of this solution was transferred under a nitrogen atmosphere to a mixture of **3a** (0.0156 g) and **4b** (0.0156 g) which had been cooled to 0 °C in an ice bath. The reaction was stirred for several minutes, ice was added, and the reaction mixture was extracted with benzene (3 × 5 mL). The combined benzene extracts were dried over anhydrous magnesium sulfate, and dodecane (0.012 g) was added to the solution. The amounts of unreacted **3a** and **4a** were determined by GLC analysis by using the dodecane as an internal standard. The relative reaction rates of **3a** and **4a** with lithium methylamide were determined in a similar manner. The product distributions (**7a** and **8a**) in the reaction of **3a** and **4b** with lithium pyrrolidide were determined by reacting pure **3a** or **4b** with an equimolar amount of lithium pyrrolidide, working up the reaction as described above, evaporating the benzene, and analyzing the product by ^1H NMR spectroscopy.

Acknowledgment. We gratefully acknowledge the financial support of this work by a Texas Woman's University Institutional Research Grant.

Registry No. **3a**, 41071-35-6; **3b**, 41071-37-8; **3c**, 57139-33-0; **3d**, 57139-34-1; **3e**, 57139-36-3; **3f**, 57139-40-9; **3g**, 97315-84-9; **4a**, 41071-34-5; **4b**, 41071-36-7; **7a**, 97315-85-0; **7b**, 97315-86-1; **7c**, 97315-87-2; **7d**, 97315-88-3; **7e**, 97315-89-4; **7f**, 97315-90-7; **7g**, 97315-97-4; **7h**, 97315-98-5; **7i**, 97315-99-6; **8a**, 97315-91-8; **8b**, 97315-92-9; **8c**, 97315-93-0; **8d**, 97315-94-1; **8e**, 97315-95-2; **8f**, 97315-96-3; piperidine, 110-89-4; lithium pyrrolidide, 4439-90-1; pyrrolidine, 123-75-1; lithium methylamide, 67601-96-1; methyl *p*-nitrobenzohydroxamate, 1613-79-2.

Supplementary Material Available: Analytical data for benzamidoximes (1 page). Ordering information is given on any current masthead page.

Annulation Reactions Leading to Naphthalene Derivatives. New Syntheses of Natural 1,2- and 1,4-Naphthoquinones

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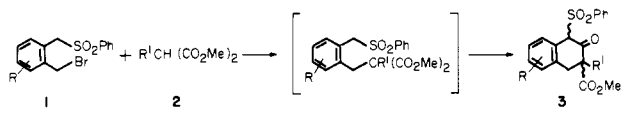
1-(Phenylsulfonyl)-2-oxo-3-(methoxycarbonyl)-1,2,3,4-tetrahydronaphthalene derivatives with various C-3 substituents were effectively prepared by a one-step cyclization involving 1-[(phenylsulfonyl)methyl]-2-(bromomethyl)benzene derivatives and monosubstituted malonic esters. A high yield one-step decarboxylation–desulfonylation of the above products by lithium iodide led to C-3-substituted 2-naphthalenols **7a–g** whereas prior C-1 alkylation of the cyclization products provided 1,3-dialkylated 2-naphthalenols **6a,b**. Oxidations of compounds **7** to *o*-naphthoquinones **8a–f** and further oxidations of the above products to substituted 2-hydroxy-1,4-naphthoquinones provided a new pathway to naturally occuring naphthoquinones like phthiocol (**9**), droserone methyl ether (**10**), and lapachol (**15**).

Regioselective annulation methodology for the formation of carbocycles fused to aromatic and heteroaromatic rings is a research area of utmost importance in providing new pathways for the construction of polycyclic natural compounds. Apart from the sequential Friedel–Crafts cyclization, there has been, during recent years, extensive utilization of one-step processes ensuring the formation of two carbon–carbon bonds, namely Diels–Alder reactions of *o*-quinodimethane species[1] and Michael-induced ring closure (MIRC) reactions,[2] to give new rings fused to aromatics. In the MIRC reactions a variety of aromatic derivatives have been used as 1,4-dipole synthons, supplying four carbons to the newly formed cyclohexane ring.

We recently initiated an annulation pathway, similar to the above in purpose but conceptually different, in which bifunctional aromatic or heteroaromatic compounds, having both electrophilic and nucleophilic centers, can function as versatile 1,4-dipole synthons in a substitution–acylation scheme. The success of such a regioselective annulation route depended on the choice of the two functions on the annulating reagents, to ensure

Scheme I



effective intermolecular reactivity instead of self-annihilation and byproduct formation under the reaction conditions. Furthermore, the problem of a regioselective bifunctionalization leading to the required annulating reagents had to be solved. We have found that activation of vicinal benzylic centers by Br and SO_2Ph groups provides a fulfillment of these requirements. Thus, 1-(bromomethyl)-2-[(phenylsulfonyl)methyl]-substituted aromatic[3] or heteroaromatic[4] derivatives, obtained via regioselective radical bromination of the unsubstituted methyl group in the presence of a vicinal (phenylsulfonyl)methyl group,[5] react with various substrates to provide new and effective pathways for the generation of bicyclic and tricyclic systems.

We report on the annulation reactions leading to functionalized naphthalene derivatives and on the potentialities of the latter as versatile synthetic intermediates to afford, inter alia, naturally occurring naphthoquinones.

