An efficient method for the one-pot construction of the 1*H*-naphtho[2,3-*c*]pyran-5,10-dione system

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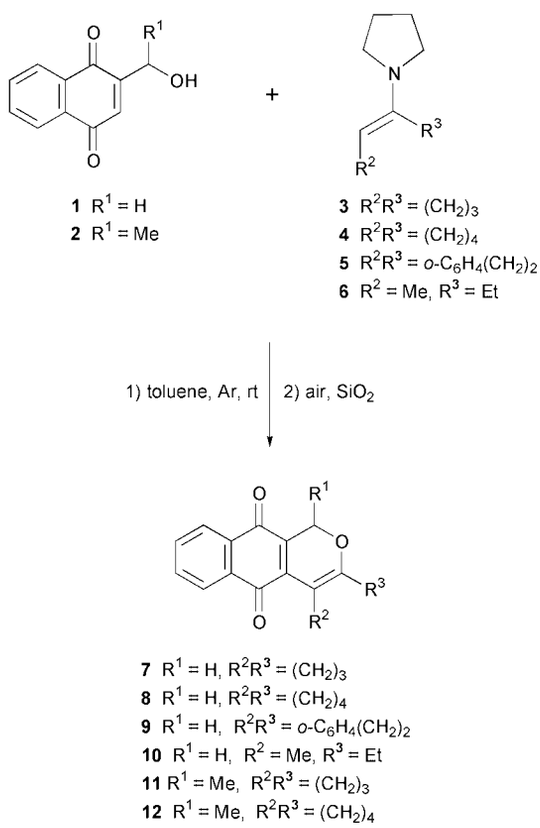
2-(1-Hydroxyalkyl)-1,4-naphthoquinones are found to react with pyrrolidino enamines in toluene to give 1*H*-naphtho[2,3-*c*]pyran-5,10-diones in good yields *via* a tandem conjugate addition–cyclization sequence, followed by an elimination of pyrrolidine. 2-Hydroxymethyl-1,4-naphthoquinone and morpholino enamines undergo a similar sequence, without loss of morpholine, to yield 3-morpholino-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-diones. The 3-morpholino group of these products can be replaced with a hydro, a hydroxy, or a methoxy group. Imines also react with 2-(1-hydroxyalkyl)-1,4-naphthoquinones to give the corresponding 1*H*-naphtho[2,3-*c*]pyran-5,10-diones, including a natural product (pentalongin). The utility of these reactions is demonstrated in the synthesis of pyranonaphthoquinone antibiotics, *viz.* (±)-eleutherin and (±)-isoeleutherin.

Compounds based on the 1*H*-naphtho[2,3-*c*]pyran-5,10-dione skeleton have aroused considerable interest amongst synthetic chemists, because some members of this family have been found in Nature and shown to possess a variety of biological properties.[1] A number of interesting methods have been reported for the preparation of this class of compounds.[2] Most of them, however, are based on multi-step conversions, although Aldersley *et al.*[2b] have prepared 3-phenyl-1*H*-naphtho[2,3-*c*]-pyran-5,10-dione in one step using the conjugate additions of phenacylpyridinium ylide to 2-(aryloxymethyl)-1,4-naphthoquinones and most recently De Kimpe and co-workers[2g] have reported on its application to the first total synthesis of isagarin. We found that 2-(1-hydroxyalkyl)-1,4-naphthoquinones reacted with enamines or imines[3] to give 1*H*-naphtho-[2,3-*c*]pyran-5,10-dione derivatives in one pot, *via* a tandem conjugate addition–cyclization sequence. The method was successfully applied to very rapid access to biologically active natural products, such as pentalongin,[4] eleutherin,[5] and isoeleutherin.[5] In this paper, details of this new general construction of the 1*H*-naphtho[2,3-*c*]pyran-5,10-dione system are reported.[6]

Results and discussion

We began by investigating the reactions of 2-(1-hydroxyalkyl)-1,4-naphthoquinones **1** and **2** with enamines **3**–**6**, in expectation of the formation of 1*H*-naphtho[2,3-*c*]pyran-5,10-dione derivatives **7**–**12** through addition of enamines to quinones in the 1,4-addition manner at the 3-position, followed by intramolecular cyclization of the resulting zwitterion intermediates. As expected, when the reactions were carried out in toluene at room temperature under argon, and followed by usual aqueous work-up and subsequent purification by preparative TLC (PLC) on silica gel, the expected products **7**–**12** were obtained as shown in Scheme 1. The products were, in general, dark red solids. The results are summarized in Table 1, which indicates that the yields were generally good. The reaction proved to be applicable to a stable enamine, 3-pyrrolidino-1,2-dihydronaphthalene **5**, though the yield of the expected product **9** was moderate (entry 3). It should be noted that the use of 1-pyrrolidinopropene, derived from propanal, resulted in the formation of complicated mixtures of products, presumably arising from the further addition of this enamine to the initially formed intermediate. The reaction of 2-(1-hydroxy-1-methylethyl)-1,4-naphthoquinone with 1-pyrrolidinocyclohexene in toluene was very sluggish, and the starting quinone was recovered almost quantitatively. This may be attributed to the steric interactions during the reaction. Heating of the reaction mixture at reflux temperature resulted in the formation of an intractable mixture of products.



