Coccidiostatic Agents: Synthesis of some Analogs of (±)-Frenolicin B

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Received 28 November 1994; revised 1 March 1995

Starting from juglone derivative **5**, a series of frenolicin B analogs **15** ($R^1 = R^2 = Me$), **19a** ($R^1 = H$, $R^2 = Ph$), and **19b** ($R^1 = Ph$, $R^2 = H$) were obtained via the key β-hydroxy ester intermediate **10** in a twelve step synthesis.

Coccidiosis is a parasitic disease, which is triggered by a protozoan organism of the genus *Eimeria*. This disease is endemic in large scale poultry farming. Due to increased drug resistance of poultry coccidiosis against the customary antibiotics, efforts are well underway towards the development of novel or modified drugs, which have been shown to have anticoccidial activity against *Eimeria tenella* in chickens. Recently, frenolicin B has been shown to have a synergistic effect in combination with ionophoric anticoccidial antibiotics against which *Eimeria* field isolates had developed resistance.[1] Consequently, this has generated a burst of efforts to synthesize frenolicin B, as well as some analogs, as anticoccidial agents for biological evaluation.

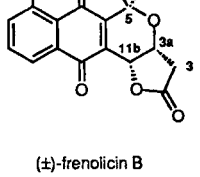
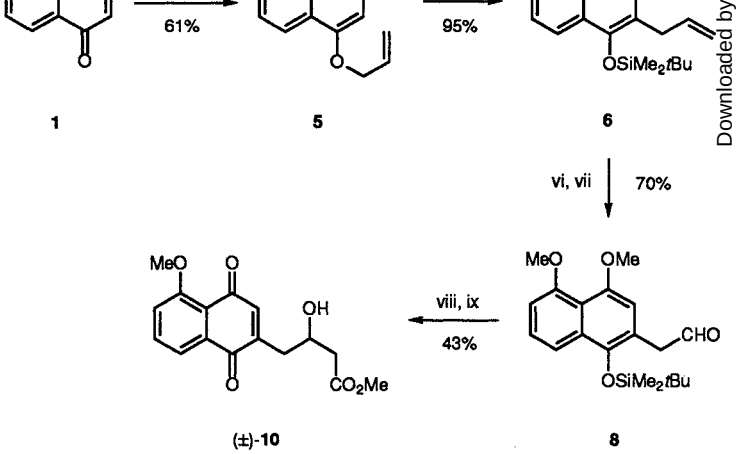


Figure 1 (±)-frenolicin B

Recently, Visnick achieved a straightforward synthesis of (±)-frenolicin B in several steps from the easily available juglone derivative **5**.[2] We describe herein the total synthesis of three racemic frenolicin B analogs **15**, **19a** and **19b**, following a modified version of the Visnick methodology. The synthesis is based on: (a) the condensation of hydroquinones with aldehydes or ketones under acidic conditions to generated the fused pyran ring and (b) the oxidative cyclization of acid derivatives in methanol/pyridine, in order to generate the lactone ring.

In accordance with Yoshii,[3] the key β-hydroxy ester intermediate **10** was synthesized following the multistep sequence as described in Scheme 1.

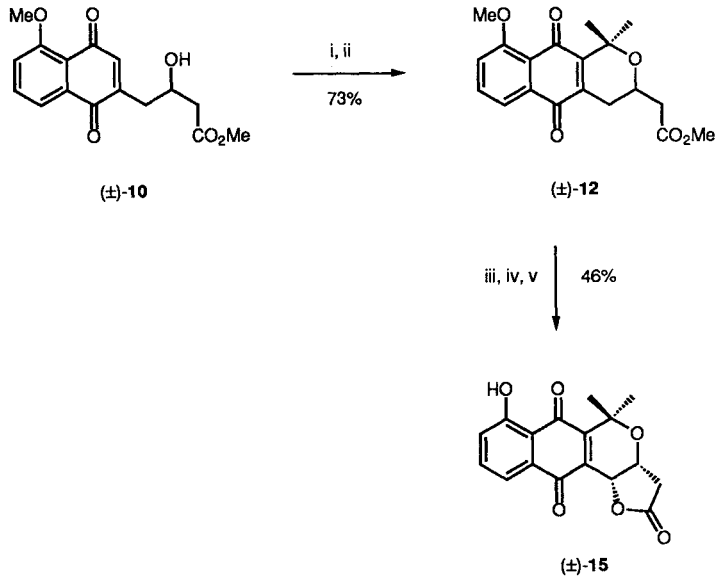
Juglone **1** was first *O*-methylated with methyl iodide using silver(I) oxide to yield **2** in 93%, which was reduced with aqueous sodium dithionite ($Na_2S_2O_4$) affording the corresponding hydroquinone intermediate **3** (99%) as an air sensitive solid. Subsequent C-1 *O*-alkylation with allyl bromide and potassium carbonate gave **4** (81%), followed by methylation of the remaining phenolic group with dimethyl sulfate in aqueous sodium hydroxide which led to **5** as a white solid (82%). Aromatic Claisen rearrangement of this allylic ether **5** in *N,N*-dimethylformamide (DMF), followed by silylation with *tert*-butyldimethylchlorosilane and imidazole led to the naphthylsilyl ether intermediate **6** (95%). Treatment of **6** with catalytic osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide (NMO) as cooxidant afforded diol **7** (88%) as a white solid, which was converted into the corresponding naphthyl acetaldehyde **8** in 79% yield after oxidative cleavage with lead tetraacetate in methanol.[4] Subsequent Mukaiyama aldol condensation[5] of **8** with *tert*-butyl(1-methoxyvinyloxy)dimethylsilane gave **9** (51%), followed by oxidation with cerium(IV) ammonium nitrate (CAN) in aqueous acetonitrile which led to the key β-hydroxy ester **10** in 83.5% yield. This type of 2-(β-hydroxy ester) 1,4-naphthoquinone is often used as a key intermediate in the preparation of pyronaphthoquinone antibiotics.[2,6,7]



i : MeI, Ag_2O, CH_2Cl_2, (→ **2**, 93%) ; ii : $Na_2S_2O_4$, AcOEt, (→ **3**, 99%) ; iii : allyl bromide, K_2CO_3, acetone, (→ **4**, 81%) ; iv : Me_2SO_4, $NaOH_{aq}$, dioxane (82%) ; v : a) DMF, 140°C ; b) $tBuMe_2SiCl$, DMAP, imidazole ; vi : OsO_4, NMO, acetone, H_2O, (→ **7**, 88%) ; vii : $Pb(OAc)_4$, MeOH (79%) ; viii : $TiCl_4$, $CH_2CH(OMe)(OSi\ tBuMe_2)$, CH_2Cl_2, (→ **9**, 51%) ; ix : CAN_{aq}, CH_3CN (84%).

Scheme 1

There are several reports in the literature which describe the condensation of aldehydes with hydroquinone as a general route to fused pyran rings.[3,8] In a preliminary study we prepared the dimethyl analog **15** as described in Scheme 2.

