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Multiple and Regioselective Introduction of Protected Sulfates into Carbohydrates Using Sulfuryl Imidazolium Salts

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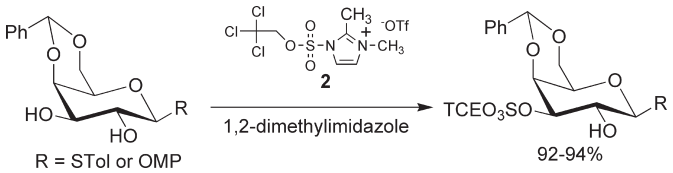

Selective incorporation of trichloroethyl (TCE)-protected sulfates into monosaccharides was examined using reagent **2**. In general, sulfation of 4,6-*O*-benzylidene acetals of galactosides and glucosides (2-OH versus 3-OH sulfations) proceeded in good to excellent yield and selectivity. Sulfation occurred predominantly at the 2-OH in 4,6-*O*-benzylidene acetals of α-glucosides and at the 3-OH in 4,6-*O*-benzylidene acetals of *β*-galactosides and *β*-glucosides. Good yields and selectivity was also achieved for the 3-OH in 3,4-diols of glucosides and galactosides. A glucoside bearing a 2-amino moiety and 6-OH group gave mainly the *N*-sulfated product in good yield. Selective sulfation of the primary 6-OH in galactose and glucose derivatives bearing one or two free secondary hydroxyl groups was also achieved usually in good yield and selectivity. Reagent **2** was also effective for the direct disulfation of diols of glucosides and galactosides, and trisulfated monosaccharides could be prepared from the disulfated compounds.

Introduction

Sulfated carbohydrates play key roles in a wide range of biological processes such as blood clotting,[1] viral entry into cells,[1] amyloidogenesis,[2] neurite outgrowth,[3] and tumor growth and metastasis.[4,5] Consequently, it is hardly surprising that natural and synthetic sulfated poly- and oligosaccharides have been shown to exhibit useful therapeutic properties such as anticoagulant,[1] anticancer,[6] and antiviral activity.[7] A synthetic multisulfated pentasaccharide has been developed as an anticoagulant and has recently been approved for clinical use.[8] Therefore the development of new and improved methods for constructing sulfated oligosaccharides is of some importance. The synthesis of sulfated oligosaccharides typically involves first constructing a fully protected precursor in which the hydroxyl groups that ultimately bear the sulfate group(s) are protected in a manner orthogonal to those that will not be sulfated. The protecting groups on the hydroxyls that are to be sulfated are then removed, and the resulting free hydroxyl groups are sulfated, usually with a sulfur trioxide-amine or amide complex, and then all other protecting groups are removed to give the desired product. However, good yields of the sulfation reactions can be difficult to attain especially when multiple sulfations are necessary.[9] Moreover, the sulfated products are highly polar and can be difficult to purify and manipulate for the final deprotections. It was realized some time ago that these shortcomings could be eliminated and/or reduced by

(1) Capilla, I.; Linhardt, R. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 391.
(2) Kisilevsky, R.; Ancsin, J. B.; Szarek, W. A.; Petanceska, S. *Amyloid* **2007**, *14*, 21.
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(4) Yip, G. W.; Smollich, M.; Gotte, M. *Mol. Cancer Ther.* **2006**, *5*, 2139.
(5) Sasisekharan, R.; Shriver, Z.; Venkataraman, G.; Narayanasami, U. *Nat. Rev. Cancer* **2002**, *2*, 521.
(6) For example, see: Karoli, T.; Liu, L.; Fairweather, J. K.; Hammond, E.; Li, C. P.; Cochran, S.; Bergefall, K.; Trybala, E.; Addison, R. S.; Ferro, V. *J. Med. Chem.* **2005**, *48*, 8229.
(7) Witvrouw, M.; Pannecouque, C.; De Clercq, E. Polysulfates: Chemistry and potential as antiviral drugs. In *Carbohydrates in Drug Design*; Witczak, Z. J., Nieforth, K. A., Eds.; Marcel Dekker: New York, 1997; pp 157−207.
(8) Petitou, M.; van Boeckel, C. A. A. *Angew. Chem.* **2004**, *43*, 3118.
(9) For example see: Orgueira, H. A.; Bartolozzi, A.; Schell, P.; Litjens, R. E.; Palmacci, E. R.; Seeberger, P. H. *Chem.—Eur. J.* **2003**, *9*, 140.

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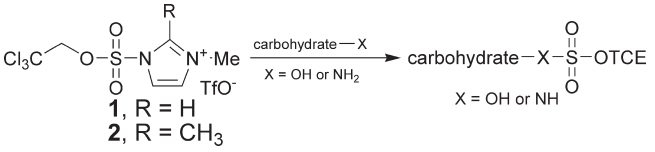
SCHEME 1



introducing the sulfate group(s) at the monosaccharide stage as a protected sulfate diester(s).[10−14] We recently reported the 2,2,2-trichloroethyl (TCE) group as a sulfate protecting group for the synthesis of sulfated carbohydrates.[15] TCE-protected sulfate esters can be readily introduced into carbohydrates using sulfuryl imidazolium salts **1** or **2** (Scheme 1).[15,16] The resulting sulfated products are stable to many of the conditions that are commonly encountered during carbohydrate syntheses, and the sulfate group is readily deprotected in excellent yield using mild reducing conditions such as Zn-ammonium formate or Pd/C and ammonium formate.[15,16]

Regioselective incorporation of protecting groups is one tactic that is employed to minimize the number of synthetic operations during the synthesis of carbohydrates.[17] There are numerous examples of the regioselective incorporation of unprotected sulfate groups into carbohydrates either directly by reacting glycosides sulfur trioxide adducts or, more commonly, reacting stannanediyl acetals or stannyl ethers of glycosides with sulfur trioxide adducts.[18] Perlin and co-workers have reported the regioselective incorporation of phenyl sulfates into monosaccharides by treating diols of monosaccharides with NaH and then phenyl chlorosulfate.[19] However, issues concerning the introduction and removal of this protecting group have prevented it from being widely used in the synthesis of complex sulfated carbohydrates. We wished to examine whether trichloroethyl-protected sulfate esters could be regioselectively introduced directly into monosaccharides using reagent **2**. Here we report the results of our studies on the direct regioselective incorporation of trichloroethyl-protected sulfate groups into monosaccharides using reagent **2**. We also present the synthesis of multiply sulfated monosaccharides using the sulfate protecting group strategy.

