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Note

Synthesis of 4-deoxy-4-thioarabinofuranosyl disaccharides, analogs of Mycobacterial arabinogalactan

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The first chemical synthesis of disaccharides, octyl 5-O-(4-deoxy-4-thio-α-D-arabinofuranosyl)-α-D-arabinofuranoside **1** and octyl 5-O-(4-deoxy-4-thio-β-D-arabinofuranosyl)-α-D-arabinofuranoside **2** incorporating 4-deoxy-4-thioarabinose is described. Designed to mimic components of mycobacterial arabinogalactan, a major and essential constituent of the cell wall of tuberculosis and related bacteria, the compounds may disrupt cell wall biogenesis. A variety of coupling methods have been investigated before finding satisfactory techniques useful for thiofuranoses. Reductive deprotection of the sulfur-containing species is problematic, though lithium naphthalenide has proved to be an effective technique.

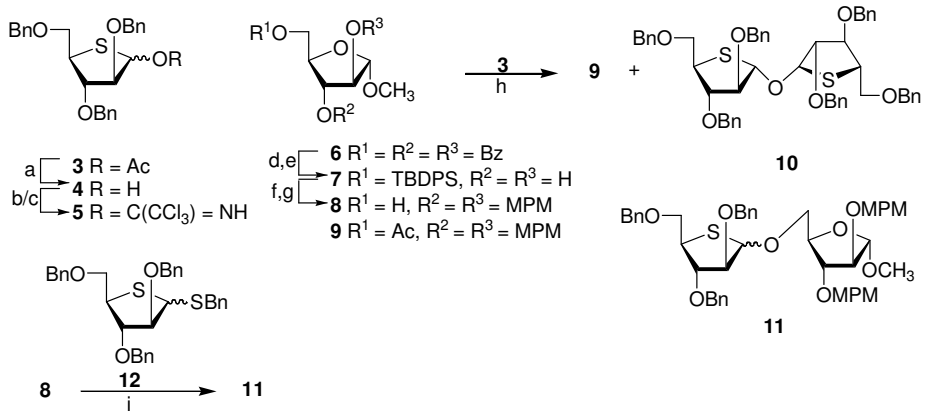
Keywords: Tuberculosis, glycosyl inhibitors, Mycobacterial arabinogalactan, thiofuranoses thioarabinofuranosyl disaccharides

The reemergence of tuberculosis and related opportunistic mycobacteria as serious public health problems, and especially the spread of multi-drug resistant tuberculosis, have focused renewed efforts to elucidate the complex biology of these organisms[1]. One outcome of these studies is an increased molecular understanding of the complex cellular envelope that is characteristic of the mycobacteria. The bacterial cell wall has long been a preferred target for antibiotics because of the inherent specificity that can be achieved. Mycobacterial arabinogalactan and arabinomannan are unusual polysaccharides that are major components of the tuberculosis bacillus[2], and the integrity of the arabinogalactan at least appears to be vital to the organism[3]. Since neither D-arabinofuranose nor D-galactofuranose, the monomers composing arabinogalactan, are found in mammalian cells, the biosynthetic steps generating and utilizing these substances may represent outstanding therapeutic targets. Disruption of arabinan metabolism, in particular, may compromise arabinogalactan, arabinomannan, and mycolylation.

The variety of arabinofuranose linkages found in mycobacterial arabinan suggests that there may be a family of related arabinosyltransferases, since glycosyltransferases are typically highly specific for a particular interglycosidic linkage. Typical of many glycosyltransferases is the presence of a divalent metal cation at the active site[4]. Since several natural and synthetic arabinosyl glycosides are known to be substrates of mycobacterial arabinosyltransferases[5], it is hypothesized that simple arabinosyl disaccharides incorporating a sulfur atom that could potentially chelate the putative cation might function as specific inhibitors. Based on the preponderant linkage found in mycobacterial arabinogalactan, the specific target was the α-octyl glycoside of 4-deoxy-4-thioarabinofuranosyl-(α-1,5)-arabinofuranoside **1**, though it was expected to also obtain the β-1,5 counterpart **2** and therefore, thought it also warranted testing. The octyl glycoside was chosen since the corresponding oxygen in the ring analog was a known substrate.

