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SYNTHESES OF $PGF_{2\alpha}$ AND CLOPROSTENOL

N. R. A. BEELEY, R. PEEL and J. K. SUTHERLAND*

Chemistry Department, University of Manchester, Manchester M13 9PL, England

and

J. J. HOLOHAN, K. B. MALLION* and G. J. SEPENDA

Process Development Department, Pharmaceuticals Division, I.C.I. Ltd., Hurdsfield Industrial Estate, Macclesfield, Cheshire SK10 2NA, England

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Abstract—Prins reaction of norbornadiene leads to an efficient synthesis of the ketoacid (**5**) which is cleaved regio- and stereo-specifically with acids to 5-*exo*-substituted norbornan-2-one-7-carboxylic acids. Baeyer Villiger oxidation of these ketones leads to bridged lactones, e.g. **18**, which can be converted into derivatives of the Corey aldehyde (**1**). In particular, the chlorolactone **19** is converted efficiently into the aldehyde **32** which, by four different routes, can be converted into known precursors of prostanoids.

In connection with a synthetic problem we observed[1] that a variant of the Prins reaction could be used to homologate conjugated dienes. Norbornadiene, though not formally a conjugated diene, reacts in a conjugate manner with most electrophiles, giving nortricyclane derivatives as the major or sole products.[2] Stereochemically the attack of electrophile is predominantly *exo* while the neutralisation of the nortricyclyl carbonium ion is not stereoselective. Should the hydroxymethylation of norbornadiene take such a course then it was apparent that such a product could be a potential precursor for the Corey aldehyde (**1**), widely used in the synthesis of prostaglandins.[3] To achieve this, cleavage of the C-1 and C-2 and C-3 and C-4 bonds of structure **2** was necessary, together with the introduction of oxygen functions at C-1 and C-4 with retention of configuration.

In the event, reaction of norbornadiene with $H.CO_2H$–H_2CO† gave a mixture which could be separated by distillation into three crude fractions. The most volatile (*ca* 10%) was nortricyclylformate, the major fraction (*ca* 60%) was the mixture of formates (**2**), while the residue contained **2**, the dimer **4**,‡ and other unidentified components. The diformates were readily hydrolysed to the mixture of fiols **3** which on oxidation with Jones' reagent gave the crystalline ketoacid **5**. The constitution of **5** was established by Wolff–Kishner reduction to the known[4] tricyclo-[2.2.1.$0^{2,6}$]heptan-3-carboxylic acid. From the crystallisation mother liquors an isomeric ketoacid could be isolated; the epimeric relationship of the two acids was established by equilibration of the ester **6** with NaOMe–MeOH yielding a mixture of the two esters. It was also possible to obtain the ketoacid **5** in 61% yield by oxidation[5] of the Prins adduct with Jones' reagent. The isomeric acid **16** was formed in *ca* 10% yield but remained in the crystallisation mother liquors. This must arise from a Prins adduct formally derived by *endo* attack on norbornadiene; this proportion of *endo* attack is unexpected and it could be formed by hydride migration in the *exo* intermediate **7**.

With plentiful supplies of the acid **5** available attention was now turned to the opening of the cyclopropyl ring,[6] which was accomplished using 45% HBr in CH_3CO_2H, 10NHCl 40% HI in H_2O, and $HClO_4$ in CH_3CO_2H to give **8**, **9**, **10** and **11** in good yield. In the latter reaction the acetate **11** was formed together with the γ-lactone **17**; both could be hydrolysed to the same hydroxyacid **12** which on heating regenerated the γ-lactone. These informative reactions confirmed the stereochemistry of the ketoacid **5**, and established the regio- and stereo-chemistry of the ring opening. The ketoester **6** also ring-opened with $HClO_4$–CH_3CO_2H and HBr–AcOH. In one experiment when the HBr–AcOH inadvertently contained some Br_2 a dibromide was obtained; the first order NMR spectrum of this compound (Fig. 1) confirmed the regio- and stereo-chemistry proposed. On reaction with Zn in AcOH at 20° the dibromide was transformed into the monobromide **8**. On treatment with base the haloacids **8**, **9**, and **10** were converted into **5**. The reasons for the remarkably regiospecific cleavage of **5** are not obvious; similar regiospecific cleavage is observed with the isomer **16**. In both cases the field effect of the carboxyl could destabilise positive charge developing β to it to a greater extent than a γ charge.

The oxygen required at C-4 was introduced by Baeyer-Villiger oxidation of the bromo- and chloro-acids. Use of peracetic acid buffered by sodium acetate gave 71% of **18** and 74% of **19**. The crystallisation mother liquors were composed mainly of the isomeric oxidation products in which CH_2 migration had occurred. Baeyer–Villiger oxidation of the iodo-acid **10** took an unexpected course, yielding, after methylation (CH_2N_2) and chromatography, the lactones **20** and **21** in poor yield. Since it was likely that

†The preparation of compounds **2**, **3**, **5**, **9**, **19**, and **17** has been done independently by Bindra, Grodski, Schaaf and Corey,[11] and these have been used in prostaglandin syntheses in a manner different from that described herein. The acid **5** has been resolved by these workers. We thank Professor Corey for informing us of his work before publication.

‡Oxidation of the residue with Jones' reagent gave the acid **5** and a neutral fraction containing the dione corresponding to **4** which reacted with HBr–AcOH to give a readily purified dibromide. Elimination of HBr then gave a pure sample of the dione.

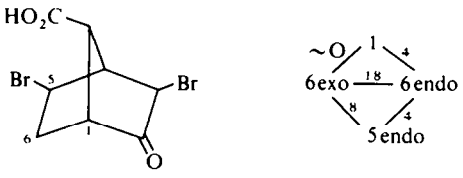


Figure 1. H-H Couplings in Hz.

20 was being formed by acid catalysed rearrangement[7] of **21**, the methyl ester **14** was oxidized (*m*-chloroperbenzoic acid) and the reaction isomerised [*p*-toluenesulphonic acid–benzene) to give **20** in 81% yield.† The oxidative elimination of iodine is not without precedent: Ogata[8] has shown that oxidation of cyclohexyl iodide yields products derivable from the interaction of cyclohexene, iodonium ion, and solvent. In our case it appeared that oxidative elimination occurred to form the norbornene, the double bond of which was too hindered to react with any electrophile present, but which underwent a rapid Baeyer–Villiger oxidation. Oxidation of an authentic sample of **23**‡ to **20** and **21** provided some support for this view.

Since Baeyer–Villiger oxidation of the ketoacid gave the lactone **24** in acceptable yield we investigated its reaction with HBr–AcOH. It proved to be much less reactive than the ketoacid but under forcing conditions the lactone **25** could be isolated in *ca* 50% yield.

The conversion of **18** and **19** into a cyclopentanoid of the required functionality formally requires opening of the lactone ring and displacement of halogen by carboxylate with inversion of configuration. Treatment of **18** and **19** with aqueous base effected 1,3-elimination to form the parent lactone **24**; none of the required lactone was formed. This very facile elimination is probably due to a most favourable geometrical relationship between proton and halogen similar to that established in the norbornane series by Nickon.[9] Two general solutions to the problem are possible, *viz* (a) use of a strong nucleophile for sp^2 carbon which is weakly basic, e.g. NH_2OH, NH_2NH_2, $O^{\ominus}OH$, and (b) alteration of the molecule to produce a less favourable geometry for elimination. In the event, reaction of **18** with NH_2OH in collidine gave the γ-lactone **26** in 52% yield but a substantial amount of elimination was also occurring. Preliminary experiments on the chlorolactone **19** showed the mixture of γ-lactone and elimination product (4:1) was formed in high yield using NH_2OH in isopropanol/H_2O. This procedure was not developed further since a satisfactory solution had been found using the second strategy. Treatment of **18** with HBr–AcOH gave the bromoester **31** which, on treatment with 8% NaOH gave the acid **26** (79%) while on reaction with 8% $NaHCO_3$ the acetate **27** (82%) was obtained.§

A formal total synthesis[3] of various prostaglandins was completed by reduction of the acid **27** to the alcohol **29** both by the mixed-anhydride procedure and, in better yield, by desulphurisation of the thiophenyl ester. However, for practical reasons it was best that the Corey aldehyde be protected as the *p*-phenylbenzoate; direct acylation of the hydroxy acid **26** was not possible since elimination to **25** occurred, presumably from the mixed anhydride. It was possible to prepare the Corey alcohol **30** by the sequence phenacyl ester formation, acylation, removal of phenacyl ester,[10] diborane reduction, but this was clearly not an attractive, practical route.¶ Our failure to develop a practical one-pot conversion of acid to aldehyde led to our abandonment of this route.

