Synthesis of the *o*-Quinones and Dihydro Diols of Polycyclic Aromatic Hydrocarbons from the Corresponding Phenols

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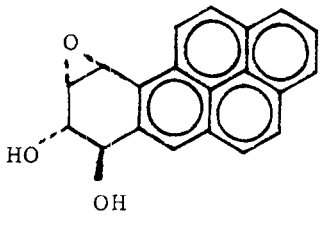
Terminal-ring *trans*-dihydro diol metabolites have been implicated as the ultimate carcinogenic forms of polycyclic aromatic hydrocarbons. Synthesis of these dihydro diols from the related polycyclic phenols in two steps via oxidation to the corresponding *o*-quinones with either Fremy's salt [$(KSO_3)_2NO$] or phenylseleninic anhydride followed by stereospecific reduction with lithium aluminum hydride is described. The non-K-region quinones and *trans*-dihydro diols of naphthalene, anthracene, phenanthrene, benz[*a*]anthracene, benzo[*a*]pyrene, and 7,12-dimethylbenz[*a*]anthracene are synthesized via this approach. Although poor yields (1–4%) were previously reported for the reduction of non-K-region quinones, an improved experimental procedure has been developed which affords the *trans*-dihydro diols free of the isomeric *cis*-dihydro diols in generally good yields. Major byproducts are the corresponding hydroquinones, previously undetected, and the related tetrahydro diols. The latter are the major products of reduction of the poorly soluble quinones of benzo[*a*]pyrene and benz[*a*]anthracene and are shown to arise through further reduction of the dihydro diols. Since the tetrahydro diols are convertible to dihydro diols and the hydroquinones are reoxidizable to quinones, good overall conversions of quinones to dihydro diols are attainable. *trans*-3,4-Dihydroxy-3,4-dihydro-7,12-dimethylbenz[*a*]anthracene synthesized in these studies is the most potent tumorigenic hydrocarbon metabolite tested to date.

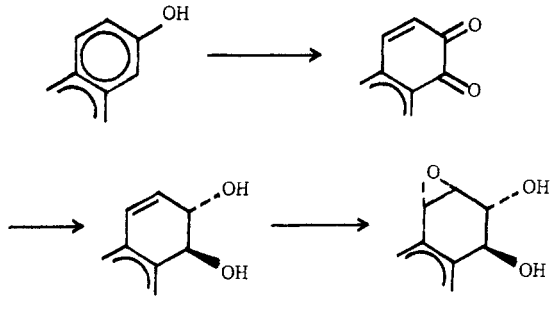
The carcinogenic activity of the common environmental pollutant benzo[*a*]pyrene has recently been shown to be due to a diol epoxide metabolite, *anti*-BPDE,[1] which binds



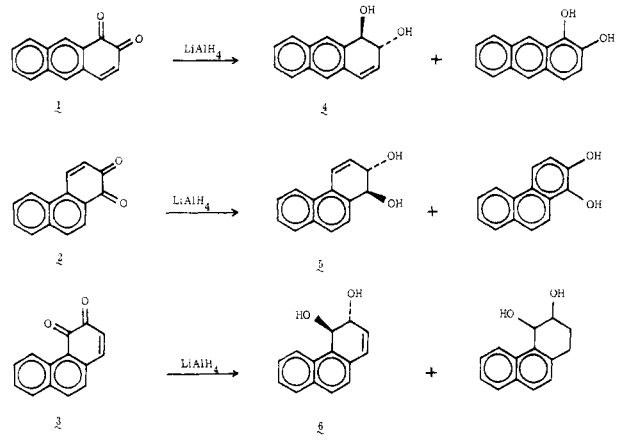
anti-BPDE

covalently to DNA in rodent, bovine, and human tissue in vivo.[2] Major binding occurs on the 2-NH_2 group of guanosine, and the structure and absolute stereochemistry of the BPDE–guanosine adduct have been fully elucidated.[2d] Analogous diol epoxide metabolites have subsequently been implicated as the principal ultimate carcinogenic forms of benz[*a*]anthracene,[3,4] 7-methylbenz[*a*]anthracene,[5] dibenz[*a*,*h*]anthracene,[6] chrysene,[7] 7,12-dimethylbenz[*a*]anthracene,[8–10] and 3-methylcholanthrene.[11,12]

