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A General Method for the Synthesis of Sugar 2-*C*-Sulfonic Acids by 1 → 2 Arylthio Group Migration in Acid-Sensitive Thioglycosides.[1] Direct Transformation of Thiotrityl Ethers into *C*-Sulfonic Acids

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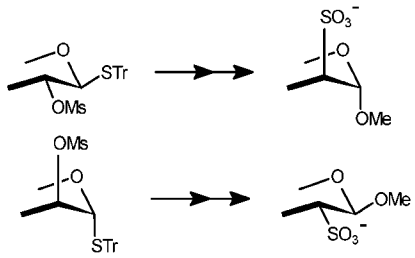
ABSTRACT



Fully protected triphenylmethyl 2-*O*-mesyl-1-thio-*β*-D-gluco- (14) and -α-D-mannopyranoside (28) were transformed by a stereoselective intramolecular 1 → 2 *trans*-arylthio migration into methyl 2-*S*-triphenylmethyl-α-D-manno- (15) and -*β*-D-glucopyranoside (29), respectively, using $NaOCH_3$ as nucleophile. The 2-*S*-triphenylmethyl ethers (15 and 29) were directly oxidized to sugar 2-*C*-sulfonic acids by using oxone ($2KHSO_5$, $KHSO_4$, K_2SO_4). Compounds (21, 23, 32, and 35) are the first representatives of secondary sugar *C*-sulfonic acids.

The chloroplast membranes of all photosynthesizing plants contain a glycolipid bearing a sugar component with a *C*-sulfonyl group.[2] The most common representative of these sugar sulfonic acids is 6-deoxy-6-sulfo-D-glucose (6-sulfoquinovose), which is one of the strongest acids occurring in nature. The biosynthesis of 6-sulfoquinovose very probably follows the reversed pathway of glycolysis, and the two starting compounds are 3-sulfoglyceraldehyde and dihydroxyacetone phosphate.[3] Chemical syntheses of various 6-deoxy-6-sulfohexoses have been published.[4]

Pyranose *C*-sulfonates as mimics of charged ulosonic acid species have been prepared using a nucleophilic addition reaction.[5] Quite recently, the preparation of anomeric α-D-GlcpNAc 1-*C*-sulfonate has been also reported.[6] To the best

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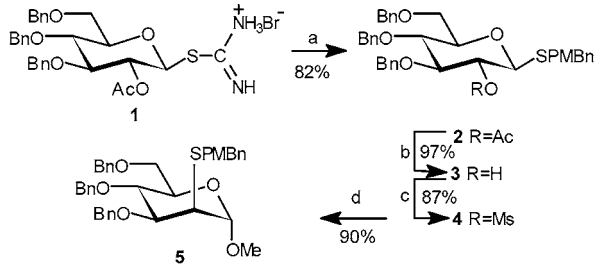
our knowledge, the synthesis of secondary sugar sulfonic acids has not yet been disclosed, although such derivatives might successfully mimic the building blocks of sulfated polysaccharides which have very important biological properties.

Our approach to 2-sulfonic acid sugars is based upon stereospecific 1,2-alkyl/arylthio group migration[7−10] and the use of an easily removable arylthio group to regenerate the 2-SH, followed by oxidation. Trityl, *p*-methoxybenzyl, and 2′-methylnaphthyl β-D-thioglycosides were prepared from appropriate isothiouronium salts (**1**[11] and **10**[12]) using trityl chloride, *p*-methoxybenzyl bromide, and 2′-methylnaphthyl bromide as arylation agents (Schemes 1−3).

Scheme 1. Preparation of Protected *p*-methoxybenzyl β-D-thioglucosides: Transformation of Compound **4** into Protected Methyl 2-Thio(p-methoxybenzyl)-α-D-mannopyranoside[a]

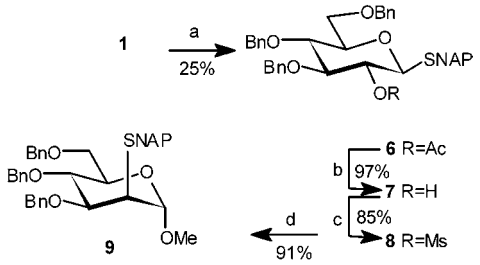


[a] Key: (a) 3.5 equiv of Na_2CO_3, 1.8 equiv of Na_2SO_3, CH_2Cl_2, H_2O, rt, 1.5 h, 1.3 equiv of PMBnBr, Hunig's base, CH_2Cl_2, rt, 24 h; (b) NaOMe/MeOH, rt, overnight; (c) 1.3 equiv of MsCl, 0.15 equiv of DMAP, dry pyridine, rt, overnight; (d) 5 equiv of NaOMe, MeOH, reflux, 4 h.

