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An improved synthesis of benzyl 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-D-*erythro*-pentofuranoside, an intermediate in the synthesis of 4′-thionucleosides*

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ABSTRACT

Treatment of methyl 3,5-di-*O*-benzyl-2-deoxy-α,β-D-*erythro*-pentofuranoside with α-toluenethiol and conc. hydrochloric acid gave 3,5-di-*O*-benzyl-2-deoxy-D-*erythro*-pentose dibenzyl dithioacetal (**21**). Mesylation of **21** and ring closure gave benzyl 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-α,β-L-*threo*-pentofuranoside. Inversion of configuration at C-4 of **21** was achieved by the Mitsunobu reaction, to produce 4-*O*-benzoyl-3,5-di-*O*-benzyl-2-deoxy-L-*threo*-pentose dibenzyl dithioacetal. Successive debenzoylation, mesylation, and ring closure then gave the title compound. Several new dithioacetal derivatives of 2-deoxy-D-*erythro*-pentose were prepared in exploratory routes to the described thio sugar or as intermediates.

INTRODUCTION

The preparation of methyl 2-deoxy-4-thio-α,β-D-*erythro*-pentofuranosides (**5**) has been described by Nayak and Whistler[1,2] in a 15-step synthesis starting from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. Fu and Bobek[3] published an alternative route that comprises 14 steps from L-arabinose. Neither of these routes is suitable for the preparation of the relatively large amounts of the thio sugar intermediate required for nucleoside synthesis. A shorter route to the 2-deoxy-4-thio-D-*erythro*-pentofuranoside moiety (**31**), suitably derivatised to allow direct condensation with a protected pyrimidine base, is now described.

DISCUSSION

The initial strategy involved introduction of iodine or bromine substituents at C-4 of a protected 2-deoxy-D-*erythro*-pentose derivative (**2**), wich inversion of configuration to give **3**. It was hoped that introduction of a sulphur nucleophile (→**4**), with another inversion at C-4, deprotection at C-1, and ring closure, would lead to the thio sugar **5**.

2-Deoxy-D-*erythro*-pentose diethyl dithioacetal (**6**) was prepared (57%) by reacting 2-deoxy-D-*erythro*-pentose (2-deoxy-D-ribose) with ethanethiol and conc. hydrochloric acid[4]. Treatment of **6** with benzaldehyde and conc. hydrochloric acid gave

* Dedicated to Professor Grant Buchanan on the occasion of his 65th birthday.
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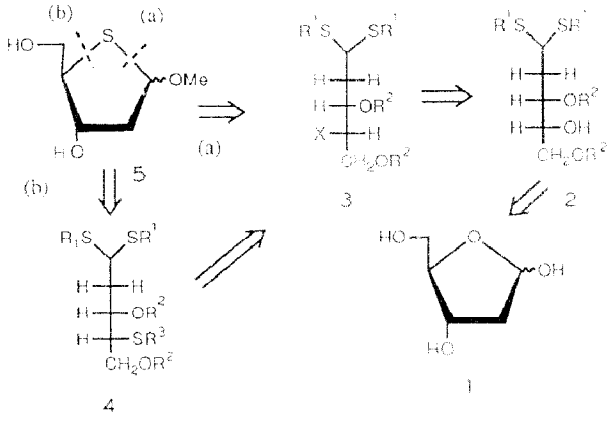


3,5-*O*-benzylidene-2-deoxy-D-*erythro*-pentose diethyl dithioacetal (**7**, 65%), the ^{1}H-n.m.r. spectrum of which contained one singlet for PhC*H*, which indicated that only one diastereoisomer was present. Attempted iodination of **7** using the Rydon reagent (tripbenyl phosphite methiodide)[5] caused decomposition, possibly due to the acid sensitivity of the benzylidene group. Similarly, attempted iodine exchange of the mesylate **8** and the *p*-bromobenzenesulphonate (**9**) of **7**, using NaI/acetone[6] or MgI_2/ether[7], failed at room temperature and at the reflux temperature. Attempted iodination of 5-hydroxy-2-phenyl-1,3-dioxane[8], used as a model compound, was also unsuccessful.

