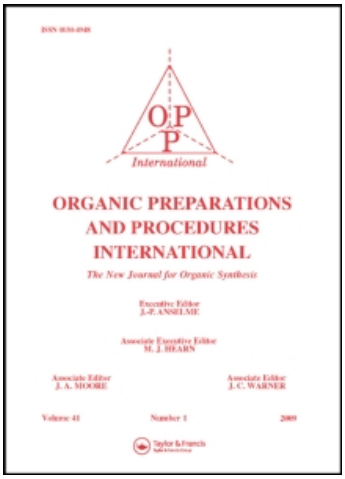

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A PRACTICAL PROCEDURE FOR THE SYNTHESIS OF 3-((E)-5-(2,3,4,5-TETRAMETHOXY-6-METHYLPHENYL)-3METHYLPENT-3-ENYL)-2,2-DIMETHYLOXIRANE

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A PRACTICAL PROCEDURE FOR THE SYNTHESIS OF 3-((E)-5-(2,3,4,5-TETRAMETHOXY-6-METHYLPHENYL)-3-METHYLPENT-3-ENYL)-2,2-DIMETHYLOXIRANE

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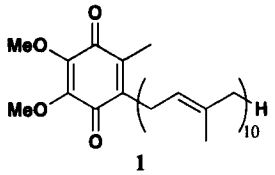
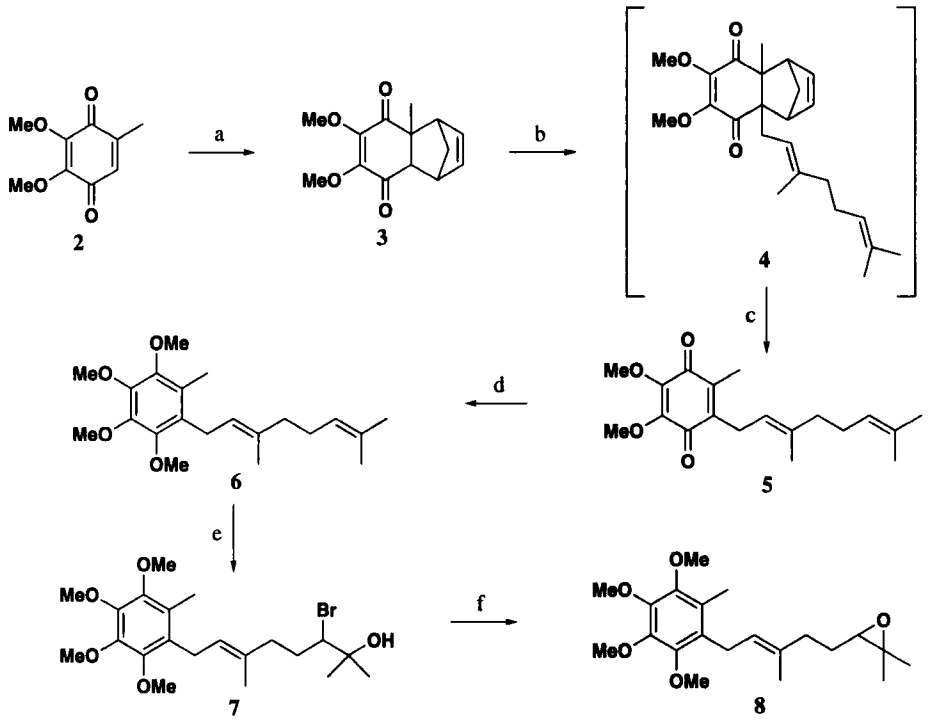
3-[(E)-5-(2,3,4,5-Tetramethoxy-6-methylphenyl)-3-methylpent-3-enyl]-2,2-dimethyloxirane (**8**) is a key intermediate for total synthesis of coenzyme Q10 (**1**) and has previously been synthesized from *p*-cresol *via* bromination, methylation, Grignard reaction and epoxidation.[1,2] However, this procedure is not attractive for the large-scale preparation of **8** due to drawbacks such as low yield (ca. 30% overall yield), low reaction temperature (–78°C), chromatographic separation and the use of several expensive and hazardous reagents. Therefore, a practical method for synthesis of **8** is desirable. Herein, we report a new efficient and convenient method for the preparation of **8** from commercially available starting material **2**.



