JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02968 • Publication Date (Web): 03 Jan 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Total Synthesis of Rhodonoids A, B, E and F, Enabled by Singlet Oxygen Ene Reactions

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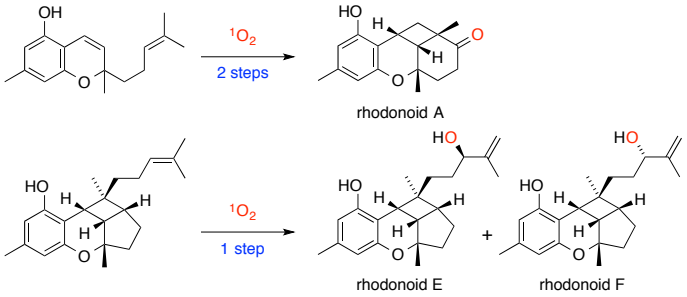
Abstract



Singlet oxygen is a versatile reagent for the selective oxidation of organic compounds under mild reaction conditions. It is frequently invoked in biosynthetic pathways, so it is especially suitable for application in the biomimetic synthesis of natural products. Herein, we show that use of the singlet oxygen ene reaction, combined with [2+2] cycloadditions, leads to concise, divergent and redox-economic total syntheses of several polycyclic members of the rhodonoid family of meroterpenoids.

Introduction

Rhodonoids A-G (**1**-**7**, Figure 1) are a family of polycyclic meroterpenoids isolated from *Rhododendron capitatum*.[1] Despite their sterecochemically rich structures, the rhodonoids were all found as partial racemates. This implies that key steps in their biosynthesis might not be under enzymatic control, which makes the rhodonoids attractive targets for biomimetic synthesis.[2] We have previously reported a divergent synthesis of rhodonoids C and D via a biomimetic cascade reaction that involves ring opening of an epoxide intermediate.[3] A similar strategy was independently developed by Hsung and Tang,[4] who also used epoxide ring opening chemistry in their total syntheses of rhodonoids A, B, E and F.[5] Herein, we propose that singlet oxygen ene reactions[6] are involved in the biosynthesis of rhodonoids A, B, E and F. Application of these

photooxygenation reactions in a biomimetic strategy has enabled a concise route to rhodonoid natural products that minimises redox reactions and protecting group operations.

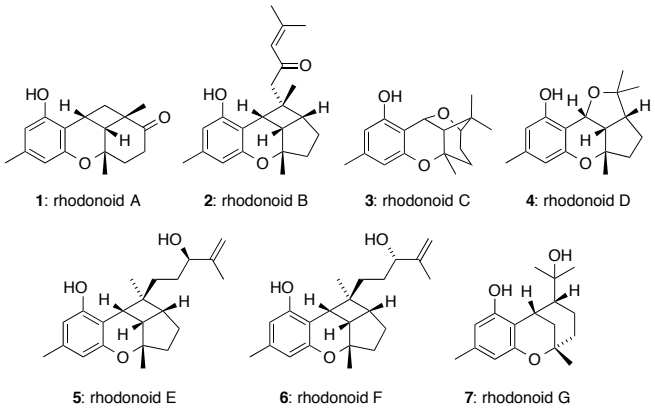
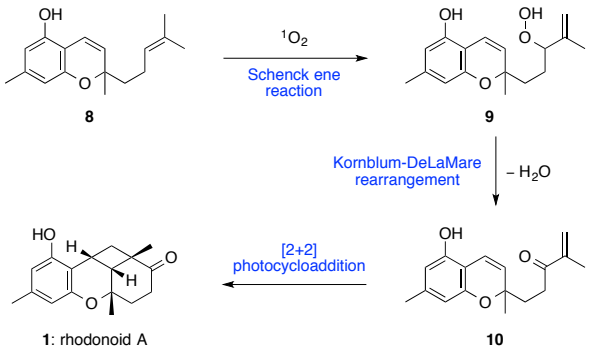


Figure 1. Rhodonoids A-G, partially racemic meroterpenoids from *Rhododendron capitatum*.

