Synthesis and Absolute Configuration of Nocardione A and B, Furano-*o*-naphthoquinone-Type Metabolites of *Nocardia* sp. with Antifungal, Cytotoxic, and Enzyme Inhibitory Activities[‡]

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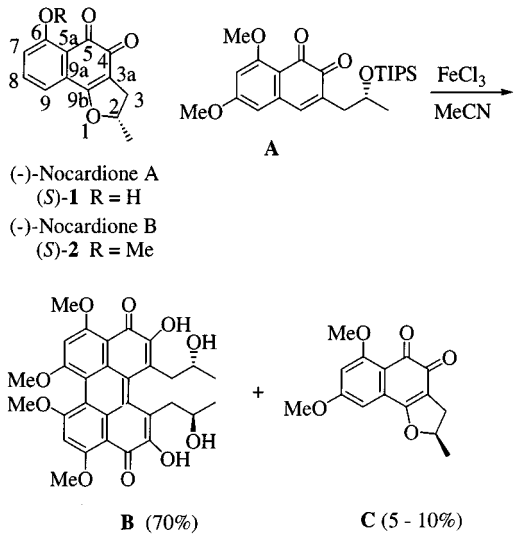
(±)-Nocardione A (**1**), (*S*)-(−)-nocardione A, and (*R*)-(+)-nocardione B (**2**) were synthesized by starting from the enantiomers of propylene oxide and 5-benzyloxy (or methoxy)-1-tetralone. The absolute configurations of the naturally occurring (−)-**1** and (−)-**2** were established as (*S*).

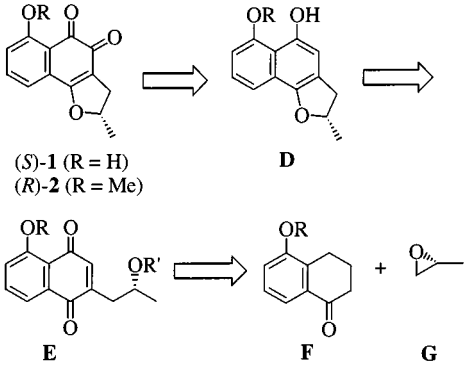
Introduction

In 2000 Otani et al. isolated two new furano-*o*-naphthoquinones, (−)-nocardione A (**1**, Scheme 1) and (−)-nocardione B (**2**) as new tyrosine phosphatase inhibitors with moderate antifungal and cytotoxic activities.[1] Due to the scarcity of the materials (only 8 mg of **1** and 0.3 mg of **2** were obtained from 4.5 L of the culture broth of *Nocardia* sp. TP-A0248), their absolute configuration remained unknown. In order to solve this problem, we undertook a synthesis of optically active **1** and **2** with known absolute configuration. After the completion of our synthesis, we noticed the work of Merlic et al.[2] who oxidized an *o*-naphthoquinone **A** with ferric chloride to give a calphostin-type compound, **B**, and nocardione-type compound **C**. The latter compound was obtained only as a minor product, and therefore this reaction could not be employed in the synthesis of nocardiones.



Scheme 1. Structures of (−)-nocardione A (**1**), B (**2**), and related compounds

As shown in Scheme 2, our plan was to build the unstable *o*-naphthoquinone system at a later stage in the synthesis, and envisage **D** as an intermediate for building up **1** and **2**. For the construction of the dihydrofuran ring a Mitsunobu reaction was considered the method of choice.



Scheme 2. Retrosynthetic analysis of **1** and **2**

This suggested **E** as an ideal intermediate, which could be synthesized from 5-alkoxy-1-tetralone **F** and (*R*)-propylene oxide **G**.

Results and Discussion

Scheme 3 summarizes the synthesis of (±)-nocardione A (**1**) and (*R*)-(+)-nocardione B (**2**). Commercially available 5-methoxy-1-tetralone (**3**) was treated with lithium hexamethyldisilazide (LHMDS), followed by (*S*)-propylene oxide (**4**) in the presence of scandium triflate in dry toluene[3] to give hydroxy ketone **5**. The hydroxy group of **5** was protected as 2,2,2-trichloroethoxycarbonate (Troc), which was known to be readily removable under reducing conditions,

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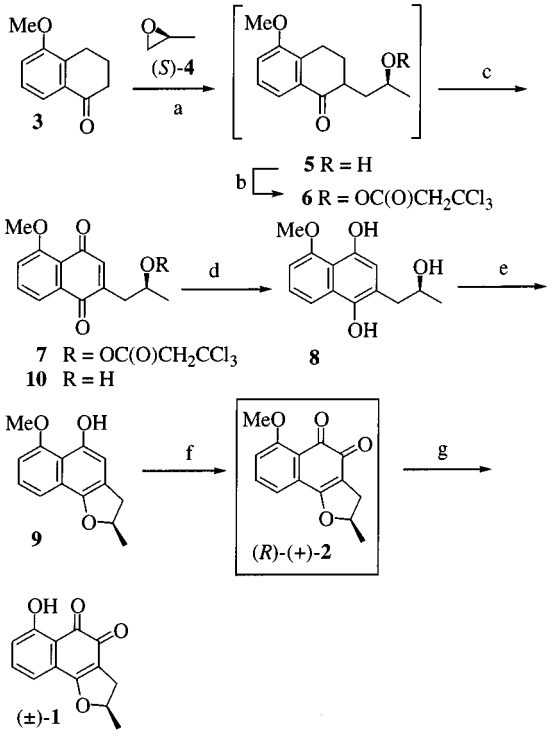


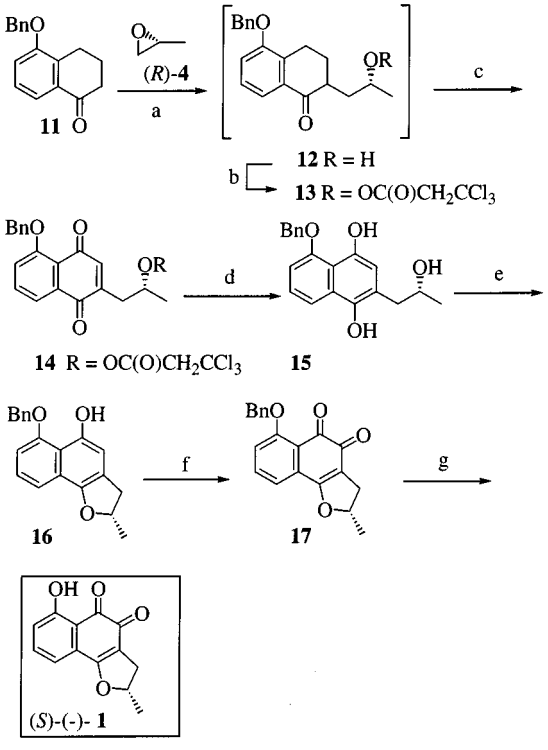
Scheme 3. Synthesis of (±)-nocardione A (**1**) and (*R*)-(+)-nocardione B (**2**); reagents and conditions: (a) 1.0 M LHMDS in hexane, toluene, −4−0 °C, 1 h then 10 mol % $Sc(OTf)_3$, room temp., 22 h; (b) $Cl_3CCH_2OC(O)Cl$, C_5H_5N, CH_2Cl_2, 0 °C, 30 min, then room temp., 11 h; (c) SeO_2, 1,4-dioxane, reflux 15 h (32%, 3 steps); (d) powdered Zn, AcOH, under Ar, room temp., 2 h (81%); (e) $EtO_2CN{=}NCO_2Et$, Ph_3P, THF, room temp., 17 h (28%); (f) $(PhSeO)_2O$, THF, 50 °C, 0.5 h (71%); (g) $AlCl_3$, 0 °C, 0.5 h, then room temp., 13.5 h, (quant.)

to furnish **6**. Conversion of **6** to *p*-naphthoquinone **7** was executed with selenium dioxide in 32% overall yield based on (*S*)-**4** (3 steps). Reduction of the quinone **7** with zinc and acetic acid to hydroquinone **8** was accompanied with concomitant removal of the Troc group, giving **8**. The hydroquinone **8** was so easily oxidized in air that the crude product had to be completely reduced by catalytic hydrogenation with palladium−charcoal to give pure hydroquinone **8**.

