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Efficient acid-promoted per-O-sulfation of organic polyols

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This paper is dedicated to Professor Genrikh A. Tolstikov on the occasion of his 75th birthday

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ABSTRACT

An efficient protocol for the preparation of per-O-sulfated organic compounds is reported. Sulfation of polyols with the $Et_3N{\cdot}SO_3$ complex in DMF in the presence of triflic acid allowed acceleration of the reaction at lower temperature. The efficiency of the developed protocol is demonstrated by the transformation of a series of organic polyols and phenols related to oligosaccharides, cyclitols, lignans and flavonoids.

The biological importance of poly-O-sulfated compounds necessitates the development of efficient methods for their preparation from the parent polyols. The most commonly used reagents for the synthesis of poly-O-sulfated derivatives include the complexes of sulfur trioxide with tertiary amines or amides, for example, $Et_3N{\cdot}SO_3$, $Py{\cdot}SO_3$ and $DMF{\cdot}SO_3$. These reagents were used in the syntheses of poly-O-sulfated organic compounds, particularly of heparin[1–3] and fucoidan[4–7] fragments, the anticancer drug PI-88,[8] oligo-O-sulfated flavonoid glycosides,[9] *myo*-inositol hexasulfate[10,11] and others.

O-Sulfation of organic compounds containing several OH-groups may require elongation of reaction times up to several days, increasing the temperature up to 95 °C and the use of a large excess of the sulfating complex. Thus, per-O-sulfation of carbohydrates with the complexes $Et_3N{\cdot}SO_3$ or $Py{\cdot}SO_3$ is usually carried out at 50–65 °C,[2,3,7,8] while $DMF{\cdot}SO_3$ appears to be more reactive

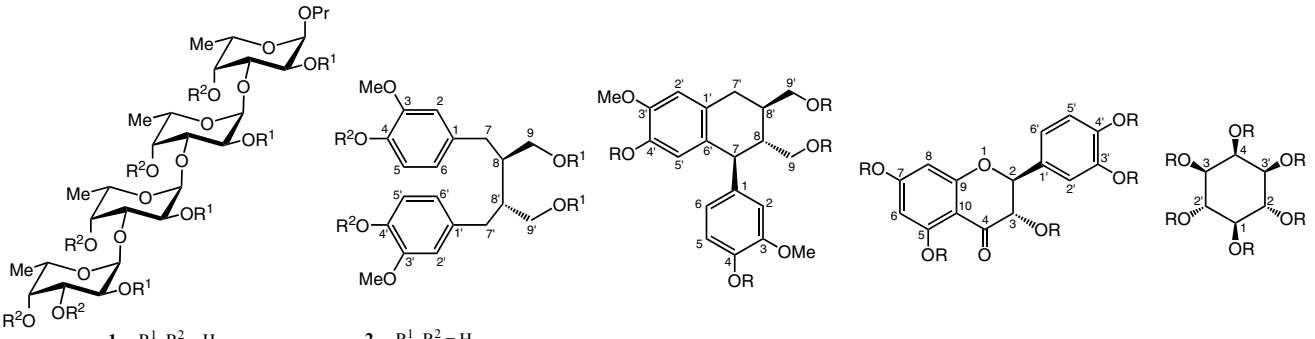

Figure 1. Polyhydroxylated substrates **1**–**5** and their products of O-sulfation.

