JOURNAL OF NATURAL PRODUCTS

Article

Cite This: J. Nat. Prod. 2017, 80, 2751-2755

pubs.acs.org/jnp

Stereocontrolled Semisyntheses of Elliptone and 12aβ-Hydroxyelliptone

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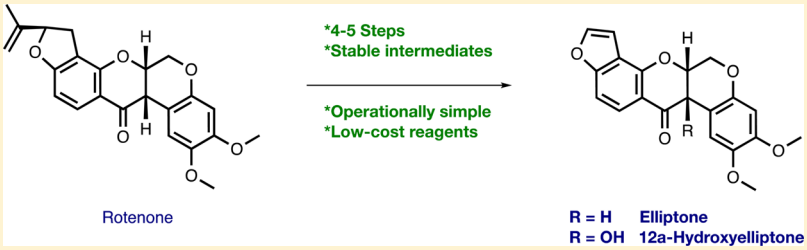
Supporting Information



ABSTRACT: Operationally simple, stereocontrolled semisyntheses of the anticancer rotenoids elliptone and 12aβ-hydroxyelliptone, isolated from *Derris elliptica* and *Derris trifoliata*, respectively, are described. Inspired by the work of Singhal, elliptone was prepared from rotenone via a dihydroxylation-oxidative cleavage, chemoselective Baeyer−Villiger oxidation, and acid-catalyzed elimination sequence. Elaboration of elliptone to 12aβ-hydroxyelliptone was achieved via a diastereoselective chromium-mediated Étard-like hydroxylation. The semisynthesis of elliptone constitutes an improvement over previous methods in terms of safety, scalability, and yield, while the first synthesis of 12aβ-hydroxyelliptone is also described.

Natural rotenoids form the bioactive constituents of many traditional plant preparations used for crop protection and fishing in tropical parts of the world.[1,2] As powerful inhibitors of mitochondrial respiration, there has been a steady increase in the number of rotenoids being investigated as potential anticancer agents.[3,4] The most abundant and well-characterized members of the rotenoid family, rotenone (**1**), rotenolone (**2**), deguelin (**3**), and tephrosin (**4**) (Figure 1), have been shown to be nanomolar-active inhibitors of mitochondrial Complex I, and we suggest this finding may explain their well-documented anticancer activities.[3,4]

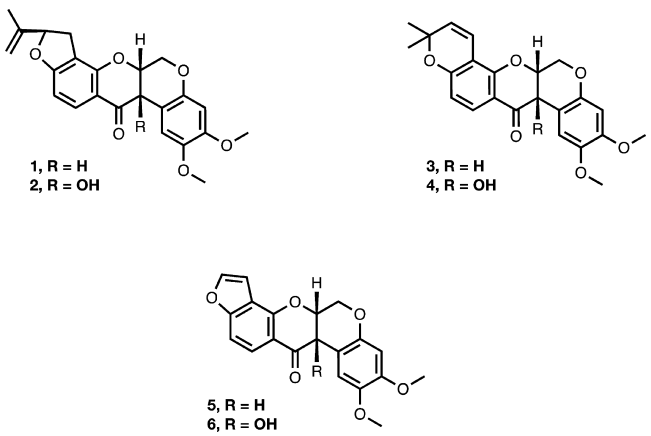


Figure 1. Structures of the rotenoids rotenone (**1**), rotenolone (**2**), deguelin (**3**), tephrosin (**4**), elliptone (**5**), and 12aβ-hydroxyelliptone (**6**).

First isolated from *Derris elliptica* by Harper in 1939,[5] elliptone (**5**) (Figure 1) represents one of the many natural rotenoids whose biological activity remains, in our view, underexplored.[4a,6] Isolated from *Derris trifoliata* by Ito in 2004,[6] 12aβ-hydroxyelliptone (**6**) (Figure 1) was found, alongside elliptone (**5**), to possess cancer chemopreventive properties comparable to those of β-carotene; however, despite these promising results, no further biological studies have been reported to date.[6]

