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Reaction of 1,2-Orthoesters with HF−Pyridine: A Method for the Preparation of Partly Unprotected Glycosyl Fluorides and Their Use in Saccharide Synthesis

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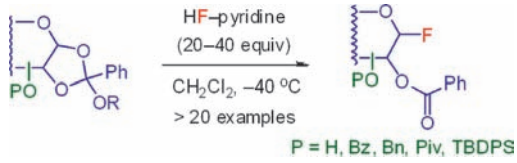
ABSTRACT



Glycosyl fluorides can be prepared in an efficient manner by treatment of pyranose- or furanose-derived 1,2-orthoesters, with hydrogen fluoride pyridine (HF−py). The method is compatible with the presence of a variety of protecting groups, including *tert*-butyldiphenyl silyl ethers, and can be applied to sugar derivatives with free hydroxyl groups, thus avoiding the need for the protection−deprotection steps.

Oligosaccharides have been recognized as fundamental compounds in many biological recognition processes.[1] Consequently, glycosylation, the key event in their preparation, receives continuous attention.[2,3] Efficiency in this process often relies on the choice of the glycosyl donor[4] and the minimization of protecting group manipulations,[5] this being, for example, by strategic placement of rationally designed protecting groups[6] or by regioselective coupling of polyol glycosyl acceptors.[7] In this regard, the regioselective glycosylation of polyol acceptors with partially unprotected glycosyl donors appears as an attractive alternative.[8] The latter strategy can be useful in orthogonal[9] (or semiorthogonal)[10] glycosylation strategies and has been incorporated in a two-directional approach for the convergent

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(1) (a) Varki, A. *Glycobiology* **1993**, *3*, 97–130. (b) Reuter, G.; Gabius, H. J. *Cell. Mol. Life Sci.* **1999**, *55*, 368–422. Burton, D. R.; Dwek, R. A. *Science* **2006**, *313*, 627–628. (c) McReynolds, K. D.; Gervay-Hague, J. *Chem. Rev.* **2007**, *107*, 1533–1552.

(2) Toshima, K.; Tatsuta, K. *Chem. Rev.* **1993**, *93*, 1503–1531.

(3) (a) Boons, G.-J. *Tetrahedron* **1996**, *52*, 1095–1121. (b) Demchenko, A. V. *Lett. Org. Chem.* **2005**, *2*, 580–589. (c) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900–1934.

(4) Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 823–938.

(5) Baeschlin, D. K.; Green, L. G.; Hahn, M. G.; Hinzen, B.; Ince, S. J.; Ley, S. V. *Tetrahedron: Asymmetry* **2000**, *11*, 173–197.

(6) Litjens, R. E. J. N.; van den Bos, L. J.; Codée, J. D. C.; Overkleeft, H. S.; van der Marel, G. A. *Carbohydr. Res.* **2007**, *342*, 419–429.

(7) Fraser-Reid, B.; López, J. C.; Gómez, A. M.; Uriel, C. *Eur. J. Org. Chem.* **2004**, 1387–1395.

(8) (a) Boons, G.-J.; Zhu, T. *Synlett* **1997**, 809–811. (b) Matsuo, I.; Isomura, M.; Miyazaki, T.; Sakakibara, T.; Ajisaka, K. *Carbohydr. Res.* **1998**, *305*, 401–413. (c) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545–9554. (d) López, J. C.; Agocs, A.; Uriel, C.; Gómez, A. M.; Fraser-Reid, B. *Chem. Commun.* **2005**, 5088–5090.

(9) (a) Kanie, O.; Ito, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1994**, *116*, 12073–12074. (b) Demchenko, A. V.; Pornsuriyasak, P.; De Meo, C.; Malysheva, N. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3069–3072. (c) Pornsuriyasak, P.; Demchenko, A. V. *Chem.—Eur. J.* **2006**, *12*, 6630–6646. (d) Kaeothip, S.; Pornsuriyasak, P.; Rath, N. P.; Demchenko, A. V. *Org. Lett.* **2009**, *11*, 799–802.

