

A Stereoselective Synthesis of Methyl β -C-Lactoside through the Tether Approach

Gilles Rubinstenn, Jean-Maurice Mallet and Pierre Sinay*

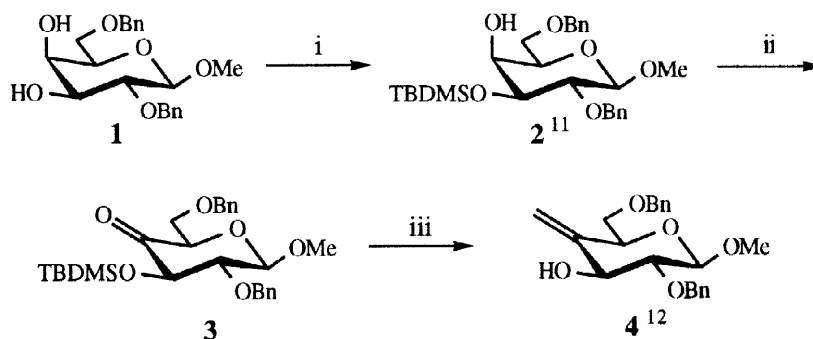
Ecole Normale Supérieure, Département de Chimie associé au CNRS, 24 rue Lhomond,
75231 Paris cedex 05, France

Received 9 March 1998; accepted 19 March 1998

Abstract: Methyl β -C-lactoside (β -D-Galp-C(1 $\rightarrow$ 4)- β -Glc p-OMe) is stereoselectively synthesized by radical coupling of phenyl Se- β -D-galactopyranoside **5** onto *exo*-methylene-sugar **4**, which are temporarily connected through a silaketal tether. © 1998 Elsevier Science Ltd. All rights reserved.

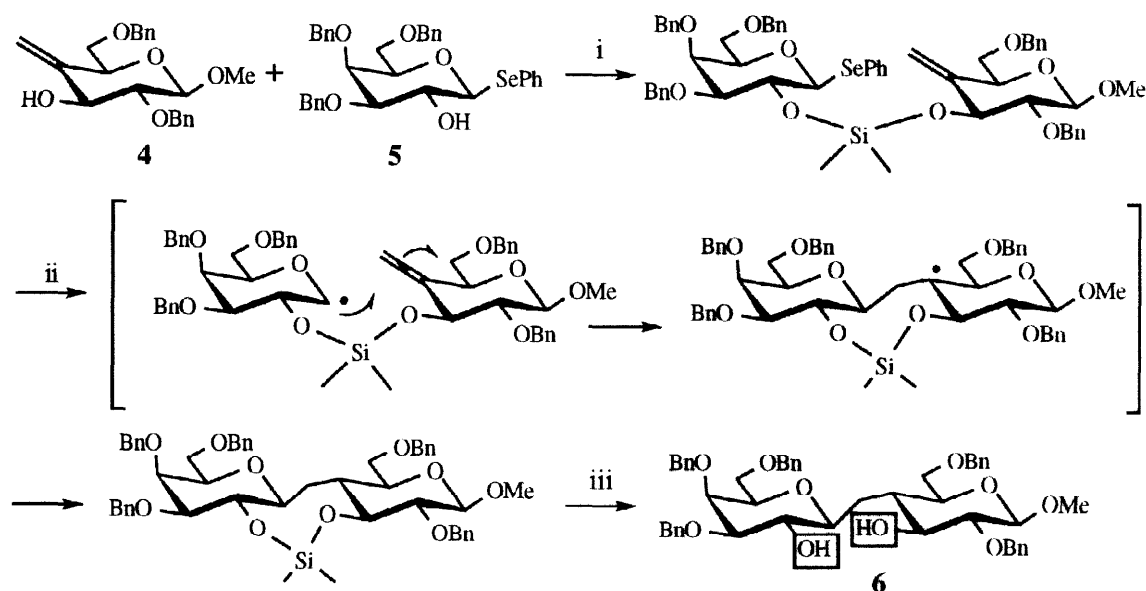
C-disaccharides are *sensu stricto* defined as close analogues of regular disaccharides in which the interglycosidic oxygen atom has been replaced by a methylene group. These mimetics cannot be hydrolyzed *in vivo* by glycosidases, a property which qualifies them as stable potential surrogates of biologically active oligosaccharides¹. Since the report on the first chemical synthesis of a C-disaccharide², a great deal of attention has been devoted to their preparation³ and also to the study of their conformation, either in solution⁴ or complexed with a protein⁵.