Ring closure of **8** to give tricyclic naphthol **9** with inversion of configuration at C-2 could be accomplished under the classical Mitsunobu conditions employing triphenylphosphane and diethyl azodicarboxylate (DEAD)[4] in a rather poor yield of 28%. The use of new reagents for Mitsunobu reactions, as developed by Tsunoda et al.,[5] did not improve the yield. Oxidation of **9** to (*R*)-nocardione B was first attempted with Fremy's salt. However, this resulted in the ring opening of **9** to give back naphthoquinone **10**. Fortunately, Barton's benzeneseleninic anhydride $[(PhSeO)_2O]$[6] smoothly oxidized **9** to furnish (*R*)-nocardione B (**2**) as dextrorotatory orange needles, m.p. 156.0−157.0 °C, $[\alpha]_D^{27} = +72.6$ ($CHCl_3$). Although these m.p. and specific rotation values were somewhat different from those reported for natural (−)-nocardione B {m.p. 79−81 °C; $[\alpha]_D^{27} = -29.8$ ($CHCl_3$)},[1] its major ^1H and ^{13}C NMR signals perfectly coincided with those of our synthetic material. The natural product was apparently contaminated with impurities, as evidenced by additional ^1H and ^{13}C NMR signals observed in its spectra. To ascertain the homogeneity of our synthetic material, (*R*)-(+)-**2** was analyzed by HPLC on a chiral stationary phase, and shown to be enantiomerically pure. Unfortunately, no sample of the natural **2** was available to allow its HPLC analysis. Since the naturally occurring nocardione B is levorotatory, its absolute configuration was determined as (*S*), although there is a slight possibility that impurities in the natural **2** might have reversed the sign of its optical rotation. The overall yield of (*R*)-nocardione B (**2**) was 5.1% based on (*S*)-propylene oxide (6 steps).

Finally, demethylation of (*R*)-nocardione B (**2**) was accomplished by treatment with aluminum chloride in dichloromethane.[7] This step caused complete racemization of the product, and (±)-nocardione A (**1**) was obtained as dark red needles, m.p. 156.0−157.0 °C. HPLC analysis of this compound on a chiral stationary phase revealed it to be racemic. All our attempts to effect demethylation without racemization were unsuccessful. A logical alternative to circumvent this difficulty was to use a more readily removable protective group for the phenolic hydroxy group than the methyl group.

Accordingly, (*S*)-(−)-nocardione A (**1**) was synthesized as shown in Scheme 4 by employing a benzyl group as the



Scheme 4. Synthesis of (*S*)-(−)-nocardione A (**1**); reagents and conditions: (a) 1.0 M LHMDS in hexane, toluene, −4−0 °C, 1 h; then 10 mol % $Sc(OTf)_3$, room temp., 21 h; (b) $Cl_3CCH_2OC(O)Cl$, C_5H_5N, CH_2Cl_2, 0 °C, 20 min then room temp., 1 h; (c) SeO_2, 1,4-dioxane, reflux 15 h (36%, 3 steps); (d) powdered Zn, AcOH, under Ar, room temp., 2 h (81%); (e) $EtO_2CN{=}NCO_2Et$, Ph_3P, THF, room temp., 19 h (19%); (f) $(PhSeO)_2O$, THF, 50 °C., 0.5 h (78%); (g) H_2, 10% Pd/C, DMF, room temp., 10 min (50%)

protective group, which could be removed successfully (vide infra). Known 5-benzyloxy-1-tetralone (**11**)[8] and (*R*)-propylene oxide (**4**) were converted into benzyl-protected nocardione A (**17**) in the same manner as described above for the synthesis of (*R*)-nocardione B via **12**, **13**, **14**, **15**, and **16**. In this case, too, the Mitsunobu-type ring closure of **15** to give **16** proceeded with the rather miserable yield of 19%. The final deprotection step was carefully examined to achieve an acceptable yield. A large amount (40−50 wt% of the substrate **17**) of palladium−charcoal was added to **17** in DMF, and the mixture was stirred under hydrogen for 5−10 min. Longer reaction time caused decrease in the yield of **1**. Solvents such as THF or ethyl acetate and acetic acid did not give reproducible yields. After hydrogenation, the dark brown-red color of the mixture turned pale blue. Then hydrogen atmosphere was replaced with air to cause oxidation of the generated hydroquinone as evidenced by the color change of the solution to dark red. (*S*)-nocardione A (**1**) was obtained as dark red needles, m.p. 172.5−173.5 °C, $[\alpha]_D^{21} = -56.0$ ($CHCl_3$).

Again, as in the case of (*R*)-**2**, the m.p. and specific rotation values were somewhat different from those reported for the natural (−)-nocardione A {m.p. 115−120 °C; $[\alpha]_D^{20} = -85.4$ ($CHCl_3$)}. However, its major ^1H and ^{13}C NMR signals were in perfect agreement with those of our synthetic material. In the ^1H NMR spectrum of the natural product, we could recognize some additional signals due to impurities. HPLC analysis of the synthetic (*S*)-(**−**)-**1** proved it to be enantiomerically pure. Here again, no comparison sample of the natural **1** was available. The naturally occurring (**−**)-**1** was thus determined to be with (*S*) absolute configuration. The overall yield of (*S*)-(**−**)-**1** was 2.2% based on (*R*)-**4** (7 steps).

In conclusion, (±)-nocardione A (**1**), (*S*)-(**−**)-nocardione A (**1**), and (*R*)-(**+**)-nocardione B (**2**) were synthesized, and the absolute configurations of the naturally occurring and levorotatory **1** and **2** were determined as (*S*). Further improvements are awaited to achieve a better yield in the ring closure step (**8** → **9** and **14** → **15**).

Experimental Section

Boiling and melting points: Uncorrected values. − Melting points: Yanaco MP-S3. − $[\alpha]_D$: Jasco DIP-1000, Jasco P-1010. − IR: Jasco IRA-102, Jasco FT/IR460. − ^1H NMR: Jeol JNM-EX 90A (90 MHz), Jeol JNM-LA 400, (TMS at $\delta_H = 0.00$ or $CHCl_3$ at $\delta_H = 7.26$ or CH_3OH at $\delta_H = 3.30$ as internal standard). − ^{13}C NMR: Jeol JNM-LA 400 (100 MHz), ($CDCl_3$ at $\delta_C = 77.0$ or CD_3OD at $\delta_C = 49.0$ as an internal standard). − MS: Jeol JMS-AX 505HA. − CC: Merck Kieselgel 60 Art. no. 1.07734 or Kanto Chemical silica gel 60N (spherical, neutral). − TLC: 0.25 mm Merck silica gel plates (60F-254). − HPLC: Column: Daicel Chiralpak AD − RH® (4.6 mm ×150 mm). UV detector: SSC − 5200. Pump unit: SSC − Flow system 3100. Recorder: SIC − chromatocoder 12. − UV-Vis: Hitachi U-2010.

