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A NOVEL SYNTHESIS OF SPIROCHROMENES

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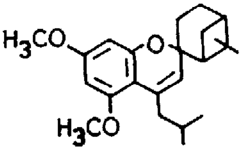
ABSTRACT : The Mitsunobu coupling of cyclic tertiary ethynyl carbinols followed by the Claisen rearrangement of the ethers obtained provides a short, novel entry to spirochromene systems.

In connection with the synthesis of Robustadial, an antimalarial compound isolated from the Eucalyptus robusta leaves[1], we became interested in the chemistry of spirochromenes. The synthesis of a few spirochromenes (1, 2) which are important intermediates in the synthesis of Robustadial and its analogs were reported recently by Salomon et al[2]. There has also been considerable interest in the study of spirochromenes due to their photochromic properties[3]. The methodology available in the literature[4] for the construction of spirobenzopyran systems and the one adopted by Salomon et al[2,5] in their recent synthesis of Robustadial and its analogs is outlined in Scheme I from a retrosynthetic perspective. These routes entail several



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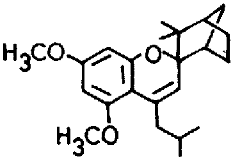

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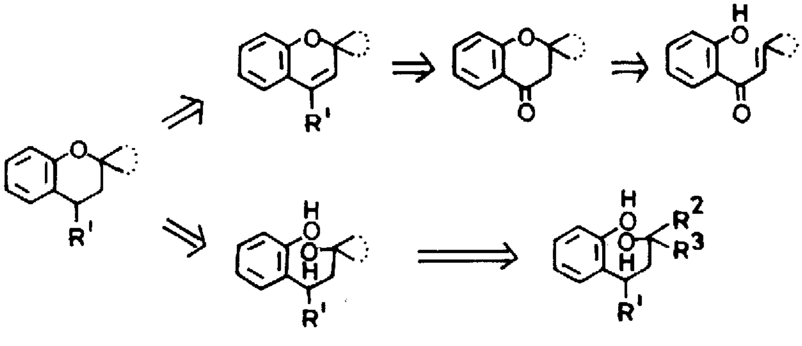
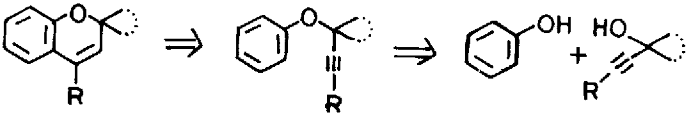
Scheme I



steps; the condensation step does not furnish a single olefin and the stereochemistry at the spirocarbon is also not ensured.

An alternative route which is conceptually different and is based on a pericyclic transformation, outlined in Scheme II, has not been explored so far. Since α , α -dimethylpropargyl aryl ethers undergo the Claisen rearrangement with great ease (about 600 times faster than the corresponding aryl propargyl ethers[6]) it can be expected that cyclic tertiary ethynyl aryl ethers will rearrange readily to the spirochromenes with great ease. Realisation of the target molecule by this route would however depend very much on the feasibility of synthesising such cyclic tertiary ethynyl aryl ethers.

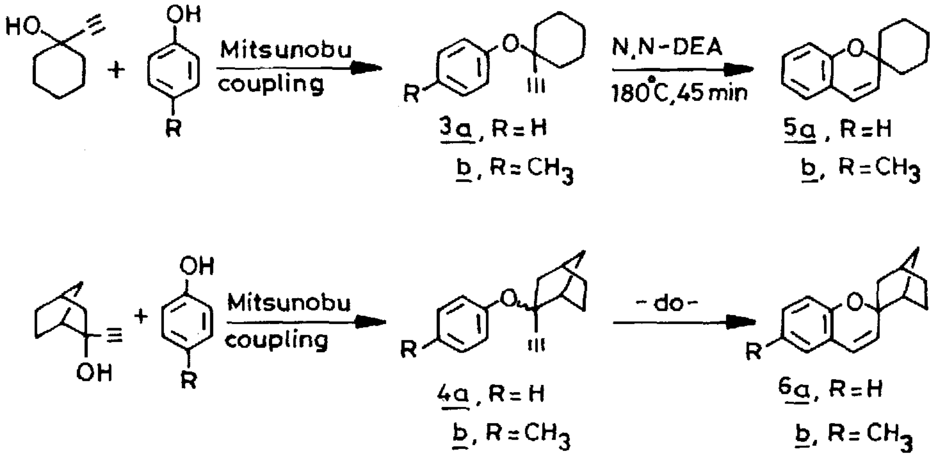
Scheme II



The preparation of the halides of tertiary ethynyl carbinols is often complicated by acetylene-allene rearrangements[7]. In cases where the halides are known, they are marked by their poor reactivity to nucleophilic displacement reactions[8]. In this communication we demonstrate the viability of the alternative route outlined in Scheme II for the synthesis of spirochromenes.

