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Mild and rapid method for the generation of *o*-quinone methide intermediates. Synthesis of puupehedione analogues

Alejandro F. Barrero,[a,*] José F. Quílez del Moral,[a] M. Mar Herrador,[a] Pilar Arteaga,[a] Manuel Cortés,[b] Julio Benites[a] and Antonio Rosellón[a]

[a]*Department of Organic Chemistry, Institute of Biotechnology, University of Granada, Avda. Fuentenueva, 18071 Granada, Spain*
[b]*Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 306, Correo 22, Santiago, Chile*

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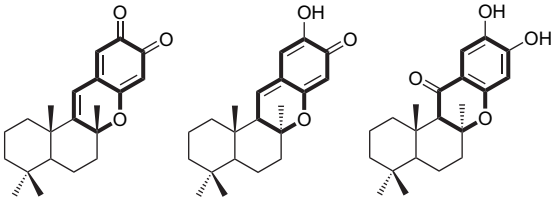
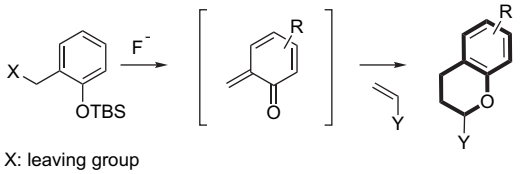
Abstract—A route to simpler analogues to bioactive puupehedione derivatives involving a hetero Diels–Alder cycloaddition of a *o*-quinone methide is described. These intermediate species are generated via fluoride-induced desilylation of silyl derivatives of *o*-hydroxybenzyl iodides. Remarkable short reaction times and very mild experimental conditions are the main features of this method.

1. Introduction

The benzopyran moiety is contained in a variety of natural products, many of which present interesting biological properties.[1] Among them, puupehedione (**1**) and other related marine derivatives, as puupehenone (**2**) and 15-oxo-puupehenol (**3**), have been attracting our attention during the last years due to the wide range of biological properties they present, including antitumor, antiviral antimalarial, antibiotic antituberculosis, antioxidant, insecticidal and antifungal activities.[2]



Thus, as a part of a programme to identify useful anti-angiogenic agents, some of us proved that some puupehedione-related derivatives completely inhibited the in vivo angiogenesis in the CAM assay at doses equal or lower than 30 nmol/egg, which makes them attractive drugs for further evaluation.[3] The scarce availability of many bioactive compounds from their natural sources together with the impracticality of many syntheses for producing amounts of materials appropriate for clinical follow-up has led to much research to develop simpler and more accessible analogues for broad biological evaluation.[4] In this context, we devised that the benzopyran nucleus of these compounds could be generated by reaction of *o*-quinone methides intermediates, obtained via fluoride-induced desilylation *o*-silyloxybenzyl derivatives, with appropriate dienophiles (Scheme 1). Although different reports on this subject were described by Rokita et al.,[5] this group used the *o*-quinone methide in DNA alkylating studies. Thus, to our knowledge, the only use of this reaction in organic synthesis was described by Young et al., in their synthesis of (±)-thielocin Alβ.[6]



Scheme 1.

o-Quinone methides are extremely reactive transient species, which undergo dimerisation processes in the absence of nucleophiles or electron-rich alkenes.[7] Although different strategies have been reported for their generation, most of them rely on the use of catalysts, acidic or basic conditions, high temperatures or long reaction times.[8] Among the recent advances in this subject,[9] special relevance should be given to the works of Pettus et al., which include a low-temperature anionic method for generating *o*-quinone methides and their enantioselective cycloaddition with a chiral enol ether.[10]

Keywords: Cyclisation; Epoxides; Titanium; Radical reaction; Terpenoids.
* Corresponding author. Tel./fax: +34 958 243318; e-mail: afbarre@ugr.es

