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Synthesis of 1,3-disubstituted naphtho[2,3-*c*]pyran-5,10-diones

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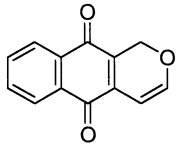
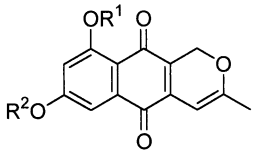
Abstract—Two convenient and simple methods for the synthesis of 1,3-disubstituted naphtho[2,3-*c*]pyran-5,10-diones, which involve the introduction of acylmethyl groups onto 2-(1-hydroxyethyl)-1,4-naphthoquinones and subsequent base- and acid-induced ring closure, were developed.

1. Introduction

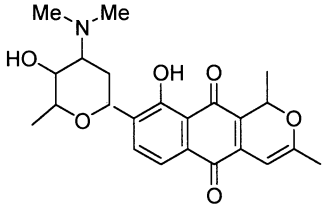
Naphtho[2,3-*c*]pyran-5,10-diones are an important class of compounds due to their broad range of biological activities.[1–4] Their useful biological activities have made these compounds attractive synthetic objectives. The development of new synthetic strategies for the synthesis of pyranonaphthoquinones is still very popular in synthetic organic chemistry.[4,5]



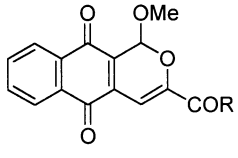
1 (pentalongin)



2a R^1= Me, R^2 = Me (dehydroherbarin)
2b R^1= H, R^2 = H
2c R^1= H, R^2 = Me



3 (3543R1)



4 (R = OMe, NR^1R^2)

A particular group of naturally occurring 3,4-dehydropyranonaphthoquinones, which include examples such as pentalongin **1**, dehydroherbarin **2a** and the pigments **2b**, **2c**, were found to possess interesting antimicrobial, antiparasitic and phytotoxic activities.[6–8] In addition, several 1,3-disubstituted-3,4-dehydropyranonaphthoquinones have been reported to possess significant antineoplastic activity. Compound **3** (3543R1), a metabolite produced by *Streptomycin tanashiensis* K3543, was recently identified as a very active neoplasm inhibitor.[9] The synthetic C(3)-carbonyl substituted pyranonaphthoquinones **4** have been found as very effective antitumor chemotherapeutics.[10]

In fact, several methods[11–13] have been developed for the synthesis of 3,4-dehydropyranonaphthoquinones but their use is generally limited. An interesting method has been developed for the synthesis of 3-aryl substituted pentalongin derivatives in a one-pot procedure from phenacylpyridinium ylides and 2-(phenoxymethyl)-1,4-naphthoquinone.[14a,b] However, this procedure is not applicable for the synthesis of 1,3-disubstituted pentalongin derivatives. Concerning the synthesis of 1,3-disubstituted pentalongin derivatives, only two procedures have been described so far. The first procedure concerned a tandem conjugate addition-cyclization sequence between 2-(1-hydroxyalkyl)-1,4-naphthoquinone and enamines and imines.[15b] The second procedure involved a difficult multi-step conversion, including oxidation with DDQ and Diels Alder cyclocondensation.[10]

We report herein two simple and convenient one-pot syntheses of a series of 1,3-disubstituted naphtho[2,3-*c*]pyran-5,10-diones via introduction of acylmethyl groups onto 2-(1-hydroxyethyl)-1,4-naphthoquinone by using acylmethylpyridinium ylides and a final intramolecular cyclization.

2. Results and discussion

The starting material **10,** i.e. 1,4-dimethoxy-2-(1-hydroxyethyl)naphthalene, is a suitable substrate for the synthesis of

Keywords: 1,3-disubstituted naphtho[2,3-c]pyran-5,10-diones; 1,4-naphthoquinones; acylmethylation.

