The Acetoxyfulvene Synthesis of Prostaglandins. Part 1.[1] Synthesis of the Corey Aldehyde

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A short and practical alternative synthesis of the Corey aldehyde (2), a key intermediate in prostaglandin synthesis, is described. 6-Acetoxyfulvene (7) underwent a Diels–Alder reaction with 2-chloroacrylonitrile to give 7-acetoxymethylene-2-chlorobicyclo[2.2.1]hept-5-ene-2-carbonitrile (8) which was converted sequentially into 2-chloro-7-*anti*-formylbicyclo[2.2.1]hept-5-ene-2-carbonitrile (10) and its 7-*syn*-isomer (11). The factors controlling the stereochemistry at C(7) in the *anti*- and *syn*-aldehydes (10) and (11) are discussed in detail.

In a study of the effect of structural modification of prostaglandin $F_{2\alpha}$ (1) on the separation of reproductive [2] from smooth muscle activity, we wished to synthesise a series of analogues with modified side chains. Shortly after we began the study, Corey [3] published a synthesis ideally suited to our purpose in which the two side chains of $F_{2\alpha}$ (1) were sequentially elaborated by Wittig-type reactions from the aldehyde (2). Unfortunately, Corey's synthesis of this key aldehyde (2) was unsuitable for large scale preparations for the following reasons.

First, a key step in the synthesis is the construction of the 7-substituted bicycloheptene (4) by a Diels–Alder reaction of 2-chloroacrylonitrile with 5-methoxymethylcyclopenta-1,3-diene (3). 5-Alkylcyclopentadienes are known to rearrange through a 1,5-hydrogen shift to the 1-alkyl isomers [5-methylcyclopentadiene has a half-life of 40 min at 20 °C (ref. 4)] and Corey's group had to use a catalyst [copper(II) tetrafluoroborate] to enable their 5-methoxymethyl analogue to participate in the Diels–Alder reaction before it could rearrange to the 1-isomer (5). Nevertheless even under the most carefully controlled conditions, some isomerisation did take place before Diels–Alder cycloaddition and the required bicycloheptene (4) was obtained contaminated with its isomer (6) and had to be purified by chromatography. We found that on a moderate scale (2 mol) the unwanted isomer (6) became the major (and sometimes the sole) product. The use of thallium(I) cyclopentadienide was claimed [3] to give a product less prone to isomerisation which yielded a higher proportion of required bicycloheptene. However, we ruled this out as a viable large-scale alternative on toxicity grounds.[5]

Secondly, the synthesis used a number of other toxic and hazardous reagents. For example, chloromethyl ethers used in the preparation of the 5-substituted cyclopentadiene (3) are invariably contaminated with significant amounts of the potent, volatile carcinogen bischloromethyl ether;[6,7a] in the later stages of the synthesis boron tribromide [7b] was used to cleave the methyl ether; and finally the resulting primary alcohol was oxidised to the aldehyde (2) using the pyrophoric Collins reagent.[8]

We now describe an alternative synthesis of the Corey aldehyde (2) which avoids these problems and which has been used both on the large scale in the laboratory and also in the manufacture of the prostaglandin analogues

[1] Preliminary communication, E. D. Brown, R. Clarkson, T. J. Leeney, and G. E. Robinson, *J.C.S. Chem. Comm.*, 1974, 642; B.P. 1,353,922.

[2] M. Dukes, W. Russell, and A. L. Walpole, *Nature*, 1974, **250**, 330.

[3] (*a*) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 5675; (*b*) E. J. Corey, U. Koelliker, and J. Neuffer, *ibid.*, 1971, **93**, 1489; (*c*) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *ibid.*, p. 1491.

[4] S. McLean and P. Haynes, *Tetrahedron*, 1965, **21**, 2329.

[5] E. C. Taylor and A. McKillop, *Accounts Chem. Res.*, 1970, **3**, 338; E. L. Browning, 'Toxicity of Industrial Metals,' Butterworths, London, 1961.

