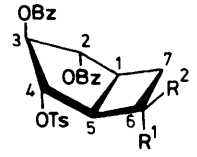
Functionalised Carbocycles from Carbohydrates. Part 5.[1] The Synthesis of the Epoxybicyclo[3.2.0]heptanone Ethylene Acetal Prostaglandin Intermediate

Robert J. Ferrier,* Petpiboon Prasit, and Peter C. Tyler
Department of Chemistry, Victoria University of Wellington, Private Bag, Wellington, New Zealand

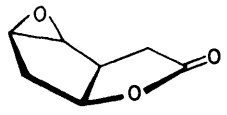
Treatment of the ethylene dithioacetal (4) of the bicyclo[3.2.0]heptanone derivative (3) with base gave specifically the hydroxy epoxide (8) which, with most nucleophiles, reacted at C-2 to give analogues of the starting material (4). The iodo dibenzoate (9) was then converted into the iodo lactone (11) from which the prostaglandin intermediate (6) has already been made. The corresponding ethylene acetal (5) was converted into the analogous epoxide (13) and thence into the diol (17) and the epoxybicyclo-[3.2.0]heptanone ketal (7) which is a preferred, optically pure intermediate for prostaglandin synthesis.

In the preceding paper [1] we show that the methyl ketone (1) can be made by photochemical ring closure of a nonadienulose derivative, and that the cyclobutanol (2) and the derived ketone (3) are obtainable from compound (1). Compound (2) gave access to the epoxy lactone (6) [1] which is an advanced intermediate used in one general synthetic route to the prostaglandins and which we have made previously from a D-glucose derivative by a different strategy.[2] A related intermediate used in another approach to these compounds is the acetal (7) which has advantages over the epoxy lactone in that, on treatment with nucleophiles, it undergoes opening of the epoxide ring with enhanced regioselectivity of the type required for the introduction of prostaglandin ω-chains.[3,4] Since the epoxybicyclo[3.2.0]heptanone acetal (7) has clear similarities both to the ketone (3) [1] and to the previously obtained lactone (6) [2] it became our next synthetic objective.

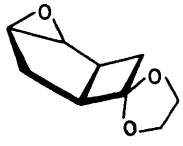
Initially it proved troublesome to prepare the spiro-acetal (5) of the cyclobutanone (3) using ethane-1,2-diol, and this was unexpected since related ketones have been reported to react efficiently with this reagent; [5] because of this, and also because the dithioacetal group could be readily removed from the dithio analogue (4), this compound was used in model studies. Several attempts to displace the sulphonyloxy group directly gave mixed products, but when the triester was treated with potassium carbonate in dry methanol it afforded specifically (t.l.c., ^{1}H n.m.r. evidence) the crystalline epoxide (8) (Scheme) which, with sodium iodide in the presence of toluene-*p*-sulphonic acid, also gave a single product. This, on benzoylation, afforded the iodo dibenzoate (9), and hydrolysis of the dithioacetal ring gave the crystalline iodo ketone (10) which, on Baeyer–Villiger oxidation, afforded the iodo lactone (11) which we have encountered twice previously [1,2] as a synthetic precursor of the epoxy lactone (6). This sequence therefore establishes the structure of the epoxide (8) and shows that it did not rearrange under the basic conditions of its formation as was possible through the presence of the hydroxy group *trans*-related to the three-membered ring.[6] Previously it has been found that *endo*-2,3-epoxide rings fused within bicyclo[3.2.0]heptanes undergo preferential ring opening by *exo*-nucleophilic attack at the site nearer the ring junction,[3,4] and the present results are consistent with this. While 'diaxial ring opening' has been invoked to account for this observation,[3] this explanation requires the assumption of a specific envelope conformation by the cyclopentane ring, and it is not apparent that the transition state (8a), leading to the observed product in the present case, should be strongly favoured. It does, however, give rise to products without involving increased interactive strain between the developing hydroxy group and the cyclobutyl ring atoms, and