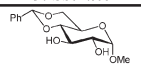
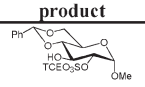
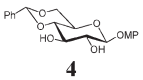
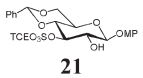
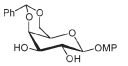
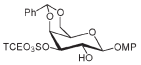
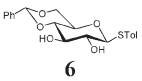
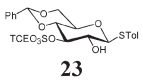
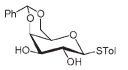
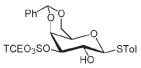
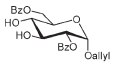
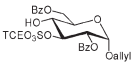
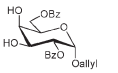
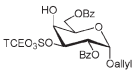
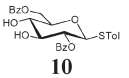
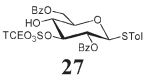
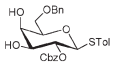
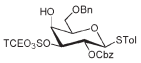
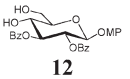
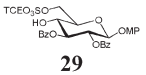
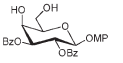
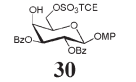
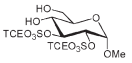
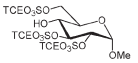
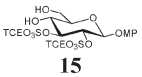
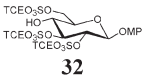
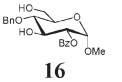
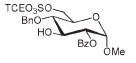
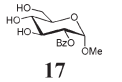
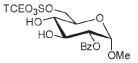
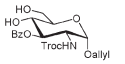
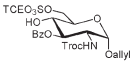
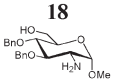
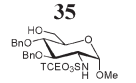
Results and Discussion

Our studies began with selective sulfations of 4,6-*O*-benzylidene acetals of galactosides and glucosides (2-OH versus 3-OH sulfations, Table 1, entries 1−5). Adding 1.2 equiv of **2** and 1.5 equiv of 1,2-dimethylimidazole (DMI) in a single batch to a solution of α-glucoside **3** in methylene chloride gave the 2-sulfated product **20** as the major product in a 58% yield (entry 1). The 2,3-disulfated product was isolated in a 5% yield. Increasing the amount of reagent **2** and DMI to 2.0 and 2.5 equiv, respectively, and adding them as separate solutions in CH_2Cl_2 dropwise slowly to a solution of **3** in methylene chloride increased the yield of **20** to 68% (entry 1) and disulfated product to 15%. None of the 3-sulfated product was produced in either case. Alternatively, we found that a similar yield of **20** and disulfated product could be obtained by adding reagent **2** in a single portion to a solution of **3** and then introducing a solution of DMI slowly over several hours. Subjecting β-glycosides **4** and **5** and β-thioglycosides **6** and **7** to the same conditions (adding a solution of 2.5 equiv of DMI in methylene chloride slowly to a solution of the carbohydrate and 2.0 equiv of reagent **2**) led to the selective formation of the 3-*O*-monosulfated products **22**−**24** in good to excellent yields (entries 3−5) with the exception being glucoside **4**, which gave the 3-*O*-monosulfated product **21** in a 60% yield and the corresponding disulfated product in an 18% yield (entry 2). In most cases the monosuflated products were readily separated from disulfated products by silica gel chromatography except when glucoside **4** was the substrate. Attempts to increase the yield of compound **21** by increasing the amount of sulfating agent and DMI did not result in a significant increase in isolated yield mainly because multiple columns were required to separate the mono- and disulfated products. Both the *O*- and *S*-galactosides **5** and **7** exhibited better selectivity and higher yields than their glucoside counterparts **4** and **6**, and *S*-glycosides **6** and **7** gave better selectivity than *O*-glycosides **4** and **5**. Indeed, both galactosides **5** and **7** as well as both S-glycosides **6** and **7** gave excellent yields of the 3-*O*-monosulfated products even when subjected to a large excess of **2** and DMI (entries 3−5), and only trace amounts of disulfated products or what appeared to be 2-*O*-monosulfated products were formed.

The regioselectivity of acylation or sulfonation reactions involving 2,3-diols of 4,6-*O*-benzylidene glucopyranoside and galactopyranoside substrates under basic conditions is dependent upon the reagents, the precise reaction conditions, and the stereochemistry and nature of the anomeric substituent.[17b] However, in general, 4,6-*O*-benzylidene acetals of α-glucosides usually exhibit greater regioselectivity for the 2-OH,[17a,b,20,21] while 4,6-*O*-benzylidene acetals of