(1) For leading references on cyclization via *o*-quinodimethane species, see: Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 7609. Oppolzer, W. *Pure Appl. Chem.* **1981**, *53*, 1181.

(2) For leading references, see, e.g.: Eisenhut, W.; Renfroe, H. B.; Schmid, H. *Helv. Chim. Acta* **1965**, *48*, 375. Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. Broom, N. J.; Sammes P. G. *J. Chem. Soc., Chem. Commun.* **1978**, 162. Kraus, G. A.; Sugimoti, H. *Tetrahedron Lett.* **1978**, 2263. Li, T.; Wu, Y. L. *J. Am. Chem. Soc.* **1981**, *103*, 7007. Dodd, J. H.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, 3593. Chenard, B. L.; Dolson, M. G.; Sercel, A. D.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 318.

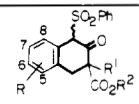
(3) Ghera, E.; Ben-David, Y. *Tetrahedron Lett.* **1983**, 3533.

(4) Ghera, E.; Ben-David, Y.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 774.

(5) Ghera, E.; Plemenitas, A.; Ben-David, Y. *Synthesis* **1984**, 504. Alternative pathways, via bromination of corresponding benzyl alcohols, have been also utilized for the preparation of annulation reagents (see Experimental Section).

0022-3263/85/1950-3355$01.50/0

Table I. Physical Data for the Cyclization Products 3a–i[a]



	% yield	^{1}H NMR chem shifts,[b] δ
3a, R = H; R^1 = Me; R^2 = Me	92	1.53 and 1.57 (2 s, 3 H), 3.34 and 3.83 (2 s, 3 H), 3.06–3.54 (m, 2 H), 4.85 and 5.01 (2 s, 1:6, 1 H), 7.12–7.76 (m, 9 H)
3b, R = H; R^1 = Et; R^2 = Me	95	0.72 and 1.01 (2 t, 3 H), 1.90–2.14 (m, 2 H), 3.01–3.48 (m, 2 H), 3.33 and 3.81 (2 s, 3 H), 4.84 and 5.01 (2 s, 1:8, 1 H), 7.09–7.68 (m, 9 H)
3c, R = H; R^1 = $CH_2CH{=}CH_2$; R^2 = Et	82	0.78 and 1.32 (2 t, 3 H), 2.64–2.78 (m, 2 H), 2.95–3.60 (m, 2 H), 3.66–4.24 (m, 2 H) 4.84 and 5.01 (2 s, 1:7, 1 H), 5.00–5.26 (m, 2 H), 5.51–6.12 (m, 1 H), 7.11–7.81 (m, 9 H)
3d, R = 8-OMe; R^1 = Me; R^2 = Me	81	1.60 (s, 3 H), 3.35 (s, 3 H), 3.56 (s, 3 H), 3.07–3.88 (m, 2 H), 5.45 and 5.62 (2 s, 1:6, 1 H), 6.54–7.79 (m, 8 H)
3e, R = 8-OMe; R^1 = Et; R^2 = Me	87	1.06 (t, 3 H), 2.10 (q, 2 H), 3.05–3.93 (m, 8 H), 5.45 and 5.58 (2 s, 1:8, 1 H), 6.55–7.80 (m, 8 H)
3f, R = 6-OMe; R^1 = Et; R^2 = Me	95	1.00 and 1.96 (2 t, 3 H), 1.96–2.16 (m, 2 H), 3.15–3.77 (m, 2 H), 3.37 (s, 3 H), 3.82 (s, 3 H), 4.74 and 4.94 (2 s, 1:6, 1 H), 6.81–7.80 (m, 8 H)
3g, R = 5-Me; R^1 = Et; R^2 = Me	99	1.03 and 1.19 (2 t, 3 H), 1.84–2.06 (m, 2 H), 2.38 (s, 3 H), 3.02–3.57 (m, 2 H), 3.33 and 3.82 (2 s, 3 H), 4.83 and 4.97 (2 s, 1:8, 1 H), 6.78–7.81 (m, 8 H)
3h, R = 5-Me; R^1 = CH_2CO_2Et; R^2 = Me	97	1.24 (t, 3 H), 2.34 (s, 3 H), 2.88 (s, 2 H), 3.33 (s, 3 H), 3.57–4.21 (m, 4 H), 4.85 and 5.03 (2 s, 1:7, 1 H), 6.93–7.79 (m, 8 H)
3i, R = H; R^1 = $CH_2CH_2CH(OCH_2)_2$; R^2 = Et	87	0.78 (t, 3 H), 1.70–2.07 (m, 4 H), 2.99–4.00 (m, 8 H), 4.81–5.0 (m, 2 H), 7.11–7.78 (m, 9 H)

[a] The yields represent chromatographically isolated mixtures of two stereoisomers homogeneous by TLC, which gave satisfactory C, H analyses within 0.4% of calculated values. [b] Chemical shifts given twice for the same protons represent the signals of the two stereoisomers.

