The First Total Synthesis of Grandinal, a New Phloroglucinol Derivative Isolated from *Eucalyptus grandis*

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The first total synthesis of grandinal (**1**) is accomplished by biomimetic cycloaddition of the jensenone derivative (**2**) and the *o*-quinone methide (**3**) generated by oxidation of grandinol (**4**).

Grandinal (**1**) is an isopentyl phloroglucinol dimer, isolated from *Eucalyptus grandis*, which showed attachment-inhibiting activity against the blue mussel *Mytilus edulis galloprovincialis*, and antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis*.[1] Grandinal (**1**) has a unique pyran skeleton and this structure was established by spectral and chemical investigations. Biogenetically, grandinal (**1**) is proposed to be formed by Diels–Alder cycloaddition of the jensenone derivative (**2'**) and the *o*-quinone methide (**3**) generated by oxidation of grandinol (**4**) (Figure 1).

Herein, we report an efficient total synthesis of grandinal (**1**) via biomimetic cycloaddition of the jensenone derivative (**2**) and the *o*-quinone methide (**3**).

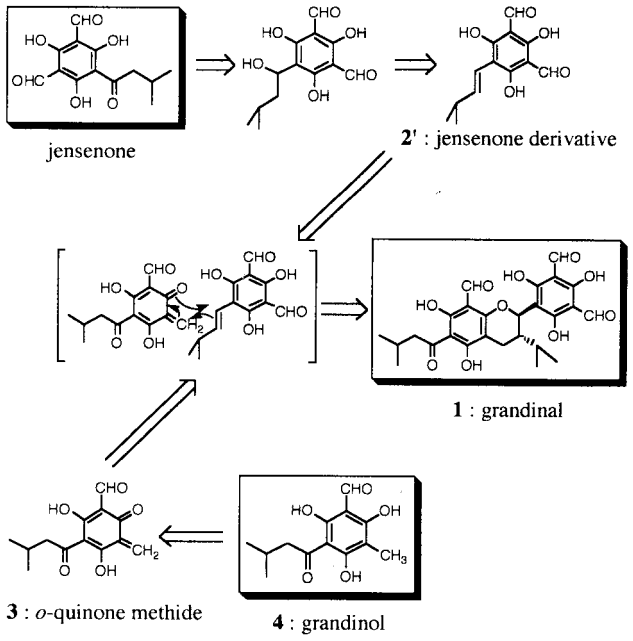
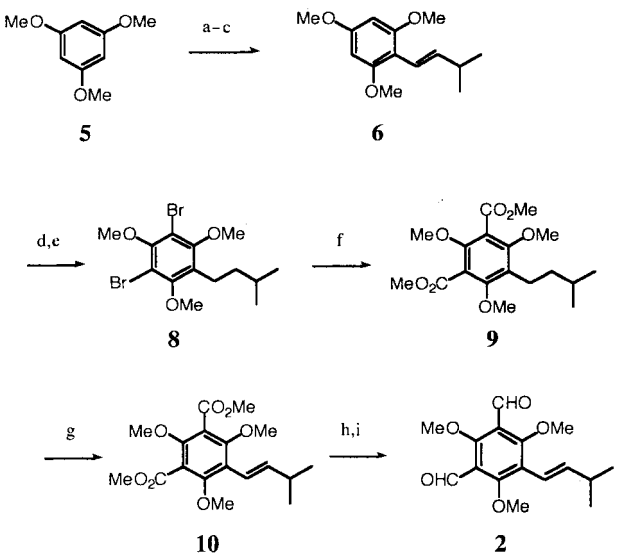


Figure. 1. Proposed biogenetic pathway for grandinal (**1**).

We prepared grandinol (**4**) by an alternate and improved procedure in three steps in 13% overall yield.[2]

Synthesis of the jensenone derivative (**2**) was started from **5** (Scheme 1). An isovaleryl group was readily introduced by a reaction with isovaleryl chloride. Reduction of the isovaleryltrimethoxybenzene with LAH and subsequent dehydration by irradiation in $CHCl_3$ gave the styrene compound (**6**).[3]

