ORGANIC LETTERS

2012
Vol. 14, No. 5
1342–1345

Stereoselective, Electrophilic α-*C*-Sialidation

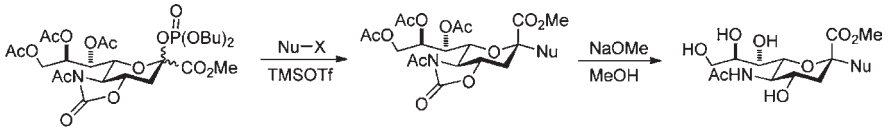
Amandine Noel,[†] Bernard Delpech,[†] and David Crich*[,†,‡]

Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles, CNRS, 1 Avenue de la Terrasse, 91190 Gif-sur-Yvette, France, and Department of Chemistry, Wayne State University, Detroit, Michigan 48202, United States

dcrich@chem.wayne.edu

Received January 31, 2012

ABSTRACT



Nu-X = allyltributylstannane, TMS enol ethers, excellent yield and α-selectivity

5-*N*-Acetyl-5-*N*,4-*O*-oxazolidinone protected α- and β-sialyl phosphates react with allyltributylstannane and a variety of trimethylsilyl enol ethers to give α-sialyl *C*-glycosides in high yield and excellent selectivity. Elimination to give the 2,3-glycal is minimized by the presence of the oxazolidinone ring. The oxazolidinone ring can be subsequently cleaved under mild conditions at room temperature leaving in place the native acetamide group.

Because of resistance to hydrolytic enzymes and their ability to mimic native *O*-glycosides, the *C*-glycosides have enjoyed considerable attention from synthetic and medicinal chemists.[1] One of the earliest,[2] most reliable, and widely applied approaches to *C*-glycosides has been the reaction of electrophilic glycosyl donors, typically under Lewis acid catalysis with *C*-nucleophiles such as alkenes, silyl enol ethers, and allylsilanes. Interestingly, however, following Paulsen's report that treatment of chloride **1** with allyltrimethylsilane in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) leads exclusively to the elimination product **3** (Scheme 1),[3] this method has not been applied in the sialic and ulosonic acid series with the exception of the low yield formation of a *C*-aryl glycoside **4** from the anomeric acetate **2** (Scheme 1).[4]

The formation of *C*-sialosides by the trapping of anomeric radicals generated from **1** and related radical precursors avoids the problem of elimination but is typically unselective.[3,5] This being the case, sialic and ulosonic acid *C*-glycosides are typically generated by alkylation of enolate anions or their equivalents, most commonly generated reductively from thioglycosides or the corresponding sulfones, when excellent α-selectivity is observed.[1c,e,g,6]

[†] CNRS.

[‡] Wayne State University.

(1) (a) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Pergamon: Oxford, 1995. (b) *C-Glycoside Synthesis*; Postema, M. H. D., Ed.; CRC: Boca Raton, FL, 1995. (c) Yuan, X. J.; Linhardt, R. J. *Curr. Top. Med. Chem.* **2005**, *5*, 1393–1430. (d) Du, Y.; Linhardt, R. J. *Tetrahedron* **1998**, *54*, 9913–9959. (e) Beau, J.-M.; Gallagher, T. *Top. Curr. Chem.* **1997**, *187*, 1–54. (f) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55–83. (g) Somsak, L. *Chem. Rev.* **2001**, *101*, 81–135. (h) Skrydstrup, T.; Vauzeilles, B.; Beau, J.-M. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, pp 495–530. (i) Beau, J.-M.; Vauzeilles, B.; Skrydstrup, T. In *Glycoscience*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer: Berlin, 2001; Vol. 3, pp 2679–2724. (j) Gyorgydeak, Z.; Pelyvas, I. F. In *Glycoscience*; Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds.; Springer: Berlin, 2001; Vol. 1, pp 691–747. (k) Postema, M. H. D.; Piper, J. L.; Betts, R. L. *Synlett* **2005**, 1345–1358. (l) Postema, M. H. D.; Calimente, D. In *Glycochemistry: Principles, Synthesis, and Applications*; Wang, P. G., Bertozzi, C. R., Eds.; Dekker: New York, 2001; pp 77–131. (m) Boons, G.-J.; Demchenko, A. V. In *Carbohydrate-Based Drug Discovery*; Wong, C.-H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 1, pp 55–102. (n) Bertozzi, C. R.; Bednarski, M. D. In *Modern Methods in Carbohydrate Synthesis*; Khan, S. H., O'Neill, R. A., Eds.; Harwood: Amsterdam, 1996; pp 316–351.

