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Anodic Oxidation as a Synthetic Expedient to Naphthoquinone and Anthraquinone Ketals †

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Abstract: *Some naphthoquinone and anthraquinone ketals have been prepared by anodic oxidation. Regioselective hydrolysis of the above diketals into monoketals is also described. Diels-Alder reaction of (E)-1-methoxybuta-1,3-diene with the monoketal of 1,4-dihydro-4,4-dimethoxy-5-benzyloxynaphthalene proceeded in a regioselective manner.*

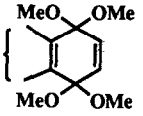
Introduction

The preparation of quinone bisketals **1** was first reported by Belleau and Weinberg in 1963,[2] and since then much efforts have been devoted to the studies on the synthesis of quinone bisketals **1** and quinone monoketals **2**.[3] Amongst all known preparations of quinone bisketals, anodic oxidation, whose mechanism was proposed by Swenton,[4] has been established unquestionably as the method of choice.

As key starting materials, quinone ketals have been employed to the synthesis of many interesting organic molecules.[5] In this regard, the most useful reactions of quinone monoketals are 1,2-additions[6] and 1,4-additions[7] as well as Diels-Alder cycloadditions[8] and

† Dedicated to Professor Huang Yao Zeng, Shanghai Institute of Organic Chemistry, Academia Sinica, on the occasion of his 80th birthday.

acid-catalyzed additions.[9]



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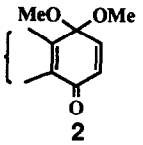

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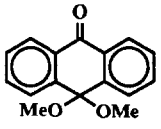
Our need for the identification and synthesis of new A_1 adenosine receptor ligands[10] inspired our quest to prepare new molecules containing the framework of 10,10-dimethoxyanthrone (**3**). Notwithstanding the fact that several naphthoquinone ketals are known, the parent skeleton **3** has not yet been prepared. In this note, we would like to disclose the synthesis of **3** from anthracene, utilizing an anodic oxidation procedure. In addition, the recent work of Carreño[11] also prompted us to report our approach to synthesize a derivative of **3**.



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Results and Discussion

As outlined in scheme I, it is likely that the 10,10-dimethoxyanthron framework could be assembled by a combination of an anodic oxidation, a selective hydrolysis of a quinone ketal, and a Diels-Alder reaction of monoketals. The most important key compound **10** was prepared via a six-step route consisting of mainly conventional reactions. Thus, a Friedel-Crafts acylation converted 1,4-dimethoxybenzene (**4**) to its corresponding ketoacid **5**,[12] which was reduced by a Clemmensen reaction to acid **6**.[12] Again, an intramolecular Friedel-Crafts cyclization of **6** gave ketone **7**.[13] On selective bromination, ketone **7** furnished bromide **8**.[14] Dehydrobromination and aromatization then afforded phenol **9** from **8**.[15] Finally, the phenol **9** was protected as its benzyl ether **10**.[16]

The next stage of this program called for the construction of the naphthoquinone bisketal **11**, and the monoketals **12** and **13**. Expectedly, compound **11** was obtained from compound **10** by anodic oxidation.[3b,4] This reaction was carried out in 2% methanolic potassium hydroxide under constant current electrolysis in a single compartment cell. In this manner, the dimethoxy derivative **10** was electrochemically oxidized to **11** in 73% yield. Fortunately, both compounds **12** and **13** were obtained by selective hydrolysis of **11** using

two different conditions as illustrated in Scheme 1.[3b] The isomeric compounds **12** and **13** were distinguished by ^{1}H-^{1}H 2D-NOESY spectra. In the 2D-NOESY spectrum of compound **12**, the six methoxy protons obviously correlate with the vinylic hydrogens. On the other hand, in the 2D-NOESY spectrum of **13**, the methoxy protons correlate not only with both the vinylic hydrogens, but also with the methylenic hydrogens of the benzyloxy group. The regioselective acid hydrolysis of **11** to **12** is presumably due to the participation of the benzyloxy group. On the other hand, the preferential absorption of the less crowded side of **11** on silica gel might cause the formation of **13**.

