3. Naphthopyranquinone Antibiotics: Novel Enantioselective Syntheses of Frenolicin B and Some of Its Stereoisomers

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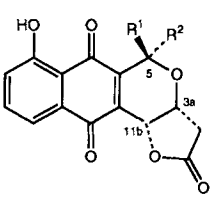
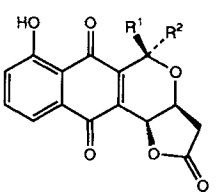
Two new enantioselective syntheses of the naphthopyranquinone antibiotic frenolicin B (**1**), of its enantiomer **2**, and of its diastereoisomers **3** and **4** were accomplished using two different routes from optically active β-hydroxy esters (*R*)- and (*S*)-**11** and **18**. β-Hydroxy esters (*R*)- and (*S*)-**11** were prepared stereoselectively from optically active sulfenylacetates (*S*)- and (*R*)-**10**, respectively (*Scheme 2, Method A*). Alternatively, compound **18** was obtained in excellent yield by enantioselective hydrogenation of the corresponding β-keto ester **17**, using a chiral ruthenium-complex catalyst (*Scheme 3, Method B*). Subsequently, compounds (*S*)-**11** and **18** were transformed into frenolicin B (**1**). In analogy, stereoisomers **2**–**4** were prepared from (*S*)- and (*R*)-**11** in good yields.

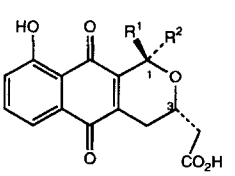
1. Introduction. – Frenolicin B (**1**), a metabolite of *Streptomyces roseofulvus*, is a member of an important family of naturally occurring naphthopyranquinones which contain an isochroman and a 1,4-naphthoquinone moiety. The stereoisomers **2**–**4** of **1** and also kalafungin (**5**), deoxyfrenolicin (**6**), isoeleutherin (**7**), and eleutherin (**8**) (*Fig. 1*) belong to this same family, all of which show biological activity as antibiotics, anti-



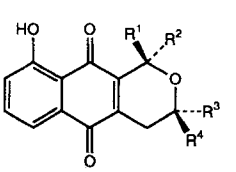
1 R^1 = Pr, R^2 = H, Frenolicin B
3 R^1 = H, R^2 = Pr
5 R^1 = Me, R^2 = H, Kalafungin



2 R^1 = H, R^2 = Pr
4 R^1 = Pr, R^2 = H



6 R^1 = Pr, R^2 = H, Deoxyfrenolicin



7 R^1 = R^3 = Me, R^4 = H, Isoeleutherin
8 R^1 = R^4 = Me, R^2 = R^3 = H, Eleutherin

Fig. 1. *Natural naphthopyranquinones containing an isochroman and a 1,4-naphthoquinone moiety*

mycotics and, in some cases, also antineoplastic activity [1] [2]. Their mode of action has not been established yet. It is believed that a bioreductive alkylation is involved since these compounds show the structural features which seemed necessary to allow them to function as precursors to electrophilic quinonemethides, subsequent to *in vivo* reduction [3] [4].

The broad spectrum of biological activities of this growing family of naphthopyranquinone antibiotics, as well as the potentiating effect of frenolicin B (**1**) and of diverse analogs on ionophoric compounds used for the treatment of coccidiosis in animals, led to numerous syntheses of these bioactive compounds [5–10]. The absolute configuration of **1** has been assigned by chemical and spectral (optical rotatory dispersion spectrum) data by comparison with those of isoeleutherin (**7**) [11]. The configuration of **7** has previously been shown to be (1*R*,3*R*) [12] [13]. In more recent studies, some suitable crystals of frenolicin B could be obtained for an X-ray analysis [14]. These structural data confirmed the original assignment of the absolute configuration as being (3a*R*,5*R*,11b*R*).

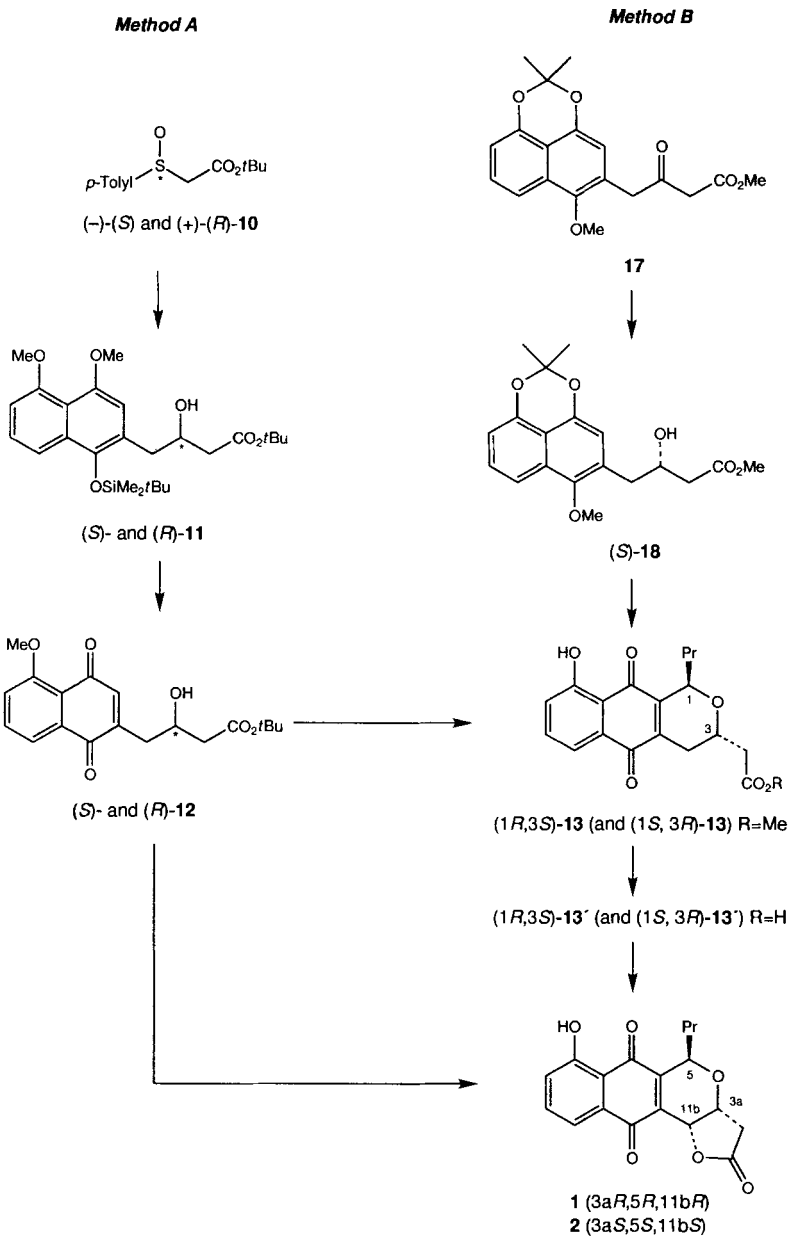
Enantioselective syntheses in this area have been scarce [15][1]). Recently, we reported the synthesis of racemic analogs of frenolicin B [16], starting from the commercially available juglone (**15**). We wish now to disclose the full details of two enantioselective total syntheses of frenolicin B (**1**) and of its enantiomer **2**, as well as of the two diastereoisomers **3** and **4**, from optically active β-hydroxy esters **11** and **18**. These latter ones were generated from sulfenyl esters **10** (*Method A*) and from β-keto ester **17**, respectively (*Method B*) (*Scheme 1*).

2. Synthesis of Frenolicin B (1) and of Stereoisomers 2–4 from Optically Active Sulfinylacetates 10. – The synthetic utility of organic sulfur compounds has recently been reviewed, and survey dealing with some general aspects of asymmetric synthesis have been published [17] [18]. Recently, we have reported the synthesis of racemic analogs of frenolicin B from commercially available juglone (**15**; see below) *via* a *Mukaiyama* aldol condensation of naphthaleneacetaldehyde **14** with *tert*-butyl dimethylsilyl ketene acetal of *tert*-butyl acetate [19]. Now, the optically pure natural frenolicin B (**1**) and its stereoisomers **2–4** were synthesized by use of (+)-(*R*)- and (−)-(*S*)-*tert*-butyl (4-tolylsulfinyl)-acetate ((+)-(*R*)- and (−)-(*S*)-**10**, resp.) in the highly stereoselective aldol-type condensations [20] [21] of naphthaleneacetaldehyde **14** which was obtained as described previously [14] [16] (*Scheme 2*). *Andersen* [22], and *Mislow* and coworkers [23] showed that the optically active sulfoxides (−)-(*S*)- and (+)-(*R*)-**10** were readily obtained in 70 and 64% yield from the corresponding menthyl sulfinates (+)-(*R*)- and (−)-(*S*)-**9**, respectively, by S_N2 displacement of the *O*-menthyl group, using the magnesium enolate of *tert*-butyl acetate. The absolute configuration at the S-center of **10** was determined by ORD (positive *Cotton* effect at 250 nm) [23] and the enantiomeric purity easily determined by ^{1}H-NMR in the presence of a chiral europium(III) complex [24] [25]. In analogy to a literature procedure [26], the β-hydroxy esters (*S*)- and (*R*)-**11** were then prepared in 69 and 78% yield from (−)-(*S*)- and (+)-(*R*)-**10**, respectively, by condensation of naphthaleneacetaldehyde **14** in THF at −78° in the presence of *tert*-butylmagnesium bromide, followed by desulfurization with aluminium amalgam in THF/H_2O. These aldol-type condensations occur with high asymmetric induction. Enantiomer (*S*)-**11** was obtained with 96% ee from (+)-(*R*)-**9** and (*R*)-**11** with 93.5% ee from (−)-(*S*)-**9b**. These results

[1]) *Hubschwerlen* completed a chiral synthesis of frenolicin B (**1**) which also confirms the absolute configuration of this natural product [15a].

show that chemical yields and enantioselectivities are higher than for most aldol-type condensations of ester enolates. As pointed out already by *Solladie* [21], the use of a *Grignard* reagent as base, such as *t*-BuMgBr, favors the formation of highly chelated enolates but also acts as *Lewis*-acid catalyst. As described earlier, the absolute configuration of the generated *β*-hydroxy esters is easily predictable by comparison of the analyti-

Scheme 1



cal data of some known compounds [21]. Enantiomeric excess was determined with achiral columns by capillary supercritical fluid chromatography (SFC), after conversion of the enantiomeric alcohols **11** into their diastereoisomeric esters using (*S*)-*Trolox* methyl esters [27].

