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Synthesis of β-*C*-*galacto*-Pyranosides with Fluorine on the Pseudoanomeric Substituent

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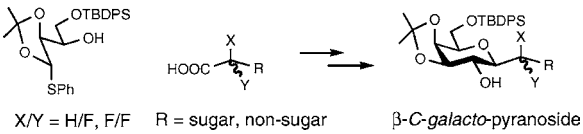
ABSTRACT



***β*-*C*-*galacto*-Pyranosides with CHF and CF_2 substitutes for the glycosidic oxygen were prepared through a four-step sequence starting from a central 1-thio-1,2-*O*-isopropylidene acetal alcohol and different α-fluoro- and α,α-difluoro acids. The key step in the synthesis is the oxocarbenium cyclization of an intermediate enol ether-thioacetal to a C1-substituted glycal.**

Exact *C*-glycosides **2**, analogues of *O*-glycosides **1** in which the glycosidic oxygen is replaced by a methylene moiety, have attracted attention as hydrolytically stable mimetics of their parent *O*-glycosides (Figure 1).[1] However, the effectiveness of *C*-glycosides as *O*-glycoside mimetics could be compromised by electronic effects associated with replacing an oxygen with a methylene.[2] For example, *C*-glycosides are likely to be less accurate mimetics in cases where the glycosidic oxygen acts as a hydrogen bond acceptor. Receptor binding could also be adversely affected by the greater flexibility of *C*-glycosides with respect to the intersaccharide bonds.[3−5] Against this backdrop, we were interested in *C*-glycosides such as **3** and **4** with one or two fluorines on

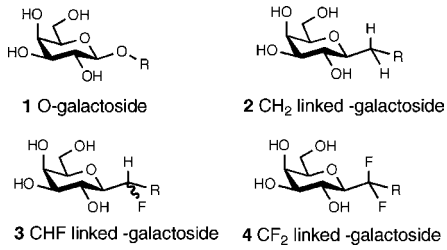


Figure 1. *O*- vs *C*-glycosides.

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(1) For *C*-glycoside reviews: Postema, M. H. D. *C-Glycoside Synthesis*; CRC Press: Boca Raton, Fl, 1995. Levy, D. E.; Tang, C. *The Synthesis of C-Glycosides*; Pergamon: Oxford, 1995. Beau, J.-M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1−54. Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700−717. Du, Y.; Linhardt, R. J.; Vlahov, J. R. *Tetrahedron* **1998**, *54*, 9913−9959. Postema, M. H. D.; Piper, J. L.; Betts, R. L. *Synthesis* **2005**, 1345−1358. Yuan, X.; Linhardt, R. J. *Curr. Top. Med. Chem.* **2005**, *5*, 1393−1430. Levy, D. E. In *The Organic Chemistry of Sugars*; Levy, D. E., Fügedi, P., Eds.; CRC Press/Taylor & Francis: Boca Raton, 2005; p 269−348.

(2) For examples of relative activity of *O*-glycosides and their exact *C*-glycoside analogues: Acton, E. M.; Ryan, K. J.; Tracy, M.; Arora, S. K. *Tetrahedron Lett.* **1986**, *27*, 4245−4248. Wei, A.; Boy, K. M.; Kishi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9432−9436. Uchiyama, T.; Vassilev, V. P.; Kajimoto, T.; Wong, W.; Huang, H.; Lin, C.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1995**, *117*, 5395−5396. Xin, Y.-C.; Zhang, Y.-M.; Mallet, J.-M.; Glaudemans, C. P. J.; Sinaÿ, P. *Eur. J. Org. Chem.* **1999**, 471−476. Link, J. T.; Sorensen, B. K. *Tetrahedron Lett.* **2000**, *41*, 9213−9217. Mikkelsen, L. M.; Hernáiz, M. J.; Martín-Pastor, M.; Skrydstrup, T.; Jiménez-Barbero, J. *J. Am. Chem. Soc.* **2002**, *124*, 14940−14951. Yang, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 3818−3822.

(3) Jiménez-Barbero, J.; Espinosa, J. F.; Asensio, J. L.; Cañada, F. J.; Poveda, A. *Adv. Carbohydr. Chem. Biochem.* **2001**, *56*, 235−284.

