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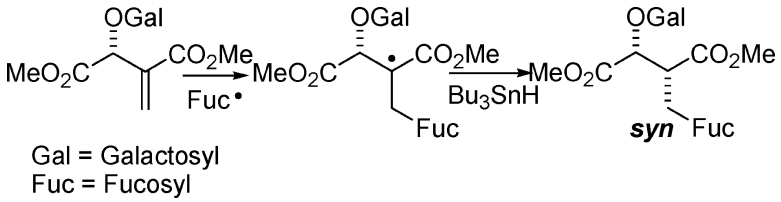

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Synthesis of Postulated Molecular Probes: Stereoselective Free-Radical-Mediated *C*-Glycosylation in Tandem with Hydrogen Transfer

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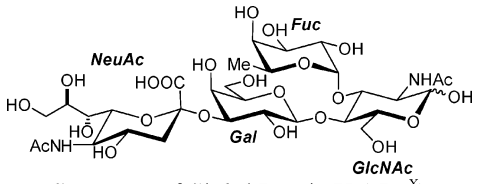
Abstract: Reported herein is a strategy employing an addition reaction in tandem with a hydrogen-transfer reaction for the elaboration of *C*-glycoside-based sialyl Lewis X (sLe^X) analogues. Significant stereocontrol was noted when alkyl radicals were reacted with a series of alkoxytaconates. Transition states were proposed to explain the obtained selectivity. Further reaction between an anomeric-centered fucosyl-derived radical and a galactosylated hydroxytaconate provided easy access to *C*,*O*-diglycosides as mimics of sLe^X. In this case, two 1,3-distant stereocenters were created with high diastereoselectivity using free radical intermediates in a tandem process.

The present study stems from our interest in what could appear to be unrelated scientific issues: the discovery of new synthetic methodologies that allow for diastereoselective modifications[1−3] of acyclic free radical intermediates, and the development of sialyl Lewis X (sLe^X) mimetics as antagonists of *E*- and *P*-selectins. The latter originates from our interest in altering the biological effects mediated by the interaction between posttranslationally modified proteins (e.g., glycoproteins) and their receptors.[4]



Structure of Sialyl Lewis X (sLe^X)

The selectin-dependent vascular adhesion of neutrophils, in response to pro-inflammatory stimuli, is an example of such. Disrupting the interactions between *E*- and *P*-selectins and their respective ligands, ESL-1 (*E*-selectin ligand-1) and PSGL-1 (*P*-selectin glycoprotein ligand-1), which are located at the surface of neutrophils and malignant cells, is believed to be promising as a new treatment for inflammatory diseases[5] or certain forms of invasive cancer.[6]

At the molecular level, recent X-ray diffraction analysis of sLe^X (alone as well as attached to the PSGL-1 *N*-terminus) bound to *P*-selectin clearly established[7] the main pharmacophores to be the sialylated galactose (NeuAc-Gal) and fucose (Fuc) subunits through electrostatic attraction and H-bonding, the *N*-acetylglucosamine (GlcNAc) only acting as a tether. Similar conclusions were empirically reached through structure−activity relationship studies, aimed at preventing the interactions between *E*- and *P*-selectins and their sLe^X-containing ligands, as the replacement of the GlcNAc subunit of sLe^X, while unattached to the protein, by different tethers (cyclic as well as acyclic) led to potent antagonists in competition-based assays.[8]

(1) For reviews on the synthetic usefulness of free-radical-mediated reactions see: (a) *Radicals in Organic Synthesis, Volume 1: Basic Principles*; Renaud, P., Sibi, M. P., Eds/; Wiley-VCH: Weinheim, Germany, 2001. (b) *Stereochemistry of Radical Reactions: Concepts Guidelines, and Synthetic Applications*; Curran, D. P., Porter, N. A., Giese, B., Eds.; Wiley-VCH: New York, 1996.