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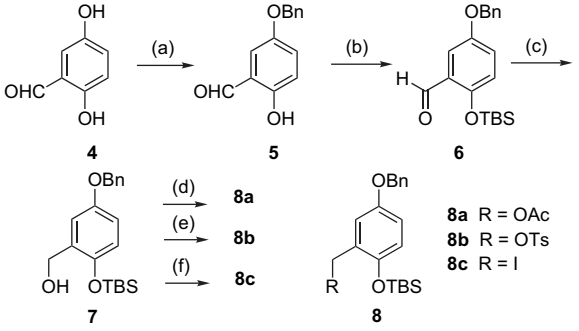
To start the development of this synthetic method, we addressed the search of the corresponding oxa-dienic precursor starting from commercial 2,5-dihydroxybenzaldehyde, **4**, following the straightforward transformations shown in Scheme 2.

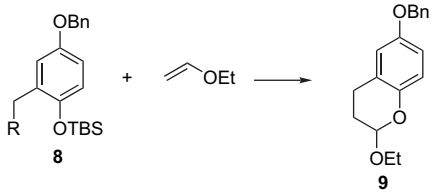


Scheme 2. Reagents and conditions: (a) $NaHCO_3$, KI, BnBr, CH_3CN, reflux, 24 h, 51%; (b) TBSCl, imidazole, DMF, rt, 4 h, 82%; (c) $NaBH_4$, MeOH, rt, 2 h, 98%; (d) Ac_2O, Py, rt, 42 h, 94%; (e) TsCl, Py, DMAP, reflux, 7 h, 68%; (f) Ph_3P, imidazole, I_2, CH_3CN/toluene, 60 °C, 10 min, 83%.

Thus, **4** was monobenzylated using the mixture BnBr, KI and $NaHCO_3$[11] to afford **5** in a 51% yield. An additional 36% of the corresponding dibenzylated derivative was also obtained. Protection of the hydroxyl group of **5** as silyl ether and subsequent treatment with $NaBH_4$ furnished primary alcohol **7**. Different leaving groups were then installed on this primary position (**8a**–**8c**) in order to test our hypothesis. The results obtained in the reaction of these derivatives with ethyl vinyl ether in the presence of TBAF are shown in Table 1.

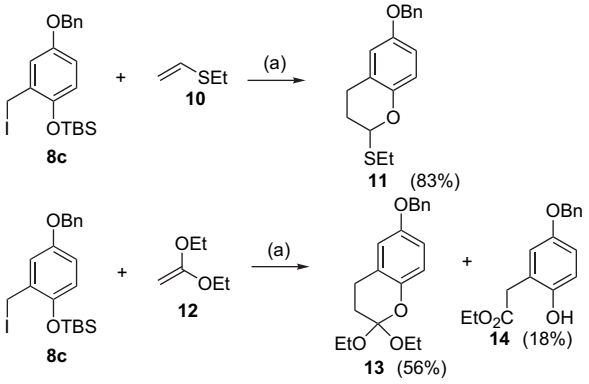
When the corresponding acetate or tosylate benzyl derivatives were treated for 10 min with TBAF (1.5 equiv) in the presence of 100 equiv of ethyl vinyl ether in DCM at 0 °C, only decomposition of starting material was observed. The hoped-for conversion took place when iodide was used as leaving group (entry 3, Table 1). More efficient conversion (up to 88%) occurred when benzene was used as solvent (entry 5, Table 1) (surely due to the less solubility in benzene of the potential nucleophilic salt TBAI, by-product of the reaction). It is worth noting that this yield was obtained in a very short reaction time, 2 min, and at room temperature, which are unprecedently mild experimental conditions for this kind of reaction. Although the use of the corresponding enol ether as the solvent for the reaction has been reported to increase the yield in many of these hetero Diels–Alder processes,[12] different assays were performed in order to check to what extent the quantity of ethyl vinyl ether could be lowered (entries 6–9, Table 1). Thus, an acceptable yield was still obtained using 35 equiv of ethyl vinyl ether, only a moderate result was found when the quantity of this reagent was reduced to 20 equiv, while the use of 10 equiv led to minor quantities of the desired adduct.