We have recently described a strategy for the synthesis of various α -C-(1 $\rightarrow$ 4) disaccharides⁶ based on a 9-*endo trig* radical cyclisation from two tethered monosaccharides. In this approach the temporarily covalent attachment was achieved through a silacetal or ketal tether between the hydroxyl group on C-2' of a anomeric radical precursor and the primary hydroxyl group on C-6 of an exomethylene sugar at C-4, the so-called 6,2' pair. We consistently observed an α -selectivity in this process, which parallels the one observed in the intermolecular version⁷. The 6,2' tether is probably flexible enough not to significantly counterbalance the kinetic anomeric effect which dictates the α -selectivity. From the outset of the tethering project, we have suspected that the array of hydroxyl group inherently present in monosaccharides might well offer a unique and potentially flexible way of achieving fine tuning of the selectivity of the C-glycosylation step. In accordance with this, we would like to report in this letter on the use of 3,2' pair for a selective synthesis of methyl β -C-lactoside⁸. The radical acceptor **4**⁹ has been prepared from methyl 2,6-di-O-benzyl β -D-galactopyranose **1**¹⁰ as shown in scheme 1.



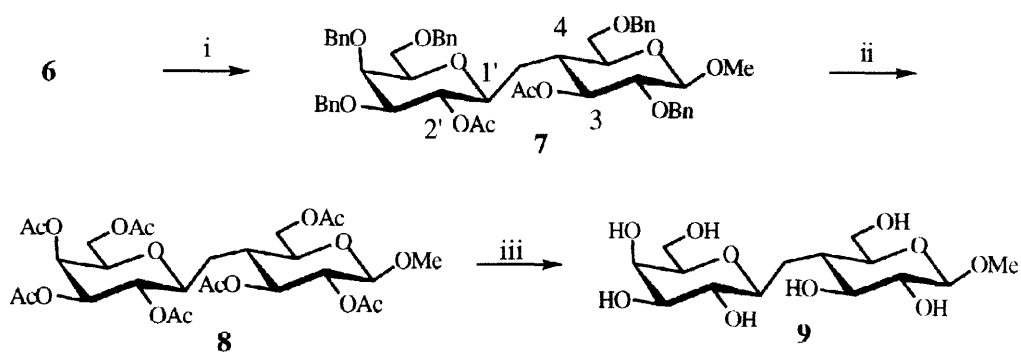
Scheme 1. Reagents. i: TBDMSCl (1.2 equiv), Et₃N (2 equiv), DMAP (0.4 equiv), DMF, RT, 20h, 96%. ii : PCC (4 equiv), 4Å molecular sieves, CH₂Cl₂, RT, 30 min, 85%. iii : 1) Tebbe reagent (2.5 equiv), THF/Pyridine, -60°C $\rightarrow$ RT; 2) aq. HF, THF, RT, 24h, 61%.

The alcohols **4** and **5**^{6d} were efficiently connected together through a dimethyl silaketal tether. An 8-*endo trig* radical cyclisation reaction, followed by desilylation, selectively afforded the methyl β -C-lactoside derivative **6**, in 45% overall yield, as shown in scheme 2.