Diels-Alder cycloaddition of monoketal **13** with (*E*)-1-methoxy-1,3-butadiene in toluene at 120°C afforded the chromatographically separable adduct **14** (68%) as a white solid. The regioselectivity of this reaction is in agreement with both the steric and electronic factors.[17] In this case, the two aforementioned factors are in the same direction, leading to the "*ortho*-adduct " as the major product. The structure of **14** was suggested by ^{1}H-NMR, ^{13}C-NMR, and 2D-NOESY spectrometry. Unequivocal evidence for the structure of **14** was also obtained by an X-ray analysis.[18]

However, it should be mentioned that compounds **12** and **13** are unstable on thermolysis. Further efforts in employing them as dienophiles in Diels-Alder reactions were hampered by their thermal decomposition. Attempts to dehydrogenate **14** to yield a 1-benzyloxy-substituted derivative of **3** were however unfruitful.

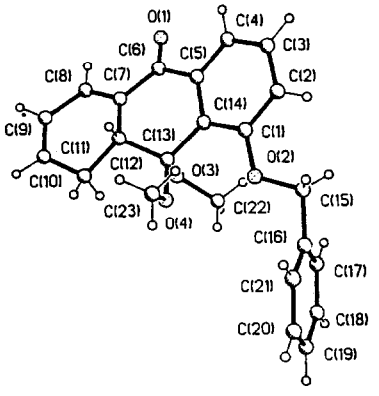
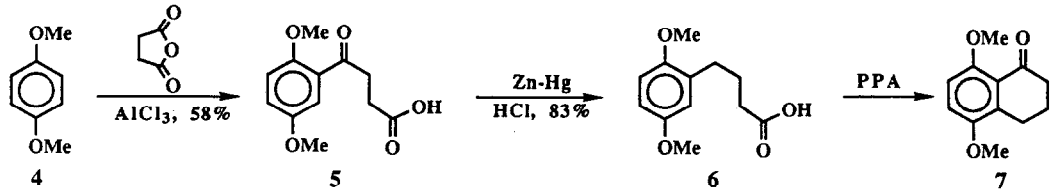
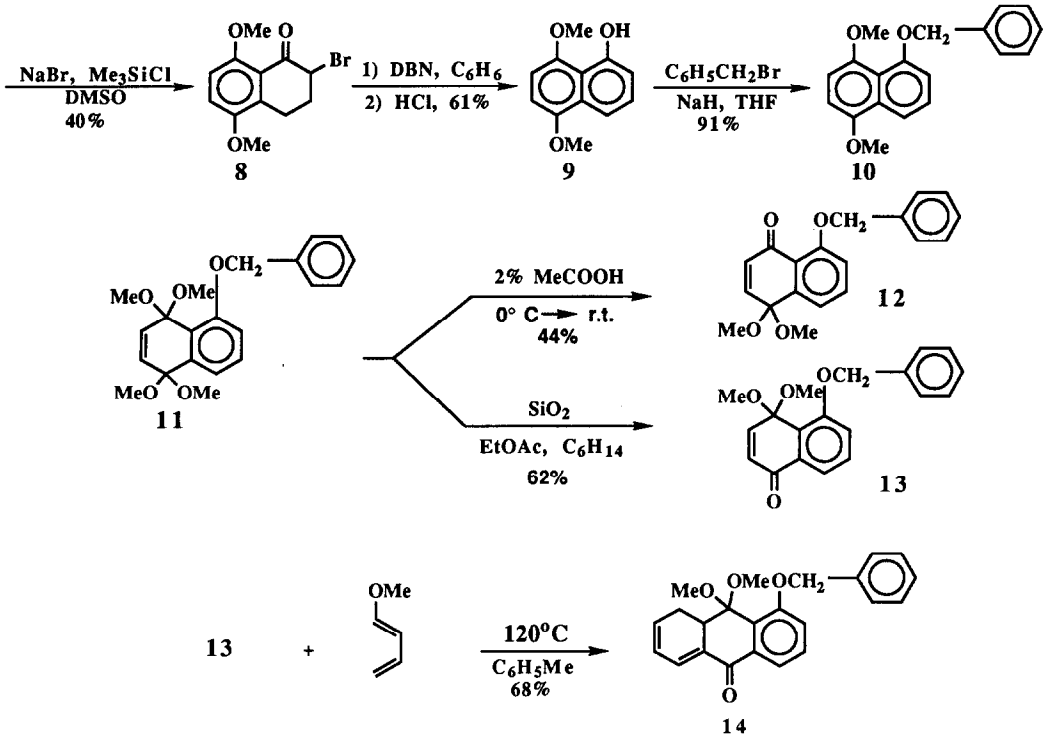