Table II. Physical Data for 2-Naphthalenols 7a–g[a]

compd	mp, °C	% yield	^{1}H NMR chem shifts, δ
7a, R = H; R^1 = Me	162–163[b]	94	2.39 (s, H), 5.10 (s, OH), 7.02–7.73 (m, 6 H)
7b, R = H; R^1 = Et	77–78[c]	99	1.32 (t, 3 H), 2.80 (q, 2 H), 5.02 (s, OH), 7.06–7.69 (m, 6 H)
7c, R = H; R^1 = $CH_2CH{=}CH$	63–64	63	3.56 (d, J = 6 Hz, 2 H), 5.23–5.28 (br d, 2 H), 5.87–6.29 (m, 1 H), 7.12–7.77 (m, 6 H)
7d, R : 8-OMe; R = Me	124–125	83	2.48 (s, 3 H), 3.96 (s, 3 H), 5.04 (s, 1, OH), 6.74–7.54 (m, 5 H)
7e, R = 8-OMe; R^1 = Et	96–97	81	1.31 (t, 3 H), 2.79 (q, 2 H), 3.96 (s, 3 H), 5.09 (s, 1, OH), 6.67–7.54 (m, 5 H)
7f, R = 6-OMe; R^1 = Et	87	75	1.30 (t, 3 H), 2.77 (q, 2 H), 3.86 (s, 3 H), 4.91 (s, OH), 6.98–7.55 (m, 5 H)
7g, R = 5-Me; R^1 = Et	76–77	88	1.33 (t, 3 H), 2.64 (s, 3 H), 2.84 (q, 2 H), 4.96 (s, OH), 7.06–7.72 (m, 5 H)

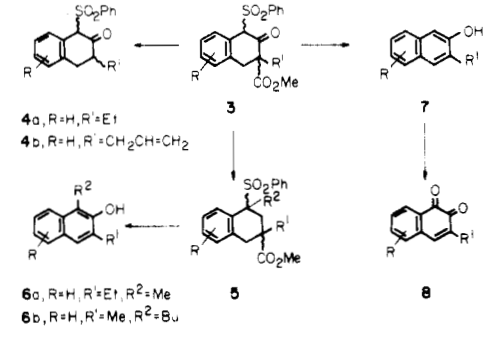
[a] All new compounds gave satisfactory analyses within 0.4% of calculated values. [b] Lit.[24] mp 161–162 °C. [c] Lit.[25] mp 78 °C.

Results and Discussion

The reactions of variously substituted malonates (**2**) with bromosulfones (**1**), using an excess of sodium hydride in tetrahydrofuran solution, resulted in the immediate alkylation of the malonate, followed by intramolecular acylation of the α-sulfonyl carbanion to give the bicyclic products **3** (Scheme I). This sequence starts with the alkylation step, as proven by the isolation of the corresponding products (shown in parenthesis in Scheme I), when only 1 equiv of base was used.

The sequential two-step process, as monitored by TLC, is complete in about 30 min, and the products **3a–i** (Table I), though homogeneous on TLC, were a mixture of two diastereomers from which the main isomer (80–85% of the total amount) could usually be separated by crystallization. The isomeric ratio was determined by the integration of the α-phenylsulfonyl protons in the ^{1}H NMR spectrum. Exposure of the major diastereomers to the reaction conditions (NaH, THF) resulted in the formation of the initial diastereomeric ratio. Thus, the observed stereoselectivity is due to thermodynamic control. Although we have no unambiguous basis for assigning the stereochemistry in the formed ring, we assume a cis relationship between the phenylsulfonyl and R^1 groups in the major diastereomers of **3a–i**: the C-1 hydrogen at the bulky $PhSO_2$ group is expected to adopt a pseudoaxial orientation, and consequently, its cis arrangement to the C-3 carboxylate group will result in NMR absorption at relatively lower field, as was found for the main epimers (Table I). Use of methyl rather than ethyl esters in the cyclization reactions was preferred in order to facilitate subsequent S_N2 hydrolyses. Accordingly, addition of Me_2SO to the reaction mixture, after completion of cyclization, and subsequent warming

Scheme II



(70 °C) led to the decarboxylation of the bicyclic products, (**4a–b**, Scheme II). The isolation of decarboxylated products was, however, less practical, particularly in the case of methoxy-substituted bicyclic derivatives, in view of their lower stability (in comparison with **3**) and the tendency for aromatization of the newly formed ring by the elimination of the phenylsulfinate group.

A general and very effective method for decarboxylation and concomitant desulfonylation of the bicyclic products **3**, leading to high yields of variously C-3-substituted 2-naphthalenols **7** (Table II), consisted of refluxing for a short time compounds **3** with $LiI{\cdot}2H_2O$ in 2,6-lutidine. The S_N2 dealkylation of methyl esters induced by lithium iodide is well documented,[6] and decarboxylations effected by this reagent have also been reported.[7] Occurrence of

(6) McMurry, J. *Org. React.* (*N. Y.*) **1976**, *24*, 187.
(7) Kende, A. S.; Roth, B.; Sanfilippo, P. J.; Blacklock, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 5808.

