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A study of the homonuclear Diels–Alder dimerisations of hydroxybutenyl and pentadienyl coumarins

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Abstract

The synthesis of dimeric coumarins via homonuclear Diels–Alder reactions is described.

Keywords: Diels–Alder reactions; dimeric coumarins.

For many years plants of rutaceous origin have been used extensively in ethnic medicine. Phytochemical examination of these plants have yielded numerous natural products including several dimeric coumarin derivatives, e.g. phebalin[1] (**1a**), thamnosin[2] (**1b**) and toddasin[3] (**1c**). These dimers are believed to possess physiological properties but exist at extremely low concentrations of the order of 0.01% w/w, which has prohibited investigations into their biological activities. A total synthesis of these dimers could prove lucrative in the development of biologically active lead compounds.

It is generally believed that the biosynthesis of these dimers is through a Diels–Alder addition of two diene units, one acting as the diene and the other as a dienophile. It was envisaged that in vitro Diels–Alder dimerisation of suitable monomeric dienyl coumarins would hence lead to the required coumarin dimers. In 1990, Reisch et al.[4] reported a synthesis of thamnosin (**1b**) in 7% yield by Diels–Alder dimerisation of 7-methoxy-6-(3′-methyl-1′,3′-butadienyl)coumarin (**2c**) in the presence of fused $ZnCl_2$. To date no reports have appeared in the literature on the synthesis of phebalin (**1a**) and toddasin (**1c**). In this paper, we report our studies on the homonuclear Diels–Alder dimerisation of hydroxybutenyl and pentadienyl coumarins with a view to the synthesis of phebalin (**1a**) and toddasin (**1c**).

Diels–Alder dimerisations can be carried out thermally or catalysed by Lewis acids or mineral acids. Initial attempts were made to synthesise phebalin (**1a**) via a thermally induced Diels–Alder dimerisation of 7-methoxy-8-(3′-methyl-1′,3′-butadienyl)coumarin (**2a**), prepared by the iodina-

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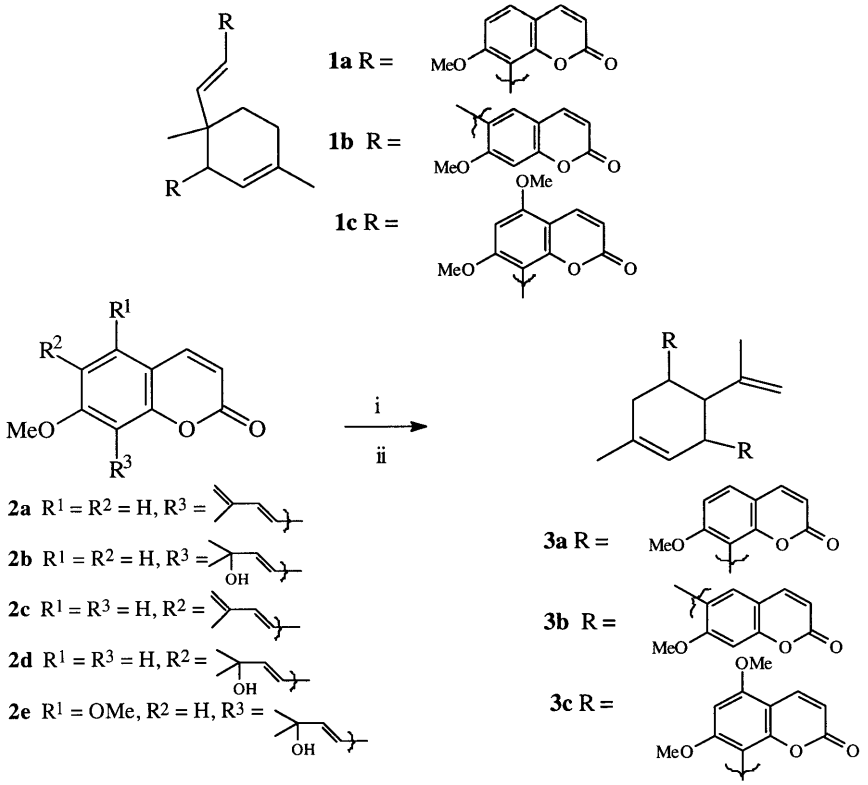
tion of 7-hydroxycoumarin, followed by methylation, a palladium acetate catalysed Heck reaction and subsequent dehydration. Thermal dimerisation was carried out by heating the diene (**2a**) neat as well as in a high boiling point solvent, e.g. liquid paraffin. In both cases starting material was the major compound to be recovered (Scheme 1).