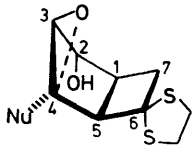
(1) R^1 = COMe, R^2 = H
(2) R^1 = OH, R^2 = H
(3) R^1R^2 = O
(4) R^1R^2 = $-SCH_2CH_2S-$
(5) R^1R^2 = $-OCH_2CH_2O-$



(6)



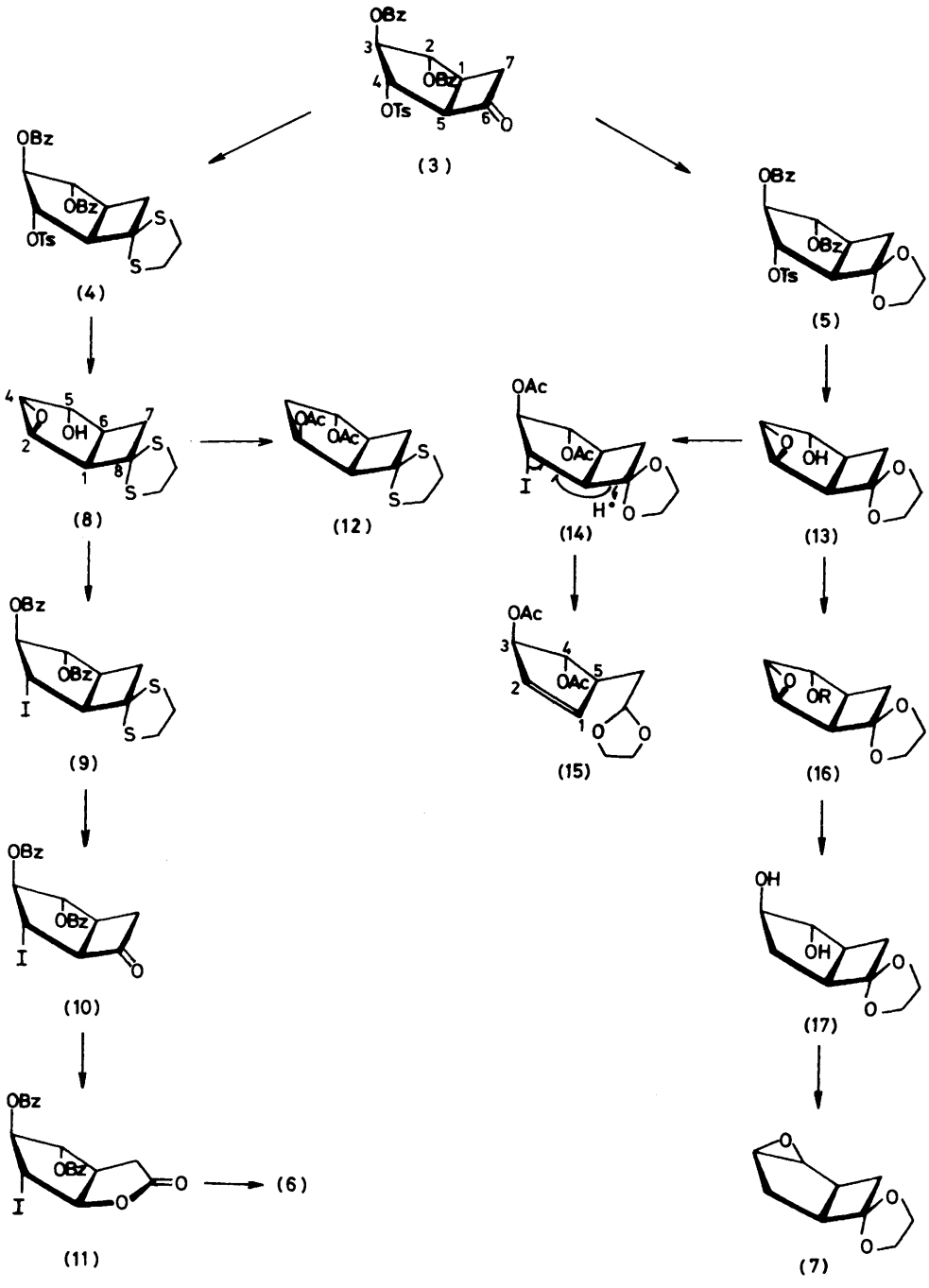
(7)