To overcome the acylation problem it was necessary to change the carboxyl functionality while the OH was still protected; the lactone **19** was a suitable stage at which to do this. The aldehyde **32** can be prepared *via* the primary alcohol[11] but the overall yields are not high and the most satisfactory route to this rather unstable compound is by Rosenmund reduction[12] of the acid chloride. In the first route (Scheme 1) the aldehyde was condensed with the anion of dimethyl 2-oxoheptylphosphonate to give mainly the crystalline enone **34** contaminated with the elimination product **33** which could be prepared by stirring **34** with aqueous sodium hydroxide. Reduction of **34** with $NaBH_4$ or $ZnBH_4$ gave the mixture of epimeric alcohols **35** which was converted to the γ-lactones **36** using Corey's procedure[13] ($NaOH/H_2O_2$); this method was superior to both the hydroxylamine route and the acidolysis procedure. The mixture of alcohols and the derived acetates was identical to that obtained by a different route.[14]

Three routes have been developed for the synthesis of cloprostenol; they are attractive in that they allow the synthesis of the intermediate **41** from the acid **19** by 'one-pot', ambient temperature reactions. The starting point was the acid chloride of **19**, purified and free of catalyst poisons, which undergoes Rosenmund reduction to the aldehyde **32** (*ca* 90%). The aldehyde could be isolated, but was rather unstable and thus in all the routes to be described, the Rosenmund reaction mixture was used directly.

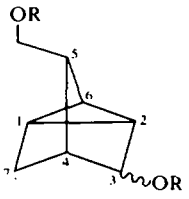
In Scheme 2 to enone **41** the Rosenmund reaction mixture was treated with *p*-toluenesulphonic acid in dry methanol at ambient temperature when **32** underwent smooth cleavage of the lactone ring and acetalisation of the formyl group to afford the soluble monocyclic hydroxyester **37**. Addition of an excess of aqueous alkali then brought about a sequence of three rapid, efficient (tlc) reactions. Ester hydrolysis gave the acid **38** which cyclised spontaneously to the lactone **39** this finally suffering hydrolysis to the hydroxyacid **40** (sodium salt). The reaction mixture, still at ambient temperature, was then brought to *ca* 0.5–1.0N HCl to promote two further very clean (tlc) stages, *viz* rapid relactonisation to **39** followed by slower (*ca* 3hr) deprotection to the very water-soluble hydroxy-aldehyde (**1**). This compound has been prepared

†Oxidation of the trichloroethyl **15** ester with *m*-chloroperbenzoic acid gave the bridged lactone **22** uncontaminated with γ-lactone, but the conditions required to remove the protective group brought about partial isomerisation to the γ-lactone.

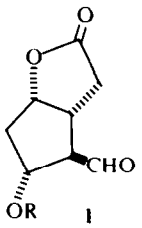
‡The ester **23** was prepared from the dimethyl acetal of norborn-5-en-2-on-7-carboxaldehyde by hydrolysis, CrO_3 oxidation, and methylation (CH_2N_2).

§Since AcOH is the common solvent for the sequence **5** → **8** → **31** and the conversions **31** → **26** or **27** only require treatment of the residue with aqueous base, these conversions could be carried out as 'one-pot' processes with addition of the appropriate reagents. The overall yield **5** → **26** was 46%.

¶**26** could also be prepared from the benzyl ester of **19** by the sequence $NaOH/H_2O_2$, *p*-$PhC_6H_4CO.Cl$/pyridine, H_2/Pd.



2 R = CHO
3 R = H



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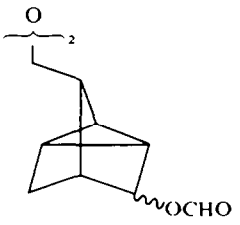

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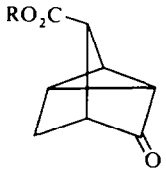
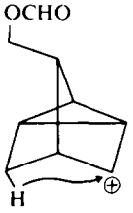


5 R = H
6 R = Me



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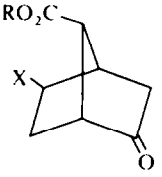
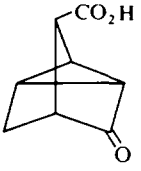


8 R = H X = Br
9 R = H X = Cl
10 R = H X = I
11 R = H X = OAc
12 R = H X = OH
13 R = Me X = OAc
14 R = Me X = I
15 R = CH_2CCl_3 X = I



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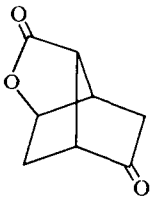

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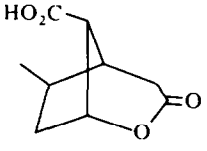
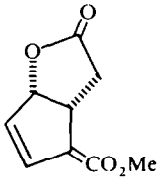


18 X = Br
19 X = Cl



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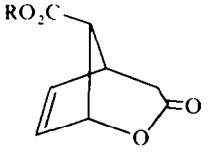
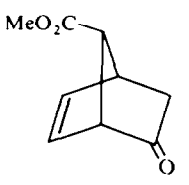


21 R = Me
22 R = CH_2CCl_3



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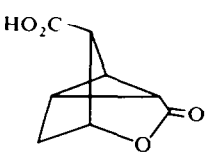

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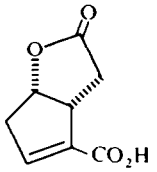

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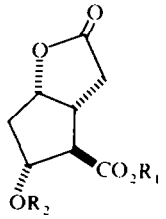
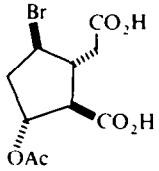


26 $R_1 = H$, $R_2 = H$
27 $R_1 = H$, $R_2 = Ac$
28 $R_1 = H$, $R_2 = COC_6H_4Ph\text{-}p$



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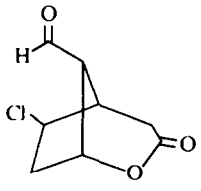
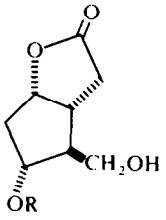
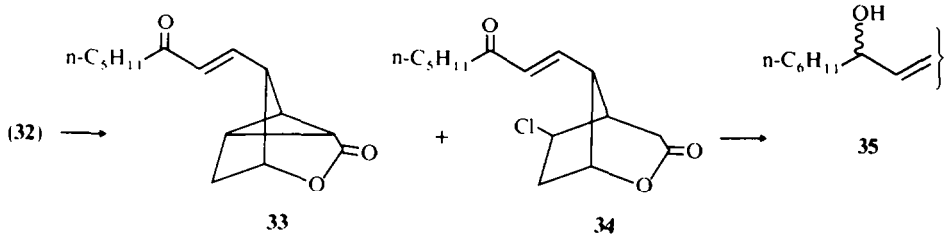


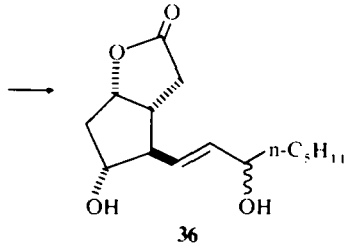
32



29 R = Ac
30 R = $CO.C_6H_4Ph\text{-}p$



33 **34** **35**



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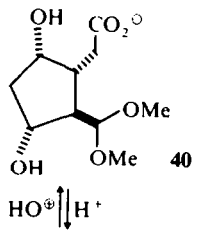