Our recent success on the application of the Mitsunobu coupling reaction for the preparation of aryl ethers of ethynylcarbinols, especially α,α -diaryl and α,α -dimethylpropargyl aryl ethers[9] prompted us to extend this method for the synthesis of cyclic tertiary ethynyl carbinols, despite the lack of precedence in the literature for the Mitsunobu reaction on tertiary carbinols[10]. Reaction of 1-ethynylcyclohexanol with phenol and p-cresol, under Mitsunobu coupling conditions[11], at room temperature furnished the corresponding ethers **3a** and **3b** in about 38% yield along with some dehydrated product viz. 1-ethynylcyclohexene. Similarly, the Mitsunobu coupling of 2-ethynyl-endo-2-norbornanol with phenol and p-cresol, at room temperature, furnished the ethers **4a** and **4b** in 35% yield along with some amount of the corresponding dehydrated product. The reaction was free from any acetylene-allene rearrangement or Wagner-Meerwein shifts. The ethers **3a**, **3b**, **4a** and **4b**, obtained by column chromatography over silica, were homogenous on HPLC and TLC[12]. The spectral data of **4a** and **4b** were in accordance with the gross structures, but their exact stereochemistry could not be ascertained with the data on hand. The Mitsunobu coupling reaction on secondary alcohols is known to proceed by an S_N2 pathway leading to inversion of configuration[13] but this aspect has not been investigated thus far on tertiary alcohols[14]. A surprising observation in the Mitsunobu coupling of these tertiary carbinols was that an exclusive dehydration of the alcohols occured when the reaction was carried out at 0°C[15].

The ethers 3a, 3b, 4a, and 4b underwent a facile Claisen rearrangement in N,N-diethylaniline at 180°C during a period of 45 minutes yielding the chromenes 5a, 5b, 6a and 6b respectively as pale yellow liquids in 90-95% yield. The transformation of the ethers 4a and 4b to the spirochromenes 6a and 6b under these conditions was markedly clean. The stereochemistry of 6a and 6b is based mainly on mechanistic considerations[16].



Thus, a few spirochromenes have been synthesised by our new route. The ethers of the type 3 and 4 may also serve as important synthetic intermediates in the synthesis of spirochromanones by the catalysed Claisen rearrangement[17]. The synthetic utility of these ethers and the total synthesis of Robustadial by the above route is currently in progress.

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11. The reaction was performed by the addition of DEAD to a solution of TPP, the alcohol and the phenol in dry benzene, under argon, at R.T.

12. Spectral data of representative compounds :
    4a : ir (CCl_4) : $3300cm^{-1}$, $3020cm^{-1}$, $2930cm^{-1}$, $1600cm^{-1}$.
    ^1H nmr (CCl_4/TMS) : 1.0-2.4 (complex m), 2.5 (s), 6.5-7.2 (m).
    MS : m/z 212 (M^+), 94 (base peak).
    4b : ir (CCl_4) : $3020cm^{-1}$, $2930cm^{-1}$, $1625cm^{-1}$, $1600cm^{-1}$.
    ^1H nmr (CCl_4/TMS) : 1.0-2.5 (complex m), 5.6(d), 6.2(d), 6.4-7.1(m).

13. (i) Mitsunobu, O., Synthesis, 1 (1981).

    (ii) See also ref. 10.

14. Assignment of the stereochemistry of 4a and 4b, as well as the study of the stereochemical course in such reactions is in progress.

15. Dehydration of β-hydroxy carboxylic acids under the Mitsunobu conditions is known in literature (Adam, W., Narita, N., and Nishizawa, Y., J. Am. Chem. Soc., 106, 1843 (1984)), but the dehydration of tertiary alcohols under such mild, neutral conditions is surprising. The exclusive dehydtation occuring at low temperatures is being investigated.

16. On the basis of the well established mechanism of aryl propargyl ether Claisen rearrangement (Hepworth, J.D., in Comprehensive Heterocyclic Chemistry; vol.3, eds. Katritzky, A.R., Rees, C.W., Boulton, A.J., and McKillop, A., Pergamon Press, Oxford, 1984 ; pp. 743), the final step involves an electrocyclic ring closure of a heterotriene system. This should proceed from the less hindered exo- side leading to the ethers 6a and 6b.

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