(8a)

the higher selectivity found for compound (8) than is reported for the dioxolane (7) is in keeping with this explanation since the *endo*-sulphur atom adjacent to the epoxide ring would further inhibit the production of a compound having an *endo*-hydroxy group at C-4. The presence of the hydroxy group at C-2 can also be invoked as a factor inhibiting nucleophilic attack at C-3.

In the hope that the epoxide (8) would react with lithium aluminium hydride to give the required 2,3-diol, the reduction was carried out and the product was acetylated. The ester gave a ^{1}H n.m.r. spectrum which indicated that a diol had been produced as required, but the two ester ring-protons were not coupled, which suggests that the ester groups were at C-2 and C-4 and thus that deoxygenation had occurred at C-3 and that the product was the diacetate (12). This can be accounted for by nucleophilic ring opening by hydride complexed by the hydroxy group at C-2, and thus directed to attack at the adjacent position. The coupling exhibited by the lower field ring ester proton of compound (12) (10.4, 7.3, and 7.3 Hz) is quite inconsistent with values found for many *endo*-protons at C-2 or C-4 in compounds of the present series. This is consistent with the oxygenated group at C-4 of compound (12) having been produced from the epoxide (8) by nucleophilic attack at C-3 and having the *endo*-configuration.



Scheme.

With important aspects of the reactivity of compounds (4) and (8) established, attention was turned to the dioxolane (5) which was prepared in high yield by use of bis(trimethylsilyl)ethane-1,2-diol with trimethylsilyl trifluoromethanesulphonate as catalyst.[7] Conversion into the crystalline epoxide (13) was uneventful and this, on treatment with sodium iodide in the presence of toluene-*p*-sulphonic acid, gave an iodo product which was converted into the diacetate (14) and treated with tributyltin hydride. Previously,[2] compound (11) had been efficiently converted into the corresponding deoxy epoxide (6) by initial deiodination with this reagent, but the iodo diacetate (14) reacted differently affording two products, one of which had ^{1}H and ^{13}C n.m.r. spectra consistent with it being the cyclopentene (15), and the other was a related, unsaturated diacetate. A proposed mechanism for the formation of the first product is shown in the Scheme and is a radical analogue of the reaction by which the cyclobutanol (2), under basic conditions, undergoes cleavage of the C-5–C-6 bond and loss of the C-4 substituent with formation of a cyclopentene ring system.[1]

Alternative methods therefore were sought to open the epoxide ring of compound (13), and direct reduction with lithium aluminium hydride was precluded on the grounds of the experience gained with the analogous epoxide (8). Compound (13) was therefore converted into the t-butyldimethylsilyl ether (16) which, on treatment with lithium aluminium hydride, opened in the anticipated fashion to give a silyl ether which, on mild acid-catalysed hydrolysis, gave the diol (17). By analogy with the reaction undergone by the analogous 6,7-diol derived from compound (11), it was anticipated that compound (17) would be converted with high efficiency into the required epoxide (7) on treatment with tosylimidazole.[2] However, when treated with this reagent or with 2,4,6-triisopropylphenylsulphonylimidazole [8] it gave the expected product (7) and a second product, believed to be the alternative *exo*-epoxide, in a *ca.* 1 : 1 ratio.* Treatment of the diol (17) with diethyl azodicarboxylate and triphenylphosphine appeared to give the *exo*-epoxide specifically, in agreement with previous findings.[2]

The required epoxide (7) had a complex, highly specific ^{1}H n.m.r. spectrum which was identical to that obtained for the racemic compound [4] and supplied through the courtesy of Drs. R. F. Newton and S. M. Roberts of Glaxo Ltd.