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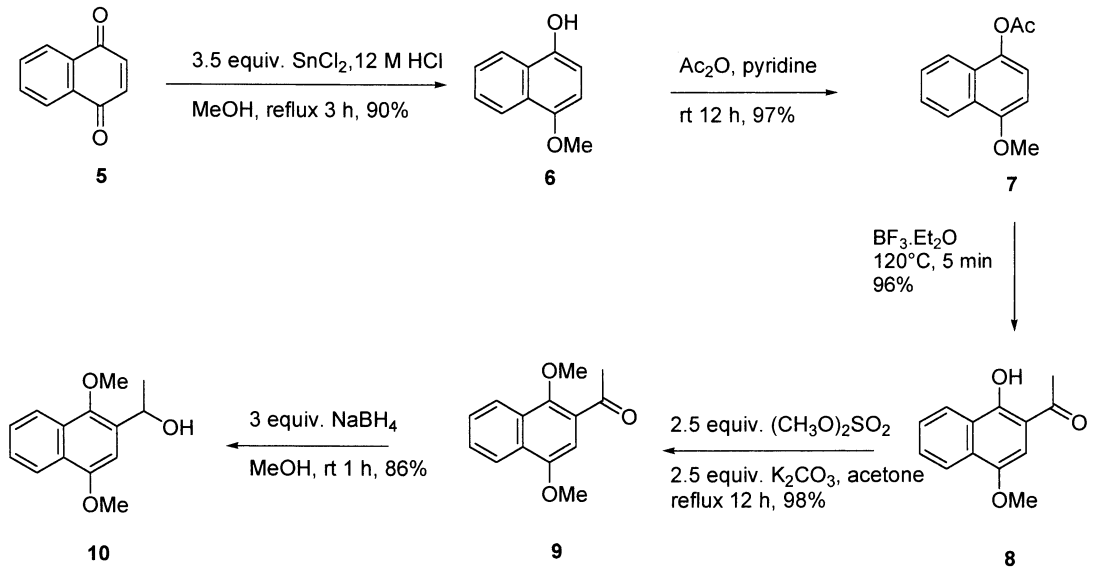
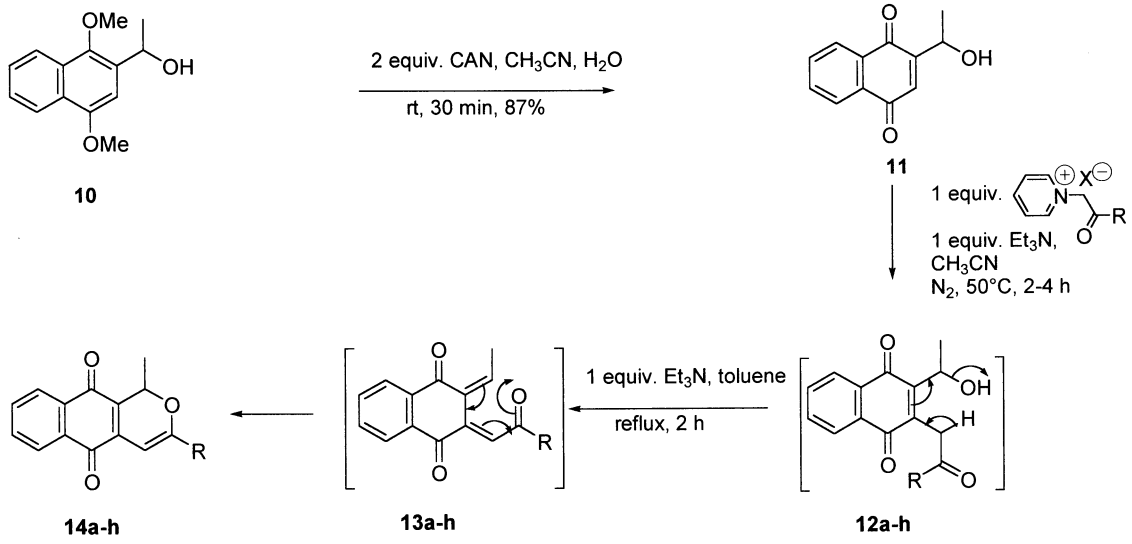


Scheme 1.

1,3-disubstituted naphtho[2,3-*c*]pyran-5,10-diones. The synthesis of compound **10** is shown in Scheme 1. Naphthoquinone **5** was smoothly reduced by treatment with tin(II) chloride and concentrated hydrogen chloride in methanol under reflux for 3 hours to afford 4-methoxy-1-naphthol **6** in 90% yield. 4-Methoxy-1-naphthol **6** was acetylated with acetic anhydride in pyridine at room temperature for 12 hours to give the corresponding acetate **7** in 97% yield.[13] This compound **7** underwent Fries rearrangement[13] with $BF_3{\cdot}Et_2O$ at 120°C for five minutes to afford the



a R = 4-ClC_6H_4 (63%)

b R = 4-FC_6H_4 (62%)

c R = 4-MeC_6H_4 (65%)

d R = 4-$CH_3OC_6H_4$ (61%)

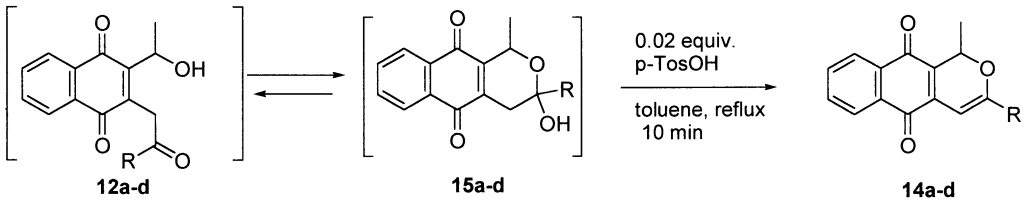
e R = 2,4-$(CH_3O)_2C_6H_3$ (67%)

f R = C_6H_5 (66%)

g R = $C(CH_3)_3$ (64%)

h R = CH_3 (68%)

Scheme 2.



a R = 4-ClC_6H_4 (95%) (**14a**)

b R = 4-FC_6H_4 (90%) (**14b**)

c R = 4-MeC_6H_4 (97%) (**14c**)

d R = 4-$OCH_3C_6H_4$ (92%) (**14d**)

Scheme 3.

2-acetyl-4-methoxy-1-naphthol **8** in 96% yield. 2-Acetyl-4-methoxy-1-naphthol **8** was treated with an excess of dimethyl sulfate and potassium carbonate in dry acetone under reflux[16] to afford the corresponding 2-acetyl-1,4-dimethoxynaphthalene **9** in 98% yield, which underwent smooth reduction with sodium borohydride[16] in methanol to form the alcohol **10** in 86% yield.

