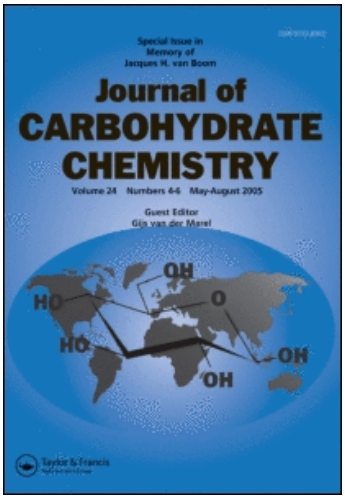

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COMMUNICATION

SYNTHETIC STUDIES OF THE 5-AMINOPENTOSE 2-SULFATE COMPONENT OF THE LIPOSIDOMYCINS

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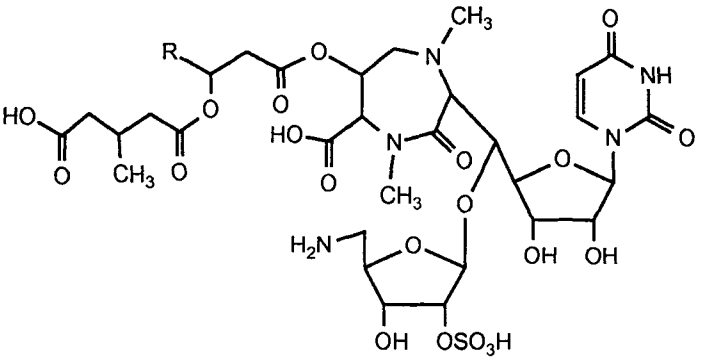
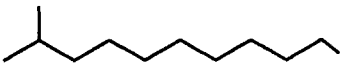
The liposidomycins are a family of novel lipid-containing nucleoside antibiotics that were recently found in the culture filterate and mycelia of *Streptomyces griseosporeus*.[1] These antibiotics inhibit formation of the lipid intermediate in bacterial peptidoglycan synthesis.[1,2] The primary site of

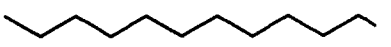


1 R =

2 R =

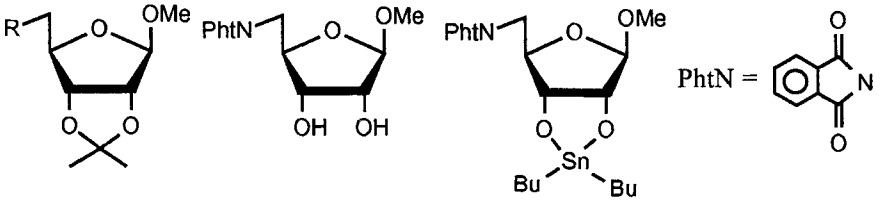


3 R =



action of liposidomycin C was found to be phospho-*N*-acetylmuramyl-pentapeptide transferase from *E. coli* Y-10 in peptidoglycan synthesis.[3] The structures of liposidomycins A, B, and C were proposed as **1**, **2**, and **3**, respectively, on the basis of degradation and spectroscopic studies,[2,4] but six stereogenic centers in the lipid and diazepinone moieties remain unassigned. The overall structure as well as the diazepinone and 5-aminopentose 2-sulfate components are very unique. The present work reports synthetic studies related to the 5-amino-5-deoxy-β-D-riboside 2-sulfate part of the liposidomycins.

Introduction of an amino group at C-5 of methyl β-D-ribofuranoside was straightforward. Tosylate **4** was treated with the potassium salt of the phthalimide in the presence of sodium iodide in refluxing DMF to afford the protected amino sugar **5** in 84% yield. Hydrolysis of **5** in methanol using aqueous 2N HCl gave crystalline diol **6**[5] in 80% yield. Direct selective sulfation at C-2 of diol **6** was not satisfactory, however, protection of the hydroxy group at C-3 of **6** and subsequent sulfation were carried out successfully. Several methods were investigated for this transformation as described below. Diol **6** was first transformed into 2,3-*O*-stannylene sugar **7** in almost quantitative