Experimental

The n.m.r. spectra were measured in deuteriochloroform solution with a Varian FT 80A instrument and the optical rotations in chloroform within the concentration range 0.5—2%. Light petroleum refers to that fraction boiling in the range 60—80 °C.

(1S,5R)-2-exo,3-endo-*Dibenzoyloxy*-4-exo-*tosyloxyspiro*-{*bicyclo*[3.2.0]*heptane*-6,2′-[1,3]-*dithiolane*} (4).—The ketone (3) (880 mg) was stirred for 10 min at 0 °C in dichloromethane (10 ml) in the presence of ethane-1,2-dithiol and catalytic boron trifluoride–diethyl ether (0.2 ml), and then for 2 h at 20 °C. Further dichloromethane was added and the solution was washed successively with aqueous potassium hydroxide solution and water. After the organic phase had been dried the solvent was removed and the *dithiolane* (4) (910 mg, 99%) was crystallised twice from ethyl acetate–light petroleum, m.p. 94—95 °C; $[\alpha]_D$ +22° (Found: C, 60.4; H, 4.7; S, 16.1. $C_{30}H_{28}O_7S_3$ requires C, 60.4; H, 4.7; S, 16.2%); δ 2.30 (3 H, s, $C_6H_4CH_3$), 2.8—3.1 (2 H, m, 7-H_2), 3.3 (1 H, m, 1-H), 3.29 and 3.31 (together 4 H, 2 × s, 2 × CH_2S), 3.5 (1 H, m, 5-H), 5.27 (1 H, dd, $J_{4,5}$ 2.3, $J_{3,4}$ 4.0 Hz, 4-H), 5.60 (1 H, dd, $J_{2,3}$ 3.5, $J_{1,2}$ 2.0 Hz, 2-H), 5.74 (1 H, t, 3-H), and 7.1—8.1 (14 H, ArH).

(1′R,2′R,4′S,5′R,6′S)-5′-*Hydroxy*-3′-*oxaspiro*{[1,3]-*dithiolane*-2,8′-*tricyclo*[4.2.0.0^{2,4}]*octane*} (8).—The triester (4) (230 mg) was shaken in methanol–dichloromethane (16 ml; 1 : 3) with potassium carbonate (200 mg) at 20 °C for 30 min and the mixture was then filtered through Celite. The solvent was removed, the residue was dissolved in chloroform, and the solution was washed with saturated aqueous sodium chloride. The aqueous phase was back-extracted with chloroform (× 3) and the combined chloroform solutions were dried and the solvent was removed. Preparative t.l.c. (p.l.c.) of the residue gave the *epoxide* (8) (70 mg, 86%) which was crystallised from ethyl acetate–light petroleum, m.p. 85—86 °C; $[\alpha]_D$ +131° (Found: C, 50.3; H. 6.2; S, 30.0. $C_9H_{12}O_2S_2$ requires C, 50.0; H, 5.6; S, 30.0%); δ_H 1.8 (1 H, s, OH), 2.4—2.8 (3 H, m, 6′-H and 7′-H_2), 3.1—3.3 (5 H, s and m, 2 × CH_2S and 1′-H), 3.65—3.75 (2 H, m, 2′- and 4′-H), and 4.14 (1 H, s, 5′-H).

(1S,5S)-2-exo,3-endo-*Dibenzoyloxy*-4-exo-*iodospiro*{*bicyclo*[3.2.0]*heptane*-6,2′-[1,3]-*dithiolane*} (9).—A solution of the crude epoxide (8), prepared from the triester (4) (300 mg), in acetonitrile (2 ml) was cooled to 0 °C and stirred, and sodium iodide (0.2 g) and toluene-*p*-sulphonic acid monohydrate (0.15 g) were added. The mixture was stirred at 20 °C for 1 h, pyridine (3 ml) and benzoyl chloride (0.5 ml) were then added, and the solution was kept at 20 °C for 15 h. Chloroform was added and the solution was washed successively with dilute hydrochloric acid, aqueous sodium hydroxide, and water and, after being dried, was evaporated to give the *iodo dibenzoate* (9) (270 ml, 97%). Purification by p.l.c. gave the product (188 mg, 68%), $[\alpha]_D$ 0° (Found: C, 50.3; H, 4.0; I, 23.2; S, 11.8. $C_{23}H_{21}IO_4S_2$ requires C, 50.0; H, 3.8; I, 23.0; S, 11.6%); δ_H 2.95 (2 H, m, 7-H_2), 3.1—3.4 (5 H, m, 2 × CH_2S and 1-H), 3.65 (1 H, m, 5-H), 4.91 (1 H, t, $J_{4,5} = J_{3,4}$ 4.5 Hz, 4-H), 5.32 (1 H, dd, $J_{2,3}$ 3.2, $J_{1,2}$ 1.1 Hz, 2-H), 5.96 (1 H, dd, 3-H), and 7.2—8.1 (10 H, ArH).