Scheme I



Scheme II



The stereospecific syntheses of *anti*- and *syn*-BPDE initially devised in this laboratory[13] and by Yagi et al.[14]

(1) *anti*-BPDE: *trans*-7,8-dihydroxy-*anti*-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene; depicted is the anti isomer in which the epoxide oxygen atom and the benzylic hydroxyl group are on opposite faces of the molecule; in the syn isomer these groups are on the same face. Alternative nomenclatures are also employed.[2b]

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have subsequently been modified[2b,15,16] and adapted to the synthesis of the analogous derivatives of benz[a]anthracene (BA),[17,18] benzo[e]pyrene,[19,20] triphenylene,[19] chrysene,[21,22] dibenz[a,c]anthracene,[23] and dibenz[a,h]anthracene.[21,24] However, these methods have proven not readily applicable to the synthesis of the related metabolites of the most potent carcinogenic hydrocarbons, such as 7-methylbenz[a]anthracene (MBA), 7,12-dimethylbenz[a]anthracene (DMBA), and 3-methylcholanthrene, which bear alkyl substituents.[25]

We, therefore, undertook investigation of an alternative synthetic route (Scheme I) involving in the crucial steps oxidation of a benzo ring β-phenol to the corresponding o-quinone followed by reduction of the latter to the related *trans*-dihydro diol, the normal synthetic precursor of the diastereomeric diol epoxides.[2b] Although terminal-ring o-quinones derived from polyarenes larger than anthracene were apparently unknown prior to these studies, we assumed them to be synthetically accessible through oxidation of the related phenols with either Fremy's salt $[(KSO_3)_2NO]$[26] or with Barton's reagent, phenylseleninic anhydride.[27] The reduction step presented the most serious challenge, since prior literature indicated reductions of non-K-region[28] o-quinones with metal hydride reagents to be poorly efficient.[2b] Thus, reduction of 1,2-anthraquinone (1) with $LiAlH_4$ is reported by Jerina[29] to afford a 5% yield of the desired *trans*-1,2-dihydro diol 4 (Scheme II) along with the difficulty separable *cis*-1,2-dihydro diol (5%) and the corresponding tetrahydro diols (20%). Analogous reactions of the 1,2- and 3,4-phenanthraquinones (2 and 3) were even less satisfactory, providing only 4% and 1%, respectively, of the corresponding *trans*-dihydro diols 5 and 6.[29] On the other hand, reduction of K-region o-quinones with $LiAlH_4$ in ether was shown earlier to afford good yields of the related *trans*-dihydro diols,[30-32] while reduction of quinones of all types with $NaBH_4$ in dimethylformamide provided the corresponding hydroquinones.[33]

Results

Reinvestigation of the reduction of non-K-region o-quinones with $LiAlH_4$ has now led to development of an improved experimental procedure which affords substantially enhanced yields of the desired *trans*-dihydro diols of anthracene (4), phenanthrene (5 and 6), and other polycyclic aromatic ring systems. Reactions were conducted in a Soxhlet apparatus with the quinone in a fritted-glass thimble and ether as the extraction solvent. *Precautions for the complete exclusion of moisture were scrupulously observed.* Excess hydride was decomposed by addition of partially hydrated sodium sulfate mixed with Celite which furnished the inorganic residue in easily filterable form. Filtration afforded the *trans*-dihydro diols of anthracene and phenanthrene (26–61%) as the sole neutral products free by NMR analysis of the *cis*-dihydro diols and the related tetrahydro diols, except in the case of phenanthrene-3,4-dione which also furnished 3,4-dihydroxy-1,2,3,4-tetrahydrophenanthrene (40%). Treatment of the Celite-adsorbed residue with dilute acetic acid in ethyl acetate liberated the free hydroquinones, the principal byproducts. The latter, due to the tendency to decompose in air, were normally isolated as the corresponding hydroquinone diacetates. Since the hydroquinones can be recycled back to the quinones via oxidation with various reagents (e.g., $FeCl_3$[34] or *N*-chlorosuccinimide),[35] good overall conversions of the quinones to *trans*-dihydro diols are attainable. Although the hydroquinones are major products of these reactions, their formation was not previously described except in a recent brief communication by Kundu[34] which reports 3,4-dihydroxydibenz[a,h]anthracene to be a product of reduction of dibenz[a,h]anthracene-3,4-dione with $LiAlH_4$.