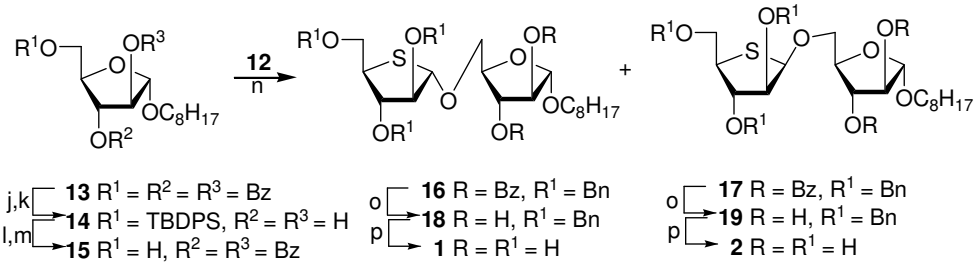
Initially, it was envisioned conversion of the 4-thioarabinose **3** (Ref. 6) to its trichloroacetimidate, which would be coupled with a suitably protected octyl arabinoside[7]. Trichloroacetimidate couplings are rare for thiosugars, and in this case conversion was poor, and the resulting imidate was unstable. Consequently, attention was turned to a Sn(IV) coupling sequence[8]. For the initial model studies, the more readily accessible methyl glycoside was used, rather than the octyl derivative.

Methyl 2,3,5-tri-O-benzoyl α-D-arabinofuranoside **6** (Ref. 9) was selectively converted to *tert*-butyldiphenylsilyl ether **7** (Ref. 10) after deacylating with methanolic ammonia followed by protecting the primary hydroxyl group with *tert* butyldiphenylsilyl chloride (TBDPSCl) in DMF (**Scheme I**). Etherification of compound **7** with *p*-methoxybenzyl chloride (MPMCl) in NaH and deprotection of silyl group with tetrabutylammonium fluoride (TBAF) resulted in model glycosyl acceptor **8**. Treatment of compound **8** with thiosugar **3** (Ref. 6) in $SnCl_4$ (Ref. 8) produced, after chromatographic separation, traces of the desired



Reagents and conditions: (a) CH_3OH, 1M $NaOCH_3$, RT, 2 hr; (b) CH_2Cl_2, Cl_3CCN, K_2CO_3, RT, 48 hr; (c) CH_2Cl_2, Cl_3CCN, NaH, RT, 5 hr; (d) CH_3OH, NH_3, RT, 12 hr; (e) tert butyldiphenylsilyl chloride (TBDPSCl), imidazole, DMF, RT, 3 hr; (f) *p*-methoxybenzyl chloride (MPMCl), NaH, DMF, tetrabutylammonium bromide (TBABr), 0°-RT, 12 hr; (g) tetrabutylammonium fluoride (TBAF), THF, 0°-RT, 3 hr; (h) $SnCl_4$, CH_3CN, 0°-RT, 1 hr; (i) *N*-bromosuccinimide (NBS), CH_3CN, 4A molecular sieves, RT, 0.5 hr, 74%.

Scheme I



Reagents & conditions: (j) CH_3OH, NH_3, RT, 12 hr; (k) TBDPSCl, imidazole, DMF, RT, 4 hr; (l) benzoyl chloride (BzCl), pyridine, 0°-RT, 12 hr; (m) TBAF, CH_3CN, 0°-RT, 12 hr; (n) NBS, CH_3CN, 4A molecular sieves, RT, 0.5 hr; (o) CH_3OH, NH_3, RT, 3 hr; (p) THF, lithium naphthanelide, -23° C, 2 hr.

Scheme II

adduct **11** as a mixture of α and β anomers (1:1), but surprisingly the major product was the symmetrical α-1,1 arabinoside **10**, along with acetylated starting material **9**.

With availability of alternative benzyl-2,3,5-tri-O-benzyl-4-deoxy-4-thio-D-thioarabinofuranosyl donor **12** (Ref. 6), attention was next turned to the coupling procedure of Nicolaou *et al.*[11] Treatment of acceptor **8** with *N*-bromosuccinimide (NBS) in acetonitrile in the presence of **12** gave a satisfactory yield of the desired disaccharide **11**, albeit as a mixture of anomers. Thus, with a coupling method in hand, the focus was now on the octyl series for synthesis of target compounds **1** and **2**.

