

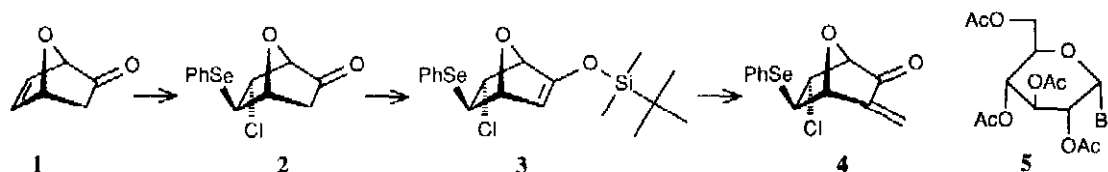
SYNTHESIS OF α -(1 \rightarrow 3)- AND α -(1 \rightarrow 4)-LINKED C-DISACCHARIDES USING (+)-7-OXABICYCLO[2.2.1]HEPT-5-EN-2-ONE ("NAKED SUGAR").

R. Mampuya Bimwala and Pierre Vogel*

Section de Chimie de l'Université de Lausanne, 2, rue de la Barre, CH 1005 Lausanne, Switzerland

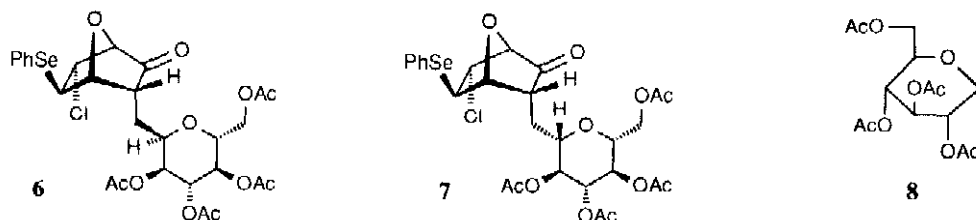
Summary. The α -(1 \rightarrow 3)- and α -(1 \rightarrow 4)-linked C-disaccharides derived from D-glucose and L-mannose have been obtained with high stereoselectivity via the addition of 2,3,4,6-tetra-O-acetyl-glucopyranosyl radical to (1S,4R,5R,6R)-6-endo-chloro-3-methylidene 5-benzeneselenenyl-7-oxabicyclo[2.2.1]heptan-2-one.

The replacement of the interglycosidic oxygen atom in disaccharides by a methylene group generates a class of interesting analogues of disaccharides, namely the C-disaccharides, which constitute potential inhibitors of glycosidases¹ and disaccharidases.² Since the first synthesis of a β -(1 \rightarrow 6)-C-disaccharide (D-glc-C- β -(1 \rightarrow 6) D-GlcOMe) by Rouzaud and Sinay,³ several approaches to C-disaccharides have been proposed.⁴ Some of them rely on the condensation of an electrophilic and a nucleophilic reagent, both derived from a natural, protected carbohydrate³⁻⁵ (see e.g. the syntheses of methylene bridge analogues of maltose,⁶ cellobiose,⁶ sucrose⁷ and β , β -trehalose⁴), others are based on the addition of glycosyl radicals to α -methylene lactones derived from a carbohydrate, leading to α -(1 \rightarrow 2)-C-disaccharides such as methylene bridge analogues of kojibiose, ristobiose, and α -L-fucopyranosyl (1 \rightarrow 2)-D-galactose.⁹ We report a new approach to the synthesis of (1 \rightarrow 3)- and (1 \rightarrow 4)-C-disaccharides which apply the addition of O-tetracetyl-D-glucopyranosyl radical to a 3-methylidene-7-oxabicyclo[2.2.1]heptan-2-one system derived from optically pure (+)-7-oxabicyclo[2.2.1]hept-5-en-2-one (**1**), a "naked sugar".¹⁰



