Tetrahedron Letters,Vol.30,No.35,pp 4731-4734,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

BIOMIMETIC RADICAL CYCLISATIONS: SYNTHESIS AND BIOSYNTHESIS OF BENZODIHYDRO-PYRANS AND -FURANS

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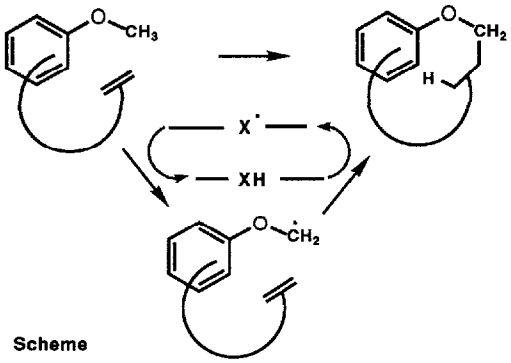
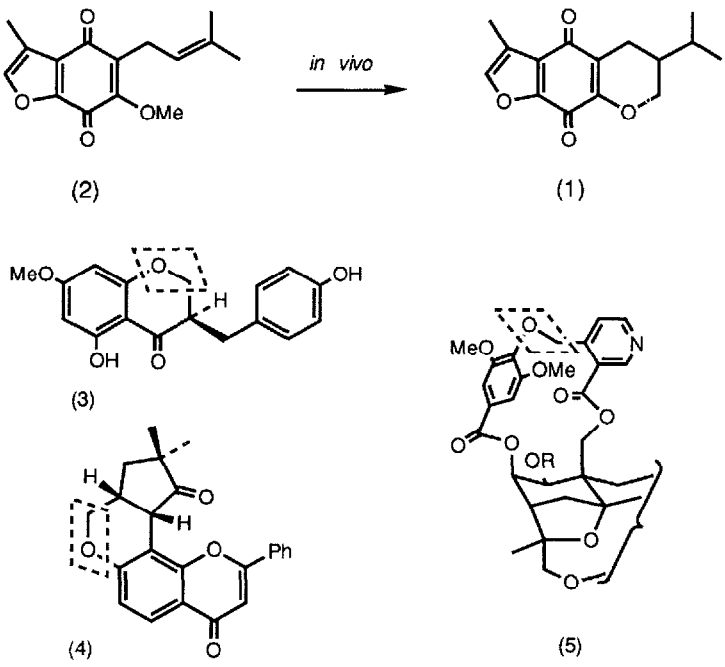
Aryloxymethylene radicals generated by decarboxylation of the thiohydroxamate esters derived from acids (8a), (10a), and (12) undergo 6-endo cyclisation yielding (9), (11), and (14) respectively, mimicking the unusual biosynthetic reactions involved in formation of (1), (3), and (4) in nature.

A number of diverse natural products contain a structural moiety which appears to be derived by addition of an aromatic methoxy group to a double bond, as generalised in the Scheme; hydrogen abstraction, by an unknown cofactor, to a carbon radical or cation must precede cyclisation.



Scheme

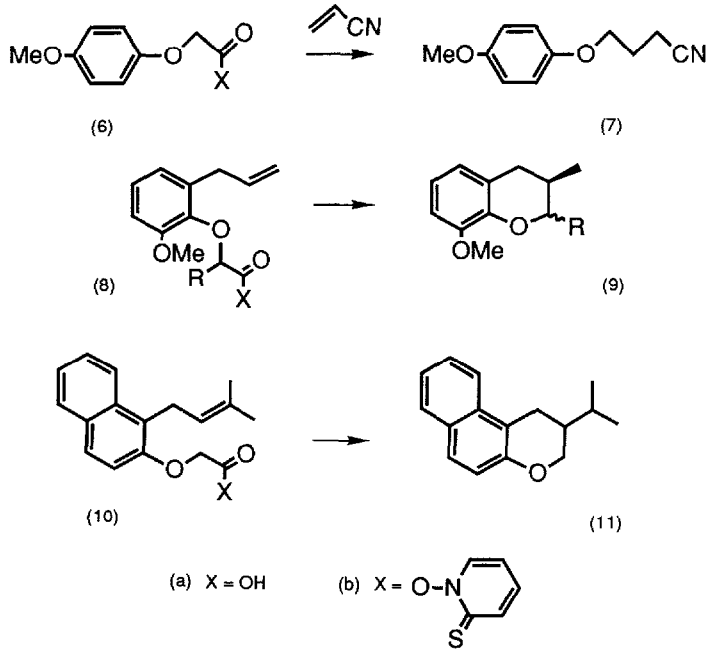
A new ring results, five or six membered, and the overall reaction may involve no net change in oxidation level, as for example in the biosynthesis of scabequinone (1) which is considered to be formed from the methoxybenzoquinone (2) in Cyperus species.[1] Similar examples are homoisoflavonoids, such as the benzylchromanone (3),[2] and stachyoidin (4).[3] Alternatively the cyclisation is, at face value, oxidative, as in the case of eucomin[4] and the cathate unit (5) of cathedulin E3 and E4.[5]



