

# Biomimetic total synthesis of forbesione and desoxymorellin utilizing a tandem Claisen/Diels–Alder/Claisen rearrangement †

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A concise synthesis of forbesione (**1**) and desoxymorellin (**3**) is presented. Central to the strategy is a biomimetic Claisen/Diels–Alder/Claisen reaction cascade that proceeds in a regioselective manner and produces the desired scaffold exclusively. The observed regioselectivity and product distribution of the Claisen/Diels–Alder/Claisen reaction are attributed to the electronic effects of the xanthone oxygen (O10), the C9 carbonyl group and the nature of the C1 functionality.

## Introduction

Gamboge, the dried resin collected from tropical trees of the genus *Garcinia*, and particularly from *G. hanburyi*, has been used traditionally for pigments and folk medicines.<sup>1</sup> Isolation of the bioactive constituents of gamboge has yielded a family of caged xanthonoids, representative members of which include forbesione (**1**),<sup>2</sup> hanburin (**2**),<sup>3</sup> desoxymorellin (**3**),<sup>4</sup> morellin (**4**),<sup>5</sup> and the bractatins **5**, **6** and **7**<sup>6</sup> (Fig. 1).

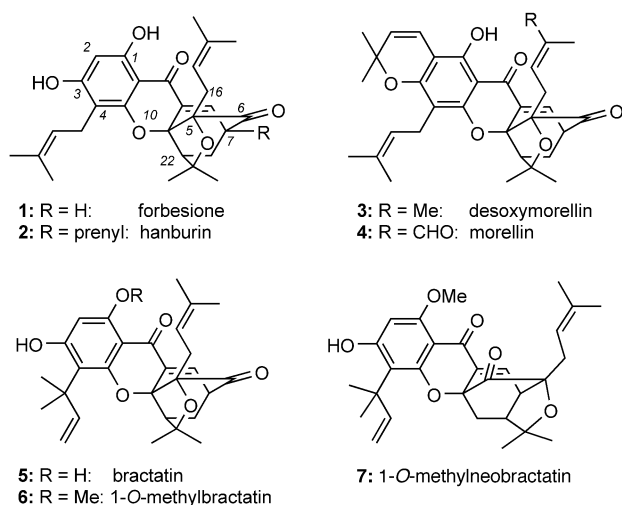


Fig. 1 Selected natural products from *Garcinia* plants.

The caged motif of these natural products, purportedly responsible for their biological activities,<sup>7</sup> has been proposed by Quillinan and Scheinmann to arise in Nature through a tandem Claisen/Diels–Alder reaction.<sup>8</sup> This biomimetic scenario has been recently explored by Nicolaou and Li during their synthesis of 1-O-methylforbesione.<sup>9</sup> Despite this and related synthetic advances,<sup>10</sup> the total synthesis of a caged *Garcinia* natural product has not yet been achieved. Herein, we describe a biomimetic synthesis of forbesione (**1**) and desoxymorellin (**3**) and present a rationalization of the regioselectivity observed during the C-ring Claisen/Diels–Alder rearrangement.

## Results and discussion

The retrosynthetic approach toward **1** and **3** is shown in Fig. 2. Disconnection of desoxymorellin (**3**) across the pyran ring suggests a synthetic entry to this natural product from forbesione (**1**) via propargylation of the C3 hydroxyl group and subsequent Claisen cyclization.<sup>11</sup> Inspired by the proposed biosynthetic scenario, we expected **1** to arise from rearrangement of tris-allyloxy precursor **8**, the fused ring system of which can be traced to xanthone **9**. Successful implementation of such a strategy would require control over the regioselectivity of both the A-ring Claisen rearrangement, *i.e.* prenylation at C4 over C2, and formation of the desired caged motif during the C-ring Claisen/Diels–Alder reaction. Reduction of this plan to practice is illustrated in Scheme 1.