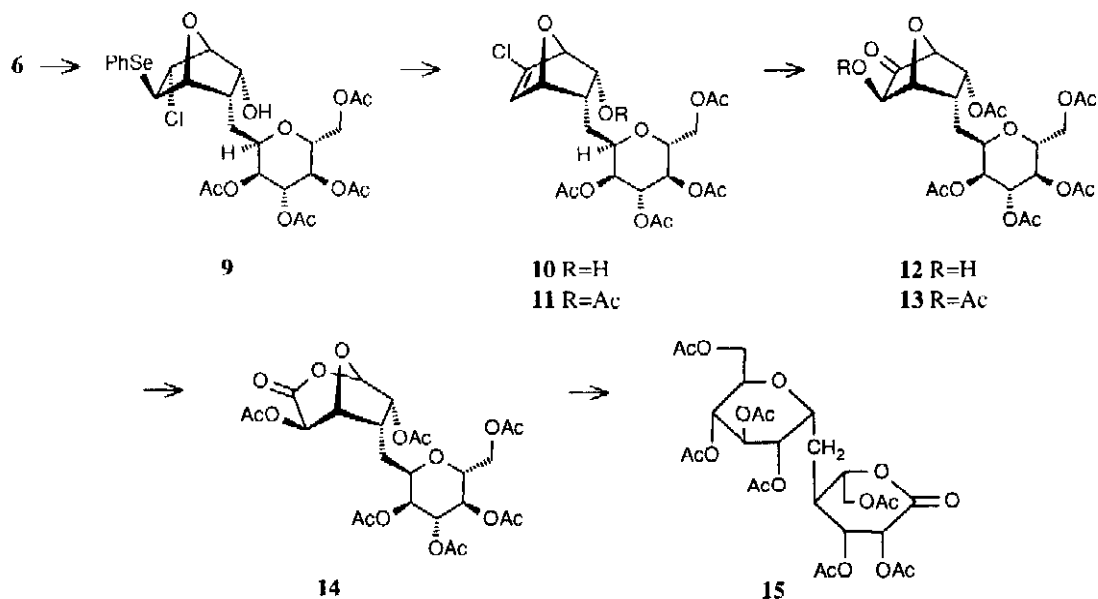
Under kinetically controlled conditions, the reaction of benzeneselenenyl chloride with **1** gave adduct **2** nearly quantitatively.¹¹ The high regioselectivity of this electrophilic addition has been attributed to the electron-releasing effect of the homoconjugated carbonyl moiety due to favourable through-bond $n(\text{CO})-\sigma\text{C}(1),\text{C}(2)-p\text{C}(6)$ interactions.¹² Treatment of the enol ether **3** derived from **2**¹¹ with the Eschenmoser's salt¹³ ($\text{H}_2\text{C}=\text{NMe}_2\text{I}$, 1.5 equivalent) in boiling anhydrous THF containing 1 equiv. of HMPT (24 h) afforded the methyleneketone **4** in 84%

yield (colourless oil, $[\alpha]_D^{25} = -49.1$, ($c=1.8$, CH_2Cl_2)). When a solution of Bu_3SnH (1 equiv.) in absolute benzene containing 5 mol% of AIBN was added slowly (automatic syringe, 30 min) to a boiling solution of **4** and acetobromoglucose **5** (1.3 equiv.) in benzene (total reactions time: 1 h), a mixture was obtained from which the α -C-glucoside **6** (48.5%),¹⁴ the β -C-glucoside **7** (6.0%) and the reduced glucose derivative **8** were separated and isolated by column chromatography on silica gel. Under these conditions, no trace of products resulting from the



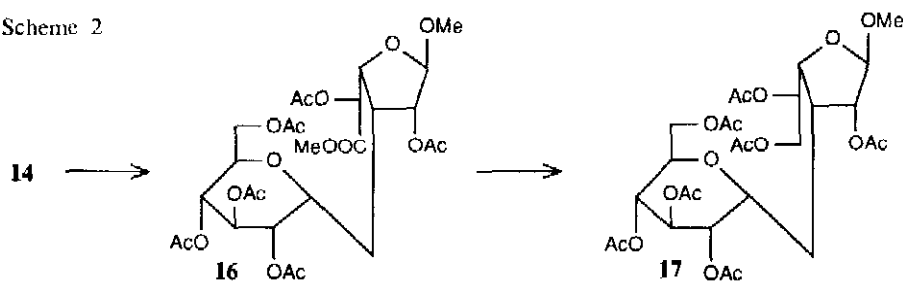
reduction of the chloride or/and of the phenylselenide functions could be detected in the crude reaction mixture (by 360 MHz ^1H -NMR). Furthermore, no trace of the C(3) *exo* stereomer of **6** could be seen, thus pointing out the high *exo* face selectivity of the hydrogen transfer from Bu_3SnH to the radical intermediate resulting from the quenching of the glycosyl radical by enone **4**. The *endo* configuration of centre C(3) C-linked to the glucose moiety was determined by the observation (double irradiation experiments) of a vicinal coupling constant of 6 Hz between H-C(4) and H-C(3) of the bicyclic system¹⁵ and NOE between H-C(5) and the CH_2 -C(3) protons. The α configuration of the "anomeric" centre C(1') of the C-glucoside was expected for the major product^{8,9,16} and was confirmed by the vicinal coupling constant $^3J(\text{Heq-C}(1'), \text{Hax-C}(2')) = 4 \text{ Hz}$ ^{8,9,17} measured in its ^1H -NMR spectrum. These features were also found in the ^1H -NMR spectra of the derivatives **9-14** described here-below.