(2) For stereoselective free-radical-based hydrogen-transfer reactions, see: (a) Guindon, Y.; Murtagh, L.; Caron, V.; Landry, S. R.; Jung, G.; Bencheqroun, M.; Faucher, A.-M.; Guérin, B. *J. Org. Chem.* **2001**, *66*, 5427. (b) Bouvier, J.-P.; Jung, G.; Liu, Z.; Guérin, B.; Guindon, Y. *Org. Lett.* **2001**, *3*, 1391. (c) Guindon, Y.; Faucher, A.-M.; Bourque, E.; Caron, V.; Jung, G.; Landry, S. R. *J. Org. Chem*. **1997**, *62*, 9276. (d) Guindon, Y.; Rancourt, J. *J. Org. Chem.* **1998**, *63*, 6554. (e) Guindon, Y.; Liu, Z.; Jung, G. *J. Am. Chem. Soc.* **1997**, *119*, 9289. (f) Guindon, Y.; Slassi, A.; Rancourt, J.; Bantle, G.; Bencheqroun, M.; Murtagh, L.; Ghiro, E.; Jung, G. *J. Org. Chem*. **1995**, *60*, 288. (g) Guindon, Y.; Yoakim, C.; Gorys, V.; Ogilvie, W. W.; Delorme, D.; Renaud, J.; Robinson, G.; Lavallée, J.-F.; Slassi, A.; Jung, G.; Rancourt, J.; Durkin, K.; Liotta, D. *J. Org. Chem*. **1994**, *59*, 1166. (h) Giese, B.; Damm, W.; Wetterich, F.; Zeitz, H. G.; Rancourt, J.; Guindon, Y. *Tetrahedron Lett.* **1993**, *34*, 5885. (i) Guindon, Y.; Lavallée, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701.

(3) For stereoselective free-radical-based allylation reactions, see: (a) Guindon, Y.; Houde, K.; Prévost, M.; Cardinal-David, B.; Landry, S. R.; Daoust, B.; Bencheqroun, M.; Guérin, B. *J. Am. Chem. Soc.* **2001,** 123, 8496. (b) Guérin, B.; Chabot, C.; Mackintosh, N.; Guindon, Y. *Can. J. Chem.* **2000**, *78*, 852. (d) Guindon, Y.; Jung, G.; Guérin, B.; Ogilvie, W. W. *Synlett* **1998**, 213. (e) Guindon, Y.; Guérin, B.; Chabot, C.; Ogilvie, W. W. *J. Am. Chem. Soc.* **1996**, *118*, 12528. (f) Guindon, Y.; Guérin, B.; Chabot, C.; Mackintosh, N.; Ogilvie, W. W. *Synlett* **1995**, 449.

(4) (a) Bhunia, A.; Jayalakshmi, V.; Benie, A. J.; Schuster, O.; Kelm, S.; Rama Krishna, N.; Peters, T. *Carbohydr. Res.* **2004**, *339*, 259. (b) Ideo, H.; Seko, A.; Ishizuka, I.; Yamashita, K. *Glycobiology* **2003**, *13*, 713R. (c) Thomas, B. E.; Kaila, N. *Med. Res. Rev.* **2002**, *22*, 566. (d) Beum, P. V.; Cheng, P. W. *Adv. Exp. Med. Biol*. **2001**, *491*, 279.

(5) Alper, J. *Science* **2003**, *301*, 159.

(6) Hopfner, M.; Alban, S.; Schumacher, G.; Rothe, U.; Bendas, G. *J. Pharm. Pharmacol*. **2003**, *55*, 697.

(7) Somers, W. S.; Tang, J.; Shaw, G. D.; Camphausen, R. T. *Cell* **2000**, *103*, 467.