Subsequent oxidation of (*S*)- and (*R*)-**11** with cerium(IV) ammonium nitrate (CAN) using $MeCN/H_2O$ as solvent afforded the 1,2-naphthoquinone derivatives (*S*)- and (*R*)-**12** in 80 and 74% yield, respectively, and proceeded without any loss of enantiomeric purity, *i.e.* 96 and 93.5%, respectively (by SFC). Successive fractional recrystallization in AcOEt/hexane gave the optically pure β-hydroxy esters (*S*)- and (*R*)-**12** in 53 and 50% overall yields and with ee > 98% as determined by SFC.

The 1,4-naphthoquinone derivatives **12** were converted in quantitative yield by reduction with Zn powder in aqueous HCl solution and dioxane/Et_2O into the corresponding amorphous grey *p*-quinols. Several reports have appeared in the literature describing the condensation of *p*-quinols with aldehydes as a route to fused pyran rings [28]. *Visnick et al.* [14] indicated that with butanal under acidic conditions, a kinetic product was observed which showed a 1,3-*cis*-relationship of the alkyl groups on the formed pyran ring. Upon thermodynamic equilibration, a favorable 3.5:1 (*trans*/*cis*) diastereoisomer ratio resulted. This efficient process was used for the preparation of frenolicin B (**1**) and of its stereoisomers. Pure diastereoisomeric naphthopyranoquinones (1*R*,3*S*)- and (1*S*,3*R*)-**13** were obtained from (*S*)- and (*R*)-**12** in 35 and 49% yields, respectively, by the following sequence of reactions (without purification of the intermediates): *1*) condensation of butanal with the *p*-quinols in Et_2O saturated with gaseous HCl (23.5% in weight) at 25° for 2.5 h leading to mixtures of two stereoisomers containing predominantly the *trans* isomers (*trans*/*cis* 3.8:1), *2*) esterification of the free acids with MeOH, *3*) oxidation of the resulting products with CAN in $MeCN/H_2O$ which led in quantitative yield to the corresponding mixtures of naphthopyranquinones (3.8:1), *4*) demethylation of the methyl ether group with BCl_3 in CH_2Cl_2 at −78°, and *5*) fractional crystallization from AcOEt/hexane which afforded the desired pure *trans*-stereoisomers **13**. However, the precise details of the cyclization mechanism have not been elucidated. Nevertheless, a mechanism which would be consistent with these results [14] suggests that the pure *cis*-esters were formed by a kinetically controlled pathway. Conversely, the pure *trans*-esters **13** would then be formed as the thermodynamically controlled products (due to equilibration). It is worth noting that the described process leads to rapid equilibration of the diastereoisomers (*cis*/*trans*) with 3.8:1 ratio. The pure *trans*-esters were isolated from the reaction mixture by subsequent fractional crystallization (see above).

Melting points and spectral data (IR, ^{1}H-NMR, MS) of (1*R*,3*S*)- and (1*S*,3*R*)-**13** were identical with those of the derivative obtained by degradation of natural frenolicin B (**1**). The specific rotation of our products were in good agreement with the reported values[2]). The relative configuration of the dihydropyran ring in the quinone derivatives **13** follows from the analysis of the ^{1}H-NMR spectral data (see *Table 1*). We note in particular the long-range coupling constants between the allylic protons. For both derivatives, large coupling constants (J(3,4'ax') = 10–11 Hz) indicate the axial position of H–C(3) and consequently the equatorial position of the substituent at C(3). Small

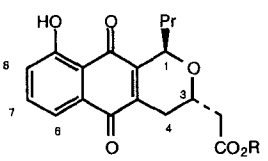
[2]) (1*R*,3*S*)-**13**: $[\alpha]_D = +107$ ($c = 0.1$, $CHCl_3$); natural derivative from **1**: $[\alpha]_D = +108$ ($c = 0.1$, $CHCl_3$); (1*S*,3*R*)-**13**: $[\alpha]_D = -108$ ($c = 0.1$, $CHCl_3$).

homoallylic coupling constants (J(1,4'ax') = 2.00 and J(1,4'eq') = 0 Hz) for H–C(1) in the spectrum of **13** unequivocally show its pseudoequatorial position and consequently the *trans*-arrangement with respect to H–C(3). The ORD spectrum of compounds **13** shown in *Fig. 2* were measured to confirm the absolute configuration of the dihydropyran moiety and also of the β-hydroxy esters **12** involved in the preparation. One would anticipate that the chirality of C(3) is not affected by the reaction conditions and that the mechanism previously established is consistent with the results. Indeed the chirality of (1*R*,3*S*)-**13** turned out to be identical to the one of the derivative obtained by degradation of natural frenolicin B (established as being (1*R*,3*S*)). The absolute configurations of the enantiomers **13** are in agreement with the ORD curves (*Fig. 2*).

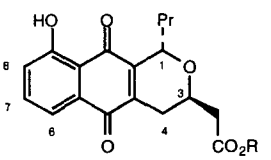
To convert the enantiomers **13** into frenolicin B (**1**) and into its diastereoisomer **3**, we first applied the procedure shown in *Scheme 1*. Saponification of the methyl ester group with lithium hydroxide (LiOH) in aqueous THF afforded the corresponding acids (1*R*,3*S*)-(92%) and (1*S*,3*R*)-**13'** (85%); next, oxidative cyclization of these products in MeOH/

Table 1. *Coupling Constants* J [Hz] *of (1*R,3S*)-***13** *and* **13'** *and (1*S,3R*)-***13** *and* **-13'**

	J(1,4'ax')	J(3,4'ax')	J(3,4'eq')	J(4'ax',4'eq')	J(6,7)	J6,8)	J(7,8)	J(3,CH_2–C(3))
(1*R*,3*S*)-**13**	2.00	10.45	3.45	19.20	7.85	1.75	7.85	
(1*R*,3*S*)-**13'**	2.00	10.45	3.50	19.20	7.85	1.75	7.85	6.35
(1*S*,3*R*)-**13**	2.00	10.45	3.45	19.20	7.85	1.80	7.85	
(1*S*,3*R*)-**13'**	2.00	10.45	3.50	19.20	7.85	1.80	7.85	6.35



(1*R*,3*S*)-**13** R=Me
(1*R*,3*S*)-**13'** R=H



(1*S*,3*R*)-**13** R=Me
(1*S*,3*R*)-**13'** R=H

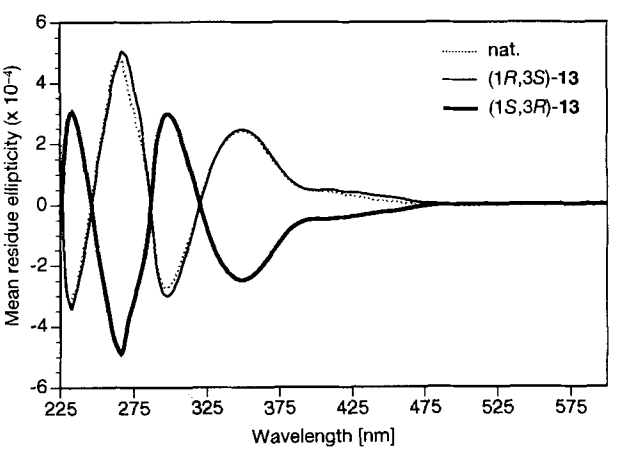
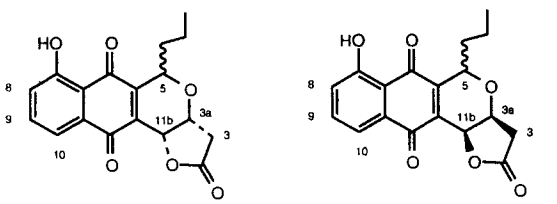


Fig. 2. *ORD Spectra of (1*R,3S*)- and (1*S,3R*)-***13** *and of the corresponding natural derivative*

pyridine gave **1** in 40 and **2** in 55% yields, respectively. At this stage, comparison of the analytical data of (1*R*,3*S*)- and (1*S*,3*R*)-**13′**, and **1** and **2** with those of natural deoxyfrenolicin (**6**) and natural frenolicin B (**1**), respectively, showed excellent correlations[3]). As aforementioned, the relative orientation of the dihydropyran substituents unambiguously follows from the analysis of their ^{1}H-NMR spectra (*Tables 1* and *2*). Thus, the dihydropyran substituents in the enantiomers **13′** are in a *trans*-orientation and the lactone moiety in the enantiomers **1** and **2** is *cis*-connected. The ORD curves (*Figs. 3* and *4*) suggest that (1*R*,3*S*)-**13′** and **1** have the same chirality as natural deoxyfrenolicin (**6**; 1*R*,3*S*) and natural frenolicin B (**1**; (3a*R*,5*R*,11b*R*)), whereas (1*S*,3*R*)-**13′** and **2** show mirror-image shaped curves.