1 $R^1 = R^2 = H$

10 $R^1 = Me$, $R^2 = H$

11 $R^1 = Me$, $R^2 = Bn$

6 $R^1 = R^2 = R^3 = H$

7 $R^1,R^3 = PhCH_2$, $R^2 = H$

8 $R^1,R^3 = PhCH<$, $R^2 = Ms$

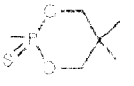
9 $R^1,R^3 = PhCH<$, $R^2 = Brs$

12 $R^1 = R^3 = Bn$, $R^2 = H$

13 $R^1 = R^2 = Bn$, $R^3 = H$

14 $R^1 = R^3 = Bn$, $R^2 = Ms$

15 $R^1 = R^3 = Bn$, $R^2 =$ 

16 $R^1 = R^3 = Bn$, $R^2 =$ 

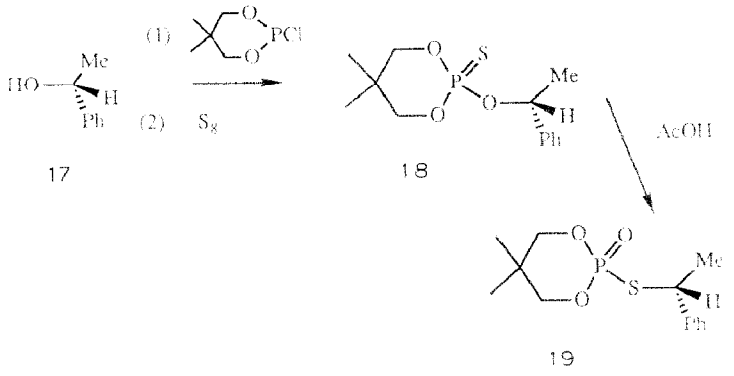
Brs = *p*-bromobenzenesulphonate

Since substitution reactions on ring systems are difficult to perform[9,10], HO-3,5 were protected so that substitution would take place at an acyclic secondary position. Methyl 3,5-di-*O*-benzyl-2-deoxy-α,β-D-*erythro*-pentofuranoside (plus a little pyranoside) (**11**, 93%) was prepared from **10** by adapting the method of Czernecki *et al.*[11], which used benzyl bromide, sodium hydride, and tetrabutylammonium iodide (1:10 stoichiometry) in tetrahydrofuran. Reaction of **11** with ethanethiol and conc. hydrochloric acid gave **12** (81%) and 3,4-di-*O*-benzyl-2-deoxy-D-*erythro*-pentose diethyl dithioacetal (**13**, 8%). Reaction of **12** with the Rydon reagent in *N,N*-dimethylformamide at room temperature gave two faster moving components in t.l.c., which were only partially characterised due to their instability (^{1}H- and ^{13}C-n.m.r. and u.v. spectroscopy, and f.a.b.-mass spectrometry) as 5-benzyloxypent-3-enol diethyl dithioacetal (57%) and 3,5-dibenzyloxypent-3-enol diethyl dithioacetal[12] (4%). It was thought that the desired 4-iodo product might have been an intermediate in the formation of the alkene but, at −20°, no reaction occurred and, at 0°, alkene was formed. With tetrahydrofuran or benzene as solvent, there was no reaction at room temperature and alkene was formed at 50°. Attempted iodine exchange of the mesylate **14** or bromine exchange of **12** were unsuccessful. Fleet[13] has reported that the rates of nucleophilic substitution reactions at a secondary carbon in carbohydrates can be decreased by as much as 10^{-4} if there is an oxygen substituent β to the leaving group.

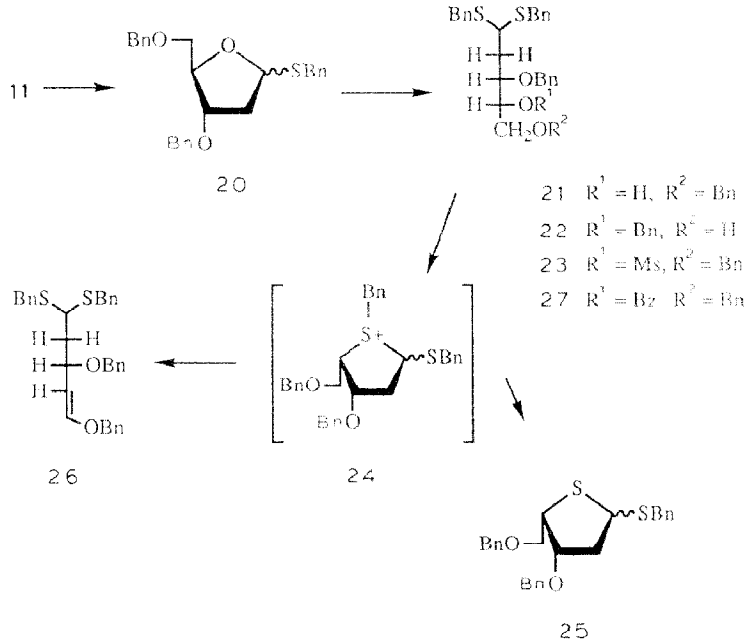
An attempt was then made to adapt the method of Bruzik and Stec[14,15] for the stereospecific conversion of an alcohol into a sulphide by conversion into the thionophosphorinane derivative **18** which, on treatment with acetic acid, rearranges with retention of configuration at the α-carbon into the thiolophosphorinane derivative **19**. Hydrolysis with base then gives the sulphide[16]. Thus, 3,5-di-*O*-benzyl-2-deoxy-4-*O*-(5,5-dimethyl-1,3,2-dioxaphosphorin-2-yl)-D-*erythro*-pentose diethyl dithioacetal (**15**) was prepared (38%) by reacting **12** with 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane[17] in benzene at 5° using triethylamine as the base. Reaction of **15** with elemental sulphur in benzene gave 3,5-di-*O*-benzyl-2-deoxy-4-*O*-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorin-2-yl)-D-*erythro*-pentose diethyl dithioacetal (**16**, 86%). Compound **16** could also be obtained directly (77%) from the alcohol **12** without the isolation of the intermediate phosphite. However, attempted rearrangement of **16** in either acetic acid or trifluoroethanol at various temperatures resulted in no reaction and, in the presence of trifluoroacetic acid, extensive decomposition resulted. The resistance of **16** to acid-catalysed rearrangement may be due to the bulky side groups which interfere with formation of the ion-pair.

When 5-*O*-tosyl-L-arabinose dibenzyl dithioacetal is heated in dry acetone containing sodium iodide and barium carbonate, a ring-closure reaction occurs[11] to form benzyl 1,5-dithio-α,β-L-arabinopyranosides and Blumberg *et al.*[19] proved that this reaction proceeded with inversion of configuration at C-5. These results provide the basis for a new strategy for the synthesis of thio sugars since sulphur now originates from C-1, rather than C-4 as outlined above and used[1-3] in previous preparations of methyl 2-deoxy-4-thio-α,β-D-*erythro*-pentofuranoside (**5**).

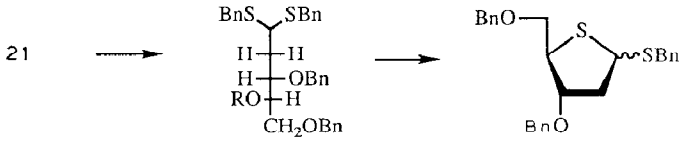
Using this new strategy, methyl 3,5-di-*O*-benzyl-2-deoxy-α,β-D-*erythro*-pento-



side (**11**) was reacted with α-toluenethiol and conc. hydrochloric acid at 42° to give 3,5-di-*O*-benzyl-2-deoxy-D-*erythro*-pentose dibenzyl dithioacetal (**21**, 85%). The reaction proceeded slowly at lower temperature and the intermediate, benzyl 3,5-di-*O*-benzyl-2-deoxy-1-thio-α,β-D-*erythro*-pentofuranoside (**20**) could be isolated. 3,4-Di-*O*-benzyl-2-deoxy-D-*erythro*-pentose dibenzyl dithioacetal (**25**) was formed, as a by-product of this reaction, from the pyranose sugar. When the mesylate (**23**) of **21** was heated in dry acetone that contained sodium iodide and barium carbonate for 40 h, 40% of **25** was obtained. When mesylate **23** was heated under reflux with acetone and barium carbonate for 18 h, the alkene **26** was obtained. It is possible that the cyclic sulphonium ion **24** is formed initially, but, instead of debenzylation to give **25**, an E2 type elimination occurs *via* base-catalysed abstraction of H-5.