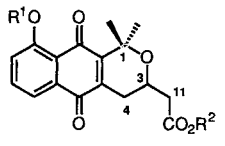


Scheme 2 i : HCl_{aq}, Zn_{act}, dioxane/Et_2O (1:1), (→ **11**, 84%) ; ii : a) HCl_g-Et_2O, acetone ; b) CAN_{aq}, CH_3CN (87%) ; iii : BCl_3, CH_2Cl_2, (→ **13**, 97%) ; iv : KOH, MeOH, (→ **14**, 92%) ; v : MeOH, pyridine, O_2, Δ (52%).

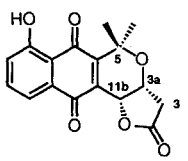
Reduction of 1,4-naphthoquinone **10** with zinc powder in a two phase system of Et_2O/HCl (aq) gave the corresponding hydroquinone **11** in 84% yield. Treatment of **11** with acetone in a saturated gaseous HCl – diethyl ether solution led to the fused pyran ring intermediate, which was oxidized with aqueous CAN to the corresponding naphthoquinone **12** in 87% yield. Demethylation with boron trichloride (BCl_3) in CH_2Cl_2 afforded **13** (97%). Subsequent saponification with potassium hydroxide in MeOH gave the racemic deoxyfrenolicin analog **14** in 92% yield. Oxidative cyclization of **14** in methanol/pyridine, involving a quinone methide intermediate in the oxidative process[6,8,9], gave the (±)-dimethyl analog **15** in 52% yield after recrystallization from MeOH. The relative orientation of the substituents in the naphthoquinones **12–15** follows unambiguously from the analysis of their ^1H NMR spectra (Table 1) and from our knowledge concerning the stereospecific formation of the lactone leading to a *cis* arrangement of H-C(3a) and H-C(11b). For **12**, **13** and **14** a large coupling constant ($J_{3-4\Psi a}$ = 11 Hz) indicates the axial position of H-C(3) and consequently the equatorial position of the substituent at C(3). Therefore, the small vicinal coupling observed for **15** (J_{3a-11b} = 2.5 Hz) proves the *cis* configuration of the lactone system.

Reduction of the quinone **10** with zinc and hydrochloric acid led to the corresponding hydroquinone **11** in 84% yield. Treatment of **11** with benzaldehyde in a saturated gaseous HCl – diethyl ether solution at −5 °C for 5 min led to a mixture of two tricyclic stereoisomers containing predominantly the *cis*-isomer (94:6; *cis*/*trans*), which was oxidized quantitatively with CAN to the corresponding mixture of quinones **16a** and **b** (94:6). Fractional crystallization of the diastereomeric mixture from acetonitrile, afforded the pure (±)-*cis*-isomer **16a** in 75% overall yield. The pure (±)-*trans*-isomer **16b** was obtained in a similar fashion. Treatment of **11** with benzaldehyde in a saturated gaseous HCl – diethyl ether solution at r.t. over 2 h led to a diastereomeric mixture of the tricyclic

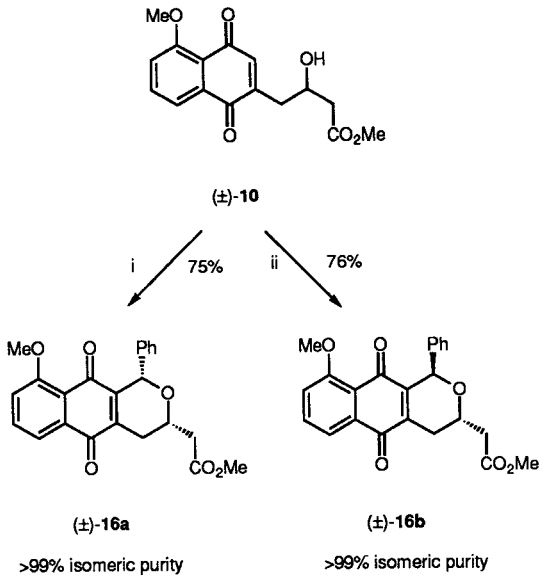
Table 1. ^1H NMR Spectra Data (*J*, Hz) of **12–15**



12 : $R^1 = R^2$ = Me
13 : R^1 = H, R^2 = Me
14 : $R^1 = R^2$ = H

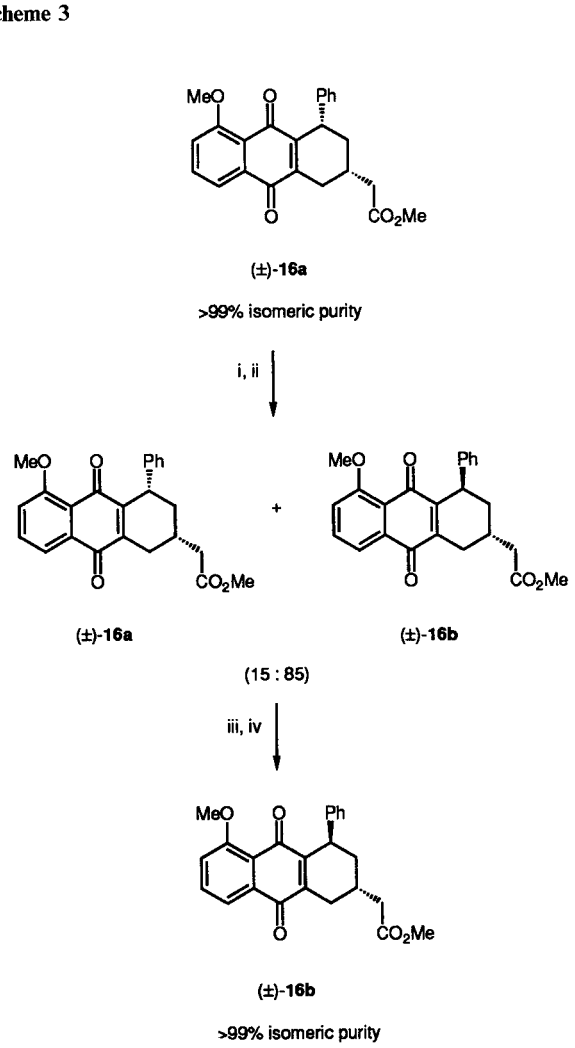


	$J_{3-4\psi ax}$	$J_{3-4\psi eq}$	J_{3-11}	$J_{3-11'}$	$J_{11-11'}$	$J_{4\psi ax-4\psi ax}$	$J_{3-3'}$	$J_{3'-3a}$	J_{3a-11b}
12	11.00	3.00	5.50	7.75	15.00	18.50			
13	11.00	3.00	5.50	7.75	15.00	18.50			
14	11.00	3.00			6	18.50			
15							18.00	4.50	2.50



i : a) HCl_{aq}, Zn_{act}, dioxane/Et_2O (1:1), (→ **11**) ; b) HCl_g-Et_2O, PhCHO, -5°C, 5min ; c) CAN_{aq}, CH_3CN, (→ **16a+16b**) ; d) Fractional crystallization, CH_3CN.
ii : a) HCl_{aq}, Zn_{act}, dioxane/Et_2O (1:1), (→ **11**) ; b) HCl_g-Et_2O, PhCHO, r.t., 2hr ; c) CAN_{aq}, CH_3CN, (→ **16a+16b**) ; d) Fractional crystallization, CH_3CN.