(10) Penney, C. L.; Perlin, A. S. *Carbohydr. Res.* **1981**, *93*, 241–246.
(11) Proud, A. D.; Prodger, J. C.; Flitsch, S. L. *Tetrahedron Lett.* **1997**, *38*, 7243.
(12) Karst, N. A.; Islam, T. F.; Avci, F. Y.; Lindhardt, R. J. *Tetrahedron Lett.* **2004**, *45*, 6433.
(13) Liu, Y.; Lien, I.-F.; Ruttgaizer, S.; Dove, P.; Taylor, S. D. *Org. Lett.* **2004**, *6*, 209.
(14) Simpson, L. S.; Widlanski, T. S. *J. Am. Chem. Soc.* **2006**, *128*, 1605.
(15) Ingram, L.; Taylor, S. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 3503.
(16) Ingram, L. J.; Desoky, A.; Ali, A. M.; Taylor, S. D. *J. Org. Chem.* **2009**, *74*, 6479.
(17) (a) Robertson, J.; Stafford, P. M. Selective hydroxyl protection and deprotection. In *Carbohydrates*; Osborn, H. M. I., Ed.; Elsevier Science Ltd.: Oxford, U.K., 2003; pp 9−68. (b) Haines, A. Relative reactivities of hydroxyl groups. In *Adv. Carbohydr. Chem. Biochem.*; Tipson, R. S., Horton, D., Eds.; Academic Press: New York, NY, 1976; Vol. 33, pp 11−110.
(18) (a) Hirano, S. *Carbohydr. Res.* **1973**, *27*, 265. (b) Jacquinet, J.-C.; Rochepeau-Jobron, L.; Combal, J.-P. *Carbohydr. Res.* **1998**, *314*, 283. (c) Belot, F.; Jacquinet, J.-C. *Carbohydr. Res.* **2000**, *325*, 93. (d) Belot, F.; Jacquinet, J.-C. *Carbohydr. Res.* **2000**, *326*, 88. (e) Pazynina, G. V.; Severov, V. V.; Maisel, M. L.; Belyanchikov, I. M.; Bovin, N. V. *Mendeleev Commun.* **2008**, *18*, 238. (f) Blanchard, S.; Turecek, F.; Gelb, M. H. *Carbohydr. Res.* **2009**, *344*, 1032. (g) Lubineau, A.; Lemoine, R. *Tetrahedron Lett.* **1994**, *35*, 8795. (h) Langston, S.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **1994**, *77*, 2341. (i) Manning, D. D.; Bertozzi, C. R.; Pohl, N. L.; Rosen, S. D.; Kiessling, L. L. *J. Org. Chem.* **1995**, *60*, 6254. (j) Zhang, Y.-M.; Brodzky, A.; Sinay, P. *Tetrahedron: Asymmetry* **1998**, *9*, 2451. (k) Dechaux, E.; Savy, P.; Bouyain, S.; Monneret, C.; Florent, J.-C. *J. Carbohydr. Chem.* **2000**, *19*, 485. (l) Malleron, A.; Hersant, Y.; Narvor, C. L. *Carbohydr. Res.* **2006**, *341*, 29. (m) Cui, Y.; Colsch, B.; Alonso, C.; Baumann, N.; Tabet, J.-C.; Mallet, J.-M.; Zhang, Y. *Glycoconj. J.* **2008**, *25*, 147. (n) Tano, C.; Son, S.-Y.; Furukawa, J-i.; Furuike, T.; Sakairi, N. *Electrophoresis* **2008**, *29*, 2869.
(19) (a) Abdel-Makil, M. M.; Perlin, A. S. *Carbohydr. Res.* **1989**, *190*, 39. (b) Abdel-Makil, M. M.; Perlin, A. S. *Carbohydr. Res.* **1989**, *189*, 123.
(20) For some specific examples, see: (a) Pelyvas, I. F.; Lindhorst, T. K.; Streicher, H.; Thiem, J. *Synthesis* **1991**, 1015. (b) Lu, X.-A.; Chou, C.-H.; Wang, C.-C.; Hung, S.-C. *Synlett* **2003**, *9*, 1364. (c) Kim, S.; Chang, H.; Kim, W. *J. Org. Chem.* **1985**, *50*, 1752. (d) Abbas, S. A.; Haines, A. H. *Carbohydr. Res.* **1975**, *39*, 358. (e) Carey, F. A.; Hodgson, K. O. *Carbohydr. Res.* **1970**, *12*, 463.

TABLE 1. Selective Sulfations with Reagent 2

Entry	Substrate	Equiv 2/ equiv DMI	Major product	% Yield major product
1	 **3**	1.2/1.5[a] 2.0/2.5[b]	 **20**	58[a] 68[b]
2	 **4**	2.0/2.5[a] 2.0/2.5[b]	 **21**	55[a] 60[b]
3	 **5**	2.0/2.5[b] 5.0/6.0[a]	 **22**	85[b] 92[a]
4	 **6**	2.0/2.5[b] 5.0/6.0[a]	 **23**	71[b] 78[a]
5	 **7**	2.0/2.5[b] 5.0/6.0[a]	 **24**	88[b] 94[a]
6	 **8**	1.5/2.0[c]	 **25**	70
7	 **9**	1.5/2.0[c]	 **26**	77
8	 **10**	1.5/2.0[c]	 **27**	70
9	 **11**	2.2/3.0[c] 6.0/7.0[c]	 **28**	78[c] 83[c]
10	 **12**	2.0/2.5[b]	 **29**	60
11	 **13**	2.0/2.5[b]	 **30**	68
12	 **14**	1.5/2.0[b] 3.0/4.0[a]	 **31**	68[b] 75[a]
13	 **15**	3.0/4.0[a]	 **32**	72
14	 **16**	1.5/2.0[c]	 **33**	68
15	 **17**	1.2/1.5[b]	 **34**	65
16	 **18**	1.5/2.0[b]	 **35**	79
17	 **19**	1.5/2.0[c]	 **36**	75

[a]Added in a single portion to a solution of the carbohydrate in CH_2Cl_2 and stirred for 24−40 h. [b]A solution of DMI in CH_2Cl_2 was added dropwise over 4−6 h to a solution of carbohydrate and reagent **2** in CH_2Cl_2, and the mixture was stirred for 24−30 h. [c]A solution of DMI was added dropwise over 6 h to a solution of the carbohydrate. Reagent **2** was added in 3 portions over 6 h.

β-galactosides and, to a lesser extent, β-glucosides usually exhibit greater selectivity for the 3-OH.[22−24] 4,6-*O*-Benzylidene galactopyranosides usually exhibit greater regioselectivity than 4,6-*O*-benzylidene glucopyranosides.[17a,b] The regioselectivity exhibited by carbohydrates **3**−**7** with reagent **2** is consistent with these general reactivity patterns. 4,6-*O*-Benzylidene-β-glucopyranosides usually exhibit a lower degree of regioselectivity than 4,6-*O*-benzylidene-α-glucopyranosides,[17a,b] and this is also consistent with our results (entries 1 and 2). However, β-thioglucoside **6** exhibits very good regioselectivity for the 3-OH and was considerably greater than that exhibited by β-glucoside **4** (entries 2 and 4).