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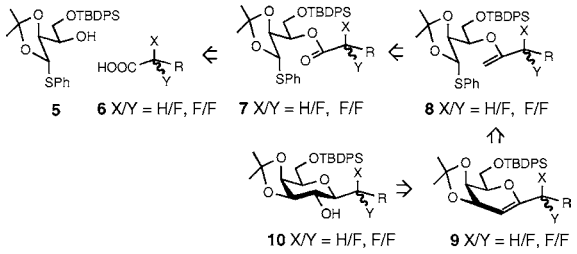
the pseudoanomeric substituent.[6,7] Given the electronegativity properties of fluorine, such structures may function as closer mimetics of *O*-glycosides, compared to the unsubstituted methylene analogues.[6,8] In this context, the CF_2 moiety has been considered an electronic isostere of oxygen. However, the generality of this tenet has been questioned, and it has been suggested that the CHF group may be a closer isopolar substitute for oxygen.[9,10] Fluorine substitution on the pseudoanomeric carbon substituent could also have a pronounced influence on the conformational behavior about the intersaccharide torsions.[11] This situation is analogous to distortion of the natural conformation of the sugar residue in nucleosides by introduction of a 2-fluoro substituent.[12] Thus, *C*-glycosides with one or two fluorine substituents on the pseudoanomeric carbon are potentially useful mechanistic probes for interrogation of carbohydrate recognition. Herein we describe the synthesis of such fluorinated β-*C*-galactosides.

An obvious strategy for *C*-glycosides such as **3** and **4** is the reaction of alcohol and keto derivatives with fluorinating agents.[13] Although several methodologies to synthesize these precursors have been developed,[1] the fluorination of such highly substituted substrates can be problematic. A convergent approach in which fluorine is introduced in simpler precursors is potentially more general, and in this context, we envisaged a variation of our previously reported *C*-glycoside synthesis.[14] Accordingly, a fluorinated *C*-glycoside such as **10** may be obtained from the stereoselective hydroboration−oxidation of the C1-substituted galactal **9** (Scheme 1). The latter is expected from the thioacetal-enol

Scheme 1



ether **8**, via an oxocarbenium ion cyclization. Precursors such as **8** could be assembled in a convergent fashion through an esterification−methylenation sequence starting from the 1-thio-1,2-*O*-isopropylidene alcohol **5** and different mono- or difluoroacids **6**. Because the original methodology was applied to systems which did not contain an electronegative substituent in the eventual pseudoglycosidic position, there was some concern that the presence of one or more fluorine substituents in this location could have deleterious effects at different stages in the synthetic sequence, in particular, on the oxocarbenium ion cyclization (i.e., **8** → **9**).[15] A second issue that had to be addressed was synthesis of more complex examples of the fluorinated acid precursors **6**.

Acid precursors **6**, for several biologically interesting *C*-glycolipids,[16] *C*-disaccharides,[17,18] and benzylic *C*-glycosides[19] were required (Table 1). The monofluoride acid precursors were used as a mixture of enantiomeric or diastereomeric fluorides, with the anticipation that the corresponding epimeric fluoro-*C*-glycosides would be chromatographically separable. 2-Fluorohexanoic acid **6a**[20] was prepared from the mesylate derivative of the methyl ester following a known procedure, and α-fluorophenylacetic acid **6e**[21] was commercially available. Initial attempts to prepare carbohydrate-derived fluorides **6c** and **6d** following variations of the procedure used for **6a** led to complex mixtures. In an alternative approach, **6c** was obtained by reaction of aldehyde **11**[22] with the sodium salt of triethyl 2-fluoro-2-phospho-

(4) For an example where *O*- and *C*-glycosides bind in different conformations with respect to the intersaccharide torsions: Espinosa, J. F.; Montero, E.; Vian, A.; García, J. L.; Dietrich, H.; Schmidt, R. R.; Martín-Lomas, M.; Imberty, A.; Cañada, F. J.; Jiménez-Barbero, J. *J. Am. Chem. Soc*. **1998**, *120*, 1309−1318.

(5) Gabius, H.-J. *Pharm. Res.* **1998**, *15*, 23−30. Dam, T. K.; Brewer, C. F. *Chem. Rev*. **2002**, *102*, 387−429.

