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Synthesis of 5-*O*-methylembelin

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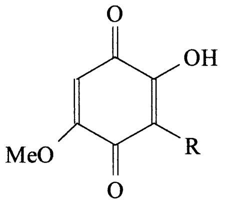
Abstract—A general synthetic route to 3-alkyl-2-hydroxy-5-methoxy-1,4-benzoquinones and the total synthesis of 5-*O*-methylembelin is reported based upon ring expansion of substituted cyclobutenes. © 2001 Elsevier Science Ltd. All rights reserved.

Mangroves (trees or shrubs whose roots are covered by salt water at least part of the time) usually grow in saline habitats. They dominate approximately one-fourth of the world's coastal ecosystems throughout the tropic and subtropic regions of the world.[1] Mangroves are sources of food and drink for man and animals, medicinal decoctions, oils and fats, food, twine for fishing floats and boat anchors, and fish poisons. In Philippines, more than 140,000 hectares of mangrove swamps are in existence. Ecologically, mangroves are important in maintaining and building the soil, as a reservoir in the tertiary assimilation of wastes, and in the global cycle of certain gases. They also serve as a natural habitat for wildlife, birds and shellfish.

Aegiceras corniculatum (syn. *Aegiceras majus*) is a shrub or small tree which is commonly known in the Philippines as 'saging–saging' and belongs to the family Aegicerataceae.[2,3] The presence of saponins and diterpenes in *A. corniculatum* was reported by a number of investigators.[4–7] Examination of an orange pigment by Hensens and Lewis[8] yielded the hydroquinones embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone) and rapanone (3,5-dihydroxy-3-tridecyl-1,4-benzoquinone). There was no biological activity reported for these components. An ethnobotanical survey of mangrove vegetation[9] in Southeast Asia revealed that the leaves and bark of *A. corniculatum* contained toxic chemicals. Juvenile fish (Tilapia) were killed instantly when exposed to extracts of this species.[10]

The compound 5-*O*-methylembelin (**1**) was isolated by Gomez et al.[11] and demonstrated toxicity to fish (*Tilapia nilotica*) at a concentration of 1 ppm within a period of 75 min. Also the growth of the fungi *Pythium ultimum* was inhibited by the presence of 5-*O*-methylembelin.[11]



5-O-Methylembelin(**1**); R = $C_{11}H_{23}$
Maesonin(**2**); R = (Z) $(CH_2)_9CH{=}CH(CH_2)_3CH_3$
Irisoquin(**3**); R = $C_{18}H_{37}$

5-*O*-methylembelin was originally synthesized in a low yield by Joshi and Kamat[12] by derivation of the known compound embelin. In 1983, Kubo et al.[13] reported the synthesis of another related benzoquinone, maesonin (**2**), in a net overall yield of 16%.

In 1985, Wong et al.[14] reported the synthesis of a related 5-methoxy-2-hydroxy-3-alkylbenzoquinone, irisoquin (**3**), in a net overall yield of 5%. Irisoquin demonstrated cytotoxic activity with cultured KB and P 388 cells ($ED_{50}=1.8$ and 0.03 μg/mL, respectively).

The goals of this research were to develop a general synthetic route to 3-alkyl-2-hydroxy-5-methoxy-1,4-benzoquinones and to complete the total synthesis of 5-*O*-methylembelin (**1**).

1. Results and discussion

As previously mentioned, 5-*O*-methylembelin (**1**) is toxic to fish.[11] Therefore, the goal of this research was to provide a synthetic route to 5-*O*-methylembelin (**1**) so that additional material can be made available for further cytotoxic studies. The goal was also to choose a novel synthetic route that is general enough to provide additional analogs which vary in the length of the alkyl side chain.

Keywords: 5-*O*-methylembelin; 3-alkyl-2-hydroxy-5-methoxy-1,4-benzoquinones; ring expansion of cyclobutenes.