(1S,5S)-2-exo,3-endo-*Dibenzoyloxy*-4-exo-*iodo*-6-*oxobicyclo*[3.2.0]*heptane* (10).—The iodinated thioacetal (9) (45 mg) in acetone (2 ml) containing water (0.25 ml) was stirred with *N*-iodosuccinimide (0.1 g) and cadmium carbonate (0.1 g) for 20 min at 20 °C. The products were partitioned between chloroform and aqueous sodium hydrogen sulphite and the material in the organic phase was passed through a short column of silica gel to give the *iodo ketone* (10) (36 mg, 93%) which was recrystallised from ethyl acetate–light petroleum, m.p. 128—130 °C; $[\alpha]_D$ +169° (Found: C, 52.9; H, 3.8. $C_{21}H_{17}IO_5$ requires C, 52.9; H, 3.6); δ_H 3.0—3.6 (3 H, m, 1-H and 7-H_2), 4.2 (1 H, m, 5-H), 4.69 (1 H, s, 4-H), 5.57 (1 H, s, 2-H) and 6.00 (1 H, s, 3-H).

(1R,5R)-6-exo,7-endo-*Dibenzoyloxy*-8-exo-*iodo*-3-*oxo*-2-*oxabicyclo*[3.3.0]*octane* (11).—The iodo ketone (10) (14 mg) was treated in 70% aqueous acetic acid (1 ml) with 30% hydrogen peroxide (0.1 ml) at 0 °C for 2 h and at 20 °C for 3 h. The solvent was removed to leave the iodo lactone which, after purification by p.l.c. and crystallisation from ethanol, had m.p. and mixed m.p. 162—164 °C, $[\alpha]_D$ +11° (lit.,[9] m.p. 162—164 °C; $[\alpha]_D$ +11°); the ^{1}H n.m.r. spectrum was identical to that of previous samples.

Treatment of the Epoxide (8) *with Lithium Aluminium Hydride.*—The epoxide (10 mg) was shaken in diethyl ether (1 ml) for 4 h with lithium aluminium hydride (10 mg). Excess of hydride was destroyed with ethyl acetate and the mixture was filtered through Celite. The solvent was removed and the residue was acetylated with acetyl chloride in pyridine. The product gave a ^{1}H n.m.r. spectrum with the following features: δ_H 2.01 and 2.10 (total 6 H, 2 × s, 2 × Ac), 2.2—2.9 (5 H, m, 1-H and 3- and 7-H_2), 3.21 (4 H, s, 2 × SCH_2), 3.5 (1 H, m, 5-H), 4.96 (1 H, d, *J* 4.5 Hz, 2-H), and 5.37 (1 H, dt, *J* 10.4, 7.3, and 7.3 Hz, 4-H). This is consistent with the compound being the diacetate (12).

