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11-DEOXYHOMOPROSTACYCLIN ANALOGUES

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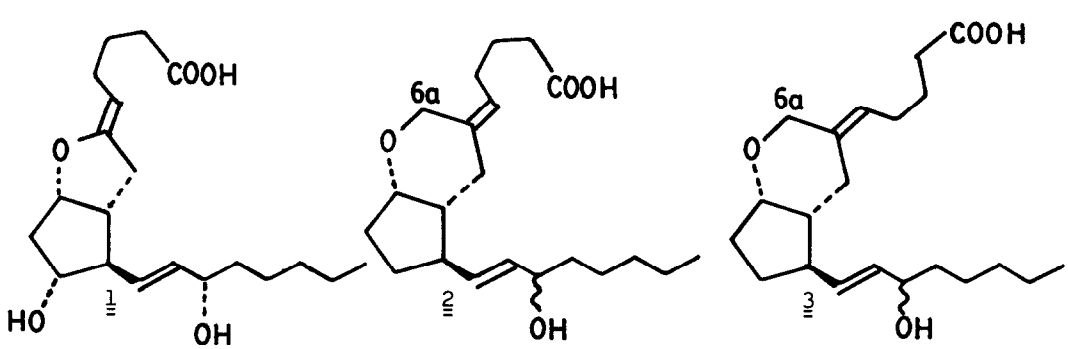
Summary: A short synthesis of 11-deoxyhomoprostacyclin analogues 2 and 3 is described. The key step involves an organocuprate conjugate addition - enolate alkylation reaction.

A good deal of effort has been directed towards the synthesis of analogues of prostacyclin (1) which retain the remarkable biological properties of the parent molecule[2] and yet are sufficiently stable to be used therapeutically.[2] In this communication we describe the synthesis of prostacyclin analogues 2 and 3 in which the additional 6a-methylene group confers stability by transforming the labile enol ether of prostacyclin (1) into an allylic ether grouping. The synthesis of the 11α-hydroxylated derivatives of 2 and 3 has recently been reported.[3]



a, α-OH
b, β-OH

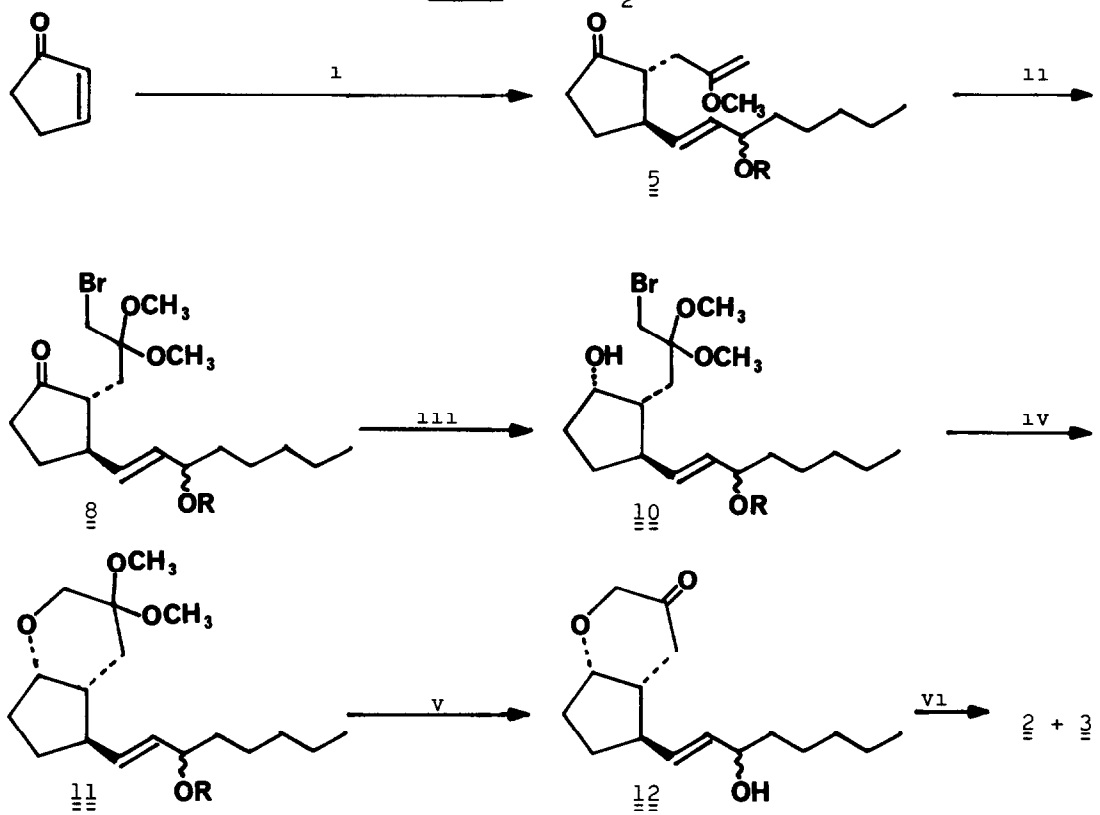
Our interest in the conjugate addition-enolate alkylation reaction for the synthesis of 11-deoxyprostaglandins[4] led us to investigate ways of exploiting this procedure for the synthesis of 2 and 3. The most successful approach was the one shown in the scheme.[5] Treatment of cyclopent-2-enone with mixed cuprate 4[6] and alkylation of the intermediate enolate with 2-methoxyallyl bromide[7] in liquid ammonia gave a mixture of the desired alkylation product 5 and the unalkylated ketone 6 These compounds have similar chromatographic properties in several solvent systems and the isolation of 5 was further hampered by the ease with which it was hydrolysed to the diketone 7.[5] However, 5[5] could be obtained in pure form by chromatography on silver nitrate impregnated silica. Preparation of 5 using the conjugate addition-chlorotrimethylsilane trapping-enolate regeneration and alkylation procedure[8] gave a lower overall yield than the one-pot procedure.