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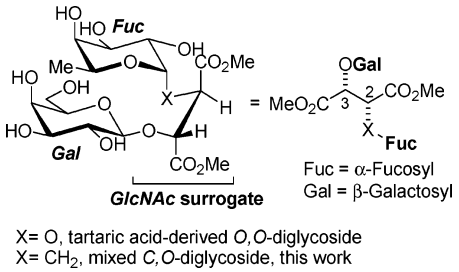
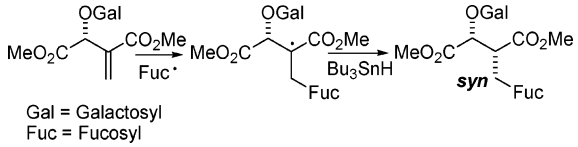


Figure 1. Tartrate-derived *O*,*O*- and *C*,*O*-diglycosides as GlcNAc mimics.

Scheme 1



In this regard, we became interested in testing the value of *O*,*O*-diglycosides derived from dimethyl tartrate (Figure 1, X = O) as sLe^X analogues, for both theoretical and practical reasons.

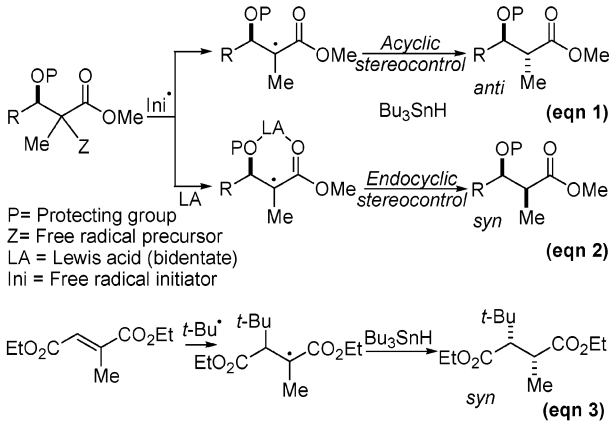
On one hand, previous studies by our group have shown that the preferred conformation of tartrate derivatives involves both esters being *anti*-oriented, to minimize electrostatic repulsion, and the ethereal oxygens (Figure 1, X = O) *gauche* to each other.[9] This led us to hypothesize that the tartrate moiety could be an acceptable surrogate to GlucNAc. Indeed, if fucose and galactose subunits were attached to it, they could adopt a conformation similar to the sLe^X bioactive one.[7] On the other hand, apart from being crucial for the conformational bias described above, the presence of ester functionalities should enable the coupling of members of this "trisaccharide" family to other chemical entities (e.g., proteins, peptides, polymer support, etc.). These "postulated molecular probes" could be of use in various biochemical techniques: affinity chromatography, cell sorting, etc.

A number of studies were launched to prepare these tartrate derivatives (*O*,*O*-diglycosides) to test these hypotheses. It quickly became obvious that efforts also had to be directed toward the synthesis of derivatives with intrinsic gain in stability against acid- and glycosidase-mediated hydrolysis. This led us to look at mixed *C*,*O*-diglycosides (Figure 1, X = CH_2) in which one of the oxygens is replaced by a methylene. A new chemical strategy to the synthesis of this series of molecules first had to be designed and tested, which is the object of the study reported herein.

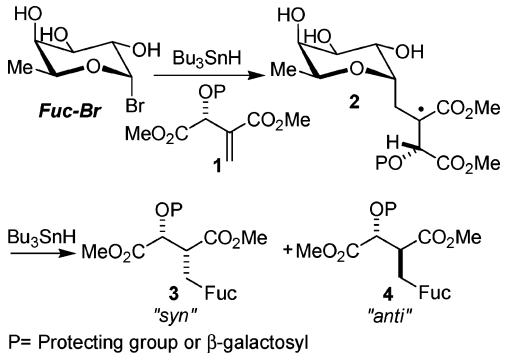
From the beginning of this project, we were interested by the use of free radical intermediates to establish the relative stereochemistry of the acyclic tether, as illustrated in Scheme 1. In fact, we were inspired by a number of reports on the stereoselective free-radical-mediated synthesis of β-alkoxy esters.