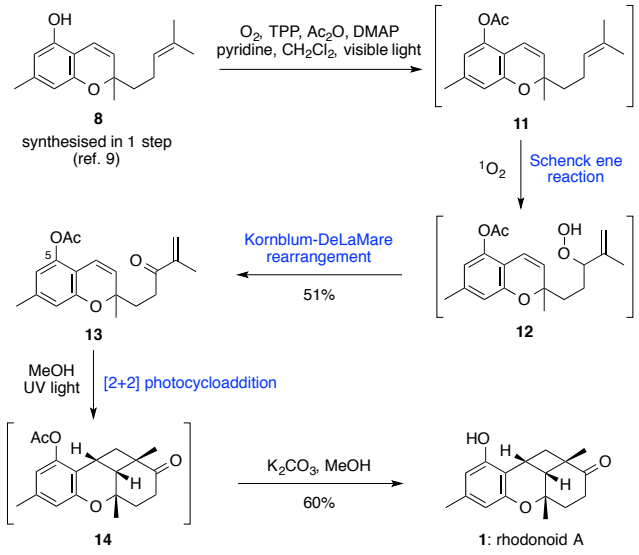
Results and Discussion

Chromene **8** has already been shown to the be the likely biosynthetic precursor of rhodonoids C and D (**3** and **4**) via biomimetic synthesis,[3,4] so we thought it might also be the precursor of rhodonoid A (**1**) (Scheme 1). A singlet oxygen ene reaction (often called the Schenck ene reaction) of the prenyl side chain of chromene **8** could give hydroperoxide **9** as an inconsequential mixture of diastereomers. A Kornblum-DeLaMare rearrangement[7] of **9** would give the enone **10**, which could undergo an intramolecular [2+2] photocycloaddition [8] to give rhodonoid A (**1**). A [2+2] photocycloaddition of a protected version of **10** was used in Hsung and Tang's total synthesis of **1**.[5]



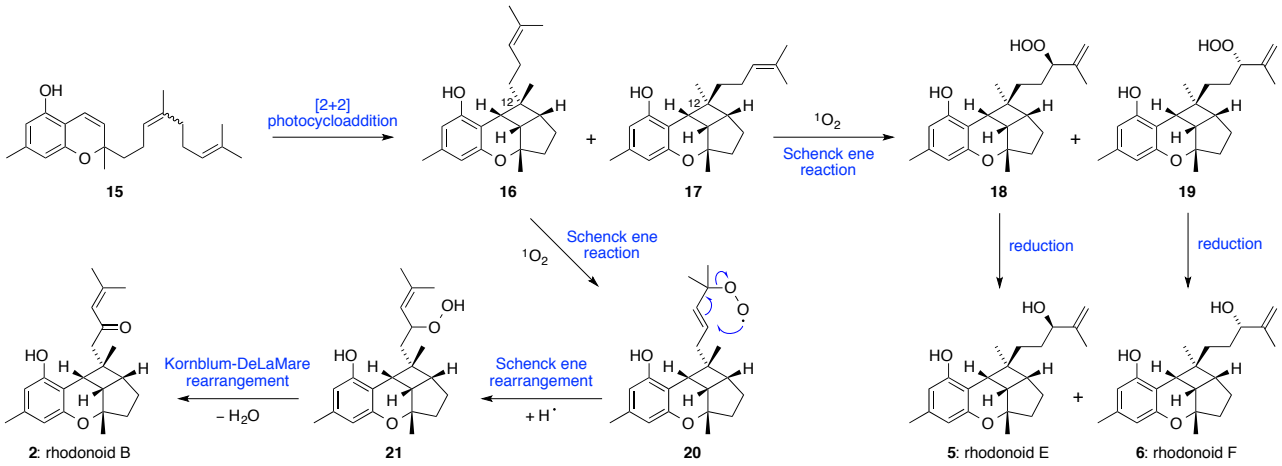
Scheme 1. Proposed Biosynthesis of Rhodonoid A

Given that exposure to light is necessary for both the generation of singlet oxygen (required for the Schenck ene reaction, **8** → **9**) and the intramolecular [2+2] cycloaddition (**10** → **1**), we hoped to develop a one-pot, photochemical method for the direct conversion of **8** into **1**. Although this goal has proven elusive, we have developed an efficient two-step sequence to convert **8** into **1** (Scheme 2). Firstly, a one-pot Schenck ene reaction and subsequent Kornblum-DeLaMare rearrangement of chromene **8**[9] was achieved using visible light and tetraphenylporphyrin (TPP) as the sensitizer to generate singlet oxygen, with excess pyridine, Ac_2O and catalytic DMAP to activate the hydroperoxide rearrangement. The C-5 phenol was also acetylated during this step to give **13** in 51% yield. These reaction conditions were first reported by Laroche and Nay in their studies on the biomimetic photooxygenation of resinic diterpenes.[10] No [2+2] photocycloaddition of **13** was observed under these reaction conditions with visible light. Enone **13** was therefore dissolved in MeOH and exposed to UV light to form **14**, which was hydrolysed in the same pot by addition of K_2CO_3, giving rhodonoid A (**1**) in 60% yield.[5] This two-step (31% overall yield) sequence compares favourably to the previous synthesis of rhodonoid A by Hsung and Tang, which required six steps (11% overall yield) to convert **8** into **1**.[5]



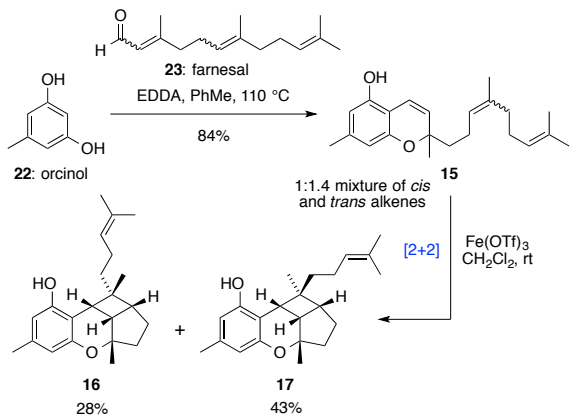
Scheme 2. Biomimetic Total Synthesis of Rhodonoid A

