New Syntheses of Phenanthrenes and of Related Systems by Intramolecular Annulation Processes

Eugene Ghera,* Rakesh Maurya, and Yoshua Ben-David

Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot 76100, Israel

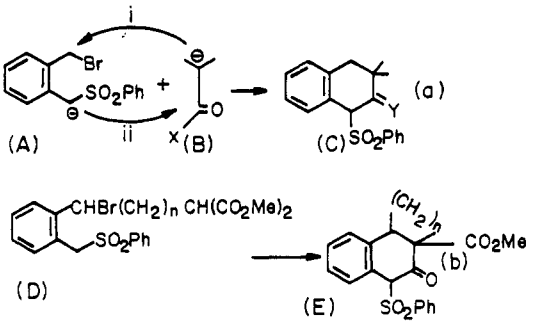
Received August 27, 1987

A regio- and stereoselective intramolecular double annulation, which converts monocyclic aromatic compounds into partly reduced phenanthrenes, is described. Methoxy- (**9a,c**) and [(*tert*-butyldimethylsilyl)oxy]benzene derivatives (**9b**) with a (5-bromoalkyl)malonate side chain and an ortho-located (phenylsulfonyl)methyl group were synthesized and submitted to base-promoted intramolecular double cyclization to afford tricyclic **10a-c**, which were further transformed into 1,2,3,4-tetrahydro-10-phenanthrenol derivatives **11a-c**. Application of the annulation process to the bromides **20**, containing a cyclopentane in the side chain, resulted in the synthesis of tetracyclic stereoisomers with the skeletal structure of aromatic steroids (**22**). The extension of the annulation methodology to the bromo sulfone **26** led to the stereoselective formation of the benz[*e*]indene derivative **27**, which was further converted to 2,3-dihydrobenz[*e*]inden-4-ol (**28**) and the new *o*-quinone **29**.

Formation of two carbon-carbon bonds in one vessel under the same reaction conditions enables an efficient and more rapid transformation of simple into more complex molecules. In this context, the intramolecular formation of two carbon-carbon bonds can provide an effective construction of two new carbon rings in one operation, and the Diels-Alder intramolecular cycloadditions[1] are an outstanding example of the importance of such processes.

We have recently investigated new 4C + 2C reactions of bifunctionalized aromatic annulating reagents (A) with various substrates (B) to afford products (C) in a chemoselective manner, both carbon-carbon bonds being formed sequentially in one vessel under the same reaction conditions, with step (i) preceding (ii), as shown in Scheme I, eq a.[2] Following the successful elaboration of this annulation, we envisioned its intramolecular applicability, with A and B as moieties of one compound (D), to afford by double cyclization tricyclic angular systems (E) (eq b). Recent attempts in this direction, which led to the synthesis of cyclobuta[*a*]naphthalenes, have confirmed the viability of this approach.[3] In the present paper we describe the utilization of intramolecular annulation for the synthesis of angular polycyclic condensed systems, the main target being related to the synthesis of partly reduced and regioselectively substituted phenanthrenes. The interest for an innovative approach to such systems seems justified in view of the widespread presence of the phenanthrene nucleus in various natural compounds.[4]

Scheme I[a]



[a] X = OMe or CH_2R; Y = O or CH_2R, OH.

Results and Discussion

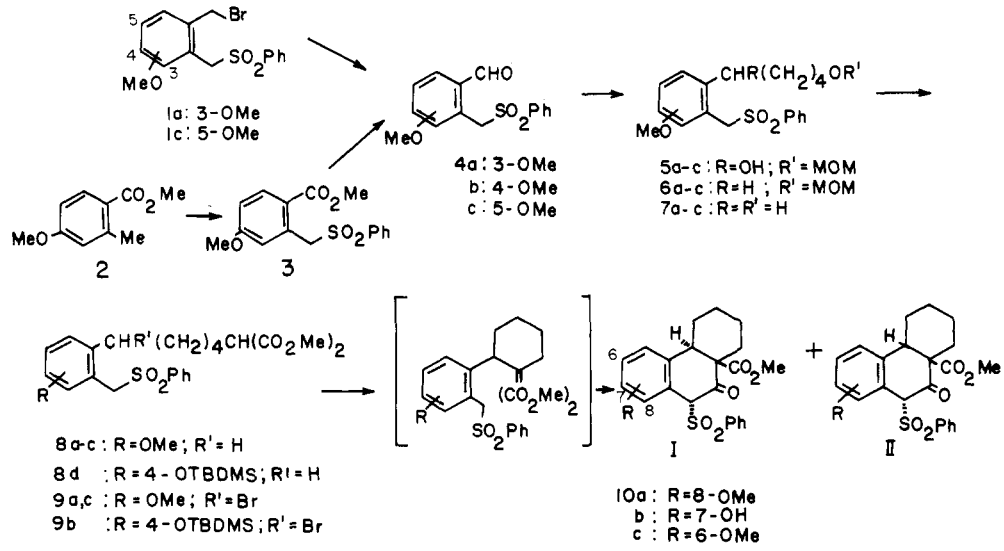
As adequate intermediates for the proposed annulation reactions, we have chosen to utilize aromatic compounds having a (phenylsulfonyl)methyl substituent and an ortho-located aliphatic side chain, terminated with a malonate group (**8a-c**, Scheme II). Radical bromination, which occurs regioselectively in the malonate side chain, would then provide the functionalities required for the double cyclization. The additional incorporation of methoxy substituents at various positions of the aromatic ring in order to determine their influence on the efficiency of the annulation process was considered to be of interest in view of the presence of such groups in natural polycyclic compounds for which the obtained products could serve as synthetic models. Moreover, such substitution could enable the conversion of the aromatic rings of the cyclized systems into nonaromatic oxygenated carbon rings via Birch reduction.

During the initial attempts for the synthesis of intermediates required for cyclizations, we utilized the readily available methoxy-substituted aromatic bromo sulfones **1a** and **1c**[5] for coupling reactions involving the benzylic bromide group and appropriate Grignard reagents, but the yields obtained, even in the presence of copper catalysts,[6] were unsatisfactory. Wittig reactions of phosphoranes derived from **1a** and **1c** with appropriate aldehydes were even less successful, probably because of the concomitant base-induced deprotonation of the acidic α-sulfonyl methylene group. Similarly, the attempted construction of the aliphatic side chain, prior to the introduction of the sulfone, proved ineffective in our hands. High yields of compounds **5a-c** could be, however, obtained by reacting aldehydes **4a-c**[7] with the Grignard reagent derived from the methoxymethyl ether of 4-bromobutanol,[8] this reaction

(1) For a recent review, see: E. Ciganek, *Organic Reactions*; Wiley: New York, 1984; Vol. 32, pp 1-374.
(2) (a) Ghera, E.; Ben-David, Y. *J. Org. Chem.* **1985**, *50*, 3355. (b) Ghera, E.; Ben-David, Y. *Tetrahedron Lett.* **1985**, *26*, 6253.
(3) Ghera, E.; Maurya, R. *Tetrahedron Lett.* **1987**, *28*, 709. For some preliminary data on intramolecular annulations, see: Ghera, E.; Ben-David, Y. *Tetrahedron Lett.* **1983**, *24*, 3533.
(4) For some recent new approaches to phenanthrenes, see, inter alia: Padwa, A.; Doubleday, C.; Mazzu, A. *J. Org. Chem.* **1977**, *42*, 3271. Kende, A. S.; Curran, D. P. *J. Am. Chem. Soc.* **1979**, *101*, 1857. Cossey, A.; Gunther, M. J.; Mander, L. N. *Tetrahedron Lett.* **1980**, *21*, 3309. Bell, M. R.; Herrmann, J. L.; Akullian, V. *Synthesis* **1981**, 357. Jackson, A. H.; Shannon, P. V. R.; Taylor, P. V. *J. Chem. Soc., Perkin Trans. 2* **1981**, 286. Boger, D. L.; Mullican, M. D. *Tetrahedron Lett.* **1982**, *23*, 4551. Trost, B. M.; Murayama, E. *Tetrahedron Lett.* **1982**, *23*, 1047. Lakhvich, F. A.; Khlebnicova, T. S.; Akhrem, A. A. *Synthesis* **1985**, 784. Carvalho, C. F.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1913.
(5) Ghera, E.; Plemenitas, A.; Ben-David, Y. *Synthesis* **1984**, 504.
(6) Tamura, M.; Kochi, Y. *Synthesis* **1971**, 303.
(7) The methods chosen for the preparation of aldehydes **4a-c** depended on the immediate availability of starting materials. See Experimental Section.
(8) Kulkarni, S. V.; Patil, V. D. *Heterocycles* **1982**, *18*, 163. For the method of preparation of the MOM ether, see: Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1975**, 276.