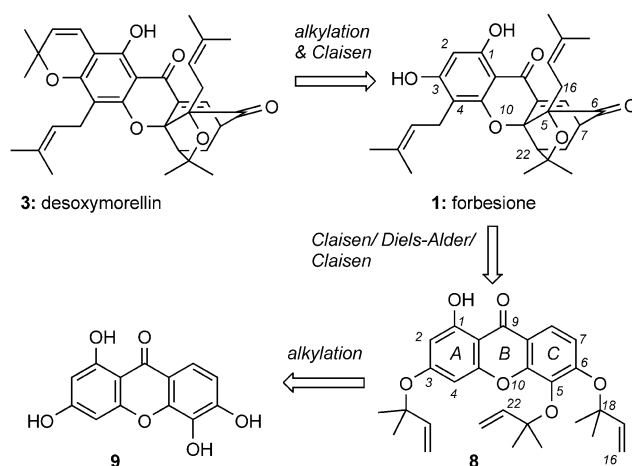
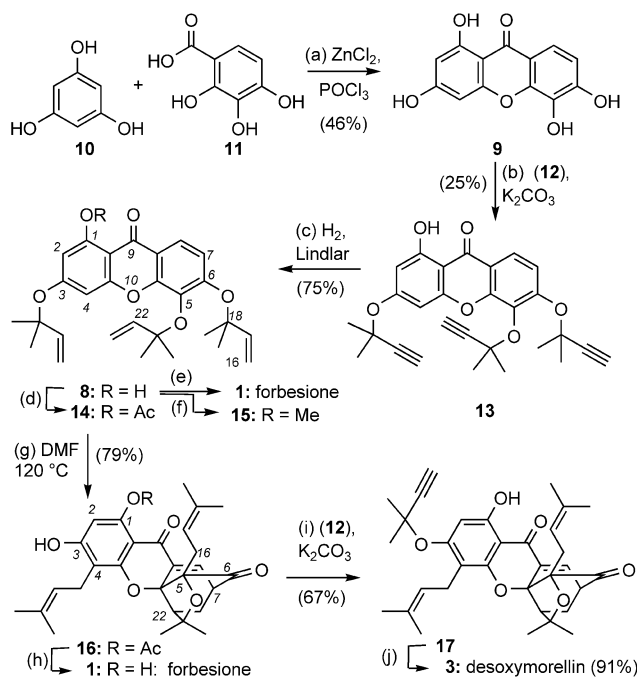


Fig. 2 Strategic bond disconnections of **3** and **1**.

Our synthetic studies commenced with a  $ZnCl_2$  mediated condensation of phloroglucinol (**10**) with 2,3,4-trihydroxybenzoic acid (**11**) in  $POCl_3$ <sup>12</sup> to produce xanthone **9** in 46% yield (Scheme 1). Several conditions were tested for the conversion of **9** to allyl ether **8**. Among them, the best results were obtained using a two step procedure that involved propargylation of the more reactive C3, C5 and C6 phenols to form **13**, followed by partial reduction of the installed alkynes. Although the reduction afforded **8** in respectable yields (75%), the propargylation of **9** was found to be unexpectedly difficult.<sup>13</sup> Use of 2-chloro-2-methylbutyne (**12**) in the presence of KI and

† Electronic supplementary information (ESI) available: <sup>1</sup>H and <sup>13</sup>C NMR spectra for compounds **1**, **3**, **8** and **9**. See <http://www.rsc.org/suppdata/ob/b3/b311833a/>



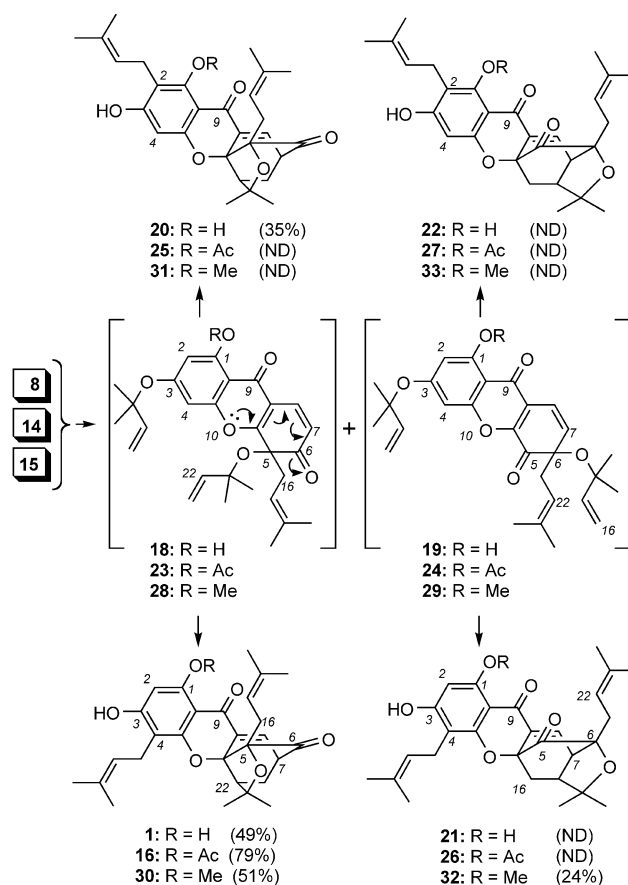
**Scheme 1** Reagents and conditions: (a) 1.0 equiv. of **10**, 1.0 equiv. of **11**, 6.5 equiv. of  $\text{ZnCl}_2$ ,  $\text{POCl}_3$ , 65 °C, 3 h, 46%; (b) 3.3 equiv. of **12**, 3.3 equiv. of  $\text{K}_2\text{CO}_3$ , 5.1 equiv. of **12**, 10 mol%  $\text{CuI}$ ,  $(\text{CH}_3)_2\text{CO}$ , 45 °C, 6 h, 25%; (c) 10%  $\text{Pd/BaSO}_4$ , quinoline,  $\text{EtOAc}$ , 25 °C, 6 h, 75%; (d) 25 equiv. of pyridine, 25 equiv. of  $\text{Ac}_2\text{O}$ , 10 mol%  $\text{DMAP}$ ,  $\text{CH}_2\text{Cl}_2$ , 35 °C, 24 h, 85%; (e)  $\text{DMF}$ , 120 °C, 1 h, 49% of **1** and 35% of **20**; (f) 5.0 equiv. of  $\text{Cs}_2\text{CO}_3$ , 5.0 equiv. of  $\text{MeI}$ ,  $\text{DMF}$ , 25 °C, 15 min, 61%; (g)  $\text{DMF}$ , 120 °C, 1 h, 79%; (h) 0.5 M  $\text{K}_2\text{CO}_3$  (aq),  $\text{MeOH}$ , 25 °C, 6 h, 91%; (i) 1.5 equiv. of  $\text{KI}$ , 3.0 equiv. of  $\text{K}_2\text{CO}_3$ , 20 equiv. of **12**, 10 mol%  $\text{CuI}$ ,  $(\text{CH}_3)_2\text{CO}$ , 55 °C, 6 h, 67%; (j)  $\text{DMF}$ , 120 °C, 4 h, 91%.

