

Synthesis of oligosaccharide mimetics

Pierre Sinay

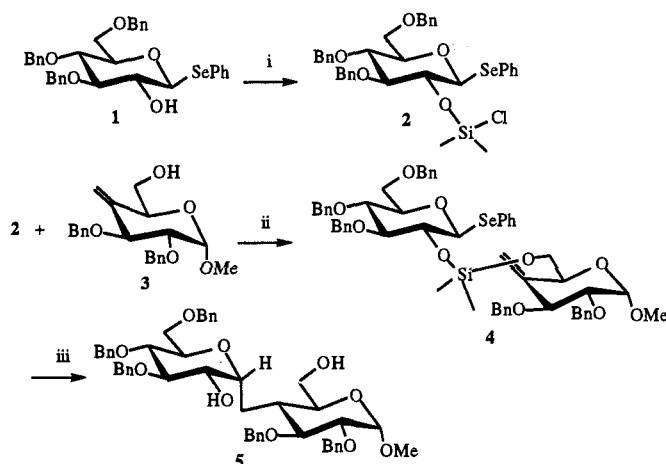
*Ecole Normale Supérieure, Département de Chimie
24, Rue Lhomond, 75231 Paris Cedex 05, France*

Abstract : A variety of *C*-disaccharides have been selectively and expeditiously synthesized through the so-called tether approach.

Introduction

Recent advances in glycoscience have clearly demonstrated that specific synthetic oligosaccharides can be promising medicinal agents. A now well established case is a synthetic pentasaccharide heparin fragment (ref. 1) which displays selective antithrombotic activity. The tetrasaccharide Sialyl Lewis^x and derivatives thereof (ref. 2) are also currently considered as potential anti-inflammatory agents. Obviously, other candidates should emerge in a near future. The emergence of these rather complex polyhydroxylated molecules is indeed the consequence of the rapid progresses which have been observed in the past in the selective synthesis of oligosaccharides (ref. 3). A possible disadvantage of such drugs is their inherent vulnerability. Glycosidases are cleaving glycosidic bonds and thus may *in vivo* degrade synthetic oligosaccharides rather rapidly. There is thus a need for non-hydrolysable mimetics. A great deal of attention has recently been devoted, in this respect, to the preparation of *C*-disaccharides (ref. 4), members of a challenging novel class of disaccharide mimetics, in which the interglycosidic oxygen atom is replaced by a methylene group. These products are conformationally close to their natural counterparts (ref. 5) and cannot be chemically or biochemically hydrolyzed. They are thus probably going to emerge as attractive new tools in glycobiology.

We have recently discovered (ref. 6) an expeditious synthetic entry into methyl α -*C*-maltoside (scheme 1), based on a 9 *endo-trig* radical cyclisation reaction from two tethered monosaccharides.



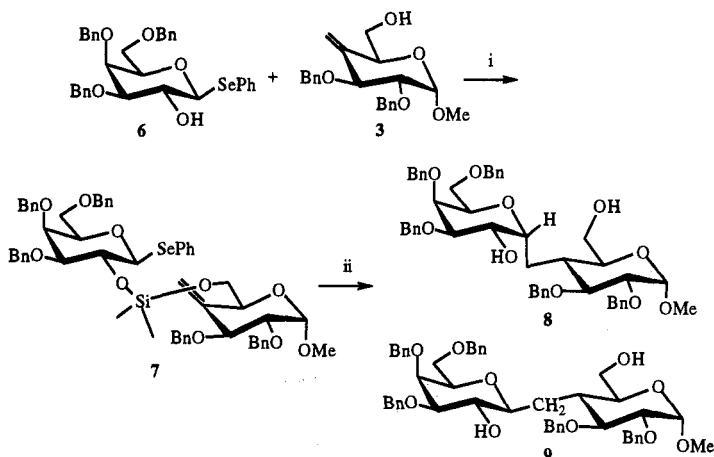
Scheme 1: Reagents: i) 1) BuLi , 2) Me_2SiCl_2 , ii) 3, imidazole, THF; iii) Bu_3SnH , toluene, reflux then aq. HF/THF (40% overall yield).