(6) For examples of difluoromethylene-linked *C*-furanosides: Herpin, T. F.; Motherwell, W. B.; Tozer, M. J. *Tetrahedron: Asymmetry* **1994**, *5*, 2269−2282. Herpin, T. F.; Motherwell, W. B.; Weibel, J.-M. *J. Chem. Soc., Chem. Commun*. **1997**, 923−924.

(7) For reviews on fluorinated carbohydrates: Card, P. J. *J Carbohydr. Chem*. **1985**, *4*, 451−487. *Fluorinated Carbohydrates, Chemical and Biochemical Aspects*; Taylor, N. F., Ed.; ACS Symp. Ser. 374; American Chemical Society: Washington, DC, 1996. Plantier-Royon, R.; Portella, C. *Carbohydr. Res*. **2000**, *327*, 119−146.

(8) For discussions on fluorinated compounds in medicinal chemistry: Welch, J. T.; Eswaraksrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991. *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, 1994. *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symp. Ser. 639; American Chemical Society: Washington, DC, 1996. Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem*. **2004**, *5*, 637−643.

(9) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619−8683.

(10) Blackburn, G. M.; Kent, D. E.; Kolkmann, F. *J. Chem. Soc., Perkin Trans. I* **1984**, 1119−1125. Thatcher, G. R. J.; Campbell, A. S. *J. Org. Chem*. **1993**, *58*, 2272−2281. Nieschalk, J.; O'Hagan, D. *J. Chem. Soc., Chem. Commun*. **1995**, 719−720.

(11) The preferred *gauche* conformation in 2-fluoroethyl residues attached to electronegative substituents is well documented. For recent examples: Briggs, C. R. S.; O'Hagan, D.; Howard, J. A. K.; Yufit, D. S. *J. Fluorine Chem*. **2003**, *119*, 9−13. Briggs, C. R. S.; O'Hagan, D.; Rzepa, H. S.; Slawin, A. M. Z. *J. Fluorine Chem*. **2004**, *125*, 19−25.

(12) Meier, C.; Knispel, T.; Marquez, V. E.; Siddiqui, M. A.; De Clercq, E.; Balzarini, J. *J. Med. Chem*. **1999**, *42*, 1615−1624.

(13) Hudlicky, M. *Org. React*. **1988**, *35*, 513−637. Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561−2578.

(14) Khan, N.; Cheng, X.; Mootoo, D. R. *J. Am. Chem. Soc*. **1999**, *121*, 4918−4919. Cheng, X.; Khan, N.; Mootoo, D. R. *J. Org. Chem*. **2000**, *65*, 2544−2547.

(15) For an example of deactivation of enol ethers with one or two fluorines on the adjacent carbon: Matsumura, Y.; Asai, T.; Shimada, T.; Nakayama, T.; Urushihara, M.; Morizawa, Y.; Yasuda, A.; Yamamoto, T.; Fujitani, B.; Hosoki, K. *Chem. Pharm. Bull*. **1995**, *43*, 353−355. Chang, C. S.; Negishi, M.; Nakano, T.; Morizawa, Y.; Matsumura, Y.; Ichikawa, A. *Prostaglandins* **1997**, *53*, 83−90.

(16) Yang, G.; Franck, R. W.; Bittman, R.; Samadder, P.; Arthur, G. *Org. Lett*. **2001**, *3*, 197−200. Yang, G.; Franck, R. W.; Byun, H.-S.; Bittman, R.; Samadder, P.; Arthur, G. *Org. Lett*. **1999**, *1*, 2149−2151. Yang, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Angew. Chem., Int Ed*. **2004**, *43*, 3818−3822. Dondoni, A.; Perrone, D.; Turturici, E. *J. Org. Chem*. **1999**, *64*, 5557−5564. Cipolla, L.; Nicotra, F.; Vismara, E.; Guerrini, M. *Tetrahedron* **1997**, *53*, 6163−6170.

