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A STEREOCONTROLLED SYNTHESIS OF A NOVEL PROSTACYCLIN ANALOG "ALLENE-CARBACYCLIN". APPLICATION OF MOLECULAR MECHANICS CALCULATIONS TO ORGANIC SYNTHESIS.

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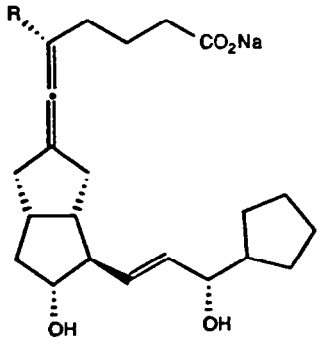
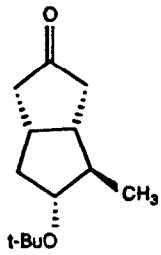
Abstract

The synthesis of a novel Prostacyclin/Carbacyclin analog 1a has been achieved in a stereocontrolled manner starting from the readily available bicyclic ketone 3. A key strategic feature of the synthesis is a nucleophilic acetylide anion addition to 3, the stereochemistry of which is predicted by MM2 calculations.

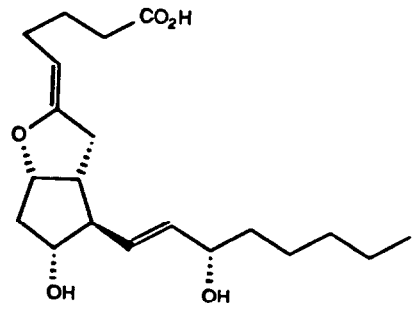
The search for therapeutically effective prostacyclin 2[1] mimics continues unabated. In this letter, we disclose a) the synthesis of novel allenic carbacyclin analogs which exhibit a high eudismic ratio for the different allenic isomers and provide important information on the "active shape" of the prostacyclin molecule at its platelet receptor and b) the utility and novelty of electrostatic probe calculations in the prediction of the stereochemical outcome of nucleophilic attack at an sp2 carbon atom.



1a R=H
1b R=CH3



11



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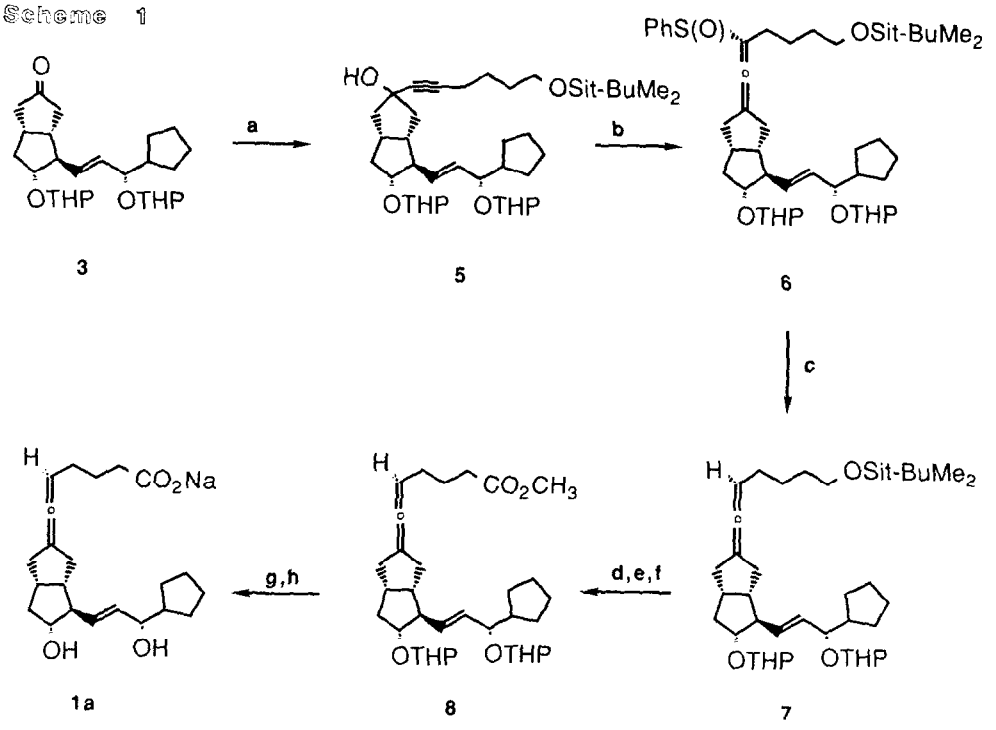
"Allene-Carbacyclin" 1a is predicted by our molecular modelling calculations[2] to be able to adopt the active shape conformation of PGI_2 **2** at the platelet receptor.