Scheme 2. Reagents. i : 1) **5**, Me_2SiCl_2 (4.4 equiv), BuLi (1.1 equiv), THF, $-78^\circ\text{C} \rightarrow \text{RT}$; 2) **4** (1 equiv), Imidazole (2.5 equiv), THF, RT. ii : Bu_3SnH (2 equiv), AIBN (0.3 equiv), PhMe, 110°C , 17h. iii : Bu_4N^+ , F^- (2 equiv) THF, RT, 45% (over the three steps)

In order to confirm the structure of **6**¹³ and the absolute configuration of the two asymmetric centres created during the reaction, it was converted into the diacetate **7**, where the two protons signals H-3 and H-2' are deshielded, acting as convenient reporter groups for the direct assignment of the overall stereochemical outcome of the reaction ($J_{3,4}$ 11.5 Hz, calling for a trans diaxial relationship between H-3 and H-4; $J_{1',2'}$ 9.5 Hz, calling for a second trans diaxial relationship between H-1' and H-2'). As shown in scheme 3, **7** was readily converted into peracetate **8**¹⁴, then further into the title methyl β -C-lactoside **9**¹⁵.



Scheme 3. Reagents : i : Ac_2O / pyridine, 99%. ii : 1) H_2 , Pd/C, MeOH. 2) Ac_2O / pyridine, 91%
iii : K_2CO_3 , MeOH, 91%

The observed β -selectivity is probably the result of a strongly favorable conformational bias given by the tethered system¹⁶. The more rigid 3,2' tether - compared to the previously used 6,2' - presumably delivers the double bond from the β -face of the sugar radical (scheme 2).

In conclusion, we have demonstrated here that silaketal tethering through the 3,2' pair is particularly well suited for the synthesis of the biologically relevant C-lactose skeleton. We may say that the 3,2' set is

a "matched pair" for the preparation of C-lactose. The silaketal tethering strategy¹⁷ offers a unique way to control the selectivity of the C-glycosylation step through the judicious choice of an appropriate set of hydroxyl groups.

