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A new and efficient method for *o*-quinone methide intermediate generation: application to the biomimetic synthesis of the benzopyran derived natural products (±)-lucidene and (±)-alboatrin

Raphaël Rodriguez,[a] John E. Moses,[b] Robert M. Adlington[a] and Jack E. Baldwin*[a]

[a] *The Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, UK OX1 3TA. E-mail: jack.baldwin@chem.ox.ac.uk*

[b] *The School of Pharmacy, University of London, 29-39 Brunswick Square, London, UK WC1N 1AX*

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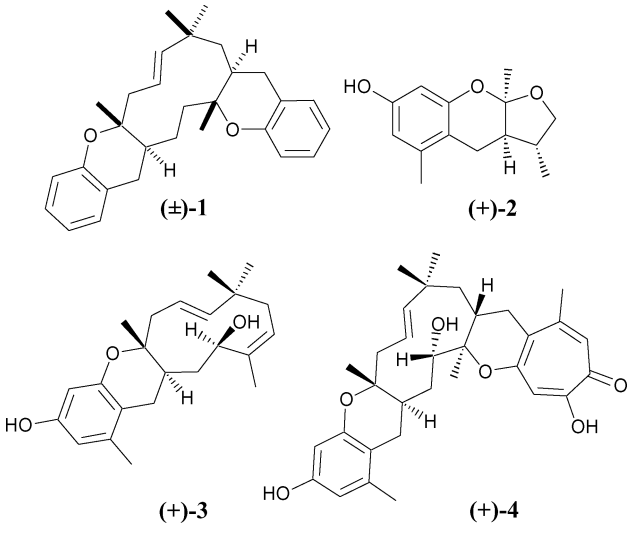
Lucidene and alboatrin are complex benzopyran derived natural products. A key step in their biogenesis may involve a hetero Diels–Alder cycloaddition between an *o*-quinone methide intermediate with a simple, or activated tri-substituted olefin. Experimental evidence is provided to support this hypothesis, with the biomimetic synthesis of both (±)-lucidene and (±)-alboatrin successfully achieved using a new and efficient method for *o*-quinone methide generation.

Introduction

In recent years many structurally novel benzopyran derived natural products have been isolated from organisms as diverse as plants, animals, insects and fungi (Scheme 1). Many of these compounds display interesting biological properties including activity against *Plasmodium falciparum*,[1] phytotoxic properties,[2] erythropoietin gene expression,[3] and acetylcholine esterase inhibition.[4] As part of our continuing efforts directed towards the biomimetic synthesis of natural products, we became interested in studying these class of benzopyranic natural products which include (±)-lucidene **1**,[5] (+)-alboatrin **2**,[2] (+)-pughiinin A **3**,[1] and (+)-epolone A **4**[3] (Scheme 1), and in developing methodology that would allow ready access to the common benzopyran core structure. We have recently reported a biomimetic synthesis of (±)-alboatrin **2**, which involved a novel hetero Diels–Alder cycloaddition of an *o*-quinone methide intermediate and a readily accessible dienophile.[6a] We now wish to report a complete account of these studies which include a new method for the generation of *o*-quinone methide intermediates, and their application towards the biomimetic synthesis of complex natural products.



Scheme 1

o-Quinone methides are highly reactive transient species, which have been applied as intermediates in the synthesis of several natural products.[6,7] Such compounds are known to react with nucleophiles in 1,4-Michael addition type fashion, or with a range of dienophiles to perform [4 + 2] cycloaddition to provide benzopyran type structures. Many strategies have been established in order to generate *o*-quinone methides *in situ*. However, problems with such protocols often include undesirable high temperatures,[7,8] long reaction times,[4,7,8] the need for catalysis,[7,9] and/or acidic[7] or basic conditions,[7,10a] which can induce problematic side reactions. In addition, the *o*-quinone methide precursors necessary for use with existing methodologies are often unstable and relatively inaccessible.[7] Thus, we chose to investigate alternative methodologies for the generation of *o*-quinone methides for the application towards natural product synthesis.

Results and discussion

We have previously reported the generation of *o*-quinone methide by the thermal driven dehydration of an *o*-hydroxybenzyl alcohol precursor **5**.[6c] Although this method proved synthetically useful, the reaction temperatures necessary to facilitate dehydration were undesirable and potentially disruptive to delicate structures. However, we were keen to build upon this methodology and uncover a more attractive *o*-quinone methide precursor. We envisaged a solution to the problem might involve activation of the benzyl alcohol moiety of the *o*-quinone methide precursor, thus facilitating dehydration through a more attractive acetyl leaving group. To investigate our hypothesis, we prepared the *o*-quinone methide precursors **6a** and **6b** (Scheme 2), since benzopyran sub units are common structural features of several natural products (Scheme 1). Although *o*-acetoxymethylphenols (including **6b**) have been described in the literature, members of this class of compounds have been reported as being labile structures which "can be conserved for several days in dilute solution but polymerise rapidly as soon as they are pure".[10a] Their reported synthesis is likewise unattractive; for example Loubinoux has reported the need for a six-step synthesis of *o*-acetoxymethylphenol (**6b**) from salicylaldehyde.[10b] Perhaps as a consequence, reports of potential *o*-acetoxymethylphenols to serve as *o*-quinone methide synthons are limited to base promoted chemistry, followed by *in situ* nucleophilic Michael addition.[10a] We have been unable to find reports of their use for *o*-quinone methide generation under purely thermal conditions.

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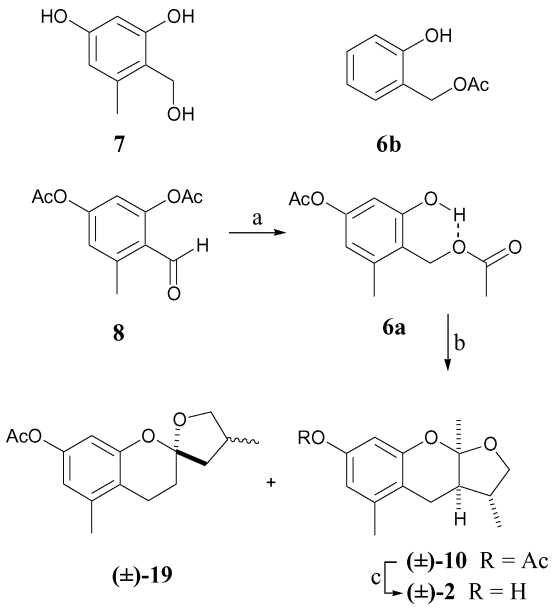


Scheme 2 *Reagents and conditions*: (a) BH_3–MS (1 equiv.), THF, 0 °C, to rt, 1 h, 84%; (b) (±)-4,5-dihydro-2,4-dimethylfuran **9** (1equiv.), benzene, reflux, 36 h, 93% overall; (c) K_2CO_3 (3 equiv.), DCM–MeOH–H_2O (12 : 7 : 1), rt, 6 h, 97%.

In order to avoid the lengthy reported synthesis of **6b**,[10b] we chose to investigate conditions that would allow selective acylation of the primary alcohol moiety of commercially available *o*-hydroxybenzyl alcohol **5**. Subsequently, it was discovered that this selectivity could indeed be achieved by careful control of the reaction temperature and rate of addition of the acylating reagent, leading to the synthesis of **6b** in an impressive 89% yield. In order to prepare **6a**, we considered that a related selective acylation of the corresponding hydroxymethyl-orcinol derivative **7** could also be used. However, upon reduction of the corresponding aldehydic precursor, compound **7** was found to be unstable and rapidly decomposed under the reaction conditions. To address this problem, it was reasoned that suitable protection of the phenolic position may prevent premature decomposition. To this end, diacetate **8**[11] was prepared, which we reasoned could be reduced to the corresponding alcohol, and that such a compound may facilitate *o*-quinone methide formation under thermal conditions from an *o*-acetoxymethylphenol **6a**, itself generated *via* a transesterification mechanism. In practice, the transfer of the phenolic acetate to the adjacent benzyl alcohol group occurred during the reduction of **8** with borane–DMS complex, thus giving the stable compound **6a**[12] (Fig. 1)[13] with a gratifying 84% yield. The proton NMR of **6a** displayed a sharp signal at 8.23 ppm, characteristic of a hydrogen bond between the phenolic OH and the benzylic acetate. This was encouraging since it was envisaged that such a hydrogen bond may facilitate the elimination of acetic acid through a six-membered ring transition state, furnishing the desired *o*-quinone methide under relatively mild conditions.

