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Stereoselectivity, regioselectivity and mechanism in the intramolecular 'citran' bicyclisation of chromenes †

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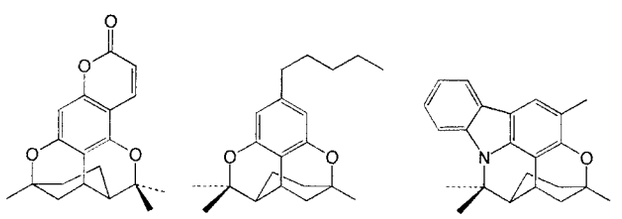
Stereochemical evidence suggests that acid catalysed citran formation proceeds *via* electrocyclisation of a dienone, and that pyrolysis of 'farnesylidenemalonic acid' proceeds with retention of configuration at the newly formed 8-olefin bond, indicating the operation of forward and reverse Diels–Alder processes respectively; 1,3-dihydroxynaphthalene reacts with citral in pyridine to yield chromene and citran products in a regioselective fashion.

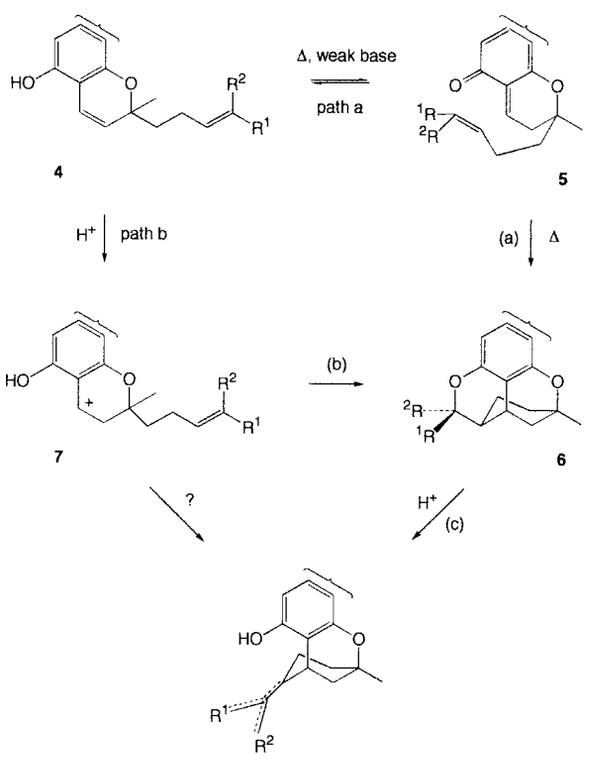
Meroterpenoid structures in which a resorcinol (1,3-dihydroxybenzene) or a phloroglucinol (1,3,5-trihydroxybenzene) nucleus has been alkylated with a prenyl moiety with subsequent cyclisation, are found in many natural sources. One type, the tetracyclic 'citran' ring system, typifies such natural products as deoxybruceol **1**,[1] mahanimbidine **2**[2] and cannibicitran **3**.[3] The



1 **2** **3**

most versatile and high yielding synthesis of the citran structure involves the condensation of an appropriate phenol with citral under mild base conditions.[4] For example deoxybruceol **1** was formed in good yield on heating 5,7-dihydroxycoumarin with citral in pyridine, and mahanimbidine **2** was synthesised by a similar pyridine catalysed reaction between citral and 3-hydroxy-4-methoxycarbazole. The reaction pathway has been shown to involve the initial formation of a chromene of type **4**, with subsequent intramolecular bicyclisation, and this pathway appears to be of biosynthetic importance.