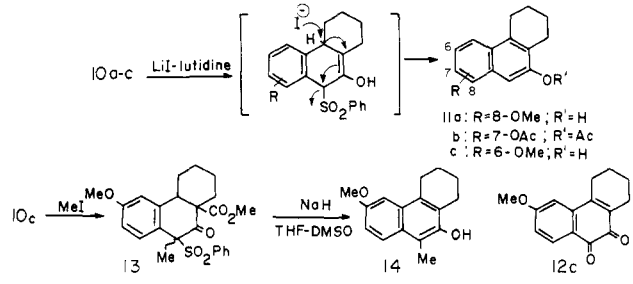
0022-3263/88/1953-1912$01.50/0

Scheme II



being sufficiently rapid to compete with the interfering metalation of the α-sulfonyl methylene group. Optimal conditions for the subsequent reductive dehydroxylation of **5a–c** to **6a–c** were found to be dependent on the location of the methoxy group in the ring. While utilization of triethylsilane[9] afforded sluggish results, compound **6c** could be best obtained by the reduction of the mesylate of **5c** with $LiAlH_4$. The preparation of mesylates from **5a** and **5b** resulted, however, in partial elimination, and therefore, direct dehydration of alcohols followed by catalytic hydrogenation was used to obtain **6a** and **6b**, respectively. Cleavage of the methoxymethyl ether, conversion to iodide, and condensation of the latter with malonic ester to give malonates **8a–c** was readily achieved by standard procedures. Radical bromination of **8a** and **8c** proceeded with complete regioselectivity, providing the intermediates **9a** and **9c**, respectively. Compound **8b**, however, when submitted to identical reaction conditions, underwent spontaneous dehydrobromination, due to the electron-donating effect of the *p*-methoxy group, and therefore, the change of the methoxy group for another protecting group was required, as will be shown further. Intramolecular double cyclization of **9a** and **9c**, respectively, was effected by using an excess of potassium *tert*-butoxide in tetrahydrofuran and *tert*-butyl alcohol to give 88–89% of phenanthrene derivatives (**10a** and **10c**). The bicyclic intermediate (shown in brackets) was usually not detected unless an insufficient amount of base was used in the reaction. The proton NMR spectra showed that the cyclizations proceeded stereoselectively, leading to the formation of mainly one product, with a small amount of a minor diastereomer (10–15%) also present. Thus, an 87:13 diastereomeric ratio was determined for **10c** by the help of $CHSO_2Ph$ proton signals in the NMR spectrum of the mixture (at δ 5.00 and 5.18) and by chromatographic separation. Similarly, cyclization of bromide **9a** afforded a 9:1 diastereomeric pair of the tricyclic products **10a**. No change in configuration was observed when each of the diastereomers of **10c** was submitted to the basic conditions of the cyclization, and we assumed, therefore, that the products were configurationally different at the ring junction. Examination of molecular models of the bicyclic intermediate (in brackets, Scheme II) revealed that the attack of the α-sulfonyl carbanion on the equatorial methoxycarbonyl group, which

Scheme III



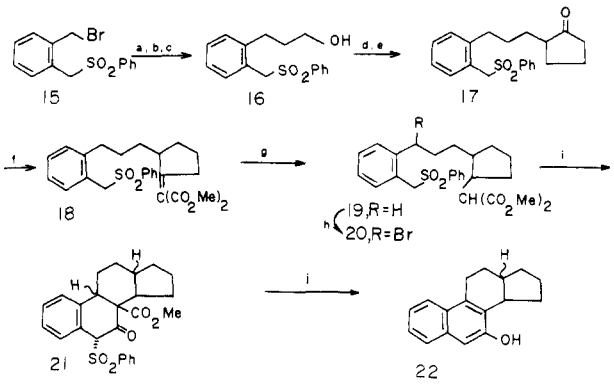
should result in a trans ring junction, involves less hindering interactions than the attack on the axial ester. Unambiguous confirmation for the assumed configuration of the major cyclization product (**10c-I**) was obtained by single-crystal X-ray analysis, which showed, indeed, a trans ring junction, with the angular ester group axially oriented in the periferial chair ring, while the sulfone adopts a trans arrangement versus the carboxylate group. On the basis of the previously mentioned equilibration experiments, a similar trans relationship between the sulfone and the ester group can be assigned in the minor diastereomer; hence the rings in **10c–II** should be cis fused.

Further transformations of the obtained products indicated the synthetic utility of the annulation process. Decarboxylation and desulfonylation of **10a** and **10c** were readily achieved in one operation on heating with lithium iodide in 2,6-lutidine, similar to some transformations we described in other systems.[2a] The initial decarboxylation is probably followed by the attack of the iodide anion on the enolic intermediate (Scheme III), thus ensuring aromatization via desulfonylation, and affording 10-phenanthrenol derivatives **11a** and **11c** in 75% and 79% yields, respectively. The availability of the latter provides a route to the corresponding *o*-quinones: treatment of **11c** with *m*-chloroperbenzoic acid gave the quinone **12c** in moderate yield (50%). The presence of the C-9 sulfone group in the cyclized products allows the regioselective alkylation in the phenanthrene bridge, as exemplified by the methylation of **10c** to **13**, and further conversion to the 9-methyl-10-phenanthrenol derivative **14**. Decarboxylation and desulfonylation were achieved concomitantly by heating **13** with sodium hydride in THF to which small amounts of DMSO and methanol were added.

Next, the applicability of the annulation process for the preparation of potential models for the synthesis of aro-

(9) Adlington, M. G.; Orfanopoulos, M.; Fry, J. L. *Tetrahedron Lett.* **1976**, 2955.

Scheme IV[a]



[a] (a) $NaCH(CO_2Me)_2$, DMF; (b) DMSO–H_2O, Δ; (c) $LiAlH_4$, THF; (d) MsCl, TEA, CH_2Cl_2; NaI, acetone; (e) pyrrolidine enamine of cyclopentanone, toluene, Δ; (f) $CH_2(CO_2Me)_2$, $TiCl_4$, pyridine, THF; (g) H_2, Pt–C, MeOH, $HClO_4$, 750 psi; (h) NBS, CCl_4, hν; (i) *t*-BuOK, *t*-BuOH–THF; (j) LiI, lutidine.

matic steroids was investigated. As a first step in this direction, the annulation using aromatic precursors with an oxygen group para to the malonate side chain had to be effected. In view of the inability to obtain a stable bromo derivative by radical bromination of **8b**, the methoxy group of the latter was demethylated by use of boron tribromide in methylene chloride and the hydroxyl group was converted to a benzoate. The presence of an electron-attracting ester group on the aromatic ring enabled the formation of a stable bromide on reaction with *N*-bromosuccinimide (NBS), but attempts of intramolecular cyclization, under various basic conditions, resulted in the formation of polymers. In a further search for an appropriate protecting group, we found that a para silyloxy group sufficiently weakens the electron-donating effect (in relation to the methoxy group) and thus ensures the formation of a stable bromide (**9b**). The latter underwent successful cyclization by use of potassium *tert*-amyloxide in a solution of THF and *tert*-amyl alcohol to afford, after the cleavage of the silyl group, 65% of **10b**, obtained as well stereoselectively as a 9:1 diastereomeric pair. Aromatization of the central ring proceeded as in the previously described regioisomeric systems to afford an air-sensitive diol, which was characterized as the diacetate **11b**.