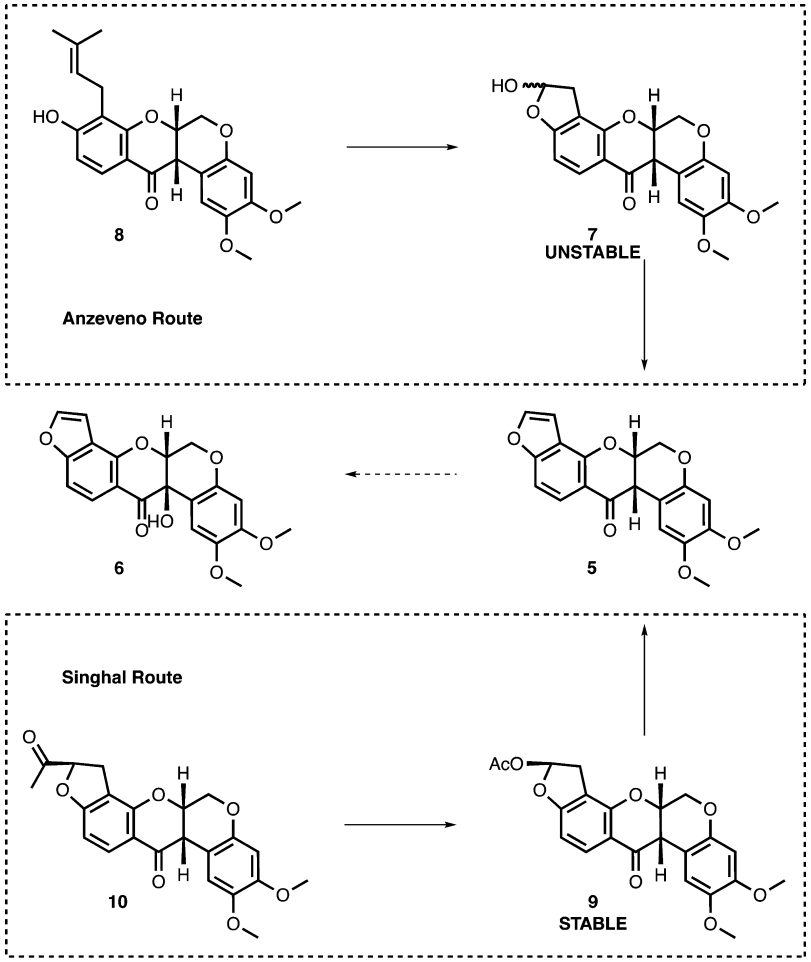
As part of an extensive investigation into the chemistry and biochemistry of the natural rotenoids underway in our laboratory, we sought efficient, operationally simple semisynthetic routes to elliptone (**5**) and 12aβ-hydroxyelliptone (**6**) from inexpensive rotenone (**1**). Our preference for semisynthesis over total synthesis originated from a desire to obtain enantiomerically pure rotenoids in the shortest and most scalable of sequences possible.

Previous efforts toward elliptone (**5**) have been restricted to a lengthy total synthesis of the racemic form, reported by Fukami in 1965,[7] and two semisyntheses of the natural enantiomer from derivatives of rotenone (**1**), described by Anzeveno and Singhal in 1979 and 1982, respectively.[8,9] In contrast, no synthesis of 12a-hydroxyelliptone (**6**) has been reported to date.

Received: June 19, 2017
Published: October 17, 2017

DOI: 10.1021/acs.jnatprod.7b00527
J. Nat. Prod. 2017, 80, 2751−2755

Scheme 1. Comparison of the Semisyntheses of Elliptone (6) Reported by Anzeveno[8a] and Singhal[9a] and Our Proposed Hydroxylation of Elliptone (5) to 12aβ-Hydroxyelliptone (6)



RESULTS AND DISCUSSION

In evaluating the two reported semisyntheses of elliptone (**5**) it was noted that the Anzeveno route suffered from a low overall yield,[8a] involved the use of many hazardous reagents and solvents, and proceeded via an intermediate lactol, **7** (Scheme 1), accessed via an oxidative cleavage of rot-2′-enonic acid (**8**),[8b] that proved particularly susceptible to degradation in our hands. Additionally, the preparation of lactol **7** required a high (7.5 mol %) loading of highly toxic and expensive osmium tetroxide catalyst.[8a] The Singhal route seemed to be more appealing, proceeding via the stable lactol acetate **9** (Scheme 1) accessed by chemoselective Baeyer–Villiger oxidation of the known norketone **10**.[9] However, this short publication lacked experimental conditions, procedures, and characterization data, and we were unable to successfully recreate the key Baeyer–Villiger chemistry using the reported *meta*-chloroperoxybenzoic acid (see also below).[9a]

