Stereo-controlled Synthesis of Prostaglandin Synthons [1]

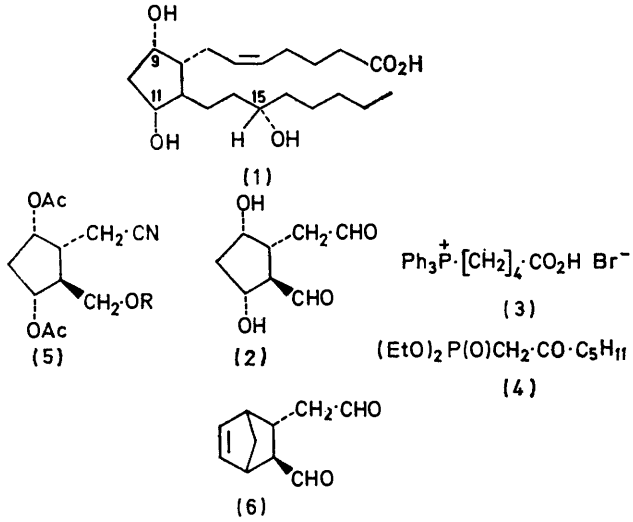
By **Geraint Jones,* Ralph A. Raphael,** and **Susan Wright,** Imperial Chemical Industries Limited, Pharmaceuticals Division, Alderley Park, Macclesfield SK10 4TG, and Department of Chemistry, University of Cambridge, Cambridge CB2 1EW

Novel cyclopentanoid precursors [(±)-*c*-2-cyanomethyl-*t*-3-methoxymethylcyclopentane-*r*-1,*c*-4-diyl diacetate (22) and (±)-*c*-2-cyanomethyl-*t*-3-triphenylmethoxymethylcyclopentane-*r*-1,*c*-4-diyl diacetate (34)] for the prostanoids have been prepared by oxidative cleavage of 5,6-bisalkoxymethylnorbornenes [(11b) and (26)], and their utility has been demonstrated by conversion into known lactone intermediates [(25) and (35)] for prostaglandin synthesis.

A RETROSYNTHETIC analysis of the problem of a flexible prostaglandin synthesis usually involves carrying out two Wittig type transformations on the 5,6- and 13,14-double bonds, which leads on the one hand to the heavily substituted cyclopentane dialdehyde synthon (2) having all except one of the stereochemical centres of the natural prostanoids already incorporated, and on the other hand to the two synthons (3) and (4) for attaching in turn the respective carboxylic and alkyl side-chains. Schemes based on this analysis have the

[1] Preliminary account, G. Jones, R. A. Raphael, and S. Wright, *J.C.S. Chem. Comm.*, 1972, 609.

flexibility derived from the fact that the side-chains are attached at a late stage to the same basic cyclopentane skeleton, thus offering considerable opportunity for



systematic variation of the side-chains. The mode of selective protection and generation of the key cyclopentane dialdehyde synthon gives rise to a number of alternative approaches.[2a-d] In the approach to be described the potential two-carbon aldehyde group was an ether of the corresponding alcohol and the potential 9- and 11-hydroxy-groups were *O*-acetyl derivatives.

The synthetic strategy for the introduction of the *cis*-9,11-dihydroxy-system was derived from the consideration that a double bond, incorporated in a norbornene system by means of a [2 + 4] Diels–Alder addition reaction with cyclopentadiene, can be a latent source of two carbonyl functions. Such a dicarbonyl compound could be a suitable precursor for the simultaneous regiospecific insertion, by Baeyer–Villiger oxidation, of the 9- and 11-oxygen atoms. These oxygen atoms, thus introduced would bear the same *cis* relationship to the main carbon skeleton as did the original carbon–carbon double bond. A comparison of this synthetic process for incorporating the 9- and 11-oxygen functions with the biosynthetic process,[3] which involves, at least in principle, a cycloaddition of oxygen [4] to a skipped polyenoic acid followed by reductive cleavage of the intermediate dioxonorbornene peroxide, reveals the route's biomimetic origins. Similar considerations have resulted in other prostaglandin syntheses based on norbornene precursors.[5,6]

The problem of synthesising a substituted cyclopentane (2) having four asymmetric centres by this retrosynthetic analysis resolves itself to that of preparing a *trans*-disubstituted norbornene derivative bearing readily distinguishable two-carbon and one-carbon side-chains, potentially at an aldehyde oxidation level. On account of the paucity of dienophiles having differentiable two-carbon and one-carbon pendant groups and the great wealth of dienophiles having two single-carbon appendages, we decided to introduce the two-carbon side-chain by sequential addition of two single-carbon units. We now describe the execution of the foregoing synthetic plan.

A Diels–Alder reaction between cyclopentadiene and β-formylacrylic acid pseudo-ester, a photorearrangement product of furfuraldehyde, gave exclusively in an exothermic reaction at room temperature the *cis,endo*-norbornene (7). The ester acetal (8),[7] having two readily distinguishable single-carbon *trans*-oriented side-chains, was prepared from the *cis*-Diels–Alder adduct (7) by epimerisation of the aldehydic carbon atom with acidic methanol under reflux. Thus, two stereochemical centres present in the final prostaglandin molecule were stereospecifically introduced.

As a preliminary experiment the oxidative cleavage of norbornene (15) itself was investigated. This was satisfactorily cleaved to the dialdehyde (16) with osmium tetraoxide and sodium periodate in aqueous dioxan. The dialdehyde was converted by treatment with an excess of methylmagnesium iodide and Jones oxidation into 1,3-diacetylcyclopentane (17). Baeyer–Villiger oxidation of the diketone with *m*-chloroperbenzoic acid was very slow. A rapid oxidation was observed when buffered trifluoroperacetic acid [8] was used as oxidant. The oxidation proceeded with no competing migration of the methyl groups and with complete retention of configuration at the migrating centres, yielding exclusively *cis*-1,3-diacetoxycyclopentane (18).

The cleavage sequence, thus established, made stringent demands on the range of usable protecting groups and it was apparent that ether groups offered the best prospect of surviving the requirements of this reaction path. Suitable protection of the two oxygen functions in the ester acetal (8) by ether formation was necessary. Reduction of the ester acetal (8) with lithium aluminium hydride gave the alcohol (9), which was freed from diolic impurities by filtration through silica gel. Benzylation of the alcohol gave the benzyl ether (10). Hydrolysis of the benzyl ether in 40% aqueous dioxan and sulphuric acid followed by reduction with lithium aluminium hydride and methylation gave,

[2] (*a*) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 5675; (*b*) D. Brewster, M. Myers, J. Ormerod, M. E. Spinner, S. Turner, and A. C. B. Smith, *J.C.S. Chem. Comm.*, 1972, 135; (*c*) I. Ernest, R. J. Friary, J. Gosteli, G. Nestler, H. Raman, R. Sitrin, Ch. Suter, J. K. Whitesell, and R. B. Woodward, *J. Amer. Chem. Soc.*, 1973, **95**, 6853; (*d*) J. K. Sutherland and R. Peel, Third International Symposium of the Chemical Society, 1973.