1 R^1 = H
2 R^1 = Me

3 R^2R^3 = $(CH_2)_3$
4 R^2R^3 = $(CH_2)_4$
5 R^2R^3 = *o*-$C_6H_4(CH_2)_2$
6 R^2 = Me, R^3 = Et

7 R^1 = H, R^2R^3 = $(CH_2)_3$
8 R^1 = H, R^2R^3 = $(CH_2)_4$
9 R^1 = H, R^2R^3 = *o*-$C_6H_4(CH_2)_2$
10 R^1 = H, R^2 = Me, R^3 = Et
11 R^1 = Me, R^2R^3 = $(CH_2)_3$
12 R^1 = Me, R^2R^3 = $(CH_2)_4$

Scheme 1

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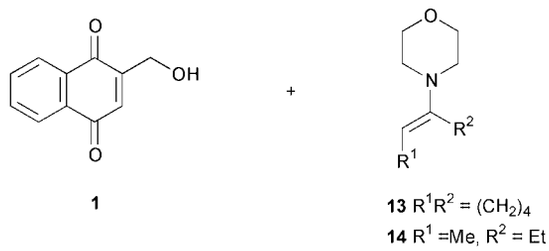
Table 1 Preparation of 1*H*-naphtho[2,3-*c*]pyran-5,10-diones **7**–**12** from 2-(1-hydroxyalky1)-1,4-naphthoquinones **1** or **2** and pyrrolidine enamines **3**–**6**

Entry	Quinone	Enamine	Product (yield/%)[a]
1	**1**	**3**	**7** (81)
2	**1**	**4**	**8** (83)
3	**1**	**5**	**9** (48)
4	**1**	**6**[b]	**10** (81)
5	**2**	**3**	**11** (73)
6	**2**	**4**	**12** (62)

[a] Yields of purified products (PLC on SiO_2). [b] A mixture of stereoisomers was used.

We next investigated the reactions of 2-hydroxymethyl-1,4-naphthoquinone **1** with morpholino enamines **13** and **14** in place of pyrrolidine enamines. It was found that the reactions gave 3-morpholino-3,4-dihydro-1*H*-naphthopyran-5,10-diones **15** and **16**, respectively, in fair yields, as a single diastereomer in each case, as outlined in Scheme 2. These products were



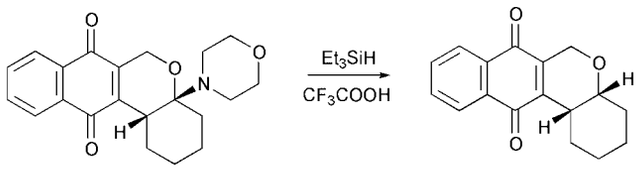
1 + **13** $R^1R^2 = (CH_2)_4$; **14** R^1 = Me, R^2 = Et

15 $R^1R^2 = (CH_2)_4$ 64%
16 R^1 = Me, R^2 = Et 55%

Scheme 2

sufficiently stable to be purified by PLC on silica gel. The formation of these 3-morpholino derivatives may be ascribed to the lower basicity of morpholine compared with that of pyrrolidine. The stereochemistry of **15** was tentatively determined by comparing its ^{1}H NMR spectrum with that of **17**, whose stereochemistry was unambiguously determined as described below. The *cis*-configuration of 3-Et and 4-Me in **16** was evident by ^{1}H NMR NOE experiments. Thus, irradiation of the signal at δ 1.15 due to 4-Me resulted in enhancements of the signals at δ 1.72 due to one of the methylene protons of 3-Et (12%) and at δ 0.98 due to the methyl protons of 3-Et (8.7%), while any enhancement of the signals due to the morpholine protons was not observed.

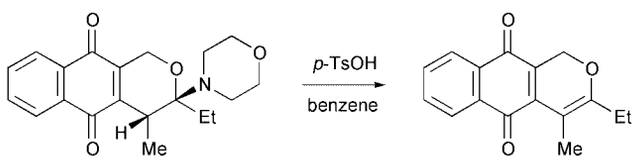
In order to demonstrate the synthetic usefulness of these morpholinonaphthopyrandiones **15** and **16**, transformations into some related derivatives were then studied. Compound **15** was treated with triethylsilane in TFA at room temperature to provide the corresponding dihydro derivative **17** in fair yield as a single diastereomer (Scheme 3). The stereochemistry of this product was also confirmed by NOE experiments between the two conjunctive protons; an 8.4% enhancement of the signal at



15 **17** 60%

Scheme 3

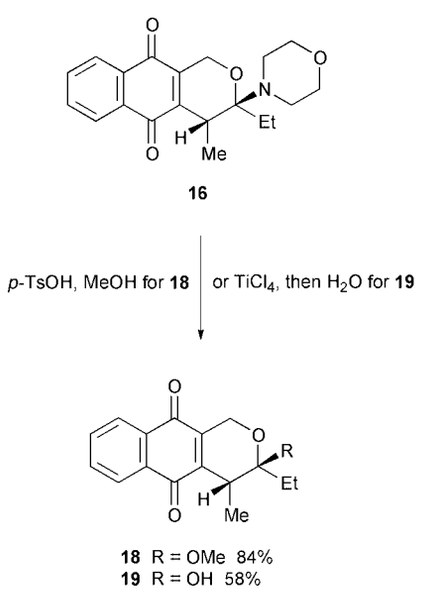
δ 2.7–2.8 due to the 12b-H on irradiation of the signal at δ 3.6–3.65 due to the 4a-H. The *cis* stereochemical outcome of this reduction is a result of the attack by a hydride on the intermediate oxonium ion from the least hindered face. Treatment of **16** with toluene-*p*-sulfonic acid in benzene resulted in elimination of morpholine to give **10** in high yield (Scheme 4). The



