Photosynthetic Routes to Prostaglandins. Synthesis of Prostaglandin-C_2 and Analogues [1]

By **Noelle M. Crossland** and **Stanley M. Roberts,*** The Ramage Laboratories, Department of Chemistry and Applied Chemistry, University of Salford, Salford, Lancashire M5 4WT
Roger F. Newton,* Exploratory Research Department, Glaxo–Allenburys Research Ltd., Ware, Hertfordshire SG12 0DJ

The 5-*endo*-7-*anti*-disubstituted bicyclo[2.2.1]heptan-2-ones (1)—(5) afforded the aldehydes (6)—(10) respectively on photolysis. The hydroxy-aldehyde (10) is a known intermediate in the synthesis of prostaglandin-C_2. The aldehydes (7)—(9) were converted into the 11,12-dehydroprostaglandin-$F_{2\alpha}$ derivatives (14)—(18).

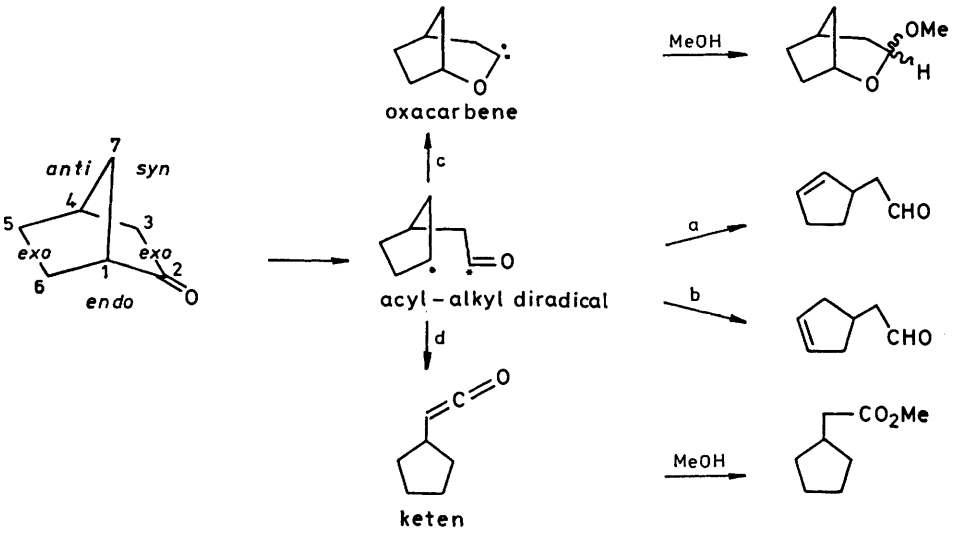
THE photochemistry of norbornan-2-one and its derivatives has been investigated at length.[2] Photolysis of simple norbornan-2-ones leads to excitation of the carbonyl chromophore and α-cleavage between C_1 and C_2 followed by one or more of the following events (see Scheme); (*a*) abstraction of H-7-*syn* by the acyl radical; (*b*) abstraction of H-6-*endo* by the acyl radical; (*c*) formation of an oxacarbene; (*d*) abstraction of H-3 by the alkyl radical. When a choice is available, the acyl radical generally prefers to abstract H-7-*syn* (path a) rather than H-6-*endo* (path b).[3] This preference is virtually nullified when a substituent is introduced at C-4 in the norbornanone skeleton.[4] When a substituent is introduced in the *syn*-configuration at C-7 the cyclopent-3-enylacetaldehyde (path b) forms the major product with lesser amounts of the ring-expanded product (path c).[5] Substitution at C-7-*syn* and C-6-*endo* leads to the ring-expansion reaction (path c) becoming predominant with a minor amount of product resulting from H-3 transfer (path d) and further reaction of the keten.[6] Ring-expansion reactions are observed to be favoured for norbornan-2-ones having a cyclopropyl ring fused adjacent to the carbonyl group.[7]

Substitution at C-3 in the norbornan-2-one can extend the range of products formed by causing α-cleavage of the bond C^2–C^3 to become competitive with the C^1–C^2 cleavage.[8]

In this paper, we show that 5-*endo*-,7-*anti*-disubstituted norbornanones react through pathway (a) after photo-excitation and that prostaglandin-C_2 and analogues can be prepared in this manner.

