Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gsrp20

β-D-Arabinosyl 1-C-sulfonic acid

Walter S. Won [a] & Spencer Knapp [a]
[a] Department of Chemistry and Chemical Biology , Rutgers The State University of New Jersey , 610 Taylor Road, Piscataway , NJ , 08854 , USA
Published online: 10 Aug 2012.

To cite this article: Walter S. Won & Spencer Knapp (2013) β-D-Arabinosyl 1-C-sulfonic acid, Journal of Sulfur Chemistry, 34:1-2, 33-37, DOI: 10.1080/17415993.2012.706814

To link to this article: http://dx.doi.org/10.1080/17415993.2012.706814

Journal of Sulfur Chemistry, 2013
Vol. 34, Nos. 1–2, 33–37, http://dx.doi.org/10.1080/17415993.2012.706814

β-D-Arabinosyl 1-*C*-sulfonic acid†

Walter S. Won and Spencer Knapp*

Department of Chemistry and Chemical Biology, Rutgers The State University of New Jersey, 610 Taylor Road, Piscataway, NJ 08854, USA

(*Received 31 May 2012; final version received 24 June 2012*)

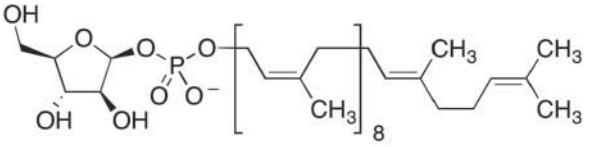
A short synthetic route to β,D-arabinofuranosyl 1-*C*-sulfonic acid (**7**), a possible biomimetic for the arabinofuranosyl anomeric phosphate, is described. The furanosyl 1-*C*-sulfonate was prepared by buffered dimethyldioxirane oxidation of an *S*-acetyl-1-thio-β-arabinofuranose derivative. Deprotection under mild conditions allowed isolation of the free sulfonic acid without desulfonylation.

Keywords: thioacetate; bioisostere; arabinosyltransferase; tuberculosis; arabinogalactin

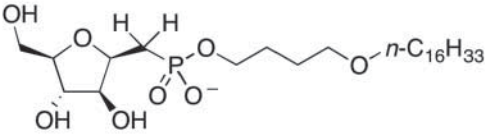
1. Introduction

One approach to the synthesis of enzyme inhibitors is to replace a strong-binding functional group of the substrate with another group of similar size, shape, and charge, but one that resists the action of the enzyme in question (for a recent review, see (*1*)). Suitable "biomimetic" replacements for phosphate, for example, might include sulfate, thiosulfate, phosphonate, seleninate, among many others. In as much as anomeric phosphates play an important role in carbohydrate biosynthesis and processing, a variety of substrate mimics have been prepared that contain replacement functional groups at C-1 (*2*). Some of these have likewise shown inhibition of the enzymes whose substrate served as the guide for their design. For example, decaprenol-β-phosphoarabinofuranose (DPA, **1**, Figure 1) is the naturally occurring donor substrate for arabinosyltransferase (AraT) in the biosynthesis of the arabinogalactin cell-wall component of *Mycobacterium tuberculosis*. A phosphonate ester analog (**2**), prepared by Centrone and Lowary ((*3*), for DPA analogs,

*Corresponding author. Email: spencer.knapp@rutgers.edu
†This paper is dedicated with affection to Professor Eric Block on the occasion of his 70th birthday, and in recognition of his many contributions to organic and natural products chemistry.



1, DPA



2

Figure 1. Structures of DPA and a phosphonate analogue.