Scheme 1



Reduction of ketone **6** with NaBH_4 (THF/MeOH 1:1, 0°C , 10 min) furnished the *endo* alcohol **10** (96%, colourless oil, $[\alpha]_{\text{D}}^{25} = +18.8$ ($c=1.3$, CH_2Cl_2)). Oxidative elimination of the phenylselenide (mCPBA, CH_2Cl_2 , -78°C , 20 min) gave the corresponding chloroalkenol **10** (96%, colourless oil, $[\alpha]_{\text{D}}^{25} = +33.6$ ($c=1.3$, CH_2Cl_2)) which was acetylated with Ac_2O /pyridine and dimethylaminopyridine (DMAP: catalyst) into **13** (97%, colourless oil, $[\alpha]_{\text{D}}^{25} = +65.7$ ($c=0.87$, CH_2Cl_2)). Double hydroxylation of the chloroalkene **11** with H_2O_2 and OsO_4 (catalyst) in THF (0°C , 3 h) afforded the 3-*exo*-hydroxy-7-oxabicyclo[2.2.1]heptan-2-one derivative **12** nearly quantitatively.^{11b} Acetylation (Ac_2O /pyridine/DMAP) of **12** gave **13** (94%, m.p. $170\text{--}171^\circ\text{C}$: $[\alpha]_{\text{D}}^{25} = +112.9$ ($c=0.52$, CH_2Cl_2)).¹⁸ Baeyer-Villiger oxidation of ketone **13** with mCPBA/ NaHCO_3 (CH_2Cl_2 , 20°C , 15 h) gave the urono-6,1-lactone **14** (94%, colourless oil, $[\alpha]_{\text{D}}^{25} = +99$ ($c=1$, CH_2Cl_2)) with high regioselectivity, as for the Baeyer-Villiger oxidation of related 7-oxabicyclo[2.2.1]heptan-2-ones substituted at C(3-*exo*) by ester moieties.¹⁹ Treatment of lactone **14** with anhydrous MeOH containing a trace amount of K_2CO_3 (20°C , 45 min) led to the formation of the corresponding methyl furanuronate which was reduced *in situ* by addition of NaBH_4 (20°C , 4 h) into the corresponding methyl 4-C-substituted 4-deoxy-L-mannohexonate. Acidification of the solution with 1N HCl (pH 2-3) and stirring at 40°C overnight led to a complex mixture of partially acetylated 4-deoxy-4-C-(α -D-glucopyranosylmethyl)-L-mannono- δ -lactone. After solvent evaporation to dryness (several evaporations with toluene), and acetylation (Ac_2O /pyridine/DMAP) the peracetylated derivative **15** was isolated (62%, colourless oil, $[\alpha]_{\text{D}}^{25} = +12.4$ ($c=0.8$, CH_2Cl_2)).²⁰

Scheme 2



Under acidic conditions, the methanolysis of uronolactone **14** ($\text{MeOH} + \text{SOCl}_2$, 20°C , 3 h) gave the methyl (methylfuranoside)uronate **16**. Reduction with LiAlH_4 (6 equiv.) in anhydrous THF (20°C , 150 min), followed by acidic treatment (2N HCl, pH=3, $0^\circ\text{--}60^\circ\text{C}$), drying by azeotropic distillation (toluene) and acetylation (Ac_2O /pyridine/DMAP, 20°C , 15 h), afforded methyl 2,5,6-tri-O-acetyl-3-C-[(2',3',4',6'-tetra-O-acetyl- α -D-glucopyranosyl)methyl]-L- α -manno-furanoside (**17**) (65%, colourless oil, $[\alpha]_{\text{D}}^{25} = +17.5$ ($c=1.2$, CH_2Cl_2)).