Scheme 1. (i) $ZnCl_2$, $CHCl_3$, reflux, 18 h (argon); (ii) TFA/silica gel–benzene, 2 h

Lewis acid catalysed dimerisation of the diene (**2a**) was then attempted. The reaction conditions were similar to those reported by Reisch et al.[4] The diene (**2a**) and freshly fused $ZnCl_2$ in $CHCl_3$ were refluxed for 18 h and, after work-up, yielded a mixture of products. Preparative TLC separation resulted in the isolation of one major product in 20% yield. Crystallisation from methanol yielded colourless crystals with a melting point of 212°C. The positive mode electrospray ionisation mass spectrum showed a signal (MH^+) at m/z 485 indicating that the product was a dimer. The ^1H NMR spectrum had resonances at δ 1.25 (3H, singlet) and 1.77 (3H, singlet) due to two methyl groups. A singlet at δ 3.88 integrating for six hydrogens indicated the presence of two methoxyl groups. The appearance of two sets of double doublets at δ 6.20 ($J=9$ Hz) and 7.57 ($J=9$ Hz) each integrating for two hydrogens and the two multiplets at 6.8 and 7.25, each due to two aromatic protons indicated the presence of two coumarin units, substituted at adjacent positions. Multiplets at δ 2.10 (2H), 2.59 (1H) and 3.82 (2H) suggest that the two pentadienyl side chains of the monomer have been involved in cyclisation resulting in the formation of a cyclohexene ring. The presence of a vinylic $=CH_2$ was indicated by a broad singlet at δ 4.4. Another broad singlet at δ 5.47 may be due to an olefinic proton. Based on these values structure (**3a**) was assigned to the product. The ^1H NMR

spectrum did not show the presence of any doublets due to *cis* or *trans* olefinic hydrogens and hence the product was not phebalin (**1a**). For phebalin to have been formed, the external double bond of the diene should have acted as the dienophile. However the structure assigned for (**3a**) was formed when the internal double bond acts as the dienophile. This structure was further confirmed by X-ray crystallographic analysis (Fig. 1).

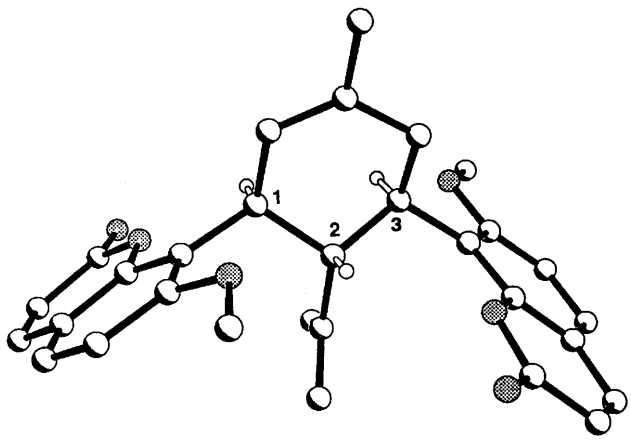


Figure 1. X-ray structure of **4a** ($ZnCl_2$)

In their synthesis of thamnosin (**1b**), Reisch et al.[4] reported that under the same reaction conditions dimerisation of 7-methoxy-6-(3′-methyl-1′,3′-butadienyl)coumarin (**2c**) occurred around the external double bond of the dienophile. Therefore this reaction was repeated using exactly the same reaction conditions. The reaction produced one major product (**3b**) in 18% yield with a melting point of 226°C. The ^{1}H NMR spectrum of this compound was similar to that obtained for dimer (**3a**) and indicated that it too was formed as a result of dimerisation around the internal double bond of the dienophile. Unfortunately, this compound was not sufficiently crystalline for X-ray analysis.