Singlet oxygen ene reactions were also invoked in the biosynthesis of rhodonoids B, E and F (Scheme 3). Chromene **15** (as a mixture of *E* and *Z* alkene isomers) could undergo a [2+2] photocycloaddition to give the tetracyclic diastereomers **16** and **17** (epimers at C-12). Singlet oxygen ene reaction of tetracycle **17** could form the diastereomeric hydroperoxides **18** and **19**, reduction of which would give rhodonoid E (**5**) and rhodonoid F (**6**) respectively. Rhodonoid B (**2**) could arise from singlet oxygen ene reaction of tetracycle **16** to give peroxy radical **20**. This reactive radical intermediate could undergo a Schenck ene rearrangement[11] and H atom abstraction to give hydroperoxide **21**, followed by Kornblum-DeLaMare rearrangement to give **2**.



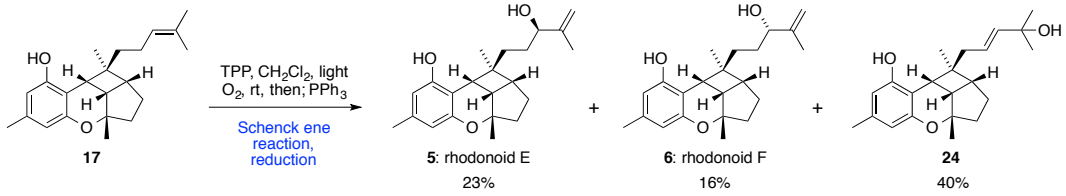
Scheme 3. Proposed Biosynthesis of Rhodonoids B, E, and F

Divergent synthesis of tetracycles **16** and **17** was achieved using Hsung and Tang's $Fe(OTf)_3$-mediated cationic [2+2] cyclization. Firstly, orcinol (**22**) was condensed with technical grade farnesal (**23**, a complex mixture of isomers) in the presence of EDDA to give chromene **15** as a 1:1.4 mixture of *cis* and *trans* isomers (Scheme 4).[12] These *cis* and *trans* alkenes were previously prepared as by Hsung and Tang as pure stereoisomers, but we carried out a divergent intramolecular [2+2] cycloaddition on the mixture to give **16** and **17** in 28% and 43% yield respectively. Tetracycles **16** and **17** were separable by careful flash chromatography on silica gel. Attempted [2+2] photocycloaddition of **15** using UV light resulted in decomposition.



Scheme 4. Divergent Synthesis of Tetracycles 16 and 17[5]

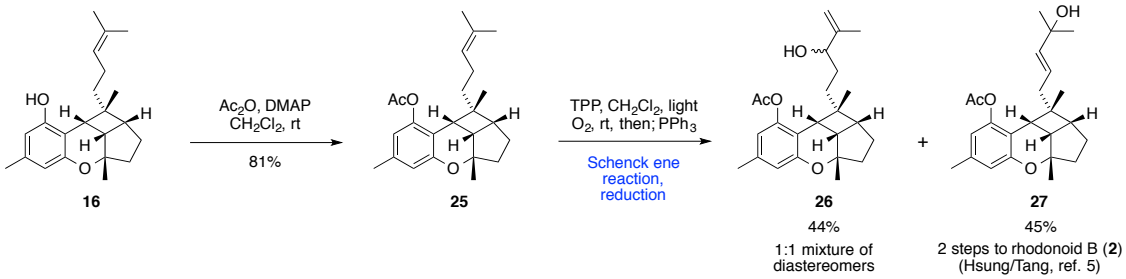
Visible light-mediated singlet oxygen ene reaction of tetracycle **17** using TPP as the sensitizer followed by reduction of the hydroperoxide intermediates with PPh_3 gave rhodonoid E (**5**) in 23% yield, rhodonoid F (**6**) in 16% yield, and tertiary alcohol **24** in 40% yield (Scheme 5). These compounds were separable by careful flash chromatography using silica gel doped with silver nitrate.[13] If our biosynthetic speculation on the origin of rhodonoids E and F is correct, then **24** is a plausible "undiscovered natural product". Previously, Hsung and Tang converted **17** into **5** and **6** (28% and 26% overall yield, respectively) via a four-step sequence involving ring opening of an epoxide intermediate.[4]



Scheme 5. Biomimetic Total Synthesis of Rhodonoids E and F

Finally, we used singlet oxygen chemistry to enable a formal synthesis of rhodonoid B (**2**) via the generation of tertiary alcohol **27**, which has been converted into **2** by Hsung and Tang in two further steps.[5] First, tetracycle **16** was acetylated under standard conditions to give **25**. Singlet oxygen ene reaction of **25** followed by reduction of the hydroperoxide products using PPh_3 gave **27** in 45% yield, alongside an inseparable mixture of secondary allylic alcohol diastereomers **26** in

44% yield (Scheme 6). Hsung and Tang's previous synthesis of rhodonoid B required seven steps (37% yield) to convert **16** into **27**, compared to our two-step protocol (36% yield).[5]



Scheme 6. Formal Total Synthesis of Rhodonoid B

Conclusion

We have significantly shortened the step count of previous total syntheses of rhodonoids A, B, E and F through the strategic use of singlet oxygen as a mild and selective oxidant. The 3-step total synthesis of rhodonoid A features a one-pot singlet ene reaction and Kornblum-DeLaMare rearrangement, followed by a [2+2] photocycloaddition, to rapidly assemble a complex polycyclic framework.