In continuing studies directed toward the synthesis of model compounds for aromatic steroids, we next prepared an intermediate with a five-membered ring fused into the side chain so as to provide, on cyclization, the B and C rings of the tetracyclic steroid framework (Scheme IV). It was of interest to determine whether the increased rigidity and additional hindrance imposed upon the system by a cis- or trans-fused carbon ring within the side chain would interfere with the cyclization process. As shown in Scheme IV, the synthesis of the required intermediate started from bromo sulfone **15**, which was converted to the alcohol **16**, via condensation with the sodium salt of dimethyl malonate, followed by decarboxylation and reduction. Conversion of **16** to the corresponding iodide, by using standard procedures, and the reaction of the latter with the pyrrolidine enamine of cyclopentanone gave the product **17**, which was condensed with malonic ester in the presence of titanium tetrachloride and pyridine,[10] to afford the crystalline olefin **18**. The sterically hindered double bond in **18** was successfully hydrogenated under pressure, by using Pt on carbon as catalyst and adding a small amount of $HClO_4$ to the methanol solution to afford **19** (89%) as a 3:1 stereoisomeric pair, according to the ^1H NMR shifts of the ester methyl groups. Regioselective bromination of the stereoisomeric pair **19** and base-promoted cyclization of the bromides **20**, under our usual conditions, afforded a 57% yield of tetracyclic stereoisomers **21**, homogeneous in TLC. The presence of three stereoisomers is evidenced by the three singlets in ^1H NMR at δ 4.85, 5.00, and 5.10 assigned to the α-sulfonyl protons. The structure of the cyclized products was confirmed by the lithium iodide–lutidine aromatization reaction, which converted **21** into the crystalline product **22** (72%), obtained in the 3:1 ratio of cis- and trans-fused stereoisomers, as evidenced by the ring B aromatic proton singlet signals (δ 6.97 and 6.98, 3:1). The analogous stereoisomeric ratio observed in **19** and **22** suggests a similar ability of both stereoisomeric **19** to cyclize. Utilization of appropriate intermediates in the above scheme may possibly be applicable for the synthesis of estrogenic steroids.

While the ring closure involving the acylation of the α-sulfonyl carbanion leads invariably to a six-membered ring, the size of the periferial ring obtained by the initial cyclization can be varied according to the length of the malonate side chain. Accordingly, the cyclization of the intermediate **26** with a five-carbon alkyl diester side chain was investigated next. As shown in Scheme V, this intermediate was prepared by the homologation of alcohol **16** to **24** via the nitrile **23**. Analogously to the previously described procedures, alcohol **24** was converted to the malonate **25** and then to bromide **26**. The base-promoted cyclization of **26**, under conditions slightly different from those previously utilized, resulted in the stereoselective formation of a single product **27**, decarboxylation having already occurred under the cyclization conditions, to afford a 61% yield in the three-step sequential transformation. In view of the equilibrating conditions of the reaction, the more stable cis ring fusion[11] can be assigned to the benzhydrindanone derivative **27**. Desulfonylation induced by lithium iodide afforded 2,3-dihydrobenz[*e*]inden-4-ol **28** (86%), which underwent oxidation with a $CuCl–O_2$ complex[12] to give the novel quinone **29** in 75% yield.

In summary, we have developed an intramolecular double annulation process which provides a new access to polycyclic condensed angular systems, enabling the regioselective introduction of substituents in the newly formed rings. The results so far obtained justify the utilization of the developed methodology for various synthetic targets, comprising the synthesis of polycyclic natural compounds.

Experimental Section

Melting points were determined on a Reichert hot-stage microscope and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ on Varian T-80 or Bruker 270-MHz instruments and referenced to Me_4Si as an internal standard. IR spectra were recorded on a Mattson apparatus. Merck silica gel 60 was used for column chromatography, and TLC data were obtained with precoated Merck 60F-254 silica gel on aluminum sheets. 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 via a syringe. THF was freshly distilled from sodium–benzophenone under nitrogen. *tert*-Butyl alcohol and *tert*-amyl alcohol were dried by distillation from potassium.

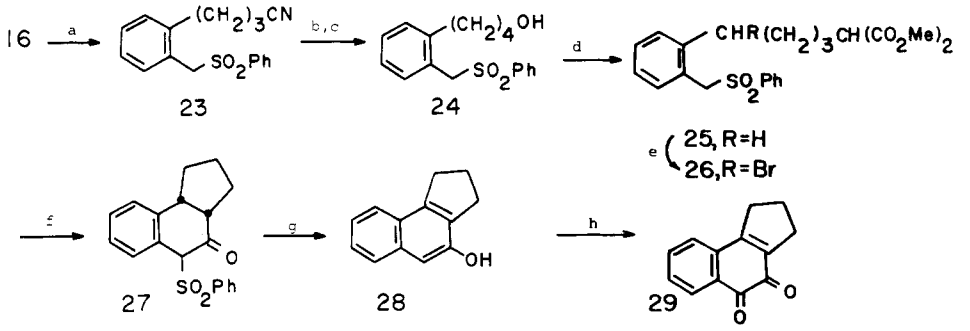
3-Methoxy-2-[(phenylsulfonyl)methyl]benzaldehyde (4a). The bromide **1a**[5] (3.55 g, 10 mmol) was refluxed for 16 h with an excess of AgOAc (2.82 g, 17 mmol) in 200 mL of dry C_6H_6. After

(10) Lehnert, W. *Tetrahedron* **1973**, *29*, 635.

(11) Concannon, P. W.; Ciabattoni, J. *J. Am. Chem. Soc.* **1973**, *95*, 3284.

(12) Capdevielle, P.; Maumy, H. *Tetrahedron Lett.* **1983**, *24*, 5611.

Scheme V[a]



[a] (a) MsCl, TEA, CH_2Cl_2; KCN, DMF; (b) Dibal; HCl–H_2O; (c) $LiAlH_4$; (d) MsCl, TEA, CH_2Cl_2; NaI, acetone; $NaCH(CO_2Me)_2$, DMF; (e) NBS, CCl_4, hν; (f) *t*-BuOK, *t*-BuOH, THF; (g) LiI, lutidine; (h) CuCl, O_2, CH_3CN.

cooling, the mixture was filtered, the solid washed thoroughly with warm $CHCl_3$, and the filtrate concentrated in vacuo. The residue was dissolved in 50 mL of dry THF and added to a suspension of $LiAlH_4$ (0.38 g, 10 mmol) in dry ether (50 mL) at 5 °C. After being stirred for 30 min, the cold reaction mixture was treated successively with aqueous saturated Na_2SO_4 and then dry Na_2SO_4, filtered, and evaporated. To the cooled (0 °C) and stirred solution of the residue in acetone (40 mL) was added dropwise 5 mL of a 2.65 M solution of Jones' reagent (13.25 mmol). After 10 min, when the conversion to a less polar product was completed (TLC monitoring), the mixture was poured into cold aqueous $NaHCO_3$ and extracted with ether containing 20% $CHCl_3$. The organic layer was washed with brine and dried (Na_2SO_4). After filtration and solvent removal, the residue crystallized to give 2.32 g (80% overall yield) of **4a**. An analytical sample had the following characteristics: mp 148–150 °C (from hexane–$CHCl_3$); ^1H NMR δ 3.50 (s, 3 H), 5.13 (s, 2 H), 6.92–7.72 (m, 8 H), 10.08 (s, 1 H). Anal. Calcd for $C_{15}H_{14}O_4S$: C, 62.07; H, 4.82. Found: C, 61.90; H, 4.72.

5-Methoxy-2-[(phenylsulfonyl)methyl]benzaldehyde (4c) was prepared as above from **1c** in 88% overall yield: mp 86 °C; ^1H NMR δ 3.87 (s, 3 H), 4.89 (s, 2 H), 6.98–7.63 (m, 8 H), 9.80 (s, 1 H). Anal. Calcd for $C_{15}H_{14}O_4S$: C, 62.07; H, 4.82. Found: C, 62.10; H, 4.71.

