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SYNTHESIS OF A NOVEL PROSTACYCLIN ANALOG CONTAINING THE BICYCLO[3.1.0]HEXANE RING SYSTEM. APPLICATION OF MOLECULAR MECHANICS CALCULATIONS TO ORGANIC SYNTHESIS

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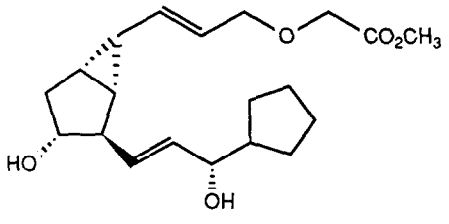
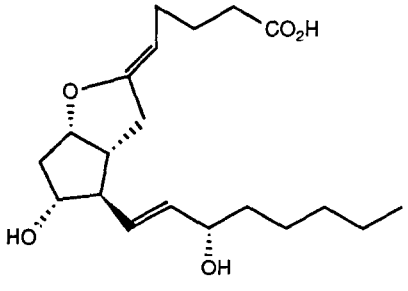
Abstract

The synthesis of a novel prostacyclin analog I has been achieved, incorporating as a key strategic feature a regio-controlled epoxide ring opening (as predicted by MM2 calculations) of a readily available prostaglandin synthon.

As part of our program representing a computational approach towards the design of novel prostacyclin[1] II mimics which can adopt an "active shape" conformation[2] at the platelet receptor, we chose to synthesize the novel PGI_2 analog I.



I

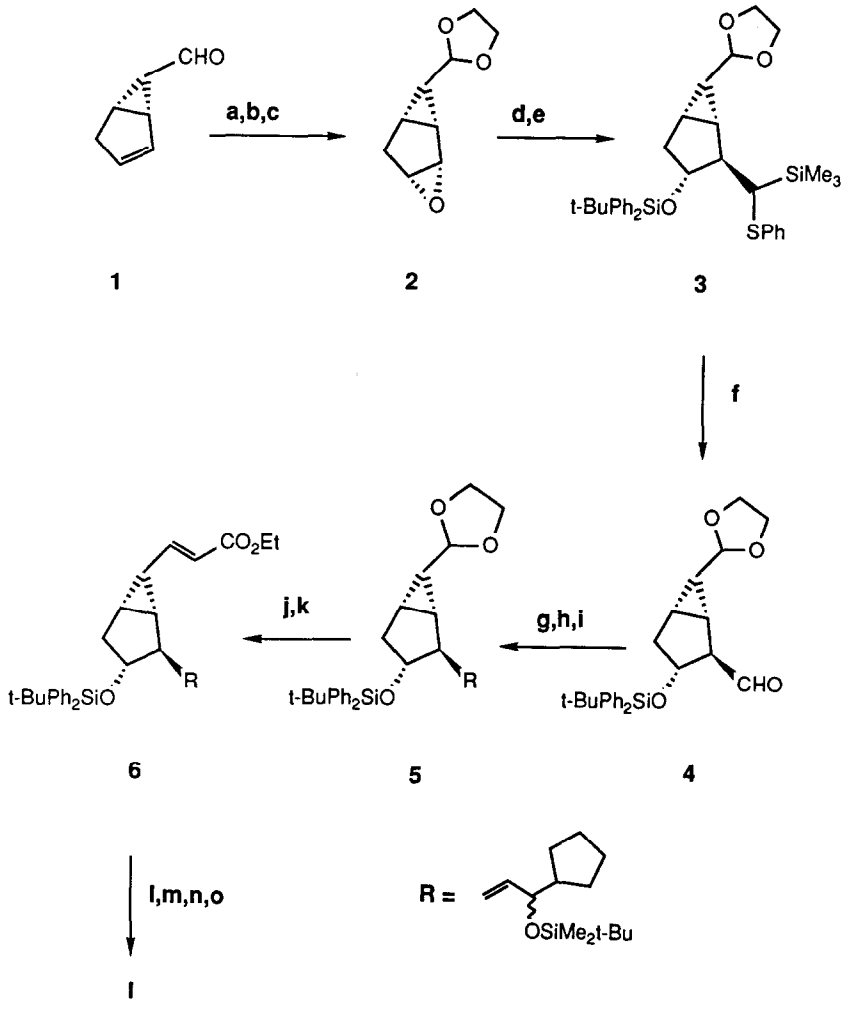


II

A preliminary retrosynthetic analysis of the target structure indicated that the bicyclic epoxide 2 would be a key synthon in the synthetic scheme. A MM2 conformational analysis of this molecule[3] indicated that nucleophilically triggered epoxide ring opening should occur exclusively at C-12 (PG numbering) via the more stable boat transition state.