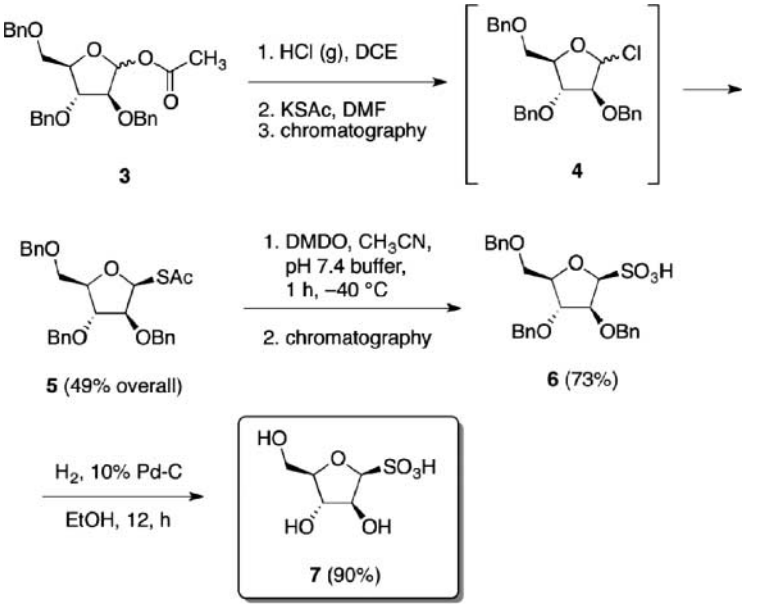
see (*4*)), was shown to prevent the growth of *M. tuberculosis* strain $H_{37}Rv$ at an minimum inhibitory concentration of 3.13 μg/mL, possibly (although not definitively) as the result of AraT inhibition.

Anomeric 1-*C*-sulfonates, which are not common in Nature (a single example, sodium paeoniflorin sulfonate, isolated from processed *Paeonia lactiflora* roots, was suggested to be an artifact of isolation (*5*)), have been suggested (*6*) as enzyme-resistant mimics of negatively charged carbohydrate derivatives, where the negative charge is that of a carboxylate, *O*-phosphate, or *O*-sulfate group. The ability to incorporate a negative charge at the anomeric position of carbohydrates might serve more generally as a way to bind positively charged protein side-chain residues or metals, including those that may occur in an enzyme active site. Previous studies have shown that *pyranosyl* anomeric 1-*C*-sulfonates can be prepared by direct oxidation of the *S*-acetyl-1-thio precursor, and that the products are stable and easily purified and isolated as their triethylammonium salts (*6*). We set about to prepare analogously a *β*-arabinofuranosyl 1-*C*-sulfonate as a start toward DPA analogs based on sulfonates or sulfonate esters, and are pleased to report the synthesis of the title compound as a first entry in this class.

2. Results and discussion

Treatment of 1-*O*-acetyl-2,3,5-tris-*O*-(phenymethyl)-*β*-D-arabinofuranose (*7*) **3** with gaseous hydrochloric acid (HCl) (*8*) in dichloroethane solution (Scheme 1) gave the anomeric chloride **4** as a mixture of isomers that was not characterized, but instead the solution was concentrated and then treated directly with a solution of excess potassium thioacetate in dimethylformamide (DMF). Chromatography of the product mixture on silica gel removed the *alpha* anomer and other impurities, and gave the *beta* thioacetate **5** in 49% overall yield. The *beta*-arabinofuranose stereochemistry was assigned based on the H-1/H-2 coupling constant of 5.2 Hz. Among 1-*O*-acetyl arabinofuranoses, the *beta* anomer typically has an H-1/H-2 coupling constant of ~5 Hz, whereas for the *alpha* anomer it is close to 0 Hz (see *e.g.* (*9*(a)). For the more general discussion of arabinofuranoside proton coupling constants, see (*9*(b)).

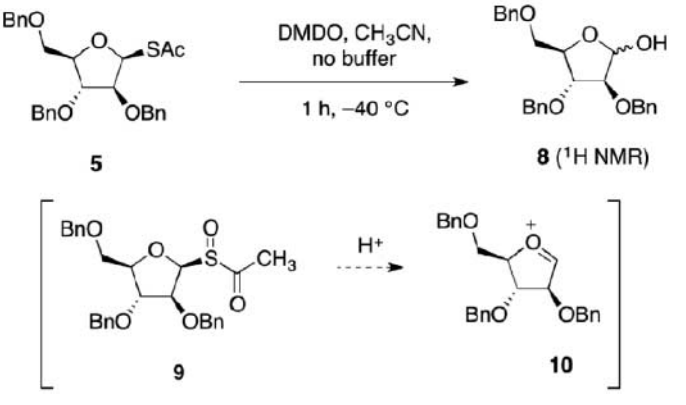
Thioacetate **5** (as a solution in 3:1 acetonitrile/phosphate buffer, pH 7.4) was rapidly oxidized by addition to a cold solution of excess dimethyldioxirane (DMDO) in acetone. Chromatography on silica gave the sulfonic acid **6** directly, without the need to convert to a sulfonate salt, and the acid form was stable to storage in the freezer for days. Debenzylation of **6** by catalytic hydrogenolysis occurred smoothly in ethanol solution. Isolation of the pure, deprotected sulfonic acid **7** required



Scheme 1. Synthesis of the title compound.

only filtration and concentration. Characterization by ^{1}H and ^{13}C NMR spectroscopy as well as negative ion mass spectrometry secured the structure. In particular, the H-1/H-2 (carbohydrate numbering) coupling constant of 4.8 Hz indicates that the *beta*-arabinofuranosyl stereochemistry is retained in **7**.

