Tetrahedron Letters No. 26, pp 2215 - 2218, 1975. Pergamon Press. Printed in Great Britain.

A NOVEL APPROACH TO THE SYNTHESIS OF PROSTANOIDS[1]

Andrew Greene and Pierre Crabbé *
C.E.R.M.O., Université Scientifique et Médicale
38041 Grenoble, France.

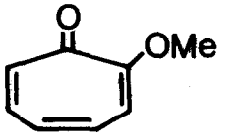
(Received in UK 8 May 1975; accepted for publication 15 May 1975)

A considerable effort has been devoted to synthetic studies of natural and modified prostaglandins[1,2]. We have been engaged in a research programme having as its objective a new chemical synthesis that would allow access to natural prostaglandins as well as to many modified prostaglandins, not readily obtainable by other synthetic schemes.

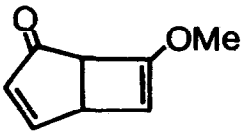
We wish to report a synthesis of dl-11-deoxy-PGE_1 (9b) which illustrates the simplicity of the method.

Irradiation of readily available[3] α-tropolone methyl ether (1) in anhydrous methanol solution for 4 hr at room temperature, with a Hanau TQ 150 high-pressure mercury arc lamp (quartz filter) sequentially induced a valence tautomerisation of the tropolone ring and a skeletal rearrangement to afford 7-methoxy-3,6-bicyclo[3.2.0]heptadiene-2-one (2)[4] in yields higher than 80% after distillation. The substituted cyclopentenone (2) was reduced selectively to the cyclopentanone (3) [ν_{max} 3070, 1735 and 1630 cm^{-1} ; n.m.r. 4.75 (s, vinyl H), 3.60 ppm (s, OMe)[5] ; m/e 138 (M^+)], in 90% yield, by hydrogenation over prehydrogenated platinum in ethyl acetate solution.

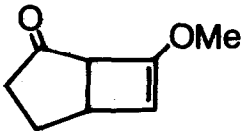
Ozonolysis of the enol ether double bond of the bicyclic intermediate (3) at -78° in 5:1 methylene chloride-methanol solution was followed by treatment of the ozonide with liquid sulfur dioxide[6], thus affording the dimethyl acetal (4) [ν_{max} 1750-1730 cm^{-1} ; n.m.r. 4.25 (d, J = 5 Hz, acetal H), 3.70 (s, Me ester), 3.35 and 3.32 ppm (2 x OMe) ; m/e 185 (M^+ - OMe)[7] ; $FeCl_3$ test : positive] in 70% yield. Alkylation of the keto-ester (4) at position 8[8] was performed by reaction with potassium hydride in dimethyl sulphoxide[9] under an argon atmosphere, followed by treatment with ethyl 7-iodoheptanoate[10,11] providing the diester (5) [ν_{max} 1745-1730 cm^{-1} ; n.m.r. 4.25 (d, J = 6 Hz, acetal H), 4.05 (q, J = 7 Hz, $C\underline{H}_2Me$), 3.60 (s, Me ester), 3.35 (s, 2 x OMe), 1.20 ppm (t, J = 7 Hz, $CH_2\underline{Me}$) ; m/e 341 (M^+ - OMe)] in ca. 60% yield.



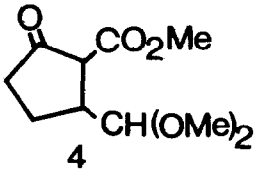
1



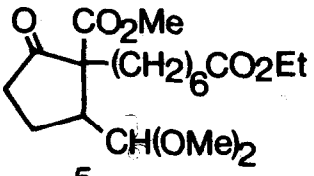
2



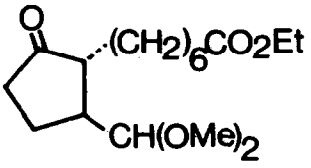
3



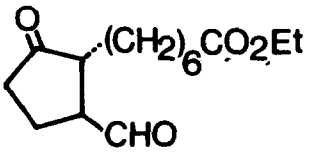
4



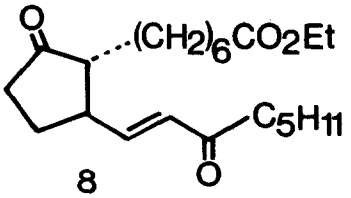
5



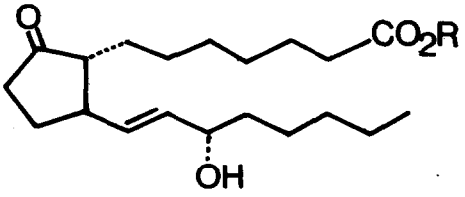
6



7



8



9 a, R = Et
b, R = H

Decarboxylation of compound (5), a key-step in the synthesis, was smoothly effected with sodium cyanide in hexamethylphosphoric triamide for one hour at 70° under dry argon[12], affording in 90% yield the keto-ester (6) [ν_{max} 1730 cm^{-1}; n.m.r. 4.20 (d, J = 5 Hz, acetal H), 4.05 (q, 7 Hz, $C\underline{H}_2Me$), 3.35 (s, 2 x OMe), 1.20 ppm (t, J = 7 Hz, $CH_2\underline{Me}$) ; m/e 283 (M^+ - OMe)]. The sensitive acetal group is not affected by these mild reaction conditions. Treatment of ketone (6) with ethanolic potassium acetate, known equilibration conditions[13], led to unchanged material thus confirming the trans relationship between the substituents on the cyclopentanone. Cleavage of the acetal protecting group in the intermediate (6) with p-toluenesulphonic acid in acetone liberated the aldehyde (7)[14] [ν_{max} 2720, 1730 cm^{-1} ; n.m.r. 9.75 (d, J = 2 Hz, CHO), 4.05 (q, J = 7 Hz, $C\underline{H}_2Me$), 1.20 ppm (t, J = 7 Hz, $CH_2\underline{Me}$)] in nearly quantitative yield.

