Carbohydrate Research, 136 (1985) 411–418
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

Note

Formation of methyl 5-thiopentopyranosides in the D-*arabino*, L-*lyxo*, D-*ribo*, and D-*xylo* series from methyl 5-thio-3-*O*-toluene-*p*-sulphonyl-α-D-xylopyranoside*

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(Received April 18th, 1984; accepted for publication, May 17th, 1984)

Conventional syntheses of all of the 5-thio-D-pentoses have now been reported[1–3] and each involves a displacement reaction on a suitable furanose 5-sulphonate derivative by a sulphur nucleophile. Thus, starting with 1,2-*O*-isopropylidene-3,5-di-*O*-toluene-*p*-sulphonyl-α-D-xylofuranose, Owen and co-workers[4] synthesised methyl 5-thio-3-*O*-toluene-*p*-sulphonyl-α-D-xylopyranoside (**1**) and converted it into methyl 2,3- and 3,4-anhydro-α-D-ribopyranosides (**2** and **3**). The possibility existed that **1** was a potential source of 5-thio-D-*ribo* compounds by way of displacement reactions at C-3. Likewise, opening of the epoxide rings in **2** and **3** could lead to 5-thio-D-*arabino* and 5-thio-L-*lyxo* products, respectively, as well as 5-thio-D-*xylo* compounds. We have examined these possibilities and now report our results.

The sulphonate **1** was prepared by a modification of the earlier route[4] (see Experimental) and converted into the dibenzoate **4**, which was unaffected on heating with sodium benzoate in *N,N*-dimethylformamide. This result was not unexpected, because **4** presumably exists in the $^4C_1$ conformation and any attacking nucleophile is subject to steric hindrance from the axial MeO-1. A similar lack of reactivity has been observed[5] in pyranose derivatives, and the same considerations clearly apply to thiopyranoses. However, the benzoyloxy groups of **4** are suitably placed for the sulphonate group to undergo intramolecular displacement leading to either of the benzoxonium ions **6** or **7** (Scheme 1) which, in the presence of water, would yield orthoacids that should then collapse to give the "equatorial hydroxyl–axial ester"[6] *ribo*-dibenzoates **8** and **9**. Indeed, when **4** was heated in moist *N,N*-dimethylformamide containing sodium benzoate, **8** and **9** were obtained in modest

*5-Thiopyranoses, Part VII. For Part VI, see ref. 1.
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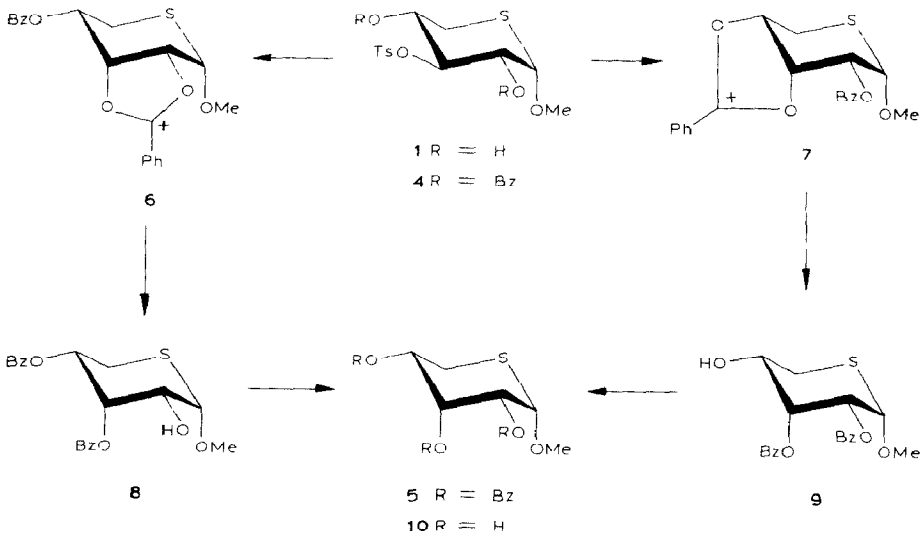
0008-6215/85/$ 03.30