(*S*)-(+)-5-Methoxy-2-{2′-(2′′,2′′,2′′-trichloroethoxycarbonyl)-oxy}propyl-1,4-naphthalenedione (7). − (i) Alkylation with (*S*)-(−)-Propylene Oxide: A 1.0 M solution of LHMDS in *n*-hexane (243 mL) was cooled in an ice bath at −5−0 °C. To this solution was added a solution of **3** (39 g, 216 mmol) in toluene (170 mL) dropwise via cannula over 1.0 h under Ar. After having been stirred for 1.5 h at −5−0 °C, a solution of (*S*)-(−)-propylene oxide (4.10 g, 71 mmol) in toluene (38 mL) was added dropwise via cannula over 10 min, and then $Sc(OTf)_3$ (3.9 g, 8 mmol) was added in one portion. The resulting mixture was stirred at room temperature under Ar for 22 h. The mixture was diluted with Et_2O (200 mL) and filtered through a celite pad. The residue on the pad was washed thoroughly with EtOAc (300 mL). The combined filtrates were washed with sat. aq. NH_4Cl, 5% HCl and brine (each 200 mL). All the aqueous layers were combined and extracted with EtOAc (500 mL). The second extract was washed with brine (200 mL). All the organic layers were combined, dried with Na_2SO_4, filtered, and concentrated in vacuo to give 43.7 g of the crude product. This was purified twice by silica gel chromatography (400 g, EtOAc/*n*-hexane 1:2−4:1 as eluent, then 600 g, EtOAc/*n*-hexane 1:3−1:1 as eluent) to give an inseparable mixture of the diastereomers of **5** (9.89 g) as a red oil. − IR (film): $\tilde{\nu}_{max} = 3450$ (s, OH), 1680 (s, C=O), 1580 (m, C=C). − ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.23$ (d, $J = 6.4$ Hz, 1.1 H, CH_3CH), 1.27 (d, $J = 6.4$ Hz, 1.5 H, CH_3CH), 1.42 (d, $J = 6.4$ Hz, 0.4 H, CH_3CH), 1.51 (ddd, $J = 15.0$, 5.1 Hz, 2.7 Hz, 0.5 H), 1.60 (ddd, $J = 14.0$, 8.2 Hz, 4.2 Hz, 0.5 H), 1.82−2.01 (m, 1 H), 2.02−2.15 (m, 1 H), 2.17−2.30 (m, 1 H), 2.66−2.85 (m, 2 H), 3.06 (dt, $J = 18.0$, 4.9 Hz, 0.5 H), 3.11 (dt, $J = 18.0$, 4.2 Hz, 0.5 H), 3.87 (s, 3 H, OCH_3), 3.90−4.05 (m, 1 H), 7.02 (d, $J = 8.0$ Hz, 1 H, Ar−*H*), 7.28 (t, $J = 8.4$ Hz, 1 H, Ar−*H*), 7.64 (dd, $J = 8.0$, 1.0 Hz, 0.5 H, Ar−*H*), 7.65 (d, $J = 8.0$ Hz, 0.5 H, Ar−*H*). Because the obtained material was an inseparable diastereomeric mixture, it was impossible to assign each NMR peak correctly at this stage.

(ii) Protection of the Hydroxy Group of 5: To an ice cooled solution of **5** (9.83 g) and pyridine (7.45 mL, 92 mmol) in CH_2Cl_2 (50 mL) was added a solution of 2,2,2-trichloroethyl chloroformate (10.7 g, 50 mmol) in CH_2Cl_2 (50 mL) over 30 min. After the resulting mixture was stirred for 30 min, an additional amount of 2,2,2-trichloroethyl chloroformate (2.0 g, 9.4 mmol) in CH_2Cl_2 (2 mL) was added to it. The mixture was stirred at room temperature for 10 h. Again, an additional portion of 2,2,2-trichloroethyl chloroformate (3.0 g, 14 mmol) in CH_2Cl_2 (3 mL) was added. After having been stirred for an additional 30 min, the mixture was diluted with Et_2O (750 mL), washed with sat. aq. $CuSO_4$ (150 mL), water (2 × 150 mL), and brine (150 mL). It was then dried with Na_2SO_4, filtered, and concentrated in vacuo to give 22.0 g of the crude product as a red oil. This oil was purified twice by silica gel chromatography {400 g, EtOAc/*n*-hexane 1:4 as eluent, then Kanto Chemical silica gel 60N (spherical, neutral) 210 g EtOAc/*n*-hexane 1:10−1:1 as eluent} to give an inseparable mixture of the diastereomers of **6** (16.1 g) as a red oil. − IR (film): $\tilde{\nu}_{max} = 1760$ (s, O−C=O), 1680 (s, C=O), 1600 (s, C=C), 1580 (s, C=C). − ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.40$ (d, $J = 6.3$ Hz, 1.5 H, CH_3CH), 1.41 (d, $J = 6.3$ Hz, 1.5 H, CH_3CH), 1.58−1.94 (m, 3 H), 2.20−2.36 (m, 1.5 H), 2.48−2.55 (m, 0.5 H), 2.58−2.81 (m, 2 H), 3.09 (ddd, $J = 18.0$, 9.0 Hz, 4.4 Hz, 0.5 H), 3.86 (s, 3 H, OCH_3), 4.73 (d, $J = 12.0$ Hz, 0.5 H, Cl_3CCH_2), 4.74 (d, $J = 12.0$ Hz, 0.5 H, Cl_3CCH_2), 4.77 (d, $J = 12.0$ Hz, 0.5 H, Cl_3CCH_2), 4.80 (d, $J = 12.0$ Hz, 0.5 H, Cl_3CCH_2), 5.06−5.19 (m, 1 H, CH_2CHOC=O), 7.01 (d, $J = 8.3$ Hz, 1 H, Ar−*H*), 7.27 (t, $J = 8.0$ Hz, 1 H, Ar−*H*), 7.61 (dd, $J = 8.0$, 1.0 Hz, 0.5 H, Ar−*H*), 7.63 (d, $J = 8.0$ Hz, 0.5 H, Ar−*H*). Because the obtained material was an inseparable diastereomeric mixture, it was impossible to assign each NMR peak correctly at this stage.

