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Formal Radical Cyclization onto Benzene Rings: A General Method and Its Use in the Synthesis of *ent*-Nocardione A

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Received November 26, 2003

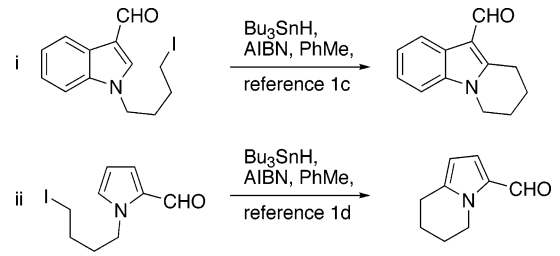
An indirect method is described for effecting radical cyclization onto a benzene ring. Cross-conjugated dienones **6**, which are readily prepared from phenols, undergo radical cyclization (**6** → **7** → **8**), and the products (**8**) are easily aromatized. The method has been applied to the synthesis of *ent*-nocardione A (**21**).

Introduction

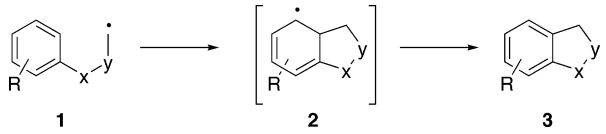
While radical cyclization onto double bonds is now a standard synthetic method, related closures onto aromatic rings represent a much less developed area. Radical cyclization onto certain heterocycles is reasonably well-known,[1] and typical examples are shown in Scheme 1. In contrast, the corresponding closure onto benzene rings (see Scheme 2) is usually a difficult process, and is not well understood.[1b,2] Such reactions can be achieved, however, by application of xanthate-based methods, as illustrated in Scheme 3,[3−5] but these often involve quite harsh procedures, and the development of a milder process that operates under standard free radical cyclization conditions (R_3SnH, catalytic AIBN, refluxing PhH) would undoubtedly be useful.

We report an indirect method for achieving the same overall transformation as that shown in Scheme 2. Our approach[6,7] (Scheme 4) involves converting the starting benzenoid compound into a cross-conjugated ketone (**4** → **6**) carrying an alkoxy substituent terminating in a homolyzable group. The ketone readily undergoes radical cyclization,[8] and the product (**8**) is easily rearomatized (**8** → **9**), so that the overall result is similar to that summarized in Scheme 2.

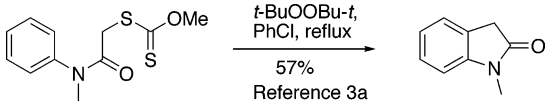
SCHEME 1



SCHEME 2



SCHEME 3



(1) For typical examples of cyclization onto heteroaromatic rings, see: (a) Murphy, J. A.; Sherburn, M. S. *Tetrahedron* **1991**, *47*, 4077−4088. (b) Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun*. **1995**, 977−978. (c) Moody, C. J.; Norton, C. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2639−2643. (d) Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111−8128. (e) Marco-Contelles, J.; Rodríguez-Fernández, M. *Tetrahedron Lett*. **2000**, *41*, 381−384. (f) Escolano, C.; Jones, K. *Tetrahedron Lett*. **2000**, *41*, 8951−8955. (g) Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Romero, Y.; Muchowski, J. M. *Tetrahedron Lett*. **2000**, *41*, 10181−10184. (h) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747−2762. (i) Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett*. **2002**, *43*, 4191−4193. (j) Gagosz, F.; Zard, S. Z. *Org. Lett*. **2002**, *4*, 4345−4348. (k) Du, W.; Curran, D. P. *Org. Lett*. **2003**, *5*, 1765−1768. (l) Flanagan, S. R.; Harrowven, D. C.; Bradley, M. *Tetrahedron Lett*. **2003**, *44*, 1795−1798.

(2) (a) Crich, D.; Hwang, J.-T. *J. Org. Chem*. **1998**, *63*, 2765−2770. (b) Cf.: Crich, D.; Sannigrahi, M. *Tetrahedron* **2002**, *58*, 3319−3322.

(3) (a) Axon, J.; Boiteau, L.; Boivin, J.; Forbes, J. E.; Zard, S. Z. *Tetrahedron Lett*. **1994**, *35*, 1719−1722. (b) Liard, A.; Quiclet-Sire, B.; Saicic, R.; Zard, S. Z. *Tetrahedron Lett*. **1997**, *38*, 1759−1762. (c) Cholleton, N.; Zard, S. Z. *Tetrahedron Lett*. **1998**, *39*, 7295−7298. (d) Hoang-Cong, X.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett*. **1999**, *40*, 2125−2126. (e) Ly, T.-M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *Tetrahedron Lett*. **1999**, *40*, 2533−2536. (f) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed*. **2000**, *39*, 731−733. (g) Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun*. **2002**, 1692−1693. (h) Quiclet-Sire, B.; Zard, S. Z. *J. Chem. Soc., Chem. Commun*. **2002**, 2306−2307. (i) Zard, S. Z. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 672−685.

(4) For oxidative cyclizations initiated by radical formation from β-dicarbonyl compounds, see: Snider, B. B. *Chem. Rev*. **1996**, *96*, 339−363.

(5) For methods that do not involve xanthates, see: (a) Ishibashi, H.; Nakamura, N.; Ito, K.; Kitayama, S.; Ikeda, M. *Heterocycles* **1990**, *31*, 1781−1784. (b) Curran, D. P.; Liu, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1377−1393. (c) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1994**, *50*, 2107−2114. (d) Rosa, A. M.; Lobo, A. M.; Branco, P. S.; Prabhakar, S. *Tetrahedron* **1997**, *53*, 285−298. (e) Bowman, W. R.; Mann, E.; Parr, J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2991−2999. (f) Harrowven, D. C.; Nunn, M. I. T.; Fenwick, D. R. *Tetrahedron Lett*. **2002**, *43*, 3185−3187. (g) Fiumana, A.; Jones, K. *Tetrahedron Lett*. **2000**, *41*, 4209−4211.

(6) Preliminary communication: Clive, D. L. J.; Fletcher, S. P.; Zhu, M. *J. Chem. Soc., Chem. Commun*. **2003**, 526−527.

(7) Preliminary communication: Clive, D. L. J.; Fletcher, S. P. *J. Chem. Soc., Chem. Commun*. **2003**, 2464−2465.

(8) Cf.: Villar, F.; Equey, O.; Renaud, P. *Org. Lett*. **2000**, *2*, 1061−1064.

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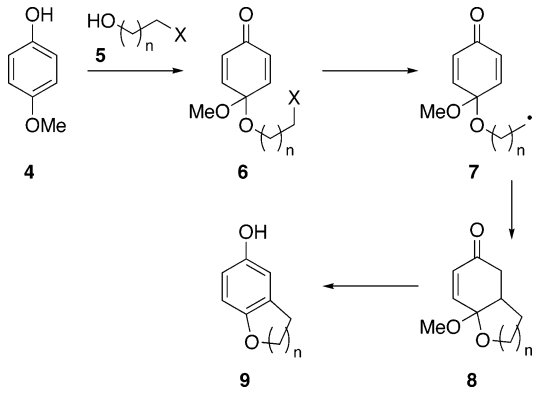
Published on Web 04/17/2004

SCHEME 4



The cross-conjugated ketones are available (Scheme 4) by oxidation of *p*-methoxyphenols in the presence of an excess of an α,*ω*-halo alcohol (**5**), which is used as solvent. Alternatively, the starting phenol can carry a *p*-alkoxy group already bearing a homolyzable substituent, and in that case the oxidation is done in MeOH. Typical examples of these approaches are shown in Table 1. We generally use $PhI(OAc)_2$ (ca 1.1 equiv) as the oxidizing agent, but have also used DDQ (see later, Scheme 6, **28** → **29**).

The intermediate quinone ketals are sensitive to acid, and so the oxidation must be done in the presence of K_2CO_3 (ca. 2.2 equiv),[9] and during chromatographic purification, a small amount of Et_3N should be added to all solvents used. In some cases the oxidation is done with *iodo* alcohols (Table 1, entries 1 and 2, right-hand columns; Table 2, entry 3), but 4-iodobutanol could not be used since it reacts with $PhI(OAc)_2$. Generally, chloro alcohols are satisfactory, and the resulting chlorides can be converted into the corresponding iodides by heating with anhydrous NaI; yields were better when this step is done in DME rather than in acetone. In the preparation of **12a** (Table 1), evaporation of excess of 4-chlorobutanol (which produces THF and HCl[10]) was done in the presence of solid K_2CO_3.

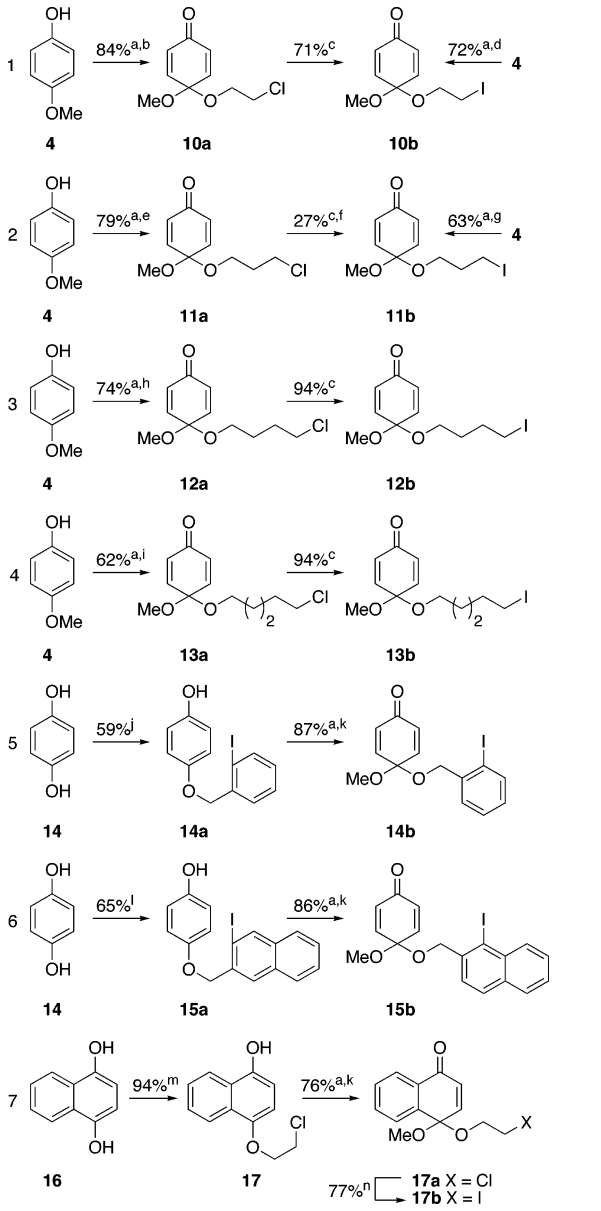
In those cases where a phenol, bearing an *ω*-haloalkoxy group in the para position, is readily available (Table 1, entries 5−7), then oxidation in MeOH is an alternative route that is experimentally convenient, because the excess of solvent is easily removed. Iodides **14a** and **15a** were made by alkylating hydroquinone with the appropriate benzylic bromide (see the Experimental Section).

Chloride **17** was chosen as a starting material simply because its preparation is straightforward. We noticed that the oxidation of **17** to **17a** is peculiar in that it does not work well unless a trace of EtOAc is present. This phenomenon was observed repeatedly in a series of experiments in which the outcome was uniformly successful when EtOAc was added, and unsuccessful when it was omitted. However, we did not attempt to identify the mechanistic basis of this intriguing observation.

The examples in Table 2 establish that the general oxidation works satisfactorily when an additional methoxy substituent is present. A methyl group para to the phenolic hydroxyl is also tolerated, although in the single example of this type (entry 3), the yield was only 48%.

The radical cyclizations proceeded without incident (see Tables 3 and 4) when dilute toluene solutions of stannane (0.07−0.12 M) and initiator (0.005−0.011 M) were added over 3−5 h to a hot (85 °C) solution (0.030−0.040 M) of the substrate in the same solvent. We arbitrarily avoided refluxing the solvent, and suspect, on the basis of a single experiment, that our milder conditions give a better result. Yields were generally above 75%. It appears necessary to use iodides in these reactions, as in two cases where bromides were examined [the bromide correspond-

TABLE 1.

