Tetrahedron Letters No. 29, pp 2951 - 2954, 1972. Pergamon Press. Printed in Great Britain.

PHOTOCHEMICAL CYCLOADDITIONS IN THE PROSTAGLANDIN SERIES

Pierre Crabbé[1], Gustavo A. García and Carlos Ríus

Facultad de Química, Universidad Nacional Autónoma de México

México 20, D. F., México

(Received in USA 8 May 1972; received in UK for publication 13 June 1972)

The prostaglandin molecule offers an attractive opportunity for photochemical reactions. The preparation of such novel prostanoic derivatives can be achieved either by total synthesis or by cycloaddition to naturally occurring substances. We wish to report the synthesis of four prostanoid [2+2]cycloadducts using both approaches.

Irradiation of the conjugated ketone (2) [ν_{max} 1735, 1710 cm^{-1}; λ_{max} 209 nm, log ε 4.11; n.m.r. 3.6 (CO_2Me), 6.21 (dd, $J_{1,2}$ 6 Hz, $J_{1,3}$ 2 Hz, C-10 vinylic H), 7.61 ppm (dd, $J_{2,1}$ 6 Hz, $J_{2,3}$ 2.5 Hz, C-11 vinylic H); m/e 274 (M^+)], readily obtained from (1)[2], in methylene chloride solution saturated with ethylene with a Hanau Q-18 high pressure ultraviolet lamp at low temperature, affords the cyclobutyl-ketone (3) [70%; ν_{max} 1740, 1610 cm^{-1}; m/e 302 (M^+)], along with isomeric material. Sodium borohydride reduction of ketone (3), followed by brief exposure to acid, provides the lactone (4) [ν_{max} 1770, 1610 cm^{-1}; m/e 272 (M^+)], separated from the 9β-hydroxy-acid also formed during the reduction. The n.m.r. spectrum of (4) displays a triplet at 4.71 ppm ($J_{8,9H}$ 7 Hz; $J_{9,10H}$ 7 Hz) corresponding to the proton at C-9. Examination of the geometry of the tricyclic lactone (4) with molecular models indicates that such a triplet is only compatible with the α-configuration of the cyclobutyl moiety.