Oxidative demethylation[16] of alcohol **10** with 2 equivalents of cerium(IV) ammonium nitrate in aqueous acetonitrile at room temperature gave the corresponding quinone **11** in 87% yield. The introduction of an acylmethyl group onto quinone **11** was accomplished by using *N*-acylmethyl-pyridinium salts and triethylamine in acetonitrile under nitrogen at 50°C for 2ndash;4 hours.[14a–d] Several substituted phenacylmethyl units were introduced, including methyl-, chloro-, fluoro- and methoxysubstituted derivatives. The final intramolecular cyclization of compounds **12** was performed with 1 equivalent of triethylamine in acetonitrile under reflux for 2 hours.[14a,b] Unfortunately, in our hands this procedure was not successful. In this case, the hydroxyl group of compound **12** is a weak leaving group, compared to bromo or aryloxy groups in the case of the reported procedure.[14a,b] However, the intramolecular cyclization of compounds **12** has been modified successfully by using 1 equivalent of triethylamine in toluene under reflux for two hours (Scheme 2). Under these condition the corresponding 3,4-dehydronaphtho[2,3-*c*]pyran-5,10-diones **14** were obtained in acceptable yields (61–66%). Also the title compounds **14** with two aliphatic substituents at the 1- and 3-position became easily accessible in 64–68% yield (compounds **14g, h**).

The mechanism of the cyclization reaction of compounds **12** is outlined in Scheme 2.[14a,b] In order to confirm the mechanism of the reaction, attempts were made to isolate the intermediates **12**. Unfortunately, the reaction products were obtained as a mixture of compound **12** and **15** in a 1:4 ratio. In other words, compounds **12** were not stable and easily underwent the intramolecular addition to give compounds **15**. Crystallization allowed the isolation of the pure compounds **15b,c**. These results initiated us to develop a new method for the synthesis of 1,3-disubstituted-3,4-dehydronaphtho[2,3-*c*]pyran-5,10-diones **14**.

The second procedure for the synthesis of 3,4-dehydronaphtho[2,3-*c*]pyran-5,10-diones **14** is outlined in Scheme 3. The intramolecular condensation of compounds **12** into compounds **15** was performed in toluene, which allowed the complete dehydration by treatment with 0.02 equiv. of p-toluenesulfonic acid over a period of 10–20 minutes, affording compounds **14** in excellent yields of 90–97%.

In conclusion, two convenient and simple methods for the synthesis of 1,3-disubstituted naphtho[2,3-*c*]pyran-5,10-diones from 2-(1-hydroxyethyl)-1,4-naphthoquinone **10** are described. By means of the first method, the novel quinones **14a–g** were obtained in 61–68% yield, while by the second method, the quinones **14a–d** were obtained in 90–97% yield.

3. Experimental

Melting points were determined on a Buchi 535 apparatus. ^1H NMR spectra (270 MHz) and ^{13}C NMR spectra (67 MHz) were recorded with a Jeol JNM-EX 270 NMR spectrometer. IR spectra were measured with a Perkin Elmer Model 983 spectrophotometer. Mass spectra were recorded with a Varian- MAT 112 mass spectrometer (70 eV).

3.1. Compound data

3.1.1. 4-Methoxy-1-naphthol 6. To a solution of 15.8 g (0.1 mol) of 1,4-naphthoquinone **5** in MeOH (200 mL) was added dropwise a solution of 66.5 g (0.35 mol) $SnCl_2$ in 12 M HCl (70 mL) at room temperature over a period of 20 minutes. The solution was then refluxed for 3 hours and cooled to room temperature. Then MeOH was removed to 1/5 of the starting volume and the residue was poured in cold water to give a precipitate, which was filtered and dissolved in CH_2Cl_2. The organic solution was dried ($MgSO_4$), and the solvent was removed *in vacuo* to give 13.4 g of compound **6** (77% yield, white solid, mp 126–126.5°C, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ: 8.20–8.23 (1H, m, H-8), 8.09–8.13 (1H, m, H-5), 7.48–7.52 (2H, m, H-7 and H-6), 6.71 (1H, d, J=8.1 Hz, H-2), 6.62 (1H, d, J=8.1 Hz, H-3), 3.94 (3H, s, OMe). ^{13}C NMR ($CDCl_3$) δ:

149.7 (C-1), 145.0 (C-4), 125.9 (C-7), 125.7 (C-2), 125.3 (Cquat), 122.3 (Cquat), 122.0 (C-6), 121.3 (C-3), 107.9 (C-5), 103.4 (C-8), 55.8 (OMe). IR (KBr): 3416 (OH), 1635, 1597, 1456, 1359, 1266, 1093, 1022 cm^{-1}. MS, m/z (%): 174 (M^+, 100), 160 (28), 131 (48), 103 (38), 77 (41). Anal. Calcd. $C_{11}H_{10}O_2$: C 75.84%, H 5.79%; found: C 75.71%, H 5.70%.