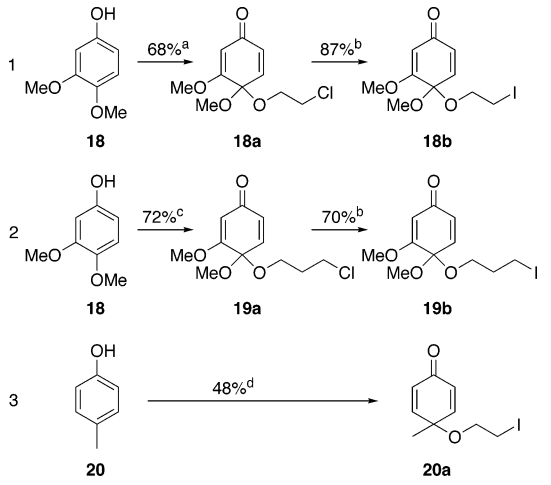


[a] $PhI(OAc)_2$, K_2CO_3. [b] 2-Chloroethanol. [c] Anhydrous NaI, acetone, reflux. [d] 2-Iodoethanol. [e] 3-Chloropropanol. [f] Not optimized, since direct route from **4** was developed. [g] 3-Iodopropanol. [h] 4-Chlorobutanol. [i] 5-Chloropentanol. [j] 1-(Bromomethyl)-2-iodobenzene, DMF, K_2CO_3. [k] MeOH. [l] 2-Bromomethyl-3-iodonaphthalene, DMF, K_2CO_3. [m] 2-Chloroethanol, HCl. [n] Anhydrous NaI, DME, reflux.

(9) Cf.: (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927−3903. (b) Fleck, A. E.; Hobart, J. A.; Morrow, G. W. *Synth. Commun.* **1992**, *22*, 179−187.

(10) Heine, H. W.; Siegfried, W. *J. Am. Chem. Soc.* **1954**, *76*, 489−490.

TABLE 2.

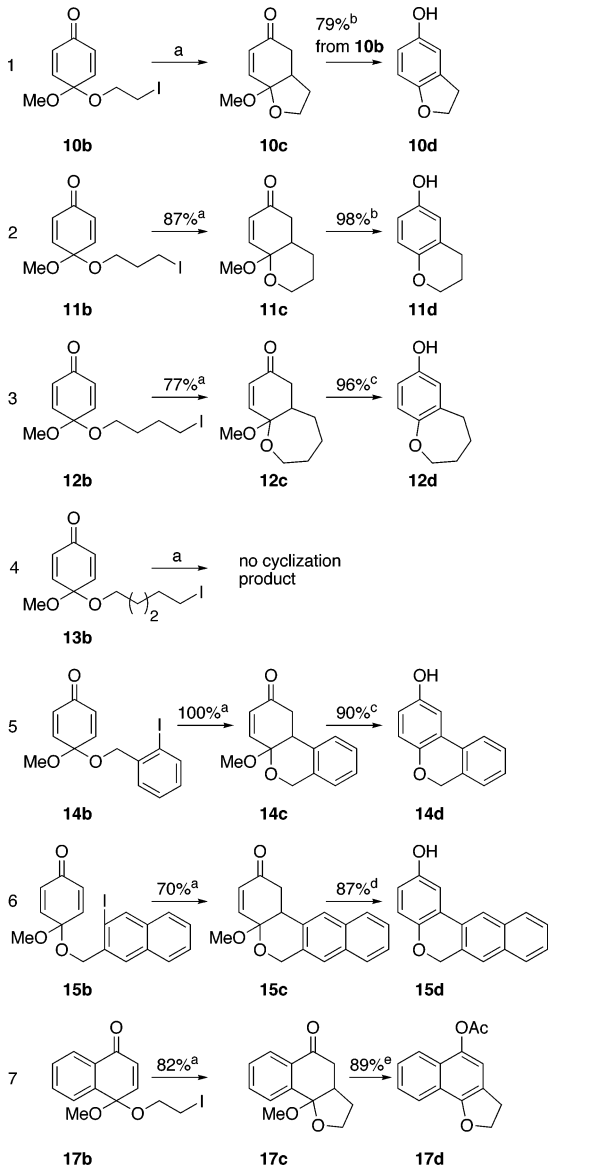


[a] 2-Chloroethanol, $PhI(OAc)_2$, K_2CO_3. [b] Anhydrous NaI, acetone, reflux. [c] 3-Chloropropanol, $PhI(OAc)_2$, K_2CO_3. [d] 2-Iodoethanol, $PhI(OAc)_2$, K_2CO_3.

ing to **14b**, and the bromide corresponding to **37** (see Scheme 7)], cyclization did not occur (the **14b** analog[11]) or was a minor pathway (the **37** analog), and we suspect that preferential reduction of the dienone system takes place. Of all the iodides listed in Tables 3 and 4, only **13b** failed to undergo radical cyclization.

The last step of the overall sequence is acid-catalyzed aromatization, and in all the examples we examined the methoxy group is expelled in preference to the heterocyclic oxygen; in entry 3 of Table 4, where no methoxy group is present, the heterocyclic ring opens. $TsOH \cdot H_2O$ is usually satisfactory, but HCO_2H and AcOH can also be used (see **31** → **32**), and yields for the aromatization are generally above 87%. The crude products from the radical cyclization can be used directly without purification (Table 3, entry 1). The aromatization of **17c** (Table 3) and **20b** (Table 4) was initially problematic, and the expected phenols could not be isolated. However, in situ acetylation, achieved by acid treatment in the presence of Ac_2O, overcomes the problems and delivers the acetates **17d** and **20c** in 89% and 69% yield, respectively. The aromatization of **18c** and **19c** was arbitrarily done in the presence of 4 Å molecular sieves.

TABLE 3.



[a] Bu_3SnH, AIBN, PhMe, 85 °C, except for entry 1, where Ph_3SnH was used. [b] TsOH, PhMe. [c] TsOH, acetone, CH_2Cl_2. [d] TsOH, 4 Å molecular sieves, CH_2Cl_2. [e] TsOH, Ac_2O.

Manipulation of the Radical Cyclization Products before Aromatization

As illustrated in Tables 3 and 4, our general process affords phenols; it can, however, be modified easily so as to produce products with hydrogen, alkyl, or aryl groups in place of the normal phenolic hydroxyl.

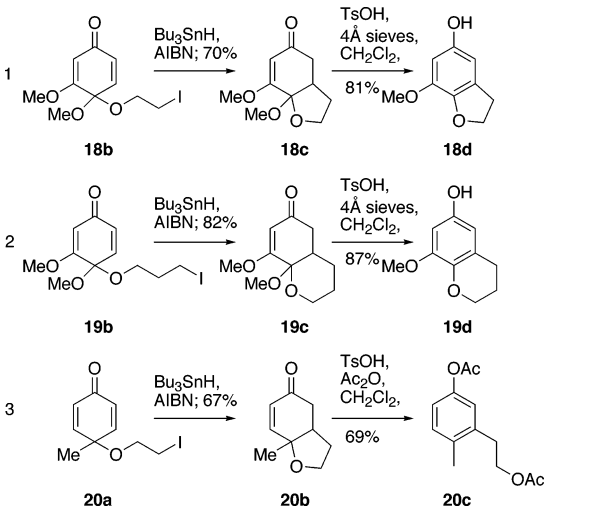
Reduction of the radical cyclization products with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ proceeds normally and aromatization of the resulting alcohols results in loss of the hydroxyl group (Table 5, entries 1, 4, and 5). In the case of entry 5, aromatization occurs so easily that silica chromatography of the reduction product **19e** gives some of the aromatized product **19f**, while corresponding treatment of **18e** is devoid of such complications. The prearomatization substrates shown in Table 3 were always chromatographed in the presence of Et_3N, but this precaution was arbitrarily not taken for the examples in Table 5.

Acid treatment of **18g** and **19g** (Table 5, entries 6−9) gives results that depend on the precise conditions. In the presence of 4 Å molecular sieves, aromatization and formation of an intermediate enone occurs (**18g** → **18h** + **18i**; **19g** → **19h** + **19i**) and both the aromatized methyl ethers (**18h**, **19h**) and the enones (**18i**, **19i**) can be isolated. In the absence of molecular sieves, the normal aromatization products (**18h**, **19h**) are formed along with the corresponding phenols (**18j**, **19j**) resulting from aromatization of the enone (**18i**, **19i**). The enones can themselves be aromatized (**18i** → **18j**, 89%; **19i** → **19j**, 81%).

When the radical cyclization products are treated with a Grignard reagent, a tertiary alcohol is, of course, formed (Table 5, entries 2, 3, 6, and 8), and aromatization gives

(11) (2-Bromophenyl)methanol was isolated.

TABLE 4.



products carrying an alkyl or aryl group originating from the Grignard reagent.

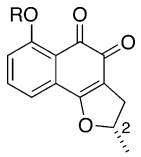
Another modification to the normal sequence that can be made is to trap the intermediate radical arising from the closure step,[8] and this was done in the case of iodide **14b** (Scheme 5). When the iodide was heated with allyltributyltin and AIBN, radical **14i** underwent Keck allylation, ultimately giving **14k**, after acid treatment. α-Keto radicals, such as **14i**, appear to react only at carbon, and we later found (see Scheme 6, compound **30**) a case where reaction at oxygen, while geometrically favorable, did not occur at all.

The results summarized in the above tables and schemes show clearly that the present radical cyclization method is a very effective route to benzo-fused oxygen heterocycles and gives access to substitution patterns not easily accessible by other methods.

We have also applied our method to the synthesis of a sensitive natural product, as described in the next section.

Application to Natural Product Synthesis: Synthesis of Nocardione A

During the course of the above work the *o*-quinone (−)-nocardione A (**21**)[12] came to our attention. The prior



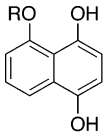
21 R = H
22 R = Me

synthesis of optically pure material[13,14] had revealed that the structure presents a number of difficult synthetic problems, but it seemed clear that the compound should be accessible by our radical methodology, and its construction would be a more demanding test than the examples we had examined so far. It would also represent a worthwhile synthetic target on account of its potentially important biological properties. In the event, we prepared *ent*-nocardione A in 22% overall yield from juglone.

Nocardione A is produced by a microorganism tentatively identified as the Gram-positive bacterium *Nocardia* sp TP-A0248.[12] The compound is a cdc25B tyrosine phosphatase inhibitor, a property that is noteworthy because 50% of cancers of the head and neck[15] and 32% of breast cancers[16] are associated with elevated expression of cdc25B tyrosine phosphatase. The general class of protein tyrosine phosphatases are key enzymes in the signal transduction pathway of a wide range of cellular processes,[17] and inhibitors of such enzymes merit study as leads in drug design and as tools to elucidate the role of phosphorylation pathways.[18] Nocardione A also has moderate antifungal and cytotoxic activity,[12] and causes cell death with characteristics of apoptosis in U937 human myeloid leukemia cell lines.[12]

Previous synthetic work[13] on nocardione A initially relied on deprotection of the congener nocardione B (**22**), but attempts to effect the required demethylation caused epimerization at C(2). The successful route[13] was based on *O*-benzyl protection and use of a Mitsunobu displacement to generate the delicate dihydrofuran unit (19%). Surprisingly, the debenzylation needed to release the phenolic hydroxyl proved difficult (50%).

After extensive exploratory work, we settled on the route summarized in Scheme 6 (which leads to *ent*-nocardione A).[7] Juglone (**23**) was protected as its allyl ether (Ag_2O, allyl bromide, 79%) and then reduced to the hydroquinone level ($Na_2S_2O_4$) (**23** → **24** → **25**). The hydroquinone could be alkylated (**25** → **26**) with the trifluoromethanesulfonate prepared[19] from (−)-ethyl lactate.[20] This step required some optimization and, although a systematic survey of reaction conditions was not made, we did investigate a number of solvents (acetone, DMF, DMSO, CH_2Cl_2), bases (K_2CO_3, Cs_2CO_3), and ethyl lactate derivatives (mesylate and trifluoromethanesulfonate), using the *O*-benzyl (**35a**), *O*-meth-



35a R = Bn
35b R = $MeOCH_2$

oxymethyl (**35b**), and allyl (**25**) hydroquinones. We also

(12) Isolation: Otani, T.; Sugimoto, Y.; Aoyagi, Y.; Igarashi, Y.; Furumai, T.; Saito, N.; Yamada, Y.; Asao, T.; Oki, T. *J. Antibiot*. **2000**, *53*, 337−344.