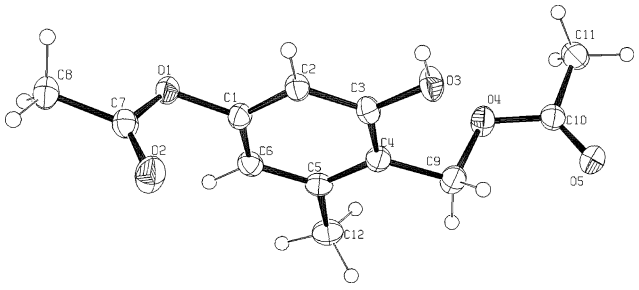


Fig. 1 X-Ray structure of **6a**.

To investigate the potential of compounds **6a** and **6b** as *o*-quinone methide precursors, several readily available dienophiles were exposed to both compounds under a range of reaction conditions. The results from these studies are summarised in Table 1. Generally, the reaction times, temperatures required and yields obtained compare favourably with those described for other methods,[4,7,8,14] and the reaction could be performed on very hindered dienophiles such as α-pinene. To further demonstrate the usefulness of this new method for *o*-quinone methide generation, we decided to investigate its potential towards the biomimetic synthesis of benzopyran containing natural products. With this in mind, we focused our initial efforts towards the synthesis of alboatrin (±)-**2**.

(+)-Alboatrin[2] **2** is a phytotoxic benzopyran natural product reported in 1988 by Ichihara *et al.*, and later structurally corrected by Murphy *et al.*[15] The biosynthesis of (+)-alboatrin **2** may be proposed to proceed through a hetero Diels–Alder cycloaddition of an orcinol-derived *o*-quinone methide **16**, and (*R*)-4,5-dihydro-2,4 dimethylfuran **9** (Fig. 2). Indeed, Wilson *et al.* have made a similar connection and demonstrated in a recent study its feasibility as a major pathway to the structurally related natural product (−)-xyloketal A **17** and (−)-xyloketal D **18**[4] (Fig. 3). In order to provide further biosynthetic details regarding the origin of (+)-**2**, and to further evaluate our methodology towards natural product synthesis, dienophile (±)-4,5-dihydro-2,4-dimethylfuran **9** was prepared according to the procedure of Wilson *et al.*[4] Thereafter, simple heating of **6a** in the presence of (±)-**9** afforded (±)-acetylalboatrin **10** as the major isolated product (63% yield), (±)-acetyl-*epi*-alboatrin[16] (5% yield), and an inseparable mixture [3 : 2] of diastereoisomers (±)-**19** (25% yield). De-acylation of (±)-**10** gave target (±)-alboatrin, for which spectral data were identical to the natural material [^{1}H, ^{13}C].[2] The structure of (±)-**2** was also confirmed by X-ray analysis and was found to be in agreement with Murphy's proposal[15] (Fig. 4).[13] With the successful application

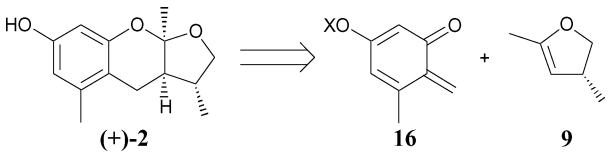


Fig. 2 Biomimetic analysis of alboatrin (+)-**2**.

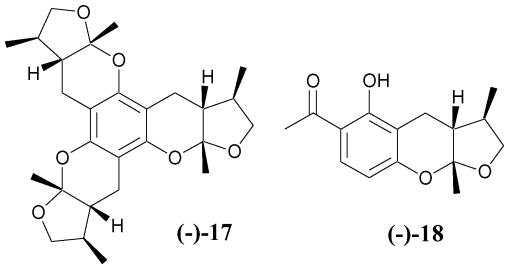


Fig. 3

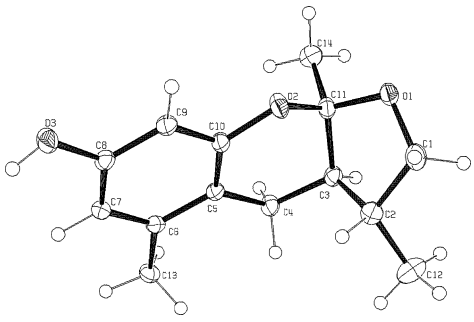
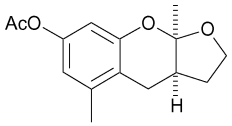
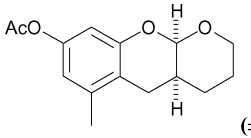
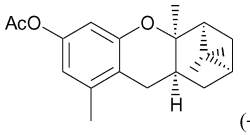
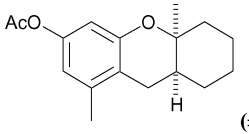
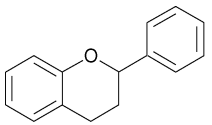


Fig. 4 X-Ray structure of (±)-**2**.

Table 1 *o*-Quinone methide (*o*-QMS) hetero-Diels–Alder cycloaddition products

o-QMS precursor	Dienophile	Temperature/°C	Time/h	Yield (%)[a]	Adduct
6a	(±)-4,5-Dihydro-2,4-dimethylfuran **9**[b]	80	36	63[d]	Acetylalboatrin (±)-**10**
6a	4,5-Dihydro-2-methylfuran	100	12	78[e]	 (±)-**11**
6a	3,4-Dihydro-2*H*-pyran	100	12	72[e]	 (±)-**12**
6a	(1*R*)-(+)-α-Pinene	140	12	30[e]	 (−)-**13**
6a	1-Methylcyclohexene	140	12	60[e]	 (±)-**14**
6b	Styrene	100	12	79[e]	 **15**
(Other *o*-quinone methide precursors)		(90	6.5	64)[14a]	
		(60	10.5	42)[14a]	
		(190	2	68)[14a]	
		(90–110	12	56)[14b]	
6a	α-Humulene **20**	140	12	53[e]	(±)-**24**[e]
6b	α-Humulene **20**	130	12	52[f]	(±)-**22**
				38[f]	(±)-**1**/(±)-**23** [2.5 : 0.7][h]
6b	α-Humulene **20**	130	12	0[g]	(±)-**22**
				71[g]	(±)-**1**/(±)-**23** [2.5 : 0.7][h]

[a] Yields were calculated after column chromatography. Reactions were performed in a sealed tube under argon. [b] This compound was synthesised in four steps starting from propionic acid.[4] [c] Dienophile used as solvent at 0.85 M. [d] The yield quoted refers to a mixture of epimers in a ratio of [12.6 : 1] in favour of (±)-**10**. [e] Compound (±)-**25** was prepared by deacetylation of compound (±)-**24** (see Experimental section). [f] The reaction has been carried out in toluene using 2.05 equiv. of **6b**. [g] The reaction has been carried out in toluene using 4.10 equiv. of **6b**. [h] Ratios have been determined by ^{1}H NMR.

of this methodology towards the synthesis of (±)-**2**, we next decided to re-investigate the biomimetic synthesis of (±)-lucidene, employing this newly developed approach.

(±)-Lucidene is a bis(benzopyranyl) sesquiterpene isolated from the root bark of *Uvaria lucida ssp. lucida*[5] in racemic form. The co-isolation of α-humulene **20** from the same species led to speculation that lucidene is the product of two consecutive inverse demand hetero Diels–Alder cycloadditions of **20**, with two equivalents of *o*-quinone methide **21** (Fig. 5).[5] This hypothesis is attractive on the grounds that FMO theory supports the regiochemical and *syn*-stereochemical aspects[17] of such inverse electron demand hetero Diels–Alder processes, since electronic factors would favour addition to the more electron rich tri-substituted double bonds at the expense of the more sterically hindered di-substituted double bond. It has also been reported that (*E*) double bonds in medium sized rings show a higher reactivity than otherwise expected on account of steric strain.[18] We have previously provided convincing evidence to support this biosynthetic proposal, where thermolysis of *o*-hydroxybenzyl alcohol **5** was used to generate the *o*-quinone methide intermediate (Scheme 3).[19] A summary of our previous study is provided in Table 2.[6c] The experimental results demonstrated that the naturally occurring diastereomer (±)-lucidene **1**, is the favoured bis-adduct of α-humulene **20** with unsubstituted *o*-quinone methide **21** at high temperature. The isolation of monoadduct (±)-**22** *en route* to lucidene, offers positive evidence that a similar pathway may occur in the biosynthesis of (±)-lucidene **1**. However, it was appreciated that the temperatures employed in the cycloaddition reaction were excessive.