Thus, if the configuration at C-4 of **21** can be inverted, the subsequent ring-closure reaction would produce a thio sugar with the desired 2-deoxy-D-*erythro* configuration. Application of the Mitsunobu reaction for the esterification of alcohols with the inversion of configuration[20,21] was investigated. Reaction of **21** with benzoic acid, diethyl azodicarboxylate, and triphenylphosphine in tetrahydrofuran at room temperature gave (40%) 4-*O*-benzoyl-3,5-di-*O*-benzyl-2-deoxy-L-*threo*-pentose dibenzyl dithioacetal (**28**). Increasing the temperature did not increase the yield greatly but shortened the reaction time. Increasing the ratio of the reagents to **21** also did not affect the yield. Benzoylation of **21** gave **27**. The ^{1}H-n.m.r. spectra of **28** and **27** contained multiplets for H-4 centred at 5.3 and 5.5 p.p.m., respectively, which confirmed that inversion of configuration at C-4 had occurred.



28 R = Bz
29 R = H
30 R = Ms

31

Debenzoylation of **28** gave 3,5-di-*O*-benzyl-2-deoxy-L-*threo*-pentose dibenzyl dithioacetal (**29**, 98%). Compounds **21** and **29**, which differed only in the configuration at C-4, had different ^{1}H-n.m.r. spectra with doublets for HO centred at 4.96 and 4.87 p.p.m., respectively. Further evidence to suggest that **21** and **29** were stereoisomers was provided by the different optical rotations. Reaction of **29** with mesyl chloride in pyridine yielded 97% of mesylate **30**. Attempted synthesis of **30** from **21** in one step by a Mitsunobu reaction with methanesulphonic acid was unsuccessful.

3,5-Di-*O*-benzyl-2-deoxy-4-*O*-methanesulphonyl-L-*threo*-pentose dibenzyl dithioacetal (**30**) was heated under reflux in dry acetone, sodium iodide, and barium carbonate, to give benzyl 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-α,β-D-*erythro*-pentofuranoside (**31**, 38%). The ^{1}H-n.m.r. spectra of the thio sugars **25** and **31** were similar, but there were some striking differences in the ^{13}C-n.m.r. spectra. For example, the chemical shifts of the resonances of C-1β were 80.77 p.p.m. for **25** and 83.04 p.p.m. for **31**. The ^{13}C-n.m.r. spectra indicated that, for each thio sugar, one anomer predominated due to the steric requirements of the ring-closure reaction. For compound **31**, the two anomers can easily be separated by reverse-phase h.p.l.c. and the ^{1}H-n.m.r. spectrum of the predominant isomer is clearly consistent with that expected for the β anomer.

The above synthesis of the thio sugar **31** involved a 7-step synthesis from 2-deoxy-D-*erythro*-pentose with an overall yield of 11%. This yield could be increased to 25% by recycling unreacted intermediates (*cf.* the overall yield of 4% in the 14-step synthesis[3] from L-arabinose). The product **31** is now available in reasonable quantities for the synthesis of new nucleosides.

EXPERIMENTAL

General procedures. — Melting points were determined in a Gallenkamp apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. The ^{1}H- and ^{13}C-n.m.r. spectra (internal Me_4Si for ^{1}H and ^{13}C) were recorded on a JEOL GX270 or FX90Q instrument. Positive-ion f.a.b.-mass spectra were obtained with a Kratos MS80 RF instrument, using glycerol or 3-nitrobenzyl alcohol as a matrix. T.l.c. was performed on Silica Gel 60 F_{254} (Merck) with detection by u.v. absorbance or by charring with sulphuric acid. Silica Gel 60 (70–230 mesh, 7734, Merck) was used for column chromatography. Elemental analyses were performed in the microanalytical laboratory of this Department.

The following solvents were distilled before use: pyridine (from KOH), methanol (from Mg), tetrahydrofuran (from Na/benzophenone), and dichloromethane (from P_2O_5). Calcium-chloride-dried benzene was further dried over sodium wire. Acetone was dried with anhydrous potassium carbonate.

2-Deoxy-D-erythro-*pentose diethyl dithioacetal* (**6**). — Conc. hydrochloric acid (5 mL) was added dropwise to a stirred mixture of 2-deoxy-D-*erythro*-pentose (5 g, 37 mmol) and ethanethiol (5 g, 81 mmol) at 0°. Stirring was continued at 0° for 30 min, and the mixture was then poured into ice–water (50 mL), neutralised with sodium hydrogen carbonate, and extracted with chloroform (3 × 40 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (chloroform–methanol, 19:1) of the residue gave **6** (5.1 g, 56%), as a colourless oil, $[\alpha]_D^{25}$ −15° (*c* 1.4, ethanol). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 1.00–1.35 (t, 6 H, 2 CH_3CH_2S), 1.50–2.18 (m, 2 H, H-2,2), 2.40–2.82 (m, 4 H, 2 CH_3CH_2S), 3.10–3.78 (m, 4 H, H-3,4,5,5), 3.95–4.19 (m, 1 H, H-1), 4.20–4.74 (m, 3 H, HO-3,4,5).

Anal. Calc. for $C_9H_{20}O_3S_2$: C, 45.0; H, 8.3. Found: C, 45.0; H, 8.5.