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and multiple sulfation with this reagent is performed at temperatures as low as −5 °C in good yield.[12] Also a rapid microwave-based protocol was developed for the synthesis of per-O-sulfated organic molecules.[13]

Herewith we report an improved protocol for the preparation of per-O-sulfated derivatives of polyhydroxy organic compounds, which was developed for the synthesis of highly sulfated fragments and analogues of natural polysaccharide fucoidans. These polysaccharides exhibit an interesting spectrum of important biological activities including anticoagulant, antiangiogenic and antimicrobial as well as the ability to inhibit selectin mediated inflammation.[14,15]

Our study towards the preparation of per-O-sulfated polyols was started with attempts to synthesize nonasulfate **1b** from tetrasaccharide **1** (Fig. 1).[6] Its selectively tetrasulfated derivative **1a** was recently obtained by us[6] via sulfation of the appropriate selectively substituted tetraol precursor with Py·SO_3 (5 equiv per OH-group) within 1 h in DMF at 20 °C. This protocol appeared to be inefficient for per-O-sulfation of tetrasaccharide **1** affording a mixture of partially O-sulfated products and only traces of target compound **1b** (Table 1, entry 1).

Treatment of **1** with Py·SO_3 in pyridine at elevated temperature, as was applied[7] for the per-O-sulfation of the β-octyl glycoside analogue of tetrasaccharide **1**, also produced a mixture of partially sulfated derivatives (entry 2). This result was probably connected with the low solubility of sulfated products and their precipitation from the reaction mixture. Application of DMF-Py (3:1 v/v) as a solvent system, which increases the solubility and prevents precipitation, resulted in the formation of a mixture of products with an increased degree of sulfation, but again no target completely sulfated compound **1b** was obtained (entry 3). Attempts at per-O-sulfation of **1** with Py·SO_3 in DMF were also unsuccessful (entry 4). In this case, the reaction was accompanied by cleavage of the glycoside bonds and gave a very complex mixture of products. Application of the complex $Et_3N·SO_3$ under the same conditions was free of degradation but not efficient enough to give persulfate **1b** (entry 5).

Surprisingly, we found that the addition of triflic acid (TfOH) to the reaction mixture significantly promoted O-sulfation with $Et_3N·SO_3$ and allowed the reaction to be run at 0 °C in a shorter time. This was demonstrated by NMR analysis of reaction mixtures obtained after sulfation of **1** using the $Et_3N·SO_3$ complex in DMF in the presence of different amounts of TfOH (Fig. 2) which varied from 0.3 to 1.6 equiv of TfOH per OH-group. The use of 1.6 equiv[16] of TfOH resulted in the clear formation of per-O-sulfated product **1b** (entry 6).

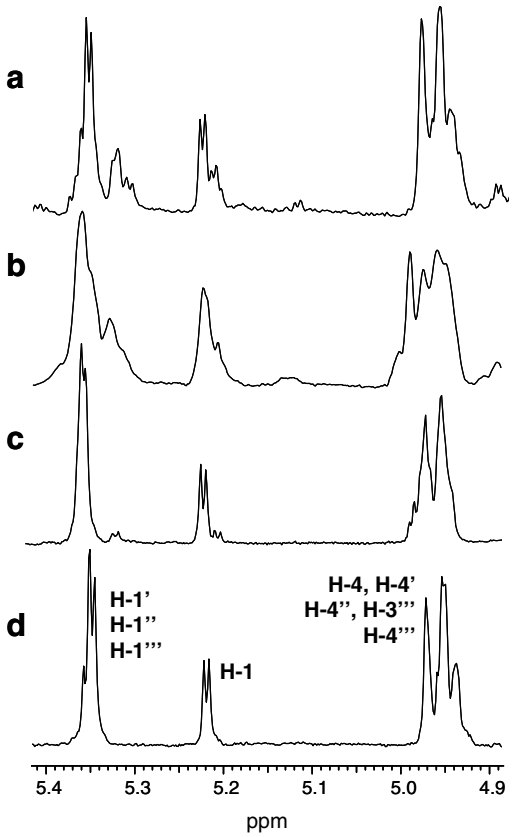
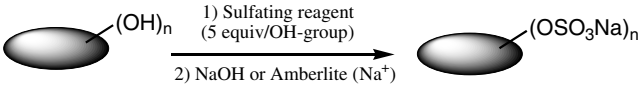


Figure 2. Anomeric regions in the ^1H NMR spectra of the products of O-sulfation of tetrasaccharide **1** by $Et_3N·SO_3$ (5 equiv/OH-group) in DMF in the absence (a) and in the presence of 0.3 (b), 1.0 (c) and 1.6 equiv (d, entry 6 in Table 1) of TfOH per OH-group.