4-Methoxy-2-[(phenylsulfonyl)methyl]benzaldehyde (4b). A mixture of ester **2**[5] (1.80 g, 10 mmol), *N*-bromosuccinimide (1.87 g, 10.5 mmol), and azobisisobutyronitrile (AIBN) (0.1 g) in 120 mL of CCl_4 was refluxed by lamp irradiation. After 1 h (TLC monitoring), the mixture was cooled and filtered and the filtrate evaporated in vacuo. To the residue dissolved in DMF (40 mL) was added an excess of $PhSO_2Na$ (2.46 g, 15 mmol), and the mixture was heated for 5 h at 100 °C. After cooling, the reaction mixture was poured into water and the precipitated crystals were filtered and dried to give 2.49 g (78%) of ester **3**: mp 114–115 °C (from $CHCl_3$–hexane); ^1H NMR δ 3.68 (s, 3 H), 3.80 (s, 3 H), 5.08 (s, 2 H), 6.84–7.92 (m, 8 H). Anal. Calcd for $C_{16}H_{16}O_5S$: C, 60.00; H, 5.00. Found: C, 60.15; H, 5.06.

The ester **3** (2.60 g, 8.12 mmol) was reduced with $LiAlH_4$ and then oxidized with Jones' reagent, as described for **4a**, to give 2.17 g (92%) of **4b**: mp 117–118 °C; ^1H NMR δ 3.86 (s, 3 H), 5.03 (s, 2 H), 6.94–7.77 (m, 8 H), 9.66 (s, 1 H). Anal. Calcd for $C_{15}H_{14}O_4S$: C, 62.07; H, 4.82. Found: C, 62.22; H, 4.76.

1-[1-Hydroxy-5-(methoxymethoxy)-1-pentyl]-5-methoxy-2-[(phenylsulfonyl)methyl]benzene (5c). The Grignard reagent, prepared by warming (60 °C, 1 h) a mixture of 0.31 g (13 mmol) of Mg and 4-bromo-1-(methoxymethoxy)butane[8] (2.7 g, 13.7 mmol), in THF (15 mL), was added at 25 °C dropwise during 1 h to a stirred solution of the aldehyde **4c** (2.5 g, 8.6 mmol) in 100 mL of dry C_6H_6, under argon. After an additional 30 min of stirring, the reaction mixture was poured into cold aqueous NH_4Cl and extracted with $CHCl_3$. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated. Chromatographic purification of the residue (ether–pentane, 4:1) gave 3.3 g of **5c** as an oil (94%): ^1H NMR δ 1.49–1.87 (m, 6 H), 3.32 (s, 3 H), 3.50 (t, J = 6 Hz, 2 H), 3.80 (s, 3 H), 4.44 (br s, 2 H), 4.58 (s, 2 H), 4.60 (m, 1 H), 6.69–7.67 (m, 8 H). Anal. Calcd for $C_{21}H_{28}O_6S$: C, 61.76; H, 6.86. Found: C, 61.59; H, 6.92.

1-(5-Hydroxy-1-pentyl)-5-methoxy-2-[(phenylsulfonyl)-methyl]benzene (7c). To a solution of **5c** (0.408 g, 1 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added triethylamine (0.45 mL) and methanesulfonyl chloride (0.15 mL). After 3 h, the cold reaction mixture was diluted with THF (20 mL) and a suspension prepared from $LiAlH_4$ (0.5 g) in THF (50 mL) was slowly added with stirring, until no more reaction was observed. The resulting mixture was stirred for 2 h at 25 °C, then quenched, and filtered, as described before. The crude product gave, after chromatographic purification (pentane–ether, 2:1), 0.325 g of **6c** as an oil homogeneous on TLC, which, without further characterization, was dissolved in CH_3OH (10 mL) containing 1.5 mL of aqueous 10% HCl, and the mixture was refluxed for 2 h, then poured into aqueous $NaHCO_3$ and ice, and extracted with $CHCl_3$. The organic layer was dried (Na_2SO_4), filtered, and evaporated in vacuo to give 0.285 g of **7c** (82% from **5c**) as an oil: ^1H NMR δ 1.42–1.64 (m, 6 H), 2.36 (t, J = 6 Hz, 2 H), 3.61 (t, J = 6 Hz, 2 H), 3.77 (s, 3 H), 4.32 (s, 2 H), 6.58–7.68 (m, 8 H). Anal. Calcd for $C_{19}H_{24}O_4S$: C, 65.51; H, 5.88. Found: C, 65.64; H, 5.95.

1-[6,6-Bis(methoxycarbonyl)-1-hexyl]-5-methoxy-2-[(phenylsulfonyl)methyl]benzene (8c). The alcohol **7c** (0.696 g, 2 mmol) was converted to its mesylate as shown for **5c**. To the crude product, obtained by concentration in vacuo of the reaction mixture, were added acetone (50 mL) and NaI (0.9 g, 6 mmol), and the mixture was refluxed for 2 h, then diluted with water, and extracted with ether containing 20% $CHCl_3$. The organic layer was washed successively with aqueous sodium thiosulfate and brine and dried (Na_2SO_4). Filtration and removal in vacuo of the solvent gave the crude iodide. In a separate reaction flask, a mixture of NaH (80% oil dispersion, washed with dry hexane, net wt 72 mg, 3 mmol), DMF (12 mL), and dimethyl malonate (0.41 g, 3.1 mmol) was stirred under argon at room temperature for 30 min. The crude iodide in THF (6 mL) was then added and the resulting mixture stirred at 50 °C for 5 h, then poured into cold aqueous NaCl, and extracted with ether containing 20% $CHCl_3$ (×3). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (pentane–ether, 2:3) gave 0.67 g of **8c** (73% yield from **7c**): mp 72–73 °C (hexane–$CHCl_3$); ^1H NMR δ 1.26–1.96 (m, 8 H), 2.24–2.35 (m, 2 H), 3.34 (t, J = 6 Hz, 1 H), 3.73 (s, 6 H), 3.78 (s, 3 H), 4.31 (s, 2 H), 6.63–7.79 (m, 8 H). Anal. Calcd for $C_{24}H_{30}O_7S$: C, 62.33; H, 6.49. Found: C, 62.45; H, 6.38.

1-[1-Hydroxy-5-(methoxymethoxy)-1-pentyl]-3-methoxy-2-[(phenylsulfonyl)methyl]benzene (5a). Aldehyde **4a** (2.9 g, 10 mmol) underwent the Grignard reaction as described for **4c** to give 3.49 g of **5a** (85%): mp 77–78 °C; ^1H NMR δ 1.58–1.82 (m, 6 H), 3.18 (s, 3 H), 3.33 (s, 3 H), 3.51 (t, J = 6 Hz, 2 H), 4.59 (s, 2 H), 4.71 (AB q, J = 14 Hz, 2 H), 5.03 (br s, 1 H), 6.51 (dd, J = 2 and 5 Hz, 1 H), 7.14–7.67 (m, 7 H). Anal. Calcd for $C_{21}H_{28}O_6S$: C, 61.76; H, 6.86. Found: C, 61.62; H, 6.96.

1-[1-Hydroxy-5-(methoxymethoxy)-1-pentyl]-4-methoxy-2-[(phenylsulfonyl)methyl]benzene (5b). A Grignard reaction of aldehyde **4b** (2.9 g, 10 mmol) as described for **4c** gave 3.30 g of **5b** (81%), as an oil: ^1H NMR δ 1.45–1.68 (m, 6 H), 3.33 (s, 3 H), 3.50 (t, J = 6 Hz, 2 H), 3.64 (s, 3 H), 4.49 (AB q, J = 9 Hz, 2 H), 4.58 (s, 2 H), 4.76 (m, 1 H), 6.37 (d, J = 3 Hz, 1 H), 6.89 (dd, J = 3 and 9 Hz, 1 H), 7.34–7.81 (m, 6 H). Anal. Calcd for $C_{21}H_{28}O_6S$: C, 61.76; H, 6.86. Found: C, 61.54; H, 6.91.