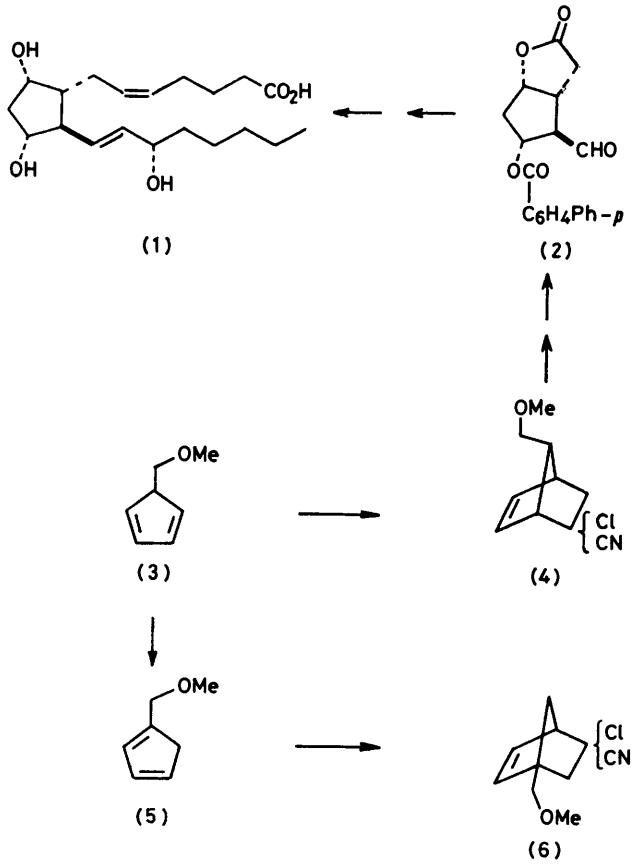
[6] L. S. Frankel, K. S. McCallum, and L. Collier, *Environ. Sci. Technol.*, 1974, **8**, 356.

[7] N. Irving Sax, 'Dangerous Properties of Industrial Materials,' Van Nostrand–Rheinhold, New York, 1975, (*a*) p. 631, (*b*) p. 468.

[8] L. F. Fieser and M. Fieser, 'Reagents for Organic Synthesis,' Wiley, New York, 1976, p. 146.

cloprostenol [9] ('Estrumate'*) and fluprostenol [9] ('Equimate'*).

The fundamental problem of the Corey synthesis,

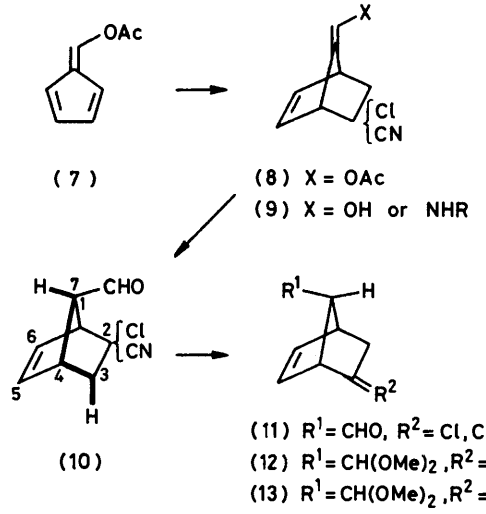


the diene isomerisation, was avoided by using 6-acetoxyfulvene (7) (prepared in two simple steps from cyclopentadiene [10]) as the diene in the Diels–Alder reaction. A further advantage of this approach is that the enol acetate function in acetoxyfulvene (7), which becomes the formyl group in the Corey aldehyde (2), is present at the correct oxidation level.

6-Acetoxyfulvene (7) smoothly underwent a Diels–Alder reaction with 2-chloroacrylonitrile in refluxing cyclohexane to give the 7-acetoxymethylenebicycloheptenes (8) as a mixture of epimers at C(2). Acid-catalysed hydrolysis of the enol acetates (8) in acetone gave only the aldehydes (10) with the 'wrong', *anti*- † stereochemistry at C(7). This assignment was based on the n.m.r. spectrum, which showed a long range coupling (J 3 Hz, demonstrated by double resonance) between the C(7) proton and the C(3) *endo*-proton *via* the planar **W** conformation [11] shown. Models revealed that this coupling would only be present in the aldehyde with the *anti*-stereochemistry at C(7).