We connect the effect of TfOH with its ability to liberate free SO_3 from the amine complex in situ, which is the most reactive sulfation agent. The TfOH promoted O-sulfation protocol was shown to be efficient for the sulfation of polyol substrates of other types. Thus, sulfation of the lignan secoisolariciresinol **2**[17] with the $SO_3·NEt_3$ complex in DMF at 0 °C in the absence of acid gave, in 40 min, selectively disulfated derivative **2a** (entry 7). Its exhaustive sulfation required both increasing the temperature up to 20 °C and elongation of the reaction time (24 h, entry 8), while per-O-sulfation in the presence of TfOH (1.0 equiv per OH-group, entry

Table 1
Per-O-sulfation of polyol substrates



Entry	Polyol	Amount of TfOH, equiv/OH-group	Temperature (°C)	Reaction time	Sulfation agent	Reaction products	Yield (%)[14]
1	**1**	0	20	1 h	Py·SO_3, DMF	Mixture of partially sulfated products	—
2	**1**	0	55	72 h	Py·SO_3, Py	Mixture of partially sulfated products	—
3	**1**	0	55	72 h	Py·SO_3, DMF/Py (3:1 v/v)	Mixture of partially sulfated products	—
4	**1**	0	55	72 h	Py·SO_3, DMF	Mixture of partially sulfated and degradation products	—
5	**1**	0	55	72 h	$Et_3N·SO_3$, DMF	Mixture of partially sulfated products	—
6	**1**	1.6	0	24 h	$Et_3N·SO_3$, DMF	**1b**	77
7	**2**	0	0	40 min	$Et_3N·SO_3$, DMF	**2a**	57
8	**2**	0	20	24 h	$Et_3N·SO_3$, DMF	**2b**	81
9	**2**	1.0	0	90 min	$Et_3N·SO_3$, DMF	**2b**	75
10	**3**	1.0	0	90 min	$Et_3N·SO_3$, DMF	**3a**	53
11	**4**	1.0	0	24 h	$Et_3N·SO_3$, DMF	**4a**	60
12	**5**	1.6	0	24 h	$Et_3N·SO_3$, DMF	**5a**	61

9) was complete within 90 min at 0 °C. This protocol was also efficient for per-O-sulfation of isolariciresinol[17] **3** (entry 10), the flavonoid dihydroquercetin[17] **4** (entry 11) and cyclitol *myo*-inositol **5** (entry 12), and gave the corresponding per-O-sulfated products **3a**-**5a** in practical yields. The necessary amounts of TfOH to convert phenols **3** and **4** were determined by us within preliminary experiments. It should be noted that O-sulfation of flavonoid derivatives using the $SO_3{\cdot}NEt_3$ complex in dimethylacetamide at 65 °C was shown[9] to be inapplicable for exhaustive O-sulfation of all phenolic OH-groups. Compound **5a** was prepared previously by sulfation of *myo*-inositol with chlorosulfonic acid or oleum under heating (Fig. 1).[10,11]

In conclusion, an improved protocol for the synthesis of persulfated derivatives of polyols containing multiple alcoholic and phenolic OH-groups has been reported. The applicability of this method was demonstrated by the preparation of per-O-sulfated derivatives of polyols of interest for pharmacology investigations as well as examples related to lignans, flavonoids, cyclitols, and oligosaccharides.