RESULTS AND DISCUSSION

Photolysis of 5-endo-7-anti-*Disubstituted Norbornan-2-ones.*—The norbornanones (1)—(5) required for this study were prepared by the reaction of the appropriate 3-*endo*-substituted tricyclo[3.2.0.0^{2,7}]heptan-6-one with cyanide ion, or a cuprate reagent, as we have described previously.[9-12]



SCHEME

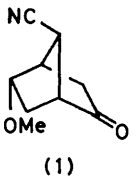
Photolyses of the ketones (1)—(5) were conducted using dilute solutions in methanol with sodium hydrogencarbonate as a buffer. A medium-pressure Hanovia lamp and Pyrex apparatus were employed. In all cases, analytical t.l.c. indicated a clean conversion to product(s).

After 72 h the bicyclic ketone (1) had been converted into a product, homogeneous by t.l.c., which was characterised as the cyano-aldehyde (6) [$\nu_{max.}$ 2 240 and 1 725 cm^{-1}; $\delta(CDCl_3)$ *inter alia* 9.4 (br s, 1 H, CHO), 6.5 (q, 1 H, CH=)].

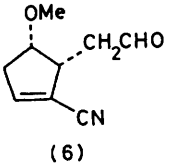
The aldehydes (7)—(10) were obtained on photolysis of the ketones (2)—(5) respectively, in modest yields (37—53%) after preparative chromatography. Spectral data were in accord with the proposed structures; particularly characteristic was the low-field (δ *ca.* 6.2) doublet in the n.m.r. spectra, a signal which has been observed previously for cyclopentenes bearing this substitution pattern.[13]

This new synthetic route to PG-C_2 is very efficient in that the use of protecting groups is minimised. The key photolysis step introduces the *endo*-cyclic double bond in the required position; simultaneously the embryonic α-side chain of the prostaglandin is released in the correct oxidation state at C-6 (prostaglandin numbering) for immediate chain-extension to be realised.

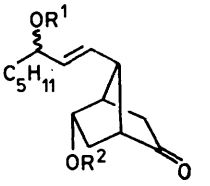
We employed the same strategy to construct some

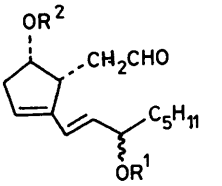


(1)

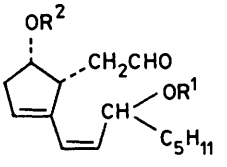


(6)

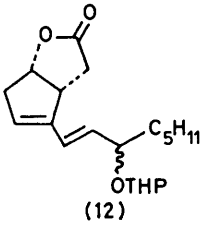




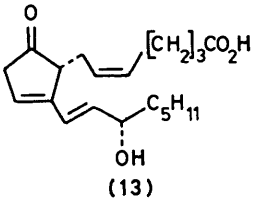
(2) $R^1 = R^2 = Si(Me)_2Bu^t$ (7)
(3) $R^1 = Si(Me)_2Bu^t$; $R^2 = Me$ (8)
(4) $R^1 = Si(Me)_2Bu^t$; $R^2 = CH_2Ph$ (9)
(5) $R^1 = THP$; $R^2 = H$ (10)



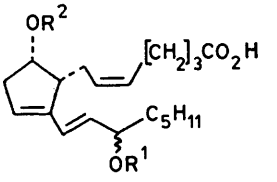
(11)



(12)



(13)



(14) $R^1 = R^2 = Si(Me)_2Bu^t$
(15) $R^1 = Si(Me)_2Bu^t$; $R^2 = Me$
(16) $R^1 = Si(Me)_2Bu^t$; $R^2 = CH_2Ph$
(17) $R^1 = H$; $R^2 = Me$
(18) $R^1 = COMe$; $R^2 = Me$

Chromatography separated the aldehydes (7)—(10) from trace amounts of a second photolytic product. We were unable to obtain pure samples of this second photoproduct, but we tentatively assign the structure (11) to these components on the basis of n.m.r. spectra of mixtures rich in these compounds. These spectra show that the minor products possess an aldehyde unit but the absence of a signal $6.5 \geqslant \delta \geqslant 6.0$ indicates some modification of the diene unit.