The epoxide 2 was assembled as in Scheme I. The readily available cyclopropane carboxaldehyde 1[4] was protected as its ethylene ketal (ethylene orthocarbonate,[5] CSA, CH_2Cl_2) and converted to 2 using standard methodology (1,3-dibromo,5,5-dimethylhydantoin, acetone/water, 25°C, 5 hrs followed by NaOH/MeOH, 61% for the two steps[6]). 2 was found to be, in general, rather unreactive towards cuprate reagents (with the exception of divinylcopper lithium, 74%)[7]. However, ring opening was found to occur in high yield upon exposure to the carbanion derived from phenylthiomethyl trimethylsilane[8]. The stereochemistry of the single reaction product regioisomer[9] was determined by combining interpretation of the 200 MHz NMR spectrum, conformational energy calculations and Haasnoot's modified Karplus equation derived vicinal JJ(H-H) coupling constants[10]. The resultant carbinol was silylated (t-$BuMe_2SiCl$,DMF, imidazole) and treated with one equivalent of m-CPBA (-20°C,CH_2Cl_2) to afford aldehyde 4 directly upon work up.[11] This sensitive material was promptly exposed to cyclopentylcarboxymethylene triphenylphosphorane[12] (PhH,25°C,63%) to afford the α,β unsaturated enone. The remainder of the synthesis proved to be uneventful, 1,2-reduction of the enone ($NaBH_4$,-30°C) and silylation of the resultant carbinols (t-$BuMe_2SiCl$,DMF,imidazole, 90% for two steps) afforded an epimeric mixture of protected C-15 alcohols 5. Demasking of the protected aldehyde (PPTS, acetone/water, 25°C) and homologation ($Ph_3P{=}CHCO_2Et$, THF, 25°C, 20 hrs) afforded exclusively the (E)-unsaturated ester 6 in high yield (85%). Reduction to the allylic alcohol (DIBAL-H, $PhCH_3$,-70°C) followed by modified Williamson ether synthesis[13] and treatment with ethereal diazomethane provided the protected 3-oxa derivative (64%, 3 steps) which upon exposure to standard desilyation conditions (TBAF, THF, 25°C) afforded a mixture of I and its 15(R)-epimer which were separated chromatographically.

I was found to be only weakly active as an antiplatelet agent in comparison to prostacyclin. Further refinements of the receptor model[2] are currently in progress in our laboratory.



Reagents

a) ethylene orthocarbonate, CSA, CH_2Cl_2; b) 1,3,dibromo 5,5 dimethylhydantoin, acetone/H_2O; c) NaOH(1 equiv.) in MeOH;
d) PhSCH(Li)$SiMe_3$, THF, 0°C; e) t-$BuMe_2SiCl$, DMF, imidazole;
f) m-CPBA(1 equiv), CH_2Cl_2-20°C, $CuSO_4$ work up.
g) $Ph_3P{=}CH_2C(O)CH_2$-  , PhH, 25°C; h) $NaBH_4$, MeOH,-30°C;
i) t-$BuMe_2SiCl$,DMF, imidazole; j) PPTS, acetone/H_2O;
k) $Ph_3P{=}CHCO_2Et$, THF, RT, 10 hrs; l) DIBAL-H, $PhCH_3$,-70°C; m) n-BuLi, $ClCH_2CO_2Li$, DMF, DMSO, THF, 25°C; n) CH_2N_2, Et_2O; o) TBAF, THF, 25°C.

Acknowledgements

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References

1. For background information see R.C. Nickolson, M.H. Town, and H. Vorbruggen, Med. Res. Reviews, 1985, 5 1.

2. A tentative receptor model was developed by comparing minimum energy conformations of known active and inactive prostacyclin analogs using methods available in CHEMLAB. Compound I was conceived, geometrically relaxed by force field methods and shown to meet the requirements of the model during the synthetic planning phase of the work (with S.E. Radak).

3. MM2 and PRDDO force field calculations indicate that for the bicyclo[3,1,0]hexane ring system the boat conformation is favored over the chair by approximately 2.7 K cal. Attack at C-12 is favored over C-11 as the boat conformation is retained in the transition state of only the former. A detailed examination of this and the bicyclo[3,2,0]heptane ring systems will appear in a forthcoming full paper.

4. D.L. Garin, J. Chem. Soc., Chem. Commun., 1973, 403.

5. D.H.R. Barton, C.C. Dawes, and P.D. Magnus, J. Chem. Soc., Chem. Commun., 1975, 482.

6. Yields refer to chromatographically pure material with consistent NMR, Ir, ms/microanalytical data.

7. A survey of the reactivity of 2 with a variety of nucleophiles will appear in the full paper.

8. P.J. Kocienski, Tetrahedron Lett., 1980, 21 1559.

9. This compound is, of course, a mixture of diastereomers due to the phenylthiomethyl trimethylsilyl function.

10. C.A.G. Haasnoot, F.A.A.M. de Leeuw and C. Altona, Tetrahedron, 1980, 36 2783.

11. The aldehyde 4 could also be obtained from the corresponding vinyl derivative by sequential glycolization (Y. Van Rheenen, R.C. Kelly and D.Y. Cha, Tetrahedron Lett., 1976 1973) and periodate cleavage ($NaIO_4$, MeOH, 0^oC).

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