The formation of the *anti*-aldehyde (10) followed from protonation of the enol acetate (8) on the less hindered *syn*-face of the molecule. Enolisation of the aldehyde had clearly not taken place during hydrolysis and so more vigorous conditions were tried. However, establishment of equilibrating conditions for the *anti*-aldehyde (10) which did not cause extensive decomposition proved extremely difficult. Strongly basic conditions were totally unsatisfactory but prolonged treatment with dilute acid (2N-hydrochloric acid at 84 °C for 4 days) gave the *syn*-aldehydes (11) in moderate yield. The *syn*-stereochemistry was confirmed by the n.m.r. spectrum, which showed no coupling between the C(3) *endo*- and C(7) protons.

Although we could now obtain the required aldehyde (11) it was clear that we needed to improve the yield and shorten the time taken for the isomerisation to have a viable route. During the isomerisation of the aldehyde (10) C(7) clearly must become sp^2 hybridised. This is known to be disfavoured [12] as it increases angle strain in an already strained system. To help overcome the energy barrier to the formation of the intermediate (9) we decided to investigate isomerisation of the Schiff's bases corresponding to the aldehydes (10) and (11). This approach, designed to take advantage of the fact that tautomerism between imine and enamine takes place more readily than that between aldehyde and enol,[13] was amply justified. Treatment of the *anti*-aldehyde (10) with *p*-chloroaniline at room temperature, overnight, gave the *syn*-aldehyde (11) in high yield.



Before proceeding with the remainder of the synthesis it was necessary to protect the aldehyde function with a

* Trade marks of I.C.I.

† Used here to indicate that the 7-substituent was on the opposite side of the one carbon bridge to the double bond.

[9] N. S. Crossley, *Prostaglandins*, 1975, **10**, 5; D. Binder, J. Bowler, N. S. Crossley, J. Hutton, M. Senior, L. Slater, P. Wilkinson, and N. C. A. Wright, *Prostaglandins*, 1974, **6**, 87.

[10] K. Haffner, G. Schulz, and K. Wagner, *Annalen*, 1964, **678**, 39.

[11] V. Mark, *Tetrahedron Letters*, 1974, 299.

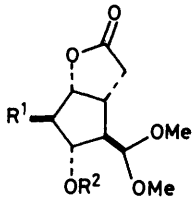
[12] H. C. Brown and J. Muzzio, *J. Amer. Chem. Soc.*, 1966, **88**, 2811.

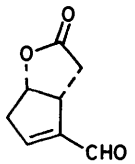
[13] For example, the Schiff's base from isobutyraldehyde and *p*-bromoaniline contains 18% of the enamine form at equilibrium (A. de Savignac and A. Lattes, *Bull. Soc. chim. France*, 1970, 4476).

group which could ultimately be removed without destroying the labile aldehyde (2). The dimethyl acetal group seemed the obvious choice and the acetals (12) were readily prepared using trimethyl orthoformate.

We now had available a straightforward six-stage synthesis of the acetals (12) complete with the appropriate functionality and stereochemistry needed to produce the Corey aldehyde. (2).

The remainder of the reaction sequence was analogous to that described by Corey. Hydrolysis of the chloronitrile (12) with sodium hydroxide in ethanolic dimethyl sulphoxide gave the crystalline ketone (13) in high yield. A Baeyer–Villiger reaction with alkaline hydrogen peroxide followed by iodo-lactonisation with potassium iodide–iodine gave the iodohydrin (14). The iodohydrin (14) was esterified with *p*-phenylbenzoyl chloride and the resulting iodo-ester (15) was deiodinated with tri-n-butyltin hydride to yield the acetal (16), the precursor of the Corey aldehyde (2).





(14) $R^1 = I$, $R^2 = H$

(15) $R^1 = I$, $R^2 = CO \cdot C_6H_4Ph\text{-}p$

(16) $R^1 = H$, $R^2 = CO \cdot C_6H_4Ph\text{-}p$

(17)

Deprotection of the acetal (16) initially caused problems as the aldehyde (2) readily lost 4-phenylbenzoic acid to give the αβ-unsaturated aldehyde (17). However the elimination was avoided by carrying out the hydrolysis of the acetal (16) in a two-phase system (2% propan-2-ol–chloroform and concentrated hydrochloric acid) and gave the Corey aldehyde (2) in high yield.