In weak base (*e.g.* pyridine) the bicyclisation has been shown to proceed through tautomerisation of the chromene **4** to the quinomethane **5** [Scheme 1, path (a)] followed by an intramolecular [2 + 4] cycloaddition to yield the citran **6**. When $R^1 \neq R^2$ in **4**, three new chiral centres result and we have shown that in the pyridine-catalysed reaction the geometry of the acyclic double bond is retained in the products.[5] However the same reaction may be induced by acid catalysis, and in this case the possibility of a non-stereospecific proton-initiated process [path (b)] must be considered. This could lead to **6** together with its geometric isomer (R^1 and R^2 reversed), besides tricyclic products **8**,[4] proceeding through carbocations of which only the first, **7**, is shown. Because of the geometrical arrangement, a fully concerted acid-catalysed **4**→**6** conversion appears very unlikely.



4 **5** **7** **6** **8**

Scheme 1

In this paper we set out evidence that the bicyclisation process under acid catalysis does in fact proceed by an intramolecular Diels–Alder reaction, and that the role of the catalyst is to facilitate the tautomerisation which provides the necessary cyclohexadienone intermediate *e.g.* **5**. Further, we report on a closely related thermal reaction and demonstrate that it operates *via* a retro-Diels–Alder mechanism, and finally we examine a new case of regioselective phenol–2,4-dienal condensation, and rationalise the outcome.

We began by examining a system in which the stereochemistry of both acid- and base-catalysed cyclisations can be examined and compared. The first reaction studied was the pyridine-catalysed condensation between phloroglucinaldehyde (2,4,6-trihydroxybenzaldehyde) **9** and 2*E*/*Z*,6*E*-farnesal (2*E*/*Z*,6*E*-trimethyldodeca-2,6,10-trienal) **10** at 50 °C. A relatively low temperature was used to enable isolation of intermediate

† Experimental section is available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/b0/b001310m/

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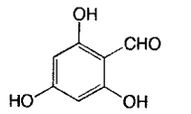
chromenes, at the expense of overall yields. Previous studies have shown that these reactions are not sensitive to the 2*E*- or 2*Z*- configuration of the 2-enal involved. The products were the two regioisomeric citrans **11a** and **11b** (1 : 3), along with the chromene **12** and the bis-chromene **13**. Using chemical shift criteria for the methyl at C-7′ developed in earlier work [5] it was



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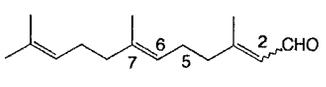

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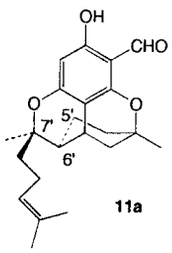
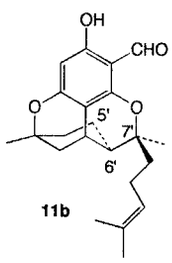
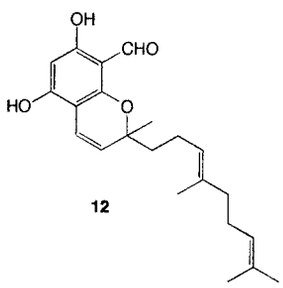


11a



11b



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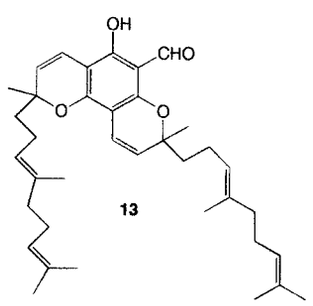