Table 2. *Coupling Constants* J [Hz] *of* **1**–**4**

	J(3,3′)	J(3′,3a)	J(3a,11b)	J(5,11b)	J(5,CH_2–C(5))	J(5,CH_2–C(5))	J(8,9)	J(8,10)	J(9,10)
1	17.70	5.20	3.00		10.35	3.00	7.85	2.25	7.85
2	17.70	5.20	3.00		10.35	3.00	7.85	2.25	7.85
3	17.35	4.35	2.45	1.95	6.75		7.15	2.45	7.15
4	17.35	4.35	2.45	1.95	6.75		7.15	2.45	7.15



1 (3a*R*,5*R*,11b*R*)
3 (3a*R*,5*S*,11b*R*)

2 (3a*S*,5*S*,11b*S*)
4 (3a*S*,5*R*,11b*S*)

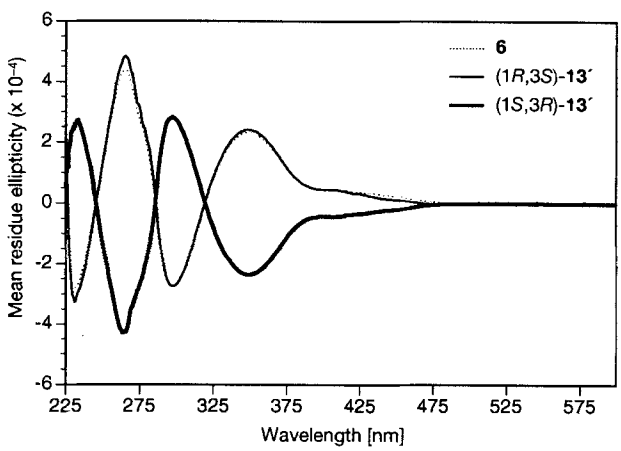


Fig. 3. *ORD Spectra of (1*R,*3*S*)- and of (1*S,*3*R*)-***13′*** *and of natural deoxyfrenolicin* (**6**)

[3]) (1*R*,3*S*)-**13**: $[\alpha]_D = +103$ ($c = 0.1$, $CHCl_3$), m.p. 179°; (1*S*,3*R*)-**13**: $[\alpha]_D = -103$ ($c = 0.1$, $CHCl_3$), m.p. 175°; natural deoxyfrenolicin (**6**): $[\alpha]_D = +105$ ($c = 0.1$, $CHCl_3$), m.p. 179°; synthetic **1**: $[\alpha]_D = +230$ ($c = 0.1$, $CHCl_3$), m.p. 170°; **2**: $[\alpha]_D = -225$ ($c = 0.1$, $CHCl_3$), m.p. 170°; natural frenolicin B (**1**): $[\alpha]_D = +228$ ($c = 0.1$, $CHCl_3$), m.p. 170°.

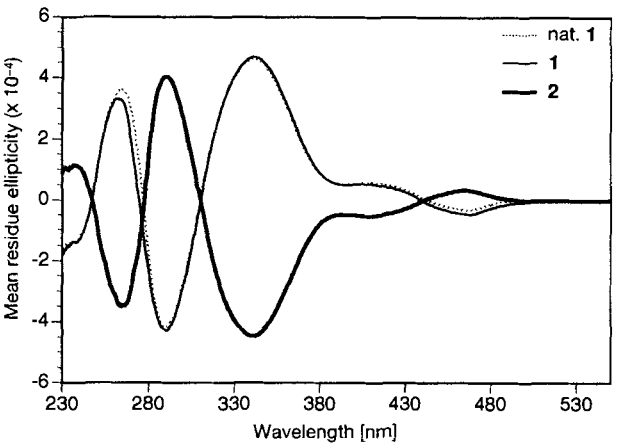


Fig. 4. *ORD Spectra of* **1** (3a*R*,5*R*,11b*R*) *and of* **2** (3aS,5S,*11b*S), *and of natural frenolicin B*

Having achieved successfully the synthesis of **1** and **2**, we focused our attention on the preparation of stereoisomers **3** and **4** starting from the corresponding optically pure β-hydroxy esters (*S*)- and (*R*)-**12**, and using the same reaction sequence without isolation of any intermediates, as outlined in *Scheme 2*. Reduction of quinones (*S*)- and (*R*)-**12** with Zn powder and aqueous HCl solution in dioxane/Et_2O gave the corresponding amorphous *p*-quinols as grey solids; these compounds were treated without any further purification with butanal in Et_2O saturated with gaseous HCl (8.5% in weight) at room temperature for 6 h yielding mixtures of two stereoisomers which contained predominantly the *cis*-isomers (*trans*/*cis* 1:4). Oxidation of the resulting mixtures with CAN in MeCN/H_2O and demethylation with BCl_3 in CH_2Cl_2 at −78° led simultaneously to demethylation of the methyl-ether group and to deprotection of the *tert*-butyl ester function. Further oxidative cyclization with air in MeCN/MeOH/pyridine gave the desired stereoisomers **3**

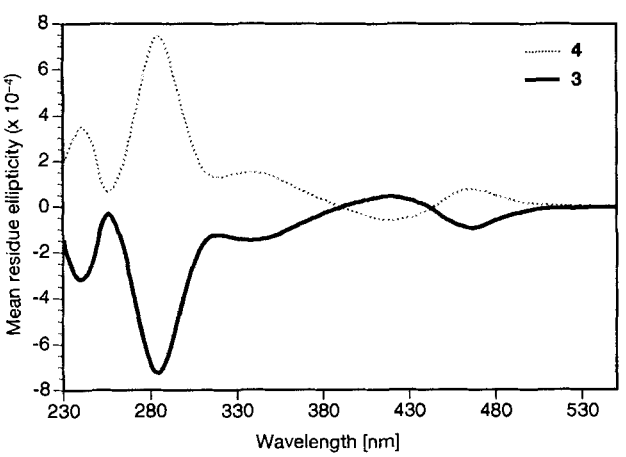
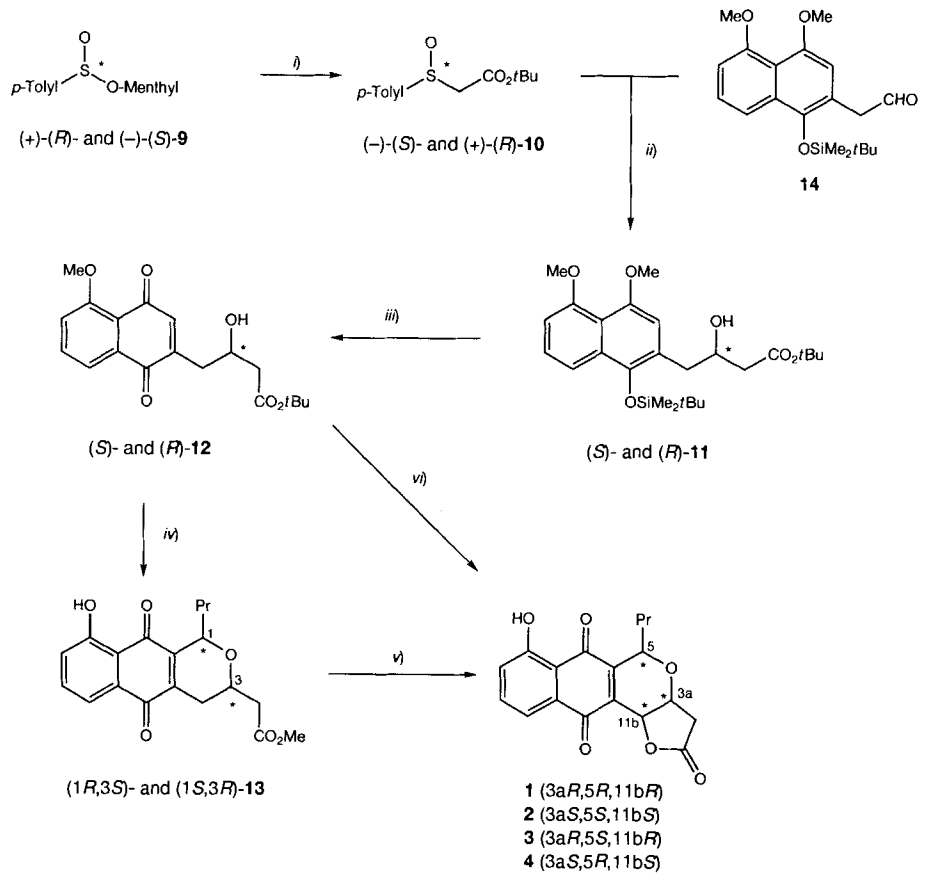


Fig. 5. *ORD Spectra of* **3** (3a*R*,5*S*,11b*R*) *and of* **4** (3a*S*,5*R*,11b*S*)

