Stereoselective Synthesis of α-*C*-L-Fucopyranosyl Containing *C*-Disaccharides

El Djouhar Rekaï , Gilles Rubinstenn, Jean-Maurice Mallet and Pierre Sinaÿ*

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

Fax : +33 (0) 1 44 32 33 97; e-mail : Pierre.Sinay@ens.fr

Stephan N. Müller and Bernd Giese

Institut für Organische Chemie der Universität Basel, St Johanns Ring 19, CH-Basel, Switzerland

Fax: +41 (061) 267 1105; e-mail : giese@ubaclu.unibas.ch

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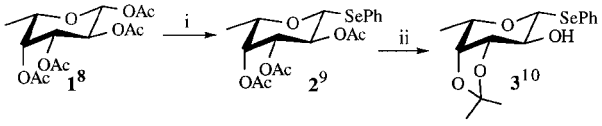
Abstract: A variety of α-*C*-L-fucopyranosyl containing *C*-disaccharides were stereoselectively synthesized by radical coupling of phenyl 3,4-*O*-isopropylidene-Se-β-L-fucopyranoside onto an appropriate *exo*-methylene-sugar, which is temporarily tethered.

In 1983, we reported[1] the first synthesis of a *C*-disaccharide, coining the now accepted name for a molecule which is a close analogue of a regular disaccharide in which the interglycosidic oxygen atom has been replaced by a methylene group. The rationale behind this synthetic chemical challenge was the construction of disaccharide mimics which cannot be hydrolyzed *in vivo* by glycosidases, a property which potentially appoints them as stable mimics of biologically active oligosaccharides. A critical question then is to appreciate to what extent such a replacement - which eradicates the *exo*-anomeric effect - significantly affects the conformation of the molecule, a consequence of dramatic effect for the preservation of the biological activity. From these premises, it is not surprising that a great deal of attention has recently been devoted to the stereoselective synthesis of *C*-disaccharides[2], and also to the study of their conformation[3].

Among natural monosaccharides, L-fucose (6-deoxy-L-galactose) is an important component of biologically active oligosaccharides. A typical example is the α-L-fucose containing sialyl Lewis^x tetrasaccharide, a molecule which is claimed to be responsible for the attachment of neutrophiles to the endothelium, a phenomenon of critical importance for the recruitment of leukocytes to a site of inflammation[4]. This hypothesis has resulted in a recent intense activity in the synthesis of mimics[5].

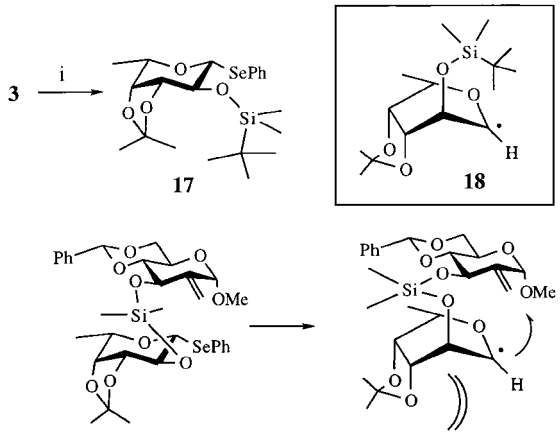
We would like to demonstrate in this letter that the tether approach[6] is remarkably well suited to the stereoselective synthesis of various α-*C*-L-fucopyranosyl containing *C*-disaccharides[7]. The crystalline radical donor **3** constantly used in this study has conveniently been prepared in three steps from the known fully acetylated L-fucose **1**[8], as shown in Scheme 1.



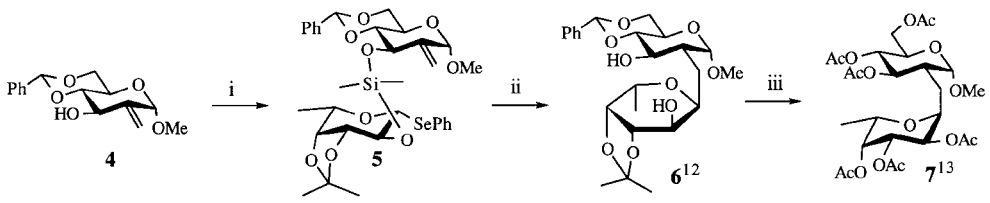
Scheme 1. Reagents: i) PhSeH / BF_3Et_2O, CH_2Cl_2, 0°C, 94% ; ii) a) MeONa/ MeOH, rt; b) 2,2-dimethoxypropane / CSA, CH_2Cl_2, rt, 83%

