Total Synthesis of Two Naphthoquinone Antibiotics, Psychorubrin and Pentalongin, and Their C(1)-Substituted Alkyl and Aryl Derivatives

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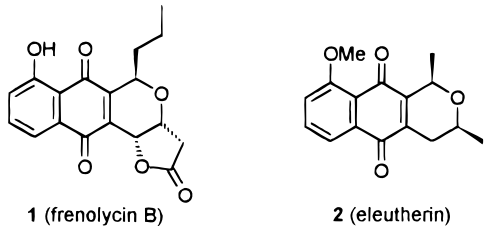
The synthesis of 1-alkyl- and 1-aryl-1*H*-naphtho[2,3-*c*]pyran-5,10-diones, bearing a C(3)−C(4) double bond, was performed by two alternative cyclization strategies of 2,3-disubstituted 1,4-naphthoquinones. Lemieux−Johnson oxidation of 2-allyl-3-hydroxymethyl-1,4-dimethoxynaphthalenes and subsequent oxidative demethylation of the intermediate 3,4-dihydro-5,10-dimethoxy-1*H*-naphtho-[2,3-*c*]pyran-3-oles to the corresponding 3,4-dihydro-3-hydroxy-1*H*-naphtho[2,3-*c*]pyran-5,10-diones gave, after acid-catalyzed dehydration, the desired 1*H*-naphtho[2,3-*c*]pyran-5,10-diones. Alternatively, the pyranonaphthoquinone ring system was constructed by intramolecular acid-catalyzed condensation of (3-hydroxymethyl-1,4-naphthoquinone-2-yl)acetaldehyde acetals. Using this synthetic approach, the synthesis of two naturally occurring naphthoquinone antibiotics, pentalongin and psychorubrin, is reported.

Introduction

The synthesis of naturally occurring pyranonaphthoquinones such as frenolycin B (**1**),[1] eleutherin (**2**),[2] and nanaomycin A (**3**)[3] has been of great interest for many

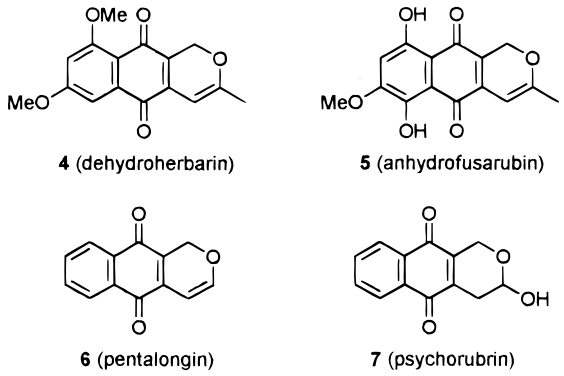


1 (frenolycin B) **2** (eleutherin)

3 (nanaomycin A)

years because these compounds have been found to show important physiological activities against Gram-positive bacteria, fungi, and mycoplasmas. Furthermore, it has been suggested that these pyranonaphthoquinones may exhibit antitumor activity because their proposed mechanism of action, namely as "bioreductive dialkylating agents", resembles that of alkylating antibiotics such as the mitomycins.[4]

Although the synthesis of various pyranonaphthoquinones has been extensively investigated in the literature,[5] a particular group of pyranonaphthoquinone antibiotics bearing a C(3)−C(4) double bonds has received much less attention.[6] Examples of this group of 3,4-dehydro-pyranonaphthoquinones include dehydroherbarin (**4**),[7] anhydrofusarubin (**5**),[8] and pentalongin (**6**),[9] and



4 (dehydroherbarin) **5** (anhydrofusarubin)

6 (pentalongin) **7** (psychorubrin)

also these pyranonaphthoquinones show significant antimicrobial activities.[10] Pentalongin (**6**) for example, which was isolated from *Pentas longiflora* Oliv. (Rubiaceae), shows antifungal and antiparasital activity, and the powder from the roots of *P. longiflora* is used by the

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(1) Iwai, Y.; Kora, A.; Takahashi, Y. *J. Antibiot.* **1978**, *31*, 959.

(2) Schmid, H.; Ebnöther, A. *Helv. Chim. Acta* **1951**, *64*, 1041.

(3) (a) Omura, S.; Tanaka, H.; Koyama, Y.; Katagiri, M. *J. Antibiot.* **1974**, *27*, 363. (b) Tanaka, H.; Koyama, Y.; Marumo, H.; Oiwa, R.; Katagiri, M.; Nagai, T.; Omura, S. *J. Antibiot.* **1975**, *28*, 860. (c) Tanaka, H.; Koyama, Y.; Nagai, T.; Omura, S. *J Antibiot.* **1975**, *28*, 868.

(4) Moore, H. W. *Science* **1977**, *197*, 527.

(5) Naruta, Y.; Maruyama, K. Recent Advances in the Synthesis of Quinonoid Compounds. In *The Chemistry of Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley: New York, 1988; Vol. II, p 241.

(6) Aldersley, M. F.; Dean, F. M.; Hamzah, A. S. *Tetrahedron Lett.* **1986**, *27*, 255. (b) Aldersley, M. F.; Chishti, S. H.; Dean, F. M.; Douglas, M. E.; Ennis, D. S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2163.

(7) Kadkol, M. V.; Golpalkrishnan, K. S.; Narasimhachari, N. *J. Antibiot.* **1971**, *24*, 245. (b) Nagarajan, R.; Narasimhachari, N.; Kadkol, M. V.; Gopalkrishnan, K. S. *J. Antibiot.* **1971**, *24*, 249.

(8) Tatum, J. H.; Baker, R. A. *Phytochemistry* **1983**, *22*, 543. (b) Parisot, D.; Devys, M.; Férézou, J.-P.; Barbier, M. *Phytochemistry* **1983**, *22*, 1301.

(9) Hari, L.; De Buyck, L. F.; De Pooter, H. L. *Phytochemistry* **1991**, *30*, 1726. (b) De Kimpe, N.; Van Puyvelde, L.; Schripsema, J.; Erkelens, C.; Verpoorte, R. *Magn. Reson. Chem.* **1993**, *31*, 329.

(10) Baker, R. A.; Tatum, J. H.; Nemec, S., Jr. *Phytopathology* **1981**, *71*, 951. (b) Baker, R. A.; Tatum, J. H.; Nemec, S., Jr. *Mycopathologia* **1990**, *111*, 9.