$\text{K}_2\text{CO}_3$ <sup>14</sup> under  $\text{CuI}$  catalysis was essential for this alkylation which, despite all efforts, proceeded in only 25% yield. Despite the low alkylation yield, this strategy offered the most expedient route to xanthone **8**, the putative biosynthetic precursor to the target natural products.

With compound **8** in hand, the stage was set to study the proposed biosynthetic hypothesis for the synthesis of forbesione.<sup>8</sup> Drawing on previous experience with related structures,<sup>10</sup> we heated **8** in  $\text{DMF}$  at 120 °C and obtained a mixture of forbesione (**1**) (49%) together with isoforbesione (**20**) (35%) (for the structure of **20** see Scheme 2). Although these results demonstrated the excellent regioselectivity of the C-ring Claisen/Diels–Alder reaction for the formation of the desired caged structure, the excitement was attenuated by the concomitant formation of isomers **1** and **20**. This issue was circumvented by converting the C1 hydroxyl group of **8** to its corresponding acetate **14**. Heating **14** in  $\text{DMF}$  gave rise to 1-*O*-acetylforbesione (**16**) exclusively and, after deprotection, afforded forbesione (**1**) in 71% combined yield.<sup>15</sup> Finally, with forbesione in hand, attention was turned toward the synthesis of desoxymorellin (**3**). This was accomplished by propargylation of the C3 phenol of **1** followed by Claisen rearrangement of the resulting alkyne **17**. This sequence produced desoxymorellin (**3**) from **1** in 61% combined yield.

The exclusive formation of the desired caged motif upon exposure of precursors **8** and **14** to the Claisen/Diels–Alder conditions deserves additional comments. Such selectivity is particularly intriguing in light of the results reported by Nicolaou and Li,<sup>9</sup> heating 1-*O*-methylated precursor **15** in  $\text{DMF}$  at 120 °C afforded a mixture of adducts, the major compounds of which were identified as 1-*O*-methylforbesione (**30**) and 1-*O*-methylneoforbesione (**32**) (for the structures of **30** and **32** see Scheme 2). Scheme 2 illustrates all possible pathways of this reaction cascade.

In principle, precursor **8** can open its rearrangement cascade by delivering a prenyl group to either the C5 or C6 center,



**Scheme 2** Derivatization of the C1-hydroxyl group and its effect on the Claisen/Diels–Alder reaction cascade.

forming intermediates **18** and **19**, respectively (Scheme 2).<sup>16</sup> Intermediate **18** is responsible for the desired caged structure and could lead, after Claisen rearrangement of the C3 allyloxy unit, to forbesione (**1**) and/or isoforbesione (**20**).<sup>17</sup> In a similar manner, intermediate **19** could lead to an isomeric caged structure, the so-called neo skeleton,<sup>6</sup> ultimately forming neoforbesione (**21**) and/or isomer **22**. Similar structures are expected with precursors **14** and **15**.