(iii) Oxidation with SeO_2: A mixture of **6** (16.0 g) and SeO_2 (8.7 g, 78 mmol) in 1,4-dioxane (170 mL) was heated under reflux for 11 h under Ar. The resulting solution was diluted with EtOAc (500 mL) and washed with water and brine (each 350 mL). The aqueous layers were combined and extracted with EtOAc (2 × 500 mL). The organic layers were combined, washed with brine (350 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo to give 19.3 g of the crude product as a red oil. This was purified by silica gel chromatography (1 kg, EtOAc/*n*-hexane 1:2−2:3 as an eluent) to give 9.58 g [32% from (*S*)-propylene oxide in 3 steps] of **7** as an amorphous and sticky solid; $[\alpha]_D^{26} = +17.4$ ($c = 0.57$ in $CHCl_3$). − IR (KBr): $\tilde{\nu}_{max} = 1755$ (s, O−C=O), 1660 (s, C=O), 1630 (s, C=C), 1590 (s, C=C). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (d, $J = 6.4$ Hz, 3 H, C*H*$_3$CH), 2.72 (ddd, $J = 14.0$, 8.8 Hz, 0.8 Hz, 1 H, C*H*$_2$CH), 2.96 (ddd, $J = 14.0$, 4.4 Hz, 0.8 Hz, 1 H, C*H*$_2$CH), 4.00 (s, 3 H, C*H*$_3$O), 4.69 (s, 2 H, Cl_3CCH_2O), 5.09−5.19 (m, 1 H, $CH_3CHOC{=}O$), 6.76 (s, 1 H, CO−C*H*=C), 7.30 (dd, $J = 8.4$ Hz, 0.8 Hz, 1 H, Ar−*H*), 7.68 (dd, $J = 8.4$, 7.6 Hz, 1 H, Ar−*H*), 7.76 (dd, $J = 7.6$, 0.8 Hz, 1 H, Ar−*H*). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.1, 35.7, 56.3, 74.3, 76.3, 94.2, 117.7, 119.3, 119.5, 134.0, 134.7, 138.9, 143.6, 153.3, 159.3, 183.8, 184.8. − $C_{17}H_{15}Cl_3O_6$ (421.7) calcd. C 48.42, H 3.59; found C 48.52, H 3.64.

(*S*)-(+)-2-(2′-Hydroxypropyl)-5-methoxy-1,4-naphthalenediol (8): To a degassed solution of **7** (9.28 g, 22 mmol) in AcOH (45 mL), which was well cooled in an ice bath, was added powdered zinc (9.0 g, 138 mmol) in one portion. The ice bath was removed and the resulting suspension was stirred vigorously at room temperature for 1 h under Ar. The mixture was diluted with EtOAc (700 mL) and washed with sat. aq. $NaHCO_3$ (2 × 200 mL), water (1 × 200 mL), and brine (1 × 200 mL). The aqueous layers were combined and extracted with EtOAc (400 mL). The second extract was washed with brine (1 × 200 mL). All the organic layers were combined, dried with Na_2SO_4 under Ar, filtered, and concentrated in vacuo to give 8.26 g of the crude product as a black oil. This was purified by chromatography on silica gel (830 g, EtOAc/*n*-hexane 1:3−1:0 as eluent) to give 6.10 g of a dark red oil. (At this point, TLC analysis showed that the obtained product had been partially oxidized to quinone in the course of the purification operations. The crude product was therefore reduced to obtain a single hydroquinone product employing the following conditions). The obtained oil and 10% Pd/C (600 mg) in EtOAc (30 mL) were vigorously stirred at room temperature under H_2. The mixture was filtered and the filtrate was concentrated in vacuo to give 5.58 g of a gummy product. This was crystallized from EtOAc/*n*-hexane to give 4.99 g of a solid, which was well washed with Et_2O/*n*-pentane (1:3) to give 4.42 g (81%) of pale brown powder. This was recrystallized from benzene/*n*-hexane to give an analytical sample of **8** as pale brown powder; m.p. 109.0−110.0 °C (benzene/*n*-hexane). − $[\alpha]_D^{27} = +14.9$ ($c = 0.545$ in MeOH). − IR (KBr): $\tilde{\nu}_{max} = 3400$ cm^{-1} (s, O−H), 3300−2200 (br, O−H), 1640 (m, C=C), 1610(s, C=C), 1515 (m, C=C). − ^{1}H NMR (400 MHz, CD_3OD): δ = 1.18 (d, $J = 6.1$ Hz, 3 H, C*H*$_3$CH), 2.80 (dd, $J = 14.0$, 6.6 Hz, 1 H, C*H*$_2$CH), 2.85 (dd, $J = 14.0$, 4.6 Hz, 1 H, C*H*$_2$CH), 3.97 (s, 3 H, C*H*$_3$O), 4.05−4.17 (m, 1 H, C*H*OH), 6.55 (s, 1 H, Ar−*H*), 6.79 (d, $J = 8.0$ Hz, 1 H, Ar−*H*), 7.24 (t, $J = 8.0$ Hz, 1 H, Ar−*H*), 7.75 (d, $J = 8.0$ Hz, 1 H, Ar−*H*). − ^{13}C NMR (100 MHz, CD_3OD): δ = 23.1, 41.7, 56.5, 70.1, 105.0, 113.9, 115.5, 116.9, 123.2, 126.0, 129.6, 144.1, 148.2, 157.3. − $C_{14}H_{16}O_4$ (248.3) calcd. C 67.73, H 6.50; found C 67.72, H 6.47.

(*R*)-(−)-2,3-Dihydro-6-methoxy-2-methylnaphtho[1,2-*b*]furan-5-ol (9): To a degassed solution of Ph_3P (4.52 g, 17.2 mmol) and **8** (4.07 g, 16.4 mmol) in THF (400 mL) was added, dropwise, a solution of DEAD (3.00 g, 17.2 mmol) in THF (32 mL) over 2 h under Ar at room temperature. The resulting mixture was stirred for 17 h at room temperature. It was then concentrated in vacuo to give a black tar, which was purified twice by chromatography on silica gel {600 g, EtOAc/*n*-hexane 1:3 as eluent, then 200 g, EtOAc/*n*-hexane 1:6 as eluent) to give 1.07 g (28%) of **9** as pale yellow powder. This was recrystallized from *n*-hexane to give an analytical sample as pale yellow plates; m.p. 98.0−99.0 °C (*n*-hexane). − $[\alpha]_D^{26} = -14.0$ ($c = 1.00$ in MeOH). − IR (KBr): $\tilde{\nu}_{max} = 3450$ cm^{-1} (s, O−H), 1640 (m, C=C), 1600 (s, C=C), 1515 (m, C=C). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (d, $J = 6.3$ Hz, 3 H, C*H*$_3$CH), 2.93 (dd, $J = 15.0$, 7.8 Hz, 1 H, C*H*$_2$CH), 3.42 (dd, $J = 15.0$, 9.0 Hz, 1 H, C*H*$_2$CH), 4.04 (s, 3 H, C*H*$_3$O), 5.00−5.10 (m, 1 H, CH_2CHOAr), 6.72 (d, $J = 7.6$ Hz 1 H, Ar−*H*), 6.75 (s, 1 H, Ar−*H*), 7.27 (dd, $J = 8.5$, 7.6 Hz, 1 H, Ar−*H*), 7.48 (dd, $J = 8.5$, 1.0 Hz, 1 H, Ar−*H*), 8.93 (s, 1 H, Ar−O*H*). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 38.4, 55.9, 79.6, 103.6, 107.1, 113.9, 115.4, 121.7, 121.8, 125.2, 147.5, 148.2, 156.2. − $C_{14}H_{14}O_3$ (230.3) calcd. C 73.03, H 6.13; found C 73.36, H 6.22.

