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A two-step biomimetic synthesis of antimalarial robustadials A and B

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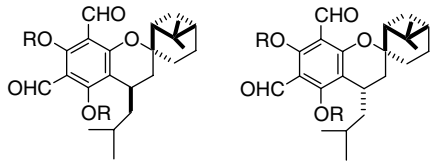
Abstract—The antimalarial robustadials A and B have been synthesized in two steps starting from commercially available phloroglucinol comprising a key biomimetic three-component reaction that involves in situ generation of an *o*-quinone methide via Knoevenagel condensation and subsequent Diels–Alder cycloaddition with (−)-β-pinene.

Robustadials A **1a** and B **1b** were isolated as antimalarial compounds from the leaves of *Eucalyptus robusta.*[1] They exhibited strong in vivo activity against *Plasmodium berghei*.[1] Several structurally similar phloroglucinol–terpene adducts (euglobals) occur widely in various species of *Eucalyptus* and are reported to show diverse biological activities such as Epstein–Barr Virus inhibitory, antileishmanial, antimalarial, etc.[2] The correct structure of robustadials was established by total synthesis of robustadial dimethyl ethers, **2a** and **2b**.[3,4]



1a: R = H
2a: R = CH_3

1b: R = H
2b: R = CH_3

As a part of our continuing program to explore naturally occurring phloroglucinol compounds for their biological potential,[5,6] we have developed a short and efficient method for the synthesis of robustadials A **1a** and B **1b** for evaluation of their antimalarial activity. There have been no further reports on the antimalarial activity of these compounds or other related compounds.

There have been some reports on the total synthesis of robustadials by different routes involving varying number of steps. Further, most of the syntheses were for dimethyl ether derivatives of robustadials and a few were of key precursors required for robustadial synthesis. Salomon et al. have synthesized robustadial dimethyl ethers from 2,4-dimethoxy-6-hydroxyacetophenone via condensation with (+)-nopinone, followed by cyclization and introduction of isobutyl and diformyl functionalities (8 steps, overall yield 2.5%).[3] Majewski and Bantle reported a stereoselective synthesis of one of the key intermediates involved in the synthesis of robustadials via Prins reaction.[7] Furthermore, Koser and Hoffman synthesized the dimethyl robustadial skeleton (which lacks the diformyl functionality) via a five-step procedure starting from 3,5-dioxo-cyclohexanecarboxylic acid methyl ester involving condensation, Diels–Alder cycloaddition and aromatization to yield the chroman skeleton.[8] Majewski et al. reported stereoselective syntheses of dimethyl robustadials via amine catalyzed cyclization as a key step for formation of the chroman skeleton (8 steps, overall yield 0.5%).[9] Recently, Aukrust and Skattebol reported a synthesis of robustadial A **1a** starting from (−)-nopol involving Friedel–Crafts condensation of an α,β-unsaturated acid derivative with phloroglucinol to yield the chromone skeleton in the key step (6 steps, overall yield 4%).[10] In

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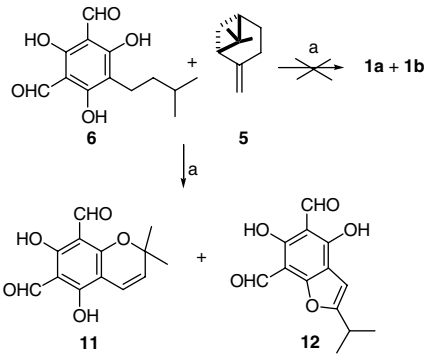
this letter, we report a simple and efficient two-step synthesis of robustadials A and B from commercially available phloroglucinol **9** with an overall yield of 27% involving Knoevenagel condensation followed by Diels–Alder cycloaddition as a key biomimetic step. This strategy should also give ready access to related euglobals and s-euglobals in higher yields.[6]

Biogenetically, robustadials A **1a** and B **1b** have been proposed to be formed from the Diels–Alder cycloaddition of *o*-quinone methide, **3** generated from jensenone **4** with (−)-β-pinene **5**.[2,11] Based on the proposed biogenesis, our retrosynthetic analysis of **1** is depicted in Scheme 1. The ring skeleton of **1** could be constructed from *o*-quinone methide, **3** via a Diels–Alder cycloaddition reaction with **5**. The key intermediate, *o*-quinone methide, **3** could be generated by the oxidation of diformylated synthon **6** or by coupling of phenol **7** and aldehyde **8** via a Knoevenagel condensation.