Indeed, we and others[1−3,10,11] have shown that free-radical-based hydrogen-transfer processes can be used to produce α-alkyl-β-alkoxy esters with high stereocontrol. As described in Scheme 2, high *anti* selectivity was obtained when α-bromo or α-(phenylselenyl) esters reacted with tributyltin hydride and

Scheme 2



Scheme 3. Addition of 1-Fucosyl Radical to β-Alkoxytaconate **2** in Tandem with a Hydrogen-Transfer Reaction



a free radical initiator (e.g., Et_3B; see eq 1). The addition of bidentate Lewis acids in such reactions was found to reverse the sense of stereoselectivity (coined *the endocyclic effect*;[2d,i] see eq 2), the *syn* compounds being predominant.

Interestingly, replacing the β-alkoxy substituent by an ester was reported[12] to lead to a *syn* stereochemistry, as shown in eq 3. Indeed, good stereoselectivity was noted when hindered radicals were added on diethyl 2-methylfumarate. The synthesis of our proposed targets, as described in Scheme 3, would involve the addition of radicals to β-alkoxytaconates, in which both an ester and an alkoxy group are present at the stereodeterminant center. Thus, the first question: What would be the combined effects of these functionalities on the stereoselectivity of the hydrogen-transfer reaction? A second, and perhaps even more interesting question arose: Could an anomeric-based free radical, generated from a glycosyl halide, be a suitable reactive species for the addition to an α-alkoxytaconate as a radical trap? One could then envisage controlling two new noncontiguous

(8) See for example: (a) Kolb, H. C.; Ernst, B. *Chem.—Eur. J.* **1997**, 1571. (b) Jahnke, W.; Kolb, H. C.; Blommers, M. J. J.; Magnani, J. L. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2603. (c) Kolb, H. C.; Ernst, B. *Pure Appl. Chem.* **1997**, *69*, 1879.

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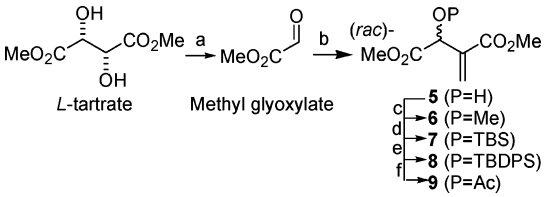
(11) (a) Hartung, J.; Gottwald, T.; Spehar, K. *Synthesis* **2002**, 1469. (b) Hartung, J. *Eur. J. Org. Chem.* **2001**, *4*, 619. (c) Hartung, J.; Kneuer, R. *Eur. J. Org. Chem.* **2000**, 1677. (d) Guindon, Y.; Guérin, B.; Landry, S. R. *Org. Lett.* **2001**, *3*, 2293. (e) Hartung, J.; Schwarz, M.; Svoboda, I.; Fuess, H.; Duarte, M. T. *Eur. J. Org. Chem.* **1999**, *6*, 1275. (f) Guindon, Y.; Denis, R. C. *Tetrahedron Lett.* **1997**, *39*, 339. (g) Hartung, J.; Gallou, F. *J. Org. Chem.* **1995**, *60*, 6706.

(12) Bulliard, M.; Zeitz, H.-G.; Giese, B. *Synlett* **1991**, 423.

Scheme 4[a]



[a] Reagents and conditions: (a) HIO_4, THF; (b) DABCO, methyl acrylate, THF, 68%; (c) Ag_2O, MeI, CH_2Cl_2, 75%; (d) (TBS)Cl, imidazole, CH_2Cl_2, 82%; (e) TBDPSCl, imidazole, CH_2Cl_2, 83% (f) Ac_2O, 2,6-lutidine, CH_2Cl_2, −50 °C, 82%.

stereogenic centers in this novel tandem process, as illustrated in Scheme 3.

The first stereocenter would result from a selective α-*C*-glycosylation under stereoelectronic control, as pioneered by Giese and others.[13] The second stereocenter would result from a hydrogen-transfer reaction involving the intermediate free radical adduct **2**, to give the "*syn*" isomer **3**. These are the hypotheses we seek to test in this first study.