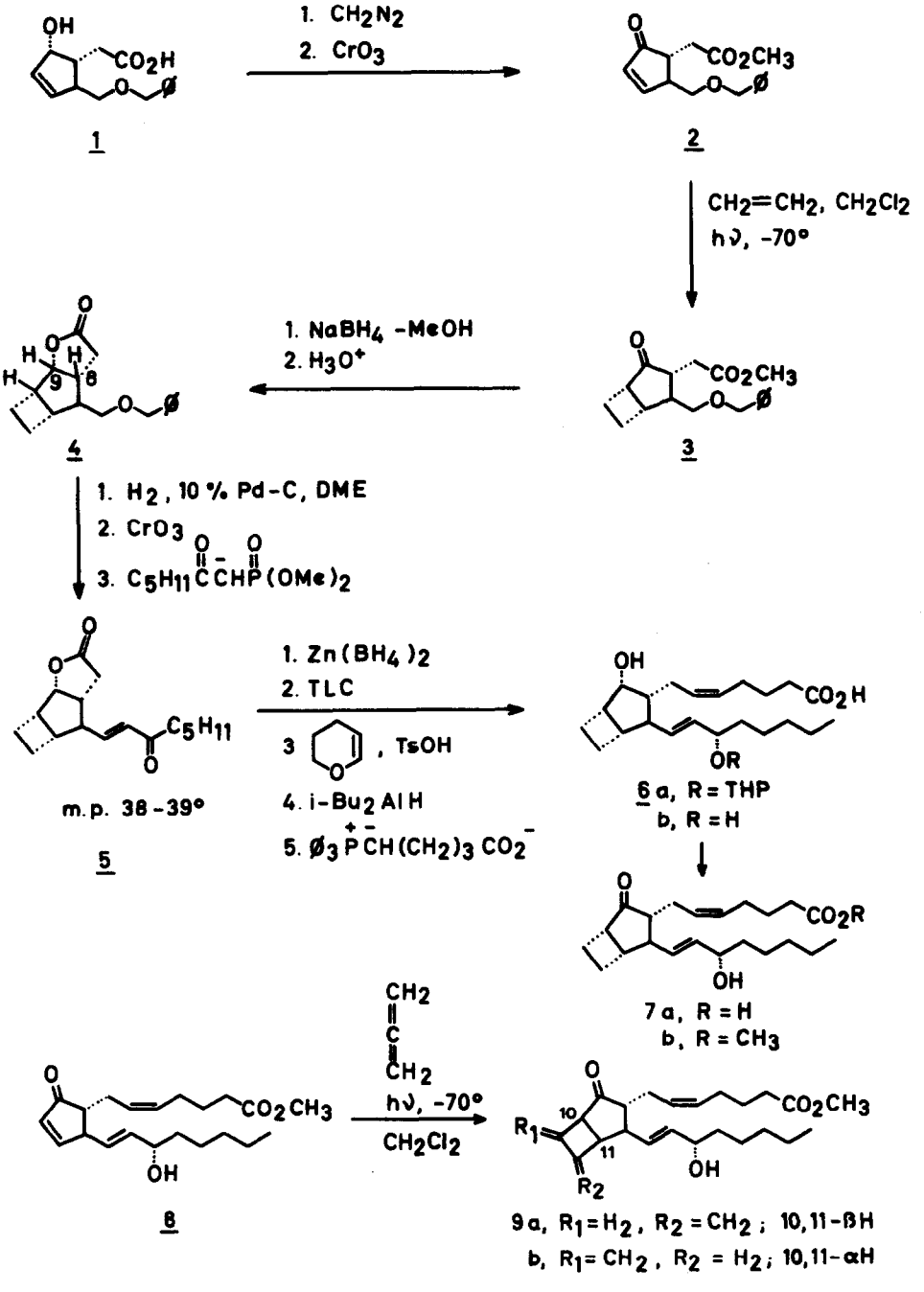
The synthetic intermediate (4) is then submitted to the sequence of reactions (see Chart) described previously[3]. Hydrogenolysis of the benzyl ether group and oxidation[4] of the primary alcohol gives the corresponding aldehyde, which is alkylated with the sodium salt of dimethyl 2-oxoheptylphosphonate to afford the crystalline enone (5) [ν_{max} 1770,

1695, 1625 cm^{-1}; λ_{max} 228 nm, log ε 4.19; n.m.r. 0.88 (Me), 6.12 (*d*, 16 Hz; 14-H), 6.68 ppm (dd, J 16 Hz, J 8 Hz; 13-H; m/e 276 (M^+)].

Reduction of the carbonyl at C-15 is followed by separation of the required 15(S)-alcohol derivative [ν_{max} 3450, 1770, 1670 cm^{-1}; n.m.r. 0.88 (Me), 5.52 ppm (m, vinylic H); m/e 278 (M^+)] from its 15(R)-isomer [ν_{max} 3400, 1770, 1670 cm^{-1}; n.m.r. 0.88 (Me), 5.52 ppm (m, vinylic H); m/e 278 (M^+)] by preparative TLC. The concluding steps of the synthesis are shown on the Chart. Whereas mild acid hydrolysis of the 15α-tetrahydropyranyl ether derivative (6a), obtained after alkylation of the lactol, completes the synthesis of dl-10α,11α-ethylene-11-desoxy-$PGF_{2\alpha}$ (6b) [ν_{max} 3450, 1710 cm^{-1}; n.m.r. 0.88 (Me), 4.12 (CO_2H, 9-OH, 15-OH), 5.46 ppm (4 vinylic H)], oxidation[5] of (6a) followed by acid treatment provides the corresponding prostaglandin belonging to the E-series (7a) [ν_{max} 3450, 1740, 1710 cm^{-1}; n.m.r. 0.88 (Me), 5.51 ppm (m, 4 vinylic H)].