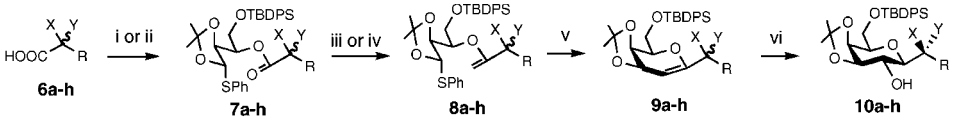
(17) Hiruma, K.; Kajimoto, T.; Weitz-Schmidt, G.; Ollmann, I.; Wong, C.-H. *J. Am. Chem. Soc*. **1996**, *118*, 9265−9270. Shibata, K.; Hiruma, K.; Kanie, O.; Wong, C.-H. *J. Org. Chem*. **2000**, *65*, 2393−2398.

(18) Denton, R. W.; Cheng, X.; Tony, K. A.; Dilhas, A.; Hernández, J. J.; Canales, A.; Jiménez-Barbero, J.; Mootoo, D. R. *Eur. J. Org. Chem*. **2007**, 645−654.

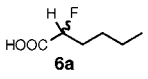
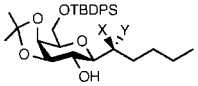
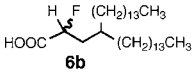
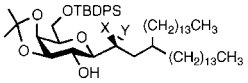
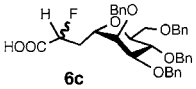
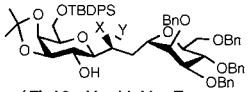
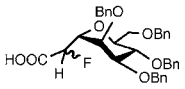
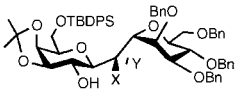
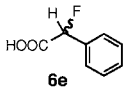
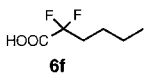
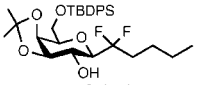
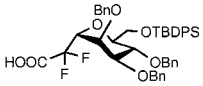
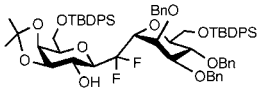
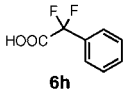
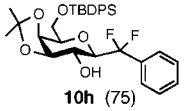
(19) Schmidt, R. R.; Dietrich, H. *Angew. Chem., Int. Ed. Engl*. **1991**, *30*, 1328−1329.

(20) Focella, A.; Bizzarro, F.; Exon, C. *Synth. Commun.* **1991**, *21*, 2165−2170.

Table 1. Synthesis of Fluoro *C*-Glycosides



(i) **6a-f, h** + **5**, DCC, DMAP, C_6H_6; (ii) **6g** + **5**, 2,4,6-trichlorobenzoyl chloride; Et_3N, THF then **5**, DMAP, toluene; (iii) Tebbe reagent; (iv) Takai reagent; (v) MeOTf, DTBMP, CH_2Cl_2, MS 4A; (vi) BH_3. Me_2S, THF; then Na_2O_2

6a-h	**7a-h** (%)	**8a-h** (%)	**9a-h** (%)	**10a-h** (%)*
 **6a**	**7a** (95)	**8a** (83)	**9a** (73)	 (*R*)-**10a** X = H, Y = F (*S*)-**10a** X = F, Y = H (70)
 **6b**	**7b** (95)	**8b** (95)	**9b** (80)	 (*R*)-**10b** X = H, Y = F (*S*)-**10b** X = F, Y = H (61)
 **6c**	**7c** (86)	**8c** (80)	**9c** (71)	 (*R*)-**10c** X = H, Y = F (*S*)-**10c** X = F, Y = H (70)
 **6d**	**7d** (68)	**8d** (77)	**9d** (83)	 (*R*)-**10d** X = H, Y = F (*S*)-**10d** X = F, Y = H (63)
 **6e**	**7e** (78)	**8e** (00)	–	--
 **6f**	**7f** (85)	**8f** (55)	**9f** (81)	 **10f** (70)
 **6g**	**7g** (76)	**8g** (63)	**9g** (82)	 **10g** (86)
 **6h**	**7h** (92)	**8h** (50)	**9h** (75)	 **10h** (75)

* Note the change in priorities of the carbon substituents attached to fluorinated carbon in **10d** relative to **10a**−**c**.