3.1.2. 1-Acetoxy-4-methoxynaphthalene 7. A mixture of 10.0 g (0.057 mol) of 4-methoxy-1-naphthol **6**, Ac_2O (20 mL) and pyridine (30 mL) was stirred at room temperature for 24 hours.[13] The reaction mixture was poured in cold water and extracted twice with EtOAc. The extract was washed with 2M HCl, water and dried ($MgSO_4$). Then the solvent was evaporated *in vacuo* to give 12 g of product **7** (97% yield, white solid, mp 53–54°C, hexane). ^1H NMR ($CDCl_3$) δ: 8.25–8.27 (1H, m, H-8), 7.75–7.78 (1H, m, H-5), 7.38–7.45 (2H, m, H-7 and H-6), 7.05 (1H, d, J=8.6 Hz, H-2), 6.58 (1H, d, J=8.6 Hz, H-3), 3.78 (3H, s, OMe), 2.28 (3H, s, Me). ^{13}C NMR ($CDCl_3$) δ: 169.6 (C=O), 153.2 (C-1), 139.7 (C-2), 127.2 (Cquat), 126.6 (C-6), 125.9 (Cquat), 125.4 (C-7), 122.1 (C-5), 120.6 (C-8), 117.5 (C-2), 102.6 (C-3), 55.2 (OMe), 20.5 (Me). IR (KBr): 1751 (C=O), 1624, 1594, 1579, 1458, 1264, 1087, 883, 766 cm^{-1}. MS, m/z (%): 216 (M^+, 11), 174 (77), 159 (63), 131 (10), 105 (10), 91 (12), 77 (15), 43 (100). Anal. Calcd. $C_{13}H_{12}O_3$: C 72.21%, H 5.59%; found: C 72.34%, H 5.69%.

3.1.3. 2-Acetyl-4-methoxy-1-naphthol 8. A flask, containing 10 g (0.046 mol) of 1-acetoxy-4-methoxynaphthalene **7**, was heated to 120°C and then $BF_3.Et_2O$ (5 mL) was added by a syringe.[13] After 5 min, the mixture was treated cautiously with cold water (20 mL). The reaction mixture was extracted twice with EtOAc. The extract was washed with $NaHCO_3$, dried ($MgSO_4$), and the solvent was evaporated *in vacuo* to give 12.2 g of compound **8**, which was purified by flash chromatography to obtain 9.6 g of pure product **8** (96% yield, white solid, mp 115–116°C, hexane). ^1H NMR ($CDCl_3$) δ: 13.65 (1H, s, Ar-OH), 8.42 (1H, d, J=8.4 Hz, H-8), 8.17 (1H, d, J=8.4 Hz, H-5), 7.28–7.69 (2H, m, H-7 and H-6), 6.74 (1H, s, H-3), 3.95 (3H, s, OMe), 2.64 (3H, s, Me). ^{13}C NMR ($CDCl_3$) δ: 203.6 (C=O), 153.3 (C-4), 147.3 (C-1), 130.2 (C-3), 129.6 (C-7), 126.5 (C-6), 125.9 (Cquat), 124.3 (C-8), 121.8 (C-5), 111.9 (Cquat), 100.7 (C-2), 55.6 (OMe), 26.9 (Me). IR (KBr): 3414 (OH), 1626 (C=O), 1590, 1573, 1453, 1392, 1237, 1109, 1022 cm^{-1}. MS, m/z (%): 216 (M^+, 18), 202 (42), 187 (23), 160 (30), 159 (29), 129 (29), 94 (46), 43 (100). Anal. Calcd. $C_{13}H_{12}O_3$: C 72.21%, H 5.59%; found: C 72.29%, H 5.68%.

3.1.4. 2-Acetyl-1,4-dimethoxynaphthalene 9. A mixture of 14.0 g (49.2 mmol) of 2-acetyl-4-methoxy-1-naphthol **8**, 17.6 g (123.4 mmol) of dimethyl sulfate and 15.48 g (123.48 mmol) of potassium carbonate in dry acetone (200 mL) was stirred vigorously and refluxed for 24 hours.[16] The mixture was cooled to room temperature, and filtered to remove potassium carbonate. The filtrate was evaporated in vacuo and the residue was poured in water and extracted twice with ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$) and the solvent was evaporated in vacuo to give 15.0 g of crude product. The product was purified by chromatography on a silica gel column (hexane/ethyl acetate, 10/1) to give 13.6 g of compound **9** in 98% yield as a colorless oil. ^1H NMR ($CDCl_3$) δ: 8.19–8.25 (1H, m, H-5), 8.15–8.19 (1H, m, H-8), 7.56–7.63 (2H, m, H-6 and H-7), 6.68 (1H, s, H-2), 4.01 (3H, s, OMe), 3.96 (3H, s, OMe), 2.82 (3H, s, Me). ^{13}C NMR ($CDCl_3$) δ: 199.7 (C=O), 151.8 (C-4), 153.4 (C-1), 129.0 (C-3), 128.7 (Cquat), 127.7 (C-7), 127.2 (Cquat), 127.1 (C-6), 123.2 (C-5), 122.5 (C-8), 102.1 (C-2), 63.8 (3H, s, OMe), 55.7 (OMe), 30.9 (Me). IR (NaCl): 1661 (C=O), 1595, 1453, 1368, 1225, 1103 cm^{-1}. MS, m/z (%): 230 (M^+, 100), 215 (85), 188 (34), 187 (40). Anal. Calcd. $C_{14}H_{14}O_3$: C 73.03%, H 6.13%; found: C 72.76%, H 5.94%.