[3] D. A. van Dorp, R. K. Beerthuis, D. H. Nugteren, and H. Vonkeman, *Biochim. Biophys. Acta*, 1964, **90**, 204; S. Berstrom, H. Danielsson, and B. Samuelsson, *ibid.*, p. 207.

[4] E. J. Corey, G. W. J. Fleet, and M. Kato, *Tetrahedron Letters*, 1973, 3963.

[5] D. Brewster, M. Myers, J. Ormerod, P. Otter, A. C. B. Smith, M. E. Spinner, and S. Turner, *J.C.S. Perkin I*, 1973, 2796.

[6] J. Katsube, H. Shimomura, and M. Matsui, *Agric. and Biol. Chem. (Japan)*, 1971, **35**, 1828.

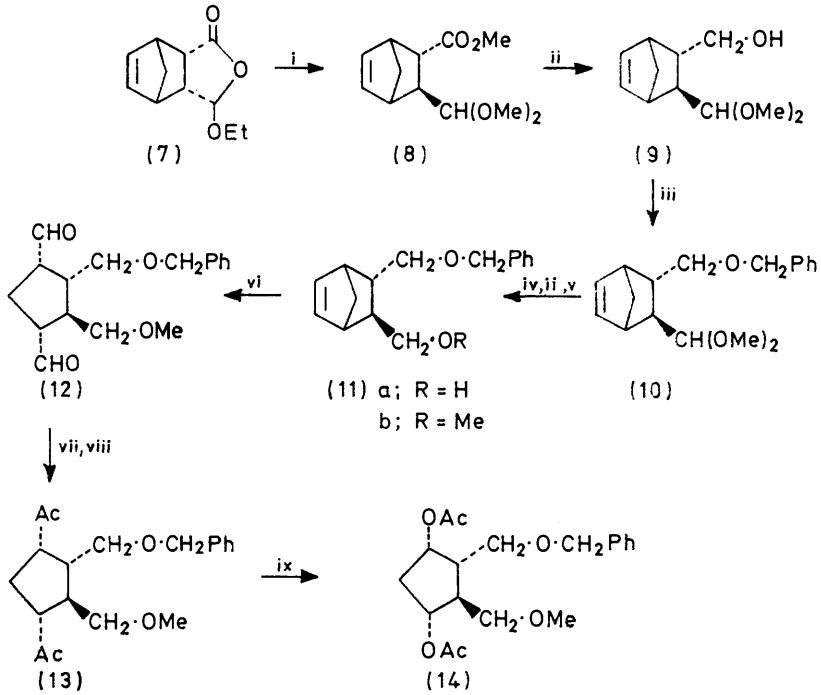
[7] V. M. Andreev and A. V. Usova, *Izvest. Akad. Nauk S.S.S.R., Ser. khim.*, 1966, 4273.

[8] W. D. Emmons and G. B. Lucas, *J. Amer. Chem. Soc.*, 1955, **77**, 2287.

after distillation, the benzyl methyl diether (11b) in 83% overall yield from the benzyl ether acetal (10).

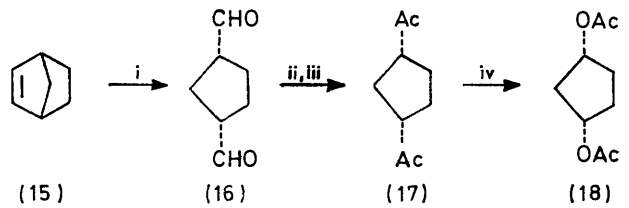
The benzyl methyl diether (11b) was cleaved by a series of reactions analogous to those described for the model series, and gave the diacetate (14) in 28% overall yield from the diether (11b). A cyclopentanoid derivative bearing the four stereochemical centres found in natural prostaglandins was thus available.

The primary and secondary acetates could be separated by chromatography on silica gel and were characterised individually by spectroscopic methods. The purified secondary acetate, however, even when kept in glass vessels at room temperature, rapidly reverted to an equilibrium mixture of both acetates. As only the secondary acetate (19) is potentially convertible into a prostanoid, any primary acetate was discarded.



Reagents: i, MeOH–H_2SO_4; ii, $LiAlH_4$–Et_2O; iii, $PhCH_2Br$–NaH–$(MeO{\cdot}CH_2)_2$; iv, dioxan–H_2SO_4 aq.; v, MeI–NaH–$(MeO{\cdot}CH_2)_2$; vi, OsO_4–$NaIO_4$–aq. dioxan; vii, MeLi; viii, Jones reagent; ix, $CF_3{\cdot}CO_3H$–Na_2HPO_4–CH_2Cl_2

The introduction of the single-carbon residue which would ultimately become C-6 (prostaglandin numbering) of the prostaglandin molecule was next investigated. It was anticipated that this could be achieved by debenzylation, tosylation, and displacement of the

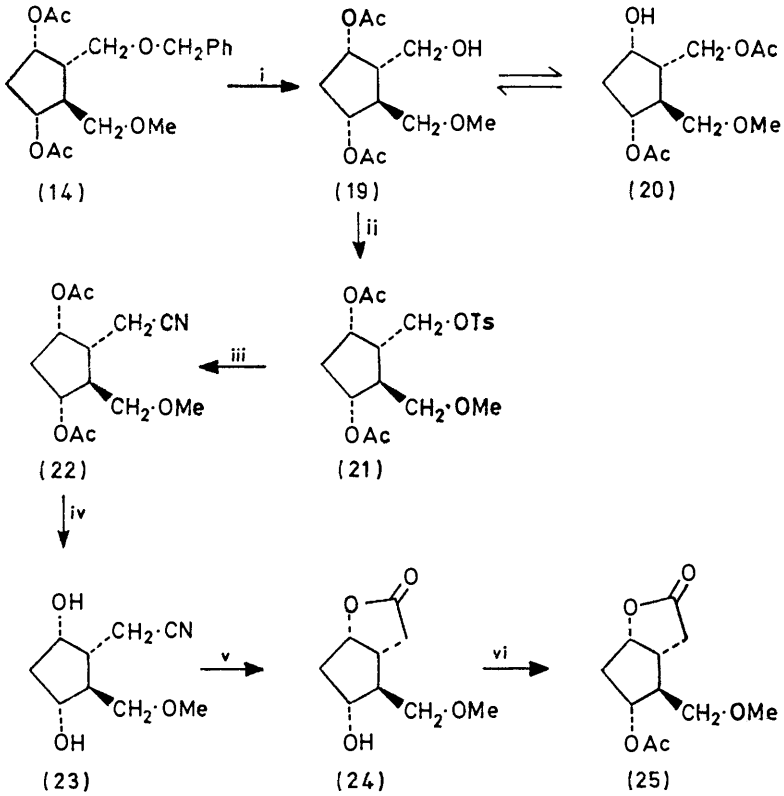


Reagents: i, OsO_4–$NaIO_4$–aq. dioxan; ii, MeMgI; iii, Jones reagent; iv, $CF_3{\cdot}CO_3H$–Na_2HPO_4–CH_2Cl_2