Experimental Section

General Information. All chemicals used were purchased from commercial suppliers and used as received. All reactions were performed under an inert atmosphere of N_2 unless otherwise stated. All organic extracts were dried over anhydrous magnesium sulfate. Thin layer chromatography was performed using aluminium sheets coated with silica gel. Visualization was aided by viewing under a UV lamp and staining with ceric ammonium molybdate stain followed by heating. All R_f values were measured to the nearest 0.05. Flash chromatography was performed using 40-63 micron grade silica gel. Melting points were recorded on a digital melting point apparatus and are uncorrected. Infrared spectra were recorded using an FT-IR spectrometer as the neat compounds. High field NMR was recorded using a 600 MHz spectrometer (^{1}H at 600 MHz, ^{13}C at 150 MHz) or a 500 MHz spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz). The solvent used for NMR spectra was $CDCl_3$

unless otherwise specified. ^{1}H chemical shifts are reported in ppm on the δ-scale relative to TMS (δ 0.0) and ^{13}C{^{1}H} NMR are reported in ppm relative to chloroform (δ 77.16). Multiplicities are reported as (br) broad, (s) singlet, (d) doublet, (t) triplet, (q) quartet and (m) multiplet. All *J*-values were rounded to the nearest 0.1 Hz. ESI high resolution mass spectra were recorded on a Q-TOF mass spectrometer. Photochemistry with UV light was performed using a generic brand commercial LED UV light globe; wavelength: 365 nm. Photochemical reactions with visible light were performed with a conventional commercial LED desk lamp at 240 V with a 4 W 5000 K 32 mA globe.

2,7-dimethyl-2-(4-methylpent-3-en-1-yl)-2*H*-chromen-5-ol (8). To a solution of 4-methylresorcinol (10.0 g, 80.6 mmol, 1.0 equiv) in PhMe (250 mL) at room temperature was added citral (12.3 mL, 80.6 mmol, 1.0 equiv) and ethylenediamine diacetate (430 mg, 2.42 mmol, 0.03 equiv). The reaction was stirred at reflux for 3 h. The mixture was cooled to room temperature, then concentrated *in vacuo* and purified via flash column chromatography on SiO_2 (8:1, hexanes:EtOAc) to afford chromene **8** as an orange oil (17.2 g, 66.6 mmol, 82%). Data for **8** matched that previously reported in the literature.[5] Data for **8**: R_f 0.40 (5:1, hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (d, J = 10.0 Hz, 1H), 6.24 (s, 1H), 6.11 (s, 1H), 5.49 (d, J = 10.0 Hz, 1H), 5.10 (t, J = 7.1 Hz, 1H), 4.71 (br s, 1H), 2.20 (s, 3H), 2.13 – 2.07 (m, 2H), 1.72 (dd, J = 10.7, 5.9 Hz, 1H), 1.66 (s, 3H), 1.66 – 1.63 (m, 1H), 1.58 (s, 3H), 1.37 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 154.1, 151.0, 139.5, 131.6, 127.2, 124.2, 117.0, 109.9, 108.3, 106.7, 78.2, 41.1, 26.2, 25.7, 22.7, 21.5, 17.6.

2,7-dimethyl-2-(4-methyl-3-oxopent-4-en-1-yl)-2*H*-chromen-5-yl acetate (13). Using modified conditions reported by Nay *et al*.,[10] chromene **8** (450 mg, 1.80 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (30 mL), followed by addition of tetraphenylporphyrin (TPP) (22 mg, 0.036 mmol, 0.02 equiv), pyridine (8.70 mL, 108 mmol, 60 equiv), Ac_2O (17.0 mL, 180 mmol, 100 equiv) and DMAP (4 mg, 0.036 mmol, 0.02 equiv). The reaction was stirred at room temperature in a borosilicate glass test tube while exposed to visible light at a distance of 10 cm from the irradiation vessel and with O_2 bubbled through the solution for 36 h. The reaction was then quenched by

addition of distilled H_2O (40 mL). The organic phase was then separated, and the aqueous phase further extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were then washed with 0.5 M $CuSO_{4(aq)}$ (3 x 60 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified via flash chromatography (neat CH_2Cl_2) to give the desired enone **13** (283 mg, 1.13 mmol, 51%) as a white solid. Data for **13**: R_f 0.30 (9:1, hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.48 (s, 1H), 6.41 (s, 1H), 6.33 (d, J = 10.0 Hz, 1H), 5.92 (s, 1H), 5.71 (d, J = 1.6 Hz, 1H), 5.49 (d, J = 10.0 Hz, 1H), 2.83 (dddd, J = 69.0, 17.1, 10.1, 5.4 Hz, 2H), 2.29 (s, 3H), 2.25 (s, 3H), 2.08 – 1.93 (m, 2H), 1.90 – 1.79 (m, 3H), 1.38 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 201.6, 169.3, 153.8, 146.3, 144.3, 139.7, 128.6, 124.9, 117.4, 115.0, 114.7, 111.3, 78.3, 35.8, 32.5, 26.9, 21.6, 20.9, 17.7; IR (neat) 2925, 1769, 1676, 1451, 1190; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{19}H_{23}O_4$ 315.1591; Found 315.1591.