Table 1. Reaction of **8a–c** with ethyl vinyl ether



Entry	R	Temperature (°C)	Time	Solvent	Equiv of dienophile	Yield (%)
1	OAc	0	10	DCM	100	0
2	OTs	0	10	DCM	100	0
3	I	0	10	DCM	100	40
4	I	0	2	DCM	100	41
5	I	25	2	Benzene	100	88
6	I	25	2	Benzene	50	87
7	I	25	2	Benzene	35	70
8	I	25	2	Benzene	20	45
9	I	25	2	Benzene	10	5–10

Having found the conditions to efficiently achieve the generation and ensuing cycloaddition of the *o*-quinone methide derived from **8c**, we then turned our efforts to study the versatility of this process. Thus, two variations of this protocol were studied. On one hand, **8c** was caused to react with other dienophiles as **10** and **12** (Scheme 3).

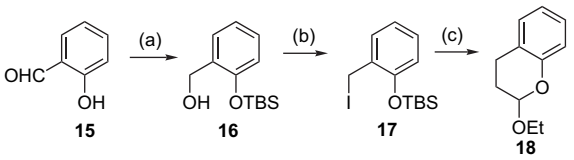


Scheme 3. Reagents and conditions: (a) TBAF, benzene, rt, 2 min.

The results found with **10** and **12** showed that the reaction proceeded as satisfactorily as it did when ethyl vinyl ether was employed. With respect to the formation of the alkylthiochroman derivative **11**, it should be remarked that although *o*-quinone methides have been reported to undergo [4+2] cycloadditions with vinyl ethers, furans, enamines and imines, to the best of our knowledge, this is the first report of a sulfide ether acting as a dienophile in a cycloaddition reaction with an in situ generated *o*-quinone methide. Furthermore, the synthesis of **11** is of additional interest since different thiochromone derivatives related to it are contained in a patent useful for the treatment of Alzheimer disease, Down syndrome, vascular dementia and parkinsonism.[13] Other noteworthy adduct include the direct formation of the *o*-alkyl phenol derivative **14**, since *o*-functionalized phenols are ubiquitous among natural products.[14,12]

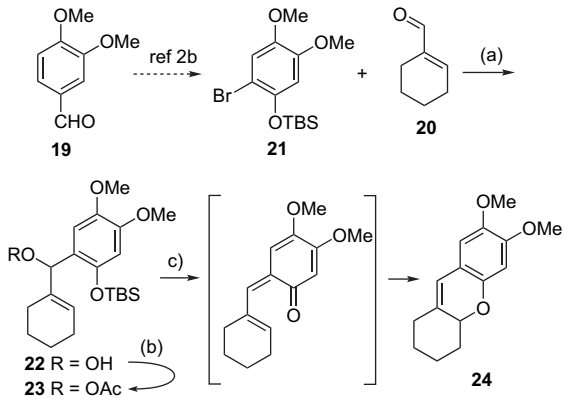
The second variation introduced with the aim of widening the scope of this procedure was the use of a different oxa-dienic moiety. Thus, starting from commercial 2-hydroxybenzaldehyde (**15**), the corresponding *o*-silyloxybenzyl iodide, **17**, was obtained after straightforward transformations (Scheme 4). When this compound was caused to react with ethyl vinyl ether, the reaction was found to proceed similarly. TLC monitoring and NMR control of the reaction

crude showed that chroman **18** was the only compound generated. The noticed volatility of **18** is postulated to account for the moderate yields obtained.



Scheme 4. Reagents and conditions: (a) (i) TBSCl, imidazole, DMF, rt, 4 h; (ii) $NaBH_4$, MeOH, rt, 2 h, 81% in two steps; (b) Ph_3P, imidazole, I_2, CH_3CN/toluene, 60 °C, 10 min, 73%; (c) TBAF, ethyl vinyl ether, benzene, rt, 2 min 51%.