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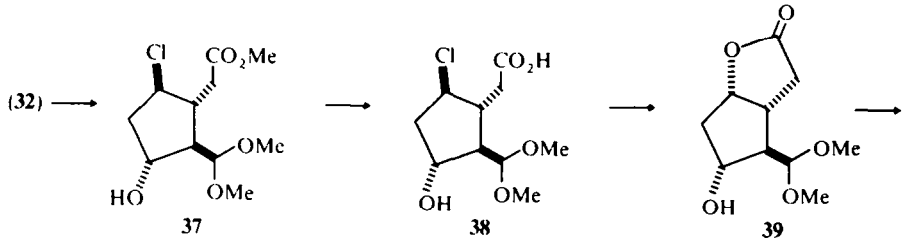
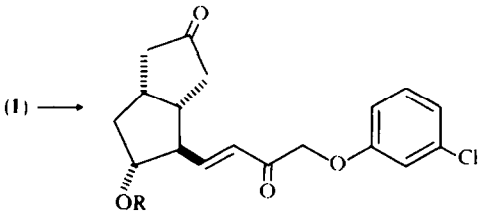
Scheme 1

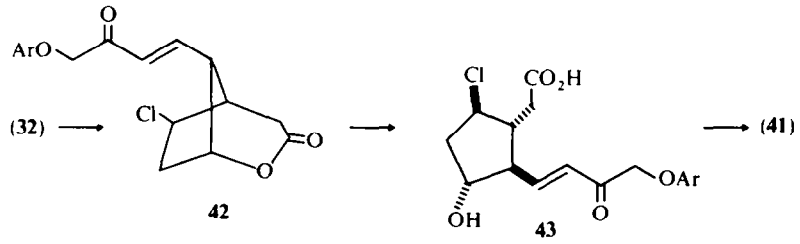


37 **38** **39**



41 R = H
45 R = $CO.C_6H_4Ph\text{-}p$

Scheme 2.

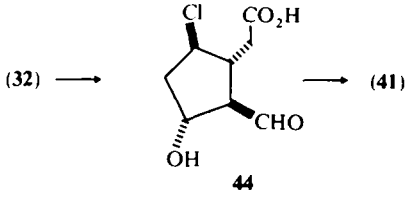


Scheme 3.

previously (but also not isolated) in low yield *via* a different route and was reported as insufficiently stable to survive chromatographic separation.[13] However, in the 0.5–1.0N HCl solution in which it was produced in this investigation it was stable with only traces of elimination over 36 hr. On treatment of the aqueous solution with excess potassium carbonate and then the phosphonate *m*-$ClC_6H_4OCH_2COCH_2PO(OMe)_2$,[15] **1** rapidly gave crystalline **41** isolated in 36% yield from **19**. (A similar condensation but under different conditions has been reported by E. J. Corey *et al.* in the $F_{2\alpha}$ series).[13]

In Scheme 3 to the enone **41**, the Rosenmund reaction mixture was treated directly with potassium carbonate and the phosphonate to afford the crystalline enone **42** [29% from **19**] which could be, but was not normally, isolated, the reaction mixture being treated with dilute acid to produce the hydroxyacid **43** and then with excess potassium carbonate which promoted efficient cyclisation to the required **41** [13.5% from **19**]. [If isolated *crude* **42** was separately taken to **41** the overall yield from **19** was 25.5%].

In Scheme 4, the mixture from the Rosenmund reduction was acidified with dilute acid to effect hydrolysis of **32** to give mainly the monocyclic aldehyde **44** which, without isolation was treated with excess potassium carbonate and the phosphonate. Rapid reactions led to the enone **41** [33% from **19**]. The enone **41** was *p*-phenylbenzoylated to give an intermediate **45** on an established route to the prostanoid chloprostenol. These routes constitute a relatively short and efficient synthesis of prostaglandins and related compounds.



Scheme 4.

EXPERIMENTAL

M.ps were determined on a Kofler block and are uncorrected. IR spectra were recorded on a Perkin–Elmer 257 instrument in $CHCl_3$ soln. NMR spectra were recorded at 60 MHz on a Perkin–Elmer R12B, at 90 MHz on a Perkin–Elmer R32, and at 100 MHz on a Varian HA100 using $CDCl_3$ as solvent unless otherwise specified. High resolution mass spectra were measured on A.E.I.MS9 and MS30 instruments. Tlc was carried out on Merck silica gel F_{254} plates. The statement "worked up in the usual way" implies that the organic extract was washed with saturated brine, dried over Na_2SO_4 or $MgSO_4$, and the solvent evaporated under reduced pressure.

Anti-5-oxo-tricyclo[2.2.1.$0^{2,6}$]*heptan-3-carboxylic acid* (**5**)

Norbornadiene (368 g) was added dropwise to a soln of paraformaldehyde (124 g) in 98% formic acid (2 l) containing H_2SO_4 (10 ml); the stirred soln initially warmed up to 50°. After addition of norbornadiene was complete the soln was stirred for a further 12 hr. Most of the formic acid was removed *in vacuo* and the residue dissolved in diethyl ether and filtered through a pad of Celite. After washing with $NaHCO_3$ aq the organic extract was worked up in the usual way to give a mixture which was distilled under vacuum to give nortricyclyl formate (40 g) b.p. 35–40°/0.05 mm and **2** (620 g; 79%) b.p. 92–102°/0.05 mm, ν_{max} 1720 cm^{-1}, τ 1.97 (2 H, s), 5.18 (0.5 H), 5.26 (0.5 H), 5.90 (1 H, d), 6.03 (1 H, d).

(a) A solution of CrO_3 (214 g) in conc H_2SO_4 (184 ml) and water (800 ml) was added dropwise to a stirred soln of the diformate (123 g) in acetone (2 l) while maintaining the temp of the mixture at 5°. Celite (300 g) was suspended in the acetone soln prior to addition of the oxidant. After stirring for a further 12 hr at 25° the liquid was decanted, most of the acetone removed *in vacuo*, and the residue filtered through Celite. The filtrate was extracted with EtOAc (×4) and the extracts worked up in the usual way to give **5** m.p. 143–146° (62 g; 65%) after trituration with ether. Recrystallisation from Me_2CO–petroleum ether b.p. 60–80° gave a sample m.p. 145–147°; (Found: C, 63.3; H, 5.1. $C_8H_8O_3$ Requires: C, 63.2; H, 5.3%), τ [$(CD_3)_2CO$] 7.02 (1 H, s), 8.6 (1 H, t).

Fractional crystallisation (Me_2CO–petroleum ether b.p. 60–80°) of the mother liquors gave the *syn*-acid **16**, m.p. 119–121°, (Found: C, 63.2; H, 5.3%), τ [$(CD_3)_2CO$] 7.10 (1 H, s), 8.66 (1 H, t).

The methyl esters of **5**, b.p. 94°/0.55 m, (Found: C, 65.4; H, 6.1. $C_9H_{10}O_3$ Requires: C, 65.1; H, 6.1%), τ 6.95 (1 H, s), 8.53 (1 H, t) and of **16**, b.p. 100°/0.12 mm. (Found: C, 64.8: H, 5.9%), were prepared by treatment with ethereal diazomethane. Methyl ester **6** (420 mg) on reflux with NaOMe in MeOH for 3 hr gave starting ester (209 mg) and the ester of **16** (147 mg).

(b) The diformate (40 g) in EtOH (200 ml) and water (100 ml) was cooled to 0° and 8° NaOH aq (220 ml) added dropwise with stirring. After addition was complete most of the EtOH was removed *in vacuo* and the residue extracted with EtOAc (6 × 80 ml). Work-up in the usual way gave the viscous diol (27.6 g), b.p. 160°/0.02 mm, τ [$(CD_3)_2CO$] 6.19 ($\frac{1}{2}$H), 6.27 ($\frac{1}{2}$H), 6.54 ($\frac{2}{2}$H), (Mass measurement: found 140.0842. $C_8H_{12}O_2$ Requires: 140.0837). A soln of CrO_3 (70 g), conc H_2SO_4 (61 ml), and water (500 ml) was added dropwise with stirring to a cooled soln of the diol (27.6 g) in AnalaR acetone (500 ml). After addition was complete the soln was stirred at ambient temp for 16 hr. Excess oxidant was destroyed by addition of sodium metabisulphite soln and most of the acetone removed under reduced pressure. The residue was extracted with EtOAc (5 × 200 ml) and worked up in the usual way to give **5** (15.79 g after recrystallisation).