16 **10** 90%

Scheme 4

3-morpholino group of **16** could be replaced cleanly by a methoxy group on treatment with toluene-*p*-sulfonic acid in methanol to produce **18** in good yield. The 3-hydroxy derivative **19** was obtained in moderate yield on treatment with titanium(IV) tetrachloride and quenching of the resulting salts with water (Scheme 5). Each of the compounds **18** and **19** was



18 R = OMe 84%
19 R = OH 58%

Scheme 5

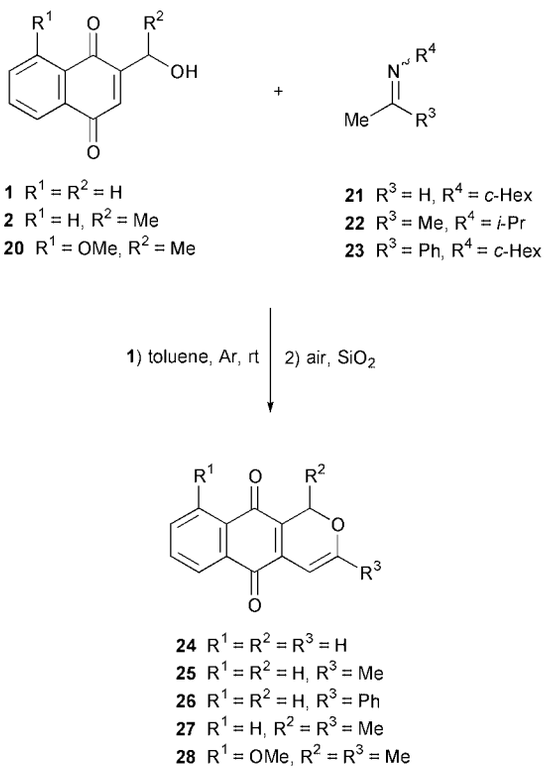
produced as a single diastereomer, and their stereochemistry was determined by comparing their ^{1}H NMR spectra with that of **16**, whose stereochemistry was unambiguously determined as described above.

Subsequently, envisaging that imines would tautomerize to their enamine forms in the reaction mixtures and should undergo a similar reaction sequence with the (hydroxyalkyl)-naphthoquinones **1**, **2** and **20** to lead to the formation of the desired naphthopyrandiones, we investigated the reactions of **1**, **2** and **20** with imines **21**–**23**. It was found that the sequence proceeded smoothly and gave somewhat complicated mixtures compared with those from using enamines, from which the corresponding 1*H*-naphtho[2,3-*c*]pyran-5,10-dione derivatives

Table 2 Preparation of 1*H*-naphtho[2,3-*c*]pyran-5,10-diones **24**–**28** from 2-(1-hydroxyalkyl)-1,4-naphthoquinones **1**, **2**, or **20** and imines **21**–**23**

Entry	Quinone	Imine	Product (yield/%)[a]
1	**1**	**21**[b]	**24**[c] (44)
2	**1**	**22**	**25** (60)
3	**1**	**23**[b]	**26** (39)
4	**2**	**22**	**27** (53)
5	**20**	**22**	**28** (55)

[a] Yields of purified products (PLC on SiO_2). [b] A mixture of stereoisomers was used. [c] Pentalongin (ref. 4).



Scheme 6

24–**28** were isolated in moderate to fair yields (Scheme 6). The results are summarized in Table 2. Compound **24** is an antibiotic (pentalongin) isolated from *Pentas longiflora*.[4] Although the yields were somewhat lower than those using enamines, the use of imines may offer an advantage, because these imines are generally easier to prepare than are the corresponding enamines.

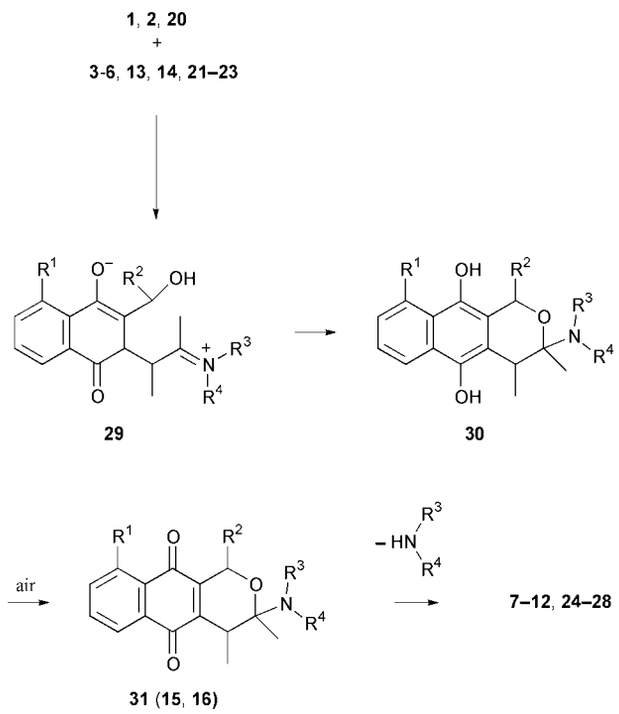
The reactions forming naphthopyrandione derivatives **7**–**12**, **15**, **16** and **24**–**28** are thought to proceed *via* the conjugate addition of enamines or imines at the 3-position of the (hydroxyalkyl)naphthoquinones **1**, **2** and **20** to form the iminium intermediates **29**, which is followed by intramolecular cyclization to give the dihydroquinone intermediates **30**. These intermediates are then oxidized upon exposure to air to give the aminonaphthopyrandione products **31** (**15** and **16**). In the case of using pyrrolidine enamines or imines the elimination of an amine occurs during work-up and/or purification procedures to give **7**–**12** and **24**–**28** (Scheme 7).