Figure 1. A perspective view of compound **14**

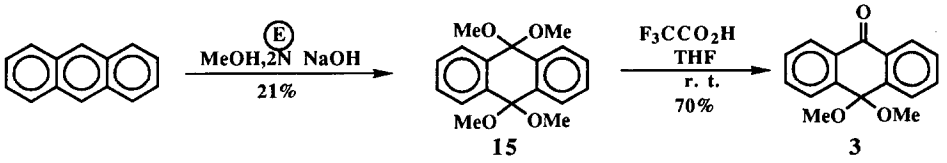
Scheme I





In view of the fact that a derivative of **3** could not be realized by using the above assemblage steps, we therefore turned our attention to a direct synthesis of the parent **3** itself. Indeed, the bisketal **15** was obtained from anthracene by an anodic oxidation in refluxing methanol. The low yield of **15** is mainly due to the poor reactivity of C-9 and C-10, as compared with the methoxy substituted **10**. The bisketal **15** was then selectively hydrolyzed by treatment with trifluoroacetic acid to give the monoketal **3** (**Scheme 2**), whose structure was unambiguously confirmed by NMR spectrometry. To our best knowledge, this is the first time that anthrancene was electrochemically oxidized to the corresponding bisketal.

Scheme 2



In conclusion, we have prepared two novel bisketals **11** and **15**. They were selectively hydrolyzed to their corresponding monoketals **12**, **13** and **3**, respectively. Compound **13** underwent regioselective Diels-Alder reaction and subsequent loss of methanol to give **14**, which can be regarded as a dihydro-derivative of **3**.

Experimental Section

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Cryospec WM-250 (250 MHz) and are reported in ppm (δ) downfield from internal TMS standard. Mass spectra were recorded on a VG Micromass 7070F instrument. Elemental analyses were performed at Shanghai Institute of Organic Chemistry, Academia Sinica, China. Melting points were measured on a hot-stage microscope and are uncorrected. Merck silica gel (60 F_{254}) precoated on aluminum sheet was used for TLC study and Merck silica gel (70-230 or 230-400 mesh) was used for column chromatography unless stated otherwise. Basic silica gel was prepared by washing with 5% aqueous ammonium hydroxide, then distilled water, and was finally dried at 110°C overnight prior to chromatography. All compounds were dried over anhydrous sodium sulfate. Almost all reactions were performed under nitrogen atmosphere.

β-(2,5-Dimethoxybenzoyl)-propionic acid (5).[12] Succinic anhydride (5.8 g, 0.06 mol) and 1,4-dimethoxybenzene (7.2 g, 0.05 mol) were added with stirring to nitrobenzene (48 mL) under nitrogen. Aluminum chloride (15.6 g, 0.12 mol) was added slowly at 0°C. The resulting mixture was stirred overnight in an ice bath and then at room temperature for 24 hours. The solution was poured into ice-water (150 mL) and 20% aqueous sodium hydroxide was added until it became alkaline. The aqueous solution which was extracted with ether (3 x 100 mL) and was acidified with dilute hydrochloric acid to induce precipitation. The crude precipitate was filtered and recrystallized from methanol and water (1:1) to give **5** as needles (7.2 g, 58%), m.p. 101-101.5°C: ^{1}H-NMR ($CDCl_3$) δ 2.64-2.92 (t, *J*=6 Hz, 2H), 3.28-3.57 (t, *J*=6 Hz, 2H), 3.76 (s, 3H), 3.87 (s, 3H), 6.97-7.37 (m 3H); MS *m/e* 238 (M^+). Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.49; H, 5.92. Found: C, 60.43; H, 5.81.

γ-(2,5-Dimethoxyphenyl)-butyric acid (6).[12] Mossy zinc (14 g, 0.2 mol) and mercuric chloride (1.4 g, 0.02 mol) was added to dilute hydrochloric acid (0.8 mL conc. HCl, 20 mL water) with stirring for 10 minutes. Dilute hydrochloric acid was decanted and the mossy zinc was washed with water (2 x 50 mL), Then aqueous hydrochloric acid (20 mL conc. HCl, 10 mL water) was added to the mossy zinc followed by a solution of compound **5**

(6.4 g, 0.038 mol) in toluene (40 mL). The reaction mixture was refluxed for 18 hours., then cooled to room temperature and poured into cold water (100 mL). The solution was extracted with ethyl acetate (3 x 80 mL). The organic layer was washed with brine (3 x 15 mL), dried over sodium sulfate and evaporated to give the product **6** (5.6 g, 93%) as white solid, m.p. 148-149°C: ^{1}H-NMR ($CDCl_3$) δ 1.73-2.77 (m, 6H), 3.72 (s, 6H), 6.64 (s, 3H); MS *m/e* 224 (M^+). Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.74 ; H, 7.47.