To probe for further biosynthetic details, we applied our new method of *o*-quinone methide generation toward the synthesis of (±)-lucidene **1**, as a comparison with our previous method which employed an unactivated *o*-quinone methide precursor **5**.[6c] In the former case the reaction was carried out in toluene at 130–140 °C, as opposed to heating in xylene at 170 °C. When α-humulene was heated in the presence of 2.05 equivalents of compound **6b**, monoadduct (±)-**22**[20] was obtained in 52% yield, along with a mixture of bis-adducts (±)-**1**/(±)-**23** in 38% yield, which favoured the natural product (±)-lucidene **1** [2.5 : 0.7]. The same reaction using 4.10 equivalents of precursor **6b** gave an inseparable mixture of compound (±)-**1**/(±)-**23** in the same ratio as above, with an encouraging 71% yield. In this case, no trace of mono-adduct or tris-adduct compounds were detected. In order to investigate the effect of temperature on the diastereoselectivity of the second cycloaddition process, compound (±)-**22** was exposed to 2.0 equivalents of **6b** in benzene at 90 °C for 36 hours. A mixture of compounds (±)-**1**/(±)-**23** in 32% yield was obtained, with a similar ratio in favour of compound **1** [2.5 : 0.6].

In the same manner, we synthesised compound (±)-**25** (Fig. 6)[13] by condensation of precursor **6a** with α-humulene (**20**) (53% yield) to provide adduct (±)-**24** and subsequent deacetylation under basic conditions (82% yield) (Scheme 4). We believe this building block constitutes a useful starting material for the biomimetic synthesis of pughiinin A **3** and epolone A **4** in racemic form.

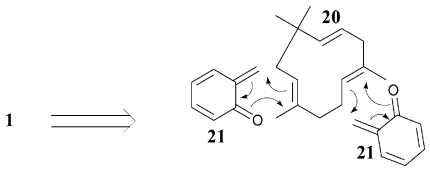
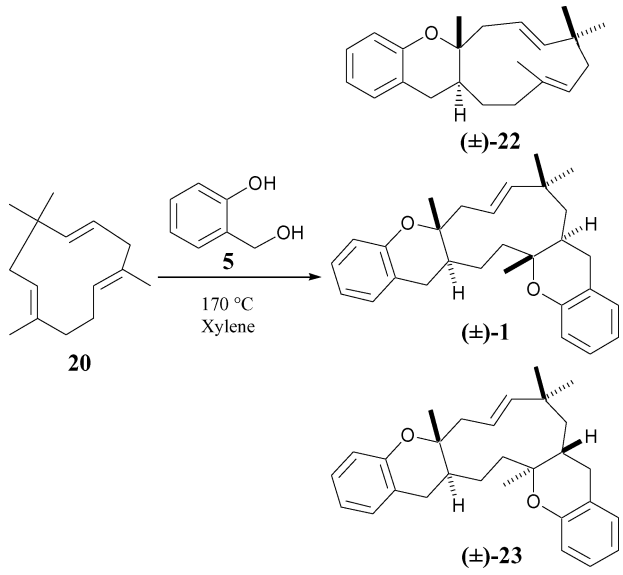


Fig. 5 Biomimetic analysis of lucidene.



Scheme 3

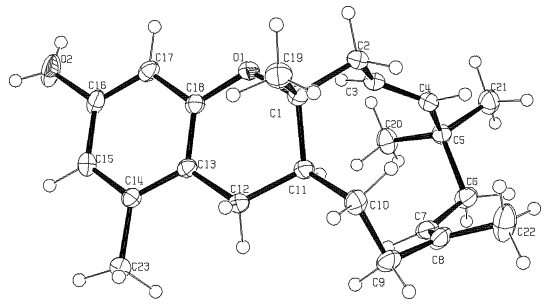
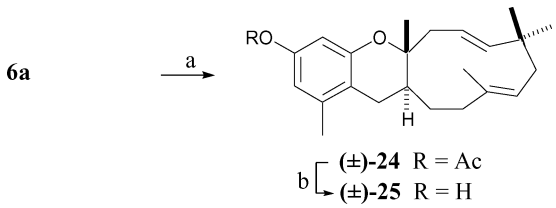


Fig. 6 X-Ray structure of **25**.



Scheme 4 *Reagents and conditions*: (a) neat humulene **20** (5 equiv.), 140 °C, 12 h, 53% overall; (c) K_2CO_3 (1.1 equiv.), DCM–MeOH–H_2O (12 : 7 : 1), rt, 6 h, 82%.

Conclusion

In conclusion, we have developed a new and efficient method for *o*-quinone methide generation from *o*-acetoxymethyl-phenols.

Table 2

Humulene **20** (equiv.)	*o*-Hydroxybenzyl alcohol **5** (equiv.)	Solvent	Temp./°C	Yield of (±)-**22** (%)	Yield of mixture (±)-1/(±)-23 (%) [ratio]
1	2.05	Xylene	170	28	17 [2.5 : 1]
1	2.05	Acetonitrile–water 1 : 1	170	32	7
1	2.05	1,4-Dioxane	170	23	4
1	6	Xylene	170	—	45 (trace of tris-adduct)[21]

The described methodology required no added acid,[7] base[7,10b] or catalyst[7,9] for the formation of the Diels–Alder adducts. The elimination of acetic acid was not found to be detrimental to the reaction. The reaction times, temperatures required and yields obtained compare favourably with those described for traditional methods.[4,7,8,14] The reaction can be performed on very hindered dienophiles such as α-pinene and on complex non-conjugated polyene such as α-humulene with high regio-, chemo- and stereoselectivity. Our novel method has been applied to a rapid biomimetic synthesis of the complex natural products (±)-alboatrin **2** and (±)-lucidene **1**. Application to the biomimetic syntheses of (±)-pughiinin A **3** and (±)-epolone A-**4** are objectives.

Experimental

All solvents and reagents were purified by standard techniques,[22] or used as supplied from commercial sources as appropriate. Solvents were removed under reduced pressure using a Buchi R110 or R114 Rotavapor fitted with a water condenser. Final traces of solvent were removed from samples using an Edwards E2M5 high vacuum pump with pressures below 2 mmHg. All experiments were carried out under inert atmosphere unless otherwise stated. ^{1}H NMR spectra were recorded at 200, 400 and 500 MHz using, Bruker DPX200, DQX400 and Bruker AMX500 instruments. For ^{1}H spectra recorded in $CDCl_3$, CD_3OD, C_6D_6, chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Proton assignments and stereochemistry are supported by ^{1}H–^{1}H COSY and NOESY where necessary. Data are reported in the following manner: chemical shift (integration, multiplicity, coupling constant if appropriate). Coupling constants (J) are reported in Hertz to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded at 50.2, 100.6 and 125.8 MHz using Bruker DPX200, Bruker DQX400, and Bruker AMX500 instruments. Carbon spectra assignments are supported by DEPT-135 spectra, ^{13}C–^{1}H (HMQC) correlations where necessary. Chemical shifts are quoted in ppm and are referenced to the appropriate residual solvent peak. Flash column chromatography was carried out using Sorbsil™ C60 (40–63 mm, 230–40 mesh) silica gel. Thin layer chromatography was carried out on glass plates pre-coated with Merck silica gel 60 F_{254} which were visualised by quenching of UV fluorescence or by staining with 10% w/v ammonium molybdate in 2 M sulfuric acid or 1% w/v potassium permanganate in aqueous alkaline solution followed by heat, as appropriate. Melting points were recorded using a Cambridge Instruments Gallen™ III Kofler Block melting apparatus or a Buchi 510 capillary apparatus and are uncorrected. Infrared spectra were recorded either as a thin film between NaCl plates on a Perkin-Elmer Paragon 1000 Fourier Transform spectrometer with internal referencing. Absorption maxima are reported in wavenumbers (cm^{-1}) and the following abbreviations are used: w, weak; m, medium; s, strong; br, broad. Low resolution mass spectra were recorded on V. G. Micromass ZAB 1 F and V. G. Masslab instruments as appropriate with modes of ionisation being indicated as CI, EI, ES or APCI with only molecular ions. High resolution mass spectrometry was measured on a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer and on a VG autospec chemical ionisation mass spectrometer.