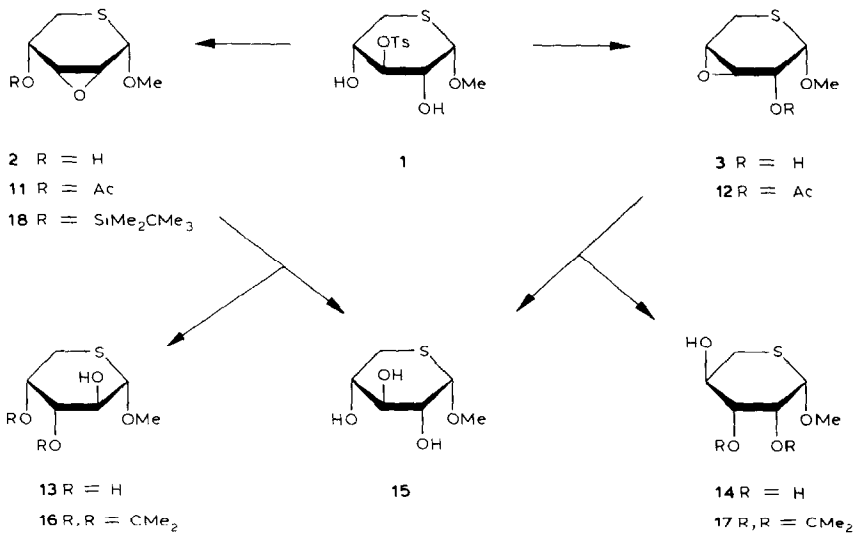
yield, the bulk of the starting material being recovered. Treatment of **8** or **9** with methanolic sodium methoxide furnished material chromatographically indistinguishable from the known[3] methyl 5-thio-α-D-ribopyranoside (**10**). Benzoylation of **10**, **8**, or **9** gave the same tribenzoate **5**. The esterification patterns of **8** and **9** followed from their ^{1}H-n.m.r. spectra. Thus, the H-2 signal of the 3,4-dibenzoate **8** appeared as a triplet at δ 4.19, well upfield from the signals for H-3 (δ 5.94) and H-4 (δ 5.40). The large value (11.5 Hz) of $J_{4,5a}$ clearly indicated the $^4C_1$ conformation, and thus HO-2 is in the expected equatorial orientation. Similar considerations applied to the 2,3-dibenzoate **9**, where the signal for H-4 appeared as an octet at δ 4.31, well upfield of those for H-2 (δ 5.45) and H-3 (δ 5.85); again, $J_{4,5a}$ was large (11.0 Hz), indicating the $^4C_1$ conformation and an equatorial disposition for HO-4. The tribenzoate **5** also exists in the $^4C_1$ conformation ($J_{4,5a}$ 11.5 Hz).