Dihydro diol/hydroquinone product ratios were markedly diminished by traces of moisture or by the use of the conventional paper thimbles presumably employed by previous investigators.[29,30] Phenolic byproducts potentially arising through dehydration of the dihydro diols were not detected. This mode of decomposition may, however, be significant in the original procedure of Booth et al.[30] which employs strong acid (H_2SO_4) to decompose the product aluminum salts.

Having achieved some degree of mastery of the quinone reduction step, we turned our attention to the synthesis of the required polycyclic o-quinones. Initial experiments were conducted with phenylseleninic anhydride. Oxidation of sodium 1- and 2-naphthoxide (generated in situ through reaction with NaH) with $(PhSeO)_2O$ gave 1,2-naphthoquinone in 65% and 73% yields, respectively, confirming the earlier findings of Barton.[27] 1,4-Naphthoquinone was also isolated as a minor product (10%) from oxidation of 1-naphthol. Similar oxidation of 2-hydroxyanthracene and 2-hydroxyphenanthrene, both β-type phenols, afforded smoothly the corresponding o-quinones anthracene-1,2-dione and phenanthrene-1,2-dione (Table I). On the other hand, attempted analogous oxidation of 3-hydroxyphenanthrene, also a β-type phenol, failed to provide the expected 3,4-dione but instead furnished 2,2-dihydroxybenz[e]indan-1,3-dione (7).

Extension of this reaction to the larger polycyclic ring systems of carcinogenic hydrocarbons also afforded smoothly the corresponding o-quinones from β-type phe-

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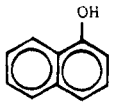
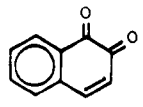
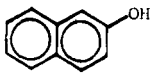
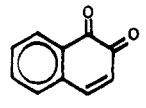
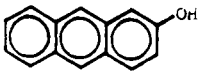
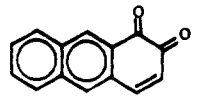
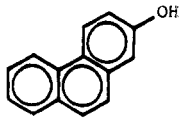
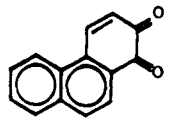
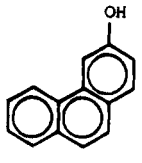
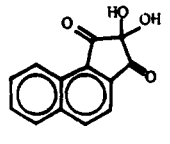
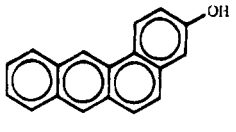
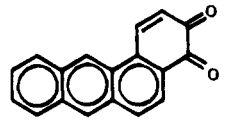
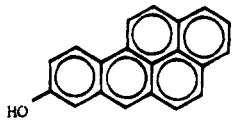
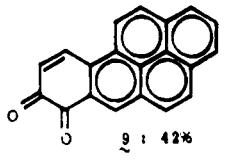
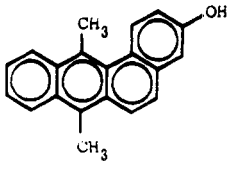
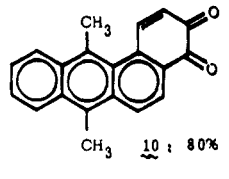
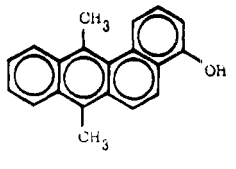
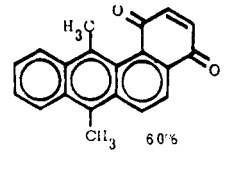
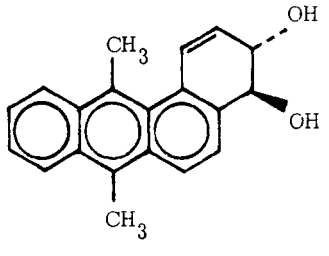
Table I. Oxidation of Polycyclic Phenols with $(PhSeO)_2O$