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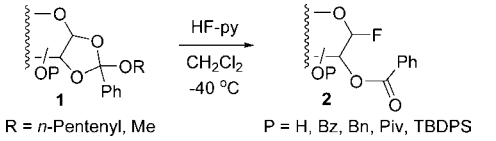
synthesis of oligosaccharides.[11] In this context, we believe that the design of methods that allow the direct exchange of anomeric leaving groups between partially unprotected sugar building blocks (glycosyl donors or acceptors) would be useful.[12]

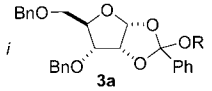
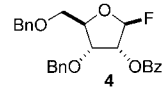
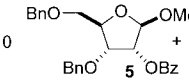
Glycosyl 1,2-orthoesters, first introduced in glycosylation studies by Kochetkov and co-workers,[13−15] have been revitalized by the advent of *n*-pentenyl orthoesters (NPOEs).[16,17] Other research groups have also illustrated the value of 1,2-orthoesters in oligosaccharide synthesis.[18,19]

Scheme 1. Transformation of 1,2-Orthoesters into Glycosyl Fluorides



We have recently described the transformation of partially unprotected *n*-pentenyl glycosides (NPGs),[20] and thioglycosides,[21] into glycosyl fluorides[22] mediated by bis(pyridine)iodonium tetrafluoroborate[23]/HF−pyridine[24] or *N*-iodosuccinimide/HF−pyridine.[25] These methods, however, could not be applied to partially unprotected NPOE substrates because addition of IF across the double bond was the preferred reaction. In this manuscript, we disclose that furanose- and pyranose-derived 1,2-*O*-alkyl orthoesters, **1**, can be efficiently transformed into glycosyl fluorides, **2**, upon treatment with the HF−pyridine complex[26,27] (Scheme 1), and that this transformation can be applied to partly unprotected substrates. In this reaction, HF−pyridine plays a dual role as the acid, necessary to promote unravelling of the 1,2-orthoester,[28] and as the source of the nucleophilic fluoride ion.

Table 1. HF−Pyridine Mediated Transformation of 1,2-Orthoesters into Furanosyl Fluorides in CH_2Cl_2 at −40 °C

entry	substrate	HF-py (equiv)	product(s)	yield (%)
i	 **3a**	20	 **4**	72[a]
ii	**3a**	40	**4**	100[a]
iii	**3b**	40	**4**	82[a]
iv	**3a**	10	 + **4** **5**	42[b]

series: **a**) R = Me, **b**) R = *n*-pentenyl — 24%

[a] Addition of **3** to a precooled solution of HF−py in CH_2Cl_2. [b] Addition of the HF−py complex to a solution of **3** in CH_2Cl_2.

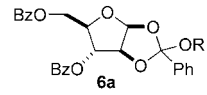
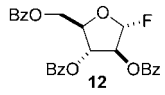
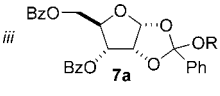
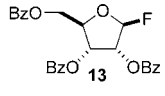
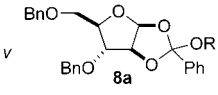
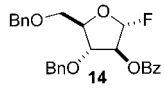
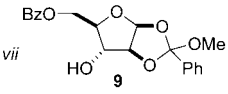
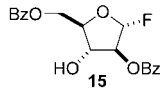
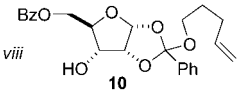
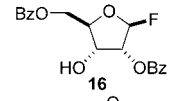
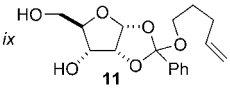
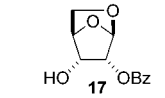
We first studied the HF−pyridine mediated transformation of ribose 1,2-orthoesters **3** (Table 1). The reactions, which took place smoothly at −40 °C in CH_2Cl_2,[29] were usually completed within 5−10 min. In some instances, the yield of glycosyl fluoride could be improved by increasing the amount of HF−pyridine (Table 1, entry *i* vs *ii*). *n*-Pentenyl orthoesters (NPOEs), e.g., **3b**, could also be used in the preparation of glycosyl fluorides (Table 1, entry *iii*). Finally, from an experimental standpoint, it is crucial that the orthoester be added to the solution of HF−pyridine in CH_2Cl_2, to avoid acid-catalyzed rearrangement to glycosides (Table 1, entry *iv*).