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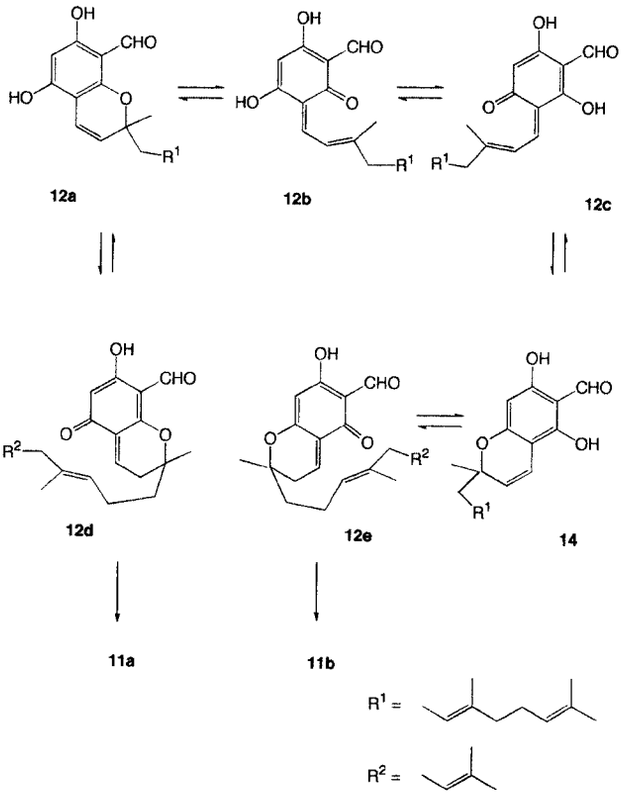
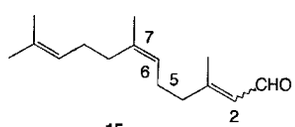
clear that both **11a** and **11b** retained the 6*E*-geometry of the original farnesal.

The formation of two regioisomeric citrans may be rationalised as illustrated in Scheme 2. Prototropic shifts allow equilibration of the initial chromene product **12a** with the cyclohexadienone tautomer **12d**, which reacts by an intramolecular 4 + 2 cycloaddition to yield the citran **11a**. Alternatively chromene **12a** can undergo electrocyclic opening to cyclohexadienone **12b** which can switch the geometry of the exocyclic double bond [1,4] to form the isomeric intermediate **12c**. The last can in turn close to the unobserved chromene **14** from which the second citran **11b** is formed, by way of **12e**, as shown. In a converse manner, phloroglucinaldehyde reacted with 2*E*/*Z*,6*Z*-farnesal **15** to give the regioisomeric citrans **16a** and **16b** (1 : 3), both retaining the 6*Z*-configuration, the chromene **17** and the bis-chromene **18**. The four citrans **11a**,**b** and **16a**,**b** were chromatographically and spectroscopically distinguishable.

The chromene **12** was then refluxed in benzene with (+)-camphorsulfonic acid. Only the same two citrans as formed in the pyridine-catalysed reaction were produced, *i.e.* **11a** and **11b** (1 : 1), the acyclic double bond geometry being retained though regiochemical rearrangement occurred. The difference in citran ratio between base and acid conditions is thought to reflect differences in thermodynamic stabilities between the ionised and protonated intermediates involved. Similar acid treatment of chromene **17** led to the citran **16a** only, the farnesal 6*Z*-geometry again being retained. The chromene **17** reacts with acid more rapidly than **12** and since only one citran is found in this case, the more readily occurring bicyclisation apparently



Scheme 2



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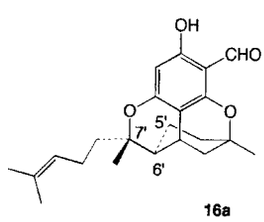
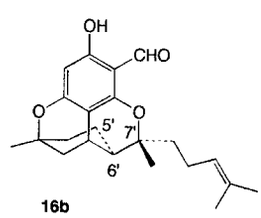
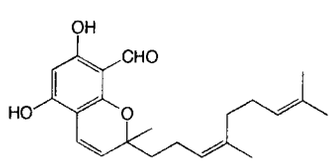


16a



16b



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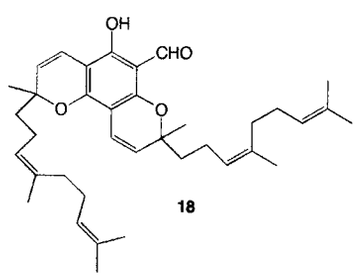