Scheme 3



i : $Na_2S_2O_4$, CH_2Cl_2 ; ii : HCl_g-Et_2O, r.t., 18hr ; iii : CAN_{aq}, CH_3CN ; iv : Fractional crystallization, CH_3CN.

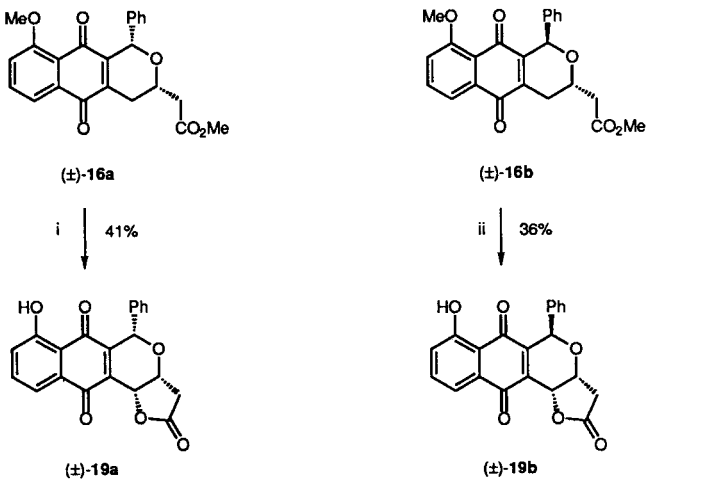
Scheme 4

derivatives containing predominantly the *trans*-isomer (15:85; *cis*/*trans*), which was oxidized quantitatively with CAN to give the corresponding mixture of naphthoquinones **16a** and **b** (15:85). Further fractional crystallization from acetonitrile yielded the pure (±)-*trans*-isomer **16b** in 76% (Scheme 3).

A mechanism consistent with these results suggests that the pure (±)-*cis*-ester **16a** was formed as the kinetically controlled product after fractional crystallization of the diastereomeric mixture. Conversely, the pure (±)-*trans* ester **16b** was formed as the thermodynamically controlled product due to equilibration. To complete our investigation, reduction of pure (±)-*cis*-**16a** isomer with sodium dithionite, followed by subsequent acid catalyzed epimerization, afforded mainly the thermodynamically more stable *trans* form (85:15), which led to pure (±)-*trans*-isomer **16b** after oxidation (CAN) and subsequent fractional crystallization (Scheme 4).

The relative configuration of the dihydropyran ring in quinones **16a** and **b** follows from the analysis of the ^1H NMR spectra (Table 2), in particular the long range coupling constants between allylic protons. For both isomers large coupling constants ($J_{3-4\Psi a} = 10.5–11$ Hz) indicate the axial position of H-C(3) and consequently the equatorial position of the substituent at C(3). Relatively high homoallylic couplings ($J_{1-4\Psi a} = 3.5–4$ Hz and $J_{1-4\Psi eq} = 2.5$ Hz) for H-C(1) in the spectrum of **16a**, unequivocally show its pseudoaxial position and consequently the *cis* configuration of the dihydropyran substituents. On the other hand, smaller values of H-C(1) homoallylic couplings observed for **16b** ($J_{1-4\Psi a} = 1.8$ Hz and $J_{1-4\Psi eq} = 0$ Hz) prove its *trans* configuration.

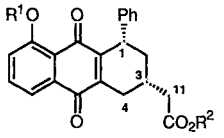
Both **16a** and **b** were demethylated with BCl_3 to give pure (±)-*cis*-**17a** (95%) and pure (±)-*trans*-**17b** (72%), respectively. Saponification of the methyl esters **17a** and **17b** with lithium hydroxide in aqueous THF afforded the corresponding racemic acids, i.e. **18a** (70%) and **18b**



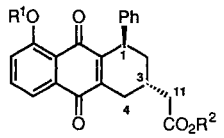
i : a) BCl_3, CH_2Cl_2, (→ **17a**, 95%) ; b) LiOH, THF-H_2O (5:1), (→ **18a**, 70%) ; c) MeOH, pyridine, O_2, Δ (60%).
ii : a) BCl_3, CH_2Cl_2, (→ **17b**, 72%) ; b) LiOH, THF-H_2O (5:1), (→ **18b**, 79%) ; c) MeOH, pyridine, O_2, Δ (59%).

Scheme 5

Table 2. ^{1}H NMR Spectral Data (J, Hz) of **16a, b, 17a, b** and **18a, b**



16a: $R^1 = R^2 = Me$
17a: $R^1 = H$, $R^2 = Me$
18a: $R^1 = R^2 = H$

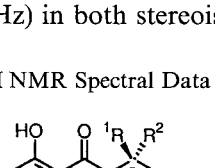


16b: $R^1 = R^2 = Me$
17b: $R^1 = H$, $R^2 = Me$
18b: $R^1 = R^2 = H$

	$J_{1-4\psi ax}$	$J_{1-4\psi eq}$	$J_{3-4\psi ax}$	$J_{3-4\psi eq}$	J_{3-11}	$J_{3-11'}$	$J_{11-11'}$	$J_{4\psi ax-4\psi ax}$
16a	3.50	2.50	11.00	2.50	6.50	7.50	16.00	18.00
16b	1.80		10.50	3.50	6.00	7.50	16.50	19.00
17a	4.00	2.50	10.50	2.50	6.00	7.00	16.00	18.00
17b	1.80		10.50	3.50	6.00	7.50	16.00	19.00
18a	4.00	2.50	10.50	2.50	6.00	7.00	16.00	18.00
18b	1.80		10.50	3.50	6.00	7.50	16.00	19.00

(79%). In the final stage, oxidative cyclization in methanol/pyridine gave the desired derivatives **19a** (61%) and **19b** (59%), respectively (Scheme 5). The configuration of the side chains on the pyran rings were confirmed by the ^{1}H NMR data. The value of the long range coupling constant for **19a** ($J_{5-11b} = 2.0$ Hz) clearly indicates the pseudoequatorial position of H-C(11b) and consequently the pseudoaxial position of H-C(5). Similarly the value for **19b** of $J_{5-11b} = 0$ Hz is in good agreement with the pseudoequatorial position of H-C(5) (Table 3). This is completed by the small values obtained for J_{3a-11b} (2.0–3.5 Hz) in both stereoisomers.

Table 3. ^{1}H NMR Spectral Data (J, Hz) of **19a** and **b**



19a: $R^1 = H$, $R^2 = Ph$
19b: $R^1 = Ph$, $R^2 = H$

	$J_{3-3'}$	$J_{3'-3a}$	J_{3a-11b}	J_{5-11b}
19a	16.00	4.25	2.00	2.00
19b	18.00	4.25	3.50	

To complete our work, **15**, **19a** and **19b** as well as many of the pyran intermediate compounds have been submitted to in vitro testing, to evaluate their anticoccidial activities. The antibacterial activities of **15**, **19a** and **19b** revealed that the naphthoquinone and the lactone portions were positively required for the appearance of stronger activities and that **15** and **19b** have the same in vitro activity as frenolicin B against *E. tenella*. Their precursors, the carboxylic acids, are comparatively less active, while the corresponding methyl esters are inactive.