tosylate group with cyanide ion, without undue interference from the potentially competing 1,3-acetate shift. Thus the benzyl group was removed from the diester (14) under rigorously controlled neutral conditions with 5% palladium–carbon in ethanol. The presence of acid or base catalysed the easy rearrangement of the secondary acetate to the primary acetate (20), and an equilibrium mixture (40 : 60 by n.m.r.) was obtained.

In face of the difficulties raised by the acetate rearrangement, the one-carbon unit was incorporated in modest overall yield (25%) by tosylation of the secondary acetate (19) in pyridine solution and displacement of the resulting tosylate with cyanide ion in dimethyl sulphoxide.

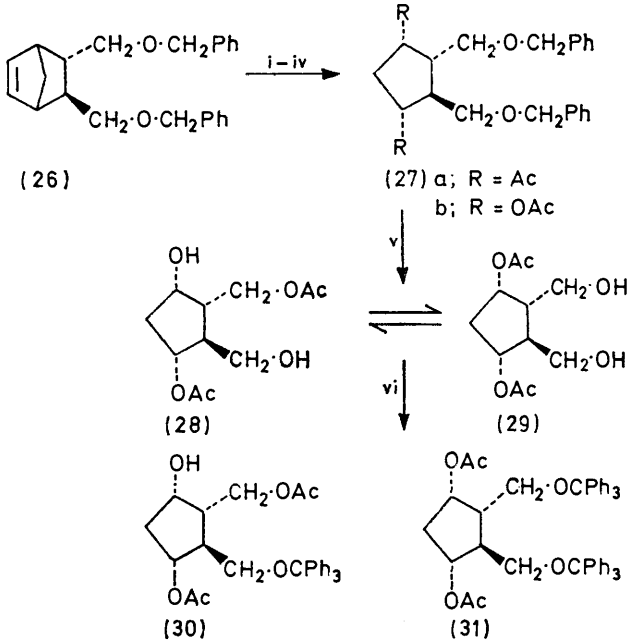
The utility of this intermediate nitrile (22) as a prostaglandin synthon was most readily demonstrated by its conversion into the lactone acetate [2a] (25), whose transformation into natural prostaglandins has been described by the Harvard group. This procedure would not be part of the most direct route to the prostanoids, but the link-up with the lactone acetate (25) offered a ready method of rapidly confirming the stereochemical and structural assignments made so far and also of formally completing the synthesis. Alkaline hydrolysis of the ester functions in the nitrile (22) with potassium carbonate in methanol, followed by hydrolysis of the nitrile group with concentrated hydrochloric acid, gave directly the hydroxy-lactone (24) in 93% yield. Acetylation gave, in 96% yield, the acetoxy-lactone (25), identical (t.l.c.; n.m.r. and i.r. spectroscopy) with the authentic material.



Reagents: i, 5% Pd/C–H_2–EtOH; ii, TsCl–pyridine; iii, NaCN–Me_2SO; iv, K_2CO_3–MeOH; v, conc. HCl; vi, Ac_2O

The foregoing synthesis can undoubtedly be made more efficient. An inordinate amount of synthetic energy is expended in constructing the relatively simple unsymmetrically substituted norbornene *trans* benzyl methyl diether (11b). Even though these stages are all relatively efficient a more direct route utilising a symmetrically substituted norbornene diether and postponing differentiation until a later stage could have advantages. The troublesome acetate shift could then be used to advantage as a means of distinguishing between the primary alcoholic functions on the two faces of the cyclopentane ring. Thus, the conversion of an accessible symmetrically substituted norbornene derivative into a useful prostaglandin synthon offered an attractive solution and is now considered.

trans-5,6-Bis(benzyloxymethyl)bicyclo[2.2.1]hept-2-ene (26) was prepared by direct benzylation of the known diol.[9] The dibenzyl ether was conveniently cleaved by reductive ozonolysis to the dialdehyde. The crude dialdehyde was treated immediately with an excess of methyl-lithium in ether to yield the diol mixture, which was oxidised with Jones reagent to the diketone (27a). Baeyer–Villiger oxidation of the diketone gave the diacetate (27b). The benzyl groups were removed with 5% palladium–carbon in ethanol and the acetate rearrangement, which enables a distinction to be made between the two primary alcoholic functions, was brought about by refluxing the diol in pyridine. The equilibrium mixture thus obtained in 90% overall yield, consisting of the primary acetate (28) (60%) and the secondary acetate (29) (40%) (n.m.r.), was treated with triphenylmethyl chloride to give the

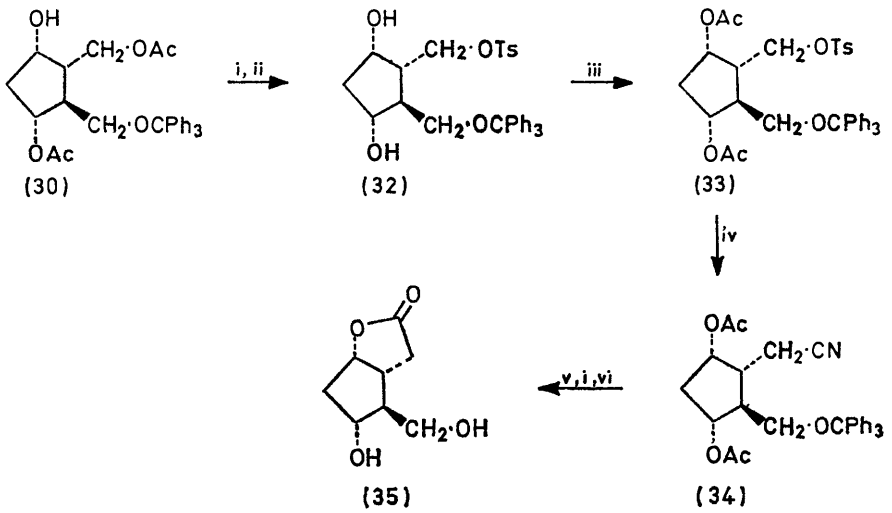


Reagents: i, O_3 or OsO_4–$NaIO_4$ aq. dioxan; ii, MeLi; iii, Jones oxidation; iv, $CF_3{\cdot}CO_3H$–Na_2HPO_4–CH_2Cl_2; v, 5% Pd/C–H_2–EtOH; vi, Ph_3CCl–pyridine

[9] M. Hara, Y. Odaira, and S. Tsutsumi, *Tetrahedron*, 1866, **22**, 95.

bistriphenylmethoxy-derivative (31) and the diacetate (30) in 44% overall yield from the dibenzyl ether (27). Thus, the primary alcoholic functions on the two faces of the cyclopentane ring were differentiated and a crystalline intermediate (30) was obtained.