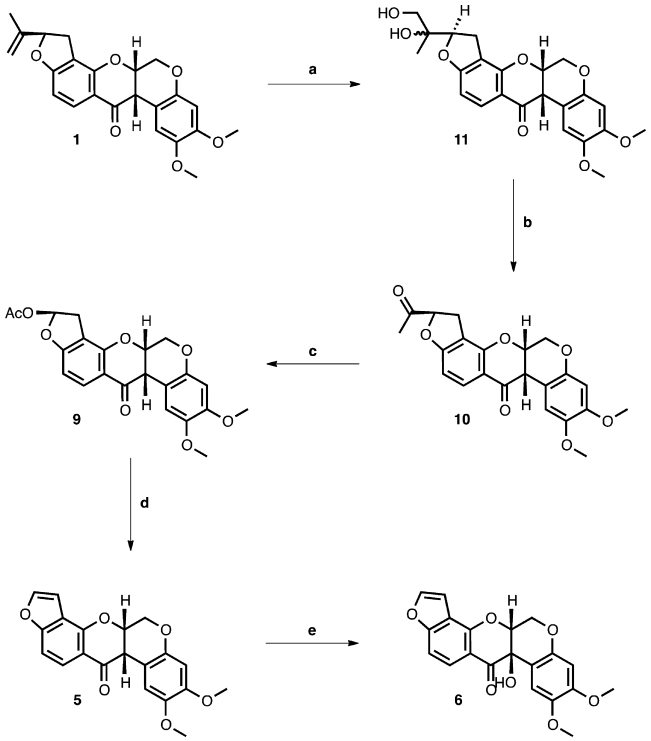
Inspired by the chemistry of Singhal,[9a] an alternative preparation of the lactol acetate (**9**) from rotenone (**1**) was sought, anticipating that formal elimination of the acetoxy group under acidic conditions would indeed deliver elliptone (**5**) in a concise manner. Building upon the success of the previous semisynthesis of tephrosin (**4**),[10] we reasoned that chromium-mediated Étard-like hydroxylation of elliptone (**5**) would provide 12aβ-hydroxyelliptone (**6**) as a single diastereoisomer (Scheme 1).

Dihydroxylation of rotenone (**1**) with 0.4 mol % OsO_4 in the presence of excess citric acid[11] provided the diastereoisomeric *vic*-diols (**11**) of amorphigenol in an excellent yield of 92%. Next, the oxidative cleavage of the *vic*-diols (**11**) with aqueous periodic acid provided the corresponding rotenone 6′-norketone (**10**) in an overall yield of 72% over two steps (Scheme 2). Importantly, both the dihydroxylation and oxidative cleavage reactions could be carried out on a multigram scale without any notable decrease in yield.

The subsequent chemoselective Baeyer–Villiger reaction of the norketone **10** was more challenging. The use of traditional oxidants such as *meta*-chloroperoxybenzoic acid,[9a] peracetic acid, and trifluoroperacetic acid proved unproductive with reactions suffering variously from incomplete conversion of the norketone **10** or the formation of complex mixtures of unidentifiable polar byproducts. More encouraging results were obtained using Oxone,[12] the potassium peroxymonosulfate-containing triple salt, which afforded the mono-oxygenated lactol acetate (**9**) as the only identifiable product. Variations in the amount of Oxone employed, the reaction temperature, and the inclusion of either weakly acidic or basic additives were next to be investigated with a view to improving both the yield and rate of the reaction. Ultimately, however, lactol acetate (**9**) could only be isolated in modest yields of 35–38% upon treatment of the norketone **10** with 8.0 equiv of Oxone under neutral conditions. Complete consumption of the substrate was

DOI: 10.1021/acs.jnatprod.7b00527
J. Nat. Prod. 2017, 80, 2751–2755

Scheme 2[a]



[a]Reagents and conditions: (a) OsO_4 (0.4 mol %), NMO, citric acid, acetone−H_2O (4:1), rt, 22 h, 92%; (b) H_5IO_6, H_2O, rt, 4.5 h, 78%; (c) Oxone, MeCN−H_2O (10:1), rt, 28 h, 35%; (d) PTSA, toluene, 80 °C, 1.5 h, 76%; (e) $K_2Cr_2O_7$, HOAc: H_2O (2:1), 60 °C, 0.5 h then rt, 18 h, 63%.

observed after 28 h by LCMS and analysis by TLC complicated by the highly similar retention factors of starting material and product. Although low yielding the reaction could readily be performed on larger scales, providing sufficient material for the elimination step.

Treatment of lactol acetate (**9**) with *para*-toluenesulfonic acid in toluene at 80 °C proceeded smoothly to afford elliptone (**5**) in 76% yield.[9a] Pleasingly, the Étard-like hydroxylation of elliptone (**5**) with $K_2Cr_2O_7$ in aqueous HOAc afforded 12a*β*-hydroxyelliptone (**6**) in 63% yield as a single diastereoisomer. The stereochemical outcome of this reaction may be attributed to the pericyclic ene and [2,3] sigmatropic rearrangement steps of the Étard reaction,[10] in conjunction with the "butterfly wing" architecture of the substrate.