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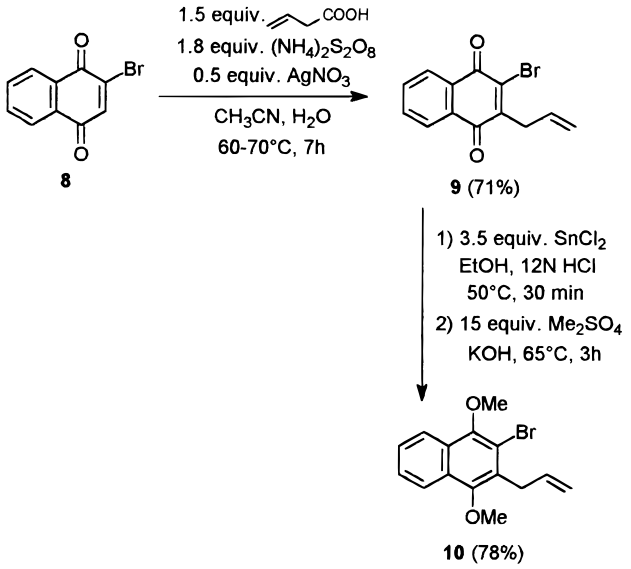
Scheme 1



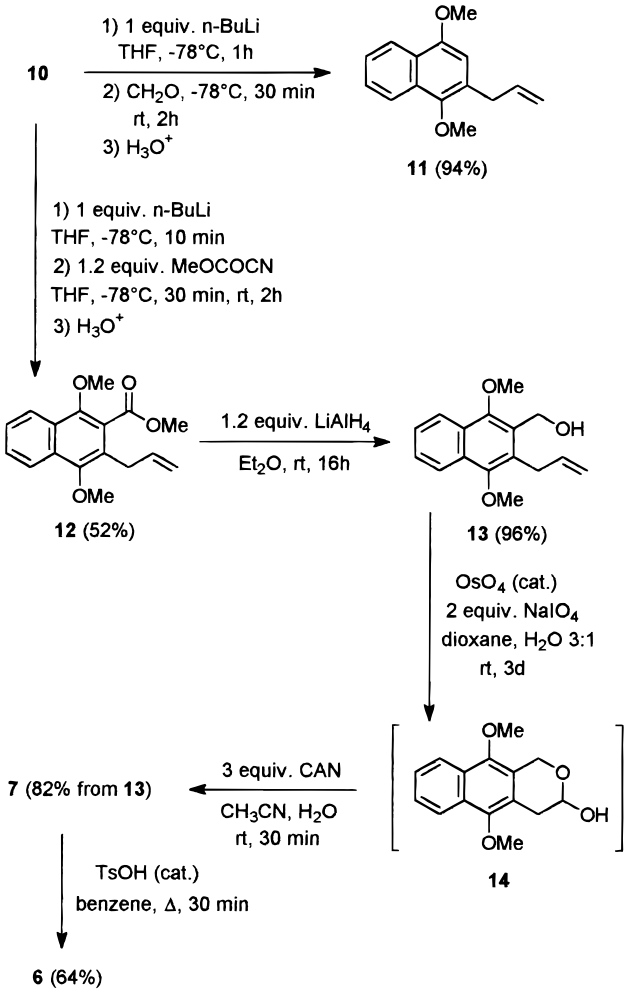
traditional healers of the Dispensary of Traditional Medicine of Curphametra (Butare, Rwanda) to treat the skin disease pityriasis versicolor.[9]

In view of the interesting physiological activities of pentalongin (**6**) and other pyranonaphthoquinones of the 3,4-dehydro series, we wanted to develop a general synthetic strategy allowing the synthesis of a series of pentalongin-based antibiotics for SAR studies. Pentalongin (**6**) was obtained before by dehydration of psychorubrin (**7**), another natural naphthoquinone antibiotic with significant antitumor activity, isolated from *Psychotria rubra*.[11] Pentalongin was also synthesized by a photochemical [2+2] addition of 2-chloro-1,4-naphthoquinone and acrolein dimethyl acetal and subsequent treatment of the resulting 1-dimethoxymethyl-1,2-dihydrocyclobuta[*b*]naphthalene-3,8-dione with *p*-toluenesulfonic acid,[12] but this photochemical procedure was completely unsuccessful in our hands, despite several attempts. Therefore, in this paper, we present the first total synthesis of two naturally occurring pyranonaphthoquinone antibiotics, pentalongin (**6**) and psychorubrin (**7**), by a new synthetic route, as a general strategy for the synthesis of 1*H*-naphtho[2,3-*c*]pyran-5,10-diones. Using this synthetic approach, a series of unnatural analogues of pentalongin (**6**) bearing alkyl and aryl substituents at the C(1) and C(3) positions of pentalongin will be synthesized.

Results and Discussion

The synthesis of pentalongin (**6**) and psychorubrin (**7**) is presented in Schemes 1 and 2, starting from 2-bromo-1,4-naphthoquinone (**8**), which is readily available from 1-hydroxynaphthalene through oxidative bromination with *N*-bromosuccinimide.[13] Radical allylation of this naphthoquinone **8** with vinylacetic acid, using ammonium persulfate and silver nitrate in aqueous acetonitrile, allowed the introduction of an allyl side chain at C(2).

Scheme 2

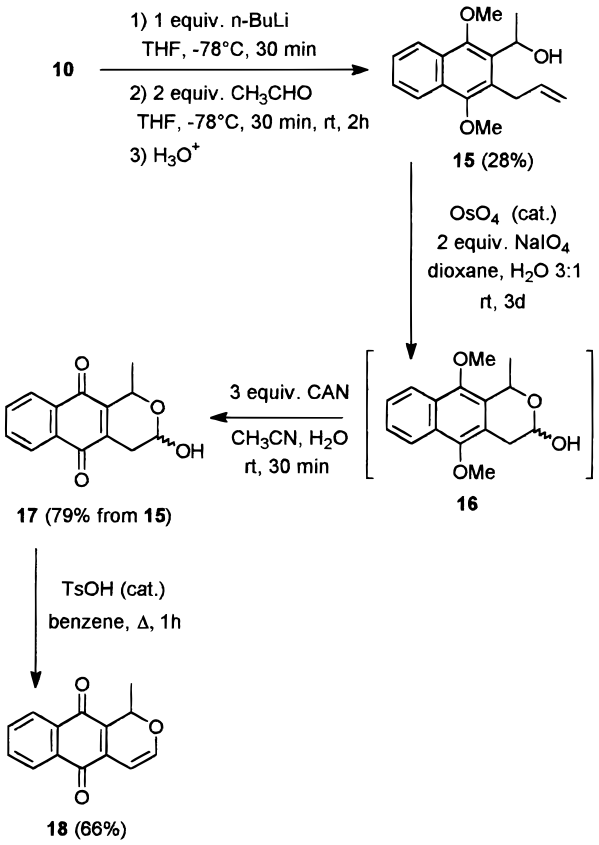


The resulting 2-allyl-3-bromo-1,4-naphthoquinone (**9**) was subjected to a conventional reductive methylation by means of tin(II) chloride and dimethyl sulfate to yield 2-allyl-3-bromo-1,4-dimethoxynaphthalene (**10**).

