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Calix[4]quinone. Part 2: Intramolecular Michael-addition of calix[4]diquinone

Ker-Ming Yang, Ming-Dar Lee, Rong-Fua Chen, Yi-Lin Chen and Lee-Gin Lin*

Institute of Applied Chemistry, Chinese Culture University, Taipei 11114, Taiwan, ROC

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Abstract—The oxidation of calix[4]arene dibenzoate **1** with chlorine dioxide yielded the corresponding calix[4]diquinone **2** and an intramolecular Michael-addition product **3**. Reaction of diquinone **2** with ethylene glycol under acidic conditions produced the half-protected ketal derivative **4**. The removal of benzoate moieties from compound **4** in basic conditions produced a phenoxide anion, which underwent intramolecular Michael-addition and yielded product **5**. In acidic ketal cleavage conditions, the ketal moieties of product **5** were removed, but the intramolecular Michael-addition structure was maintained in the product **6**.

1. Introduction

Calix[4]quinone, which is a sort of calix[4]arene comprising cyclic arrays of *p*-quinone and methylene residues, was first synthesized by a direct oxidation of calix[4]arene with chlorine dioxide in 1986.[1] However, the exact structure of calix[4]quinone which was confirmed by X-ray crystallography was reported later by Morita and co-workers from a very different multi-step synthetic approach.[2b] Since then, several papers on this new calixarene system had been published,[2–4] and among these reports, the *p*-hydroxycalix[4]arene and calix[4]quinone pair have been proposed as the enzyme redox model and/or electron transfer system.[4]

In our previous work,[5] we have established the use of chlorine dioxide to introduce an oxygen atom at the calixarenes *para*-position, and the synthesis of *p*-monohydroxycalix[4]arene was achieved in a subsequent route. It was anticipated that the calix[4]diquinone molecule would also behave similar to its calix[4]monoquinone counterpart, and that the corresponding *p*-dihydroxycalix[4]arene could be achieved accordingly. However, we were surprised to find that the calix[4]diquinone derivatives behaved quite differently from calix[4]monoquinone, and a totally different set of calix[4]arene derivatives was produced. In this paper, we report on the intramolecular Michael-addition behavior of the calix[4]diquinone molecular system.

2. Results and discussion

2.1. Calix[4]arene dibenzoate 1

Although, the calix[4]arene 1,3-dibenzoate **1** could be prepared according to the literature procedure,[6] undesired side products were frequently observed during the preparation. It was later shown that the majority of the side product was calix[4]arene tetrabenzoate with a '1,3-alternate' conformation,[7] and this tetrabenzoate became the only product when a large excess of NaH was used in the synthesis. Further investigations indicated that the reaction conditions for the calix[4]arene 1,3-dialkyl ethers[8] were also suitable for the preparation of the calix[4]arene dibenzoate **1**, in which the calix[4]arene was refluxed with large excess of benzoyl chloride in CH_3CN in the presence of K_2CO_3 to afford calix[4]arene dibenzoate **1** in over 80% yield.

2.2. Calix[4]diquinone dibenzoate 2

When calix[4]arene dibenzoate **1** was oxidized with chlorine dioxide in phosphate-buffered solution at room temperature, a procedure described by L. Rosik,[1] a pale orange minor product **3** was obtained along with the bright yellow calix[4]diquinone **2** (Fig. 1). Calix[4]diquinone **2** was purified from the reaction mixture by a simple recrystallization, but the isolation of product **3** required column chromatography. The structure of calix[4]diquinone **2** was accurately assigned based on all available spectral data, whereas, the structural assignment of compound **3** presented some uncertainty.

The FAB-mass spectral data indicated that compound **3** has a molecular weight of 678 a.m.u, which was 18 a.m.u more then the expected calix[4]diquinone's mass; and the ^1H

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* Corresponding author; e-mail: lglin@faculty.pccu.edu.tw