Table III. Physical Data for 1,2-Naphthalenediones 8a–f[a]

compd	prep. method[b]	mp, °C	% yield	^{1}H NMR chem shifts, δ
8a, R = H; R^1 = Me	A	123[c]	72	2.05 (d, J = 1 Hz, 3 H), 7.21–7.72 (m, 4 H), 8.03 (dd, J = 8, 2 Hz, 1 H)
8b, R = H; R^1 = Et	A	96–97	86	1.17 (t, 3 H), 2.43 (q, 2 H), 7.16–7.72 (m, 4 H), 8.03 (dd, J = 8, 2 Hz, 1 H)
8c, R = H; R^1 = $CH_2CH{=}CH_2$	B	85–86	56	3.20 (dd, J = 6, 1 Hz, 2 H), 5.06–5.29 (br d, 2 H), 5.67–5.87 (m, 1 H), 7.20–7.72 (m, 4 H), 8.05 (dd, J = 8, 2 Hz, 1 H)
8d, R = 8-OMe; R^1 = Me	B	154[d]	57	2.03 (d, J = 1 Hz, 1 H), 3.97 (s, 3 H), 6.84 (d, J = 7 Hz, 1 H), 7.0 (d, J = 8.5 Hz, 1 H), 7.14 (sps, 1 H), 7.53 (dd, J = 8.5, 7 Hz, 1 H)
8e, R = 6-OMe; R^1 = Et	B	139–140	61	1.16 (t, 3 H), 2.46 (q, 2 H), 3.89 (s, 3 H), 6.74–7.06 (m, 3 H), 8.03 (d, J = 8 Hz, 1 H)
8f, R = 5-Me; R^1 = Et	A	106–107	74	1.17 (t, 3 H), 2.47 (s, 3 H), 2.49 (q, 2 H), 7.17–7.44 (m, 3 H), 7.90 (dd, J = 7, 1 Hz, H)

[a] All new products gave satisfactory C,H analyses within 0.4% of calculated values. [b] Methods A and B are explained in the Experimental Section. [c] Lit.[26] mp 122 °C. [d] Lit.[14a] mp 155 °C; ^{1}H NMR, IR, and UV spectra were identical with those reported.

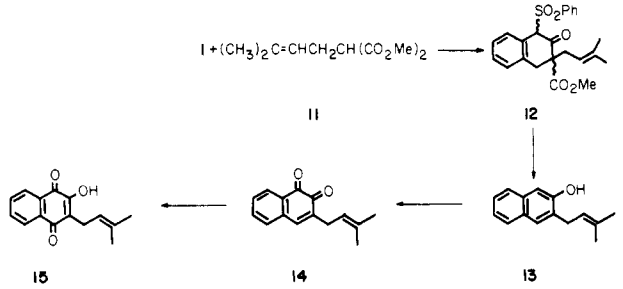
concomitant desulfonylation and the readiness with which this multistep process now takes place are probably due to the driving force for aromatization. The lithium-induced elimination of phenylsulfinates is less effective in other systems, where aromatization is not involved. In the case of an ethyl ester (**3c**), the decarboxylation–desulfonylation reaction required more time, and the yield of **7c** was lower, as expected for a less effective initial nucleophilic dealkylation of the ethyl ester. Recovery of some starting material in the above case confirms that the initial nucleophilic attack occurs on the ester group.

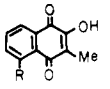
The cyclized products **3** offer possibilities of further transformations as well. Thus a two-step synthesis of 1,3-disubstituted 2-naphthlenols **6a,b** proceeds smoothly via alkylation of **3** with an alkyl halide in acetone in presence of K_2CO_3 to yield **5** and subsequent elimination of the carboxylate and sulfinate groups by treatment with sodium hydride in THF–Me_2SO at 70 °C. The alternative aromatization procedure with lithium iodide was much less effective for the above C-1-alkylated products **5** than for the compounds **3**.

The new synthesis of variously C-3-substituted 2-naphthalenols **7** compares favorably with other multistep routes to analogous compounds[8] and thus provides a new entry, via oxidation, into the class of 1,2-naphthoquinones with C-3 side chains. Fremy's salt, which is frequently used for the oxidation of naphthols to naphthoquinones,[9] is inconvenient due to the required high dilution of the aqueous reaction mixture and may afford lower yields as a result of substitution of the aromatic rings.[10] Other reagents used for β-naphthol oxidations[11] provided disappointing yields (<50%) when applied to compounds **7a–e**. Although an *o*-quinone can be cleaved on prolonged treatment with peracids[12] either *m*-chloroperbenzoic acid or cuprous chloride–oxygen complex[13] (methods A and B, respectively, Table III) afforded good yields of naphthoquinones **8a–f** by simple experimental methods.

8-Methoxy-3-methyl-1,2-naphthoquinone (**8d**), a natural quinone isolated from the wood of tropical trees,[14b] was thus obtained by the oxidation of **7d** with the CuCl–O_2 complex and identified by its physical and spectral properties and by its conversion, in 62% yield, to another naturally occurring 1,4-naphthoquinone, droserone 5-methyl ether (**10**), which we obtained by the modification of a previously reported method[14a] consisting of air oxidation of **8d** in presence of an aqueous base.

Scheme III





9, R=H
10, R=OMe

The conversion of C-3-substituted 1,2-naphthoquinones into correspondingly substituted 2-hydroxy-1,4-naphthoquinones provides a new route to C-3-prenylated 1,4-naphthoquinones, which play an important role in biological processes.[15] Previous syntheses of such compounds were based on reactions that couple a quinone[16] or a hydroquinone[17] with the required olefin, but the yields were usually low to moderate because of the sensitivity of the allylic side chain to the reaction conditions. Improvements of this approach were achieved mainly by modifying the naphthoquinone prior to the coupling reaction.[18,19] Our annulation approach evades these difficulties by providing the prenyl side chain already at the cyclization stage, as exemplified by the synthesis of lapachol (**15**),[20] a naphthoquinone with potent antitumor[21] activity isolated from