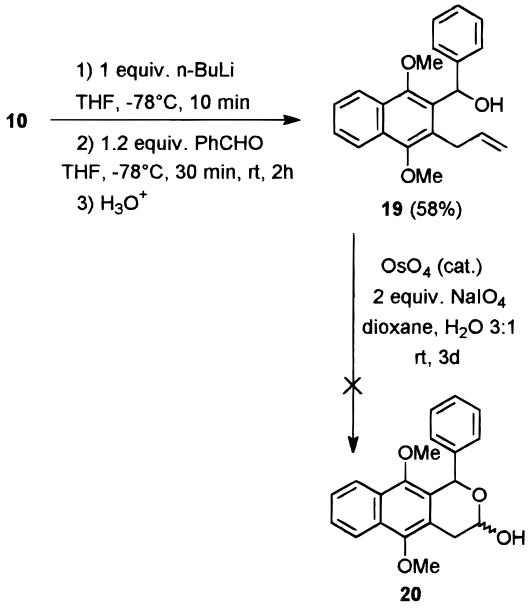
Direct conversion of this bromonaphthalene **10** to alcohol **13** via condensation with anhydrous formaldehyde was attempted by reaction of **10** with 1 equiv of *n*-butyllithium in tetrahydrofuran at −78 °C and treatment of the intermediate lithium salt with anhydrous formaldehyde (by bubbling formaldehyde gas, generated by heating anhydrous paraformaldehyde, through the solution) (Scheme 2). Unfortunately, the reaction gave only the debrominated 2-allyl-1,4-dimethoxynaphthalene (**11**) which was obtained in 94% yield from the reaction mixture, indicating, however, under these circumstances, the complete conversion of **10** into its lithium salt by bromine−lithium exchange. The desired alcohol **13** was obtained via the introduction of a methoxycarbonyl group and subsequent reduction of this functional group with lithium aluminum hydride. Methoxycarbonylation of bromonaphthalene **10** to **12** was carried out by bromine−lithium exchange and subsequent condensation of the transient anion formed with methyl choroformate or methyl cyanoformate, the latter providing a better yield of 52%. With methyl choroformate, compound **12** was obtained only in 33% yield. In either case, the 2-allyl-1,4-dimethoxynaphthalene (**11**) was a side product (up to 25%) from the methoxycarbonylation reaction, but it could be separated easily from ester **12** by flash chroma-

(11) Hayashi, T.; Smith, F. T.; Lee, K. H. *J. Med. Chem.* **1987**, *30*, 2005.
(12) Naito, T.; Makita, Y.; Yazaki, S.; Kaneko, C. *Chem. Pharm. Bull.* **1986**, *34*, 1505.
(13) Heinzman, S. W.; Grunwell, J. R. *Tetrahedron Lett.* **1980**, *21*, 4305.

Scheme 3



Scheme 4



tography. No efforts were made to improve the yields of the conversion of **10** to **12**, because the difficulties for introducing the methoxycarbonyl group were thought to be mainly of steric origin. Lemieux−Johnson oxidation of the alcohol **13** with catalytic osmium(VIII) tetroxide and excess of sodium periodate resulted in lactol **14** as the sole product. Because this acetal was found to undergo spontaneous elimination of water in anhydrous solvents, it was reacted immediately with cerium(IV) ammonium nitrate to afford psychorubrin (**7**) in an overall yield of 82% yield from alkenol **13**. The spectral data of the synthetic psychorubrin were in complete accordance with those of the natural product.[11] Finally, pentalongin (**6**) was obtained by treatment of psychorubrin (**7**) with *p*-toluenesulfonic acid in benzene under reflux for 30 min.[11] After recrystallization from methanol, pentalongin (**6**) was obtained as red needles with physical and spectral data identical to the natural product.[9] This is the first report on the total synthesis of pentalongin, obtained in 14% overall yield from 2-bromo-1,4-naphthoquinone (**8**).

For the preparation of 1-methylpentalongin (**18**) using the same synthetic pathway, the bromonaphthalene **10** was treated with 1 equiv of *n*-butyllithium in dry tetrahydrofuran at −78 °C, and condensation of the intermediate anion with acetaldehyde at the same temperature gave alcohol **15** in 28% yield after flash chromatography. Lemieux−Johnson oxidation of alkenol **15** with catalytic osmium(VIII) tetroxide and excess of sodium periodate lead to the formation of lactol **16** as a mixture of stereoisomers.[14] The *cis*- and the *trans*-isomers were formed in a ratio of ca. 2:1. Lactol **16** underwent spontaneous dehydration in anhydrous solvents and was therefore immediately oxidized with cerium(IV) ammonium nitrate to afford the pyranonaphthoquinone 1-methylpsychorubrin (**17**) as a mixture of stereoisomers in a ratio of 31:69, in an overall yield of 79% from alcohol **15**. The cis- and *trans*-isomers were not separated but were reacted with *p*-toluenesulfonic acid in benzene under reflux to give 1-methylpentalongin (**18**) as the sole product in 66% yield (Scheme 3).

Finally, the possibility of introducing a phenyl group at C(1) of pentalongin using the same synthetic route was investigated (Scheme 4). Therefore, the naphthyl anion derived from 2-allyl-3-bromo-1,4-dimethoxynaphthalene (**10**), obtained by bromine−lithium exchange utilizing *n*-butyllithium, was condensed with benzaldehyde at −78 °C, resulting in alcohol **19**. Unfortunately, lactol **20** could not be obtained by Lemieux−Johnson oxidation of the alcohol **19**, which resulted only in a complex reaction mixture, and thus the introduction of an aryl group at C(1) of pentalongin necessitated another synthetic approach (vide infra).

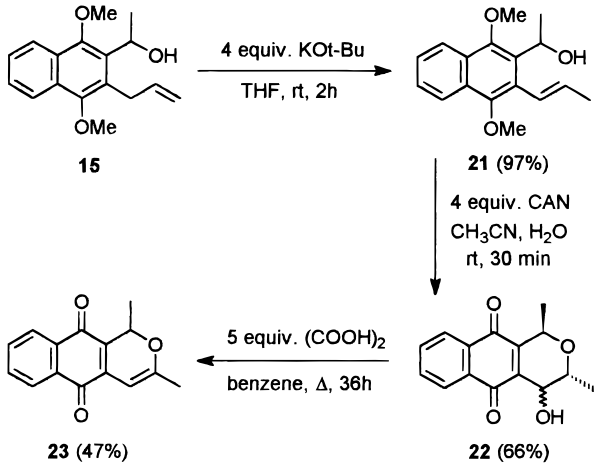
The synthesis of 1,3-dimethylpentalongin (**23**) is outlined in Scheme 5. Isomerization of the double bond in alkenol **15** to the conjugated vinylic position was performed with potassium *tert*-butoxide in dry tetrahydrofuran. It was found that oxidative demethylation of alcohol **21** with 4 equiv of cerium(IV) ammonium nitrate not only oxidized the dimethyl ether to the 5,10-quinonoid system but induced simultaneous oxidative cyclization of the alkenol moiety, resulting in a mixture of stereoisomeric 4-hydroxypyranonaphthoquinones **22** in a total yield of 66%.[15] Elimination of water from the stereoisomers **22** could not be performed with *p*-toluenesulfonic acid and necessitated the use of 5 equiv of anhydrous oxalic acid in benzene under reflux for 36 h. The resulting 1,3-dimethylpentalongin (**23**) was isolated in 47% yield after flash chromatography (Scheme 5).