noacetate,[23,24] followed by hydrogenation and hydrolysis steps (Scheme 2). This protocol was also used for **6b** but is not applicable to fluoroacids such as **6d**, which contain a 3-alkoxy substituent. For **6d**, the fluorination of an allylsilane precursor was explored.[25] The known carbohydrate alkene **12**[22] was subjected to a cross metathesis with allyltrimethylsilane under an atmosphere of ethylene to give **13**.[26] Treatment of the mixture of allylsilanes **13** with Selectfluor provided an approximately 1:1 mixture of diastereomeric allylic fluorides, which was processed to **6d** via a standard oxidative sequence. Known difluorides **6f** and **6h** were obtained by treatment of the ketoester precursors with DAST.[27] This procedure was not successful for the more complex carbohydrate difluoride **6g**. Therefore, using a

(21) Reynolds, G. A.; Hauser, C. A. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, pp 708−710. Purrington, S. T.; Woodard, D. L. *J. Org. Chem*. **1990**, *55*, 3423−3424.

(22) Wong, C.-H.; Moris-Varas, F.; Hung, S.-C.; Marron, T. G.; Lin, C.-C.; Gong, K. W.; Weitz-Schmidt, G. *J. Am. Chem. Soc*. **1997**, *119*, 8152−8158.

(23) Sano, S.; Ando, T.; Yokoyama, K.; Nagao, Y. *Synlett* **1998**, 777−779. Bargiggia, F.; Dos Santos, S.; Piva, O. *Synthesis* **2002**, 427−437. Moon, H. R.; Kim, H. O.; Jeong, L. S. *J. Chem. Soc., Perkin Trans. I* **2002**, 1800−1804. Sano, S.; Saito, K.; Nagao, Y. *Tetrahedron Lett.* **2003**, *44*, 3987−3990. Suzuki, Y.; Sato, M. *Tetrahedron Lett.* **2004**, *45*, 1679−1681.

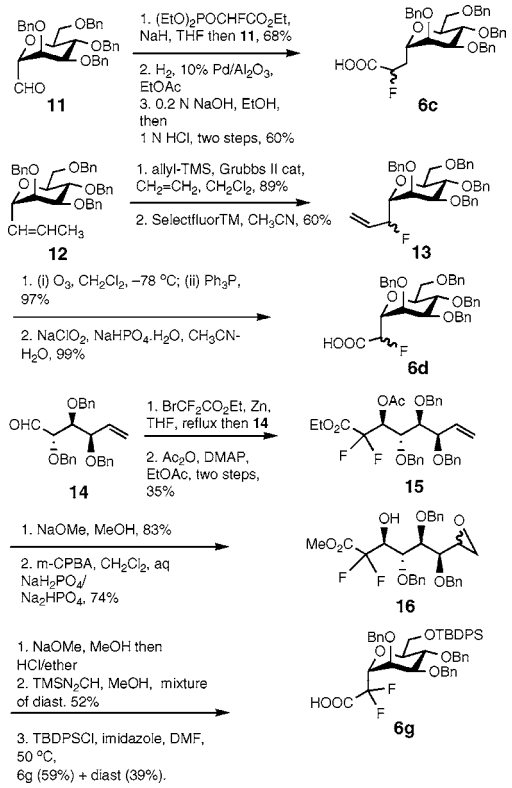
(24) For a related Julia procedure: Zajc, B.; Kake, S. *Org. Lett*. **2006**, *8*, 4457−4460.

(25) Thibaudeau, S.; Gouverneur, V. *Org. Lett*. **2003**, *5*, 4891−4893.

(26) Chen, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Org. Lett*. **2004**, *6*, 4077−4080.

(27) For **6f**: Dubowchik, G. M.; Padilla, L.; Edinger, K.; Firestone, R. A. *J. Org. Chem*. **1996**, *61*, 4676−4684. For **6h**: Middleton, W. J.; Bingham, E. M. *J. Org. Chem*. **1980**, *45*, 2883−2887. Hägele, G.; Haas, A. *J. Fluorine Chem*. **1996**, *76*, 15−19.