(*R*)-(+)-2,3-Dihydro-6-methoxy-2-methylnaphtho[1,2-*b*]furan-4,5-dione [(+)-Nocardione B (2)]: To a solution of $(PhSeO)_2O$ (865 mg, 3.8 mmol) in THF (10 mL), heated at 49 °C, was added a solution of **9** (2.00 g, 5.0 mmol) in THF (8.5 mL) dropwise through a dropping funnel under Ar. The resulting mixture was stirred for 0.5 h at 50±1 °C, then cooled to room temperature and diluted with EtOAc (150 mL). The EtOAc solution was washed with water (100 mL), sat. aq $NaHCO_3$, (100 mL), and brine (100 mL). The aqueous layers were combined and extracted with EtOAc (2 × 150 mL). The organic solutions were combined, washed with brine (100 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo to give 2.38 g of an orange powder. This was purified twice by chromatography on silica gel {Kanto Chemical silica gel 60N (spherical, neutral) 270 g, EtOAc/*n*-hexane 1:1−3:1 as eluent, then Kanto Chemical silica gel 60N (spherical, neutral) 350 g, EtOAc/*n*-hexane 3:1 as eluent} to give 649 mg (71%) of **2** as an orange powder. This was recrystallized from EtOAc/*n*-hexane to give an analytical sample of **2** as orange needles; m.p. 156.0−157.0 °C (EtOAc/*n*-hexane). {ref.[1] m.p. 79−81 °C}. − $[\alpha]_D^{27} = +72.6$ ($c = 0.32$ in $CHCl_3$). {ref.[1] $[\alpha]_D^{27} = -29.8$ ($c = 0.32$ in $CHCl_3$)}. − IR (KBr): $\tilde{\nu}_{max} = 1690$ (m, C=O), 1660 (s, C=O), 1620 (s, C=C), 1580 (s, C=C), 1465 (s, C=C), 1405 (m), 1300 (s), 1275 (w), 1250 (w, C− O−C), 1035 (s, C− O−C), 900 (m), 800 (m). {ref.[1] IR (KBr): $\tilde{\nu}_{max} = 1650$, 1620, 1580, 1300, 1270, 1030.} − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56 (d, $J = 6.4$ Hz, 3 H, C*H*$_3$CH), 2.72 (dd, $J = 15.0$, 7.3 Hz, 1 H, C*H*$_2$CH), 3.26 (dd, $J = 15.0$, 9.8 Hz, 1 H, C*H*$_2$CH), 3.99 (s, 3 H, C*H*$_3$O), 5.17−5.27 (m, 1 H, CH_2CHOAr), 7.17 (d, $J = 8.8$ Hz 1 H, Ar−*H*), 7.28 (d, $J = 7.3$ Hz 1 H, Ar−*H*), 7.59 (dd, $J = 8.8$, 7.3 Hz, 1 H, Ar−*H*). {ref.[1] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56 (d, $J = 6.3$ Hz, 3 H, C*H*$_3$CH), 2.71 (dd, $J = 15.2$, 7.3 Hz, 1 H, C*H*$_2$CH), 3.25 (dd, $J = 15.2$, 9.6 Hz, 1 H, C*H*$_2$CH), 3.98 (s, 3 H, C*H*$_3$O), 5.22 (m, 1 H, CH_2CHOAr), 7.17 (d, $J = 8.5$ Hz, 1 H, Ar−*H*), 7.27 (d, $J = 8.3$ Hz, 1 H, Ar−*H*), 7.58 (t, $J = 8.3$ Hz, 1 H, Ar−*H*).} − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0 (10-C), 33.6 (3-C), 56.4 (6-O*C*H$_3$), 84.1 (2-C), 114.6 (3a-C), 116.6 (9-C), 117.3 (7-C), 118.1 (5a-C), 129.7 (9a-C), 135.8 (8-C), 161.8 (6-C), 169.2 (9b-C), 175.6 (4-C), 180.4 (5-C). {ref.[1] ^{13}C NMR: (100 MHz, $CDCl_3$): δ = 21.9 (10-C), 33.5 (3-C), 56.2 (6-O*C*H$_3$), 84.1 (2-C), 114.3 (3a-C), 116.7 (9-C), 117.3 (7-C), 118.1 (5a-C), 129.5 (9a-C), 135.8 (8-C), 161.8 (6-C), 169.3 (9b-C), 175.5 (4-C), 180.2 (5-C)}. The signals due to 3a-C and 5a-C were assigned on the basis of HMBC experiments. The ^{1}H and ^{13}C NMR spectra of the natural (−)-**2** contain additional peaks due to unknown impurities. − $C_{14}H_{12}O_4$ (244.2) calcd.

C 68.85, H 4.95; found C 68.92, H 5.12. − UV-Vis (MeOH) λ_{max} (ε): 230 (22000), 259 (20000), 397 (6000). {ref.[1] 201 (20300), 230 (15900), 258 (13200), 395 (3700)}. − UV-Vis (0.01 N HCl: MeOH 1:9) λmax (ε): 231 (20000), 259 (19000), 400 (5800). {ref.[1] 233 (13600), 258 (13500), 396 (4000)}. − UV-Vis (0.01 N NaOH/MeOH 1:9) λ_{max} (ε): 230 (19000), 259 (18000), 400 (5300). {ref.[1] 207 (8300), 231 (11900), 259 (11300), 396 (3000)}. − The HPLC conditions were as follows: Column, Daicel Chiralpak AD − RH® (4.6 mm ×150 mm); eluent, H_2O/MeCN (2:1); flow rate, 0.6 mL/min; Detection at λ = 230 nm; sample concentration and injection volume, 0.1 mg/mL in MeCN solution × 0.5 μL. Under these conditions, (*S*)-**2** was detected at t_R = 15.4 min, and (*R*)-**2** was detected at t_R = 18.9 min, ca.100% *ee*.

(±)-2,3-Dihydro-6-hydroxy-2-methylnaphtho[1,2-*b*]furan-4,5-dione [(±)-Nocardione A (1)]: To a solution of (+)-**2** (250 mg, 1.02 mmol) in CH_2Cl_2 (7.5 mL) in an ice bath was added finely powdered $AlCl_3$ (2.05 g, 15.4 mmol) in one portion. The resulting mixture was vigorously stirred at room temperature for 13.5 h, and then poured into crashed-ice/water (100 mL). To this mixture was added conc. HCl (100 mL). After having been stirred vigorously for several minutes, the mixture was extracted with EtOAc (2 × 150 mL). The extracts were combined, washed with brine (250 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo to give 249 mg of crude (±)-**1**. This was purified by chromatography on silica gel (30 g, $CHCl_3$/EtOAc 10:1 as an eluent) to give 236 mg of (±)-**1** as a dark red powder {quant., 5.1% in 7 steps from (*S*)-**4**.}. This was recrystallized from EtOAc/*n*-hexane to give an analytical sample of (±)-**1** as dark red needles: m.p. 156.0−157.0 °C (EtOAc/*n*-hexane). − IR (KBr): $\tilde{\nu}_{max}$ = 1660 (sh., C=O), 1640 (s, C=O), 1615 (s, C=C), 1580 (s, C=C), 1480 (m), 1450 (s), 1410 (m), 1305 (s), 1240 (m, C− O−C), 1030 (s, C− O−C). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$CH), 2.72 (dd, *J* = 15.6, 7.2 Hz, 1 H, C*H*$_2$CH), 3.26 (dd, *J* = 15.6, 10 Hz, 1 H, C*H*$_2$CH), 5.20−5.27 (m, 1 H, CH$_2$C*H*OAr), 7.11 (dd, *J* = 8.8, 0.8 Hz, 1 H, Ar−*H*), 7.19 (dd, *J* = 7.2, 0.8 Hz, 1 H, Ar−*H*), 7.53 (dd, *J* = 8.8, 7.2 Hz, 1 H, Ar−*H*), 11.9 (s, 1 H, O−*H*). {ref.[1] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$CH), 2.73 (dd, *J* = 15.6, 7.3 Hz, 1 H, C*H*$_2$CH), 3.27 (dd, *J* = 15.6, 9.8 Hz, 1 H, C*H*$_2$CH), 5.25 (m, 1 H, CH$_2$C*H*OAr), 7.13 (d, *J* = 8.8 Hz, 1 H, Ar−*H*), 7.2 (d, *J* = 7.3 Hz, 1 H, Ar−*H*), 7.54 (dd, *J* = 8.8, 7.3 Hz, 1 H, Ar−*H*), 11.95 (s, 1 H, O−*H*).} − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0 (10-C), 33.5 (3-C), 84.6 (2-C), 113.4 (5a-C), 115.2 (3a-C), 117.6 (9-C), 123.3 (7-C), 127.4 (9a-C), 137.6 (8-C), 164.4 (6-C), 169.2 (9b-C), 175.0 (4-C), 185.4 (5-C). {ref.[1] ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.45 (10-C), 34.04 (3-C), 85.04 (2-C), 113.99 (5a-C), 115.67 (3a-C), 117.98 (9-C), 123.77 (7-C), 128.0 (9a-C), 138.03 (8-C), 164.96 (6-C), 169.58 (9b-C), 175.53 (4-C), 185.93 (5-C)}. The ^{1}H and ^{13}C NMR spectra were identical with those of the natural (−)-**1**, although in the ^{1}H NMR spectrum of (−)-**1**, some signals due to impurities were observable. − $C_{13}H_{10}O_4$ (230.2) calcd. C 67.82, H 4.38; found C 67.85, H 4.47. − The product was nearly racemic, as revealed by its HPLC analysis on Chiralpak AD-RH ® (vide infra). Experimental $[\alpha]_D$ value of the product was $[\alpha]_D^{26}$= +0.7 (*c* = 0.36, $CHCl_3$).