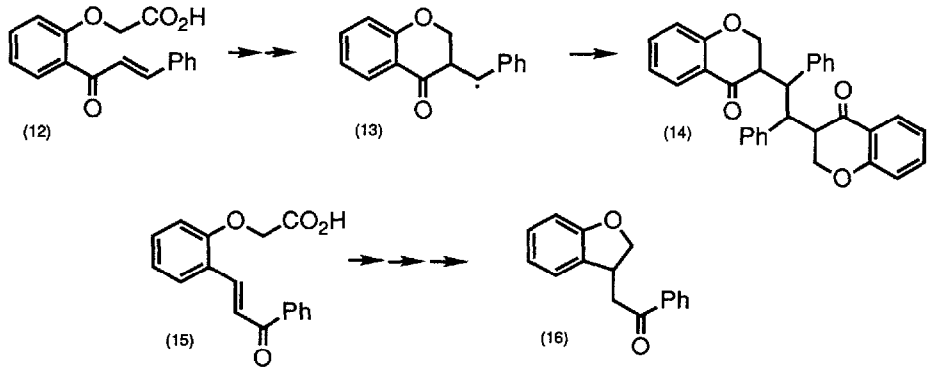
Since a priori we inclined towards a radical mechanism, we sought to test its viability by examination of the cyclisation of aryloxymethylene radicals and perhaps to develop a new biomimetic synthetic method. For our purposes we chose to employ the radical decarboxylation strategy of Barton and his coworkers[6] to generate the desired radicals. This method requires the formation of a thiohydroxamate ester, e.g. (6b), from reaction of an aryloxyethanoyl chloride with the sodium salt of thiopyridone N-oxide, followed by photolysis in the presence of a suitable hydrogen donor.

As a first test we looked at a simple intermolecular case, and fragmented ester (6b) using the above conditions and tributyltin hydride-azoisobutyonitrile in the presence of acrylonitrile; we were pleased to find a modest yield of desired nitrile (7), the product from addition of p-methoxyphenoxymethylene radicals to acceptor, and quenching by hydrogen abstraction. The yield was not optimised but we moved on immediately to investigate two intramolecular cases designed to form a 3-alkylchroman ring system, paralleling the proposed biosynthesis of this substructure of scabequinone, i.e. (8, R=H), and (10). 2-Allyl-5-methoxyphenol was prepared by Claisen rearrangement of 2-allyloxyanisole, and converted to the aryloxyacetate (8, R=H, X=OEt) by reaction with ethyl bromoacetate-potassium carbonate-sodium iodide. The corresponding acid, acid chloride, and thiohydroxamate (8b, R=H)

were prepared conventionally. 1-Dimethylallyl-2-naphthol was synthesised by alkylation of 2-naphthol with isoprene and trimethylsilyl iodide, and similarly converted via (10a) to (10b). Photolysis (tungsten lamp) of (8b, R=H) and (10b) in refluxing benzene with t-butanethiol gave the desired products (9, R=H), 66%, and (11), 57%, from non-oxidative 6-exo cyclisation. Much lower yields of (11) were found in photolysis of (10b) at room temperature, when 1-dimethylallyl-2-naphthol methyl ether became a significant product (from radical trapping by hydrogen before cyclisation). Cyclisation of (8b, R=Me) was also readily effected, 70%, giving the expected cis/trans mixture (1:1) of stereoisomers (9, R=Me).



We then extended this study to include an analogue of the homoisoflavonoid system (3). The aryloxyacetic acid (12) derived from 2'-hydroxychalcone was decarboxylated as before (but at higher concentration); under the conditions used the major product proved to be the dimers (14), overall yield 44%; one (non-centrosymmetric) stereoisomer dominated. Again the desired 6-exo radical cyclisation has taken place; the conditions for termination of radical (13) by hydrogen have not yet been explored. Finally we also demonstrated that 5-exo ring closure is feasible by using the acid (15) from 2-hydroxychalcone; the saturated ketone (16) was smoothly isolated (51%). All product structures were substantiated by high field ^{1}H and ^{13}C n.m.r. and m.s.



Thus in conclusion we have observed that aryloxymethylene radicals can be generated, and that they do add intramolecularly to both electron rich and electron poor double bonds in a net non-oxidative manner, mimicking the biological process. A biological radical process is thus at least chemically sensible.

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(Received in UK 20 June 1989)