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SYNTHESIS OF THE COUMARIN, SESIBIRICIN

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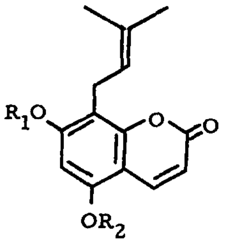
The natural coumarin, sesibiricin[1] (1) is unusual in that it possesses two 3, 3-dimethylallyl substituents, one attached to oxygen, the other to carbon. Thus a projected synthesis from the readily available 5, 7-dihydroxycoumarin (6) would necessitate regioselective O-prenylation and C-prenylation of this diphenol. Since we have previously demonstrated[2, 3] that dimethylallyl ethers of 7-hydroxy-5-methoxycoumarin undergo Claisen rearrangement exclusively to C-8, a suitable synthetic precursor of 1 would contain the 7-(1, 1-dimethyl)-allyloxy grouping. Starting from 6 or the corresponding diacetate (7), selective functionalisation of the oxygen at C-7 would not however be expected since it is known[3, 4] that the 5-oxygen is the more readily alkylated. Thus the first step is necessarily protection of the C-5 hydroxyl, preferably as the 3, 3-dimethylallyl ether, since this is the substituent present in sesibiricin. The question arises as to whether this function would survive the three-step insertion[2] of the isoprenyl group at C-8, in particular the Claisen rearrangement step, since such ethers are unstable[5] at 190°. However, the facile rearrangement of 8 to 3 at low temperature during the synthesis[2] of coumurrayin (4) led us to anticipate that a selective rearrangement of the bis-ether (9) might be possible.

The synthesis of 9 was achieved by two routes. In the more direct but less efficient sequence, reaction of 3 with 3, 3-dimethylallyl bromide, K_2CO_3 in acetone gave mainly the bisether (10, 52%) but fortuitously provided the desired monoether (11) , m.p. 143.5-145°, as the only other major product (23%). That 11 was a 7-hydroxycoumarin followed from its UV behaviour[5] and its stepwise conversion (vide infra) to 4 . The derived[2] dimethylpropargyl ether (12), on Lindlar hydrogenation, furnished 9 which significantly was found from TLC



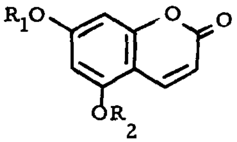
1: R_1=Me, R_2= $CH_2CH{=}CMe_2$

2: R_1=H, R_2= $CH_2CH{=}CMe_2$

3: R_1=H, R_2=Me

4: R_1=R_2=Me

5: R_1=Me, R_2=H



8: R_1= $CMe_2CH{=}CH_2$, R_2=Me

9: R_1= $CMe_2CH{=}CH_2$, R_2= $CH_2CH{=}CMe_2$

10. R_1=R_2= $CH_2CH{=}CMe_2$

11: R_1=H, R_2= $CH_2CH{=}CMe_2$

12: R_1= $CMe_2C{\equiv}CH$, R_2= $CH_2CH{=}CMe_2$

13: R_1= $CH_2CH{=}CMe_2$, R_2=H

14: R_1= $CH_2CH{=}CMe_2$, R_2= $CMe_2C{\equiv}CH$

and NMR to contain a small percentage of the desired phenol (2). The selective Claisen rearrangement of the 1, 1-dimethylallyl ether of 9 was quantitatively accomplished by heating at 130° for 1 hr. The sole rearrangement product (2) was readily converted (MeI, K_2CO_3 in acetone) into sesibiricin (1), m.p. 121-122°, in high yield. The structure of the synthetic sesibiricin and therefore that of the monoether (11) was verified by conversion of 1 into coumurrayin (4) via acid hydrolysis to 5 and methylation. A more efficient six-step synthesis of 1 (25% overall from 7) was achieved by improving the synthetic route to the key intermediate (12). Thus treatment of the diacetate (7) with excess 3, 3-dimethylallyl bromide, K_2CO_3 in 1, 2-dimethoxyethane gave, after hydrolysis 10 (8%) and the two isomeric monoethers (11 and 13). Direct dimethylpropargylation gave a mixture of 12 and 14, 50% and 14% respectively from 7, which were conveniently separated by TLC.

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