(2) (a) Ogawa, T.; Pernet, A. G.; Hanessian, S. *Tetrahedron Lett.* **1973**, *14*, 3543–3546. (b) Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479–1482. (c) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978.

(3) Paulsen, H.; Matschulat, P. *Liebigs Ann.* **1991**, 487–495.

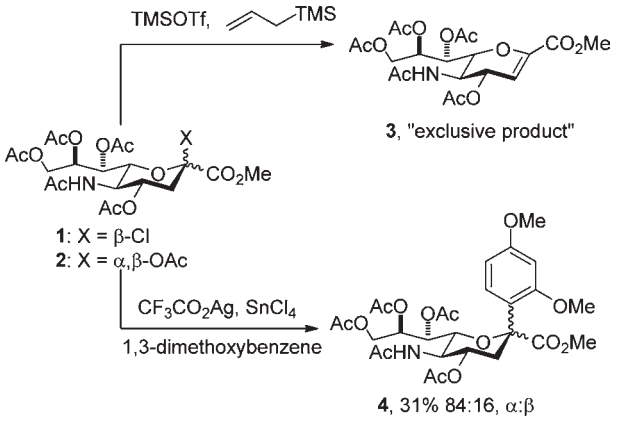
(4) (a) Kuribayashi, T.; Ohkawa, N.; Satoh, S. *Tetrahedron Lett.* **1998**, *39*, 4537–4540. (b) Kuribayashi, T.; Mizuno, Y.; Gohya, S.; Satoh, S. *J. Carbohydr. Chem* **1999**, *18*, 371–382.

(5) (a) Nagy, J. O.; Bednarski, M. D. *Tetrahedron Lett.* **1991**, *32*, 3953–3956. (b) Waglund, T.; Claesson, A. *Acta Chem. Scand.* **1991**, *46*, 73–76.

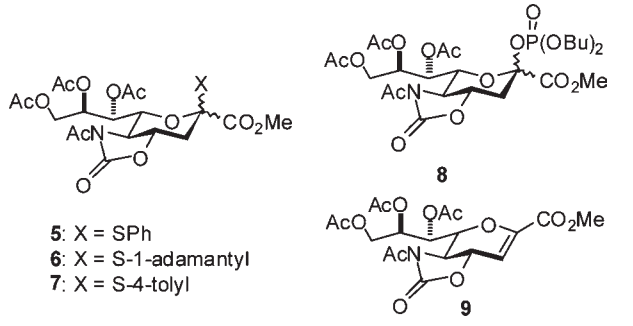
(6) (a) Luthman, K.; Orbe, M.; Waglund, T.; Claesson, A. *J. Org. Chem.* **1987**, *52*, 3777–3784. (b) Crich, D.; Ritchie, T. J. *J. Chem. Soc., Chem. Commun.* **1988**, 985–986. (c) Wallimann, K.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 1520–1532. (d) Vlahov, I. R.; Vlahova, P. I.; Linhardt, R. J. *J. Am. Chem. Soc.* **1997**, *119*, 1480–1481. (e) Abdallah, Z.; Doisneau, G.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5209–5212. (f) Watanabe, T.; Hirai, G.; Kato, M.; Hashizume, D.; Miyagi, T.; Sodeoka, M. *Org. Lett.* **2008**, *10*, 4167–4170.