1

The synthetic route to **8** is depicted in *Scheme 1*. The Diels-Alder cycloaddition of **2** with cyclopentadiene provided **3** in nearly quantitative yield. The reaction time was reduced from 4 days in CH_2Cl_2 to only 24 h by using AcOH as catalyst and solvent at room temperature.[3] According to the procedure for the preparation of an analogue,[4] enolization of **3** by potassium *t*-butoxide and subsequent geranylation in anhydrous THF/DMF led smoothly to compound **4**, which, without any purification, was induced to undergo thermal elimination of cyclopentadiene at 100°C/6 Torr for 4 h to afford compound **5** (91% yield). Reduction of **5** with $Na_2S_2O_4$ in acetone and subsequent methylation of the resulting substituted hydroquinone with Me_2SO_4 in the presence of NaOH furnished ether **6** in 96% yield in a one-pot procedure. The bromination/addition of **6** with NBS in THF/H_2O at –10°C subsequent treatment of the resulting bromoalcohol **7** with K_2CO_3 in CH_3OH in the absence of light, afforded the desired epoxide **8** in 76% yield.

In conclusion, we have developed a facile and practical procedure for the preparation of **8** starting from commercially available starting material 2,3-dimethoxy-5-methylquinone (**2**) with an overall yield of 65% from **2**. This procedure is superior as a practical, high yield synthesis because of the mild reaction conditions and the use of inexpensive reagents.



a) Cyclopentadiene, AcOH, r.t., 24 h, 99%; b) *t*-BuOK, geranyl bromide, THF, DMF, -25°C; c) 100°C/6 Torr, 91% (two steps); d) $Na_2S_2O_4$, H_2O, acetone, 0.5 h, r.t., then NaOH, $(CH_3)_2SO_4$, 2 h, r.t., 96%; e) NBS, THF, H_2O, 4 h, -10°C; f) K_2CO_3, CH_3OH, 10°C, 76% (two steps)

Scheme 1

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded with a Bruker DMX500 using TMS as an internal standard. Chemical shifts (δ) are expressed in ppm. GC-MS spectra were recorded on Finnigan Voyager instrument. Elemental analyses were performed on a Carlo-Erba 1006 elemental analyzer.

4,5-Dimethoxy-2-methyltricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione (3).- A solution of **2** (10 g, 0.05 mol) and freshly distilled cyclopentadiene (11 g, 0.16 mol) in AcOH (30 mL, 0.5 mol) was stirred at room temperature for 24 h. The reaction mixture was adjusted to pH 8 with 2N aq. NaOH (30 mL) and extracted with AcOEt (3 x 40 mL). The combined organic extracts were washed with water (3 x 30 mL) and dried over $MgSO_4$. The solvent was evaporated in *vacuo* and the crude product was purified over silica gel (hexane:EtOAc, 6:1) to give **3** (13.48 g, 99%) as a pale red oil. ^{1}H NMR: (400MHz, $CDCl_3$): δ 6.16 (dd, 1H, J = 2.28, 4.44Hz,), 6.02 (dd, 1H, J = 2.24, 4.08 Hz,), 3.94 (s, 3H, CH_3O), 3.93 (s, 3H, CH_3O), 1.31 (s, 3H, CH_3), 3.43 (s, 1H), 3.09 (s, 1H), 2.84 (d, 1H, J = 1.56 Hz), 1.67, 1.56 (AB, 2H, J = 7.28 Hz)

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.65; H, 6.68

2-[(*E*)-3,7-Dimethyl-2,6-octadienyl]5,6-dimethoxy-3-methyl-1,4-benzoquinone (5).- To a mixture of t-BuOK (6 g, 53 mmol) in anhydrous THF/DMF (90 mL/30 mL) was added dropwise a solution of **3** (10.8 g, 44 mmol) in anhydrous THF/DMF (30 mL/10 mL) at –25°C during 1.5 h, and then a solution of geranyl bromide (9.4 g, 44 mmol) in anhydrous THF/DMF (15 mL/5 mL) was slowly added at the same temperature. The reaction mixture was stirred for 2 h at –25°C and water (200 mL) was added and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with saturated aq. NaCl (3 x 40 mL) and dried over Na_2SO_4, filtered and concentrated in *vacuo*. The crude product was distilled at 100°C/6Torr for 4 h to provided crude 13.8 g of **5** (95% purity determined by GC-MS), which was further purified by chromarography on silica gel (hexane: EtOAc, 4:1) as a pale red oil (12.64g, 91%). ^{1}H NMR: (400 MHz,$CDCl_3$): δ 4.95 (s, 1H, $CH=C(CH_3)_2$), 4.88 (t, 1H, J = 7 Hz, CH=C), 3.99 (s, 3H, CH_3O), 3.98 (s, 3H, CH_3O), 3.11 (d, 2H, J = 7 Hz, $ArCH_2$), 2.02 (s, 3H, $ArCH_3$), 1.94 (s, 2H, CH_2), 1.74 (s, 3 H, CH_3), 1.67 (s, 3H, CH_3), 1.55 (s, 3H, CH_3). GC-MS (m/z): 320 (M^+ + 2H, 8), 318 (M^+, 14), 303 (18), 275 (37), 249 (30), 235 (100), 217 (85), 197 (58), 196 (50), 69 (83), 66 (5).