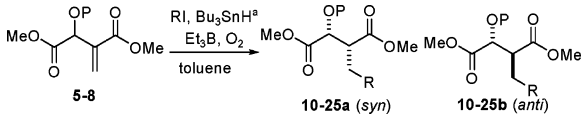
Results and Discussion

A Baylis−Hillman condensation was used to synthesize our target radical traps, as illustrated in Scheme 4. The reaction between methyl acrylate and methyl glyoxylate, obtained from HIO_4-mediated oxidative cleavage of dimethyl tartate, gave the alcohol **5** in good yield, which was subsequently converted to the various ethers **6**, **7**, and **8** as well as to the acetate **9**.

To these substrates were added various alkyl radicals, all generated from their corresponding iodides, using Et_3B/O_2 as the initiator. As seen in Table 1, only modest *anti*[14] selectivity was noted when the free alcohol **5** was used as the substrate (entries 1−4). Similar results were obtained for the methyl ether **6** when primary and secondary alkyl radicals were added (entries 5−7). Interestingly, a reversal of diastereoselectivity was observed when the *tert*-butyl radical was added (entry 8). With the silyl ethers **7** and **8**, the results were much more consistent in terms of *syn* preference. In both cases, the diastereocontrol increased with the steric encumbrance of the alkyl radical (Me < *i*-Pr < c-Hex < *t*-Bu), the TBDPS series giving a better ratio (entries 13−16) than their TBS counterparts (entries 9−12). Of particular importance, bearing in mind the planned tandem sequence, is the 11:1 *syn*:*anti* ratio obtained using cyclohexyl radical in conjunction with the TBDPS ether **8** (entry 15).

Figure 2 illustrates the importance of the ester group on the stereogenic center for the hydrogen-transfer reaction to proceed with *syn* selectivity. Indeed, compounds **17** and **18** (R = CO_2-Me) were obtained in a *syn*-selective manner,[2d] whereas **26** and **27** (R = Me) were produced with no (or even slightly *anti*) selectivity.

Table 1. Addition of Alkyl-Derived Free Radicals in Tandem with a Diastereoselective Hydrogen-Transfer Reaction[a]



entry	radical trap	R	products	ratio[b] (*syn*:*anti*)	yield (%)
1	**5** (P = H)	Me	10a,b	1:2	77
2	**5** (P = H)	*i*-Pr	11a,b	1:3	68
3	**5** (P = H)	c-Hex	12a,b	1:2.5	64
4	**5** (P = H)	*t*-Bu	13a,b	1:1.5	68
5	**6** (P = Me)	Me	14a,b	1:2.5	75
6	**6** (P = Me)	*i*-Pr	15a,b	1:1	70
7	**6** (P = Me)	c-Hex	16a,b	1:2	80
8	**6** (P = Me)	*t*-Bu	17a,b	5:1	86
9	**7** (P = TBS)	Me	18a,b	2.5:1	59
10	**7** (P = TBS)	*i*-Pr	19a,b	4.5:1	84
11	**7** (P = TBS)	c-Hex	20a,b	6:1	91
12	**7** (P = TBS)	*t*-Bu	21a,b	11:1	83
13	**8** (P = TBDPS)	Me	22a,b	7:1	63
14	**8** (P = TBDPS)	*i*-Pr	23a,b	9:1	68
15	**8** (P = TBDPS)	c-Hex	24a,b	11:1	67
16	**8** (P = TBDPS)	*t*-Bu	25a,b	17:1	81

[a] Conditions: to a solution of the olefin and the halide (0.05M) in toluene was slowly added (0.5 mL/h) Bu_3SnH (2 equiv, 1 M) in toluene. Initiation was accomplished using Et_3B (0.2 equiv) every 20 min. [b] Ratios of crude product mixtures were determined by ^1H NMR.

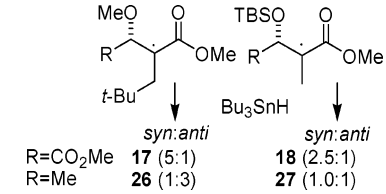


Figure 2. Importance of the β-positioned ester functionality on the *syn* selectivity during the hydrogen-transfer reaction.

