Pergamon

Tetrahedron Letters 40 (1999) 3165–3168

TETRAHEDRON LETTERS

Total Stereoselective Syntheses of β-C-*manno*-Pyranosides and of β-C(1→3)-linked Disaccharides

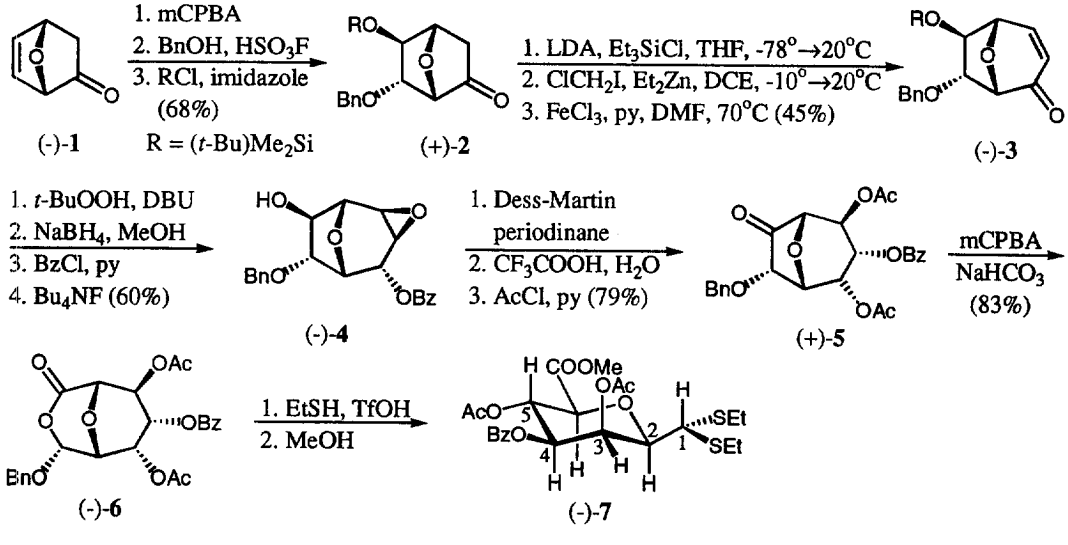
Patrick Gerber and Pierre Vogel*

Section de Chimie de l'Université de Lausanne, BCH, CH 1015 Lausanne-Dorigny, Switzerland.
e-mail: pierre.vogel@ico.unil.ch; fax: +41 21 692 39 75

Received 25 January 1999; accepted 23 February 1999

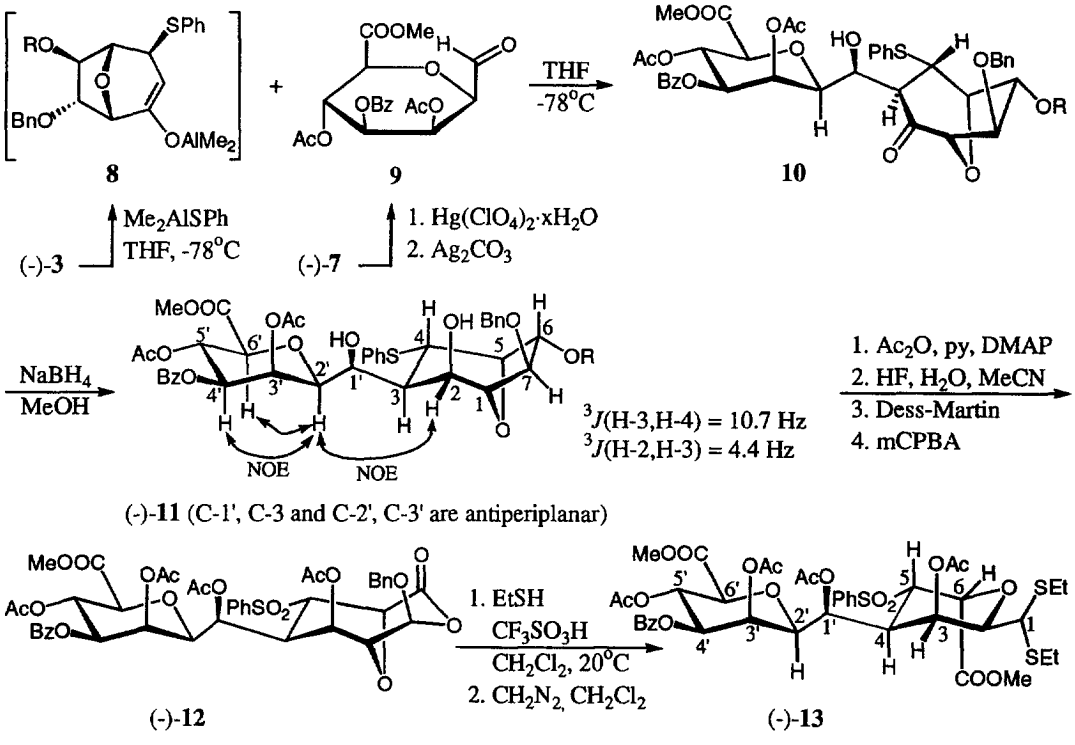
Abstract: (-)-7-Oxabicyclo[2.2.1]hept-5-en-2-one has been converted to (-)-6-*exo*-[(*tert*-butyl)dimethylsilyloxy]-7-*endo*-benzyloxy-8-oxabicyclo[3.2.1]oct-3-en-2-one and methyl 3,5-di-O-acetyl-2,6-anhydro-4-O-benzoyl-D-*glycero*-D-*galacto*-heptouronate that were condensed with Me_2AlSPh into a single aldol which was transformed into a β-D-Man*p*-CH(OAc)(1→3)-α-L-Gul*A*p-$CH(SEt)_2$ derivative.