In conclusion, we have developed operationally simple four- and five-step semisyntheses of elliptone (**5**) and 12a*β*-hydroxyelliptone (**6**) from rotenone (**1**). Also described is the preparation of elliptone (**5**), improving upon the methods of Anzeveno[8] and Singhal[9] in terms of scalability and yield. Dihydroxylation of rotenone (**1**) followed by oxidative cleavage provided norketone **10**, which was susceptible to chemoselective Baeyer−Villiger oxidation with excess Oxone to afford lactol acetate (**9**).[9] Acid-catalyzed elimination according to Singhal's procedure afforded elliptone (**5**).[9] A highly diastereoselective Étard-like hydroxylation of elliptone (**5**) gave 12a*β*-hydroxyelliptone (**6**), the mechanistic details of which we have discussed previously.[10] With the desired natural products in hand biological investigations are ongoing, and the results will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points for crystalline compounds were obtained using a Büchi melting point B-545 melting point apparatus. Optical rotations were recorded on an Anton-Paar MCP 100 polarimeter. $[\alpha]_D$ values are reported in 10^{-1} deg cm^2 g^{-1} at 598 nm; concentration (c) is given in g (100 mL)$^{-1}$. Infrared spectra were recorded on a PerkinElmer Spectrum One spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 Cryo Ultrashield (500 MHz) spectrometer. Low-resolution mass spectra (LRMS) were recorded using an LCMS system (Agilent series LC with an ESCi Multi-Mode Ionization Waters ZQ spectrometer using MassLynx 4.1 software). High-resolution mass spectra (HRMS) were recorded using a Micromass Q-TOF. Thin-layer chromatography retention factors (R_f) are quoted to the nearest 0.05. Flash column chromatography was carried out according to the method of Still.[14] Yields refer to chromatographically and spectroscopically pure compounds, for which full analytical data are given. (6a*S*,12a*S*,5′*R*)-Rotenone (**1**) (95% purity) was purchased from Molekula Fine Chemicals as an off-white amorphous solid and was crystallized from EtOH (×3) to give colorless plates [mp 162−163 °C (lit. 163 °C)].[13] All other solvents and reagents were used as obtained from commercial sources.

The (trivial) nomenclature and numbering systems used for the assignments in this article are well established in this natural product family.[1c,d,13] See also Figure 2.

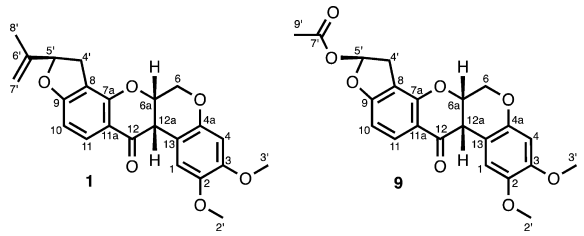


Figure 2. Representative atom-numbering schemes for rotenone (**1**) and lactol acetate (**9**), from which all products in this study derive.