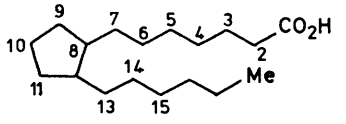
Synthesis of Prostaglandin-C_2 (PG-C_2) and Analogues.—The hydroxy-aldehyde (10) exists mainly as the bicyclic lactol: full structure elucidation was carried out on this unstable lactol and on the more stable lactone (12) which was isolated in high yield after Jones oxidation. The photolytic generation of the hydroxy-aldehyde (10) secures another pathway to PG-C_2 (13) utilising the prescribed methods from this known intermediate.[14]

PG-C_2 analogues. Thus the aldehydes (7)—(9) were reacted with the appropriate Wittig reagent to give the 9-alkoxy-derivatives (14)—(16) of 9-deoxo-PG-C_2. The silyloxy-bond in the acid (15) was cleaved by treatment with acetic acid in aqueous tetrahydrofuran over a period of four days to give the prostanoid (17) which partially acetylated under the reaction conditions to give the ester (18).

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded on a Varian EM 360 or a Perkin-Elmer R32 spectrometer in $CDCl_3$ unless otherwise stated. I.r. spectra were recorded on a Perkin-Elmer 257 spectrophotometer. Mass spectra were obtained using MS 12 and MS 9025 instruments. Silica gel MFC and alumina type H were used for column chromatography and silica gel G for t.l.c. Anhydrous magnesium sulphate was used as a drying agent for solutions in organic solvents.

Light petroleum refers to the fraction of b.p. 60—80 °C. The preparations of the bicycloheptanones (1),[9] (2),[11] (3),[12] (4),[12] and (5) [12] have been described. The octenylcyclopentenes (14)—(18) are named as derivatives of prostanoic acid, (19).



(19)

Photolysis Procedure.—The bicyclo[2.2.1]heptan-2-one (0.5 g) was dissolved in dry methanol (80 ml) containing sodium hydrogencarbonate (0.5 g). Argon was bubbled through the solution for 30 min, before commencement of irradiation using a medium-pressure mercury lamp and a Pyrex filter.

The solution was evaporated and the residue taken up in chloroform (30 ml). The solution was washed with water (30 ml) and the aqueous wash back-extracted with chloroform (3 × 30 ml). The combined organic extracts were dried and evaporated and the residue was purified by preparative chromatography.

(2-*Cyano*-5α-*methoxycyclopent*-2-*enyl*)*acetaldehyde* (6). This was obtained from the cyanonorbornanone (1) after 72 h, as an oil (50%); $\nu_{max.}$ 2 240 and 1 725 cm^{-1}; δ 9.4 (1 H, br s, CHO), 6.5 (1 H, q, H-3), 4.05 (1 H, m, H-5), 3.1 (3 H, s, OMe), and 3.25—2.50 (5 H, m, H-1 + 2 × CH_2); it gave a 2,4-dinitrophenylhydrazone derivative, m.p. 133—135 °C (Found: M^+, 345.017 4. $C_{15}H_{15}N_5O_5$ requires M, 345.017 3).