The use of pH 7.4 buffer in the DMDO oxidation of **5** was required for conversion to the sulfonic acid **6**. Without the buffer, the oxidation led instead to the hydrolysis product, reducing sugar **8** (Scheme 2), as determined by examination of the ^{1}H NMR spectrum of the crude reaction mixture (the ^{1}H NMR spectrum matched that of authentic (commercially available) **8**: (*10*)). This situation differs from the DMDO oxidation of *S*-acetyl-1-thiopyranoses (*6*), which delivers the sulfonates directly, and these are evidently stable to acid conditions (the product itself is a strong acid). As prepared from **5**, sulfonic acid **6** is also stable to acid, so the hydrolysis must have occurred earlier in the conversion.



Scheme 2. Unintended hydrolysis during unbuffered DMDO oxidation.

One possibility (Scheme 2) is that after initial oxidation of the thioacetate to an *S*-oxide (**9**), protonation occurs on the S=O, converting the AcSOH residue into a good leaving group. Analogous *O*-protonation of anomeric sulfoxides by triflic acid also leads to rapid departure of the RSOH group under mild conditions, as in the Kahne glycosylation procedure (*11*). Protonation of a *later S*-oxidized intermediate derived from **9**, such as the *S*-acetyl sulfone (*12*) Ara*f*-SO_2Ac, or the sulfonic/acetic mixed anhydride Ara*f*-SO_2OAc, and then the oxonium ion formation is an alternative possibility. The *O*-benzyl-protected arabinofuranosyl system of **5** may be described as "armed," (*13*) that is to say, relatively electron rich at the anomeric position. In contrast, the *S*-acetyl-1-thiopyranose systems described earlier are all per-*O*-acetates, hence they are "disarmed," or less electron rich, and thus perhaps less likely to suffer oxonium formation (**10**) as a competing pathway.

While **7** cannot be described as a close structural mimic of DPA (**1**), it can potentially be converted by *O*-alkylation (*14*) to sulfonate esters of long-chain alcohols that might more closely resemble **1**. However, studies on long-chain sulfone and phosphinate arabinofuranosyl derivatives indicate that even modest anti-mycobacterial activity is difficult to achieve with phosphate mimics, and is dependent on chain length in a way that cannot be easily rationalized based on possible inhibition of AraT (*3*, *4*). Sulfonic acid **7** might also be converted into a sulfonate derivative capable of electrophilically modifying an enzyme active site nucleophile, although this has not yet been attempted.

3. Experimental section

3.1. *S-Acetyl-2,3,5-tris-O-(benzyl)-1-thio-β-D-arabinofuranose (5)*

A solution of 500 mg (1.08 mmol) of 1-*O*-acetyl-2,3,5-tris-*O*-(benzyl)-α, β-D-arabinofuranose in 10 mL of anhydrous dichloroethane was treated with anhydrous HCl by bubbling the gas into the solution for a period of 20 min. The reaction mixture was stirred at room temperature for 30 min and then was concentrated to afford crude 2,3,5-tri-*O*-(phenylmethyl)-D-arabinofuranosyl chloride as a yellow syrup. A solution of this product in 5 mL of dry DMF was added to a solution of 1.23 g (0.018 mol) of potassium thioacetate in 10 mL of dry DMF via cannulation at –40°C. After 1 h, the reaction mixture was concentrated and then taken up in 20 mL of dichloromethane. The solution was filtered through a pad of Celite, concentrated, and then chromatographed on silica gel with 10:1 hexane/ethyl acetate as the eluent to afford 254 mg (49%) of 5 as thick oil:

R_f 0.45 (4:1 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.37 (m, 15H), 6.10 (d, 1H, J=5.2 Hz), 4.55 (s, 2H), 4.55 and 4.51 (ABq, 2 H, J=11.8 Hz), 4.50 and 4.60 (ABq, 2H, J=11.8 Hz), 4.20 (dd, 1H, J=4.6, 5.2 Hz), 4.18 (ddd, 1H, J=4.0, 5.6, 6.8 Hz), 4.04 (app t, 1 H, J=4.0 Hz), 3.61 (dd, 1H, J=5.2, 10.0 Hz), 3.55 (dd, 1H, J=6.8, 10.4 Hz), 2.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4, 138.1, 137.7, 137.1, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.7, 127.6, 84.7, 83.4, 82.4, 82.3, 73.3, 72.3, 71.9, 70.0, 31.1; FAB-MS m/z 502 MNa^+.