Inasmuch as the necessary tethering and removal of the silicon connection are high-yielding processes, this potentially general route offers a fascinating direct way to build up promptly a disaccharide mimetic. The silaketal stratagem is, so to say, entropically mimicking an evanescent and very simple *C*-glycosyl transferase (unknown enzyme), the tether (enzyme) bringing together the glycosyl donor (phenyl Se-glycoside) and the glycosyl acceptor (*exo* methylene sugar), the tributyltin hydride (coenzyme) triggering the condensation, and the removal of the transient tether achieving the release of the *C*-disaccharide.

After scheme 1, which provides a typical example, we would like, in this lecture, to demonstrate that indeed this methodology is flexible and provides compounds of potential biological significance.

The use of selenophenyl galactopyranosides for the synthesis of α and β *C*-disaccharides

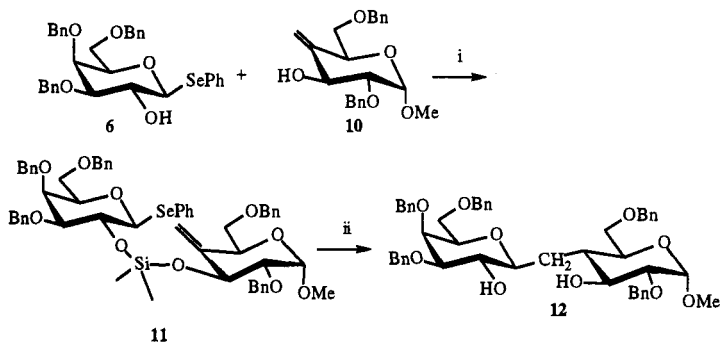
Galactose is frequently found in natural oligosaccharides and we thus concentrated on the problem of the selective synthesis of galactose based *C*-disaccharides. A comparison of schemes 2 and 3 nicely demonstrates that the array of hydroxyl groups which is present in monosaccharides provides a flexible way of achieving a fine tuning of the stereoselectivity.



Scheme 2 (ref. 7): Reagents: i) 1) **6**, BuLi, 2) Me₂SiCl₂, 3) **3**, imidazole, THF; ii) Bu₃SnH, toluene, reflux then aq HF/ THF (60% overall yield, ratio **8/9** =3/1).

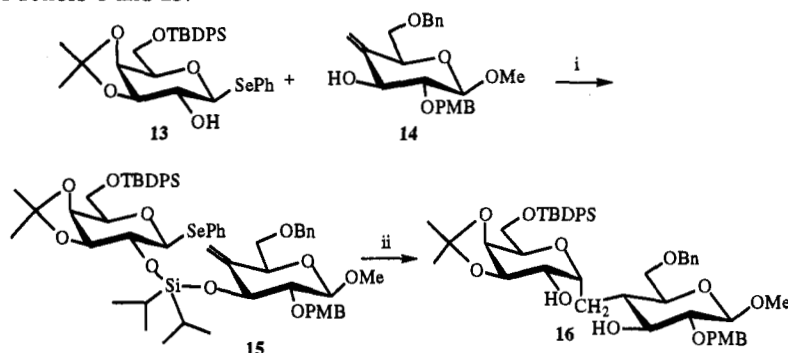
When the galactopyranosyl donor **6** was tethered with the primary hydroxyl group of **3**, selective α -*C*-galactosylation was observed, via a 9-*endo trig* cyclisation process. Although the selectivity was rather limited (ref. 7), compared to the corresponding *C*-glucosylation (Scheme 1), it indicates that this type of tethering induces an α -*C*-glycosylation.

When the same galactopyranosyl donor **6** was now tethered with alcohol **10** (scheme 3), the selectivity of the *C*-galactosylation at C-4 was nicely reversed, and the *C*-lactoside derivative was obtained.



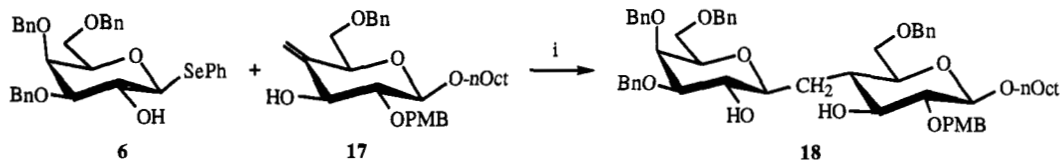
Scheme 3: Reagents: i) 1) **6**, BuLi, 2) Me₂SiCl₂, 3) **10**, DMAP, THF; ii) Bu₃SnH, toluene, reflux; then nBu₄NF / THF (44% overall yield).