All reactions which required air or moisture sensitive reactants and solvents were carried out in oven- or flame-dried glassware under a positive pressure of dry Ar. Reaction solvents and liquid reagents were purified before use. Acetone and dioxane were distilled under Ar, THF from Na with benzophenone ketyl as indicator, CH_2Cl_2 from powdered CaH_2, DMF over ninhydrin and kept over 4Å molecular sieves. All other reactants were "reagent-grade" unless described otherwise. Anal. TLC: 2.5 × 10 cm precoated TLC plates, SiO_2 60F-254, layer thickness 0.25 mm (Merck, Darmstadt, Germany). Flash chromatography (FC): Merck SiO_2 60 (70–230 Mesh ASTM).[10] Mp: Büchi-SMP-20 apparatus; uncorrected. IR: Nicolet-7199 FT-IR spectrometer; solids in KBr pellets, liquids as thin films.

^{1}H NMR Spectra: Bruker-AC-250 apparatus, at 250 MHz; in $CDCl_3$; TMS as internal standard; chemical shift of signal centers, J values are in Hz. MS: Finnigan MS9-AEI or Mat90.

Compounds **2–10** and **12–19** gave C,H analysis ± 0.3%; except **7**, C + 0.6%.

5-Methoxy-1,4-naphthoquinone (2):
A stirred mixture of juglone **1** (100 g, 0.58 mol), iodomethane (71.5 mL, 1.15 mol) and silver(I) oxide (199.6 g, 0.86 mol) in 1800 mL of CH_2Cl_2 was kept under Ar for 22 h at r.t. Some additional silver(I) oxide (20 g, 0.086 mol) and iodomethane (7.5 mL, 0.115 mol) were added and the reaction mixture was stirred for an additional 4 h. The reaction mixture was then filtered through Decalite, the cake washed with CH_2Cl_2 and the filtrate concentrated and recrystallized from EtOH to yield **2** (101 g, 93%) as a red solid. Mp 186–187 °C.

IR (KBr): ν = 1649, 1583, 1471, 1299, 1276, 1253, 1020, 855, 829, 777 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 4.02 (s, 3H), 6.68 (s, 2H), 7.32 (dd, 1H, J = 8.00, 1.00), 7.69 (t, 1H, J = 8.00), 7.75 (dd, 1H, J = 8.00, 1.00).

MS: m/z = 188 (M^+), 170 (18%), 160 (20), 159 (26), 132 (18), 131 (33), 130 (35), 114 (25), 105 (15), 104 (55), 102 (58), 76 (62), 75 (23), 63 (30), 62 (20), 50 (18), 39 (15).

5-Methoxy-1,4-naphthalenediol (3):
To a solution of sodium dithionite (826 g, 4.76 mol) in water (3 L) was added a solution of **2** (105.4 g, 0.56 mol) in EtOAc (2 L). The resulting two phase solution was stirred for 1.5 h, the organic layer separated, and the aqueous phase extracted with EtOAc. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated. The resulting solid was dried to afford **3** (105.2 g, 98.8%) as a light-brown solid. Mp > 100 °C (dec.).

IR (KBr): ν = 3362, 3274, 1637, 1610, 1415, 1269, 1049, 881, 818, 749 cm^{-1}.

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 4.05 (s, 3H), 4.67 (s, 1H), 6.58 (d, 1H, J = 8.00), 6.73 (d, 1H, J = 8.00), 6.93 (d, 1H, J = 7.00), 7.31 (t, 1H, J = 7.00), 7.70 (d, 1H, J = 7.00), 8.96 (s, 1H).

MS: m/z = 190 (M^+), 175 (85%), 147 (30), 103 (20), 91 (18).

4-Allyloxy-8-methoxy-1-naphthalenol (4):
A solution of **3** (105 g, 0.553 mol), potassium carbonate (191 g) and

allyl bromide (140.3 mL, 1.66 mol) in acetone (2 L) was heated at reflux for 18 h. The reaction mixture was filtered and evaporated to dryness. The resulting solid was dissolved in EtOAc (1 L) and washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed (EtOAc/hexane, 1:4) to afford **4** (104 g, 81%) as a yellow crystalline product. Mp 101–102°C.

IR (KBr): ν = 3381, 1631, 1600, 1407, 1262, 1233, 1061, 1028, 822, 803, 756 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 4.06 (s, 3H), 4.63 (m, 2H), 5.30 (m, 1H), 5.48 (m, 1H), 6.15 (m, 1H), 6.77 (s, 2H), 6.84 (dd, 1H, J = 7.00, 1.00), 7.34 (t, 1H, J = 7.00), 7.90 (dd, 1H, J = 7.00, 1.00), 8.96 (s, 1H).

MS: m/z = 230 (M^+), 189 (100%), 174 (20).

1-Allyloxy-4,5-dimethoxynaphthalene (5):
To a stirred solution of **4** (78.2 g, 0.34 mol) and dimethyl sulfate (290 mL, 3.04 mol) in dioxane (1.5 L) under Ar at r.t. was added 40% aq NaOH (1.3 L). The reaction mixture was stirred for an additional 18 h at r.t., diluted with water (2 L), and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried and evaporated. The residue was crystallized from MeOH to give **5** (61 g, 82%) as a beige solid. Mp 102°C.

IR (KBr): ν = 1593, 1466, 1277, 1053, 804, 755 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 3.92 (s, 3H), 3.97 (s, 3H), 4.65 (m, 2H), 5.31 (m, 1H), 5.49 (m, 1H), 6.16 (m, 1H), 6.75 (s, 2H), 6.91 (dd, 1H, J = 8.00, 1.00), 7.39 (t, 1H, J = 8.00), 7.91 (dd, 1H, J = 8.00, 1.00).

MS: m/z = 244 (M^+), 204 (15%), 203 (100), 45 (42).

(2-Allyl-4,5-dimethoxy-1-naphthyloxy)-*tert*-butyldimethylsilane (6):
A solution of **5** (56.5 g, 0.234 mol) in degassed DMF (800 mL) was heated to 140°C for 3 h under Ar. The resulting solution was cooled to r.t. whereupon DMF (200 mL), imidazole (38.1 g, 0.56 mol), *tert*-butyldimethylchlorosilane (42.2 g, 0.28 mol) and dimethylaminopyridine (DMAP; 1.42 g, 0.012 mol) were added. The reaction mixture was stirred for 48 h at r.t. and then diluted with sat. aq $NaHCO_3$ (500 mL). The mixture was then extracted with Et_2O, the organic layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed (EtOAc/hexane, 1:4) to afford **6** (79.8 g, 95%) as a yellow oil.

IR (film): ν = 2955, 2930, 2858, 1600, 1509, 1387, 1261, 1073, 835, 780 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 0.142 (s, 6H), 1.10 (s, 9H), 3.52 (m, 2H), 3.90 (s, 3H), 3.95 (s, 3H), 5.12 (m, 2H), 5.95 (m, 1H), 6.66 (s, 1H), 6.80 (dd, 1H, J = 8.00, 1.00), 7.32 (t, 1H, J = 8.00), 7.65 (dd, 1H, J = 8.00, 1.00).

MS: m/z = 58 (M^+), 260 (50%), 73 (100), 59 (23).