(6a*S*,12a*S*,5′*R*,6′*R*)- and (6a*S*,12a*S*,5′*R*,6′*S*)-Amorphigenol (11). A solution of OsO_4 (420 μL, 0.041 mmol, 2.5 wt % in *t*-BuOH) was added in one portion to a solution of (6a*S*,12a*S*,5′*R*)-rotenone (**1**) (4.00 g, 10.2 mmol), *N*-methylmorpholine-*N*-oxide (1.43 g, 12.2 mmol), and citric acid (7.80 g, 40.6 mmol) in acetone (160 mL) and H_2O (40 mL). The mixture was stirred at room temperature for 22 h. EtOAc (200 mL) was added followed by a saturated aqueous Na_2SO_3 solution (200 mL), and the two phases were mixed vigorously for 0.5 h. The organic layer was separated, washed with H_2O (3 × 200 mL) and brine (200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude pale yellow solid was crystallized from MeOH−H_2O (approximately 1:1) to afford a 55:45 unassigned diastereoisomeric mixture of (6a*S*,12a*S*,5′*R*,6′*S*)- and (6a*S*,12a*S*,5′*R*,6′*R*)-amorphigenol (**11**) as white needles (3.98 g, 92%): mp 181−184 °C; R_f 0.05 (*n*-hexane−EtOAc; 1:1); $[\alpha]^{20}_D$ −89 (c 0.1 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3600−3200br, 1668m (C=O)^{ketone}, 1604m, 1515m, 1348m, 1317m, 1287m, 1214m, 1201m, 1181m, 1058m, 1009m, 909m, 816m; NMR data for the major diastereoisomer δ_H (500 MHz, $CDCl_3$) 1.21 [3H, s, C(8′)H$_3$], 2.29 [1H, dd, J 10.0, 5.0 Hz, C(7′)HH′OH], 2.40 [1H, s, C(6′)OH], 3.18 [1H, app d, J 12.0 Hz, C(4′)HH′], 3.18 [1H, app d, J 12.0, Hz, C(4′)HH′], 3.52 [1H, ddd, J 14.0, 10.0, 5.0 Hz, C(7′)HH′OH], 3.73 [1H, ddd, J 14.0, 10.0, 5.0 Hz, C(7′)HH′OH], 3.76 [3H, s, C(2′)H$_3$], 3.81 [3H, s, C(3′)H$_3$], 3.84 [1H, d, J 4.5 Hz, C(12a)H], 4.18 [1H, app d, J 15.0 Hz, C(6)HH′], 4.61 [1H, dd, J 15.0, 3.5 Hz, C(6)HH′], 4.86 [1H, app t, J 12.0 Hz, C(5′)H], 4.93 [1H, ddd, J 4.5, 3.5, 1.0 Hz, C(6a)H], 6.45 [1H, s, C(4)H], 6.47 [1H, d, J 11.0 Hz, C(10)H], 6.75 [1H, s, C(1)H], 7.82 [1H, d, J 11.0 Hz, C(11)H]; δ_C (125 MHz, $CDCl_3$) 19.3 [C(8′)H$_3$], 27.0 [C(4′)H$_2$], 44.6 [C(12a)H], 55.9 [C(3′)H$_3$], 56.3 [C(2′)H$_3$], 66.2 [C(6)H$_2$], 66.8 [C(7′)H$_2$], 72.2

DOI: 10.1021/acs.jnatprod.7b00527
J. Nat. Prod. 2017, 80, 2751−2755

[C(6a)H], 73.4 [C(6′)], 87.3 [C(5′)H], 100.9 [C(4)H], 104.6 [C(10)H], 104.7 [C(13)], 110.3 [C(1)H], 113.4 [C(8)], 113.5 [C(11a)], 129.9 [C(11)H], 143.9 [C(2)], 147.4 [C(4a)], 149.5 [C(3)], 157.9 [C(7a)], 166.9 [C(9)], 189.0 [C(12)]; NMR data for the minor diastereoisomer δ_H (500 MHz, $CDCl_3$) 1.17 [3H, s, C(8′)H_3], 2.09 [1H, dd, *J* 10.0, 5.0 Hz, C(7′)HH′OH], 2.55 [1H, s, C(6′)OH], 3.16 [1H, dd, *J* 19.5, 12.0 Hz, C(4′)HH′], 3.23 [1H, dd, *J* 19.5, 12.0 Hz, C(4′)HH′], 3.56 [1H, ddd, *J* 14.0, 10.0, 5.0 Hz, C(7′)HH′OH], 3.76 [3H, s, C(2′)H_3], 3.80 [1H, ddd, *J* 14.0, 10.0, 5.0 Hz, C(7′)HH′OH], 3.81 [3H, s, C(3′)H_3], 3.85 [1H, d, *J* 4.5 Hz, C(12a)H], 4.18 [1H, app d, *J* 15.0 Hz, C(6)HH′], 4.62 [1H, dd, *J* 15.0, 4.0 Hz, C(6)HH′], 4.86 [1H, app t, *J* 12.0 Hz, C(5′)H], 4.93 [1H, ddd, *J* 4.5, 3.5, 1.0 Hz, C(6a)H], 6.45 [1H, s, C(4)H], 6.47 [1H, d, *J* 11.0 Hz, C(10)H], 6.75 [1H, s, C(1)H], 7.83 [1H, d, *J* 11.0 Hz, C(11)H]; δ_C (125 MHz, $CDCl_3$) 19.7 [C(8′)H_3], 27.3 [C(4′)H_2], 44.6 [C(12a)H], 55.9 [C(3′)H_3], 56.3 [C(2′)H_3], 66.2 [C(6)H_2], 68.6 [C(7′)H_2], 72.2 [C(6a)H], 72.9 [C(6′)], 90.0 [C(5′)H], 100.9 [C(4)H], 104.6 [C(10)H], 104.8 [C(13)], 110.3 [C(1)H], 113.3 [C(8)], 113.7 [C(11a)], 129.9 [C(11)H], 143.9 [C(2)], 147.4 [C(4a)], 149.5 [C(3)], 157.9 [C(7a)], 166.6 [C(9)], 189.0 [C(12)]; LRMS *m*/*z* found 429.2, $C_{23}H_{25}O_8$ $[M + H]^+$ requires 429.2; HRMS *m*/*z* found 451.1354, $C_{23}H_{24}O_8Na$ $[M + Na]^+$ requires 451.1363.

