PROSTAGLANDIN ANALOGUES; THE SYNTHESIS OF NEW PROSTANOIDS FROM NATURAL SAFROLE[1]

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ABSTRACT: The synthesis of new modified prostanoids (2,3) using natural safrole (1) as starting material is described.

Prostaglandins (PG) can be called "tomorrow drugs"[3] due their ubiquitous formation in human tissue and organs and their several powerful biological effects.[4] However, it is also apparent that the natural PG will not find clinical application, since they induce a broad spectrum of side effects. A hundred PG analogues have already been prepared, posseding a variety of structural modifications at the five-membered carbocyclic ring, at the side chains of PG system,[5] as well as analogues having heterocyclic rings and even secoprostanoids.[6]

In the present study we describe our results in a research effort to synthesize new PG hybrid analogues 2 and 3 from the natural safrole (1) isolated from sassafraz oil. The hybrid character of these new analogues can be summarized by the presence of a 9,11-bis oxa ring[7] and by the endocyclic form of the Δ^{13} double bond with a carbon-carbon linkage between C-6 and C-14.

A convenient and attractive synthetic route to 2 is illustrated in Scheme 1. Starting from 1 the aldehyde 4 was prepared by the previous described sequence.[2] Treatment of 4 with ethyl acetate phosphonium bromide produced a clean mixture of E/Z olefins 5 in 93% yield.[8] Subsequent hydrogenation of 5 using Pd/C as catalyst furnished quantitatively the saturated ester 6, with the appropriate α-chain length. The synthesis of the new analogues 2 was completed by introducing the alcoholic moiety of the w-chain by initial treatment of 6 with the mixed anhydride[9] prepared using n-hexanoic acid and trifluoro acetic anhydride, obtained from trifluoro acetic acid and phosphorous pentoxide, affording the acylated adduct 7[8] in 65% yield after column chromatography, followed by benzylic reduction using sodium borohydride, to produce the desired hybrid analogue 2 after alkaline hydrolysis.

The synthetic route adopted to synthesize the acetic acid hybrid analogue 3 is shown in the Scheme 2, using the acid 9, prepared from 1 as previously described.[2] Ultimately the compound 3, synthetisezed by the same synthetic methodology, may be seen as a new hybrid analogue of PG having as principal structural features both of nonsteroid anti inflammatory agents and PG.

In conclusion, the synthesis of these new PG derivatives 2 and 3 using safrole as the starting material can be run in as high as 39% and 45% overall yield, respectively. Morever, using the proper modifications in the synthetic route we can obtain other hybrid compounds having structural variations in the amyl moiety of the w-chain.[10]

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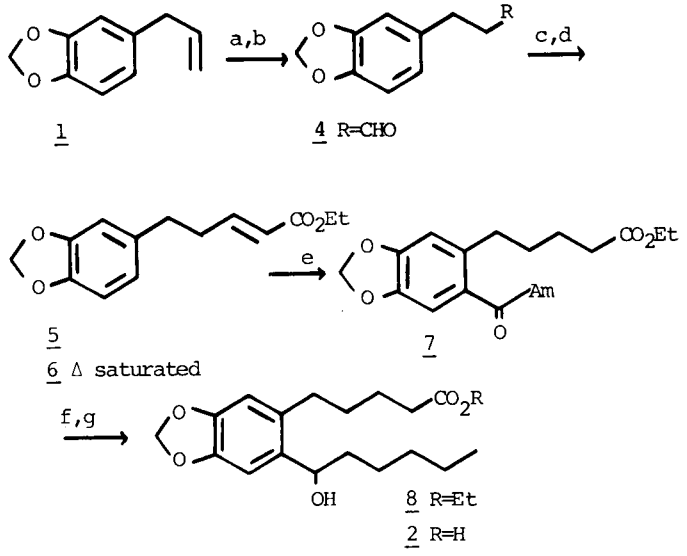
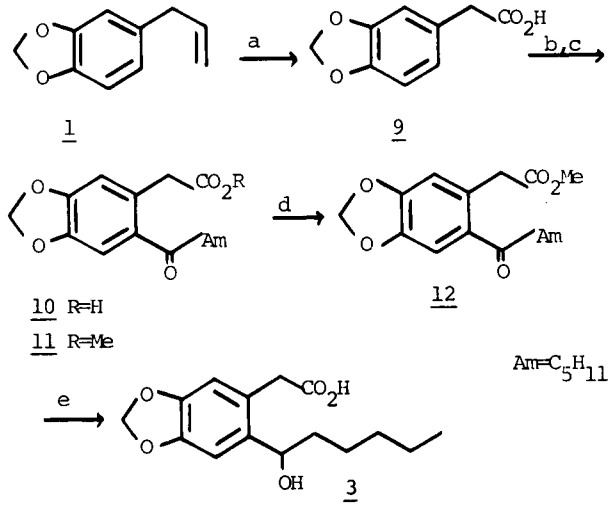
SCHEME 1



1 4 R=CHO 5 6 Δ saturated 7 8 R=Et 2 R=H

a) $NaBH_4$, BF_3. Et_2O, diglime, 20°C, 1h; 30% H_2O_2, 6N NaOH, reflux, 4h (78%); b) PDC, CH_2Cl_2, rt, 18h (92%); c) $Ph_3PCHCO_2Et.Br$, THF, reflux (93%); d) H_2, 10% Pd/C, AcOEt (98%); e) $C_5H_{11}CO_2H$, $(CF_3CO)_2O$, $HClO_4$ cat. (65%); f) $NaBH_4$, MeOH, 0°C (90%); g) K_2CO_3, MeOH:H_2O (4:1), rt (95%).

SCHEME 2



1 9 10 R=H 11 R=Me 12 3 Am=C_5H_{11}

a) reference 2; b) CH_2N_2, Et_2O:dioxane (4:1), rt (100%); c) $C_5H_{11}CO_2H$, $(CF_3CO)_2O$, $HClO_4$ cat., 48h (62%); d) $NaBH_4$, MeOH, 0°C (90%); e) K_2CO_3, MeOH:H_2O (4:1), rt, 18h (98%).