Tricyclo[2.2.1.$0^{2,6}$]*heptan-3-carboxylic acid*

The acid **5** (573 mg), powdered KOH, and hydrazine hydrate (2 ml) in triethyleneglycol (25 ml) were heated at

140–150° for 1.5 hr. Solvent was distilled off until the reflux temp reached 220°, at which stage the soln was refluxed for a further 3 hr. The cooled soln was poured into water, acidified and extracted with ether (4 × 50 ml). Work-up in the usual way gave the acid, m.p. 49–50° (petroleum ether b.p. 60–80°) (Lit.[4] m.p. 49–50.6°).

Reaction of ketoacid (5) *with hydrogen bromide*

The acid **5** (21.5 g) in glacial AcOH (150 ml) and 45% HBr in AcOH (40 ml) was heated at 60° for 1 hr. The cooled soln was poured in water and extracted with EtOAc (× 4). Work-up in the usual way gave **8** (29.1 g), m.p. 183.5–185.5° (acetone-petroleum ether b.p. 60–80°), (Found: C, 41.2; H, 3.9; Br, 34.3. $C_8H_9O_3Br$ Requires: C, 41.4; H, 3.9; Br, 34.3%), τ [$(CD_3)_2CO$] 5.66 (1 H, m). Esterification with diazomethane gave the *methyl ester*, m.p. 90–91° (petroleum ether b.p. 60–80°), (Found: C, 43.9; H, 4.5; Br, 32.4. $C_9H_{11}O_3Br$ Requires: C, 43.7; H, 4.5; Br, 32.3%).

If the ring-opening reaction was carried out in the presence of bromine the ketoacid (4 g) gave the *dibromide* (Fig. 1) (7.06 g), m.p. 188–193°, (Found: C, 31.0; H, 2.5; Br, 50.8. $C_8H_8O_3Br_2$ Requires: C, 30.8; H, 2.6; Br, 51.2%). Reduction of the dibromide with Zn dust and AcOH for 1 hr at ambient temp gave **8** (69%).

Reduction of **8** (2.1 g) with Zn dust (4.66 g) and AcOH (30 ml) (12 hr reflux) gave *norbornan-2-one-7-anti-carboxylic acid* (0.96 g) m.p. 104–106° (benzene–petroleum ether b.p. 60–80°), (Found: C, 62.2; H, 6.7. $C_8H_{10}O_3$ Requires: C, 62.3; H, 6.5%).

When **8** (411 mg) was dissolved in 1N NaOH (20 ml) and left for 10 min acidification gave **5** (201 mg).

Reaction of the ketoacid (**5**) *with hydrochloric acid*

The ketoacid **5** (12.9 g) and conc HCl (75 ml) was refluxed for 1.25 hr. On cooling a solid (15.8 g) precipitated. Recrystallisation gave **9** m.p. 157–160° (benzene–petroleum ether b.p. 60–80°), (Found: C, 51.1; H, 4.8; Cl, 18.4. $C_8H_9O_3Cl$ Requires: C, 50.9; H, 4.8; Cl, 18.8%), τ [$(CD_3)_2CO$] 5.67 (1 Hm).

Reaction of the ketoacid (**5**) *with hydriodic acid*

The ketoacid **5** (20 g) was refluxed in 57% HI (60 ml) for 1 hr. After addition of sodium metabisulphite soln the mixture was extracted with EtOAc (× 6). Work-up in the usual way gave **10** (33.5 g) m.p. 227–228° (Me_2CO–EtOAc). (Found: C, 34.6; H, 3.2; I, 45.0. $C_8H_9O_3I$ Requires: C, 34.3; H, 3.2; I, 45.3%), τ ($(CD_3)_2CO$] 5.75 (1 H, q).

Reaction of the ketoacid with perchloric acid

The ketoacid **5** (4.1 g), glacial AcOH (50 ml), and 70% aqueous perchloric acid were refluxed for 6.25 hr. The black soln was poured into water (250 ml) and extracted with EtOAc (1 × 130, 3 × 80 ml). Work-up in the usual way gave a residue which was dissolved in $NaHCO_3$ aq and extracted with EtOAc (× 3). Work-up in the usual way gave **17** (1.36 g), m.p. sublimes (acetone–petroleum ether b.p. 60–80°), (Found: C, 63.2; H, 5.2. $C_8H_8O_3$ Requires: C, 63.2; H, 5.3%), ν_{max} 1790, 1760 cm^{-1}, τ 5.15 (1 H, bs), 6.76 (1 H, bs), 7.01 (1 H, bs).

Acidification of the bicarbonate soln and extraction with EtOAc (× 5) gave, after work-up in the usual way, a brown solid (2.53 g). Recrystallisation from acetone–petroleum ether b.p. 60–80° gave **11** (1.35 g), m.p. 186–187°, (Found: C, 56.9; H, 5.9. $C_{10}H_{12}O_5$ Requires: C, 56.6; H, 5.7%), τ (D_5-pyridine) 4.98 (1 H, m), 8.08 (3 H, s). Esterification with diazomethane gave **13** m.p. 101.5–103° (petroleum ether b.p. 60–80°), (Found: C, 58.4; H, 6.3. $C_{11}H_{14}O_5$ Requires: C, 58.4; H, 6.2%), τ 5.12 (1 H, m), 6.28 (3 H, s), 8.00 (3 H, s).

Dissolution of **17** (1.03 g) in 0.5N NaOH (50 ml), followed by acidification 30 min later, gave after EtOAc extraction (× 8) **12** (0.81 g) m.p. 165–167°, (Found: C, 56.5; H, 6.0. $C_8H_{10}O_4$ Requires: C, 56.5; H, 5.9%), τ(D_5-pyridine) 5.71 (1 H, m). On sublimation the acid was converted to **17**. Hydrolysis of **11** under the same conditions for 1.5 hr also gave **12**.

The acid **12** with toluene-*p*-sulphonyl chloride and pyridine gave a *tosylate*, m.p. 125–126° (CCl_4), (Found: C, 56.9; H, 5.4; S, 9.2. $C_{16}H_{18}O_6S$ Requires: C, 56.8; H, 5.4; S, 9.5%), τ 5.30 (1 H, m).

The acid **12** on oxidation with Jones's reagent gave *norbornan-2,5-dione-7-carboxylic acid* (70%) m.p. 150–151°, (Found: C, 57.4; H, 4.7 $C_8H_8O_4$ Requires: C, 57.1; H, 4.8%).

Baeyer–Villiger oxidation of bromo-acid **8**

A mixture of **8** (18.6 g), anhyd NaOAc (2.82 g), 40% peracetic acid (20 ml), and glacial AcOH (175 ml) was stirred at ambient temp for 12 hr. Excess oxidant was destroyed by addition of sodium metabisulphite, the soln diluted with water, and then sat with NaCl. Extraction with EtOAc and work-up in the usual way gave a crystalline residue which was triturated with ether to give **18** (14.1 g) m.p. 178–182° (dec) (acetone–petroleum ether b.p. 60–80°), (Found: C, 38.6; H, 3.7; Br, 32.3. $C_8H_9O_4Br$ Requires: C, 38.6; H, 3.6; Br, 32.1%), τ [$(CD_3)_2CO$] 4.98 (1 H, bs), 5.40 (1 H, m).

The methyl ester of **8** was oxidized with *m*-chloroperbenzoic acid in CH_2Cl_2 to the *methyl ester of* **18** (70%), m.p. 113–114° (CCl_4), (Found: C, 41.2; H, 4.3; Br, 30.4. $C_9H_{11}O_4Br$ Requires: C, 41.1; H, 4.2; Br, 30.4%), τ 5.90 (1 H, m), 6.26 (3 H, s), 6.70 (1 H, bs).