The synthesisof a prostaglandin synthon from a symmetrically substituted norbornene derivative could thus be completed by the addition of the one-carbon unit as a nitrile group. Deacetylation of the diacetate (30) with potassium carbonate gave a triol, which was selectively tosylated on the single primary alcoholic function. The oily monotosylate (32) was reacetylated and the tosyl group was displaced with cyanide ion, yielding the key prostanoid intermediate nitrile (34).



Reagents: i, K_2CO_3–MeOH; ii, TsCl–pyridine; iii, Ac_2O; iv, NaCN–Me_2N·CHO; v, 80% AcOH–H_2O;] vi, conc. HCl

In order formally and rapidly to complete this synthesis the intermediate nitrile was converted by detritylation (80% AcOH–H_2O; 25°) followed by deacetylation and hydrolysis of the nitrile function to afford directly the lactone diol (35), which has been elaborated to a natural prostaglandin by the Harvard group.[10]

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. I.r. spectra (for thin films in the case of oils and for Nujol mulls in the case of solids) were recorded with a Perkin-Elmer 157 spectrophotometer. N.m.r. spectra were obtained with a Varian A60 or HA100 spectrometer for solutions in deuteriochloroform. Mass spectra were obtained with an A.E.I. MS9 double-focusing spectrometer operating at 70 eV.

3-Dimethoxymethylbicyclo[2.2.1]*hept-5-en-2-ylmethanol* (9).—A solution of the crude ester (8) (39·5 g) [7] in ether (150 ml), was added slowly with stirring to a suspension of lithium aluminium hydride (10 g) in ether (21). Stirring was then continued for 1 h. Saturated ammonium chloride solution was added dropwise until a granular precipitate had formed. The solution was filtered, dried ($MgSO_4$), and evaporated (32·1 g). Chromatography on Florisil gave the pure *alcohol* (21·2 g) (61%). Distillation gave a sample of b.p. 98° at 0·6 mmHg (Found: C, 67·0; H, 9·0. $C_{11}H_{18}O_3$ requires C, 66·6; H, 9·1%), $\nu_{max.}$ 3390 (OH) and 3040 (norbornene CH) cm^{-1}, τ ($CDCl_3$) 3·86 (1H, q, =CH), 4·05 (1H, q, =CH), 5·83 [1H, d, J 4·2 Hz, C*H*$(OMe)_2$], 6·63 (s) and 6·72 (s) [$CH(OCH_3)_2$], 6·5—7·5 (5H, complex), 8·06 (1H, complex, H-5), and 8·5—8·8 (3H, complex, H-7a, H-7b, and H-6).

5-Benzyloxymethyl-6-dimethoxymethylbicyclo[2.2.1]*hept-2-ene* (10).—A solution of the alcohol (9) (31·2 g) in 1,2-dimethoxyethane (50 ml) was added to a suspension of oil-free sodium hydride (10·2 g) in 1,2-dimethoxyethane (250 ml) under nitrogen. The mixture was stirred at room temperature for 1 h, benzyl bromide (28·4 g) was added, and the mixture was refluxed on a steam-bath for 16 h. Sodium carbonate solution (10% w/v; 50 ml) was added cautiously and the product was extracted into ether (×4). The extract was washed with water (×2), dried, and evaporated (yield 44·4 g, 98%). Distillation gave a *sample* of b.p. 155—158° at 0·05 mmHg (Found: C, 74·8; H, 8·2%; M^+, 288·172. $C_{18}H_{24}O_3$ requires C, 75·0; H, 8·45%; M, 288·1725), $\nu_{max.}$ 3040 cm^{-1} (norbornene CH), τ ($CDCl_3$) 2·73 (5H, complex, ArH), 3·90 (1H, q, =CH), 4·10 (1H, q, =CH), 5·60 (2H, q, O·CH_2Ar), 5·86 [1H, d, J 8·0 Hz, C*H*$(OMe)_2$], 6·72 (s) and 6·75 (s) [$CH(OCH_3)_2$], 6·2—7·5 (4H, complex), 7·92 (1H, complex, H-2), and 8·5—9·0 (3H, complex, H-7a, H-7b, and H-3).

3-Benzyloxymethylbicyclo[2.2.1]*hept-5-en-2-ylmethanol* (11a).—A solution of the ether acetal (10) (84·4 g) in dioxan (1 l) was treated with aqueous (650 ml) sulphuric acid (9 ml) and refluxed on a steam-bath for 1 h. The solution was neutralised with sodium carbonate solution (15% w/v) and extracted with ether (×4). The extract was washed with brine, dried ($MgSO_4$), and concentrated to afford the ether aldehyde (75 g), $\nu_{max.}$ 2720 (CHO) and 1725 cm^{-1}, which was reduced immediately without further purification.

A solution of the aldehyde ether (75 g) in ether (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (5 g) in ether (1000 ml). The solution

[10] E. J. Corey, H. Sherahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *J. Amer. Chem. Soc.*, 1971, **93**, 1490.

was then stirred for a further 30 min and set aside overnight. Saturated aqueous ammonium chloride was added slowly until a granular precipitate separated. The ethereal suspension was filtered and the solution was washed with brine, dried ($MgSO_4$), and evaporated (72·2 g). Distillation gave a *sample* of b.p. 155—160° at 0·1 mmHg (Found: C, 78·5; H, 8·0. $C_{16}H_{20}O_2$ requires C, 78·65; H, 8·25%), $\nu_{max.}$ 3333 (OH), and 3030 (norbornene CH) cm^{-1}, τ ($CDCl_3$) 2·73 (5H, complex, ArH), 3·81 (1H, q, =CH), 4·10 (1H, q, =CH), 5·54 (2H, s, O·CH_2Ph), 6·2—7·5 (7H, complex), 8·06 (1H, complex, H-6), and 8·5—8·9 (3H, complex, H-7a, H-7b, and H-5).