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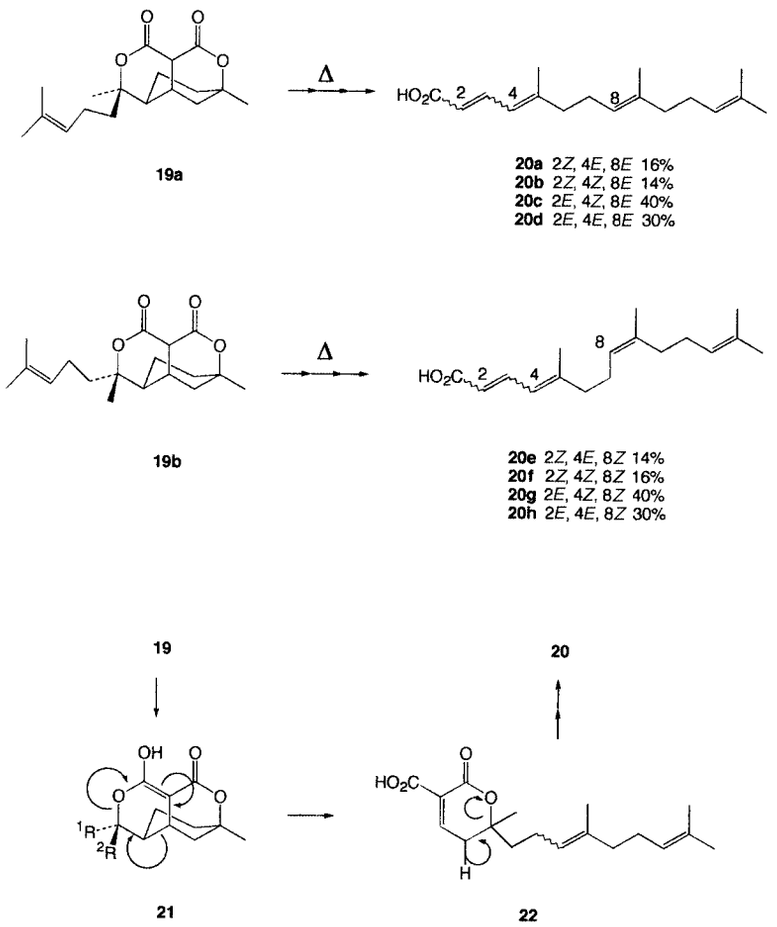
becomes faster than the rate-determining step of the reorientation process.

Thus despite complexities in the reactions, both the acid- and the base-catalysed bicyclisations are stereospecific and it



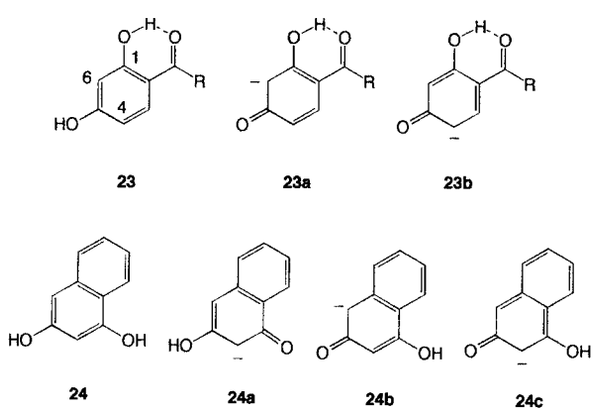
Scheme 3

becomes reasonable to view both types of reaction as proceeding through an *o*-quinomethane, followed by intramolecular [2 + 4] cycloaddition as in Schemes 1 and 2. These processes then differ only in the mode of catalysis of the *o*-hydroxystyrene→*o*-quinomethane tautomerism. The tricyclic products **8** may arise by the well established acid-induced cleavage of the citrans **6** [Scheme 1, path (c)].[4]

