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Note

New syntheses of methyl 5-thio-β-D-arabinopyranoside and (+)-biotin †

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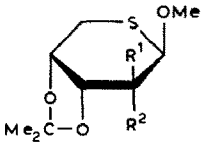
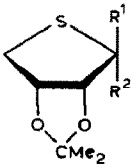
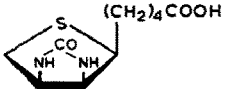
Previously one of us reported [2] that methyl 3,4-*O*-isopropylidene-2-*O*-methanesulfonyl-5-thio-β-D-ribopyranoside (**1**) readily underwent ring contraction in methanol to give 2,5-dideoxy-2,5-epithio-D-arabinose dimethyl acetal (**2**). It was of interest to examine this reaction with the corresponding D-arabinose derivative **3** because the expected product **4** is a potential precursor for a new synthesis of (+)-biotin (**5**). A number of syntheses of **5** from monosaccharides have been reported previously, e.g., also from D-arabinose [3,4], from D-glucose [5,6], and from D-mannose [7].







5

1 R^1 = H; R^2 = OMs **2** R^1 = H; R^2 = $CH(OMe)_2$

3 R^1 = OMs; R^2 = H **4** R^1 = $CH(OMe)_2$; R^2 = H

We have already described [8,9] two syntheses of methyl 5-thio-β-D-arabinopyranoside (**11**) and we now give a third and more convenient variation. Treatment of the dithioacetal **6** with *N*-bromosuccinimide in methanol [10] gave a mixture of the α and β anomers of the furanoside **7** which was converted into the diacetate **8**.

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† Thiopyranoses, Part 14. For Part 13, see ref 1.

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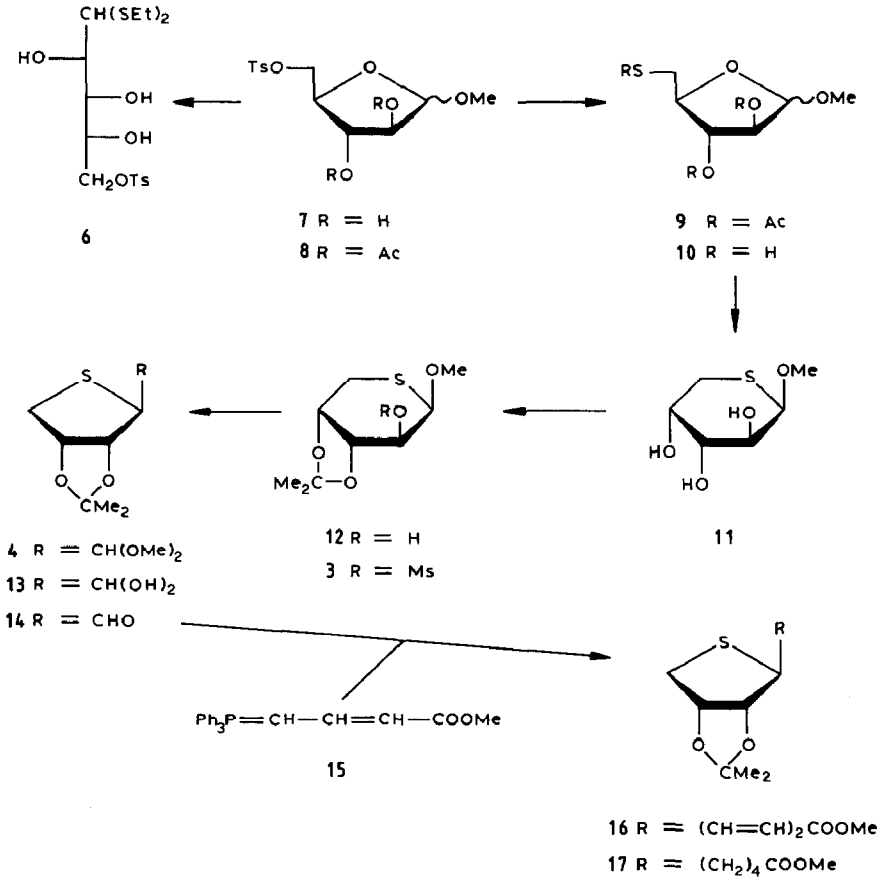
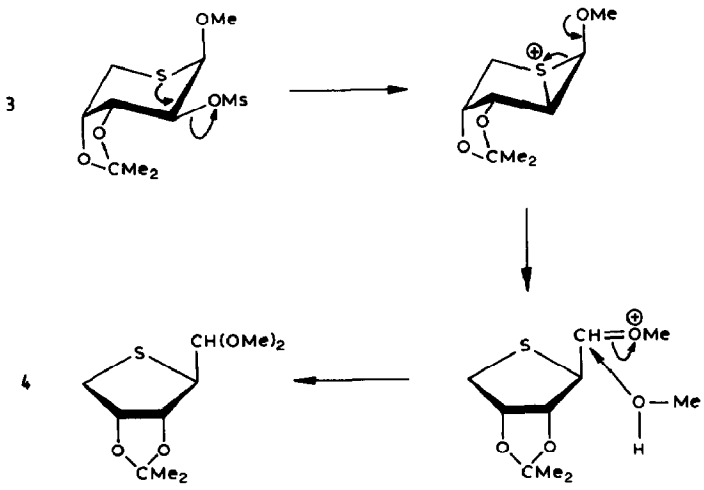