2-Acetoxymethylphenol (6b)[6a]

To a stirred solution of 2-hydroxybenzyl alcohol **5** (5.0 g, 40.2 mmol) in dry DCM (80 ml) was added slowly at 0 °C pyridine (3.3 ml, 40.2 mmol) and acetyl chloride (2.9 ml, 40.2 mmol) under nitrogen. The reaction mixture was then warmed to room temperature and stirred one hour. The reaction mixture was quenched with a saturated solution of ammonium chloride (100 ml) and washed three times with a saturated solution of copper sulfate (3 × 100 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford **6b** as a colourless oil (6.0 g, 89%) which was used without further purification. R_F 0.3 [80 : 20 30–40 petroleum ether (PE) : EtOAc]; ν_{max}/cm^{-1} (film) 3369 (s), 1711 (s), 1490 (m), 1458 (m), 1383 (m), 1281 (s), 1244 (s), 909 (s), 734 (s); δ_H (200 MHz, $CDCl_3$) 2.12 (3H, s), 5.13 (2H, s), 6.88–7.00 (2H, m), 7.22–7.35 (2H, m), 7.81 (1H, s); δ_C (100 MHz, $CDCl_3$) 21.0, 63.4, 117.9, 120.6, 121.7, 131.3, 132.3, 155.6, 173.9; m/z (ES−) 165.14 ([M − H]$^-$). **6b** was stable for over three months at 0 °C.

2-Phenylchroman (15)[14]

In a sealed tube was stirred 2-acetoxymethylphenol **6b** (200 mg, 1.2 mmol) in styrene (1.4 ml, 12.2 mmol) at 100 °C, under argon for 12 hours. After evaporation of excess of styrene under reduced pressure, the yellow oil was purified by flash silica gel chromatography (98 : 2 30–40 PE : EtOAc) to give **15** as a white solid (200 mg, 79%). Mp = 40–41 °C; R_F 0.6 (95 : 5 30–40 PE : EtOAc); ν_{max}/cm^{-1} (film) 3063 (m), 3029 (m), 2927 (m), 2846 (m), 1582 (s), 1488 (s), 1455 (s), 1235 (s), 754 (s); δ_H (200 MHz, $CDCl_3$) 2.02–2.32 (2H, m), 2.77–2.89 (1H, ddd, J 16.5, 5.0, 3.5 Hz), 2.96–3.13 (1H, m), 5.10 (1H, dd, J 9.5, 3.0 Hz), 6.89–6.99 (2H, m), 7.12–7.25 (2H, m), 7.32–7.51 (5H, m); δ_C (50 MHz, $CDCl_3$) 25.1, 30.0, 77.8, 117.0, 120.4, 121.9, 126.0 (2C), 127.4, 127.9, 128.6 (2C), 129.6, 141.8, 155.2.

2,4-Dihydroxy-6-methylbenzaldehyde[11]

Phosphorous oxychloride (5.6 ml, 60.5 mmol) was added dropwise over 10 minutes to stirring DMF (20 ml) at −10 °C under nitrogen, and the mixture stirred for a further 20 minutes. Orcinol (7.5 g, 60.5 mmol) in DMF (25 ml) was then added to the solution at −10 °C and the mixture allowed to warm to room temperature over 2 hours. To the reaction was then added ice and 10% aqueous NaOH until pH 9–10 was achieved, and a precipitate formed. The mixture was then heated to boiling for 10 minutes then cooled to room temperature. The acidity was then adjusted to pH 3, and the precipitate then formed was filtered and washed with water until neutral, then dried in a vacuum desiccator to give the 2,4-dihydroxy-6-methylbenzaldehyde as a yellow solid (3.5 g, 38%) which was used without further purification. Mp = 178–180 °C; R_F 0.2 (75 : 25 30–40 PE : EtOAc); ν_{max}/cm^{-1} (KBr) 3080 (m), 2926 (m), 1628 (s), 1482 (s), 1303 (s), 1233 (s), 1170 (s); δ_H (400 MHz, MeOD) 2.50 (3H, s), 6.11 (1H, d, J 2.0 Hz), 6.22 (1H, d, J 2.0 Hz), 10.02 (1H, s); δ_C (100 MHz, MeOD) 17.3, 100.5, 110.8, 113.0, 145.3, 166.2, 166.5, 193.2; HRMS (APCI) Calculated for $C_8H_9O_3$ ([M + H]$^+$): 153.0552, Found: 153.0551.

2,4-Diacetoxy-6-methylbenzaldehyde (8)[11]

To a stirred solution of 2,4 dihydroxy-6-methylbenzaldehyde (4.0 g, 26.3 mmol) in dry DCM (100 ml) was slowly added at 0 °C pyridine (4.6 ml, 58.0 mmol) and acetyl chloride (2.0 ml, 29.0 mmol) under nitrogen. The reaction mixture was warmed to room temperature, stirred two hours and then cooled to 0 °C when another quantity of acetyl chloride was slowly added (2.0 ml, 29.0 mmol). The reaction was stirred for a further two hours then quenched with a saturated solution of ammonium chloride (100 ml) and washed three times with a saturated solution of copper sulfate (3 × 150 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a yellow oil which was purified by flash silica gel chromatography (80 : 20 30–40 PE : EtOAc) to afford the desired product **8** as a colourless oil (4.4 g, 71%). R_F 0.5 (70 : 30 30–40 PE : EtOAc); ν_{max}/cm^{-1} (film) 2930 (w), 1774 (s), 1692 (s), 1610 (s), 1369 (m), 1193 (s), 1126 (s); δ_H (200 MHz, $CDCl_3$) 2.28 (3H, s), 2.34 (3H, s), 2.61

(3H, s), 6.85 (1H, d, *J* 2.0 Hz), 6.91 (1H, d, *J* 2.0 Hz), 10.30 (1H, s); δ_C (50 MHz, $CDCl_3$) 20.6, 20.9, 21.2, 114.8, 122.5, 123.9, 144.0, 153.7, 154.3, 168.4, 169.1, 188.8; *m/z* (ES+) 254.19 ([M + NH_4]$^+$).

2-Acetoxymethyl-3-methyl-5-acetoxyphenol (6a)[6a]

To a stirred solution of 2,4-diacetoxy-6-methylbenzaldehyde **8** (3.8 g, 16.1 mmol) in dry THF (90 ml) was slowly added a 2 M THF solution of borane–DMS complex (8.0 ml, 16.0 mmol) at 0 °C under nitrogen. The reaction was stirred for one hour at room temperature and was then quenched at 0 °C with water (2 ml). The mixture was evaporated to dryness under reduced pressure to give a crude product which was purified by flash silica gel chromatography (70 : 30 30–40 PE : EtOAc). The title compound was obtained as a white solid which was crystallised from ether to afford **6a** as white crystals (3.2 g, 84%). Mp = 95–96 °C; R_F 0.3 (70 : 30 30–40 PE : EtOAc); ν_{max}/cm^{-1} (film) 3413 (br), 1779 (s), 1735 (s), 1708 (s), 1599 (m), 1370 (m), 1209 (s), 1133 (s); δ_H (400 MHz, $CDCl_3$) 2.10 (3H, s), 2.27 (3H, s), 2.38 (3H, s), 5.12 (2H, s), 6.53 (1H, s), 6.54 (1H, s) 8.23 (1H, s); δ_C (100 MHz, $CDCl_3$) 19.6, 21.0, 21.2, 59.6, 109.3, 115.8, 118.8, 141.2, 152.1, 157.3, 169.5, 174.3; HRMS (ES−) Calculated for $C_{12}H_{13}O_5$ ([M − H]$^-$): 237.0763, Found: 237.0763. **Crystal data for 6a**: $C_{12}H_{14}O_5$, *M* = 238.24, monoclinic, *a* = 29.1890(14), *b* = 4.9244(3), *c* = 19.8157(11) Å, *U* = 2363.5(2) Å^3, *T* = 150 K, space group *C2/c*, *Z* = 8, μ(Mo-Kα) = 0.105 mm^{-1}, 11482 reflections measured, 2983 unique (R_{int} = 0.045) which were used in calculations. The final *wR* was 0.0599.[13]

(±)-5a(*R**),14a(*S**),(*E*)-(*E*)-5a,6,9,10,13,14,14a,15-Octahydro-5a,9,9,12-tetramethylcycloundeca[1,2-*b*]benzopyran (22)

Procedure A. In a sealed tube was stirred 2-acetoxymethylphenol **6b** (750 mg, 4.5 mmol) in dry toluene (6 ml) with α-humulene (0.52 ml, 2.2 mmol) at 130 °C, under argon for 12 hours. After evaporation of toluene under reduced pressure, the yellow oil was purified by flash silica gel chromatography (99 : 1 30–40 PE : EtOAc) to give the monoadduct (±)-**22** as a white solid (353 mg, 52%) and an inseparable mixture (346 mg, 38%), [2.5 : 0.7] of diadduct (±)-lucidene **1** and (±)-isolucidene **23** as a white solid.