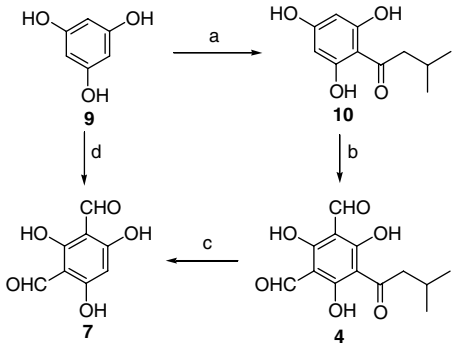
Our synthetic strategy involved initial synthesis of diformylated key precursors, **6** or **7**. Based on earlier reports[6,12] on the synthesis of several natural as well as unnatural euglobals which are structurally similar to robustadials, we initially prepared 3,5-diformyl-isopentyl phloroglucinol **6** which after treatment with DDQ in the presence of (−)-β-pinene **5** was expected to yield the desired cycloadduct. The precursor, **6** was synthesized as described earlier.[5,13]

Treatment of **6** with (−)-β-pinene **5** in the presence of DDQ in nitromethane, however, did not result in formation of the desired pair of diastereoisomers **1a** and **1b**, instead benzopyran **11** and benzofuran **12**, respectively, were formed via DDQ-mediated intramolecular cyclization of the isopentyl functionality (Scheme 2).[14] A similar type of DDQ-mediated intramolecular cyclization was reported earlier for mallotojaponin.[15]

In order to synthesize **7**, we adopted two different approaches. The first involved synthesis of the naturally occurring diformylated acyl phloroglucinol compound, jensenone **4** as reported earlier.[5] Jensenone **4** upon deacylation by refluxing in 80% sulfuric acid for 1 h resulted in the formation of **7** in 45% yield (Scheme 3). A second



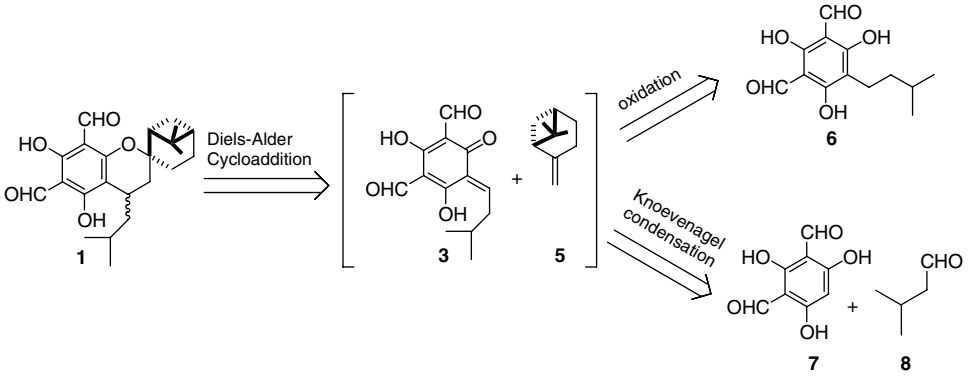
Scheme 2. Reagents and conditions: (a) DDQ, CH_3NO_2, 60 °C, 2 h, 20%.



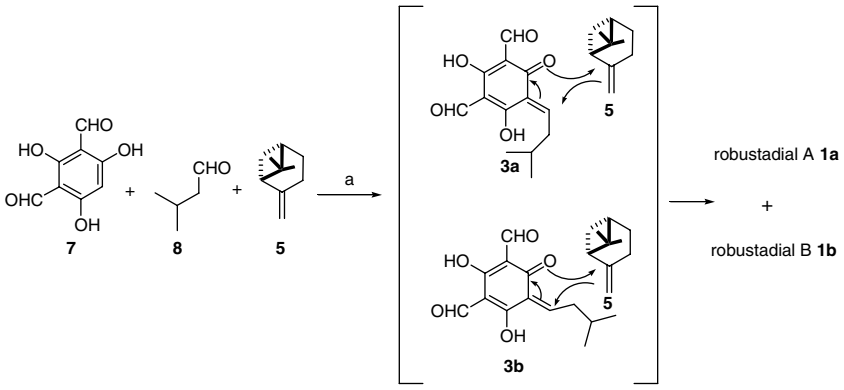
Scheme 3. Reagents and conditions: (a) $(CH_3)_2CHCH_2COCl$, $AlCl_3$, 50 °C, 40%; (b) $(CH_2)_6N_4$, TFA, 60 °C, 2 h, 40%; (c) 80% H_2SO_4, 80 °C, 1 h, 45%; (d) $POCl_3$/DMF (3 equiv each), RT, 2 h, 40%.

approach involved direct introduction of both diformyl groups onto the phloroglucinol nucleus. After investigating a number of reagents and experimental conditions, **7** was synthesized from **9** using the Vilsmeier–Haack reagent (3 equiv each of $POCl_3$ and DMF) in 40% yield (Scheme 3).[16] Diformylation of phloroglucinol compounds has been reported earlier with $Zn(CN)_2$ in 1.5% yield.[17]

Treatment of 2,4-diformyl phloroglucinol **7** with isovaleraldehyde **8** and (−)-β-pinene **5** in the presence of



Scheme 1. Retrosynthetic analysis of robustadials A **1a** and B **1b**.