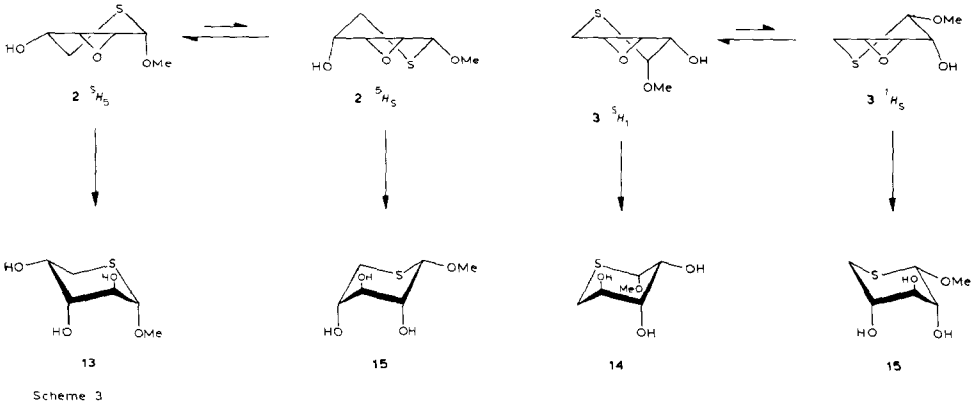
Scheme 1

The epoxides **2** and **3** were obtained from the tosylate **1** as described[4], but they were more easily separated as their acetates **11** and **12** (Scheme 2). Zemplén deacetylation then regenerated **2** and **3**. Owen and co-workers[4] showed that the preferred conformations for **11** and **12** were $^5H_5$ and $^5H_1$, respectively, from a study of their ^{1}H-n.m.r. spectra, and consideration of the spectra of the epoxides **2** and **3** led us to similar conclusions for these compounds. Thus, **2** showed a large diaxial coupling ($J_{4,5a}$ 10.0 Hz) between H-4 and H-5*a* and long-range coupling between H-1 and H-5*e* ($J_{1,5e}$ 1.5 Hz) characteristic of the $^5H_5$ conformation. The isomer **3** showed two long-range coupling constants ($J_{1,3} = J_{1,5e} = 1$ Hz), and only the $^5H_1$ conformer possesses the necessary planar W-arrangements for H-1/H-3 and H-1/H-5*e*. Diaxial opening, according to the Fürst–Plattner Rules, of epoxides **2** and **3** in their preferred conformations should lead to the *arabino* and *lyxo* products **13** and

14, whereas diaxial opening of the less-favoured conformers should give the same *xylo* compound **15** in either case (see Scheme 3). Even if the epoxides opened to give mixtures of products, it was expected that the required arabinoside **13** and lyxoside **14**, having vicinal *cis*-hydroxyl groups, would be readily separated from the accompanying xyloside **15** by formation of suitable acetals, *e.g.*, **16** and **17**.



Scheme 2



Scheme 3

When **2** or **3** was heated with aqueous sodium hydroxide for several hours, two products were formed in each case. The 2,3-epoxide **2** gave the xyloside **15** and the arabinoside **13** in the ratio 2:1, and the 3,4-epoxide **3** gave the lyxoside **14** and the xyloside **15** in the ratio 3:2. When each of these mixtures was treated with acetone and sulphuric acid, the xyloside **15** underwent some acetal formation, and

TABLE I

^{1}H-NMR DATA[a]

Compound	Chemical shifts (p.p.m.)							Coupling constants (Hz)						
	H-1	H-2	H-3	H-4	H-5	H-5'	Other signals[b,c]	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5'}$	$J_{5,5'}$	Other couplings
2	4.69	3.81	3.40	4.18	2.91	2.38	3.48 (OMe)	5.0	4.0	1.5	10.5	5.0	13.0	1.5 ($J_{1,5'}$), 1.0 ($J_{3,5'}$)
3	4.44	4.10	3.30	3.69	3.05	2.73	3.46 (OMe)	4.5	3.5	4.5	1.5	6.0	15.0	1.0 ($J_{1',3} = J_{1,5'}$)
4	4.75		5.7↔5.3		3.2↔2.7		3.40 (OMe), 2.00 (ArMe)	1.0						
5	4.87	5.58	6.14	5.58	3.39	2.65	3.51 (OMe)	4.0	2.5	2.5	11.5	4.0	12.5	1.0 ($J_{1,5'} = J_{3,5'}$)
8	4.51	4.19	5.94	5.40	3.18	2.51	3.53 (OMe)	4.0	3.5	3.0	11.5	4.0	12.5	
9	4.74	5.48	5.89	4.31	3.16	2.49	3.48 (OMe)	3.0	3.0	3.0	11.0	4.0	13.0	
16	4.41	3.91	4.02	4.48	2.89	2.66	3.42 (OMe); 1.50, 1.38 (CMe_2)	6.5	9.0	6.5	9.5	6.5	13.5	1.0 ($J_{1,5'}$)
17		4.6↔4.0			2.78	2.53	3.40 (OMe); 1.53, 1.39 (CMe_2)				4.5	10.5	11.5	
18[d]	4.56	3.54	3.03	4.12	2.99	2.01	3.36 (OMe); 0.92 (CMe_3)	5.0	4.0	1.0	10.5	4.5	13.0	1.5 ($J_{1,5'} = J_{3,5'}$)
19	5.87	4.67	4.78	4.23	3.07	2.87	2.47 (ArMe), 2.29 (SAc), 1.46, 1.21 (CMe_2)	4.0	0.5	3.0	7.0	6.5	13.5	

[a]In $CDCl_3$. [b]Compounds **4, 5, 8, 9**, and **19** also showed signals in the aromatic region. [c]Compounds **2, 3, 8**, and **9** also showed hydroxyl signals. [d]In CCl_4.

