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

Eric J. Tisdale, Irina Slobodov and Emmanuel A. Theodorakis *
Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093-0358, USA. E-mail: etheodor@chem.ucsd.edu; Fax: +1-858-822-0386; Tel: +1-858-822-0456

Received 25th September 2003, Accepted 23rd October 2003
First published as an Advance Article on the web 11th November 2003

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. Isolation of the bioactive constituents of gamboge has yielded a family of caged xanthonoids, representative members of which include forbesione (1), hanburin (2), desoxymorellin (3), morellin (4), and the bractatins 5, 6 and 7 (Fig. 1).

Fig. 1 Selected natural products from Garcinia plants.

The caged motif of these natural products, purportedly responsible for their biological activities, has been proposed by Quillinan and Scheinmann to arise in Nature through a tandem Claisen/Diels–Alder reaction. This biomimetic scenario has been recently explored by Nicolaou and Li during their synthesis of 1-O-methylforbesione. Despite this and related synthetic advances, 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. 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.
K₂CO₃, under Cu 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. Drawing on previous experience with related structures, we heated 8 in 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 DMF gave rise to 1-O-acetylforsbesione (16) exclusively and, after deprotection, afforded forbesione (1) in 71% combined yield. 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 Li¹⁶ heating 1-O-methylated precursor 15 in DMF at 120 °C afforded a mixture of adducts, the major compounds of which were identified as 1-O-methylforbesione (30) and 1-O-methyleneoforesione (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, forming intermediates 18 and 19, respectively (Scheme 2).¹⁶ 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).¹⁷ In a similar manner, intermediate 19 could lead to an isomeric caged structure, the so-called neo skeleton, 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.¹⁸ 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 (R = 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-methyleneoforesione (32) (24% yield). Our own results with 15 (R = Me) parallel the observations made by Nicolaou and Li¹⁶ 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 (vinyllogous ester structure). This reduces the inclination of the O-C18 bond to rupture which leads to

---

**Scheme 1** Reagents and conditions: (a) 1.0 equiv. of 10, 1.0 equiv. of 11, 6.5 equiv. of ZnCl₂, POCl₃, 65 °C, 3 h, 46%; (b) 3.3 equiv. of KI, 3.3 equiv. of K₂CO₃, 5.1 equiv. of 12, 10 mol% CuI, (CH₃)₃CO, 45 °C, 6 h, 25%; (c) 10% Pd/BaSO₄, quinoline, EtOAc, 25 °C, 6 h, 75%; (d) 25 equiv. of pyridine, 25 equiv. of Ac₂O, 10 mol% DMAP, CH₂Cl₂, 35 °C, 24 h, 85%; (e) DMF, 120 °C, 1 h, 49% of 1 and 35% of 20; (f) 5.0 equiv. of Cs₂CO₃, 5.0 equiv. of Mel, DMF, 25 °C, 15 min, 61% (g) DMF, 120 °C, 1 h, 79%; (h) 0.5 M K₂CO₃ (aq), MeOH, 25 °C, 6 h, 91%; (i) 1.5 equiv. of KI, 3.0 equiv. of K₂CO₃, 20 equiv. of 12, 10 mol% CuI, (CH₃)₃CO, 55 °C, 6 h, 67%; (g) DMF, 120 °C, 4 h, 91%.

---

**Scheme 2** Derivatization of the C1-hydroxyl group and its effect on the Claisen/Diels–Alder reaction cascade.
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 Cl 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, non-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). 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 (Et2O), dichloromethane (CH2Cl2), toluene (PhCH3) 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. Di-methyl 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 (1H NMR, 13C 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 heating apply. 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 205 Avatar FT-IR spectrometer and values are reported in cm−1 units. Optical rotations were recorded on a Jasco P-1010 polarimeter and values are reported as follows: [α]D (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.