Since neither of these dimerisation reactions yielded the products they were intended to synthesise, a new approach was adopted using acetic acid and sulphuric acid as a catalyst for the dimerisation. These reactions produced inseparable mixtures, and no worthwhile product was isolated. Subsequently the use of trifluoroacetic acid in a silica gel matrix with benzene as a catalyst was explored for dimerisation as reported by Sheu et al.[5] for the synthesis of yuehchukene from a hydroxymethylbutenylindole. 8-(3-Hydroxy-3-methylbut-2-enyl)-7-methoxycoumarin (**2b**), in the above conditions, gave a dimeric coumarin in 52% yield. [Electrospray MS-485 (MH^+)] with an identical ^{1}H NMR spectrum as to that of product (**3a**). But this product had a melting point of 231°C, which is different from that of product (**3a**). Initially it was thought that the two melting points were different because of the difference in their crystalline shapes. However, FT-IR spectroscopic analysis of the two compounds indicated that there are slight variations in the region 2800–3100 cm^{-1}. X-Ray crystallographic analysis indicated that the product is a diastereoisomer **5a**, in which the chirality around carbons C-1, C-2 and C-3 is (*R*,*R*,*S*) whereas the $ZnCl_2$ catalysed dimerisation product has (*R*,*S*,*R*) configuration (Fig. 2) and is represented by structure **4a**. The formation of these diastereoisomers may be due to the differences in the way in which the dienophile interacts with the surface of the solid support present during the reaction, i.e. silica gel/$ZnCl_2$ and the direction of approach of the diene.

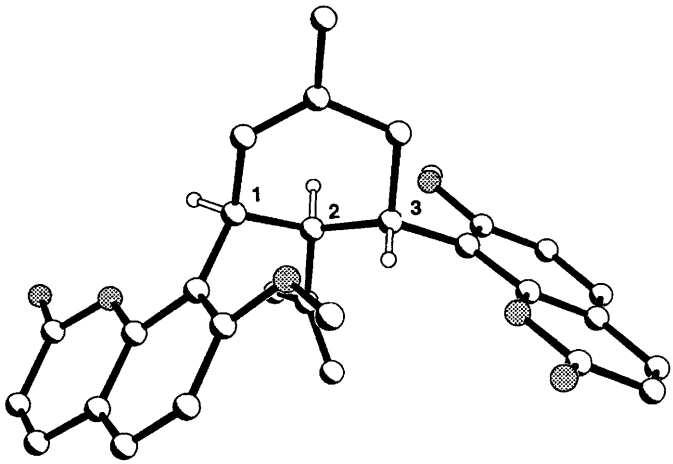


Figure 2. X-ray structure of **5a** (TFA/silica)

8-(3′-Methylbuta-1′,3′-dienyl)-7-methoxycoumarin (**2a**) underwent a similar reaction in trifluoroacetic acid/silica gel and gave a dimer in 47% yield and the product is identical in all respects with the dimer (**3a**) from alcohol (**2b**) dimerisation reaction.

The TFA/silica gel catalysed dimerisation of both 6-(3′-hydroxybut-2-enyl)-7-methoxycoumarin (**2d**) and 6-(3′-methylbut-1,3-dienyl)-7-methoxycoumarin (**2c**) gave the same product with a melting point of 213°C in yields of 42 and 40%, respectively. Positive-mode electrospray-ionisation mass spectrometry showed a parent ion (MH^+) at m/z 485. ^{1}H NMR of the major products were identical and indicated that the internal double bond of the diene acts as the dienophile and assigned the structure (**3b**). The dimers formed from the $ZnCl_2$ and CF_3COOH/silica gel reactions from **2c** and **2d** have different melting points of 226 and 213°C, respectively, and hence can be two different stereoisomers like **4a** and **5a** and can be represented structurally by **4b** and **5b**. The two products were not sufficiently crystalline for X-ray analysis.