The procedure was next applied to ribo- and arabino-orthoesters, **6**−**11** (Table 2). As previously observed, methyl or NPOEs could be used without appreciable changes in

(10) (a) Demchenko, A. V.; De Meo, C. *Tetrahedron Lett.* **2002**, *43*, 8819–8822. (b) López, J. C.; Uriel, C.; Guillamón-Martin, A.; Valverde, S.; Gómez, A. M. *Org. Lett.* **2007**, *9*, 2759–2762.
(11) (a) Zhu, T.; Boons, G. J. *Tetrahedron Lett.* **1998**, *39*, 2187–2190. (b) Zhu, T.; Boons, G. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1898–2000.
(12) Hanessian, S.; Lu, P. P.; Ishida, H. *J. Am. Chem. Soc.* **1998**, *120*, 13296–13330.
(13) (a) Kochetkov, N. K.; Khorlin, A. J.; Bochkov, A. F. *Tetrahedron Lett.* **1964**, *5*, 289–293. (b) Kochetkov, N. K. *Tetrahedron* **1987**, *43*, 2389–2436.
(14) Fraser-Reid, B.; López, J. C. Orthoesters and Related Derivatives. In *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Demchenko, A. V., Ed.; Wiley-VCH: New York, 2008; Chapter 5.1.
(15) Kong, F. *Carbohydr. Res.* **2007**, *342*, 345–373.
(16) (a) Allen, J. G.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1999**, *121*, 468–469. (b) Mach, M.; Schlueter, U.; Mathew, F.; Fraser-Reid, B.; Hazen, K. C. *Tetrahedron* **2002**, *58*, 7345–7354. (c) Lu, J.; Jayaprakash, K. N.; Schlueter, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **2004**, *126*, 7450–7457. (d) Lu, J.; Fraser-Reid, B. *Chem. Commun.* **2005**, 862–864. (e) Jayaprakash, K. N.; Lu, J.; Fraser-Reid, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5894–5898.
(17) Fraser-Reid, B.; Lu, J.; Jayaprakash, K. N.; López, J. C. *Tetrahedron: Asymmetry* **2006**, *17*, 2449–2463.
(18) (a) Bamhaoud, T.; Sanchez, S.; Prandi, J. *Chem. Commun.* **2000**, 659–660. (b) Sanchez, S.; Bamhaoud, T.; Prandi, J. *Tetrahedron Lett.* **2000**, *41*, 7447–7452. (c) Marotte, K.; Sanchez, S.; Bamhaoud, T.; Prandi, J. *Eur. J. Org. Chem.* **2003**, 3587–3598.
(19) (a) Liu, X.; Wada, R.; Boonyarattanakalin, S.; Castagner, B.; Seeberger, P. H. *Chem. Commun.* **2008**, 3510–3512. (b) Boonyarattanakalin, S.; Liu, X.; Michieletti, M.; Lepenies, B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 16791–16799. (c) Ravidà, A.; Liu, X.; Kovacs, L.; Seeberger, P. H. *Org. Lett.* **2006**, *8*, 1815–1818.
(20) Fraser-Reid, B.; Udodong, U. E.; Wu, Z.; Ottosson, H.; Merrit, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett* **1992**, 927–942.
(21) Oscarson, S. *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; *Vol. 1*, pp 93−116.
(22) Mukaiyama, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 5590–5614.
(23) Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 319–320.
(24) López, J. C.; Bernal-Albert, P.; Uriel, C.; Valverde, S.; Gómez, A. M. *J. Org. Chem.* **2007**, *72*, 10268–10271.
(25) López, J. C.; Bernal-Albert, P.; Uriel, C.; Gómez, A. M. *Eur. J. Org. Chem.* **2008**, 5037–5041.
(26) Olah, G. A.; Welch, J. T.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A. *J. Org. Chem.* **1979**, *44*, 3872–3881.
(27) The HF−pyridine complex has been used as a source of fluoride in the preparation of glycosyl fluorides :(a) Hayashi, M.; Hashimoto, S.; Noyori, R. *Chem. Lett.* **1984**, 1747–1750. (b) Szarek, W. A.; Grynkiewicz, G.; Doboszewski, B.; Hay, G. W. *Chem. Lett.* **1984**, 1751–1754. (c) Bröder, W.; Kunz, H. *Carbohydr. Res.* **1993**, *249*, 221–241. (d) Palme, M.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 959–969. (e) Lee, Y. J.; Lee, B. Y.; Jeon, H. B.; Kim, K. S. *Org. Lett.* **2006**, *8*, 3971–3974.
(28) In this context, treatment of orthoester **3a**, with $Et_3N{\cdot}HF$, less acidic than HF−pyridine but yet a good source of fluoride ion (McClinton, M. A. *Aldrichim. Acta* **1995**, *28*, 31−35), left compound **3a** unchanged.
(29) Reaction at −378 °C (HF−py, 20 equiv) was sluggish, leaving considerable amounts of unreacted 1,2-orthoester among other compounds, in a complex reaction mixture.