Having established a simple and efficient route to 1*H*-naphtho[2,3-*c*]pyran-5,10-dione derivatives, we next turned our attention to application of the present method to the synthesis of useful natural products and planned the conversion of the naphthopyrandione **28** into (±)-eleutherin **33** and (±)-isoeleutherin **34**. Eleutherin and isoeleutherin are antibiotics, found in *Eleutherin bulbosa*.[5a] The conversion was accomplished by reduction using triethylsilane in TFA, and is summarized in

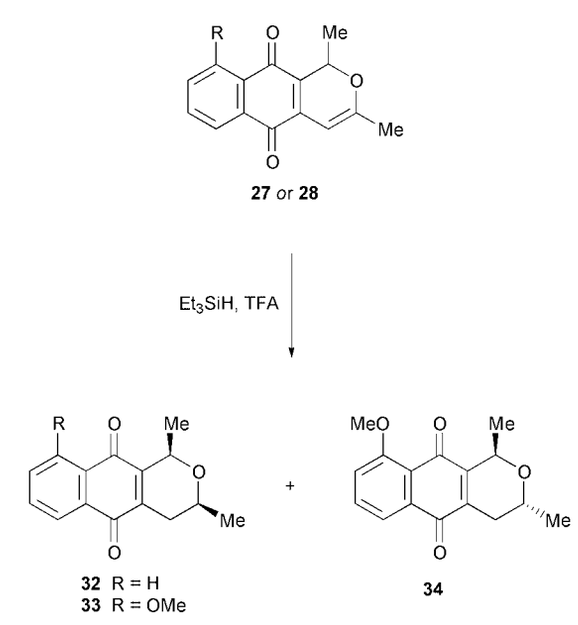
Table 3 Preparation of (±)-eleutherin **33** and its derivatives **32** and **34**

Entry	**27** or **28**	Reaction temp.	Product(s) (yield/%)[a]
1	**27**	rt	**32** (98)
2	**28**	rt	**33** (8)[b] **34** (42)[b]
3	**28**	−20 °C to rt	**33** (7)[b] **34** (56)[b]
4	**28**	−20 °C	**33** (66)

[a] Yields of purified products (PLC on SiO_2). [b] Separable by PLC on SiO_2.



Scheme 7



Scheme 8

Scheme 8 and Table 3. First, as the model reaction, compound **27** was treated with triethylsilane in TFA at room temperature. The reduction took place within minutes to afford *cis*-1,3-dimethyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione **32** [(±)-demethoxyeleutherin] exclusively in excellent yield (entry 1). Compound **28** was then subjected to reduction under the same conditions. Unfortunately, however, the reaction is less

reliable, affording a *ca.* 1 : 5 mixture of the desired product **33** along with its diastereoisomer, (±)-isoeleutherin **34**, in moderate combined yield (entry 2), while these products were easily separated from each other by PLC on silica gel. Although the low stereoselectivity in this reaction was disappointing, we reached the conclusion that the formation of **34** is a result of isomerization of the initially formed desired product **33** under the reaction conditions,[7] and reasoned that carrying out the reaction at lower temperature should suppress the isomerization and allow us to obtain the desired product **33** exclusively in satisfactory yield. As expected, the reaction at −20 °C proceeded more cleanly than that at room temperature and resulted in the formation of **33** as the sole diastereoisomer in fair yield (entry 4). We later found that the yield of **34** was improved (56%, **33** : **34** = 1 : 8) when compound **28** was treated with triethylsilane in TFA at −20 °C and then the mixture was allowed to warm gradually to room temperature (entry 3). IR and ^{1}H NMR data as well as melting points for **32**, **33**, and **34** are consistent with literature values.[5] Thus, these natural products were obtained in two steps from **20**, which was synthesized almost quantitatively in two steps ($NaBH_4$ reduction followed by oxidation with CAN) from known 1-(1-hydroxy-4,8-dimethoxynaphthalen-2-yl)ethanone as reported by Uno.[5f] So this sequence constitutes a very concise total synthesis of these natural products.

In summary, the studies recorded herein demonstrate that 1*H*-naphtho[2,3-*c*]pyran-5,10-dione and 1*H*-3,4-dihydronaphtho[2,3-*c*]pyran-5,10-dione derivatives can be prepared from readily available starting materials. The method has advantages, particularly with regard to ease of operation and applicability to the concise total synthesis of important natural products.

Experimental

All mps were recorded with a Laboratory Devices MEL-TEMP II melting-point apparatus and are uncorrected. IR spectra were determined using KBr disks (unless stated otherwise) with a Perkin-Elmer 1600 Series FT IR spectrometer. ^{1}H NMR spectra were determined in $CDCl_3$ using $SiMe_4$ as internal reference with a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz or a JEOL JNX-PMX 60 NMR spectrometer operating at 60 MHz. *J*-Values are given in Hz. Low-resolution mass spectra were recorded on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). Column chromatography was carried out on Merck Kieselgel 60 F_{254}. TLC was carried out on Merck Kieselgel 60 PF_{254}. All of the solvents used were dried over appropriate drying agents and distilled under argon prior to use.