Rhodonoid A (1). A solution of enone **13** (57 mg, 0.181 mmol, 1.0 equiv) in MeOH (3 mL) was left in a borosilicate sealed vial placed within a water condenser and irradiated from beneath with UV light at a distance of 5 cm for 24 h at room temperature. K_2CO_3 (62 mg, 0.450 mmol, 2.5 equiv) was then added in one portion and the reaction was stirred for 1 h. H_2O (5 mL) was added and the product was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were then dried under $MgSO_4$, filtered and concentrated. Purification *via* flash chromatography (9:1, hexanes:EtOAc) afforded (±)-rhodonoid A (**1**) as a white solid (30 mg, 0.110 mmol, 60%). Data for (±)-rhodonoid A (**1**) matched that previously reported in literature.[5] Data for **1**: R_f 0.20 (8:2, hexanes:EtOAc); mp 179.6 – 180.2 °C (MeOH) (lit. 180 – 181 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.34 (s, 1H), 6.21 (s, 1H), 4.59 (s, 1H), 3.80 - 3.73 (m, 1H), 2.78 (ddd, J = 18.1, 10.9, 7.1 Hz, 1H), 2.59 (d, J = 9.5 Hz, 1H), 2.42 (ddd, J = 18.3, 6.8, 3.4 Hz, 1H), 2.39 – 2.33 (m, 1H), 2.33 – 2.30 (m, 1H), 2.22 (s, 3H), 2.16 (dd, J = 12.2, 7.1 Hz, 1H), 2.03 (ddd, J = 14.0, 10.9, 6.8 Hz, 1H), 1.44 (s, 3H), 1.16 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 216.5, 154.1, 152.8, 137.5, 112.6, 112.0, 109.3, 73.5, 51.1, 43.9, 39.0, 34.1, 33.7, 25.4, 24.9, 21.9, 21.3; IR (neat) 2965, 1687, 1625, 1514,

1420, 1187, 1069; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{17}H_{21}O_3$ 273.1485; Found 273.1485.

2-(4,8-dimethylnona-3,7-dien-1-yl)-2,7-dimethyl-2*H*-chromen-5-ol (15). To a solution of 4-methylresorcinol (12.9 g, 103.9 mmol, 1.0 equiv) in PhMe (300 mL) at room temperature was added farnesal (*mixture of isomers*, 22.9 g, 103.9 mmol, 1.0 equiv) and ethylenediamine diacetate (190 mg, 10.4 mmol, 0.10 equiv). The reaction was stirred at reflux for 16 h. The mixture was cooled to room temperature, then concentrated *in vacuo*. Purification via flash column chromatography on SiO_2 (10:1, hexanes:EtOAc) then afforded chromene **15** as a 1:1.4 mixture of *cis*:*trans* stereoisomers (28.6 g, 87.6 mmol, 84%). Data for **15** matched that previously reported in the literature.[5] Data for **15**: R_f 0.50 (8:2, hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.60 (d, J = 9.9 Hz, 1H), 6.24 (d, J = 4.0 Hz, 1H), 6.11 (s, 1H), 5.49 (dd, J = 10.0, 8.4 Hz, 1H), 5.17 – 5.04 (m, 2H), 4.70 (s, 1H), 2.20 (s, 3H), 2.15 – 1.94 (m, 6H), 1.76 – 1.70 (m, 2H), 1.67 (s, 3H), 1.62 – 1.57 (m, 6H), 1.38 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 154.3, 151.2, 139.7, 139.7, 135.5, 135.4, 131.5, 127.4, 127.3, 125.0, 124.5, 124.2, 116.9, 116.8, 110.0, 110.0, 108.4, 106.9, 78.4, 78.3, 41.5, 41.2, 39.8, 32.0, 26.8, 26.7, 26.4, 26.4, 25.9, 25.8, 23.5, 22.8, 22.6, 21.6, 17.8, 17.8, 16.1; IR (neat) 2967, 1626, 1578, 1448, 1249, 1197, 1091; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{31}O_2$ 327.2319; Found 327.2319.