3,5-O-Benzylidene-2-deoxy-D-erythro-*pentose diethyl dithioacetal* (**7**). — Compound **6** (3.75 g, 15.6 mmol) was warmed gently with benzaldehyde until the mixture was homogeneous. The mixture was cooled to 0°, conc. hydrochloric acid (2 mL) was added dropwise with stirring, and, after 30 min, ethanol (35 mL) was added. The mixture was neutralised with saturated aqueous hydrogen carbonate and extracted with chloroform (3 x 40 mL), the combined extracts were dried (Na_2SO_4), and the chloroform was evaporated *in vacuo*. Column chromatography (chloroform–ethanol, 91:1) of the residue gave **7** (3.3 g, 65%), as a slightly yellow syrup, $[\alpha]_D^{25}$ −52° (*c* 3.5, ethanol). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 1.05–1.35 (m, 6 H, 2 CH_3CH_2S), 1.84–2.38 (m, 2 H, H-2,2), 2.42–2.74 (m, 4 H, 2 CH_3CH_2S), 3.23–4.18 (m, 5 H, H-1,3,4,5,5), 5.33–5.37 (d, 1 H, OH-4), 5.50 (s, 1 H, PhC*H*), 7.28–7.51 (m, 5 H, Ph). F.a.b.-mass spectrum: *m/z* 328 (M^+).

Anal. Calc. for $C_{16}H_{24}O_3S_2$: C, 58.5; H, 4.9. Found: C, 58.8; H, 4.7.

3,5-O-Benzylidene-2-deoxy-4-O-methanesulphonyl-D-erythro-*pentose diethyl dithioacetal* (**8**). — To a stirred solution of **7** (0.5 g, 1.5 mmol) in dry pyridine (5 mL) at 0° was added dropwise a solution of methanesulphonyl chloride (0.3 g, 2.6 mmol) in dry pyridine (5 mL). The mixture was allowed to attain room temperature, stirred for 18 h,

then concentrated *in vacuo*. A solution of the residue in dichloromethane was washed with 2M hydrochloric acid, M sodium carbonate, and water, dried ($MgSO_4$), and concentrated. Column chromatography (chloroform) of the residue gave **8** (0.59 g, 95%), $[\alpha]_D^{25}$ −60° (*c* 2.1, ethanol). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 1.00–1.32 (m, 6 H, 2 CH_3CH_2S), 2.10–2.30 (m, 2 H, H-2,2), 2.40–2.78 (m, 4 H, 2 CH_3CH_2S), 3.41 (s, 3 H, Ms), 3.82–4.72 (m, 5 H, H-1,3,4,5,5), 5.20 (s, 1 H, PhC*H*), 7.32–7.49 (m, 5 H, Ph). F.a.b.-mass spectrum: *m/z* 406 (M^+).

Anal. Calc. for $C_{17}H_{26}O_5S_3$: C, 50.2; H, 6.5. Found: C, 50.2; H, 6.7.

*3,5-*O*-Benzylidene-4-*O*-p-bromobenzenesulphonyl-2-deoxy-*D*-*erythro*-pentose diethyl dithioacetal* (**9**). — Compound **9** (0.69 g, 83%), prepared from **7** (0.5 g, 1.5 mmol) and *p*-bromobenzenesulphonyl chloride (0.66 g, 1.6 mmol) by the procedure described above for **8**, had $[\alpha]_D^{25}$ −47° (*c* 1.6, ethanol). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 1.00–1.30 (m, 6 H, 2 CH_3CH_2S), 1.40–1.72 (m, 2 H, H-2,2), 2.30–2.67 (m, 4 H, 2 CH_3CH_2S), 3.73–4.65 (m, 5 H, H-1,3,4,5,5), 5.65 (s, 1 H, PhC*H*), 7.38 (s, 5 H, Ph), 7.98 (s, 4 H, aromatic). F.a.b.-mass spectrum: *m/z* 547 (M^+).

Anal. Calc. for $C_{22}H_{27}BrO_5S_3$: C, 48.3; H, 5.0. Found: C, 48.6; H, 4.9.

*Methyl 3,5-di-*O*-benzyl-2-deoxy-α,β-*D*-*erythro*-pentoside* (**11**). — To a solution of 2-deoxy-D-*erythro*-pentose (50 g, 373 mmol) in dry methanol (900 mL) was added methanolic 1% hydrogen chloride (100 mL). The mixture was kept in a stoppered flask for 30 min at room temperature, then stirred with silver carbonate (10 g), filtered, and concentrated to a syrup. Traces of methanol were removed from the residue by repeated evaporation following addition of tetrahydrofuran. To a solution of the syrupy residue in dry tetrahydrofuran (470 mL) under nitrogen at 0° was added sodium hydride (50%, dispersion in oil, 39.4 g, 821 mmol) slowly with stirring. Tetrabutylammonium iodide (30.3 g, 82.1 mmol) was then added followed by benzyl bromide (140 g, 821 mmol) during 1 h. The mixture was stirred for 60 h at room temperature with the exclusion of moisture, then concentrated *in vacuo*. A solution of the residue in dichloromethane was poured into ice–water, and the organic layer was dried ($MgSO_4$) and concentrated. Column chromatography (hexane–ethyl acetate, 4:1) of the syrupy residue gave a mixture (114 g, 93%) of **11**α (R_F 0.36) and **11**β (R_F 0.47) as a colourless syrup. N.m.r. data for **11**α: ^{1}H [$(CD_3)_2SO$], δ 1.80–2.40 (m, 2 H, H-2,2), 3.40 (s, 3 H, OMe), 3.42–3.58 (d, 2 H, H-5,5), 3.86–4.40 (m, 2 H, H-3,4), 4.45–4.60 (m, 4 H, 2 PhCH_2O), 5.00–5.12 (q, 1 H, H-1), 7.17–7.56 (d, 10 H, 2 Ph); ^{13}C ($CDCl_3$), δ 38.9 (C-2), 55.1 (OMe), 70.2 (C-5), 71.5 (PhCH_2O), 73.4 (PhCH_2O), 78.6 (C-3), 82.1 (C-4), 105.2 (C-1), 127.6–128.3 (aromatic).