Some regioselective 3-OH acylations of 4,6-*O*-benzylidene-*β*-thioglucopyranosides have been reported suggesting that this may be a general phenomenon with *β*-thioglucopyranosides.[25]

Next we examined selective sulfation of carbohydrates **8**−**11** that contain free 3- and 4-OH groups. Adding solutions of reagent **2** (1.5 equiv) and DMI (2.0 equiv) slowly to a solution of carbohydrate **8** resulted in the formation of mainly disulfated product. However, when a solution of DMI (2.0 equiv) was added slowly to a solution of the carbohydrate, during which reagent **2** was added in three equal portions, followed by stirring for an additional 24 h, selective 3-*O*-sulfation of **8** was achieved in a 70% yield (entry 6, compound **25**), and only a trace amount of disulfated product and what appeared to be the 4-*O*-monosulfated product were detected. Sulfation of galactosyl derivative **9** under the same conditions gave the 3-*O*-sulfated compound **26** in a 77% yield (entry 7). Selective 3-*O*-sulfation of *S*-glucoside and *S*-galactoside derivatives **10** and **11** could also be achieved in 70% and 78% yields, respectively, using a similar approach (entries 8 and 9), though some disuflated product was obtained (approximately 10%). An 83% yield of the 3-*O*-monosulfated *S*-galactoside compound **28** was obtained by adding reagent **2** (6 equiv) in two portions over 8 h to a solution of **11** and DMI (7 equiv) followed by stirring for 20 h. Under these conditions the disulfated product was also formed in a 15% yield. Direct regioselective protection of 3,4-diols of galactosides is common with functionalization usually occurring on the less sterically hindered 3-OH, and the reaction of galactoside **9** with reagent **2** follows this pattern.[26] Several reports have appeared describing the regioselective protection (acylation, benzylation) of the 3-OH of 3,4-diols of 2-deoxy-2-amino glucosides in which the amino group is protected with an acyl or phthalimido group.[27,28] A report has appeared describing the selective benzylation of the 3-OH of a 3,4-diol of a 2-deoxy-2-azido glucosides.[29] However, we have been unable to find reports describing the protection of the 3-OH in 3,4-diols of glucosides with good regioselectivity.[30] Our results indicate that, at least for the sulfation reactions studied here, good selectivity can be achieved; however, further investigation will be required to determine if this level (or better) of selectivity can be achieved with other protecting groups and other 3,4-diols of glucosides.

The ability of reagent **2** to selectively sulfate the primary 6-OH over a secondary hydroxyl group (entries 10−16) by the slow addition of a solution of DMI to a solution of the carbohydrate and reagent **2** was examined. In most cases good selectivity was achieved (65−79% yield of 6-*O*-sulfated product, entries 11−16) when one or two secondary OH's were present, with compound **12** (entry 10) being an exception that gave the 6-*O*-sulfated product in a 60% yield. Disulfated products were isolated in 15% and 10% yields with carbohydrates **12** and **13**, respectively. No products resulting from monosulfation of just the secondary hydroxyls were detected. For compounds bearing TCE sulfates at the 2- and 3-positions (entries 12 and 13), the 6-OH could be selectively sulfated over the 4-OH in good yield by direct addition of an excess of the base and sulfating agent in a single portion. Only trace amounts of what appeared to be tetrasulfated products were formed. Attempts to selectively monosulfate methyl α- and *β*-D-glucopyranoside using 1.2 equiv of reagent **2** and 1.5 equiv of DMI led to a mixture of sulfated products.

Finally, we examined glucosamine **19** (entry 17) as a candidate for selective sulfation. We had previously found that reagent **1** does not readily sulfate amines yet is capable of sulfating alcohols in good yield, whereas reagent **2** readily sulfates both amines and alcohols.[16] Subjecting **19** to 1.5 equiv of **2** and 2.0 equiv of DMI gave the *N*-monosulfated product **36** in a 75% yield with a 10% yield of the disulfated product. Surprisingly, subjecting **19** to 1.5 equiv of reagent **1** and 2.0 equiv of 1-methylimidazole (1-MI) also gave the *N*-monosulfated product **36** in a 70% yield and only a trace amount of the disulfated product. Increasing the amount of reagent **1** and 1-MI did not result in an increase in the yield of the *N*-sulfated product **36**, however, there was an increase in the amounts of unidentified byproducts formed as well as disulfated product as determined by TLC.

Polysaccharides often contain residues that bear more than one sulfate groups. Since disulfated products were sometimes formed during the selective sulfation studies mentioned above, we anticipated that disulfation of certain carbohydrates could be achieved in good yield using reagent **2** (Table 2). As mentioned above, we were unable to obtain the disulfated products derived from 2,3-diols **5**−**7** and 3,4-diols **9** and **11**. However, 2,3-diols **3** and **4** and 3,4-diol **8** were disulfated in good yield using 3.5−5.0 equiv of reagent **2** and 4.0−6.0 equiv of DMI (entries 1−3). Surprisingly, 3,4-diol **10** gave disuflated product **43** in only a 45% yield. A considerable number of unidentified byproduct were formed as determined by TLC. Compounds **12**, **13**, **16**, **18**, and **19** were also all disulfated in good yield (entries 5−9). Attempts to disulfate compound **37** led to a complex mixture of

(21) This has been attributed to H-bonding between the 2-OH and the anomeric oxygen which leads to enhanced nucleophilicity of the 2-OH group. See: Creasey, S. E.; Gutherie, R. D. *Carbohydr. Res.* **1972**, *22*, 487.