The partially acetylated thioglycosides **2**, **6**, and **11** were deacetylated to furnish OH-2 compounds (**3** and **7**); **12** was transformed into a 4,6-*O*-benzylidene derivative (**13**). The OH-2 compounds (**3**, **7**, and **13**) were mesylated to give mesyl compounds (**4**, **8**, and **14**) ready for transformation via 1 → 2 thio migration (Schemes 1−3). These reactions were performed in methanol in the presence of 5 equiv of $NaOCH_3$ at reflux temperature for 4 h. The products were obtained in high yields and with complete stereoselectivity; starting from thio β-D-glucopyranosides, methyl 2-thio-α-D-mannopyranosides (**5**, **9,** and **15**) were formed.

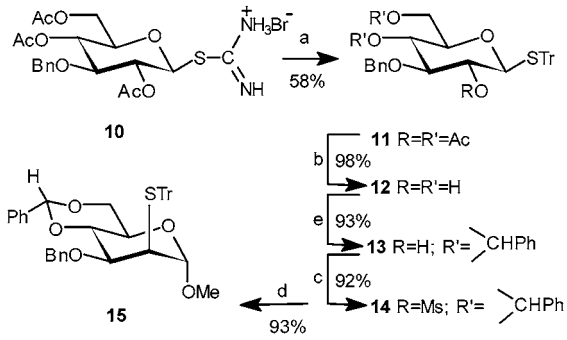
The *p*-methoxybenzyl group is commonly used for the protection of SH groups in peptide[13] and in nucleoside chemistry.[7,14] It can be removed under mild acidic (TFA, in

Scheme 2. Preparation of Protected 2′-Methylnaphthyl β-D-Thioglucopyranosides: Transformation of Compound **8** into Protected Methyl 2-Thio(2′-methylnaphthyl)-α-D-mannopyranoside[a]



[a] Key: (a) 3.5 equiv of Na_2CO_3, 1.8 equiv of Na_2SO_3, CH_2Cl_2, H_2O, rt, 1.5 h, 1.3 equiv of NAPBr, Hunig's base, CH_2Cl_2, rt, 24 h; (b) NaOMe/MeOH, rt, overnight; (c) 1.3 equiv of MsCl, 0.15 equiv of DMAP, dry pyridine, rt, overnight; (d) 5 equiv of NaOMe, MeOH, reflux, 4 h.

Scheme 3. Preparation of Protected Trityl β-D-Thioglucopyranosides: Transformation of Compound **14** into Protected Methyl 2-Thiotrityl-α-D-mannopyranoside[a]



[a]Key: (a) 3.5 equiv of Na_2CO_3, 1.8 equiv of Na_2SO_3, CH_2Cl_2, H_2O, rt, 1.5 h, 1.3 equiv of TrCl, Hunig's base, CH_2Cl_2, rt, 24 h; (b) NaOMe/MeOH, rt, overnight; (c) 1.3 equiv of MsCl, 0.15 equiv of DMAP, dry pyridine, rt, overnight; (d) 5 equiv of NaOMe, MeOH, reflux, 4 h; (e) 1.5 equiv of α,α-dimethoxytoluene, 0.2 equiv of *p*TSA·H_2O, dry DMF 50 °C, vacuum 2 h.