1-(5-Hydroxy-1-pentyl)-3-methoxy-2-[(phenylsulfonyl)-methyl]benzene (7a). To a cooled (−5 °C) solution of **5a** (0.6 g, 1.47 mmol) in dry pyridine was added dropwise freshly distilled $POCl_3$ (0.45 mL), and the mixture was stirred at −5 °C for 30 min, then poured over ice and aqueous 10% HCl, and extracted ($CHCl_3$). The organic layer was washed successively with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (pentane–ether, 1:1), then dissolved in ethyl acetate (25 mL), and submitted to hydrogenation over 10% Pd on carbon (1 h, 25 °C). The reaction mixture was filtered, the catalyst washed several times with hot ethyl acetate, and the filtrate evaporated. The residue (**6a**) was treated directly with 10% HCl in methanol as described for **6c**, to give the crystalline alcohol **7a** (0.35 g, 69% from **5a**). An analytical sample had the following characteristics: mp 90–91 °C ($CHCl_3$–hexane); ^1H NMR δ 1.51–1.66 (m, 6 H), 2.70–2.97 (m, 2 H), 3.21 (s, 3 H), 3.63 (t, J = 6 Hz, 2 H), 4.60 (s, 2 H), 6.45 (d, J = 7 Hz, 1 H), 6.84 (d, J = 7 Hz, 1 H), 7.08–7.70 (m, 6 H). Anal. Calcd for $C_{19}H_{24}O_4S$: C, 65.51; H, 5.88. Found: C, 65.75; H, 5.88.

1-(5-Hydroxy-1-pentyl)-4-methoxy-2-[(phenylsulfonyl)-methyl]benzene (7b). To compound **5b** (1.19 g, 2.92 mmol) in dry C_6H_6 (42 mL) was added *p*-TsOH (50 mg), and the mixture was refluxed in the presence of a Dean–Stark water separator. After 1 h, the mixture was poured into cold aqueous $NaHCO_3$ and extracted with ether containing 20% $CHCl_3$, and the organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (pentane–ether, 1:1), and the product was hydrogenated and then treated with acid in CH_3OH, as described for **7a**, to give **7b** (0.83 g, 82% from **5a**): mp 65 °C (from pentane); ^1H NMR δ 1.25–1.71 (m, 6 H), 2.25–2.42 (m, 2 H), 3.61 (t, J = 6 Hz, 2 H), 3.65 (s, 3 H), 4.33 (s, 2 H), 6.53–7.72 (m, 8 H). Anal. Calcd for $C_{19}H_{24}O_4S$: C, 65.51; H, 5.88. Found: C, 65.72; H, 5.82.

1-[6,6-Bis(methoxycarbonyl)-1-hexyl]-3-methoxy-2-[(phenylsulfonyl)methyl]benzene (8a) was obtained from **7a** (0.348 g, 1 mmol) as described for **8c**, in 81% yield: mp 95–96 °C (pentane–$CHCl_3$); ^1H NMR δ 1.38–2.05 (m, 8 H), 2.68–2.79 (m, 2 H), 3.21 (s, 3 H), 3.33 (t, J = 7 Hz, 1 H), 3.73 (s, 6 H), 4.59 (s, 2 H), 6.45 (d, J = 7 Hz, 1 H), 6.84 (d, J = 7 Hz, 1 H), 7.08–7.68 (m, 6 H). Anal. Calcd for $C_{24}H_{30}O_7S$: C, 62.33; H, 6.49. Found: C, 62.36; H, 6.41.

1-[6,6-Bis(methoxycarbonyl)-1-hexyl]-4-methoxy-2-[(phenylsulfonyl)methyl]benzene (8b) was obtained from **7b** (0.83 g, 2.39 mmol) as described for the preparation of **7c** (86%): mp 58–59 °C (from pentane); ^1H NMR δ 1.28–2.31 (m, 10 H), 3.34 (t, J = 7 Hz, 1 H), 3.66 (s, 3 H), 3.73 (s, 6 H), 4.34 (s, 2 H), 6.54–7.71 (m, 8 H). Anal. Calcd for $C_{24}H_{30}O_7S$: C, 62.33; H, 6.49. Found: C, 62.45; H, 6.60.

1,2,3,4,4a,9,10,10a-Octahydro-6-methoxy-10a-(methoxycarbonyl)-10-oxo-9-(phenylsulfonyl)phenanthrene (10c). To a solution of **8c** (1.17 g, 2.53 mmol) in CCl_4 (130 mL) were added NBS (0.47 g, 2.64 mmol) and benzoyl peroxide (0.1 g), and the mixture was refluxed by irradiation for 15 min (TLC monitoring). After cooling, the imide was separated by filtration, the filtrate was concentrated in vacuo, and the residue was chromatographed (pentane–ether, 2:3) to give the bromide **9c**, 1.29 g (94%), pertinent ^1H NMR shift at δ 5.11 (dd, J = 5 and 9 Hz, CHBr), which, without further characterization, was dissolved in dry THF (90 mL) and added dropwise at 25 °C during 30 min via a motor-driven syringe to a freshly prepared solution of *tert*-BuOK from 0.66 g of potassium (17 mmol) in *tert*-BuOH (65 mL). After being stirred for an additional 30 min, the reaction mixture was poured into aqueous NH_4Cl and ice and extracted with $CHCl_3$, and the combined organic layers were washed with brine, filtered, and concentrated in vacuo. Direct crystallization ($CHCl_3$–hexane) afforded 0.55 g of **10c-I**, and flash chromatography of the mother liquor (pentane–ethyl acetate, 4:1) gave 0.118 g of **10c-II**, followed by an additional 0.24 g of **10c-I** (89% total yield). The major diastereomer (**10c-I**) had the following characteristics: mp 166–168 °C; IR (KBr) 1719, 1747 cm^{-1}; ^1H NMR δ 1.60–2.36 (m, 8 H), 3.30 (s, 3 H), 3.50–3.71 (m, 1 H), 3.83 (s, 3 H), 5.00 (s, 1 H), 6.78–7.79 (m, 8 H). Anal. Calcd for $C_{23}H_{24}O_6S$: C, 64.48; H, 5.60. Found: C, 64.35; H, 5.55.

The minor diastereomer (**10c-II**) had the following characteristics: mp 101–103 °C; ^1H NMR δ 1.36–2.00 (m, 8 H), 3.40 (s, 3 H), 3.32–3.50 (m, 1 H), 3.84 (s, 3 H), 5.18 (s, 1 H), 6.80–7.98 (m, 8 H). Anal. Calcd for $C_{23}H_{24}O_6S$: C, 64.48; H, 5.60. Found: C, 64.52; H, 5.51.

1,2,3,4-Tetrahydro-6-methoxy-10-phenanthrenol (11c). A mixture containing **10c** (0.3 g, 0.7 mmol, diastereomeric pair), freshly distilled, 2,6-lutidine (5 mL), and $LiI{\cdot}3H_2O$ (0.345 g, 1.8 mmol) was heated under argon at 150 °C for 1 h, when TLC showed complete conversion to a less polar product. The lutidine was then removed under reduced pressure (0.1 mm), and the residue was chromatographed (elution with pentane containing 10% ether and 5% CH_2Cl_2) to give crystalline **11c** (0.145 g, 79%): mp 174–175 °C (from $CHCl_3$–hexane); ^1H NMR δ 1.86–1.98 (m, 4 H), 2.78 (t, J = 5 Hz, 2 H), 3.03 (t, J = 6 Hz, 2 H), 3.90 (s, 3 H), 4.97 (s, O*H*), 6.93 (s, 1 H), 7.07 (dd, J = 2 and 9 Hz, 1 H), 7.18 (d, J = 2 Hz, 1 H), 7.53 (d, J = 9 Hz, 1 H). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.94; H, 7.01. Found: C, 78.86; H, 6.92.

1,2,3,4-Tetrahydro-8-methoxy-10-phenanthrenol (11a). Compound **8a** was brominated (96%) as shown for **8c**, and the bromide (**9a**) was directly cyclized as described above, to give **10a** in 88% yield, obtained as a pair of diastereomers in ~9:1 ratio according to the ^1H NMR shifts at δ 5.66 and 5.16 (2 s, C*H*SO_2Ph) for the major and minor diastereomers. This mixture was reacted directly with $LiI{\cdot}3H_2O$ in 2,6-lutidine, as shown before, to give 75% of **11a**: mp 173–175 °C (hexane–$CHCl_3$); ^1H NMR δ 1.81–1.97 (m, 4 H), 2.09 (br s, 2 H), 2.80 (br s, 2 H), 3.96 (s, 3 H), 4.94 (s, OH), 6.75 (d, J = 7 Hz, 1 H), 7.13–7.43 (m, 3 H). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.94; H, 7.01. Found: C, 78.78; H, 6.89.