Octyl 2,3,5-tri-O-benzoyl-α-D-arabinofuranoside **13** was prepared from tribenzoate **6** *via* the intermediate glycosyl bromide (30% HBr/HOAc, 2hr, 91%) using Sn (IV) coupling[8]. As before, tribenzoate **13** was smoothly converted to octyl 5-*tert* butyldiphenylsilyl α-D-arabinofuranoside **14** after debenzoylation followed by treatment with TBDPSCl. Benzoylation of **14** and deprotection of silyl group with TBAF gave octyl 2,3-di-O-benzoyl α-D-arabinofuranoside **15**. Glycosyl acceptor **15** underwent coupling with **12** upon treatment with NBS to give a 21:31 mixture of disaccharides **16** and **17**. After separation of anomers chromatographically, the benzoyl groups of each disaccharide were deprotected, affording **18** and **19**. Various debenzylation methods, *viz*. BBr_3 (Ref. 12), $FeCl_3$ (Ref. 13), Na in liquid NH_3 (Ref. 14), and Pearlman's catalyst[15], were uniformly unsuccessful for the deblocking of **18** and **19**. However, a freshly made lithium naphthanelide[16] in THF at –23ºC was found to afford the desired products, octyl 5-O-(4-deoxy-4-thio-α-D-arabinofuranosyl)-α-D-arabinofuranoside **1** and octyl 5-O-(4-deoxy-4-thio-β-D-arabinofuranosyl)-α-D-arabinofuranoside **2** in satisfactory yield (**Scheme II**).

Experimental Section

The general procedures were same as reported earlier[17]. The solvent used in NMR is $CDCl_3$ unless otherwise stated. The structures of disaccharides were assigned on the basis of decoupling experiments in ^1H NMR.

Methyl 2,3-di-O-methoxybenzyl-α-D-arabinofuranoside, 8. Compound **7** (Ref. 10) (5.22 g, 12.97 mmol) was added to a suspension of NaH (60% dispersion in mineral oil, 1.24 g, 31.05 mmol) in dry DMF (40 mL) dropwise at 0ºC followed by methoxybenzylchloride (4.22 mL, 31.05 mmol) and tetrabutylammonium bromide (1.0 g). The reaction mixture was stirred overnight at RT. MeOH (20 mL) was added, the solution was concentrated to dryness, the oil was redissolved in CH_2Cl_2 and organic layer was washed with water, brine, dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure. The residue was column chromatographed over silica gel (cyclohexane : EtOAc, 1:1) to yield methyl 2,3-di-O-methoxybenzyl-5-O-*tert* butyldiphenylsilyl-α-D-arabinofuranoside (3.7 g, 45%). ^1H NMR: δ 7.51 (m, 10H, Ar.*H* of TBDPS), 7.18 (m, 4H, *o*-methoxy Bn*H*), 6.83 (m, 4H, *m*-methoxy Bn*H*), 4.91 (s, 1H, H-1), 4.43 (m, 4H, -CH_2 of methoxy Bn), 4.11 (m, 1H, H-4), 3.94 (m, 2H, H-5a,b), 3.80, 3.77 (s, 3H, 2×-OMe), 3.79 (m, 2H, H-2, H-3), 3.37 (s, 3H, -OMe), 1.04 (s, 9H, -CMe_3); FAB MS: *m/z* 665 $(M+Na)^+$.

Tetrabutylammonium fluoride (8 mL, 7.95 mmol) was added dropwise to a solution of methyl-2,3-di-O-methoxybenzyl-5-O-*tert*-butyldiphenylsilyl-α-D-arabinofuranoside[10] (3.65 g, 5.68 mmol) in freshly distilled THF (50 mL) at 0°C. The reaction was warmed upto RT and stirred for 3 hr. Brine water was added to the reaction mixture and extracted with EtOAc twice. The organic layer was dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure. The residue was passed through a column of silica gel (cyclohexane:EtOAc, 8:2 to 6:4) to yield **8** (1.63 g, 76%). ^1H NMR: δ 7.23 (m, 4H, *o*-methoxy Bn*H*), 6.86 (m, 4H, *m*-methoxy Bn*H*), 4.90 (s, 1H, H-1), 4.47 (m, 4H, -CH_2 of methoxy Bn), 4.10 (m, 1H, H-4), 3.93 (m, 2H, H-2, H-3), 3.82 (m, 1H, H-5a), 3.80, 3.79 (s, 3H, 2×-OMe), 3.60 (m, 1H, H-5b), 3.38 (s, 3H, -OMe), 1.86 (dd, 1H, *J*=7.9 and 4.4 Hz, 5-OH); FAB MS: *m/z* 411 $(M+Li)^+$.