REFERENCES AND NOTES

1. A mixed C,O-pentasaccharide related to heparin has recently been synthesized and shown to exhibit an antithrombotic activity similar to that of the corresponding O-pentasaccharide : Helmboldt, A.; Petitou, M.; Mallet J.-M.; Herault, J.-P.; Lormeau, J.-C.; Herbert, J.-M.; Sinaÿ, P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1507.
2. Rouzaud, D.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.*, **1983**, 1353.
3. Representative selection of stereoselective syntheses of C-disaccharides: a) Martin, O. R.; Lai, W. *J. Org. Chem.* **1993**, *58*, 176 and references therein. b) Mazéas, D.; Skrydstrup, T.; Doumeix, O.; Beau, J.-M. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1383. c) Ferritto R., Vogel P. *Tetrahedron: Asymmetry* **1994**, *5*, 2077. d) Dietrich, H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1994**, 975. e) Armstrong, R. W.; Sutherlin, D. P.; *Tetrahedron Lett.* **1994**, *35*, 7743. f) Wei, A.; Haudrechy, A.; Audin, C.; Jun, H.-S.; Haudrechy-Bretel, N.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 2160. g) Sutherlin, D. P.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 9802. h) Jarreton, O.; Skrydstrup, T.; Beau, J.-M. *J. Chem. Soc., Chem. Commun.* **1996**, 1661. i) Sutherlin, D. P.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 5267. j) Leewenburgh, M. A.; Timmers, C. M.; Van Der Marel, G. A.; Van Boom, J. H.; Mallet, J.-M.; Sinaÿ P. *Tetrahedron Lett.* **1997**, *38*, 6251. k) Vogel, P. in "Carbohydrate Mimics, Concepts and Methods" Ed. Yves Chapleur, Wiley VCH, pp 19-48 and references therein.
4. a) Wang, Y.; Goekjian, P. G.; Ryckmann, D. M.; Miller, W. H.; Babirad, S. A.; Kishi, Y. *J. Org. Chem.* **1992**, *57*, 482. b) Wei, A.; Boy, K. M.; Kishi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9432. c) Espinosa, J. -F.; Martín-Pastor, M.; Asensio, J. L.; Dietrich, H.; Martín-Lomas, M.; Schmidt, R. R.; Jiménez-Barbero, J. *Tetrahedron Lett.* **1995**, *36*, 6329. d) Espinosa, J. -F.; Cañada, F. J.; Asensio, J. L.; Martín-Pastor, M.; Dietrich, H.; Martín-Lomas, M.; Schmidt, R. R.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **1996**, *118*, 10862. e) Berthault, P.; Birlirakis, N.; Rubinstenn, G.; Sinaÿ, P. ; Desvaux, H. *J. Biomol. NMR*, **1996**, *8*, 23-35. f) Rubinstenn, G.; Sinaÿ, P. ; Berthault, P. *J. Phys Chem. A*, **1997**, *101*, 2536.
5. a) Espinosa, J.-F.; Cañada, F. J.; Asencio, J. L.; Dietrich, H.; Martin-Lomas, M.; Schmidt, R. R.; Jimenez-Barbero, J. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 303. b) ref 4d. c) Espinosa, J.-F.; Montero, E.; Vian, A.; Garcia, J. L.; Dietrich, H.; Schmidt, R. R.; Martin-Lomas, M.; Imberty, A.; Cañada, F. J.; Jimenez-Barbero, J. *J. Am. Chem. Soc.* **1998**, *120*, 1309.
6. a) Xin, Y. C.; Mallet, J.-M.; Sinaÿ, P. *J. Chem. Soc., Chem. Commun.* **1993**, 864. b) Vauzeilles, B.; Cravo, D.; Mallet, J.-M.; Sinaÿ, P. *Synlett* **1993**, 522. c) Chénéde, A.; Perrin, E.; Rekaï, E. D.; Sinaÿ, P. *Synlett* **1994**, 420. d) Mallet, A.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron: Asymmetry* **1994**, 2593.
7. a) Giese, B.; Dupuis, J. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 622. b) Adlington, R. M.; Baldwin, J. E.; Bosak, A.; Kozyrod, R. P. *J. Chem. Soc. Chem. Commun.* **1983**, 944.
8. A chemical synthesis of C-lactose has been reported^{3d}. This compound has also been converted classically into methyl β -C-lactoside, see 4d.
9. All new compounds gave satisfactory elemental analysis. NMR data were in agreement with the proposed structures.
10. a) Garegg, P. J.; Lindberg, K. B.; Swahn, C.-G. *Acta Chem. Scand. B*, **1974**, *28*, 381. b) Flowers, H. M.; *Carbohydr. Res.* **1975**, *39*, 245. This compound was prepared by benzylation of methyl 3,4-O-isopropylidene β -D-galactopyranose prepared according to : Catelani, G.; Colonna, F.; Marra, A. *Carbohydr. Res.* **1988**, *182*, 297.