In a typical reaction, the alcohols **3** and **4**[11] were connected together through a dimethyl silaketal tether to give **5**. An 8-*endo trig* radical cyclization process, followed by desilylation, afforded the protected *C*-disaccharide **6** in 49% yield as the single isomer isolated from the reaction medium. The ^{1}H NMR data[12] call for the assigned structure and for a conformation of the α-C-L-fucosyl moiety which deviated from the $^1C_4$ chair form. This deviation is indeed diagnostic for the α-L-configuration. In order to unambiguously determine the structure of **6**, it was converted into the hexacetate **7**[13] (Scheme 2). In this case, the α-L-fucosyl moiety adopts a $^1C_4$ chair conformation and the ^{1}H NMR spectrum clearly confirms this structure.

Table 1 reports the use of this strategy for the synthesis of various α-*C*-L-fucopyranosyl containing *C*-disaccharides. A characteristic feature of this strategy is that the 8-*endo-trig* radical cyclization consistently resulted in the exclusive formation of an α-*C*-*L*-fucopyranoside. This is most welcome, inasmuch that this anomery is precisely the one found in L-fucose containing glycoconjugates. In order to bring some information about the connection between radical structure and stereoselectivity of radical C-C bond formation, the phenyl Se-β-L-fucopyranoside **3** was converted into **17**[22] (Scheme 3). Upon UV irradiation in degassed benzene solution in the presence of $(Bu_3Sn)_2$, the L-fucopyranos-1-yl radical **18** was generated and shown by electron spin resonance (ESR) spectroscopy to clearly adopt a ^{2,5}B boat conformation[23]. Making the hypothesis that this is the reactive conformer, it is clear that the *exo* approach of the tethered *exo*-methylene sugar is sterically favored (Scheme 3).

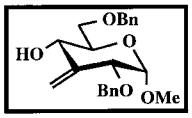
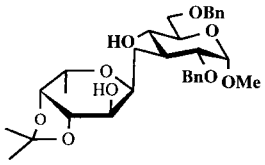
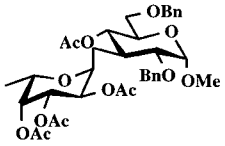
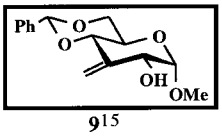
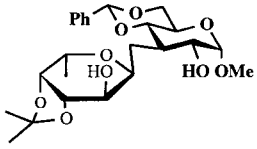
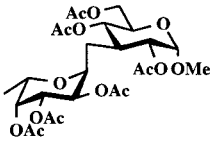
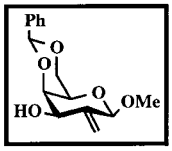
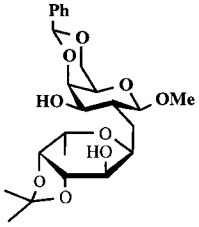
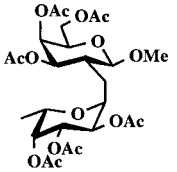


Scheme 3. Reagents: i) TBDMS-Cl, DMAP, Et_3N, DMF, 4d, 40%



Scheme 2. Reagents: i) **3**, BuLi, Me_2SiCl_2, THF, -78°C-> rt, then **4**, DMAP, THF, rt, 18h ; ii) Bu_3SnH, AIBN, toluene, 110°C, 17h then nBu_4NF, H_2O, THF, 1 h, 49% ; iii) aq 80% AcOH, 50°C, 1h, then Ac_2O, Pyr, 95%