3.1.5. 3-(1-Hydroxyethyl)-1,4-dimethoxynaphthalene 10. To a solution of 5.0 g (21.74 mmol) of 3-acetyl-1,4-dimethylnaphthalene **9** in dry MeOH (50 mL) was added 2.41g (65.25 mmol) of sodium borohydride.[16] The mixture was stirred for one hour at room temperature, then quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The extract was washed with brine, water, dried ($MgSO_4$), and the solvent was evaporated in vacuo to give 4.8 g of the crude product which was purified by chromatography on a silica gel column (hexane / ethyl acetate, 10 / 1) to give 4.3 g of compound **10** (86% yield, white solid, mp 100–102°C, hexane), (Lit.[17] 101–103°C). ^1H NMR ($CDCl_3$) δ: 8.20 (1H, d, J=8.4 Hz, H-8), 7.98 (1H, d, J=8.4 Hz, H-5), 7.45–7.51 (2H, m, H-7 and H-6), 6.86 (1H, s, H-3), 5.00–5.03 (1H, m, CH–OH), 3.96 (3H, s, OMe), 3.87 (3H, s, OMe), 1.55 (3H, d, J=6.7 Hz, Me). ^{13}C NMR ($CDCl_3$) δ: 152.4 (C-1), 145.4 (C-4), 133.2 (C-2), 128.3 (Cquat), 126.6 (C-6), 126.0 (Cquat), 125.3 (C-7), 122.4 (C-8), 121.8 (C-5), 100.9 (C-3), 64.6 (CH–OH), 63.9 (3H, s, OMe), 62.7 (OMe), 24.3 (Me). IR (KBr): 3354 (OH), 2949, 1626, 1596, 1509, 1458, 1361, 1263, 1083 cm^{-1}. MS, m/z (%): 232 (M^+, 21), 86 (32), 84 (50), 51 (57), 49 (100).

3.1.6. 3-(1-Hydroxyethyl)-1,4-naphthoquinone 11. To a solution of 4.0 g (1.7 mmol) of 3-(1-hydroxyethyl)-1,4-dimethoxynaphthalene **10** in a mixture of water (40 mL) and acetonitrile (40 mL), was added 18 g (0.034 mol) of ceric ammonium nitrate.[16] The mixture was stirred for 15 min, then poured in water and extracted with ether. The extract was washed with water, brine, dried ($MgSO_4$), and the solvent was evaporated in vacuo to give 3.02 g of compound **11** in 87% yield, as yellow powder, 87–88°C (hexane), (Lit.[17] 88–89°C). ^1H NMR ($CDCl_3$) δ: 8.06–8.11 (2H, m, H-5 and H-8), 7.73–7.78 (2H, m, H-6 and H-7), 7.01 (1H, s, H-3), 5.0-5.03 (1H, m, CH–OH), 1.52 (3H, d, J=6.2Hz, Me). ^{13}C NMR ($CDCl_3$) δ: 185.6 (C=O), 185.3 (C=O), 152.7 (Cquat), 134.1 (C-6), 133.9 (C-7), 132.9 (C-8), 132.3 (Cquat), 131.9 (Cquat), 126.5 (C-5), 126.2 (C-3), 63.3 (CH–OH), 22.6 (Me). IR (KBr): 3414 (OH), 1657 (C=O), 1617 (C=O), 1592, 1288, 1247, 1155, 1018 cm^{-1}. MS, m/z (%): 202 (M^+, 96), 187 (64), 160 (100), 159 (97).

3.1.7. 2-(1-Hydroxyethyl)-3-(acylmethyl)-1,4-naphthoquinone 12. To a solution of 0.01 mol of 2-(1-hydroxyethyl)-1,4-naphthoquinone **11** and 0.01 mol of pyridinium ylide[14a–d] in acetonitrile (40 mL), under N_2 at 50°C, was added dropwise a solution of 0.01 mol of Et_3N in

acetonitrile (10 mL). The mixture was stirred for 2–4 hours at room temperature. The solvent was evaporated in vacuo and the residue was quenched with water and extracted with CH_2Cl_2. The extract was washed with 1 M HCl, water and dried ($MgSO_4$). The solvent was evaporated in vacuo to give the crude intermediate reaction products **12** and **15** in a 1:4 ratio. These products were treated with 0.01 mol of triethylamine in toluene (10 mL), and the mixture was refluxed for 2 hours. The mixture was poured in water and extracted with EtOAc. The extract was washed with 2 M HCl, water and dried ($MgSO_4$). The solvent was evaporated in vacuo to give the crude product, which was purified by flash chromatography on silica gel (hexane/ethyl acetate, 9/1) to give the pure 2,3-disubstituted naphthoquinones **14** (first procedure).

To 1 mmol of the mixture of the intermediates **12** and **15**, dissolved in toluene (15 mL), was added 0.02 mmol of p-TsOH. The reaction mixture was refluxed for 10 min. The mixture was poured in water and extracted with EtOAc. The extract was washed with water and dried ($MgSO_4$). The solvent was evaporated in vacuo to give the crude product, which was purified by flash chromatography on silica gel (hexane/ethyl acetate, 9/1) to give the pure 2,3-disubstituted naphthoquinones **14a–d** (second procedure).