Octyl 5-O-*t*-butyl-di-phenylsilyl-α-D-arabinofuranoside, 14. Compound **13** (Ref. 8) (8.76 g, 15.26 mmol) was dissolved in MeOH (150 mL) and NH_3/MeOH (7 *N*, 100 mL) was added to it and reaction mixture was stirred overnight at RT. The solvent was evaporated under reduced pressure, *tert* butyldiphenylsilyl chloride (2.44 mL, 9.41 mmol) and imidazole (1.28 g, 18.81 mmol) were added to the residue taken in DMF (20 mL) and stirred at RT for 4 hr. Et_2O was added and the organic layer was washed with water, dried over anhyd. Na_2SO_4, filtered and concentrated. Column chromatography over silica gel (cyclohexane:EtOAc, 8.5:1.5) of the residue gave **14** (2.54 g, 60%). ^1H NMR: δ 7.67 (m, 4H, *m*-Ar.*H*), 7.43(m, 6H, *o*- and *p*-Ar.*H*), 5.08 (s, 1H, H-1), 4.20 (d, 1H, *J*=11 Hz, 3-OH), 4.07 (m, 3H, H-2, H-3, H-4), 3.78 (m, 3H, H-5a,b, -OC*H*H$(CH_2)_6CH_3$), 3.46 (m, 1H, -OCH*H*$(CH_2)_6CH_3$), 3.04 (d, 1H, *J*=11.7 Hz, 2-OH), 1.55 (m, 2H, -$OCH_2CH_2(CH_2)_5CH_3$), 1.27 (m, 10H, -$OCH_2CH_2(CH_2)_5CH_3$), 1.05 (s, 9H, -CH_3), 0.87 (t, 3H, *J*=7.0 Hz, -$O(CH_2)_7CH_3$); FAB MS: *m/z* 501 $(M+H)^+$.

Octyl 5-O-(4-deoxy-4-thio-2,3,5-tri-O-benzyl-α-D-arabinofuranosyl)-2,3-di-O-benzoyl-α-D-arabinofuranoside, 16 and octyl 5-O-(4-deoxy-4-thio-2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)-2,3-di-O-benzoyl-α-D-arabinofuranoside, 17. Compound **12** (Ref. 6) (900 mg, 1.66 mmol) and **15** (Ref. 18) (852 mg, 1.81 mmol, obtained from **14**) were dissolved separately in anhydrous CH_3CN (15 mL each) under an atmosphere of argon and molecular sieves were added to the former and stirred for 15 min. The latter solution was added to the former dropwise at RT followed by addition of NBS (321 mg, 1.8 mmol). The reaction was stirred at RT for 30 min. The reaction mixture was diluted with $CHCl_3$ and filtered through celite. The organic layer was washed with 10% aq $NaHCO_3$, brine, dried over anhyd. Na_2SO_4 and concentrated. The residue was column chromatographed over silica gel (cyclohexane:EtOAc, 9.5:0.5) to give **16** (312 mg, 21%) and **17** (450 mg, 31%).

16: ^1H NMR: δ 8.04 (m, 4H, Ar.*H*., *o*-protons of benzoyls), 7.38 (m, 21H, Ar.*H*., benzyls, *m*- and *p*-protons of benzoyls), 5.45 (broad s, 1H, H-3), 5.44 (broad s, 1H, H-2), 5.22 (s, 1H, H-1), 5.18 (d, 1H, *J*=3.2 Hz, H-1'), 4.60 (m, 6H, CH_2 of benzyls), 4.43 (m, 1H, H-4), 4.25 (dd, 1H, *J*=6.4, 3.5 Hz, H-2'), 4.01 (dd, 1H, *J*=10.5, 5.5 Hz, H-5a), 3.93 (dd, 1H, *J*=8.5, 6.4 Hz, H-3'), 3.74 (m, 4H, H-5'a, H-4', H-5b, -OC*H*H$(CH_2)_6CH_3$), 3.50 (m, 2H, H-5'b, -OCH*H*$(CH_2)_6CH_3$), 1.62 (m, 2H, -$OCH_2CH_2(CH_2)_5CH_3$), 1.31 (m, 10H, -$O(CH_2)_2(CH_2)_5CH_3$), 0.86 (t, 3H, *J*=6.6 Hz, -$O(CH_2)_7CH_3$); FAB MS: *m/z* 889 $(M+H)^+$. Anal. Calcd for $C_{53}H_{60}O_{10}S$: C, 71.51; H, 6.80. Found: C, 71.11; H, 6.85%.