5-Benzyloxymethyl-6-methoxymethylbicyclo[2.2.1]*hept-2-ene* (11b).—A solution of the alcohol (11a) (72·2 g) in 1,2-dimethoxyethane (50 ml) was added to a stirred suspension of oil-free sodium hydride (26·7 g) in 1,2-dimethoxyethane (600 ml) under nitrogen. The mixture was stirred for 1 h at room temperature, then methyl iodide (93 ml) was added dropwise. After the reaction had subsided, water was added cautiously, and the product was extracted into ether (×4). The extract was washed with brine, dried ($MgSO_4$), and evaporated (yield 71·9 g). Distillation gave a fraction of b.p. 112—116° at 0·05 mmHg [62·7 g, 83% from (10)] which consisted of the *benzyl methyl diether* (Found: C, 78·9; H, 8·6%; M^+, 258·1577. $C_{17}H_{22}O_2$ requires C, 79·0; H, 8·6%; *M*, 258·1619), $\nu_{max.}$ 3030 and 3003 (norbornene CH) cm^{-1}, τ ($CDCl_3$) 2·70 (5H, complex, ArH), 3·87 (1H, q, =CH), 4·09 (1H, q, =CH), 5·58 (2H, q, O·CH_2Ph), 6·7 (3H, s, CH_2·OCH_3), 6·4—7·4 (6H, complex), 8·14 (1H complex, H-2), and 8·5—9·0 (3H complex, H-7a, H-7b, and H-3).

Model Cleavage of Norbornene (15).—Osmium tetraoxide (0·5 g) was added to a solution of norbornene (15) (18·8 g, 0·2 mole) in dioxan (400 ml) and water (200 ml). The solution was stirred at room temperature, sodium periodate (96·4 g, 0·45 mol) was added in portions during 15 min, and the temperature was kept below 40 °C with an ice-bath. The mixture was stirred overnight, then filtered, and the solid (sodium iodate) was washed with ether. The combined filtrate and washings were evaporated and the residue was extracted with ether (4 × 300 ml). The extract was washed with brine (50 ml), dried ($MgSO_4$), and evaporated (yield 19·0 g; $\nu_{max.}$ 2720 and 1720 cm^{-1}).

A solution of the resulting dialdehyde (16) (15·0 g) in ether (50 ml) was added at room temperature over 15 min to ethereal methylmagnesium iodide [from magnesium (14·6 g) and methyl iodide (85 g)]. After stirring for 1·5 h, 2N-hydrochloric acid (120 ml) was added. The mixture was extracted with ether (4 × 250 ml) and the extract washed with brine, dried ($MgSO_4$), and evaporated (yield 14·2 g; $\nu_{max.}$ 3350 cm^{-1}). A solution of the residual diol (13·8 g) in acetone (150 ml) was oxidised with Jones reagent [11] (*ca.* 25 ml). The excess of oxidant was destroyed with propan-2-ol and the solvents were evaporated off. The residue was extracted with ether and the extract was washed with brine, dried ($MgSO_4$), and evaporated to leave *trans*-1,3-diacetylcyclopentane (13·8 g, 57%). Distillation gave a sample with b.p. 125—127° at 2·0 mmHg, $\nu_{max.}$ 1715 cm^{-1}, τ ($CDCl_3$) 7·1br (2H, t, C*H*Ac), 7·8—8·2 (6H, complex, CH_2), and 7·88 (6H, s, Ac), *m/e* 154 ($C_9H_{14}O_2$), 139, 136, 112, and 111.

The diketone (17) (1·54 g, 10 mmol) and disodium hydrogen phosphate (6·0 g) was stirred in methylene chloride (10 ml) while a mixture of trifluoroacetic anhydride (15·68 g, 75 mmol) and 90% hydrogen peroxide (1·95 ml, 75 mmol) in methylene chloride (20 ml) was added during 10 min. The mixture was then stirred for 3 h and filtered, and the solid was washed with methylene chloride. The combined filtrate and washings were washed successively with aqueous 10% sodium carbonate and brine, dried ($MgSO_4$), and evaporated to give *cyclopentane*-trans-1,3-*diyl diacetate* (1·6 g, 86%). Preparative g.l.c. gave material of b.p. 100—102° at 0·1 mmHg (Found: C, 57·8; H, 7·8. $C_9H_{14}O_4$ requires C, 58·05; H, 7·6%), $\nu_{max.}$ 1742 cm^{-1}, τ ($CDCl_3$) 4·90br (2H, CH·OAc), 7·85—8·10 (6H, complex, CH_2), and 7·95 (6H, s, OAc).

r-1,c-4-*Diacetyl*-c-2-*benzyloxymethyl*-t-3-*methoxymethylcyclopentane* (13).—Osmium tetraoxide (2 g) was added to a solution of the benzylmethyl diether (11b) (25·8 g) in dioxan (540 ml). The solution was stirred in the dark for 15 min in order to allow the osmate ester to form, and then diluted with distilled water (120 ml). Sodium periodate (54 g) in water (380 ml) was then added over 12 h. The mixture was stirred overnight in the dark. The salts were filtered off and washed with dry ether. The dioxan and ether were removed and the aldehyde was extracted from the aqueous residue with ether (×4). The extract was washed with brine, dried, and evaporated (yield 28·0 g; $\nu_{max.}$ 2720 and 1725 cm^{-1}).

The resulting dialdehyde (28·0 g) was treated immediately without further purification with ethereal methyl-lithium [from lithium (8·4 g) and methyl bromide], and the mixture was stirred for 2 h and decomposed with 2N-hydrochloric acid (*ca.* 250 ml). Extraction with ether gave an ethereal solution which was washed with brine, dried ($MgSO_4$), and evaporated (yield 29·0 g; $\nu_{max.}$ 3400 cm^{-1}).

A solution of the resulting crude diol (29·0 g) in acetone (500 ml) was oxidised with Jones reagent [11] (*ca.* 40 ml). The excess of oxidising agent was destroyed with propan-2-ol and the acetone evaporated off. Extraction with ether gave a solution which was washed with brine, dried, and evaporated to give the *diketone* (26·0 g). Filtration through Florisil followed by distillation gave material of b.p. 175—180° at 0·1 mmHg (Found: C, 71·3; H, 8·3%; M^+, 318·1896. $C_{19}H_{26}O_4$ requires C, 71·7; H, 8·2%; *M*, 318·1831), $\nu_{max.}$ 1715 cm^{-1} (C=O), τ ($CDCl_3$) 2·70 (5H, complex, ArH), 5·68 (2H, s, O·CH_2Ph), 6·70 (3H, s, CH_2·OCH_3), 6·5—8·0 (6H, complex), and 7·83 (s) and 7·87 (s) (6H, Ac).