The aldehyde (2) thus obtained was identical with a sample prepared by the literature method.

This convenient eleven-stage route to the Corey aldehyde has proved to be extremely robust and easily operated even on the kilogram scale.

EXPERIMENTAL

M.p.s were recorded on a Kofler hot-stage apparatus. I.r. spectra were recorded on a Perkin-Elmer 157 spectrophotometer and are for liquid films unless otherwise stated. ^1H N.m.r. spectra were measured on a Varian HA100 (100 MHz) spectrometer, with tetramethylsilane as internal reference. Mass spectra were determined on an A.E.I. MS9 spectrometer. T.l.c. was carried out on Merck Kieselgel $60F_{254}$ plates. All organic solutions were dried over magnesium sulphate and evaporations were carried out *in vacuo*.

6-*Acetoxyfulvene* (7).—Sodium (46 g, 2 mol) was added in small pieces to cyclohexane (1.04 l) under nitrogen with stirring. Ethanol (92 g; 95%) was added slowly to the stirred suspension and the mixture refluxed for 2 h, after which most of the sodium had dissolved. The solution was then cooled to 5 °C and freshly distilled cyclopentadiene (139.2 g, 2.1 mol) in cyclohexane (100 ml) was added over 10 min. The mixture was stirred at 5 °C for 45 min after which ethyl formate (164.8 g, 2.84 mol) was added over 20 min with the temperature <10 °C. The cooling bath was removed and the stirred mixture allowed to warm to 50 °C over 25 min, after which the mixture was distilled to remove the ethanol as an azeotrope (770 ml of distillate collected). The suspension of the sodio-derivative of 6-hydroxyfulvene was diluted with cyclohexane (200 ml) and cooled to 5 °C with stirring. Acetic anhydride (204 g, 2 mol) was added slowly over 30 min with the temperature maintained at 10 °C, after which the mixture thickened and cyclohexane (400 ml) was added to allow stirring to continue for 30 min at room temperature. Water (400 ml) was added, stirring was continued for a further 15 min, and the mixture was filtered through a pad of Celite. The filter cake was washed with cyclohexane (total 300 ml) and the washings were combined with the filtrate. The aqueous phase was separated, washed with 2% sodium hydrogen carbonate solution (400 ml) and water (400 ml), and dried to give a deep red solution of 6-acetoxyfulvene (7) in cyclohexane, which was used in the next stage. Evaporation of a sample gave a yellow oil, δ($CDCl_3$) 2.25 (3 H, s, Ac), 6.45 (4 H, m), and 7.85 (1 H, d, C*H*OAc).

7-*Acetoxymethylene*-2-*chlorobicyclo*[2.2.1]*hept*-5-*ene*-2-*carbonitrile* (8).—The foregoing solution of 6-acetoxyfulvene (7) was diluted to 1 800 ml with cyclohexane and purged with nitrogen for 15 min. 2-Chloroacrylonitrile (490 g, 5.6 mol, 2.7 equiv. based on cyclopentadiene) was added and the mixture refluxed under nitrogen for 20 h. It was then filtered through Celite and evaporated. The resulting oil was diluted with methylene chloride (200 ml) and stirred for 12 h with activated charcoal (22 g). Filtration through Celite and evaporation gave the epimeric *enol acetates* (8) (287.4 g; 61% based on cyclopentadiene) as a yellow oil which was used directly. A sample purified by dissolution in ether and filtration was a pale yellow oil, $\nu_{max.}$ (film) 2 230, 1 760, and 1 650 cm^{-1}, δ($CDCl_3$) 2.08 and 2.10 (3 H, OAc), 6.24(m) and 6.52(m) (2 H, CH=CH), and 6.84 (1 H, s, =C*H*OAc) (Found: C, 58.7; H, 4.5; Cl, 16.4; N, 6.2. $C_{11}H_{10}ClNO_2$ requires C, 59.1; H, 4.5; Cl, 15.9; N, 6.2%).