Carbohydrate mimics are potentially useful tools to study cellular interactions[1] and may become leads for drug discovery.[2] In particular C-linked disaccharides and oligosaccharides[3] offer the advantage of being resistant to acidic and enzymatic hydrolysis. They are therefore potential inhibitors of glycosidases and may represent non-hydrolyzable epitopes. Since the first synthesis of β-D-Glc*p*-CH_2(1→6)-D-Glc*p* by Rouzaud and Sinaÿ,[4] several approaches to C-disaccharides and C-linked oligosaccharides have been reported.[3,5,6] Although several proposals appeared for the preparation of β-C-*manno*-hexopyranosides[7] only three examples of C-disaccharides involving β-C-mannosides (β-D-Man*p*-CH_2(1→1)-β-D-Glc,[8] β-D-Man*p*-CH_2(1→4)-α-D-Glc*p*-OMe,[9] β-D-Man*p*-CH_2(1→6)-D-Glc[5b]) have been reported. We present here a new approach to the synthesis of β-C-*manno*-hexopyranosides starting from (1*S*,4*S*)-7-oxabicyclo[2.2.1]hept-5-en-2-one ((-)-**1**: a "naked sugar" of the first generation[10]). The method generates 6,7-dihydroxy-8-oxabicyclo[3.2.1]oct-3-en-2-one and D-*glycero*-D-*galacto*-heptouronic derivatives that can be coupled to construct new types of C-disaccharides.



0040-4039/99/$ - see front matter
PII: S0040-4039(99)00432-3

Following Le Drian's method,[11] (-)-**1** was converted into (-)-6-*endo*-(benzyloxy)-5-*exo*-hydroxy-7-oxabicyclo[2.2.1]heptan-2-one which was silylated ((*t*-Bu)Me_2SiCl, imidazole) into (+)-**2** (68%, based on (-)-**1**). Cyclopropanation of the triethylsilyl enol ether of (+)-**2** with $ClCH_2I/Et_2Zn$ (DCE, -10 to 20°C, 4 h), and subsequent oxidation with $FeCl_3$/pyridine[12] (DMF, 0-70°C, 2 h) provided enone (-)-**3** (45%, based on (+)-**2**, no purification of the intermediate compounds).[13] Successive one-pot epoxidation of (-)-**3** (*t*-BuOOH, DBU, CH_2Cl_2, 20°C, 3 h),[14] reduction of the ketone moiety with $NaBH_4$ in MeOH (0°C, 30 min), benzoylation of the *endo* alcohol so-obtained (BzCl, pyridine, 20°C, 3.5 h) and desilylation (Bu_4NF, THF, H_2O, 0°C, 3.5 h) gave (-)-**4** (66%). Dess-Martin periodinane oxidation of alcohol (-)-**4** followed by acid promoted (CF_3COOH, CH_2Cl_2, 20°C, 1 h) opening of the epoxide (with participation of the 3-*endo*-benzoyloxy group) liberated a diol which was acetylated (AcCl, pyridine, DMAP (cat.), CH_2Cl_2, 0°-20°C, 6 h) into (+)-**5** (79% based on (-)-**4**, no purification of intermediate products).[15] Baeyer-Villiger oxidation of (+)-**5** was highly regioselective and generated uronolactone (-)-**6** as expected.[16] On treatment with ethanethiol and then with MeOH under acidic conditions (CF_3SO_3H), the dithioacetal of 2,6-anhydro-heptouronic derivative (-)-**7** was obtained (72%). Its structure and conformation were deduced from its spectral data; in particular its ^{1}H-NMR spectrum showed typical coupling constants for the β-*manno*-pyranoside with ^3J(H-1,H-2) = 9.5, ^3J(H-2,H-3) = 1.0, ^3J(H-3,H-4) = 3.4, ^3J(H-4,H-5) = 10.1, ^3J(H-5,H-6) = 9.9 Hz and strong NOE's between signals of δ_H = 3.77 (H-2), 5.32 (H-4) and 4.10 ppm (H-6).