Inasmuch as lactose is a biologically relevant target, scheme 3 opens the way to the expeditious synthesis of an interesting mimetic. As shown in scheme 4, a very interesting and alternative way to control the anomery of the C-disaccharide is the substitution pattern on the galactopyranosyl radical donor. The galactosyl donor **13** was tethered with the alcohol through diisopropyl silicon tether. This last tether, which is more stable than the previous one (dimethyl), allows the easy isolation by silica gel flash chromatography of the silaketal **15**, and thus the precise evaluation of the yield of the radical cyclisation. This yield (80%), together with the remarkable α selectivity (>20: 1), clearly demonstrate, in comparison with scheme 3, the complementarity of the two galactosyl donors **6** and **13**.

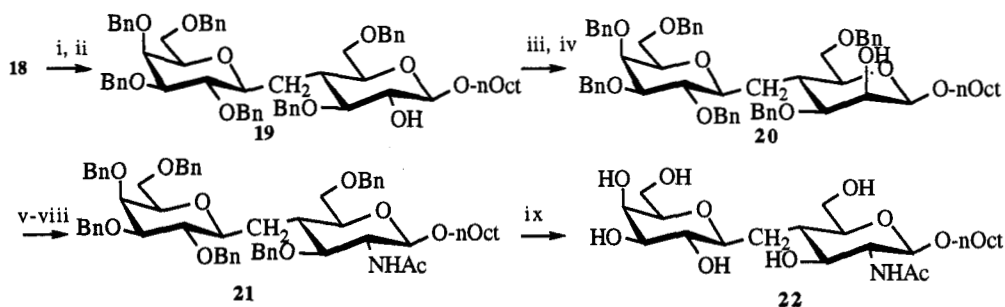


Scheme 4: Reagents: i) 1) BuLi, THF, 0° C, 2) $i\text{Pr}_2\text{SiCl}_2$, 4 equiv., -78° C to r. t., 3) Concentrate to dryness, 4) ROH, DMAP, THF, r. t. (70%); ii) Bu_3SnH , AIBN, toluene, reflux (80%)

Schemes 5 and 6 now describe the synthesis of the β -octyl glycoside of *N*-acetyl-*C*-lactosamine, a compound which is currently studied as a substrate (or inhibitor ?) for α -L-fucosyl transferases.



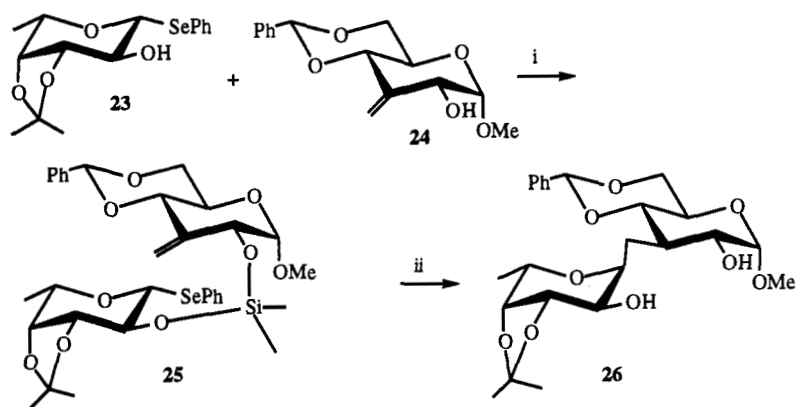
Scheme 5: Reagents: i) 1) **6**, BuLi, 2) Me_2SiCl_2 , 3) **17**, DMAP, THF; ii) Bu_3SnH , toluene, reflux; then TBAF/THF (44% overall yield). nOct = $(\text{CH}_2)_7\text{-CH}_3$; PMB = *p*-methoxybenzyl.



Scheme 6: Reagents: i) BnBr / NaH / THF (87%); ii) DDQ / H_2O / CH_2Cl_2 (72%); iii) Swern oxidation; iv) LiEt_3BH / THF; (85%, two steps); v) MsCl / Et_3N / 0°C; vi) NaN_3 / DMF / 140°C; (84%, two steps); vii) LiAlH_4 / Et_2O ; viii) Ac_2O / pyridine; ix) H_2 , Pd/C, MeOH.