Scheme 1.

Reaction of **8** with potassium thioacetate gave **9**, deacetylation of which afforded the thiol **10** which was isomerised into the pyranoside **11** in acidified methanol. The thioacetate displacement reaction was also carried out on **7** but proceeded less cleanly and in lower yield (Scheme 1).

Reaction of **11** with acetone and 2,2-dimethoxypropane in the presence of toluene-*p*-sulfonic acid gave a single product, the acetal **12**, which was treated with methanesulfonyl chloride in the presence of triethylamine to give the mesylate **3**. All attempts to isolate **3** resulted in its decomposition, so it was allowed to react directly with methanol when the desired acetal **4** was obtained, presumably by the mechanism shown in Scheme 2. Evidence for the structure **4** came from the mass spectrum which showed the expected peak at 75 mass units [$CH(OMe)_2$)] and from the ^1H NMR spectrum where the coupling constant $J_{2,3}$ (0.9 Hz) supported the *ribo* configuration (compare $J_{2,3}$ 4.0 Hz for **2** [2]). Selective deprotection of the acetal function in **4** was achieved by heating **4** in acetone which contained toluene-*p*-sulfonic acid. Evidently either sufficient water was present for hydrolysis



Scheme 2.

to occur or the reaction proceeded via trans-acetalation. The product had a low mobility in TLC, suggesting that it existed in the *gem*-diol form **13** rather than as the free aldehyde **14**. It was not characterised further but was allowed to react with the phosphorane **15** [11] when it gave the diene **16** as a 2:1 mixture of the (4*E*) and (4*Z*) forms ($J_{4,5}$ 15.1 and 10.6 Hz, respectively). Catalytic hydrogenation of **16** gave the known [7] saturated ester **17** which has previously been converted [7] into (+)-biotin (**5**). The earlier biotin syntheses [3,4] utilising D-arabinose also involved the formation of **17** but they differ from the present route in that the sulfur was introduced at a later stage.

1. Experimental

General methods.—Melting points are uncorrected. NMR spectra were recorded at 200 or 300 MHz (^{1}H) and 50 or 75 MHz (^{13}C) for solutions in $CDCl_3$ unless otherwise stated. Kieselgel 60 was used for TLC (Merck 5554) and column chromatography (Fluka 60738).

Methyl 5-thio-β-D-arabinopyranoside (**11**).—A solution of *N*-bromosuccinimide (2.2 g) in MeOH (150 mL) at 0°C was added to a stirred solution of 5-*O*-toluene-*p*-sulfonyl-D-arabinose diethyl dithioacetal (**6**, 2.0 g) in MeOH (50 mL) at 0°C during 30 min. A mixture of finely ground $Na_2S_2O_3$ (10 g) and $NaHCO_3$ (10 g) in water (30 mL) was added and the resulting suspension was stirred for a further 30 min. The suspension was poured into aq NaCl (1 L) and extracted with CH_2Cl_2. The extract was dried and concentrated to yield the furanoside **7** as a syrup (1.5 g, 98%); NMR data: ^{1}H (partial): δ 4.84 (s, 0.8 H, H-1α), 4.76 (d, 0.2 H, *J* 3.8 Hz, H-1β), 3.34 (s, 2.4 H, α-OMe), 3.32 (s, 0.6 H, β-OMe), 2.42 (s, 3 H, ArMe).

