Synthesis of euglobal-G3 and -G4

Kazuhiro Chiba,* Takaaki Arakawa and Masahiro Tada

Laboratory of Bio-organic Chemistry, Tokyo University of Agriculture and Technology, 3-5-8 Saiwai-cho, Fuchu, Tokyo 183, Japan

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

Euglobals¹ (*e.g.* 1 and 2) and robustadials² (*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 skeletons⁴ 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 Ia₁ and Ia₂ 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



euglobal-G3 1 R¹ = CHO, R² = COCH₂CHMe₂, R³, R⁴ = H euglobal-G4 2 R¹ = COCH₂CH(Me)₂, R² = CHO, R³, R⁴ = H robustadial A 3 R¹, R² = CHO, R³ = β -CH₂CHMe₂, R⁴ = H robustadial B 4 R¹, R² = CHO, R³ = α -CH₂CHMe₂, R⁴ = H

robustadial A dimethyl ether 5

 $R^1,\,R^2=CHO,\,R^3=\beta\text{-}CH_2CHMe_2,\,R^4=Me$ robustadial B dimethyl ether ${\bf 6}$

 R^1 , $R^2 = CHO$, $R^3 = \alpha$ - CH_2CHMe_2 , $R^4 = Me$



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.

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, Et₂O 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 ethanol¹⁰ (80% yield from 11). Friedel-Crafts acylation of 13 by isovaleryl chloride in TiCl₄-CH₂Cl₂ followed by deprotection¹¹ of 14 with TiCl₄ in CH_2Cl_2 at 2-methyl-6-(3-methylambient temperature gave butyryl)phloroglucinol 15 (yield 71% from 13). Formylation of 15 was accomplished by dichloromethyl methyl ether in TiCl₄-CH₂Cl₂ 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 2 Reagents and conditions: i, HC(OEt)₃, BF₃/Et₂O; ii, Raney Ni; iii, isovaleryl chloride, TiCl₄; iv, TiCl₄/CH₂Cl₂; v, CHCl₂OCH₃, TiCl₄; vi (+)- β -pinene, DDQ-MeNO₂



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 regioand 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, CHCl₃); 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 (CDCl₃) & 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); ¹³C NMR (CDCl₃) & 2064, 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 $E_{\rm [}\alpha_{\rm D}^{24}$ + 11.6 (c 0.09, CHCl₃); MS m/z: 386 (M⁺ 50), 343 (53), 251 (100), 233 (19), 193 (31) and 148 (24); UV $\lambda_{\rm max}/(1.4$ -dioxane) 276 (37 500) and 346 (5150); IR (NaCl) $\nu_{\rm max}/{\rm cm^{-1}}$: 3600–3300, 2960, 1610 and 1420; ¹H NMR(CDCl₃) & 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); ¹³C NMR(CDCl₃) & 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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