Acknowledgements

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References and notes

1. Petitou, M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3118–3133.
2. Duchaussoy, P.; Jaurand, G.; Driguez, P.-A.; Lederman, I.; Gourvenec, F.; Srassel, J.-M.; Sizun, P.; Petitou, M.; Herbert, J.-M. *Carbohydr. Res.* **1999**, *317*, 85–99.
3. Petitou, M.; Imberty, A.; Duchaussoy, P.; Driguez, P.-A.; Ceccato, M.-L.; Gourvenec, F.; Sizun, P.; Hrault, J.-P.; Perez, S.; Herbert, J.-M. *Chem. Eur. J.* **2001**, *7*, 858–873.
4. Gerbst, A.; Ustyuzhanina, N.; Grachev, A.; Khatuntseva, E.; Tsvetkov, D.; Shashkov, A.; Usov, A.; Preobrazenskaya, M.; Ushakova, N.; Nifantiev, N. *J. Carbohydr. Chem.* **2003**, *22*, 109–122.
5. Gerbst, A.; Ustyuzhanina, N.; Grachev, A.; Zlotina, N.; Khatuntseva, E.; Tsvetkov, D.; Shashkov, A.; Usov, A.; Nifantiev, N. *J. Carbohydr. Chem.* **2002**, *21*, 313–324.
6. Ustyuzhanina, N.; Krylov, V.; Grachev, A.; Gerbst, A.; Nifantiev, N. *Synthesis* **2006**, *23*, 4017–4031.
7. Hua, Y.; Gu, G.; Du, Y. *Carbohydr. Res.* **2004**, *339*, 867–872.
8. Fairweather, J.; Hammond, E.; Johnstone, K.; Ferro, V. *Bioorg. Med. Chem.* **2008**, *16*, 699–709.
9. Correia-da-Silva, M.; Sousa, E.; Pinto, M.; Duarte, B.; Marques, F. *Abstracts of Papers*, 1st International Conference on Drug Design and Discovery, Dubai, UAE, Feb 4–7, 2008; p 31.
10. Fatiadi, A. J. *Carbohydr. Res.* **1970**, *12*, 293–296.
11. Takahashi, N.; Egami, F. *Nippon Kagaku Zasshi* **1959**, *80*, 1364–1366.
12. Kuszmann, J.; Medgyes, G.; Boros, S. *Carbohydr. Res.* **2004**, *339*, 1569–1579.
13. Raghuraman, A.; Riaz, M.; Hindle, M.; Desai, U. R. *Tetrahedron Lett.* **2007**, *48*, 6754–6758.
14. Berteau, O.; Mulloy, B. *Glycobiology* **2003**, *13*, 29R–40R.
15. Cumashi, A.; Ushakova, N.; Preobrazhenskaya, M.; D'Incecco, A.; Piccoli, A.; Totani, L.; Tinari, N.; Morozevich, G.; Berman, A.; Bilan, M.; Usov, A.; Ustyuzhanina, N.; Grachev, A.; Sanderson, C.; Kelly, M.; Rabinovich, G.; Iacobelli, S.; Nifantiev, N. *Glycobiology* **2007**, *17*, 541–552.