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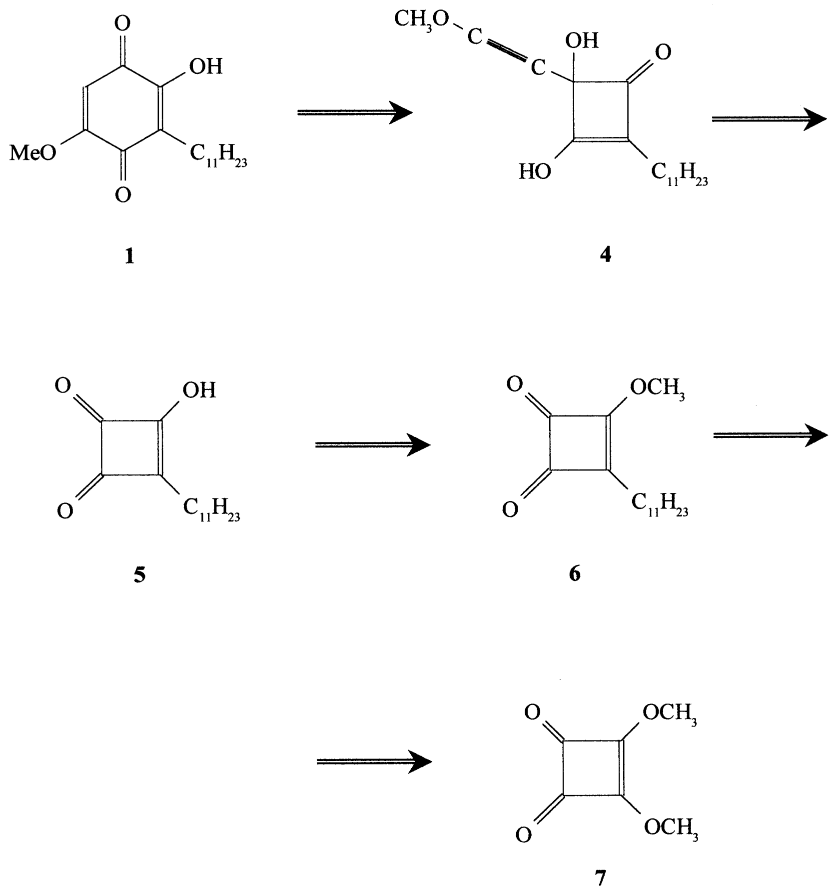
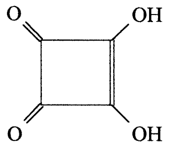


Scheme 1. Retrosynthetic analysis of 5-*O*-methylembelin (**1**).

Liebeskind[15] and co-workers reported that substitued cyclobutenes undergo ring expansion to yield substitued benzoquinones. Based on this work, the following retrosynthetic analysis of 5-*O*-methylembelin (**1**) was proposed (Scheme 1). This route provides complete selectivity of both the alkoxy and alkyl side chains. The alkoxy group was selected by using the appropriate alkoxyacetylene, and the alkyl chain was selected by using the appropriate alkylgrignard.

In 1989, Foland et al.[16] reported a similar procedure which led to the alkoxybenzoquinone having various alkyl groups at position 2 and 6 of benzoquinone. This method complements the one previously reported by Moore et al.[17] for the synthesis of 2,5-diaklylated-1,4-benzoquinones. The route developed in this paper will complement these two in providing 2,5-dialkoxyl-3alkyl-1,4-benzoquinones.

Dimethyl squarate (**7**) was obtained in 66% yield by treatment of squaric acid (**8**) with diazomethane (Aldrich Chemical Co.) following the procedure of Cohen and Cohen[18] Comparison of the spectral date (mass spectrum, infrared spectrum, proton nuclear magnetic resonsance spectrum) and the melting point with that published in the literature[18] confirmed that the product of this reaction was identical to dimethyl squarate (**7**). Dimethyl squarate (**7**) was then treated with 1.1 equiv. of undecylmagnesium bromide following the general procedure of Chickao,[19] followed by addition of 1.1 equiv. of trifluoroacetic anhydride. When the reaction was quenched with water and warmed to rt, the trifluoroacetate group was cleaved to yield the novel intermediate 3-methoxy-4-undecyl-3-cyclobutene-1,2-dione (**6**).



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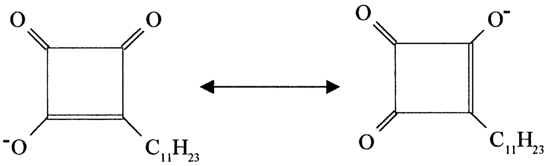
The mass spectrum of **6** showed a M^+ at *m*/*e* of 266.4 and other fragments at *m*/*e* 253.3, 223.3, 140.2, 126.2, 112.1, 97.1, 83.1, 69.1, and 55.0 (base peak). The infrared spectrum of compound **6** showed absorptions at $\nu_{\max}$ 2964 for aliphatic C–H stretching, 1794–1753 for carbonyls, and other absorptions at 1605, 1456, and 1369. The proton nuclear magnetic resonance spectrum of **6** showed a resonance at δ 4.42 (3H, s) for the methoxy group, a triplet at 2.56 (2H, t, J=7.7 Hz) for the methylene group attached to the ring, a broad multiplet at 1.22 (18H, m) which integrated for 18 protons of the undecyl chain, and a triplet at (δ 0.84 (3H, t, J=6.7 Hz) which integrated for the remaining three protons of the undecyl chain. The carbon-13 nuclear magnetic resonance spectrum of **6** showed peaks at 199 (C-1), 196 (C-3), 194 (C-2), 185 (C-4), 61 (OCH_3), and at 14–32 ppm for the undecyl chain.