conversion of the arabinoside **13** and the lyxoside **14** into the acetals **16** and **17** was incomplete. The reaction of **15** was not entirely unexpected, because formation of *trans*-acetals from 5-thiopyranoid compounds has been observed[7], although with more-forcing reagents. Accordingly, the mixtures were treated with 2,2-dimethoxypropane in the presence of an acid catalyst to ensure complete acetal formation. The product mixtures were then treated with cold, aqueous acetic acid to hydrolyse preferentially the more labile xylopyranoside *trans*-acetal(s). The acetals **16** and **17** thus obtained were easily separated from the xyloside **15**. Heating the acetals **16** and **17** with aqueous acetic acid gave the crystalline glycosides **13** and **14**. The properties of the latter were in keeping with its being the enantiomer of the known[1] D form.

The epoxide-opening reactions, particularly that of the 2,3-epoxide **2**, were at variance with expectation, and the results were compared with those for the related methyl 2,3- and 3,4-anhydro-α-D-ribopyranosides. Thus, the 2,3-epoxide reacted[8] with sodium methanethiolate mainly at C-3, and the related methyl 2,3-anhydro-4-azido-4-deoxy-α-D-ribopyranoside gave[9] equal amounts of products arising from attack at C-2 and C-3 by azide ions. There are numerous examples[10] of opening at C-4 in methyl 3,4-anhydro-β-D-ribopyranoside, but there are no reports for the related α anomer. In the case of 2,3-epoxides, C-2 is generally considered to be less reactive than C-3, because of the electron-withdrawing effect of the anomeric centre. With the epoxides **2** and **3**, an additional effect that may deter formation of the required products is the presence of the ring sulphur atom. In the preferred conformations a nucleophile attacking from an axial direction will be in *syn*-diaxial conflict with a lone-pair orbital of the sulphur atom. This type of interaction has already been pointed out[10] in the oxygen cases, but it would be expected to be even greater when oxygen is replaced by sulphur in the ring, *cf.*, the "hockey-stick effect"[11] which destabilises tetrahydrothiopyran rings containing an axial heteroatom substituent β to the sulphur atom. The conformational energy differences between the half-chair forms of **2** and **3** are probably not very large, and the ring-opening reactions may well proceed *via* the less-favoured conformations. An attempt was made to increase this energy difference (and thus force the reaction into the desired pathway) in the 2,3-epoxide **2** by converting the quasi-equatorial HO-3 into the bulky *tert*-butyldimethylsilyloxy group. The silyl ether **18** was readily prepared and was clearly in the desired $^{S}H_{5}$ conformation, but reaction with aqueous sodium hydroxide gave no recognisable products.

EXPERIMENTAL

General methods. — See Part VI[1].

*Methyl 5-thio-3-*O*-toluene-*p*-sulphonyl-α-*D*-xylopyranoside* (**1**). — A mixture of potassium thioacetate (1.4 g) and 1,2-*O*-isopropylidene-3,5-di-*O*-toluene-*p*-sulphonyl-α-D-xylofuranose (4.2 g) in *N*,*N*-dimethylformamide (30 mL) was heated at 100° for 2 h. The mixture was cooled, ether (100 mL) was added, and the mixture

was extracted repeatedly with water to remove salts and *N,N*-dimethylformamide. The ether layer was dried ($MgSO_4$) and evaporated to leave 5-*S*-acetyl-1,2-*O*-isopropylidene-5-thio-3-*O*-toluene-*p*-sulphonyl-α-D-xylofuranose (**19**) as a syrup (3.7 g), $[\alpha]_D$ −48° (*c* 1.5, chloroform) (Found: mol. wt., 402.0828. $C_{17}H_{22}O_7S_2$ calc.: mol. wt., 402.0807). A solution of **19** in methanol (65 mL) containing conc. hydrochloric acid (6.5 mL) was boiled under reflux for 5 h, before neutralising ($PbCO_3$) and filtering (Hyflo). Removal of solvents and crystallisation of the residue from ether–ethanol gave **1** (3.8 g), m.p. 128–131°, $[\alpha]_D$ +193° (*c* 0.8, chloroform); lit.[4], m.p. 130–132°, $[\alpha]$ +211°.