(1S,5R)-2-exo,3-endo-*Dibenzoyloxy*-4-exo-*tosyloxyspiro*-{*bicyclo*[3.2.0]*heptane*-6,2′-[1,3]-*dioxolane*} (5).—A solution of the ketone (3) (680 mg), bis(trimethylsilyl)ethane-1,2-diol (1 ml), and trimethylsilyl trifluoromethanesulphonate (0.5 ml) in dichloromethane (8 ml) was stirred under nitrogen for 6 h at 20 °C and was then kept at 4 °C for 15 h. Toluene was added and the solution was washed successively with water (× 2), dilute hydrochloric acid, and aqueous sodium hydrogen carbonate. The solution was then dried and the solvent was

* A method for the specific conversion of the ether (16) into the diol (7) has been devised and will be reported later.

removed to give a solid residue (740 mg, 100%). Recrystallisation from ethyl acetate–light petroleum gave the *acetal* (5) (85%), m.p. 145—146 °C; $[\alpha]_D$ −5.5° (Found: C, 63.8; H, 5.0; S, 5.8. $C_{30}H_{28}O_9S$ requires C, 63.8; H, 5.0; S, 5.7%); δ_H 2.22 (3 H, s, $C_6H_4CH_3$), 2.7 (3 H, m, 1-H and 7-H_2), 3.3 (1 H, m, 5-H), 4.00 (4 H, s, 2 × CH_2O), 5.25 (2 H, m, 2- and 4-H), 5.85 (1 H, t, $J_{2,3} = J_{3,4}$ 5.8 Hz, 3-H), and 7.0—8.0 (14 H, ArH).

(1'R,2'R,4'S,5'R,6'S)-5'-*Hydroxy*-3'-*oxaspiro*{[1,3]-*dioxolane*-2,8'-*tricyclo*[4.2.0.$0^{2,4}$]*octane*} (13).—The triester (5) (740 mg) was stirred in methanol–dichloromethane (20 ml; 1 : 1) with potassium carbonate for 1.5 h. Work-up as for compound (8) and purification by flash column chromatography [10] gave the *epoxide* (13) (205 mg, 85%) which was crystallised from ethyl acetate–light petroleum, m.p. 125—126 °C; $[\alpha]_D$ +129° (Found: C, 58.9; H, 6.5. $C_9H_{12}O_4$ requires C, 58.7; H, 6.6%); δ_H 2.1—2.6 (4 H, m, 6'-H, 7'-H_2, and OH), 3.06 (1 H, m, 1'-H), 3.60 (1 H, t, *J* 2.4 Hz, 2'-H), 3.70 (1 H, br s, 4-H), 3.93 (4 H, s, 2 × CH_2O), and 4.13 (1 H, s, 5'-H).

Reaction of the Epoxide (13) *with Iodide, and the Deiodination of Compound* (14).—A solution of the epoxide (50 mg) in acetonitrile was treated at −5 °C with sodium iodide (122 mg) and toluene-*p*-sulphonic acid (52 mg) for 1.5 h to give a chromatographically discrete product which was acetylated in pyridine with acetic anhydride—again to give another discrete product (111 mg) assumed to be the iodo diacetate (14). This was treated in refluxing benzene (5 ml) with tributyltin hydride (200 mg) and a trace of azobisisobutyronitrile for 5 min to give two products which were separated by flash column chromatography.[10] The more mobile (19 mg), assigned structure (15), gave n.m.r. spectra with the following features: δ_H 1.7—2.1 (2 H, m, CH_2), 2.05 and 2.06 (together 6 H, 2 × s, 2 × Ac), 2.8 (1 H, m, 5-H), 3.9 (4 H, m, 2 × CH_2O), 4.9—5.1 (2 H, m, 3- and 4-H), 5.5—5.7 (1 H, m, CH=), and 6.0 (2 H, m, CH= and OCHO); δ_C 21.04 ($COCH_3$), 37.52 (CH_2), 46.34 (C-5), 64.88 and 64.96 (CH_2O), 82.79 and 83.07 (C-3 and -4), 103.06 (OCO), 127.54 (C-1), 138.76 (C-2), and 170.42 p.p.m. ($COCH_3$).