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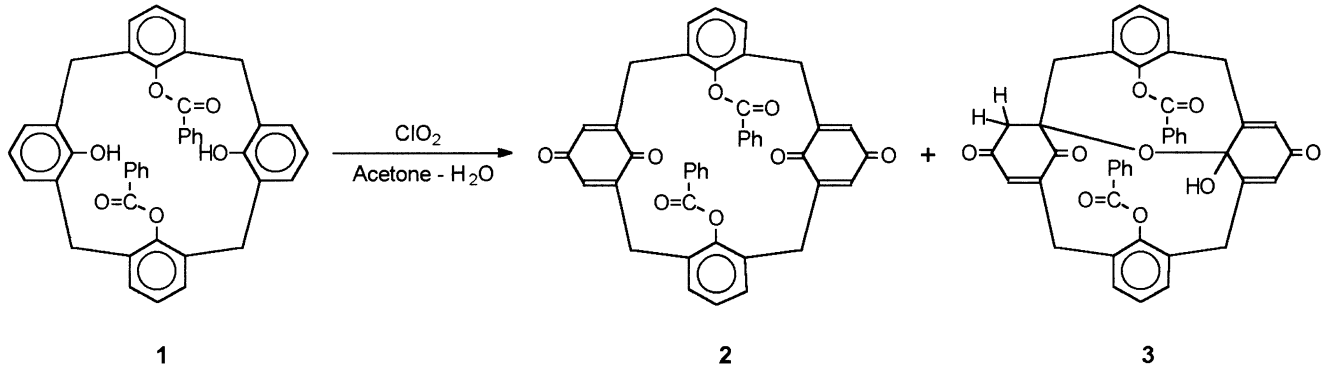

Figure 1.

NMR spectra indicated that 30 hydrogens were present in compound **3**, which was **2** hydrogens more than the expected calix[4]diquinone. These data indicated that the structure of compound **3** was equivalent to adding one water molecule onto calix[4]diquinone **2** in some fashion. Several possibilities existed for the structure of product **3**, but most of the proposed structures were shown to be incorrect when D_2O treated NMR sample indicated that only one single hydrogen was exchanged with deuterium. With the availability of the two-dimension ^1H NMR spectrum, we were able to deduce every hydrogen signal and proposed a hemiketal structure with distal (i.e. 1,3-related) transannular ether linkage for product **3**. Biali et al. reported a similar structure with proximal (1,2-related) transannular ether linkage in the oxidative studied of *p-tert*-butylcalix[4]-arene.[9] They also suggested, based on Dreiding models studies, that the distance is too long to allow the formation of a transannular bond between phenolic oxygen atom and the *meta*-position of the distal rings.[9a] Therefore, the distal transannular ether linkage in product **3** was assigned to link between the 'upper rim' oxygen atom and the *meta*-position of the distal ring. However, the exact structure for product **3** still required further evidence, e.g. a single crystal X-ray crystallography, to reveal the exact location of the hemiketal moieties.

Even though, the structure of compound **3** seemed to be the result of addition of one water molecule onto diquinone **2**, the hydration studies indicated that diquinone **2** did not convert to compound **3** in acidic conditions. It was also