Starting with the "naked sugar" **1**, α -(1 \rightarrow 3)- (Scheme 2) and α -(1 \rightarrow 4)-C-linked-disaccharides (Scheme 1) derived from D-glucose and L-mannose have been obtained readily with high stereoselectivity. Using the enantiomer of **1**, which is as readily available as **1**,¹⁰ our approach should allow one to prepare the corresponding α -(1 \rightarrow 3)- and α -(1 \rightarrow 4)-C-linked disaccharides derived from D-glucose and D-mannose. Enone **4** and its enantiomer are expected to add other carbohydrate derived radicals than 2,3,4,6-tetra-O-acetylglucopyranosyl radical^{8,9,16} and thus make possible to preparation of a large variety of C-disaccharides.

Acknowledgments. We thank *Hoffmann La Roche & Co. AG*, Basel, the *Fonds Herbette*, Lausanne, and the *Swiss National Science Foundation* for generous support.

REFERENCES AND FOOTNOTES

1. P. Lal  gerie, G. Legler, D. M. Yon, *Biochimie* **1982**, *64*, 977.
2. E. Truscheit, W. Frommer, B. Junge, L. M  ller, D. D. Schmidt, W. Wingender, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 744.
3. D. Rouzaud, P. Sina  , *J. Chem. Soc., Chem. Commun.* **1983**, 1353.
4. O. R. Martin, W. Lai, *J. Org. Chem.* **1990**, *55*, 5188 and references cited therein.
5. R. R. Schmidt, R. Preuss, *Tetrahedron Lett.* **1989**, *30*, 3409; A. Boschetti, F. Nicotra, L. Panza, G. Russo, L. Zucchelli, *J. Chem. Soc., Chem. Commun.* **1989**, 1085; S. Jarosz, B. Fraser-Reid, *J. Org. Chem.* **1989**, *54*, 4011; see also the cycloaddition approaches: e.g.: S. J. Danishefsky, S. L. DeNinno, S.-h. Chen, L. Boisvert, M. Barchachyn, *J. Am. Chem. Soc.* **1989**, *111*, 5810.
6. S. A. Babirad, Y. Wang, Y. Kishi, *J. Org. Chem.* **1987**, *52*, 1370.
7. U. C. Dyer, Y. Kishi, *J. Org. Chem.* **1988**, *53*, 3383; M. Carcano, F. Nicotra, L. Panza, G. Russo, *J. Chem. Soc., Chem. Commun.* **1989**, 642.
8. B. Giese, T. Witzel, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 450.
9. B. Giese, M. Hoch, C. Lamberth, R. R. Schmidt, *Tetrahedron Lett.* **1988**, *29*, 1375.
10. P. Vogel, D. Fattori, F. Gasparini, C. Le Drian, *Synlett.* **1990**, *1*, 173; P. Vogel, *Bull. Soc. Chim. Belg.* **1990**, *99*, 395; J.-L. Reymond, P. Vogel, *Tetrahedron: Asymmetry* **1990**, *1*, 729.
11. a) K. A. Black, P. Vogel, *J. Org. Chem.* **1986**, *51*, 5341; b) D. Fattori, E. de Guchteneere, P. Vogel, *Tetrahedron Lett.* **1989**, *30*, 7415.
12. P.-A. Carrupt, P. Vogel, *Tetrahedron Lett.* **1982**, *23*, 2563; *Helv. Chim. Acta* **1989**, *72*, 1008; *J. Org. Chem.* **1990**, *55*, 5696.