17: ^{1}H NMR: δ 8.06 (m, 4H, Ar.*H*., *o*-protons of benzoyls), 7.41 (m, 21H, Ar.*H*., benzyls, *m*- and *p*-protons of benzoyls), 5.48 (d, 1H, *J*=4.7 Hz, H-3), 5.42 (d, 1H, *J*=1.3 Hz, H-2), 5.20 (s, 1H, H-1), 5.10 (d, 1H, *J*=3.0 Hz, H-1'), 4.60 (m, 7H, H-4, CH_2 of benzyls), 4.18 (m, 2H, H-3', H-2'), 4.09 (dd, 1H, *J*=10.8, 4.0 Hz, H-5a), 3.73 (m, 3H, H-5b, H-5'a, -OC*H*H$(CH_2)_6CH_3$), 3.50 (m, 2H, H-5'b –OCH*H* $(CH_2)_6CH_3$), 3.38 (m, 1H, H-4'), 1.62 (m, 2H, -OCH_2 C$H_2(CH_2)_5CH_3$), 1.26 (m, 10H, -O$(CH_2)_2(CH_2)_5CH_3$), 0.86 (t, 3H, *J*=6.6 Hz, -O$(CH_2)_7CH_3$); FAB MS: *m/z* 895 $(M+Li)^+$. Anal. Calcd for $C_{53}H_{60}O_{10}S$: C, 71.51; H, 6.80. Found: C, 71.23; H, 6.78%.

Octyl 5-O-(4-deoxy-4-thio-2,3,5-tri-O-benzyl-α-D-arabinofuranosyl)-α-D-arabinofuranoside, 18. Compound **16** (196 mg, 0.22 mmol) was dissolved in MeOH (10 mL) and NH_3/MeOH (7 N, 10 mL) was added to it and reaction mixture was stirred for 3 hr at RT. The solvent was evaporated under reduced pressure. Column chromatography over silica gel ($CHCl_3$:MeOH, 97:3) of the residue gave **18** (130 mg, 87%). ^{1}H NMR: δ 7.26 (m, 15H, Ar.*H*), 5.09 (d, 1H, *J*=1.7 Hz, H-1'), 4.98 (s, 1H, H-1), 4.48 (m, 6H, CH_2 of benzyls), 4.18 (m, 1H, H-4), 4.15 (dd, 1H, *J*=3.7, 2.2 Hz, H-2'), 4.01 (m, 2H, H-3', H-3), 3.90 (m, 2H, H-2, H-5a), 3.72 (m, 2H, H-4', -OC*H*H$(CH_2)_6CH_3$), 3.60 (dd, 1H, *J*=9.4, 7.0 Hz, H-5'a), 3.56 (dd, 1H, *J*=10.3, 2.6 Hz, H-5b), 3.43 (m, 2H, H-5'b, -OCH*H* $(CH_2)_6CH_3$), 1.56 (m, 2H, -$OCH_2CH_2(CH_2)_5CH_3$), 1.27 (m, 10H, -O$(CH_2)_2(CH_2)_5CH_3$), 0.88 (t, 3H, *J*=6.6 Hz, -O$(CH_2)_7CH_3$); FAB MS: *m/z* 687 $(M+Li)^+$. Anal. Calcd for $C_{39}H_{52}O_8S$: C, 68.76; H, 7.69. Found: C, 68.36; H, 7.53%.

Octyl 5-O-(4-deoxy-4-thio-2,3,5-tri-O-benzyl-β-D-arabinofuranosyl)-α-D-arabinofuranoside, 19. Compound **17** (176 mg, 0.20 mmol) was dissolved in MeOH (10 mL) and NH_3/MeOH (7 N, 10 mL) was added to it as done in **16**. Column chromatography over silica gel ($CHCl_3$:MeOH, 97:3) of the residue gave **19** (113 mg, 84%). ^{1}H NMR: δ 7.31 (m, 15H, Ar.*H*), 4.94 (s, 1H, H-1), 4.73 (d, 1H, *J*=4.0 Hz, H-1'), 4.61 (m, 6H, -CH_2 of benzyls), 4.20 (m, 1H, H-4), 4.14 (dd, 1H, *J*=8.3, 3.9 Hz, H-2'), 4.06 (dd, 1H, *J*=8.2, 5.8 Hz, H-3'), 4.05 (dd, 1H, *J*=10.1, 2.5 Hz, H-5a), 3.97 (m, 2H, H-2, H-3), 3.68 (m, 2H, H-5'a, -OC*H*H$(CH_2)_6CH_3$), 3.45 (dd, 1H, *J*=14.6, 7.2 Hz, H-5'b), 3.41 (m, 1H, -OCH*H*$(CH_2)_6CH_3$)m, 3.34 (m, 1H, H-4'), 3.27 (dd, 1H, *J*=10.3, 1.6 Hz, H-5b), 1.58 (m, 2H, -$OCH_2CH_2(CH_2)_5CH_3$), 1.30 (m, 10H, -O$(CH_2)_2$ $(CH_2)_5CH_3$), 0.90 (t, 3H, *J*=6.6 Hz, -O$(CH_2)_7CH_3$); FAB MS: *m/z* 687 $(M+Li)^+$. Anal. Calcd for $C_{39}H_{52}O_8S$: C, 68.76; H, 7.69. Found: C, 68.40; H, 7.59%.