3-[1-*tert*-Butyldimethylsiloxy-4,5-dimethoxy-2-naphthyl]-1,2-propanediol (7):
To a stirred mixture of **6** (79.5 g, 0.22 mol) and NMO (60.2 g, 0.45 mol) in acetone (890 mL) and water (120 mL), was added a solution of osmium tetroxide (3 g, 11 mmol) in *t*-BuOH (120 mL) over 10 min. After 2 h at r.t., the reaction mixture was cooled to 0°C and sat. aq sodium hydrogen sulfite (600 mL) and EtOAc (500 mL) were added and the stirring was continued for an additional 15 min. The solution was filtered through Decalite, brine was added, and the aqueous phase extracted with EtOAc. The combined organic layers were washed with brine, dried and evaporated. The residue was crystallized from Et_2O/hexane (1:5) to give **7** (76.5 g, 88%) as a white solid. Mp 87–88°C.

IR (KBr): ν = 3399, 2929, 2857, 1599, 1509, 1466, 1387, 1262, 1072, 834, 780 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 0.142 (s, 3H), 0.156 (s, 3H), 1.09 (s, 9H), 2.11 (m, 2H), 2.11 (s, 2H), 3.45 (dd, 1H, J = 12.00, 6.00), 3.60 (dd, 1H, J = 12.00, 4.00), 3.93 (s, 3H), 3.97 (s, 3H), 4.00 (m, 1H), 6.66 (s, 1H), 6.83 (dd, 1H, J = 8.00, 1.00), 7.35 (t, 1H, J = 8.00), 7.63 (dd, 1H, J = 8.00, 1.00).

MS: m/z = 392 (M^+), 291 (18%), 260 (15), 217 (23), 75 (55), 73 (100), 59 (15).

1-*tert*-Butyldimethylsiloxy-4,5-dimethoxy-2-naphthaleneacetaldehyde (8):
To a stirred solution of **7** (38.25 g, 97.4 mmol) in MeOH (320 mL) at −5°C under Ar, was added lead(IV) tetraacetate (47.55 g, 0.107 mol) portionwise while maintaining the temperature below 0°C. The resulting mixture was stirred for 1.5 h at −5°C, concentrated in vacuo to half its volume and diluted with EtOAc. The resulting solution was then washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed (EtOAc/hexane, 1:1) and crystallized from Et_2O/hexane (1:5) to yield **8** (27.89, 79%) as a white solid. Mp 64–65°C.

IR (film): ν = 1720, 1600, 1506, 1385, 1258, 1066, 906, 830, 766 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 0.13 (s, 6H), 1.10 (s, 9H), 3.78 (d, 2H, J = 2.50), 3.92 (s, 3H), 3.97 (s, 3H), 6.55 (s, 1H), 6.86 (dd, 1H, J = 8.00, 1.00), 7.36 (t, 1H, J = 8.00), 7.66 (dd, 1H, J = 8.00, 1.00), 9.70 (t, 1H, J = 2.50).

MS: m/z = 360 (M^+), 303 (50%), 288 (25), 272 (25), 75 (25), 73 (100), 59 (15).

Methyl *rac*-4-[1-(*tert*-Butyldimethylsiloxy)-4,5-dimethoxy-2-naphthyl]-3-hydroxybutyrate (9):
To a stirred solution of **8** (20 g, 56 mmol) in CH_2Cl_2 (200 mL) cooled to −78°C under Ar, was added dropwise a solution of 1.0 M titanium(IV) chloride in CH_2Cl_2 (61 mL, 61 mmol) over 30 min. A solution of *tert*-butyl(1-methoxyvinyloxy)dimethylsilane (14.63 g, 77 mmol) in CH_2Cl_2 (50 mL) was added over 30 min. After 2 h of stirring at −78°C, sat. aq $NaHCO_3$ was slowly added to the mixture and the reaction was brought to r.t. The reaction mixture was subsequently filtered through Decalite, the organic phase was separated, washed with brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed (EtOAc/hexane, 1:1) and crystallized from hexane to give **9** (12.3 g, 51%) as a white solid. Mp 82–83°C.

IR (film): ν = 3528, 1722, 1599, 1510, 1462, 1381, 1262, 1072, 911, 832, 757 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 0.13 (s, 3H), 0.16 (s, 3H), 1.09 (s, 9H), 2.42 (m, 2H), 2.97 (m, 3H), 3.92 (s, 3H), 3.96 (s, 3H), 4.32 (m, 1H), 6.67 (s, 1H), 6.83 (dd, 1H, J = 8.00, 1.00), 7.33 (t, 1H, J = 8.00), 7.63 (dd, 1H, J = 8.00, 1.00).

MS: m/z = 434 (M^+), 304 (15%), 303 (60), 275 (20), 151 (20), 75 (35), 73 (100), 59 (15).

Methyl *rac*-4-(1,4-Dihydro-5-methoxy-1,4-dioxo-2-naphthyl)-3-hydroxybutyrate (10):
To a solution **9** (2.8 g, 6.4 mmol) in MeCN (60 mL), cooled to 0°C, was added dropwise a solution of CAN (10.6 g, 19.3 mmol) in water (60 mL). The reaction was allowed to warm to r.t., was stirred for 15 min at r.t., diluted with brine and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed (EtOAc/hexane, 2:1) to afford **10** (1.65 g, 83.5%) as a yellow solid. Mp 127°C.

IR (KBr): ν = 3466, 1737, 1660, 1258, 1148, 1038, 973, 777 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 2.53 (dd, 1H, J = 17.00, 8.00), 2.62 (dd, 1H, J = 17.00, 4.00), 2.65 (ddd, 1H, J = 14.00, 8.00, 1.00), 2.77 (ddd, 1H, J = 14.00, 4.50, 1.00), 3.17 (d, 1H, J = 4.50), 3.72 (s, 3H), 4.00 (s, 3H), 4.31 (m, 1H), 6.84 (t, 1H, J = 1.00), 7.29 (dd, 1H, J = 8.00, 1.00), 7.66 (t, 1H, J = 8.00), 7.78 (dd, 1H, J = 8.00, 1.00).

MS: m/z = 304 (M^+), 272 (15%), 230 (23), 203 (25), 202 (100), 174 (18), 173 (22), 159 (16), 131 (18), 115 (35), 103 (22), 77 (18), 76 (28), 71 (40), 61 (15), 43 (40), 39 (16).

Methyl *rac*-4-(1,4-Dihydroxy-5-methoxy-2-naphthyl)-3-hydroxybutyrate (11):
To a solution of **10** (1.74 g, 5.72 mmol) in a 1:1 solution of dioxane and Et_2O (63 mL) cooled to 0°C was added 18% aq HCl (20.9 mL), then zinc (3.5 g) portionwise over 30 min. The reaction was allowed to warm to r.t., treated with brine and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and evaporated. The

residue was crystallized from Et_2O to give **11** (1.47 g, 84%) as a beige solid. Mp > 150 °C (dec).