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.18. Found: C, 71.75; H, 8.23

1,2,3,4-Tetramethoxy-5-methyl-6-((*E*)-3,7-dimethylocta-2,6-dienyl)benzene (6).- To a solution of **5** (40 g, 0.10 mol) in acetone (100 mL) was added a solution of $Na_2S_2O_4$ (20 g, 0.11 mol) in water (50 mL) at room temperature. After stirring 30 min, a solution of 4N aq. NaOH (50 mL) was added. After the reaction mixture had been stirred for an additional 15 min, Me_2SO_4 (40 mL) was added dropwise at 25°C and stirring was continued at room temperature for 2 h and then refluxed for 30 min. The organic phase was separated. And the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with water (3 x 50 mL), dried over Na_2SO_4 and evaporated in *vacuo*. The oily residue was chromatographed on silica gel (hexane:EtOAc, 5:1) to give pure **6** (33.4 g, 96%) as a light yellow oil. ^{1}H NMR: (400 MHz, $CDCl_3$): δ 4.81 (s, 1H, olefin), 4.72 (s, 1H, olefin), 3.76 (s, 6H, OCH_3), 3.70 (s, 6H, OCH_3), 3.24 (d, J = 5.3Hz, 2H, CH_2), 2.09 (s, 3H, CH_3), 1.71 (s, 2H, CH_2), 1.63 (s, 2H, CH_2), 1.68 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.51 (s, 3H, CH_3). GC-MS (m/z): 350 (M^+ + 2H, 2), 349 (M^++1H, 14), 348 (63), 225 (100), 211 (25), 69 (30).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.51; H, 9.45

3-((E)-5-(2,3,4,5-Tetramethoxy-6-methylphenyl)-3-methylpent-3-enyl)-2,2-dimethyloxirane (8).- To a stirred solution of **6** (1 g, 2.9 mmol) in THF/H_2O (2.5 mL/1 mL) at –10°C was added NBS (0.5 g, 3 mmol). The reaction mixture was stirred for 4 h, and poured into water (20 mL) and extracted with AcOEt (3 x 10 mL). The organic layer was washed with saturated aq. NaCl (3 x 20 mL) and dried over Na_2SO_4 and the solvent was evaporated in *vacuo*. After cooling to room temperature, CH_3OH (10 mL) and powdered K_2CO_3 (0.28 g, 2 mmol) were added, and the reaction mixture was stirred for a further 2 h at 10°C protected from light. After removal of the solvent in *vacuo*, AcOEt (15 mL) was added and washed with water (3 x 10 mL), dried over Na_2SO_4. The solvent was evaporated in *vacuo* and the crude oil was purified by column chro-

matography (hexane:EtOAc, 9:1) to afford pure **8** (0.79 g, 76%) as a pale yellow oil. ^{1}H NMR: (400MHz,$CDCl_3$): δ 5.05 (s, 1H, olefin), 2.23 (s, 1H, CH), 3.83 (s, 6H, CH_3O), 3.71 (s, 6H, CH_3O?2), 3.22 (d, J = 6.4Hz, 2H, CH_2), 2.06 (s, 3H, CH_3), 2.00 (s, 2H, CH_2), 1.97 (s, 2H, CH_2), 1.60 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.23 (s, 3H, CH_3). GC-MS (m/z): 364 (M^+, 95), 365 (M^+ + 1H, 20), 247 (50), 225 (100), 189 (50), 173 (20), 85 (22)

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.90. Found: C, 69.45; H, 8.82

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A PRACTICAL PREPARATION OF *N,N*-PHTHALYL-L-GLUTAMIC 1,5-ANHYDRIDE

Submitted by Haining Gu[†]* and Yongxiang Jiang[††]
(08/13/04)

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N,N-Phthalyl-L-glutamic anhydride is a crucial reagent for γ-glutamylations. A useful synthetic route to glutamylaminoacids and glutamylamino peptides has been successfully established by the utilization of compounds protected by the phthalyl group.[1] The phthalyl moiety was chosen in preference to the carbobenzoxy as a protecting group because ring opening of the appropriate L-glutamic anhydride with amines is known[2] to give γ-glutamyl derivatives with the former protecting group, while yielding α-glutamyl products with the latter.

In general, phthalimidoacids have been prepared by heating mixtures of the aminoacids and phthalic anhydride slightly above the fusion point of the anhydride,[3] but the product thus obtained from L-glutamic acid was not pure when crystallized from water.[4] The condensation