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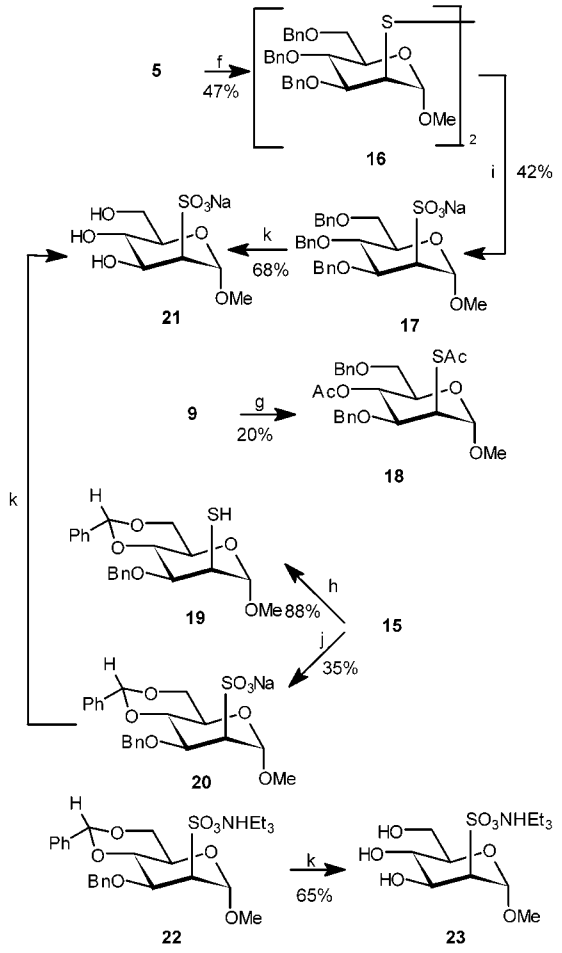
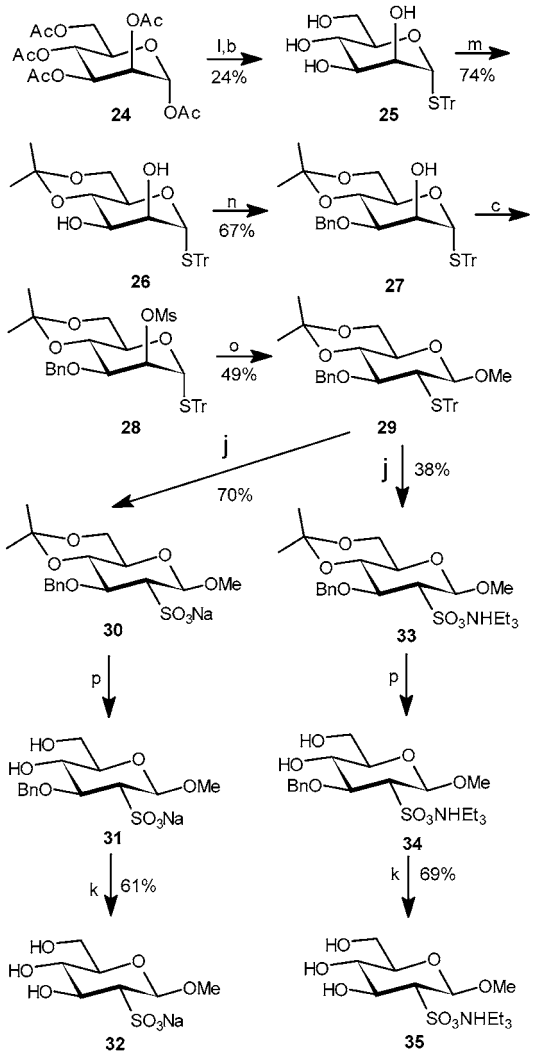
(11) Compound **1** was prepared from 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-α-glucopyranosyl bromide (Kochetkov, N. K.; Dmitriev, B. A.; Chizhov, O. S.; Klimov, E. M.; Malysheva, N. K.; Chernyak, A. Ya.; Bayramova, N. E.; Torgov, V. I. *Carbohydr. Res.* **1974**, *33*, C5−C7) by treating with thiourea (4.7 equiv) in dry boiling acetone for 15 min.

Scheme 4. Transformation of 2-Arylthioethers into 2-*C*-Sulfonic Acid Salts (Na and $NHEt_3$) of α-D-Mannopyranosides[a]



[a] Key: (f) 1.2 equiv of mercuric trifluoroacetate, 80% AcOH, rt, 4 h; (g) 8 equiv of DDQ, CH_2Cl_2, rt, 3 h; Ac_2O, pyridine, rt, 3 h; (h) 1 equiv of $AgNO_3$, 1 equiv of pyridine, dry CH_2Cl_2/dry EtOH (1/1), reflux, 1.5 h; 4 equiv of dithiothreitol, dry EtOAc, rt, overnight; (i) 18 equiv of *m*-CPBA, 2.5 equiv of NaOAc, CH_2Cl_2, rt, 4 h; (j) 2.5 equiv of Oxone, 30 equiv of KOAc, concd AcOH, rt, 5 h; (k) H_2/Pd−C, AcOH, EtOH, rt, 24 h.

Scheme 5. Preparation of Trityl 1-Thio-α-D-mannopyranoside Derivatives and Transformation of the 2-*O*-Mesyl Compound into 2-Thiotrityl Ether of Methyl β-D-Glucopyranoside: Its Oxidation by Oxone into 2-*C*-Sulfonic Acid Salts (Na and $NHEt_3$) of Methyl β-D-Glucopyranoside[a]



[a] Key: (l) 1.5 equiv of TrSH, 2 equiv of $BF_3{\cdot}Et_2O$, nitromethane, rt, overnight; (m) 2 equiv of 2-methoxypropene, 0.2 equiv of *p*TSA, dry DMF, 0 °C, 1 h; (n) 1.1 equiv of Bu_2SnO, reflux, overnight, 1.1 equiv of BnBr, dry DMF, rt, overnight; (o) 10 equiv of NaOMe, CH_2Cl_2/MeOH (1/1), reflux, 24 h; (p) TFA, CH_2Cl_2, H_2O, rt, 3 h.

the presence of anisole or phenol) or reductive[7] (sodium/liquid ammonia) conditions to regenerate SH functionality.