(22) For some examples see: (a) References 20a−20e . (b) Wang, H.; She, J.; Zhang, L.-H.; Ye, X.-S. *J. Org. Chem.* **2004**, *69*, 5774. (c) Du, Y.; Gu, G.; Wei, G.; Hua, Y.; Linhardt, R. J. *Org. Lett.* **2003**, *5*, 3627. (d) Jacquinet, J.-C. *Carbohydr. Res.* **2004**, *339*, 349.

(23) For some recent examples of some exceptions to these reactivity patterns, see ref 22b.

(24) It has been suggested that the favored reaction of the 3-OH in 4,6-*O*-benzylidene-*β*-galactopyranosides is due to its involvement in an H-bond with the axial oxygen on C-4. See: Chittenden, G. J. F.; Buchanan, J. G. *Carbohydr. Res.* **1969**, *11*, 1164.

(25) (a) Jiang, L.; Chan, T.-H. *J. Org. Chem.* **1998**, *63*, 6035. (b) Qiu, Y.; Nakahara, Y.; Ogawa, T. *Biosci. Biotechnol. Biochem.* **1996**, *60*, 986.

(26) For some examples, see: Tanahashi, E.; Katsutoshi, M.; Shibuya, M.; Igarashi, Y.; Ishida, H.; Hasewaga, A.; Kiso, M. *J. Carbohydr. Chem.* **1997**, *16*, 831. (b) Westerlind, U.; Hagback, P.; Tidbaeck, B.; Lotta, W.; Blixt, O.; Hahid, R.; Norberg, T. *Carbohydr. Res.* **2005**, *340*, 221.

(27) (a) Suami, T.; Kin-ichi, K.; Iimura, Y.; Tanabe, H. *Carbohydr. Res.* **1984**, *135*, 319. (b) Clinch, K.; Evans, G. B.; Furneaux, R. H.; Rendle, P. M.; Rhodes, P. L.; Roberton, A. M.; Rosendale, D. I.; Tyler, P. C.; Wright, D. P. *Carbohydr. Res.* **2002**, *337*, 1095. (c) Becker, B.; Thiem, J. *Tetrahedron: Asymmetry* **1994**, *5*, 2339.

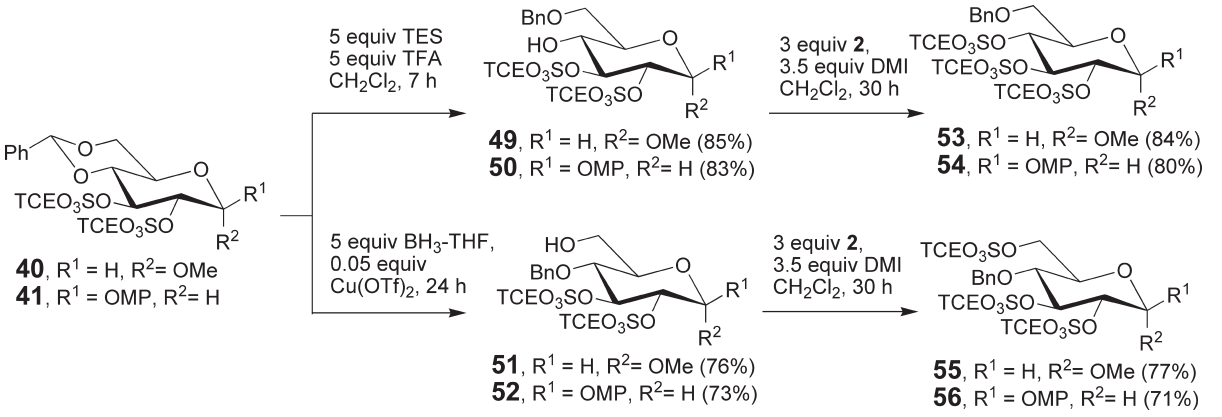
(28) This has also been achieved using di-*n*-butyltin oxide. See: Robina, I.; Lopez-Barba, E.; Fuentes, J. *Synth. Commun.* **1996**, *26*, 2847.

(29) Mayer, T. G.; Schmidt, R. R. *Eur. J. Org. Chem.* **1999**, *5*, 1153.

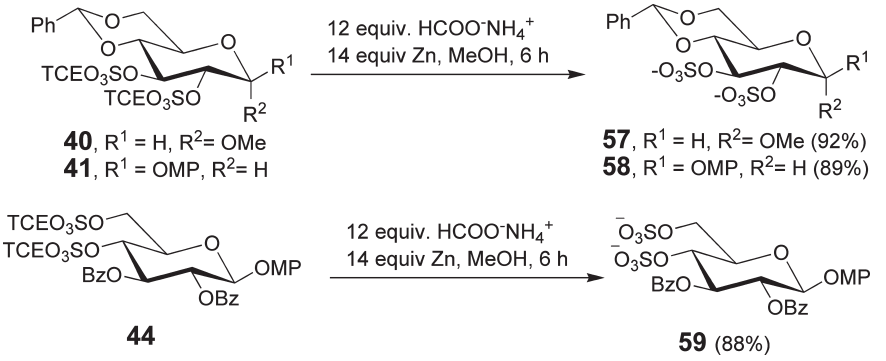
(30) Ljevakovic et al. have reported that the reaction of 1,2,6-tri-*O*-pivaloyl-*β*-D-glucopyranoside with pivaloyl chloride in pyridine gives a 59% yield of 1,2,4,6-tri-*O*-pivaloyl-*β*-D-glucopyranoside and a 30% yield of 1,2,3,6-tri-*O*-pivaloyl-*β*-D-glucopyranoside. See: Ljevakovic, D.; Tomic, S.; Tomasic, J. *Carbohydr. Res.* **1992**, *230*, 107.

(31) This is supported by the finding that attempts to sulfate the 6-OH of phenyl 3,4-di-*O*-acetyl-2-deoxy-1-thio-2-trichloroacetamido-*β*-D-galactopyranoside with reagent **2** also led to a complex mixture of products.