With the above results in mind, we felt that puupehedione analogue **24** could be expeditiously synthesized using this procedure from commercially available 3,4-dimethoxybenzaldehyde (**19**) and 1-cyclohexene-1-carboxaldehyde (**20**) (Scheme 5).



Scheme 5. Reagents and conditions: (a) **21**, THF, −78 °C, *t*BuLi, 15 min, then **20**, 15 min, 81%; (b) Ac_2O, Py, 0 °C, 1 h; (c) benzene, TBAF, 2 min, rt, 62% two steps.

It should be noted that the synthetic proposal for **24** involves an intramolecular hetero Diels–Alder cycloaddition. Thus, the success of this approach would suppose a significant widening of the possibilities of this protocol, although the ultimate aim of this synthesis is to test whether compound **24** or related derivatives would retain the activity of metabolites such as puupehedione (**1**), puupehenone (**2**) and 15-oxopuupehenol (**3**).

The synthesis of **24** began with the addition of the organolithium derived from commercial **19** to aldehyde **20** to give alcohol **22** in 81% yield (Scheme 2). Compound **22** was acetylated and treated without further purification with TBAF. The hoped-for conversion took place efficiently, a 62% of **24** being obtained as a result of an electrocyclic process.[15] Contrary to what were observed in the intermolecular version of the process, an acetate group was now found to be an efficient leaving group.

In conclusion, we have proved that *o*-quinone methides can be generated from *o*-silyloxybenzyl derivatives via fluoride-induced desilylation. These methides reacted with electron-rich alkene to afford different chroman nuclei. This new method compares favourably with existing alternatives in terms of reaction times, reaction temperatures and the ease of generation of the methide precursor. This reaction was applied to the synthesis of a simpler analogue of biologically active puupehedione-related compounds, a part of a programme to identify useful anti-angiogenic agents. In the hope of widening the possibilities offered by this method, further studies with the aim of obtaining more analogues of puupehedione and other interesting chroman derivatives are being carried out.

2. Experimental

2.1. General

All air- and water-sensitive reactions were performed in flasks flame-dried under a positive flow of argon and conducted under an atmosphere of argon. Reagents were purchased at the higher commercial quality and used without further purification, unless otherwise stated. Silica gel SDS 60 (35–70 μm) was used for flash column chromatography. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualising agent and a solution of phosphomolybdic acid in ethanol and heat as developing agent. IR spectra were recorded with a Matson model Satellite FTIR instrument as NaCl plates (films). NMR studies were performed with a Bruker ARX 400 (^{1}H 400 MHz/^{13}C 100 MHz) spectrometer. The accurate mass determination was carried out with a AutoSpec-Q mass spectrometer arranged in a EBE geometry (Micromass Instrument, Manchester, UK) and equipped with a FAB (LSIMS) source.

2.1.1. General procedure for the generation of benzopyranes via *o*-methide quinone intermediates. To a solution of iodo derivative (0.22 mmol) in dry benzene (4 mL) was added 1.08 mL of ethyl vinyl ether and the resulting solution is stirred for 5 min. Then, it was added 0.32 mL of a 1 M solution of TBAF. The mixture was further stirred for 2 min and then diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by column chromatography.

2.2. Synthesis of oxa-dienic precursors

2.2.1. Synthesis of 8c.

2.2.1.1. 5-(Benzyloxy)-2-(*t*-butyldimethylsilyloxy) benzaldehyde (6). To a solution of 2 g (14.5 mmol) of commercial 2,5-dihidroxybenzaldehide (**4**), 1.388 g (16.53 mmol) of $NaHCO_3$ and 0.241 g (1.45 mmol) of KI in 30 mL of dry acetonitrile heated to 60 °C, 2.23 mL of BnBr (3.22 g, 18.85 mmol) were added. The reaction mixture was then stirred under argon at reflux for 24 h. The solvent was removed to afford a crude product, which was re-dissolved in EtOAc (50 mL) and washed with 1 N HCl and brine. The residue was purified by column chromatography. Eluting with hexane/EtOAc, 3:1, afforded 1692 mg of the corresponding monobenzylated derivative **5** (51%).[16] To a solution of 1090 mg of **5** in 30 mL of DCM under argon was added imidazole (810 mg, 12.05 mmol) and TBSCl (1090 mg, 7.23 mmol). The reaction was stirred at room