Procedure B. In a sealed tube was stirred 2-acetoxymethylphenol **6b** (1.5 g, 9.0 mmol) in dry toluene (6 ml) with α-humulene (0.52 ml, 2.2 mmol) at 130 °C, under argon for 12 hours. After evaporation of toluene under reduced pressure, the yellow oil was purified by flash silica gel chromatography (99 : 1 30–40 PE : EtOAc) to give a white solid (641 mg, 71%) which was an inseparable mixture [2.5 : 0.7] of diadduct (±)-lucidene **1** and (±)-isolucidene **23**. The compounds (±)-**1** and (±)-**23** were separated, for the purpose of characterisation by preparative HPLC. A reverse phase Hypersil C18 (25 cm × 0.25 inch) column was found to achieve the required separation with an aqueous acetonitrile solvent system (4 : 1 MeCN : H_2O).

Compound (±)-22. Mp = 118 °C; R_F 0.7 (98 : 2 30–40 PE : EtOAc); ν_{max}/cm^{-1} (KBr) 3056 (w), 2986 (m), 2928 (s), 2852 (m), 1584 (m), 1492 (s), 1456 (s), 1250 (s), 1136 (m), 1040 (m), 982 (s), 757 (s); δ_H (500 MHz, $CDCl_3$) 1.06 (3H, s), 1.10 (3H, s), 1.15 (3H, s), 1.17 (1H, m), 1.38 (1H, dd, *J* 13.0, 11.0 Hz), 1.68, (3H, s), 1.80 (1H, dd, *J* 12.5, 4.0 Hz), 1.88 (1H, dd, *J* 13.0, 11.0 Hz), 1.94 (1H, ddd, *J* 12.5, 9.0, 5.5 Hz), 2.16 (1H, dd, *J* 13.0, 7.5 Hz), 2.22 (1H, t, *J* 12.5 Hz), 2.35 (1H, dd, *J* 14.5, 10.0 Hz), 2.50 (1H, dd, *J* 16.5, 12.5 Hz), 2.58 (1H, dt, *J* 14.5, 2.0 Hz), 2.96 (1H, dd, *J* 16.5, 5.5 Hz), 5.06 (1H, br dd, *J* 12.5, 4.0 Hz), 5.16 (1H, dd, *J* 16.0, 2.0 Hz), 5.24 (1H, ddd, *J* 16.0, 10.0, 2.0 Hz), 6.86 (1H, d, *J* 7.5 Hz), 6.87 (1H, t, *J* 7.5 Hz), 7.10 (1H, d, *J* 7.5 Hz), 7.15 (1H, t, *J* 7.5 Hz); δ_C (125 MHz, $CDCl_3$) 17.2, 20.2, 24.3, 29.5, 30.3, 30.4, 35.6, 37.8, 38.2, 41.4, 43.1, 80.2, 117.0, 119.2, 121.0, 121.8, 123.1, 127.2, 128.8, 136.5, 142.0, 154.0; HRMS (CI+) Calculated for $C_{22}H_{31}O$ ([M + H]$^+$): 311.2375, Found: 311.2378.

(±)-5a(*R**),10a(*S**),16a(*R**),18a(*S**)-(*E*)-5a,6,9,10,10a,16a,17,18,18a,19-Decahydro-5a,9,9,16a-tetramethyl-11*H*-cycloundeca[1,2-*b*:5,6-*b*′]bisbenzopyran (lucidene) (1)[5]

Mp = 208–211 °C; R_F 0.6 (98 : 2 30–40 PE : EtOAc); ν_{max}/cm^{-1} (film) 2921 (s), 1610 (w), 1585 (m), 1487 (s), 1454 (s), 1378 (m), 1304 (m), 1259 (s), 1220 (m), 753 (m); δ_H (500 MHz, $CDCl_3$) 1.09 (1H, dd, *J* 14.0, 5.5 Hz), 1.09 (3H, s), 1.13 (3H, s), 1.27 (6H, s), 1.55 (1H, m), 1.71 (1H, m), 1.83 (2H, m), 1.97 (1H, m) 2.06 (1H, br m), 2.22 (1H, m), 2.58 (1H, m,), 2.59 (2H, d, *J* 7.0 Hz), 2.67 (1H, br d, *J* 16.0 Hz), 2.81 (1H, dd, *J* 17.0, 5.5 Hz), 2.82 (1H, br m), 5.65 (1H, dt, *J* 16.0, 8.0 Hz), 5.79 (1H, d, *J* 16.0 Hz), 6.76 (1H, d, *J* 8.0 Hz), 6.77 (1H, d, *J* 8.0 Hz), 6.79 (1H, td, *J* 7.0, 1.0 Hz), 6.82 (1H, td, *J* 7.0, 1.0 Hz), 7.00 (1H, d, *J* 7.0 Hz), 7.06 (1H, d, *J* 7.0 Hz), 7.07 (2H, t, *J* 7.0 Hz); δ_C (125 MHz, $CDCl_3$) 19.6, 21.3, 23.7, 26.7, 29.1, 29.6, 30.0, 31.8, 32.6, 35.7, 40.8, 46.0, 49.0, 79.4, 79.7, 116.7, 117.2, 119.3, 119.6, 121.7, 122.8, 124.5, 127.1, 127.3, 128.7, 129.1, 143.9 (2C), 153.5; HRMS (CI+) Calculated for $C_{29}H_{37}O_2$ ([M + H]$^+$): 417.2794, Found: 417.2782.

(±)-5a(*R**),10a(*R**),16a(*S**),18a(*S**)-(*E*)-5a,6,9,10,10a,16a,17,18,18a,19-Decahydro-5a,9,9,16a-tetramethyl-11*H*-cycloundeca[1,2-*b*:5,6-*b*′]bisbenzopyran (isolucidene) (23)

Mp = 121 °C; R_F 0.6 (98 : 2 30–40 PE : EtOAc); ν_{max}/cm^{-1} (film) 2919 (s), 1610 (w), 1586 (s), 1499 (s), 1456 (s), 1377 (m), 1310 (m), 1254 (s), 1141 (m), 1102 (m), 1032 (m), 940 (w), 754 (s); δ_H (500 MHz, $CDCl_3$) 1.05 (1H, m), 1.05 (3H, s), 1.09 (3H, s), 1.15 (1H, br m), 1.20 (3H, s), 1.26 (3H, s), 1.55–1.68 (3H, m), 1.87–2.04 (3H, m), 2.41 (1H, dd, *J* 13.0, 7.5 Hz), 2.50–2.62 (3H, m), 2.78 (1H, dd, *J* 16.5, 5.5 Hz), 2.83 (1H, dd, *J* 16.5, 5.5 Hz), 5.48 (1H, ddd, *J* 15.5, 7.0, 6.0 Hz), 5.55 (1H, d, *J* 15.5 Hz), 6.76 (1H, d, *J* 7.5 Hz), 6.78 (1H, d, *J* 7.5 Hz), 6.82 (2H, t, *J* 7.5 Hz), 7.03 (1H, d, *J* 7.5 Hz), 7.05 (1H, d, *J* 7.5 Hz), 7.09 (1H, t, *J* 7.5 Hz), 7.10 (1H, t, *J* 7.5 Hz); δ_C (125 MHz, $CDCl_3$) 19.1, 20.9, 24.4, 29.6, 30.7, 30.8, 30.9, 32.6, 36.3, 38.3, 41.3, 47.6, 48.4, 79.6, 80.6, 116.7, 116.7, 119.3, 119.5, 121.6, 121.6, 122.5, 127.2, 127.3, 128.4, 128.8, 143.5, 153.4, 153.6; HRMS (CI+) Calculated for $C_{29}H_{37}O_2$ ([M + H]$^+$): 417.2794, Found: 417.2784.