reaction yields (Table 2, entries: *i* vs *ii*; *iii* vs *iv*; and *v* vs *vii*). The use of benzyl or benzoyl substituents at *O*-3 and *O*-5 does not seem to affect the yield of glycosyl fluorides. Glycosyl fluorides **15** and **16** (Table 2, entries *vii* and *viii*, respectively), with secondary OH groups, were obtained uneventfully. However, orthoester **11** with a primary 5-OH group furnished 1,5-anhydro derivative **17**, upon treatment with HF−pyridine (Table 2, entry *ix*).

Table 2. Reaction of Ribo- And Arabino-1,2-orthoesters, **6**−**11**, with HF−Pyridine in CH_2Cl_2 at −40 °C

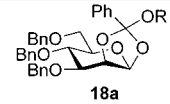
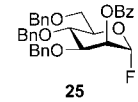
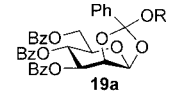
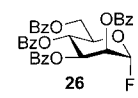
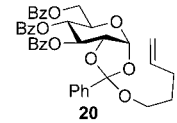
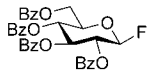
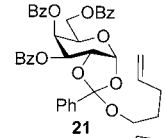
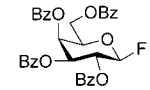
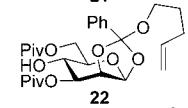
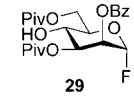
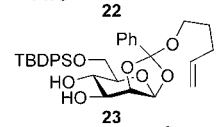
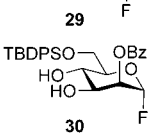
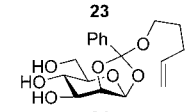
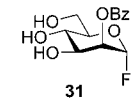
entry	substrate	HF-py (equiv)	product	yield (%)
i	 **6a**	20	 **12**	95
ii	**6b**	20	**12**	79
iii	 **7a**	20	 **13**	100
iv	**7b**	20	**13**	100
v	 **8a**	40	 **14**	91
vi	**8b**	40	**14**	93
vii	 **9**	20	 **15**	91
viii	 **10**	20	 **16**	53
ix	 **11**	20	 **17**	40

series: **a**) R = *n*-pentenyl, **b**) R = Me

Similarly, pyranosyl 1,2-orthoesters **18**−**24** afforded pyranosyl fluorides **25**−**31**, under the same reaction conditions (Table 3). Notably, similar yields were obtained from either *n*-pentenyl, methyl, or allyl 1,2-orthoesters (Table 3, entries: *iii*, *iv*, *v*). Diol **23** was readily prepared by silylation of triol **24**, the latter having been uneventfully obtained by de-*O*-benzoylation (NaOMe/MeOH) of **19a**.

The reaction is compatible with the presence of secondary hydroxyl groups in the 1,2-orthoester (Table 3, entries *viii*, *ix*). In addition, the excellent yield of **30** shows that fluoridation is so rapid that it can even compete with HF−pyridine mediated de-*O*-silylation (Table 3, entry *ix*). Equally remarkable is that triol **24** could be successfully transformed into glycosyl fluoride **31**, in 83% yield[30] (Table 3, entry *x*). Finally, although most of the transformations depicted in Table 3 were performed with mannose orthoesters, glucose- or galactose-derived 1,2-orthoesters could also be successfully transformed into pyranosyl fluorides (Table 3, entries *vi* and *vii*, respectively).