*Why is the Claisen/Diels–Alder reaction regioselective?* The answer may lie in the electronic effects of both the xanthone oxygen (O10) and the C9 carbonyl group. The C9 carbonyl group of precursor **8** is *para* to the C6 allyloxy unit and thus, it can accept electron density from the C6 oxygen. This contributes to a weakening of the ether bond to the C18 alkyl fragment facilitating its rupture.<sup>18</sup> In addition, as shown in structure **18** (Scheme 2), the xanthone oxygen (O10) is *meta* to the C6 carbonyl group thereby stabilizing it by resonance. Such a stabilization effect cannot be achieved at the C5 carbonyl group of intermediate **19**. In precursor **8**, the combination of such effects leads to the exclusive formation of **18** over **19** and ultimately, the desired caged scaffold (combined isolated yield for **1** and **20**: 84%). Similar effects are operative in the rearrangement of 1-*O*-acetylated precursor **14** ( $\text{R} = \text{Ac}$ ) and lead to the isolation of **16** in 79% yield. In these two cases, we were not able to isolate any products having the neo structure. However, when the 1-*O*-methylated precursor **15** (prepared as shown in Scheme 1) was subjected to similar reaction conditions, it produced 1-*O*-methylforbesione (**30**) (51% yield) together with 1-*O*-methylneoforbesione (**32**) (24% yield). Our own results with **15** ( $\text{R} = \text{Me}$ ) parallel the observations made by Nicolaou and Li<sup>9</sup> and provide further evidence of the role played by the C9 carbonyl group. In **15**, the withdrawing effect of the carbonyl is attenuated by the presence of the C1 methyl ether (vinylogous ester structure). This reduces the inclination of the O–C18 bond to rupture which leads to

intermediates **28** and **29** and thus, the formation of isomers **30** and **32**.

The outcome of the tandem Claisen/Diels–Alder/Claisen rearrangement of **8**, **14** and **15** and its dependency on the nature of the C1 functionality is in agreement with the structures that constitute the family of caged *Garcinia* natural products. These naturally occurring compounds share a common caged structure exemplified by the simplest among them, forbesione (**1**). The only exception to this trend is provided by the structure of 1-*O*-methylneobractatin (**7**), which contains the alternative, neo scaffold (Fig. 1). This compound was isolated from extracts of the dried and powdered leaves of *Garcinia bracteata* as a minor constituent along with 1-*O*-methylbractatin (**6**).<sup>6</sup> The presence of the seemingly innocuous 1-*O*-methyl group seems to explain the concomitant formation of both **7** and **6** from **15**. This suggests that the 1-*O*-methyl group was incorporated by Nature prior to the tandem Claisen/Diels–Alder/Claisen rearrangement.

In conclusion, we describe a concise synthesis of forbesione (**1**) and desoxymorellin (**3**). As such, this report constitutes the first total synthesis of a caged *Garcinia* natural product. Our approach rests upon a biomimetic tandem Claisen/Diels–Alder/Claisen reaction, the regioselectivity of which can be modulated by the functionalizations present in the xanthone precursor(s). Of particular interest is the finding that functionalization of the C1 hydroxyl group of the starting xanthone can affect the outcome of this reaction cascade *via* remote electronic effects. Conscientious exploration of such effects could lead to the synthesis of other *Garcinia* natural products as well as designed analogs.

## Experimental

### General notes

All reagents were commercially obtained (Aldrich, Acros) at highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive liquids and solutions were transferred *via* syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at approximately 20 mmHg. All non-aqueous reactions were carried out under anhydrous conditions, *i.e.* using flame-dried glassware, under an argon atmosphere and in dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF), diethyl ether (Et<sub>2</sub>O), dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), toluene (PhCH<sub>3</sub>) and benzene (PhH) were purified by passage through a bed of activated alumina. Pyridine, triethylamine (TEA) and boron trifluoride etherate were distilled from calcium hydride prior to use. Dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) were distilled from calcium hydride under reduced pressure (20 mmHg) and stored over 4Å molecular sieves until needed. Phloroglucinol (**10**) and 2,3,4-trihydroxybenzoic acid (**11**) were commercially available and used without any additional purification. Yields refer to chromatographically and spectroscopically (<sup>1</sup>H NMR, <sup>13</sup>C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) and visualized under UV light and/or developed by dipping in solutions of 10% ethanolic phosphomolybdic acid (PMA) or *p*-anisaldehyde and applying heat. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded

on a Nicolet 320 Avatar FT-IR spectrometer and values are reported in cm<sup>-1</sup> units. Optical rotations were recorded on a Jasco P-1010 polarimeter and values are reported as follows: [α]<sup>T</sup><sub>D</sub> (c: g/100 ml, solvent). High-resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions.