Procedure C. In a sealed tube was stirred compound (±)-**22** (130 mg, 0.42 mmol) in dry benzene (0.5 ml) with 2-acetoxymethylphenol **6b** (140 mg, 0.84 mmol) at 90 °C, under argon during 36 hours. After evaporation of benzene under reduced pressure, the yellow oil was purified by flash silica gel chromatography (99 : 1 30–40 PE : EtOAc) to give a white solid (56 mg, 32%) which was an inseparable mixture [2.5 : 0.6] of (±)-lucidene **1** and (±)-isolucidene **23**. The mixture of two compounds was crystallized from hexane to afford selectively white crystals of (±)-**1**.

(±)-3a(*R**),9a(*R**)-2,3,3a,9a-Tetrahydro-5,9a-dimethyl-7-acetoxy-4*H*-furo[2,3-*b*]chroman (3-nor-methyl-acetyl-alboatrin) (11)[6a]

In a sealed tube was stirred 2-acetoxymethyl-3-methyl-5-acetoxyphenol **6a** (203 mg, 0.85 mmol) in 4,5-dihydro-2-methylfuran (1.0 ml, 10.9 mmol) at 100 °C, under argon for 12 hours. After evaporation under reduced pressure, the yellow oil obtained was purified by flash silica gel chromatography (95 : 5 30–40 PE : EtOAc) to give (±)-**11** as a white solid (175 mg, 78%). Mp = 115–117 °C; R_F 0.2 (90 : 10 30–40 PE : EtOAc); ν_{max}/cm^{-1} (film) 3056 (w), 2982 (w), 1757 (s), 1597 (m), 1482 (w), 1368 (w), 1265 (w), 1213 (w), 1109 (w), 736 (s); δ_H (400 MHz, $CDCl_3$) 1.51 (3H, s), 1.75–1.85 (1H, m), 2.01–2.09 (1H, m), 2.21 (3H, s), 2.26 (3H, s), 2.43–2.49 (1H, m), 2.78 (1H, s), 2.79 (1H, s), 3.95 (1H, dd, *J* 16.5, 8.5 Hz), 4.03 (1H, td, *J* 8.5, 3.0 Hz), 6.43 (1H, br s), 6.50 (1H, br s); δ_C (100 MHz, $CDCl_3$) 19.4, 21.2, 22.4,

23.5, 29.0, 40.5, 66.7, 106.3, 108.2, 115.0, 115.3, 138.1, 149.5, 153.8, 169.7; HRMS (ES+) Calculated for $C_{15}H_{19}O_4$ ([M + H]$^+$): 263.1283, Found: 263.1289.

(±)-4a(*R**),10a(*S**)-3,4,4a,10a-Tetrahydro-6-methyl-8-acetoxy-2*H*,5*H*-pyrano[2,3-*b*]chroman (12)[6a]

In a sealed tube was stirred 2-acetoxymethyl-3-methyl-5-acetoxyphenol **6a** (203 mg, 0.85 mmol) in 3,4-dihydro-2*H*-pyran (1.0 ml, 10.9 mmol) at 100 °C, under argon for 12 hours. After evaporation under reduced pressure, the yellow oil obtained was purified by flash silica gel chromatography (95 : 5 30–40 PE : EtOAc) to give (±)-**12** as a colourless oil (161 mg, 72%). R_F 0.3 (90 : 10 30–40 PE : EtOAc); ν_{max}/cm^{-1} (film) 3055 (m), 2934 (w), 1759 (s), 1598 (m), 1422 (m), 1265 (s), 1217 (s), 1093 (s), 897 (m), 739 (s); δ_H (400 MHz, $CDCl_3$) 1.62–1.70 (5H, m), 2.18 (3H, s), 2.26 (3H, s), 2.50 (1H, dd, *J* 16.5, 4.5 Hz), 2.72 (1H, dd, *J* 16.5, 6.5 Hz), 3.69–3.73 (1H, m), 3.98–4.04 (1H, m), 5.28 (1H, d, *J* 2.5 Hz), 6.49 (1H, s), 6.50 (1H, s); δ_C (100 MHz, $CDCl_3$) 19.4, 21.2, 23.6, 24.4, 26.5, 31.6, 62.7, 96.3, 107.8, 115.6, 116.4, 138.3, 149.4, 153.3, 169.7; HRMS (CI+) Calculated for $C_{15}H_{19}O_4$ ([M + H]$^+$): 263.1283, Found: 263.1288.

(−)-1(*S*),3(*R*),4a(*S*),10a(*R*)-6,10a,11,11-Tetramethyl-8-acetoxybicyclo[3.1.1]heptan[2,3-*b*]chroman (13)[6a]

In a sealed tube was stirred 2-acetoxymethyl-3-methyl-5-acetoxyphenol **6a** (203 mg, 0.85 mmol) in (1*R*)-(+)-α-pinene (1.0 ml, 6.3 mmol) at 140 °C, under argon for 12 hours. After evaporation under reduced pressure, the yellow oil obtained was purified by flash silica gel chromatography (99 : 1 30–40 PE : EtOAc) to give (±)-**13** as a viscous colourless oil (81 mg, 30%). $[\alpha]_D^{25} = -2.9$ (*c* = 1, $CHCl_3$); R_F 0.6 (98 : 2 30–40 PE : EtOAc); ν_{max}/cm^{-1} (film) 2922 (s), 1758 (s), 1559 (s), 1483 (m), 1369 (m), 1256 (s), 1216 (s), 1127 (s), 1015 (m), 739 (s); δ_H (500 MHz, $CDCl_3$) 1.04 (3H, s), 1.16 (1H, d, *J* 10.5 Hz), 1.28 (3H, s), 1.31 (3H, s), 1.32–1.35 (1H, m), 1.81–1.84 (1H, m), 2.04–2.15 (2H, m), 2.17 (1H, t, *J* 5.5 Hz), 2.24 (3H, s), 2.25 (3H, s), 2.43 (1H, dd, *J* 15.0, 5.0 Hz), 2.47–2.53 (1H, m), 2.73 (1H, dd, *J* 15.0, 6.0 Hz), 6.40 (1H, d, *J* 2.5 Hz), 6.49 (1H, d, *J* 2.5 Hz); δ_C (125 MHz, $CDCl_3$) 19.2, 21.2, 23.2, 26.8, 27.5, 28.0, 29.3, 34.2, 34.5, 40.2, 40.4, 54.9, 84.0, 108.3, 114.9, 121.3, 136.8, 149.3, 157.3, 169.7; HRMS (ES+) Calculated for $C_{20}H_{27}O_3$ ([M + H]$^+$): 315.1960, Found: 315.1963.

(±)-4a(*S**),9a(*S**)-2,3,4,4a,9,9a-Hexahydro-4a,8-dimethyl-6-acetoxy-1*H*-xanthene (14)[6a]

In a sealed tube was stirred 2-acetoxymethyl-3-methyl-5-acetoxyphenol **6a** (203 mg, 0.85 mmol) in 1-methylcyclohexene (1.0 ml, 8.5 mmol) at 140 °C, under argon for 12 hours. After evaporation under reduced pressure, the yellow oil was purified by flash silica gel chromatography (99 : 1 30–40 PE : EtOAc) to give (±)-**14** as a white solid (141 mg, 60%). Mp = 100–101 °C; R_F 0.6 (98 : 2 30–40 PE : EtOAc); ν_{max}/cm^{-1} (film) 2933 (s), 1758 (s), 1596 (s), 1370 (m), 1265 (s), 1218 (s), 1125 (s), 737 (s); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, s), 1.24–1.31 (2H, m), 1.36–1.44 (2H, m), 1.48–1.52 (1H, m), 1.57–1.75 (3H, m), 1.93 (1H, br d, *J* 13.5 Hz), 2.18 (3H, s), 2.24 (1H, d, *J* 17.0 Hz), 2.25 (3H, s), 2.81 (1H, dd, *J* 17.0, 6.5 Hz), 6.40 (1H, d, *J* 2.0 Hz), 6.44 (1H, d, *J* 2.0 Hz); δ_C (100 MHz, $CDCl_3$) 19.4, 21.2, 21.7, 25.4, 25.6, 27.1, 28.8, 36.8, 38.3, 74.7, 108.0, 114.3, 116.4, 138.4, 149.1, 153.8, 169.8; HRMS (CI+) Calculated for $C_{17}H_{23}O_3$ ([M + H]$^+$): 275.1647, Found: 275.1644.