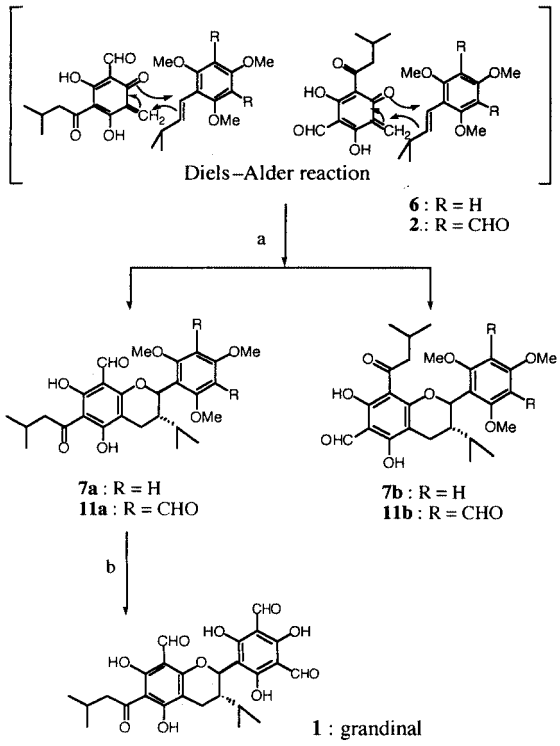
In order to investigate the feasibility of cycloaddition, we have implemented Diels–Alder cycloaddition of grandinol (**4**) and the styrene compound (**6**) using DDQ (Scheme 2). Generation of the *o*-quinone methide as diene by DDQ led to cycloaddition with the styrene compound (**6**) as dienophile. The reaction was carried out in nitromethane at 60 °C[4] and consequently gave the desired product **7a** and the regioisomer **7b**. This result indicated that two *o*-quinone methide species were generated by oxidation with DDQ leading to two regioisomers. Thus, we succeeded Diels–Alder cycloaddition between grandinol (**4**) and the styrene compound (**6**).



Conditions
(a) Isovaleryl chloride, $AlCl_3$, 0 °C, 3 h, 84%. (b) LAH, 0 °C, 3 h, 97%.
(c) $CHCl_3$, irradiation, 2.5 h, 100%. (d) Pt_2O, H_2, 12 h, 100%.
(e) Br_2, CH_2Cl_2, 15 h, 83%. (f) *t*-BuLi / THF, –78 °C, then $ClCO_2Me$, 2 h, 52%.
(g) 1) NBS, AIBN, CCl_4, reflux, 1 h. 2) DBU, THF : DMF = 1 : 1, 20 h, 60%.
(h) DIBAL, CH_2Cl_2, –78 °C, 2 h, 77%. (i) PDC, CH_2Cl_2, 17 h, 79%.

Scheme 1.

Further, the styrene compound (**6**) was reduced by treatment with Pt_2O under H_2 atomosphere to yield the alkylbenzene. Aromatic bromination of the alkylbenzene using Br_2 gave **8**. Two methyl ester groups of **9** were introduced adding $ClCO_2Me$ via lithium–bromide exchange reaction of **8** using *t*-BuLi. Allyl bromination of **9** with NBS in the presence of



Conditions

(a) DDQ, nitromethane, 60 °C, 3 days, **8a**=24%, **8b**=30%, **9a**=14%, **9b**=18%.
(b) $BBr_3S(Me)_2$, $ClCH_2CH_2Cl$, 70 °C, 20 h, 55%.

Scheme 2.

AIBN as a radical initiator and subsequent elimination with DBU gave **10**. DIBAL reduction led to the desired diol styrene compound. Finally, oxidation of the diol styrene compound was accomplished using PDC. The jensenone derivative (**2**) was thus synthesized in nine steps in 13% overall yield as shown in Scheme 1.[3,5,6]

Having successfully prepared the desired compounds, the jensenone derivative (**2**) was subjected to Diels–Alder cycloaddition under the same conditions (Scheme 2). Purification by column chromatography of the reaction mixture furnished the desired product **11a** in 14% yield and the regioisomer **11b** in 18% yield.[7]

Finally, **11a** was subjected to deprotection of the hydroxy groups with $BBr_3S(Me)_2$.[6] Since the reaction product was identical with the natural product on the basis of comparisons of spectral data and HPLC,[1] we accomplished the first synthesis of grandinal (**1**) (Scheme 2).