N.m.r. data for **11**β: ^{1}H [$(CD_3)_2SO$], δ 2.05–2.45 (m, 2 H, H-2,2), 3.30 (s, 3 H, OMe), 3.42–3.60 (m, 2 H, H-5,5), 4.00–4.43 (m, 2 H, H-3,4), 4.43–4.65 (d, 4 H, 2 PhCH_2O), 5.02–5.18 (q, 1 H, H-1), 7.20–7.50 (d, 10 H, 2 Ph); ^{13}C ($CDCl_3$), δ 39.3 (C-2), 54.9 (OMe), 70.2 (C-5), 72.0 (PhCH_2O), 73.3 (PhCH_2O), 80.0 (C-3), 82.8 (C-4), 105.4 (C-4), 127.6–128.3 (aromatic).

*3,5-Di-*O*-benzyl-2-deoxy-*D*-erythro-pentose diethyl dithioacetal* (**12**). — Conc. hydrochloric acid (11.2 mL) was added dropwise to a stirred mixture of **11** (28 g, 85.3 mmol) and ethanethiol (11.7 g, 188 mmol) at 0°, and stirring was continued for 20 h at

room temperature. The mixture was worked-up as described for **6**, except that hexane–ethyl acetate (4:1) was used in the column chromatography. The first component eluted (R_f 0.29), isolated as a colourless syrup, was **12** (29.1 g, 81%), $[\alpha]_D^{25}$ −24° (*c* 2.4, ethanol). N.m.r. data: ^{1}H [$(CD_3)_2SO$], δ 1.00–1.28 (m, 6 H, 2 CH_3CH$_2$S), 1.80–2.10 (m, 2 H, H-2,2), 2.33–2.72 (m, 4 H, 2 CH$_3$CH_2S), 3.38–3.59 (d, 2 H, H-5,5), 3.70–4.08 (m, 3 H, H-1,3,4), 4.33–4.75 (m, 4 H, 2 PhCH_2O), 4.95–5.05 (d, 1 H, HO-4), 7.20–7.43 (d, 10 H, 2 Ph); ^{13}C ($CDCl_3$), δ 14.4 (*C*H$_3$CH$_2$S), 23.5 and 24.3 (CH$_3$*C*H$_2$S), 37.5 (C-2), 47.8 (C-5), 70.9 (C-3), 71.8 (C-4), 72.8 (Ph*C*H$_2$O), 73.4 (Ph*C*H$_2$), 77.5 (C-1), 127.8–128.4 (aromatic). F.a.b.-mass spectrum: *m/z* 420 (M^+).

Anal. Calc. for $C_{23}H_{32}O_3S_2$: C, 65.7; H, 7.7. Found: C, 65.9; H, 7.7.

The next fraction (R_f 0.12) was 3,4-di-*O*-benzyl-2-deoxy-D-*erythro*-pentose diethyl dithioacetal (**13**; 2.8 g, 8%), isolated as a colourless syrup. N.m.r. data: ^{1}H [$(CD_3)_2SO$], δ 1.05–1.30 (m, 6 H, 2 CH_3CH$_2$S), 1.80–2.10 (m, 2 H, H-2,2), 2.30–2.72 (m, 4 H, 2 CH$_3$CH_2S), 3.40–3.60 (d, 2 H, H-5,5), 3.75–4.10 (m, 3 H, H-1,3,4), 4.31–4.75 (m, 4 H, 2 PhCH_2O), 4.70–4.82 (d, 1 H, HO-4), 7.30 (s, 10 H, 2 Ph); ^{13}C ($CDCl_3$), δ 14.4 (CH$_3$CH$_2$S), 23.5 and 24.5 (CH$_3$CH$_2$S), 38.7 (C-2), 48.1 (C-5), 61.4 (C-3), 72.3 (PhCH$_2$O), 73.1 (PhCH$_2$O), 77.1 (C-4), 81.1 (C-1), 127–128.4 (aromatic).

*3,5-Di-*O*-benzyl-2-deoxy-4-*O*-methanesulphonyl*-D-erythro-*pentose diethyl dithioacetal* (**14**). — Compound **14** (1.8 g, 100%), $[\alpha]_D^{25}$ −35° (*c* 2.2, ethanol), was prepared from **15** (1.5 g, 3.6 mmol) and methanesulphonyl chloride (0.62 g, 5.4 mmol) by the procedure used for the preparation of **8**, except that column chromatography was not performed. ^{1}H-N.m.r. data [$(CD_3)_2SO$], δ 1.00–1.30 (m, 6 H, 2 CH_3CH$_2$S), 1.77–2.08 (m, 2 H, H-2,2), 2.31–2.75 (m, 4 H, 2 CH$_3$CH_2S), 3.17 (s, 3 H, Ms), 3.54–4.17 (m, 4 H, H-1,3,5,5), 4.38–4.85 (m, 4 H, 2 PhCH_2O), 4.93–5.15 (m, 1 H, H-4), 7.25–7.40 (d, 10 H, 2 Ph). F.a.b.-mass spectrum: *m/z* 498 (M^+).

Anal. Calc. for $C_{24}H_{34}O_5S_3 \cdot 0.5H_2O$: C, 56.8; H, 7.0. Found: C, 56.9; H, 6.9.

*3,5-Di-*O*-benzyl-2-deoxy-4-*O*-(5,5-dimethyl-1,3,2-dioxaphosphorinan-2-yl)*-D-erythro-*pentose diethyl dithioacetal* (**15**). — To a stirred solution of 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane[17] (0.8 g, 4.7 mmol) and dry triethylamine (0.8 mL, 5.7 mmol) in dry benzene (20 mL) at 0° was added dropwise a solution of **12** (1.0 g, 2.4 mmol) in dry benzene (10 mL). After 10 min, the mixture was filtered and the benzene was removed *in vacuo*. Column chromatography (hexane–ethyl acetate, 9:1) of the residue gave **15** (0.5 g, 38%), as a colourless syrup. ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 0.64 (s, 3 H, Me-5′), 1.10–1.25 (m, 9 H, 2 CH_3CH$_2$S and Me-5′), 1.80–2.10 (m, 2 H, H-2,2), 2.40–2.70 (m, 4 H, 2 CH$_3$CH_2S), 3.20–3.35 (t, 2 H, H-5,5), 3.59–3.61 (d, 2 H, H-1,3), 3.90–4.10 (m, 4 H, H-4′,4′,6′,6′), 4.40–4.53 (m, 4 H, 2 PhCH_2O), 4.65–4.70 (d, 1 H, H-4), 7.20–7.36 (m, 10 H, 2 Ph). F.a.b.-mass spectrum: *m/z* 553 (M^+).

