A New Approach to the Synthesis of the Prostanoids

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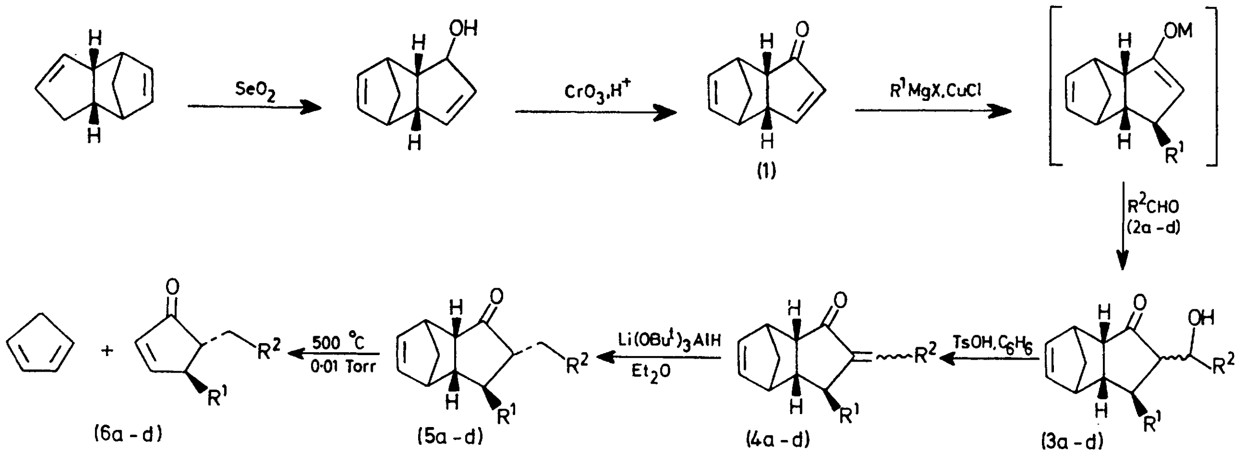
Summary A short, simple synthesis of PGA_1-type compounds, wherein the assembly of fragments leaves scope for variations at a later stage is described; this method involves the use of a bicyclo[2.2.1]heptene as a protecting group and precursor of the conjugated enone system, present in the final products.



SCHEME

a; $R^1 = Bu^n$, $R^2 = Me$
b; $R^1 = Bu^n$, $R^2 = [CH_2]_4CO_2Me$
c; $R^1 = Oct^n$, $R^2 = [CH_2]_6Me$
d; $R^1 = Oct^n$, $R^2 = [CH_2]_5CO_2Me$
Oct^n = n-octyl; Ts = p-$MeC_6H_4SO_2$

IN this note we describe a new approach to (±)-PGA-type compounds; few syntheses of these compounds have been reported.[1]† Since chemical conversion of the PGA class into B,[2] C,[3] E,[4] and F[4] classes has been accomplished, using synthetic or natural sources,[5] these routes thus constitute a total synthesis of primary prostaglandins.[6] Jones oxidation of the allylic alcohol derived from *endo*-dicyclopentadiene by SeO$_2$ treatment[8] gives rise to the pure *endo*-ketone (**1**) (42% overall yield) which easily undergoes Cu^I-catalysed addition of Grignard reagents[9] derived from butyl or octyl bromide.

As shown in the Scheme the anionic species formed *in situ* react with the aldehydes (**2a**—**d**)‡ to produce the crude ketones (**3a**—**d**) which are dehydrated to the corresponding αβ-unsaturated ketones (**4a**—**d**) [80—94% from (**2**)] by heating at reflux in C_6H_6 with a catalytic amount of TsOH. Quantitative reduction with Li(OBu^t)$_3$AlH[10] gives the ketones (**5a**—**d**) having *trans*-stereochemistry assigned by analogy with earlier work[9] and from the fact that steric factors due to the shape of molecules (**3**) allow only *exo*-approach of the bulky reducing agent.