3.5.6-Tetrahydroxyxanthone (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 ZnCl2 (7.00 g, 51.5 mmol) was added POCI3 (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% EtOAc–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 MgSO4, filtered and concentrated. The crude material was column chromatographed (65–70% EtOAc–hexane) to yield 1,3,5,6-tetrahydroxyxanthone (9) (0.04 g, 46%).

3.5.6-Tris (1,1-dimethylprop-2-ynyl)-1-hydroxyxanthan-9-one (13). To a round-bottomed flask containing xanthone 9 (95.9 mg, 0.36 mmol), KI (197.4 mg, 1.19 mmol), K2CO3 (164.3 mg, 1.19 mmol) and Cul (7.0 mg, 36.9 mmol) was added dry acetone (5.00 mL) and 2-chloro-2-methylbut-3-yne (0.21 µL, 29.6 µmol). The reaction mixture was then degassed and stirred under an atmosphere of H2 (1 atm) 459.1802, found 459.1819.

3.5.6-Tris (1,1-dimethylallyl)-1-hydroxyxanthan-9-one (8). To a solution of xanthone 13 (96.5 mg, 0.21 mmol) in EtOAc (4 mL) was added 10% Pd/BaSO4 (9.7 mg) and quinoline (3.5 µL, 29.6 µmol). The reaction mixture was then degassed and stirred under an atmosphere of H2. To decrease the reaction time, an additional amount of 10% Pd/BaSO4 (9.7 mg) was added to the reaction mixture every hour until the reaction was complete by TLC (20% EtOAc–hexane). After five additional reactions 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% EtOAc–hexane) to yield alkene 8 (73.4 mg, 75%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.79 (s, 1H), 7.50 (d, $J = 8.8$ Hz), 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);

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 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, 7.27, 27.5, 27.0; HRMS calc. for C$_{20}$H$_{17}$O$_{5}$ (M + H$^+$) 546.227, found 546.227.

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$_2$Cl$_2$ (10.0 mL) at 0°C was added pyridine (1.13 mL, 14.0 mmol), DMAP (6.8 mg, 0.05 mmol) 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$_2$O–hexane). The reaction mixture was then partitioned between Et$_2$O and saturated NaHCO$_3$ (aq). The Et$_2$O layer was then washed with brine, dried over MgSO$_4$ filtered and concentrated. The crude material was then purified by column chromatography (15% Et$_2$O–hexane) to yield acetoxy 14 (239.4 mg, 85%).

14. IR (film) max$_{325}$ 1751, 1657, 1596, 1539, 1516; HRMS calc. for C$_{21}$H$_{23}$O$_5$N$_2$ (M + H$^+$) 442.1556, found 442.1546.

1-Acetoxy-3,5,6-tris(1,1-dimethylallyloxy)xanthen-9-one (14). For desoxymorellin (3). A round-bottomed flask containing forbesione (I) (71.6 mg, 0.15 mmol), KI (38.4 mg, 0.23 mmol), K$_2$CO$_3$ (63.9 mg, 0.46 mmol) and C$_6$H$_6$ (2.9 mg, 15.4 mg) was added dry acetone (5.0 mL) and 2-chloro-2-methylbutyl-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$_2$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$_2$O and water. The water layer was back-extracted one time, and the combined Et$_2$O layers were dried over MgSO$_4$ filtered and concentrated. The crude material was column chromatographed (10–80% CHCl$_3$–hexane) to yield alkylene 17 (54.8 mg, 67%); 17: yellow solid; $R_f =$ 0.6 (70% Et$_2$O–hexane); IR (film) max$_{325}$ 3271, 2926, 1737, 1639, 1125; $^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.59 (s, 1H), 7.46 (d, $J = 6.8$ Hz, 1H), 6.20 (bs, 1H), 6.04 (s, 1H), 5.26–5.23 (m, 1H), 5.11 (d, $J = 6.8$ Hz, 1H), 4.34–4.37 (m, 2H), 2.59–2.56 (m, 2H), 2.50 (d, $J = 9.2$ Hz, 1H), 2.35 (dd, $J = 13.6$, 6.8 Hz, 1H), 1.82 (s, 3H), 1.77 (d, $J = 1.3$, 6.8 Hz, 1H), 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); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 203.1, 179.4, 163.9, 163.0, 157.9, 135.4, 134.9, 133.9, 133.1, 121.1, 117.7, 105.6, 101.0, 97.0, 90.5, 85.4, 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$_{23}$H$_{21}$O$_5$ (M + H$^+$) 546.227, found 446.2275.