Hydrolysis of the dithioacetal (-)-**7** ($Hg(ClO_4)_2·xH_2O$, MeCN, 20°C, then: Ag_2CO_3, MeCN/$CHCl_3$, 20°C) liberated the unstable aldehyde **9** which was reacted with the aluminum enolate **8** generated by addition of Me_2AlSPh[17] to enone (-)-**3**. Out of four possible diastereomeric aldols only **10** was formed. Because of its

instability it was not isolated but reduced with $NaBH_4$ (MeOH, 0°C) to give diol (-)-**11** in 56% overall yield (based on (-)-**7**)). Repeating the same experiments starting from (±)-**1** instead of (-)-**1**, diol (±)-**11** was obtained, thus proving the homochiral matching of the aldol condensation of racemic (±)-**3** and (±)-**7**.

Acylation of diol (-)-**11** (Ac_2O, pyridine, DMAP, 20°C, 1 h) followed by desilylation (40% aqueous HF, MeCN, 0°C, 2 h) and Dess-Martin periodinane oxidation (CH_2Cl_2, 20°C, 45 min) furnished a ketone, the Baeyer-Villiger oxidation of which (mCPBA, $NaHCO_3$, $CHCl_3$, 20°C, 16 h) gave (-)-**12**. Subsequent treatment with $EtSH/CF_3SO_3H/CH_2Cl_2$, 20°C, 15 min) and with CH_2N_2 (CH_2Cl_2, 20°C) produced the β-D-C-*manno*-pyranoside (-)-**13** (61% based on (-)-**11**, without purification of the intermediate products).

The structure of (-)-**11**[18] was established by its ^{1}H-NMR spectrum. Strong NOE's between signals of protons H-2', H-4' and H-6' confirmed that no epimerization had occurred during the aldol condensation. *Trans*-configuration of H-3 and H-4 was confirmed by ^3J(H-3,H-4) = 10.7 Hz; the *cis* configuration between H-2 and H-3 was given by ^3J(H-2,H-3) = 4.4 Hz. The (1'*S*) configuration was deduced from the Zimmerman-Traxler mode of aldolisation[19] and by analogy with related aldol reactions[6] (*exo* face of enone (-)-**3** adds the nucleophile; *endo* face of enolate **8** reacts with the aldehyde due to the bulk of the PhS group; for steric reasons the *exo* face of ketone **10** is preferred for the reduction by $NaBH_4$). Strong NOE's between H-2 and H-2' and a weaker NOE between H-1' and H-4 as well as ^3J(H-1',H-2') = 9.5 Hz and ^3J(H-1',H-3) = 3.8 Hz confirmed the conformation shown for (-)-**11**. The structure of (-)-**13** was also given by its spectral data.[20] The α-L-*gulo*-pyranoside structure of C-1 to C-7 and the conformation shown for (-)-**13** was confirmed by the ^{1}H-NMR data (^3J(H,H) and NOE's). It demonstrates that the acidic conditions used for the uronolactone opening epimerize, in this case, the carboxylic moiety (less steric repulsions for the $PhSO_2$···HOOC moiety in the L-*gulo* than in the D-*manno* uronic acid).

Work is underway in our laboratory to use (-)-**13** and (-)-**3** and other templates[3] to generate C-linked oligosaccharides with β-C-D-*manno*-pyranoside units.

Acknowledgments. We thank the *Swiss National Science Foundation* and the *Fonds Herbette* for financial support.