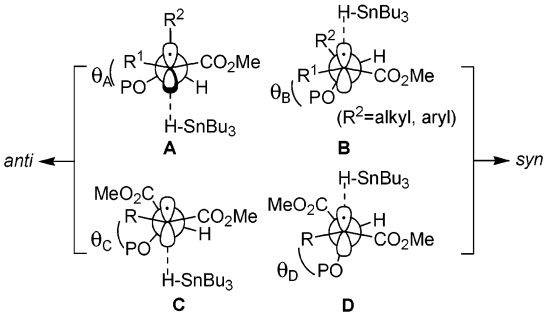


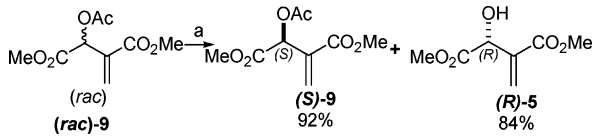
Figure 3. Proposed transition states.

These results could be rationalized using variants of transition states that we and others have previously suggested[2,3] to explain the experimental results obtained in a hydrogen-transfer reaction involving carbon-centered free radicals flanked on one side by a stereogenic center bearing an oxygen and on the other side by an ester (Scheme 2, eqs 1 and 3). Minimization of intramolecular dipole−dipole interactions and of the allylic 1,3-strain in these π-delocalized radicals prompted us to propose two transition states: **A** leading to the *anti* and **B** leading to the *syn* products (Figure 3). The product distribution of any specific reaction of this type would be dictated by the difference

(13) (a) Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700. (b) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 969. (c) Giese, B.; Linker, T.; Muhn, R. *Tetrahedron* **1989**, *45*, 935. (d) Giese, B.; Hoch, M.; Lamberth, C.; Schmidt, R. R. *Tetrahedron Lett.* **1988**, *29*, 1375. (e) Giese, B. *Pure Appl. Chem.* **1988**, *60*, 1655. (f) Giese, B.; Dupuis, J.; Nix, M. *Org. Synth.* **1987**, *65*, 236. (g) Giese, B.; Dupuis, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 622.

(14) The configuration of the *syn* and *anti* alcohols **10** and **11** was previously assigned; see: (a) Bhat, K. S.; Dixit, K. N.; Rao, A. S. *Indian J. Chem. Sect. B* **1985**, *24*, 509 (b) Wasmuth, D.; Arigoni, D.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 344. (c) Nakata, M.; Ishiyama, T.; Hirose, Y.; Maruoka, H.; Tatsuta, K. *Tetrahedron Lett.* **1993**, *34*, 8439. (d) Nakata, M.; Ishiyama, T.; Akamatsu, S.; Hirose, Y.; Maruoka, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 967. These known alcohols were subsequently derived in the corresponding methyl and silylated ethers and their NMR data compared. In all cases the chemical shifts of the hydrogens on the carbons bearing the ethers of the *anti* isomers were upfield of those of the *anti* compounds, and the constant couplings (H_2-H_3) of the *anti* compounds greater than their *syn* counterparts. This assignment was confirmed by X-ray analysis of compound **33a**.

Scheme 5[a]



[a] Reagents and conditions: (a) *Candida rugosa* lipase, toluene, pH 7 buffer.