SCHEME 2. Synthesis of Trisulfated Carbohydrates 53−56



SCHEME 3. Deprotection of the Sulfate Group in Multisulfated Carbohydrates



products. It is possible that upon sulfation of the 6-OH group an intramolecular reaction occurs between the sulfur at the anomeric position and C-6 resulting in loss of the sulfate group at C-6 and formation of a reactive cyclic sulfonium ion.[31]

Although we could readily prepare trisulfated compounds **31** and **32** (Table 1, entries 12 and 13) from their disulfated precursors **14** and **15**, attempts to trisulfate triols **17**, **38**, and **39** as well as to tetrasulfate methyl α- and β-D-glucopyranoside under a variety of conditions were unsuccessful in that complex mixtures of sulfated products were obtained. However, trisulfated carbohydrates **53−56** could be prepared from disulflated carbohydrates **49−52** as outlined in Scheme 2. Subjecting disulfated compounds **40** and **41** to either triethylsilane/TFA or BH_3-THF/$Cu(OTf)_2$ gave compounds **49−52**, which were then sulfated using 3 equiv of SIS **2** and 3.5 equiv of DMI to give compounds **53−56** in yields ranging from 71% to 84%.

Deprotection of the sulfate protecting groups in multisulfated carbohydrates can be readily achieved using Zn/ammonium formate as illustrated for compounds **40**, **41**, and **44** in Scheme 3.

In conclusion, we have shown that the direct regioselective incorporation of TCE-protected sulfates into monosaccharides can be achieved using reagent **2**. We have also shown that reagent **2** can also be used for the direct disulfation of monosaccharides and that trisulfated monosaccharides can also be prepared from the disulfated compounds. We expect that the procedures outlined here will prove to be very useful in the preparation of complex sulfated carbohydrates.

Experimental Section

Representative Procedure for the Selective Sulfation of Compounds 3−7, 12−15, 17, and 18 (Table 1, compound 7). Method A: Reagent **2** (1.5 g, 3.32 mmol) and DMI (0.38 g, 3.98 mmol) were added in one portion to a solution of carbohydrate **7**[32] in CH_2Cl_2 (4 mL) at 0 °C (ice bath). The reaction was stirred, gradually allowed to warm to room temperature by allowing the ice bath to melt, and then stirred for a total reaction time of 30 h. The reaction was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and concentrated to a crude brown oil. Flash chromatography (1:4, EtOAc/hexanes) gave compound **24** as a white solid (0.363 g, 94%). **Method B:** To carbohydrate **7** (0.25 g, 0.66 mmol) in dry CH_2Cl_2 (2.0 mL) at 0 °C (ice bath) was added reagent **2** (0.61 g, 1.33 mmol) followed by the addition of a solution of DMI (0.16 g, 1.67 mmol) in CH_2Cl_2 (1 mL) over 6 h using a syringe pump. The ice bath was removed, and the reaction was allowed to warm to room temperature and left stirring until the reaction was complete by TLC (approximately 24 h). The reaction was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and concentrated to a crude brown oil. Flash chromatography (1:4, EtOAc/hexanes) gave compound **24** as a white solid (0.34 g, 88%). Mp 92−94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36, (s, 3H, CH_3), 2.68 (b, 1H, OH), 3.54 (s, 1H, H5), 3.39 (t, 1H, J = 9.4, H2), 4.02, 4.35 (AB, 2H, J = 12.4 Hz, H6′, H6), 4.48 (d, 1H, J = 9.3 Hz, H1), 4.56 (d, 1H, J = 2.1 Hz, H4), 4.66, 4.86 (AB, 2H, J = 10.8 Hz, CH_2CCl_3), 4.72 (dd, 1H, J = 9.4, 2.7 Hz, H3), 5.52 (s, 1H, CHPh), 7.10 (d, 2H, J = 7.6 Hz, ArH), 7.4 (s, 5H, ArH), 7.57 (d, 2H, J = 7.6 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 65.1, 68.8, 69.3, 73.3, 78.3, 79.7,

(32) Vargas-Berenguel, A.; Meldal, M.; Paulsen, H.; Jensen, K. J.; Bock, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, *22*, 3287.

84.8, 86.8, 92.6, 100.9, 125.2, 126.2, 126.4, 128.1, 129.6, 129.9, 133.1, 134.4, 134.6, 137.1, 139.0; $[\alpha]_D^{26}$ = 49.4 (c 1.0, $CHCl_3$); HRMS (ESI) m/z = 584.9987, $C_{22}H_{24}Cl_3O_8S_2$ $(M + H)^+$ requires 584.9978.