The reverse citran→chromene reaction has not been observed for aromatic citrans. However, the bis-lactones **19a** and **19b** (the 'farnesylidenemalonic acids') can be prepared by condensation of 6*E*- and 6*Z*-farnesal respectively by condensation with malonic acid in the presence of pyridine,[5] and present a parallel structural pattern to the aromatic citrans. Pyrolysis of **19a** (200 °C; Cu bronze; 3 h) afforded four isomers of 5,9,13-trimethyltetradeca-2,4,8,12-tetraenoic acid **20a–d**, all 8*E* (Scheme 2; composition estimated by NMR), while pyrolysis of **19b** gave the four 8*Z*-stereoisomers **20e–h** (Scheme 3). Thus this thermal process can reasonably be represented as a Diels–Alder reversion from the enolic form **21** of lactone **19** to provide **22** in which the 8-olefinic bond is formed with retention of configuration. Thermal opening of the new lactone in **22** followed by decarboxylation and loss of stereochemical integrity of the conjugated 2,4-bonds gives the acids **20**. The analogous bis-lactone derived from citral (citrylidene malonic acid) undergoes a similar pyrolysis to 5,9-dimethyldeca-2,4,8-trienoic acid.[6]

Thus it appears that both the base-catalysed and the acid-catalysed formation of aromatic citrans such as **11a** and the thermal opening of the bis-lactonic citran counterparts, *e.g.* **19a** all involve a (4 + 2) cycloaddition bicyclisation step, in forward or reverse modes.

Finally in this paper we address an issue of regioselectivity in the reactions of phenols, in basic conditions, with 2,4-dienals such as citral. The chromenylation of acylphloroglucinols, as exemplified above, displays limited regioselectivity. In contrast, the parallel chemistry of acylresorcinols **23** shows marked preference for C-alkylation at C-6, initiated by the more acidic hydroxy group.[7] The intermediate phenolate in this reaction path **23a** (Scheme 4) retains the 1,2-double bond, and with

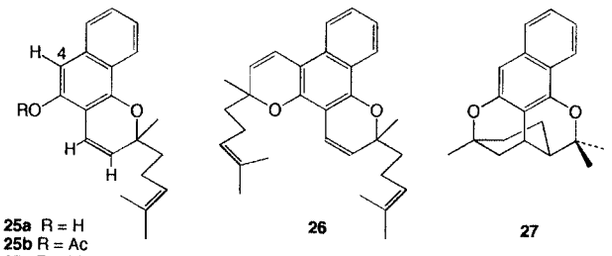


Scheme 4

it the stability of the chelated (quasi-aromatic) *o*-hydroxy carbonyl unit, while the alternative phenolate **23b** lacks this feature. Corresponding regioselectivity is shown in the chromenylation of 7-hydroxycoumarin also ascribed to retention of aromaticity of the γ-pyrone ring in the intermediate phenolate. As a further test of the control of the regioselectivity of these condensations, we chose to examine the reaction with citral of 1,3-dihydroxynaphthalene **24**, since naphthalene chemistry affords classic examples of regiochemical control dictated by retention of aromaticity in the non-reacting ring. Thus of the three possible intermediates **24a–c** (Scheme 4) it would be

expected that chromenylation might proceed predominantly through **24a** and **24b**.

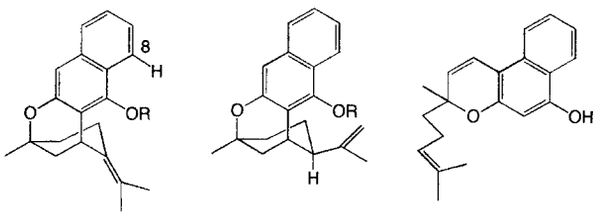
The reaction of 1,3-dihydroxynaphthalene with citral was carried out in pyridine at 40 °C for 16 h. These conditions were chosen not to give a low conversion but to maximise the number of products (four) observed by TLC. Chromatography afforded three pure compounds. The first was the monochromene **25a**.