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References and Notes

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2 K. Umehara, I. P. Singh, H. Etoh, M. Takasaki, and T. Konoshima, *Phytochemistry*, **49**, 1699 (1998).
3 Spectral data of **6** : ^{1}H NMR ($CDCl_3$, 270 MHz) δ ppm: 6.54 (1H, d, *J* = 16.5 Hz), 6.45 (1H, dd, *J* = 16.5 Hz, 6.7 Hz), 6.13 (2H, s), 3.82 (6H, s), 3.80 (3H, s), 2.44 (1H, octet, *J* = 6.7 Hz), 1.08 (6H, d, *J* = 6.7 Hz) ; ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ ppm: 159.4 (s), 158.9 (2s), 140.1 (d), 116.9 (d), 108.4 (s), 91.0 (2d), 55.7 (2q), 55.3 (q), 33.1 (d), 22.9 (2q). Spectral data of **2** : ^{1}H NMR ($CDCl_3$, 270 MHz) δ ppm: 10.33 (2H, s), 6.47 (1H, dd, *J* = 16.2 Hz, 6.8 Hz), 6.28 (1H, d, *J* = 16.2 Hz), 3.93 (3H, s), 3.81 (6H, s), 2.51 (1H, octet, *J* = 6.8 Hz), 1.10 (6H, d, *J* = 6.8 Hz) ; ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ ppm: 188.1 (2d), 165.7 (2s), 164.0 (s), 145.5 (d), 123.5 (s), 120.5 (2s), 114.9 (d), 65.1 (q), 62.2 (2q), 32.6 (d), 22.1 (2q).
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5 T. Tanaka, H. Mikamiyama, K. Maeda, and C. Iwata, *J. Org. Chem.*, **63**, 9782 (1998).
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7 Spectral data of **11a** : HRFAB-MS [*m/z* 543.2230 $(M+H)^+$ + 0.1 mmu for $C_{29}H_{35}O_{10}$] ; UV $\lambda_{max.}$ (MeOH) nm (log ε) : 250 (4.10), 275 (4.35), 334 (3.38) ; IR $\nu_{max.}$ (NaCl) cm^{-1} : 1695, 1624, and 1127 ; ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm: 15.50 (1H, s), 14.34 (1H, s), 10.33 (2H, s), 9.87 (1H, s), 5.38 (1H, d, *J* = 10.6 Hz), 4.04 (3H, s), 3.88 (6H, s), 2.98 (2H, d, *J* = 6.7 Hz), 2.76 (1H, dd, *J* = 17.1 Hz, 5.2 Hz), 2.75 (1H, m), 2.32 (1H, dd, *J* = 17.0 Hz, 13.3 Hz), 2.24 (1H, septet, *J* = 6.7 Hz), 1.55 (1H, double septet, *J* = 6.7 Hz, 3.6 Hz), 0.97 (6H, d, *J* = 6.7 Hz), 0.96 (3H, d, *J* = 6.7 Hz), 0.75 (3H, d, *J* = 6.7 Hz) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm: 206.5 (s), 190.9 (d), 187.2 (2d), 172.0 (s), 167.9 (4s), 161.5 (s), 122.3 (s), 120.2 (2s), 103.8 (s), 103.4 (s), 102.6 (s), 76.5 (d), 66.0 (q), 65.0 (2q), 52.7 (t), 37.8 (d), 27.6 (d), 25.0 (d), 22.7 (2q), 21.1 (q), 18.3 (t), 15.3 (q). Spectral data of **11b** : HRFAB-MS [*m/z* 543.2230 $(M+H)^+$ – 0.2 mmu for $C_{29}H_{35}O_{10}$] ; UV $\lambda_{max.}$ (MeOH) nm (log ε): 250 (4.29), 283 (4.40), 334 (3.66) ; IR $\nu_{max.}$ (NaCl) cm^{-1} : 1686, 1616, and 1131 ; ^{1}H NMR ($CDCl_3$, 500 MHz) δ ppm: 15.26 (1H, s), 13.30 (1H, s), 10.32 (2H, s), 10.20 (1H, s), 5.45 (1H, d, *J* = 10.7 Hz), 4.03 (3H, s), 3.91 (6H, s), 2.80 (1H, dd, *J* = 16.2 Hz, 4.9 Hz), 2.68 (1H, m), 2.64 (1H, dd, *J* = 15.0 Hz, 6.4 Hz), 2.48 (1H, dd, *J* = 15.0 Hz, 7.3 Hz), 2.35 (1H, dd, *J* = 16.2 Hz, 12.4 Hz), 2.02 (1H, septet, *J* = 6.7 Hz), 1.60 (1H, double septet, *J* = 7.0 Hz, 3.0 Hz), 0.99 (3H, d, *J* = 7.0 Hz), 0.80 (3H, d, *J* = 7.0 Hz), 0.66 (3H, d, *J* = 6.7 Hz), 0.61 (3H, d, *J* = 6.7 Hz) ; ^{13}C NMR ($CDCl_3$, 125 MHz) δ ppm: 205.1 (s), 192.5 (d), 186,8 (2d), 169.8 (s), 168.7 (s), 167.5 (3s), 163.1 (s), 121.5 (s), 119.2 (2s), 104.7 (s), 103.9 (s), 101.6 (s), 76.5 (d), 66.2 (q), 64.8 (2q), 52.7 (t), 37.7 (d), 27.5 (d), 24.8 (d), 22.5 (q), 22.2 (q), 21.1 (q), 18.3 (t), 15.5 (q).