In analogy with the former synthesis, treatment of alkenol **13** with potassium *tert*-butoxide in dry tetrahy-

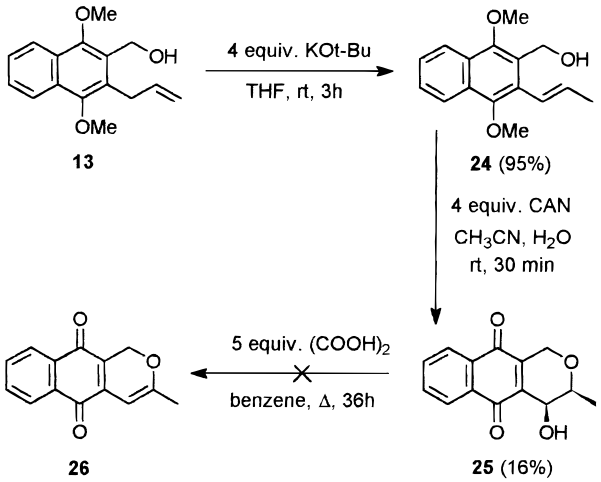
(14) Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1197.

(15) Chorn, T.A.; Giles, R. G. F.; Green, I. R.; Mitchell, P. R. K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1249.

Scheme 5



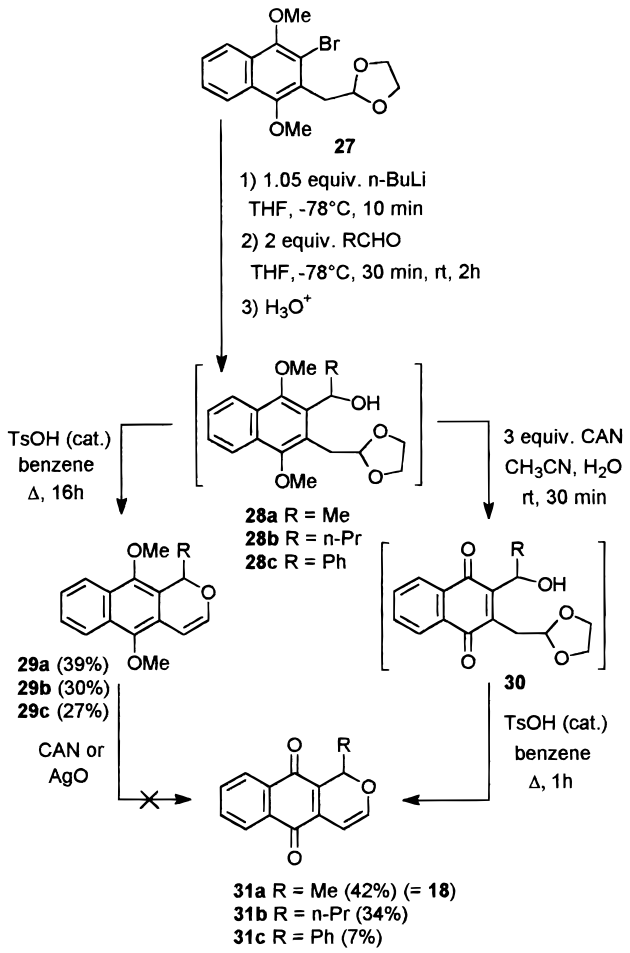
Scheme 6



drofuran induced the allylic double bond to isomerize to the conjugated vinylic position in alcohol **24**, as illustrated in Scheme 6. Oxidative cyclization and simultaneous oxidative demethylation of the alcohol **24** by the use of 4 equiv of cerium(IV) ammonium nitrate afforded a complex reaction mixture from which only one epimer, namely, the *cis*-isomer **25**, could be isolated in a yield of 16% by means of flash chromatography. The small coupling constant of 2 Hz between H(3) and H(4) implies that H(3) is axial and H(4) is pseudoequatorial; the C(3) methyl is therefore equatorial, and the C(4) hydroxy group pseudoaxial. Curiously, when the alcohol **25** was reacted with an excess of anhydrous oxalic acid, under the same conditions as those used for the dehydration of alcohols **22**, the desired 3-methylpentalongin (**26**) could not be detected in the reaction mixture (Scheme 6).

In Scheme 7, the use of an acetal protected aldehyde **27** is demonstrated as an alternative synthetic approach for the synthesis of C(1)-substituted alkyl- or aryl-1*H*-naphtho[2,3-*c*]pyran-5,10-diones. Acetal **27**, as a starting material, is available in an overall yield of 34% from 1-hydroxynaphthalene in six steps.[16] The use of 1.05 equiv of *n*-butyllithium in dry tetrahydrofuran at −78 °C caused bromine−lithium exchange, and condensation of the transient anion with an aldehyde afforded alcohols **28**. These intermediates **28** were not purified, and

Scheme 7



treatment with *p*-toluenesulfonic acid or flash chromatography on silica gel resulted in the formation of naphthopyranes **29**. In an attempt to oxidize these pyranonaphthalenes **29** to the desired pyranonaphthoquinones **31**, using the common oxidizing agents cerium(IV) ammonium nitrate or silver(II) oxide, only complex reaction mixtures were obtained. Therefore, in an alternative approach, oxidative demethylation was carried out prior to the acid-catalyzed cyclization and elimination of water. The intermediate acetals **28** were treated first with 3 equiv of cerium(IV) ammonium nitrate, but the intermediate acetals **30** could not be purified; elution over silica, as well as treatment of the crude acetals **30** with *p*-toluenesulfonic acid, allowed the desired 1-alkyl- or 1-phenyl-1*H*-naphtho[2,3-*c*]pyran-5,10-diones **31** to be isolated in 42% (**31a**, R = Me), 34% (**31b**, R = *n*-Pr), and 7% (**31c**, R = Ph) yield (Scheme 7).

In conclusion, the synthesis of a series of C(1)- and C(3)-substituted alkyl- and aryl-1*H*-naphtho[2,3-*c*]pyran-5,10-diones was performed by two alternative synthetic pathways. Using this methodology, the first total synthesis of two naturally occurring naphthoquinones, pentalongin and psychorubrin, was completed.

Experimental Section

General Methods. ^{1}H NMR (270 MHz) and ^{13}C NMR (68 MHz) peak assignments were performed with the aid of the DEPT technique, 2D-COSY spectra, and HETCOR spectra. Dry tetrahydrofuran (THF) was obtained by distillation from sodium−benzophenone ketyl. Diethyl ether was dried and

(16) Joshi, B. S.; Jiang, Q.; Rho, T.; Pelletier, S. *J. Org. Chem.* **1994**, *59*, 8220.

distilled from sodium. Other solvents were used without further purification.