10.1021/ol300255q
Published on Web 02/15/2012

Scheme 1. Attempted Electrophilic *C*-Sialylation



In our laboratory, we have developed the *N*-acetyloxazolidinone protected thioglycosides **5** and **6** as highly α-selective donors for the synthesis of *O*-sialosides,[7] while closely related oxazolidinones lacking the *N*-acetyl group have been developed and employed by the Takahashi,[8] De Meo,[9] and other groups.[10] Subsequently, Wong and coworkers converted the thioglycoside **7** to the anomeric phosphates **8** and showed that they are also excellent α-sialoside donors.[11] We now describe the use of this class of compounds as highly α-selective electrophilic *C*-sialosyl donors, thereby opening up the electrophilic manifold as a facile route into the sialic acid *C*-glycosides.



Initial experiments employing **6** and standard thioglycoside activating systems such as the combinations of 1-benzenesulfinyl piperidine[12] and diphenyl sulfoxide[13] with trifluoromethanesulfonic anhydride, and the *N*-iodosuccinimide–trifluoromethanesulfonic acid pair[14] were unsatisfactory owing to competing reaction with the nucleophile. We turned, therefore, to the phosphates **8** that are activated under standard Lewis acidic conditions compatible with electron-rich olefins. Screening experiments revealed TMSOTf to be a suitable Lewis acid capable of promoting the reaction of **8** with allyltrimethylsilane at −78 °C in dichloromethane. These conditions were therefore adopted as standard and applied to a range of allylmetals and silyl enol ethers as reported in Table 1. In addition to the use of dichloromethane as solvent, and in view of the strong α-directing effect exerted in sialidations in general by the use of acetonitrile-containing solvents, we also studied the use of a 2:1 mixture of dichloromethane and acetonitrile as solvent (Table 1).

With allyltrimethylsilane as a nucleophile (Table 1, entries 1 and 2), the allyl *C*-glycosides **10** were obtained in moderate to good yields, but poor selectivity irrespective of the solvent employed. With the more nucleophilic allyltributylstannane, **10** was obtained in high yield from the α-anomer of the sialyl phosphate **8α** (Table 1, entry 3), but only a moderate yield was obtained from the *β*-anomer ***8β*** (Table 1, entry 4) irrespective of the solvent employed. The selectivity for the formation of **10** was essentially complete when allyltributylstannane was used as the nucleophile, with only the α-anomer being formed, unimpacted by the configuration of the donor employed and either of the solvents studied (Table 1, entries 3 and 4). The stereochemistry of the two anomers of the *C*-allyl sialoside was assigned on the basis of NOE correlations between the allylic methylene group and the axial hydrogens at C4 and 6 in the *β*-anomer and between the allylic methylene group and the axial hydrogen at C3 for the α-anomer. The stereochemistry of all subsequent *C*-sialosides was assigned analogously as described in the Supporting Information. Turning to the use of silyl enol ethers as nucleophiles, the application of trimethylsiloxyethene gave the *C*-sialoside **11** in high yield and exquisite α-selectivity both in dichloromethane and in the mixture with acetonitrile (Table 1, entries 5 and 6). A lower yield was, however, observed when the *β*-phosphate ***8β*** was employed as the donor in dichloromethane. With the trimethylsilyl enol ether derived from pinacolone (Table 1, entries 7 and 8), the yields were generally good, irrespective of the configuration of the donor, and the selectivities were high and in favor of the α-anomer in dichloromethane. However, interestingly, a much lower selectivity was noted when the combination of dichloromethane and acetonitrile was the solvent. With acetophenone trimethylsilyl enol ether, good yields and excellent α-selectivities also were obtained from either anomer of the donor (Table 1, entries 9 and 10). Finally, with

(7) (a) Crich, D.; Li, W. *J. Org. Chem.* **2007**, *72*, 2387–2391. (b) Crich, D.; Li, W. *J. Org. Chem.* **2007**, *72*, 7794–7797. (c) Crich, D.; Wu, B. *Org. Lett.* **2008**, *10*, 4033–4035. (d) Crich, D.; Navuluri, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 3049–3052. (e) Sun, B.; Jiang, H. *Tetrahedron Lett.* **2011**, *52*, 6035–6038. (f) Wang, Y.-J.; Jia, J.; Gu, Z.-Y.; Liang, F.-F.; Li, R.-C.; Huang, M.-H.; Xu, C.-S.; Zhang, J.-X.; Men, Y.; Xing, G.-W. *Carbohydr. Res.* **2011**, *346*, 1271–1276.