(*R*)-(−)-5-Benzyloxy-2-[2′-(2′′,2′′,2′′-trichloroethoxycarbonyl)-oxy]propyl-1,4-naphthalenedione (14). − (i) Alkylation with (*R*)-(+)-Propylene Oxide: A 1.0 M LHMDS in *n*-hexane solution (308 mL) was cooled in an ice/MeOH bath at −5−0 °C. To this solution was added a solution of **11** (64.6 g, 256 mmol) in toluene (250 mL) dropwise via cannula over 1.0 h under Ar. After having been stirred for 1 h at −4−0 °C, a solution of (*R*)-(+)-propylene oxide (5.97 g, 103 mmol) in toluene (50 mL) was added dropwise via cannula over 15 min, and then $Sc(OTf)_3$ (5.0 g, 10.3 mmol) was added in one portion. The resulting mixture was stirred at room temperature under Ar for 21 h. The mixture was cooled in an ice bath, quenched with sat. aq. NH_4Cl (300 mL), and filtered through a celite pad. The residue on the pad was washed with EtOAc (300 mL). The biphasic filtrate was separated. The upper organic phase was washed with 5% HCl and brine (each 300 mL). All the aqueous layers were combined and extracted with EtOAc (300 mL). All the organic layers were combined, dried with Na_2SO_4, filtered, and concentrated in vacuo to give 83.7 g of the crude product. This was purified by silica gel chromatography (1 kg, EtOAc/*n*-hexane, 1:4−1:2) to give 20.2 g of an inseparable diastereomeric mixture of **12** as a pale orange solid. − IR (KBr): $\tilde{\nu}_{max}$ = 3300 (s, OH), 1680 (s, C=O), 1595 (s, C=C), 1580 (s, C=C). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 6.3 Hz, 1.2 H, C*H*$_3$CH), 1.27 (d, *J* = 6.1 Hz, 1.5 H, C*H*$_3$CH), 1.43 (d, *J* = 6.3 Hz, 0.3 H, C*H*$_3$CH), 1.52 (ddd, *J* = 15.0, 5.1 Hz, 2.7 Hz, 0.5 H), 1.56−1.65 (m, 0.5 H), 1.83−2.01 (m, 0.5 H), 2.01−2.16 (m, 1 H), 2.17−2.40 (m, 1.5 H), 2.66−3.03 (m, 2 H), 3.15 (dt, *J* = 18.0, 5.1 Hz, 0.5 H), 3.20 (dt, *J* = 18.0, 4.2 Hz, 0.5 H), 3.90−4.06 (m, 1 H), 5.09 (d, *J* = 12.0 Hz, 1 H, ArC*H*$_2$O), 5.13 (d, *J* = 12.0 Hz, 1 H, ArC*H*$_2$O), 7.09 (d, *J* = 8.3 Hz, 1 H, Ar−*H*), 7.26 (t, *J* = 8.0 Hz, 1 H, BnOAr−*H*), 7.35−7.47 (m, 5 H, Ar−*H*), 7.65 (dd, *J* = 8.3, 1.0 Hz, 0.5 H, BnOAr−*H*), 7.67 (dd, *J* =8.3, 1.0 Hz, 0.5 H, BnOAr−*H*). Since the obtained material was a diastereomeric mixture, it was impossible to assign each NMR peak correctly at this stage. − HRMS (EI) [M^+] ($C_{20}H_{22}O_3$): calcd. 310.1569; found 310.1569.

(ii) Protection of the Hydroxy Group of 12: To an ice-cooled solution of **12** (20.0 g) and pyridine (11.4 g, 142 mmol) in CH_2Cl_2 (125 mL) was added a solution of 2,2,2-trichloroethyl chloroformate (16.4 g, 25 mmol) in CH_2Cl_2 (25 mL) over 20 min. The resulting mixture was stirred for 1 h, and then concentrated in vacuo to1/4 volume. This was diluted with EtOAc (300 mL). The EtOAc solution was washed with water (2 × 200 mL) and brine (200 mL), dried with Na_2SO_4, filtered, and concentrated to give 47.0 g of a crude product as an oil. This was purified by silica gel chromatography (400 g, EtOAc/*n*-hexane 1:3 as eluent) to give 19.1 g of pure fractions as a solid and 13.8 g of impure fractions as an oil. The latter was further purified by silica gel chromatography (300 g, EtOAc/*n*-hexane 1:7 as eluent) to give 8.08 g of pure fractions as an oil. All of the pure fractions were combined, which solidified to give 27.0 g of an inseparable and sticky diastereomeric mixture of **13**. − IR (KBr): $\tilde{\nu}_{max}$ = 1745 (s, O−C=O), 1680 (s, C=O), 1600 (m, C=C), 1585 (s, C=C). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.406 (d, *J* = 6.3 Hz, 1.5 H, C*H*$_3$CH), 1.413 (d, *J* = 6.3 Hz, 1.5 H, C*H*$_3$CH), 1.64 (ddd, *J* = 15.0, 8.6 Hz, 3.9 Hz, 0.34 H), 1.73 (ddd, *J* = 15.0, 9.0 Hz, 4.9 Hz, 0.31 H), 1.79−1.95 (m, 0.72 H), 2.20−2.29 (m, 0.75 H), 2.35 (ddd, *J* = 13.0, 8.8 Hz, 4.4 Hz, 0.54 H), 2.52 (ddd, *J* = 15.0, 9.5 Hz, 4.6 Hz, 0.56 H), 2.59−2.69 (m, 1 H), 2.74−2.89 (m, 1 H), 3.13−3.23 (m, 1 H), 4.72 (d, *J* = 12.0 Hz, 0.5 H, Cl_3CCH_2), 4.75 (d, *J* = 12.0 Hz, 0.5 H, Cl_3CCH_2), 4.78 (d, *J* = 12.0 Hz, 0.5 H, Cl_3CCH_2), 4.79 (d, *J* = 12.0 Hz, 0.5 H, Cl_3CCH_2), 5.06−5.19 (m, 1 H, CH$_2$C*H*OC=O), 5.09 (d, *J* = 12.0 Hz, 1 H, ArOCH_2), 5.12 (d, *J* = 12.0 Hz, 1 H, ArOCH_2), 7.08 (dd, *J* = 8.3, 1.0 Hz, 1 H, BnOAr−*H*), 7.26 (t, *J* = 7.9 Hz, 1 H, BnOAr−*H*), 7.35−7.47 (m, 5 H, Ar−*H*), 7.63 (dd, *J* = 7.8, 1.0 Hz, 0.5 H, BnOAr−*H*), 7.65 (dd, *J* =7.8, 1.0 Hz, 0.5 H, BnOAr−*H*). Since the product was an inseparable diastereomeric mixture, it was impossible to assign each NMR peak correctly at this stage. − HRMS (EI) [M^+] ($C_{23}H_{23}Cl_3O_5$): calcd. 484.0611; found 484.0618.