Baeyer–Villiger oxidation of chloroacid **9**

The chloroacid **9** (4.8 g) was oxidized as for **8** to give **19** (3.30 g), m.p. 175–178° (acetone–petroleum ether b.p. 60–80°), (Found: C, 46.8; H, 4.3; Cl, 17.5. $C_8H_9O_4Cl$ Requires: C, 47.0; H, 4.4; Cl, 17.3%), τ [$(CD_3)_2CO$], 4.96 (H, bs), 5.41 (1 H, m).

Baeyer–Villiger oxidation of the iodoacid esters **14** *and* **15**

(a) The ester **14** (1.294 g) in EtOAc (20 ml) containing 40% peracetic acid (5 ml) and NaOAc (4 g) was stirred at ambient temp for 35 hr. After addition of water the aqueous layer was extracted with EtOAc (× 4). The organic extracts were washed with sodium metabisulphite soln and $NaHCO_3$ aq and then worked up in the usual way to give a mixture of **21** with some **20** (NMR). The mixture was dissolved in benzene (20 ml) containing toluene-*p*-sulphonic acid (500 mg) and set aside for 24 hr. Work-up in the usual way (ether extraction) gave **20** (629 mg), τ, 3.94 (2 H, m), 4.41 (1 H, m) 6.30 (3 H, s), ν_{max} 1780, 1740 cm^{-1}.

(b) The iodoacid **10** (10 g), pyridine (2.86 g), dicyclohexylcarbodiimide (7.37 g), and trichlorethanol (5.34 g) were stirred at ambient temp in CH_2Cl_2 (60 ml) for 24 hr. The dicyclohexylurea was filtered off and washed with CH_2Cl_2. The combined filtrate was washed with $NaHCO_3$ aq and worked up in the usual way **15** (14.5 g), m.p. 117–118° (EtOAc), (Found: C, 29.1; H, 2.4; Cl, 26.0; I, 30.4. $C_{10}H_{10}O_3Cl_3I$ Requires: C, 29.2; H, 2.5; Cl, 25.9; I, 30.8%). A mixture of 40% peracetic acid (120 ml) containing NaOAc (20 g) was added slowly to **15** (39.1 g) in EtOAc (200 ml). After 5 min an exothermic reaction began and the soln refluxed. The rate of addition was controlled to avoid over-vigorous reaction and after completion of addition the mixture, now containing a white solid, was stirred overnight. 2N HCl was added and the mixture extracted with $CHCl_3$ (× 5). Work-up in the usual way gave **22** (25.7 g), m.p. 108–109° (CCl_4), (Found: C, 40.1; H, 3.1; Cl, 34.3. $C_{10}H_{10}O_4Cl_3I$ Requires: C, 40.1; H, 30.0; Cl, 35.5%), τ 3.50 (1 H, q), 3.70 (1 H, q), 4.62 (1 H, bs), 5.29 (2 H, s), ν_{max} 1765 cm^{-1}.

The δ-lactone **22** (73 mg) in benzene (15 ml) containing toluene-*p*-sulphonic acid (200 mg) was set aside for 24 hr. After addition of EtOAc, work-up in the usual way gave the *γ-lactone* of **20** as a viscous oil (70 mg), γ_{max} 1795, 1765 cm^{-1}, τ 3.88 (2 H, m), 4.38 (1 H, m), 5.25 (2 H, s).

Refluxing **22** (319 mg) in 90% AcOH (4 ml) and benzene (8 ml) with Zn dust (1.2 g) gave, after filtration, addition of 2N HCl and work-up in the usual way, the *γ-lactone* acid of **20**

(162 mg) m.p. 117–119° (acetone–petroleum ether b.p. 60–80°), (Found: C, 56.8; H, 5.3. $C_8H_8O_3$ Requires: C, 57.1; H, 4.8%) ν_{max} 1785, 1720 cm^{-1}, τ [$(CD_3)_2CO$] 3.85 (1 H, m), 4.05 (1 H, m), 4.45 (1 H, m).

Baeyer–Villiger oxidation of ketoacid **5** *and ketoester* **6**

The acid **5** (3.06 g) was stirred with 40% peracetic acid (10 ml) in glacial AcOH (30 ml) for 12 hr. Sodium metabisulphite was added, the soln diluted with water and extracted with EtOAc (× 5) and then worked up in the usual way to give **24** (1.8 g) m.p. 178.5–181° (acetone–petroleum ether b.p. 60–80°), (Found: 57.2; H, 4.9. $C_8H_8O_4$ Requires: C, 57.1; H, 4.8%), τ 5.30 (1 H, bs).

Oxidation of **6** (740 mg) with *m*-chloroperbenzoic acid (1.128 g) in CH_2Cl_2 (11 ml) gave after work-up an oil (780 mg). Two crystallisations from benzene–petroleum ether b.p. 60–80° gave the *methyl ester* of **24**, m.p. 60–61°, (Found: C, 59.3; H, 5.6. $C_9H_{10}O_4$ Requires: C, 59.3; H, 5.5%), τ 5.26 (1 H, bs). Chromatography on silica gel with ether as eluant gave the *isomeric lactone* (28 mg). m.p. 96.5–97.5 (CCl_4) (Found: C, 59.6; H, 5.6%), τ 5.78 (1 H, t).

Reaction of the lactone **24** *with hydrogen bromide*

The lactone **24** (1.02 g) in 45% HBr in AcOH (20 ml) was refluxed for 19 hr. The soln was evaporated to dryness and a further portion of 45% HBr in AcOH (45 ml) was added. After 60 hr reflux the soln was again evaporated to dryness. The black residue was dissolved in EtOH and treated with charcoal. After filtration through a pad of Celite evaporation gave a light brown crystalline residue. Recrystallisation from $CHCl_3$ gave **25** (507 mg) m.p. 152–157°, (Found: C, 57.3; H, 5.0. $C_8H_8O_4$ Requires: C, 57.1; H, 4.8%), τ [$(CD_3)_2CO$] 3.20 (1 H, m), 4.83 (1 H, t), ν_{max} 1785, 1710 cm^{-1}.

Reaction of the bromolactone **18** *with sodium hydroxide*

The bromoacid **18** (68 mg) dissolved in water (5 ml) containing NaOH (30 mg) was set aside for 10 min. Acidification, extraction with EtOAc (× 4), and work-up in the usual way gave **24** (41 mg) identical with the compound previously prepared.

Preparation of the lactone acid **26**

(a) The lactone **18** (6.11 g), hydroxylamine hydrochloride (6.82 g), and collidine (200 ml) were heated at 120° for 2 hr. The cooled soln was acidified to pH 1 with HI and continuously extracted with ether for 56 hr. Evaporation of the ether extract gave a residue which on trituration with $CHCl_3$ gave **26** (1.58 g), m.p. 150–152°, (acetone–petroleum ether b.p. 60–80°), (Found: C, 51.6; H, 5.3. $C_8H_{10}O_5$ Requires: C, 51.6; H, 5.4%), τ (CF_3CO_2H) 4.5 (1 H, m), 5.06 (1 H, m). The mother liquors were esterified with diazomethane and chromatographed on silica gel. Elution with ether–acetone (9:1) first gave the methyl ester of **24** (1.087 g) and then the *methyl ester of* **26** (636 mg), m.p. 71–73° (benzene–petroleum ether b.p. 60–80°), (Found: C, 54.4; H, 6.1. $C_9H_{12}O_5$ Requires: C, 54.0; H, 6.0%), τ 4.98 (1 H, dt), 5.52 (1 H, q), ν_{max} 1770, 1730 cm^{-1}.