Table 1

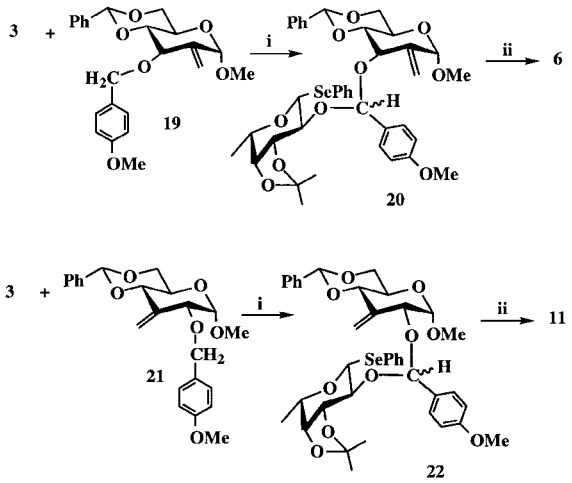
Entry	*C*-fucosyl acceptor	*C*-disaccharide	Coupling constants[a] (Hz)	Yield[b] (%)	Acetylated *C*-disaccharide	Coupling constants (Hz)
A	 **8**[14]	 **11**[18]	$J_{1,2}$ = 3.5 $J_{2,3}$ = 11 $J_{3,4}$ = 10 $J_{4,5}$ = 10 $J_{1',2'}$ = 2.5 $J_{2',3'}$ = 3 $J_{3',4'}$ = 7 $J_{4',5'}$ = 2	41	 **14**	$J_{1,2}$ = 3 $J_{2,3}$ = 11 $J_{3,4}$ = 10.5 $J_{4,5}$ = 10.5 $J_{1',2'}$ = 5 $J_{2',3'}$ = 9 - $J_{4',5'}$ = 2
B	 **9**[15]	 **12**[19]	$J_{1,2}$ = 3.5 $J_{2,3}$ = 11 $J_{3,4}$ = 10.5 $J_{4,5}$ = 9.0 $J_{1',2'}$ = 3.5 $J_{2',3'}$ = 4 $J_{3',4'}$ = 6.5 $J_{4',5'}$ = 2	57	 **15**	$J_{1,2}$ = 3.5 $J_{2,3}$ = 11.5 $J_{3,4}$ = 11 $J_{4,5}$ = 10 $J_{1',2'}$ = 5.5 $J_{2',3'}$ = 9.5 $J_{3',4'}$ = 3.5 $J_{4',5'}$ = 2.5
C	 **10**[16]	 **13**[20]	$J_{1,2}$ = 9.0 $J_{2,3}$ = 11.5 $J_{3,4}$ = 3.5 $J_{4,5}$ = 0 $J_{1',2'}$ = 4.0 $J_{2',3'}$ = 5.5 $J_{3',4'}$ = 6.5 $J_{4',5'}$ = 2.0	38 [c]	 **16**	$J_{1,2}$ = 9.0 $J_{2,3}$ = 11.5 $J_{3,4}$ = 3.0 $J_{4,5}$ = 1.0 $J_{1',2'}$ = 6.0 $J_{2',3'}$ = 10.5 $J_{3',4'}$ = 3.5 $J_{4',5'}$ = 1.5

a) after addition of CCl_3-CO-NCO in $CDCl_3$ (entries A, B) or C_2D_6CO + $CDCl_3$ (entry C). b) Yields refer to chromatographically homogeneous compounds and are calculated for the three steps: tethering, radical cyclisation , and detethering. c) **13** is the major isomer (*galacto* structure at the reducing end); another isomer[21] (*talo* structure) was also isolated (*galacto:talo* 2.8/1); 38 % refers to the overall yield *galacto+talo*

The final H-abstraction by the newly formed radical consistently occurred from the β-side as has been previously observed[6b-d,7a] (Table 1, entries A and B). In the case of the *galacto* compound (entry C) approach from the β–side is hindered by the axial *C*-4 hydroxyl group, so that a mixture of diastereoisomers has been obtained.

We have previously reported on the use of a temporary ketal connection for the successful synthesis of a *C*-disaccharide[24]. In this respect, the *p*-methoxybenzyl ether offers an interesting option, which has elegantly been promoted by T. Ogawa[25] in a similar context. As reported in Scheme 4, the *C*-disaccharides **6** and **11** can also be prepared using this variation on the theme in 60% and 42% overall yield, respectively[26]. One advantage of this route is that the *p*-methoxybenzyl ether, which may act as a protecting group for the preparation of the appropriate *exo*-methylene derivative, can be directly be used for the tethering.

In conclusion, we have demonstrate that - with two variations - tethering of the easily available phenyl Se-β-L-fucopyranoside with a carbohydrate allylic alcohol allows, through an *8-endo-trig* cyclization process, the rather expeditious and stereoselective synthesis of various α-*C*-L-fucopyranosyl containing *C*-disaccharides.



Scheme 4. Reagents : i) DDQ, 4 Å MS. CH_2Cl_2 20°C, 2h30, (**20**: 77%; **22**:83 %) ii) Bu_3SnH, AIBN 110°C, 17h then DDQ, CH_2Cl_2, H_2O (**6** : 60%; **11** : 42%)

References and notes

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(9) All new compounds gave satisfactory elemental analysis. NMR data were in agreement with the proposed structures.