(8) For general syntheses of 3-substituted β-naphthols, see, e.g.: Khorana, M. L.; Pandit, S. Y. *J. Indian Chem. Soc.* **1963**, *40*, 789. Fields, D. L. *J. Org. Chem.* **1971**, *36*, 3002.
(9) Zimmer, H.; Larkin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229.
(10) See, E.G.: Teuber, H. J. *Org. Synth.* **1972**, *52*, 88.
(11) "Houben-Weyl Method of Organic Chemistry"; Georg Thieme Verlag: Stuttgart, Vol. VII/3b, pp 15–30. Horspool, W. M. *Rev. Chem. Soc.* **1969**, *23*, 204.
(12) French, H. E.; Sears, K. *J. Am. Chem. Soc.* **1948**, *70*, 1278. Karr, P.; Schneider, L. *Helv. Chem. Acta* **1947**, *30*, 859.
(13) Capdevielle, P.; Maumy, H. *Tetrahedron Lett.* **1983**, 5611.
(14) (a) Sidhu, G. S.; Sankaram, A. V. B.; Mahmood, Ali S. *Indian J. Chem.* **1968**, *6*, 681. (b) Thomson, R. H. "Naturally Occurring Quinones"; Academic Press, London, 1971.
(15) See, e.g.: Bentley, R.; Campbell, I. M. In "The Chemistry of Quinonoid Compounds"; Patai, S., Ed.; Wiley: London, 1974; pp 683–736.
(16) For the peroxide alkylation method, see: Fieser, L. F. *J. Am. Chem. Soc.* **1948**, *70*, 3174. Baillie, A. C.; Thomson, R. H. *J. Chem. Soc. C* **1968**, 48. For acid-catalyzed condensations with aldehydes, see: Hooker, S. C. *J. Am. Chem. Soc.* **1936**, *58*, 1163. Thomson, R. H. *J. Chem. Soc.* **1953**, 1196.
(17) Fieser, L. F.; Campbell, W. P.; Fry, E. M.; Gates, D. M. *J. Am. Chem. Soc.* **1936**, *61*, 2559.
(18) Snyder, C. D.; Rapport, H. *J. Am. Chem. Soc.* **1974**, *96*, 8046.
(19) Evans, D. A.; Hoffman, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 1983.
(20) For previous syntheses of lapachol, see: Fieser, L. F. *J. Am. Chem. Soc.* **1927**, *49*, 857. Pettit, G. R.; Houghton, L. E. *Can. J. Chem.* **1968**, *46*, 2471. Burnett, A. R.; Thomson, R. H. *Chem. Ind. (London)* **1968**, 1771.
(21) Rao, K. V.; McBride, T. J.; Oleson, J. J. *Cancer Res.* **1968**, *28*, 1952. Lagrota, M. H. C.; Wigg, M. D.; Pereira, L. O. B.; Fonseca, M. E. F.; Pereira, N. A.; Guimares, J. C. *Rev. Microbiol.* **1983**, 21.

the heartwood of tropical trees.

Annulation of the bromosulfone **1** (R = H) with the prenylated malonate **11** (Scheme III) under our usual cyclization conditions gave **12** (stereoisomeric mixture), which was converted without separation to **13** by LiI-induced aromatization in a 66% overall yield (from **1**). Oxidation with the $CuCl-O_2$ complex gave the *o*-quinone **14** (76%). The conversion of the latter to lapachol was first attempted by using aqueous base in an oxygen atmosphere (as for **10**), but the yields were disappointing. Similarly, exposure to oxidation by oxygen in a solution of *t*-BuOK in *tert*-butyl alcohol, a method used previously to obtain 2-hydroxy-1,4-quinones from tetralones,[22] afforded only 25–30% of **15**. A substantially improved yield (64%) of lapachol was obtained by submitting to the above oxidation method the corresponding hydroquinone, which was readily formed by shaking a benzene solution of **14** with aqueous sodium dithionite. Phthiocol (**9**), a metabolic product of the human tubercle bacillus,[23] was analogously obtained in 86% yield from the quinone **8a**.

In summary, we believe that the new annulation method provides an effective route to a wide range of naphthalene derivatives, including naturally occurring naphthoquinones of biological interest.

Experimental Section

Melting points were determined on a hot-stage microscope and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ with a Varian T-80 spectrometer. IR spectra were recorded on a Perkin-Elmer 462 spectrometer, and UV spectra were obtained on a Carry 118 instrument. Flash chromatography with silica gel was used for purification of compounds, and precoated Merck Kieselgel 60 F_{254} plates were used for thin-layer chromatography (TLC) tests. All air- and moisture-sensitive reactions were carried out in flame-dried, argon-flushed, two-necked flasks sealed with rubber septa, and the reagents were introduced with a syringe. The substituted malonates were prepared from malonic esters and the corresponding bromides by well-known procedures. Methoxy derivatives (R = OMe) of bromo sulfone **1** were obtained as shown previously.[5] The preparation of a methyl derivative of **1**, used for cyclizations leading to **3g–h** is described below.