temperature for 4 h and then diluted with EtOAc and washed with H_2O, 1 N HCl, saturated $NaHCO_3$ and brine and worked up as usual. The product obtained was purified by chromatography on silica gel (hexane/EtOAc, 4:1) to give 960 mg (82% yield) of **6** as yellow oil. IR (film) ν: 3065, 3034, 2955, 2930, 2858, 1681, 1611, 1489, 1426, 1388, 1273, 1211, 1155, 1026, 908, 841, 782 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 6H), 1.00 (s, 9H), 5.02 (s, 2H), 6.81 (d, J=9.0 Hz, 1H), 7.12 (dd, J=9.0, 3.4 Hz, 1H), 7.36 (d, J=3.4 Hz, 1H), 7.45–7.30 (m, 5H), 10.39 (1H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.4, 18.1, 25.6, 70.2, 110.8, 121.4, 124.1, 127.0, 127.3, 127.8, 128.3, 136.5, 153.0, 153.1, 189.2 ppm. HRFABMS calcd for $C_{20}H_{26}O_3NaSi$ $[M+Na]^+$ 365.1549, found 365.1551.

2.2.1.2. [5-Benzyloxy-2-(*t*-butyldimethylsilyloxy)-phenyl] methanol (7). To a solution of 265 mg of $NaBH_4$ (7 mmol) in MeOH (11 mL) was added **6** (400 mg, 1.02 mmol) in 6 mL of MeOH. The mixture was stirred at room temperature and refluxed for 2 h. MeOH was then removed and the resulting crude re-dissolved in EtOAc and washed with 2 N HCl and brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography (hexane/*t*-BuOMe 6:1) to give 398 mg (98%) of **7**. IR (film) ν: 3402, 3064, 3035, 2955, 2929, 2885, 2858, 1606, 1585, 1494, 1463, 1381, 1268, 1222, 1155, 1027, 902, 839, 780, 736, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 6H), 0.95 (s, 9H), 4.58 (s, 2H), 4.95 (s, 2H), 6.66 (d, J=8.8 Hz, 1H), 6.71 (dd, J=8.8, 3.0 Hz, 1H), 6.92 (d, J=3.0 Hz, 1H), 7.20–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.4, 18.0, 25.7, 61.1, 70.3, 114.2, 114.6, 118.9, 127.4, 127.7, 128.4, 132.4, 137.2, 146.8, 153.2 ppm. HRFABMS calcd for $C_{20}H_{28}O_3NaSi$ $[M+Na]^+$ 367.1705, found 367.1698.

2.2.1.3. 4-Benzyloxy-1-(*t*-butyldimethylsilyloxy)-2-iodomethylbenzene (8c). A solution of 114 mg of **7** (0.33 mmol), 130 mg of PPh_3 (0.5 mmol), 34 mg of imidazole (0.5 mmol) and 127 mg of I_2 (0.5 mmol) in 2 mL of acetonitrile and 8 mL of toluene was heated at 60 °C for 10 min. The reaction mixture was then diluted with EtOAc and subsequently washed with saturated $Na_2S_2O_3$, brine, dried and evaporated. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 4:1) on silica gel to afford 125 mg (83%) of **8c** as yellowish oil. IR (film) ν: 3068, 3036, 2955, 2930, 2884, 2857, 1599, 1581, 1492, 1454, 1267, 1154, 906, 838, 781, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.27 (s, 6H), 1.05 (s, 9H), 4.42 (s, 2H), 4.97 (s, 2H), 6.68 (d, J=8.8 Hz, 1H), 6.78 (dd, J=8.8, 3.0 Hz, 1H), 6.94 (d, J=3.0 Hz, 1H), 7.30–7.45 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −3.9, 1.8, 18.4, 26.0, 61.1, 70.6, 115.9, 116.5, 119.4, 127.6, 128.0, 128.6, 130.3, 137.1, 147.5, 152.9 ppm. HRFABMS calcd for $C_{20}H_{27}O_2NaSiI$ $[M+Na]^+$ 477.0718, found 477.0723.