16. *General conditions for per-O-sulfation*: To a stirred solution of polyol (0.1 mmol) in DMF (5 ml) was added $SO_3{\cdot}NEt_3$ complex (5 equiv per OH). The reaction mixture was kept for 10 min at 0 °C, then the necessary amount of TfOH was added dropwise at −20 °C. The temperature was allowed to rise to 0 °C and the reaction mixture was stirred for the appropriate time and in the cases of **1a**, **2a**–**c** and **5a** was quenched with excess of 1 M aq NaOH. The aqueous phase was separated and washed with CH_2Cl_2 (2 × 1 ml), then loaded onto a Sephadex G-15 column (40 × 3 cm) and eluted with water; the fractions containing the product were combined and freeze-dried to give the persulfates as amorphous substances. Compounds **2a** and **2b** were recrystallized from EtOH to give pure compounds as white crystals. In the case of the preparation of **3a** and **4a**, the reaction mixture was quenched with excess Et_3N and MeOH, stirred for 30 min and concentrated at 30 °C. The residue was purified by flash column chromatography on silica gel 60 (40–63 μm, E. Merck) with elution by CH_2Cl_2: MeOH–Et_3N = 4:1:0.1, the fractions containing the target product were combined and concentrated at <30 °C. The residue was dissolved in water and treated with Amberlite IR-120 (Na^+) cation exchange resin for 2 h. The resin was filtered off, and the filtrate was concentrated to a volume of 1 mL, and then subjected to gel-permeation chromatography on a Sephadex G-15 gel column as described above for **1a** and **5a**. *Selected data of O-sulfated products*: *Compound* **1b**: $[\alpha]_D$ −107 (*c* 1, H_2O); ^1H NMR (500 MHz, D_2O): 5.41 (3H, s br, H-1′, H-1″, H-1‴), 5.24 (1H, d, H-1, $J_{1,2}$ = 3.4 Hz), 4.95–4.89 (5H, m, H-4, H-4′, H-4″, H-3‴, H-4‴), 4.59–4.50 (5H, m, H-2, H-2′, H-2″, H-2‴, H-5‴), 4.46–4.29 (5H, m, H-3, H-3′, H-5′, H-3″, H-5″), 4,23 (1H, q, H-5, $J_{5,6}$ = 6.7 Hz), 3.66 (1H, m, OC*H*H′), 3.58 (1H, m, OCH*H*′), 1.64 (2H, m, Pr), 1.36–1.30 (12H, m, 12 H-6), 0.93 (3H, t, Pr, *J* = 7.4 Hz); MS-ESI $C_{27}H_{39}Na_9O_{44}S_9$ $[M+H]^+$; calcd: 1562.746, found: 1562.740. *Compound* **2a**: $[\alpha]_D$ −30 (*c* 1, H_2O); ^1H NMR (500 MHz, D_2O): 6.76 (2H, d, *J* = 8.6 Hz, H-5), 6.62 (4H, s br, H-2, H-6), 4.21 (2H, dd, *J* = 5.1 Hz, *J* = 9.4 Hz, H-9a), 4.06 (2H, dd, *J* = 6.8 Hz, *J* = 10.2 Hz, H-9b), 3.70 (6H, s, CH_3), 2.72 (2H, dd, *J* = 5.1 Hz, *J* = 13.7 Hz, H-7a), 2.57 (2H, dd, *J* = 9.4 Hz, *J* = 13.7 Hz, H-7b), 2.07 (2H, m, H-8); ^{13}C NMR (125 MHz, D_2O): 149.2 (C-3), 145.9 (C-4), 133.3 (C-1), 123.7 (C-6), 116.8 (C-5), 114.5 (C-2), 70.6 (C-9), 57.1 (Me), 41.0 (C-8), 35.7 (C-7); MS-ESI $C_{20}H_{24}Na_2O_{12}S_2$ $[M+Na]^+$; calcd: 589.04, found: 