c-2-*Benzyloxymethyl*-t-3-*methoxymethylcyclopentane*-r-1,c-4-*diyl Diacetate* (14).—Trifluoroperacetic acid [from trifluoroacetic anhydride (172 g) and 90% hydrogen peroxide (21·4 ml)] in methylene chloride (300 ml) was added dropwise, at a rate such as to maintain reflux, to a stirred slurry of the crude diketone (13) (26·0 g), disodium hydrogen phosphate (112·5 g), and methylene chloride (500 ml). The mixture was then stirred for an additional 2 h and the solids were filtered off. The filtrate was washed with sodium carbonate solution (10% w/v) and water, dried ($MgSO_4$), and evaporated (yield 19·0 g). Chromatography on Florisil [elution with petroleum–ether (2 : 1 v/v)] gave the *diacetoxy-ether* [9·8 g, 28% for the four stages from the olefin (11b)]. Distillation gave a sample of b.p. 175—180° 0·2 mmHg (Found: C, 65·1; H, 7·5%; M^+, 350·1694. $C_{19}H_{26}O_6$ requires C, 65·1; H, 7·5%; *M*, 350·1729), $\nu_{max.}$ 1735 cm^{-1} (C=O), τ ($CDCl_3$) 2·70 (5H, s, ArH), 4·77 (1H, complex, C*H*·OAc), 4·97 (1H, complex, C*H*·OAc), 5·54 (2H, q, O·CH_2Ph), 6·3—6·7 (4H, complex, CH_2·OMe and

[11] K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 1946, 39.

CH_2·OCH_2Ph), 6·70 (3H, s, CH_2·OCH_3), 7·6—8·4 (4H, complex, CH), and 8·02 (s) and 8·08 (s) (6H, OAc).

c-2-*Hydroxymethyl*-t-3-*methoxymethylcyclopentane*-r-1,c-4-*diyl Diacetate* (19) *and* c-3-*Acetoxymethyl*-c-4-*hydroxy*-t-2-*methoxymethylcyclopentan*-r-1-*yl Acetate* (20).—A solution of the diacetoxy-diether (14) (3·2 g) in ethanol (50 ml) was hydrogenated at S.T.P. over 5% palladium–carbon (3·8 g) for 30 min. The catalyst was filtered off and washed with ethanol and the solvent evaporated off (yield 2·3 g, 97%). This material freshly prepared consists essentially of the diacetate alcohol (19); however, it rearranges slowly in a glass vessel to the diacetate alcohol (20).

Pure samples of each of these diacetates could be obtained by separation on a silica gel column [continuous elution with ethyl acetate–hexane (1 : 1 v/v)]. The diacetoxy-ol (19) showed $\nu_{max.}$ 3450 and 1735 cm^{-1}, τ ($CDCl_3$) 4·78 (1H, complex, C*H*·OAc), 5·0 (1H, complex, C*H*·OAc), 6·3—6·6 (4H, complex, CH_2O), 6·66 (3H, complex, OCH_3), 7·0—7·4br (1H, OH), 7·5—8·2 (4H, complex, CH), and 7·94 (s) and 7·97 (s) (6H, OAc).

The other diacetoxy-ol (20) showed $\nu_{max.}$ 3550 and 1735 cm^{-1}, τ ($CDCl_3$) 5·0 (1H, m, C*H*·OAc), 5·5—6·0 (3H, complex, C*H*·OH and CH_2·OAc), 6·56 (2H, q, CH_2·OMe), 6·70 (3H, s, CH_2·OCH_3), 7·1—7·4br (1H, OH), 7·7—8·2 (4H, complex, CH), and 7·95 (s) and 7·97 (s) (6H, OAc).

c-2-*Cyanomethyl*-t-3-*methoxymethylcyclopentane*-r-1,c-4-*diyl Diacetate* (23).—The freshly prepared diacetoxy-ol (19) (1·45 g) was dissolved in pyridine (15 ml) and treated with toluene-*p*-sulphonyl chloride (2·7 g) for 3 days at 0°. The mixture was poured onto ice and extracted with ether (×4). The extract was washed with 50% hydrochloric acid, dried (Na_2SO_4–K_2CO_3), and evaporated to give an oil (2·0 g).

To a solution of this crude tosylate (21) (2·0 g) in dimethyl sulphoxide (10 ml) was added finely powdered sodium cyanide (0·3 g), and the mixture was heated on a steam-bath for 10 h. The mixture was poured into brine and extracted with ether. The extract was washed with brine, dried (Na_2SO_4–K_2CO_3) and evaporated (yield 1·1 g). Chromatography on silica gel (45 g) [elution with petroleum–ethyl acetate (3 : 1 v/v)] gave the pure *diacetoxy-nitrile* [0·378 g, 25% for the four stages from the diacetate (14)] [Found: *m/e* 270·1363. $C_{13}H_{20}NO_5$ (M + 1) requires 270·1341], $\nu_{max.}$ 2250 (C≡N) and 1735 (C=O) cm^{-1}, τ ($CDCl_3$) 4·84 (1H, m, C*H*·OAc), 5·05 (1H, m, C*H*·OAc), 6·5 (2H, d, CH_2·OMe), 6·71 (3H, s, OCH_3), 7·44 (2H, m, CH_2·CN), 7·6—8·3 (4H, complex, CH), and 7·94 (s) and 8·02 (s) (6H, OAc).

6-*Methoxymethyl*-3-*oxo*-2-*oxabicyclo*[3.3.0]*octan*-7-*yl Acetate* (25).—The nitrile (22) (156 mg), absolute methanol (2·5 ml), and anhydrous, finely ground potassium carbonate (200 mg) were mixed and stirred at ambient temperature for 30 min. N-Hydrochloric acid (3·0 ml) was added and the mixture was stirred for 5 min. The solvent was removed under high vacuum and the residue heated on a steam-bath with concentrated hydrochloric acid (3 ml) for 2 h. The acid was removed under high vacuum and the product extracted into ethyl acetate (×4). The extract was dried ($MgSO_4$) and evaporated (yield 100 mg, 98%). Preparative t.l.c. gave the hydroxy-lactone (47 mg) as a viscous oil, $\nu_{max.}$ 3400 and 1770 cm^{-1}.