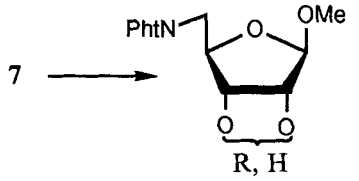
4 R = OTs
5 R = NPht

6

7

yield by treatment with dibutyltin oxide in refluxing methanol. Reaction of **7** was carried out with various electrophilic reagents such as acetyl chloride, benzyl(Bn) bromide, trityl(Tr) chloride, *t*-butyldimethylsilyl(TBDMS) chloride, and methoxyethoxymethyl(MEM) chloride. The results are summarized in Table 1. Although the reactions of 2',3'-*O*-stannylene nucleosides with various electrophiles have been extensively studied,[6] similar studies of the reaction of 2,3-*O*-stannylene ribosides are rare. Acetylation and benzylation of 2,3-*O*-stannylene riboside **7** gave a 1:1 mixture of 2- and 3-protected derivatives, while tritylation and silylation afforded 2-ethers as the major products. The reaction of **7** with MEM chloride unexpectedly provided 2,3-*O*-methylene acetal

TABLE 1. Reaction of 2,3-*O*-Stannylene Acetal 7 with Electrophiles

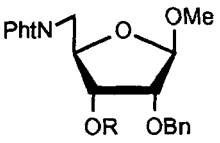


8 R = Ac **9** R = $PhCH_2$
10 R = Tr **11** R = TBDMS
12 R = - CH_2 -

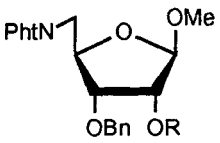
reagent	solvent	temp.	time	product	yield	isomers (2-/3-)
CH_3COCl	Et_3N	r.t.	10min.	**8**	70%	1/1
$PhCH_2Br/Bu_4NBr$	toluene	reflux	12h	**9**	98%	1/1
$TrCl/Bu_4NBr$	toluene	reflux	2h	**10**	55%	7.5/1
$TBDMSCl/Bu_4NBr$	toluene	reflux	2h	**11**	65%	3/1
$MEMCl/Bu_4NBr$	DMF	reflux	2h	**12**	60%	

12.[7] However, the reaction of **7** with methoxymethyl(MOM) chloride gave neither methylene acetal **12** nor the MOM ether. These results suggest that the two oxygen atoms of the MEM group are somehow related to the formation of **12**.

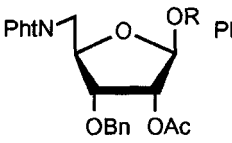
Benzyl ether **9** was chosen for the further elaboration because of the need for a participating group at C-2 and convenience in separation and handling. Fractional crystallization of **9** in methanol gave crystalline 2-*O*-benzyl ether **9a** {mp 107-108 °C, $[\alpha]_D$ +14.1° (*c* 0.22, $CHCl_3$)} and subsequent flash column chromatography of the residue from the crystallization afforded pure 3-*O*-benzyl ether **9b** {syrup, $[\alpha]_D$ -12.1° (*c* 0.19, $CHCl_3$)}. Assignments of **9a** and **9b** were



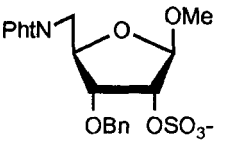
9a R = H
14a R = Ac

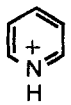


9b R = H
14b R = Ac



15 R = Ac
16 R = 





17

readily made on the basis of the ^1H and ^{13}C NMR spectral data of **9a** and **9b** and of their acetyl derivatives **14a** and **14b**.[8] For the model study for the synthesis of liposidomycins, glycosidation and sulfation at C-2 of compound **9b** were carried out. Reaction of **9b** with acetic acid-acetic anhydride in the presence of a catalytic amount of sulfuric acid in methylene chloride afforded diacetate **15** { $[\alpha]_D$ +16.2° (*c* 0.37, $CHCl_3$)} in 70% yield. Reaction of **15** and cyclohexanol in methylene chloride in the presence of tin(IV) chloride gave β-glycoside **16**[9] in 58% yield. Reaction of **9b** with sulfur trioxide-pyridine complex in pyridine at room temperature provided 2-*O*-sulfate salt **17**[10] in almost quantitative yield.