3.2. *(2S,3S,4R,5R)-3,4-Bis(phenylmethoxy)-5-[(phenylmethoxy)methyl]tetrahydrofuran-2-sulfonic acid (6)*

To a stirred solution of 200 mg (0.418 mmol) of 5 in 10 mL of 3:1 v/v acetonitrile/sodium phosphate dibasic buffer (pH 7.4, Aldrich) was added 20 mL of freshly prepared DMDO (0.079 M solution in acetone) at –40°C. After 1 h at –40°C, the reaction mixture was concentrated and then chromatographed on silica gel with 9:0.5:0.5 dichloromethane/methanol/hexane as the eluent to afford 148 mg (73%) of the 1-C-sulfonic acid 6: R_f 0.23 (9:0.5:0.5 dichloromethane/methanol/hexane);

^{1}H NMR (400 MHz, CD_3OD) δ 7.15–7.43 (m, 15H), 4.86 and 4.56 (ABq, 2H, J=12.6 Hz), 4.80 (d, 1H, J=5.2 Hz), 4.57 and 4.51 (ABq, 2H, J=11.6 Hz), 4.49 and 4.41 (ABq, 2H, J=12.0 Hz), 4.34 (dd, 1H, J=4.8, 5.2 Hz), 4.15 (app t, 1H, J=4.8 Hz), 4.08 (ddd, 1H, J=5.2, 6.0, 10.4 Hz), 3.77 (dd, 1H, J=6.4, 10.4 Hz), 3.67 (dd, 1H, J=6.0, 10.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 137.9, 137.9, 137.8, 128.1, 127.9, 127.8, 127.5, 127.4, 127.3, 127.2, 89.0, 82.6, 82.5, 82.2, 72.9, 72.8, 71.7, 70.6; NI-FAB-MS m/z 483 M^-.

3.3. *(2S,3S,4R,5R)-3,4-Dihydroxy)-5-(hydroxymethyl)tetrahydrofuran-2-sulfonic acid (7)*

A mixture of 148 mg (0.305 mmol) of the 1-C-sulfonate 6, 15 mg of 10% Pd/C, and 10 mL of ethanol was stirred overnight under a hydrogen atmosphere. The reaction mixture was filtered through a pad of Celite, which was washed with ethanol. The filtrate was concentrated to afford 59 mg (90%) of the product 7 as a white solid: mp 55–60°C; $[\alpha]_D$ –7.0°(c 0.33, 1:1 ethanol/methanol); ^{1}H NMR (400 MHz, CD_3OD) δ 4.72 (d, 1H, J=4.8 Hz), 4.26 (dd, 1H, J=3.6, 4.4 Hz), 4.11 (app t, 1H, J=4.0 Hz), 3.91 (ddd, 1H, J=4.4, 6.0, 8.4 Hz), 3.77 (dd, 1H, J=6.4, 12.0 Hz), 3.71 (dd, 1H, J=4.4, 12.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 89.1, 86.4, 77.1, 76.2, 62.1; NI-FAB-MS m/z 213 M^-.

Acknowledgements

We are grateful to the NIH (AI055760) for financial support. H-1 and C-13 NMR spectra of compounds **5**, **6**, and **7** are available in the Supplementary Material.