Acetylation of **7** with Ac_2O (1.0 mL) in pyridine (2.0 mL), in the usual way, afforded the diacetate **8** as a syrup (1.6 g, 86%); NMR data: ^1H (partial): δ 4.89 (s, 0.8 H, H-1α), 4.86 (d, 0.2 H, J 4.2 Hz, H-1β), 3.36 (s, 2.4 H, α-OMe), 3.26 (s, 0.6 H, β-OMe), 2.45 (s, 3 H, ArMe), 2.08 (s, 6 H, 2 OAc).

A solution of **8** in DMF (6 mL) that contained potassium thioacctate (1.2 g) was left overnight at room temperature and then partitioned between ether and water. The ether extract was dried and concentrated to a syrup which was further purified by chromatography (1 : 1 ether–light petroleum) to give the thioacetate **9** as a syrup (1.1 g, 89%); NMR data: ^1H (partial): δ 3.38 (s, 3 H, OMe), 2.37 (s, 2.4 H, α-SAc), 2.35 (s, 0.6 H, β-SAc), 2.12 (s, 6 H, 2 OAc).

A solution of **9** in MeOH (13 mL) that contained NaOMe [from sodium (80 mg)] was left under N_2 for 15 min at room temperature when concd HCl (0.8 mL) was added and the mixture was heated under reflux for 4 h. After neutralisation ($PbCO_3$), filtration, and removal of solvents, crystallisation of the residue from EtOH gave **11** [0.39 g, 60% (45% overall yield from **6**)]; mp and mixed mp 176–178°C.

*Methyl 3,4-O-isopropylidene-5-thio-β-*D*-arabinopyranoside* (**12**) (with Dr. N.M. Munkombwe).—A mixture of **11** (1.0 g), acetone (38 mL), 2,2-dimethoxypropane (20 mL), and toluene-*p*-sulfonic acid (1.0 g) was stirred at room temperature for 15 min before being neutralised (Na_2CO_3) and filtered. The filtrate was concentrated to a syrup which was redissolved in CH_2Cl_2 and filtered through silica. Removal of solvents gave **12** as a syrup (1.07 g, 88%), $[\alpha]_D$ −25° (*c* 1.2, $CHCl_3$). Mass spectrum: *m/z* 220.0769 ($C_9H_{16}O_4S$ calcd *m/z* 220.0769 for M^+). NMR data: ^1H, δ 4.58 (d, 1 H, $J_{1,2}$ 2.4 Hz, H-1), 4.43 (dt, 1 H, $J_{3,4}$ 5.8, $J_{4,5a}$ 3.9, $J_{4,5b}$ 6.5 Hz, H-4), 4.15 (dd, 1 H, $J_{2,3}$ 7.6 Hz, H-3), 3.98 (dt, 1 H, $J_{2,OH}$ 7.9 Hz, H-2), 3.41 (s, 3 H, OMe), 2.93 (dd, 1 H, $J_{5a,5b}$ 13.7 Hz, H-5a), 2.70 (dd, 1 H, H-5b), 2.41 (d, 1 H, OH), 1.52, 1.37 (2 s, 6 H, CMe_2); ^{13}C, δ 109.4 (CMe_2), 83.8 (C-1), 77.9, 76.4, 73.6 (C-2,3,4), 56.6 (OMe), 28.0 (C-5), 25.9, 25.0 (CMe_2).

*2,5-Dideoxy-2,5-epithio-3,4-O-isopropylidene-*D*-ribose dimethyl acetal* (**4**).—A solution of methanesulfonyl chloride (0.2 mL) in dry CH_2Cl_2 (2 mL) was added slowly with stirring and cooling (ice bath) to a solution of **12** (0.32 g) and Et_3N (0.35 mL) in dry CH_2Cl_2 (3 mL). After 30 min, MeOH (5 mL) and $NaHCO_3$ (0.5 g) were added and the mixture was left stirring overnight. The mixture was partitioned between water and CH_2Cl_2, and the organic extract was dried, concentrated, and purified by chromatography (3 : 1 ether–light petroleum) to give **4** as a syrup (0.30 g, 82%); $[\alpha]_D$ −77° (*c* 1.0, CH_2Cl_2). Mass spectrum: *m/z* 234.0973 ($C_{10}H_{18}O_4S$ calcd *m/z* 234.0926 for M^+). NMR data: ^1H (C_6D_6), δ 5.03 (dd, 1 H, $J_{2,3}$ 0.9, $J_{3,4}$ 5.7 Hz, H-3), 4.66 (ddd, 1 H, $J_{4,5a}$ 4.9, $J_{4,5b}$ 1.4 Hz, H-4), 4.02 (d, 1 H, $J_{1,2}$ 3.8 Hz, H-1), 3.54 (dd, 1 H, H-2), 3.09, 2.98 (2 s, 6 H, 2 OMe), 2.98 (dd, 1 H, $J_{5a,5b}$ 12.0 Hz, H-5a), 2.81 (dd, 1 H, H-5b) 1.56, 1.17 (2 s, 6 H, CMe_2); ^{13}C, δ 110.9 (CMe_2), 107.9 (C-1), 84.6, 84.3 (C-3,4), 56.2, 55.5 (2-OMe), 56.0 (C-2), 38.4 (C-5), 26.7, 24.6 (CMe_2).