1,2,3,4-Tetrahydro-6-methoxy-9,10-phenanthrenequinone (12). To a stirred solution of **11c** (27 mg, 0.12 mmol) in dry CH_2Cl_2 (1 mL) at 10 °C was added portionwise *m*-chloroperbenzoic acid (30 mg, 85%, 0.15 mmol) during 5 min. After an additional 5 min, the mixture was diluted with CH_2Cl_2 and washed successively with aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered, and the filtrate evaporated in vacuo. Column chromatography of the residue (pentane–ether, 1:1, and 5% CH_2Cl_2) gave 14 mg of **12** (50%) as orange crystals: mp 134–136 °C; ^1H NMR δ 1.68–1.87 (m, 4 H), 2.45–2.71 (m, 4 H), 3.91 (s, 3 H), 6.78–7.00 (m, 2 H), 8.06 (d, J = 8 Hz, 1 H). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.38; H, 5.78. Found: C, 74.51; H, 5.72.

1,2,3,4-Tetrahydro-6-methoxy-9-methyl-10-phenanthrenol (14). To a solution of **10c** (43 mg, 0.1 mmol, diastereomeric pair) in acetone (5 mL) were added anhydrous K_2CO_3 (46 mg, 0.3 mmol) and 1 mL of MeI, the stirred mixture was refluxed for 2 h, then cooled, and filtered, and the filtrate was concentrated to give a residue, which was purified by chromatography (pentane–ether, 2:1, and 5% CH_2Cl_2), affording 42 mg of **13** (96%) as a diastereomeric mixture, homogeneous on TLC, which was dissolved in dry THF (8 mL) and added to a reaction flask containing NaH (pentane-washed 80% oil dispersion, net wt 90 mg, 3.75 mmol), under argon. After addition of DMSO (0.6 mL) and MeOH (0.06 mL), the reaction mixture was stirred at 60 °C for 1 h, then poured into ice and aqueous 10% HCl, and extracted with $CHCl_3$. The residue was chromatographed (pentane–ether, 4:1) to give 13 mg of **14**: 56%; mp 136–138 °C; ^1H NMR δ 1.83–1.99 (m, 4 H), 2.49 (s, 3 H), 2.75–2.77 (br s, 2 H), 2.97–3.03 (br s, 2 H), 3.91 (s, 3 H), 4.74 (s, OH), 7.05–7.21 (m, 2 H), 7.82 (d, J = 9 Hz, 1 H). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.34; H, 7.44. Found: C, 79.15; H, 7.42.

Demethylation of 8b and Preparation of *tert*-Butyldimethylsilyl Ether 8d. To a cooled (−78 °C) solution of **8b** (0.304 g, 0.66 mmol) in dry CH_2Cl_2 (15 mL) under argon was added BBr_3 (409 mg, 1.6 mmol) dropwise. After the mixture was stirred for 5 min at −78 °C, the temperature was increased to 0 °C and stirring was continued for 1.5 h, after which aqueous $NaHCO_3$ and ice were added and the mixture was extracted with $CHCl_3$. The organic extract was washed with brine, dried (Na_2SO_4), evaporated, and the product purified by chromatography (ether–pentane, 1.5:1) to give 0.29 g of an oil, homogeneous on TLC, which was dissolved in DMF (2 mL). Imidazole (0.26 g, 3.8 mmol) and *tert*-butyldimethylchlorosilane (0.31 g, 2.06 mmol) were added, and the mixture was stirred at 25 °C with TLC monitoring. After 6 h, the mixture was diluted with ether and successively washed with 5% aqueous HCl, aqueous $NaHCO_3$, and brine. The organic layer was dried (Na_2SO_4), filtered, and evaporated and the residue chromatographed (pentane–ether, 3:1) to give **8d** (0.34 g, 92% from **8b**) as an oil: ^1H, NMR δ 0.15 (s, 6 H), 0.95 (s, 9 H), 1.24–2.20 (m, 10 H), 3.33 (t, J = 7 Hz, 1 H), 3.73 (s, 6 H), 4.31 (s, 2 H), 6.67–7.69 (m, 8 H). Anal. Calcd for $C_{29}H_{42}O_7SSi$: C, 61.92; H,

7.47. Found: C, 61.75; H, 7.40.

Bromination of 8d and Cyclization to 10b. To a solution of the silyl ether **8d** (0.164 g, 0.29 mmol) in CCl_4 (18 mL) were added NBS (64 mg, 0.36 mmol), dry $NaHCO_3$ (8 mg), and benzoyl peroxide (5 mg), and the mixture was mildly refluxed by lamp irradiation for 10 min (TLC monitoring). After cooling to 0 °C, the mixture was filtered and the filtrate evaporated in vacuo at <40 °C. The residue (crude **9b**) was dried (by adding and then removing in vacuo 5 mL of dry benzene), then dissolved in dry THF (30 mL), and added dropwise 30 min with a motor-driven syringe to a stirred solution of *tert*-AmOK (0.36 g, 2.9 mmol) in a mixture of THF (70 mL) and *tert*-AmOH (15 mL), under argon, at 10–15 °C. After being stirred for an additional 30 min, the reaction mixture was worked up as for **10c** and showed the presence, in TLC, of the cyclized product as a silyl ether less polar than **9b** and of the polar deprotected product **10b**. This mixture was dissolved in 10 mL of $CHCl_3$ to which 1 mL of $BF_3{\cdot}OEt_2$ was added, and kept under argon overnight, at room temperature, when TLC showed complete conversion to **10b**. After dilution with $CHCl_3$ and successive washings with aqueous $NaHCO_3$ and brine, the organic layer was dried (Na_2SO_4), filtered, and concentrated and the crude product purified by chromatography (pentane–ether, 1:3) to give 78 mg of **10b** (65% from **8d**) as a diastereomeric pair (~9:1), from which the pure major diastereomer (**10b**-I) was obtained by crystallization ($CHCl_3$–hexane): mp 218–220 °C; ^1H NMR δ 1.53–2.30 (m, 8 H), 3.26 (s, 3 H), 3.28–3.57 (m, 1 H), 4.98 (s, 1 H), 6.64–7.85 (m, 8 H). Anal. Calcd for $C_{22}H_{22}O_6S$: C, 63.77; H, 5.31. Found: C, 63.58; H, 5.30.

Preparation of Diacetate 11b. The diastereomeric mixture (**10b**) was reacted with $LiI{\cdot}H_2O$ as shown for **10c**, and the crude product was acetylated under usual conditions (acetic anhydride in pyridine, 12 h) to give, after chromatographic purification, the diacetate **11b**: 55%; mp 114–116 °C; ^1H NMR δ 1.83–2.26 (m, 4 H), 2.33 (s, 3 H), 2.36 (s, 3 H), 2.62–2.77 (br s, 2 H), 3.03–3.16 (br s, 2 H), 7.13–7.46 (m, 3 H), 7.95 (d, J = 9 Hz, 1 H). Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.48; H, 6.04. Found: C, 72.29; H, 5.91.

1-(3-Hydroxy-1-propyl)-2-[(phenylsulfonyl)methyl]benzene (16). To the sodium salt of dimethyl malonate, prepared from 9.6 mmol of NaH and 10 mmol of diester in 30 mL of DMF (as for **8c**), was added 2.6 g (8 mmol) of bromo sulfone **15** (Aldrich) in dry THF (7 mL). After being stirred at 25 °C for 30 min, the reaction mixture was poured into aqueous NH_4Cl and ice, and the formed precipitate was separated by filtration and redissolved in $CHCl_3$. The solution was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The obtained crystalline product was dissolved in DMSO (80 mL) to which NaCl (0.2 g) and H_2O) (1 mL) were added, and the reaction mixture was stirred under argon at 160–170 °C for 4 h, then cooled, diluted with 250 mL of ethyl acetate, washed with brine, dried (Na_2SO_4), filtered, concentrated in vacuo, and purified by chromatography (ether–pentane, 1:1). The product, homogeneous on TLC, was dissolved without further characterization in dry THF (20 mL), and a suspension of $LiAlH_4$ (0.38 g, 10 mmol) in THF (40 mL) was added dropwise to the cooled solution (at 0 °C), until TLC showed complete conversion to a more polar product. Workup, as shown before, and chromatographic purification (ether–pentane, 4:1) gave 1.18 g of **16** (51% from **15**): mp 96 °C; ^1H NMR δ 1.63–1.93 (m, 3 H), 2.60 (t, J = 7 Hz, 2 H), 3.60 (t, J = 5 Hz, 2 H), 4.44 (s, 2 H), 7.02–7.83 (m, 9 H). Anal. Calcd for $C_{16}H_{18}O_3S$: C, 66.21; H, 6.21. Found: C, 66.43; H, 6.28.