*Methyl 2,4-di-O-benzoyl-5-thio-3-O-toluene-*p*-sulphonyl-α-D-xylopyranoside* (**4**). — The diol **1** (4.0 g) was dissolved in pyridine (10 mL) to which benzoyl chloride (3 mL) was added with stirring and cooling. After 15 h at room temperature, work-up in the usual way gave **4** (5.9 g), m.p. 166–167° (from ethanol), $[\alpha]_D$ +121° (*c* 1, chloroform) (Found: C, 59.8; H, 4.8. $C_{27}H_{26}O_8S_2$ calc.: C, 59.8; H, 4.8%). When first prepared, this compound had m.p. 119–121°, but later preparations had the higher melting point.

Methyl 2,3,4-tri-O-benzoyl-5-thio-α-D-ribopyranoside (**5**). — (*a*) *From* **10**. Treatment of methyl 5-thio-α-D-ribopyranoside[3] (**10**, 55 mg) with benzoyl chloride (0.05 mL) in pyridine (1 mL) for 24 h at room temperature gave, after the usual work-up, **5** (0.12 g), m.p. 108–109° (from light petroleum), $[\alpha]_D$ +8.4° (*c* 0.6, chloroform) (Found: C, 66.2; H, 5.1. $C_{27}H_{24}O_7S$ calc.: C, 66.0; H, 4.9%).

(*b*) *From* **4**. A solution of the tosylate **4** (0.50 g) in *N,N*-dimethylformamide (25 mL) containing water (0.25 mL) and sodium benzoate (0.50 g) was boiled under reflux for 30 h and then the solvents were removed under reduced pressure. The residue was triturated with dichloromethane, and the extract was evaporated to give a mixture which was chromatographed on silica gel (13.5 g) with benzene–ether (9:1; 10-mL fractions).

Fractions 6–7 contained **4** (0.30 g), m.p. and mixture m.p. 166–167°.

Fractions 8–10 contained the syrupy 3,4-dibenzoate **8** (72 mg) which, on benzoylation, gave the tribenzoate **5** (65 mg), m.p. 104–105°.

Fractions 12–18 contained the syrupy 2,3-dibenzoate **9** (45 mg) which, on benzoylation, gave **5** (40 mg), m.p. 106–108°.

Methyl 4-O-acetyl-2,3-anhydro-5-thio-α-D-ribopyranoside (**11**) *and methyl 2-O-acetyl-3,4-anhydro-5-thio-α-D-ribopyranoside* (**12**). — To a solution of the tosylate **1** (4.60 g) in dichloromethane (20 mL) was added a cold solution of sodium methoxide [from sodium (0.39 g)] in methanol (10 mL). After 15 min, the mixture was neutralised (CO_2), ether (100 mL) was added to complete salt precipitation, and the mixture was filtered (Hyflo). The filtrate was evaporated and the residue was treated with acetic anhydride (4 mL) and pyridine (8 mL) overnight. Work-up in the usual way gave a mixture (2.80 g) of **11** and **12**, which were separated by chromatography on silica gel (110 g). Elution with benzene–ether (23:2) gave **11** (1.77 g), m.p. 59–60° (from light petroleum), $[\alpha]_D$ +301° (*c* 0.8, chloroform); lit.[4], m.p. 43–52°, $[\alpha]_D$ +290°. Further elution with benzene–ether (1:1) gave syrupy **12** (0.93 g), $[\alpha]_D$ +225° (*c* 2.5, chloroform); lit.[4] $[\alpha]_D$ +238°.

*Methyl 2,3- and 3,4-anhydro-5-thio-α-*D*-ribopyranosides* (**2** *and* **3**). — The acetates **11** and **12** (0.90 g) were each dissolved in dichloromethane (10 mL), and sodium methoxide [from sodium (20 mg)] in methanol (1 mL) was added. When the reactions were complete, ether (20 mL) was added and each mixture was filtered through a short column of silica gel (1 g). Evaporation of the filtrates gave **2** and **3** (0.60 g). The 2,3-epoxide **2** had m.p. 56–58° (from ether–light petroleum, $[\alpha]_D$ +307° (*c* 0.8, chloroform); lit.[4] $[\alpha]_D$ +307°. The 3,4-epoxide **3** had m.p. 50–52° (from ether–light petroleum, $[\alpha]_D$ +252° (*c* 1.3, chloroform); lit.[4], m.p. 52–53°, $[\alpha]_D$ +268°.