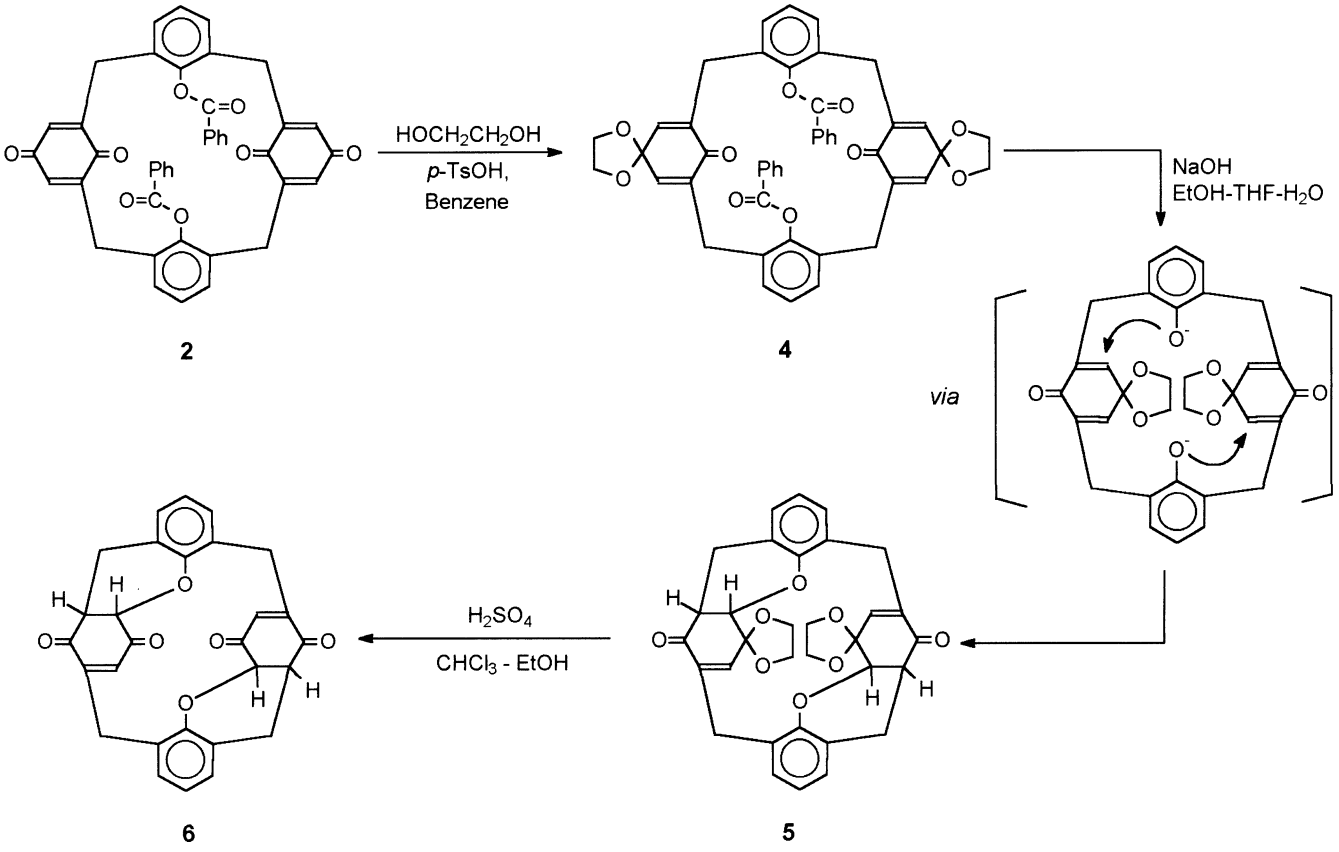

Figure 2.

noticed that the hemiketal structure of compound **3** was exceptionally stable, as an attempt to cleave the hemiketal moieties by refluxing compound **3** with 6N HCl for 96 h produced no trace of diquinone **2** and/or any degraded compounds. These results implied that instead of adding one water molecule onto diquinone **2** in an acidic oxidation reaction, compounds **2** and **3** were both produced simultaneously in chlorine dioxide oxidation via a different mechanism.

During the preparation of diquinone **2**, the oxidation was attempted in one instance without the buffer solution. Although the oxidation reaction proceeded as with the buffer solution conditions, the amount of compound **3** was increased and the diquinone **2** was no longer able to be isolated directly from the reaction mixture by a simple recrystallization. The separation of this mixture by column chromatography resulted in 32% of diquinone **2** and 19% of compound **3**. The amount of compound **3** was largely increased from less than 1% to 19% in this reaction. This result turned our attention to search for better reaction conditions for the chlorine dioxide oxidation, and preliminary results indicated that a pH 9 buffer system gave a better overall yield of both oxidative products **2** and **3**. A detailed study on the effect of pH on the chlorine dioxide oxidation is already underway in our laboratory.

2.3. Calix[4]diquinone dibenzoate monoketal 4

As in case of calix[4]monoquinone tribenzoate,[5] the ketalization of calix[4]diquinone dibenzoate **2** also produced only the corresponding half-protected ketal derivative **4** (Fig. 2). One may speculate that steric hindrance of the diquinone **2** is much smaller as compared with the previous monoquinone case, and hence, the failure of the formation of the fully protected quinones may not arise strictly from the benzoate moieties. We suggest that the molecular structure of calix[4]arene contains a smaller opening on the 'lower rim', and steric hindrance from the calix[4]arene itself may prevent the formation of the 'lower rim' cyclic ketal structure. The position of the masked carbonyl, on this assumption, was assigned to the less hindered 'upper rim'.