5,8-Dimethoxy-1-tetralone (7).[13] The acid **6** (33 g, 0.15 mol) and polyphosphoric acid (330 g) were stirred together at 70°C for 1 hour, then was poured into ice-water (600 mL). The water solution was extracted with ether (3 x 200 mL), washed with brine (3 x 30 ml) and dried over sodium sulfate. The organic solvent was evaporated under vacuum to give the tetralone **7** (21g) which was chromatographed on a short silica gel column (150 g, 230-400 mesh) using hexane containing 33% ethyl acetate as an eluent to give yellowish crystals of **7** (18.5 g, 60%), m.p. 53.5-54.5°C: ^{1}H-NMR ($CDCl_3$) δ 1.94-2.27 (m, 2H), 2.5-3.0 (m, 4H), 3.82 (s, 3H), 3.85 (s, 3H), 6.66-7.27(m, 2H); MS *m/e* 206 (M^+). Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.07; H, 6.83.

2-Bromo-5,8-dimethoxy-1-tetralone (8).[14] To a solution of sodium bromide (3.1 g, 30 mmol) in dry acetonitrile (20 mL), trimethylsilyl chloride (3.3 g, 30 mmol) was added. After 15 minutes, compound **7** (2.1 g, 10 mmol) and then dimethylsulfoxide (2.3 g, 30 mmol) were added. After 1.5 hours, the mixture was poured into water (100 mL) and was extracted with ether (3 x 40 mL). The organic layer was dried over sodium sulfate, and evaporated under vacuum. The residue was purified by chromatography on a silica gel column (100 g, 70-230 mesh) using petroleum ether (30-60°C) and ether as an eluent in a gradient manner to give the product **8** (1.14 g, 40%), m.p. 85-86°C: ^{1}H-NMR ($CDCl_3$) δ 2.33-2.56 (m, 2H), 2.90-3.20 (m, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 4.44-4.79 (m, 1H), 6.73-7.24 (m, 2H); MS *m/e* 285 (M^+). Anal. Calcd. for $C_{12}H_{13}O_3Br$: C, 50.55; H, 4.59. Found: C, 50.22, H, 4.77.

5,8-Dimethoxy-1-naphthol (9).[15] To a solution of bromo-ketone **8** (0.5 g, 1.8 mmol) dissolved in toluene (10 mL) was added DBN (0.26 mL, 2.13 mmol). The solution was stirred at room temperature for 28 hours. After this time, the mixture was diluted with ether (50 mL), the organic layer was washed with 5% aqueous hydrochloric acid (10 mL), then dried over sodium sulfate. The mixture was evaporated to dryness, and the residue was chromatographed on a silica gel column (30 g, 70-230 mesh) using hexane containg 25% ether as an eluent to give the product **9** (0.22 g, 61%), m.p. 144-

144.5°C: ^{1}H-NMR ($CDCl_3$) δ 3.95 (s, 3H), 3.97 (s, 3H), 6.63 (s, 2H), 6.82-7.79 (m, 3H), 9.43 (s, 1H); MS *m/e* 204 (M^+). Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 69.79; H, 5.73.

1-Benzyloxy-5,8-dimethoxy-naphthalene (10).[16] To a solution of compound **9** (2 g, 10 mmol) in tetrahydrofuran (20 mL), 80% sodium hydride (0.5 g, 0.016 mol) was added. The mixture was stirred for 10 minutes, then benzyl bromide (2 mL) was added. The mixture was further stirred at 60°C for 24 hours. The mixture was cooled to room temperature and was diluted with ethyl acetate (100 mL). The organic layer was washed successively with water (10 mL), brine (10 mL) and dried over sodium sulfate. The mixture was evaporated to dryness and the residue was chromatographed on a silica gel column (60 g, 70-230 mesh) using petroleum ether (30-60°C) and ether as an eluent in a gradient manner to give the product **10** (2.65 g, 92%), m.p. 105-105.5°C: ^{1}H-NMR ($CDCl_3$) δ 3.86 (s, 3H), 3.94 (s, 3H), 5.22 (s, 2H), 6.86 (s, 2H), 7.07-7.85 (m, 8H); MS *m/e* 294 (M^+). Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.55; H, 6.12. Found: C, 77.40; H, 6.03.