Scheme 4. Reagents and conditions: (a) CH_3COOH, CH_3COONa, MW, 1000 W, 4 min, 68%.

sodium acetate in acetic acid under microwave irradiation (1000 W) for 4 min resulted in formation of the desired products in a combined yield of 68% (Scheme 4). Similar results were obtained when the reaction was carried out under conventional heating at 80 °C for 2 h.

The *o*-quinone methide is generated in situ by addition of isovaleraldehyde to phloroglucinol followed by dehydration (Knoevenagel-like condensation). (−)-β-Pinene **5** can undergo the cycloaddition reaction with *o*-quinone methides, **3a** and **3b** via two distinct orientations and each can lead to two pairs of diastereoisomers. However, only one pair of diastereoisomers, **1a** and **1b** were formed which indicated selectivity in the Diels–Alder cycloaddition. This regioselective preference for formation of two isomers arises because the oxygen of the *o*-quinone methide only attacks the more substituted terminus of the pinene double bond.

Diastereoisomers **1a** and **1b** were separated by reverse phase preparative HPLC[18] and were characterized from spectral data, viz. UV, NMR, MS, IR and optical rotation.[19] All previously published papers reported data for the dimethyl ethers of robustadials except for that of Aukrust and Skattebol who reported spectral data for robustadial A only.[10] Hence, the structures were finally confirmed by synthesis of robustadial dimethyl ethers, **2a** and **2b** prepared by treatment of a mixture of **1a** and **1b** with methyl iodide in the presence of potassium carbonate in acetone (70% yield). The diastereoisomers **2a** and **2b** were separated by preparative-TLC[20] and were characterized by comparison of their UV, NMR, MS, IR and optical rotations with the literature data.[3,4]

In conclusion, we have reported a short and efficient two-step synthesis of antimalarial robustadials A **1a** and B **1b** starting from commercially available phloroglucinol **9** in an overall yield of 27%. This methodology should also be useful for the synthesis of euglobals in which an isobutyl group is present on the pyran ring.

Acknowledgements

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14. Compounds **11** and **12**: A mixture of 3,5-diformyl-1-isopentylphloroglucinol (**6**, 150 mg, 0.60 mmol), (−)-β-pinene (**5**, 0.186 ml, 1.19 mmol) and DDQ (10 mg) in nitromethane (10 ml) was heated at 60 °C for 2 h. The solvent was evaporated and the crude product was purified by silica gel column chromatography (5% EtOAc in hexane) to yield two products. 5,7-Dihydroxy-6,8-diformyl-2*H*-chromene (**11**, 30 mg, 21%): Cream white solid; mp 106–108 °C; IR (KBr): ν_{max} 3369, 2928, 1642, 1440, 1314, 1178, 112 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 13.39 (s, 1H), 13.16 (s, 1H), 10.16 (s, 1H), 10.06 (s, 1H), 6.57 (d, $J = 10.1$ Hz, 1H), 5.54 (d, $J = 10.1$ Hz, 1H), 1.25 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 191.9, 191.8, 168.9, 165.7, 163.0, 125.8, 114.5, 104.0, 103.9, 100.9, 80.5, 28.5; EIMS: m/z 248 $[M]^+$, 233, 205, 103, 77, 65, 53. 4,6-Dihydroxy-5,7-diformyl-2-isopropyl-benzofuran (**12**, 35 mg, 24%): Yellow oil; IR (Neat): ν_{max} 3412, 2927,

1647, 1451, 1301, 1212, 1137, 1064 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 13.43 (s, 1H), 12.83 (s, 1H), 10.32 (s, 1H), 10.21 (s, 1H), 6.47 (s, 1H), 3.06 (m, 1H), 1.34 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 193.4, 189.6, 166.0, 164.5, 164.4, 160.0, 110.8, 105.6, 101.6, 97.7, 28.0, 20.7; EIMS: m/z 248 $[M]^+$, 233, 220, 205, 107, 91, 77, 65, 41.