Octyl 5-O-(4-deoxy-4-thio-α-D-arabinofuranosyl)-α-D-arabinofuranoside, 1. Freshly made Li-Naphthanelide[16] in THF (3 mL) was added to compound **18** (60 mg, 0.08 mmol) dissolved in THF (2 mL) dropwise at –23ºC under argon for 2 hr. Water was added and solvents were evaporated off with coevaporation of toluene. Column chromatography over silica gel ($CHCl_3$:MeOH, 9:1) gave **1** (8 mg, 26%) besides recovering the unreacted starting material **18** (8 mg). ^{1}H NMR (CD_3OD): δ 5.01 (d, 1H, *J*=4.5 Hz, H-1'), 4.82 (d, 1H, *J*=1.6 Hz, H-1), 4.04 (dd, 1H, *J*=7.1, 4.6 Hz, H-2'), 3.98 (m, 2H, H-3, H-4), 3.91 (dd, 1H, *J*=3.62, 1.76 Hz, H-2), 3.87 (m, 2H, H-4', OH), 3.76 (m, 1H, H-5a), 3.70 (m, 2H, H-3', -OC*H*H$(CH_2)_6CH_3$), 3.57 (m, 2H, H-5'a, H-5b), 3.42 (m, 2H, H-5'b), 3.40 (m, 1H, -OCH*H*$(CH_2)_6CH_3$), 1.58 (m, 1H, -$OCH_2CH_2(CH_2)_5CH_3$), 1.29 (m, 10H, -O$(CH_2)_2(CH_2)_5CH_3$), 0.90 (t, 3H, *J*=6.6 Hz, -O$(CH_2)_7$ CH_3; FAB MS: *m/z* 417 $(M+Li)^+$. Anal. Calcd for $C_{18}H_{34}O_8S.H_2O$: C, 50.45; H, 8.40. Found: C, 50.47; H, 7.98%.

1.7 Octyl 5-O-(4-deoxy-4-thio-β-D-arabinofuranosyl)-α-D-arabinofuranoside, 2. Freshly made Li-Naphthanelide[16] (3 mL) was added to compound **19** (21 mg, 0.08 mmol) in THF (2 mL) dropwise at –23ºC under argon as done in **1**. Column chromatography over silica gel ($CHCl_3$:MeOH, 9:1) gave **2** (5 mg, 39%). ^{1}H NMR (D_2O): δ 4.98 (s, 1H, H-1), 4.95 (d, 1H, *J*=3.5 Hz, H-1'), 4.09 (m, 5H, H-4, H-3', H-2', H-2, H-3), 3.93 (dd, 1H, *J*=14.5, 3.5 Hz, H-5a), 3.84 (dd, 1H, *J*=11.6, 4.8 Hz, H-5'a), 3.71 (m, 2H, H-5b, -OC*H*H$(CH_2)_6CH_3$), 3.62 (m, 1H, H-5'b), 3.50 (m, 1H, -OCH*H*$(CH_2)_6CH_3$,), 3.26 (m, 1H, H-4'), 1.60 (m, 2H, -$OCH_2CH_2(CH_2)_5CH_3$), 1.30 (m, 10H, -O$(CH_2)_2$ $(CH_2)_5CH_3$), 0.88 (t, 3H, *J*=6.6 Hz, -O$(CH_2)_7CH_3$); FAB MS: *m/z* 411 $(M+H)^+$. Anal. Calcd for $C_{18}H_{34}O_8S$: C, 52.66; H, 8.34. Found: C, 52.25; H, 8.22%.

Acknowledgments

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