(13) Synthesis of optically pure material: Tanada, Y.; Mori, K. *Eur. J. Org. Chem*. **2001**, 4313−4319.

(14) Synthesis of racemic material: Yang, H.; Lu, W.; Bao, J. X.; Aisa, H. A.; Cai, J. C. *Chinese Chem. Lett*. **2001**, *12*, 883−886; *Chem. Abstr*. **2002**, *136*, 102216.

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(16) Galaktionov, K.; Lee, A. K.; Eckstein, J.; Draetta, G.; Meckler, J.; Loda, M.; Beach, D. *Science* **1995**, *269*, 1575−1577.

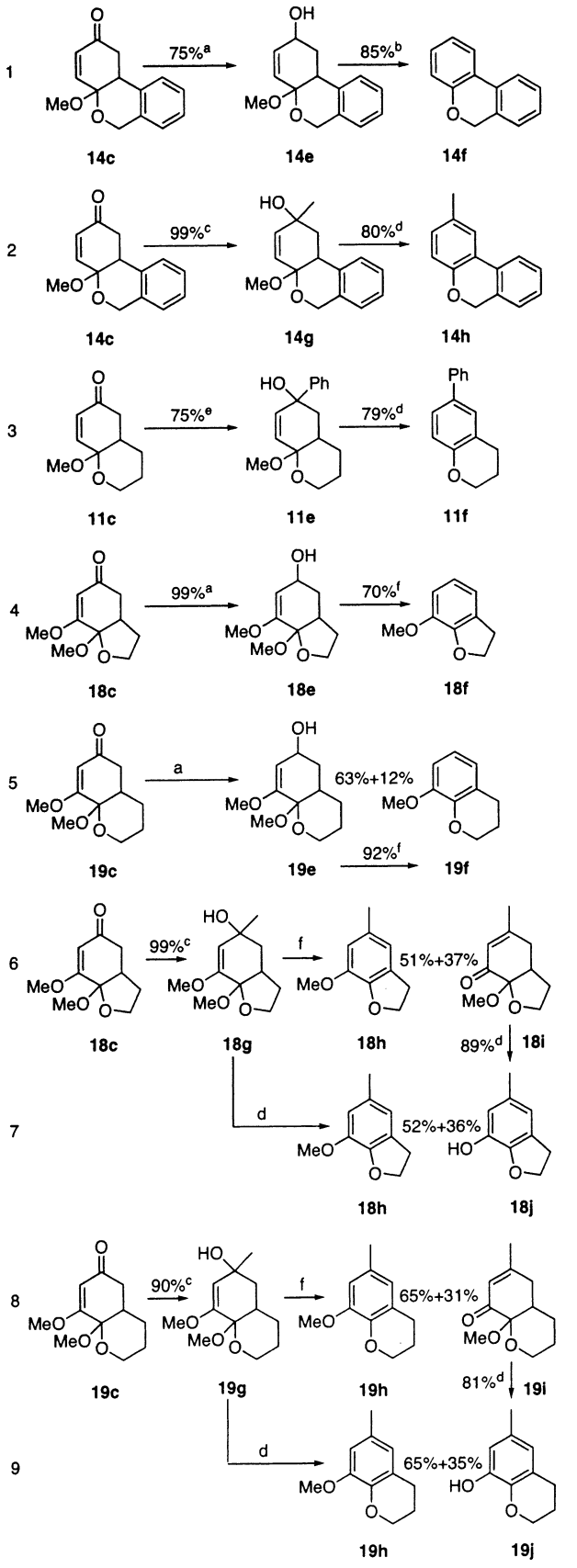
(17) Dunphy, W. G.; Kumagai, A. *Cell* **1991**, *67*, 189−196.

(18) (a) Blaskovich, M. A.; Kim, H. O. *Expert Opin. Ther. Pat*. **2002**, *12*, 871−905. (b) Walton, K. M.; Dixon, J. E. *Annu. Rev. Biochem*. **1993**, *62*, 101−120.

(19) (a) Effenberger, F.; Burkard, U.; Willfahrt, J. *Liebigs Ann. Chem*. **1986**, 314−333. (b) Effenberger, F.; Burkard, U.; Willfahrt, J. *Angew. Chem., Int. Ed. Engl*. **1983**, *95*, 65−66.

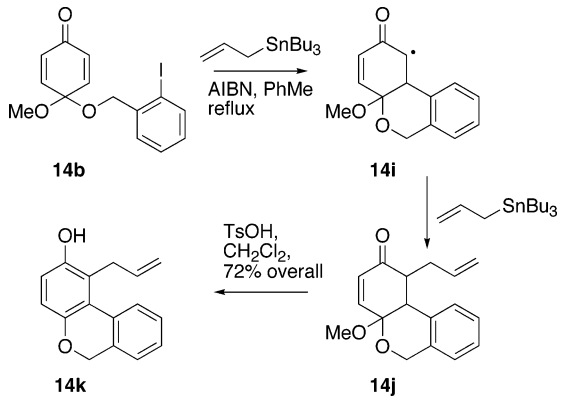
(20) Commercial samples of ethyl (−)-lactate are probably ca. 97% ee. See: Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc*. **1984**, *106*, 4192−4201 and references therein.

TABLE 5.

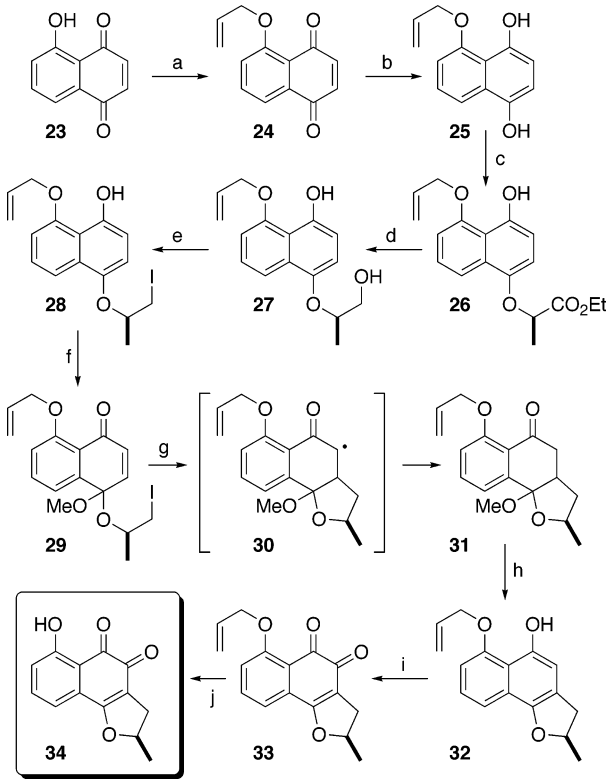


[a] $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH. [b] TsOH·acetone, $CHCl_3$. [c] MeMgCl, THF. [d] TsOH, CH_2Cl_2. [e] PhMgBr, THF. [f] TsOH, 4 Å molecular sieves, CH_2Cl_2.

SCHEME 5



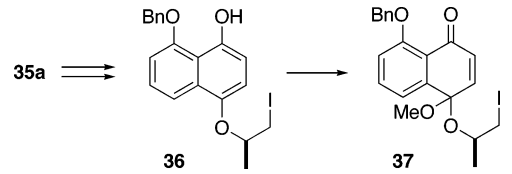
SCHEME 6 [a]



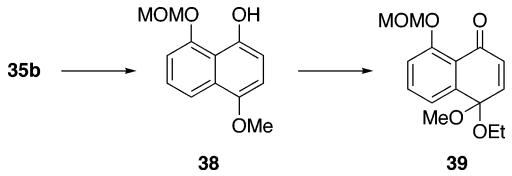
[a] Reagents and conditions: (a) allyl bromide, Ag_2O, CH_2Cl_2, reflux, 11 h, 79%; (b) $Na_2S_2O_4$, ether−water, 40 min, 100%; (c) triflate of ethyl (−)-lactate, Cs_2CO_3, CH_2Cl_2, −78 °C, 18 h, 50%, 88% corrected for recovered **25**; (d) $LiAlH_4$, THF, 10 min, 100%; (e) Ph_3P, imidazole, I_2, THF, 12 h, 89%; (f) DDQ, MeOH, K_2CO_3, 4 min, 87%; (g) Bu_3SnH and AIBN (addition over 9 h), heat 6 h more, PhMe, 85 °C, 82%; (h) AcOH, $CHCl_3$, 2 h, 88%; (i) $[PhSe(O)]_2O$, THF, 12 min, 96%, 82% after recrystallization; (j) 10 mol % of $Pd(PPh_3)_4$, dimedone, THF, 4 min, 74%.

examined a Mitsunobu reaction between **35a** and ethyl lactate, but the yield of coupling product was poor and extensive amounts of quinone were generated. These experiments guided us to the conditions summarized in Scheme 6, and we accepted the modest yield (50%) for the alkylation (**25** → **26**) since much hydroquinone could be recovered, so that the corrected yield was 88%. In addition, alkylation occurred only at the required phenolic hydroxyl under the optimized conditions, and the process appeared to work with clean inversion of the

SCHEME 7



SCHEME 8

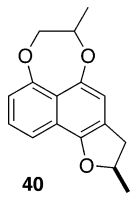


lactate stereochemistry (as judged by ^{19}F NMR examination of the Mosher ester derived from alcohol **27**). This mechanistic outcome requires that ethyl (+)-*R*-lactate be used to make natural nocardione A, but we decided to go ahead with the very much cheaper *S*-isomer.

The ester was then reduced (Scheme 6, $LiAlH_4$, 100%, **26** → **27**); surprisingly, reduction of the corresponding ester in the methoxymethyl series (derived from **35b**) gave erratic results. With alcohol **27** in hand, iodide **28** was easily obtained by reaction with Ph_3P, I_2, and imidazole (89%). At this point, oxidation with DDQ in MeOH afforded (87%) the substrates **29** required for the key radical cyclization. Our choice of DDQ, as opposed to $PhI(OAc)_2$, was based on earlier studies in the benzyl series, where the corresponding transformation (see Scheme 7, **36** → **37**) was very inefficient when $PhI(OAc)_2$ was used as the oxidant.

An alternative method for making cross-conjugated ketones such as **29** was investigated briefly: the hydroquinone *O*-methyl ether **38** (Scheme 8) was treated with DDQ in neat ethyl lactate, but we did not isolate the expected product and obtained instead the mixed acetal **39**.

Radical cyclization of **29** (Scheme 6) under standard conditions (slow addition of a dilute solution of stannane and initiator to a dilute solution of the substrate at 85 °C) gave the desired product **31** in 82% yield; evidently, the intermediate radical **30** is quenched by stannane rather than undergoing closure through oxygen onto the double bond of the allyl group. Quantitative rearomatization to **32** occurred on storing the cyclization product in $CDCl_3$; use of HCO_2H gave some **32**, but an appreciable amount of the cyclic ether **40** (as a mixture of two



isomers) was also formed. Treatment of **31** with DBU in refluxing PhMe (12 h) caused no change, but satisfactory rearomatization (**31** → **32**) was easily achieved by using AcOH in $CHCl_3$ at room temperature (88%).

The naphthol **32** was next converted (96%) into the *o*-quinone **33** by the action of $[PhSe(O)]_2O$.[21] The quinone was recrystallized (82% yield after recrystallization) and treated with $(Ph_3P)_4Pd$ in the presence of dimedone to remove the allyl protecting group and release *ent*-nocardione A (74%).