Preparation of 1-Methyl-2-(bromomethyl)-3-[(phenylsulfonyl)methyl]benzene. A mixture of 2,6-dimethyl methyl benzoate (4.88 g, 0.03 mol), NBS (5.34 g, 0.03 mol), and benzoyl peroxide (1 g) in CCl_4 (250 mL) was refluxed with lamp irradiation for 30 min (TLC monitoring), cooled, filtered, and concentrated at reduced pressure. To the residue dissolved in DMF (180 mL) was added sodium benzene sulfinate (8.2 g, 0.05 mol), and the reaction mixture was stirred 1 h at room temperature, poured into ice-water (1 L), and extracted with ether. Chromatography (1:1 pentane–ether) gave an oil, homogeneous in TLC, which was dissolved in dry THF (100 mL) and added to a suspension of $LiAlH_4$ (0.95 g, 0.025 mol) in dry THF (80 mL) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was treated with aqueous saturated Na_2SO_4 (2 mL) and then dry Na_2SO_4 and filtered, and the filtrate was evaporated to give 4.16 g (51% overall yield) of 1-methyl-2-(hydroxymethyl)-3-[(phenylsulfonyl)-methyl]benzene: mp 118–120 °C (from chloroform–hexane); ^1H NMR δ 2.49 (s, 3 H), 4.51 (s, 2 H), 4.70 (s, 2 H), 6.49–7.76 (m, 8 H). Anal. Calcd. for $C_{15}H_{16}O_3S$: C, 65.21; H, 5.84. Found: C, 65.32; H, 5.86.

The above compound (0.552 g, 2 mmol) in dry CH_2Cl_2 (4 mL) was added dropwise, under argon, to a stirred mixture, cooled to −20 °C, which was initially prepared by adding Me_2S (0.186 g, 3 mmol) at 0 °C to a suspension of NBS (0.54 g, 3 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was further stirred at 0 °C for 3 h, then poured into ice–water, and extracted (CH_2Cl_2). The organic layer was washed with aqueous $NaHCO_3$ and brine, dried, and evaporated. Crystallization (chloroform–hexane) gave 0.51 g of the bromo sulfone (86%): mp 141–143 °C; ^1H NMR δ 2.41 (s, 3 H), 4.49 (s, 2 H), 4.64 (s, 2 H), 6.69–7.81 (m, 8 H). Anal. Calcd for $C_{15}H_{15}BrO_2S$: C, 53.10; H, 4.42. Found; C, 53.36; H, 4.30.

General Procedure for the Preparation of 3a–i (Table I). Sodium hydride (80% dispersion in mineral oil, net weight 0.145 g, 6 mmol) was washed twice with dry pentane under argon. A solution of the malonate **2** (1.2 mmol) in dry THF (7 mL) was added and the mixture was stirred at room temperature. The bromo sulfone **1** (1 mmol) in dry THF (8 mL) was added after 30 min to the reaction mixture (except for the preparation of **3h**, which required immediate addition of the bromo sulfone, after the malonate). After 5 min TLC indicated formation of two products (the more polar being the alkylated intermediate), and after 30 min TLC showed complete conversion to the less polar of the two products formed initially. The reaction mixture was then poured into cold aqueous NH_4Cl and extracted twice with chloroform. The combined organic layers were washed twice with saturated NaCl solution, dried (Na_2SO_4), and evaporated. Chromatography on silica afforded the bicyclic product (elution with 1:1 or 2:1 pentane–ether, depending on substitution) as a crystallizable mixture of two stereoisomers homogeneous on TLC. Identical reaction results were obtained in bigger scale reactions (5–10 mmol).

Preparation of 1-(Phenylsulfonyl)-2-oxo-3-ethyl-1,2,3,4-tetrahydronaphthalene (4a) and 1-(Phenylsulfonyl)-2-oxo-3-(2-propen-1-yl)-1,2,3,4-tetrahydronaphthalene (4b). To the reaction mixture containing **3b**, formed by the above procedure from malonate **2** (R = Et) and bromo sulfone **1** (R = H), was added Me_2SO (1 mL), and the resulting mixture was stirred at 60–70 °C for 1 h, when TLC showed almost full conversion to a less polar product. Aqueous NaCl (0.1 mL) was then added and warming continued for 20 min. Quenching with aqueous (5%) HCl, extraction with chloroform, and chromatographic purification (pentane and 30% ether) gave 0.226 g of **4a** (72%) as a crystallizable stereoisomeric mixture: ^1H NMR δ 0.80–2.28 (m, 5 H), 2.64–3.49 (m, 3 H), 4.83 and 5.16 (2 s, 1 H), 7.04–7.82 (m, 9 H). Anal. Calcd for $C_{18}H_{18}O_3S$: C, 68.78 H, 5.77. Found: C, 68.81; H, 5.68.

In a similar manner was obtained **4b** (crystalline mixture of stereoisomers): 0.2 g (61% overall yield); ^1H NMR, δ 2.10–3.40 (m, 5 H), 4.85 (s, 1 H), 4.91–5.28 (m, 2 H), 5.45–5.90 (m, 1 H), 7.07–7.75 (m, 9 H). Anal. Calcd for $C_{19}H_{18}O_3S$: C, 69.93; H, 5.56. Found: C, 69.62; H, 5.81.