**1,3,5,6-Tetrahydroxanthone (9)**. To a round-bottomed flask containing phloroglucinol (**10**) (1.0 g, 7.93 mmol) and 2,3,4-trihydroxybenzoic acid (**11**) (1.35 g, 7.93 mmol) and ZnCl<sub>2</sub> (7.00 g, 51.5 mmol) was added POCl<sub>3</sub> (15.0 mL). The reaction vessel was then equipped with a reflux condenser and stirred under argon at 65 °C. The onset of a red color indicated the formation of the xanthone product. After 3 h, the reaction was shown to be complete by TLC (80% Et<sub>2</sub>O–hexane). It was then cooled to 25 °C and poured into a beaker of ice. The reaction mixture was then partitioned between water and EtOAc. The water layer was back-extracted several times and the combined EtOAc layers dried over MgSO<sub>4</sub>, filtered and concentrated. The crude material was column chromatographed (65–70% Et<sub>2</sub>O–hexane) to yield 1,3,5,6-tetrahydroxanthone (**9**) (0.94 g, 46%). **9**: yellow solid; *R*<sub>f</sub> = 0.25 (80% Et<sub>2</sub>O–hexane); IR (film) *v*<sub>max</sub> 3482, 1593, 1293, 1161, 786; <sup>1</sup>H NMR (400 MHz, d<sub>6</sub>-acetone) δ 13.10 (s, 1H), 9.14 (br s, 3H), 7.57 (d, *J* = 9.2 Hz, 1H), 6.93 (d, *J* = 9.2 Hz, 1H), 6.37 (d, *J* = 2.0 Hz, 1H), 6.18 (d, *J* = 2.0 Hz, 1H); <sup>13</sup>C NMR (100 MHz, d<sub>6</sub>-acetone) δ 180.68, 165.44, 164.41, 158.34, 151.77, 146.55, 132.92, 117.17, 114.54, 113.42, 102.87, 98.64, 94.53; HRMS calc. for C<sub>13</sub>H<sub>8</sub>O<sub>6</sub> (M + H<sup>+</sup>) 261.0394, found 261.0389.

**3,5,6-Tris(1,1-dimethylprop-2-ynyloxy)-1-hydroxyxanthone-9-one (13)**. To a round-bottomed flask containing xanthone **9** (95.9 mg, 0.36 mmol), KI (197.4 mg, 1.19 mmol), K<sub>2</sub>CO<sub>3</sub> (164.3 mg, 1.19 mmol) and CuI (7.0 mg, 36.9 μmol) was added dry acetone (5.00 mL) and 2-chloro-2-methylbut-3-yne (0.21 mL, 1.84 mmol). The reaction vessel was then equipped with a reflux condenser and the reaction was stirred under argon while heating at 45 °C. The reaction was monitored by TLC (30 and 80% Et<sub>2</sub>O–hexane) until complete. After 6 h, the reaction mixture was allowed to cool to 25 °C and acidified with AcOH. The reaction mixture was then partitioned between EtOAc and water. The water layer was back-extracted once and the combined EtOAc layers dried over MgSO<sub>4</sub>, filtered and concentrated. The crude material was column chromatographed (5% Et<sub>2</sub>O–hexane) to yield **13** (42.2 mg, 25%). **13**: yellow solid; *R*<sub>f</sub> = 0.4 (30% Et<sub>2</sub>O–hexane); IR (film) *v*<sub>max</sub> 3292, 2990, 2116, 1600, 1132; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 12.82 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 6.71 (d, *J* = 2.0 Hz, 1H), 2.71 (s, 1H), 2.68 (s, 1H), 2.34 (s, 1H), 1.82 (s, 6H), 1.79 (s, 6H), 1.77 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 180.3, 162.6, 162.5, 156.6, 156.1, 152.1, 135.2, 120.8, 115.8, 115.6, 103.8, 101.1, 97.5, 85.0, 84.7, 77.4, 75.2, 75.0, 74.0, 73.7, 73.6, 72.6, 30.5, 29.68, 29.65; HRMS calc. for C<sub>28</sub>H<sub>26</sub>O<sub>6</sub> (M + H<sup>+</sup>) 459.1802, found 459.1819.

**3,5,6-Tris(1,1-dimethylallyloxy)-1-hydroxyxanthone-9-one (8)**. To a solution of xanthone **13** (96.5 mg, 0.21 mmol) in EtOAc (4 mL) was added 10% Pd/BaSO<sub>4</sub> (9.7 mg) and quinoline (3.5 μL, 29.6 μmol). The reaction mixture was then degassed and stirred under an atmosphere of H<sub>2</sub>. To decrease the reaction time, an additional amount of 10% Pd/BaSO<sub>4</sub> (9.7 mg) was added to the reaction mixture every hour until the reaction was complete by TLC (20% Et<sub>2</sub>O–hexane). After five additions and a total of 6 h, the reaction mixture was filtered through a plug of silica gel and concentrated under reduced pressure. The crude material was column chromatographed (5% Et<sub>2</sub>O–hexane) to yield alkene **8** (73.4 mg, 75%). **8**: yellow oil; *R*<sub>f</sub> = 0.55 (30% Et<sub>2</sub>O–hexane); IR (film) *v*<sub>max</sub> 2982, 1597, 1436, 1285, 1128;