phenol	product, yield
	 65%
	 73%
	 54%
	 56%
	 7 : 48%
	 8 : 36%
	 9 : 42%
	 10 : 80%
	 60%

nols. Thus, oxidation of 3-hydroxy-BA, 8-hydroxybenzo[a]pyrene, and 3-hydroxy-DMBA with $(PhSeO)_2O$ furnished BA-3,4-dione (**8**), benzo[a]pyrene-7,8-dione (**9**), and DMBA-3,4-dione (**10**), respectively. However, 4-hydroxy-DMBA, an α-type phenol, provided principally DMBA-1,4-dione (**11**, 60%) with a lesser percentage (12%) of the desired DMBA-3,4-dione. This is the first example of oxidation of a phenol with $(PhSeO)_2O$ to furnish predominantly a *p*-quinone. Initially, we were led astray on the structural assignment of the 1,4-dione, since the 3,4-dione was anticipated to be the major isomer of analogy with similar oxidation of 1-naphthol, and the NMR data did not unequivocally distinguish these two isomeric structures. However, agreement between the physical and spectral properties of the minor isomeric quinone obtained from oxidation of 4-hydroxy-DMBA and authentic DMBA-3,4-dione produced from oxidation of 3-hydroxy-DMBA confirmed unequivocally the assignment of the major isomer as DMBA-1,4-dione.

Oxidation with Fremy's salt was also investigated as an alternative synthetic route to the desired quinones. This path was not explored initially because of two potential serious drawbacks: (a) the anticipated poor solubility of the polyarene phenols in the partially aqueous media normally employed in these oxidations and (b) the likelihood of undesirable side reactions involving a free-radical mechanism,[26] particularly on the alkyl-substituted polycyclic compounds. However, these difficulties proved less serious than anticipated. Oxidation of 3-hydroxy-BA, 8-hydroxybenzo[a]pyrene, and 3-hydroxy-DMBA with Fremy's salt in aqueous methanol afforded **8**, **9**, and **10**, respectively, in good yield. On the other hand, attempted analogous oxidation of 3-hydroxyphenanthrene failed to provide the expected bay-region 3,4-quinone, affording instead only the unchanged phenol. In other studies conducted in this laboratory,[36] oxidation of 3-hydroxy-MBA with Fremy's salt afforded smoothly MBA-3,4-dione, while attempted analogous oxidation of 2-hydroxy-MBA to the bay-region 1,2-dione also failed. Therefore, this method provides a practical alternative to Barton's reagent for oxidations of this type, but both methods are ineffectual for the synthesis of sterically restricted (i.e., bay region) *o*-quinones.