25a R = H
25b R = Ac
25c R = Me

26

27



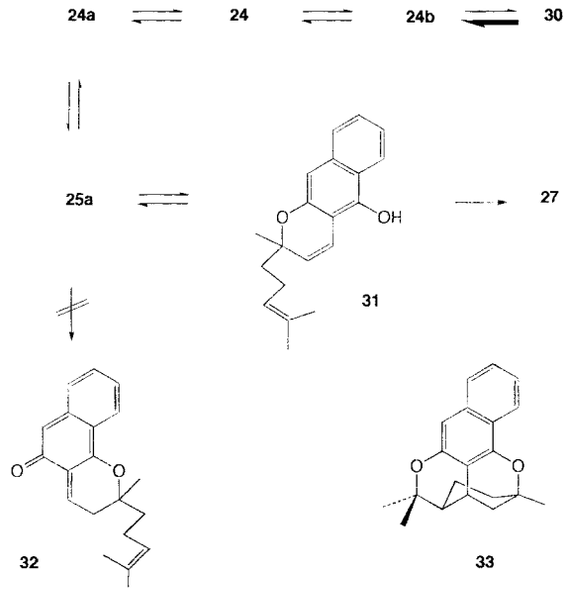
28a R = H
28b R = Ac
28c R = Me

29a R = H
29b R = Ac
29c R = Me

30

The site of the new pyran ring was established by NMR examination of the derived methyl ether **25b** and acetate **25c**. The former showed a strong NOE (7%) on the aromatic 4-H on irradiating the *O*-methyl protons, and the latter displayed shifts in the olefinic chromene protons which are documented as concordant with a *peri* relationship.[8] Only structure **25a** fits both these observations. From spectroscopic data the second product was the bis-chromene **26**, and the third proved to be the citran **27**. The orientation shown for this citran was demonstrated by acid-catalysed opening of the more susceptible heterocyclic ring, to a mixture of the isomeric isopropylidene **28a** and isopropenyl **29a** compounds. These were characterised as their *O*-acetyl (**28b**, **29b**) and *O*-methyl (**28c**, **29c**) derivatives. The *O*-acetates **28b** and **29b** both displayed upfield shifts (−0.46 ppm from the corresponding methyl ethers) of the *peri* naphthalenic protons (8-H) attributed to the acetate carbonyl, thus fixing the structures of **28a**, **29a** and **27**. The compound formed in trace quantities, observed on TLC but not isolated, was probably the monochromene **30**, on the evidence of the formation of the bis chromene **26**. On repeating the reaction in refluxing toluene with *tert*-butylamine as base, no monochromene products were observed and the citran **27** was isolated in 65% yield.

These results may be rationalised by the sequence shown in Scheme 5. Under the reaction conditions, 1,3-dihydroxynaphthalene equilibrates with the phenolates **24a** and **24b**. Intermediate **24a** reacts with citral to yield the observed chromene **25a**. This product can further isomerise to chromene **31**, by the general mechanisms outlined in Scheme 2, and this chromene undergoes bicyclisation to the observed citran **27**.



Scheme 5

Chromene **25a** does not lead on to citran **33**, since the required cyclohexadienone intermediate **32** loses the aromaticity of the non-reacting ring. Phenolate **24b** may have reacted with citral to form chromene **30**, but since this can only have been a trace product, it is presumably an unfavoured terminus in the equilibria, possibly because of *peri* hydrogen interactions. Thus it may be concluded that the maximisation of aromatic character in competing intermediates can be a significant factor in determining regioselectivity in the condensation reactions of 2,4-dienals with substituted resorcinols.

Acknowledgements

This paper is dedicated, on behalf of his many research students, as a memorial to the life and work of Leslie Crombie. We shall remember his kindly support, encouragement and great enthusiasm, with much gratitude and affection.

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