Synthesis of euglobal-G3 and -G4

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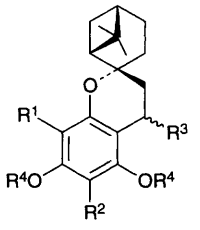
The first, concise synthesis of euglobals is accomplished by biomimetic cycloaddition of β-pinene and quinone methides generated by oxidation of grandinol

Euglobals[1] (*e.g.* **1** and **2**) and robustadials[2] (*e.g.* **3** and **4**) were isolated from *Eucalyptus* spp. as inhibitors of the Epstein–Barr virus activation,[3] or as antimalarial compounds. These compounds have unique chroman or spirochroman skeletons. Recently, the construction of these skeletons[4] and derivatives has been investigated. Salomon *et al.* reported the synthesis of robustadial A and B dimethyl ethers (**5** and **6**) by a pyrrolidine-catalysed condensation of (+)-nopione with 2,4-dimethoxy-6-hydroxyacetophenone.[5] Koser *et al.* synthesized precursors of **5** and **6** by the cycloaddition of 1-oxabutadiene species and β-pinene.[6] We have also reported an electrochemical generation of *o*-quinone methides and their cycloaddition with α-phellandrene to yield the euglobal Ia_1 and Ia_2 skeletons.[7]

Presently, we envisioned that synthesis of natural euglobals could be readily accessible by the cycloaddition of terpenes and quinone methides (**A** or **B**), and directed our attention to grandinol **7** which was also isolated from *Eucalyptus* spp. That is, *in situ* generation of **A** or **B** by the oxidative activation of the benzylic site of **7** and subsequent cycloaddition with terpenes was expected to simply give natural euglobals.



euglobal-G3 **1** R^1 = CHO, R^2 = $COCH_2CHMe_2$, R^3, R^4 = H

euglobal-G4 **2** R^1 = $COCH_2CH(Me)_2$, R^2 = CHO, R^3, R^4 = H

robustadial A **3** R^1, R^2 = CHO, R^3 = β-CH_2CHMe_2, R^4 = H

robustadial B **4** R^1, R^2 = CHO, R^3 = α-CH_2CHMe_2, R^4 = H

robustadial A dimethyl ether **5**

R^1, R^2 = CHO, R^3 = β-CH_2CHMe_2, R^4 = Me

robustadial B dimethyl ether **6**

R^1, R^2 = CHO, R^3 = α-CH_2CHMe_2, R^4 = Me

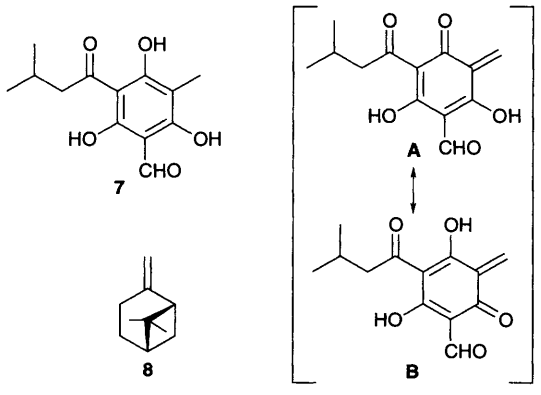
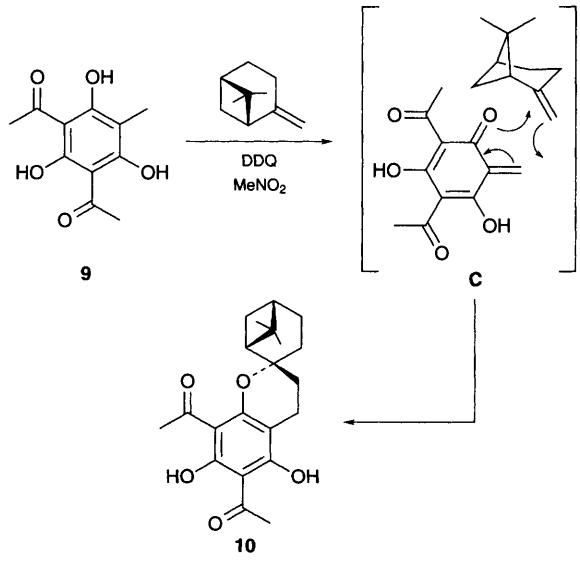


Fig. 1

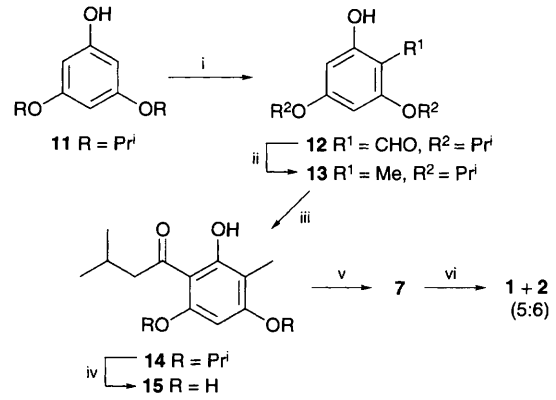
First, as a model study, we tried the oxidative generation of a corresponding quinone methide **C** from 2,6-diacetyl-4-methylphloroglucinol **9**.[8] Although the intermolecular cycloaddition of *o*-quinone methides and unactivated alkenes has been proven difficult, 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) oxidation of **9** in the presence of β-pinene in nitromethane gave the desired cycloadduct **10** after standing for 1 h at 50 °C (yield 84%). The reaction was successful only in nitromethane. The desired product was not obtained in MeOH, PhH, DMF, Et_2O or MeCN.