Table 3. Reaction of Pyranose 1,2-Orthoesters, **18**−**24**, with HF−Pyridine (20 equiv) in CH_2Cl_2 at −40 °C, Leading to Pyranosyl Fluorides, **25**−**31**

entry	substrate	product	yield (%)
i	 **18a**	 **25**	80
ii	**18b**	**25**	100
iii	 **19a**	 **26**	93
iv	**19b**	**26**	91
v	**19c**	**26**	84
vi	 **20**	 **27**	94
vii	 **21**	 **28**	92
viii	 **22**	 **29**	93
ix	 **23**	 **30**	88
x	 **24**	 **31**	83

series: **a**) R = *n*-pentenyl, **b**) R = Me, **c**) R =allyl

A single glycosyl fluoride was obtained in each case, to which we have assigned an *anti*-1,2-orientation based on comparison with literature data, mechanistic grounds, and on the observed ^{1}H NMR couplings.[31]

To illustrate the usefulness of this transformation when used in combination with selective activation strategies, we have carried out the synthesis of trisaccharide **34** (Scheme 2). Thus, fluoride **15** (Table 2, entry *vii*) was glycosylated with NPOE **6a** [NIS, $Yb(OTf)_3$][32] to give disaccharide **32**, which was now used as a donor in the glycosylation of NPG **33**, to yield linear trisaccharide **34**.

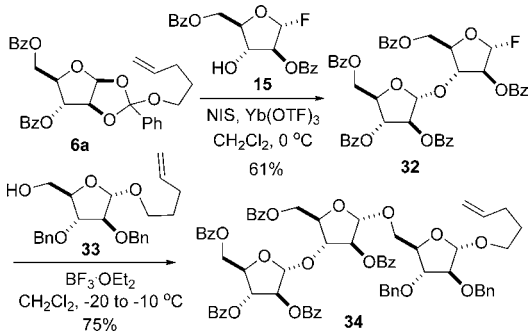
Finally, we have performed the synthesis of tetrasaccharide **39** by using fluoride triol **31**, as the key intermediate (Scheme 3). Thus, NPOE **19a** was used to regioselectively[33] glyco-

(30) Neither 1,6-anhydro derivative formation or 1,2,6 internal orthoester formation were observed:Hiranuma, S.; Kanie, O.; Wong, C.-H. *Tetrahedron Lett.* **1999**, *40*, 6423–6426.

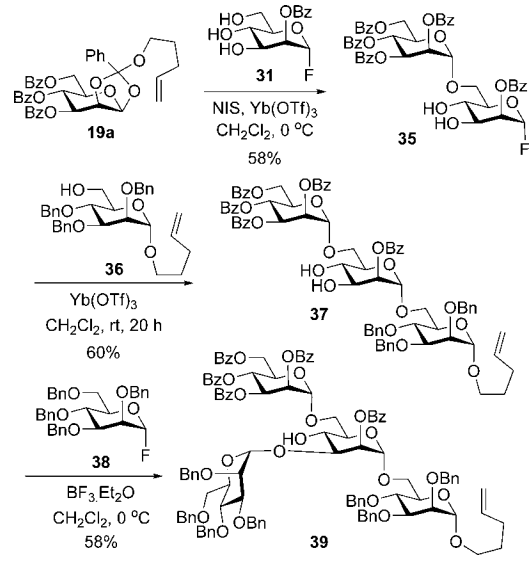
(31) (a) Hall, L. D.; Steiner, P. R.; Pedersen, C. *Can. J. Chem.* **1970**, *48*, 1155–1165. (b) Hall, L. D.; Manville, J. F.; Bhacca, N. S. *Can. J. Chem.* **1969**, *47*, 1–17.

(32) (a) Jayaprakash, K. N.; Radhakrishnan, K. V.; Fraser-Reid, B. *Tetrahedron Lett.* **2002**, *43*, 6953–6955. (b) Jayaprakash, K. N.; Fraser-Reid, B. *Synlett* **2004**, 301–305.