(±)-4,5-Dihydro-2,4-dimethylfuran (9), Prepared by the method of Wilson *et al.*[4]

Bp = 100 °C at atmospheric pressure; δ_H (400 MHz, C_6D_6) 0.86 (3H, d, *J* 7.0 Hz), 1.67 (3H, d, *J* 2.0 Hz), 2.72–2.82 (1H, m), 3.70 (1H, dd, *J* 8.5, 6.5 Hz), 4.21 (1H, dd, *J* 9.5, 8.5 Hz), 4.43–4.44 (1H, m); δ_C (100 MHz, C_6D_6) 13.6, 20.9, 37.8, 77.1, 101.4, 155.0.

(±)-3(*R**),3a(*R**),9a(*R**)-2,3,3a,9a-Tetrahydro-3,5,9a-trimethyl-7-acetoxy-4*H*-furo[2,3-*b*]chroman (acetylalboatrin) (10)[6a]

In a sealed tube was stirred 2-acetoxymethyl-3-methyl-5-acetoxyphenol **6a** (200 mg, 0.84 mmol) with (±)-4,5-dihydro-2,4-dimethylfuran **9** (82 mg, 0.84 mmol) in benzene (1 ml) at 80 °C under argon for 36 hours. After evaporation under reduced pressure, the colourless oil obtained was purified by flash silica gel chromatography (98 : 2 30–40 PE : EtOAc) to give the spiroacetal (±)-**19** as a viscous colourless oil (57 mg, 25%, as an inseparable mixture [3 : 2 from ^{1}H NMR] of two diastereoisomers, R_F 0.5 (90 : 10 30–40 PE : EtOAc)), and (±)-acetylalboatrin **10** and (±)-acetyl-*epi*-alboatrin as a white solid (158 mg, 68%, as a mixture [12.6 : 1 from ^{1}H NMR], R_F 0.3 (90 : 10 30–40 PE : EtOAc)).

Data for (±)-10. ν_{max}/cm^{-1} (film) 3054 (s), 2987 (s), 1760 (m), 1603 (m), 1421 (s), 1262 (s), 1215 (m), 896 (s), 752 (s); δ_H (200 MHz, $CDCl_3$) 1.04 (3H, d, *J* 6.0 Hz), 1.50 (3H, s), 1.93 (1H, ddd, *J* 11.0, 4.5, 3.0 Hz), 2.12–2.17 (1H, m), 2.22 (3H, s), 2.26 (3H, s), 2.71–2.73 (2H, m), 3.52 (1H, t, *J* 8.0 Hz), 4.17 (1H, t, *J* 8.0 Hz), 6.42 (1H, d, *J* 2.0 Hz), 6.49 (1H, d, *J* 2.0 Hz); δ_C (100 MHz, $CDCl_3$) 15.9, 19.5, 21.2, 22.0, 22.8, 35.4, 47.9, 74.1, 107.1, 108.3, 114.9, 115.3, 138.1, 149.5, 153.6, 169.7; HRMS (ES+) Calculated for $C_{16}H_{21}O_4$ ([M + H]$^+$): 277.1440, Found: 277.1431. The ^{1}H NMR spectra of the mixture of acetylalboatrin and acetyl-*epi*-alboatrin displayed signals which compare favourably with the structure of *epi*-alboatrin described by Murphy *et al.* (ref. 15). *e.g.* for acetyl-epi-alboatrin δ_H (200 MHz, $CDCl_3$) 0.85 (3H, d, *J* 7.0 Hz); for epi-alboatrin δ_H (200 MHz, $CDCl_3$) 0.88–0.90 (3H, d, *J* 7.0 Hz). The two epimers could be separated and characterised by GCMS, LRMS (CI+) 277 for each. The Dept 135 experiment of the mixture of two spiroacetals (±)-**19** displays two new CH_2's for each compound and the disappearance of one CH and one CH_3. The ^{1}H NMR spectra also confirms the disappearance of one CH_3 for each compound and the HRMS of the mixture of compounds is in agreement with both proposed structures calculated for $C_6H_{21}O_4$ ([M + H]$^+$): 277.1440, Found: 277.1431. Likewise the structure of the spiroacetal compounds (±)-**19** was in agreement with quinone methide derived products described by Wilson *et al.*[4] in an analogous study.

(±)-3(*R**),3a(*R**),9a(*R**)-2,3,3a,9a-Tetrahydro-3,5,9a-trimethyl-7-hydroxy-4*H*-furo[2,3-*b*]chroman (alboatrin) (2)[2]

To a stirred solution of (±)-acetylalboatrin **10** and (±)-acetyl-*epi*-alboatrin [12.6 : 1] (480 mg, 1.74 mmol) in 9 ml of DCM–MeOH–H_2O (12 : 7 : 1) was added potassium carbonate (721 mg, 5.21 mmol) at room temperature under nitrogen. The mixture was stirred for 6 hours and was then extracted with ethyl acetate (3 × 50 ml). The combined organic layers were washed with a saturated solution of ammonium chloride (3 × 50 ml), dried over magnesium sulfate and concentrated under reduced pressure. The crude obtained was purified by flash silica gel chromatography (98 : 2 30–40 PE : EtOAc) to give a white solid. The solid was crystallised from ether to afford (±)-alboatrin **2** (368 mg, 97%) as white crystals.

Mp = 148–149 °C; R_F 0.1 (90 : 10 30–40 PE : EtOAc); ν_{max}/cm^{-1} (film) 3400 (s), 2958 (m), 1620 (s), 1599 (s), 1494 (m), 1462 (m), 1335 (m), 1204 (m), 1148 (s), 1117 (s), 986 (m), 845 (m); δ_H (200 MHz, $CDCl_3$) 1.04 (3H, d, *J* 6.5 Hz), 1.51 (3H, s), 1.93 (1H, ddd, *J* 11.0, 4.5, 3.5 Hz), 2.01–2.14 (1H, m), 2.19 (3H, s), 2.68 (2H, br s), 3.51 (1H, t, *J* 8.5 Hz), 4.17 (1H, t, *J* 8.5 Hz), 4.80 (1H, br s), 6.26 (1H, s), 6.29 (1H, s); δ_C (100 MHz, $CDCl_3$) 16.0, 19.4, 21.5, 23.2, 35.5, 48.4, 74.0, 101.9, 107.5, 109.6, 110.0, 138.2,

153.7, 155.1; HRMS (ES−) Calculated for $C_{14}H_{17}O_3$ ([M − H]$^-$): 233.1178, Found: 233.1180. **Crystal data for 2**: $C_{14}H_{18}O_3$, M = 234.30, monoclinic, a = 8.8435(3), b = 13.4040(5), c = 10.6982(3) Å, U = 1221.60(7) Å^3, T = 150 K, space group $P2_1/n$, Z = 4, μ(Mo-Kα) = 0.088 mm^{-1}, 1990 reflections measured, 2890 unique (R_{int} = 0.024) which were used in calculations. The final wR was 0.0498.[13]

(±)-5a(*R**),14a(*S**),(*E*)-(*E*)-5a,6,9,10,13,14,14a,15-Octahydro-5a,9,9,12,16-pentamethyl-18-acetoxycycloundeca[1,2-*b*]benzopyran (24)

In a sealed tube was stirred 2-acetoxymethyl-3-methyl-5-acetoxyphenol **6a** (203 mg, 0.85 mmol) with α-humulene (1 ml, 4.35 mmol) at 140 °C, under argon for 12 hours. The yellow mixture obtained was purified by flash silica gel chromatography (pure 30–40 PE, then 99 : 1 30–40 PE : EtOAc) to give (±)-**24** as a white solid (173 mg, 53%). Mp = 130–132 °C; R_F 0.4 (90 : 10 30–40 PE : EtOAc); ν_{max}/cm^{-1} (film) 2925 (s), 1761 (s), 1598 (s), 1452 (m), 1367 (m), 1211 (s), 1126 (s), 1046 (m), 911 (m); δ_H (400 MHz, $CDCl_3$) 1.02 (3H, s), 1.04 (3H, s), 1.05 (3H, s), 1.14 (1H, td, J 13.0, 8.0 Hz), 1.34 (1H, dd, J 13.0, 11.0 Hz), 1.62 (3H, s), 1.75 (1H, dd, J 12.5, 4.0 Hz), 1.79–1.88 (2H, m), 2.07–2.18 (3H, m), 2.21–2.30 (1H, m), 2.22 (3H, s), 2.26 (3H, s), 2.50 (1H, br d, J 14.5 Hz), 2.82 (1H, dd, J 16.5, 5.5 Hz), 5.00 (1H, dd, J 11.5, 4.0 Hz), 5.09 (1H, dd, J 16.0, 1.5 Hz), 5.16 (1H, ddd, J 16.0, 10.0, 2.0 Hz), 6.42 (1H, d, J 2.5 Hz), 6.44 (1H, d, J 2.5 Hz); δ_C (100 MHz, $CDCl_3$) 16.1, 18.1, 18.8, 19.9, 23.3, 26.1, 29.3, 29.5, 34.4, 36.8, 37.1, 40.3, 41.8, 78.7, 106.8, 112.9, 117.0, 119.7, 122.0, 135.2, 136.3, 140.9, 148.1, 153.3, 168.5; HRMS (ES+) Calculated for $C_{25}H_{35}O_3$ ([M + H]$^+$): 383.2586, Found: 383.2581.