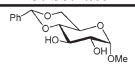
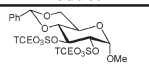
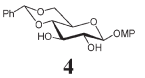
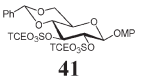
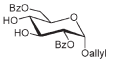
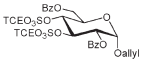
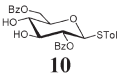
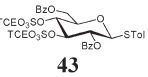
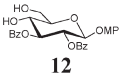
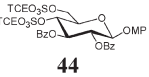
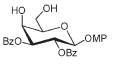
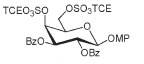
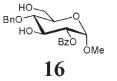
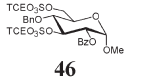
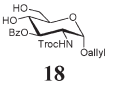
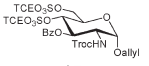
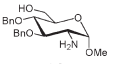
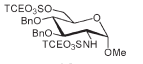
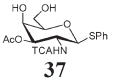
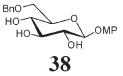
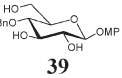
Representative Procedure for the Selective Sulfation of Compounds 8−11, 16, and 19 (Table 1, compound 8). To carbohydrate **8**[33] (0.1 g, 0.23 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C (ice bath) was added reagent **2** (0.053 g, 0.11 mmol), followed by the addition of a solution of DMI (0.16 g, 1.67 mmol) in CH_2Cl_2 (2 mL) over 8 h using a syringe pump. During the addition of the DMI two portions of reagent **2** (0.053 g, 0.11 mmol for each portion) was added after 3 and 6 h and the ice batch was removed after the initial 1 h. The reaction was left stirring until the reaction was complete by TLC (approx 24 h). The reaction was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$) and concentrated to brown crude oil. Flash chromatography (1:4, EtOAc/hexanes) gave compound **25** as a colorless syrup (0.1 g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.63 (br, 1H, OH), 3.79 (t, 1H, J = 9.4 Hz, H4), 4.03 (m, 2H, H5, 1H of allyl CH_2), 4.19 (AB, 1H, J = 12.7 Hz, the second H of allyl CH_2), 4.46, 4.92 (AB system, 2H, J = 12.4 Hz, H6, H6′), 4.7 (s, 2H, CH_2CCl_3), 5.07−5.14 (m, 2H, H2, 1H of olefinic CH_2), 5.21−5.29 (m, 3H, 1H of olefinic CH_2, H3, H1), 5.77 (m, 1H, olefinic H), 7.41−7.61 (m, 6H, ArH), 8.09 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.01, 68.6, 69.0, 70.17, 70.91, 79.9, 84.73, 92.5, 95.23, 118.3, 128.6, 128.7, 129.0, 129.9, 130.1, 132.8, 133.7, 133.71, 165.7, 167.7; $[\alpha]^{26}_D$ = 56.8 (c 1.0, $CHCl_3$); HRMS (ESI) m/z = 639.0286, $C_{25}H_{26}Cl_3O_{11}S$ $(M + H)^+$ requires 639.0261.

Representative Procedure for the Multiple Sulfation of Compounds 3, 4, 8, 10, 12, 13, 16, 18, and 19 (Table 2, compound 3). To carbohydrate **3**[34] (0.25 g, 0.85 mmol) in CH_2Cl_2 (3.4 mL) at 0 °C (ice bath) were added DMI (0.32 g, 3.4 mmol) and reagent **2** (1.16 g, 2.54 mmol). The ice bath was removed, and the reaction was allowed to warm to room temperature and then stirred for 15 h. After 15 h, additional aliquots of DMI (0.163 g, 1.7 mmol) and reagent **2** (0.778 g, 1.69 mmol) were added at room temperature. Upon completion by TLC (approximately 30 h) the reaction was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), and concentrated to crude brown oil. Flash chromatography (1:5, EtOAc/hexanes) gave compound **40** as a white solid (0.56 g, 94%). Mp 128−130 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.51 (s, 3H, OCH_3), 3.8−3.72 (m, 2H, H4, H6′), 3.79 (ddd, 1H, J = 9.8, 9.7, 4.6 Hz, H5), 4.35 (dd, 1H, J = 10.4, 4.6 Hz, H6), 4.42, 4.51 (AB system, 2H, J = 11.1 Hz, CH_2CCl_3), 5.68 (dd, 1H, J = 9.3, 3.6 Hz, H2), 4.83, 4.9 (AB, 2H, J = 11.0 Hz, CH_2CCl_3), 5.17 (t, 1H, J = 9.6 Hz, H3), 5.25 (d, 1H, J = 3.1 Hz, H1), 5.51 (s, 1H, CHPh), 7.35 (m, 3H, ArH), 7.46 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.1, 62.3, 68.6, 78.53, 78.8, 79.5, 80.1, 80.4, 92.4, 92.4, 97.5, 102.8, 126.4, 128.7, 129.9, 135.8; $[\alpha]^{26}_D$ = 44.0 (c 1.0, $CHCl_3$); HRMS (ESI) m/z = 702.8589, $C_{18}H_{20}Cl_6O_{12}S_2$ $(M + H)^+$ requires 702.8606.

Representative Procedure for the Selective Opening of the Benzylidene Acetal in Compounds 40 and 41 Using Borane/Tetrahydrofuran/Copper(II) Triflate (Scheme 2, compound 51).[35] To a solution of borane/tetrahydrofuran (1 M in THF, 1.41 mL, 1.41 mmol) was added carbohydrate **40** (0.2 g, 0.28 mmol) at room temperature under argon. The mixture was stirred for 10 min, and freshly dried copper(II) triflate (0.0051 g, 0.014 mmol) was added to the solution. After stirring for 24 h, the mixture was cooled to 0 °C (ice bath), and the reaction was quenched with triethylamine (0.1 mL, 0.7 mmol) and methanol (1 mL, *caution:* hydrogen gas was evolved). The resulting mixture was concentrated at reduced pressure followed by coevaporation with methanol. Flash chromatography (1:4, EtOAc/hexanes) gave compound **51** as a colorless syrup (0.15 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (s, 1H, OH), 3.42 (s, 3H, OCH_3), 3.69−3.86 (m, 4H, H6, H6′, H5, H4), 4.61−4.65 (m, 2H, 1H of CH_2Ph, H2), 4.75−4.94 (m, 5H, 1H of CH_2Ph, $2CH_2CCl_3$), 5.15−5.21 (m, 2H, H3, H1), 7.34 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.56, 60.53, 70.78, 74.96, 75.21, 79.04, 80.24, 80.30, 83.38, 92.32, 92.64, 96.21, 128.3, 128.4, 128.6, 136.6; $[\alpha]^{26}_D$ = 68.6 (c 1.0, $CHCl_3$); HRMS (ESI) m/z = 721.9020, $C_{18}H_{26}Cl_6NO_{12}S_2$ $(M + NH_4)^+$ requires 721.9027.