13. J. L. Roberts, P. S. Borromeo, C. D. Poulter, *Tetrahedron Lett.* **1977**, 1621.
14. Spectral data of **6**: $^1\text{H-NMR}$ (CDCl_3 , 250 MHz) δ_{H} 7.65, 7.35 (m, C_6H_5); 5.15 (t, $^3J=7$, H-C(3')); 5.0 (dd, 7, 4, H-C(2')); 4.92 (m, 6, 1, H-C(4)); 4.90 (t, 7, H-C(4')); 4.50 (d, $J=5.5$, H-C(1)); 4.32 (ddd, 5.5, 3, 1, H-C(6)); 4.30 (m, 6, 4, H-C(1')); 4.28 (dd, $^2J=12.2$, $^3J=7$, $\text{H}_1\text{C}(6')$); 4.10 (dd, $^2J=12.2$, $^3J=5$, $\text{H}_2\text{C}(6')$); 3.72 (m, $^3J=7$, 4, H-C(5')); 3.62 (d, 3, H-C(5)); 2.75 (m, $J=6$, H-C(3)); 2.12-2.02 (4s, 4AcO); 1.98-1.85 (m, $^2J=15$, $^3J=6$), 1.70 (m, $^2J=15$, $\text{H}_2\text{C-C}(3)$). IR (CHCl_3) ν 3010-2880, 1770-1730, 1440, 1370 cm^{-1} ; $[\alpha]_{\text{D}}^{25} = +24.3$ ($c=2.1$, CH_2Cl_2).
15. W. L. Nelson, D. R. Allen, *J. Heterocyclic Chem.* **1972**, *9*, 561; F. Kienzle, *Helv. Chim. Acta* **1975**, *58*, 1180; C. Mahaim, P. Vogel, *Ibid.* **1982**, *65*, 866.
16. H.-G. Korth, R. Sustmann, B. Giese, B. R  ckert, K. S. Gr  ninger, *Chem. Ber.* **1990**, *123*, 1891; H.-G. Korth, J.-P. Praly, L. Somsak, R. Sustmann, *Ibid.* **1990**, *123*, 1155.
17. a) R. U. Lemieux, J. D. Stevens, *Can. J. Chem.* **1965**, *43*, 2059; b) B. Giese, J. Dupuis, M. Nix, *Org. Synthesis* **1987**, *65*, 236.
18. Spectral data of **13**: $^1\text{H-NMR}$ (CDCl_3 , 250 MHz) δ_{H} 5.25 (t, 8.5, H-C(3')); 5.18 (dd, 8.5, 1.0, H-C(2')); 4.98 (m, 8.5, 1.0, H-C(4')); 4.98 (m, 8.5, 1.0, H-C(4')); 4.96 (s, H-C(3-endo)); 4.95 (m, H-C(4)); 4.68 (d, 6, H-C(1)); 4.60 (d, 6, H-C(6-exo)); 4.25 (dd, $^2J=12.2$, $^3J=6$, $\text{H}_1\text{C}(6')$); 4.2 (m, H-C(1')); 4.05 (dd, $^2J=12.2$, $^3J=5$, $\text{H}_2\text{C}(6')$); 2.62 (m, H-C(5)); 2.12-2.0 (6s, 6 Ac), 1.90-1.65 (m, $\text{CH}_2\text{-C}(5)$). IR (CHCl_3) ν 3010-2960, 1785, 1750, 1430, 1370, 1210, 1030, 900 cm^{-1} .
19. a) Y. Auberson, P. Vogel, *Helv. Chim. Acta* **1989**, *72*, 278; b) see also: K. R  ser, P.-A. Carrupt, P. Vogel, E. Honegger, E. Heilbronner, *Helv. Chim. Acta* **1990**, *73*, 1.
20. Spectra data of **15**: $^1\text{H-NMR}$ (CDCl_3 , 250 MHz) δ_{H} 5.42 (dd, 7.5, 2.2, H-C(2)); 5.30 (t, 9, H-C(3')); 5.22 (m, H-C(3)); 5.10 (dd, 9, 5.5, H-C(2')); 5.02 (t, 9, H-C(4')); 4.38 (m, H-C(1')); 4.33 (m, H-C(5)); 4.22 (m, 3H $\text{H}_1\text{C}(6)$, $\text{H}_2\text{C}(6)$, Ha-C(6')); 4.02 (dd, $^2J=12.2$, $^3J=2.5$, Hb-C(6')); 3.88 (m, H-C(5')); 2.20 (m, H-C(4)) 2.1-2.0 (7s, 7Ac); 2.0-1.85 (m, $\text{CH}_2\text{-C}(4)$). IR (CHCl_3) ν 3010-2960, 1790, 1745, 1430, 1370, 1210, 1160, 1030, 900 cm^{-1} .

(Received in France 23 December 1990)