2.4. Intramolecular Micheal-addition products 5 and 6

It was anticipated, as in previous cases,[5] that the benzoate moieties of dibenzoate **4** should be easily removed and produce the corresponding calix[4]diquinone diketal product. It was also expected that the resultant product, which possessed a C_{2v} symmetry would display a simple ^{1}H NMR spectrum with one exchangeable hydrogen signal. To our surprise, the basic hydrolysis product **5** displayed a very complex but well-defined ^{1}H NMR spectrum with a set of three doublets and one unusually upfield double doublet for the calix[4]arene's methylene hydrogens. We were more surprised to notice that no hydrogen signal disappeared when the NMR sample was treated with D_2O. This information not only indicated that the phenolic hydroxy hydrogen was non-existant but also implied that a proton was adjacent to calixarene's methylene bridge in the structure of hydrolysis product **5**. The only rational explanation for such phenomenon was that the phenoxide anion, which was produced in basic hydrolysis of the phenyl benzoate moieties, added to the nearby conjugate enone system in 1,4-addition fashion forming a Michael-addition product **5**. The intramolecular 1,4-addition that occurred would hinder the free rotation, and the product **5** was expected to possess chirality similar to the spiro products reported by Biali.[9] This unique structure of intramolecular Michael-addition product **5** was established with two-dimension ^{1}H NMR spectrum and all the hydrogen signals were assigned accurately.

The ketal moieties in monoketal **5** were very stable and can only be cleaved by refluxing with strong acid, but the intramolecular phenyl–cyclohexyl ether linkage was retained in hydrolysis conditions. We were surprised to notice that the hydrolysis product **6**, which possessed an 1,4-diketone structure did not undergo double keto-enol tautomerization to give the stable aromatic hydroquinone structure in acidic conditions. We believe that the rigid structure of compound **6** is one of the reasons for its failure to undergo keto-enol tautomerization, and a simple molecular structure model does indicate the inflexible structure of compound **6**.

3. Experimental

3.1. General

All reagents were obtained from Commercial Chemical Companies and used without further purification. Melting points were taken in capillary tubes on a Mel-Temp apparatus (Laboratory Devices, Cambridge, MA) and were uncorrected. ^{1}H NMR spectra were recorded on Burker DMX-300 WB and/or Burker DMX-500 SB spectrometer and chemical shifts were reported as δ values in ppm relative to TMS (δ=0.00) as an internal standard. IR spectra were recorded on Perkin–Elmer Paragon 1000 FT-IR Spectrometer, FAB-MS spectra were taken on a JOEL JMS-HX 102 spectrometer, and elemental analyses were taken on a Perkin–Elmer 24°C analyzer. Chromatographic separations were performed with Merck silica gel (230–400 mesh ASTM) on columns of 25 mm diameter filled to height of 150 mm. TLC analyses were carried out on Merck aluminum back silica gel 60 F_{254} plates (absorbant thickness 0.2 mm).

3.1.1. 25,27-Dibenzoyloxy-26,28-dihydroxycalix[4]arene (1). A solution of 2.12 g (5.00 mmol) of calix[4]arene, 0.69 g (5.00 mmol) of K_2CO_3, and 1.15 mL (1.40 g, 10.0 mmol) of benzoyl chloride in 100 mL of CH_3CN was refluxed for 10 h. The solvent was removed, and the residue was treated with water to give a white solid. The solid material was collected and recrystallized from $CHCl_3$ and CH_3OH to give 2.47 g (78%) of colorless crystals: mp 262–264°C (lit.[6] mp 262–264°C). The spectral properties of this product was identical to the literature reported.[6]

3.1.2. 25,27-Dibenzoyloxy-26,28-calix[4]diquinone (2) and intramolecular Michael-addition product 3. *Method A: with pH 7 buffer solution*. A slurry of 3.35 g (5.30 mmol) of **1** was dissolved in 150 mL of acetone, and 50 mL of concentrated buffer solution[10] was added. A portion of 115 mL of yellowish ClO_2 aqueous solution[11] was then added, and the reaction mixture was stirred at room