(8) Tanaka, H.; Nishiura, Y.; Takahashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 7124–7125.

(9) (a) Farris, M. D.; De Meo, C. *Tetrahedron Lett.* **2007**, *48*, 1225–1227. (b) Harris, B. N.; Patel, P. P.; Gobble, C. P.; Stark, M. J.; De Meo, C. *Eur. J. Org. Chem.* **2011**, 4023–4027.

(10) (a) Hanashima, S.; K., S.; Ito, Y.; Yamaguchi, Y. *Eur. J. Org. Chem.* **2009**, 4215–4220. (b) Liang, F.-F.; Chen, L.; Xing, G.-W. *Synlett* **2009**, 425–428. (c) Hanashima, S. *Trends Glycosci. Glycobiol.* **2011**, *23*, 111–121.

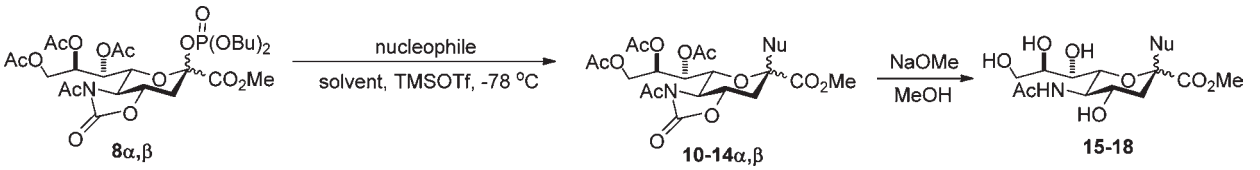
(11) Hsu, C.-H.; Chu, K.-C.; Lin, Y.-S.; Han, J.-L.; Peng, Y.-S.; Ren, C.-T.; Wu, C.-Y.; Wong, C.-H. *Chem.—Eur. J.* **2010**, *16*, 1754–1760.

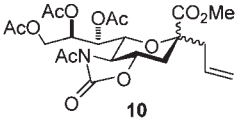
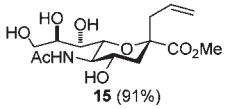
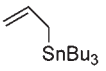
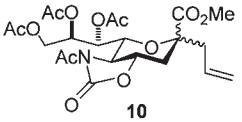
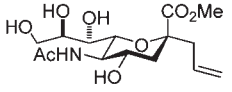
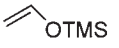
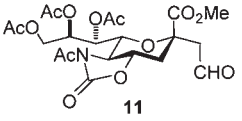
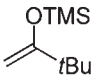
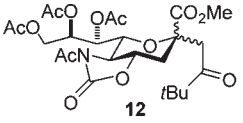
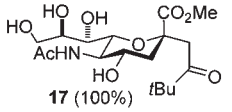
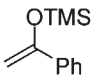
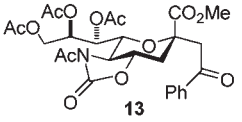
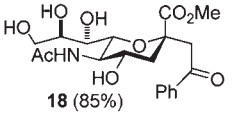
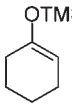
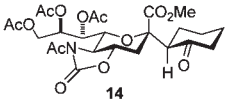
(12) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015–9020.

(13) Codée, J. D. C.; van den Bos, L. J.; Litjens, R. E. J. N.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H.; van der Marel, G. A. *Tetrahedron* **2004**, *60*, 1057–1064.

(14) (a) Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 1331–1334. (b) Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313–4316.