Anal. Calc. for $C_{28}H_{41}O_7PS_2$: C, 60.8; H, 7.5. Found: C, 61.1; H, 7.6.

*3,5-Di-*O*-benzyl-2-deoxy-4-*O*-(5,5-dimethyl-2-thiono-1,3,2-dioxaphosphorinan-2-yl)*-D-erythro-*pentose diethyl dithioacetal* (**16**). — To a stirred solution of **15** (0.45 g, 0.81 mmol) in dry benzene (5 mL) at 10° was added elemental sulphur (54 mg, 1.67 mmol). The mixture was stirred at room temperature for 24 h, then concentrated *in vacuo*. Column chromatography (hexane–ethyl acetate, 9:1) of the residue gave **16** (0.49 g,

86%), isolated as a colourless syrup, $[\alpha]_D^{25}$ −10° (*c* 1.5, ethanol). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 0.76 (s, 3 H, Me-5'), 1.00–1.28 (m, 9 H, 2 CH_3CH_2S and Me-5'), 1.85–2.10 (m, 2 H, H-2,2), 2.38–2.70 (m, 2 CH_3CH_2S), 3.60–4.23 (m, 8 H, H-1,3,5,5,4',4',6',6'), 4.44–4.75 (m, 4 H, 2 $PhCH_2O$), 4.75–4.89 (m, 1 H, H-4), 7.22–7.39 (m, 10 H, 2 Ph). F.a.b.-mass spectrum; *m/z* 584 (M^+).

Anal. Calc. for $C_{28}H_{41}O_5PS_3$: C, 57.5; H, 7.1. Found: C, 57.6; H, 7.2.

3,5-Di-O-benzyl-2-deoxy-D-erythro-*pentose dibenzyl dithioacetal* (**21**). — Conc. hydrochloric acid (150 mL) was added dropwise to a stirred mixture of compound **11** (77.5 g, 236 mol) and α-toluenethiol (147 g, 1.19 mol) at room temperature. The temperature was then raised to 40°, stirring was continued for 18 h, and the mixture was worked-up as described for **12**. The first fraction (R_F 0.58 and 0.53; hexane–ethyl acetate, 4:1) eluted from the column, and isolated as a colourless syrup, was benzyl 3,5-di-*O*-benzyl-2-deoxy-1-thio-α,β-D-*erythro*-pentofuranoside (**20**; 3 g, 3%). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 1.35–2.35 (m, 2 H, H-2,2), 3.30–4.12 (m, 6 H, H-3,4,5,5 and $PhCH_2S$), 4.36–4.59 (m, 4 H, 2 $PhCH_2O$), 4.94–5.12 (m, 1 H, H-1), 7.15–7.43 (m, 15 H, 3 Ph). F.a.b.-mass spectrum: *m/z* 420 (M^+).

Anal. Calc. for $C_{26}H_{28}O_3S$: C, 74.3; H, 6.7. Found, C, 74.4; H, 6.5.

The second fraction (R_F 0.29) eluted and isolated as a colourless syrup was **21** (109 g, 85%), $[\alpha]_D^{25}$ −102° (*c* 2.0, ethanol). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 1.83–2.10 (m, 2 H, H-2,2), 3.32–3.44 (d, 2 H, H-5,5), 3.66–3.81 (m, 7 H, H-1,3,4 and 2 $PhCH_2S$), 3.95–4.47 (m, 4 H, 2 $PhCH_2O$), 4.95–4.97 (d, 1 H, OH-4), 7.05–7.35 (m, 20 H, 4 Ph). F.a.b.-mass spectrum *m/z* 298 $[M-2\ SBn]^+$.

Anal. Calc. for $C_{33}H_{36}O_3S_2$: C, 72.8; H, 6.7. Found: C, 73.0; H, 6.5.

The third fraction (R_F 0.22) eluted was 3,4-di-*O*-benzyl-2-deoxy-D-*erythro*-pentose dibenzyl dithioacetal (**22**; 6.4 g, 5%), isolated as a colourless syrup. ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 1.85–2.12 (m, 2 H, H-2,2), 3.33–3.88 (m, 9 H, H-1,3,4,5,5 and 2 $PhCH_2S$), 3.98–4.64 (m, 4 H, 2 $PhCH_2O$), 4.70–4.74 (t, 1 H, OH-5), 7.08–7.35 (m, 20 H, 4 Ph). F.a.b.-mass spectrum: *m/z* 544 (M^+).

Anal. Calc. for $C_{33}H_{36}O_3S_2$: C, 72.8; H, 6.7. Found: C, 72.6; H, 6.6.

3,5-Di-O-benzyl-2-deoxy-4-O-methanesulphonyl-D-erythro-*pentose dibenzyl dithioacetal* (**23**). — Compound **23** (4.6 g, 100%), prepared from **21** (4.0 g, 7.4 mmol) and methanesulphonyl chloride (1.3 g, 11.3 mmol) by the procedure used for the preparation of **8** except that silica gel chromatography was not performed, had $[\alpha]_D^{25}$ −41° (*c* 2.3, dichloromethane). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 1.80–2.13 (m, 2 H, H-2,2), 3.12 (s, 3 H, Ms), 3.52–4.00 (m, 8 H, H-1,3,5,5 and 2 $PhCH_2S$), 4.00–4.60 (m, 4 H, 2 $PhCH_2O$), 4.87–5.09 (m, 1 H, H-4), 6.96–7.41 (m, 20 H, 4 Ph). F.a.b.-mass spectrum: *m/z* 531 $[M-PhCH_2]^+$.

Anal. Calc. for $C_{34}H_{38}O_5S_3$: C, 65.6; H, 6.2. Found: C, 65.3; H, 6.3.