As already indicated, in preliminary work along similar lines to those of our optimized route summarized in Scheme 6, we had used *O*-benzyl protection, but removal of the *O*-benzyl group in the last step of the synthesis could be achieved in only 43% yield. We also explored *O*-MOM protection, but found that reduction of the ester unit (cf. **26** → **27**) then gave variable yields, and at the end of the sequence (cf. **33** → **34**) the MOM group could not be removed without opening the dihydrofuran ring. Therefore, we tried the *O*-allyl group, and found that it was satisfactory, as described above. Its use, in combination with the radical cyclization methodology, allows construction of *ent*-nocardione A in overall yield of 22% from juglone (**23**).

Conclusion

The radical methodology described in this article represents a powerful method for making benzo-fused oxygen heterocycles; the approach is amenable to a number of modifications, and has been applied in the synthesis of *ent*-nocardione A.

Experimental Section

4-(2-Chloroethoxy)-4-methoxycyclohexa-2,5-dienone (10a). $PhI(OAc)_2$ (143 mg, 0.443 mmol) and K_2CO_3 (122 mg, 0.886 mmol) were tipped into a flask that was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. After 5 min 2-chloroethanol (1 mL) was injected and, after a further 10 min, a solution of **4** (50 mg, 0.40 mmol) in 2-chloroethanol (1 mL) was added dropwise over ca. 6 min. A further portion of 2-chloroethanol (1 mL) was used as a rinse, which was added rapidly. Stirring was continued for 50 min and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O, and the combined organic extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was kept under oil pump vacuum (0.3 mmHg) for 50 min to remove the excess of 2-chloroethanol. Flash chromatography of the residue over silica gel (1 × 24 cm), using 1:10:90 to 1:20:80 Et_3N−EtOAc−hexane, gave **10a** (68.0 mg, 84%) as an oil: FTIR ($CHCl_3$, cast) 2962, 1689, 1674, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.39 (s, 3 H), 3.61 (t, J = 5.9 Hz, 2 H), 3.81 (t, J = 5.9 Hz, 2 H), 6.23−6.25 (m, 1 H), 6.27−6.29 (m, 1 H), 6.77−6.79 (m, 1 H), 6.81−6.83 (m, 1 H) (strictly an AA′BB′ system); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.7 (t), 50.7 (q), 60.1 (t), 92.6 (s), 130.1 (d), 142.8 (d), 184.9 (s); exact mass m/z calcd for $C_9H_{11}{}^{35}ClO_3$ 204.03673, found 204.03697.

4-(2-Iodoethoxy)-4-methoxycyclohexa-2,5-dienone (10b). Acetone (1 mL, dried over K_2CO_3) was added to a mixture of **10a** (37.0 mg, 0.183 mmol) and anhydrous NaI (85.2 mg, 0.568 mmol). The mixture was stirred and refluxed for 45 h, cooled, and evaporated. The residue was partitioned between water and Et_2O, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (26 × 1.2 cm), using first hexane and then EtOAc−hexane mixtures up to 1:10 EtOAc−hexane, gave **10b** (38.4 mg, 71%) as an oil: FTIR (CH_2Cl_2, cast) 2940, 2832,

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1688, 1638, 1617, cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.35 (t, $J = 6.8$ Hz, 2 H), 3.42 (s, 3 H), 3.84 (t, $J = 6.8$ Hz, 2 H), 6.25−6.32 (m, 2 H), 6.78−6.88 (m, 2 H) (strictly an AA′BB′ system); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 2.3 (t), 50.9 (q), 63.8 (t), 92.6 (s), 130.1 (d), 143.0 (d), 184.9 (s); exact mass *m*/*z* calcd for $C_9H_{11}IO_3$ 293.97531, found 293.97605. If we were to do this experiment again we would use DME as the reaction solvent, and Et_3N during the chromatography.

4-(2-Iodoethoxy)-4-methoxycyclohexa-2,5-dienone (10b). $PhI(OAc)_2$ (143 mg, 0.443 mmol) and K_2CO_3 (122 mg, 0.886 mmol) were tipped into a flask that was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. After 5 min, 2-iodoethanol (1 mL) was injected and, after a further 5 min, a solution of **4** (52.3 mg, 0.422 mmol) in 2-iodoethanol (1 mL) was added dropwise over ca. 7 min. A further portion of 2-iodoethanol (0.5 mL) was used as a rinse, which was added rapidly. Stirring was continued for 1.5 h and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was diluted with water and extracted with Et_2O. The combined organic extracts were washed with 1 N aqueous $Na_2S_2O_3$, water, and brine, dried ($MgSO_4$), and evaporated. The residue was kept under oil pump vacuum (0.3 mmHg) for 24 h to remove the excess of 2-iodoethanol. Flash chromatography of the residue over silica gel (1 × 28 cm), using 1:10:90 Et_3N−EtOAc−hexane, gave **10b** (89.7 mg, 72%) as an oil.

2,3-Dihydrobenzofuran-5-ol (10d). A solution of Ph_3SnH (0.07 mL, 0.27 mmol) and AIBN (4.8 mg, 0.030 mmol) in PhMe (5 mL) was added over 4 h (syringe pump) to a stirred and heated (85 °C) solution of **10b** (47.8 mg, 0.163 mmol) in PhMe (10 mL). Heating was continued for 2 h after the addition, the mixture was cooled to room temperature, and $TsOH·H_2O$ (5 mg) was added. Stirring was continued for 30 min and the mixture was partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel, using 1:4 EtOAc−hexane, gave the **10d**[22] (17.4 mg, 79%) as a white solid: mp 108−110 °C.

8a-Methoxy-6-phenyl-3,4,4a,5,6,8a-hexahydro-2*H*-chromen-6-ol (11e). PhMgBr (0.60 mL, 0.60 mmol, 1 M in THF) was added at a fast dropwise rate to a stirred solution of **11c** (55.0 mg, 0.302 mmol) in THF (5 mL). Stirring was continued for 2 h and the mixture was then cooled to 0 °C and quenched with water. The solvent was evaporated and the residue was partitioned between water and Et_2O. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:20:30 Et_3N−EtOAc−hexane, gave **11e** (59.5 mg, 75%) as a colorless solid: mp 131−133 °C; FTIR (CH_2Cl_2 cast) 3406, 3033, 2862, 1490, 1274, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.22−1.32 (m, 2 H), 1.68−1.81 (m, 3 H), 1.96−2.06 (m, 1 H), 2.19 (s, 1 H), 2.44 (t, $J = 13.2$ Hz, 1 H), 3.36 (s, 3 H), 3.60−3.68 (m, 2 H), 5.85 (dd, $J = 5.2$, 2 Hz, 1 H), 6.07 (d, $J = 5.2$, 1 H), 7.23−7.27 (m, 3 H), 7.47 (d, $J = 7.6$ Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.2 (t), 24.4 (t), 33.5 (d), 42.5 (t), 48.0 (q), 61.5 (t), 74.8 (s), 96.0 (s), 126.0 (d), 126.8 (d), 127.4 (d), 128.2 (d), 135.6 (d), 144.6 (s); exact mass *m*/*z* calcd for $C_{16}H_{20}O_3$ 260.14124, found 260.14086.

6-Phenylchroman (11f). $TsOH·H_2O$ (10 mg) was added to a stirred solution of **11e** (47.8 mg, 0.184 mmol) in CH_2Cl_2 (10 mL), and stirring was continued for 1 h. The mixture was then partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:4 CH_2Cl_2−hexane, gave **11f**[23] (30.5 mg, 79%) as a colorless solid: mp 43−44 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.01−2.06 (m, 2 H), 2.85 (t, $J = 6.8$ Hz, 2 H), 4.22 (t, $J = 5.2$ Hz, 2 H), 6.86 (d, $J = 8.2$ Hz, 1 H), 7.26−7.34 (m, 3 H), 7.38−7.42 (m, 2 H), 7.52−7.55 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.4 (t), 25.0 (t), 66.6 (t), 117.0 (d), 122.4 (s), 126.0 (d), 126.5 (d), 126.7 (d), 128.4 (d), 128.6 (d), 133.3 (s), 141.0 (s), 154.6 (s); exact mass *m*/*z* calcd for $C_{15}H_{14}O$ 210.10446, found 210.10445.

4a-Methoxy-1,2,6,10b-tetrahydro-4a*H*-benzo[*c*]chromen-2-ol (14e). $CeCl_3·7H_2O$ (76.7 mg, 0.206 mmol) and then $NaBH_4$ (23.4 mg, 0.618 mmol) were added to a stirred and cooled (−78 °C) solution of **14c** (47.7 mg, 0.206 mmol) in dry MeOH (5 mL). After the addition the cooling bath was removed and stirring was continued for 55 min. Water was added and the mixture was extracted with $CHCl_3$. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel, using 1:15:35 Et_3N−EtOAc−hexane, gave **14e** (35.9 mg, 75%) as an oil [which was a single isomer (^1H NMR)]: FTIR (CH_2Cl_2, cast) 3378, 2942, 2858, 1496 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.76 (dt, $J = 10.5$, 13.3 Hz, 1 H), 2.17−2.23 (m, 1 H), 2.15 (br s, 1 H), 2.82 (dd, $J = 13.5$, 3.0 Hz, 1 H), 3.38 (s, 3 H), 4.41 (q, $J = 4.9$ Hz, 1 H), 4.75 (AB q, $J = 15.0$ Hz, $\Delta\nu_{AB} = 13.2$ Hz, 2 H), 6.01 (apparent AB q, $J = 10.5$ Hz, $\Delta\nu_{AB} = 7.8$ Hz, 2 H), 6.98 (d, $J = 7.2$ Hz, 1 H), 7.13−7.22 (m, 3 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 40.4 (d), 41.2 (t), 49.1 (q), 62.8 (t), 67.86 (d), 67.87 (d), 95.8 (s), 123.5 (d), 125.2 (d), 126.2 (d), 126.8 (d), 128.8 (d), 132.2 (s), 135.0 (s), 136.5 (d); exact mass *m*/*z* calcd for $C_{14}H_{16}O_3$ 232.10994, found 232.11016.

6*H*-Benzo[*c*]chromene (14f). $TsOH·H_2O$ (35.1 mg, 0.201 mmol) was added to a stirred solution of **14e** (35.9 mg, 0.155 mmol) in a mixture of $CHCl_3$ (10 mL) and acetone (1 mL), and stirring was continued overnight [TLC control (silica, hexane or 5% EtOAc−hexane) suggested the reaction was over within 4 min]. The mixture was evaporated and the residue was partitioned between hexane and water. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:20 CH_2Cl_2−hexane, gave **14f**[24] (23.7 mg, 85%) as an oil.

1-Allyl-4a-methoxy-6,10b-dihydro-1*H*,4a*H*-benzo[*c*]-chromen-2-one (14j). AIBN (10 mg, 0.061 mmol) and allyltributyltin (170 mg, 0.512 mmol) were added to a stirred solution of **14b** (83.5 mg, 0.256 mmol) in PhMe (5 mL), and the mixture was then refluxed for 34 h, cooled, and evaporated. Flash chromatography of the residue over silica gel, using 1:5:45 Et_3N−EtOAc−hexane, gave a solid, which appeared to be a mixture of isomers corresponding to the desired product (**14j**) (^1H NMR). TLC analysis (silica, 30% EtOAc−hexane), showed two close spots. The crude material was used directly for the next step.

1-Allyl-6*H*-benzo[*c*]chromen-2-ol (14k). $TsOH·H_2O$ (20 mg, 0.11 mmol) was added to a stirred solution of **14j** (mixture of isomers) in CH_2Cl_2 (4 mL). After 45 min, acetone (10 mL) was added and stirring was continued overnight, since it was not clear from TLC examination (silica, 30% EtOAc−hexane) of the mixture if the reaction was over. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 20% EtOAc−hexane, gave **14k** (44.1 mg, 72%) as an oil: FTIR (CH_2Cl_2, cast) 3418, 3076, 2976, 2835, 1635, 1571 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.71 (apparent dt, $J = 2.3$, 2.1 Hz, 2 H), 4.81−4.85 (br m, 1 H), 4.89 (s, 2 H), 5.24 (dq, $J = 17.3$, 1.6 Hz, 1 H), 5.35 (dq, $J = 10.3$, 1.8 Hz, 1 H), 6.25−6.34 (m, 1 H), 6.80 (d, $J = 8.6$ Hz, 1 H), 6.89 (d, $J = 8.6$ Hz, 1 H), 7.23 (br d, $J = 6.4$ Hz, 1 H), 7.28 (td, $J = 7.3$, 1.1 Hz, 1 H), 7.33 (td, $J = 7.5$, 1.4 Hz, 1 H), 7.62 (d, $J = 7.7$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 33.0 (t), 69.3 (t), 116.2 (d), 116.6 (d), 117.2 (t), 121.3 (s), 124.8 (s), 124.9 (d), 126.0 (d), 127.2 (d), 127.9 (d), 130.3 (s), 134.0 (s), 135.6 (d), 150.0 (s), 150.5 (s); exact mass *m*/*z* calcd for $C_{16}H_{14}O_2$ 238.09938, found 238.09982.