(6a*S*,12a*S*,5′*R*)-Rotenone-6′-norketone (10). A diastereomeric mixture of (6a*S*,12a*S*,5′*R*,6′*R*)- and (6a*S*,12a*S*,5′*R*,6′*S*)-amorphigenol (**11**) (2.00 g, 4.67 mmol) was added in one portion to a solution of periodic acid (4.26 g, 18.7 mmol) in H_2O (200 mL). The suspension was stirred vigorously at room temperature for 4.5 h before it was extracted with EtOAc (4 × 80 mL). The combined organic extracts were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude off-white solid was crystallized from MeOH to afford (6a*S*,12a*S*,5′*R*)-rotenone-6′-norketone (**10**) as white needles (1.44 g, 78%): mp 194−196 °C (lit. mp 198−199 °C);[9b] R_f 0.20 (*n*-hexane−EtOAc; 1:1); $[\alpha]^{20}_D$ −60 (*c* 0.1 in $CHCl_3$) (no lit. value); ν_{max} (neat)/cm^{-1} 2910w, 1714 (C═O)^{ketone}, 1681 (C═O)^{ketone}, 1607m, 1514m, 1457m, 1349m, 1305m, 1254m, 1238m, 1215m, 1196m, 1145m, 1092m, 1005m, 910m, 818m; δ_H (500 MHz, $CDCl_3$) 2.30 [3H, s, C(8′)H_3], 3.33 [1H, dd, *J* 16.0, 10.0 Hz, C(4′)HH′], 3.36 [1H, dd, *J* 16.0, 10.0 Hz, C(4′)HH′], 3.76 [3H, s, C(2′)H_3], 3.81 [3H, s, C(3′)H_3], 3.86 [1H, d, *J* 4.0 Hz, C(12a)H], 4.18 [1H, d, *J* 12.0 Hz, C(6)HH′], 4.61 [1H, dd, *J* 12.0, 3.0 Hz, C(6)HH′], 4.93 [1H, dd, *J* 4.0, 3.0 Hz, C(6a)H], 5.13 [1H, m, C(5′)H], 6.45 [1H, s, C(4)H], 6.58 [1H, d, *J* 8.5 Hz, C(10)H], 6.74 [1H, s, C(1)H], 7.87 [1H, d, *J* 8.5 Hz, C(11)H]; δ_C (125 MHz, $CDCl_3$) 26.3 [C(8′)H_3], 29.3 [C(4′)H_2], 44.6 [C(12a)H], 55.9 [C(3′)H_3], 56.3 [C(2′)H_3], 66.2 [C(6)H_2], 72.4 [C(6a)H], 87.3 [C(5′)H], 100.9 [C(4)H], 104.5 [C(13)], 105.0 [C(10)H], 110.3 [C(1)H], 111.9 [C(8)], 114.0 [C(11a), 130.3 [C(11)H], 143.9 [C(2)], 147.4 [C(4a)], 149.6 [C(3)], 157.9 [C(7a)], 166.3 [C(9)], 188.9 [C(12)], 206.7 [C(6′)]; LRMS *m*/*z* found 397.1, $C_{22}H_{21}O_7$ $[M + H]^+$ requires 397.1; HRMS *m*/*z* found 397.1295, $C_{22}H_{21}O_7$ $[M + H]^+$ requires 397.1287.