Benzyl 3,5-Di-O-benzyl-2-deoxy-1,4-dithio-L-threo-*pentofuranoside* (**25**). — A mixture of **23** (1.5 g, 2.4 mmol), sodium iodide (3.8 g, 25 mmol), barium carbonate (7.5 g, 38 mmol), and dry acetone (45 mL) was boiled under reflux for 42 h, then filtered. The solids were washed with chloroform, and the combined filtrate and washings were washed with water, aqueous 5% sodium thiosulphate, and water, dried ($MgSO_4$), and

concentrated. Column chromatography (hexane–ethyl acetate, 9:1) of the residue gave **25** (R_F 0.32), isolated as a slightly yellow syrup (0.42 g, 40%), and **23** (R_F 0.09; 0.45 g, 30%). N.m.r. data: ^{1}H [$(CD_3)_2SO$], δ 1.81–2.50 (m, 2 H, H-2,2), 3.38–3.96 (m, 5 H, H-3,5,5 and PhCH_2S), 4.13–4.53 (m, 6 H, H-1,4 and 2 PhCH_2O), 7.26–7.33 (m, 15 H, 2 Ph); ^{13}C ($CDCl_3$), δ 37.0 (C-2α,β), 40.4 (C-5α), 41.9 (C-5β), 47.6 (C-4α), 48.9 (C-4β), 50.9 (PhCH$_2$Sα), 51.6 (PhCH$_2$Sβ), 69.5 (C-3β), 70.4 (C-3α), 71.6 (PhCH$_2$Oα,β), 73.3 (PhCH$_2$Oα,β), 80.8 (C-1α,β), 127.1–128.9 (aromatic). F.a.b.-mass spectrum: *m/z* 436 (M^+).

Anal. Calc. for $C_{26}H_{28}O_2S_2$: C, 71.5; H, 6.5; S, 14.7. Found: C, 71.7; H, 6.8; S, 14.4.

3,5-Di-O-benzyl-2,4-dideoxy-D-glycero-*pent-4-enose dibenzyl dithioacetal* (**26**). — A mixture of **23** (120 mg, 0.23 mmol), barium carbonate (0.5 g, 2.5 mmol), and dry acetone (5 mL) was boiled under reflux for 18 h, then worked-up as described for **25**, to give **26** (R_F 0.36; hexane–ethyl acetate, 9:1), isolated as a clear syrup (40 mg, 39%). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 3.38–4.60 (m, 11 H, H-2,2,5, 2 PhCH_2O, and 2 PhCH_2S), 5.30–5.70 (m, 1 H, H-1), 6.20–6.56 (d, 1 H, H-4), 7.02–7.48 (m, 20 H, 4 Ph).

Anal. Calc. for $C_{33}H_{34}O_3S_2 \cdot H_2O$: C, 72.8; H, 6.7. Found: C, 72.8; H, 6.6.

4-O-Benzoyl-3,5-di-O-benzyl-2-deoxy-D-erythro-*pentose dibenzyl dithioacetal* (**27**). — To a stirred solution of **21** (0.5 g, 0.92 mmol) in dry pyridine (3 mL) was added a solution of benzoyl chloride (0.14 g, 1 mmol) in dry pyridine (2 mL) dropwise at 0°. After 10 min, methanol (10 mL) was added, the solvent was removed *in vacuo*, and a solution of the residue in dichloromethane was washed with 2M hydrochloric acid, M sodium carbonate, and water, dried ($MgSO_4$), and concentrated. Column chromatography (hexane–ethyl acetate, 9:1) of the residue gave **27** (0.41 g, 69%), isolated as a slightly yellow syrup, $[\alpha]_D^{25}$ −52.0° (*c* 1.7, dichloromethane). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 1.88–2.20 (m, 2 H, H-2,2), 3.51–4.08 (m, 8 H, H-1,3,5,5 and 2 PhCH_2S), 4.08–4.60 (m, 4 H, 2 PhCH_2O), 5.38–5.60 (m, 1 H, H-4), 6.92–8.04 (m, 25 H, 5 Ph).

Anal. Calc. for $C_{40}H_{40}O_4S_2 \cdot H_2O$: C, 72.5; H, 6.4. Found: C, 72.7; H, 6.3.

4-O-Benzoyl-3,5-di-O-benzyl-2-deoxy-L-threo-*pentose dibenzyl dithioacetal* (**28**). — To a stirred solution of **21** (54.1 g, 99.3 mmol), triphenylphosphine (39.1 g, 149 mmol), and benzoic acid (18.2 g, 149 mmol) in dry tetrahydrofuran (800 mL) was added a solution of diethyl azodicarboxylate (26.0 g, 149 mmol) in dry tetrahydrofuran (200 mL) dropwise at room temperature. The mixture was stirred at room temperature for 18 h, then concentrated *in vacuo*. Column chromatography (hexane–ethyl acetate, 85:15) of the residue gave **21** (31 g, 57%) and **28** (25.8 g, 40%) isolated as a white solid, $[\alpha]_D^{25}$ −52° (*c* 0.7, dichloromethane). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 1.84–2.17 (m, 2 H, H-2,2), 3.62–4.01 (m, 8 H, H-1,3,5,5 and 2 PhCH_2S), 4.04–4.54 (m, 4 H, 2 PhCH_2O), 5.22–5.39 (m, 1 H, H-4), 6.98–7.99 (m, 25 H, 5 Ph). F.a.b.-mass spectrum: *m/z* 525 $[M - SCH_2Ph]^+$.

Anal. Calc. for $C_{40}H_{40}O_4S_2$: C, 74.0; H, 6.2. Found: C, 74.3; H, 6.4.

3,5-Di-O-benzyl-2-deoxy-L-threo-*pentose dibenzyl dithioacetal* (**29**). — To a stirred solution of **28** (88.8 g, 137 mmol) in dichloromethane (500 mL) was added a solution of sodium methoxide (11.1 g, 206 mmol) in methanol (205 mL) dropwise at 0°. The mixture was allowed to attain room temperature during 3 h, poured into aqueous

5% NaH_2PO_4, and extracted with dichloromethane. The extract was washed with aqueous 5% sodium hydrogen carbonate and water, dried ($MgSO_4$), and concentrated. Column chromatography (hexane–ethyl acetate, 4:1) of the residue gave **29** (72.0 g, 98%), isolated as a colourless syrup, $[\alpha]_D^{25}$ −75.6° (*c* 1.9, ethanol). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 1.84–2.08 (m, 2 H, H-2,2), 3.32–4.83 (m, 9 H, H-1,3,4,5,5 and 2 PhCH_2S), 4.00–4.55 (m, 4 H, 2 PhCH_2O), 4.86–4.88 (d, 1 H, OH-4), 7.06–7.34 (m, 20 H, 4 Ph). F.a.b.-mass spectrum *m/z* 297 [M − 2 SCH_2Ph + H]$^+$.