Scheme 2. *Synthesis of* **1–4** *According to* Method A



i) $MeCO_2t$-Bu, Et_2O/THF, $^iPr_2NMgBr$, r.t. (70% of (*S*)-**10**, 99%ee; 64% of (*R*)-**10**, 99% ee). *ii*) 1. *t*-BuMgBr, THF, −78°; 2. Al-Hg, THF/H_2O, r.t. (69% of (*S*)-**11**, 96% ee; 78% of (*R*)-**11**, 93.5% ee). *iii*) 1. CAN, MeCN/H_2O, 0° to r.t.; 2. crystallization (53% of (*S*)-**12**, > 98% ee; 50% of (*R*)-**12**, > 98% ee). *iv*) 1. HCl_{aq}, Zn_{act}, dioxane/Et_2O, r.t.; 2. PrCHO, HCl_g in Et_2O (23.8%), 2.5 h; 3. MeOH; 4. CAN, MeCN/H_2O, 0° to r.t.; 5. BCl_3, −78°, CH_2Cl_2; 6. crystallization (35% of (1*R*,3*S*)-**13**; 49% of (1*S*,3*R*)-**13**). *v*) 1. LiOH, THF/H_2O, r.t. (92% of (1*R*,3*S*)-**13'**; 85% of (1*S*,3*R*)-**13'**); 2. pyridine, MeOH, MeCN, O_2, reflux, 16 h (40% of **1**; 55% of **2**). *vi*) 1. HCl_{aq}, Zn_{act}, dioxane/Et_2O, r.t.; 2. PrCHO, HCl_g in Et_2O (8.5%), 6 h; 3. CAN, MeCN/H_2O, 0° to r.t.; 4. BCl_3, −78°, CH_2Cl_2; 5. pyridine, MeOH, MeCN, O_2, reflux, 16 h (32% of **3**; 25% of **4**).

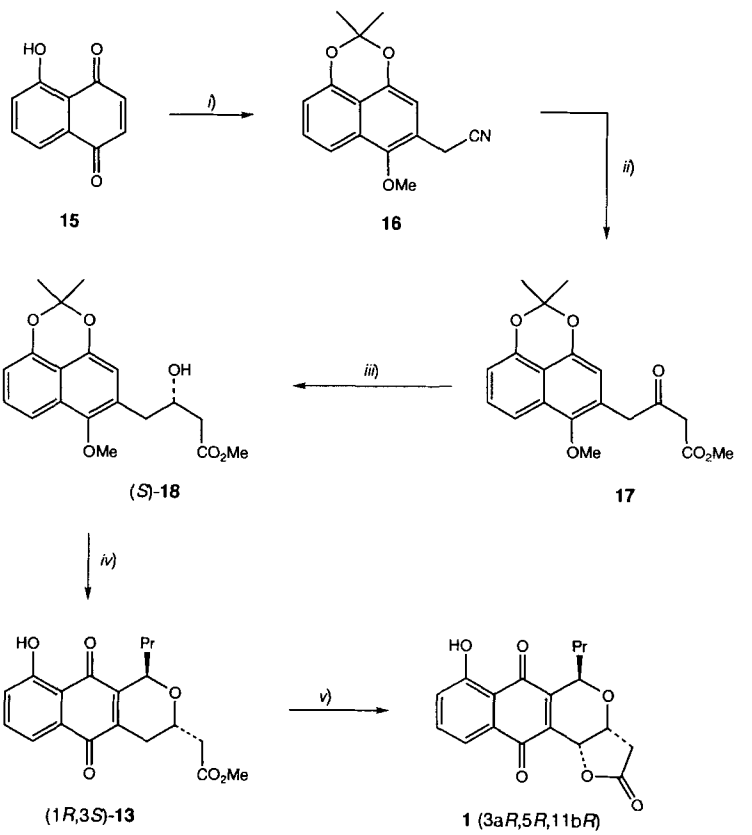
and **4** as diastereoisomer mixtures. Purification by flash chromatography (FC) on silica gel with AcOEt/hexane 2:1 afforded the pure stereoisomers **3** (3a*R*,5*S*,11b*R*) from (*S*)-**12** and **4** (3a*S*,5*R*,11b*S*) from (*R*)-**12** in 32 and 25% yields, respectively.

The characteristic coupling constants derived from ^{1}H-NMR spectra of **3** and **4** are summarized in *Table 2* and underscore, as previously mentioned, the presence of a *cis*-fused 2*H*-furo[3,2-*b*]naphtho[2,3-*d*] pyran system and indicate the pseudoequatorial position of H–C(11b) and consequently the pseudoaxial position of H–C(5). The ORD curves of **3** and **4** (*Fig. 5*) show the shapes of miror images, confirming the absolute configuration for **3** (3a*R*,5a*S*,11b*R*) and **4** (3a*S*,5*R*,11b*S*).

3. Synthesis of Frenolicin B (1) from Optically Active β-Hydroxy Ester (*S*)-18. – Homogeneous asymmetric hydrogenation of functionalized ketones with transition-metal complex catalyst offers an attractive tool for stereoselective organic synthesis. With many substrates, the homogeneous ruthenium-catalyzed hydrogenation procedure is superior to the heterogeneous version [29] and compares well with selectivities of biochemical transformations [30].

The second approach for the enantioselective synthesis of frenolicin B(**1**), made use of the prochiral β-keto ester **17** which led to the desired β-hydroxy ester (*S*)-**18** by homogeneous asymmetric hydrogenation in high chemical and optical yields (*Scheme 3*). Commercially available juglone (**15**) was reduced with aqueous sodium dithionite, ketalized

Scheme 3. *Synthesis of* **1** *According to* Method B



i) 1. $Na_2S_2O_4$; 2. $(Me)_2C(OMe)_2$, $BF_3 \cdot OEt_2$, 3 h; 3. Et_2NH, $(CH_2O)_n$, 70°, 2.5 h; 4. KCN, [18]crown-6, DMF, 70°, 2 h; MeI, K_2CO_3, 70°, 3 h (35% of **16**). *ii*) $BrCH_2CO_2Me$, Zn_{act}, THF, 60°, 1.5 h (79% of **17**). *iii*) H_2, [Ru{(*S*)-biphemp}]Cl_2, 60°/60 bar (97% of **18**, 98% ee). *iv*) 1. PrCHO, HCl_g in Et_2O, 2. AgO, HNO_3, dioxane; 3. H_2SO_4, benzene, r.t.; 4. crystallization (56% of (1*R*,3*S*)-**13**). *v*) 1. LiOH, THF/H_2O, r.t., 4 h; 2. pyridine, MeOH, O_2, reflux, 24 h (71%).

with dimethoxypropane in the presence of $BF_3 \cdot Et_2O$ according to the procedure of *Yoshii* [31], and the resulting intermediate was immediately treated with paraformaldehyde and Et_2NH at 70° for 2.5 h affording a 2-[(diethylamino)methyl]naphthalen-1-ol adduct. Subsequent treatment with KCN and [18]crown-6, followed by methylation with MeI in the presence of anh. K_2CO_3 at 70° in DMF led to the naphthodioxinacetonitrile **16** in 35% overall yield (from **15**) [32].

Since the discovery of the addition of zinc ester enolates to nitriles by *Blaise* in 1905 [33], this general route to β-keto esters has found little application [33], because of low yield and of some competing side reactions. As pointed out by *Hannick* and *Kishi* [34], treatment of **16** with ethyl bromoacetate in the presence of activated Zn dust in refluxing THF allowed us to obtain, after acidic hydrolysis, the β-keto ester **17** in 79% yield. At this stage, we focused our attention on the asymmetric hydrogenation of oxo esters catalyzed by chiral cationic diphosphine complexes [36] [37]. Thus, the asymmetric hydrogenation of **17** was performed in MeOH using [Ru{(*S*)-biphemp}]Cl_2 (prepared *in situ* from [Ru{(*S*)-biphemp}](OAc)$_2$ and HCl; biphemp = 6,6′-dimethyl-2,2′-biphenylenebis[diphenylphosphine]) with a substrate/catalyst ratio of 100 at 60° under 60 bar H_2 pressure. Under these conditions, β-hydroxy ester **18** was obtained in > 98% ee and 97% yield after purification by FC on silica gel. The ee value was determined by HPLC using a *Chiralpack AD* column. The absolute configuration (*S*) of this chiral β-hydroxy ester was consistent with the mechanistic consideration which has been established during enantioselective hydrogenation of 3-oxocarboxylic esters [38] [39]. The chirality of the biphemp ligand is controlling the facial selectivity at the carbonyl function. With the optically pure (*S*)-β-hydroxy ester **18** in hand, the stage was set for the pyran ring annulation. Treatment of **18** with butanal in Et_2O saturated with gaseous HCl (24.5% by weight) at 25° for 2.5 h led to a mixture of two stereoisomers containing predominantly the *cis*-isomer (*cis*/*trans* 4:1) which was oxidized quantitatively with silver(I) oxide in dioxane to the corresponding mixture of quinones (1*S*,3*R*)- and (1*R*,3*S*)-**13** (*cis*/*trans* 4:1). As mentioned previously, our preliminary studies had indicated that **18** condenses with butanal under acidic conditions to afford the 1,3-*cis*-diastereoisomer *via* kinetic control. Conversely, allowing the reaction to equilibrate resulted in a *trans*/*cis* 1.5:1 products ratio under thermodynamic control. While oxidation under the initial conditions with CAN gave irreproducible results, we found that with AgO, the reaction proceeded without any complication in dioxane. Acid-catalyzed epimerization of the latter mixture (conc. H_2SO_4/benzene, 0°, 0.5 h) gave mainly the desired *trans*-isomer (1*R*,3*S*)-**13** (4:1 mixture of *trans*/*cis*-isomers), which could be isolated in pure form with 56% yield by fractional crystallization. Finally, *trans* ester (1*R*,3*S*)-**13** was saponified with LiOH in aqueous THF to afford optically pure deoxyfrenolicin (**6**). Subsequent oxidative cyclization in the presence of air in MeOH/pyridine gave **1** in 71% yield from (1*R*,3*S*)-**13**.