Starting materials

1-Pyrrolidinocyclopentene **3**, 1-pyrrolidinocyclohexene **4**, and 1-morpholinocyclohexene **13** were commercially available. 3-Pyrrolidino-1,2-dihydronaphthalene **5**,[8] 3-pyrrolidinopent-2-ene **6**,[8] 3-morpholinopent-2-ene **14**,[8] *N*-ethylidenecyclohexylamine **21**,[9] *N*-isopropylideneisopropylamine **22**,[10] and *N*-(1-phenylethylidene)cyclohexylamine **23**,[10] were prepared following the appropriate procedures reported previously.

2-Hydroxymethyl-1,4-naphthoquinone 1

This compound was initially prepared according to the route developed by Antonini *et al.*[11] Unfortunately, however, we were unable to obtain this compound both in pure form and in good yield. The following route was therefore attempted. To a stirred solution of 1,4-dimethoxynaphthalene-2-carbaldehyde[5f] (1.5 g, 7.1 mmol) in THF (20 cm^3) was added $NaBH_4$ (0.83 g, 21 mmol) and stirring was continued for 70 min at room temperature. Usual work-up followed by recrystallization from hexane–EtOAc gave (1,4-dimethoxynaphthalen-2-yl)methanol[9] (1.5 g, 99%) as a white solid; mp 74–76 °C; ν_{max}/cm^{-1} 3400 and 1628; δ_H (60 MHz) 2.40 (1H, br s), 3.89 (3H, s), 3.95 (3H, s), 4.87 (2H, br s), 6.75 (1H, s), 7.25–7.55 (2H, m) and 7.85–8.3 (2H, m).

This alcohol (1.4 g, 6.5 mmol) was dissolved in MeCN (56 cm^3) and a solution of CAN (7.2 g, 13 mmol) in water (6.5 cm^3) was added at 0 °C. After the mixture had been stirred for 3 min at the same temperature, usual work-up followed by recrystallization from CCl_4 gave **1** (1.2 g, 99%) as yellow needles; mp 117–118 °C (lit.,[11] 111–112 °C).

2-(1-Hydroxyethyl)-1,4-naphthoquinone[12] 2

To a stirred solution of (1,4-dimethoxynaphthalen-2-yl)-magnesium bromide, generated from the reaction of 2-bromo-1,4-dimethoxynaphthalene[5f] (1.3 g, 5.0 mmol) with magnesium turnings (0.13 g, 5.2 mmol) in THF (18 cm^3) at reflux temperature for 1 h, was added dropwise acetaldehyde (1.4 g, 32 mmol) at 0 °C. After 1 h the mixture was worked up as usual. Purification of the residue by column chromatography on SiO_2 gave 1-(1,4-dimethoxynaphthalen-2-yl)ethanol[12] (1.0 g, 89%) as a yellow solid; mp 99–101 °C (lit.,[12] 101–102 °C).

This compound (0.83 g, 3.6 mmol) was oxidized with CAN (2.8 g, 5.2 mmol) as described for the preparation of **1** to give **2** (0.42 g, 58%) as a yellow solid; mp 92–94 °C (from hexane–Et_2O) (lit.,[12] 88–89 °C).

2-(1-Hydroxyethyl)-8-methoxy-1,4-naphthoquinone 20

1-(1-Hydroxy-4,8-dimethoxynaphthalen-2-yl)ethanone[5f] (0.55 g, 2.3 mmol) was treated with $NaBH_4$ (0.26 g, 6.8 mmol) in THF (25 cm^3), as described for the reduction of 1,4-dimethoxynaphthalene-2-carbaldehyde, to give 2-(1-hydroxyethyl)-4,8-dimethoxy-1-naphthol (0.52 g, 96%) as a yellow viscous oil: R_f 0.31 (2 : 1 EtOAc–hexane) (Found: C, 68.0; H, 6.6. $C_{14}H_{16}O_4$ requires C, 67.75; H, 6.5%); ν_{max}/cm^{-1} 3404, 1634 and 1611; δ_H (60 MHz) 1.58 (3H, d, *J* 6.3), 2.77 (1H, d, *J* 4.6), 3.95 (3H, s), 4.06 (3H, s), 5.31 (1H, quint, *J* 5.8), 6.84 (1H, d, *J* 7.6), 6.90 (1H, s), 7.30 (1H, dd, *J* 8.4 and 7.6), 7.83 (1H, d, *J* 8.4) and 9.30 (1H, s).

This compound (0.33 g, 1.3 mmol) was oxidized with CAN (1.4 g, 2.6 mmol), as described for the preparation of **1**, to give **20** (0.28 g, 92%) as a yellow solid; mp 98–104 °C (from CCl_4) (Found: C, 67.05; H, 5.2. $C_{13}H_{12}O_4$ requires H, 67.25; H, 5.2%); ν_{max}/cm^{-1} 3510, 3400, 3172, 1662, 1648 and 1626; δ_H (60 MHz) 1.50 (3H, d, *J* 6.5), 2.58 (1H, d, *J* 3.6), 4.11 (3H, s), 4.98 (1H, m), 6.90 (1H, d, *J* 1.1), 7.30 (1H, dd, *J* 7.6 and 1.8), 7.68 (1H, t, *J* 7.6) and 7.73 (1H, dd, *J* 7.6 and 1.8).