2.2.2. Synthesis of 17.

2.2.2.1. 1-(*t*-Butyldimethylsilyloxy)-2-iodomethyl benzene (17). This compound was prepared starting from commercial 2-hydroxybenzaldehyde, **15**. Following the same procedures used for **8c**, this compound was subsequently protected as silyl ether, reduced to give phenol **16**,[17] and treated with I_2 in the presence of PPh_3 to give the iodo derivative **17** in an 60% overall yield. Compound **17**, colourless oil. IR (film) ν: 3069, 3036, 2955, 2929, 2885, 2858, 1599, 1581, 1491, 1454, 1361, 1266, 1202, 1155, 1040, 924, 832, 781, 753, 704, 662 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.36 (s, 6H), 1.13 (s, 9H), 4.52 (s, 2H), 6.82 (dd, J=8.1, 1.0 Hz, 1H), 6.92 (dt, J=7.6, 1.0 Hz, 1H), 7.19 (ddd, J=1.6, 8.0, 7.6 Hz, 1H), 7.35 (dd, J=1.6, 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −3.9, 1.8, 18.4, 25.8, 118.6, 121.4, 129.4, 129.7, 130.7, 153.5 ppm. HRFABMS calcd for $C_{13}H_{21}ONaSiI$ $[M+Na]^+$ 371.0304, found 371.0300.

2.3. Reactions of heterocyclisation. Synthesis of chromanes

2.3.1. 6-(Benzyloxy)-2-ethoxychroman (9). After subjecting **8c** (133 mg, 0.3 mmol) to the heterocyclisation conditions, the resulting crude was purified by column chromatography on silica gel. Eluting with hexane/*t*-BuOMe (6:1) furnished 74 mg of **9** (88%) as a colourless oil. IR (film) ν: 3032, 2926, 2856, 1754, 1612, 1465, 1454, 1377, 1192, 1058, 877 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 1.19 (t, J=7.1 Hz, 3H), 1.93 (m, 1H), 2.03 (m, 1H), 2.60 (ddd, J=3.6, 5.9, 16.3 Hz, 1H), 2.97 (ddd, J=6.1, 11.7, 17.2 Hz, 1H), 3.63 (dq, J=7.0, 9.8 Hz, 1H), 3.88 (dq, J=7.0, 9.8 Hz, 1H), 4.99 (s, 2H), 5.22 (t, J=2.8 Hz, 1H), 6.70 (s, 1H), 6.76 (s, 2H), 7.30–7.45 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 20.9, 26.6, 63.6, 70.6, 96.8, 114.2, 115.1, 117.5, 123.3, 127.5, 127.9, 128.6, 137.5, 146.3, 152.8 ppm. HRFABMS calcd for $C_{18}H_{20}O_3Na$ $[M+Na]^+$ 307.1310, found 307.310.