4. Conclusion. – Among the presented two novel synthetic asymmetric routes to **1**, we clearly favor the second approach based on homogeneous asymmetric hydrogenation of a β-keto ester, which has several advantages compared to the first route (see above) and to the various other routes reported in the literature. Even with yet unoptimized conditions, the overall yield with this new approach was superior to the other routes. Multigram quantities of **1** could easily be prepared from commercially available juglone (**15**). In addition, this efficient and versatile process can also be extented to the other

diastereoisomers of frenolicin B (**1**) and eventually to various other types of naphthopyranquinone antibiotics.

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Experimental Part

General. All reactions which require 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 over Na with benzophenone ketyl as indicator, CH_2Cl_2 from powdered CaH_2 and DMF over ninhydrin and kept over 4-Å 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 (*E. Merck & Co.*, Darmstadt, Germany). Flash chromatography (FC): *E. Merck* SiO_2 *60* (70–230 mesh ASTM), according to [39]. M.p.: *Büchi-Smp-20* apparatus; uncorrected. IR: *Nicolet-7199* FT-IR spectrometer; solids in KBr pellets, liquids as thin films; characteristic bands in cm^{-1}. ^{1}H-NMR Spectra: *Bruker-AC-250* apparatus, at 250 MHz; in $CDCl_3$; $SiMe_4$ as internal standard; chemical shift of signal centers and ranges in ppm (δ), *J* in Hz. MS: *Finnigan MS9-AEI* or *Mat90*; *m/z* (rel. %).

*(−)-(S)-*tert*-Butyl (4-Tolylsulfinyl)acetate* ((−)-(*S*)-**10**). To a soln. of EtMgBr (prepared from Mg (8.25 g) and EtBr (25.35 ml)) in Et_2O (550 ml) under Ar, $(i\text{-}Pr)_2NH$ (48 ml, 0.339 mol) was added. After heating under reflux for 30 min, the mixture was cooled to −40° and diluted with THF (15 ml). To this mixture were added dropwise 30.6 ml of AcO(*t*-Bu) (0.212 mol) and 25 g of (+)-(*R*)-menthyl toluene-4-sulfinate ((+)-(*R*)-**9**, 0.085 mol) in Et_2O (125 ml) and THF (15 ml). After 18 h at −40°, the mixture was transferred onto a sat. NH_4Cl soln. and extracted with $CHCl_3$. The combined org. layers were washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by FC (silica gel, AcOEt/hexane 1:1): 15.10 g (70%) of (−)-(*S*)-**10**. Yellow oil. $[\alpha]_D = -149.2$ (*c* = 2.25, EtOH); ee > 99%. IR (KBr): 3040*m*, 2979*w*, 2929*w*, 1724*s*, 1596*w*, 1495*w*, 1456*w*, 1292*s*, 1161*m*, 1084*m*, 1052*m*, 840*w*, 812*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 1.40 (*s*, *t*-Bu); 2.42 (*s*, Me); 3.56 (*d*, *J* = 2.15, 1 aliph. H); 3.80 (*d*, *J* = 2.15, 1 aliph. H); 7.34 (*d*, *J* = 1.25, 2 arom. H); 7.59 (*d*, *J* = 1.25, 2 arom. H). MS: 254 (M^+), 198 (20), 140 (18), 139 (100), 91 (15), 57 (40), 43 (18), 41 (17). Anal. calc. for $C_{13}H_{18}O_3S$ (248.372): C 61.39, H 7.13; found: C 61.4, H 7.2.

*(+)-(R)-*tert*-Butyl (4-Tolylsulfinyl)acetate* ((+)-(*R*)-**10**). As described for (−)-(*S*)-**10**, with (−)-(*S*)-menthyl toluene-4-sulfinate ((−)-(*S*)-**9**): (+)-(*R*)-**10** (13.73 g, 64%). Yellow oil. $[\alpha]_D = +150.8$ (*c* = 2.25, EtOH); ee > 99%. IR, ^{1}H-NMR, MS: identical to those of (−)-(*S*)-**10**. Anal. calc. for $C_{13}H_{18}O_3S$ (248.372): C 61.39, H 7.13; found: C 61.3, H 7.2.

*(S)-*tert*-Butyl 1-[(*tert*-Butyl)dimethylsilyloxy]-β-hydroxy-4,5-dimethoxynaphthalene-2-butanoate* ((*S*)-**11**). To a soln. of (−)-(*S*)-**10** (2.75 g, 10.8 mmol) in THF (700 ml), cooled at −78°, was added dropwise within 20 min a soln. of *t*-BuMgBr (150 ml, 0.24 mol; prepared from 5.31 g of Mg, 30.8 ml of *t*-BuBr, and 150 ml of Et_2O). The mixture was then stirred for 30 min at −78°, and naphthaleneacetaldehyde **14** (3.54 g, 9.8 mmol) in THF (50 ml) was added. After 20 h at −78°, the mixture was poured into a sat. NH_4Cl soln. and extracted with $CHCl_2$. The combined org. layers were washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by FC (silica gel, AcOEt/hexane 1:1) affording 5.21 g of a yellow oil. To this latter product diluted in THF (1500 ml) and H_2O (1500 ml) was added aluminium amalgam (52.1 g), the temp. being maintained between 15 and 20°. The mixture was then left overnight under vigorous stirring. After filtration and washing with $CHCl_3$, the soln. was dried (Na_2SO_4) and evaporated. The residue was purified by FC (silica gel, AcOEt/hexane 1:1): (*S*)-**11** (2.76 g, 69%); ee 96%. Yellow oil. IR (KBr): 3503*m*, 2956*w*, 2931*w*, 2858*w*, 1727*s*, 1600*m*, 1509*w*, 1464*w*, 1388*w*, 1262*m*, 1147*m*, 1076*m*, 834*w*, 780*w*. ^{1}H-NMR: 0.138 (*s*, Me); 0.158 (*s*, Me); 1.09 (*s*, *t*-Bu); 1.42 (*s*, *t*-Bu); 2.30 (*d*, *J* = 5.80, 2 aliph. H); 2.91 (*dd*, *J* = 13.45, 7.00, 1 aliph. H); 2.99 (*dd*, *J* = 13.45, 6.25, 1 aliph. H); 3.20 (*s*, OH); 3.93 (*s*, MeO); 3.96 (*s*, MeO); 4.28 (*m*, 1 aliph. H); 6.69 (*s*, 1 arom. H); 6.83 (*dd*, *J* = 7.85, 1.25, 1 arom. H); 7.33 (*t*, *J* = 7.85, 1 arom. H); 7.64 (*dd*, *J* = 7.85, 1.25, 1 arom. H). MS: 476 (M^+), 420 (30), 403 (20), 331 (18), 303 (50), 288 (35), 275 (18), 260 (18), 229 (20), 75 (35), 73 (100), 57 (40), 41 (20). Anal. calc. for $C_{26}H_{40}O_6Si$ (476.686): C 65.51, H 8.46; found: C 65.2, H 8.7.

(R)-tert-Butyl 1-[(tert-Butyl)dimethylsilyloxy]-β-hydroxy-4,5-dimethoxynaphthalene-2-butanoate ((*R*)-**11**). As described for (*S*)-**11**, with (+)-(*R*)-**10** (2.44 g, 9.6 mmol), *t*-BuMgBr (150 ml, 0.24 mol; prepared from 4.70 g of Mg, 27.5 ml of *t*-BuBr, and 150 ml of Et_2O), and **14** (3.14 g, 8.77 mmol). To the intermediate yellow oil (4.47 g) aluminium amalgam (44.7 g) was added. FC (silica gel, AcOEt/hexane 1:1) yielded (*R*)-**11** (2.64 g, 78%); ee 93.5%. Yellow oil. IR, ^{1}H-NMR, MS: identical to those of (*S*)-**11**. Anal. calc. for $C_{26}H_{40}O_6Si$ (476.686): C 65.51, H 8.46; found: C 62.8, H 8.5.