2-[3-[2-[(Phenylsulfonyl)methyl]phenyl]propyl]cyclopentanone (17). The alcohol **16** (0.78 g, 2.69 mmol) was converted to the mesylate and then to the iodide, as shown before for **7c**. The crude iodide was added to a solution of the pyrrolidine enamine of cyclopentanone (0.41 g, 3 mmol)[10] in dry toluene (6 mL), and the reaction mixture was refluxed under argon for 18 h. Then water was added, and the mixture was refluxed for an additional 30 min, cooled, poured into cold 10% aqueous HCl, and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo. Chromatography (ether–pentane, 2:3) gave 0.52 g of **17** (54% from **16**): mp 65 °C (from ether–pentane); ^1H NMR δ 1.29–2.41 (m, 13 H), 4.38 (s, 2 H), 7.02–7.68 (m, 9 H). Anal. Calcd for $C_{21}H_{24}O_3S$: C, 70.79; H, 6.74. Found: C, 70.68; H, 6.72.

Preparation of the Olefin 18. A solution containing 1.2 mL of $TiCl_4$ in 2.8 mL of CCl_4 was added dropwise to stirred anhydrous THF (12 mL) in an argon-flushed flask at 0 °C. To the resulting yellow precipitate were added, successively, with stirring, the ketone **17** (0.4 g, 1.12 mmol) in THF (0.5 mL), dimethyl malonate (0.18 g, 1.35 mmol) in THF (0.5 mL), and then pyridine (5 mL, dropwise addition during 45 min). The temperature was then increased to 25 °C, and stirring was continued for 18 h, after which the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give, after chromatographic purification (ether–pentane, 3:7), 0.25 g of **18**, mp 79–80 °C (ether–pentane), and 73 mg of unchanged **17** (47%, 58% net): ^1H NMR δ 1.43–1.93 (m, 8 H), 2.32–2.77 (m, 4 H), 2.82–3.25 (m, 1 H), 3.70 (s, 3 H), 3.75 (s, 3 H), 4.38 (s, 2 H), 7.02–7.70 (m, 9 H). Anal. Calcd for $C_{26}H_{30}O_6S$: C, 66.38; H, 6.38. Found: C, 66.54; H, 6.42.

Hydrogenation of Olefin 18. A mixture containing the olefin **18** (0.2 g, 0.42 mmol), MeOH (3 mL), 5% Pt on carbon (0.18 g), and one drop of 70% $HClO_4$ was hydrogenated at 750 psi. After 13 h (TLC test), the mixture was filtered, the catalyst was thoroughly washed with hot ethyl acetate, and the filtrate was washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatography (ether–pentane, 30:70) gave 178 mg (89%) of **19** as a 3:1 stereoisomeric mixture (oil): ^1H NMR δ 1.26–1.82 (m, 12 H), 2.29–2.47 (m, 2 H), 3.25–3.39 (m, 1 H), 3.67 and 3.71 (2 s, 1:3, 6 H), 4.38 (s, 2 H), 7.03–7.71 (m, 9 H). This mixture was used in the next steps without separation of stereoisomers.

Preparation of 20 and Cyclization to 21. A mixture of **19** (60 mg, 0.13 mmol), NBS (25 mg, 0.14 mmol), and AIBN (catalytic amount) in CCl_4 (2 mL) was refluxed by illumination for 5 min. The cooled mixture was filtered, the filtrate was evaporated in vacuo, and the residue was purified by a short chromatography (pentane–ether, 7:3) to give 70 mg of **20**: 100% yield; ^1H NMR δ 1.31–2.35 (m, 12 H), 3.20–3.48 (m, 1 H), 3.70 and 3.72 (2 s, 1:3, 6 H), 4.47 (AB q, J = 14 Hz, 2 H), 5.04–5.25 (m, 1 H), 6.92–7.78 (m, 9 H). The bromide was dissolved, without further characterization, in dry THF (2 mL) and added dropwise, during 15 min, to a stirred, freshly prepared solution of *tert*-BuOK (from 32 mg of K, 0.83 mmol) in *tert*-BuOH (2 mL) under argon, at room temperature. After the mixture was stirred for an additional 30 min, it was poured into aqueous NH_4Cl and extracted with ethyl acetate, the organic layer was washed with brine, dried, and filtered, and the filtrate was evaporated in vacuo and chromatographed (ether–pentane, 30:70) to give 28 mg of **21** (57% from **19**) as a mixture of three stereoisomers (oil): homogeneous in TLC; ^1H NMR δ 0.88–2.68 (m, 12 H), 3.18, 3.19, 3.80 (3 s, 3 H), 3.39–3.76 (m, 1 H), 4.85, 5.00, 5.10 (3 s, 1 H, C*H*SO_2Ph), 7.05–7.89 (m, 9 H); MS, m/e (relative intensity) 438 (9) (M^+), 297 (100) (M–SO_2Ph).

Preparation of 22. A mixture of **21** (50 mg, 0.11 mmol), $LiI{\cdot}3H_2O$ (45 mg, 0.33 mmol), and 2,6-lutidine (1.5 mL) was heated to reflux (150 °C) under argon for 2 h, then cooled, poured over cold 10% HCl, and extracted with ethyl acetate. Workup (as shown for **11c**) gave the stereoisomers **22** (19 mg, 72%): mp 120–122 °C; ^1H NMR δ 1.25–3.34 (m, 12 H), 5.05 and 5.09 (2 s, O*H*), 6.97 and 6.98 (2 s, 3:1, 1 H), 7.28–7.94 (m, 9 H); MS, m/e (relative intensity) 238 (100) (M^+), 209 (57), 195 (40), 157 (42). Anal. Calcd for $C_{17}H_{18}O$: C, 85.71; H, 7.56. Found: C, 85.76; H, 7.48.

1-(3-Cyano-1-propyl)-2-[(phenylsulfonyl)methyl]benzene (23). Alcohol **16** (1.2 g, 4.14 mmol) was converted to the mesylate, as shown before. To the crude product in DMF (20 mL) was added KCN (0.67 g, 10 mmol), and the mixture was stirred at 60 °C overnight, then poured over ice and brine, and extracted with ether. Workup in the usual manner and chromatography (ether–pentane, 6:4) gave **23** (0.95 g, 77%): mp 63 °C (ether–pentane); ^1H NMR δ 1.79–1.98 (m, 2 H), 2.26–2.77 (m, 4 H), 4.39 (s, 2 H), 7.06–8.04 (m, 9 H). Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.23; H, 5.68. Found: C, 68.15; H, 5.68.

1-(4-Hydroxy-1-butyl)-2-[(phenylsulfonyl)methyl]benzene (24). To a solution of **23** (0.95 g, 3.16 mmol) in dry CH_2Cl_2 (9 mL) was added at 0 °C a 1 M solution of Dibal in hexane (3.2 mL, 3.2 mmol). After 1 h, the mixture was quenched with aqueous (5%) HCl, then stirred for an additional 30 min, and extracted with CH_2CL_2. The organic layer was washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and evaporated in vacuo. The crude product, homogeneous by TLC, was dissolved

in THF (15 mL) and added to a suspension of $LiAlH_4$ (0.1 g, 2.6 mmol) at 0 °C, under argon. After being stirred for 30 min, the reaction mixture was quenched and worked up, as shown before, to give, after chromatographic purification (ether–pentane, 4:1), 0.66 g of **24** (oil, 69% from **23**): ^1H NMR δ 1.47–1.63 (m, 4 H), 2.37–2.55 (m, 2 H), 3.63 (br s, 2 H), 4.40 (s, 2 H), 7.02–7.71 (m, 9 H). Anal. Calcd for $C_{17}H_{20}O_3S$: C, 67.10; H, 6.58. Found: C, 67.12; H, 6.53.