temperature for 48 h. The pale yellow solid material was collected and recrystallized three times from $CHCl_3$ and CH_3OH to give 1.52 g (47%) of **2** as an yellow crystals: mp 298–299°C; ^{1}H NMR ($CDCl_3$) δ 8.24 (bs, 4H, *o*-Ar′*H*), 7.74–7.77 (m, 2H, *p*-Ar′*H*), 7.57–7.60 (m, 4H, *m*-Ar′*H*), 6.92–7.07 (m, 6H, Ar*H*), 6.34 (bs, 4H, quinone-*H*), 3.47 (bs, 8H, ArCH_2Ar); IR (KBr) cm^{-1}: 1732 (s, C═O), 1655 (s, C═O); FAB-MS *m/z*: 661 (M^++1), 662 (M^++2). Anal.[12] Calcd for $C_{42}H_{28}O_8$: C, 76.36; H, 4.27. Calcd for $C_{42}H_{28}O_8$·1/2$CHCl_3$: C, 70.86; H, 3.99. Found: C, 70.88; H, 3.90.

The mother liquor was concentrated and subjected to column chromatography separation with $CHCl_3$ as an eluent. The first eluted component, after recrystallization from $CHCl_3$ and CH_3OH, weighing 0.15 g (4%) was the yellow compound **2**. The second eluted product, after recrystallization from $CHCl_3$ and CH_3OH, weighing 0.02 g (0.5%) was the yellow product **3**; mp 296–297°C; ^{1}H NMR ($CDCl_3$) δ 8.36 (d, *J*=7.5 Hz, 2H, *o*-Ar′*H*), 8.32 (d, *J*=7.5 Hz, 2H, *o*-Ar′*H*), 7.75 (t, *J*=7.5 Hz, 1H, *p*-Ar′*H*), 7.72 (t, *J*=7.5 Hz, 1H, *p*-Ar′*H*), 7.61 (t, *J*=7.5 Hz, 2H, *m*-Ar′*H*), 7.58 (t, *J*=7.5 Hz, 2H, *m*-Ar′*H*), 7.19 (bd, *J*=7.0 Hz, 1H, *m*-Ar*H*), 7.08 (bd, *J*=7.5 Hz, 1H, *m*-Ar*H*), 6.92 (t, *J*=7.5 Hz, 1H, *p*-Ar*H*), 6.87–6.91 (m, 2H, *m*-Ar*H*), 6.78 (t, *J*=7.7 Hz, 1H, *p*-Ar*H*), 6.41–6.43 (m, 2H, quinone-*H* and COC*H*), 6.25 (s, 2H, quinone-*H*), 3.88–3.89 (m, 1H, COC*H*), 3.58–3.68 (3d, 3H, ArCH_2Ar), 3.42 (d, *J*=13.7 Hz, 1H, ArCH_2Ar), 3.34 (d, *J*=13.6 Hz, 1H, ArCH_2Ar), 3.21 (d, *J*=14.0 Hz, 1H, ArCH_2Ar), 2.53 (s, 1H, ArOH_2), 2.51 (d, *J*=14.0 Hz, 1H, ArCH_2Ar), 1.99 (d, *J*=14.0 Hz, 1H, ArCH_2Ar); IR (KBr) cm^{-1}: 3503 (s, OH), 1722 (s, C═O), 1659 (s, C═O); FAB-MS *m/z*: 678 (M^+), 680 (M^++2). Anal. Calcd for $C_{42}H_{30}O_9$: C, 74.34; H, 4.42. Calcd for $C_{42}H_{30}O_9$·H_2O: C, 72.41; H, 4.60. Found: C, 72.56; H, 4.38.

Method B: without buffer solution. A slurry of 3.34 g (5.28 mmol) of **1** was dissolved in 150 mL of acetone, and 50 mL of water was added. A portion of 115 mL of yellowish ClO_2 aqueous solution was then added, and the reaction mixture was stirred at room temperature for 48 h. The organic solvent was removed, and a large amount of water was added to generate a pale yellow solid. The solid material was collected, dissolved in $CHCl_3$, and subjected to column chromatography separation with $CHCl_3$ as an eluent. The first eluted component, after recrystallization from $CHCl_3$ and CH_3OH, weighing 1.17 g (32.5%) was the yellow compound **2**. The second eluted product, after recrystallization from $CHCl_3$ and CH_3OH, weighing 0.66 g (19%) was the yellow product **3**.