4-(3-Iodonaphthalen-2-ylmethoxy)phenol (15a). A solution of 2-bromomethyl-3-iodonaphthalene (0.23 g, 0.66 mmol) in THF (3 mL) was added dropwise over 25 min to a stirred

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mixture of hydroquinone (0.364 g, 3.30 mmol) and K_2CO_3 (0.229 g, 1.66 mmol) in THF (10 mL). A further portion of THF (1 mL) was used as a rinse, which was added quickly. The flask was transferred to an oil bath, and stirring was continued overnight at 60 °C. The mixture was cooled, poured into water, neutralized with 10% hydrochloric acid, and extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:4 EtOAc−hexane, gave **15a** (0.1637 g, 65%) as a solid: mp 124−126 °C; FTIR (CH_2Cl_2 cast) 3368, 3051, 1204, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.68 (s, 1 H), 5.09 (s, 2 H), 6.76−6.79 (m, 2 H), 6.89−6.93 (m, 2 H), 7.46−7.50 (m, 2 H), 7.69−7.72 (m, 1 H), 7.77−7.80 (m, 1 H), 7.93 (s, 1 H), 8.39 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 74.8 (t), 94.2 (s), 116.1 (d), 116.3 (d), 126.5 (d), 126.7 (d), 126.8 (d), 127.4 (d), 128.0 (d), 132.7 (s), 134.3 (s), 135.4 (s), 138.6 (d), 149.9 (s), 152.7 (s); exact mass *m*/*z* calcd for $C_{17}H_{13}IO_2$ 375.99603, found 375.99672.

4-(3-Iodonaphthalen-2-ylmethoxy)-4-methoxycyclohexa-2,5-dienone (15b). $PhI(OAc)_2$ (0.164 g, 0.510 mmol) and K_2CO_3 (0.140 g, 1.02 mmol) were tipped into a flask that was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. MeOH (6 mL) was added, and a solution of **15a** (0.16 g, 0.43 mmol) in MeOH (4 mL) was injected dropwise over ca. 5 min. A further portion of MeOH (2 mL) was used as a rinse, which was added rapidly. Stirring was continued for 2 h and the reaction was quenched with saturated aqueous $NaHCO_3$. The mixture was partitioned between water and Et_2O, and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 2:15:90 Et_3N−EtOAc−hexane, gave **15b** (0.1471 g, 86%) as an oil: FTIR (CH_2Cl_2 cast) 3053, 1638, 1383, 1105, 1066 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.45 (s, 3 H), 4.74 (s, 2 H), 6.32 (dt, J = 10, 1.5 Hz, 2 H), 6.95 (dt, J = 10, 1.5 Hz, 2 H), 7.44−7.50 (m, 2 H), 7.66−7.69 (m, 1 H), 7.76−7.79 (m, 1 H), 7.84 (s, 1 H), 8.34 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 50.9 (q), 68.8 (t), 93.0 (s), 94.3 (s), 126.5 (d), 126.76 (d), 126.82 (d), 127.3 (d), 127.9 (d), 130.1 (d), 132.7 (s), 134.3 (s), 135.8 (s), 138.6 (d), 143.2 (d), 185.1 (s); exact mass *m*/*z* calcd for $C_{18}H_{15}IO_3$ 406.00659, found 406.00562.

4a-Methoxy-6,12b-dihydro-1*H*,4a*H*-naphtho[2,3-*c*]-chromen-2-one (15c). A solution of Bu_3SnH (0.117 mL, 0.422 mmol) and AIBN (7.1 mg, 0.042 mmol) in PhMe (10 mL) was added over 3 h (by syringe pump) to a stirred and heated (80 °C) solution of **15b** (0.143 g, 0.352 mmol) in PhMe (50 mL). Heating at 80 °C was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 2:20:80 Et_3N−EtOAc−hexane, gave **15c** (0.070 g, 70%) as an oil: FTIR (CH_2Cl_2 cast) 3053, 1631, 1270, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.81 (dd, J = 16.5, 5, 0.5 Hz, 1 H), 2.90 (dd, J = 16.5, 10.5 Hz, 1 H), 3.49 (s, 3 H), 3.53 (dd, J = 10.5, 5 Hz, 1 H), 5.03 (d, J = 2.5 Hz, 2 H), 6.10 (d, J = 10, 0.5 Hz, 1 H), 6.94 (d, J = 10.5 Hz, 1 H), 7.40−7.44 (m, 2 H), 7.54 (s, 1 H), 7.60 (s, 1 H), 7.73−7.78 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 41.8 (q), 43.2 (t), 49.6 (d), 63.6 (t), 95.8 (s), 122.6 (d), 125.9 (d), 126.1 (d), 126.2 (d), 127.3 (d), 127.5 (d), 130.4 (d), 130.8 (s), 132.2 (s), 132.7 (s), 132.7 (s), 143.1 (d), 197.9 (s); exact mass *m*/*z* calcd for $C_{18}H_{16}O_3$ 280.10995, found 280.10993.

6*H*-Naphtho[2,3-*c*]chromen-2-ol (15d). $TsOH·H_2O$ (5 mg) was added to a stirred mixture of **15c** (68.0 mg, 0.243 mmol) and 4 Å molecular sieves (ca. 100 mg) in CH_2Cl_2 (7 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:20 EtOAc−CH_2Cl_2, gave **15d** (52.7 mg, 87%) as a colorless solid: mp 200−201 °C; FTIR (CH_2Cl_2 cast) 3452, 3048, 1489, 1194 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.55 (s, 1 H), 5.19 (s, 2 H), 6.74 (dd, J = 9, 3 Hz, 1 H), 6.91 (d, J = 8.5 Hz, 1 H), 7.38 (d, J = 3 Hz, 1 H), 7.42−7.48 (m, 2 H), 7.60 (s, 1 H), 7.76−7.80 (m, 1 H), 7.84−7.88 (m, 1 H), 8.05 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 69.0 (t), 109.9 (d), 116.6 (d), 118.5 (d), 120.9 (d), 123.2 (d), 123.8 (s), 126.2 (two coincident d), 127.5 (d), 128.0 (s), 128.1 (d), 130.6 (s), 132.9 (s), 133.5 (s), 149.4 (s), 150.6 (s); exact mass *m*/*z* calcd for $C_{17}H_{12}O_2$ 248.08372, found 248.08336.

4-(2-Chloroethoxy)-4-methoxy-4*H*-naphthalen-1-one (17a). A solution of **17**[25] in EtOAc was evaporated and the residue was kept for 10 min (and no longer) under oil pump vacuum (0.1 mmHg). When material that had been too thoroughly dried was used, the following experiment did not work and a blue color developed.

$PhI(OAc)_2$ (110 mg, 0.342 mmol) and K_2CO_3 (95.0 mg, 0.688 mmol) were tipped into a flask that was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. After 5 min, freshly distilled MeOH (10 mL) was injected and, after a further 10 min, a solution of **17** (69.8 mg, 0.314 mmol) in MeOH (5 mL) was added dropwise over ca. 3 min. Stirring was continued for 25 min and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was partitioned between water and Et_2O, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and evaporated. The residue was kept under oil pump vacuum (0.3 mmHg) overnight. Flash chromatography of the residue over silica gel, using 2% Et_3N−hexane and then 1:10:40 Et_3N−EtOAc−hexane, gave **17a** (60.7 mg, 76%) as an oil: FTIR ($CHCl_3$, cast) 2963, 1678, 1631, 1601, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.19 (s, 3 H), 3.44−3.49 (m, 1 H), 3.52−3.60 (m, 2 H), 3.66−3.71 (m, 1 H), 6.58 (dd, J = 10.5, 0.8 Hz, 1 H), 6.92 (dd, J = 10.5, 0.5 Hz, 1 H), 7.49 (apparent t, J = 7.7 Hz, 1 H), 7.65 (apparent t, J = 7.3 Hz, 1 H), 7.74 (apparent d, J = 7.9 Hz, 1 H), 8.06 (apparent d, J = 7.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 42.6 (t), 51.3 (q), 63.8 (t), 94.9 (s), 126.4 (d), 126.8 (d), 129.5 (d), 131.4 (s), 132.6 (d), 133.6 (d), 139.5 (s), 143.6 (d), 183.6 (s); exact mass *m*/*z* calcd for $C_{12}H_{10}{}^{35}ClO_2$ (M − OMe) 221.03693, found 221.03698.

4-(2-Iodoethoxy)-4-methoxy-4*H*-naphthalen-1-one (17b). DME (10 mL, dried over Na/Ph_2CO) was added to a stirred mixture of **17a** (70.0 mg, 0.275 mmol) and anhydrous NaI (412 mg, 2.75 mmol). The mixture was stirred and refluxed for 22 h, cooled, and poured into water. The aqueous phase was extracted with Et_2O and the combined organic extracts were washed with $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel, using 1:10:90 Et_3N−EtOAc−hexane, gave **17b** (72.8 mg, 77%) as an oil: FTIR ($CHCl_3$, cast) 2937, 1673, 1630, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.15−3.23 (m, 2 H), 3.20 (s, 3 H), 3.47 (apparent dt, J = 10.2, 6.1 Hz, 1 H), 3.69 (apparent dt, J = 9.8, 6.7 Hz, 1 H), 6.58 (d, J = 10.5 Hz, 1 h), 6.93 (d, J = 10.5 Hz, 1 H), 7.50 (apparent dt, J = 7.3, 1.3 Hz, 1 H), 7.66 (apparent dt, J = 7.3, 1.4 Hz, 1 H), 7.76 (apparent dq, J = 7.8, 0.6 Hz, 1 H), 8.06 (apparent dq, J = 7.9, 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 2.4 (t), 51.4 (q), 64.4 (t), 94.8 (s), 126.4 (d), 126.8 (d), 129.5 (d), 131.4 (s), 132.6 (d), 133.7 (d), 139.6 (s), 143.7 (d), 183.7 (s); exact mass *m*/*z* calcd for $C_{13}H_{13}IO_3$ 343.99094, found 343.99073.

9b-Methoxy-2,3,3a,9b-tetrahydro-4*H*-naphtho[1,2-*b*]furan-5-one (17c). A solution of Bu_3SnH (0.08 mL, 0.3 mmol) and AIBN (10 mg, 0.061 mmol) in PhMe (5 mL) was added over 3 h (syringe pump) to a stirred and heated (95 °C) solution of **17b** (72.8 mg, 0.212 mmol) in PhMe (15 mL). Heating was continued for 30 min after the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 1:10:40 Et_3N−EtOAc−hexane, gave **17c** (37.7 mg, 82%) as an oil [which was a single isomer (^1H NMR)]: FTIR ($CHCl_3$, cast) 2947, 2893, 1692, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.73−1.79 (m, 1 H), 2.35−2.42 (m, 1 H), 2.69 (dd, J = 16.0, 8.7 Hz, 1 H), 2.82 (dd, J = 16.0, 5.7 Hz, 1 H), 3.06−3.12 (m, 1 H), 3.20 (s, 3 H), 4.06 (dt, J = 8.3, 5.8 Hz, 1 H), 4.17

(25) Laatsch, H. *Liebigs Ann. Chem.* **1980**, 140−157.

(dt, J = 8.4, 6.0 Hz, 1 H), 7.43 (t of m, J = 7.3 Hz, 1 H), 7.64 (td, J = 7.2, 1.4 Hz, 1 H), 7.70 (dq, J = 7.9, 0.5 Hz, 1 H), 7.91 (dq, J = 8.1, 0.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.4 (t), 39.0 (d), 40.6 (t), 51.2 (q), 67.3 (t), 105.8 (s), 126.0 (d), 127.5 (d), 129.0 (d), 131.8 (s), 134.4 (d), 140.2 (s), 196.7 (s); exact mass m/z calcd for $C_{13}H_{14}O_3$ 218.09430, found 218.09453.