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16. Synthesis of **7**: To a solution of phloroglucinol dihydrate **9** (1.0 g, 6.17 mmol) in ethyl acetate (15 ml), dimethyl formamide (1.43 ml, 18.5 mmol) and phosphoryl chloride (1.73 ml, 18.5 mmol) were added and the reaction mixture was allowed to stir at room temperature for 2 h. Water (10 mL) was added and the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and finally dried over sodium sulfate. Silica gel column chromatography using 20% EtOAc in hexane gave **7** (0.45 g, 40%). 1,3-Diformyl-2,4,6-trihydroxybenzene **7**: Cream white solid; mp 218–220 °C; IR (KBr): ν_{max} 2959, 2576, 1645, 1441, 1399, 1259, 1195, 1097 cm^{-1}; ^1H NMR ($CDCl_3$: CD_3OD-4: 1, 300 MHz): δ 10.08 (s, 2H), 5.84 (s, 1H); ^{13}C NMR ($CDCl_3$: CD_3OD-4: 1, 75 MHz): δ 192.5, 170.1, 104.5, 94.6; CIMS: m/z 183 $[M+1]^+$.[17]
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18. Diastereoisomers, **1a** and **1b** were separated by reverse phase HPLC using a Shimadzu HPLC (USA manufacturing Inc.) system consisting of Princeton SPHER-100, C18 (100 A, 5 μ, 250 × 10.0 mm) column using methanol:water:acetic acid 100:5:3 as the mobile phase with a flow rate of 3.5 ml/min. Diastereoisomers, **1a** and **1b** eluted with retention times of 27.42 and 29.61 min, respectively.
19. Synthesis of robustadials A **1a** and B **1b**: A mixture of 1,3-diformyl-2,4,6-trihydroxybenzene (**7**, 0.2 g, 1.09 mmol), isovaleraldehyde (**8**, 0.24 ml, 2.18 mmol), (−)-β-pinene (**5**, 0.51 ml, 3.27 mmol) and sodium acetate (10 mg) in acetic acid (5 ml) was heated in a domestic microwave oven (1000 W, 4 min). On cooling, the solvent was removed under reduced pressure, ethyl acetate was added and the resultant mixture was washed with water and finally dried over sodium sulfate. The product was purified by silica gel column chromatography (5% EtOAc in hexane) to give robustadials A and B as a yellow oil (0.29 g, 68%). The mixture of diastereoisomers (70 mg) was separated by semi-preparative HPLC.[18] Robustadial A (**1a**, 20 mg): Yellow oil, $[\alpha]_D$ +71.19 (*c* 0.45, $CHCl_3$); UV ($CHCl_3$) λ_{max} 283 (ε 19,400), 300 (14,800), 350 (3200); IR (Neat): ν_{max} 3373, 2922, 1730, 1635, 1541, 1435, 1306, 1162, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 13.45 (br s, 2H), 10.14 (s, 1H), 10.04 (s, 1H), 2.90 (m, 1H), 2.26–1.72 (m, 11H), 1.48–1.43 (m, 1H), 1.30–1.22 (m, 1H), 1.24 (s, 3H), 1.01 (s, 3H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.24, 191.78, 169.42, 168.10, 164.12, 105.85, 104.62, 104.06, 85.90, 48.16, 42.54, 40.51, 38.97, 38.19, 30.49, 27.52, 26.50, 25.92, 25.44, 24.77, 24.02, 23.24, 20.94; CIMS: m/z 387 $[M+1]^+$, 251 ($M–C_{10}H_{16}$); Robustadial B (**1b**, 24 mg): Yellow oil, $[\alpha]_D$ −66.17 (*c* 0.45, $CHCl_3$); UV ($CHCl_3$) λ_{max} 283 (ε 17,030), 300 (13,400), 350 (2800); IR (Neat): ν_{max} 3373, 2925, 1733, 1634, 1544, 1440, 1383, 1302, 1178, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 13.48 (br s, 2H), 10.14 (s, 1H), 10.03 (s, 1H), 2.93 (m, 1H), 2.31–2.18 (m, 3H), 2.10–1.85 (m, 6H), 1.78–1.67 (m, 2H), 1.56 (d, $J = 9.1$ Hz, 1H), 1.30 (s, 3H), 1.25–1.20 (m, 1H), 1.03 (s, 3H), 0.98 (d, $J = 6.7$ Hz, 3H), 0.92 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.29, 191.77, 169.72, 168.11, 164.0, 105.99, 104.94, 103.94, 85.34, 50.58, 42.65, 40.36, 38.94, 38.18, 28.14, 27.16, 26.88, 25.75, 25.58, 24.74, 23.96, 23.42, 21.07; CIMS: m/z 387 $[M+1]^+$, 251 ($M–C_{10}H_{16}$).
20. The diastereoisomers **2a** and **2b** were separated by preparative TLC using 5% EtOAc in hexane as the mobile phase (R_f 0.31 and 0.27, respectively, triple run).