When compound **5** was treated with AcOH in the presence[15] of mercuric trifluoroacetate, disulfide formation occurred, and the product could be directly oxidized into the desired C_2-sulfonic acid derivative (**17**) by *m*-CPBA.

The 2-SNAP congener (**9**) was stable in the presence of AcOH; it could be oxidatively cleaved using DDQ, although a benzyl group was also removed during the reaction. The product obtained after acetylation proved to be methyl 4-*O*-acetyl-2-*S*-acetyl-3,6-di-*O*-benzyl-α-D-mannopyranoside (**18**).

The most promising results were obtained with the 2-*S*-trityl derivative (**15**). Its hydrolysis resulted in the SH-2 compound (**19**) which was oxidized into a 2-SO_3Na product (**20**) using Oxone ($2KHSO_5$, $KHSO_4$, K_2SO_4) as the oxidation agent in the presence of potassium acetate in glacial acetic acid. Hydrolysis and oxidation can be performed in one step; treatment of compound **15** with Oxone provided directly the C_2-sulfonic acid derivative (**20**) in good yield (Scheme 4).

Compounds **17** and **20** were hydrogenolyzed in ethanol in the presence of 10% Pd−C catalyst to give compound **21**.[16]

(12) Compound **10** was obtained from 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-α-D-glucopyranosyl bromide (Finan, P. A.; Warren, C. D. *J. Chem. Soc.* **1962**, 3089) as in ref 11.

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When compound **20** was purified by column chomatography in dichloromethane−methanol 65:35 (containing 1% TEA), the TEA salt (**22**) was formed. Hydrogenolysis of **22** gave the TEA salt (**23**).

The easy transformation of the sugar thiotrityl ethers into sugar *C*-sulfonic acid prompted us to prepare suitably protected trityl 1-thio-α-D-mannopyranoside to be used for the synthesis of 2-*C*-sulfonic acid of D-glucose.

Penta-*O*-acetyl-α-D-mannopyranose (**24**) was treated with triphenylmethanethiol in the presence of $BF_3 \cdot Et_2O$. The syrupy product was isolated after column chromatography and its deacetylation resulted in the crystalline triphenylmethyl 1-thio-α-D-mannopyranoside (**25**). The OH-4,6 were protected by isopropylidenation (**25** → **26**), and the OH-3 of compound **26** was selectively activated by dibutyltin acetal followed by treatment with benzyl bromide in DMF to give **27**. The OH-2 of **27** was mesylated, and the fully protected compound **28** was treated with 10 equiv of NaOMe in dichloromethane−methanol (1:1) at reflux for 24 h. The intramolecular thiotrityl migration proceeded with excellent stereoselectivity and methyl 3-*O*-benzyl-4,6-*O*-isopropylidene-2-*S*-trityl-*β*-D-glucopyranoside (**29**) was isolated. The $^3J_{1,2}$= 5.9 Hz coupling constant confirmed the *β*-gluco-configuration. Oxidation of the thiotrityl ether into *C*-sulfonic acid proceeded smoothly without the hydrolysis of the isopropylidene group. The sodium salt of the oxidized product (**30**) could be isolated by organic solvent extraction. Converting the Na salt into triethylamine salt (**33**) increased the product solubility in organic solvents. The isopropylidene groups of the salts (**30** and **33**) were hydrolyzed with diluted TFA in dichloromethane at rt to give compounds **31** and **34**. The purification was easy in these forms and the benzyl group could be removed by catalytic hydrogenolysis (Pd on Carbon) using ethanol containing traces of acetic acid (Scheme 5).

The end products with gluco configuration (**32** and **35**) were characterized by ^{1}H- and ^{13}C NMR spectra.

In summary, the 1,2-*trans*-thiotrityl glycosides are excellent starting compounds for the preparation of 1,2-*trans*-2-*C*-sulfonic acid salts of methyl glycosides. Compounds **21**, **23**, **32**, and **35** are, to the best of our knowledge, the first secondary *C*-sulfonic acids described in the literature. Their biological investigation is in progress.

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(16) All of the synthesized compounds exhibited spectral (^{1}H NMR, ^{13}C NMR) and analytical (MS) data were fully consistent with the assigned structures.