Bromination of 5 in methanol gave the required α-bromoketal 8[5] together with the bicyclic acetal 9.[5,9] Stereospecific reduction of 8 with potassium tri-(sec-butyl)borohydride gave the α-alcohol 10[5] which underwent cyclisation on treatment with sodium hydride in tetrahydrofuran (THF) to give ketal 11.[5] Hydrolysis and desilylation of 11 using aqueous oxalic acid on silica gel[10] gave the ketone 12.[5]

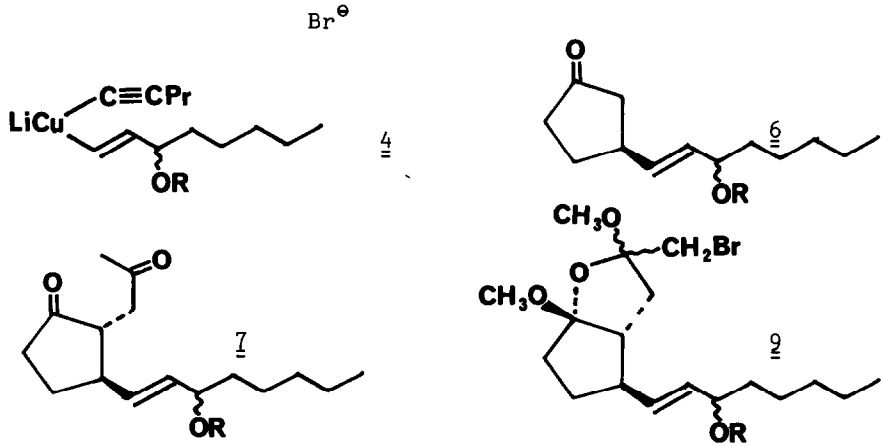
Finally, treatment of ketone 12 with the Wittig reagent derived from (4-carboxybutyl)triphenylphosphonium bromide completed the synthesis. The crude reaction product, which contained 2 and 3 together with dec-5-endioic acid derived from self-condensation of the Wittig reagent, was purified by short-path chromatography.[11] The least polar 5E-, 15β-diastereomer 3b was eluted first followed by an inseparable mixture of 3a and 2b followed by the most polar component, the 5Z-, 15α-diastereomer 2a.[5,12] The 5E and 5Z-configurations were readily assigned using ^{1}H NMR spectroscopy, the Z-isomers exhibit a characteristic[3] AB system (J = 15Hz) for the 6a-protons whereas the E-isomers show only a broad, ill-defined, multiplet.

Analogues 2 and 3 were inhibitors of collagen-induced platelet aggregation but they were appreciably (ca. 10^{-3}) less active than prostacyclin

SCHEME (R = $SiMe_2{}^tBu$)



Reagents: (i) 4, ether, -78° then 2-methoxyallyl bromide, NH_3(l) (16%).
(ii) Br_2, MeOH, NaOAc, -78°, 10 min (44% 8, 18% 9).
(iii) KHB(sec-Bu)$_3$, THF, -40° (93%).
(iv) NaH, THF, reflux, 2 days (58%).
(v) 10% aq. oxalic acid, SiO_2, CH_2Cl_2, r.t., 2 days (79%).
(vi) $Ph_3\overset{\oplus}{P}(CH_2)_4COOH$ $\overset{\ominus}{Br}$, KO^{t}Bu, THF, r.t., 2 h (80%).



Acknowledgements

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References and Footnotes

1. Present address: School of Chemical Sciences, University of East Anglia, Norwich NR4 7TJ, England.
2. For a review of the synthesis and biological properties of prostacyclin and prostacyclin analogues see K.C. Nicolaou, G.P. Gasic, W.E. Barnette, Angew. Chem. Int. Ed., 1978, 17, 293.
3. W. Skuballa, Tetrahedron Letters, 1980, 3261.
4. A.J. Dixon, R.J.K. Taylor, R.F. Newton, J.C.S. Perkin I, 1981, 1407.
5. All synthetic compounds are racemic and, unless otherwise shown, are mixtures of 15R- and 15S- diastereomers. All new compounds gave satisfactory elemental analyses or high resolution mass spectral data and their IR and NMR spectra were consistent with the assigned structures.
6. E J. Corey, D J. Beames, J. Am. Chem. Soc., 1972, 94, 7210.
7. R.M. Jacobson, R.A. Raths, J.H. McDonald, J. Org. Chem., 1977, 42, 2245.
8. J.W. Patterson, J.H. Fried, J. Org. Chem., 1974, 39, 2506; E.S. Binkley, C.H. Heathcock, J. Org. Chem., 1975, 40, 2156.
9. The crude mixture of 5 and 6 was usually directly brominated and then 8 was separated from 6 and 9 by silica gel chromatography.
10. F. Huet, A. Lechevalier, M. Pellet, J.M. Conia, Synthesis, 1978, 63.
11. On silica gel (Merck 7729) acidified to ca. pH 4.5 with trifluoroacetic acid using ethylacetate-light petroleum (3:7) as eluant. This procedure gave 2 and 3 contaminated with small amounts of dec-5-enoic acid. An alternative and more efficient method of purification consists of
    (i) conversion of the crude reaction product to the corresponding t-butyldimethylsilyl esters
    (ii) chromatography, the diester of dec-5-enoic acid is very non-polar and readily removed
    (iii) saponification.
12. The assignment of stereochemistry at C-15 was based on the general rule that 15α- compounds are usually more polar on the TLC than the corresponding 15β-epimers.

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