Acetic Acid 2,3-Dihydronaphtho[1,2-*b*]furan-5-yl Ester (17d). Ac_2O (ca 1 mL) was added with stirring to **17c** (16.0 mg, 0.0734 mmol), followed by $TsOH\cdot H_2O$ (5 mg). A yellow color developed immediately. Stirring was continued for 3.5 h, the Ac_2O was evaporated under oil pump vacuum, and the residue was taken up in Et_2O. The solution was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel, using 1:20 EtOAc−hexane, gave **17d**[26] (14.7 mg, 89%) as an oil.

4-(2-Chloroethoxy)-3,4-dimethoxycyclohexa-2,5-dienone (18a). $PhI(OAc)_2$ (0.230 g, 0.714 mmol) and K_2CO_3 (0.197 g, 1.43 mmol) were tipped into a flask that was then closed by a septum and flushed with N_2. After 5 min, 2-chloroethanol (1 mL) was injected and, after a further 10 min, a solution of **18** (100 mg, 0.649 mmol) in 2-chloroethanol (2.5 mL) was added dropwise over ca. 6 min. A further portion of 2-chloroethanol (1 mL) was used as a rinse, which was added rapidly. Stirring was continued for 1 h and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was partitioned between water and CH_2Cl_2, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and evaporated. The residue was kept under oil pump vacuum overnight to remove the excess of 2-chloroethanol. Flash chromatography of the residue over silica gel, using 1:40:60 Et_3N−EtOAc−hexane, gave **18a** (0.151 g, 68%) as a yellow oil: FTIR (CH_2Cl_2 cast) 3076, 2942, 1308, 1174 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.27 (s, 3 H), 3.52−3.56 (m, 2 H), 3.67−3.72 (m, 5 H), 5.55 (d, J = 2 Hz, 1 H), 6.22 (dd, J = 10.4, 2 Hz, 1 H), 6.52 (d, J = 10.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 42.5 (t), 51.5 (q), 56.0 (q), 64.1 (t), 93.8 (s), 104.0 (d), 131.0 (d), 140.1 (d), 168.8 (s), 185.9 (s); exact mass m/z calcd for $C_{10}H_{13}ClO_4$ 232.05023, found 232.05016.

4-(2-Iodoethoxy)-3,4-dimethoxycyclohexa-2,5-dienone (18b). Dry acetone (10 mL) was added to a stirred mixture of **18a** (0.42 g, 1.8 mmol) and anhydrous NaI (2.71 g, 18.1 mmol) and the mixture was refluxed for 48 h, cooled, and partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel, using 1:1 EtOAc−hexane, gave **18b** (510.8 mg, 87%) as a yellow oil, which was used directly in the next step.

7,7a-Dimethoxy-2,3,3a,7a-tetrahydro-4*H*-benzofuran-5-one (18c). A solution of Bu_3SnH (0.956 mL, 3.55 mmol) and AIBN (58.3 mg, 0.355 mmol) in PhMe (15 mL) was added over 3 h (by syringe pump) to a stirred and heated (85 °C) solution of **18b** (960 mg, 2.96 mmol) in PhMe (40 mL). Heating at 85 °C was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel, using 2:98 Et_3N in EtOAc, gave **18c** (0.417 g, 70%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2944, 2834, 1664, 1612, 1317 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.69−1.80 (m, 1 H), 2.20−2.28 (m, 1 H), 2.37 (dd, J = 16.4, 7.4 Hz, 1 H), 2.54 (dd, J = 16.4, 7.4 Hz, 1 H), 2.78 (quintet, J = 6.8 Hz, 1 H), 3.37 (s, 3 H), 3.71 (s, 3 H), 4.00−4.10 (m, 2 H), 5.31 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 30.3 (t), 38.8 (t), 40.9 (d), 51.3 (q), 56.1 (q), 68.1 (t), 102.9 (d), 103.7 (s), 171.3 (s), 196.6 (s); exact mass m/z calcd for $C_{10}H_{14}O_4$ 198.08920, found 198.08962.

7-Methoxy-2,3-dihydrobenzofuran-5-ol (18d). $TsOH\cdot H_2O$ (3 mg) was added to a stirred mixture of **18c** (18.0 mg, 0.0910 mmol) and 4 Å molecular sieves (ca 100 mg) in CH_2Cl_2 (5 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:20 EtOAc−CH_2Cl_2, gave **18d**[22] (12.2 mg, 81%) as a solid: 110−111 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.15 (t, J = 8.7 Hz, 2 H), 3.80 (s, 3 H), 4.57 (t, J = 8.7, 2 H), 5.09 (s, 1 H), 6.30−6.34 (m, 2 H).

7-Methoxy-5-methyl-2,3-dihydrobenzofuran (18h) and 5-Methyl-2,3,3a,7a-tetrahydro-4*H*-benzofuran-7-one (18i). $TsOH\cdot H_2O$ (5 mg) was added to a stirred mixture of **18g** (98.0 mg, 0.429 mmol) and 4 Å molecular sieves (ca. 100 mg) in CH_2Cl_2 (15 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with water. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 5:1 EtOAc−hexane, gave **18h** (41.3 mg, 51%) as a colorless solid and **18i** (33.1 mg, 37%) as an oil. Compound **18h** data: mp 46−48 °C; FTIR (CH_2Cl_2 cast) 2935, 1620, 1203 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.27 (s, 3 H), 3.16 (t, J = 8.4 Hz, 2 H), 3.83 (s, 3 H), 4.57 (t, J = 8.4 Hz, 2 H), 6.53 (s, 1 H), 6.62 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.1 (q), 30.6 (t), 55.9 (q), 71.6 (t), 111.9 (d), 117.4 (d), 127.9 (s), 130.6 (s), 144.0 (s), 146.1 (s); exact mass m/z calcd for $C_{10}H_{12}O_2$ 164.08372, found 164.08344.

Compound **18i** data: FTIR (CH_2Cl_2 cast) 2976, 1484, 1252 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70−1.74 (m, 1 H), 1.90 (s, 3 H), 2.19−2.26 (m, 2 H), 2.39−2.46 (m, 1 H), 2.64−2.66 (m, 1 H), 3.44 (s, 3 H), 3.94−4.05 (m, 2 H), 5.84 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.3 (s), 30.4 (t), 33.6 (t), 43.5 (q), 51.9 (q), 67.3 (t), 101.4 (s), 125.3 (d), 160.0 (s), 192.4 (s); exact mass m/z calcd for $C_{10}H_{14}O_3$ 182.09430, found 182.09465.

7-Methoxy-5-methyl-2,3-dihydrobenzofuran (18h) and 5-Methyl-2,3-dihydrobenzofuran-7-ol (18j). $TsOH\cdot H_2O$ (5 mg) was added to a stirred solution of **18g** (28.0 mg, 0.138 mmol) in CH_2Cl_2 (5 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 3:1 EtOAc−hexane, gave **18h** (12.0 mg, 52%) and **18j** (6.8 mg, 36%) as colorless solids. Compound **18j** data: mp 95−97 °C; FTIR (CH_2Cl_2 cast) 3361, 3031, 1718, 999 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.23 (s, 3 H), 3.18 (t, J = 8.8 Hz, 2 H), 4.57 (t, J = 8.8 Hz, 2 H), 4.96 (s, 1 H), 6.40 (s, 1 H), 6.57 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.9 (q), 30.5 (d), 71.9 (d), 115.6 (d), 117.2 (d), 127.7 (s), 131.1 (s), 139.7 (s), 144.4 (s); exact mass m/z calcd for $C_9H_{10}O_2$ 150.06808, found 150.06840.

5-Methyl-2,3-dihydrobenzofuran-7-ol (18j). $TsOH\cdot H_2O$ (5 mg) was added to a stirred solution of **18i** (30.0 mg, 0.165 mmol) in CH_2Cl_2 (5 mL), and stirring was continued for 1 h. The mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel, using 1:3 EtOAc−hexane, gave **18j** (22.1 mg, 89%) as a colorless solid, spectroscopically identical with material obtained previously.

4-(2-Iodoethoxy)-4-methylcyclohexan-2,5-dienone (20a). $PhI(OAc)_2$ (529 mg, 1.64 mmol) and K_2CO_3 (452 mg, 3.28 mmol) were tipped into a flask that was then closed by a septum and flushed with N_2. The flask was placed in an ice bath and the contents were stirred. After 5 min, 2-iodoethanol (2 mL) was injected and, after a further 5 min, a solution of freshly distilled *p*-cresol (**20**) (162 mg, 1.49 mmol) in 2-iodoethanol (2 mL) was added dropwise over ca. 5 min. A further portion of 2-iodoethanol (1 mL) was used as a rinse, which was added rapidly. Stirring was continued for 130 min and the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL). The mixture was partitioned between water and Et_2O, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with 1 N aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$), and evaporated. The residue was kept under oil pump vacuum (0.4

(26) Semmelhack, M. F.; Bozell, J. J. *Tetrahedron Lett.* **1982**, *23*, 2931−2934.

mmHg) for 18 h to remove the excess of 2-iodoethanol. Flash chromatography of the residue over silica gel (24 × 1.8 cm^2), using 1:10:90 Et_3N−EtOAc−hexane, gave **20a** (198.9 mg, 48%) as an oil: FTIR ($CHCl_3$, cast) 2977, 2928, 1674, 1631, 1605 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.42−1.45 (m, 3 H), 3.15−3.20 (m, 2 H), 3.48−3.53 (m, 2 H), 6.24−6.29 (m, 2 H), 6.75−6.80 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.5 (t), 26.3 (q), 66.3 (t), 72.6 (s), 130.2 (d), 151.0 (d), 184.8 (s); exact mass *m*/*z* calcd for $C_9H_{11}IO_2$ 277.98038, found 277.98014.

7a-Methyl-2,3,3a,7a-tetrahydro-4*H*-benzofuran-5-one (20b). A solution of Bu_3SnH (0.09 mL, 0.3 mmol) and AIBN (10 mg, 0.061 mmol) in PhMe (5 mL) was added over 3 h (syringe pump) to a stirred and heated (95 °C) solution of **20a** (74.9 mg, 0.269 mmol) in PhMe (10 mL). Heating was continued for 20 min after the addition. The solvent was evaporated under water pump vacuum (the product is volatile), and flash chromatography of the residue over silica gel, using 1:10:90 Et_3N−EtOAc−hexane (and evaporation of appropriate fractions under water pump vacuum), gave **20b** (27.3 mg, 67%) as an oil. A distilled sample (Kugelrohr oven at 120 °C, 40 mmHg) solidified at ca. 0 °C, but the solid melted below room temperature: FTIR (CH_2Cl_2, cast) 2970, 2878, 1683 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.43 (s, 3 H), 1.69−1.78 (m, 1 H), 2.14−2.21 (m, 1 H), 2.40−2.46 (m, 1 H), 2.59 (apparent d, *J* 4.0 Hz, 2 H), 3.76 (sextet, *J* = 4.5 Hz, 1 H), 3.86 (q, *J* = 8.0 Hz, 1 H), 5.88 (d, *J* = 10.2 Hz, 1 H), 6.52 (dd, *J* = 10.2, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.7 (q), 31.6 (t), 38.1 (t), 43.3 (d), 66.0 (t), 78.9 (s), 128.0 (d), 152.7 (d), 197.6 (s); exact mass *m*/*z* calcd for $C_9H_{12}O_2$ 152.08372, found 152.08378.