3.1.8. 3-(4-Fluorophenyl)-3-hydroxy-1-methyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione 15b. The crude reaction mixture of compound **12b** and **15b** was recrystallized in hexane to give the pure compound **15b** as a red powder, mp 128–129°C (hexane). ^{1}H NMR ($CDCl_3$) δ: 1.68 (3H, d, J=6.6 Hz, Me), 2.37 (1H, s, CH_3), 2.53 (1H, dd, J_1=16.5 Hz, J_2=2.6 Hz, ABY system, H-4a), 3.23 (1H, dd, J_1=16.5 Hz, J_2=2.0 Hz, ABY system, H-4b), 5.15–5.19 (1H, m, H-1), 7.09 (2H, dd, J=7.9 Hz and J=8.5 Hz, H-3′, H-5′), 7.64 (2H, dd, J=7.9 Hz and J=8.5 Hz, H-2′ and H-6′), 7.71–7.78 (2H, m, H-7 and H-8), 8.06–8.12 (2H, m, H-6 and H-9); ^{13}C NMR ($CDCl_3$) δ: 183.7 (C=O), 183.4 (C=O), 162.7 (d, $^1J_{CF}$=247.9, CF), 144.9 (Cquat), 140.3 (Cquat), 139.2 (Cquat), 133.8 (C-7), 133.6 (C-8), 132.9 (Cquat), 131.2 (Cquat), 127.0 (C-3′), 126.9 (C-5′, C-5), 126.3 (C-9), 115.4 (C-2′), 115.0 (C-6′), 94.9 (C-3), 65.8 (C-1), 34.5 (C-4), 20.4 (Me). IR (KBr): 3452 (OH), 1666 (C=O), 1637 (C=O), 1595, 1509, 1452, 1406, 1336, 1185, 1078 cm^{-1}. MS, m/z (%): 338 (M^+, 40), 320 (60), 208 (33), 127 (39), 100 (10), 93 (100). Anal. Calcd. $C_{20}H_{15}O_4F$: C 71.00%, H 4.47%; found: C 71.06%, H 4.67%.

3.1.9. 3-Hydroxy-3-(4-methylphenyl)-1-methyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione 15c. The crude reaction mixture of compound **12c** and **15c** was recrystallized in hexane to give the pure compound **15c** as a red powder, mp 136–138°C (hexane). ^{1}H NMR ($CDCl_3$) δ: 1.67 (3H, d, J=6.9 Hz, Me), 2.37 (1H, s, CH_3), 2.55 (1H, dd, J_1=18.6 Hz, J_2=2.3 Hz, ABX system, H-4a), 3.21 (1H, dd, J_1=18.6 Hz, J_2=3.5 Hz, ABX system, H-4b), 5.10–5.18 (1H, m, H-1), 7.26 (2H, d, J=7.9 Hz, H-2′, H-6′), 7.62 (2H, d, J=7.9 Hz, H-3′ and H-5′), 7.68–7.75 (2H, m, H-7 and H-8), 8.05–8.16 (2H, m, H-6 and H-9); ^{13}C NMR ($CDCl_3$) δ: 183.8 (C=O), 183.5 (C=O), 145.1 (Cquat), 141.5 (Cquat), 139.6 (Cquat), 133.9 (Cquat), 133.7 (C-7), 133.5 (C-8), 132.3 (Cquat), 131.8 (Cquat), 129.4 (C-3′), 129.1 (C-5′, C-5), 128.5 (C-9), 126.2 (C-2′), 124.8 (C-6′), 95.1 (C-3), 65.7 (C-1), 34.4 (C-4), 21.1 (Me), 20.5 (Me). IR (KBr): 3440 (OH), 1662 (C=O), 1644 (C=O), 1592, 1515, 1457, 1405, 1296, 1044 cm^{-1}. MS, m/z (%): 334 (M^+, 16), 317 (100), 284 (12), 204 (83), 203 (13), 125 (90). Anal. Calcd. $C_{21}H_{18}O_4$: C 75.43%, H 5.43%; found: C 75.56%, H 5.47%.

3.1.10. 3-(4-Chlorophenyl)-1-methyl-1*H*-naphtho[2,3-*c*]pyrane-5,10-dione 14a. Compound **14a** was synthesized according to the first and the second procedure in 63% and 95% yield, respectively; red powder, mp 142–143°C (hexane). ^{1}H NMR ($CDCl_3$) δ: 1.46 (3H, d, J=6.7 Hz, Me), 5.85–5.87 (1H, m, H-1), 6.63 (1H, s, H-4), 7.37 (2H, dd, J=8.6 Hz, and J=2.0 Hz, H-3′, H-5′), 7.67–7.69 (2H, m, H-7 and H-8), 7.72 (2H, dd, J=8.6 Hz, and J=2.0 Hz, H-2′ and H-6′), 8.04–8.11 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$) δ: 182.5 (C=O), 181.7 (C=O), 157.7 (C-3), 136.7 (Cquat), 135.9 (Cquat), 133.9 (C-8), 133.2 (C-7), 132.6 (Cquat), 131.8 (Cquat), 131.7 (Cquat), 128.8 (C-3′, C-5′), 128.1 (Cquat), 127.4 (C-2′, C-6′), 126.4 (C-6), 125.9 (C-9), 92.7 (C-4), 69.9 (C-1), 17.9 (Me). IR (KBr): 1667 (C=O), 1642 (C=O), 1589, 1543, 1481, 1334, 1265, 1006 cm^{-1}. MS, m/z (%): 338/336 (M^+, 1), 286 (13), 105 (11), 99 (23), 89 (24), 71 (30), 43 (100). Anal. Calcd. $C_{20}H_{13}O_3Cl$: C 71.33%, H 3.89%; found: C 70.93%, H 3.77%.