Photochemical cycloaddition of allene[6] to PGA_2-methyl ester (8) from Plexaura Homomalla[7] gives a mixture of isomeric (methylene)10,11-ethylene-11-desoxy-PGE_2 methyl esters of which two are reported here. Preparative TLC allows to isolate the major isomer (9a) [22%; ν_{max} 3430, 1745-1735 cm^{-1}; n.m.r. 0.89 (Me), 3.65 (CO_2Me), 4.10 (15α-OH), 4.97 (d, J 15 Hz, $C=CH_2$), 5.46 ppm (m, 4 vinylic H); m/e 370 (M^+-H_2O), 357 (M^+-OMe)]. The configuration of the methylenecyclobutane bridge is probably α in (9a), since its Cotton effect ($[\theta]_{302}$ -5,570; a -63) is reminiscent of that exhibited by the methyl ester (7b) ($[\theta]_{303}$ -3,860) obtained by cycloaddition of ethylene to (8).

The structure of the photoadduct (9b) [15%; ν_{max} 3430, 1745-1735 cm^{-1}; n.m.r. 0.89 (Me), 3.66 (CO_2Me), 4.10 (15α-OH), 4.88 (d, J 16 Hz, $C=CH_2$), 5.49 ppm (m, 4 vinylic H); m/e 370 (M^+-H_2O), 357 (M^+-OMe)], is based on its UV maximum at 300 nm (log ε 2.38), typical of a β,γ-unsaturated keto-system. In addition, the β-stereochemistry of the methylenecyclobutane moiety in (9b) is supported by the intense negative chiroptical properties ($[\theta]_{304}$ -14,850; a -142), in agreement with the extension of the octant rule for this homo-conjugated chromophore[6,8].


1. CH_2N_2
2. CrO_3
1
2
$CH_2=CH_2$, CH_2Cl_2
hν, -70°
3
1. $NaBH_4$ -MeOH
2. H_3O^+
4
1. H_2, 10 % Pd-C, DME
2. CrO_3
3. $C_5H_{11}\overset{O}{C}\overset{-}{C}HP(OMe)_2$
m.p. 38-39°
5
1. $Zn(BH_4)_2$
2. TLC
3 , TsOH
4. i-Bu_2AlH
5. $\phi_3\overset{+}{P}\overset{-}{C}H(CH_2)_3CO_2^-$
6 a, R = THP
b, R = H
7 a, R = H
b, R = CH_3
8
$CH_2=C=CH_2$
hν, -70°
CH_2Cl_2
9 a, $R_1=H_2$, $R_2=CH_2$; 10,11-βH
b, $R_1=CH_2$, $R_2=H_2$; 10,11-αH

Acknowledgments: G.A.G. and C.R. express their gratitude to the U.N.A.M. for pre-doctoral fellowships. The authors thank Dr. O. Halpern, Syntex Research, Palo Alto, California, for a supply of extracts of gorgonians and for informing us of his findings about the 15(S)-configuration of PGA_2 isolated from marine corals.

REFERENCES

1. Author to whom inquiries may be addressed at Syntex, S. A., Apartado Postal 10-820, Mexico 10, D. F., Mexico.
2. P. Crabbé and A. Guzmán, Tetrahedron Letters, 115 (1972).
3. E.J. Corey, S.M. Albocino, U. Koelliker, T.K. Schaaf, and R.K. Varma, J. Amer. Chem. Soc., 93, 1491 (1971), and references cited therein.
4. J.C. Collins, W.W. Hess, and F.J. Frank, Tetrahedron Letters, 3363 (1968).
5. K. Bowden, I.M. Heilbron, E.R.H. Jones, and B.C.L. Weedon, J. Chem. Soc., 39 (1946).
6. P. Crabbé, A. Cruz, and J. Iriarte, Photochem. Photobiol., 7, 829 (1968); P. Sunder-Plassman, P.H. Nelson, P.H. Boyle, A. Cruz, J. Iriarte, P. Crabbé, J.A. Zderic, J.A. Edwards, and J.H. Fried, J. Org. Chem., 34, 3779 (1969).
7. W.P. Schneider, R.D. Hamilton, and L.E. Rhuland, J. Amer. Chem. Soc., 94, 2122 (1972).
8. E. Bunnenberg, C. Djerassi, K. Mislow, and A. Moscowitz, J. Amer. Chem. Soc., 84, 2823 (1962).