[2-(3′-*t*-*Butyldimethylsilyloxyoct*-1′E-*enyl*)-5-*t*-*butyldimethylsilyloxycyclopent*-2-*enyl*]*acetaldehyde* (7). This was obtained from the bis(silyloxy)-ketone (2) as an oil (37%); $\nu_{max.}$ 1 735 cm^{-1}; δ 9.7 (1 H, s, CHO), 6.05 (1 H, d, *J* 16 Hz, H-3), 5.4 (2 H, m, H-1′, H-2′), 4.5 (1 H, m, H-3′), 4.05 (1 H, m, H-5), 3.5 (1 H, m, H-1), 2.85—1.35 (12 H, m, 6 × CH_2), 0.85 (21 H, s, 7 × Me), and 0.05 (12 H, s, 2 × $SiMe_2$).

[2-(3′-*t*-*Butyldimethylsilyloxyoct*-1′E-*enyl*)-5α-*methoxycyclopent*-2-*enyl*]*acetaldehyde* (8). This was obtained from the ketone (3) as an oil (39%); $\nu_{max.}$ 1 730 cm^{-1}; δ 9.85 (1 H, s, CHO), 6.2 (1 H, d, *J* 16 Hz, H-3), 5.5 (2 H, m, H-1′, H-2′), 4.0 (2 H, m, H-5, H-3′), 3.25 (3 H, s, OMe), 3.5 (1 H, m, H-1), 2.9—1.1 (12 H, m, 6 × CH_2), 0.85 (12 H, s, 4 × Me), and 0.05 (6 H, s, $SiMe_2$).

[2-(3′-*t*-*Butyldimethylsilyloxyoct*-1′E-*enyl*)-5α-*benzyloxycyclopent*-2-*enyl*]*acetaldehyde* (9). This was obtained from the norbornanone (4) as an oil (45%); $\nu_{max.}$ 1 730 cm^{-1}; δ 9.85 (1 H, s, CHO), 7.25 (5 H, m, Ph), 6.15 (1 H, d, *J* 17 Hz, H-3), 5.7—5.3 (2 H, m, H-1′, H-2′), 4.4 (2 H, s, OCH_2), 4.35—3.8 (2 H, m, H-5, H-3′), 3.40 (1 H, m, H-1), 2.9—1.10 (12 H, m, 6 × CH_2), 0.85 (12 H, s, 4 × Me), and 0.05 (6 H, s, $SiMe_2$) (Found: M^+, 456.306 0. $C_{28}H_{44}O_3Si$ requires M, 456.306 0).

[2-(3′-*Tetrahydropyranyloxyoct*-1′E-*enyl*)-5α-*hydroxycyclopent*-2-*enyl*]*acetaldehyde* (10). This was obtained from the hydroxy-ketone (5) as an oil (53%); $\nu_{max.}$ 3 400 cm^{-1}; δ 6.3 (1 H, d, *J* 17 Hz, H-3), 5.6 (3 H, m, H-1, H-1′, H-2′), 4.65 (2 H, m, H-3′ + OCHO), 4.3—3.1 (4 H, m, H-5 + OH + OCH_2), 2.85—1.15 (19 H, m, H-1 + 9 × CH_2), and 0.85 (3 H, t, Me) (Found: $[M - H_2O]^+$, 318.220 2. $C_{20}H_{30}O_3$ requires $M - H_2O$, 318.219 5).

6-(3′-*Tetrahydropyranyloxyoct*-1′-*enyl*)-2-*oxabicyclo*[3.3.0]-*oct*-6-*en*-3-*one* (12). To a stirred solution of the hydroxyaldehyde (lactol) (10) (0.10 mmol) in diethyl ether (2 ml) was added Jones reagent (0.25 ml, 0.25 mmol). After 1 h the mixture was extracted with diethyl ether (4 × 20 ml) and the combined ether extracts were washed with a saturated solution of sodium hydrogencarbonate (2 × 20 ml). The aqueous washings were back-extracted with diethyl ether (4 × 20 ml) and the combined organic fractions were dried and evaporated. Preparative chromatography over alumina using ethyl acetate–light petroleum (15 : 85) as eluant gave the *lactone* (12) (50%) as an oil; $\nu_{max.}$ 1 770 cm^{-1}; δ 6.25 (1 H, d, *J* 14 Hz, H-7), 5.70—5.10 (3 H, m, H-1, H-1′, H-2′), 4.60 (2 H, m, H-3′ + OCHO), 4.20—3.30 (3 H, m, H-5 + OCH_2), 2.90—1.10 (18 H, m, 9 × CH_2), and 0.87 (3 H, t, Me) (Found: M^+, 334.214 2. $C_{20}H_{30}O_4$ requires M, 334.214 2).