2.3.2. 6-(Benzyloxy)-2-(ethylthio)chroman (11). After subjecting **8c** (100 mg, 0.22 mmol) to the heterocyclisation conditions but using ethyl vinyl sulfide as dienophile, the resulting crude was purified by column chromatography on silica gel. Eluting with hexane/*t*-BuOMe (4:1) furnished 55 mg of **11** (83%) as a colourless oil. IR (film) ν: 2964, 2927, 2869, 1732, 1608, 1494, 1453, 1376, 1265, 1193, 1076, 987, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 1.24 (t, J=7.4 Hz, 3H), 2.02 (m, 1H), 2.21 (m, 1H), 2.37–2.78 (m, 3H), 2.88 (ddd, J=6.4, 10.2, 16.6 Hz, 1H), 4.93 (s, 2H), 5.46 (t, J=4.0 Hz, 1H), 6.62 (s, 1H), 6.68 (s, 2H), 7.20–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 22.9, 24.7, 27.4, 70.6, 80.2, 114.5, 115.3, 118.1, 122.6, 127.5, 127.9, 128.6, 137.5, 146.6, 153.2 ppm. HRFABMS calcd for $C_{18}H_{20}O_2SNa$ $[M+Na]^+$ 307.1310, found 307.1310.

2.3.3. 6-(Benzyloxy)-2,2-diethoxychroman (13). After subjecting **8c** (131 mg, 0.28 mmol) to the heterocyclisation conditions but using 1,1-diethoxyethene as dienophile, the resulting crude was purified by column chromatography on silica gel. Eluting with hexane/*t*-BuOMe (20:1) furnished 53 mg of **13** (56%) and 16 mg of **14** (18%). Compound **13**, colourless oil. IR (film) ν: 2976, 2928, 1729, 1613, 1496, 1442, 1380, 1205, 1091, 1047, 969, 879, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J=7.1 Hz, 6H), 2.00 (t, J=6.8 Hz, 2H), 2.77 (t, J=6.8 Hz, 2H), 3.62 (m, 4H), 4.92 (s, 2H), 6.60–6.85 (m, 3H), 7.20–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 23.9, 27.8, 57.4, 70.6, 112.4, 114.1, 114.7, 117.4, 122.8, 127.6, 127.9, 128.6, 137.4, 148.5, 153.0 ppm. Compound **14**, colourless oil. IR (film) ν: 3417, 2979, 2931, 2869, 1730, 1709, 1505, 1196, 1027, 737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J=7.2 Hz,

3H), 2.68 (t, J=6.4 Hz, 2H), 2.84 (t, J=6.4 Hz, 2H), 4.12 (q, J=7.2 Hz, 2H), 4.96 (s, 2H), 6.70–6.81 (m, 3H), 7.20–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 24.9, 35.3, 61.4, 70.7, 114.1, 117.0, 118.0, 122.8, 127.6, 127.8, 127.9, 128.6, 128.7, 137.4, 148.5, 153.0, 177.0 ppm. HRFABMS calcd for $C_{18}H_{20}O_4Na$ $[M+Na]^+$ 323.1260, found 323.1261.

2.3.4. 2-Ethoxychroman (18). After subjecting **17** (125 mg, 0.4 mmol) to the heterocyclisation conditions, the resulting crude was purified by column chromatography on silica gel. Eluting with hexane/*t*-BuOMe (6:1) furnished 33 mg of **18**[18] (51%). Compound **18**, colourless oil. IR (film) ν: 2955, 2923, 2853, 1732, 1605, 1456, 1376, 1262, 1097, 1015, 802, 743 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J=7.1 Hz, 6H), 1.87 (m, 1H), 1.98 (m, 1H), 2.57 (ddd, J=3.9, 5.7, 16.8 Hz, 1H), 2.91 (ddd, J=5.7, 11.2, 16.8 Hz, 1H), 3.58 (dq, J=7.0, 9.7 Hz, 1H), 3.82 (dq, J=7.1, 9.7 Hz, 1H), 5.18 (t, J=3.0 Hz, 1H), 6.75–6.85 (m, 2H), 6.95–7.10 (m, 2H). HRFABMS calcd for $C_{11}H_{14}O_2Na$ $[M+Na]^+$ 201.0892, found 323. 201.0884.