(10) Selected data for **3:** m.p. 77°C (Hexane). $[\alpha]_D^{20}$ -12 (c 1, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ : 7.64-7.18 (m, 5H, Ph), 4.59 (d, 1H, $J_{1,2}$ 10.3 Hz, H-1), 4.02-3.93 (m, 2H, H-3, H-4), 3.8 (dq, 1H, $J_{5,4}$ 2.5 Hz, $J_{5,6}$ 6.25 Hz, H-5), 3.54-3.42 (m, 1H, H-2), 2.38 (d, 1H, $J_{OH,2}$ 2.21 Hz, OH), 1.36 (d, 3H, H-6), 1.31 and 1.26 (2s, 6H, CH_3).

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(12) Selected data for **6 :** $[\alpha]_D^{20}$ + 32 (c 0.57, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ : 4.75 (d, 1H, $J_{1,2}$ 3 Hz, H-1), 4.35 (dd, 1H, $J_{3',4'}$ 7.5, $J_{4',5'}$3.5 Hz, H-4'), 4.20-4.13 (dq, 1H, $J_{5',6'}$6.5, $J_{5',4'}$2 Hz, H-5'), 4.08-4.03 (dt, 1H, $J_{1',2'}$2.5, $J_{1',CH2}$ 7 Hz, H-1'), 3.95 (t, 1H, $J_{3,2} = J_{3,4}$ 9.5 Hz, H-3), 3.51 (t, 1H, $J_{4,5}$ 9.5 Hz, H-4), 3.39 (s, 3H, *O*-CH_3), 2.02-1.82 (m, 3H, H-2, CH_2 bridge), 1.55, 1.38 (2s, 6H, CH_3), 1.28 (d, 3H, H-6').

(13) Selected data for **7 :** ^{1}H NMR (400 MHz, $CDCl_3$): δ : 5.11 (dd, 1H, $J_{2',3'}$ 10.5 Hz, $J_{3',4'}$ 3 Hz, H-3'), 4.98 (t, 1H, $J_{4,3} = J_{4,5}$ 10 Hz, H-4), 4.84 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.22 (dddd, 1H, $J_{1',CHa}$ 1.77 Hz, $J_{1',2'}$ 5.87 Hz, $J_{1',CHb}$ 11.83 Hz, H-1'), 2.08 (m, 1H, H-2), 1.89 (dddd, 1H, $J_{CHb,CHa}$ 15.4 Hz, $J_{CHb,2}$ 7.1 Hz, CH_b), 1.46 (dddd, 1H, $J_{CHa,2}$ 4.23 Hz, CH_a), 1.16 (d, 3H, $J_{6',5'}$ 6.5 Hz, H-6').

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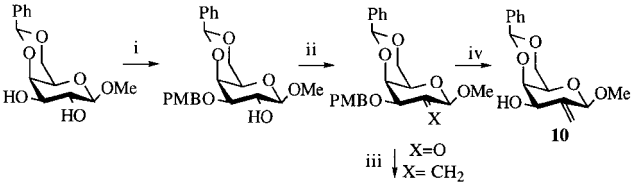
(15) Compound **9** was prepared by selective reductive opening ($NaBH_3CN$, M.S. 4 Å, THF, HCl, diethyl ether, 95%) of the known 4,6-*O*-benzylidene acetal : Yoshimura, J.; Kawauchi, N.; Yasumori, T.; Sato, K-I.; Hashimoto, H. *Carbohydr. Res.* **1984**, *133*, 255.

(16) Compound **10** was prepared from known[17] methyl 4,6-*O*-benzylidene β-D-galactopyranoside (Scheme 5).



Scheme 5. Reagents : i) a) Bu_2SnO / M.S. 4Å / CH_3CN, b) Bu_4NI / PMBCl, 79% ; ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 ; iii) Tebbe reagent / CH_2Cl_2/ THF / Pyr : 22/7/1, 90% ; iv) DDQ / CH_2Cl_2/ H_2O, 88%

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(18) Selected data for **11**: $[\alpha]_D^{20}$ + 35 (c 1.58, $CHCl_3$).

(19) Selected data for **12 :** mp: 191°C (Ethyl Acetate); $[\alpha]_D^{20}$ + 31 (c 1.1, $CHCl_3$).

