THE SYNTHESIS OF A NEW HYBRID PROSTANOID FROM NATURAL SAFROLE .[1]

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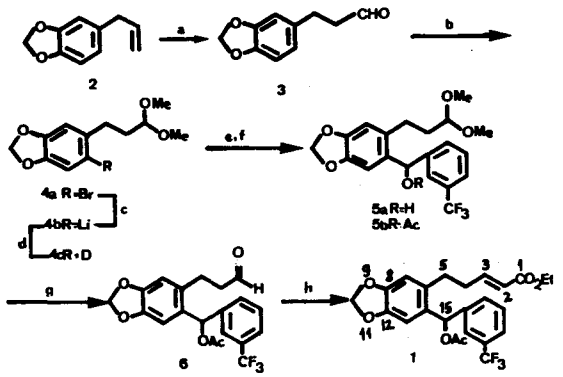
ABSTRACT:The synthesis of a new hybrid prostanoid (1), using natural safrole (2) is described.

Much of the past decade's research in prostaglandins (PG) synthesis, seeking therapeutically useful prostanoids, has been directed toward the preparation of structurally modified analogs which might possess greater tissue selectivity and be of longer duration in their action. A hundred PG analogs have already been prepared,possessing a variety of structural modifications at the the carbocyclic ring, at both the side chains of the PG system, and even heterocyclic analogs have been described.[2]

In our previous reports we have described the synthesis of new PG[3] analogs using safrole (2) as an useful starting material.[4] In this paper we described the synthesis of an hybrid PG analog, i.e., the m-trifluoromethyl acetate derivative 1,having as the main structural feature the presence of a 9,11-bis oxa ring and an endocyclic "bridge" form of the C-13 double bond with a carbon linkage between C-6 and C-14.[5,6]

The synthetic route applied for the preparation of this new hybrid analog is shown in Scheme 1. The synthetic strategy outlined here, differs from that previosly described by the inversion of polarity at the C-6 position of safrole (2)[4],using herein lithiated species as an intermediate to introduce the w-chain of the new prostanoid 1. Starting from 2, the aldehyde 3[7] was prepared by regioselective oxidation of the terminal position of the allyl moiety of the natural product, using the previosly described sequence.[4] Treatment of a methanolic solution of 3 at 0°C, with bromine in the presence of a catalytic ammount of 2,2-dimethoxypropane[8] furnished the bromo-dimethyl ketal 4a in 85% yield.[9] This compound could be lithiated through bromine-lithium specific exchange[10]by using a n-butyl lithium solution in n-hexane at -78° C. The formation of the aryl lithium intermediate 4b could be ascertained by deuterium incorporation,[11] followed by PMR analysis of the deutered dimethyl ketal 4c. The PMR spectrum of 4c shows only a broad singlet signal corresponding to two aromatic

SCHEME 1



a) As described in ref. 4; b) Br_2, (3.4 eq.) $MeOH$, 2,2-DMP (cat.), 0°C, 30 min (85%); c) nBuLi (2,05 eq.), THF, - 78°C, 1h; d) D_2O exc.; e) (to give 5a) m-$CF_3C_6H_4$ (2.0 eq.), -78°C→ r.t., THF, 2h (85%); f)(to give 5b) Ac_2O,%-DMAP, r.t. 30h; chromatography over florisil (67%); g) 15% H_2SO_4, $(CH_3)_2CO$, r.t., 2h (100%); h) ϕ_3P= $CHCO_2Et$ (1.72 eq.), THF, reflux, 12h (82%).

para-hydrogens.[12] The w-chain of the new analog 1 was introduced by trapping the lithium derivative 4b with m-trifluorobenzaldehyde,[13] to afford benzylic alcohol 5a[9] in 85% yield. This rather unstable compound was treated in the usual manner (Ac_2O, 4-DMAP (cat.), r.t., overnight) to give the corresponding acetate 5b in 67% yield, after chromatographic purification.[9] The synthesis of the analog 1 was completed by bis-homologation of the acidic chain. Acid treatment of oily acetate 5b provided, quantitatively, the aldehyde 6.[9] Subsequent treatment of 6 with c.a. 1.7 equivalents of ethyl phosphonium acetate bromide[15] in THF produced, in 82% yield, the new desired analog 1 as an oily product.[9]

On this way, the synthesis of the new hybrid PG analog 1, using safrole (2) as the starting material, could be run in as high as 30% overall yield. Morever, by using different aromatic aldehydes in the nucleophyllic addition step of this synthetic sequence, we can obtain several other hybrid compounds with variations in the w-chain.

These derivatives are expected to present a higher biological half-life due to hindering of beta-oxidation, a common degration step in the metabolism of PG compounds.

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