References

(1) Meanwell, N.A. *J. Med. Chem.* **2011,** *54,* 2529–2591.
(2) (a) Nicotra, F.; Ronchetti, F.; Russo, G. *J. Org. Chem.* **1982,** *47,* 4459–4462; (b) Casero, F.; Cipolla, L.; Lay, L.; Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.* **1996,** *61,* 3428–3432; (c) Junker, H.-D.; Fessner, W.-D. *Tetrahedron Lett.* **1998,** *39,* 269–272; (d) Gaurat, O.; Xie, J.; Valery, J.-M. *Tetrahedron Lett.* **2000,** *41,* 1187–1189; (e) Wen, X.; Hultin, P.G. *Tetrahedron Lett.* **2004,** *45,* 1773–1775; (f) Zhu, X.; Stolz, F.; Schmidt, R.R. *J. Org. Chem.* **2004,** *69,* 7367–7370; (g) Vidal, S.; Bruyere, I.; Malleron, A.; Auge, C.; Praly, J.-P. *Bioorg. Med. Chem.* **2006,** *14,* 7293–7301; (h) Knapp, S.; Ajayi, K. *Tetrahedron Lett.* **2007,** *48,* 1945–1949; (i) Lopez, M.; Drillaud, N.; Bornaghi, L.F.; Poulsen, S.-A. *J. Org. Chem.* **2009,** *74,* 2811–2816; (j) Czifrak, K.; Somsak, L. *Carbohydr. Res.* **2009,** *344,* 269–277.
(3) (a) Centrone, C.A.; Lowary, T.L. *Bioorg. Med. Chem.* **2004,** *12,* 5495–5503; (b) Centrone, C.A.; Lowary, T.L. *J. Org. Chem.* **2002,** *67,* 8862–8870; (c) Centrone, C.A.; Lowary, T.L. *J. Org. Chem.* **2003,** *68,* 8115–8119.
(4) (a) Joe, M.; Lowary, T.L. *Carbohydr. Res.* **2006,** *341,* 2723–2730; (b) Owen, D.J.; Davis, C.B.; Hartnell, R.D.; Madge, P.D.; Thomson, R.J.; Chong, A.K.J.; Coppel, R.L.; von Itzstein, M. *Bioorg. Med. Chem. Lett.* **2007,** *17,* 2274–2277; (c) Smellie, I.A.; Bhakta, S.; Sim, E.; Fairbanks, A.J. *Org. Biomol. Chem.* **2007,** *5,* 2257–2266; (d) Davis, C.B.; Hartnell, R.D.; Madge, P.D.; Owen, D.J.; Thomson, R.J.; Chong, A.K.J.; Coppel, R.L.; von Itzstein, M. *Carbohydr. Res.* **2007,** *342,* 1773–1780; (e) Wilkinson, B.L.; Long, H.; Sim, E.; Fairbanks, A.J. *Bioorg. Med. Chem. Lett.* **2008,** *18,* 6265–6267; (f) Ayers, B.; Long, H.; Sim, E.; Smellie, I.A.; Wilkinson, B.L.; Fairbanks, A. *Carbohydr. Res.* **2009,** *344,* 739–746.
(5) Hayes, P.Y.; Lehmann, R.; Penman, K.; Kitching, W.; De Voss, J.J. *Tetrahedron Lett.* **2005,** *46,* 2615–2618.
(6) Knapp, S.; Darout, E.; Amorelli, B. *J. Org. Chem.* **2006,** *71,* 1380–1389.
(7) Maryanoff, B.E.; Reitz, A.B.; Tutwiler, G.F.; Benkovic, S.J.; Benkovis, P.A.; Pilkis, S.J. *J. Am. Chem. Soc.* **1984,** *106,* 7851–7853.
(8) Yu, X.-J.; Li, G.-X.; Qi, X.-X.; Deng, Y.-Q. *Bioorg. Med. Chem. Lett.* **2005,** *15,* 683–685.
(9) (a) Wang, Z.; Prodhomme, D.R.; Buck, J.R.; Park, M.; Rizzo, C.J. *J. Org. Chem.* **2000,** *65,* 5969–5985; (b) Mizutani, K.; Kasai, R.; Nakamura, M.; Tanaka, O.; Matsuura, H. *Carbohydr. Res.* **1989,** *185,* 27–38.
(10) Zeng, J.; Vedachalam, S.; Xiang, S.; Liu, X.-W. *Org. Lett.* **2011,** *13,* 42–45.
(11) (a) Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.* **1993,** *115,* 1580–1581; (b) Alonso, I.; Khiar, N.; Martin-Lomas, M. *Tetrahedron Lett.* **1996,** *37,* 1477–1480.
(12) Adam, W.; Hadjiarapoglou, L. *Tetrahedron Lett.* **1992,** *33,* 469–470.
(13) (a) Mootoo, D.R.; Konradsson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988,** *110,* 5583–5584; (b) Fraser-Reid, B.; Wu-Z.; Udodong, U.; Ottosson, H. *J. Org. Chem.* **1990,** *55,* 6068–6070.
(14) Kevill, D.N.; Rissmann, T.J. *J. Chem. Soc., Perkin Trans.* **1984,** *2,* 717–720.