(20) Selected data for **13 :** mp: 108 °C (Cyclohexane/Ethyl Acetate). $[\alpha]_D^{20}$ - 36 (c 1, $CHCl_3$).

(21) Selected data for the *talo* compound : mp: 112°C (Cyclohexane/ Ethyl Acetate). $[\alpha]_D^{20}$ - 41 (c 2, $CHCl_3$). ^{1}H NMR (400 MHz; $CDCl_3$): δ : 4.43 (d, 1H, $J_{1,2}$ 2Hz, H-1), 4.27 (dd, 1H, $J_{3',4'}$ 7.5 Hz, $J_{3',2'}$ 4.5 Hz, H-3'), 4.17-4.09 (m, 2H, H-6b, H-4), 4.04 (dddd, 1H, $J_{5',4'}$ 2 Hz, $J_{5',6'}$ 6.5 Hz, H-5'). ^{1}H NMR (400 MHz; C_2D_6CO + $CDCl_3$)+ CCl_3-CO-NCO): δ: 5.28 (dd, 1H, $J_{3,2}$ 5 Hz, $J_{3,4}$ 3.5 Hz, H-3), 5.06 (dd, 1H, $J_{2',1'}$ 3 Hz, $J_{2',3'}$ 4.5 Hz, H-2'), 4.81 (d, 1H, $J_{1,2}$ 2.5 Hz, H-1).

(22) Selected data for **17** : m.p. : 81-82 °C (Hexane). $[\alpha]_D^{20}$ + 43 (c 0.46, $CHCl_3$). ^{1}H NMR (250 MHz; $CDCl_3$): δ : 7.61-7.16 (m, 5H, H-ar), 4.74 (d, 1H, $J_{1,2}$ 8.67 Hz, H-1), 3.95 (m, 2H, H-3, H-4), 3.76 (m, 2H, H-2, H-5), 1.44 et 1.29 (2s, 6H, CH_3), 1.32 (d, 3H, $J_{6,5}$ 6.25 Hz, H-6), 0.85 (s, 9H, tbutyl), 0.04 and 0.00 (2s, 6H, 2 CH_3-Si).

(23) ESR data of **18** at 280K; g value : 2.00295; hyperfine splittings (G) : $a(H_\alpha)$ 18.45; $a(H_\beta)$ 1.40; $a(H_\gamma)$ 3.75; $a(H'_\gamma)$ 3.75. For a discussion of ESR coupling constants in carbohydrate radicals, see: a) Dupuis, J.; Giese, B.; Rügge, D.; Fischer, H.; Korth, H.-G. Sustmann, R. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 896. b) Korth, H.-G.; Sustmann R.; Dupuis, J.; Giese, B. *J. Chem.Soc. Perkin Trans. II* **1986**,1453.

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(26) Typical procedure : tethering : A solution of **19** (220 mg, 1.1 equiv) and **3** (165 mg, 1 equiv) in anhydrous dichloromethane (2 mL) was added to a mixture of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (145 mg, 1.15 equiv), molecular sieves 4 Å (900 mg) in anhydrous CH_2Cl_2 (8 mL) at 0°C in the dark. The solution was stirred for 45 min at 0°C then 1h30 at r.t. An aqueous solution of Na_2CO_3 and $Na_2S_2O_5$ was added. The reaction mixture was filtered through celite; the organic layer was separated, dried ($MgSO_4$), and concentrated. Column chromatography (Cyclohexane / Ethyl Acetate / Triethylamine : 6/1/0.01) of the residue gave **20** (300 mg, 84%) as a mixture of two isomers 70/30 (NMR). Cyclisation : A solution of **20** (270 mg, 0.365 mmol) in anhydrous, degassed toluene (15 mL) was refluxed under argon. A solution of Bu_3SnH (246 µL, 2.5 equiv.), AIBN (12 mg, 0.2 equiv.) in anhydrous, degassed toluene (2.5 mL), was added slowly (syringe pump, 17h) to the refluxing solution. The reaction mixture was refluxed for 1 h, and concentrated. Detethering : DDQ (1.23 g, 14 equiv) was added to a solution of the residue in a mixture (CH_2Cl_2 / H_2O : 20/1) (11.5 mL). The reaction mixture was stirred for 1h30 at rt, diluted with CH_2Cl_2, washed with aq. Na_2CO_3, aq. $Na_2S_2O_5$, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography (CH_2Cl_2 / Acetone : 5/1) to give **6** (60%).