Method C: with pH 9 buffer solution. A slurry of 3.35 g (5.30 mmol) of **1** was dissolved in 150 mL of acetone, and 50 mL of concentrated buffer solution[13] was added. A portion of 115 mL of yellowish ClO_2 aqueous solution was then added, and the reaction mixture was stirred at room temperature for 60 h. The pale yellow solid material was collected and recrystallized three times from $CHCl_3$ and CH_3OH to give 1.88 g (54%) of **2** as an yellow crystals.

The mother liquor was concentrated and subjected to column chromatography separation with $CHCl_3$ as an eluent. The first eluted component, after recrystallization from $CHCl_3$ and CH_3OH, weighing 0.27 g (8%) was the yellow compound **2**. The second eluted product, after recrystallization from $CHCl_3$ and CH_3OH, weighing 0.11 g (3%) was the yellow product **3**.

3.1.3. 25,27-Dibenzoyloxy-26,28-calix[4]diquinone-5,17-bis(ethylene ketal) (4). A slurry of 0.99 g (1.50 mmol) of **2**, 5.6 mL (6.20 g, 100 mmol) of ethylene glycol, and 0.10 g of *p*-TsOH in 70 mL of benzene was equipped with a Dean–Stark water trap and refluxed for 48 h. The solvent was removed, and the residue was treated with water to leave a pale yellow solid. The solid material was collected and recrystallized from $CHCl_3$ and CH_3OH to afford 0.81 g (72%) of light yellow crystals: mp 315–317°C; ^{1}H NMR ($CDCl_3$) δ 8.46 (d, *J*=7.6 Hz, 4H, *o*-Ar′*H*), 7.70 (t, *J*=7.6 Hz, 2H, *p*-Ar′*H*), 7.57 (t, *J*=7.7 Hz, 4H, *m*-Ar′*H*), 7.09 (bs, 4H, *m*-Ar*H*), 6.86 (m, 2H, *p*-Ar*H*), 6.11 (bs, 4H, quinone-*H*), 3.88 (bs, 8H, ketal-*H*), 3.44 (bs, 4H, ArCH_2Ar), 3.13 (bs, 4H, ArCH_2Ar); IR (KBr) cm^{-1}: 1732 (s, C═O), 1655 (s, C═O); FAB-MS *m/z*: 749 (M^++1). Anal. Calcd for $C_{46}H_{36}O_{10}$: C, 73.80; H, 4.81. Calcd for $C_{46}H_{36}O_{10}$·1/2H_2O: C, 72.92; H, 4.89. Found: C, 72.63; H, 4.90.

3.1.4. Intramolecular Michael-addition product 5—product of basic hydrolysis of compound 4. A slurry of 0.75 g (1.00 mmol) of **4** was dissolved in 40 mL of THF, and a portion of 25 mL of ethanolic alkali solution (1.54 g of NaOH dissolved in 7 mL of water and 18 mL of ethanol) was added. The reaction mixture was refluxed for 20 h, and was neutralized with diluted HCl. The solvent was removed to leave an oily residue, and a large amount of water was then added to induce an off white solid. The solid material was collected and recrystallized from $CHCl_3$ and CH_3OH to afford 0.33 g (61%) of pale yellow crystals: mp 325–327°C; ^{1}H NMR ($CDCl_3$) δ 7.01 (s, 2H, C═C*H*), 7.00 (d, *J*=7.5 Hz, 2H, *m*-Ar*H*), 6.69 (d, *J*=7.4 Hz, 2H, *m*-Ar*H*), 6.52 (t, *J*=7.5 Hz, 2H, *p*-Ar*H*), 4.36–4.37 (m, 2H, OC*H*), 4.31 (dd, *J*=11.2, 6.1 Hz, 2H, ketal-*H*), 4.25 (dd, *J*=14.8, 7.7 Hz, 2H, ketal-*H*), 4.15 (dd, *J*=11.4, 6.4 Hz, 2H, ketal-*H*), 3.99 (dd, *J*=14.0, 7.0 Hz, 2H, ketal-*H*), 3.38 (d, *J*=12.8 Hz, 2H, ArCH_2Ar), 3.31 (d, *J*=15.8 Hz, 2H, ArCH_2Ar), 3.25 (d, *J*=12.8 Hz, 2H, ArCH_2Ar), 3.08–3.10 (m, 2H, COC*H*), 3.22 (dd, *J*=15.9, 5.8 Hz, 2H, ArCH_2Ar); IR (KBr) cm^{-1}: 1673 (s, C═O); FAB-MS *m/z*: 541 (M^++1). Anal. Calcd for $C_{32}H_{28}O_8$: C, 71.11; H, 5.19. Calcd for $C_{32}H_{28}O_8$·1/2H_2O: C, 69.94; H, 5.28. Found: C, 69.82; H, 5.25.