11. Selected data for **2** : $[\alpha]_{\text{D}}^{20} +2$ (c 1, CHCl_3). $^1\text{H-NMR}$ (400MHz, CDCl_3) : 7.39-7.30 (m, 10H, H-arom), 4.92, 4.65 (AB, 2H, J_{AB} 11.0Hz, CH_2Ph), 4.67, 4.63 (AB, 2H, J_{AB} 12.0Hz, CH_2Ph), 4.29 (d, 1H, $J_{1,2}$ 8.0Hz, H-1), 3.86 (d, 1H, $J_{6a,6b}$ 10.0, $J_{5,6a}$ 5.5Hz, H-6a), 3.82 (d, 1H, $J_{3,4}$ 3.5Hz, H-4), 3.80 (dd, 1H, $J_{5,6b}$ 5.5Hz, H-6b), 3.71 (dd, 1H, $J_{2,3}$ 8.5Hz, H-3), 3.66 (ddd, 1H, H-5), 3.59 (s, 3H, OMe), 3.48 (dd, 1H, H-2), 2.52 (s, 1H, OH), 0.95 (s, 9H, *t*BuSi), 0.14 (s, 3H, MeSi), 0.11 (s, 3H, MeSi).
12. Selected data for **4** : mp 86.5°C (diisopropyl ether/pentane) $[\alpha]_{\text{D}}^{20} +19$ (c 1, CHCl_3). $^1\text{H-NMR}$ (400MHz, CDCl_3) : 7.38-7.31 (m, 10H, H-arom), 5.34 (m, 1H, $=\text{CH}_2$), 5.05 (m, 1H, $=\text{CH}_2$), 4.93, 4.66 (AB, 2H, J_{AB} 11.5Hz, CH_2Ph), 4.64 (s, 2H, CH_2Ph), 4.46 (d, 1H, $J_{1,2}$ 7.0Hz, H-1), 4.18-4.09 (m, 2H, H-5, H-3), 3.91 (d, 1H, $J_{6a,6b}$ 10.0, $J_{5,6a}$ 4.5Hz, H-6a), 3.76 (dd, 1H, $J_{5,6b}$ 4.0Hz, H-6b), 3.59 (s, 3H, OMe), 3.24 (dd, 1H, $J_{2,3}$ 7.5Hz, H-2).
13. Selected data for **6** : $[\alpha]_{\text{D}}^{20} +15$ (c 0.3, CHCl_3). $^1\text{H-NMR}$ (400MHz, CDCl_3) : 7.53-7.30 (m, 25H, H-arom), 4.97, 4.75 (AB, 2H, J_{AB} 11.5Hz, CH_2Ph), 4.90, 4.61 (AB, 2H, J_{AB} 11.5Hz, CH_2Ph), 4.77, 4.60 (AB, 2H, J_{AB} 12.0Hz, CH_2Ph), 4.63, 4.60 (AB, 2H, J_{AB} 12.0Hz, CH_2Ph), 4.51, 4.43 (AB, 2H, J_{AB} 12.0Hz, CH_2Ph), 4.29 (d, 1H, $J_{1,2}$ 7.5Hz, H-1), 3.97 (d, 1H, $J_{3',4'}$ 3.0Hz, H-4'), 3.86 (d, 1H, $J_{6a,6b}$ 11.0, $J_{5,6a}$ 2.0Hz, H-6a), 3.80 (dd, 1H, $J_{1',2'}$ 9.5, $J_{2',3'}$ 9.5Hz, H-2'), 3.70 (dd, 1H, $J_{5,6b}$ 5.5Hz, H-6b), 3.61-3.47 (m, 5H, H-5, H-3, H-5', H-6'a, H-6'b), 3.60 (s, 3H, OMe), 3.40 (dd, 1H, H-3'), 3.33 (ddd, 1H, $J_{1',4h}$ 2.0, $J_{1',4h'}$ 8.0Hz, H-1'), 3.27 (dd, 1H, $J_{2,3}$ 8.5Hz, H-2), 2.16 (ddd, 1H, $J_{4,4h}$ 2.0, $J_{4h,4h'}$ 15.5Hz, H-4h), 1.92 (dddd, 1H, $J_{3,4}$ 11.5, $J_{4,4h}$ 5.5Hz, H-4), 1.62 (ddd, 1H, H-4h'). 4h and 4h' refer to the interglycosidic methylene. The β anomery was also strongly suggested by $^4\text{C}_1$ chair form conformation observed for the D-galactosyl residue of **6**. In the case of an α anomery, a large conformational deviation from $^4\text{C}_1$ is expected. This deviation, when existing, is indeed diagnostic for the α configuration^{6d}.