(iii) Oxidation with SeO_2: A mixture of **13** (26.8 g) and SeO_2 (12.2 g, 110 mmol) in 1,4-dioxane (240 mL) was heated under re-

flux for 15 h. The resulting solution was diluted with EtOAc (1000 mL), and washed with water and brine (each 500 mL). The aqueous layers were combined, and extracted with EtOAc (750 mL). The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated in vacuo to give 34.3 g of the crude product as a red oil. This was purified by silica gel chromatography (1 kg, EtOAc/*n*-hexane 1:3 as eluent) to give 15.9 g of pure fractions and 6.3 g of impure fractions. The latter was further purified by silica gel chromatography {Kanto Chemical silica gel 60N (spherical, neutral) 560 g, EtOAc/*n*-hexane 1:3 as eluent} to give pure fractions. All of the pure fractions were combined and kept in vacuo to give 18.0 g of **14** as a red amorphous and sticky solid. [36% from (*R*)-propylene oxide in 3 steps]; $[\alpha]_D^{25} = -17.6$ (c = 1.22 in MeOH). − IR (KBr): $\tilde{\nu}_{max}$ = 1755 (s, O−C=O), 1660 (s, C=O), 1630 (s, C=C), 1585 (s, C=C). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (d, J = 6.4 Hz, 3 H, CH_3CH), 2.73 (ddd, J = 14.0, 8.6 Hz, 0.8 Hz, 1 H, CH_2CH), 2.98 (ddd, J = 14.0, 4.2 Hz, 1.2 Hz, 1 H, CH_2CH), 4.71 (s, 2 H, Cl_3CCH_2), 5.10−5.19 (m, 1 H, CHOC=O), 5.31 (s, 2 H, ArOCH_2−Ar), 6.78 (s, 1 H, CO−CH=C), 7.32 (d, J = 8.3 Hz, 1 H, BnOAr−H), 7.34 (t, J = 7.4 Hz, 1 H, Ar−H), 7.42 (t, J = 7.4 Hz, 2 H, Ar−H), 7.57 (d, J = 7.4 Hz, 2 H, Ar−H), 7.63 (dd, J = 8.3, 7.4 Hz, 1 H, BnOAr−H), 7.66 (dd, J = 8.3, 1.0 Hz, 1 H, BnOAr−H). − ^{13}C NMR (100 MHz, CD_3OD): δ = 20.5, 37.2, 71.6, 75.7, 77.5, 96.1, 120.5, 121.1, 121.2, 128.0, 128.5, 128.9, 129.5, 135.6, 136.1, 137.9, 140.0, 145.9, 155.1, 159.7, 185.5, 186.0. − $C_{23}H_{19}Cl_3O_6$ (497.8) calcd. C 55.50, H 3.85; found C 55.60, H 4.10.

(*S*)-(−)-5-Benzyloxy-2-(2′-hydroxypropyl)-1,4-naphthalenediol (15): To a well ice-cooled and degassed solution of **14** (17.8 g, 36 mmol) in AcOH (85 mL) was added powdered zinc (17.8 g, 272 mmol) in one portion. After removal of the ice bath, the resulting suspension was stirred at room temperature for 2 h under Ar. An additional portion of powdered zinc (2 g) was added. After having been stirred for an additional 20 min, the mixture was filtered. The solid residue was washed well with EtOAc (500 mL). The filtrates were combined and washed with water (2 × 250 mL). All of the aqueous layers were combined and extracted with EtOAc (250 mL). The organic layers were combined, washed with sat. aq. $NaHCO_3$ (2 ×150 mL), brine (1×200 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo to give 15.7 g of a crude product as a yellow solid. This was recrystallized from EtOAc/*n*-hexane to give 5.58 g (48%) from the first crop of **15** and 2.68 g (23%) of the second crop of **15** as white powder. The mother liquor (3.58 g) was purified by chromatography on silica gel (EtOAc/*n*-hexane 1:3 as eluent) to give 1.66 g of a pale brown solid. This powder was washed thoroughly with Et_2O to give 1.16 g (10%) of **15** as faint yellow powder. The total amount of **15** was 9.36 g (81%); m.p. 138.0−139.0 °C (EtOAc/*n*-hexane). − $[\alpha]_D^{27} = -24.0$ (c = 1.00 in $CHCl_3$). − IR (KBr): $\tilde{\nu}_{max}$ = 3400 (s, OH), 1640 (s, C=C), 1610 (s, C=C). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (d, J = 6.4 Hz, 3 H, CH_3CH), 2.84 (dd, J = 15.0, 7.1 Hz, 1 H, CH_2CH), 2.95 (dd, J = 15.0, 2.4 Hz, 1 H, CH_2CH), 4.29−4.38 (m, 1 H, CHOH), 5.27 (s, 2 H, ArOCH_2−Ar), 6.56 (s, 1 H, CO−CH=C), 6.87 (d, J = 7.8 Hz, 1 H, BnOAr−H), 7.31 (dd, J = 8.5, 7.8 Hz, 1 H, BnOAr−H), 7.35−7.47 (m, 3 H, Ar−H), 7.47−7.52 (m, 2 H, Ar−H), 7.90 (dd, J = 8.5, 7.8 Hz, 1 H, BnOAr−H), 8.93 (s, 1 H, ArOH). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.2, 40.3, 70.8, 71.5, 105.3, 113.1, 114.7, 116.6, 120.6, 124.9, 128.0, 128.1, 128.7, 128.9, 135.4, 143.4, 147.0, 155.0. − $C_{20}H_{20}O_4$ (324.4) calcd. C 74.06, H 6.21; found C 74.13, H 6.57.