3-O-(1,1-Dimethylpropargyl)forbesione (17). To a round-bottomed flask containing forbesione (I) (71.6 mg, 0.15 mmol), KI (38.4 mg, 0.23 mmol), K$_2$CO$_3$ (63.9 mg, 0.46 mmol) and C$_6$H$_6$ (2.9 mg, 15.4 mg) was added dry acetone (5.0 mL) and 2-chloro-2-methylbutyl-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$_2$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$_2$O and water. The water layer was back-extracted one time, and the combined Et$_2$O layers were dried over MgSO$_4$ filtered and concentrated. The crude material was column chromatographed (10–80% CHCl$_3$–hexane) to yield alkylene 17 (54.8 mg, 67%); 17: yellow solid; $R_f =$ 0.6 (70% Et$_2$O–hexane); IR (film) max$_{325}$ 3271, 2926, 1737, 1639, 1125; $^{1}$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.59 (s, 1H), 7.45 (d, $J = 6.8$ Hz, 1H), 6.20 (bs, 1H), 6.04 (s, 1H), 5.26–5.23 (m, 1H), 5.11 (d, $J = 6.8$ Hz, 1H), 4.34–4.37 (m, 2H), 2.59–2.56 (m, 2H), 2.50 (d, $J = 9.2$ Hz, 1H), 2.35 (dd, $J = 13.6$, 6.8 Hz, 1H), 1.82 (s, 3H), 1.77 (d, $J = 1.3$, 6.8 Hz, 1H), 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); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 203.1, 179.4, 163.9, 163.0, 157.9, 135.4, 134.9, 133.9, 133.1, 121.1, 117.7, 105.6, 101.0, 97.0, 90.5, 85.4, 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$_{23}$H$_{21}$O$_5$ (M + H$^+$) 546.227, found 446.2275.
\[ J = 10.0 \text{ Hz}, 1H \), 5.53 (d, \( J = 9.6 \text{ Hz}, 1H \)), 5.24–5.21 (m, 1H), 4.45–4.42 (m, 1H), 3.50 (dd, \( J = 6.4, 4.8 \text{ Hz}, 1H \)), 3.38–3.26 (m, 2H), 2.58 (d, \( J = 8.0 \text{ Hz}, 1H \)), 2.50 (d, \( J = 9.2 \text{ Hz}, 1H \)), 2.35 (dd, \( J = 13.2, 4.0 \text{ Hz}, 1H \)), 1.78 (s, 3H), 1.72 (s, 1H), 1.69 (s, 3H), 1.46 (s, 6H), 1.38 (s, 3H), 1.36 (dd, \( J = 13.2, 9.6 \text{ Hz}, 1H \)), 1.30 (s, 3H), 1.04 (s, 3H); \( ^{13}C \) NMR (100 MHz, CDCl\(_3\)) \( \delta = 203.2, 179.3, 160.3, 121.8, 118.3, 116.8; \) HRMS calc. for C\(_{29}\)H\(_{38}\)O\(_2\) (M + H\(^+\)) 531.2741, found 531.2741.

Acknowledgements

Financial support from the NIH (CA086079) is gratefully acknowledged. We also thank the San Diego Chapter of the ARCS Foundation for their support through graduate student fellowships to E. J. T.

References

13 For a recent account on this topic, see: T. R. Pettus and C. Hoarau, Synlett., 2003, 127–137.
17 The trisubstituted alkene cannot participate as a dienophile during the Diels–Alder reaction due to its decreased reactivity.