The methyl ester of **26** was acetylated (Ac_2O–pyridine) to give the *acetate*, m.p. 89–90.5° (CCl_4), (Found: C, 54.8; H, 5.8. $C_{11}H_{14}O_6$ Requires: C, 54.5; H, 5.8%), τ 4.64 (1 H, q), 4.92 (1 H, m), 7.99 (3 H, s), ν_{max} 1775, 1740, 1735 cm^{-1}. The methyl ester of **26** was also *p*-phenylbenzoylated to give an *ester* identical to that obtained from Jones's oxidation of the Corey aldehyde **1** R = *p*-phenylbenzoyl) followed by treatment with diazomethane, m.p. 145–146° (MeOH), (Found: C, 69.7; H, 5.3. $C_{22}H_{20}O_6$ Requires: C, 69.5; H, 5.3%).

(b) Reflux of **19** (303 mg) with NaOAc (618 mg), hydroxylamine hydrochloride (522 mg), water (3.5 ml) and isopropanol (7.5 ml) for 12 hr gave a 4:1 mixture of **26**:**24** (272 mg). Similar reaction of **18** gave a 4:5 ratio.

(c) The bromolactone (5.98 g) in 48% HBr–AcOH (23 ml) and AcOH (7 ml) was heated at 100° for 1 hr. The cooled soln was poured into water, extracted with EtOAc (× 4), and worked up in the usual way to give **31** (6.24 g), τ [$(CD_3)_2CO$] 4.64 (1 H, q), 5.68 (1 H, m), 8.00 (3 H, s). Recrystallisation from ether–petroleum ether b.p. 60–80° gave a solid, m.p. 110–113° but satisfactory analyses could not be obtained due to ready loss of HBr.

The acetate **31** (4.7 g) was dissolved in excess 8% NaOH aq and set aside from 30 min. After acidification to pH 1 with HCl the soln was continuously extracted with ether for 39 hr. After evaporation of the extract the product was triturated with ether to give **26** (2.69 g).

The acetate **31** (3.51 g) was stirred in water (25 ml) containing $NaHCO_3$ (1.92 g) for 1 hr. The soln was acidified to pH 1 with 2N HCl and extracted with EtOAc (× 5). Work-up in the usual way gave **27**, m.p. 177–184°, (acetone–petroleum ether b.p. 60–80°), (Found: C, 52.5; H, 5.3. $C_{10}H_{12}O_6$ Requires: C, 52.6; H, 5.3%), τ (CF_3CO_2H), 4.32 (1 H, q). 4.63 (1 H, m), 7.81 (3 H, s).

(d) The ketoacid **5** (24.12 g) was dissolved in 45% HBr in AcOH (90 ml) and heated at 60° for 1 hr. The excess reagent was distilled off and the crystalline residue dissolved in glacial AcOH (200 ml). NaOAc (2.42 g) and 40% peracetic acid (32 ml) were added and the soln stirred at room temp for 12 hr. Conc H_2SO_4 (24 ml) was added and the soln stirred for a further 12 hr. Sodium metabisulphite was then added and the soln diluted with water, saturated with NaCl, and extracted with EtOAc (× 5). Work-up in the usual way gave an oil which was dissolved in water (100 ml) and a soln of NaOH (40.5 g) in water (50 ml) added dropwise with stirring and cooling. After 1 hr at ambient temp the soln was acidified to pH 1 with 10N HCl and the volume reduced to *ca* 50% by warming *in vacuo*. Continuous extraction with ether for 3·5 hr gave an oil (11 g) and **26** (1.36 g). Extraction for a further 37 hr gave the acid (12.1 g). The yield based on **5** is 46%.

Preparation of the acetoxy alcohol **29**

(a) The acid **27** (1.135 g) in THF (40 ml) at 0° was treated sequentially with Et_3N (0.505 g) and ethyl chloroformate (0.543 g) and the mixture stirred for 15 min. The solid was filtered off and $NaBH_4$ (0.7 g) added to the filtrate. After 3 hr at 0° 2N HCl was added and the mixture extracted with EtOAc (× 5). Work-up in the usual way gave **29** as an oil (0.443 g), τ 5.00 (2 H,)m, 6.42 (2 H, d), 7.96 (3 H, s), ν_{max} 3500, 1780, 1740 cm^{-1}, (Mass measurement Found: 214.0835. $C_{10}H_{14}O_5$ Requires: 214.0841).

(b) The γ-lactone **27** (1.135 g) was added to dicyclohexylcarbodiimide (1.032 g), pyridine (0.396 g), and thiophenol (0.55 g) in CH_2Cl_2 (50 ml) and the mixture stirred overnight. The urea was filtered off and washed with EtOAc. The soln was washed with 2N HCl, $NaHCO_3$ aq and worked up in the usual way to give the *thiolo ester* (1.544 g), ν_{max} 1780, 1740, 1695 cm^{-1}, m^+ 320. A portion of the thiolo ester (995 mg) in EtOH (15 ml) was stirred with W2 Raney Ni for 1.5 hr. After filtration through a pad of Celite and washing the pad with EtOAc, evaporation of the solvent gave **29** (593 mg).

Preparation of the Corey alcohol **30**

The acid **26** (739 mg) in water (10 ml) was neutralised with 5% NaOH aq (phenolphthalein) then a solution of *p*-bromophenacyl bromide (1.22 g) in MeOH was added and the mixture refluxed for 1.25 hr. On cooling **28** (736 mg) separated, m.p. 158–160° (acetone–petroleum ether b.p. 60–80°) (Found: C, 50.5; H, 4.4; Br, 21.0. $C_{16}H_{15}BrO_4$ Requires: C, 50.2; H, 4.0; Br, 20.9%). The phenacyl ester (344 mg), *p*-phenylbenzoyl chloride (365 mg) and pyridine (6 ml) were stored at ambient temp for 2.5 hr. The soln was poured into water, extracted with $CHCl_3$ (× 3) and worked up in the usual way to give the *phenylbenzoate* (423 mg), m.p. 161–163° (acetone–petroleum ether b.p. 60–80°) (Found: C, 62.0; H, 4.3; Br, 14.1. $C_{29}H_{23}O_5Br$ Requires: C, 61.8; H, 4.1; Br, 14.2%). This ester (104 mg) in glacial AcOH (10 ml) was stirred with Zn dust (960 mg) for 1.25 hr. The mixture was diluted with ether, filtered, and the filtrate concentrated. Excess $NaHCO_3$ aq was added and the soln extracted with ether. The aqueous phase was then acidified with 2N H_2SO_4 and extracted with CH_2Cl_2 (× 4). Work-up in the usual way gave **28** (52 mg), m.p. 174.5–175.5° (EtOAc–petroleum ether

b.p. 60–80°), (Found: C, 68.9; H, 5.1. $C_{21}H_{18}O_6$ Requires: C, 68.8; H, 5.0%), which was identical to a sample prepared by Jones's oxidation of the Corey aldehyde **1** R = *p*-PhC$_6$H$_4$CO).

Diborane was passed into a soln of **28** (366 mg) in THF (5 ml) at 0°. After 45 min water was added and the soln extracted with EtOAc (× 5) and worked up in the usual way to give **30** (171 mg), m.p. 150–152°, identical with an authentic sample.

Scheme 1. *Preparation of the γ-lactone diol* **36**

The chloroacid **19** (5.193 g) in THF (50 ml) containing one drop of DMF was cooled to 0° and oxalyl chloride (2.33 ml) added dropwise. After the vigorous effervescence had subsided the flask was aspirated for a few min and then a soln of lithium tri-t-butoxyaluminium hydride (*ex* 2.114 g LAH) in THF (50 ml) was added and the mixture stirred for 30 min. at 0°. 1N HCl was added carefully, followed by EtOAc. The aqueous layer was further extracted with EtOAc (× 3) and the combined organic extracts were shaken with $NaHCO_3$ aq and then worked up in the usual way to give a dark oil which was chromatographed on silica gel. Elution with ether–acetone (9:1) gave the crystalline alcohol (2.529 g), m.p. 96–99° (acetone–petroleum ether b.p. 60–80°) τ 5.10 (1 H, m), 5.74 (1 H, q), 6.07 (2 H, d, J ≡ 8 Hz).