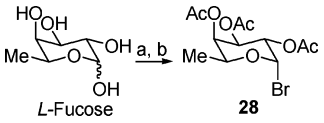
in energy between these transition states. As reported before,[2] *anti* products were prevalent when P was small (e.g., methyl or benzyl) and R^2 significant from a steric standpoint (isopropyl or higher alkanes). The ratios dropped when the steric encumbrance of P or R^1 increased (see Figure 2, formation of **26** and **27**). In those cases, minimization of the now important allylic 1,2-strain, by increasing the angle θ_A (Figure 3), placed OP in the trajectory of the incoming hydride reagent in **A**, thus raising the energy of this *anti*-leading transition state. In the case of hydroxytaconate-derived radicals, the presence of an additional electron-withdrawing group on the oxygen-bearing stereogenic center would change the delicate balance between steric and electronic factors by affecting the latter. Indeed, the dipole moment is no longer defined solely by the C−O bond in these cases, due to the presence of the additional ester functionality. We therefore suggest that, as seen in transition state **C**, the resulting angle θ_C, between R and OP, is greater than the corresponding θ_A for transition state **A**, thus impeding the approach of the incoming reagent in the case of transition state **C**. Similarly, since θ_D is thought to be greater than θ_B, by invoking the same electronic argument, the top face attack should be facilitated in **D**. Thus, having increased the energy of transition state **C** and decreased that of **D**, one would expect the *anti* preference to be lower in the present cases. In this particular situation, increasing the steric encumbrance of R and OP should further increase θ_C and θ_D, so far facilitating the top face attack of the reagent, at the expense of the bottom face, thus allowing the *syn* products to be favored as experimentally noted. ESR studies[15] to evaluate the ground-state conformation of such radicals are planned to support the aforementioned hypothesis.

Knowing the controlling factors of the free radical addition−hydrogen-transfer sequence, we then turned our attention to the second objective of our study aiming at the synthesis of our pseudo-trisaccharides: the addition of an anomeric-centered free radical to a chiral taconate-derived radical trap. Kinetically controlled enzyme-based resolution (Scheme 5) of the racemic acetate **9**, using *Candida rugosa* lipase,[16] afforded the enantiopure alcohol (*R*)-**5**, which was converted to the TBDPS ether (*R*)-**8**.

To a toluene solution containing the silyl ether (*R*)-**8** and the known[17] peracetylated bromofucoside **28** (see the preparation in Scheme 6) was slowly added tributyltin hydride in the presence of Et_3B and O_2.

As illustrated by entry 1 (Table 2), exciting results were observed. First, as expected, stereoselective attack of the radical

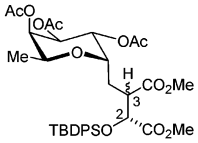
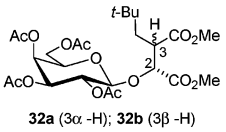
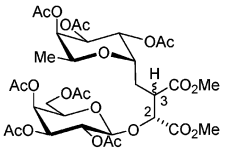
Scheme 6[a]



[a] Reagents and conditions: (a) Ac_2O, pyridine, DMAP; (b) HBr, AcOH, quantitative.

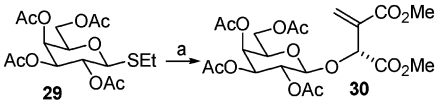
Table 2. Diastereoselective *C*-Glycosylation in Tandem with Hydrogen Transfer Involving Free Radical Intermediates

R^1X + Radical Trap $\xrightarrow[O_2,\ \text{toluene, } 23^\circ C]{Bu_3SnH^a,\ Et_3B}$ Products

Entry	R^1X	Radical Trap	Products	Yield% (*syn:anti*)
1	**28**	(*R*)-**8**	 **31a** (3α -H); **31b** (3β -H)	61 (12:1)
2	***t*-BuI**	**30**	 **32a** (3α -H); **32b** (3β -H)	-[c] (>20:1)
3	**28**	**30**	 **33a** (3α -H); **33b** (3β -H)	92 (7:1)

[a] Conditions: to a solution of the olefin and the halide (0.05 M) in toluene was slowly added (0.5 mL/h) Bu_3SnH (2 equiv, 1 M) in toluene. Initiation was accomplished using Et_3B (0.2 equiv) every 20 min. [b] Ratios of crude product mixtures were determined by ^1H NMR. [c] Products were not isolated.