Reduction of the polycyclic *o*-quinones obtained in the foregoing syntheses was also carried out with $LiAlH_4$ by the procedure outlined earlier. Reduction of DMBA-3,4-dione by this method afforded pure *trans*-3,4-dihydroxy-3,4-dihydro-DMBA (**12**; mp 182–184 °C, 43%).[37] The



12

integrated 270-MHz NMR spectrum of **12** was entirely consistent with the assigned structure and with NMR data reported by Tierney et al.,[38] who obtained **12** as a minor product (<0.1%) from oxidation of DMBA with ascorbic acid–ferrous sulfate–EDTA. The H_1 signal of **12** appeared at low field, consistent with its assigned bay-region location. The H_2 proton was found as a doublet of doublets at δ 6.13 coupled to H_1 and H_3 ($J_{1,2}$ = 9.5 Hz, $J_{2,3} \simeq$ 2.2 Hz). The relatively large value of $J_{3,4}$ (11.5 Hz) confirms the trans stereochemical relationship of the hydroxyl

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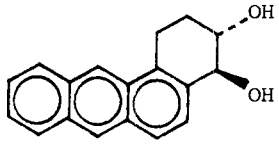
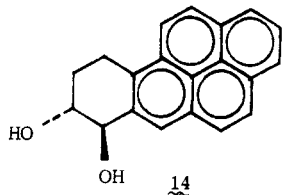
groups and indicates that this dihydro diol exists in solution predominantly in the diequatorial conformation;[19,39] smaller couplings are expected for the cis isomer or for the trans-diaxial conformer.[19,39] Investigations of the carcinogenic activity of **12** reveal it to be *more potent than DMBA, the most biologically active carcinogenic hydrocarbon commonly employed in carcinogenesis research*[24,40] *and the most tumorigenic hydrocarbon metabolite tested to date.*[41]

Reduction of BA-3,4-dione (8) and benzo[*a*]pyrene-7,8-dione (**9**) with $LiAlH_4$ by the same method furnished principally the related tetrahydro diol derivatives, **13** and **14**. Presumably **13** and **14** arise through further reduction



13

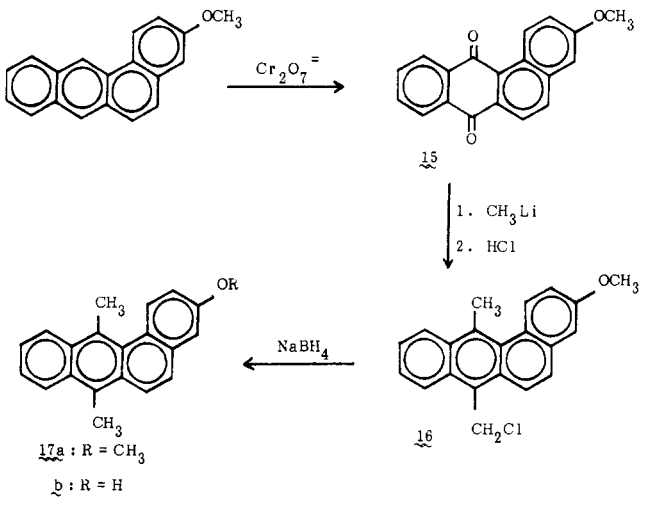


14

of the initially formed dihydro diol intermediates. This is likely since reduction of aromatic olefins with $LiAlH_4$ has been well-documented,[42] and the quinones **8** and **9** proved particularly poorly soluble in ether, necessitating prolonged reaction periods for their complete extraction from the Soxhlet thimble. In order to test experimentally the facility of aromatic dihydro diols to undergo reduction to tetrahydro diols, we reacted *trans*-1,2-dihydroxy-1,2-dihydronaphthalene, obtained initially in 61% yield from reduction of 1,2-naphthoquinone (2-h reaction), with $LiAlH_4$ for an additional 14 h under identical experimental conditions. In accord with expectation, 1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene was obtained as a major product of the reaction (dihydro/tetrahydro product ratio = 1).

The polycyclic aromatic phenols required for these studies, with the exception of 3-hydroxy-DMBA[37] (**17b**), were synthesized by the published methods cited in the Experimental Section. 3-Hydroxy-DMBA was prepared from 3-methoxy-BA[43] via the sequence of oxidation to the quinone (**15**) with sodium dichromate in acetic acid, transformation of the latter to the (chloromethyl)-DMBA derivative (**16**) by reaction with methyllithium and HCl by Newman's method,[43] and reduction with $NaBH_4$ (Scheme III).[37] The latter reagent is more convenient than stannous chloride previously employed for this purpose[44,45] and affords equally high yields. Demethylation with lithium thiomethoxide[46] afforded 3-hydroxy-DMBA (**17b**).