5,7-Dimethoxy-8-(3′-hydroxybut-3-enyl)coumarin (**2e**), a possible intermediate in the synthesis of toddasin (**1c**), underwent dimerisation in the presence of TFA/silica gel to yield two major products. One of the products (22% yield), from its mass spectrum, ^{1}H NMR and X-ray analysis, was shown to be (**3c**) similar to the other internal dimers (Fig. 3). The configuration of the three carbons in this case is (*R*,*S*,*R*) and can be assigned structure **4c**. The second compound obtained in 30% yield was also found to be an internal dimer with a mol. wt of 658. X-Ray crystallographic analysis (Fig. 4) revealed that in this instance trifluoroacetic acid has added onto the double bond of the central cyclohexene ring system and hence was assigned the structure **6** (Scheme 2).

All these reactions indicate that the internal double bond of the diene prefers to act as the dienophile, even though it is expected that there would be less steric hindrance for the external double bond of the diene to act as the dienophile. A possible explanation for the preferential use of the internal double bond of the diene may be due to the way in which the monomer is held by the solid support that is present during the reaction. It is perceived that the methoxyl group(s) present on the monomer coordinates to the surface of the silica gel and $ZnCl_2$ in a manner which restricts the approaching diene and results in products with specific stereochemistry.

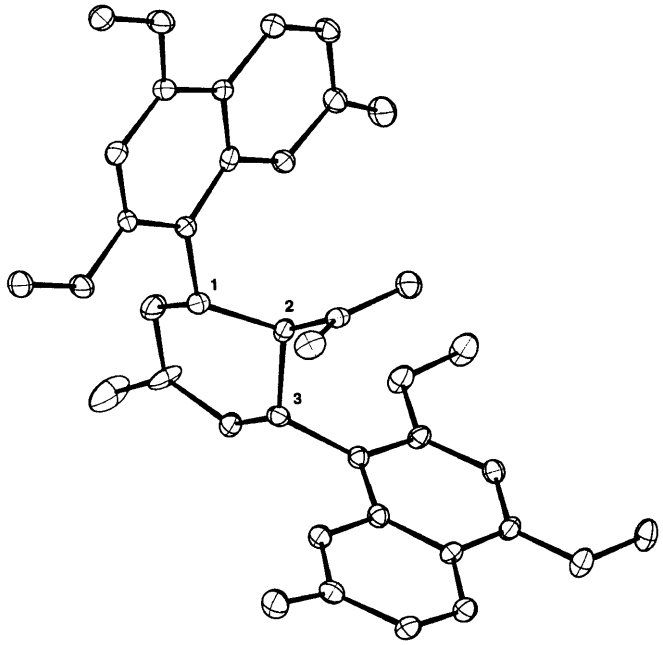


Figure 3. X-ray structure of **4c**

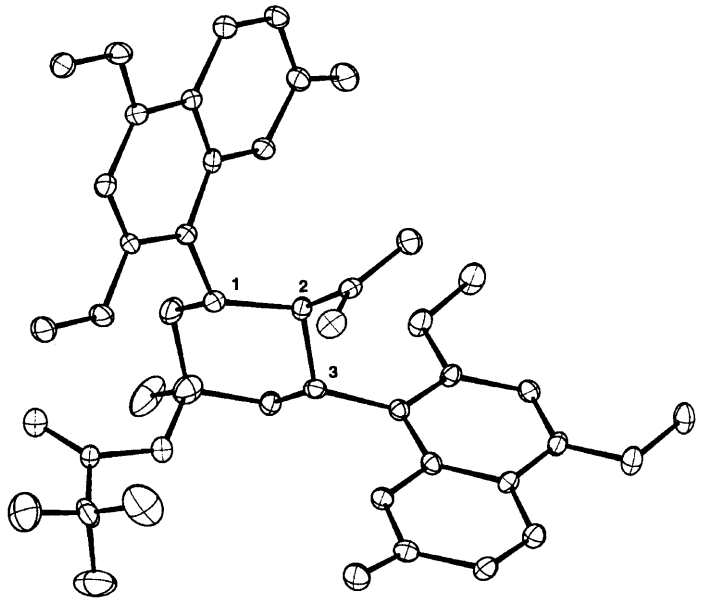
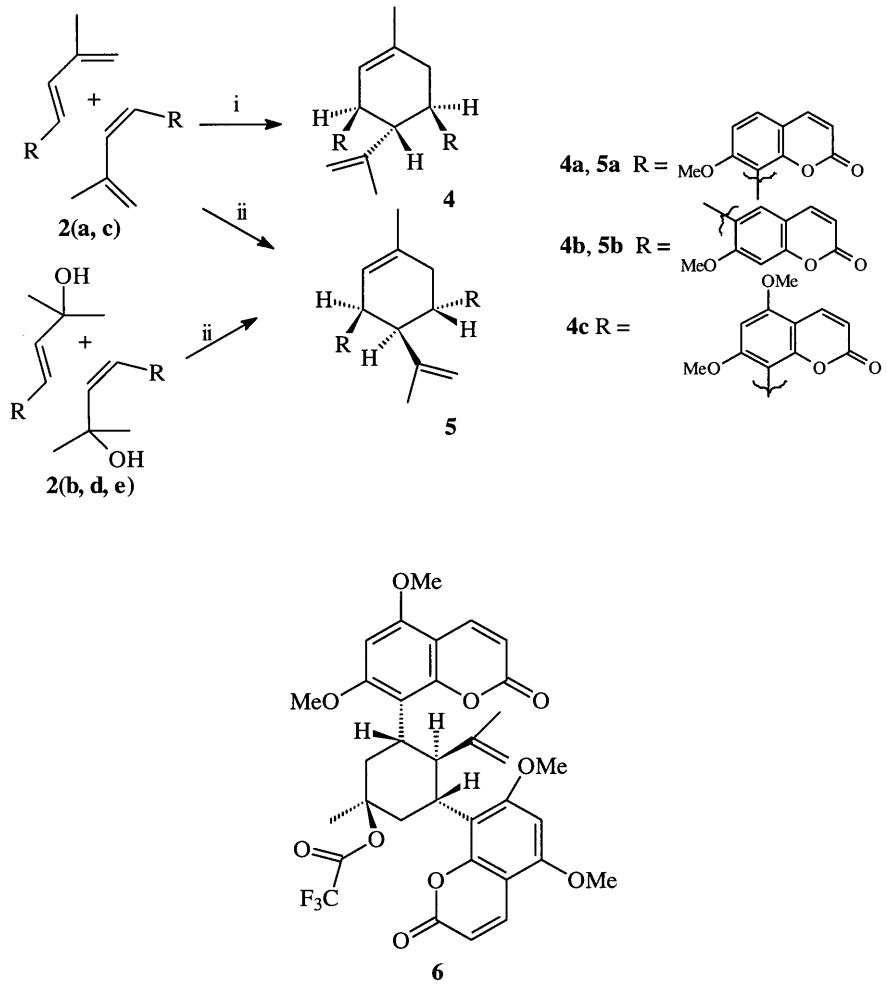


Figure 4. X-ray structure of **6**

A study of antimicrobial activity of the dimer (**3c**) in 5 mM concentrations against five microbial organisms—*Cornybacterium ammoniagenes* (B-4246), *Bacillus megaterium* (B-3701), *Pseudomonas aeruginosa* (B-23), *Bacillus licheniformis* (B-14368) and *Pseudomonas fragi* (B-727)—with pathogenic properties was carried out using the diffusion disc method with an



Scheme 2. (i) $ZnCl_2$, $CHCl_3$, reflux, 18 h (argon); (ii) TFA/silica gel–benzene, 2 h

incubation period of 24 and 48 h. Dimer **3c** is found to inhibit the growth of *Bacillus licheniformis* and is inactive against the other four organisms. Other intermediates used in the synthesis of **3c**, like 5,7-dihydroxycoumarin, 5,7-dimethoxycoumarin, 5,7-dimethoxy-8-iodocoumarin and 5,7-dimethoxy-8-(3′-hydroxy-3′-methylbutenyl)coumarin (**2e**), were found to be inactive against all the microorganisms used. Work is under way to study **3c** as well as other dimers **3a** and **3b** for their activities against more virulent pathogenic organisms.

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