*Methyl (2*E*, 4*E/Z*, 6*S*, 7*R*, 8*S*)-6,9-epithio-7,8-(isopropylidenedioxy)nona-2,4-dienoate* (**16**).—A solution of **4** (0.1 g) in acetone (10 mL) that contained toluene-*p*-sulfonic acid (0.2 g) was heated under reflux for 3 h and then neutralised with

Table 1
^{1}H NMR chemical shifts (ppm)

Compound	H-2	H-3	H-4	H-5	H-6	H-7	H-8	H-9a	H-9b	OMe	CMe_2
16e	5.90	7.25	6.31	6.04	3.92	4.67	4.96	3.03	2.96	3.74	1.54, 1.33
16z	5.95	7.62	6.18	5.73	4.35	4.57	4.93	3.14	3.04	3.77	1.57, 1.33
17	2.32	←——	1.7–1.3	——→	3.20	4.46	4.87	3.02	2.88	3.67	1.51, 1.32

Table 2
^{1}H NMR coupling constants (Hz)

Compound	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9a}$	$J_{8,9b}$	$J_{9a,9b}$	$J_{2,4}$	$J_{3,5}$	$J_{4,6}$
16e	15.3	11.0	15.1	7.8	2.5	5.9	4.9	2.3	12.9	0.5	0	0.5
16z	15.2	11.7	10.6	10.8	3.4	6.0	5.4	2.0	12.8	0.5	1.0	0.8
17	7.3				2.8	6.0	5.3	2.7	12.8			

Table 3
^{13}C NMR chemical shifts (ppm)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	OMe	O_2CMe_2	$O_2C\mathit{Me}_2$
16e	167.0	121.7	143.6	129.3	139.0	55.2	87.7	83.3	37.1	51.6	112.2	26.8, 25.0
16z	167.0	123.4	138.4	128.1	136.0	55.2	88.8	83.3	36.8	50.3	113.2	27.2, 25.2
17	174.0	33.9	24.5	29.7	27.8	54.0	88.5	83.0	36.2	51.5	111.7	26.8, 24.9

Na_2CO_3 (0.4 g) and water (0.4 mL). The mixture was filtered and concentrated to leave a syrup which was dissolved in CH_2Cl_2 (12 mL). A solution of (3-methoxycarbonyl-2-propen-1-yl)triphenylphosphonium bromide (0.25 g) in water (10 mL) was added followed by 0.25 M NaOH (2 mL). The mixture was stirred vigorously under N_2 for 30 min at room temperature. The organic layer was washed with dil HCl, then with aq $KHCO_3$, and finally dried, filtered, and concentrated to a syrup which was purified by chromatography (2:3 ether–light petroleum) to give **16** as a syrup (30 mg, 26%) in which the (2*E*) **16e** and (2*Z*) **16z** diastereoisomers were present in the ratio 2:1. For NMR data, see Tables 1–3.

Methyl (6S,7R,8S)-6,9-epithio-7,8-(isopropylidenedioxy)nonanoate (**17**).—The diene **16** (18 mg) in MeOH (2 mL) was hydrogenated at atmospheric pressure in the presence of Pd (20 mg) for 48 h. The catalyst was removed by filtration and the filtrate was concentrated to a syrup which was purified by chromatography (2:3 ether–light petroleum) to give **17** (5 mg, 28%) (contaminated with a small amount of hydrocarbon material). For NMR data, see Tables 1–3.

Acknowledgments

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