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 12.79 (s, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 9.2 Hz, 1H), 6.53 (d, *J* = 2.4 Hz, 1H), 6.42 (d, *J* = 2.0 Hz, 1H), 6.27–6.13 (m, 3H), 5.30–5.16 (m, 5H), 5.02 (dd, *J* = 10.8, 0.8 Hz, 1H), 1.581 (s, 6H), 1.577 (s, 6H), 1.56 (s, 6H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 180.3, 163.6, 162.5, 156.9, 156.6, 152.1, 143.5, 143.4, 143.2, 135.4, 120.0, 116.5, 115.6, 114.1, 114.0, 112.9, 103.3, 101.3, 97.4, 83.5, 82.2, 81.1, 27.4, 27.3, 27.0; HRMS calc. for C<sub>28</sub>H<sub>32</sub>O<sub>6</sub> (M + H<sup>+</sup>) 465.2272, found 465.2278.

#### 1-Acetoxy-3,5,6-tris(1,1-dimethylallyloxy)xanthen-9-one (14).

To a solution of **8** (259.5 mg, 0.56 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10.0 mL) at 0 °C was added pyridine (1.13 mL, 14.0 mmol), DMAP (6.8 mg, 55.9 μmol) and acetic anhydride (1.32 mL, 14.0 mmol). After the addition, the reaction mixture was warmed to 35 °C. After 24 h, the reaction was judged to be complete by TLC (30% Et<sub>2</sub>O–hexane). The reaction mixture was then partitioned between Et<sub>2</sub>O and saturated NaHCO<sub>3</sub> (aq). The Et<sub>2</sub>O layer was then washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The crude material was purified by column chromatography (15% Et<sub>2</sub>O–hexane) to yield acetate **14** (239.4 mg, 85%). **14**: colorless oil; *R*<sub>f</sub> = 0.6 (70% Et<sub>2</sub>O–hexane); IR (film) *v*<sub>max</sub> 2981, 1775, 1655, 1598, 1126; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.78 (d, *J* = 9.2 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.95 (d, *J* = 2.8 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 6.28–6.13 (m, 3H), 5.32–5.15 (m, 5H), 5.02 (dd, *J* = 10.8, 1.2 Hz, 1H), 2.46 (s, 3H), 1.56 (s, 6H), 1.55 (s, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 174.5, 169.5, 161.2, 157.7, 156.1, 151.4, 150.5, 143.41, 143.36, 143.2, 135.4, 120.6, 117.5, 116.9, 114.3, 113.9, 112.8, 110.6, 108.6, 104.0, 83.4, 82.1, 81.4, 27.3, 27.2, 27.0, 21.4; HRMS calc. for C<sub>30</sub>H<sub>34</sub>O<sub>7</sub> (M + H<sup>+</sup>) 507.2377, found 507.2391.

#### 3,5,6-Tris(1,1-dimethylallyloxy)-1-methoxyxanthen-9-one

**(15)**. To a solution of xanthone **8** (45.0 mg, 0.10 mmol) in DMF (1.00 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (157.8 mg, 0.48 mmol) and MeI (30.2 μL, 0.48 mmol). TLC (80% Et<sub>2</sub>O–hexane) of the reaction mixture 15 min after the addition indicated that the reaction was complete. The reaction mixture was then acidified with AcOH and partitioned between Et<sub>2</sub>O and water. The Et<sub>2</sub>O layer was washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated. The crude material was then column chromatographed (65% Et<sub>2</sub>O–hexane) to give methyl ether **15** (28.3 mg, 61%). **15**: colorless oil; *R*<sub>f</sub> = 0.2 (70% Et<sub>2</sub>O–hexane); IR (film) *v*<sub>max</sub> 2980, 1657, 1596, 1419, 1118; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.84 (d, *J* = 8.4 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 6.38 (d, *J* = 2.0 Hz, 1H), 6.29–6.15 (m, 3H), 5.33–5.15 (m, 5H), 5.01 (dd, *J* = 10.4, 0.8 Hz, 1H), 3.93 (s, 3H), 1.60 (s, 6H), 1.55 (s, 12H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 175.8, 175.2, 161.7, 161.1, 158.4, 155.5, 150.9, 143.7, 143.4, 143.3, 135.0, 120.8, 118.2, 116.7, 113.8, 112.6, 106.5, 98.3, 98.2, 83.2, 81.9, 80.9, 56.1, 27.2, 27.1, 26.8; HRMS calc. for C<sub>29</sub>H<sub>34</sub>O<sub>6</sub> (M + H<sup>+</sup>) 479.2428, found 479.2431.