Table 1. Electrophilic *C*-Sialylation and Subsequent Oxazolidinone Cleavage



	donor	nucleophile	product	CH_2Cl_2 yield	CH_2Cl_2 α:β[a]	2:1 CH_2Cl_2:MeCN yield	2:1 CH_2Cl_2:MeCN α:β[a]	hydrolysis (yield)
1	8α		 **10**	75%	1:1	60%	3:7	
2	8β			54%	3:2	48%	3:7	**15** (91%)
3	8α		 **10**	81%	100:0	80%	100:0	
4	8β			36%	100:0	33%	100:0	**16** (95%)
5	8α		 **11**	82%	100:0	74%	100:0	–
6	8β			46%	100:0	74%	100:0	–
7	8α		 **12**	72% + 9% **9**	82:18	57% + 8% **9**	3:2	
8	8β			80%	85:15	74%	3:2	**17** (100%)
9	8α		 **13**	62% + 28% **9**	100:0	85%	100:0	
10	8β			91%	100:0	64% + 24% **9**	100:0	**18** (85%)
11	8α		 **14**	81%	100:0	87%	100:0	–
12	8β			70%	100:0	88%	100:0	–

[a] Anomeric ratios were determined by integration of the ^{1}H NMR spectra of the crude reaction mixtures.

trimethylsiloxycyclohexene, an excellent yield of a single diastereomer **14** was obtained from both phosphates **8**. This compound was assigned as the equatorial *C*-glycoside on the basis of NOE measurements. The *R*-configuration adjacent to the ketone is tentatively assigned on the basis of the open, antiperiplanar transition state model shown in Figure 1.[15]

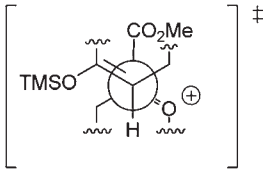


Figure 1. Proposed transition state for the formation of **14**.

Four of the C-sialosides (**10α** and **10*β***, **12** and **13**) were subjected to a deacetylation and concomitant cleavage of the oxazolidinone ring with sodium methoxide in methanol at room temperature, all in good yields (Table 1, entries 1/2, 3/4, 7/8, and 9/10). Importantly, the spectroscopic data for the *C*-sialosides **15** and **16** correlate with those described earlier in the literature[3] for these known substances and thereby confirm the configurational assignments made on the basis of NOE measurements. The ability to cleave the oxazolidinone selectively under mild, practical conditions, leaving in place the acetamide typically found in the sialic acid glycosides, is one advantage presented by the *N*-acetyloxazolidinone protected donors **5**–**8**, as compared with the *N*-deacetyl analogs studied by

(15) Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 629–660.

Takahashi and De Meo,[8,9] which require much harsher conditions for removal of the oxazolidinone ring, followed by *N*-acetylation.

Overall, the use of the 5-*N*,4-*O*-oxazolidinone protecting group adds the stereoselective electrophilic *C*-glycosylation route to the existing methods for the formation of the sialic acid *C*-glycosides and, in doing so, opens up a new avenue for the synthesis of glycomimetics. Furthermore, the 5-*N*,4-*O*-protecting group for the sialic acid donors joins the 4,6-*O*-benzylidene acetal group in the hexopyranoside class of donors in displaying an apparent commonality of mechanism for the formation of both the *C*- and *O*-glycosides.[16] In particular, its ability to direct electrophilic *C*- and *O*-glycosylation to the formation of equatorial glycosides is remarkable and closely resembles the parallel effect of the benzylidene acetal in mannopyranosylation.[17] While the underlying reasons for this selectivity are not yet entirely clear, we maintain that they are related to a combination of the restriction of conformational mobility imposed by the *trans*-fused oxazolidinone ring and its powerful electron-withdrawing effect due the coplanarity of the carbonyl dipole with the mean plane of the pyranose ring.[18]

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

(16) (a) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144–1153. (b) Aubry, S.; Sasaki, K.; Sharma, I.; Crich, D. *Top. Curr. Chem.* **2011**, *301*, 141–188.

(17) (a) Crich, D.; Sharma, I. *Org. Lett.* **2008**, *10*, 4731–4734. (b) McGarvey, G. J.; LeClair, C. A.; Schmidtmann, B. A. *Org. Lett.* **2008**, *10*, 4727–4730.

(18) Crich, D. *J. Org. Chem.* **2011**, *76*, 9193–9209.

The authors declare no competing financial interest.