References and Notes

1. See e.g.: Varki, A. *Glycobiology* **1993**, *3*, 97-130; Feizi, T. *Curr. Opin. Struct. Bio.* **1993**, *3*, 701-710; Varki, A. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 7390-7397; Morenem, K. W.; Trimble, R. B.; Hersovics, A. *Glycobiology* **1994**, *4*, 113-125; Rye, P. D.; Bovin, N. V.; Vlasora, E. V.; Walker, R. A. *Ibid.* **1995**, *5*, 385-389.
2. See e.g.: MacLean, G. D.; Reddish, M.; Koganty, M.; Wong, T.; Gandhi, S.; Smodenski, M.; Samuel, J.; Nabholtz, J. M.; Longenecker, B. M. *Cancer Iummunol. Immunother.* **1993**, *36*, 215-222; Vhahov, I. R.; Vhahova, P. I.; Linhardt, R. J. *J. Am. Chem. Soc.* **1997**, *119*, 1480-1481; Platt, F. M.; Reinkensmeier, G.; Dwek, R. A.; Butters, T. D. *J. Biol. Chem.* **1997**, *272*, 19365-19372; Mehta, A.; Lu, X.; Block, T. M.; Blumberg, B. S.; Dwek, R. A. *Proc. Nat. Acad. Sci. USA* **1997**, *94*, 1822-1827; Sinaÿ, P. *Pure & Appl. Chem.* **1997**, *69*, 459-463; Kraehenbuehl, K.; Picasso, S.; Vogel, P. *Helv. Chim. Acta* **1998**, *81*, 1439-1479 and ref. cited therein; Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1-8.
3. Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*, Tetrahedron Organic Chemistry Series, Eds.: Baldwin, J. E.; Magnus, P. D. Pergamon-Elsevier Science Ltd., Oxford, **1995**; Postema, M. H. D. *C-Glycoside Synthesis*, CRC, Boca Raton, FL, **1995**; Vogel, P.; Ferritto, R.; Kraehenbuehl, K.; Baudat, A. *Carbohydrate Mimics, Concept and Methods*, Ed: Chapleur, Y.; Wiley-VCH, Weinheim, **1998**, Chap. 2, p. 19-48; Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913-9959.
4. Rouzaud, D.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1983**, 1353-1354.