2.4. Synthesis of the puupehedione analogue 24

2.4.1. Synthesis of alcohol 22. A 1.7 M solution of *tert*-butyllithium in pentane (3.4 mL) was added at −78 °C to a solution of **21** (1800, 5.17 mmol) in diethyl ether (75 mL), under argon atmosphere. After stirring for 30 min at this temperature, **20** (625 mg, 5.69 mmol) was added and the mixture was further stirred for 15 min at −78 °C. The reaction crude was diluted with ether and then water was added. The organic layer was then washed with brine, dried and concentrated to give a crude, which was chromatographed on silica gel column (H/E, 2:1) to give 1582 mg of **22** (81%) as a colourless oil. IR (film) ν: 3507, 2966, 2950, 2929, 2856, 1609, 1510, 1463, 1446, 1400, 1255, 1202, 1114, 1008, 909, 837, 780 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 3H), 0.22 (s, 3H), 0.99 (s, 9H), 1.50–1.65 (m, 4H), 1.79–2.00 (m, 2H), 2.03 (m, 2H), 3.80 (s, 6H), 5.28 (br s, 1H), 5.70 (br s, 1H), 6.37 (s, 1H), 6.81 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −3.9, 22.6, 22.7, 25.0, 25.6, 25.9, 55.9, 56.3, 72.2, 103.6, 111.0, 122.6, 123.9, 138.9, 143.4, 146.9, 148.4 ppm. HRFABMS calcd for $C_{21}H_{34}O_4SiNa$ $[M+Na]^+$ 378.2226, found 378.2217.

2.4.2. Acetate 23. To a solution of 150 mg (0.40 mmol) of **22** in 2 mL of pyridine was added 1 mL of Ac_2O at 0 °C. After stirring for 15 min at this temperature, the reaction mixture was worked up as usual to give 160 mg of **23**, which was used without further purification. Colourless oil. IR (film) ν: 3507, 2950, 2931, 2857, 1739, 1612, 1510, 1447, 1400, 1232, 1204, 1115, 1015, 902, 839, 780 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.21 (s, 3H), 0.23 (s, 3H), 1.99 (s, 9H), 1.52–1.70 (m, 4H), 1.82 (m, 1H), 1.93–2.06 (m, 3H), 2.08 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 5.55 (br s, 1H), 6.38 (s, 1H), 6.42 (br s, 1H), 6.79 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −3.9, 21.3, 22.3, 22.5, 25.0, 25.7, 25.9, 55.9, 56.5, 72.9, 103.4, 111.2, 120.4, 123.6, 135.9, 143.4, 147.2, 148.9, 169.9 ppm.

2.4.3. Synthesis of 24. To a solution in benzene (5 mL) of the above crude containing **23** was added 0.5 mL of a 1 M solution of TBAF. The mixture was further stirred for 2 min and then diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by column chromatography to afford 60 mg of **24** (62% for two steps). Colourless oil. IR (film) ν: 3032, 2926, 2856, 1754, 1612, 1465, 1454, 1377, 1192, 1058, 877 cm^{-1}. ^{1}H NMR (400 MHz, $CD_3)_2CO$) δ 1.23 (qt, J=3.6, 12.9 Hz, 1H), 1.42 (qt, J=3.6, 12.9 Hz, 1H), 1.61 (m, 1H), 1.70 (m, 1H), 1.78 (m, 1H), 1.97 (m, 1H), 2.06 (m, 1H), 2.97 (br d, J=14.3 Hz, 1H), 3.64 (s, 3H), 3.68 (s, 3H), 4.79 (br dd, J=5.5, 10.9 Hz, 1H), 5.91 (t, J=1.9 Hz, 1H), 6.25 (s, 1H), 6.46 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CD_3)_2CO$) δ 24.9, 27.4, 33.3, 35.8, 56.2, 57.1, 77.6, 101.3, 111.8, 114.4, 116.9, 136.1, 144.4, 148.4, 150.5 ppm. HRFABMS calcd for $C_{15}H_{18}O_3$ $[M]^+$ 246.1256, found 246.1255.

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