(1*R*,1a*R*,1a^1*S*,3a*S*,8b*S*)-1,3a,6-trimethyl-1-(4-methylpent-3-en-1-yl)-1a,1a^1,2,3,3a,8b-hexahydro-1*H*-4-oxabenzo[*f*]cyclobuta[*cd*]inden-8-ol (16) and (1*S*,1a*R*,1a^1,3a*S*,8b*S*)-1,3a,6-trimethyl-1-(4-methylpent-3-en-1-yl)-1a,1a^1,2,3,3a,8b-hexahydro-1*H*-4-oxabenzo[*f*]cyclobuta[*cd*]inden-8-ol (17). Using a modified procedure from Tang *et al*.,[5] $Fe(OTf)_3$ (50 mg, 0.099 mmol, 0.3 equiv) was added in one portion to a solution of a 1:1.4 *cis:trans* mixture of chromene **15** (100 mg, 0.306 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) under N_2 at –78 ºC. The reaction was warmed to room temperature and left to stir for 12 h, then quenched with sat. $NaHCO_{3(aq)}$ (30 mL). The product was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were washed with brine (60 mL). The organic phase was dried over $MgSO_4$,

filtered and concentrated *in vacuo*. Careful flash chromatography on silica gel (50:1, hexanes:EtOAc) then afforded **17** as a white solid (42 mg, 0.131 mmol, 43%) followed by **16** as an off white solid (28 mg, 0.086 mmol, 28%). Data for **16** and **17** matched that previously reported in literature.[5] Data for **16**: R_f 0.20 (20:1, hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.32 (s, 1H), 6.18 (s, 1H), 4.94 (t, J = 4.9 Hz, 1H), 4.46 (br s, 1H), 3.12 (d, J = 9.7 Hz, 1H), 2.57 (dd, J = 9.8, 8.2 Hz, 1H), 2.42 (td, J = 8.3, 3.6 Hz, 1H), 2.22 (s, 3H), 2.05 (dt, J = 12.9, 7.5 Hz, 1H), 1.86 – 1.61 (m, 5H), 1.60 (s, 3H), 1.49 (s, 3H), 1.38 (s, 3H), 1.32 (s, 3H), 1.28 – 1.11 (m, 2H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 154.7, 153.9, 137.5, 130.7, 125.4, 111.6, 108.7, 108.3, 83.7, 46.2, 42.4, 40.2, 38.6, 36.1, 31.2, 30.5, 26.4, 26.1, 25.8, 23.5, 21.4, 17.7; IR (neat) 2950, 1626, 1452, 1375, 1054; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{31}O_2$ 327.2319; Found 327.2319. Data for **17**: R_f 0.20 (20:1, hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.32 (s, 1H), 6.17 (s, 1H), 5.17 (t, J = 7.0 Hz, 1H), 4.48 (s, 1H), 3.06 (d, J = 9.6 Hz, 1H), 2.56 (dd, J = 9.6, 7.7 Hz, 1H), 2.47 (t, J = 7.5 Hz, 1H), 2.22 (s, 3H), 2.18 – 2.04 (m, 1H), 2.03 – 1.91 (m, 2H), 1.76 (ddd, J = 13.3, 11.6, 5.1 Hz, 1H), 1.71 (s, 3H), 1.70 – 1.59 (m, 4H), 1.63 (s, 3H), 1.36 (s, 3H), 0.76 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 154.6, 154.1, 137.6, 131.4, 125.1, 111.5, 108.5, 108.2, 83.5, 46.8, 44.4, 42.4, 39.1, 38.6, 35.6, 27.4, 25.9, 25.7, 22.9, 21.3, 17.8, 15.1; IR (neat) 2927, 1625, 1584, 1453, 1251, 1052; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{31}O_2$ 327.2319; Found 327.2318.

Rhodonoid E (5), rhodonoid F (6) and (1*S*,1a*R*,1a^1*S*,3a*S*,8b*S*)-1-(((*E*)-4-hydroxy-4-methylpent-2-en-1-yl)-1,3a,6-trimethyl)-1a,1a^1,2,3,3a,8b-hexahydro-1*H*-4-oxabenzo[*f*]-cyclobuta[*cd*]inden-8-ol (24). To a borosilicate glass test tube containing **17** (188 mg, 0.661 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added tetraphenylporphyrin (8 mg, 0.013 mmol, 0.02 equiv). O_2 was bubbled through the solution while it was stirred at room temperature and exposed to visible light at a distance of 10 cm from the irradiation vessel for 6 h. PPh_3 (350 mg, 1.32 mmol, 2.0 equiv) was then added and the reaction was stirred for a further 16 h under N_2. The solution was then concentrated *in vacuo* and purified via flash chromatography (9:1, CH_2Cl_2:EtOAc) to give (±)-rhodonoid E (**5**) as a white solid (49 mg, 0.150 mmol, 23%) and a mixture of (±)-rhodonoid F (**6**) and allylic alcohol **24** (133 mg,