2-*Chloro*-7-anti-*formylbicyclo*[2.2.1]*hept*-5-*ene*-2-*carbonitrile* (10).—The enol acetates (8) (447 g, 2 mol) were dissolved in acetone (2 l), 0.1N-hydrochloric acid (2 l) was added, and the mixture was refluxed under nitrogen for 21 h, cooled, adjusted to pH 4 with solid sodium hydrogen carbonate, and evaporated to remove acetone. The stirred aqueous residue was treated with methylene chloride (1 l) and adjusted to pH 7 using solid sodium hydrogen carbonate. The aqueous phase was separated and the organic phase washed with water (2 × 2 l) and dried. Evaporation gave the epimeric anti-*aldehydes* (10) (33.7 g, 93%) as an oil. Bulb-to-bulb distillation of a sample gave a waxy solid, m.p. 74—78 °C, $\nu_{max.}$ (film) 2 700, 2 230, and 1 720 cm^{-1}, δ($CDCl_3$) 1.75 (dd) and 2.26 (dd) (*J* 14 and 3 Hz) [1 H, 2 : 1 ratio, *endo*-C(3)H], 2.54 (dd) and 2.82 (dd) (*J* 14 and 4 Hz) [1 H, 1 : 2 ratio, *exo*-C(3)H], 2.86(m, *J* 3 Hz) [1 H, *syn*-C(7)H], 3.4(m) [C(5)H], 3.85(m) [C(1)H], 6.22(m) and 6.46(m) (2 H, CH=CH), and 9.63s and 9.57s (1 : 2 ratio, CHO) (Found: C, 59.9; H, 4.5; Cl, 19.3; N, 7.0. C_9H_8ClNO requires C, 59.5; H, 4.4; Cl, 19.7; N, 7.7%).

2-*Chloro*-7-syn-*formylbicyclo*[2.2.1]*hept*-5-*ene*-2-*carbonitrile* (11).—*Method A*. A solution of the *anti*-aldehydes

(10) (100 mg) in dioxan (2 ml) was purged with nitrogen. 2N-Hydrochloric acid (0.5 ml) was added and the stirred mixture heated at 84 °C for 4 days under nitrogen, cooled and diluted with methylene chloride (5 ml). The aqueous phase was separated and the organic layer washed with saturated aqueous sodium hydrogen carbonate (2 × 2 ml), dried, and evaporated to give the epimeric syn-*aldehydes* (11) (70 mg, 70%) as an oil, purified by bulb-to-bulb distillation, $\nu_{max.}$ 2 700m, 2 200, and 1 720 cm^{-1}, $\delta(CDCl_3)$ 1.82 and 2.30 [total 1 H, d, *endo*-C(3)H], 2.52 and 2.86 [total 1 H, dd, *exo*-C(3)H], 2.90 and 3.13 [total 1 H, s, C(7)H], 6.2 and 6.5 (total 2 H, m, CH=CH), and 9.52 and 9.60 (total 1 H, d, CHO) (Found: C, 59.3; H, 4.4; Cl, 19.2; N, 7.6. C_9H_8ClNO requires C, 59.5; H, 4.4; Cl, 19.6, N, 7.7%).

Method B. The *anti*-aldehydes (10) (337 g, 1.86 mol) and *p*-chloroaniline (284 g, 2.2 mol, 1.2 equiv.) were dissolved in propan-2-ol (2.7 l) containing acetic acid (335 ml) and the solution was stirred at room temperature, under nitrogen, for 24 h. The bulk of the solvent was evaporated off and the residue stirred with 2N-hydrochloric acid (1 250 ml) and methylene chloride (1 250 ml) for 30 min. The organic phase was separated and the aqueous phase extracted with methylene chloride (500 ml). The combined organic phase was washed with 2N-hydrochloric acid (1 250 ml) and 10% sodium chloride solution (2 × 1 l), dried, and evaporated to yield the epimeric *syn*-aldehydes (11) (364.8 g) as a dark viscous oil suitable for use in the next reaction.