2-Allyl-3-bromo-1,4-naphthoquinone (9). To a stirred suspension of 2-bromo-1,4-naphthoquinone (**8**)[13] (500 mg, 2.10 mmol), silver nitrate (110 mg, 1.05 mmol), and vinylacetic acid (270 mg, 3.15 mmol) in acetonitrile (50 mL) was added dropwise over 15 min a solution of ammonium persulfate (860 mg, 3.78 mmol) in water (25 mL). Stirring was continued for 7 h at 60−70 °C, and then the reaction mixture was poured into cold water and extracted with ethyl acetate. The extract was washed with aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated at reduced pressure. Recrystallization from methanol gave pure 2-allyl-3-bromo-1,4-naphthoquinone (**9**) (410 mg, 71%), mp 79 °C.

2-Allyl-3-bromo-1,4-dimethoxynaphthalene (10). To a solution of 2-allyl-3-bromo-1,4-naphthoquinone (**9**) (500 mg, 1.8 mmol) in 95% ethanol (20 mL) at 50 °C was added a solution of tin(II) chloride (1.2 g, 6.34 mmol) in concentrated hydrochloric acid (1.2 mL). After 30 min at the same temperature, cold water (100 mL) was added. A white solid precipitated and was isolated by filtration. The precipitate was mixed with dimethyl sulfate (3.42 g, 27 mmol), and to the resulting suspension was added dropwise at 0 °C a 50% potassium hydroxide solution (10 mL). Stirring was continued for 3 h at 65 °C, and then the reaction mixture was poured into cold water, extracted with ether, washed with aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and evaporated at reduced pressure. Flash chromatography on silica gel with 20% chloroform in pentane as eluent gave 2-allyl-3-bromo-1,4-dimethoxynaphthalene (**10**) (430 mg, 78%), mp 57 °C.

2-Allyl-1,4-dimethoxynaphthalene (11). A 2.5 M solution of *n*-butyllithium in hexane (0.4 mL, 1 mmol) was added dropwise at −78 °C to a solution of 2-allyl-3-bromo-1,4-dimethoxynaphthalene (**10**) (0.307 g, 1 mmol) in tetrahydrofuran (10 mL) under a nitrogen atmosphere, and stirring was continued at the same temperature for 1 h. Then, anhydrous formaldehyde gas (generated by heating paraformaldehyde at 100−150 °C) was bubbled through the solution along with a nitrogen stream during 30 min, and the solution was allowed to warm to room temperature over a period of 2 h. The mixture was poured into 2 N HCl, extracted with ether, dried ($MgSO_4$), and evaporated at reduced pressure. Flash chromatography (chloroform/pentane, 2/8) gave pure 2-allyl-1,4-dimethoxynaphthalene (**11**) (0.21 g, 94%) as a colorless liquid.

Methyl (3-Allyl-1,4-dimethoxynaphthalene-2-yl)carboxylate (12), 2-Allyl-3-(1-hydroxyethyl)-1,4-dimethoxynaphthalene (15), and 2-Allyl-3-(hydroxyphenylmethyl)-1,4-dimethoxynaphthalene (19). A 2.5 M solution of *n*-butyllithium in hexane (0.4 mL, 1 mmol) was added dropwise at −78 °C to a solution of 2-allyl-3-bromo-1,4-dimethoxynaphthalene (**10**) in dry THF (5 mL) under a nitrogen atmosphere, and stirring was continued at the same temperature for 30 min. A solution of acetaldehyde (88 mg, 2 mmol), methyl cyanoformate (102 mg, 1.2 mmol), or benzaldehyde (130 mg, 1.2 mmol), respectively, in dry THF (2 mL) was then added, and the resultant mixture was stirred for 10 min at −78 °C and then allowed to warm to room temperature over a period of 2 h. The mixture was poured into 2 N hydrogen chloride, extracted with ether, dried ($MgSO_4$), and evaporated at reduced pressure. Compounds **12**, **15**, and **19** were isolated after flash chromatography on silica gel with ethyl acetate/hexane as the eluent. Side products were not isolated or identified.

Methyl (3-allyl-1,4-dimethoxynaphthalene-2-yl)carboxylate (12): yield, 150 mg, 52% (ethyl acetate/hexane, 5/95). ^{1}H NMR ($CDCl_3$): δ 3.62−3.65 (2H, m, CH_2), 3.89 (3H, s, MeO), 3.93 (3H, s, MeO), 3.98 (3H, s, MeO), 5.02−5.09 (2H, m, CH=CH_2), 5.87−6.02 (1H, m, CH=CH_2), 7.47−7.58 (2H, m, H-6 and H-7), 8.06−8.11 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$): δ 31.48 (CH_2), 52.22 (OMe), 62.46 (MeO), 63.52 (MeO), 115.88 (CH=CH_2), 122.62 and 122.98 (=CH-5 and =CH-8), 125.21 (=C_{quat}), 125.48 (=C_{quat}), 126.27 and 127.37 (=CH-6 and =CH-7), 127.56 (=C_{quat}), 129.54 (=C_{quat}), 136.40 (*C*H=CH_2), 150.28 (=*C*−OMe), 150.38 (=*C*−OMe), 168.23 (C=O). IR (NaCl, cm^{-1}): 1730 (C=O). MS *m*/*z* (%): 286(M^+, 90), 255(14), 240(20), 239(100). Anal. Calcd for $C_{17}H_{18}O_4$: C 71.31, H 6.34. Found C 71.34, H 6.57. **2-Allyl-3-(1-hydroxyethyl)-1,4-dimethoxynaphthalene (15):** yield, 76 mg, 28% (ethyl acetate/hexane, 20/80). **2-Allyl-3-(1-hydroxyphenylmethyl)-1,4-dimethoxynaphthalene (19):** yield: 193 mg, 58% (ethyl acetate/hexane, 10/90).