Accordingly, we planned to synthesize natural euglobals by the oxidative activation of **7** with DDQ in nitromethane as a key step. We chose phloroglucinol diisopropyl ether **11** as a starting material in order to regulate the alkylation and acylation to the highly nucleophilic phloroglucinol aromatic carbons.[9] The methyl group was first introduced to give **13** by the formylation of **11** followed by deoxygenation by excess Raney Ni in refluxing aqueous ethanol[10] (80% yield from **11**). Friedel–Crafts acylation of **13** by isovaleryl chloride in $TiCl_4$–CH_2Cl_2 followed by deprotection[11] of **14** with $TiCl_4$ in CH_2Cl_2 at ambient temperature gave 2-methyl-6-(3-methylbutyryl)phloroglucinol **15** (yield 71% from **13**). Formylation of **15** was accomplished by dichloromethyl methyl ether in $TiCl_4$–CH_2Cl_2 to give **7** in 42% yield. Finally, DDQ oxidation of **7** in nitromethane in the presence of 3 equiv. of (+)-β-pinene successively gave **1** and **2** (60% yield, **1** : **2** = 6 : 5). The spectral data and optical rotations of the synthesized euglobals were identical† with those of the natural compounds established the absolute configuration of euglobal-G3 and -G4.[1f]

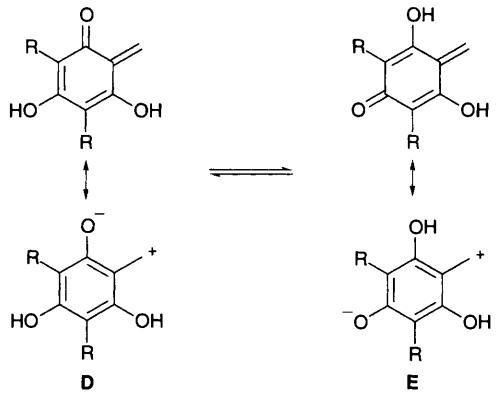
A proposed cycloaddition route is *via* generation of quinone methides which subsequently form cycloadducts with β-pinene.



Scheme 1



Scheme 2 *Reagents and conditions*: i, $HC(OEt)_3$, BF_3/Et_2O; ii, Raney Ni; iii, isovaleryl chloride, $TiCl_4$; iv, $TiCl_4/CH_2Cl_2$; v, $CHCl_2OCH_3$, $TiCl_4$; vi (+)-β-pinene, DDQ–$MeNO_2$



Scheme 3

As *o*-quinone methide intermediates (*e.g.* **A**, **B** or **C**) are equivalent to a corresponding zwitterion (*e.g.* **D**), the polar transition state might be stabilized in solvents with high dielectric constant like nitromethane. The reaction was regio- and stereo-selective to give only the same isomers already isolated as natural products. These results suggest that the present cycloaddition reaction is similar to the biogenetic synthesis,[12] and can be applied to the syntheses of varied natural euglobals and robustadials in biomimic short steps.

Footnote

† *Selected data* for euglobal-G3 **1**. $[\alpha]_D^{24}$ + 9.3 (*c* 0.15, $CHCl_3$); MS *m/z*: 386 (M^+, 51), 343 (39), 251 (100), 193 (22), 148 (28) and 93 (27); UV λ_{max} (1,4-dioxane)/nm(ε): 278 (37 000) and 338 (34 000); IR(NaCl) ν_{max}/cm^{-1}: 3600–3300, 2950, 1620, 1430, 1295 and 1185; ^1H NMR ($CDCl_3$) δ 15.39 (1 H, s), 14.45 (1 H, s), 10.03 (1 H, s), 2.99 (2 H, d, *J* 6.75 Hz), 2.57 (2 H, t, *J* 6.48 Hz), 2.27 (1 H, sept, *J* 6.75 Hz), 2.18 (1 H, t, *J* 5.13 Hz), 2.08–1.96 (5 H, m), 1.96–1.83 (2 H, m), 1.62 (1 H, d, *J* 9.99 Hz), 1.31 (3 H, s), 1.04 (3 H, s), and 1.00 (6 H, d, *J* 7.02 Hz); ^{13}C NMR ($CDCl_3$) δ 206.4, 191.8, 171.3, 168.3, 161.9, 104.4, 103.3, 101.1, 84.9, 52.7, 49.6, 40.6, 38.3, 31.9, 28.5, 27.5, 26.6, 25.1, 24.8, 23.3, 22.8 and 15.4 For euglobal-G4 **2**. $[\alpha]_D^{24}$ + 11.6 (*c* 0.09, $CHCl_3$); MS *m/z*: 386 (M^+ 50), 343 (53), 251 (100), 233 (19), 193 (31) and 148 (24); UV λ_{max}/(1,4-dioxane) 276 (37 500) and 346 (5150); IR (NaCl) ν_{max}/cm^{-1}: 3600–3300, 2960, 1610 and 1420; ^1H NMR($CDCl_3$) δ 15.37 (1 H, s), 13.18 (1 H, s), 10.19 (1 H, s), 3.00 (2 H, d, *J* 7.02 Hz), 2.58 (2 H, t, *J* 6.75 Hz), 2.29–2.24 (2 H, m), 2.19 (1 H, t, *J* 5.94 Hz), 2.06–1.86 (7 H, m), 1.63 (1 H, d, *J* 9.99 Hz), 1.30 (3 H, s), 1.03 (3 H, s), 0.97 (3 H, d, *J* 4.05 Hz) and 0.95 (3 H, d, *J* 3.78 Hz); ^{13}C NMR($CDCl_3$) δ 205.7, 192.5, 169.9, 166.9, 163.3, 104.7, 104.3, 100.4, 86.7, 53.1, 49.4, 40.4, 38.3, 31.3, 28.7, 24.8, 24.7, 23.4, 22.8, 22.7, 19.2 and 15.2.

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