The alcohol (1.135 g) in CH_2Cl_2 (5 ml) was added to a soln of CrO_3 (3.575 g) and pyridine (5.74 ml) in CH_2Cl_2 (100 ml) and stirred at ambient temp for 15 min. After addition of EtOAc the organic soln was decanted, washed with 1 N HCl and worked up in the usual way to give **32** (645 mg), τ 0.24 (1 H, s), 4.78 (1 H, m), 5.60 (1 H, m), which solidified on trituration with ether. This compound could not be purified readily and was used as soon as possible after preparation.

Dimethyl 2-oxoheptylphosphonate (2.763 g) was dissolved in dry dimethoxy ethane (175 ml) and sodium hydride (486 mg of 50% dispersion in paraffin) added in portions with vigorous stirring. The soln was cooled to −30° and a soln of **32** (1.57 g) in dimethoxyethane (10 ml) added. The mixture was kept at −15° to −20° for 40 min then diluted with a mixture of ether and EtOAc, water added, and worked up in the usual way. The product was chromatographed on silica gel. After removal of paraffin elution with ether gave three fractions (i) mainly **34** (298 mg), (ii) pure **34** (826 mg), and (iii) the *tricyclic enone* **33** (50 mg). The *enone* **34** was recrystallised from benzene-petroleum ether b.p. 60–80°, m.p. 65–67°, τ 3.08 (1 H, dd, J = 15 and 7 Hz), 3.76 (1 H, d, J = 15 Hz), 5.18 (1 H, d, J = 4 Hz), 5.68 (1 H, q, J = 4 Hz). The tricyclic enone **33** was an oil, τ 3.44 (1 H, dd, J = 15 and 5 Hz), 3.76 (1 H, d, J = 15 Hz), 5.60 (1 H, bs).

Zinc borohydride soln (20 ml of a soln prepared from 4.24 g $NaBH_4$ and 290 ml ether) was added to **34** (419 mg) in dimethoxyethane (20 ml). After stirring at ambient temp for 2 hr the soln was diluted with EtOAc, shaken with 10N HCl and worked up in the usual way to give **35** (415 mg), τ 4.22 (2 H, m), 5.27 (1 H, m), 5.72 (1 H, m), 5.92 (1 H, m).

The epimers **35** (421 mg) in THF (10 ml) were treated with 9.5% NaOH aq (6.2 ml) and 30% H_2O_2 (3 ml). After 20 min a few drops of 2N HCl were added and the soln extracted with EtOAc (× 3). After washing the extracts with sodium metabisulphite work-up in the usual way gave **36** (330 mg) as an oil. Comparison of this sample with an authentic 1:1 mixture of the C-15 epimers of **36** by tlc, and NMR established their identity. Similar comparison of the diacetates confirmed the assignment of structure.

6-exo-*Chloro*-3-*oxo*-2-*oxabicyclo*-[3.2.1]*octane*-8-*anti-carbonyl chloride* [*acid chloride of acid* **19**]

The acid **19** (6.0 g) was suspended in dry toluene (24 ml) containing a catalytic quantity of dry DMF (0.15 ml) under an argon atmosphere. $SOCl_2$ (3.174 ml) was then added and the suspension stirred and heated at 50° until a clear soln was obtained (usually in about 4 hr). (The evolved gases were led through a $CaCl_2$ tower to a water scrubber). Heating was continued for a further 30 min and then most of the excess $SOCl_2$ and residual HCl and SO_2 dioxide removed, by holding the soln, still at 50°, under a slight vacuum (*ca* 20" water) for 30 min. Addition of hexane (22 ml) over 10 min then precipitated most of the product as a dense white crystalline solid. With the heating bath removed, precipitation was completed by the addition of more hexane (26 ml). The mixture was stirred for 1 hr, periodically evacuating and refilling the reaction vessel with argon. The supernatant liquors were then removed *in situ* by suction through a sinter-tipped glass tube pushed through the suspension to the bottom of the flask at the same time keeping the contents under positive argon pressure from a balloon. The residual solid was stirred overnight with dry toluene (14.6 ml) and then the suspension was treated with hexane (29 ml) and stirred a further 1 hr before removing the supernatant liquors as previously described. The residue was finally stirred for 2 hr with fresh hexane (29 ml) which was again removed by suction *in situ*. The hexane-damp, white, moisture-sensitive, crystalline acid chloride now free from catalyst poisons, was used directly in the next stage but could be vacuum dried (6.02 g) (92%), ν_{max} (mull) 1762, 1722 cm^{-1}. τ [$(CD_3)_2CO$] 4.85 (1 H, m), 5.3 (1 H, m), 6.0 (1 H, bs).

6-exo-*Chloro*-3-*oxo*-2-*oxabicyclo*-[3.2.1]*octane*-8-*anti-carboxyaldehyde* **32**

A soln of the acid chloride (6.02 g) in AR acetone (48 ml) was added from a syringe *via* a septum cap to a soln of dimethylaniline (4.36 ml) in AR acetone (27 ml) containing 3% Pd/C (2.18 g) all under argon. The argon was exchanged for H_2 and with the reaction vessel connected to a gas-burette supplying H_2 at NTP, the mixture was vigorously stirred. Theoretical H_2 uptake was observed after 40–60 min. After exchange of H for argon, the mixture containing **32** (*ca* 90%) was used directly. Crude **32** could be obtained as a gum containing EtOAc (*ca* 10%) as follows. The soln was filtered through Hyflo and evaporated to a residue which was partitioned between EtOAc (120 ml) and 2N HCl (1 × 30 ml, 1 × 20 ml). The combined aqueous layers were extracted with EtOAc (30 ml) and the combined organic layers washed with brine (3 × 20 ml), dried and evaporated to give crude **32** as a gum (5.087 g), τ 0.24 (1 H, s), 4.78 (1 H, m), 5.60 (1 H, m). Tlc R_f *ca* 0.5 (10% v/v MeOH/$CHCl_3$) visualised by UV and ceric sulphate. Attempts to purify **32** by column chromatography led to decomposition. The compound was fairly stable in soln but darkened at room temp when isolated.

Scheme 2. 4*β*-[4-(3-*Chloro-phenoxy*-3-*oxobut*-1-trans-*enyl*]-2.3.3a*β*6 a*β*-*tetrahydro*-5*α*-*hydroxy*-2-*oxocyclopenteno* [*b*] *furan* **41**

The complete Rosenmund mixture containing **32** (*ca* 5.09 g) was treated under argon with toluene-*p*-sulphonic acid (monohydrate) (4.53 g) in dry MeOH (22 ml) and stirred overnight at ambient temp. Tlc showed clean conversion to **37** R_f *ca* 0.8 (10% v/v MeOH/$CHCl_3$) visualised by ceric sulphate (non-UV-active). [Hydroxyester **37** could be isolated as follows: a soln of crude **32** (*ca* 5.09 g) isolated as described, in MeOH (20 ml) containing toluene-*p*-sulphonic acid (0.20 g) was allowed to stand overnight. Saturated $NaHCO_3$ aq (6–8 ml) was added and most of the MeOH was evaporated. The residue was partitioned between EtOAc (80 ml) and water (30 ml) followed by brine (30 ml). The EtOAc was evaporated to a gum (5.4 g) which was chromatographed on a Kieselgel 60 column eluted with 5% Pr^{i}OH/Ph.CH_3 to afford **37** as a gum (3.98 g), τ 5.85 (3 H, m), 6.33 (3 H, s), 6.60 (3 H, s), 6.64 (3 H, s)].