Lactol Acetate (9). Oxone (6.21 g, 20.2 mmol) was added in one portion to a solution of (6a*S*,12a*S*,5′*R*)-rotenone-6′-norketone (**10**) (1.00 g, 2.53 mmol) in MeCN (60.0 mL) and H_2O (6.0 mL). The mixture was stirred at room temperature for 28 h. Saturated aqueous $NaHCO_3$ solution (100 mL) was added followed by EtOAc (100 mL), and the two phases were mixed vigorously for 0.5 h. The organic layer was separated, washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude pale yellow solid was purified by flash column chromatography (*n*-hexane−EtOAc, 3:1) to afford lactol acetate (**9**) as a white amorphous solid, which crystallized from MeOH as white needles (360 mg, 35%): mp 193−194 °C (no lit. value);[9a] R_f 0.20 (*n*-hexane−EtOAc, 2:1) (after two elutions); $[\alpha]^{20}_D$ −294 (*c* 0.1 in $CHCl_3$) (no lit. value);[9a] ν_{max} (neat)/cm^{-1} 2935w, 1754m (C═O)^{ester}, 1670m (C═O)^{ketone}, 1601m, 1510m, 1458m, 1346m, 1251m, 1214m, 1192m, 1171m, 1050m, 913m, 816m; δ_H (500 MHz, $CDCl_3$) 2.10 [3H, s, C(9′)H_3], 3.12 [1H, dd, *J* 10.5, 1.5 Hz, C(4′)HH′], 3.39 [1H, dd, *J* 10.5, 8.5 Hz, C(4′)HH′], 3.76 [3H, s, C(2′)H_3], 3.79 [3H, s, C(3′)H_3], 3.87 [1H, d, *J* 4.0 Hz, C(12a)H], 4.18 [1H, d, *J* 12.0 Hz, C(6)HH′], 4.62 [1H, dd, *J* 12.0, 3.0 Hz, C(6)HH′], 4.97 [1H, app t, *J* 4.0 Hz, C(6a)H], 6.44 [1H, s, C(4)H], 6.60 [1H, d, *J* 8.5 Hz, C(10)H], 6.73 [1H, s, C(1)H], 6.84 [1H, dd, *J* 8.5, 1.5 Hz, C(5′)H], 7.88 [1H, d, *J* 8.5 Hz, C(11)H]; δ_C (125 MHz, $CDCl_3$) 21.0 [C(8′)H_3], 32.7 [C(4′)H_2], 44.7 [C(12a)H], 55.9 [C(3′)H_3], 56.3 [C(2′)H_3], 66.2 [C(6)H_2], 72.5 [C(6a)H], 99.4 [C(5′)H], 100.9 [C(4)H], 104.4 [C(13)], 105.4 [C(10)H], 110.2 [C(1)H], 111.1 [C(8)], 114.4 [C(11a)], 130.1 [C(11)H], 143.9 [C(2)], 147.4 [C(4a)], 149.6 [C(3)], 157.8 [C(7a)], 165.0 [C(9)], 169.6 [C(7′)], 189.1 [C(12)]; LRMS *m*/*z* found 413.1, $C_{22}H_{21}O_8$ $[M + H]^+$ requires 413.1; HRMS *m*/*z* found 413.1249, $C_{22}H_{21}O_8$ $[M + H]^+$ requires 413.1236.

(6a*S*,12a*S*)-Elliptone (5). *para*-Toluenesulfonic acid monohydrate (36.9 mg, 0.194 mmol) was added to a solution of lactol acetate (**9**) (400 mg, 0.971 mmol) in dry toluene (40.0 mL) under an atmosphere of nitrogen. The mixture was heated at 80 °C for 1.5 h, cooled to room temperature, and diluted with EtOAc (40 mL). Saturated aqueous $NaHCO_3$ solution (20 mL) was added, and the two phases were mixed vigorously for 0.5 h. The organic layer was separated, washed with H_2O (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude off-white solid was purified by flash column chromatography (*n*-hexane−EtOAc, 2:1) to afford (6a*S*,12a*S*)-elliptone (**5**) as a white amorphous solid (259 mg, 76%): R_f 0.25 (*n*-hexane−EtOAc, 2:1); $[\alpha]^{20}_D$ +46 (*c* 0.1 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 1679m (C═O)^{ketone}, 1613m, 1596w, 1514m, 1464m, 1388m, 1333m, 1214m, 1193m, 1090m, 913m, 820m; δ_H (500 MHz, $CDCl_3$) 3.75 [3H, s, C(2′)H_3], 3.79 [3H, s, C(3′)H_3], 3.94 [1H, d, *J* 4.0 Hz, C(12a)H], 4.24 [1H, d, *J* 12.0 Hz, C(6′)HH′], 4.72 [1 H, dd, *J* 12.0, 3.0 Hz, C(6)HH′], 5.08 [1H, ddd, *J* 4.0, 3.0, 1.0 Hz, C(6a)H], 6.46 [1H, s, C(4)H], 6.76 [1H, s, C(1)H], 6.92 [1H, d, *J* 2.5 Hz, C(5′)H], 7.14 [1H, d, *J* 8.5 Hz, C(10)H], 7.56 [1H, d, *J* 2.5 Hz, C(4′)H], 7.89 [1H, d, *J* 8.5 Hz, C(11)H]; δ_C (125 MHz, $CDCl_3$) 44.7 [C(12a)H], 55.9 [C(3′)H_3], 56.3 [C(2′)H_3], 66.2 [C(6)H_2], 72.9 [C(6a)H], 101.0 [C(4)H], 104.5 [C(13)], 104.9 [C(5′)H], 106.7 [C(10)H], 110.3 [C(1)H], 113.6 [C(8)], 117.2 [C(11a)], 124.0 [C(11)H], 143.9 [C(2)], 145.0 [C(4′)H], 147.4 [C(4a)], 149.6 [C(3)], 156.0 [C(7a)], 160.3 [C(9)], 189.9 [C(12)]; LRMS *m*/*z* found 353.1, $C_{20}H_{17}O_6$ $[M + H]^+$ requires 353.1; HRMS *m*/*z* found 375.0826, $C_{20}H_{16}O_6Na$ $[M + Na]^+$ requires 375.0839.