Representative Procedure for the Selective Opening of the Benzylidene Acetal in Compounds 40 and 41 Using Triethysilane/TFA (Scheme 2, compound 49).[36] To the fully protected sugar **40** (0.7 g, 0.976 mmol) in CH_2Cl_2 (6 mL) was added dropwise triethysilane (0.779 mL, 4.88 mmol) followed by trifluoroacetic acid (0.37 mL, 4.88 mmol). The reaction was stirred at room temperature for 9 h until there was no starting material remaining. The reaction was diluted with CH_2Cl_2, carefully quenched with triethylamine, and concentrated to crude syrup. Flash chromatography (1:5, EtOAc/hexanes) gave compound **49** as a colorless syrup (0.6 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.2 (d, 1H, J = 3.5 Hz, OH), 3.4 (s, 3H, OCH_3),

TABLE 2. Multiple Sulfations with Reagent 2

Entry	Substrate	Equiv 2/ equiv DMI	Product	% Yield
1	 **3**	5.0/6.0	 **40**	94
2	 **4**	3.5/4.0	 **41**	85
3	 **8**	6.0/7.0	 **42**	80
4	 **10**	5.0/6.0	 **43**	45
5	 **12**	6.0/7.0	 **44**	83
6	 **13**	6.0/7.0	 **45**	80
7	 **16**	5.0/6.0	 **46**	77
8	 **18**	5.0/6/0	 **47**	84
9	 **19**	5.0/6.0	 **48**	88
10	 **37**	5.0/6.0	Complex mixture	ND
11	 **38**		Complex mixture	ND
12	 **39**		Complex mixture	ND

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(34) Yoza, K.; Amanokura, N.; Ono, Y.; Akao, T.; Shinmori, H.; Reinhoudt, D. N. *Chem.—Eur. J.* **1999**, *5*, 2722.
(35) Shie, C.; Tzeng, Z.; Kulkarni, S.; Uang, B.; Hsu, C.; Hung, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1665.
(36) Deninno, M. P.; Etienne, J. B.; Duplantier, K. C. *Tetrahedron Lett.* **1995**, *36*, 669.

3.6 (ddd, 1H, J = 10.9, 5.6, 5.2 Hz, H5), 3.8 (m, 2H, H6, H6′), 3.9 (ddd, 1H, J = 9.0, 8.9, 3.4 Hz, H4), 4.6 (m, 3H, H2, CH_2Ph), 4.8 (m, 4H, $2CH_2CCl_3$), 5.0 (t, 1H, J = 9.4 H3), 5.1 (d, 1H, J = 3.0 Hz, H1), 7.3 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.8, 69.0, 69.1, 70.5, 73.9, 78.5, 80.2, 83.7, 92.3, 92.6, 96.3, 127.8, 128.2, 128.6, 137.0; $[\alpha]^{25}_D$ = 96.2 (c 1.0, $CHCl_3$); HRMS (ESI) m/z = 704.8768, $C_{18}H_{23}Cl_6O_{12}S_2$ $(M + H)^+$ requires 704.8762.

Representative Procedure for the Synthesis of Trisulfated Carbohydrates, Compounds 53−56 (Scheme 2, compound 55). Prepared according to the general procedure described above for the multiple sulfations. Carbohydrate **51** (0.1 g, 0.14 mmol), CH_2Cl_2 (2 mL), DMI (0.07 g, 0.73 mmol), reagent **2** (0.3 g, 0.65 mmol), reaction time 30 h. Flash chromatography (1:4, EtOAc/hexanes) gave compound **55** as colorless syrup (0.092 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.44 (s, 3H, OCH_3), 3.72 (t, 1H, J = 9.5, 9.1 Hz, H4), 3.94 (d, 1H, J = 9.5 Hz, H5), 4.42−4.5 (m, 2H, H6, H6′), 4.55, 4.99 (AB system, 2H, J = 10.5 Hz, CH_2Ph), 4.63−4.89 (m, 7H, H2, $3CH_2CCl_3$), 5.16−5.21 (m, 2H, H3, H1), 7.35 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.0, 68.1, 70.8, 75.0, 75.6, 78.4, 79.7, 80.3, 80.5, 82.9, 92.2, 92.4, 92.5, 96.2, 128.6, 128.8, 135.8 $[\alpha]^{26}_D$ = 41.8 (c 1.0, $CHCl_3$); HRMS (ESI) m/z = 914.7466, $C_{20}H_{24}Cl_9O_{15}S_3$ $(M + H)^+$ requires 914.7474.

Representative Procedure for the Deprotection of the Sulfate Moiety in Compounds 40, 41, and 44 (Scheme 3, compound 57). To a suspension of ammonium formate (0.105 g, 1.67 mmol) in MeOH (1.4 mL) was added carbohydrate **40** (0.1 g, 0.14 mmol) followed by zinc dust (0.13 g, 1.98 mmol). The reaction was stirred for 6 h at room temperature after which no starting material was detected by TLC. The reaction was filtered through Celite, and the filtrate was concentrated. Flash chromatography of the residue (20:4:1 CH_2Cl_2/MeOH/NH_4OH) afforded a white solid that was lyophilized (3×) to yield **57** as a white powder (0.061 g, 92%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.29 (s, 3H, OCH_3), 3.48−3.58 (m, 2H, H4, H5), 3.71 (t, 1H, J = 9.7 Hz, H6′), 3.94−3.99 (dd, 1H, J = 9.9, 3.1 Hz, H2), 4.12−4.16 (dd, 1H, J = 10.16, 5.9 Hz, H6), 4.45 (t, 1H, J = 9.3 Hz, H3), 5.09 (d, 1H, J = 3.1 Hz, H1), 5.54 (s, 1H, CHPh), 7.1 (br, 8H, $2NH_4$), 7.28 (m, 3H, ArH), 7.49 (m, 2H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 54.6, 62.6, 68.4, 74.9, 75.7, 80.0, 98.9, 100.9, 126.0, 127.4, 128.0, 137.7; $[\alpha]^{26}_D$ = 53.8 (c 1.0, H_2O); HRMS (ESI) m/z = 441.0168, $C_{14}H_{17}O_{12}S_2$ requires 441.0161.

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Supporting Information Available: Experimental procedures and characterization data for all novel compounds except compounds **24**, **25**, **40**, **49**, **51**, **55**, and **57**; ^{1}H and ^{13}C NMR spectra for all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.