*Reaction of methyl 2,3-anhydro-5-thio-α-*D*-ribopyranoside* (**2**) *with aqueous sodium hydroxide.* — The epoxide **2** (1.37 g) was treated with boiling 0.5M sodium hydroxide for 6 h. The solution was cooled, neutralised (CO_2), and extracted with dichloromethane to remove any remaining **2**. The aqueous layer was then continuously extracted with ethyl acetate to give a syrupy mixture (1.05 g) of glycosides which was stirred with 2,2-dimethoxypropane (3 mL), acetone (9 mL), and toluene-*p*-sulphonic acid (0.12 g) for 30 min. After neutralisation (Na_2CO_3) and solvent removal, the residue was partitioned between water and dichloromethane. The organic extract was dried ($MgSO_4$), filtered, and evaporated to give a syrup which was dissolved in 80% acetic acid (12 mL). After 3 h at room temperature, the acetic acid was removed under reduced pressure and the residue was partitioned between water and dichloromethane. Evaporation of the water layer and crystallisation of the residue from ethyl acetate gave methyl 5-thio-α-D-xylopyranoside[1] (**15**, 0.46 g), m.p. and mixture m.p. 112–113°. The dichloromethane layer was evaporated to give syrupy methyl 3,4-*O*-isopropylidene-5-thio-α-D-arabinopyranoside (**16**, 0.45 g), $[\alpha]_D$ +112° (*c* 1,2, chloroform) (Found: mol. wt., 220.0766. $C_9H_{16}O_4S$ calc.: mol. wt., 220.0769). The acetal **16** was treated at 100° with aqueous 80% acetic acid (5 mL) for 1 h. Removal of solvent and recrystallisation from ethyl acetate gave methyl 5-thio-α-D-arabinopyranoside[1] (**13**, 0.34 g), m.p. and mixture m.p. 122–124°.

*Reaction of methyl 3,4-anhydro-5-thio-α-*D*-ribopyranoside* (**3**) *with aqueous sodium hydroxide.* — A solution of **3** (0.46 g) in 0.5M sodium hydroxide (15 mL) was boiled under reflux for 15 h. Work-up as in the previous experiment gave dichloromethane and aqueous layers. The dichloromethane layer yielded syrupy methyl 2,3-*O*-isopropylidene-5-thio-β-L-lyxopyranoside (**17**, 0.18 g), $[\alpha]_D$ +229° (*c* 1, chloroform) (Found: mol. wt., 220.0769. $C_9H_{16}O_4S$ calc.: mol. wt., 220.0769). Hydrolysis of **17** with aqueous acetic acid, as in the previous experiment, gave methyl 5-thio-β-L-lyxopyranoside (**14**, 64 g), m.p. 152–153°, $[\alpha]_D$ +318° (*c* 0.6, methanol) (Found: C, 39.7; H, 6.7. $C_6H_{12}O_4S$ calc.: C, 40.0; H, 6.7%); lit.[1], for D form, m.p. 152–154°, $[\alpha]_D$ −295°. The aqueous layer was chromatographed on Zerolit FF ($^-$OH) resin by elution with water to give, first, **14** (17 mg), m.p. 152–154°, and then the xyloside **15** (70 mg), m.p. and mixture m.p. 112–113°.

*Methyl 2,3-anhydro-4-*O*-*tert*-butyldimethylsilyl-5-thio-α-*D*-ribopyranoside* (**18**). — The 2,3-epoxide **2** (0.11 g) was dissolved in *N*,*N*-dimethylformamide (1.0

mL) to which were added imidazole (0.11 g) and *tert*-butyldimethylsilyl chloride (0.13 g), and the mixture was left at room temperature overnight. Ether was added, and the mixture was washed with dilute hydrochloric acid and aqueous sodium carbonate, and dried ($MgSO_4$). The extract was filtered through a little silica gel to give **18** (0.19 g) as a syrup, $[\alpha]_D$ +207° (*c* 1.5, chloroform).

ACKNOWLEDGMENTS

We thank Dr. M. N. S. Hill and Mr. I. McKeag for recording n.m.r. spectra, Messrs. P. Kelly and S. Addison for the mass spectra and mass measurements, Mr. D. Dunbar for elemental analyses, and the University of Zambia for a Staff Development Fellowship (to N.M.M.).

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