3.1.5. Intramolecular Michael-addition product 6—product of acidic hydrolysis of compound 5. *Method A: p-TsOH as catalyst*. A slurry of 0.43 g (0.80 mmol) of **5** and 0.04 g of *p*-TsOH in 200 mL of acetone was refluxed for 6 h. The color of the reaction mixture was gradually change from colorless to greenish yellow, and finally to brown. The organic solvent was removed, and the residue was treated with water to leave an yellowish solid. The solid material was collected and recrystallized from $CHCl_3$ and *n*-hexane to afford 0.27 g (75%) of yellow crystals: mp over 455°C; ^{1}H NMR ($CDCl_3$) δ 7.06 (d, *J*=7.4 Hz, 2H, *m*-Ar*H*), 6.82 (d, *J*=7.5 Hz, 2H, *m*-Ar*H*), 6.71 (s, 2H, C═C*H*), 6.67 (t, *J*=7.5 Hz, 2H, *p*-Ar*H*), 4.71–4.72 (m, 2H, OC*H*), 3.52 (d, *J*=12.8 Hz, 2H, ArCH_2Ar), 3.36–3.40 (m, 4H, ArCH_2Ar), 3.18–3.20 (m, 2H, COC*H*), 2.79 (dd, *J*=15.9, 5.6 Hz, 2H,

ArCH_2Ar); IR (KBr) cm^{-1}: 1686 (s, C=O); FAB-MS *m/z*: 453 (M^++1). Anal. Calcd for $C_{28}H_{20}O_6$: C, 74.34; H, 4.42. Calcd for $C_{28}H_{20}O_6{\cdot}CH_3OH$: C, 71.88; H, 5.00. Found: C, 71.85; H, 4.83.

Method B: H_2SO_4 as catalyst. A slurry of 0.20 g (0.37 mmol) of **5** dissolved in 150 mL of $CHCl_3$ and 50 mL of 60% of ethanol, and a portion of 15 mL of conc. H_2SO_4 was then slowly added as a catalyst. The reaction mixture was refluxed for 18 h., and the color of the reaction mixture changed from colorless to a greenish yellow. The reaction mixture was washed, sequentially with, water three times, saturated $NaHCO_3$ solution, and finally water. The organic portion was separated and dried with $MgSO_4$. The filtrate was concentrated and recrystallized from $CHCl_3$ and *n*-hexane to afford 0.14 g (84%) of yellow crystals.

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10. Concentrated aqueous buffer solution was obtained by dissolving 4.36 g of $Na_2HPO_4{\cdot}2H_2O$ and 2.42 g of $NaH_2PO_4{\cdot}2H_2O$ in 100 mL of deionized water. A pH 7 buffer solution was afforded, when this concentrated solution was diluted five times in volume.
11. Aqueous chlorine dioxide solution was prepared by mixing equal volume of sodium chlorite solution ($NaClO_2{\cdot}2H_2O$, 31.60 g, 0.25 mol in 500 mL of deionized water) and sodium persulfate solution ($Na_2S_2O_8$, 29.70 g, 0.25 mol in 500 mL of deionized water). The solution was then stored in a brown bottle at 0°C prior being used.
12. All the new compounds, which were submitted to Elemental Analysis (EA), were dried at 120°C under vacuum for 48 h prior to the analysis. If the analysis value was different from the calculated value, the sample was dried at 140°C under vacuum for 48 h prior to another analysis. The drying period will be increased further, if the sample still received a different EA value from the theoretical value. The procedure was continued until a constant EA value was attained.
13. Concentrated aqueous buffer solution was obtained by dissolving 2.86 g of $Na_2B_4O_7{\cdot}10H_2O$ and 2.76 mL of 1N HCl in 100 mL of deionized water. A pH 9 buffer solution was afforded, when this concentrated solution was diluted 5 times in volume.