Scheme III



Discussion

Synthesis of the non-K-region *trans*-dihydro diols of polycyclic hydrocarbons from the related phenols via oxidation with $(KSO_3)_2NO$ or $(PhSeO)_2O$ to the quinone followed by reduction with $LiAlH_4$ provides a convenient general route to these biologically important metabolites. Moreover, it permits synthesis for the first time of the previously inaccessible bay-region dihydro diol metabolites of the most potent carcinogenic hydrocarbons which bear alkyl substituents, such as the 3,4-dihydro diol of DMBA (**12**).

While oxidation of the majority of the polycyclic phenols in Table I with $(PhSeO)_2O$ furnished only the corresponding *o*-quinones, two exceptions were noted. Oxidation of 3-hydroxyphenanthrene with the selenium reagent afforded unexpectedly the oxidized benz[*e*]indan derivative **7** with one less carbon atom. Since 3-hydroxyphenanthrene is the only phenol in Table I in which the adjacent α position anticipated to undergo oxidative attack lies in a bay region, steric crowding is apparently an important determining factor. While details of the mechanism are obscure, there is precedent in the reported conversion of lanost-1-en-3-one to the *A*-nor-3-one by treatment with phenylseleninic anhydride.[47] The other exceptional case was oxidation of 4-hydroxy-DMBA, the first example of predominant formation of the para rather than the ortho quinone. This is particularly remarkable, since oxidation takes place preferentially in an exceptionally sterically restricted molecular region. Apparently, this is due to the enhanced susceptibility to electrophilic attack in the 1-position of 4-hydroxy-DMBA caused by the serious distortion from planarity of the molecule due to steric crowding in the bay region[48] which diminishes aromaticity and increases the electron density in the 1-position.

The Teuber reaction[26] (i.e., oxidation of phenols with Fremy's reagent) appears to provide a practical alternative to the Barton reaction and has the advantage that $(KSO_3)_2NO$ is more economical to prepare than $(PhSeO)_2O$. Both methods appear similar in their scope and limitations, and neither is applicable to the synthesis of bay-region *o*-quinones such as phenanthrene-3,4-dione. Since yields are not consistently superior by either method, the choice of reagents is likely to be dictated by reagent cost and actual yield in individual cases.

The improved experimental procedure for the reduction of polycyclic *o*-quinones described herein provides a practical synthetic route to the biologically important

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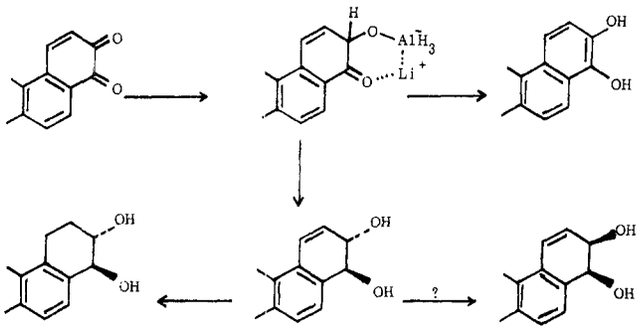
(48) X-ray crystallographic data indicate DMBA itself to be nonplanar: Iball, J. *Nature (London)* **1964**, *201*, 916.