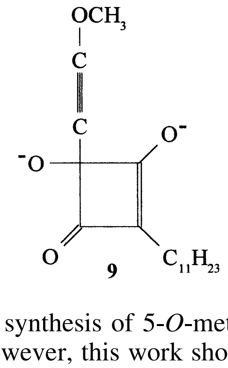
The methoxy group was then cleaved by treatment with *p*-toluenesulfonic acid in aqueous methanol in 98% yield following the procedure of Chickao[19] to yield compound

5. The mass spectrum showed a M^+ at *m/e* 253.3 and other fragments at 223.3, 195.2, 177.2, 168.2, 149.2, 140.1, 126.1, 112.1 (base peak), 95.1, 81.1, 69.1, and 55.0. The infrared spectrum showed absorptions at 2912, 1809, 1724, 1543, 1363, and 1077. The proton nuclear magnetic resonance spectrum showed a resonance at (δ 2.6 (2H, t, J=7.62 Hz) for the methylene protons on the carbon attached to the ring, a broad multiplet at 1:3 (18H, m) which integrated for 18 protons, and a triplet at 10.85 (2H, t, J=6.6 Hz) which integrated for the 3 protons on the terminal methyl group. The proton attached to the oxygen did not appear in the spectrum due to deuterium exchange with the deuterated solvent. The carbon-13 nuclear magnetic resonance spectrum showed peaks at 201 (C-1 and C-3), 194 (C-2), 189 (C-4), and 14–32 ppm (undecyl chain).

Methoxy acetylene was prepared following the procedure of Jones et al.[20] Treatment of compound methoxy acetylene with 1 equiv. of butylithium produced the anion of methoxyacetylene by abstraction of the acetylenic proton. The anion was then added to compound **5** in the ratio of two to one. The first equivalent of methoxyacetylene abstracted the proton attached to the oxygen on carbon **3**. This allowed the equilibrium shown below to be established.



The second equivalent was then added to carbon 2 to produce intermediate **9**. Due to the solubility of the intermediate in water, and its reaction with silica gel, the lithium cations in the reaction had to be removed by the use of an ion exchange resin. The ion exchange resin was filtered, and the solvent was removed in vacuo. Due to decomposition of the sample upon standing, the residue was immediately dissolved in *p*-xylene and refluxed for 3 h. The solvent was removed in vacuo, and comparison of gas chromatographic retention time with that of 5-*O*-methylembelin indicated that compound **1** was formed. The residue was placed on an octadecylsilane high pressure liquid chromatography column, and 5-*O*-methylembelin was obtained. Compound **1** was identified by comparison with an authentic sample isolated from *A. corniculatum.*



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In conclusion, the synthesis of 5-*O*-methylembelin (**1**) has been achieved. However, this work should be continued in order to increase yields and thus allow the formation of the series of analogs. Since benzoquinones are biologically active due to the electron transport phenomenon, the probability is high that analogs may have biological activity of some type at an even higher level than that of 5-*O*-methylembelin.

2. Experimental

2.1. Data for compounds

2.1.1. 3,4-Dimethoxy-3-cyclobutene-1,2-dione (7). A suspension of 3,4-dihydroxy-3-cyclobutene-1,2-dione (**8**) (5.7 g, 50 mmol) in ether (125 mL) was cooled and stirred, and into it was distilled ethereal diazomethane which was prepared by addition of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (from Diazald, 65 g, 0.30 mmol) in ether (400 mL) to a solution of potassium hydroxide (15 g) in water (24 mL) and ethanol (76 mL). The solution was warmed and concentrated at rt to yield 3,4-dimethoxy-3-cyclobutene-1,2-dione (**7**) (4.7 g, 33 mmol, 67%, mp 55°C). ^{1}H NMR (δ 4.3 (s); ^{13}C NMR 61.01 (OMe), 184.84 (olefinic) and 189.54 ppm (carbonyl); IR (KBr) 3025, 2964, 1820, 1734, 1605, 1493, 1361, and 1037 cm^{-1}; MS *n/e* 142.1 (base peak), 128.1, 114.1, 99.0, 86.0, 68.0, 56.0; exact mass calcd for $C_6H_6O_4$ 142.1112; found 142.1109

2.1.2. Undecylmagnesium bromide. A solution of undecylbromide (1.57 g, 7 mmol) in THF (50 mL) over a period of 4 h was added dropwise to a suspension of magnesium (187 mg, 7.7 mmol) turning in dry refluxing THF (50 mL).