3.1.11. 3-(4-Fluorophenyl)-1-methyl-1*H*-naphtho[2,3-*c*]pyrane-5,10-dione 14b. Compound **14b** was synthesized according to the first and the second procedure in 62% and 90% yield, respectively; red powder, mp 154–155°C (hexane). ^{1}H NMR ($CDCl_3$) δ: 1.47 (3H, d, J=6.5 Hz, Me), 5.85–5.92 (1H, m, H-1), 6.62 (1H, s, H-4), 7.10 (2H, dd, J=8.4 Hz, and J=8.6 Hz, H-3′, H-5′), 7.66–7.73 (2H, m, H-7 and H-8), 7.80 (2H, dd, J=8.4 Hz, and J=8.6 Hz, H-2′ and H-6′), 8.06–8.13 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$) δ, 182.7 (C=O), 181.8 (C=O), 164.2 (d, $^1J_{CF}$=247.9, CF), 158.0 (C-3), 136.2 (Cquat), 133.9 (C-7), 133.1 (C-8), 132.7 (Cquat), 131.7 (Cquat), 129.7 (Cquat), 129.6 (Cquat), 128.4 (C-9), 128.3 (C-6), 127.7 (Cquat), 126.4 (C-6′), 125.9 (C-2′), 115.8 (C-3′), 115.5 (C-5′), 91.9 (C-4), 69.9 (C-1), 17.9 (Me). IR (KBr): 1655 (C=O), 1640 (C=O), 1586, 1533, 1495, 1331, 1297, 1156 cm^{-1}. MS, m/z (%): 320 (M^+, 2), 304 (18), 99 (26), 89 (36), 57 (44), 43 (100). Anal. Calcd. $C_{20}H_{13}O_3F$: C 74.99%, H 4.09%; found: C 75.03%, H 3.93%.

3.1.12. 1-Methyl-3-(4-methylphenyl)-1*H*-naphtho[2,3-*c*]pyrane-5,10-dione 14c. Compound **14c** was synthesized according to the first and the second procedure in 65% and 97% yield, respectively; red powder, mp 122–126°C (hexane). ^{1}H NMR ($CDCl_3$) δ: 1.47 (3H, d, J=6.7 Hz, Me), 2.40 (Ar-*Me*), 5.86–5.93 (1H, m, H-1), 6.65 (1H, s, H-4), 7.24 (2H, d, J=9.4 Hz, H-3′, H-5′), 7.68–7.75 (4H, m, H-7, H-8, H-2′ and H-6′), 8.06–8.13 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$) δ: 183.0 (C=O), 181.7 (C=O), 159.4 (C-3), 141.3 (Cquat), 136.5 (Cquat), 133.9 (C-8), 133.0 (C-7), 132.8 (Cquat), 131.8 (Cquat), 130.7 (Cquat), 129.4 (C-3′, C-5′), 127.4 (Cquat), 126.4 (C-9), 126.3 (C-2′, C-6′), 125.9 (C-6), 91.7 (C-4), 69.8 (C-1), 21.5 (Ar-*M*e), 17.8 (Me). IR (KBr): 1667 (C=O), 1639 (C=O), 1538, 1333, 1300, 814 cm^{-1}. MS, m/z (%): 316 (M^+, 1), 301 (9), 286 (20), 103 (20), 99 (24), 71 (50), 43 (100). Anal. Calcd. $C_{21}H_{16}O_3$: C 79.73%, H 5.10%; found: C 79.86%, H 5.19%.

3.1.13. 1-Methyl-3-(4-methoxyphenyl)-1*H*-naphtho[2,3-*c*]-pyrane-5,10-dione 14d. Compound **14d** was synthesized according to the first and the second procedure in 61% and 92% yield, respectively; red powder, mp 152–153°C (hexane). ^{1}H NMR ($CDCl_3$) δ: 1.46 (3H, d, J=6.7 Hz, Me), 3.85 (OMe), 5.85–5.88 (1H, m, H-1), 6.57 (1H, s, H-4), 6.94 (2H, d, J=9.2 Hz, H-3′, H-5′), 7.26–7.69 (2H, m, H-7 and H-8), 7.75 (2H, d, J=9.2 Hz, H-2′ and H-6′), 8.05–8.08 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$) δ: 183.0 (C=O), 181.6 (C=O), 161.9 (C-4′), 159.3 (C-3), 136.6 (Cquat), 133.9 (C-8), 132.9 (C-7), 132.9 (Cquat), 131.8 (Cquat), 128.1 (C-3′, C-5′), 126.8 (Cquat), 126.4 (C-9), 126.0 (Cquat), 125.8 (C-6), 114.0 (C-6′, C-2′), 90.8 (C-4), 69.8 (C-1), 55.4 (OMe), 17.8 (Me). IR (KBr): 1662 (C=O), 1639 (C=O), 1591, 1538, 1500, 1333, 1300, 1268, 1256, 1175 cm^{-1}. MS, m/z (%): 332 (M^+, 1), 316 (7), 103 (13), 89 (75), 85 (17), 71 (33), 57 (43), 43 (100). Anal. Calcd. $C_{21}H_{16}O_4$: C 75.89%, H 4.85%; found: C 75.62%, H 4.68%.