Scheme IV



trans-dihydro diol metabolites of carcinogenic hydrocarbons, certain of which (notably **12**) are otherwise synthetically inaccessible. Several features of these reductions are deserving of comment. The principal products, in addition to the *trans*-dihydro diols, were the corresponding hydroquinones and tetrahydro diols (Scheme IV). The isomeric *cis*-dihydro diols were not detected as significant products. Since the tetrahydro diols are the synthetic precursors of the *trans*-dihydro diols in the established synthesis[2b] and the hydroquinones are reoxidizable to quinones,[34,35] high overall conversions of quinones to *trans*-dihydro diols are attainable in principle. The tetrahydro diol products which arise through further reduction of the initially formed dihydro diols become major products when reaction time must be prolonged due to the poor solubility of the quinone involved. Attempts to substitute tetrahydrofuran or other more efficient solvents for ether in these reactions led only to increased recovery of hydroquinone products. A similar finding was noted earlier in the reduction of K-region quinones with $LiAlH_4$.[31]

Experimental Section

General Methods. The NMR spectra were obtained on a Varian T60 or Bruker 270 NMR spectrometer with tetramethylsilane as internal standard in $CDCl_3$ unless specified otherwise. Elemental analyses were carried out by Atlantic Micro Lab, Inc. 1- and 2-naphthol were purchased from the Aldrich Chemical Co. and purified by distillation before use. 1,2-Naphthoquinone (Aldrich) was purified by chromatography on silica gel eluted with benzene–CH_2Cl_2. 2- and 3-phenanthrol were prepared by alkali fusion of the corresponding sulfonates which were prepared from phenanthrene by the reported procedure.[49] Phenylseleninic anhydride (PSA),[50] Fremy's salt $[ON(SO_3K)_2]$,[26] and phenanthrene-3,4-dione[51] were synthesized according to literature methods. 8-Hydroxybenzo[*a*]pyrene was synthesized from 7-oxo-7,8,9,10-tetrahydrobenzo[*a*]pyrene by a procedure analogous to that described for synthesis of 9-hydroxybenz[*a*]anthracene.[43] 3-Hydroxybenz[*a*]anthracene was synthesized from benz[*a*]anthracene by the method of Fu et al.[43]

General Procedure for the Oxidation of Phenols Using Phenylseleninic Anhydride. Into a solution of the phenol (10 mmol) in anhydrous THF (400 mL) was added a suspension of NaH (12–15 mmol) in THF (25 mL) (the commercially available 50% dispersion of NaH in oil was washed with hexane several times to remove the oil prior to use). The mixture was maintained at reflux for 10 min, cooled to room temperature, and then treated with PSA (30–35 mmol, dried in vacuo at 90 °C for 2 h). The reaction mixture was refluxed for 40 min, cooled, diluted with ether (600 mL) in a separatory funnel, and washed in sequence with water (2 × 100 mL), 5% sodium bicarbonate solution (2 × 100 mL), and water (2 × 100 mL). The organic layer was dried over anhydrous $MgSO_4$. Removal of the solvent and chromatography of the residue on silica gel (J. T. Baker analyzed reagent deactivated prior to use with 10% water by weight) gave on elution with hexane (500–800 mL) diphenyl diselenide (8–13 mmol). Further elution with benzene (300 mL) followed by 1:1 benzene–methylene chloride (200 mL) afforded unreacted phenol (10–40%). Further elution with methylene chloride followed by 1:1 methylene chloride–ethyl acetate provided the quinone (55–70%). The latter was further purified by crystallization from benzene or benzene–methylene chloride. A column residence time of no more than 10 min for the chromatography is ensured by application of slight pressure with N_2 gas.

Oxidation of 1- and 2-Naphthol. 1-Naphthol (300 mg, 2 mmol) on oxidation with PSA (3.0 g, 8.33 mmol) gave naphthalene-1,2-dione [mp 139 °C dec (lit.[52] mp 145 °C), 214 mg (65%)], and naphthalene-1,4-dione [mp 119 °C dec (lit.[52] mp 126 °C), 33 mg (10%)]. The NMR spectra of these quinones matched closely the reported NMR spectra.[53] 2-Naphthol (430 mg, 3 mmol) on oxidation with PSA (5 g, 13.9 mmol) gave 345 mg (73%) of naphthalene-1,2-dione identical in its physical properties with that obtained from oxidation of 1-naphthol.