2-*Chloro*-7-syn-*dimethoxymethylbicyclo*[2.2.1]*hept*-5-*ene*-2-*carbonitrile* (12).—The *syn*-aldehydes (11) (360 g) dissolved in a mixture of methanol (3 l), trimethyl orthoformate (318 g, 3 mol), and toluene-4-sulphonic acid monohydrate (19.0 g, 0.1 mol) were refluxed for 21 h. The solution was allowed to cool, sodium carbonate (8.4 g, 0.1 mol) was added to neutralise the acid, and the solvent was evaporated off. The residue was diluted with methylene chloride (100 ml) and vigorously stirred as hexane (3.5 l) was added. The black tar thus precipitated was separated and the solution filtered through Celite. The filtrate was evaporated, the residue redissolved in methylene chloride (450 ml); the solution was washed with water (2 × 250 ml), dried, and evaporated to give the epimeric *acetals* (12) [287 g, 63% from the *anti*-aldehyde (10)] as an oil, $\nu_{max.}$ 2 220 cm^{-1}, $\delta(CDCl_3)$ 1.7 and 2.18 [total 1 H, d, *endo*-C(3)H], 3.35 (6 H, d, OMe), 4.24 [1 H, d, C*H*$(OMe)_2$], and 6.1 and 6.35 (total 2 H, m, CH=CH) (Found: C, 57.8; H, 6.3; Cl, 15.6; N, 6.0. $C_{11}H_{14}ClNO_2$ requires C, 58.0; H, 6.2; Cl, 15.6; N, 6.2%).

syn-7-*Dimethoxymethylbicyclo*[2.2.1]*hept*-5-*en*-2-*one* (13).—A solution of the acetals (12) (214 g, 0.94 mol) in ethanol (2.1 l) and dimethyl sulphoxide (470 ml) was purged with nitrogen. Sodium hydroxide pellets (80 g, 2 mol) were added and the mixture refluxed under nitrogen for 20 h, cooled, diluted with water (2.5 l), and extracted with methylene chloride (4 × 1.25 l). The combined organic phase was washed with water (4 × 2 l), dried, and evaporated to give the *ketone* (13) (127 g, 74%) as a semi-crystalline mass suitable for use in the next stage. Bulb-to-bulb distillation of a sample gave the ketone (13), m.p. 44—45 °C, $\nu_{max.}$ (Nujol) 1 740 cm^{-1}, $\delta(CDCl_3)$ 1.97 (2 H, m, CH_2), 2.52 [1 H, d, C(7)H], 3.0 and 3.12 (each 1 H, m, bridgehead H), 3.24 and 3.29 (each 3 H, s, OCH_3), 4.38 [1 H, d, C*H*$(OMe)_2$], and 5.98 and 6.44 (each 1 H, m, CH=CH) (Found: C, 65.5; H, 7.7. $C_{10}H_{14}O_3$ requires C, 65.9; H, 7.7%).

trans-6-*Dimethoxymethyl*-cis-7-*hydroxy*-trans-8-*iodo*-cis-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (14).—A solution of the ketone (13) (364 g, 2 mol) in toluene (2.4 l) was stirred and cooled to 0 °C (bath at −10 °C) and a pre-cooled solution of sodium hydroxide (128 g, 3.2 mol) in water (2.4 l) was added. Hydrogen peroxide solution (29% w/v; 236 ml, 2 mol) was added dropwise to the stirred mixture while maintaining the temperature at 0 °C. The mixture was stirred at 0 °C for 4 h and the aqueous phase separated and washed with methylene chloride (3 × 1.5 l). The pale yellow aqueous solution was adjusted to pH 6 with glacial acetic acid and a solution of potassium iodide (664 g, 4.0 mol) and iodine (508 g, 2 mol) in water (2.4 l) was added at room temperature. After stirring for 16 h methylene chloride (2 l) was added followed by solid sodium disulphite to remove the excess of iodine. The separated aqueous layer was extracted with methylene chloride (2 × 1.5 l) and the combined organic phases were washed with water (500 ml), dried, and evaporated to give the *iodohydrin* (14) (373 g, 54%) as a solid which crystallised from ethyl acetate–hexane as needles, m.p. 90 °C, $\nu_{max.}$ (Nujol) 3 400 and 1 780 cm^{-1}, $\delta(C_5D_5N)$ 3.32 (6 H, d, OMe), 4.42 (2 H, m, CHI and C*H*OH), 4.62 [1 H, d, C*H*$(OMe)_2$], and 5.12 (1 H, m, CHO-CO) (Found: C, 35.3; H, 4.5%; M^+, 342 $C_{10}H_{15}IO_5$ requires C, 35.1; H, 4.4%; *M*, 342).