Scheme 2. Synthesis of Fluorinated Acids



variation of a known strategy,[28] **15**, a suitable precursor to **6g**, was first prepared by the reaction of the Reformatsky-like reagent from methyl bromodifluoroacetate and the known aldehyde **14**.[29] This led to a mixture of epimeric alcohols, from which **15** was separated and subjected to epoxidation with *m*CPBA. Base-mediated cyclization of the epoxide mixture provided an approximately 1:1 mixture of the desired tetrahydropyran and the epimeric cyclization product. The difluoroacid **6g** was obtained after silylation of the primary alcohol, chromatographic separation, and hydrolysis of the ester.

The four-step C-glycosidation sequence—esterification—ester methylenation—oxocarbenium cyclization—hydroboration was successful in all cases except for fluorophenylacetic acid **6c** (Table 1). Esterification reactions were performed under standard DCC conditions, except for the reaction of difluoroacid **6h**, for which the Yamaguchi protocol was more effective.[30] Ester methylenation was successfully performed using the Tebbe or Takai reagent, except for the reaction of the fluorophenylacetate **7e**, which yielded an intractable mixture.[31,32] The key oxocarbenium ion cyclizations were promoted with methyl triflate in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) and freshly activated, powdered molecular sieves. Early experiments suggested that these fluorinated glycal products were more sensitive to base (than the analogues without fluorine), and this required attention to the concentration of DTBMP used. In the event, products **9a**−**d** and **9g**,**h** were obtained in generally good yields. The hydroboration−oxidation on the glycals was performed using borane-dimethyl sulfide under standard conditions and afforded the desired mono- and difluoro-*C*-glycosides **10a**−**d** and **10g**,**h**, with no evidence of the diastereomeric hydroboration products. For the monofluoro compounds, an approximately 1:1 ratio of chromatographically separable, (*R*) and (*S*) epimers were obtained.

For assignment of the configuration at the fluorinated carbon (*R*)-**10a** was prepared by repeating the *C*-glycosidation protocol on enantiomerically pure (*R*)-2-fluorohexanoic acid. Epimeric fluorides (*R*)-**10b**/(*S*)-**10b** and (*R*)-**10c**/(*S*)-**10c** were then tentatively assigned by NMR comparisons with (*R*)-**10a**/(*S*)-**10a** (see Supporting Information). *J*/NOE NMR data, molecular mechanics and molecular dynamics calculations were used to assign (*R*)-**10d** and (*S*)-**10d**.[33]

We also examined the H NMR of epimers (*R*)-**10a** and (*S*)-**10a** for evidence of intramolecualr O−H−F hydrogen bonding. Interestingly, for solutions in C_6D_6 that were pretreated with alumina, the OH proton in (*R*)-**10a** appeared as a doublet of doublets, whereas the corresponding signal for (*S*)-**10a** was a doublet, suggesting that hydrogen bonding was significant in the former but not in the latter. The generality of these observations remains to be evaluated.

In summary, a convergent synthesis of β-*C*-galactosides with one or two fluorine substituents on the pseudoanomeric substituent has been developed. This method is especially appropriate for analogues that contain highly substituted aglycone segments as, for example, in *C*-disaccharides.

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Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Marcotte, S.; D'Hooge, F.; Ramadas, S.; Feasson, C.; Pannecoucke, X.; Quirion, J. *Tetrahedron Lett.* **2001**, *42*, 5879−5882. Li, Y.; Drew, M. G. B.; Welchman, E. V.; Shirastava, R. K.; Jiang, S.; Valentine, R.; Singh, G. *Tetrahedron* **2004**, *60*, 6523−6531.

(29) Skaanderup, P. R.; Hyldtoft, L.; Madsen, R. *Monatsh. Chem.* **2002**, *133*, 467−472.

(30) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993. White, J. D.; Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 8593−8595.

(31) Pine, S. H.; Shen, G. S.; Hoang, H. *Synthesis* **1991**, 165−167.

(32) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668−2670. Postema, M. H. D.; Calimente, D.; Liu, L.; Behrmann, T. L. *J. Org. Chem.* **2000**, *65*, 6061−6068.

(33) Pérez-Castells, J.; Hernández-Gay, J. J.; Denton, R. W.; Tony, K. A.; Mootoo, D. R.; Jiménez-Barbero, J. *Org. Biomol. Chem.* **2007**, DOI: 10.1039/B615752A.