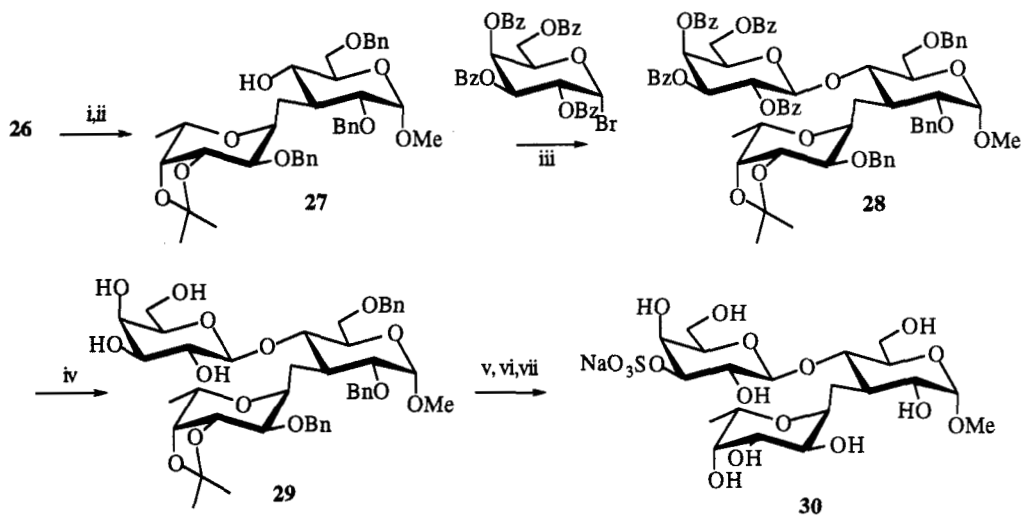
The use of a selenophenyl fucoside for the synthesis of α -C-disaccharides

Another important application of our methodology is the preparation of *C*-disaccharides based on L-Fucose. Scheme 7 is a typical example, whereby the *C*-disaccharide α has been obtained as the only isomer in an excellent 57% overall yield (tethering, cyclisation, untethering).



Scheme 7: Reagents: i) **23**, BuLi , Me_2SiCl_2 (4.4 equiv.), THF , $-78^\circ\text{C} \rightarrow 20^\circ\text{C}$, **24** (1 equiv.), imidazole (2.5 equiv.), THF , r.t. ii) Bu_3SnH (2 equiv.), AIBN (0.3 equiv.), PhMe , 110°C , 17h then Bu_4NF , THF , r.t. (60% overall yield)

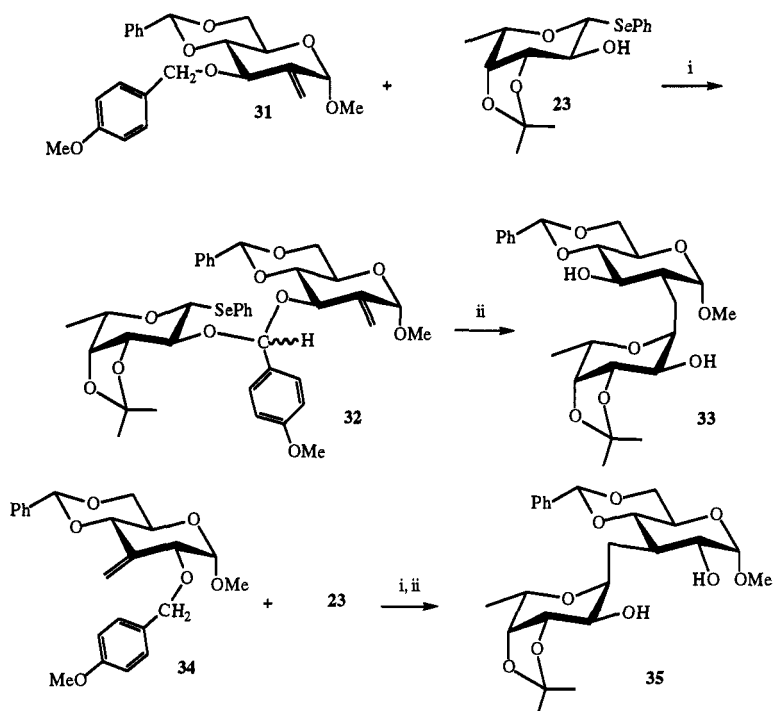
Such a disaccharide has now been transformed into a mixed O-C-sulfated trisaccharide, as shown in the scheme 8.