15α- (*and* 15β-) *t*-*Butyldimethylsilyloxy*-9α-*methoxyprosta*-5Z,11Z,13E-*trienoic acid* (15). To a suspension of (4-carboxybutyl)triphenylphosphonium bromide (1.85 g) in dry tetrahydrofuran (50 ml) was added a solution of n-butyl-lithium in hexane (1.9M, 4.4 ml) with stirring. Maintaining an inert atmosphere above the reaction, the aldehyde (8) (0.53 g) in dry tetrahydrofuran (20 ml) was added. After 18 h water (30 ml) was added, followed by ice-cold 4N sulphuric acid. The solution was extracted with diethyl ether (6 × 30 ml) and the combined organic fractions were washed with water (2 × 30 ml). The aqueous phases were back-extracted with diethyl ether (2 × 30 ml) and the combined ether extracts were dried and evaporated. The residue was taken up in the minimum quantity of diethyl ether (*ca.* 2 ml), cooled, and filtered to remove triphenylphosphine oxide. The filtrate was evaporated and the residue chromatographed over silica using ethyl acetate–light petroleum as eluant to give the *acid* (15) (60%); $\nu_{max.}$ 1 720 cm^{-1}; δ 8.1 (1 H, m, CO_2H), 6.15 (1 H, d, *J* 16 Hz, H-11), 5.75—5.25 (4 H, m, H-5, H-6, H-13, H-14), 4.05 (2 H, m, H-9, H-15), 3.30 (3 H, s, OMe), 2.5—1.0 (19 H, m, H-8, 9 × CH_2), 0.8 (12 H, m, 4 × Me), and 0.05 (6 H, s, $SiMe_2$) (Found: M^+, 464.332 2. $C_{27}H_{48}O_4Si$ requires M, 464.334 3).

15α- (*and* 15β-) *t*-*Butyldimethylsilyloxy*-9α-*benzyloxyprosta*-5Z,11Z,13E-*trienoic acid* (16). Using (4-carboxybutyl)triphenylphosphonium bromide (0.58 g), n-butyl-lithium in hexane (1.9M, 1.4 ml), the aldehyde (9) (0.20 g), and the above reaction and work-up conditions, the *acid* (16) was obtained as an oil (70%); $\nu_{max.}$ 1 715 cm^{-1}; δ 10.0 (1 H, br s, CO_2H), 7.35 (5 H, m, Ph), 6.25 (1 H, d, *J* 16 Hz, H-11), 5.85—5.30 (4 H, m, H-5, H-6, H-13, H-14), 4.50 (2 H, s, OCH_2), 4.35—3.95 (2 H, m, H-9, H-15), 2.60—1.60 (19 H, m, H-8, 9 × CH_2), 0.8 (12 H, m, 4 × Me), and 0.05 (6 H, s, $SiMe_2$) (Found: M^+, 540.363 9. $C_{33}H_{52}O_4Si$ requires M, 540.363 2).

15α- (*and* 15β-) *t*-*Butyldimethylsilyloxy*-9α-*t*-*butyldimethylsilyloxyprosta*-5Z,11Z,13E-*trienoic acid* (14). This was prepared from the aldehyde (7) (0.20 g), (4-carboxybutyl)triphenylphosphonium bromide (0.24 g), and n-butyl-lithium in hexane (0.55 ml, 1.7M) using the above reaction and work-up conditions. The product was an oil, 22%; $\nu_{max.}$ 1 720 cm^{-1} (Found: M^+, 564.398 8. $C_{32}H_{60}O_4Si_2$ requires M, 564.402 7).