To the hydroxy-lactone (24) (47 mg) was added a mixture of acetic anhydride (0·25 ml) and pyridine (0·25 ml). After 3 h at ambient temperature the excess of reagents was removed *in vacuo* (< 30°) to leave an oil (52 mg). Filtration through a short silica gel (2·9 g) column gave the acetate (48 mg, 96%), identical (t.l.c.; n.m.r. and i.r.) with authentic material.[2a]

trans-5,6-*Bis*(*benzyloxymethyl*)*bicyclo*[2.2.1]*hept*-2-*ene* (26).—A solution of the diol [9] (34·8 g) in dimethoxyethane (200 ml) was added dropwise to a suspension of oil-free sodium hydride (38·1 g) in dimethoxyethane (500 ml) under nitrogen, and the mixture was stirred for 1 h at room temperature. Benzyl bromide (76·7 g) was added and the mixture was refluxed on a steam-bath for 16 h. Sodium carbonate solution (10% w/v; *ca.* 50 ml) was added slowly and the product was extracted into ether (×4). The extract was washed with water (×2), dried, and evaporated to give the *diether* (71·8 g, 99%). Distillation gave a sample of b.p. 145—150° at 0·25 mmHg (Found: C, 82·3; H, 8·0. $C_{23}H_{26}O_2$ requires C, 82·6; H, 7·8%), $\nu_{max.}$ 3040 cm^{-1} (norbornene CH), τ ($CDCl_3$) 2·75 (10H, complex, ArH), 3·88 (1H, q, =CH), 4·10 (1H, q, =CH), 4·60 (4H, m, O·CH_2Ph), 6·3—7·5 (6H, complex, CH and CH_2·O·CH_2Ph), 8·12 (1H, complex, H-6-*exo*), and 8·48—9·00 (3H, complex, H-7a, H-7b, and H-5-*endo*).

r-1,c-4-*Diacetyl*-c-2,t-3-*bis*(*benzyloxymethyl*)*cyclopentane* (27a).—Osmium tetraoxide (2 g) was added to a solution of the diether (26) (33·4 g) in dioxan (540 ml). The solution was stirred for 15 min in the dark to allow the osmate ester to form and then diluted with distilled water (120 ml). To this solution was added sodium periodate (54 g) in water (380 ml) over 12 h. The solution was stirred overnight in the dark. The salts were filtered off and washed with ether. The product was extracted into ether (×4). The extract was washed with brine, dried, and evaporated (yield 36·9 g; $\nu_{max.}$ 2720 and 1725 cm^{-1}).

The resulting crude dialdehyde (36·9 g) was treated immediately without purification with methyl-lithium [from lithium (8·4 g) in ether and methyl bromide]. The solution was then stirred for 2 h and decomposed with 2N-hydrochloric acid (*ca.* 250 ml). The product was extracted into ether (×4). The extract was washed with brine, dried, and evaporated (yield 38·2 g; $\nu_{max.}$ 3400 cm^{-1}).

A solution of the resulting crude diol (38·1 g) in acetone (500 ml) was oxidised with Jones reagent [11] (*ca.* 45 ml). The excess of oxidising agent was destroyed with propan-2-ol. The acetone was evaporated off and the residue was partitioned between ether and water. The ethereal solution was washed with brine, dried, and evaporated to give the *diketone* (35·5 g), purified by chromatography on silica gel (Found: C, 75·9; H, 7·4. $C_{25}H_{30}C_4$ requires C, 76·2; H, 7·6%), $\nu_{max.}$ 1715 cm^{-1} (C=O), τ ($CDCl_3$) 2·75 (10H, complex, ArH), 5·57 (2H, d, O·CH_2Ph), 5·72 (2H, s, O·CH_2Ph), 6·52—6·80 (4H, complex, CH_2·O·CH_2Ph), 6·8—8·3 (6H, complex, CH), and 7·9 (6H, s, Ac).

c-2,t-3-*Bis*(*benzyloxymethyl*)*cyclopentane*-r-1,c-4-*dicarbaldehyde*.—Ozone (2·4 g) was bubbled through a solution of the diether (26) (16·7 g) in methanol (200 ml) at −20 °C. During the ozonolysis the temperature was gradually lowered to −40 °C. While still at −40 °C the system was flushed with nitrogen and dimethyl sulphide (5 ml) was added. The solution was stirred at −10 °C for 1 h, at ice-bath temperature for 1 h, and finally at room temperature for 1 h. The solvent was evaporated off and the remaining oil partitioned between ether and brine. The ethereal solution was dried and evaporated. The crude dialdehyde (19·1 g), identical with the product obtained by osmium tetraoxide–sodium periodate cleavage of the olefin, was converted into *r*-1,*c*-4-diacetyl-*c*-2,*t*-3-bis(benzyloxymethyl)-cyclopentane (27a) by the procedure already described.

c-2,t-3-*Bis(benzyloxymethyl)cyclopentane*-r-1,c-4-*diyl Diacetate* (27b).—Trifluoroperacetic acid [from trifluoroacetic anhydride (172 g) and hydrogen peroxide (90%; 21·1 ml)] in methylene chloride (300 ml) was added dropwise at a rate such as to maintain steady reflux, to a stirred mixture of the crude diketone (27a) (35 g) and disodium hydrogen phosphate (112·5 g) in methylene chloride (600 ml). The mixture was then stirred for 2 h and the solids were filtered off, washed with methylene chloride, and discarded. The methylene chloride solution was neutralised with aqueous sodium hydrogen carbonate (10%), washed with brine, dried, and evaporated (yield 27·8 g). Chromatography on Florisil [elution with petroleum–ether (2 : 1 v/v)] gave the *diacetoxy-ether* (7·5 g) [19% for the four stages from the olefin (26)], purified by further chromatography on silica gel (Found: C, 70·7; H, 7·5. $C_{25}H_{30}O_6$ requires C, 70·5; H, 7·8%), $\nu_{max.}$ 1735 cm^{-1} (C=O), τ ($CDCl_3$) 2·75 (10H, complex, ArH), 4·75 (1H, complex, C*H*·OAc), 4·92 (1H, complex, C*H*·OAc), 5·65 (4H, m, CH_2Ph), 6·2—6·8 (4H, complex, CH_2·O·CH_2Ph), 7·4—8·6 (4H, complex, CH), and 8·05 (s) and 8·09 (s) (6H, OAc).