5. a) Wei, A.; Haudrechy, A.; Audin, C.; Jun, H.-S.; Haudrechy-Bretel, N.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 2160-2169; Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *J. Org. Chem.* **1996**, *61*, 1894-1897; Streicher, H.; Geyer, A.; Schmidt, R. R. *Chem. Eur.* **1996**, *2*, 502-510; Witczak, Z. J.; Chhabra, R., Chojnacki, J. *Tetrahedron Lett.* **1997**, *38*, 2215-2218; Rubinstenn, G.; Esnault, J.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1327-1336; Angelaud, R.; Landais, Y.; Parra-Rapado, L. *Tetrahedron Lett.* **1997**, *38*, 8845-8848; Bornaghi, L.; Utille, J. P.; Mekai, E. D.; Mallet, J.-M.; Sinaÿ, P.; Driguez, H. *Carbohydr. Res.* **1997**, *305*, 561-568; b) Dondoni, A.; Zuurmond, H. M.; Boscarato, A. *J. Org. Chem.* **1997**, *62*, 8114-8124; c) Sutherlin, D. P.; Armstrong, R. W. *Ibid.* **1997**, Rubinstenn, G.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron Lett.* **1998**, *39*, 3697-3700; Du, Y.; Polat, T.; Linhardt, R. J. *Ibid.* **1998**, *39*, 5007-5010; Dondoni, A.; Kleban, M.; Zuurmond, H.; Marra, A. *Ibid.* **1998**, *39*, 7991-7994.
6. Zhu, Y.-H.; Vogel, P. *Tetrahedron Lett.* **1998**, *39*, 31-34; *J. Org. Chem.* **1999**, *64*, 666-669.
7. Stork, G.; Suh, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054-7056; Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *Tetrahedron Lett.* **1992**, *33*, 737-740; Bertozzi, C. R.; Bednarski, M. *Carbohydr. Res.* **1992**, *223*, 243-253; Mazéas, D.; Skrydstrup, T.; Doumeix, O.; Beau, J. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1383-1386; Wang, X.; Gross, P. H. *J. Org. Chem.* **1995**, *60*, 1201-1206; Dorgan, B. J.; Jackson, R. F. W. *Synlett* **1996**, 859-861; Praly, J.-P.; Chen, G.-R.; Gola, J.; Hetzer, G.; Raphoz, C. *Tetrahedron Lett.* **1997**, *38*, 8185-8188.
8. Wei, A.; Kishi, Y. *J. Org. Chem.* **1994**, *59*, 88-96.
9. Wang, Y.; Babirad, S. A.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 468-481.
10. Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173-185; Reymond, J.-L.; Vogel, P. *Tetrahedron: Asymmetry* **1990**, *1*, 729-736; Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, *34*, 3979-3982; Forster, A.; Mosimann, H.; Renaud, P.; Vogel, P. *Tetrahedron: Asymmetry* **1999**, *10*, 567-571.
11. Le Drian, C.; Vionnet, J.-P.; Vogel, P. *Helv. Chim. Acta* **1990**, *73*, 161-168.
12. Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974-6981; Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* **1976**, *41*, 2073-2074.
13. Data for (-)-**3**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36-7.26 (m, 5H), 7.19 (dd, ^3J=9.9, 4.8, H-4), 6.12 (dd, ^3J=9.9, ^4J=1.1, H-3), 4.83 (br.dd, ^3J=7.0, ^4J=1.1, H-1), 4.58, 4.40 (2d, ^2J=11.2), 4.45 (br.d, ^3J=4.8, H-5), 4.30 (m, ^3J=7.0, H-7), 4.27 (br.s, H-6), 0.90 (s, 9H), 0.11, 0.10 (2s, 6H). $[\alpha]^{25}_D$=-124 (c=0.86. $CHCl_3$).
14. Yadav, V. K.; Kapoor, K. K. *Tetrahedron* **1995**, *51*, 8573-8584.
15. Data for (+)-**5**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.08 (m, 2H), 7.50 (m, 1H), 7.33 (m, 2H), 7.21-7.14 (m, 5H), 5.66 (dd, ^3J=4.6, 4.5, H-2), 5.62 (m, ^3J=4.5, 2.1, H-3), 5.05 (dd, ^3J=2.1, 2.0, H-4), 4.86 (br.dd, ^3J=7.0, 4.6, H-1), 4.73, 4.69 (2d, ^2J=11.5), 4.56 (br.dd, ^3J = 7.0, ^4J=1.2, H-7), 4.41 (m, ^3J=2.0, 1.2, H-5), 2.21, 1.93 (2s, 2AcO). $[\alpha]^{25}_D$=+3.7 (c=1.3, CH_2Cl_2).
16. Arvai, G.; Fattori, D.; Vogel, P. *Tetrahedron* **1992**, *48*, 10621-10636.
17. Itoh, A.; Ozawa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 361-364.
18. Data for (-)-**11**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.95, 7.59-7.28 (15H), 5.98 (br.d, ^3J=3.4, H-3'), 5.64 (dd, ^3J=10.2, 10.0, H-5'), 5.39 (dd, ^3J=10.2, 3.4, H-4'), 5.22 (s, OH), 4.76 & 4.57 (2d, ^2J=11.4), 4.68 (dd, ^3J=7.9, 4.4, H-2), 4.43 (m, ^3J=9.5, 3.8, H-1'), 4.30 (d, ^3J=4.3, H-6), 4.29 (s, H-5), 4.20 (dd, ^3J=7.9, 5.3, H-1), 4.08 (dd, ^3J=5.3, 4.3, H-7), 4.07 (s, OH), 4.05 (d, ^3J=10.0, H-6'), 3.88 (br.d, ^3J=9.5, H-2'), 3.80 (s, MeO), 3.64 (d, ^3J=10.7, H-4), 2.15, 1.98 (2s, 2Ac), 2.00 (ddd, ^3J=10.7, 4.4, 3.8, H-3), 0.84 (s, 9H), 0.01, -0.10 (2s, 6H). $[\alpha]^{25}_D$ = -27 (c=0.54, CH_2Cl_2).
19. Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920-1923.
20. Data for (-)-**13**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.03, 7.89, 7.70, 7.56, 7.41 (10H), 5.86 (dd, ^3J=3.3, 1.1, H-3), 5.51 (dd, ^3J=10.0, 9.9, H-5'), 5.38 (br.d, ^3J=3.5, H-3'), 5.34 (dd, ^3J=10.0, 3.5, H-4'), 5.19 (br.s, H-6), 4.97 (dd, ^3J=9.5, 3.2, H-1'), 4.33 (br.d, ^3J=9.5, H-2'), 4.23 (d, ^3J=6.5, H-5), 4.22 (d, ^3J=9.9, H-6'), 3.85, 3.78 (2s, 6H), 3.82 (d, ^3J=8.8, H-1), 3.67 (dd, ^3J=8.8, 1.1, H-2), 2.97 (ddd, ^3J=6.5, 3.3, 3.2, H-4), 2.77-2.58 (m, 4H, ^3J=7.4), 1.99, 1.985, 1.95, 1.92 (4s, 12H), 1.27, 1.22 (2t, ^3J=7.4). $[\alpha]^{25}_D$ = -39 (c=0.65, CH_2Cl_2).