2.1.3. 3-Methoxy-4-undecyl-3-cyclobutene-1,2-dione (6). A solution of 3,4-dimethoxy-3-cyclobutene-1,2-dione (**7**) (1 g, 7 mmol) in dry THF (50 mL) was cooled to −20°C, stirred, and then a solution of undecylmagnesium bromide (**6**) was added dropwise (100 mL). The mixture was stirred for 10 min, and trifluoroacetic anhydride (1.1 mL, 7.7 mmol) was added. The mixture was warmed to 0°C for 10 min, and the reaction was quenched by the addition of water (1 mL). The solvent was removed in vacuo, and the residue was dissolved in chloroform (50 mL). The solution was washed with a 5% sodium bicarbonate solution (50 mL) and dried over sodium sulfate. The chloroform was removed in vacuo, and the compound was recrystallized from chloroform and hexane to yield 3-methoxy-4-undecyl-3-cyclobutene-1,2-dione (**6**) (1.5 g, 79%, mp 78°C (dec)). ^{1}H NMR (δ 4.23 (3H, s, OMe), 2.42 (2H, t, CH_2), 1.08 (2H, m, CH_2), 0.69 (3H, t, CH_3); ^{13}C NMR 199.44 (C=O), 196.00 (C=O), 194.63 (olefinic), 184.67 (olefinic), 61.13 (methoxyl), 14–32 ppm (alkyl); IR (KBr) 2964, 2841, 1794, 1753, 1605, 1456, 1369 cm^{-1}; MS 266.4, 253.3, 223.3, 195.3, 177.3, 162.2, 149.2, 140.2, 126.2, 112.1, 97.1, 83.1, 69.1, 55.0 (base peak); exact mass calcd for $C_{16}H_{26}O_3$ 266.3806; found 266.3802.

2.1.4. 3-Hydroxy-4-undecyl-3-cyclobutene-1,2-dione (5). 3-Methoxy-4-undecyl-3-cyclobutene-1,2-dione (**6**) (100 mg, 0.4 mmol) was dissolved in water (5 mL) and methanol (5 mL), and a catalytic amount of *p*-toluenesulfonic acid. The mixture was stirred for 4 h, and the solvent was removed in vacuo. The residue was recrystallized from chloroform and methanol to yield 94 mg of **5** (99%), mp 178°C (dec). ^{1}H NMR (δ 2.58 (2H, t, CH_2), 1.28 (2H, m, CH_2), 0.87 (3H, t, CH_3); ^{13}C NMR 201.23 (C=O), 197.85

(C=O), 184.59 (olefinic), 30.82–14.52 ppm (alkyl); IR (KBr) 2912, 1809, 1724, 1543,1363, 1077 cm^{-1}; MS *m*/*e* 253.3, 223.3, 195.2, 177.2, 168.2, 149.2, 140.1, 126.1, 112.1 (base peak), 95.1, 81.1, 69.1, 55; exact mass calcd for $C_{15}H_{23}O_3$ 252.3538; found 252.3536.

2.1.5. Synthesis of compound 1. To a solution of methoxy acetylene (17.6 mg, 0.32 mmol), *n*-butyllithium (128 μL, 12.5 M) was added at −78°C in THF (5 mL) prepared as described in the literature.[21] After 10 min, the solution was added to **5** (40 mg, 0.16 mmol) in THF (20 mL) at −78°C and stirred for 10 min. The reaction was quenched by addition of ion exchange resin (40 mg). The mixture was filtered, and the solvent was removed at rt. The residue was immediately dissolved in *p*-xylene (40 mL) and refluxed for 3 h. Gas chromatographic analysis showed that 5-*O*-methylembelin (**1**) was present (t_R=21.49 min, 150–320°C, 10°/min, 5 min hold time, DB-1701 capillary column.).

The residue (20 mg) was purified on an octadecylsilane high pressure liquid chromatograph column (10 mm×25 cm; 10 μm packing, 60% methanol–water mobile phase, t_R=12.68 min). IR 3353, 2917, 2851, 1635, 1599, 1444, 1381, 1201, 1112, 839, and 687; MS *n*/*e* 308.3, 168.1 (base peak), 153.1, 139.1, 125.1, 69.1; ^{1}H NMR 7.1 (1H, s), 5.8 (1H, s), 3.83 (3H, s), 2.41 (2H, t, *J*=7.7 Hz), 1.3 (18H, m), 0.84 (3H, t, *J*=6.6 Hz); ^{13}C NMR 183.5, 182.4, 161.7, 152.0, 119.7, 102.5, 57.1, 14.33–32.15 ppm.

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