#### 1-O-Acetylforbesione (16).

A solution of acetate **14** (204.0 mg, 0.40 mmol) in DMF (4.00 mL) was heated at 120 °C and the reaction was continuously monitored by TLC (80% Et<sub>2</sub>O–hexane). While heating, the reaction mixture turned yellow providing a qualitative indication of the reaction's progress. After 1 h, the reaction mixture was diluted with toluene and concentrated several times at 60 °C under reduced pressure to remove DMF by azeotropic distillation. The crude material was purified by column chromatography (10–40% Et<sub>2</sub>O–hexane) to yield compound **16** (150.2 mg, 79%). **16**: off-white powder; *R*<sub>f</sub> = 0.25 (70% Et<sub>2</sub>O–hexane); IR (film) *v*<sub>max</sub> 2925, 1737, 1612, 1203, 733; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.34 (d, *J* = 6.8 Hz, 1H), 6.51 (br s, 1H), 6.25 (s, 1H), 5.29–5.26 (m, 1H), 4.48–4.44 (m, 1H), 3.56–3.44 (m, 3H), 2.62–2.57 (m, 1H), 2.55 (d, *J* = 9.6 Hz, 1H), 2.48 (d, *J* = 9.2 Hz), 2.39 (s, 3H), 2.31 (dd, *J* = 13.2, 4.4 Hz, 1H), 1.83 (s, 3H), 1.78 (s, 3H), 1.69 (s, 3H), 1.40 (s, 3H), 1.32 (dd, *J* = 13.2, 10.0 Hz, 1H), 1.29 (s, 3H), 1.07 (s, 3H); <sup>13</sup>C NMR

(100 MHz, CDCl<sub>3</sub>) δ 203.5, 174.2, 169.9, 159.7, 150.0, 135.2, 134.8, 134.4, 133.3, 120.6, 117.6, 112.9, 106.0, 105.9, 90.8, 84.5, 83.1, 49.1, 47.0, 30.2, 29.2, 28.9, 25.9, 25.8, 25.5, 22.7, 21.3, 18.2, 16.9; HRMS calc. for C<sub>30</sub>H<sub>34</sub>O<sub>7</sub> (M + H<sup>+</sup>) 507.2377, found 507.2388.

**Forbesione (1)**. To a solution of **16** (71.5 mg, 0.14 mmol) in MeOH (6.0 mL) at room temperature was added 0.25 mL of 0.5 M K<sub>2</sub>CO<sub>3</sub> (aq) turning the reaction mixture yellow. This addition was repeated every hour for 6 h, until a total of 1.5 mL of 0.5 M K<sub>2</sub>CO<sub>3</sub> (aq) had been added. The reaction was monitored by TLC (70% Et<sub>2</sub>O–hexane) and found to be completed after 6 h. The mixture was then acidified with AcOH, diluted with EtOAc and washed twice with water and once with brine. The EtOAc layer was dried over MgSO<sub>4</sub>, filtered and concentrated. The crude material was then purified by column chromatography (10–40% Et<sub>2</sub>O–hexane) to yield forbesione (**1**) (59.7 mg, 91%). Forbesione (**1**): yellow solid; *R*<sub>f</sub> = 0.19 (50% Et<sub>2</sub>O–hexane); IR (film) *v*<sub>max</sub> 3197, 2914, 1732, 1593, 1174; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 12.59 (s, 1H), 7.46 (d, *J* = 6.8 Hz, 1H), 6.20 (br s, 1H), 6.04 (s, 1H), 5.26–5.23 (m, 1H), 4.45–4.41 (m, 1H), 3.51 (dd, *J* = 6.8, 4.4 Hz, 1H), 3.48–3.37 (m, 2H), 2.59–2.56 (m, 2H), 2.50 (d, *J* = 9.2 Hz, 1H), 2.35 (dd, *J* = 13.6, 4.8 Hz, 1H), 1.82 (s, 3H), 1.77 (d, *J* = 1.2 Hz, 3H), 1.70 (s, 3H), 1.39 (s, 3H), 1.36 (dd, *J* = 13.6, 10.0 Hz, 1H), 1.30 (s, 3H), 1.06 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 203.1, 179.4, 163.9, 163.0, 157.9, 135.4, 134.9, 133.9, 133.3, 121.1, 117.7, 105.6, 101.0, 97.0, 90.5, 84.5, 83.2, 49.2, 47.0, 30.3, 29.2, 29.0, 25.9, 25.7, 25.6, 22.3, 18.2, 16.9; HRMS calc. for C<sub>28</sub>H<sub>32</sub>O<sub>6</sub> (M + H<sup>+</sup>) 465.2272, found 465.2275.