1-Benzyloxy-5,8-dihydro-5,5,8,8-tetramethoxy-naphthalene (11).[3b,4] The preparative anodic oxidation was performed in a single compartment cell fitted with a circular platinum gauze anode (33 mm diameter x 28 mm height), and a platinum sheet (10 mm x 10 mm) cathode. To a solution of 2% methanolic potassum hydroxide (75 mL), compound **10** (1.6 g, 5.3 mmol) which was pre-dissolved in tetrahydrofuran (20 mL) was added. The mixture was electrolyzed under 1.4 V, 0.3 A for 3 hours at 0°C. After TLC indicated that the substrate almost diappeared, the electrolyzed solution was then evaporated to dryness. Ether (150 mL) and water (30 mL) were added to the residue. The organic layer was washed with brine (2 x 25 mL) and dried over sodium sulfate. The solution was evaporated to dryness and the residue was chromatographed on a basic silica gel column (50 g, 70-230 mesh, treated with 5% ammonium water) using ethyl acetate containg 20% hexane as an eluent to give the product **11** (1.4 g, 73%), m.p. 84-85°C: ^{1}H-NMR ($CDCl_3$) δ 3.18 (s, 3H), 3.20 (s, 3H), 5.20 (s, 2H), 6.26 (q, 2H), 6.94-7.58 (m, 8H); ^{13}C-NMR ($CDCl_3$) δ 50.99 (CH_3), 70.38 (CH_2), 95.50 (C), 96.94 (C), 113.45 (CH), 118.95 (CH), 126.56 (CH), 127.22 (CH), 128.21 (CH), 130.01 (CH), 134.17 (CH), 134.17 (C), 137.52 (C), 139.28 (C), 157.01 (C). MS *m/e* 325 (M^+ - OMe). Anal. Cacld. for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.67; H, 6.85.

1,4-Dihydro-4,4-dimethoxy-8-benzyloxy-naphthalen-1-one(12).[3b] To a solution of bisketal **11** (2.4 g, 6.8 mmol) in tetrahydrofuran (40 mL), 2% aqueous acetic acid

(20 mL) was added at 0°C. After being stirred for 1 hour at 0°C, the mixture was allowed to stir for additional 8 hours at room temperature. After this period, TLC indicated that the starting material almost disappeared. The reaction mixture was then quenched with aqueous saturated sodium hydrogen carbonate solution (10 mL), and the mixture was extracted with ether (4 x 10 mL) and the organic layer was washed with brine (2 x 5 ml). Benzene (10 mL) was added to the ether solution and the organic solvents were evaporated in vacuum to give a yellow-orange oil which was chromatographed on a basic silica gel column (100 g, 70-230 mesh) using hexane containing 20% ether as an eluent to give the product **12** (0.88 g, 44%) as yellowish semi-solid: ^{1}H-NMR (acetone-d_6) δ 3.17 (s, 6H), 5.25 (s, 2H), 6.54 (d, *J*=10.4 Hz, 1H); 6.78 (d, *J*=10.4 Hz, 1H), 7.08-7.62 (m, 8H); MS *m/e* 273 (M^+ - OMe). Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.84. Found: C, 73.52; H, 5.92.

1,4-Dihydro-4,4-dimethoxy-5-benzyloxy-naphthalen-1-one(13). The bisketal **11** (2 g, 6.4 mmol) was chromatographed on a silica gel column (30 x 3 cm, 120 g, 70-230 mesh) using hexane containing 20% ethyl acetate as an eluent. The whole period of this separation was 20 hours. During this process, the bisketal was selectively hydrolyzed to a monoketal. The eluent was collected with an automatic fraction collector and the monoketal **13** (1.07 g, 62%) was eluted after the starting material,[11] m.p. 68-68.5°C: ^{1}H-NMR (acetone-d_6) δ 3.19 (s, 6H), 5.26 (s, 2H), 6.42 (d, *J*=10.4 Hz, 1H); 6.99 (d, *J*=10.4 Hz, 1H), 7.25-7.70 (m, 8H); MS *m/e* 279 (M^+ - OMe). Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.84. Found: C, 73.12; H, 5.48.