IR (KBr): ν = 3377, 1714, 1619, 1516, 1255, 1171, 1062, 846, 746 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 2.53 (m, 2H), 2.78 (ddd, 1H, J = 14.00, 6.50, 1.00), 3.10 (ddd, 1H, J = 14.00, 2.80, 1.00), 3.70 (s, 3H), 4.04 (s, 3H), 4.34 (d, 1H, J = 1.00), 4.48 (m, 1H), 6.54 (s, 1H), 6.78 (dd, 1H, J = 8.00, 1.00), 7.31 (t, 1H, J = 8.00), 7.90 (dd, 1H, J = 8.00, 1.00), 8.38 (s, 1H), 8.87 (s, 1H).

MS: m/z = 306 (M^+), 288 (30%), 257 (15), 256 (25), 232 (30), 203 (60), 189 (26), 160 (20), 135 (22), 131 (25), 115 (32), 103 (18), 77 (24), 71 (22), 59 (15), 43 (40), 39 (15).

Methyl *rac*-(3,4-Dihydro-1,1-dimethyl-9-methoxy-5,10-dioxo-1*H*-naphtho[2,3-*c*]pyran-3-yl)acetate (12):

Gaseous HCl was bubbled through 150 mL of Et_2O maintained at r.t. for 5 min using a disposable pipet. To the resulting solution, **11** (1.99 g, 6.49 mmol) was added all at once. To this suspension was added acetone (0.97 mL, 0.013 mol), and the reaction mixture was stirred at r.t. After total consumption of **11**, the reaction mixture was treated with ice, brine and EtOAc. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was diluted with MeCN (80 mL) and treated with CAN (10.7 g, 0.02 mol) dissolved in water (80 mL). After 5 min stirring at r.t., the reaction was treated with brine and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed (EtOAc/hexane, 1:2) and crystallized from MeCN to afford **12** (1.95 g, 87%) as an orange solid. Mp 190–192 °C.

IR (KBr): ν = 2965, 2928, 1731, 1656, 1622, 1587, 1474, 1437, 1276, 1034, 711 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.57 (s, 3H), 1.68 (s, 3H), 2.27 (dd, 1H, J = 18.50, 11.00), 2.61 (dd, 1H, J = 15.00, 5.50), 2.66 (d, 1, J = 15.00, 7.75), 2.85 (dd, 1H, J = 18.50, 3.00), 3.74 (s, 3H), 4.01 (s, 3H), 4.21 (m, 1H), 7.28 (dd, 1H, J = 5.50, 1.00), 7.63 (t, 1H, J = 5.50), 7.78 (dd, 1H, J = 5.50, 1.00).

MS: m/z = 344 (M^+), 330 (20%), 312 (45), 270 (30), 269 (42), 255 (85), 227 (55), 115 (15), 77 (18), 76 (25), 59 (15), 43 (64).

Methyl *rac*-(3,4-Dihydro-9-hydroxy-1,1-dimethyl-5,10-dioxo-1*H*-naphtho[2,3-*c*]pyran-3-yl)acetate (13):

To a solution of **12** (1.6 g, 4.64 mmol) in CH_2Cl_2 (50 mL) cooled to − 78 °C under Ar, was added dropwise 1.0 M boron(III) chloride in CH_2Cl_2 (5.7 mL, 5.71 mmol). After stirring for 20 min at − 78 °C, the reaction mixture was allowed to warm to r.t., and was maintained at r.t. for 15 min. The mixture was poured into a mixture of ice (1.5 g), $NaHCO_3$ (15 g) and EtOAc (30 mL). The organic layer was washed with brine, dried and evaporated. The residue was chromatographed (EtOAc/hexane, 3:7), to give **13** (1.48 g, 97%) as an orange solid. Mp 89–90 °C.

IR (KBr): ν = 3461, 2981, 2842, 1738, 1634, 1600, 1459, 1276, 1155, 1035, 771, 705 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.60 (s, 3H), 1.68 (s, 3H), 2.27 (dd, 1H, J = 18.50, 11.00), 2.61 (dd, 1H, J = 15.00, 5.50), 2.66 (dd, 1H, J = 15.00, 7.75), 2.85 (dd, 1H, J = 18.50, 3.00), 3.74 (s, 3H), 4.21 (m, 1H), 7.26 (dd, 1H, J = 5.50, 1.00), 7.58 (t, 1H, J = 5.50), 7.61 (dd, 1H, J = 5.50, 1.00), 12.24 (s, 1H).

MS: m/z = 330 (M^+), 315 (65%), 298 (50), 257 (40), 255 (50), 228 (40), 213 (50), 121 (35), 92 (20), 77 (16), 65 (18), 59 (20), 43 (90), 39 (20).

***rac*-(3,4-Dihydro-9-hydroxy-1,1-dimethyl-5,10-dioxo-1*H*-naphtho[2,3-*c*]pyran-3-yl)acetic Acid (14):**

To a solution of **13** (1.2 g, 3.63 mmol) in MeOH (160 mL) was added 0.16 N aq KOH (160 mL) and the resulting purple reaction mixture was stirred at r.t. After total consumption of **13**, the solution was acidified to pH = 1–2 with 1 N aq HCl. The aqueous phase was separated and extracted with EtOAc. The combined organic layers were washed with brine, dried and evaporated. The residue was chromatographed (CH_2Cl_2/MeOH, 10:1) and crystallized from MeOH to yield **14** (1.06 g, 92%) as an orange solid. Mp 210–212 °C.

IR (KBr): ν = 3431, 3015, 2976, 2937, 2685, 2574, 1713, 1666, 1636, 1600, 1548, 1271, 1101, 1036, 836, 769 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.60 (s, 3H), 1.68 (s, 3H), 2.27 (dd, 1H, J = 18.50, 11.00), 2.61 (dd, 1H, J = 15.00, 5.50), 2.66 (dd, 1H, J = 15.00, 7.75), 2.85 (dd, 1H, J = 18.50, 3.00), 3.74 (s, 3H), 4.21 (m, 1H), 7.26 (dd, 1H, J = 5.50, 1.00), 7.58 (t, 1H, J = 5.50), 7.61 (dd, 1H, J = 5.50, 1.00), 12.24 (s, 1H).

MS: m/z = 316 (M^+), 301 (100%), 298 (30), 283 (22), 256 (20), 255 (35), 241 (100), 213 (40), 121 (35), 92 (20), 77 (15), 63 (18), 55 (15), 43 (95), 39 (18).

***rac*-3,3a,15,11b-Tetrahydro-7-hydroxy-5,5-dimethyl-2*H*-furo[3,2-*b*]-naphtho[2,3-*d*]pyran-2,6,11-trione (15):**

A solution of **14** (0.7 g, 2.22 mmol) in MeOH (150 mL) and pyridine (0.49 mL) was brought to reflux while passing a gentle stream of oxygen through the solution. After 12 h at reflux, the solution was cooled to r.t. and the solvent evaporated. The residue was chromatographed (EtOAc/hexane, 2:1) and crystallized from MeOH, to afford **15** (0.52 g, 52%) as a yellow solid. Mp 225 °C.

IR (KBr): ν = 3431, 2980, 2938, 1774, 1670, 1643, 1616, 1577, 1458, 1261, 1177, 1044, 779, 725 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 1.66 (s, 6H), 2.70 (d, 1H, J = 18.00), 2.95 (dd, 1H, J = 18.00, 4.50), 4.57 (dd, 1H, J = 4.50, 2.50), 5.28 (d, 1H, J = 2.50), 7.30 (dd, 1H, J = 7.00, 1.50), 7.65 (t, 1H, J = 7.00), 7.67 (dd, 1H, J = 7.00, 1.50), 11.96 (s, 1H).