1-[5,5-Bis(methoxycarbonyl)-1-pentyl]-2-[(phenylsulfonyl)methyl]benzene (25). The alcohol **24** was converted to the malonate **25** as shown for the preparation of **8c** in 70% yield: mp 109 °C ($CHCl_3$–hexane); ^1H NMR δ 1.27–2.02 (m, 6 H), 2.41 (t, J = 7 Hz, 2 H), 3.34 (t, J = 7 Hz, 1 H), 3.72 (s, 6 H), 4.37 (s, 2 H), 7.02–7.69 (m, 9 H). Anal. Calcd for $C_{22}H_{26}O_6S$: C, 63.16; H, 6.22. Found: C, 63.31; H, 6.28.

2,3,3a,4,5,9b-Hexahydro-4-oxo-5-(phenylsulfonyl)benz[e]indene (27). Compound **25** (0.33 g, 0.8 mmol) was treated with NBS (as shown for **8c**) to give, after a short chromatographic purification (ether–pentane, 1:1), 0.39 g of bromide **26** (100%), which, without further characterization, was dissolved in a mixture of anhydrous THF (112 mL) and *tert*-BuOH (30 mL). Separately prepared *tert*-BuOK (from 0.2 g of K, 5.1 mmol) in *tert*-BuOH (10 mL) was added dropwise, under argon, to the solutionof **26** during 20 min. After additional stirring during 1 h at room temperature, the mixture was poured into cold aqueous NH_4Cl and brine and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), filtered, evaporated in vacuo, and chromatographed (ether–pentane, 1:4) to give 0.16 g of **27** (62%): mp 129–130 °C; IR (KBr) 1707, 1310, 1150 cm^{-1}; ^1H NMR δ 1.23–2.36 (m, 6 H), 3.57–3.99 (m, 2 H), 4.84 (s, 1 H), 6.80 (d, J = 8 Hz, 1 H), 7.06–7.82 (m, 8 H); MS, m/e (relative intensity) 326 (21) (M^+), 185 (100), (M – SO_2Ph), 184 (22), 167 (41). Anal. Calcd for $C_{19}H_{18}O_3S$: C, 69.94; H, 5.52. Found: C, 69.87; H, 5.58.

2,3-Dihydrobenz[e]inden-4-ol (28). The compound **27** was reacted with $LiI{\cdot}3H_2O$ in 2,6-lutidine, as shown for **10c** (2 h, 150 °C), to give 86% of **28**: mp 94 °C; ^1H NMR δ 2.18–2.46 (m, 2 H), 2.97–3.36 (m, 4 H), 4.94 (br s, OH), 6.98 (s, 1 H), 7.27–7.74 (m, 4 H); MS, m/e (relative intensity) 184 (100) (M^+), 183 (41), 167 (31). Anal. calcd for $C_{13}H_{12}O$: C, 84.78; H, 6.52. Found: C, 84.91; H, 6.53.

2,3-Dihydrobenz[e]indene-4,5-dione (29). Dry oxygen was bubbled into a suspension of CuCl (0.2 g) in dry CH_3CN (2.5 mL), during 30-min at 25 °C. A solution of **28** (50 mg, 0.27 mmol) in CH_3CN (1 mL) was then added to the mixture, which was stirred at 25 °C until TLC showed no more starting material (~30 min). The mixture was then diluted with water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered and evaporated in vacuo, and the residue was chromatographed (ether–pentane, 1:4) to give 41 mg of **29** (75%): mp 135–136 °C (from $CHCl_3$–pentane); IR 1657 cm^{-1}; ^1H NMR δ 1.99–2.32 (m, 2 H), 2.72–3.11 (m, 4 H), 7.34–8.11 (m, 4 H); UV (EtOH) λ_{max} 256, 345, 422 nm (log ϵ 4.27, 3.22, 3.20); MS, m/e (relative intensity) 198 (M^+), 197 (25), 170 (17), 142 (24), 141 (28). Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.79; H, 5.05. Found: C, 78.75; H, 5.02.

Acknowledgment. We thank Dr. Felix Frolow for the determination of the X-ray structure and the Israel Academy of Sciences for supporting, in part, this work by a research grant.

Oxidation Reactions of Baccharinoid B5

Bruce B. Jarvis,* S. Nilgün Cömezoğlu, and M. Estela Alvarez

Department of Chemistry and Biochemistry, University of Maryland, College Park, Maryland 20742

Received November 4, 1987

The plant derived macrocyclic trichothecene baccharinoid B5 (1) undergoes oxidative cleavage with Cr(VI) only with difficulty to give a lactone derivative. The presence of a neighboring hydroxy group was shown to impede this reaction. Peracid oxidation of 1 yields two epoxides, one of which readily undergoes acid-catalyzed intramolecular ring-opening to yield a novel tetrahydrofuran derivative.

The Brazilian shrub *Baccharis megapotamica* Spreng (Asteraceae) was shown to contain a series of potent in vivo active antileukemic agents known as the baccharinoids.[1] The first member of these sesquiterpene antibiotics reported was baccharinoid B5 (1),[2] but subsequent work has shown that the plant contains over 20 baccharinoids[3-5] whose structures are closely related to roridins, members of the macrocyclic class of trichothecene mycotoxins.[6-8] The principal distinction between the roridins and the baccharinoids is that the latter contain an A-ring oxygen functionality either in the form of an 8β-hydroxy group or, as in 1, a 9β,10β-epoxide group. The presence of this oxygen functionality, especially the 9β,10β-epoxide group, is important for the in vivo antileukemic properties of the baccharinoids.[8] The relatively in vivo inactive roridins have been chemically oxidized to baccharinoid-like derivatives that possess substantial in vivo activity against P388 mouse leukemia.[9,10] Herein, we report some oxidative conversions of baccharinoid B5 (1) in which the macrocyclic ring was the target for synthetic modification.

Results and Discussion

Upon treatment with pyridinium dichromate (PDC), the roridins undergo oxidative cleavage to yield verrucarins

(1) Kupchan, S. M.; Streelman, D. R.; Jarvis, B. B.; Dailey, R. G., Jr.; Sneden, A. T. *J. Org. Chem.* **1977**, *42*, 4221.
(2) Kupchan, S. M.; Jarvis, B. B.; Dailey, R. G., Jr.; Bright, W.; Bryan, R. F.; Shizuri, Y. *J. Am. Chem. Soc.* **1976**, *98*, 7092.
(3) Jarvis, B. B.; Pena, N. B.; Rao, M. M.; Cömezoğlu, S. N.; Cömezoğlu, F. T. In *The Chemistry of Allelopathy*; Thompson, A. C., Ed.; ACS Symposium Series, Washington, D.C., No. 268, 1984; p 149.
(4) Jarvis, B. B.; Cömezoğlu, S. N.; Rao, M. M.; Pena, N. B.; Boettner, F. E.; Tara; Williams, M.; Forsyth, G.; Epling, G. *J. Org. Chem.* **1987**, *52*, 45.
(5) Jarvis, B. B.; Cömezoğlu, S. N.; Ammon, H. L.; Breedlove, C. K.; Bryan, R. F.; Miller, R. W.; Woode, M. K.; Streelman, D. R.; Sneden, A. T.; Dailey, R. G., Jr.; Kupchan, S. M. *J. Nat. Prod.* **1987**, *50*, 815.
(6) Tamm, C. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 61.
(7) Jarvis, B. B.; Eppley, R. M.; Mazzola, E. P. In *Trichothecenes-Chemical, Biological, and Toxicological Aspects*; Ueno, Y., Ed.; Halsted-Kodansha Scientific; New York, 1983; p 20.
(8) Jarvis, B. B.; Mazzola, E. P. *Acc. Chem. Res.* **1982**, *14*, 388.
(9) Jarvis, B. B.; Stahly, G. P.; Pavanasasivam, G.; Mazzola, E. P. *J. Med. Chem.* **1980**, *23*, 1054.
(10) Jarvis, B. B.; Midiwo, J. O.; Mazzola, E. P. *J. Med. Chem.* **1984**, *27*, 239.

0022-3263/88/1953-1918$01.50/0