Acetic Acid 3-(2-Acetoxyethyl)-4-methylphenyl Ester (20c). $TsOH·H_2O$ (5 mg, 0.03 mmol) was added to a stirred solution of **20b** (13.9 mg, 0.0914 mmol) in a mixture of CH_2Cl_2 (2 mL) and Ac_2O (1 mL), and stirring was continued for 160 min. The flask was fitted with a condenser and then lowered into an oil bath preset at 110 °C. After 2 h, the mixture was cooled and the excess of Ac_2O was removed under oil pump vacuum. The mixture was partitioned between water and Et_2O, and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel, using hexane−CH_2Cl_2 mixtures from 100% hexane to 100% CH_2Cl_2, gave **20c** (14.9 mg, 69%) as an oil: FTIR ($CHCl_3$, cast) 2959, 1761, 1739, cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.03 (s, 3 H), 2.26 (s, 3 H), 2.29 (s, 3 H), 2.91 (t, *J* = 7.2 Hz, 2 H), 4.24 (t, 7.2 Hz, 2 H), 6.83−6.87 (m, 2 H), 7.13 (d, *J* = 7.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.9 (q), 21.0 (q), 21.2 (q), 32.4 (t), 63.6 (t), 119.6 (d), 122.3 (d), 131.0 (d), 133.9 (s), 137.1 (s), 148.7 (s), 169.5 (s), 170.8 (s); exact mass *m*/*z* calcd for $C_{13}H_{16}O_4$ 236.10486, found 236.10471.

5-(Allyloxy)-1,4-naphthoquinone (24). Allyl bromide (1.82 g, 1.30 mL, 15.0 mmol) and silver(I) oxide (2.61 g, 11.3 mmol) were added to a stirred solution of juglone (**23**) (1.31 g, 7.52 mmol) in CH_2Cl_2 (20 mL), and stirring was continued for 20 h. Additional portions of allyl bromide (0.84 g, 0.60 mL, 6.9 mmol) and silver(I) oxide (1.8 g, 7.8 mmol) were added, and the mixture was then refluxed for 11 h. The mixture was cooled and partitioned between water and CH_2Cl_2, and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (25 × 2.8 cm), using 1:4 EtOAc−hexane, gave **24** (1.28 g, 79%) as a yellow-orange solid: mp 54−56 °C; FTIR ($CHCl_3$, cast) 1659, 1613, 1583 cm^{-1}; ^1H NMR ($CDCl_3$, 400.1 MHz) δ 4.66 (dt, *J* = 4.8, 1.7 Hz, 2 H), 5.31 (dq, *J* = 10.7, 1.6 Hz, 1 H), 5.60 (dq, *J* = 17.4, 1.6 Hz, 1 H), 6.03 (apparent q of t, *J* = 10.7, 4.7 Hz, 1 H), 6.80 (AB q, *J* = 2.0, 10.2 Hz, $\Delta\nu_{AB}$ = 6.3 Hz, 2 H), 7.22 (dd, *J* = 8.2, 1.3 Hz, 1 H), 7.58 (t, *J* = 8.2 Hz, 1 H), 7.65 (dd, *J* = 6.3, 1.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 69.7 (t), 117.9 (t), 119.2 (d), 119.3 (d), 120.0 (s), 131.9 (d), 134.0 (s), 134.7 (d), 136.0 (d), 140.8 (d), 158.5 (s), 184.0 (s), 185.1 (s); exact mass *m*/*z* calcd for $C_{13}H_{10}O_3$ 214.06299, found 214.06276.

5-(Allyloxy)naphthalene-1,4-diol (25). A solution of $Na_2S_2O_4$ (1.92 g, 11.0 mmol) in water (10 mL) was added to a solution of **24** (0.7871 g, 3.678 mmol) in Et_2O (50 mL), and the mixture was stirred for 40 min. Water (20 mL) was added and the aqueous phase was extracted twice with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give **25** (0.7926 g, 100%) as beige flakes: mp 133−134 °C; FTIR ($CHCl_3$, cast) 3400, 3196, 2938, 1636, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.76 (dt, *J* = 4.9, 1.3 Hz, 2 H), 4.89 (s, 1 H), 5.40 (dq, *J* = 10.4, 1.0 Hz, 1 H), 5.49 (dq, *J* = 17.2, 1.3 Hz, 1 H), 6.09−6.18 (m, 1 H), 6.72 (AB q, *J* = 8.2 Hz, $\Delta\nu_{AB}$ = 19.9 Hz, 2 H), 6.82 (d, *J* = 7.7 Hz, 1 H), 7.31 (t, *J* = 7.9 Hz, 1 H), 7.74 (dd, *J* = 8.6, 0.9 Hz, 1 H), 9.03 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 70.3 (t), 106.3 (d), 109.4 (d), 110.9 (d), 115.8 (s), 115.9 (d), 119.8 (t), 125.2 (d), 126.9 (s), 131.8 (d), 143.7 (s) 148.4 (s) 155.1 (s); exact mass *m*/*z* calcd for $C_{13}H_{12}O_3$ 216.07864, found 216.07872.

(2*R*)-2-[[5-(Allyloxy)-4-hydroxynaphthalen-1-yl]oxy]-propionic Acid Ethyl Ester (26). A solution of (*S*)-2-[(trifluoromethanesulfonyl)oxy]propionic acid ethyl ester[19] (3.50 g, 14.0 mmol) in CH_2Cl_2 (10 mL) was added over 10 min to a stirred and cooled (−78 °C) mixture of **25** (0.6117 g, 3.045 mmol) and Cs_2CO_3 (0.9945 g, 3.045 mmol) in CH_2Cl_2 (15 mL). Stirring at −78 °C was continued arbitrarily for 18 h. The progress of the reaction was monitored by TLC (silica, 1:3 EtOAc−hexane); no further change seemed to occur after ca. 3 h. The mixture was quenched with saturated aqueous NH_4Cl (10 mL) and partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (23 × 2.4 cm), using 1:10 to 1:5 EtOAc−hexane mixtures, gave **26** [0.4789 g, 50% or 88% after correction for recovered **25** (0.2448 g, 40%)] as a clear, colorless oil: FTIR ($CHCl_3$, cast) 3415, 2984, 1750, 1632, 1609, 1513 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (t, *J* = 7.2 Hz, 3 H), 1.68 (d, *J* = 6.8 Hz, 3 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 4.75 (dt, *J* = 5.6, 1.8 Hz, 2 H), 4.78 (q, *J* = 6.8 Hz, 1 H), 5.39 (dq, *J* = 10.4, 1.2 Hz, 1 H), 5.48 (dq, *J* = 17.2, 1.5 Hz, 1 H), 6.08−6.18 (m, 1 H), 6.7 (s, 2 H), 6.83 (dd, *J* = 7.8, 0.7 Hz, 1 H), 7.31 (dd, *J* = 7.8, 8.5 Hz, 1 H), 7.92 (dd, *J* = 8.6, 1.0 Hz, 1 H), 9.04 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.2 (q), 18.7 (q), 61.2 (t), 70.4 (t), 74.1 (s), 106.4 (d), 108.9 (d), 109.5 (d), 115.9 (s), 116.7 (d), 119.8 (t), 125.3 (d), 128.6 (s), 131.8 (d), 146.2 (s), 149.0 (s), 154.9 (s), 172.5 (s); exact mass *m*/*z* calcd for $C_{18}H_{20}O_4$ 316.13107, found 316.13089.

8-Allyloxy-4-[(1*R*)-2-hydroxy-1-methylethoxy]naphthalen-1-ol (27). $LiAlH_4$ (0.0149 g, 0.392 mmol) was added to a stirred solution of **26** (0.1661 g, 0.5223 mmol) in THF (15 mL). After 10 min, aqueous sodium potassium tartrate (20% w/v, 5 mL) was added. The mixture was stirred for a further 20 min, and then partitioned between water and Et_2O. The aqueous phase was extracted twice with Et_2O and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (21 × 2.3 cm), using 1:1 EtOAc−hexane, gave **27** (146.9 mg, 100%) as clear, light green flakes: mp 76−78 °C; FTIR ($CHCl_3$, cast) 3414, 2975, 2932, 1630, 1609, 1512 cm^{-1}; ^1H NMR ($CDCl_3$, 400.1 MHz) δ 1.30 (d, *J* = 6.5, 3 H), 3.78−3.85 (m, 2 H), 4.50−4.59 (m, 1 H), 4.77 (dt, *J* = 5.6, 1.4 Hz, 2 H), 5.41 (dq, *J* = 10.3, 1.2 Hz, 1 H), 5.50 (dq, *J* = 17.3, 1.2 Hz, 1 H), 6.10−6.20 (m, 1 H), 6.83 (br d, *J* = 7.5, 1 H), 6.84 (AB q, *J* = 8.6 Hz, $\Delta\nu_{AB}$ = 148.2 Hz, 2 H), 7.30 (AB q, *J* = 7.8 Hz, $\Delta\nu_{AB}$ = 3.6 Hz, 1 H), 7.84 (dd, *J* = 8.5, 0.9 Hz, 1 H), 9.06 (s, 1 H), OH signal not observed in this spectrum; ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 16.2 (q), 66.6 (t), 70.4 (t), 76.6 (d), 106.2 (d), 109.3 (d), 111.3 (d), 115.8 (s), 116.1 (d), 119.7 (t), 125.2 (d), 129.3 (s), 131.7 (d), 145.7 (s), 148.7 (s), 155.0 (s); exact mass *m*/*z* calcd for $C_{16}H_{18}O_4$ 274.12051, found 274.12067.

8-Allyloxy-4-[(1*R*)-2-iodo-1-methylethoxy]naphthalen-1-ol (28). Ph_3P (0.3337 g, 1.272 mmol) and then imidazole (0.0914 g, 1.34 mmol) were added to a stirred solution of **27** (0.1255 g, 0.4547 mmol) in THF (10 mL) (Ar atmosphere). The

mixture was transferred to an ice bath (continued stirring), and I_2 (0.2620 g, 1.032 mmol) was added in one portion. After 2.5 h, the ice bath was removed and stirring was continued overnight. The mixture was partitioned between water and EtOAc. The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed with aqueous $Na_2S_2O_3$ (10% w/v), water, and dilute hydrochloric acid (5%), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (24 × 2.8 cm), using first hexane and then EtOAc−hexane mixtures up to 1:6 EtOAc−hexane, gave **28** (0.1568 g, 89%) as an oil: FTIR ($CHCl_3$, cast) 3414, 2977, 2930, 1631, 1608 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50 (d, J = 6.0, 3 H), 3.35−3.47 (m, 2 H), 4.32−4.42 (m, 1 H), 4.76 (dt, J = 5.6, 1.3 Hz, 2 H), 5.40 (dq, J = 10.5, 1.2 Hz, 1 H), 5.49 (dq, J = 17.2, 1.2 Hz, 1 H), 6.07−6.21 (m, 1 H), 6.72−6.84 (m, 3 H), 7.30 (AB q, J = 7.8 Hz, $\Delta\nu_{AB}$ = 3.6 Hz, 1 H), 7.86 (dd, J = 8.6, 0.9, 1 H), 9.06 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.4 (t), 20.3 (q), 70.3 (t), 74.6 (d), 106.3 (d), 109.2 (d), 111.1 (d), 115.9 (s), 116.5 (d), 119.7 (t), 125.3 (d), 129.3 (s), 131.7 (d), 145.3 (s), 148.9 (s), 154.9 (s); exact mass m/z calcd for $C_{16}H_{17}IO_3$ 384.02225, found 384.02247.