Anal. Calc. for $C_{33}H_{36}O_3S_2$: C, 72.8; H, 6.7. Found: C, 72.6; H, 6.9.

*3,5-Di-*O*-benzyl-2-deoxy-4-*O*-methanesulphonyl-*L-threo-*pentose dibenzyl dithioacetal* (**30**). — Compound **30** (68.2 g, 97%) was prepared from **29** (61.4 g, 113 mmol) and methanesulphonyl chloride (19.4 g, 169 mmol), as described for **8**, except that column chromatography was not performed. The product was crystallised from hexane–ethyl acetate and had m.p. 82–83°, $[\alpha]_D^{25}$ −58° (*c* 2.4, dichloromethane). ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 1.80–2.12 (m, 2 H, H-2,2), 3.11 (s, 3 H, Ms), 3.43–4.05 (m, 8 H, H-1,3,5,5 and 2 PhCH_2S), 4.09–4.60 (m, 4 H, 2 PhCH_2O), 4.64–4.88 (m, 1 H, H-4), 6.89–7.64 (m, 20 H, 4 Ph). F.a.b.-mass spectrum: *m/z* 499 [M − SCH_2Ph]$^+$.

Anal. Calc. for $C_{34}H_{38}O_5S_3$: C, 65.6; H, 6.2. Found: C, 65.5; H, 6.1.

*Benzyl 3,5-di-*O*-benzyl-2-deoxy-1,4-dithio-*α,β*-*D*-*erythro*-pentofuranoside* (**31**). — Compound **31** (7.9 g, 38%) was prepared from **30** (29.4 g, 47.7 mmol), sodium iodide (74.0 g, 494 mmol), barium carbonate (148 g, 750 mmol), and dry acetone (1 L), as in the preparation of **29**, and **30** (29 g, 39%) was also recovered. N.m.r. data: ^{1}H [$(CD_3)_2SO$], δ 1.94–2.44 (m, 2 H, H-2,2), 3.35–4.09 (m, 5 H, H-3,5,5 and PhCH_2S), 4.13–4.66 (m, 6 H, H-1,4 and 2 PhCH_2O), 7.12–7.50 (m, 15 H, 3 Ph); ^{13}C ($CDCl_3$), δ 37.0 (C-2α,β), 41.0 (C-5α), 41.3 (C-5β), 49.0 (C-4α), 49.9 (C-4β), 53.0 (PhCH_2Sα), 53.2 (PhCH_2Sβ), 71.0 (C-3β), 71.6 (C-3α), 72.9 (PhCH_2Oα), 73.1 (PhCH_2Sβ), 82.7 (C-1α), 83.04 (C-1β), 127.1–129.0 (aromatic). F.a.b.-mass spectrum: *m/z* 437 (M + H)$^+$.

Anal. Calc. for $C_{26}H_{28}O_2S_2$: C, 71.5; H, 6.5; S, 14.7. Found: C, 71.8; H, 6.7; S, 14.4.

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REFERENCES

1 U. G. Nayak and R. L. Whistler, *J. Org. Chem.*, 34 (1969) 3819–3822.
2 U. G. Nayak and R. L. Whistler, *Anal. Chem.*, 741 (1970) 131–138.
3 Y.-L. Fu and M. Bobek, *J. Org. Chem.*, 41 (1976) 3831–3834.
4 H. Zinner, H. Nimz, and H. Venner, *Chem. Ber.*, 90 (1957) 2696–2699.
5 S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, (1953) 2224–2234.
6 R. S. Tipson, M. A. Clapp, and L. H. Cretcher, *J. Org. Chem.*, 12 (1947) 133–138.
7 P. Place, M. Roumestant, and J. Gore, *Bull Soc. Chim. Fr.*, 2 (1976) 169–176.
8 N. Baggett, J. S. Brimacombe, A. B. Foster, M. Stacey, and D. H. Whiffen, *J. Chem. Soc.*, (1960) 2574–2581.
9 R. S. Tipson, *Adv. Carbohydr. Chem.*, 8 (1953) 107–215.
10 D. H. Ball and P. W. Parrish, *Adv. Carbohydr. Chem. Biochem.*, 24 (1969) 139–197; 23 (1968) 233–280.
11 S. Czernecki, C. Georgoulis, and C. Provenghiou, *Tetrahedron Lett.*, 39 (1976) 3535–3536.

12 M. R. Dyson, Ph.D. Thesis, University of Birmingham, 1989.
13 G. W. J. Fleet, *Chem. Br.*, 25 (1989) 287–292.
14 K. Bruzik and W. J. Stec, *J. Org. Chem.*, 44 (1979) 4488–4492.
15 G. R. Norman, W. M. LeSuer, and T. W. Mastin, *J. Am. Chem. Soc.*, 74 (1952) 161–163.
16 K. Bruzik and W. J. Stec, *J. Org. Chem.*, 46 (1981) 1618–1630.
17 R. S. Edmundson, *Chem. Ind. (London)*, (1965) 1220.
18 J. Harness and N. A. Hughes, *J. Chem. Soc., Chem. Commun.*, (1971) 811.
19 K. Blumberg, A. Fuccello, and T. van Es, *Carbohydr. Res.*, 70 (1979) 217–226.
20 O. Mitsunobu, *Synthesis*, 7 (1981) 1–27.
21 A. B. Smith, K. J. Hale, and R. A. Rivero, *Tetrahedron Lett.*, 27 (1986) 5813–5816.
22 O. Varela, D. Cicero, and R. M. de Lederkremer, *J. Org. Chem.*, 54 (1989) 1884–1890.