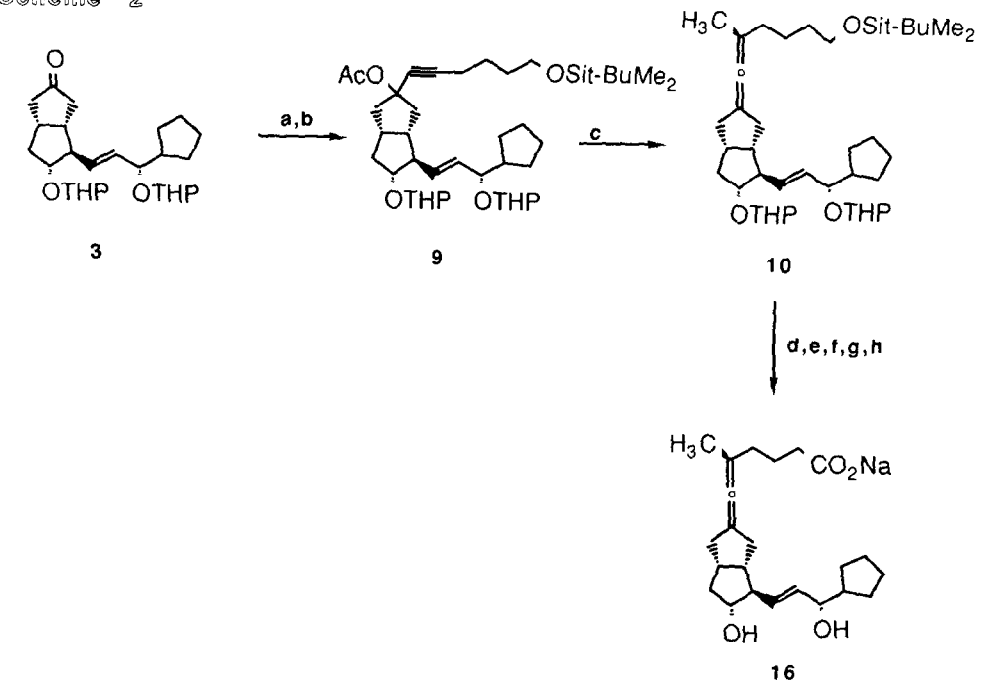
We envisaged that the critical stereochemistry at C-5 could be introduced via the stereocontrolled addition of an acetylide anion to the bicyclic ketone **3**[3]. A preliminary MM2 conformational analysis and electrostatic probe calculations on the model ketone **11** indicated that in the lowest energy conformation nucleophilic attack would occur predominantly from the si-face[4]. This prediction showed good agreement with experimental data. As shown in Scheme 1, treatment of **3** with **4** at $-20^{\circ}C$ afforded a 9:1 mixture of isomers **5**. Exposure of this mixture to phenylsulfenyl chloride triggered a [2,3] sigmatropic rearrangement of the intermediate sulfenate esters to produce the allene sulfoxides[5]. Treatment of **6** with methyllithium (Et_2O,$-70^{\circ}C$) produced a clean conversion to the required allenes **7**[6]. The remainder of the synthesis proceeded uneventfully; demasking of the primary alcohol (TBAF, THF, $25^{\circ}C$) and subsequent Jones oxidation and work up with ethereal diazomethane afforded the esters **8** in excellent overall yield. Conversion to **1a** was accomplished by removal of the secondary hydroxyl protecting groups (AcOH, THF, H_2O, 3:1:1), separation of the minor allene isomer by chromatography[7] and saponification of the carboxylic acid ester (NaOH, 1 equivalent in methanol). As expected, **1a** was found to be a potent antiplatelet agent in vivo. (ED_{50} 7 ug/kg, PGI_2 0.4 ug/kg - rat thrombocytopenia model)

To corroborate our structural assignments, the C-5 methyl allene was synthesized as shown in Scheme 2. Trapping of the intermediate alkoxide in situ with acetic anhydride afforded the propargylic acetate **9** which was treated with dimethylcopper lithium[8] (4 equivalents, Et_2O, $0^{\circ}C$) to afford the methylated allenes in >90% overall yield. This mixture was transformed to the corresponding deprotected esters as before and the allene isomers separated and individually saponified. Not surprisingly, the minor isomer **1b** was found to have essentially the same potency as **1a**, whilst the major isomer was found, interestingly enough, to have little antiplatelet activity.

Scheme 1



Scheme 2



Reagents for Scheme 1.

a) H-≡-$(CH_2)_3$OTBDMS 4, nBuLi, THF, 0°C, 92%; b) PhSCl, Et_3N, CH_2Cl_2, -70°C->25°C, 69%; c) MeLi, Et_2O, -70°C, 69%; d) n-Bu_4NF, THF, 25°C, 100%; e) Jones reagent, -25°C; f) CH_2N_2, Et_2O, 60% for 2 steps; g) HOAc, H_2O, THF (3:1:1) 25°C, 85%, h) NaOH, MeOH.

Reagents for Scheme 2.

a) H-C≡C$(CH_2)_3$OTBDMS 4,n-BuLi, THF, 0°C; b) Ac_2O (neat) 92% for 2 steps; c) Me_2CuLi (4 equivs), Et_2O, 0°C, 97%, d, e, f, g and h as above.

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. An "active shape" model was developed from an evaluation of the molecular structures of known active/inactive prostacyclin analogs using the methods available on CHEMLAB and SYBYL. For some details see S.W. Djuric, M. Miyano and J.P. Snyder, Tetrahedron Letts., in press.

3. See P.A. Aristoff, J. Org. Chem., 1981 46, 1954.

4. Molecular mechanics calculations suggest that the observed diastereofacial selectivity arises from the differentiation of the groundstate conformers rather than in the product pairs, which lie much closer in energy. Intermolecular calculations, using a charged model probe to simulate the attacking acetylide, predict a 4:1 ratio of products, close to that found. A more detailed description of this approach will be the subject of a forthcoming full paper.

5. V. VanRheenan and K.P. Shepard, J. Org. Chem. 1979 44 1582.

6. G. Neef, V. Eder and A. Seego, Tetrahedron Letts., 1980 21 903.

7. W.C. Still, M. Kahn and A. Mitra, J. Org. Chem. 1978 43 2923.

8. In accord with literature precedent, we had anticipated that cuprate induced allene formation would occur via an SN2' process leading to inversion of the stereochemistry created at the quaternary center, whilst [2,3] sigmatropic sulfenate-sulfoxide rearrangement would proceed with retention of the stereochemistry induced at the same center. See, for example, P.D. Landor, in The Chemistry of the Allenes, Ed. S.R.Landor, Academic Press 1982, p. 59, Chapter 2 and E.J. Corey and N.W. Boaz, Tetrahedron Letts., 1984 25 3063.

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