2-Allyl-3-hydroxymethyl-1,4-dimethoxynaphthalene (13). To a solution of methyl (3-allyl-1,4-dimethoxynaphthalene-2-yl)carboxylate (**12**) (570 mg, 2 mmol) in dry ether (20 mL) was added lithium aluminum hydride (91 mg, 2.4 mmol) at 0 °C. The suspension was stirred overnight at room temperature, poured into a diluted hydrochloric acid solution, and extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. Flash chromatography on silica gel with 20% ethyl acetate in hexane gave 2-allyl-3-hydroxymethyl-1,4-dimethoxynaphthalene (**13**) (495 mg, 96%), mp 83 °C. ^{1}H NMR ($CDCl_3$): δ 2.56 (1H, s broad, OH), 3.73 (2H, dt, J = 5.2 Hz, 1.8 Hz, CH_2−CH=CH_2), 3.86 (3H, s, MeO), 3.94 (3H, s, MeO), 4.83 (2H, s, CH_2OH), 4.90 (1H, dd, J = 17.2 Hz, 1.8 Hz, CH=C$H_A$$H_B$), 5.05 (1H, dd, J = 10.1 Hz, 1.8 Hz, CH=C$H_A$$H_B$), 6.11 (1H, ddt, J = 17.2 Hz, 10.1 Hz, 5.2 Hz, CH=CH_2), 7.43−7.52 (2H, m, H-6 and H-7), 8.02−8.07 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$): δ 30.32 (*C*H_2−CH=CH_2), 57.16 (CH_2OH), 62.23 (MeO), 63.18 (MeO), 115.27 (CH=*C*H_2), 122.37 and 122.52 (=CH-5 and =CH-8), 125.73 and 126.29 (=CH-6 and =CH-7), 127.67 (=C_{quat}), 128.63 (=C_{quat}), 129.11 (=C_{quat}), 138.01 (*C*H=CH_2), 150.49 (=*C*−OMe), 151.48 (=*C*−OMe). IR (NaCl, cm^{-1}): 3400 (OH), 1590, 1450, 1355, 1270, 1100, 915, 775, 735. MS *m*/*z* (%): 258(M^+, 100), 225(98). Anal. Calcd for $C_{16}H_{18}O_3$: C 74.40, H 7.02. Found C 74.03, H 6.78.

3,4-Dihydro-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran-3-ol (14). To a solution of 2-allyl-3-hydroxymethyl-1,4-dimethoxynaphthalene (**13**) (100 mg, 0.4 mmol) in water (5 mL) and dioxane (15 mL) was first added a catalytic amount of osmium(VIII) tetroxide (10 mg), and then sodium periodate (170 mg, 0.8 mmol) was added portionwise over a period of 1 h. The suspension formed was stirred for 3 days, poured into water, extracted with ether, washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. Flash chromatography on silica gel with 40% ethyl acetate in hexane gave 3,4-dihydro-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran-3-ol (**14**) (20 mg, 19%). Compound **14** was found to eliminate water rapidly when dissolved in $CDCl_3$. The crude product (purity about 90%) was used as such in the next step. ^{1}H NMR ($CDCl_3$): δ 2.97 (1H, dd, J = 16.8 Hz, 5.3 Hz, C$H_A$$H_B$), 3.29 (1H, dd, J = 16.8 Hz, 4.0 Hz, $CH_A$$H_B$), 3.89 (3H, s, MeO), 3.90 (3H, s, MeO), 4.99 and 5.19 (each 1H, each d, J = 15.5 Hz, CH_2−O), 5.42 (1H, dd, J = 5.3 Hz, 4.0 Hz, CH−OH), 7.45−7.51 (2H, m, H-7 and H-8), 8.01−8.08 (2H, m, H-6 and H-9).

Psychorubrin (7). A solution of cerium(IV) ammonium nitrate (610 mg, 1.14 mmol) in water (5 mL) was added dropwise to a solution of crude 3,4-dihydro-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran-3-ol (**14**) (100 mg, 0.38 mmol) in acetonitrile (10 mL) and water (10 mL) at 0 °C. The stirred mixture was allowed to warm to room temperature over a period of 30 min, poured into water, and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. Flash chromatography (eluent ethyl acetate 50% in hexane) gave psychorubrin (**7**) (80 mg, 82% from **13**) as a yellow powder, mp 149 °C (lit.[11] 150−152 °C). Spectral data were in accordance with those available in the literature.[11]

Pentalongin (6). A solution of psychorubrin (**7**) (330 mg, 1.4 mmol) in benzene (20 mL) was heated under reflux for 30 min with a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was allowed to cool to room temperature, dried ($MgSO_4$), and evaporated at reduced pressure. Flash chromatography (eluent 10% ethyl acetate in hexane) afforded pentalongin (**6**) (190 mg, 64%) as a red powder, mp 160−161 °C (methanol) (lit.[9] 160−161 °C). Spectral data were in accordance with those available in the literature.[9]

3,4-Dihydro-5,10-dimethoxy-1-methyl-1*H*-naphtho[2,3-*c*]pyran-3-ol (16). To a solution of 2-allyl-3-(1-hydroxyethyl)-1,4-dimethoxynaphthalene (**15**) (109 mg, 0.4 mmol) in water

(2 mL) and dioxane (6 mL) was first added a catalytic amount of osmium(VIII) tetroxide (10 mg). Then, sodium periodate (170 mg, 0.8 mmol) was added portionwise over a period of 1 h. After 3 days, the suspension was poured into water, extracted with ether, washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. Flash chromatography on silica gel with 40% ethyl acetate in hexane as eluent gave 3,4-dihydro-5,10-dimethoxy-1-methyl-1*H*-naphtho[2,3-*c*]pyran-3-ol (**16**) as a mixture of *cis*- and *trans*-isomers in a ratio of ca. 2:1 (53 mg, 48%). Compound **16** rapidly eliminated water when dissolved in $CDCl_3$. The crude product (purity about 90%) was immediately used as such in the next step.

3,4-Dihydro-3-hydroxy-1-methyl-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (17). A solution of crude 3,4-dihydro-5,10-dimethoxy-1-methyl-1*H*-naphtho[2,3-*c*]pyran-3-ol (**16**) (70 mg, 0.26 mmol) in acetonitrile (2 mL) was added dropwise to a solution of cerium(IV) ammonium nitrate (430 mg, 0.78 mmol) in water (5 mL) at 0 °C. The stirred suspension was allowed to warm to room temperature over a period of 30 min, poured into water, and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. Recrystallization from dry ether gave 3,4-dihydro-3-hydroxy-1-methyl-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (**17**) (50 mg, 79% from **15**) as a mixture of *cis*- and *trans*-isomers in a ratio of 69:31. ^{1}H NMR ($CDCl_3$): δ (*cis*-stereoisomer) 1.56 (3H, d, J = 6.9 Hz, CH_3), 2.77−2.79 (2H, m, CH_2), 3.83 (1H, broad s, OH), 5.07 (1H, q, J = 6.9 Hz, C*H*CH_3), 5.55 (1H, m, C*H*OH); (*trans*-stereoisomer) 1.63 (3H, d, J = 6.6 Hz, CH_3), 2.58 (1H, ddd, J = 18.6 Hz, 6.7 Hz, 3.3 Hz, CH_AH_B), 3.01 (1H, dt, J = 18.3 Hz, 3.0 Hz, CH_AH_B), 4.00 (1H, broad s, OH), 4.96−5.13 (1H, m, C*H*CH_3), 5.16 (1H, dd, J = 6.7 Hz, 3.0 Hz, C*H*OH), (both) 7.67−7.74 (2H, m, H-7 and H-8), 8.00−8.10 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$): δ (*cis*-stereoisomer) 20.20 (CH_3), 28.75 (CH_2), 65.07 (*C*HCH_3), 88.80 (CHOH), 126.27 (=CH-6 and =CH-9), 131.77 (=C_{quat}), 132.09 (=C_{quat}), 133.67 and 133.80 (=CH-7 and =CH-8), 139.10 (=C_{quat}), 145.23 (C_{quat}), 183.18 (C=O), 183.75 (C=O); (*trans*-stereoisomer) 21.29 (CH_3), 29.70 (CH_2), 69.18 (*C*HCH_3), 91.97 (CHOH), 126.27 (=CH-6 and =CH-9), 131.71 (=C_{quat}), 132.16 (=C_{quat}), 133.74 and 133.89 (=CH-7 and =CH-8), 139.87 (=C_{quat}), 145.57 (=C_{quat}), 183.37 (C=O), 183.61 (C=O). IR (KBr, cm^{-1}): 3370 (OH), 1660 (C=O), 1590 (C=C). MS *m*/*z* (%): 244(M^+, 12), 226(72), 211(100). Anal. Calcd for $C_{14}H_{12}O_4$: C 68.85, H 4.95. Found C 69.17, H 4.92.