1,2,3,5-Tetrahydrocyclopenta[*b*]naphtho[2,3-*d*]pyran-6,11-dione 7. Typical procedure for the reactions of 2-(1-hydroxyalkyl)-1,4-naphthoquinones with enamines or imines

To a stirred solution of 2-hydroxymethyl-1,4-naphthoquinone **1** (86 mg, 0.46 mmol) in toluene (5 cm^3) under argon was added 1-pyrrolidinocyclopentene **3** (0.12 g, 0.91 mmol), and stirring was continued overnight at room temperature. The resulting reaction mixture was diluted with Et_2O (20 cm^3) and washed successively with water, aq. NH_4Cl, and then brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to PLC on SiO_2 (1 : 5 AcOEt–hexane) to give **7** (0.12 g, 81%) as dark red needles; mp 117–119 °C (from hexane) (Found: C, 76.2; H, 4.85. $C_{16}H_{12}O_3$ requires C, 76.2; H, 4.8%); ν_{max}/cm^{-1} 1668 and 1644; δ_H (270 MHz) 2.04 (2H, quint, *J* 7.4), 2.50 (2H, t, *J* 7.4), 2.96 (2H, t, *J* 7.4), 5.28 (2H, s), 7.65–7.75 (2H, m) and 8.05–8.1 (2H, m); *m*/*z* 252 (M$^+$, 100%).

2,3,4,6-Tetrahydro-1*H*-benzo[*b*]naphtho[2,3-*d*]pyran-7,12-dione 8. Dark red needles; mp 105–107 °C (from hexane) (Found: C, 76.8; H, 5.1. $C_{17}H_{14}O_3$ requires C, 76.7; H, 5.3%);

ν_{max}/cm^{-1} 1670 and 1644; δ_H (270 MHz) 1.7–1.75 (4H, m), 2.15–2.2 (2H, m), 2.75–2.8 (2H, m), 5.00 (2H, s), 7.65–7.75 (2H, m) and 8.0–8.1 (2H, m); *m*/*z* 266 (M^+, 50%) and 210 (100).

5,6-Dihydro-8*H*-dinaphtho[2,1-*b*;2,3-*d*]pyran-9,14-dione 9. A dark red oil; R_f 0.40 (1 : 5 AcOEt–hexane) (Found: C, 80.25; H, 4.5. $C_{21}H_{14}O_3$ requires C, 80.25; H, 4.5%); ν_{max}/cm^{-1} (neat) 1678, 1669 and 1645; δ_H (270 MHz) 1.7–2.57 (2H, t, *J* 7.3), 2.93 (2H, t, *J* 7.3), 5.07 (2H, s), 7.1–7.25 (4H, m), 7.7–7.75 (2H, m) and 8.0–8.15 (2H, m); *m*/*z* 314 (M^+, 100%).

3-Ethyl-4-methyl-1*H*-naphtho[2,3-*c*]pyran-5,10-dione 10. A dark-red solid; mp 91–92 °C (from hexane) (Found: C, 75.5; H, 5.6. $C_{16}H_{14}O_3$ requires C, 75.55; H, 5.55%); ν_{max}/cm^{-1} 1665 and 1645; δ_H (270 MHz) 1.17 (3H, t, *J* 7.4), 2.18 (3H, s), 2.39 (2H, q, *J* 7.4), 4.94 (2H, s), 7.65–7.75 (2H, m) and 8.0–8.1 (2H, m); *m*/*z* 254 (M^+, 79%) and 225 (100).

5-Methyl-1,2,3,5-tetrahydrocyclopenta[*b*]naphtho[2,3-*d*]-pyran-6,11-dione 11. Dark-red needles; mp 149–151 °C (from hexane) (Found: C, 76.5; H, 5.25. $C_{17}H_{14}O_3$ requires C, 76.7; H, 5.3%); ν_{max}/cm^{-1} 1667 and 1645; δ_H (270 MHz) 1.44 (3H, d, *J* 6.8), 1.95–2.1 (2H, m), 2.4–2.55 (2H, m), 2.95–3.05 (2H, m), 5.83 (1H, q, *J* 6.8), 7.65–7.75 (2H, m) and 8.0–8.1 (2H, m); *m*/*z* 266 (M^+, 100%).

6-Methyl-2,3,4,6-tetrahydro-1*H*-benzo[*b*]naphtho[2,3-*d*]-pyran-7,12-dione 12. A red oil; R_f 0.26 (1 : 10 AcOEt–hexane) (Found: C, 77.1; H, 5.7. $C_{18}H_{16}O_3$ requires C, 77.1; H, 5.75%); ν_{max}/cm^{-1} (neat) 1670 and 1646; δ_H (270 MHz) 1.35 (3H, d, *J* 6.9), 1.5–1.65 (2H, m), 1.85–1.95 (2H, m), 2.2–2.35 (2H, m), 2.55–2.65 (1H, m), 2.8–2.95 (1H, m), 5.63 (1H, q, *J* 6.9), 7.6–7.75 (2H, m) and 8.0–8.1 (2H, m); *m*/*z* 280 (M^+, 100%).