Scheme 7[a]



[a] Reagents and conditions: (a) (*R*)-**5**, NIS, TfOH, CH_2Cl_2, −30 °C, 48%.

trap occurred on the α face of the anomeric-centered free radical, no β-anomer being detected in the crude reaction mixture. Second, the reduced products **31a** and **31b** were obtained in a 12:1 ratio, favoring the 2,3-*syn* stereochemistry.

Substituting the silyl-derived protecting group by a β-galactosyl moiety was then accomplished. Reaction between the alcohol **5** and the peracetylated 1-ethylthiogalactose **29**[18] (Scheme 7) afforded the β-galactoside **30**, the anomeric configuration resulting from the well-known anchimeric participation[19] of the C-2 acetate group.

The *tert*-butyl radical was then added to the new radical trap **30** to verify if the steric encumbrance of the sugar moiety would be sufficient to provide stereocontrol during the hydrogen-transfer step. As seen in entry 2, high stereocontrol was achieved, as only **32a** was observed by NMR. The addition of

(15) (a) Giese, B.; Damm, W.; Wetterich, F.; Zeitz, H.-G. *Tetrahedron Lett.* **1992**, *33*, 1863. (b) Giese, B.; Damm, W.; Wetterich, F.; Zeitz, H.-G.; Rancourt, J.; Guindon, Y.; *Tetrahedron Lett.* **1993**, *34*, 5885.
(16) (a) Iding, H.; Wirz, B.; Sarmiento, R.-M. R. *Tetrahedron: Asymmetry* **2003**, *14*, 1541. (b) Warwel, S.; Borgdorf, R. *Biotechnol. Lett.* **2000**, *22*, 1151. (c) Kapeller, H.; Jary, W. G.; Hayden, W.; Griengl, H. *Tetrahedron: Asymmetry* **1997**, *8*, 245.
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(19) (a) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1576. (b) Lemieux, R.; Hayami, J. *Can. J. Chem.* **1965**, *43*, 2162.

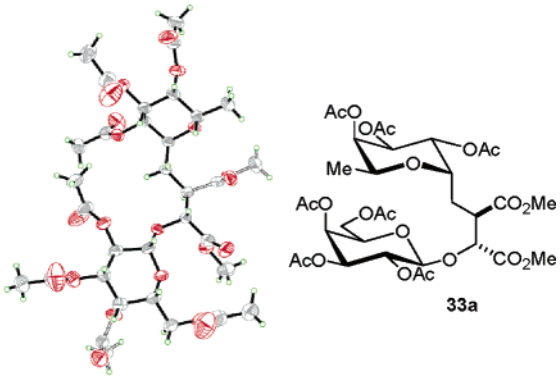

Figure 4. Structure of **33a** as determined by X-ray diffraction analysis.

the fucosyl radical derived from **28** was then performed, as described in entry 3. Once again, exclusive formation of the α-anomers was observed; **33a/b** being obtained in a 7:1 ratio as the result of the hydrogen-transfer reaction. Though the selectivity was slightly less than what we observed in the case of the addition of "secondary" radicals in the pilot study, this is nonetheless an impressive result.

X-ray crystal diffraction analysis of the desired compound **33a** confirmed the absolute and relative configurations of the newly formed stereocenters, as depicted in Figure 4. One should note the *gauche* orientation, not only between the two sugar counterparts, but also between both carboxylic ester groups. This suggests a conformational bias different from the one observed with di-*O*-tartrate-derived diethers, consequences of which will be further evaluated in relevant biological systems.

Conclusion

The present study illustrated the use of an anomeric carbon-centered free radical in an addition reaction to α,*β*-unsaturated esters, followed by a hydrogen-transfer reaction. Two 1,3-distant stereogenic centers were formed in good yield and ratio, attesting to the potential usefulness of free radical intermediates in the synthesis of highly functionalized molecules. In particular, this approach offers an original route to the synthesis of new families of pseudo-trisaccharides. The impact of such molecules and their derivatives as putative receptor antagonists, or as molecular probes, remains to be evaluated. The results of those studies will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data of new compounds (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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