1-Methylpentalongin (18). A solution of 3,4-dihydro-3-hydroxy-1-methyl-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (**17**) (30 mg, 0.12 mmol) in benzene (5 mL) was heated under reflux with a catalytic amount of *p*-toluenesulfonic acid. After 1 h, the reaction mixture was allowed to cool to room temperature, dried ($MgSO_4$), and evaporated at reduced pressure. Recrystallization from ether/pentane gave 1-methylpentalongin (**18**) (20 mg, 66%), mp 92−93 °C. ^{1}H NMR ($CDCl_3$): δ 1.45 (3H, d, J = 6.6 Hz, CH_3), 5.69 (1H, q, J = 6.6 Hz, C*H*CH_3), 6.04 (1H, d, J = 5.6 Hz, C*H*=CH−O), 6.85 (1H, d, J = 5.6 Hz, CH=C*H*-O), 7.68−7.73 (2H, m, H-7 and H-8), 8.04−8.10 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$): δ 18.08 (CH_3), 68.66 (*C*HCH_3), 96.33 (*C*H=CH−O), 125.95 and 126.45 (=CH-6 and =CH-9), 128.53 (=C_{quat}), 131.61 (=C_{quat}), 132.47 (=C_{quat}), 133.31 and 133.94 (=CH-7 and =CH-8), 134.88 (=C_{quat}), 152.07 (CH=*C*H−O), 182.29 (2 × C=O). IR (KBr, cm^{-1}): 1670 (C=O), 1650 (C=O), 1580 (C=C), 1540 (C=C). MS *m*/*z* (%): 226(M^+, 48), 211(100). Anal. Calcd for $C_{14}H_{10}O_3$: C 74.33, H 4.46. Found C 74.02, H 4.57.

***trans*-2-(1-Hydroxyethyl)-1,4-dimethoxy-3-(1-propenyl)-naphthalene (21).** To a solution of 2-allyl-3-(1-hydroxyethyl)-1,4-dimethoxynaphthalene (**15**) (620 mg, 2.3 mmol) in dry THF (20 mL) under a nitrogen atmosphere was added potassium *tert*-butoxide (1.03 g, 9.2 mmol). The suspension was stirred at room temperature for 2 h, poured into a saturated solution of ammonium chloride, extracted with ether, dried ($MgSO_4$), and evaporated at reduced pressure. Flash chromatography (eluent 20% ethyl acetate in hexane) afforded *trans*-2-(1-hydroxyethyl)-1,4-dimethoxy-3-(1-propenyl)naphthalene (**21**) (600 mg, 97%) as an oil. Spectral data were in accordance with those available in the literature.[15]

1,3-Dimethylpentalongin (23). A solution of stereoisomeric 4-hydroxypyranonaphthoquinones **22**[15] (120 mg, 0.47 mmol) in benzene (15 mL) was heated under reflux for 36 h in the presence of an excess of oxalic acid (210 mg, 2.4 mmol). Then the reaction mixture was poured into aqueous sodium hydrogen carbonate, and the organic layer was separated. The water phase was extracted twice with dichloromethane, and the combined extracts were dried ($MgSO_4$) and evaporated at reduced pressure. Flash chromatography (eluent 5% ethyl acetate in hexane) afforded 1,3-dimethylpentalongin (**23**) (50 mg, 47%) as a red powder, mp 74−75 °C. ^{1}H NMR ($CDCl_3$): δ 1.41(3H, d, J = 6.6 Hz, CH_3-1), 2.02 (3H, d, J = 0.7 Hz, CH_3-3), 5.70 (1H, q, J = 6.6 Hz, CH), 5.89 (1H, q, J = 0.7 Hz, C*H*=C−O), 7.65−7.73 (2H, m, H-7 and H-8), 8.04−8.09 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$): δ 18.11 (CH_3), 20.97 (CH_3), 69.72 (CH), 93.15 (*C*H=C−O), 125.82 and 126.34 (=CH-6 and =CH-9), 126.43 (=C_{quat}), 131.69 (=C_{quat}), 132.63 (=C_{quat}), 133.03 and 133.83 (=CH-7 and =CH-8), 136.13 (=C_{quat}), 162.73 (CH=*C*−O), 181.99 (C=O), 182.69 (C=O). IR (NaCl, cm^{-1}): 1670 (C=O), 1650 (C=O), 1580 (C=C), 1560 (C=C). MS *m*/*z* (%): 240(M^+, 34), 225(100). Anal. Calcd for $C_{15}H_{12}O_3$: C 74.99, H 5.03. Found C 74.73, H 4.99.

***trans*-2-(Hydroxymethyl)-1,4-dimethoxy-3-(1-propenyl)-naphthalene (24).** To a solution of 2-allyl-3-(hydroxymethyl)-1,4-dimethoxynaphthalene (**13**) (200 mg, 0.78 mmol) in dry THF (10 mL) under a nitrogen atmosphere was added potassium *tert*-butoxide (0.35 g, 3.12 mmol). The suspension was allowed to react for 3 h, poured into a saturated solution of ammonium chloride, extracted with ether, dried ($MgSO_4$), and evaporated at reduced pressure. Flash chromatography (eluent 20% ethyl acetate in hexane) afforded *trans*-2-(hydroxymethyl)-1,4-dimethoxy-3-(1-propenyl)naphthalene (**24**) (190 mg, 95%), mp 71−72 °C.