0.407 mmol, 63%). The mixture was then further purified *via* flash chromatography using 1% *w/w* $AgNO_3$ impregnated SiO_2 (7:3, hexanes:EtOAc) with early fractions containing allylic alcohol **24** (86 mg, 0.262 mmol, 40%) as a red oil and later fractions containing (±)-rhodonoid F (**6**) as a white solid (35 mg, 0.107 mmol, 16%). Data for (±)-rhodonoid E (**5**) and (±)-rhodonoid F (**6**) matched that previously reported.[4] Data for (±)-rhodonoid E (**5**): R_f 0.40 (9:1, CH_2Cl_2:EtOAc); mp 123.7 – 125.0 ºC ($CHCl_3$) (lit. 86 – 87 ºC)[3]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.32 (s, 1H), 6.16 (s, 1H), 4.99 (s, 1H), 4.87 (s, 1H), 4.61 (br s, 1H), 4.10 (t, J = 5.0 Hz, 1H), 3.09 (d, J = 9.6 Hz, 1H), 2.56 (dd, J = 9.6, 7.8 Hz, 1H), 2.43 (td, J = 7.8, 4.1 Hz, 1H), 2.22 (s, 3H), 2.07 – 1.94 (m, 1H), 1.76 (s, 3H), 1.73 – 1.59 (m, 6H), 1.54 – 1.49 (m, 1H), 1.35 (s, 3H), 0.73 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 154.6, 154.1, 147.7, 137.6, 111.5, 111.3, 108.6, 108.2, 83.6, 76.6, 44.5, 42.3, 42.0, 39.2, 38.8, 35.3, 29.4, 27.3, 25.7, 21.4, 17.8, 15.3; IR (neat) 2925, 1621, 1415, 1259, 1118, 1055; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{31}O_3$ 343.2268; Found 343.2280. Data for (±)-rhodonoid F (**6**): R_f 0.20 (8:2, hexanes:EtOAc); mp 149.0 – 150.6 ºC (lit. 152 – 153 ºC)[3]; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.31 (s, 1H), 6.17 (s, 1H), 4.98 (s, 1H), 4.87 (s, 1H), 4.79 (br s, 1H), 4.10 (t, J = 6.2 Hz, 1H), 3.11 (d, J = 9.6 Hz, 1H), 2.55 (dd, J = 9.6, 7.9 Hz, 1H), 2.41 (td, J = 7.4, 3.5, Hz, 1H), 2.21 (s, 3H), 2.02 – 1.95 (m, 1H), 1.87 – 1.80 (m, 1H), 1.76 (s, 3H), 1.70 – 1.50 (m, 6H), 1.34 (s, 3H), 0.73 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 154.6, 154.2, 147.6, 137.5, 111.5, 111.4, 108.7, 108.3, 83.6, 76.7, 44.7, 42.4, 42.2, 39.2, 38.8, 35.2, 29.5, 27.2, 25.6, 21.4, 17.7, 15.2; IR (neat) 2944, 1624, 1419, 1260, 1137; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{22}H_{31}O_3$ 343.2268; Found 343.2272. Data for **24**: R_f 0.20 (8:2, hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.30 (s, 1H), 6.21 (s, 1H), 5.89 – 5.87 (m, 2H), 5.01 (br s, 1H), 3.05 (d, J = 9.7 Hz, 1H), 2.59 (dd, J = 9.7, 7.7 Hz, 1H), 2.44 – 2.37 (m, 2H), 2.32 (dd, J = 12.5, 3.2 Hz, 1H), 2.21 (s, 3H), 2.0 – 1.96 (m, 1H), 1.75 – 1.56 (m, 3H), 1.36 (s, 9H), 0.79 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 154.4, 154.3, 143.3, 138.0, 123.3, 111.2, 108.4, 107.6, 83.1, 71.0, 48.9, 45.7, 42.4, 38.7, 38.2, 33.2, 29.9, 29.7, 27.4, 25.5, 21.4, 15.3; IR (neat) 2968, 1624, 1585, 1455, 1328, 1137; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{22}H_{30}O_3Na$ 365.2087; Found 365.2085.

(1*R*,1a*R*,1a^1*S*,3a*S*,8b*S*)-1,3a,6-trimethyl-1-(4-methylpent-3-en-1-yl)-1a,1a^1,2,3,3a,8b-hexahydro-1*H*-4-oxabenzo[*f*]cyclobuta[*cd*]inden-8-yl acetate (25). Following a modified procedure from Tang *et al*.,[5] Ac_2O (0.04 mL, 0.367 mmol, 2.0 equiv) was added dropwise to a solution of **16** (60 mg, 0.184 mmol, 1.0 equiv) and DMAP (33 mg, 0.275 mmol, 1.5 equiv) in CH_2Cl_2 (10 mL). The resulting mixture was stirred at room temperature for 30 min, then quenched by addition of sat. $NaHCO_{3(aq)}$ (20 mL). The resultant mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification via flash chromatography on SiO_2 (19:1, hexanes:EtOAc) afforded acetate **25** (55 mg, 0.149 mmol, 81%) as a colourless oil. Data for **25**: R_f 0.30 (19:1, hexanes:EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.60 (s, 1H), 6.48 (s, 1H), 4.94 (t, J = 7.8 Hz, 1H), 2.99 (d, J = 9.8 Hz, 1H), 2.55 (t, J = 9.1 Hz, 1H), 2.42 (td, J = 8.5, 5.8 Hz, 1H), 2.29 (s, 3H), 2.27 (s, 3H), 2.04 (dt, J = 13.1, 6.6 Hz, 1H), 1.84 – 1.67 (m, 4H), 1.66 – 1.58 (m, 1H), 1.61 (s, 3H), 1.50 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H), 1.21 – 1.12 (m, 1H), 1.01 (ddd, J = 14.0, 12.1, 5.8 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 169.2, 154.8, 149.1, 137.4, 130.7, 125.2, 116.8, 115.2, 114.7, 84.1, 46.1, 42.7, 40.7, 38.9, 36.5, 31.3, 30.6, 26.1, 25.8, 25.7, 23.3, 21.4, 21.3, 17.6; IR (neat) 2949, 1768, 1626, 1451, 1371, 1052; HRMS (ESI-TOF) m/z: $[M+H]^+$ calculated for $C_{24}H_{33}O_3$ 369.2424; Found 369.2428.