1-Methyl-3-ethyl-2-naphthalenol (6a). A stirred mixture containing the compound **3b** (0.372 g, 1 mmol), anhydrous K_2CO_3 (0.34 g), acetone (8 mL), and an excess of methyl iodide (1.5 mL) was refluxed for 1 h, when TLC showed complete conversion to a less polar product. Filtration and evaporation of the solvent gave crude **5a**, which after short chromatographic purification (2:1 pentane–ether) was dissolved in dry THF (16 mL) and added to a suspension of sodium hydride (0.96 g, 4 mmol) in THF (4 mL). To the stirred reaction mixture at 60 °C under argon were added Me_2SO (2 mL) and methanol (0.4 mL). After 30 min the reaction was quenched with cold aqueous (5%) HCl and extracted with ether (3×), and the combined organic layers were washed with brine, dried ($NaSO_4$), filtered, and evaporated. Column chromatography (pentane and 10% ether) gave **6a**: 0.119 g (63% overall yield); mp 54 °C; ^1H NMR δ 1.33 (t, 3 H), 2.52 (s, 3 H), 2.79 (q, 2 H), 4.92 (s, 1 H), 7.20–7.81 (m, 5 H). Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.78; H, 7.69.

1-Butyl-3-methyl-2-naphthalenol (6b) was prepared from **3a** by the two-step sequence as shown for **6a**, except that alkylation with butyl iodide required 24 h. Chromatographic purification gave 0.145 g of **6b** (68%): mp 72–74 °C from cold pentane); ^1H NMR δ 0.87–1.74 (m, 7 H), 2.40 (d, J = 1 Hz, 3 H), 3.00 (t, 2 H), 4.65 (sps, J = 1 Hz, 1 H), 7.19–7.91 (m, 5 H). Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.78; H, 8.52.

General Procedure for the Preparation of 2-Naphthalenols 7a–g (Table II). To the bicyclic methyl esters **3** (1 mmol) dissolved in 2,6-lutidine (6 mL) was added $LiI\cdot 2H_2O$ (0.68 g, 400 mol %), and the stirred reaction mixture was heated

(22) Baillie, A. C.; Thomson, R. H. *J. Chem. Soc. C* **1966**, 2184. Kasturi, T. R.; Arunachalam, T. *Can. J. Chem.* **1966**, *44*, 1086.
(23) Anderson, R. J.; Newmann, M. J. *J. Biol. Chem.* **1931**, *101*, 773; *103*, 197.
(24) Ebnother, A.; Meijer, T. M.; Schmid, J. *Helv. Chim. Acta* **1952**, *35*, 910.
(25) Wahl, H.; Fraemons, J. *C. R. Hebd. Seances Acad. Sci.* **1947**, *224*, 533.
(26) Weygand, F.; Schroder, K. *Chem. Ber.* **1941**, *74*, 1844.

in an oil bath at 150 °C for 1 h, when TLC showed complete conversion to a less polar product. The mixture was poured into cold aqueous (10%) HCl and extracted (3×) with chloroform. The combined organic layers were washed with 5% aqueous HCl and twice with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography (3:1 pentane–ether) to give the corresponding naphthalenol. The conversion of ethyl ester **3c** required more time (8 h), and the yield was relatively lower, as shown in the table.

Preparation of 1,2-Naphthalenediones 8a–f (Table III). Method A. To a stirred solution of naphthalenol **7** (1 mmol) in CH_2Cl_2 (6 mL) was added an excess of *m*-chloroperbenzoic acid (1.5 mmol) in a few portions during 30 min at room temperature. After about 1 h, when TLC showed absence of the starting material, the reaction mixture was poured into water and extracted twice with chloroform, and the combined organic layers were washed with aqueous 5% $NaHCO_3$ and brine, dried, and evaporated. Chromatography of the residue on a silica column (elution with 1:1 pentane-ether) afforded the red or brick-colored quinones.

Method B. Dry oxygen was bubbled into a suspension of CuCl (0.5 g) in dry CH_3CN (6 mL) during 30 min at room temperature. A solution of the corresponding naphthalenol (1 mmol) in dry CH_3CN (3 mL) was then added dropwise, and the mixture was stirred with continuous bubbling of oxygen until TLC showed no more starting material (20–30 min). Dilution with water, workup, and purification as shown for method A afforded the quinone.

Droserone Methyl Ether (10). The red *o*-quinone **8d** (0.202 g, 1 mmol) was dissolved by stirring in a 3:2 mixture of 5% aqueous NaOH and dioxane (15 mL) at 10 °C, and oxygen was bubbled into the solution during 2 h, when TLC showed complete conversion into a yellow product. The reaction mixture was then diluted with water, acidified with aqueous HCl, and extracted (3×) with chloroform. The combined organic layers were washed once with brine, dried (Na_2SO_4), and evaporated. The crystalline residue was purified by chromatography to give 0.135 g (62%)[27] of **10** as yellow needles: mp 171 °C (lit.[14a] mp 171 °C); ^{1}H NMR δ 2.06 (s, 3 H), 4.02 (s, 3 H), 7.16–7.78 (m, 3 H); UV (EtOH) λ_{max} 245, 277, 381 nm (log ϵ 4.26, 4.24, 3.80).[28]

2-Hydroxy-3-(2-methyl-2-buten-4-yl)naphthalene (13). Bromo sulfone **1** (R = H) and 2-methyl-2-buten-4-yl methyl malonate[29] **11** were reacted as shown in the general cyclization procedure to give the mixture of stereoisomers **12** (elution with 2:1 pentane–ether), which was treated with $LiI\cdot 2H_2O$ as shown for the preparation of compounds **7**. Purification by chromatography (pentane and 10% ether) gave 0.140 g of **13** (66% overall yield): mp 54–56 °C (from cold pentane); ^{1}H NMR δ 1.80 (s, 6 H), 3.51 (d, J = 7 Hz, 2 H), 5.39 (t, J = 7 Hz, 1 H), 7.13 (s, 1 H), 7.31–7.76 (m, 5 H). Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.59; H, 7.68.