Conversion of the Hydroxy Epoxide (13) *into the Epoxide* (7).—Treatment of the epoxide (13) (40 mg) with t-butyldimethylsilyl chloride (49 mg) in *N*,*N*-dimethylformamide (2 ml) containing imidazole (44 mg) [11] gave the chromatographically more mobile product (16) in 1 h at 20 °C. Toluene was added and the solution was washed with water (× 3) and evaporated to dryness under reduced pressure. The residue was dissolved in diethyl ether (3 ml) and lithium aluminium hydride (40 mg) was added. The mixture was stirred and complete reaction to give a less mobile product occurred after 3 h at 20 °C. Excess of hydride was destroyed with ethyl acetate and a little water, and the mixture was filtered through Celite and the solvent was removed. The residue was then desilylated by being kept at 35 °C for 5 h in acetic acid–water–tetrahydrofuran (5 ml; 2 : 1 : 1) and was purified by flash column chromatography to give the diol (17) (22 mg, 55%), $[\alpha]_D$ +150°; δ_H 2.1—2.35 (3 H, m, 1-H and 4-H_2), 2.45—2.55 (2 H, m, 7-H_2), 3.1 (1 H, m, 5-H), 3.92 (4 H, s, 2 × CH_2O), and 4.04 and 4.19 (together 2 H, 2 × s, 2- and 3-H). The derived diacetate gave the following ^{1}H n.m.r. resonances: δ_H 2.03 and 2.08 (together 6 H, 2 × s, 2 × Ac), 2.0—2.2 (3 H, m, 1-H and 4-H_2), 2.53 (2 H, m, 7-H_2), 2.9 (1 H, m, 5-H), 3.85 (4 H, m, 2 × CH_2O), and 5.04 (2 H, m, 2- and 3-H).

A solution of the diol (17) (37 mg) in *N*,*N*-dimethylformamide (1 ml) was added to a stirred suspension of sodium hydride in this solvent (2 ml) at 0 °C and the mixture was stirred for 20 min. After the mixture was cooled to −50 °C a solution of 2,4,6-tri-isopropylphenylsulphonylimidazole (66 mg) in the same solvent (1 ml) was added dropwise. The mixture was stirred at this temperature for 20 min, at −30 °C for 30 min, and the mixture was allowed to attain room temperature. The products (two in similar proportions) were extracted into dichloromethane, after the addition of water, and were separated by flash column chromatography. The slower product (4.2 mg, 13%) had $[\alpha]_D$ +8° and gave an identical ^{1}H n.m.r. spectrum to that of an authentic sample of the epoxide (7).[4]

Acknowledgements

We thank Ramkhamhaeng University, Bangkok, and the New Zealand Ministry of Foreign Affairs for the award (to P. P.) of leave of absence and of a Bilateral Aid Programme Post Graduate Scholarship. The work was assisted by a grant from the Wellington Medical Research Foundation.

References

1 Part 4, R. J. Ferrier and P. Prasit, preceding paper.
2 R. J. Ferrier, P. Prasit, and G. J. Gainsford, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1629.
3 R. F. Newton and S. M. Roberts, *Tetrahedron*, 1980, **36**, 2163.
4 R. J. Cave, C. C. Howard, G. Klinkert, R. F. Newton, D. P. Reynolds, A. H. Wadsworth, and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2954.
5 R. F. Newton, C. C. Howard, D. P. Reynolds, A. H. Wadsworth, N. M. Crossland, and S. M. Roberts, *J. Chem. Soc., Chem. Commun.*, 1978, 662.
6 N. R. Williams, *Adv. Carbohydr. Chem. Biochem.*, 1970, **25**, 109.
7 T. Tsunoda, M. Suzuki, and R. Noyori, *Tetrahedron Lett.*, 1980, **21**, 1357.
8 Yu. A. Berlin, O. G. Chakhmakhcheva, V. A. Efimov, M. N. Kolosov, and V. G. Korobko, *Tetrahedron Lett.*, 1973, 1353.
9 R. J. Ferrier and P. Prasit, *J. Chem. Soc., Chem. Commun.*, 1981, 983.
10 W. C. Still, M. Kahn, and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.
11 E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190.

Received 3rd *August* 1982; *Paper* 2/1358