(6a*R*,12a*R*)-12a*β*-Hydroxyelliptone (6). A solution of $K_2Cr_2O_7$ (79.0 mg, 0.269 mmol, 0.94 equiv) in H_2O (1.0 mL) was added dropwise over a period of 2 min to a solution of (6a*S*,12a*S*)-elliptone (**5**) (100 mg, 0.284 mmol) and HOAc (2.0 mL) at 60 °C. The mixture was stirred at 60 °C for 30 min, cooled to room temperature, and stirred for an additional 18 h. H_2O (20 mL) was added to the dark-green mixture, and the resulting suspension was stirred vigorously for 30 min while an off-white precipitate formed, which was collected by filtration, washed with H_2O (10 mL), and dried *in vacuo* overnight. The crude precipitate was purified by flash column chromatography (*n*-hexane−EtOAc, 2:1) to afford (6a*R*,12a*R*)-12a*β*-hydroxyelliptone (**6**) as a white amorphous solid (66.0 mg, 63%): R_f 0.15 (*n*-hexane−EtOAc, 2:1); $[\alpha]^{20}_D$ −5 (*c* 0.1 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3600−3300br, 2970w, 1739 (C═O)^{ketone}, 1680w, 1613m, 1509m, 1464m, 1366m, 1216m, 1203m, 1080m, 1025m, 813m, 743m; δ_H (500 MHz, $CDCl_3$) 3.72 [3H, s, C(2′)H_3], 3.80 [3H, s, C(3′)H_3], 4.47 [1H, s, C(6a)H], 4.56 [1H, d, *J* 12.0 Hz, C(6)HH′], 4.73 [1H, d, *J* 12.0 Hz, C(6)HH′], 4.75 [1H, s, C(12a)OH], 6.49 [1H, s, C(4)H], 6.55 [1H, s, C(1)H], 6.91 [1H, d, *J* 2.5 Hz, C(5′)H], 7.17 [1H, d, *J* 8.5 Hz, C(10)H], 7.57 [1H, d, *J* 2.5 Hz, C(4′)H], 7.88 [1H, d, *J* 8.5 Hz, C(10)H]; δ_C (125 MHz, $CDCl_3$) 55.9 [C(3′)H_3], 56.4 [C(2′)H_3], 63.8 [C(6)H_2], 67.7 [C(12a)OH], 76.7 [C(6a)H], 101.1 [C(4)H], 104.8 [C(5′)H], 107.1 [C(10)H], 108.4 [C(13)], 109.2 [C(1)H], 112.0 [C(11a)], 117.3 [C(8)], 123.9 [C(11)H], 144.0 [C(2)], 145.1 [C(4′)H], 148.4 [C(4a)], 151.2 [C(3)], 155.8 [C(7a)], 160.6 [C(9)], 192.2 [C(12)]; LRMS *m*/*z* found 351.1, $C_{20}H_{17}O_7$ $[M + H]^+$ requires 351.1; HRMS *m*/*z* found 391.0800, $C_{20}H_{16}O_7Na$ $[M + Na]^+$ requires 391.0793.

DOI: 10.1021/acs.jnatprod.7b00527
J. Nat. Prod. 2017, 80, 2751−2755

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.7b00527.

^{1}H and ^{13}C NMR spectra for compounds **1**, **5**, **6**, **9**, **10**, and **11** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research was supported by the EPSRC, BBSRC, MRC, Wellcome Trust, and ERC (FP7/2007-2013; 279337/DOS). D.A.R. thanks Cancer Research UK for funding. W.J.S.F. thanks A*STAR Singapore for funding. D.G.T. thanks AstraZeneca for funding. D.R.S. acknowledges support from a Royal Society Wolfson Research Merit award.

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DOI: 10.1021/acs.jnatprod.7b00527
J. Nat. Prod. 2017, 80, 2751−2755