14. Selected data for **8** : $[\alpha]_{\text{D}}^{20} +31$ (c 1.1, CHCl_3). $^1\text{H-NMR}$ (400MHz, acetone d-6) : 5.56 (d, 1H, $J_{3',4'}$ 3.5, $J_{4',5'}$ 1Hz, H-4'), 5.37 (dd, 1H, $J_{2,3}$ 9.5, $J_{3,4}$ 11.5Hz, H-3), 5.18 (dd, 1H, $J_{2',3'}$ 10.0Hz, H-3'), 5.08 (dd, 1H, $J_{1',2'}$ 9.5Hz, H-2'), 4.90 (dd, 1H, $J_{1,2}$ 8.5Hz, H-2), 4.61 (d, 1H, H-1), 4.53 (dd, 1H, $J_{5,6a}$ 2.0, $J_{6a,6b}$ 12.0Hz, H-6a), 4.44 (dd, 1H, $J_{5,6b}$ 5.0Hz, H-6), 4.35 (ddd, 1H, $J_{5',6'a}$ 5.0, $J_{5',6'b}$ 7.5Hz, H-5'), 4.27 (dd, 1H, $J_{6'a,6'b}$ 11.5Hz, H-6'a), 4.21 (ddd, 1H, $J_{4,5}$ 11.5Hz, H-5), 4.19 (dd, 1H, H-6'b), 3.92 (ddd, 1H, $J_{1',4h}$ 4.5, $J_{1',4h'}$ 8.0Hz, H-1'), 3.55 (s, 3H, OMe), 2.32-2.25 (m, 1H, H-4), 2.26, 2.21, 2.20, 2.16, 2.14, 2.11, 2.05 (7 s, 21H, H-Ac), 1.80, 1.75 (m, 2H, H-4h, H-4h'). $^{13}\text{C-NMR}$ (100MHz, CDCl_3) : 170.76, 170.60, 170.41, 170.35, 170.23, 170.07, 169.75 (7 C=O-Me), 101.86 (C-1), 75.40 (C-1'), 74.79 (C-5'), 73.96 (C-2), 73.57 (C-5), 72.62 (C-3'), 72.30 (C-3), 69.83 (C-2'), 68.75 (C-4'), 64.57 (C-6), 62.83 (C-6'), 56.35 (OMe), 40.67 (C-4), 27.98 (C-4h), 20.62-20.39 (7 CH_3CO).
15. Selected data for **9** : $[\alpha]_{\text{D}}^{20} -2$ (c 0.85, H_2O). MS (CI, NH_3 , m/z, %) : 355 (M+1, 100), 323 (M-OMe, 75), 340 (M-OMe+17, 40), 372 (M+18, 10). $^1\text{H-NMR}$ (500MHz, D_2O , 298K) : 4.31 (d, 1H, $J_{1,2}$ 8.5Hz, H-1), 3.96 (dd, 1H, $J_{5,6a} < 1$, $J_{6a,6b}$ 11.5Hz, H-6a), 3.93 (d, 1H, $J_{3',4'}$ 3.5Hz, H-4'), 3.72 (dd, 1H, $J_{5',6'a}$ 8.5, $J_{6'a,6'b}$ 12.0Hz, H-6'a), 3.70-3.63 (m, 4H, H-5, H-6b, H-6'b), 3.63-3.61 (m, 1H, H-5'), 3.60 (dd, 1H, $J_{2',3'}$ 9.5Hz, H-3'), 3.55 (s, 3H, OMe), 3.49 (dd, 1H, $J_{2,3}$ 9.5, $J_{3,4}$ 10.5Hz, H-3), 3.39 (dd, 1H, $J_{1',2'}$ 9.5Hz, H-2'), 3.30 (ddd, 1H, $J_{1',4h}$ 1.75, $J_{1',4h'}$ 9.5Hz, H-1'), 3.21 (dd, 1H, H-2), 2.08 (ddd, $J_{4,4h}$ 4.9, $J_{4h,4h'}$ 14.5Hz, H-4h), 1.77 (dddd, 1H, $J_{4,4h}$ 3.5, $J_{4,5}$ 10.5Hz, H-4), 1.63 (ddd, 1H, H-4h'). $^{13}\text{C-NMR}$ (125MHz, D_2O , 298K) : 104.42 (C-1), 79.71 (C-5'), 78.22 (C-5), 78.84 (C-1'), 75.92 (C-2), 75.18 (C-3'), 74.95 (C-3), 72.46 (C-2'), 70.44 (C-4'), 63.25 (C-6), 62.83 (C-6'), 58.23 (C-OMe), 41.69 (C-4), 29.61 (C-4h).
16. We consistently observed ⁶ a stereoselective reduction of the C-4 generated radical from the β side to give a gluco moiety.
17. For a review on silaketel tether, see Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, 95, 1253.