(−)-(S)-tert-Butyl 1,4-Dihydro-β-hydroxy-5-methoxy-1,4-dioxonaphthalene-2-butanoate ((*S*)-**12**). To a soln. of (*S*)-**11** (2.4 g, 5.0 mmol) in MeCN (70 ml) cooled to 0° was added dropwise a soln. of cerium(IV) ammonium nitrate (CAN; 8.28 g, 15.0 mmol) in H_2O (70 ml). The mixture was stirred at r.t. for 15 min, then transferred onto brine, and extracted with AcOEt. The combined org. layers were dried and evaporated. The residue was chromatographed (silica gel, AcOEt/hexane 2:1): 1.29 g (74%) of (*S*)-**12** with ee 96%. Recrystallization from AcOEt/hexane gave 0.925 g (53%) of orange solid. $[\alpha]_D = -299$ (*c* = 1.00, EtOH); ee > 98%. M.p. 105–106°. IR: 3517*m*, 2982*w*, 2928*w*, 2840*w*, 1728*s*, 1653*m*, 1626*m*, 1586*w*, 1472*w*, 1370*w*, 1288*m*, 1258*m*, 1150*m*, 1073*m*, 976*w*, 843*w*, 768*w*. ^{1}H-NMR: 1.46 (*s*, *t*-Bu); 2.43 (*dd*, *J* = 16.50, 8.20, 1 aliph. H); 2.49 (*dd*, *J* = 16.50, 3.80, 1 aliph. H); 2.65 (*ddd*, *J* = 14.50, 8.15, 1.00, 1 aliph. H); 2.72 (*dd*, *J* = 14.50, 4.60, 1 aliph. H); 3.34 (*d*, *J* = 4.20, 1 aliph. H); 4.00 (*s*, OH); 4.24 (*m*, 1 aliph. H); 6.84 (*t*, *J* = 1.50, 1 arom. H); 7.29 (*dd*, *J* = 7.50, 1.20, 1 arom. H); 7.66 (*t*, *J* = 7.50, 1 arom. H); 7.75 (*dd*, *J* = 7.50, 1.20, 1 arom. H). MS: 346 (M^+), 202 (60), 115 (20), 76 (18), 57 (100), 43 (18), 41 (30), 39 (18), 29 (20). Anal. calc. for $C_{19}H_{22}O_6$ (346.389): C 65.88, H 6.40; found: C 66.0, H 6.5.

(+)-(R)-tert-Butyl 1,4-Dihydro-β-hydroxy-5-methoxy-1,4-dioxonaphthalene-2-butanoate ((*R*)-**12**). From (*R*)-**11** (2.64 g, 5.5 mmol) as described for (*S*)-**12**: 1.52 g (80%) of crude (*R*)-**12** with ee 93.5%. Recrystallization from AcOEt/hexane gave 0.950 g (50%) of orange solid. $[\alpha]_D = +309$ (*c* = 1.00, EtOH); ee > 98%. M.p. 105–106°. IR, ^{1}H-NMR, MS: identical to those of (*S*)-**12**. Anal. calc. for $C_{19}H_{22}O_6$ (346.389): C 65.88, H 6.40; found: C 66.0, H 6.4.

(1R,3S)-Methyl 3,4-Dihydro-9-hydroxy-5,10-dioxo-1-propyl-1H-naphtho[2,3-c]pyran-3-acetate ((1*R*,3*S*)-**13**). To a soln. of (*S*)-**12** (0.50 g, 1.44 mmol) in dioxane/Et_2O 1:1 (60 ml) cooled to 0° were added 18% aq. HCl soln. (10.6 ml) and then portionwise within 30 min Zn (2.68 g). The mixture was allowed to warm up to r.t., then treated with brine, and extracted with AcOEt. The combined org. layers were dried and evaporated. Gaseous HCl was bubbled through Et_2O (35 ml) maintained at r.t. for 5 min using a disposable pipet. To the resulting HCl soln. (23.8% in weight), the isolated residue (0.603 g) was added all at once, followed by butanal (0.306 ml, 3.44 mmol). After consumption of the starting material, 10 ml of dry MeOH were added. The mixture was stirred for 10 min and treated with ice, brine, and AcOEt. The combined org. layers were dried and evaporated. The residue was diluted with MeCN (30 ml) and treated with a soln. of CAN (2.83 g, 5.20 mmol) in H_2O (30 ml). After 5 min stirring at r.t., the mixture was transferred onto ice, brine, and AcOEt. The combined org. layers were dried and evaporated. To this residue, dissolved in CH_2Cl_2 (50 ml) and cooled to −78° under Ar, was added dropwise 1.0M BCl_3 in CH_2Cl_2 (2.90 ml, 2.90 mmol). After 20 min at −78°, the mixture was stirred at r.t., then poured onto ice, $NaHCO_3$ soln., and AcOEt. The org. layer was washed with brine, dried, and evaporated. The residue was chromatographed (AcOEt/hexane 1:3): (1*R*,3*S*)-**13** (0.42 g, 84%). The yellow solid was recrystallized from AcOEt/hexane: 0.170 g (35%). $[\alpha]_D = +107$ (*c* = 0.10, $CHCl_3$). M.p. 124–127°. IR: 3459*m*, 2959*w*, 2872*w*, 1739*s*, 1640*m*, 1615*w*, 1575*w*, 1455*w*, 1408*w*, 1276*m*, 1249*m*, 1154*m*, 1032*m*, 985*w*, 747*w*. ^{1}H-NMR: 1.00 (*t*, *J* = 7.35, Me); 1.55 (*m*, 4 aliph. H); 2.32 (*ddd*, *J* = 19.20, 10.45, 2.00, 1 aliph. H); 2.63 (*m*, 2 aliph. H); 2.82 (*dd*, *J* = 19.20, 3.45, 1 aliph. H); 3.74 (*s*, Me); 4.28 (*m*, 1 aliph. H); 4.83 (*m*, 1 aliph. H); 7.25 (*dd*, *J* = 7.85, 1.75, 1 arom. H); 7.60 (*t*, *J* = 7.85, 1 arom. H); 7.62 (*dd*, *J* = 7.85, 1.75 1 arom. H); 12.02 (*s*, OH). MS: 344 (M^+), 312 (30), 301 (80), 271 (25), 242 (30), 241 (100), 227 (80), 213 (30), 121 (25), 55 (15), 43 (20). Anal. calc. for $C_{19}H_{20}O_6$ (344.367): C 66.27, H 5.85; found: C 66.2, H 5.8.

(1S,3R)-Methyl 3,4-Dihydro-9-hydroxy-5,10-dioxo-1-propyl-1H-naphtho[2,3-c]pyran-3-acetate ((1*S*,3*R*)-**13**). From (*R*)-**12** (0.20 g, 0.58 mmol) as described for (1*R*,3*S*)-**13**: of 0.178 g (86%) of crude. Recrystallization from AcOEt/hexane led to 0.087 g (49%) of (1*S*,3*R*)-**13**. Yellow solid. $[\alpha]_D = -108$ (*c* = 0.10, $CHCl_3$). M.p. 125.5°. IR, ^{1}H-NMR, MS: identical to those of (1*R*,3*S*)-**13**. Anal. calc. for $C_{19}H_{20}O_6$ (344.367): C 66.27, H 5.85; found: C 66.0, H 5.6.

(1R,3R)-3,4-Dihydro-9-hydroxy-5,10-dioxo-1-propyl-1H-naphtho[2,3-c]pyran-3-acetic Acid ((1*R*,3*S*)-**13′**). To a soln. of (1*R*,3*S*)-**13** (0.232 g, 0.67 mmol) in THF/H_2O 3:1 (100 ml), LiOH (0.283 g, 6.77 mmol) was added and the resulting purple mixture stirred at r.t. After total consumption of (1*R*,3*S*)-**13**, the soln. was acidified to pH 1–2 with 1N aq. HCl. The aq. phase was extracted with AcOEt, the combined org. phase washed with brine, dried, and evaporated, and the residue chromatographed (CH_2Cl_2/MeOH 10:1) and crystallized from MeOH: (1*R*,3*S*)-**13′** (0.19 g, 92%). Yellow solid. $[\alpha]_D = +103$ (*c* = 0.10, $CHCl_3$). M.p. 179°. IR: 3114*m*, 2955*w*, 2870*w*, 1723*s*, 1641*s*, 1617*m*, 1576*w*, 1459*w*, 1419*w*, 1276*s*, 1165*m*, 1076*m*, 1029*m*, 873*w*, 747*w*. ^{1}H-NMR: 1.00 (*t*, *J* = 7.40, Me); 1.65 (*m*, 4 aliph. H); 2.35 (*ddd*, *J* = 19.20, 10.45, 2.00, 1 aliph. H); 2.72 (*d*, *J* = 6.35, 2 aliph. H); 2.90 (*dd*, *J* = 19.20, 3.50,

1 aliph. H); 4.32 (*m*, 1 aliph. H); 4.87 (*m*, 1 aliph. H); 7.25 (*dd*, *J* = 7.85, 1.75, 1 arom. H); 7.59 (*t*, *J* = 7.85, 1 arom. H); 7.625 (*dd*, *J* = 7.85, 1.75, 1 arom. H); 12.02 (*s*, OH). MS: 330 (M^+), 288 (20), 287 (100), 227 (80), 213 (20), 200 (15), 121 (25), 55 (15), 43 (20), 41 (15). Anal. calc. for $C_{18}H_{18}O_6$ (330.336): C 65.65, H 5.49; found: C 65.3, H 5.4.

(1S,3R)-3,4-Dihydro-9-hydroxy-5,10-dioxo-1-propyl-1H-naphtho[2,3-c]pyran-3-acetic Acid ((1*S*,3*R*)-**13'**). From (1*S*,3*R*)-**13** (0.217 g, 0.63 mmol) in THF/H_2O 3:1 according to the above procedure: 0.175 g (85%) of (1*S*,3*R*)-**13'**. Yellow solid. $[\alpha]_D = -103$ (*c* = 0.10, $CHCl_3$). M.p. 175°. IR, ^{1}H-NMR, MS: identical to those of (1*R*,3*S*)-**13'**. Anal. calc. for $C_{18}H_{18}O_6$ (330.336): C 65.65, H 5.49; found: C 65.7, H 5.8.