3-(2-Methyl-2-buten-4-yl)-1,2-naphthalenedione 14. Compound **13** (0.52 g, 2.48 mmol) was reacted with CuCl–O_2 as shown for the preparation of 1,2-naphthalenediones (method B) with external cooling of the reaction mixture (5–10 °C). The reaction was completed (TLC) after 20 min to give after chromatographic purification (1:1 pentane–ether) 0.423 g (76%) of red crystals: mp 129–131 °C (from benzene–pentane); ^{1}H NMR δ 1.69 (s, 3 H), 1.79 (s, 3 H), 3.14 (d, J = 7 Hz, 2 H), 5.22 (t, J = 7 Hz, 1 H), 7.11 (s, 1 H), 7.32–7.61 (m, 3 H), 8.05 (dd, J = 8, 1 Hz, 1 H); IR (KBr) 1690, 1660, 1585, 1260 cm^{-1}; UV (EtOH) λ_{max} 252, 340, 419 nm (log ϵ 4.46, 3.42, 3.31). Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.81; H, 6.28.

Lapachol (15). A solution of **14** (0.226 g, 1 mmol) in benzene (20 mL) was shaken with aqueous 10% $Na_2S_2O_4$ until the color of the quinone disappeared (1–2 min). The benzene layer was washed once with brine, dried (Na_2SO_4), concentrated to 2 mL, and added at once to a solution of *t*-BuOK (200 mg) in dry *t*-BuOH (3 mL) which was initially saturated with dry oxygen by bubbling. After 5 min of stirring and continuous bubbling of O_2, the reaction mixture was poured into ice-cold aqueous HCl and extracted with benzene (2×). The combined organic layers were washed once with brine, dried (Na_2SO_4), and concentrated, and the residue was purified by chromatography (3:1 pentane–ether) to give 0.155 g of **15** (64%): mp 140–141 °C (lit.[14b] mp 140 °C); ^{1}H NMR δ 1.68 (s, 3 H), 1.78 (s, 3 H), 3.30 (dd, J = 7 Hz, 2 H), 5.21 (t, 1 H), 7.62–7.76 (m, 2 H), 8.01–8.17 (m, 2 H); UV (EtOH) λ_{max} 252, 277, 329 nm (log ϵ 4.38, 4.29, 3.48 (lit.[14b] λ_{max} 252, 278, 333 nm); Ir (KBr) 1670, 1645, 1595 cm^{-1}.

Phthiocol (9) was prepared from the quinone **8a** by the procedure shown above for compound **15** in 86% yield: mp 172–173 °C (lit.[26] mp 171–172 °C); ^{1} NMR δ 2.10 (s, 3 H), 7.63–7.77 (m, 2 H), 8.02–8.13 (m, 2 H) UV (EtOH) λ_{max} 251, 276, 335, nm (log ϵ 4.26, 4.16, 3.40); IR (KBr) 1650, 1590, 1278, cm^{-1}.

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Registry No. **1** (R = H), 88116-02-3; **1** (R = 8-OMe), 88116-09-0; **1** (R = 6-OMe), 88116-11-4; **1** (R = 5-Me), 96964-50-0; **2** (R′ = Me), 609-02-9; **2** (R′ = Et), 26717-67-9; **2** (R′ = $CH_2CH{=}CH_2$), 40637-56-7; **2** (R′ = CH_2CO_2Et), 84763-15-5; **2** (R′ = $CH_2CH_2CH(OCH_2)_2$), 96964-51-1; **3a**, 96964-52-2; **3b**, 96964-53-3; **3c**, 96964-54-4; **3d**, 96964-55-5; **3e**, 96964-56-6; **3f**, 96964-57-7; **3g**, 96964-58-8; **3h**, 96964-59-9; **3i**, 96964-60-2; **4a**, 88116-08-9; **4b**, 96964-64-6; **5a**, 96964-65-7; **5b**, 96964-67-9; **6a**, 96964-66-8; **6b**, 96964-68-0; **7a**, 17324-04-8; **7b**, 17324-05-9; **7c**, 96964-61-3; **7d**, 96964-62-4; **7e**, 88116-12-5; **7f**, 88116-14-7; **7g**, 96964-63-5; **8a**, 31907-43-4; **8b**, 89509-97-7; **8c**, 96964-69-1; **8d**, 22267-03-4; **8e**, 96964-70-4; **8f**, 96964-71-5; **9**, 483-55-6; **10**, 96964-72-6; **11**, 43219-18-7; **12**, 96964-73-7; **13**, 96964-74-8; **14**, 96964-75-9; **15**, 84-79-7; methyl 2,6-dimethylbenzoate, 14920-81-1; 1-methyl-2-(hydroxymethyl)-3-[(phenylsulfonyl)methyl]benzene, 96964-49-7.

(27) The oxidation of **8d**, as reported in ref 14a, afforded in our hands only 40% of **10**.

(28) The reported UV data for the authentic compound (λ_{max} 228, 277, 376 nm)[14b] probably contain an error. Naphthoquinones of similar structure have an UV absorption in the 240–250-nm region.[14b]

(29) Staudinger, H.; Kreis, W.; Shilt, W. *Helv. Chim. Acta* **1922**, *5*, 743.