(4a*R,12b*R**)-4a-Morpholino-2,3,4,4a,6,12b-hexahydro-1*H*-benzo[*b*]naphtho[2,3-*d*]pyran-7,12-dione 15.** Orange needles; mp 175–179 °C (from hexane–Et_2O) (Found: C, 71.1; H, 6.55; N, 3.95. $C_{21}H_{23}NO_4$ requires C, 71.35; H, 6.55; N, 3.95%); ν_{max}/cm^{-1} 1659 and 1639; δ_H (270 MHz) 1.25–2.0 (8H, m), 2.3–2.5 (2H, m), 2.55–2.7 (2H, m), 3.0–3.15 (1H, m), 3.45–3.6 (4H, m), 4.55 (1H, dd, *J* 19.6 and 1.8), 4.62 (1H, d, *J* 19.6), 7.65–7.8 (2H, m) and 8.05–8.15 (2H, m); *m*/*z* 353 (M^+, 23%), 282 (33) and 267 (100).

(3*R,4*R**)-3-Ethyl-4-methyl-3-morpholino-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione 16.** Orange needles; mp 157–159 °C (from hexane–Et_2O) (Found: C, 70.6; H, 6.85; N, 4.15. $C_{20}H_{23}NO_4$ requires C, 70.35; H, 6.8; N, 4.1%); ν_{max}/cm^{-1} 1660 and 1639; δ_H (270 MHz) 0.98 (3H, t, *J* 7.4), 1.15 (3H, d, *J* 6.9), 1.72 (1H, dq, *J* 14.3 and 7.4), 1.98 (1H, dq, *J* 14.3 and 7.4), 2.5–2.6 (2H, m), 2.8–2.9 (2H, m), 3.08 (1H, qd, *J* 6.9 and 1.6), 3.35–3.55 (4H, m), 4.50 (1H, dd, *J* 19.4 and 1.6), 4.54 (1H, d, *J* 19.4), 7.7–7.75 (2H, m) and 8.05–8.15 (2H, m); *m*/*z* 341 (M^+, 28%), 255 (68) and 199 (100).

1*H*-Naphtho[2,3-*c*]pyran-5,10-dione (pentalongin)[4] 24. A red solid; mp 160–162 °C (decomp.) (from hexane) (lit.,[4a] 160–161 °C); ν_{max}/cm^{-1} 1670 and 1652; δ_H (270 MHz) 5.16 (2H, s), 6.11 (1H, d, *J* 5.6), 6.97 (1H, d, *J* 5.6), 7.65–7.75 (2H, m) and 8.05–8.15 (2H, m).

3-Methyl-1*H*-naphtho[2,3-*c*]pyran-5,10-dione 25. Dark red crystals; mp 136–137 °C (from hexane) (Found: C, 74.05; H, 4.25. $C_{14}H_{10}O_3$ requires C, 74.35; H, 4.45%); ν_{max}/cm^{-1} 1672, 1657sh and 1626; δ_H (270 MHz) 2.04 (3H, s), 5.17 (2H, s), 5.95 (1H, s), 7.65–7.75 (2H, m) and 8.0–8.1 (2H, m); *m*/*z* 226 (M^+, 100%).

3-Phenyl-1*H*-naphtho[2,3-*c*]pyran-5,10-dione[2b,13] 26. Red prisms; mp 185–189 °C (from hexane–CH_2Cl_2) (lit.,[13] 188–191 °C).

1,3-Dimethyl-1*H*-naphtho[2,3-*c*]pyran-5,10-dione 27. Red needles; mp 81–83 °C (from hexane) (Found: C, 75.25; H, 5.0. $C_{15}H_{12}O_3$ requires C, 75.0; H, 5.05%); ν_{max}/cm^{-1} 1670, 1654 and 1622; δ_H (270 MHz) 1.41 (3H, d, *J* 6.5), 2.02 (3H, s), 5.70 (1H, q, *J* 6.5), 5.89 (1H, s), 7.6–7.75 (2H, m) and 8.0–8.1 (2H, m); *m*/*z* 240 (M^+, 46%) and 225 (100).

9-Methoxy-1,3-dimethyl-1*H*-naphtho[2,3-*c*]pyran-5,10-dione 28. Red needles; mp 133–137 °C (from hexane) (Found: C, 71.05; H, 5.1. $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.2%); ν_{max}/cm^{-1} 1653 and 1626; δ_H (270 MHz) 1.39 (3H, d, *J* 6.3), 2.00 (3H, d, *J* 1.1), 3.99 (3H, s), 5.66 (1H, q, *J* 6.3), 5.82 (1H, q, *J* 1.1), 7.23 (1H, dd, *J* 8.4 and 1.1), 7.61 (1H, dd, *J* 8.4 and 7.9) and 7.75 (1H, dd, *J* 7.9 and 1.1); *m*/*z* 270 (M^+, 58%) and 255 (100).

cis-2,3,4,4a,6,12b-Hexahydro-1*H*-benzo[*b*]naphtho[2,3-*d*]pyran-7,12-dione 17

To a stirred dark-red solution of compound **15** (0.13 g, 0.38 mmol) in TFA (0.94 cm^3) at room temperature was added dropwise Et_3SiH (0.11 g, 0.95 mmol); the solution turned brown immediately. After stirring of the mixture for 30 min, TFA was removed under reduced pressure. The residue was subjected to PLC on SiO_2 to give **17** (61 mg, 60%) as a yellow solid; mp 82–83 °C (from hexane) (Found: C, 76.15; H, 6.05. $C_{17}H_{16}O_3$ requires C, 76.1; H, 6.0%); ν_{max}/cm^{-1} 1660 and 1631; δ_H (270 MHz) 1.35–2.1 (8H, m), 2.7–2.8 (1H, m), 3.6–3.65 (1H, m), 4.60 (1H, dd, *J* 18.9 and 2.6), 4.88 (1H, d, *J* 18.9), 7.65–7.75 (2H, m) and 8.0–8.15 (2H, m); *m*/*z* 268 (M^+, 100%).