A repeated reaction using the same conditions with only one equivalent of humulene in xylene gave the same product (±)-**24** in 48% yield.

(±)-5a(*R**),14a(*S**),(*E*)-(*E*)-5a,6,9,10,13,14,14a,15-Octahydro-5a,9,9,12,16-pentamethyl-18-hydroxycycloundeca[1,2-*b*]benzopyran (25)

To a stirred solution of (±)-**24** (820 mg, 2.14 mmol) in 20 ml of a mixture (12 : 7 : 1) of DCM–MeOH–H_2O was added potassium carbonate (330 mg, 2.38 mmol) at room temperature under nitrogen. The mixture was stirred for 6 hours and then extracted with ethyl acetate (3 × 100 ml). The combined organic layers were washed with a saturated solution of ammonium chloride (3 × 100 ml), dried over magnesium sulfate and concentrated under reduced pressure. The solid obtained was purified by flash silica gel chromatography (98 : 2 30–40 PE : EtOAc) to give a white solid which was crystallised from ether to afford (±)-**25** (601 mg, 82%) as white crystals. Mp = 155–157 °C; R_F 0.4 (90 : 10 30–40 PE : EtOAc); ν_{max}/cm^{-1} (film) 3400 (s), 2925 (s), 2859 (m), 1616 (s), 1600 (s), 1461 (s), 1381 (m), 1324 (m), 1265 (m), 1145 (s), 1046 (m), 991 (m), 839 (m), 738 (s); δ_H (400 MHz, $CDCl_3$) 1.03 (3H, s), 1.05 (3H, s), 1.06 (3H, s), 1.14 (1H, td, J 13.5, 8.5 Hz), 1.34 (1H, dd, J 13.5, 10.5 Hz), 1.63 (3H, s), 1.75 (1H, dd, J 13.0, 4.5 Hz), 1.81–1.87 (2H, m), 2.04–2.17 (3H, m), 2.19 (3H, s), 2.28 (1H, dd, J 14.5, 10.0 Hz), 2.50 (1H, br d, J 14.5 Hz), 2.80 (1H, dd, J 16.5, 5.5 Hz), 4.72 (1H, br s), 5.02 (1H, d, J 12.0, 4.5 Hz), 5.11 (1H, dd, J 16.0, 1.5 Hz), 5.18 (1H, ddd, J 16.0, 10.0, 2.5 Hz), 6.20 (1H, d, J 2.5 Hz), 6.26 (1H, d, J 2.5 Hz); δ_C (100 MHz, $CDCl_3$) 17.3, 19.3, 19.9, 24.4, 27.0, 30.4, 30.7, 35.8, 38.0, 38.3, 41.5, 43.0, 79.9, 101.4, 108.6, 113.1, 121.0, 123.1, 136.7, 137.8, 142.0, 154.3, 154.7; HRMS (ES−) Calculated for $C_{23}H_{31}O_2$ ([M − H]$^-$): 339.2324, Found: 339.2331.**Crystal data for 25**: $C_{23}H_{32}O_2$, M = 240.51, monoclinic, a = 19.4765(3), b = 9.6966(2), c = 21.0587(4) Å, U = 3964.72(13) Å^3, T = 150 K, space group $P2_1/c$, Z = 8, μ(Mo-Kα) = 0.071 mm^{-1}, 32823 reflections measured, 9525 unique (R_{int} = 0.051) which were used in calculations. The final wR was 0.0524.[13]

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References

1 P. Pittayakhajonwut, M. Theerasilp, P. Kongsaeree, A. Rungrod, M. Tanticharoen and Y. Thebtaranonth, *Planta Med.*, 2002, **68**, 1017.
2 A. Ichihara, M. Nonaka, S. Sakamura, R. Sato and A. Tajimi, *Chem. Lett.*, 1988, **1**, 27.
3 P. Cai, D. Smith, B. Cunningham, S. Brown-Shimer, B. Katz, C. Pearce, D. Venables and D. Houck, *J. Nat. Prod.*, 1998, **61**, 791.
4 J. D. Pettigrew, J. A. Bexrud, R. P. Freeman and P. D. Wilson, *Heterocycles.*, 2004, **62**, 445.
5 H. Weenen and M. H. H. Nkunya, *J. Org. Chem.*, 1990, **55**, 5107.
6 For example, see: (*a*) R. Rodriguez, R. M. Adlington, J. E. Moses, A. Cowley and J. E. Baldwin, *Org. Lett.*, 2004, **6**, 3617; (*b*) J. E. Baldwin, A. V. W. Mayweg, K. Neumann and G. J. Pritchard, *Org. Lett.*, 1999, **1**, 1933; (*c*) R. M. Adlington, J. E. Baldwin, G. J. Pritchard, A. J. Williams and D. J. Watkin, *Org. Lett.*, 1999, **1**, 1937; (*d*) R. M. Adlington, J. E. Baldwin, A. V. W. Mayweg and G. J. Pritchard, *Org. Lett.*, 2002, **4**, 3009.
7 For a recent review see: R. W. Van De Water and T. R. R. Pettus, *Tetrahedron*, 2002, **58**, 5367.
8 T. Katada, S. Eguchi, T. Esaki and T. Sasaki, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2649.
9 K. Chiba, T. Hirano, Y. Kitano and M. Tada, *Chem. Commun.*, 1999, **8**, 691.
10 (*a*) B. Loubinoux, J. Miazimbakana and P. Gerardin, *Tetrahedron Lett.*, 1989, **30**, 1939; (*b*) B. Loubinoux, S. Tabbache, P. Gerardin and J. Miazimbakana, *Tetrahedron*, 1988, **44**, 6055.
11 E. M. Gruneiro and E. G. Gros, *An. Asoc. Quim. Argent.*, 1971, **59**, 259.
12 Stable at room temperature for over four months.
13 CCDC reference numbers **2** 239364, **6a** 237660, **25** 239363. See http://dx.doi.org/10.1039/b508972g for crystallographic data in CIF or other electronic format.
14 (*a*) M. Yato, T. Ohwada and K. Shudo, *J. Am. Chem. Soc.*, 1990, **112**, 5341; (*b*) S. Nakamura, M. Uchiyama and T. Ohwada, *J. Am. Chem. Soc.*, 2003, **125**, 5282.
15 S. R. Graham, J. A. Murphy and A. R. Kennedy, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3071.
16 Deacetylated to *epi*-alboatrin[15].
17 A regiochemically controlled reaction of *o*-quinone methide **21** to (−)-alloaromadendrene to provide (−)-tanzanene has been reported, see: S. K. Paknikar, K. P. Fondekar and R. Mayer, *Nat. Prod. Lett.*, 1996, **8**, 253. For related Diels–Alder approaches employing functionalized *o*-quinone methides, see for example: L. O. Chapman, M. R. Engel, J. P. Springer and J. C. Clardy, *J. Am. Chem. Soc.*, 1971, **93**, 6696; J. P. Marino and S. L. Dax, *J. Org. Chem.*, 1984, **49**, 3671; Y. Genisson, P. C. Tyler and R. N. Young, *J. Am. Chem. Soc.*, 1994, **116**, 759.
18 K. Nakanishi, T. Goto, S. Ito, S. Natori and S. Nazoe, *Natural Product Chemistry*, Academic Press, New York, 1974, vol. 1, p. 87.
19 This dehydration route to *o*-quinone methide **21** proved superior to others, see: J. I. Cunneen, E. H. Farmer and H. P. Koch, *J. Chem. Soc.*, 1943, 472.
20 Structure was confirmed by single-crystal X-ray diffraction. See reference 6*c*.
21 Mass spectrum: ([M + H]$^+$): 523.
22 D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, Pergamon Press, Oxford, 3rd edn, 1988.