***cis*-3,4-Dihydro-4-hydroxy-3-methyl-1*H*-naphtho[2,3-*c*]-pyran-5,10-dione (25).** To a solution of *trans*-2-(hydroxymethyl)-1,4-dimethoxy-3-(1-propenyl)naphthalene (**24**) (200 mg, 0.78 mmol) in acetonitrile (15 mL) and water (10 mL) was added dropwise a solution of cerium(IV) ammonium nitrate (1.69 g, 3.12 mmol) in water (5 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and, after 30 min, was poured into water and extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated at reduced pressure. Flash chromatography on silica gel with 50% ethyl acetate in hexane gave *cis*-3,4-dihydro-4-hydroxy-3-methyl-1*H*-naphtho[2,3-*c*]pyran-5,10-dione (**25**) (30 mg, 16%), mp 139−140 °C. Side products were neither isolated nor identified. ^{1}H NMR ($CDCl_3$): δ 1.45 (3H, d, J = 6.3 Hz, CH_3), 2.53 (1H, s broad, OH), 3.66 (1H, qd, J = 6.3 Hz, 2.0 Hz, C*H*−CH_3), 4.47 (1H, dd, J = 19.1 Hz, 1.6 Hz, CH_AH_B), 4.56 (1H, m, C*H*OH), 4.87 (1H, d, J = 19.1 Hz, CH_AH_B), 7.71−7.78 (2H, m, H-7 and H-8), 8.05−8.13 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$): δ 16.05 (CH_3), 61.47 (CH−OH), 63.52 (CH_2), 73.57 (*C*H−CH_3), 126.22 and 126.59 (=CH-6 and =CH-9), 131.75 (=C_{quat}), 131.80 (=C_{quat}), 134.03 and 134.19 (=CH-7 and =CH-8), 141.07 (=C_{quat}), 143.32 (=C_{quat}), 183.84 (C=O), 184.06 (C=O). IR (KBr, cm^{-1}): 3400 (OH), 1660 (C=O), 1590 (C=C). MS *m*/*z* (%): no M^+, 226($M^+ - H_2O$, 8), 201(15), 200(100), 172(75). Anal. Calcd for $C_{14}H_{12}O_4$: C 68.85, H 4.95. Found C 68.64, H 4.73.

The synthesis of 1-alkyl- and 1-phenyl-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyrans **29** is exemplified by the synthesis of **1-methyl-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran (29a).** A 2.5 M solution of *n*-butyllithium in hexane (0.6 mL, 1.4 mmol) was added dropwise at −78 °C to a solution of 2-(3-bromo-1,4-dimethoxy-2-naphthylmethyl)-1,3-dioxolane (**27**)[16] (500 mg, 1.4 mmol) in dry THF (5 mL) under a nitrogen atmosphere, and stirring was continued at the same temperature for 10 min. A solution of acetaldehyde (0.12 g, 2.8 mmol) in dry THF (2 mL) was then added, and the resultant mixture was stirred for another 30 min at −78 °C and then allowed to warm to room temperature over a period of 2 h. The reaction mixture was then poured into 2 N hydrogen chloride, extracted with ether, dried ($MgSO_4$), and evaporated at reduced pressure. The intermediate acetal **28a** could not be purified. An attempted flash chromatography on silica gel with 50% ethyl

acetate in hexane as eluent led only to the isolation of a mixture of the cyclization product **16**, together with the elimination product **29a**. The crude acetal **28a** was therefore heated under reflux for 16 h in benzene (20 mL) in the presence of a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was allowed to cool to room temperature, dried ($MgSO_4$), and evaporated at reduced pressure. Recrystallization from dry ether gave 1-methyl-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran **29a** (140 mg, 39%) as the sole product, mp 135 °C. ^{1}H NMR ($CDCl_3$): δ 1.51 (3H, d, J = 6.6 Hz, CH_3), 3.89 (3H, s, MeO), 3.95 (3H, s, MeO), 5.75 (1H, q, J = 6.6 Hz, C*H*CH_3), 6.14 (1H, d, J = 5.9 Hz, C*H*=CH−O), 6.57 (1H, d, J = 5.9 Hz, CH=C*H*-O), 7.39−7.49 (2H, m, H-6 and H-7), 7.96−8.06 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$): δ 20.66 (CH_3), 62.16 (MeO), 62.21 (MeO), 69.34 (*C*HCH_3), 98.53 (*C*H=CH−O), 118.47 (=C_{quat}), 122.33 (=CH-5 and =CH-8), 123.65 (=C_{quat}), 125.25 and 126.13 (=CH-6 and =CH-7), 127.87 (=C_{quat}), 128.87 (=C_{quat}), 143.88 (CH=*C*H−O), 144.85 (=*C*−OMe), 146.59 (=*C*−OMe). IR (KBr, cm^{-1}): 1625 (C=C), 1590, 1450, 1350, 1230, 1075, 1030, 780. MS *m*/*z* (%): 256(M^+, 97), 241(100), 227(21), 226(22). Anal. Calcd for $C_{16}H_{16}O_3$: C 74.98, H 6.29. Found C 74.87, H 6.38.

1-Propyl-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran (29b): yield, 30%, after flash chromatography (eluent 40% chloroform in pentane), mp 71−73 °C. **1-Phenyl-5,10-dimethoxy-1*H*-naphtho[2,3-*c*]pyran (29c):** yield, 27%, after flash chromatography (eluent 5% ethyl acetate in hexane), mp 78−79 °C.

The synthesis of 1-alkyl- and 1-phenyl-1*H*-naphtho[2,3-*c*]-pyran-5,10-diones (**31**) is exemplified by the synthesis of **1-methylpentalongin (31a)**. To a solution of 2-(3-bromo-1,4-dimethoxy-2-naphthylmethyl)-1,3-dioxolane (**27**)[16] (300 mg, 0.85 mmol) in dry THF (5 mL) at −78 °C under a nitrogen atmosphere was added a 2.5 M solution of *n*-butyllithium (0.36 mL, 0.89 mmol). After 10 min, a solution of acetaldehyde (70 mg, 1.7 mmol) in dry THF (2 mL) was added, and after another 30 min at −78 °C, the reaction mixture was allowed to warm to room temperature over a period of 2 h. The mixture was then poured into 2 N hydrochloric acid, extracted with ether, and evaporated at reduced pressure. To the crude product dissolved in acetonitrile (10 mL) was added dropwise a solution of cerium(IV) ammonium nitrate (1.38 g, 2.55 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature for 30 min, poured into water, and extracted with ethyl acetate. The combined extracts were washed with brine and evaporated at reduced pressure. The crude product was heated under reflux for 1 h in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid, dried ($MgSO_4$), and evaporated at reduced pressure. Flash chromatography (eluent 5% ethyl acetate in hexane) afforded 1-methylpentalongin (**31a**) (80 mg, 42%) as a red powder, mp 95 °C (methanol). For spectrometric data of **31a**, see compound **18** (vide supra). **1-*n*-Propyl-pentalongin (31b)**: yield, 34%, after flash chromatography (eluent 5% ethyl acetate in hexane), mp 98.5−99.5 °C (methanol). **1-Phenyl-pentalongin (31c)**: yield, 7%, after flash chromatography (eluent 5% ethyl acetate in hexane), mp 121 °C (methanol).

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Supporting Information Available: Spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, and MS) and elementary analyses of compounds **9**−**10**, **11**, **15**, **16**, **19**, **24**, **29b**,**c**, and **31b**,**c** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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