589.04. *Compound* **2b**: $[\alpha]_D$ −19 (*c* 1, H_2O); ^1H NMR (500 MHz, D_2O): 7.29 (2H, d, *J* = 8.1 Hz, H-5), 6.83 (4H, m, H-2, H-6), 4.25 (2H, dd, *J* = 5.1 Hz, *J* = 10.3 Hz, H-9a), 4.13 (2H, dd, *J* = 5.9 Hz, *J* = 10.3 Hz, H-9b), 3.77 (6H, s, CH_3), 2.79 (4H, m, H-7), 2.16 (2H, m, H-8); ^{13}C NMR (125 MHz, D_2O): 151.0 (C-3), 139.5 (C-4), 138.2 (C-1), 122.3 (C-5), 121.9 (C-6), 113.8 (C-2), 68.9 (C-9), 55.9 (Me), 39.5 (C-8), 34.4 (C-7); MS-ESI $C_{20}H_{22}Na_4O_{18}S_4$ $[M+Na]^+$; calcd: 792.92, found: 792.92. *Compound* **3a**: $[\alpha]_D$ −7 (*c* 1, H_2O); ^1H NMR (500 MHz, D_2O): 7.37 (1H, d, *J* = 8.3 Hz, H-5), 7.02 (1H, s, H-2′), 6.99 (1H, s, H-2), 6.89 (1H, d, *J* = 8.3 Hz, H-6), 6.77 (1H, s, H-5′), 4.24 (2H, d, *J* = 4.6 Hz, H-9′), 4.18 (1H, d, *J* = 10.2 Hz, H-9a), 4.13 (1H, d, *J* = 10.6 Hz, H-7), 3.90–3.84 (7H, m, 2 CH_3, H-9b), 3.02 (2H, m, H-7′), 2.37 (1H, m, H-8′), 2.18 (1H, t, *J* = 10.2 Hz, H-8); ^{13}C NMR (125 MHz, D_2O): 152.7 (C-3′), 150.9 (C-3), 144.7 (C-6′), 140.2 (C-4′), 139.6 (C-4), 136.7, (C-1), 133.4 (C-1′), 125.1 (C-5′), 124.1 (C-5), 123.7 (C-6), 116.2 (C-2), 114.5 (C-2′), 71.71 (C-9′), 68.3 (C-9), 57.7 (Me), 57.6 (Me), 47.7 (C-7), 43.8 (C-8), 36.1 (C-8′), 33.3 (C-7′); MS-ESI $C_{20}H_{20}Na_4O_{18}S_4$ $[M+Na]^+$; calcd: 790.9, found: 790.8. **4a**: $[\alpha]_D$ 17 (*c* 1, H_2O); ^1H NMR (500 MHz, D_2O): 7.76 (1H, d, *J* = 1.9 Hz, H-2′), 7.62 (1H, d, *J* = 8.5 Hz, H-5′), 7.55 (1H, dd, *J* = 1.9 Hz, *J* = 8.5 Hz, H-6′), 7.20 (1H, d, *J* = 2.2 Hz, H-6), 7.00 (1H, d, *J* = 2.2 Hz, H-8), 5.68 (1H, d, *J* = 11.0 Hz, H-2), 5.44 (1H, d, *J* = 11.0 Hz, H-3); ^{13}C NMR (125 MHz, D_2O): 187.9 (C-4), 162.3 (C-9), 157.4 (C-7), 151.7 (C-5), 143.9 (C-3′), 142.9 (C-4′), 133.5 (C-1′), 126.1 (C-6′), 122.8 (C-2′), 122.7(C-5′), 110.5 (C-10), 108.7 (C-6), 106.9 (C-8), 80.8 (C-2), 77.6 (C-3); MS-ESI $C_{15}H_7Na_5O_{22}S_5$ $[M+Na]^+$; calcd: 836.7, found: 836.7. *Compound* **5a**: $[\alpha]_D$ 0 (*c* 1, H_2O); ^1H NMR (500 MHz, D_2O): 5.13 (1H, br s, H-4), 5.07 (2H, br s, H-2), 4.87 (2H, br s, H-3), 4.77 (1H, br s, H-1); ^{13}C NMR (125 MHz, D_2O): 76.1 (C-4), 75.8 (C-2, 2′), 75.1 (C-3, 3′), 74.5 (C-1). Anal. Calcd (%) for $C_6H_6Na_6O_{24}S_6{\cdot}5H_2O$: C, 8.17; H, 1.83; S, 21.80; Na, 15.63. Found: C, 8.41; H, 1.93; S, 21.63; Na, 15.72.
17. Nifantiev, N.E.; Yashunsky, D.V.; Menshov, V.M.; Tsvetkov, Y.E., Tsvetkov, D.E. PCT/RU2008/000176.