Scheme 2. Synthesis of Triarabino Derivative **34** via Key Intermediate **15**



Scheme 3. Triol **31** as the Key Intermediate in the Synthesis of Branched Tetrasaccharide **39**



sylate triol **31** to give glycosyl fluoride **35** (58% yield) as the only detected disaccharide. The latter was then used to glycosylate NPG **36**, upon selective activation with $Yb(OTf)_3$, leading to trisaccharide **37**, in 60% yield, no other trisaccharide being observed. Finally, treatment of diol **37** with pyranosyl fluoride donor **38**, under the agency of $BF_3{\cdot}Et_2O$, yielded tetrasaccharide **39** in 58% yield.[34] This strategy serves to illustrate the usefulness of triol **31**, able to function as an acceptor, a donor, and an acceptor, respectively. The last steps in the synthetic sequence (i.e., **35** + **36** and then **37** + **38**) can be regarded as a two-directional strategy,[11] wherein compound **35** was first used as a donor to give trisaccharide **37**, that later functioned as an acceptor to generate tetrasaccharide **39**.

In summary, we have shown that the HF−pyridine complex can be used to successfully convert furanosyl and pyranosyl 1,2-orthoesters to glycosyl fluorides. This transformation is presumed to take place by acid -induced unraveling of the 1,2-orthoester moiety leading to an oxocarbenium (dioxolenium or trioxolenium)[35] ion that subsequently reacts with the fluoride ion. The reaction takes place rapidly, is refractory to free −OH groups in the substrate-donor, and permits the use of *tert*-butyl diphenylsilyl protecting groups. When compared with diethylaminosulfur trifluoride[36] (DAST)-mediated anomeric fluorinations on fully protected compounds, the use of HF−pyridine does not require an additional step for the liberation of the anomeric OH functionality. On the other hand, (DAST)-mediated anomeric fluorinations are not compatible with the presence of free OH groups in the molecule since they might lead to alternative reaction pathways.[37,38] The usefulness of this strategy was illustrated with the preparation of triol glycosyl fluoride **31** (which maintains a participating 2-OBz group), in just two steps from NPOE **19a**.[39] In our opinion, this reaction might prove to be useful in block, orthogonal, or two-directional strategies for oligosaccharide synthesis.[3]

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Supporting Information Available: Experimental procedures and characterization data and copies of ^1H, ^{13}C, and two-dimension NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL901630D

(33) (a) Uriel, C.; Agocs, A.; Gómez, A. M.; López, J. C.; Fraser-Reid, B. *Org. Lett.* **2005**, *7*, 4899–4902. (b) López, J. C.; Gómez, A. M.; Uriel, C.; Fraser-Reid, B. *Tetrahedron Lett.* **2003**, *44*, 1417–1420.

(34) A minor saccharide (3−5%) was also detected although its structure remains, at this time, uncertain.

(35) Fraser-Reid, B.; Grimme, S.; Piacenza, M.; Mach, M.; Schlueter, U. *Chem.−Eur. J.* **2003**, *9*, 4687–4692.

(36) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574–578.

(37) (a) Nicolaou, K. C.; Ladduwahetty, T.; Randall, J. L.; Chucholowski, A. *J. Am. Chem. Soc.* **1986**, *108*, 2466–2467. (b) Nicolaou, K. C.; Rodriguez, R. M.; Mitchell, H. J.; Suzuki, H.; Fylaktakidou, K. C.; Baudoin, O.; van Delft, F. L. *Chem.−Eur. J.* **2000**, *6*, 3095–3115.

(38) Lin, P.-C.; Adak, A. K.; Ueng, S.-H.; Huang, L.-D.; Huang, K.-T.; Ho, J. A.; Lin, C.-C. *J. Org. Chem.* **2009**, *74*, 4041–4048.

(39) 1,2-Orthoesters are normally prepared from fully acylated derivates, thus removal of the protecting groups prior to fluoride formation have the advantage of preserving the 2-*O*-acyl substituent as a masked, base stable substituent.