Thermolysis[11] of (**5a**—**d**) provided the disubstituted cyclopentenones (**6a**—**d**)§ which exhibited the following physical properties. (**6a**): ν (neat) 1705 and 1590 cm^{-1}; δ (CCl$_4$, rel. to Me$_4$Si) 6·0 (2H, apparent d of d, $J_{2,3}$ 6 and $J_{2,4}$ 1·7 Hz), 7·52 (2H, apparent d of d, $J_{2,3}$ 6 and $J_{3,4}$ 2·3 Hz); (**6b**): *m/e* 235·1699 (M^+ − OMe), 138, 95, 82 (base peak), and 81; ν (neat) 1740 (CO$_2$Me), and 1710 and 1590 (–C=C–C=O) cm^{-1}; δ (CCl$_4$, rel. to Me$_4$Si) 3·60 (s, OMe), olefinic protons as in (**6a**); (**6c**): ν (neat) 1710 and 1590 (–C=C–C=O) cm^{-1}; n.m.r. spectrum (olefinic protons) similar to that of (**6a**); (**6d**): *m/e* 305·2478 (M^+ − OMe), 85, 71, 69, and 57 (base peak); ν (neat) 1735 (CO$_2$Me), and 1700 and 1585 (–C=C–C=O) cm^{-1}; δ (CCl$_4$, rel. to Me$_4$Si) 3·59 (s, OMe), olefinic protons as in (**6d**).

This short route represents a promising pathway [four steps from the ketone (**1**), overall yield 60—90%] for the syntheses of a large variety of prostanoids.

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† The synthesis of analogues of PGA-type compounds are currently of considerable biological interest, *e.g.*, in the treatment of hypertension (J. R. Weeks, *Science*, 1973, **181**, 370).

‡ (**2a**), MeCHO; (**2b**), MeO$_2$C[CH$_2$]$_4$CHO; (**2c**), Me[CH$_2$]$_5$CHO; and (**2d**), MeO$_2$C[CH$_2$]$_5$CHO. Compounds (**2b**) and (**2d**) were obtained *via* CH$_2$I[CH$_2$]$_4$CO$_2$Me and CH$_2$I[CH$_2$]$_5$CO$_2$Me [M. E. Synerholm, *J. Amer. Chem. Soc.*, 1947, **69**, 2581; D. E. Ames, R. E. Bowman, and R. G. Mason, *J. Chem. Soc.* (*B*), 1950, 174], respectively, by Kornblum oxidation [A. P. Johnson and A. Pelter, *J. Chem. Soc.* (*B*), 1964, 520] in 80% yields.

§ Satisfactory analytical data were obtained for this compound.

[1] See *inter alia*: E. J. Corey and P. A. Grieco, *Tetrahedron Letters*, 1972, 107; J. Martel, E. Toromanoff, J. Mathieu, and H. Nomine, *ibid.*, p. 1491; E. J. Corey and G. Moinet, *J. Amer. Chem. Soc.*, 1973, **95**, 6831; E. J. Corey and J. Mann, *ibid.*, p. 6832.

[2] S. Bergstrom, R. Ryhage, B. Samuelsson, and J. Sjovall, *J. Biol. Chem.*, 1963, **238**, 3555.

[3] E. J. Corey and C. R. Cyr, *Tetrahedron Letters*, 1974, 1761.

[4] E. J. Corey and H. E. Ensley, *J. Org. Chem.*, 1973, **38**, 3187; W. P. Schneider, G. L. Bundy, and F. H. Lincoln, *J.C.S. Chem. Comm.*, 1973, 254.

[5] The richest natural source of PGA derivatives is the gorgonian *Plexaura homomalla* (ESPER): A. J. Weinheimer and R. L. Spraggins, *Tetrahedron Letters*, 1969, 59 and 5185.

[6] For a recent reviews on PGs, see P. Crabbé, *Chem. in Britain*, 1975, 132.

[7] J. Baldwin, *J. Org. Chem.*, 1966, **31**, 2441.

[8] R. B. Woodward and T. J. Katz, *Tetrahedron*, 1959, **5**, 1970.

[9] J. P. Bugel, P. Ducos, O. Gringore, and F. Rouessac, *Bull. Soc. chim. France*, 1972, 4371.

[10] W. L. Dilling and R. A. Plepys, *J. Org. Chem.*, 1970, **35**, 2971.

[11] For conditions, see J. Haslouin and F. Rouessac, *Compt. rend.*, 1973, **276**(**C**), 1691.