3.1.14. 3-(2,4-Dimethoxyphenyl)-1-methyl-1*H*-naphtho-[2,3-*c*]-pyrane-5,10-dione 14e. Compound **14e** was synthesized according to the first procedure in 67% yield; red powder, mp 143–144°C. ^{1}H NMR ($CDCl_3$) δ: 1.47 (3H, d, J=6.7 Hz, Me), 3.82 (3H, s, OMe), 3.94 (3H, s, OMe), 5.81–5.88 (1H, m, H-1), 6.90 (1H, s, H-4), 6.93 (1H, d, J=6.2 Hz, H-3′), 7.10 (1H, s, H-6′), 7.32 (1H, d, J=6.7 Hz, H-5′), 7.64–7.74 (2H, m, H-7 and H-8), 8.05–8.11 (2H, m, H-6, H-9). ^{13}C NMR ($CDCl_3$) δ: 183.0 (C=O), 181.9 (C=O), 155.9 (C-3), 153.3 (C-2′), 152.8 (C-5′), 136.4 (Cquat), 133.8 (C-8), 133.0 (C-7), 132.8 (Cquat), 131.9 (Cquat), 127.8 (Cquat), 126.4 (C-9), 125.8 (C-6), 123.0 (Cquat), 116.8 (C-6′), 113.9 (C-3′), 112.6 (C-5′), 98.0 (C-4), 69.3 (C-1), 56.1 (OMe), 55.8 (OMe), 17.6 (Me). IR (KBr): 1662 (C=O), 1640 (C=O), 1592, 1547, 1333, 1295, 1267, 1177cm^{-1}. MS, m/z (%): 362 (M^+, 1), 174 (34), 163 (13), 159 (29), 97 (29), 7 (56), 57 (100). Anal. Calcd. $C_{22}H_{18}O_5$: C 72.92%, H 5.01%; found: C 72.56%, H 4.89%.

3.1.15. 1-Methyl-3-phenyl-1*H*-naphtho[2,3-*c*]-pyrane-5,10-dione 14f. Compound **14f** was synthesized according to the first procedure in 66% yield; red powder, mp 174–175°C (hexane). ^{1}H NMR ($CDCl_3$) δ: 1.48 (3H, d, J=6.5 Hz, Me), 5.86–5.93 (1H, m, H-1), 6.87 (1H, s, H-4), 7.42–7.46 (3H, m, H-3′, H-4′ and H-5′), 7.65–7.75 (2H, m, H-7 and H-8), 7.80–7.83 (2H, m, H-2′ and H-6′), 8.06–8.13 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$) δ: 182.8 (C=O), 181.8 (C=O), 159.1 (C-3), 136.2 (Cquat), 133.9 (C-7), 133.4 (Cquat), 133.1 (C-8), 132.8 (Cquat), 131.8 (Cquat), 130.7 (C-9), 128.6 (C-3′ and C-5′), 127.8 (Cquat), 126.5 (C-6), 126.2 (C-6′, C-2′), 125.9 (C-4′), 92.3 (C-4), 69.8 (C-1), 17.9 (Me). IR (KBr): 1667 (C=O), 1639 (C=O), 1538, 1332 cm^{-1}. MS, m/z (%): 302 (M^+, 20), 288 (15), 287 (42), 197 (20), 116 (21), 115 (28), 105 (31), 99 (52), 57 (100). Anal. Calcd. $C_{20}H_{14}O_3$: C 79.46%, H 4.64%; found: C 79.36%, H 4.77%.

3.1.16. 3-(t-Butyl)-1-methyl-1*H*-naphtho[2,3-*c*]-pyrane-5,10-dione 14g. Compound **14g** was synthesized according to the first procedure in 64% yield; red powder, mp 65–65°C (hexane). ^{1}H NMR ($CDCl_3$) δ: 1.16 (9H, s, t-Butyl), 1.32 (3H, d, J=6.5 Hz, Me), 5.67–5.70 (1H, m, H-1), 5.94 (1H, s, H-4), 7.62–7.99 (2H, m, H-7 and H-8), 8.00–8.05 (2H, m, H-5, H-9). ^{13}C NMR ($CDCl_3$) δ: 183.1 (C=O), 181.9 (C=O), 172.6 (C-3), 136.4 (Cquat), 133.7 (C-8), 132.9 (C-7), 132.6 (Cquat), 131.8 (Cquat), 126.7 (Cquat), 126.3 (C-9), 125.7 (C-5), 89.6 (C-4), 69.1 (C-1), 27.3 (Me_3), 17.4 (C1-*Me*). IR (KBr): 1666 (C=O), 1650 (C=O), 1580, 1557, 1500, 1357, 1331, 1299, 1265 cm^{-1}. MS, m/z (%): 282 (M^+, 1), 225 (10), 102 (13), 187 (9), 163 (13), 160 (14), 149 (25), 129 (22), 94 (52), 57 (67), 55 (50), 43 (100). Anal. Calcd. $C_{18}H_{18}O_3$: C 76.57%, H 6.43%; found: C 76.24%, H 6.21%.

3.1.17. 1-Methyl-3-methyl-1*H*-naphtho[2,3-*c*]-pyrane-5,10-dione 14h. Compound **14h** was synthesized according to the first procedure in 68% yield; red powder, mp 83–84°C (hexane) (lit[15a] 74–75°C). ^{1}H NMR ($CDCl_3$) δ: 1.41 (3H, d, J=6.7 Hz, C1-*Me*), 2.02 (3H, s, Me), 5.69–5.71 (H, m, H-1), 5.89 (1H, s, H-4), 7.26–7.72 (2H, m, H-7 and H-8), 8.03–8.09 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$) δ: 182.9 (C=O), 182.0 (C=O), 162.7 (C3), 136.1 (Cquat), 133.9 (C-8), 133.0 (C-7), 132.6 (Cquat), 131.7 (Cquat), 126.5 (Cquat), 126.3 (C-9), 125.8 (C-6), 93.2 (C-4), 69.7 (C-1), 21.0 (C3-Me), 18.1 (C1-Me). IR (KBr): 1669 (C=O), 1654 (C=O), 1583, 1560, 1364, 1330, 1297, 1098 cm^{-1}. MS, m/z (%): 240 (M^+, 34), 225 (100), 197 (19), 168 (9), 141 (11), 115 (13), 105 (13), 43 (41).

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