Conversion of the 3-morpholino-3,4-dihydro-1*H*-naphthopyrandione 16 into the naphthopyrandione 10

A solution of compound **16** (67 mg, 0.20 mmol) and *p*-TsOH (35 mg, 0.20 mmol) in benzene (6 cm^3) was stirred overnight at room temperature. The mixture was washed successively with aq. $NaHCO_3$ and then brine, and dried over anhydrous Na_2SO_4. Evaporation of the solution gave a residue, which was purified by PLC on SiO_2 to afford compound **10** (46 mg, 90%).

(3*R, 4*R**)-3-Ethyl-3-methoxy-4-methyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione 18**

To a stirred solution of compound **16** (67 mg, 0.20 mmol) in MeOH (6 cm$_3$) containing $HC(OMe)_3$ (23 mg, 0.22 mmol) was added *p*-TsOH (35 mg, 0.20 mmol). The mixture was stirred at room temperature for 11 h, and then was neutralized by addition of $NaHCO_3$. After filtration, the filtrate was evaporated to give a residue, which was purified by PLC on SiO_2 to afford title compound **18** (47 mg, 84%) as a yellow solid; mp 84–89 °C (from hexane–Et_2O) (Found: C, 71.5; H, 6.25. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.35%); ν_{max}/cm^{-1} 1661 and 1644; δ_H (270 MHz) 0.96 (3H, t, *J* 7.6), 1.12 (3H, d, *J* 6.9), 1.70 (1H, dq, *J* 14.8 and 7.6), 1.91 (1H, dq, *J* 14.8 and 7.6), 3.04 (1H, qd, *J* 6.7 and 2.2), 3.23 (3H, s), 4.43 (1H, dd, *J* 19.7 and 2.2), 4.72 (1H, d, *J* 19.7), 7.65–7.75 (2H, m) and 8.0–8.15 (2H, m); *m*/*z* 286 (M^+, 15%), 284 (48), 254 (58) and 198 (100).

(3*R,4*R**)-3-Ethyl-3-hydroxy-4-methyl-1*H*-2,3-dihydro-naphtho[2,3-*c*]pyran-5,10-dione 19**

To a stirred solution of compound **16** (36 mg, 0.11 mmol) in DME (0.5 cm^3) at −20 °C was added $TiCl_4$ (30 mg, 0.16 mmol). The reaction mixture was stirred for 30 min at the same temperature, after which water (10 cm^3) was added to the mixture. The resulting mixture was extracted with Et_2O twice (10 cm^3 each). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by PLC on SiO_2 to give compound **19** (16 mg, 58%) as a yellow solid; mp 152–154 °C (from hexane–Et_2O) (Found: C, 70.4; H, 5.8. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%); ν_{max}/cm^{-1} 3404, 1663 and 1643 sh; δ_H (270 MHz) 1.07 (3H, t, *J* 7.3), 1.15

(3H, d, *J* 7.3), 1.71 (1H, dq, *J* 14.2 and 7.3), 1.90 (1H, dq, *J* 14.2 and 7.3), 2.18 (1H, br s), 3.50 (1H, q, *J* 7.3), 4.68 (1H, dd, *J* 19.4 and 1.9), 4.76 (1H, dd, *J* 19.4 and 1.1), 7.65–7.75 (2H, m) and 8.0–8.15 (2H, m); *m*/*z* 254 [$(M - H_2O)^+$, 100%].

cis-1,3-Dimethyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-5,10-dione [(±)-demethoxyeleutherin] 32

To a stirred solution of compound **27** (28 mg, 0.12 mol) in TFA (0.3 cm^3) at room temperature was added Et_3SiH (0.34 g, 0.29 mmol). After removal of TFA under reduced pressure the residual solid was recrystallized from hexane to give compound **32** (28 mg, 98%) as yellow needles; mp 141–144 °C (from hexane) (lit.,[5f] 143.5–145 °C).

cis-9-Methoxy-1,3-dimethyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]-pyran-5,10-dione [(±)-eleutherin] 33

A solution of compound **28** (34 mg, 0.13 mmol) in TFA (0.30 cm^3) was treated with Et_3SiH (0.36 g, 0.31 mmol) at −20 °C and the solvent was removed under reduced pressure. The residue was purified by PLC on SiO_2 to give title compound **33** (23 mg, 66%) as yellow needles; mp 157–158 °C (from hexane) (lit.,[5a] mp 155–156 °C; lit.,[5f] 158–160 °C).

trans-9-Methoxy-1,3-dimethyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]-pyran-5,10-dione [(±)-isoeleutherin] 34

A solution of compound **28** (31 mg, 0.11 mmol) in TFA (0.29 cm^3) was treated with Et_3SiH (0.33 g, 0.28 mmol) at −20 °C and the mixture was allowed to warm to room temperature. After removal of TFA the residue was purified by PLC on SiO_2 to give the title compound **34** (17 mg, 56%) as yellow needles along with **33** (2 mg, 7%). Compound **34**: mp 153–155 °C (from hexane) (lit.,[5a] 154–155 °C;[5a] lit.,[5f] 149–151 °C).

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