c-3-*Acetoxymethyl*-c-4-*hydroxy*-t-2-*triphenylmethoxymethylcyclopentan*-r-1-*yl Acetate* (30) *and* c-2,t-3-*Bistriphenylmethoxymethylcyclopentane*-r-1,c-4-*diyl Diacetate* (31).—A solution of the diacetoxy-diether (27b) (35·4 g) in ethanol (1 l) was hydrogenated at S.T.P. over 5% palladium–carbon (35 g) for 90 min. The catalyst was filtered off and washed with ethanol and the solvent was evaporated off. The residue (18·3 g, 90%) was dissolved in pyridine (24 ml) and refluxed for 16 h. The product was shown by n.m.r. spectroscopy to be a 60 : 40 mixture of the diol acetates (28) and (29), respectively. Triphenylmethyl chloride (26·9 g) was added in portions to the cooled pyridine solution. The mixture was set aside at room temperature for 96 h, then poured into ice–water, and the product was extracted with ethyl acetate (4 × 200 ml). The solution was dried, and evaporated (40·0 g). Chromatography on Florisil (800 g) [elution with petroleum (b.p. 40—60°)–ethyl acetate (8 : 1 v/v)] and crystallisation gave the *bis(triphenylmethoxymethyl)cyclopentane* (31) (4·4 g), m.p. 172—174° (Found: C, 80·3; H, 6·2. $C_{49}H_{46}O_6$ requires C, 80·5; H, 6·3%), τ ($CDCl_3$) 2·6—2·9 (30H, complex, ArH), 4·6 (1H, m, C*H*·OAc), 5·00 (1H, m, C*H*·OAc), 6·6—7·1 (4H, complex, CH_2·O), 7·4—8·5 (4H, complex, CH), and 8·12 (s) and 8·23 (s) (6H, OAc) [Found: *m/e* 653·2943. $C_{43}H_{41}O_6$ (*M* − Ph) requires 653·2903]. Further elution with petroleum (b.p. 40—60°)–ethyl acetate (3 : 1 v/v) gave the *triphenylmethoxymethylcyclopentane* (30) (9·7 g, 44%), m.p. 52—54° (Found: C, 73·5; H, 6·8. $C_{30}H_{32}O_6$ requires C, 73·7; H, 6·6%), $\nu_{max.}$ 3500 (OH) and 1735 cm^{-1} (C=O), τ ($CDCl_3$) 2·5—2·9 (15H, complex, ArH), 4·87 (1H, m, C*H*·OAc), 5·54—6·12 (2H, AB octet, CH_2·OAc), 5·88 (1H, q, C*H*·OH), 6·60—6·94 (2H, AB octet, CH_2·$OCPh_3$) 7·22br (1H, OH), 7·6—8·4 (4H, complex, CH), and 8·06 (6H, s, OAc) [Found: *m/e* 428·1973 and 351·1579. $C_{28}H_{28}O_4$ (*M* − CH_3CO_2H) requires 428·1987. $C_{22}H_{23}O_4$ requires 351·1596].

c-2-*Cyanomethyl*-t-3-*triphenylmethoxymethylcyclopentane*-r-1,c-4-*diyl Diacetate* (34).—The diacetoxy-ol (30) (9·7 g), methanol (83 ml), and anhydrous finely ground potassium carbonate (11·1 g) were mixed and stirred at ambient temperature for 2 h. N-Hydrochloric acid (166 ml) was added and the mixture was stirred for 5 min. The solvent was removed under high vacuum, the residue was extracted into ethyl acetate (4 × 200 ml), and the solution was dried and evaporated to give the triol (7·8 g) as an oil, $\nu_{max.}$ 3400 cm^{-1} (OH), τ ($CDCl_3$) 2·5—2·9 (15H, complex, ArH), 5·70 (1H, m, C*H*·OH), 5·96 (1H, m, C*H*·OH), 6·28 (2H, m, CH_2·OH), 6·92 (3H, complex, OH and CH_2·$OCPh_3$), and 7·7—8·4 (4H, complex, CH).

To an ice-cold solution of the triol (6·0 g) in pyridine (120 ml), toluene-*p*-sulphonyl chloride (2·8 g) was added with stirring. The mixture was maintained at 2° for 5 days, diluted with saturated sodium chloride solution, and extracted with ethyl acetate (4 × 200 ml). The dried extract was evaporated, final traces of pyridine being removed azeotropically with benzene. Chromatography on Florisil (225 g) [elution with petroleum (b.p. 40—60)–ethyl acetate (3 : 1 v/v)] gave, as an oil, the dihydroxy-tosylate (2·0 g), τ ($CDCl_3$) 2·1—2·4 (2H, A_2B_2, ArH), 2·6—2·9 (17H, complex, ArH), 5·5—6·1 (4H, complex, C*H*·OH and CH_2·OTs), 6·1—7·2 (4H, complex, CH·O*H* and CH_2·$OCPh_3$), 7·61 (3H, s, ArCH_3), and 7·9—8·2 (4H, complex, CH).

To a solution of the tosylate (32) (2·0 g) in pyridine (1·45 ml), acetic anhydride (3·43 ml) was added and the mixture was kept at room temperature for 72 h. The excess of reagents was removed *in vacuo* (<30°). To a solution of the resulting diacetate tosylate (33) (2·4 g) in dimethylformamide (15 ml), sodium cyanide (1 g) and a trace of sodium iodide were added and the mixture was heated at 100° for 6 h. The solvent was removed under vacuum and the product extracted into ethyl acetate. The solution was dried and evaporated (yield 1·7 g). Chromatography on Florisil (40 g) [elution with petroleum (b.p. 40—60°)–ethyl acetate (4 : 1 v/v)] gave the *nitrile* (34) (1·061 g) (Found: C, 75·0; H, 6·2. $C_{31}H_{31}NO_5$ requires C, 74·8; H, 6·3%), $\nu_{max.}$ 2250 (C≡N) and 1735 (C=O) cm^{-1}, τ ($CDCl_3$) 2·6—2·9 (15H, complex, ArH), 4·75—5·05 (2H, complex, C*H*·OAc), 6·5—6·9 (2H, m, CH_2·$OCPh_3$), 7·4—8·3 (6H, complex, CH_2·CN and C*H*), and 7·95 (s) and 8·04 (s) (6H, OAc).

7-*Hydroxy*-6-*hydroxymethyl*-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (35).—A solution of the nitrile (34) (160 mg) in 80% aqueous acetic acid (3 ml) was kept at room temperature for 24 h. The triphenylmethanol (46 mg) which separated was removed and washed with 80% aqueous acetic acid. The combined washings and filtrate were evaporated. A solution of the residue (123 mg) in methanol (3 ml) was treated with finely ground anhydrous potassium carbonate (158 mg) and stirred at ambient tempature for 40 min. N-Hydrochloric acid (2·25 ml) was added and the mixture was stirred for 5 min. The solvent was removed under high vacuum and the residue heated on a steam-bath with concentrated hydrochloric acid (3 ml) for 2 h. The acid was removed under high vacuum and the product extracted into ethyl acetate (×4). The extract was dried and evaporated (yield 78 mg, 60%). Preparative t.l.c. with benzene–methanol (3 : 1 v/v) as solvent gave the diol, identical (t.l.c.; n.m.r. and i.r.) with an authentic sample.[1]

We thank Dr. G. R. Bedford and his staff for spectroscopic and analytical determinations and Drs. W. G. M. Jones and B. W. Langley for interest and encouragement.

[4/280 *Received*, 13*th February*, 1974]