The concluding steps of the synthesis have been worked out previously[14,15]. Reaction of intermediate (7) with the sodium salt of dimethyl 2-oxoheptylphosphonate provided the expected enedione (8), characterized by the typical spectral properties of its enone chromophore[15]. After formation of the monoketal at position 9[14], reduction of the carbonyl function at position 15 with zinc borohydride yielded a mixture of 15(R) and 15(S)-isomeric alcohols. Acetic acid-water hydrolysis of the ketal gave the corresponding mixture of hydroxyketones, separated by preparative thin layer chromatography. The ester group at C-1 of the desired 15(S)-alcohol (9a) was hydrolysed with aqueous methanolic potassium carbonate to afford the crystalline dl-11-deoxy-PGE_1 (9b) [m.p. 80-82°][14], identical with an authentic sample.

The noteworthy features of this synthesis are its simplicity and its potential flexibility. Substituted tropolones are readily available from synthetic and natural sources[16], hence allowing the preparation of a large array of new prostanoids not easily secured by other routes. Moreover, the key cyclopentenone intermediate (2), through modifications at positions 10 and/or 11[8], provides an ideal entry to the primary prostaglandins as well as to yet another group of modified prostaglandins. Work along these lines is currently in progress.

Acknowledgements - We wish to thank Miss. B. Estéoule for assistance and Dr. W. Bartmann, Hoechst A.G., for a sample of dl-11-deoxy-PGE_1. This research was supported financially by a grant from the D.G.R.S.T. (contract n°73-7-1875) and the C.N.R.S. (E.R.A. n°478). A.G. is grateful to the D.G.R.S.T. for a post-doctorate research fellowship.

REFERENCES

1. Contribution N°2 from the Laboratoire de Chimie Organique, C.E.R.M.O. For N°1 see : P. Crabbé, Chemistry in Britain, 11, 132 (1975).
2. Inter alia : U. Axen, J.E. Pike and W.P. Schneider in "The Total Synthesis of Natural Products", J. ApSimon, (Ed.), Wiley-Interscience, New York, 1973, Vol.1, p.81.
3. H.C. Stevens, D.A. Reich, D.R. Brandt, K.R. Fountain and E.J. Gaughan, J. Amer. Chem. Soc., 87, 5257 (1965). Tropolone is also available from Aldrich Milwaukee, Wisconsin, U.S.A.
4. W.G. Dauben, K. Koch, S.L. Smith and O.L. Chapman, J. Amer. Chem. Soc., 85, 2616 (1963).
5. N.m.r. spectra were taken on a JEOL C-60 HL instrument in $CDCl_3$, using TMS as internal reference.
6. R.D. DeMaster, Ph.D. Dissertation, University of Minnesota ; Diss. Abstr. Int. B., 31, 5871 (1971) ; see also W.E. Noland and R.D. DeMaster, Org. Syn., 52, 135 (1972).
7. Typical of dimethylacetals ; see : W.H. McFadden, J. Wasserman, J. Corse, R.E. Lundin and R. Teranishi, Anal. Chem., 36, 1031 (1964) and references therein.
8. Prostanoic acid numbering.
9. D.M. Pond and R.L. Cargill, J. Org. Chem., 32, 4064 (1967) ; C.A. Brown, ibid., 39, 3913 (1974).
10. M.E. Synerholm, J. Amer. Chem. Soc., 69, 2581 (1947) ; D.E. Ames, R.E. Bowman and R.G. Mason, J. Chem. Soc., 174 (1950).
11. E.J. Corey and H.S. Sachdev, J. Amer. Chem. Soc., 95, 8483 (1973).
12. P. Müller and B. Siegfried, Tetrahedron Letters, 3565 (1973).
13. J.E. Pike, F.H. Lincoln and W.P. Schneider, J. Org. Chem., 34, 3552 (1969).
14. J. Bagli and T. Bogri, Tetrahedron Letters, 3815 (1972) ; id., J. Org. Chem., 37, 2132 (1972) ; F.S. Alvarez, D. Wren and A. Prince, J. Amer. Chem. Soc., 94, 7823 (1972).
15. E.J. Corey, N.M. Weinshenker, T.K. Schaaf and W. Huber, J. Amer. Chem. Soc., 91, 5675 (1969) ; E.J. Corey, T.K. Schaaf, W. Huber, U. Koelliker and N.M. Weinshenker, ibid., 92, 397 (1970) ; E.J. Corey, S.M. Albonico, U. Koelliker, T.K. Schaaf and R.K. Varma, ibid., 93, 1491 (1971) ; E.J. Corey, K.B. Becker and R.K. Varma, ibid., 94, 8616 (1972), and references cited.
16. R. Noyori, S. Makino, T. Okita and Y. Hayakawa, J. Org. Chem., 40, 806 (1975) ; D.M.G. Lloyd, "Carbocyclic Non-Benzenoid Aromatic Compounds", Elsevier Publishing Co, Amsterdam, 1966, pp.117-161, and references cited.