MS: m/z = 314 (M^+), 299 (100%), 271 (20), 257 (20), 229 (50), 201 (30), 115 (18), 92 (18), 77 (15), 55 (60), 43 (100), 39 (20).

Methyl *rac-cis*-(3,4-Dihydro-9-methoxy-5,10-dioxo-1-phenyl-1*H*-naphtho[2,3-*c*]pyran-3-yl)acetate (16a):

Gaseous hydrochloric acid was bubbled through Et_2O (80 mL) maintained at r.t. for 5 min. To this solution, **11** (1.34 g, 4.37 mmol) was added all at once. To the resulting suspension, cooled to − 5 °C, was added benzaldehyde (0.91 mL, 8.7 mmol) in one addition. After stirring for 5 min at − 5 °C, the reaction mixture was treated with ice, brine and EtOAc. The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was diluted with MeCN (50 mL) and treated with a solution of CAN (7.15 g, 13.65 mmol) in water (50 mL). After 5 min stirring at r.t., the yellow suspension was filtered, leading to a yellow solid (1.63 g) which contained predominantly the *cis*-isomer (*cis*/*trans*, 94:6). The filtrate was treated with brine and extracted with EtOAc. The organic layer was dried and evaporated to give a yellow solid (0.45 g; *cis*/*trans*, 94:6). The combined residue was chromatographed (EtOAc/hexane, 1:1) and crystallized from MeCN to afford pure (±)-*cis*-isomer **16a** (1.29 g, 75%; > 99% isomeric purity) as a yellow solid. Mp 246–247 °C.

IR (KBr): ν = 3446, 3030, 2953, 2890, 1735, 1655, 1584, 1471, 1269, 1151, 1053, 956, 745 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 2.46 (ddd, 1H, J = 18.00, 11.00, 3.50), 2.64 (dd, 1H, J = 16.00, 6.50), 2.78 (dd, 1H, J = 16.00, 6.50), 2.98 (dt, 1H, J = 18.00, 2.50), 3.69 (s, 3H), 3.85 (s, 3H), 4.13 (m, 1H), 5.81 (dd, 1H, J = 3.50, 2.50), 7.21 (dd, 1H, J = 5.50, 1.00), 7.30 (m, 5H), 7.62 (t, 1H, J = 5.50), 7.75 (dd, 1H, J = 5.50, 1.00).

MS: m/z = 392 (M^+), 319 (17%), 137 (15), 105 (25), 95 (15), 81 (58), 69 (100), 55 (16), 41 (30).

Methyl *rac-trans*-(3,4-Dihydro-9-methoxy-5,10-dioxo-1-phenyl-1*H*-naphtho[2,3-*c*]pyran-3-yl)acetate (16b):

Gaseous hydrochloric acid was bubbled through Et_2O (250 mL) maintained at r.t. for 5 min. To this solution, **11** (0.59 g, 1.94 mmol)was added all at once. To the resulting suspension cooled to − 5 °C was added benzaldehyde (0.41 mL, 3.89 mmol). The reaction mixture was allowed to warm to r.t., and was stirred for 2 h. The reaction mixture was then treated with ice (1.5 g), brine (15 mL) and EtOAc (30 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was diluted with MeCN (100 mL) and treated with a solution of CAN (3.2 g, 5.83 mmol) in water (100 mL). After 5 min stirring at r.t., the yellow suspension was filtered, leading to a yellow solid (0.412 g) which contained predominantly the *trans*-isomer (*cis*/*trans*, 15:85). The filtrate was treated with brine and extracted with EtOAc. The organic layer

was dried ($MgSO_4$) and evaporated to give a yellow solid (0.25 g; *cis*/*trans*, 15:85). The combined residue was chromatographed (EtOAc/hexane, 1:1) and recrystallized from MeCN to afford pure (±)-*trans*-isomer **16b** (0.58 g, 76%; > 99% isomeric purity) as a yellow solid. Mp 215–217 °C.

IR (KBr): ν = 3441, 3029, 2952, 1744, 1655, 1588, 1479, 1447, 1278, 1208, 1158, 1055, 1038, 952, 760, 709 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 2.46 (ddd, 1 H, J = 19.00, 10.50, 1.80), 2.52 (dd, 1 H, J = 16.50, 6.00), 2.59 (dd, 1 H, J = 16.50, 7.50), 2.85 (dd, 1 H, J = 19.00, 3.50), 3.57 (s, 3 H), 3.93 (s, 3 H), 4.00 (m, 1 H), 5.99 (d, 1 H, J = 1.80), 7.28 (m, 6 H), 7.69 (t, 1 H, J = 5.50), 7.81 (dd, 1 H, J = 5.50, 1.00).

MS: m/z = 392 (M^+), 332 (20%), 319 (57), 315 (16), 255 (25), 105 (100), 77 (30), 76 (16), 55 (15), 43 (16).

Methyl *rac-cis*-(3,4-Dihydro-9-hydroxy-5,10-dioxo-1-phenyl-1*H*-naphtho[2,3-*c*]pyran-3-yl)acetate (17a):

The same procedures was used as for **13** starting from **16a** (1.0 g, 2.55 mmol) in CH_2Cl_2 (60 mL). After crystallization from Et_2O, pure (±)-*cis*-isomer **17a** (0.93 g, 95%) was isolated as an orange solid. Mp 198–201 °C.

IR (KBr): ν = 3435, 3039, 2956, 2894, 1727, 1641, 1616, 1492, 1452, 1269, 1155, 1050, 747, 698 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 2.54 (ddd, 1 H, J = 18.00, 10.50, 4.00), 2.64 (dd, 1 H, J = 16.00, 6.00), 2.80 (dd, 1 H, J = 16.00, 7.00), 3.01 (dt, 1 H, J = 18.00, 2.50), 3.70 (s, 3 H), 4.13 (m, 1 H), 5.78 (dd, 1 H, J = 4.00, 2.50), 7.18 (dd, 1 H, J = 5.50, 1.00), 7.31 (m, 5 H), 7.58 (t, 1 H, J = 5.50), 7.64 (dd, 1 H, J = 5.50, 1.00), 11.65 (s, 1 H).

MS: m/z = 378 (M^+), 318 (18), 305 (28), 304 (15), 276 (16), 105 (100), 77 (32).

Methyl *rac-trans*-(3,4-Dihydro-9-hydroxy-5,10-dioxo-1-phenyl-1*H*-naphtho[2,3-*c*]pyran-3-yl)acetate (17b):

The same procedure was used as for **13** starting from **16b** (1.58 g, 4.03 mmol) in CH_2Cl_2 (80 mL). After crystallization from Et_2O, pure (±)-*trans*-isomer **17b** (1.09 g, 72%) was isolated as an orange solid. Mp 188–190 °C.