Continuing the telescoped sequence, the mixture was then treated rapidly at ambient temp with a soln of NaOH (7.63 g) in water (53 ml) and allowed to stand for 1 hr. Tlc now showed the Na salt (40) at R_f 0–0.1 (20% v/v $(Me_2)CO/CH_2Cl_2$) visualised with ceric sulphate (non-UV-active). 6N HCl (44 ml) was then added and the mixture set aside for 3 hr. Tlc now showed **2** as a rather diffuse spot, R_f *ca* 0.3–0.4 (40% v/v Me_2CO/CH_2Cl_2) visualised by ceric sulphate. The soln was

filtered through Hyflo to remove the catalyst washing with acetone (7 ml)–water (13 ml). The filtrate was neutralised with K_2CO_3 (*ca* 14.8 g)and then the phosphonate (8.54 g) was added, followed by acetone (22 ml) to assist its dissolution. The stirred mixture was treated with K_2CO_3 (10 g) in water (52 ml) over 45 min. After stirring for 30 min after the addition, the reaction was treated with glyoxylic acid (4.36 g) to convert the excess of the neutral phosphonate to the alkali soluble acid (A)† allowing 30 min for this reaction. The mixture was extracted with toluene (110 ml) and the aqueous layer further extracted with a toluene (65 ml)–EtOAc (44 ml) mixture. The combined organic layers were washed with sat $NaHCO_3$ aq (65 ml) [to remove (A) and excess glyoxylic acid], then 2N HCl (1 × 130 ml, 1 × 45 ml) to remove $PhNMe_2$, then brine (85 ml) and finally dried, decolourised with charcoal (1.0 g) and evaporated at *ca* 50° to *ca* 30 ml. On cooling **41** crystallised out. It was filtered off and washed with a toluene (30 ml)–hexane (22 ml) mixture, then with hexane (10 ml) and dried *in vacuo* to give **41** (3.55 g) [36% from **19**], m.p. 101–102°, ν_{max} 3360, 1755, 1695 cm^{-1}, τ [$(CD_3)_2CO$] 2.50–3.3 (5 H, m), 3.54 (1 H, d, J = 16.5 Hz), 5.04 (2 H, s), 5.00 (1 H, m), 5.85 (2 H, m), (Found: C, 60.3; H, 5.2; Cl, 10.6. $C_{17}H_{17}OCl$ Requires: C, 60.6; H, 5.1; Cl, 10.5%).

Scheme 3

A Rosenmund reduction was carried out on 0.249 × the scale described earlier. Under argon, the soln containing **32** (*ca* 1.27 g) was diluted with water (3 ml) and then the phosphonate (2.74 g) was added followed dropwise by a soln of K_2CO_3 (1.3 g) in water (10 ml) over 15 min. After 10 min tlc showed complete conversion to **42** R_f 0.7–0.8 (20% v/v Me_2CO/CH_2Cl_2) visualised by UV and ceric sulphate. [Enone **42** could be isolated as follows: The mixture was treated with glyoxylic acid (1.3 g) and K_2CO_3 (4.0 g) (as in Scheme 2) and stirred for 10 min. It was then acidified (2N HCl) to pH 6 and filtered through Hyflo washing with acetone (5 ml) and water (2 ml). The acetone was evaporated *in vacuo* at ambient temp and the residue partitioned between EtOAc (50 ml) and 2N HCl (20 ml). The aqueous layer was re-extracted with EtOAc (15 ml) and the combined organic layers were washed in turn with 2N HCl (5 ml), sat $NaHCO_3$ aq (2 × 10 ml) and NaCl aq (10 ml) then dried and evaporated to give a gum (1.543 g) which crystallised on stirring in MeOH (4 ml)–ether (10 ml). Crystalline **42** was filtered off and washed with ether (10 ml) [0.696 g (29.6%) from **1**], m.p. 111–114°, ν_{max} 1722, 1710 cm^{-1}, τ 2.5–3.3 (5 H, m), 3.45 (1 H, d, J = 16.5 Hz), 5.15 (1 H, m), 5.3 (2 H, s), 5.75 (1 H, m), (Found: C, 57.7; H, 4.5; Cl, 19.7. $C_{17}H_{16}O_4Cl_2$ Requires: C, 57.5; H, 4.5; Cl, 20.0%)].

Continuing with the telescoped process, the mixture was brought to pH 4 with 50% HCl then filtered through Hyflo. Toluene-*p*-sulphonic acid (1.13 g) was added and the soln set aside for 13 days at ambient temp. Tlc now showed **43**, R_f 0.3 (20% v/v Me_2CO/CH_2Cl_2) visualised with ceric sulphate. The pH was adjusted to 8–9 with K_2CO_3 to effect cyclisation to **41** and then glyoxylic acid (1.3 g) and K_2CO_3 (4.0 g) were added as in Scheme 2. After 1½ hr the mixture was neutralised with 2N HCl (*ca* 5 ml). The acetone was evaporated and the residue partitioned with EtOAc (2 × 90 ml) and water (30 ml). The combined organic extracts were washed successively with 2N HCl (1 × 50 ml, 1 × 30 ml), Na_2CO_3 aq (2 × 20 ml) and then brine (20 ml) and were dried and decolourised with charcoal. Evaporation of the solvent left a gum which crystallised on trituration with EtOAc (1.4 ml)–ether (14 ml) to give **41** isolated as in Scheme 2 [0.331 g, 13.5% from **19**] identical to the sample from Scheme 2.

†The formation of acid (A), *m*-$ClC_6H_4OCH_2$-$COCH{=}CHCO_2H$, was used as a device for the removal of excess phosphonate.

Scheme 3. *Non-telescoped*

Crude **42** (1.543 g) prepared as described above was dissolved in THF (18 ml) and water (6 ml) containing toluene-*p*-sulphonic acid (0.6 g) and the soln allowed to stand for 6 days at room temp. Sat K_2CO_3 aq was added to pH 8–9 and after 1½ hr the mixture was neutralised with 2N HCl. The THF was removed *in vacuo* and water (30 ml) was added. The mixture was extracted with EtOAc (2 × 90 ml) which in turn was washed with $NaHCO_3$ aq (40 ml) and brine (30 ml) and then dried and decolourised with charcoal. Evaporation of the solvent left a gum which crystallised on stirring under ether (20 ml)–EtOAc (5 ml) to afford **41** isolated as in Scheme 2 [0.567 g, 25.5% from (**19**)], identical to the sample from Scheme 2.

Scheme 4

A Rosenmund mixture prepared on 0.224 × scale of Scheme 2 containing **32** (1.138 g) was filtered free from the catalyst and then treated with toluene-*p*-sulphonic acid (1.275 g) in water (5 ml) and allowed to stand 7 days at room temp. Tlc then showed **44** as the main spot at R_f *ca* 0.2 (20% v/v Me_2CO/CH_2Cl_2) visualised by ceric sulphate. The stirred soln was treated with the phosphonate (1.96 g) followed dropwise by K_2CO_3 (3.69 g) in water (16 ml) over 1 hr. After 40 min glyoxylic acid (1.0 g) was added as in Scheme 2. After 30 min the mixture was extracted with toluene (30 ml) and then toluene–EtOAc (2:1, 2 × 30 ml). The combined organic layers were washed with 2N HCl (20 ml), sat $NaHCO_3$ (20 ml) and finally brine (20 ml). The organic phase was dried and then evaporated to a gum which crystallised on trituration with toluene to give **41**, (0.754 g) [30.6% from **19**] isolated as in Scheme 2, and identical to the sample from the latter.

4β-[4-(3-Chloro-phenoxy-3-oxobut-1-trans-enyl]-2.3.3 aβ,6 aβ-tetrahydro-5-(4-phenylbenzoyloxy)-2-oxocyclopenteno [b] furan **45**

The hydroxyenone **41** (3.36 g) was dissolved under argon in a mixture of dry toluene (20 ml), THF (10 ml) and pyridine (4 ml). The soln was treated with *p*-phenylbenzoylchloride (3.80 g) and stirred overnight. EtOAc (20 ml) was added and the mixture extracted with water (15 ml) then sat $NaHCO_3$ aq (20 ml), and finally brine. The dried extracts were evaporated to leave a solid which crystallised from acetone (25 ml)–ether (100 ml) to afford **45** (3.6 g) (70%) m.p. 139–142°, 1760, 1710, 1695 cm^{-1}, τ 1.9–3.95 (14 H, m) 3.54 (1 H, d, J = 16 Hz), 4.45–5.05 (2 H, m), 5.34 (2 H, s). (Found: C, 69.6; H, 4.9; Cl, 6.9. $C_{30}H_{25}O_6Cl$ Requires: C, 69.7; H, 4.9, Cl, 6.9%).

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