8,8a,9,10-Tetrahydro-9,9-dimethoxy-1-benzyloxy-anthracen-10-one (14).[8] The monoketal **13** (264 mg, 0.85 mmol), (*E*)-1-methoxybuta-1,3-diene (0.2 mL, 2 mmol) and toluene (0.8 mL) were placed in a sealed-tube. The mixture was heated at 120°C for 24 hours. The resulting mixture was chromatographed on a silica gel column (50 g, 70-230 mesh) using hexane containg 20% ethyl acetate as an eluent to give the product **14** (208 mg, 68%), m.p. 178-178.5°C: ^{1}H-NMR (acetone-d_6) δ 3.19 (s, 3H), 3.27 (s, 3H), 5.29 (s, 3H), 7.72-7.36 (m, 11H). MS *m/e* (M^+) (calcd for $C_{23}H_{22}O_4$) 362.1575 (found 362.1522).

Compound **14** (30 mg) was dissolved in ethyl acetate and hexane (1/2) (1 mL) and slow evaporation at room temperature yielded the single crystals which were suitable for an X-ray analysis that confirmed the molecular structure.[18]

9,10-Dihydro-9,9,10,10-tetramethoxy-anthracene (15). Anthracene (1.5 g) was suspended in a solution of 2% methanolic potassium hydroxide (75 mL) and was electrolyzed

under ambient temperature for 18 hours. Methanol was evaporated in vacuum and the residue was extracted with ether (3 x 30 mL), the organic layer was washed with water (2 x 10 mL) and combined with benzene (20 mL), then evaporated to dryness. The residue was chromatographed on a basic silica gel column (50 g, 70-230 mesh) using hexane containing 10% ether as an eluent to give product **15** (0.54 g, 21%) as white solid, m.p. 158-159°C: ^{1}H-NMR ($CDCl_3$) δ 2.95 (s, 12H), 7.58-7.86 (m, 8H); MS *m/e* 269 (M^+ - OMe). Anal. Calcd. for $C_{18}H_{20}O_4$: C, 72.00; H, 6.66. Found: C, 72.02; H, 6.77.

9,10-Dihydro-10,10-dimethoxy-anthracen-9-one (3). To a solution of bisketal **15** (0.54 g, 1.8 mmol) in tetrahydrofuran (20 mL), 5% trifluoroacetic acid (8 mL) was added, and the resulting solution was stirred at room temperature for 6 hours. At the end of this reaction, TLC indicated that the hydrolysis reaction was almost completed, then the mixture was quenched with saturated sodium hydrogen carbonate solution (10 mL), and was extracted with ether (4 x 10 mL). The ethereal layer was washed with brine (2 x 5 mL), combined with benzene (10 ml) and evaporated in vacuum. The residue was chromatographed on a basic silica gel column (30 g, 70-230 mesh) using hexane containing 5% ether as an eluent to give the product **3** (0.32 g, 70%) as white solid, m.p. 122-124°C: ^{1}H-NMR ($CDCl_3$) δ 2.93 (s, 6H), 7.75-7.72 (m, 2H), 7.75-7.82 (m, 2H), 7.90 (dd, *J*=7.8. 0.9 Hz, 2H), 8.31 (dd, J=7.8, 1.1Hz, 2H); MS *m/e* =223 (M^+ - OMe). Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.59; H, 5.51. Found: C, 75.24; H, 5.42.

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18. Compound **14**, $C_{23}H_{22}O_4$, space group $P\bar{1}$, $a = 9.120$ (2), $b = 9.240(2)$, $c = 11.615$ (1) Å, $\alpha = 108.70$ (1), $\beta = 95.06$ (1), $\gamma = 90.92$ (1)°, $Z = 2$. R_F refined to 0.041 for 2384 observed ($2\theta_{max} = 50°$) Mo$K\alpha$ data. The data collection, processing parameters, atomic co-ordinates, equivalent isotropic temperature factors, bond lengths, bond angles, anisotropic thermal parameters, hydrogen atom co-ordinates with assigned isotropic temperature factors, as well as observed and calculated structure factors for **14** are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England. Any request should be accompanied by the full literature citation for this paper. See Notice to Authors, *Tetrahedron* **40**(2), ii (1984).