15α- (*and* 15β-) *Hydroxy*-9α-*methoxyprosta*-5Z,11Z,13E-*trienoic acid* (17). To the acid (15) (60 mg) in tetrahydrofuran (10 ml) was added glacial acetic acid–water (2 : 1, 4.5 ml). After 6 d at 40 °C, water (20 ml) was added, and the solution was extracted with chloroform (6 × 30 ml). The organic extracts were washed with water (3 × 20 ml)

and the aqueous phases were back-extracted with chloroform (6 × 30 ml). The combined chloroform fractions were dried and evaporated. The residue was chromatographed over silica using glacial acetic acid–ethyl acetate–light petroleum (1 : 12 : 87) as eluant to give the hydroxy-acid (17) (22%); δ 6.15 (1 H, d, *J* 12 Hz, H-11), 5.5 (4 H, m, H-5, H-6, H-13, H-14), 4.05 (2 H, m, H-9, H-15), 3.34 (3 H, s, OMe), 2.85—1.00 (21 H, m, H-8, 2 × OH, 9 × CH_2), and 0.88 (3 H, t, Me) (Found: M^+, 350.245 0. $C_{21}H_{34}O_4$ requires *M*, 350.245 5): and the acetoxy-acid (18) (20%); δ 6.15 (1 H, d, *J* 12 Hz, H-11), 5.5 (5 H, m, H-5, H-6, H-13, H-14, H-15), 4.05 (1 H, m, H-9), 3.34 (3 H, s, OMe), 2.04 (3 H, s, OCOMe), 2.85—1.00 (19 H, H-8, 9 × CH_2), and 0.87 (3 H, t, Me) (Found: M^+, 392.256 3. $C_{23}H_{36}O_5$ requires *M*, 392.256 1).

We thank the S.R.C. and Glaxo–Allenburys Research (Ware) Ltd. for a CASE award (N. M. C.).

[8/1944 *Received*, 8*th November*, 1978]

REFERENCES

[1] Preliminary communications: N. M. Crossland, S. M. Roberts and R. F. Newton, *J.C.S. Chem. Comm.*, 1977, 886; N. M. Crossland, S. M. Roberts, R. F. Newton, and C. F. Webb, *ibid.*, 1978, 660.

[2] P. Yates, *J. Photochem.*, 1976, **5**, 91; P. Yates and R. O. Loutfy, *Accounts Chem. Res.*, 1975, **8**, 209.

[3] J. Meinwald and R. A. Chapman, *J. Amer. Chem. Soc.*, 1968, **90**, 3218.

[4] A. G. Singer, S. Wolff, and W. C. Agosta, *J. Org. Chem.*, 1977, **42**, 1327.

[5] W. C. Agosta and D. K. Herron, *J. Amer. Chem. Soc.*, 1968, **90**, 7025.

[6] Ref. 20 in P. Yates and R. O. Loutfy, *Accounts Chem. Res.* 1975, **8**, 209.

[7] P. Yates and L. Kilmury, *Tetrahedron Letters*, 1964, 1739.

[8] P. Yates and G. Hagens, *Tetrahedron Letters*, 1969, 3623.

[9] S. M. Roberts, *J.C.S. Chem. Comm.*, 1974, 948.

[10] T. V. Lee, S. M. Roberts, and R. F. Newton, *J.C.S. Perkin I*, 1978, 1179.

[11] T. V. Lee, S. M. Roberts, M. J. Dimsdale, R. F. Newton, D. K. Rainey, and C. F. Webb, *J.C.S. Perkin I*, 1978, 1176.

[12] Dutch Patent: application no. 7613429.

[13] P. Crabbé, A. Gusman, and M. Vera, *Tetrahedron Letters*, 1973, 3021, 4730.

[14] P. Crabbé and A. Cervantes, *Tetrahedron Letters*, 1973, 1319; E. J. Corey and G. Moinet, *J. Amer. Chem. Soc.*, 1973, **95**, 7185; R. C. Kelly, I. Schletter, and R. L. Jones, *Prostaglandins*, 1973, **4**, 653.