), H-C(6')), 4.20 (m, H-C(5')), 4.12 (dd, ^2J = 11.7, ^3J = 4.3), 4.06 (dd, ^3J = 5.6, 7.8, H-C(6)), 3.34 (s, MeO), 2.80 (m, H-C(3)), 2.0-2.15 (2m, CH_2-C(3)), 2.12, 2.11, 2.10, 2.07, 2.06 (5s, 5 AcO); (+)-**7**: oil, $[\alpha]_D^{25}$ = 46 (c=1, $CHCl_3$); (+)-**8**: oil, $[\alpha]_D^{25}$ = 49 (c=0.6, $CHCl_3$), ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 5.43 (t, ^3J = 9.1, H-C(3)), 5.40 (t, ^3J = 3.0, H-C(4')), 5.16 (dd, ^3J = 8.9, 4.7, H-C(2')), 5.17 (m, H-C(1)), 5.12 (dd, ^3J = 8.9, 3.0, H-C(3')), 4.92 (dd, ^3J = 9.1, 3.0, H-C(4)); 4.27 (m, H-C(1')), 4.22 (dd, ^2J = 11.6, ^3J = 7.4, H-C(6')), 4.12 (dd, ^2J = 11.6, ^3J = 4.8, H-C(6')), 3.99 (m, H-C(5')), 3.75 (m, H-C(5)), 3.30 (s, MeO), 2.49 & 1.71 (2m, H_2C(6)), 2.12, 2.10, 2.07, 2.06, 2.04, 2.03, 2.02 (7s, 7 AcO), 2.05 (m, H-C(2)), 1.65 & 1.48 (m, H_2C-C(2)). All the new compounds gave satisfactory elemental analyses.

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