trans-6-*Dimethoxymethyl*-cis-7-(4-*phenylbenzoyloxy*)-cis-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (16).—The iodohydrin (14) (361 g, 1.05 mol) was dissolved in dry toluene (1 560 ml) containing pyridine (204 ml). *p*-Phenylbenzoyl chloride (275 g, 1.27 mol) was added and the mixture stirred for 22 h at room temperature. Hexane (3.6 l) was added, the mixture stirred for 2 h at 0 °C, and the solid filtered off. The product was washed with 3 : 2 hexane–toluene (3 × 100 ml) followed by hexane (2 × 100 ml) and then dissolved in chloroform (900 ml). This solution was washed with saturated aqueous sodium hydrogen carbonate (1 l), treated with activated charcoal (30 g), and filtered through Celite. The filtrate was diluted with ethanol (2.6 l) and allowed to crystallise to give the *iodo-ester* (15) (364 g, 66%), m.p. 156—157 °C, $\nu_{max.}$ 1 780, 1 715, and 1 605 cm^{-1}, $\delta(CDCl_3)$ 3.3 and 3.43 (each 3 H, s, OCH_3), 4.41 (1 H, q, CHI), 4.61 [1 H, d, C*H*$(OMe)_2$], 5.10 (1 H, q, C*H*$OCOCH_2$), and 5.65 (1 H, t, C*H*OCOAr) (Found: C, 52.8; H, 4.6. $C_{23}H_{23}IO_6$ requires C, 52.9; H, 4.4%).

The iodo-ester (15) (109.6 g, 0.21 mol) dissolved in toluene (1 l) was purged with nitrogen for 1 h. Tri-n-butyltin hydride (77 g, 0.7 mol) was added and the solution heated at 80 °C, under nitrogen, for 22 h, then evaporated to an oil. This was diluted with pentane (500 ml) to precipitate a gum. The pentane was decanted and the residual gum crystallised from toluene to give the *acetal* (16) (79.8 g, 96%), m.p. 114 °C, $\nu_{max.}$ 1 780, 1 715, and 1 610 cm^{-1}, $\delta(CDCl_3)$ 3.36 and 3.38 (each 3 H, s, OCH_3), 4.34 [1 H, d, C*H*$(OMe)_2$], 5.04 (1 H, m, C*H*$OCOCH_2$), and 5.45 (1 H, q, C*H*OCOAr) (Found: C, 69.7; H, 6.1. $C_{23}H_{24}O_6$ requires C, 69.8; H, 6.2%).

trans-6-*Formyl*-cis-7-(4-*phenylbenzoyloxy*)-cis-2-*oxabicyclo*[3.3.0]*octan*-3-*one* (2).—The acetal (16) (39.6 g, 0.1 mol) was dissolved in chloroform (1 980 ml; washed with water to remove ethanol and dried over $CaCl_2$) containing 2% propan-2-ol and stirred vigorously at room temperature with concentrated hydrochloric acid (495 ml) for 90 min. The separated organic phase was washed with saturated aqueous sodium hydrogen carbonate (200 ml) and the separated chloroform solution evaporated in the presence of sodium hydrogen carbonate solution (50 ml). The residue was taken up in ethyl acetate (500 ml) and separated from

the hydrogen carbonate solution; the solution was then dried, and evaporated till crystallisation commenced. This gave the Corey aldehyde (2) (27.8 g, 79%), m.p. and mixed m.p. 133—134 °C, $\nu_{max.}$ 1 760, 1 720, and 1 605 cm^{-1}, $\delta(CDCl_3)$ 5.15 (1 H, m, C*H*OCOCH$_2$), 5.79 (1 H, m, C*H*O-COAr), and 9.83 (1 H, s, CHO).

[8/320 *Received*, 23*rd February*, 1978]