(1*R*,1a*R*,1a^1*S*,3a*S*,8bS)-1-(3-hydroxy-4-methylpent-4-en-1-yl)-1,3a,6-trimethyl-1a,1a^1,2,3,3a,8b-hexahydro-1*H*-4-oxabenzo[*f*]cyclobuta[*cd*]inden-8-yl acetate (26) and (1*R*,1a*R*,1a^1*S*,3a*S*,8b*S*)-1-((*E*)-4-hydroxy-4-methylpent-2-en-1-yl)-1,3a,6-trimethyl-1a,1a^1,2,3,3a8b-hexahydro-1*H*-4-oxabenzo[*f*]cyclobuta[*cd*]inden-8-yl acetate (27). To a solution of **25** (101 mg, 0.311 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) in a 25 mL borosilicate glass test tube was added tetraphenylporphyrin (TPP) (4 mg, 0.007 mmol, 0.02 equiv) and O_2 was sparged through the solution for 10 min. Visible light was applied to the solution at a distance of 10 cm from the irradiation vessel which was stirred for 6 h at room temperature. PPh_3 (163 mg, 0.621 mmol, 2.0 equiv) was then added to the solution in one portion and the reaction was stirred at room temperature under N_2 for 8 h. The reaction was concentrated *in vacuo* and purified via flash

chromatography on SiO_2 (9:1, CH_2Cl_2: EtOAc) to afford **27** (53 mg, 0.139 mmol, 45%) as a yellow oil and **26** (42 mg, 0.109 mmol, 44%) as a yellow solid and as a 1:1 mixture of diastereomers. Data for **27** matched that previously reported.[5] Data for **26**: R_f 0.50 (9:1, CH_2Cl_2:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (s, 1H), 6.47 (s overlapped, J = 6.8 Hz, 1H), 4.80 (d, J = 4.7 Hz, 1H), 4.73 (d, J = 4.7 Hz, 1H), 3.78 – 3.73 (m, 1H), 3.01 (t, J = 9.3 Hz, 1H), 2.54 (t, J = 9.3 Hz, 1H), 2.44 – 2.39 (m, 1H), 2.27 (s, 6H), 2.08 – 2.01 (m, 1H), 1.90 – 1.82 (m, 1H), 1.74 – 1.67 (m, 2H), 1.63 (s, 3H), 1.59 (s, 3H), 1.59 – 1.55 (m, 1H), 1.30 (s, 3H), 1.28 (s, 3H), 1.10 – 1.09 (m, 1H), 1.00 – 0.92 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.3, 169.2, 154.9, 154.9, 149.0, 149.0, 147.8, 147.7, 137.5, 137.5, 116.9, 116.8, 115.3, 115.2, 114.9, 114.8, 110.8, 110.7, 84.3, 84.2, 76.6, 76.5, 46.3, 46.2, 42.5, 42.4 41.0, 40.8, 39.3, 39.2, 36.4, 36.3, 30.7, 30.4, 30.2, 27.7, 27.7, 25.9, 25.7, 25.6, 25.5, 21.4, 21.4, 21.3, 17.8, 17.6; IR (neat) 2970, 1771, 1466, 1306, 1160, 1107; HRMS (ESI-TOF) m/z: $[M+Na]^+$ calculated for $C_{24}H_{32}O_4Na$ 407.2193; Found 407.2199. Data for **27**: R_f 0.35 (9:1, CH_2Cl_2:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (s, 1H), 6.47 (s, 1H), 5.43 (d, J = 16.0 Hz, 1H), 5.38 – 5.31 (m, 1H), 3.05 (d, J = 9.5 Hz, 1H), 2.54 (t, J = 9.2 Hz, 1H), 2.45 (dt, J = 8.9, 4.2 Hz, 1H), 2.28 (s, 6H), 2.08 – 1.97 (m, 2H), 1.94 – 1.84 (m, 1H), 1.76 – 1.70 (m, 2H), 1.64 – 1.59 (m, 1H), 1.28 (s, 6H), 1.22 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 169.3, 154.9, 149.0, 140.2, 137.6, 123.7, 117.0, 115.3, 114.8, 84.3, 70.7, 46.4, 42.2, 40.8, 39.4, 36.1, 34.8, 31.1, 30.0, 29.9, 26.0, 25.6, 21.4, 21.3; IR (neat) 2948, 1768, 1750, 1626, 1576, 1371, 1198; HRMS (ESI-TOF) m/z: $[M+NH_4]^+$ calculated for $C_{24}H_{36}O_4N$ 402.2639; Found 402.2639.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at https:// Experimental details including NMR spectra and Tables of ^{1}H and ^{13}C NMR data (PDF)

Acknowledgements

This work was supported by an Australian Research Council Future Fellowship awarded to J.H.G. (FT170100437).

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