Scheme 8: Reagents: i) BnBr , NaH , DMF , (100%); ii) NaBH_3CN , HCl , (70%); iii) AgOTf , collidine, 4 Å M.S., (80%); iv) MeONa/MeOH (97 %); v) Bu_2SnO , MeOH ; vi). $\text{SO}_3/\text{Me}_3\text{N}$ (70%, 3 steps); vii) H_2 , Pd/C (100%)

A careful NMR analysis of this sulfated trisaccharide **30** has been achieved, using the recently developed off-resonance ROESY method (ref. 8). It shows that this trisaccharide **30** has a rather limited internal dynamic.

The α -L-C-fucosylation can also be selectively achieved, as shown on scheme 9, either on positions 2 or 3 of D-glucose, by using a ketal tether.(ref. 9)



Scheme 9: Reagents: i) **31** (0.9 equiv.), DDQ (1 equiv.), 4Å M.S., CH₂Cl₂; ii) 1) Bu₃SnH (2.2 equiv.), AIBN (0.2equiv.), PhCH₃, 110°C, 17h; 2) DDQ (14 equiv.), CH₂Cl₂/H₂O, r.t. (**33**: 60% overall yield and **35**: 45% overall yield).

Conclusion

This lecture reports a selection of selective syntheses of C-disaccharides we have recently achieved in our group, clearly demonstrating the potentiality of the tethering approach for the practical synthesis of carbohydrate mimetics of biological relevance. A study of their biological properties is currently underway.

Acknowledgements. The lecturer would like to thank Dr. Jean-Maurice Mallet for the preparation of this manuscript and for his invaluable participation to this research programme. The selected examples have been studied by V. Colliou, E.D. Rekaï, G. Rubinstenn, B. La Ferla, and E. Untersteller.

References.

1. J. Choay, M. Petitou, J. -C. Lormeau, P. Sinay, B. Casu and G. Gatti. *Biochem. Biophys. Res. Commun.* **116**, 492 (1983).
2. Y. Ichikawa and C.H. Wong in *Complex Carbohydrates in Drug Research* (K. Bock and H. Clausen, ed.) pp 118-130, Munksgaard (1994).
3. *Modern Methods in Carbohydrate Synthesis* (S. H. Khan and R. A. O'Neill, ed.), Harwood Academic Publishers (1996).
4. For references on the synthesis of C-disaccharides and other types of carbon-linked disaccharides, see O. R. Martin and W. Lai. *J. Org. Chem.* **58**, 176 (1993). See also a) R. M. Paton and K. J. Penman. *Tetrahedron Lett.* **35**, 3163 (1994); b) D. Mazéas, T. Skrydstrup, O. Doumeix, J.-M. Beau. *Angew. Chem. Int. Ed. Engl.* **33**, 1383 (1994).
5. A. Wei and Y. Kishi. *J. Org. Chem.*, **59**, 88 (1994) and references therein.
6. Y.C. Xin, J.-M. Mallet, and P. Sinay. *J. Chem. Soc., Chem. Commun.* 864 (1993).
7. A. Mallet, J.-M. Mallet, and P. Sinay. *Tetrahedron Asymmetry* **5**, 2593 (1994).
8. a) H. Desvaux, P. Berthault, N. Birlirakis and M. Goldman. *C. R. Acad. Sci. Paris* **317**, 19 (1993); b) H. Desvaux and M. Goldman. *Mol. Phys.* **81**, 955 (1994); c) H. Desvaux and M. Goldman. *J. Chim., Phys.*, **91**, 653 (1994); d) H. Desvaux, P. Berthault, N. Birlirakis and M. Goldman; *J. Magnet. Reson. Ser A* **108**, 219 (1994); e) H. Desvaux, P. Berthault, N. Birlirakis, M. Goldman and M. Piotto. *J. Magnet. Reson. Ser A* **113**, 47 (1995).
9. a) Y.Ito and T.Ogawa. *Angew. Chem. Int. Ed. Engl.* **33**, 17 (1994); b) A.Dan, Y.Ito, and T.Ogawa. *J. Org. Chem.* **60**, 4680 (1995).