(3aR,5R,11bR)-3,3a,5,11b-Tetrahydro-7-hydroxy-5-propyl-2H-furo[3,2-b]naphtho[2,3-d]pyran-2,6,11-trione (**1**). A soln. of (1*R*,3*S*)-**13'** (0.053 g, 0.16 mmol) in MeOH/MeCN 2:1 (40 ml) and pyridine (0.230 ml) was brought to reflux while passing a gentle stream of O_2 through the soln. After 16 h at reflux, the soln. was cooled to r.t. and the solvent evaporated. The residue was chromatographed (AcOEt/hexane 2:1): **1** (0.022 g, 40%). Orange solid. $[\alpha]_D = +230$ (*c* = 0.10, $CHCl_3$). M.p. 170°. IR: 3436*s*, 2963*w*, 2934*w*, 2874*w*, 1786*s*, 1648*m*, 1620*m*, 1574*w*, 1457*w*, 1247*s*, 1154*m*, 1066*m*, 879*w*, 788*w*. ^{1}H-NMR: 1.00 (*t*, *J* = 7.15, Me); 1.75 (*m*, 4 aliph. H); 2.70 (*d*, *J* = 17.70, 1 aliph. H); 2.90 (*dd*, *J* = 17.70, 5.20, 1 aliph. H); 4.62 (*dd*, *J* = 5.20, 2.95, 1 aliph. H); 4.92 (*dd*, *J* = 10.35, 3.00, 1 aliph. H); 5.26 (*d*, *J* = 2.95, 1 aliph. H); 7.30 (*dd*, *J* = 7.85, 2.25, 1 arom. H); 7.59 (*t*, *J* = 7.85, 1 arom. H); 7.625 (*dd*, *J* = 7.85, 2.25, 1 arom. H); 11.85 (*s*, OH). MS: 328 (M^+), 287 (20), 286 (45), 285 (55), 239 (45), 229 (35), 227 (30), 201 (30), 173 (20), 139 (15), 121 (50), 115 (25), 93 (15), 92 (25), 89 (18), 77 (20), 71 (15), 65 (20), 63 (30), 55 (90), 44 (20), 43 (85), 41 (38), 39 (30), 29 (18). Anal. calc. for $C_{18}H_{16}O_6$ (328.320): C 65.85, H 4.91; found: C 65.9, H 5.0.

(3aS,5S,11bS)-3,3a,5,11b-Tetrahydro-7-hydroxy-5-propyl-2H-furo[3,2-b]naphtho[2,3-d]pryan-2,6,11-trione (**2**). From (1*S*,3*R*)-**13'** (0.148 g, 0.44 mmol) in MeOH/MeCN 2:1, according to the above procedure: 0.081 g (55%) of **2**. Orange solid. $[\alpha]_D = -225$ (*c* = 0.10, $CHCl_3$). M.p. 170°. IR, ^{1}H-NMR, MS: identical to those of **1**. Anal. calc. for $C_{18}H_{16}O_6$ (328.320): C 65.85, H 4.91; found: C 65.7, H 4.8.

(3aR,5S,11bR)-3,3a,5,11b-Tetrahydro-7-hydroxy-5-propyl-2H-furo[3,2-b]naphtho[2,3-d]pyran-2,6,11-trione (**3**). To a soln. of (*S*)-**12** (0.50 g, 1.44 mmol) in dioxane/Et_2O 1:1 (40 ml) at 0° were was added 18% aq. HCl soln. (9.40 ml) and then portionwise within 30 min period Zn (2.0 g). The mixture was allowed to warm up to r.t., then treated with brine, and extracted with AcOEt. The combined org. layers were dried and evaporated. Gaseous HCl was bubbled through Et_2O (38.5 ml) maintained at r.t. for 5 min using a disposable pipet. To the resulting soln. (8.5% in weight), the isolated residue (0.550 g) was added all at once, followed by butanal (0.320 ml, 3.60 mmol). After 6 h, the mixture was treated with ice, brine, and AcOEt. The combined org. layers were dried and evaporated. The residue was diluted with MeCN (53 ml), treated with CAN (2.95 g, 5.40 mmol), and dissolved in H_2O (53 ml). After 5 min stirring at r.t., the mixture was transferred onto ice, brine, and AcOEt. The combined org. layers were dried and evaporated. To this residue, dissolved in CH_2Cl_2 (35 ml) cooled to −78° under Ar, was added dropwise 1.0M BCl_3 in CH_2Cl_2 (3.38 ml, 3.38 mmol). After 20 min at −78°, the mixture was stirred at r.t., then poured onto ice, $NaHCO_3$ soln., and AcOEt. The org. layer was washed with brine, dried, and evaporated. The residue was chromatographed (CH_2Cl_2/MeOH 10:1) affording an orange solid (0.23 g; 4.5:1 mixture of free *cis*/*trans* acids). A soln. of this mixture in MeOH/MeCN 2:1 (100 ml) and pyridine (0.948 ml) was brought to reflux while passing a gentle stream of O_2 through it. After 16 h at reflux, the soln. was cooled to r.t. and evaporated. The residue was chromatographed (AcOEt/hexane 2:1): **3** (0.175 g, 32%). Yellow solid. $[\alpha]_D = -244$ (*c* = 0.10, $CHCl_3$). M.p. 168°. IR: 3437*s*, 2965*w*, 2918*w*, 2867*w*, 1785*s*, 1667*s*, 1641*m*, 1612*m*, 1574*w*, 1459*w*, 1405*w*, 1252*s*, 1159*m*, 1032*m*, 802*w*, 751*w*. ^{1}H-NMR: 0.90 (*t*, *J* = 7.30, Me); 1.45 (*m*, 2 aliph. H); 2.00 (*m*, 2 aliph. H); 2.74 (*d*, *J* = 17.35, 1 aliph. H); 2.90 (*dd*, *J* = 17.35, 4.35, 1 aliph. H); 4.32 (*dd*, *J* = 4.35, 2.45, 1 aliph. H); 4.75 (*m*, 1 aliph. H); 5.27 (*dd*, *J* = 2.45, 1.95, 1 aliph. H); 7.30 (*dd*, *J* = 7.15, 2.45, 1 arom. H); 7.66 (*t*, *J* = 7.15, 1 arom. H); 7.70 (*dd*, *J* = 7.15, 2.45, 1 arom. H); 11.74 (*s*, OH). MS: 328 (M^+), 287 (22), 286 (90), 285 (30), 284 (35), 257 (35), 227 (40), 213 (18), 201 (15), 121 (25), 92 (15), 63 (15), 55 (38), 44 (20), 43 (70), 41 (20), 39 (15). Anal. calc. for $C_{18}H_{16}O_6$ (328.320): C 65.85, H 4.91; found: C 65.7, H 5.0.

(3aS,5R,11bS)-3,3a,5,11b-Tetrahydro-7-hydroxy-5-propyl-2H-furo[3,2-b]naphtho[2,3-d]pyran-2,6,11-trione (**4**). From (*R*)-**12** (0.50 g, 1.44 mmol) according to the above procedure: 0.135 g (25%) of **4**. Yellow solid. $[\alpha]_D = +243$ (*c* = 0.10, $CHCl_3$). M.p. 168°. IR, ^{1}H-NMR, MS: identical to those of **3**. Anal. calc. for $C_{18}H_{16}O_6$ (328.320): C 65.85, H 4.91; found: C 65.7, H 4.8.

6-Methoxy-2,2-dimethylnaphtho[1,8-de][1,3]dioxin-5-acetonitrile (**16**). To an aq. sat. soln. of sodium dithionite (1000 ml) was added a soln. of juglone (**15**; 20 g, 0.115 mmol) in AcOEt (1000 ml). The resulting two-phase soln. was stirred for 1.5 h, the org. layer separated, and the aq. phase extracted with AcOEt. The combined org. layers were washed with H_2O, dried, and evaporated affording 22.95 g of a light-brown solid. A soln. of this product in acetone (100 ml) was then treated with dimethoxypropane (21.2 ml, 0.172 mol) and a catal. amount of $BF_3 \cdot Et_2O$. After 3 h at r.t., the mixture was poured onto ice, $NaHCO_3$ soln., and AcOEt. The

org. layer was washed with brine, dried, and evaporated. A soln. of the residue (31.75 g) and paraformaldehyde (6.90 g, 0.2 mol) in Et_2NH (96 ml, 0.92 mol) was stirred under Ar at 70° for 2.5 h. Excess Et_2NH was evaporated under reduced pressure to give an orange oil (19.21 g, 55%). This was dissolved in DMF (100 ml), and the soln. was degassed. To this soln. were added [18]crown-6 (31 g, 0.115 mmol) and KCN (11.2 g, 0.172 mol). The mixture was stirred at 70° for 2.5 h. Then anh. K_2CO_3 (31.7 g, 0.230 mol) and MeI (21.5 ml, 0.340 mol) were added. After 2.5 h at 70°, the mixture was cooled to r.t., and H_2O (200 ml) was added. The resulting mixture was extracted with Et_2O, the combined org. soln. washed with brine, dried, and evaporated, and the residue chromatographed (AcOEt/hexane 1:3) and crystallized from hexane: **16** (10.53 g, 35%). Pale brown solid. M.p. 75°. IR: 2250*m*, 1612*s*, 1507*w*, 1418*w*, 1383*m*, 1272*m*, 1148*m*, 1047*m*, 865*w*, 767*w*. ^{1}H-NMR: 1.65 (*s*, 2 Me); 3.89 (*s*, 2 aliph. H); 3.95 (*s*, MeO); 6.84 (*s*, 1 arom. H); 6.89 (*dd*, J = 7.50, 1.00, 1 arom. H); 7.47 (*t*, J = 7.50, 1 arom. H); 7.60 (*dd*, J = 7.50, 1.00, 1 arom. H). MS: 269 (M^+), 255 (15), 254 (80), 214 (90), 212 (60), 186 (16). Anal. calc. for $C_{16}H_{15}NO_3$ (269.300): C 71.36, H 5.61, N 5.20; found: C 71.2, H 5.7, N 5.2.