8-Allyloxy-4-[(1*R*)-2-iodo-1-methylethoxy]-4-methoxy-4*H*-naphthalen-1-one (29). DDQ (0.0878 g, 0.388 mmol), followed immediately by K_2CO_3 (0.0534 g, 0.387 mmol), was added to a stirred solution of **28** (0.0995 g, 0.258 mmol) in MeOH. After 4 min, aqueous $Na_2S_2O_3$ (2 mL, 10% w/v) and water (10 mL) were added. The mixture was partitioned between EtOAc and water, and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (21 × 2 cm), using 1:4 EtOAc−hexane, gave **29** (0.0938 g, 87%) as an oil [ca. 1:1.15 mixture of diastereoisomers (^1H NMR)]: FTIR ($CHCl_3$, cast) 3396, 2924, 1659, 1608, 1582 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, signals for both isomers reported, as extensive overlapping prevents allocation of signals to individual isomers) δ 1.23 (d, J = 6.2, 1.4 H), 1.35 (d, J = 6.1 Hz, 1.6 H), 2.90 (dd, J = 10.0, 7.3 Hz, 0.6 H), 3.01 (dd, J = 10.0, 3.8 Hz, 0.4 H), 3.10 (s, 1.6 H), 3.13 (s, 1.4 H), 3.20−3.33 (m, 1 H), 3.72−3.86 (m, 1 H), 4.66−4.70 (m, 2 H), 5.35 (apparent dt, J = 10.7, 1.5 Hz, 1 H), 5.68 (apparent dq, J = 17.2, 1.7 Hz, 1 H), 6.04−6.17 (m, 1 H), 6.47 (apparent dd, J = 10.4, 1.5 Hz, 1 H), 6.75 (d, J = 10.5 Hz, 0.5 H), 6.81 (d, J = 10.5 Hz, 0.5 H), 7.01 (dd, J = 8.3, 2.8 Hz, 1 H), 7.42 (dd, J = 7.8, 2.9, 1.0 Hz, 1 H), 7.58 (td, J = 8.1, 1.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.6 (t), 13.08 (t), 21.6 (q), 22.4 (q), 51.3 (q), 51.4 (q), 68.9 (d), 69.3 (d), 69.6 (two coincident t), 95.3 (s), 95.4 (s), 114.1 (d), 114.2 (d), 117.6 (t), 117.7 (t), 119.7 (d), 119.8 (d), 120.5 (s), 120.6 (s), 132.25 (d), 132.28 (d), 133.9 (d), 134.0 (d), 134.4 (two coincident d), 139.9 (d), 140.5 (d), 143.0 (s), 143.2 (s), 158.7 (s), 158.8 (s), 183.14 (s), 183.15 (s); exact mass m/z calcd for $C_{17}H_{19}IO_4$ 414.03281, found 414.03241.

(2*R*)-6-Allyloxy-9b-methoxy-2-methyl-2,3,3a,9b-tetrahydro-4*H*-naphtho[1,2-*b*]furan-5-one (31). A solution of Bu_3SnH (0.19 mL, 0.70 mmol) and AIBN (0.010 g) in PhMe (5 mL) was added over 9 h (syringe pump) to a stirred and heated (85 °C) solution of **29** (0.2246 g, 0.5399 mmol) in PhMe (10 mL). Heating at 85 °C was continued for 6 h after the addition. The solvent was evaporated, and flash chromatography of the residue over silica gel (26 × 2.8 cm), using 1:20:30 Et_3N−EtOAc−hexane, gave **31** (0.1286 g, 82%) as an oil: FTIR ($CHCl_3$, cast) 2968, 2934, 1694, 1593 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, signals for both isomers reported, as extensive overlapping prevents allocation of signals to individual isomers) δ 1.26 (d, J = 6.2 Hz, 1.5 H), 1.40 (d, J = 6.2 Hz, 1.5 H), 1.87−1.96 (m, 0.5 H), 2.01−2.12 (m, 0.5 H), 2.39−2.49 (m, 0.5 H), 2.62−2.86 (m, 2 H), 3.00−3.14 (m, 1 H), 3.13 (s, 1.5 H), 3.15 (s, 1.5 H), 4.34−4.51 (m, 1 H), 4.54−4.69 (m, 2 H), 5.31 (apparent dt, J = 10.6, 1.5 Hz, 1 H), 5.56 (dm, J = 17.2 Hz, 1 H), 5.99−6.12 (m, 1 H), 6.94 (br d, J = 8.3 Hz, 1 H), 7.32 (apparent d of quintets, J = 8.6, 0.9 Hz, 1 H), 7.52 (apparent sextet, J = 4.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz, signals for both isomers reported, as extensive overlapping prevents allocation of signals to individual isomers) δ 21.4 (q), 22.6 (q), 37.7 (t), 39.4 (t), 39.9 (d), 40.8 (d), 43.4 (t), 44.5 (t), 50.4 (q), 51.3 (q), 69.47 (t), 69.48 (t), 75.2 (d), 75.4 (d), 105.6 (s), 106.6 (s), 113.2 (d), 113.4 (d), 117.5 (two coincident t), 119.5 (d), 119.7 (d), 122.3 (s), 122.4 (s), 132.40 (d), 132.44 (d), 134.1 (d), 134.5 (d), 142.6 (s), 142.8 (s), 156.4 (s), 156.9 (s), 196.2 (s), 196.4 (s); exact mass m/z calcd for $C_{17}H_{20}O_4$ 288.13617, found 288.13558.

(2*R*)-6-Allyloxy-2-methyl-2,3-dihydronaphtho[1,2-*b*]furan-5-ol (32). AcOH (ca. 0.3 mL) was added to a stirred solution of **31** (0.0733 g, 0.253 mmol) in $CHCl_3$ (5 mL), and stirring was continued for 2 h. Evaporation of the solvent at room temperature (oil pump vacuum) and flash chromatography of the residue over silica gel (22 × 2.8 cm), using 1:10 EtOAc−hexane, gave **32** (57.6 mg, 88%) as a white solid: mp 77−78 °C; FTIR ($CHCl_3$, cast) 3423, 2972, 2928, 1641, 1605, 1524 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.50 (d, J = 6.3 Hz, 3 H), 2.92 (apparent dd, J = 16.0, 7.6 Hz, 1 H), 3.41 (apparent dd, J = 15.4, 8.9 Hz, 1 H) (formally part of an ABX system), 4.74 (apparent d, J = 5.6 Hz, 2 H), 4.99−5.06 (m, 1 H), 5.38 (dq, J = 10.5, 1.1 Hz, 1 H), 5.48 (dq, J = 17.3, 1.4 Hz, 1 H), 6.13 (ddt, J = 17.3, 10.5, 5.6 Hz, 1 H), 6.71 (d, J = 7.6 Hz, 1 H), 6.73 (s, 1 H), 7.23 (t, J = 8.2 Hz, 1 H), 7.48 (dd, J = 8.4, 0.8 Hz, 1 H), 9.00 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.9 (q), 38.4 (t), 70.2 (t), 79.6 (d), 105.1 (d), 107.1 (d), 114.2 (s), 115.6 (d), 119.6 (t), 121.6 (s), 121.9 (s), 125.1 (d), 131.8 (d), 147.5 (s), 148.3 (s), 155.2 (s); exact mass m/z calcd for $C_{16}H_{16}O_3$ 256.10995, found 256.10936.

In another experiment, an NMR sample (43.2 mg, 0.149 mmol) was left overnight in $CDCl_3$, and evaporation of the solvent, followed by flash chromatography, gave **32** (37.1 mg, 97%).

(2*R*)-6-Allyloxy-2-methyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione (33). $[PhSe(O)]_2O$[21] (70%, 0.1859 g, 0.5162 mmol) was added in one portion to a stirred solution of **32** (0.0666 g, 0.258 mmol) in THF (10 mL). After 12 min, water (20 mL) was added and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (22 × 2.2 cm), using 3:7 to 1:1 EtOAc−hexane mixtures, gave **33** (0.0676 g, 96%) as a red powder. Recrystallization from $CHCl_3$−hexane (dissolution in $CHCl_3$ and addition of hexane) gave **33** (0.574 g, 82%) as orange-red needles: mp 118−120 °C; FTIR ($CHCl_3$, cast) 2978, 1683, 1647, 1621, 1576 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.54 (d, J = 6.4, 3 H), 2.70 (apparent dd, J = 15.3, 7.3 Hz, 1 H), 3.24 (apparent dd, J = 15.3, 9.8 Hz, 1 H) (formally part of an ABX system), 4.68 (dt, J = 4.4, 1.8 Hz, 2 H), 5.15−5.24 (m, 1 H), 5.34 (dq, J = 10.7, 1.6 Hz, 1 H), 5.74 (dq, J = 17.2, 1.7 Hz, 1 H), 5.99−6.08 (m, 1 H), 7.11 (d, J = 8.6 Hz, 1 H), 7.26 (dd, 7.4, 0.8 Hz, 1 H), 7.53 (dd, 8.6, 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9 (q), 33.5 (t), 69.4 (t), 84.0 (d), 114.5 (s), 117.4 (d), 117.7 (t), 117.9 (d), 118.3 (s), 129.5 (s), 131.5 (d), 135.5 (d), 160.7 (s), 169.2 (s), 175.5 (s), 180.0 (s); exact mass m/z calcd for $C_{16}H_{14}O_4$ 270.08920, found 270.08915.

(2*R*)-6-Hydroxy-2-methyl-2,3-dihydronaphtho[1,2-*b*]furan-4,5-dione [*ent*-Nocardione A] (34). Dimedone (0.0623 g, 0.444 mmol) and then $Pd(PPh_3)_4$ (0.0259 g, 0.0223 mmol) were added to a stirred solution of **33** (0.0574 g, 0.211 mmol). Stirring was continued for 4 min, and the mixture was then evaporated (rotary evaporator) at room temperature. Flash chromatography of the reside over silica gel (24 × 1.8 cm), using 0.1:10:90 HCO_2H−EtOAc−$CHCl_3$, gave a crude red powder (0.0557 g). (Use of acid in the solvent is essential for effective purification, but recrystallization is still necessary.) Recrystallization from EtOAc−hexane gave **34** [(*R*)-(+)-nocardione A, *ent*-nocardione A] (0.0359 g, 74%) in the form of curled red needles: mp 168−169 °C [if the crystalline material is dissolved in a solvent and the solution evaporated to leave a powder, the powder changes to needles (mp 168−169 °C) at or below 158 °C]; $[\alpha]^{25}_D$ +36.8 (*c* 1.0 $CHCl_3$, 10 cm cell); $[\alpha]^{25}_D$ +49.5 (*c* 0.97 $CHCl_3$, 1 cm cell) {lit.[13] $[\alpha]^{21}_D$ −56.0 (*c* 0.97

$CHCl_3$; lit.[12] $[\alpha]^{26}_D$ −85.4 (*c* 1.0 $CHCl_3$)}; FTIR ($CHCl_3$, cast) 2961, 2925, 1643, 1615, 1589, 1499 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56 (d, $J = 6.3$, 3 H), 2.72 (apparent dd, $J = 15.4$, 7.2 Hz, 1 H), 3.25 (apparent dd, $J = 15.3$, 9.8 Hz, 1 H) (formally part of an ABX system), 5.19−5.27 (m, 1 H), 7.11 (dd, $J = 8.7$, 0.9 Hz, 1 H), 7.18 (br d, $J = 6.7$ Hz, 1 H), 7.53 (dd, $J = 8.6$, 7.3 Hz, 1 H), 11.93 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9 (q), 33.4 (t), 84.5 (d), 113.4 (s), 115.1 (s), 117.4 (d), 123.2 (d), 127.4 (s), 137.5 (d), 164.4 (s), 169.1 (s), 175.0 (s), 185.4 (s); exact mass *m*/*z* calcd for $C_{13}H_{10}O_4$ 230.05791, found 230.05774.

HPLC conditions for measurement of ee: column, chiralcell AD-RHCD-CC012 column (0.46 cm × 15 cm); eluant 2:1 water−MeCN; flow rate 0.6 mL/min; detection at 230 nm; temperature 25 °C; sample concentration and injection value 1 mL/mg in MeCN × 0.5 μL. Under these conditions (*S*)-(−)-nocardione A was detected at R_t 40.31 min, and (*R*)-(+)-nocardione A was detected at R_t 42.82 min. Our synthetic (*R*)-nocardione A had 98.55% ee.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support, Dr. X. Lu and H. Lachance for HPLC measurements, and M. Zhu for preliminary studies. S.P.F. holds an NSERC Postgraduate Scholarship.

Note Added after ASAP Posting. There was a bond missing in the structure of compounds **21** and **22** in the version posted ASAP April 17, 2004; the corrected version was posted April 20, 2004.

Supporting Information Available: NMR spectra of **10a**−**c**, **11a**−**c**,**e**, **12a**−**c**, **13a**,**b**, **14c**−**e**,**g**,**k**, 2-bromomethyl-3-iodonaphthalene, **15a**−**d**, **17a**−**c**, **18a**,**c**,**e**,**g**−**j**, **19a**−**e**,**g**,**i**, **20a**−**c**, **24**−**29**, and **31**−**34**, and experimental general techniques and procedures for **10c**, **11a**−**d**, **12a**−**d**, **13a**,**b**, **14a**−**d**,**g**−**h**, 2-bromomethyl-3-iodonaphthalene, **18e**−**g**, and **19a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO030364K