(*S*)-(−)-6-Benzyloxy-2,3-dihydro-2-methylnaphtho[1,2-*b*]furan-5-ol (16): To a degassed solution of Ph_3P (7.8 g, 29.8 mmol) and **15** (9.2 g, 28.4 mmol) in THF (920 mL) was added a solution of DEAD (5.2 g, 29.8 mmol) in THF (80 mL), dropwise over 2 h under Ar at room temperature. The resulting mixture was stirred for 3 h at room temperature. An additional portion of DEAD (0.52 g, 3.0 mmol)/Ph_3P (0.78 g, 3.0 mmol) in THF (1 mL) was added to the solution. After 16 h stirring under Ar at room temperature, the solution was concentrated in vacuo to give a black tar. This was purified twice by chromatography on silica gel (500 g, EtOAc/*n*-hexane 1:1 as eluent, then 250 g, EtOAc/*n*-hexane 1:8 as eluent) to give 1.65 g (19%) of **16** as colorless flakes. These were recrystallized from EtOAc to give an analytical sample of **16** as colorless flakes; m.p. 143.5−144.5 °C (EtOAc). − $[\alpha]_D^{29} = -2.22$ (c = 1.03 in $CHCl_3$). − IR (KBr): $\tilde{\nu}_{max}$ = 3400 (s, OH), 1640 (m, C=C), 1605 (s, C=C), 1520 (m, C=C). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (d, J = 6.3 Hz, 3 H, CH_3CH), 2.93 (dd, J = 15.0, 7.6 Hz, 1 H, CH_2CH), 3.42 (dd, J = 15.0, 8.8 Hz, 1 H, CH_2CH), 5.00−5.01 (m, 1 H, CH_2CHCH_3), 5.25 (s, 2 H, ArOCH_2−Ar), 6.72 (s, 1 H, Ar−H), 6.81 (d, J = 7.6 Hz, 1 H, BnOAr−H), 7.26 (t, J = 7.8 Hz, 1 H, BnOAr−H), 7.35−7.55 (m, 6 H, Ar−H, BnOAr−H), 8.99 (s, 1 H, OH). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 38.4, 71.5, 79.7, 105.0, 107.2, 114.1, 115.6, 121.7, 121.9, 125.2, 128.0, 128.8, 129.0, 135.3, 147.5, 148.2, 155.4. − $C_{20}H_{18}O_3$ (306.4) calcd. C 78.41, H 5.92; found C 78.41, H 6.14.

(*S*)-(−)-6-Benzyloxy-2,3-dihydro--2-methylnaphtho[1,2-*b*]furan-4,5-dione (17): To a solution of $(PhSeO)_2O$ (2.78 g, 5.4 mmol) in THF (44 mL), heated at 50 °C, was added a solution of **16** (1.53 g, 5.0 mmol) in THF (44 mL) dropwise through a cannula under Ar. The resulting mixture was stirred for 0.5 h at 50 °C, then cooled to room temperature and diluted with EtOAc (350 mL). The EtOAc solution was washed with water (150 mL), sat. aq $NaHCO_3$ (150 mL), and brine (150 mL). All of the aqueous layers were combined and extracted with EtOAc (2 ×200 mL). The organic layers were combined, dried with Na_2SO_4, filtered, and concentrated in vacuo to give 3.0 g of an orange solid. This was purified by chromatography on silica gel (80 g, EtOAc/*n*-hexane 1:1−3:1 as eluent) to give 1.24 g (78%) of **17** as an orange powder. This was recrystallized from $CHCl_3$/*n*-hexane to give an analytical sample of **17** as an orange powder; m.p. 202.0−204.0 °C ($CHCl_3$/*n*-hexane). − $[\alpha]_D^{29} = -52.1$ (c = 1.09 in $CHCl_3$). − IR (KBr): $\tilde{\nu}_{max}$ = 1680 (m, C=O), 1650 (s, C=O), 1620 (s, C=C), 1575 (s, C=C). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 (d, J = 6.4 Hz, 3 H, CH_3CH), 2.73 (dd, J = 16.0, 7.2 Hz, 1 H, CH_2CH), 3.27 (dd, J = 16.0, 9.6 Hz, 1 H, CH_2CH), 5.18−5.26 (m, 1 H, CH_2CHO), 5.28 (s, 2 H, ArOCH_2Ar), 7.22 (d, J = 8.8 Hz 1 H, BnOAr−H), 7.26−7.31 (m, 2 H, BnOAr−H, Ar−H), 7.40 (t, J = 7.6 Hz, 2 H, Ar−H), 7.57 (dd, J = 8.8, 7.2 Hz, 1 H, BnOAr−H), 7.64 (d, J = 7.6 Hz, 2 H, Ar−H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0, 33.6, 70.5, 84.2, 114.6, 117.6, 118.0, 118.4, 126.5, 127.9, 128.6, 129.7, 135.7, 135.8, 160.7, 169.3, 175.6, 180.1. − $C_{20}H_{16}O_4$ (320.3) calcd. C 74.99, H 5.03; found C 75.03, H 4.86.

(*S*)-(−)-2,3-Dihydro-6-hydroxy-2-methylnaphtho[1,2-*b*]furan-4,5-dione [(*S*)-(−)-Nocardione A (1)]: To a solution of **17** (424 mg, 1.3 mmol) in DMF (12 mL) was added 10% Pd/C (200 mg). The resulting mixture was vigorously stirred under H_2 for 6 min at room temperature until disappearance of the red color of the solution. Then, the mixture was vigorously stirred for 15 min under air in order to re-oxidize the substrate at room temperature. The mixture was filtered through a celite pad. The residue on the celite pad was washed with hot $CHCl_3$ (4 × 25 mL). The combined filtrates were diluted with EtOAc (150 mL) and washed with brine (3 × 50 mL). The aqueous layers were combined and extracted with EtOAc (2 × 50 mL) again. All of the extracts were combined, dried with

Na_2SO_4, filtered, and concentrated in vacuo to give 1.13 g of a crude oil. This was purified by chromatography on silica gel [Kanto Chemical silica gel 60N (spherical, neutral) 80 g, EtOAc/*n*-hexane 1:1 as eluent] to give 152 mg of (*S*)-**1** as red powder. {50%, 2.2% in 7 steps from (*R*)-**4**}; properties of (*S*)-**1**: dark red needles (EtOAc/*n*-hexane): m.p. 172.5−173.5 °C {ref.[1] m.p. 115−120 °C}, $[\alpha]_D^{21}$ = −56.0 (*c* = 0.97 in $CHCl_3$), {ref.[1] $[\alpha]_D^{20}$ = −85.4 (*c* = 1.0 in $CHCl_3$)}. − $C_{13}H_{10}O_4$ (230.2) calcd. C 67.82, H 4.38; found C 67.54, H 4.32. − UV-Vis (MeOH) λmax (ε): 259 (18000), 414 (4400). {ref.[1] 203 (16400), 237 (15100), 259 (18000), 416 (4900)}. − UV-Vis (0.01 N HCl/MeOH 1:9) λmax (ε): 260 (17000), 291 (5400), 415 (4300). {ref.[1] 237 (16000), 259 (18300), 415 (5000).}. − UV-Vis (0.01 N NaOH/MeOH 1:9) λ_{max} (ε): 237 (15000), 259 (12000), 473 (3200). {ref.[1] 205 (15500), 238 (16300), 259 (14400), 474 (4900)}. The IR and NMR spectroscopic data for this compound were in good agreement with those of (±)-**1** and also with the reported data.[1] The ^1H NMR spectrum of the natural product indicates that it contains some impurities. − HPLC: The HPLC conditions were as follows: Column, Daicel Chiralpak AD − RH® (4.6 mm ×150 mm); eluent, H_2O/ MeCN (2:1); flow rate, 0.6 mL/min; Detection at λ = 230 nm; Sample concentration and injection volume, 0.1 mg/mL in MeCN solution × 0.5μL. Under these conditions, (*S*)-(−)-**1** was detected at t_R = 37.6 min, and (*R*)-(+)-**1** was detected at t_R = 41.4 min: Our synthetic (*S*)-**1** was of ca.100% *ee*.

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