#### 3-O-(1,1-Dimethylpropargyl)forbesione (17).

To a round-bottomed flask containing forbesione (**1**) (71.6 mg, 0.15 mmol), KI (38.4 mg, 0.23 mmol), K<sub>2</sub>CO<sub>3</sub> (63.9 mg, 0.46 mmol) and CuI (2.9 mg, 15.4 μmol) was added dry acetone (5.0 mL) and 2-chloro-2-methylbut-3-yne (0.35 mL, 3.08 mmol). The reaction vessel was then equipped with a reflux condenser and the mixture was stirred under argon while heating at 55 °C. The reaction was monitored by TLC (70% Et<sub>2</sub>O–hexane) until complete. After 4 h, the reaction mixture was allowed to cool to 25 °C and acidified with AcOH. The reaction mixture was then partitioned between Et<sub>2</sub>O and water. The water layer was back-extracted once and the combined Et<sub>2</sub>O layers were dried over MgSO<sub>4</sub>, filtered and concentrated. The crude material was column chromatographed (10–80% CH<sub>2</sub>Cl<sub>2</sub>–hexane) to yield alkyne **17** (54.8 mg, 67%). **17**: yellow solid; *R*<sub>f</sub> = 0.6 (70% Et<sub>2</sub>O–hexane); IR (film) *v*<sub>max</sub> 3271, 2926, 1737, 1639, 1125; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 12.59 (s, 1H), 7.45 (d, *J* = 6.8 Hz, 1H), 6.89 (s, 1H), 5.22–5.18 (m, 1H), 4.42–4.38 (m, 1H), 3.50 (dd, *J* = 6.4, 4.8 Hz, 1H), 3.37–3.25 (m, 2H), 2.70 (s, 1H), 2.58 (d, *J* = 7.6 Hz, 2H), 2.49 (d, *J* = 9.6 Hz, 1H), 2.35 (dd, *J* = 13.6, 4.4 Hz, 1H), 1.742 (s, 3H), 1.736 (s, 6H), 1.71 (s, 3H), 1.68 (s, 3H), 1.38 (s, 3H), 1.34 (dd, *J* = 8.4, 4.4 Hz, 1H), 1.29 (s, 3H), 0.99 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 203.2, 179.6, 162.7, 162.1, 157.4, 134.9, 133.9, 133.6, 131.4, 122.3, 117.8, 110.6, 101.1, 98.1, 90.3, 84.7, 84.6, 83.2, 75.2, 72.7, 49.2, 47.0, 30.2, 29.6, 29.2, 28.9, 25.8, 25.7, 25.6, 22.2, 18.4, 16.7; HRMS calc. for C<sub>33</sub>H<sub>38</sub>O<sub>6</sub> (M + H<sup>+</sup>) 531.2741, found 531.2748.

**Desoxymorellin (3)**. A round-bottomed flask containing **17** (25.5 mg, 48.1 μmol) in DMF (1.00 mL) was heated at 125 °C and the reaction continuously monitored by TLC (70% Et<sub>2</sub>O–hexane). After 4 h, the reaction mixture was diluted with toluene and concentrated several times at 60 °C under reduced pressure to remove DMF by azeotropic distillation. The crude material was then purified by column chromatography (10–80% CH<sub>2</sub>Cl<sub>2</sub>–hexane) to yield desoxymorellin (**3**) (23.1 mg, 91%). Desoxymorellin (**3**): yellow solid; *R*<sub>f</sub> = 0.64 (70% Et<sub>2</sub>O–hexane); IR (film) *v*<sub>max</sub> 2925, 1737, 1594, 1438, 1141; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 12.87 (s, 1H), 7.44 (d, *J* = 6.8 Hz, 1H), 6.64 (d,

$J = 10.0$  Hz, 1H), 5.53 (d,  $J = 9.6$  Hz, 1H), 5.24–5.21 (m, 1H), 4.45–4.42 (m, 1H), 3.50 (dd,  $J = 6.4, 4.8$  Hz, 1H), 3.38–3.26 (m, 2H), 2.58 (d,  $J = 8.0$  Hz, 2H), 2.50 (d,  $J = 9.2$  Hz, 1H), 2.35 (dd,  $J = 13.2, 4.0$  Hz, 1H), 1.78 (s, 3H), 1.72 (s, 3H), 1.69 (s, 3H), 1.46 (s, 6H), 1.38 (s, 3H), 1.36 (dd,  $J = 13.2, 9.6$  Hz, 1H), 1.30 (s, 3H), 1.04 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  203.2, 179.3, 160.3, 157.6, 157.2, 134.8, 133.58, 133.55, 131.5, 126.0, 122.0, 117.7, 115.5, 108.2, 102.9, 100.5, 90.4, 84.6, 83.2, 78.4, 49.2, 47.0, 30.2, 29.2, 28.9, 28.4, 28.3, 25.9, 25.7, 25.6, 21.8, 18.3, 16.8; HRMS calc. for  $\text{C}_{33}\text{H}_{38}\text{O}_6$  ( $\text{M} + \text{H}^+$ ) 531.2741, found 531.2741.

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