IR (KBr): ν = 3447, 3032, 2950, 1743, 1645, 1620, 1492, 1455, 1274, 1156, 1043, 756, 702 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 2.50 (ddd, 1 H, J = 19.00, 10.50, 1.80), 2.56 (dd, 1 H, J = 16.00, 6.00), 2.61 (dd, 1 H, J = 16.00, 7.50), 2.88 (dd, 1 H, J = 19.00, 3.50), 3.57 (s, 3 H), 4.00 (m, 1 H), 5.96 (d, 1 H, J = 1.80), 7.23 (dd, 1 H, J = 5.50, 1), 7.29 (m, 5 H), 7.62 (t, 1 H, J = 5.50), 7.69 (dd, 1 H, J = 5.50, 1.00), 11.62 (s, 1 H).

MS: m/z = 378 (M^+), 318 (20%), 305 (30), 276 (15), 105 (100), 77 (25).

***rac-cis*-(3,4-Dihydro-9-hydroxy-5,10-dioxo-1-phenyl-1*H*-naphtho-[2,3-*c*]pyran-3-yl)acetic Acid (18a):**

The same procedure was used as for **14** starting from **17a** (0.65 g, 1.71 mmol) in THF/H_2O (5:1, 150 mL) with LiOH · H_2O (0.25 g, 5.98 mmol). Pure (±)-*cis*-isomer **18a** (0.44 g, 70%) was isolated as an orange solid. Mp 270–276 °C.

IR (KBr): ν = 3452, 3061, 3007, 2923, 2859, 2595, 2595, 1694, 1639, 1614, 1575, 1480, 1451, 1280, 1221, 1178, 1098, 1048, 734, 695 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 2.54 (ddd, 1 H, J = 18.00, 10.50, 4.00), 2.64 (dd, 1 H, J = 16.00, 6.00), 2.80 (dd, 1 H, J = 16.00, 7.00), 3.01 (dt, 1 H, J = 18.00, 2.50), 4.12 (m, 1 H), 5.78 (dd, 1 H, J = 4.00, 2.50), 7.18 (dd, 1 H, J = 5.50, 1.00), 7.31 (m, 5 H), 7.58 (t, 1 H, J = 5.50), 7.64 (dd, 1 H, J = 5.50, 1.00), 11.64 (s, 1 H).

MS: m/z = 364 (M^+), 318 (18%), 305 (25), 291 (19), 105 (100), 77 (40).

***rac-trans*-(3,4-Dihydro-9-hydroxy-5,10-dioxo-1-phenyl-1*H*-naphtho-[2,3-*c*]pyran-3-yl)acetic Acid (18b):**

The same procedure was used as for **14** starting from **17b** (1.06 g, 2.8 mmol) in THF/H_2O (5:1, 250 mL) with LiOH · H_2O (0.42 g, 9.8 mmol). Pure (±)-*trans*-isomer **18b** (0.805 g, 79%) was isolated as a yellow solid. Mp 227–232 °C.

IR (KBr): ν = 3418, 3088, 3032, 2919, 1708, 1645, 1619, 1575, 1492, 1455, 1280, 1244, 1187, 1167, 1045, 754, 700 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 2.50 (ddd, 1 H, J = 19.00, 10.50, 1.80), 2.56 (dd, 1 H, J = 16.00, 6.00), 2.61 (dd, 1 H, J = 16.00, 7.50), 2.88 (dd, J = 19.00, 3.50), 4.00 (m, 1 H), 5.96 (d, 1 H, J = 1.80), 7.23 (dd, 1 H, J = 5.50, 1.00), 7.29 (m, 5 H), 7.62 (t, 1 H, J = 5.50), 7.69 (dd, 1 H, J = 5.50, 1.00), 11.80 (s, 1 H).

MS: m/z = 364 (M^+), 318 (18%), 305 (20), 291 (19), 121 (20), 105 (100), 92 (15), 77 (40), 69 (20), 55 (18), 43 (30), 41 (15).

***rac-cis*-3,3a,5,11b-Tetrahydro-7-hydroxy-5-phenyl-2*H*-furo[3,2-*b*]-naphtho[2,3-*d*]pyran-2,6,11-trione (19a):**

The same procedure was used as for **15** starting from **18a** (0.29 g, 0.80 mmol) in MeOH (130 mL) with pyridine (0.69 mL, 8.0 mmol). Pure (±)-*cis*-isomer **19a** (0.17 g, 60.7%) was isolated as a yellow solid. Mp 217–222 °C.

IR (KBr): ν = 3434, 3064, 3036, 2927, 1800, 1669, 1647, 1619, 1574, 1490, 1281, 1144, 1065, 1011, 880, 739, 699 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 2.77 (d, 1 H, J = 16.00), 2.95 (dd, 1 H, J = 16.00, 4.25), 4.54 (dd, 1 H, J = 4.25, 2.00), 5.38 (t, 1 H, J = 2), 5.69 (d, 1 H, J = 2.00), 7.24 (dd, 1 H, J = 5.50, 1.50), 7.35 (s, 5 H), 7.58 (t, 1 H, J = 5.50), 7.64 (dd, 1 H, J = 5.50, 1.50), 11.39 (s, 1 H).

MS: m/z = 362 (M^+), 319 (20%), 318 (100), 317 (22), 316 (24), 300 (18), 275 (20), 241 (20), 240 (18), 189 (15), 127 (15), 121 (22), 105 (92), 97 (24), 83 (28), 77 (50), 69 (38), 57 (60), 55 (48), 43 (80), 41 (30), 29 (18).

***rac-trans*-3,3a,5,11b-Tetrahydro-7-hydroxy-5-phenyl-2*H*-furo-[3,2-*b*]naphtho[2,3-*d*]pyran-2,6,11-trione (19b):**

The same procedure was used as for **15** starting from **18b** (0.10 g, 0.274 mmol) in MeOH (50 mL) with pyridine (0.22 mL, 2.74 mmol). Pure (±)-*trans*-isomer **19b** (0.058 g, 59%) was isolated as a yellow solid. Mp 217–222 °C.

IR (KBr): ν = 3432, 3063, 3031, 1788, 1655, 1624, 1619, 1577, 1493, 1456, 1286, 1242, 1157, 1046, 750, 700 cm^{-1}.

^1H NMR ($CDCl_3$, 250 MHz): δ = 2.67 (d, 1 H, J = 18.00), 2.87 (dd, 1 H, J = 18.00, 4.25), 3.37 (dd, 1 H, J = 4.25, 3.50), 5.30 (d, 1 H, J = 3.50), 6.05 (s, 1 H), 7.30 (m, 6 H), 7.70 (t, 1 H, J = 5.50), 7.78 (dd, 1 H, J = 5.50, 1.50), 11.68 (s, 1 H).

MS: m/z = 362 (M^+), 319 (20%), 318 (80), 317 (28), 316 (40), 291 (20), 275 (20), 240 (20), 189 (20), 127 (15), 121 (25), 105 (100), 92 (24), 91 (15), 77 (64), 69 (25), 55 (38), 43 (58), 41 (20).

We wish to thank our colleagues from F. Hoffmann-La Roche AG, for IR spectra (Mr. A. Bubendorf), NMR (Dr. W. Arnold), MS (Dr. W. Vetter and Mr. W. Meister) and elemental analyses (Dr. St. Müller and Mr. G. Nein). We would also like to thank M. Visnick for his pioneering work which we used throughout as described in the synthetic schemes above.

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