ACKNOWLEDGEMENT

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5. Compound **6**: mp 140-145 °C; $[\alpha]_D$ -5.8° (*c* 0.24, $CHCl_3$); ^1H NMR (80 MHz, $CDCl_3$) δ 2.98 (brs, 2H), 3.31 (s, 3H), 3.90-4.27 (m, 4H), 4.77 (s, 1H), 7.62-7.90 (m, 4H); ^{13}C NMR (20.1 MHz, DMSO-d_6) δ 41.4, 54.3, 73.3, 74.4, 79.0, 108.3, 123.0, 131.5, 134.4, 167.8. Anal. Calcd for $C_{14}H_{15}O_6N$: C, 57.33; H, 5.16; N, 4.78. Found: C, 57.71; H, 5.30; N, 4.89.
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7. Compound **12**: mp 117-120 °C; $[\alpha]_D$ -32.7° (*c* 0.60, $CHCl_3$); ^1H NMR (80 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.88 (d, J=7.0Hz, 2H), 4.23-4.84 (m, 3H), 4.91 and 4.95 (AB, 2H), 5.01 (s, 1H), 7.66-7.94 (m, 4H); ^{13}C NMR (20.1 MHz, DMSO-d_6) δ 40.7, 54.7, 81.1, 82.4, 83.5, 95.0, 108.4, 122.8, 123.1, 131.4, 134.2, 134.5, 167.8. Anal. Calcd for $C_{15}H_{15}O_6N$: C, 59.01; H, 4.95; N, 4.59. Found: C, 59.19; H, 5.05; N 4.71.
8. Compound **14a**: $[\alpha]_D$ +18.3° (*c* 0.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 3H), 3.35 (s, 3H), 3.92 (m, 2H), 4.15 (dd, J=4.9, 1.2Hz, 1H), 4.49 (m, 1H), 4.55 (s, 2H), 4.85 (d, J=1.2Hz, 1H), 5.09 (dd, J=6.4, 4.9Hz, 1H), 7.28 (m, 5H), 7.70-7.88 (m, 4H). Anal. Calcd for $C_{23}H_{23}O_7N$: C, 64.93; H, 5.45; N, 3.29. Found: C, 64.62; H, 5.66; N, 3.38.

Compound **14b**: $[\alpha]_D$ +2.8° (*c* 0.29, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 2.07 (s, 3H), 3.32 (s, 3H), 3.94 (m, 2H), 4.22 (m, 1H), 4.28 (m, 1H), 4.41 and 4.55 (ABq, J=10.8Hz, 2H), 4.80 (s, 1H), 5.20 (d, J=2.7Hz, 1H), 7.23 (s, 5H), 7.69-7.85 (m, 4H); ^{13}C NMR (75.2 MHz, $CDCl_3$) δ 20.5, 40.7, 55.1, 73.2, 73.7, 77.8, 80.2, 106.3, 123.3, 127.9, 128.1, 128.4, 132.2, 134.1, 137.5, 168.5, 170.2. Anal. Calcd for $C_{23}H_{23}O_7N$: C, 64.93; H, 5.45; N, 3.29. Found: C, 65.01; H, 5.28; N, 3.40.

9. Compound **16**: $[\alpha]_D$ -16.9° (*c* 0.42, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.10-1.90 (m, 10H), 2.10 (s, 3H), 3.58 (m, 1H), 3.99 (m, 2H), 4.23-4.30 (m, 2H), 4.42 and 4.54 (ABq, J=10.7Hz, 2H), 5.09 (s, 1H), 5.21 (d, J=3.6Hz, 1H), 7.12-7.21 (m, 5H), 7.69-7.85 (m, 4H); ^{13}C NMR (75.2 MHz, $CDCl_3$) δ 20.6, 23.6, 23.9, 25.4, 30.9, 33.2, 40.6, 73.3, 74.4, 75.1, 80.7, 102.8, 123.4, 127.9, 128.1, 128.4, 132.3, 134.1, 137.7, 168.6, 170.4. Anal. Calcd for $C_{28}H_{31}O_7N$: C, 68.14; H, 6.33; N, 2.84. Found: C, 68.42; H, 6.48; N, 2.98.

10. Compound **17**: ^1H NMR (300 MHz, DMSO-d_6) δ 3.29 (s, 3H), 3.80-3.94 (m, 2H), 4.11 (m, 2H), 4.30 (d, J=9.0Hz, 1H), 4.60-4.67 (m, 2H), 5.04 (s, 1H), 7.13-7.27 (m, 5H), 7.94-7.97 (m, 4H), 8.13 (t, J=6.0Hz, 2H), 8.65 (t, J=4.5Hz, 1H), 8.94 (d, J=5.0Hz, 2H).