*Methyl 6-Methoxy-2,2-dimethyl-β-oxonaphtho[1,8-*de*][1,3]dioxin-5-butanoate* (**17**). To a suspension of activated Zn dust (14.86 g, 0.227 mmol) in refluxing anh. THF (200 ml) under Ar was added methyl bromoacetate (100 µl). After the appearance of a green color, **16** (10.20 g, 0.037 mmol) was added in one portion, and methyl bromoacetate (17.6 ml, 0.19 mol) was injected by a pump syringe within 45 min. The mixture was refluxed for an additional 10 min, diluted with THF (370 ml), and quenched with 50% aq. K_2CO_3 soln. (55 ml). Rapid stirring gave two cleanly separated layers. The combined org. solns. were washed with brine, dried, and concentrated to half of their initial volume. The layer was then poured onto 10% aq. HCl soln. and extracted with CH_2Cl_2. The combined org. solns. were washed with brine, dried, and evaporated. The residue was chromatographed (AcOEt/hexane 1:3) and crystallized from hexane: **17** (10.3 g, 79%). Yellow oil. IR: 1749*s*, 1720*s*, 1612*w*, 1506*w*, 1382*w*, 1268*s*, 1200*m*, 1047*m*, 870*w*, 759*w*. ^{1}H-NMR: 1.64 (*s*, 2 Me); 3.53 (*s*, 2 aliph. H); 3.71 (*s*, MeO); 3.86 (*s*, MeO); 3.95 (*s*, 2 aliph. H); 6.63 (*s*, 1 arom. H); 6.87 (*dd*, J = 7.45, 1.00, 1 arom. H); 7.44 (*t*, J = 7.45, 1 arom. H); 7.59 (*dd*, J = 7.45, 1.00, 1 arom. H). MS: 344 (M^+), 312 (20), 256 (15), 255 (70), 243 (23), 229 (55), 189 (28), 187 (48), 185 (65), 114 (15), 59 (36), 43 (30), 41 (34), 39 (20), 29 (15). Anal. calc. for $C_{19}H_{20}O_6$ (344.363): C 66.27, H 5.85; found: C 66.3, H 5.9.

*(S)-Methyl β-Hydroxy-6-methoxy-2,2-dimethylnaphtho[1,8-*de*][1,3]-dioxin-5-butanoate* ((*S*)-**18**). The [Rh{(*S*)-biphemp}]Cl_2 complex was prepared by mixing a soln. of [Rh{(*S*)-biphemp}](OAc)$_2$ (22.3 mg, 0.03 mmol) in CH_2Cl_2 (5 ml) with anh. HCl soln. in MeOH (0.99 ml; prepared from 50 ml of MeOH and 0.23 g (2.38 mmol) of AcCl). The volume was then completed to 10 ml with degassed MeOH (exclusion of O_2: all operations in a glove-box). The soln. of **17** (0.20 g, 0.58 mmol) in degassed MeOH (7 ml) and the freshly prepared catalyst soln. (2 ml) were kept in a 100-ml autoclave at 60°/60 bar H_2 overnight. The mixture was cooled and evaporated. The residue was chromatographed (AcOEt/hexane 1:1): **18** (0.195 g, 97%). White solid. $[\alpha]_D$ = +47 (c = 1.00, $CHCl_3$); ee 98%. M.p. 99–101°. IR: 3490*s*, 2947*w*, 1735*s*, 1613*m*, 1505*w*, 1417*w*, 1384*m*, 1268*s*, 1200*m*, 1089*m*, 1050*m*, 870*w*, 759*w*. ^{1}H-NMR: 1.65 (*s*, 2 Me); 2.52 (*d*, J = 1.00, 2 aliph. H); 2.95 (*dd*, J = 3.00, 1.00, 1 aliph. H); 3.04 (*dd*, J = 3.00, 1.00, 1 aliph. H); 3.24 (*s*, OH); 3.69 (*s*, MeO); 3.90 (*s*, MeO); 4.37 (*m*, 1 aliph. H); 6.71 (*s*, 1 arom. H); 6.83 (*dd*, J = 7.50, 1.00, 1 arom. H); 7.42 (*t*, J = 7.50, 1 arom. H); 7.59 (*dd*, J = 7.50, 1.00, 1 arom. H). MS: 328 (M^+), 287 (28), 284 (20), 241 (100), 227 (25), 213 (20), 121 (25), 55 (32), 44 (25), 43 (45), 41 (15). Anal. calc. for $C_{19}H_{22}O_6$ (346.379): C 65.88, H 6.40; found: C 65.8, H 6.3.

*(1R,3S)-Methyl 3,4-Dihydro-9-hydroxy-5,10-dioxo-1-propyl-1*H*-naphtho[2,3-*c*]pyran-3-acetate* ((1*R*,3*S*)-**13**). Gaseous HCl was bubbled through Et_2O (120 ml) maintained at r.t. for 5 min using a disposable pipet. To the resulting soln. (24.3% in weight), (*S*)-**18** (2.15 g, 6.20 mmol) was added all at once, followed by butanal (1.67 ml, 1.86 mmol). After 30 min, the mixture was treated with ice, brine, and AcOEt. The combined org. layers were dried and evaporated. The residue was diluted with dioxane (62 ml) and treated with AgO (3.0 g, 24.5 mmol). To this soln. was added 12 ml of 3N aq. $HClO_4$. After a few minutes of stirring at r.t., the mixture was transferred onto ice, brine, and $CHCl_3$. The combined org. layers were dried and evaporated. The residue was chromatographed (AcOEt/hexane 1:3.5) affording a yellow solid (2.86 g; *cis*/*trans* 95:5). To a soln. of the isolated product (2.86 g) in benzene (44 ml), concentrated H_2SO_4 (14.27 ml) was added at 0°. After 30 min at r.t., the mixture was stirred and poured onto ice and AcOEt, the org. layer washed with brine, dried, and evaporated, and the residue chromatographed (AcOEt/hexane 1:3): 1.69 g of a yellow solid (*cis*/*trans* 14:86). Further recrystallization from AcOEt/hexane led to (1*R*,3*S*)-**13** (1.18 g, 56%). Yellow solid. $[\alpha]_D$ = +108 (c = 0.10, $CHCl_3$). M.p. 124–127°. IR, ^{1}H-NMR, MS: identical to those of (1*R*,3*S*)-**13** obtained by *Method A*. Anal. calc. for $C_{19}H_{20}O_6$ (344.367): C 66.27, H 5.85; found: C 66.3, H 5.9.

*(1S,3S)-Methyl 3,4-Dihydro-9-hydroxy-5,10-dioxo-1-propyl-1*H*-naphtho[2,3-*c*]pyran-3-acetate* ((1*S*,3*S*)-**19**). As described for (1*R*,3*S*)-**13**, with gaseous HCl (24.3% in weight) in Et_2O (120 ml), (*S*)-**18** (0.96 g, 2.70 mmol), butanal (1.67 ml, 1.86 mmol), and then dioxane (29 ml), AgO (1.37 g, 11 mmol), and 6N aq. HNO_3 (53 ml). The

yellow solid (0.835 g, 87.5%; *cis/trans* 95:5) was further recrystallized from AcOEt/hexane: (1*S*,3*S*)-**19** (0.491 g, 52%). Yellow solid. $[\alpha]_D = -342$ ($c = 0.10$, $CDCl_3$). M.p. 74–75°. IR, ^{1}H-NMR, MS: identical to those of (1*R*,3*S*)-**13** obtained by *Method A*. Anal. calc. for $C_{19}H_{20}O_6$ (344.367): C 66.27, H 5.85; found: C 66.1, H 5.9.

*(3a*R,*5*R,*11b*R*)-3,3a,5,11b-Tetrahydro-7-hydroxy-5-propyl-2*H*-furo[3,2-*b*]naphtho[2,3-*d*]pyran-2,6,11-trione* (**1**). To a soln. of (1*R*,3*S*)-**13** (0.304 g, 0.89 mmol) in THF/H_2O 3:1 (152 ml), LiOH (0.372 g, 8.85 mmol) was added and the resulting purple mixture stirred at r.t. After total consumption of (1*R*,3*S*)-**13**, the soln. was acidified to pH 1–2 with 1N aq. HCl. The aq. phase was extracted with AcOEt. The combined org. layers were washed with brine, dried, and evaporated. A soln. of the residue in MeOH (122 ml) and pyridine (1.22 ml) was heated up to reflux while passing a gentle stream of O_2 through the soln. After 16 h at reflux, the soln. was cooled to r.t. and evaporated. The residue was chromatographed (AcOEt/hexane 1:1) and recrystallized from MeOH: **1** (0.206 g, 71%). Orange solid. $[\alpha]_D = +232$ ($c = 0.10$, $CHCl_3$). M.p. > 170°. IR, ^{1}H-NMR, MS: identical to those of **1** obtained by *Method A*. Anal. calc. for $C_{18}H_{16}O_6$ (328.320): C 65.85, H 4.91; found: C 65.8, H 4.9.

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