Oxidation of 2-Hydroxyanthracene. Oxidation of 2-hydroxyanthracene (200 mg, 1 mmol) with PSA (1.5 g, 4.17 mmol) gave 150 mg (54%) of anthracene-1,2-dione: mp 169–176 °C dec (lit.[54] mp 170–190 °C dec); NMR (60 MHz) δ 6.60 (d, 1, H_3, $J_{3,4}$ = 9.8 Hz), 7.40–8.10 (m, 6, H_{4-8}, H_{10}), 8.65 (s, 1, H_9).

Oxidation of 2-Hydroxyphenanthrene. 2-Hydroxyphenanthrene (390 mg, 2 mmol) on oxidation with PSA (3 g, 8.3 mmol) gave phenanthrene-1,2-dione: 230 mg (56%); mp 222 °C (benzene) (lit.[55] mp 216 °C); NMR (270 MHz) δ 6.56 (d, 1, H_3, $J_{3,4}$ = 10.4 Hz), 8.33 (d, 1, H_4), 8.13 (d, 1, H_{10}, $J_{9,10}$ = 8.55 Hz), 7.94 (d, 1, H_9), 8.28 (m, 1, H_5), 7.69 (m, 2, $H_{6,7}$), 7.89 (m, 1, H_8).

Oxidation of 3-Hydroxyphenanthrene. 3-Hydroxyphenanthrene (410 mg, 2.1 mmol) on oxidation with PSA (4 g, 11.1 mmol) and the usual workup gave 230 mg (48%) of 2,2-dihydroxybenz[*e*]indan-1,3-dione (**7**): mp 248 °C; pale yellow crystals; NMR (270 MHz, Me_2SO-d_6) δ 6.51 (s, 1, OH), 7.85 (m, 4, Ar), 8.18 (d, 1, Ar), 8.46 (d, 1, Ar), 9.11 (d, 1, OH).

Anal. Calcd for $C_{13}H_8O_4$: C, 68.42; H, 3.50. Found: C, 68.78; H, 3.89.

Oxidation of 3-Hydroxybenz[*a*]anthracene. 3-Hydroxybenz[*a*]anthracene (126 mg, 0.5 mmol) on oxidation with PSA (545 mg, 1.5 mmol) gave **8**: 94 mg (36%); dark violet crystals; mp 233 °C; NMR (270 MHz) δ 6.60 (d, 1, H_2, $J_{1,2}$ = 10.55 Hz), 7.56 (m, 2, $H_{9,10}$), 8.23 (m, 4, $H_{5,6,8,11}$), 8.43 (s, 1, H_7), 8.46 (d, 1, H_1), 8.82 (s, 1, H_{12}).

Anal. Calcd C, 83.70; H, 3.90; O, 12.39. Found: C, 83.51; H, 4.00; *m/e* 258.

Oxidation of 8-Hydroxybenzo[*a*]pyrene. Oxidation of 8-hydroxybenzo[*a*]pyrene (270 mg, 1 mmol) with PSA (2 g, 5.56 mmol) gave **9**: 120 mg (42%); sparingly soluble dark violet crystals; mp >260 °C; NMR (270 MHz) δ 6.59 (d, 1, H_9, $J_{9,10}$ = 9.8 Hz), 7.62 (d, 1, H_{12}, $J_{11,12}$ = 8.71 Hz), 8.22 (m, 5, H_{1-5}), 8.36 (d, 1, H_{11}), 8.49 (d, 1, H_{10}), 8.85 (br s, 1, H_6).

Anal. Calcd for $C_{20}H_{10}O_2$: C, 85.11; H, 3.55. Found: C, 84.94; H, 3.62.

Oxidation of 3-Hydroxy-7,12-dimethylbenz[*a*]anthracene. Oxidation of 3-hydroxy-7,12-dimethylbenz[*a*]anthracene (1.36 g, 5 mmol) with PSA (9 g, 25 mmol) yielded **10**: 1.14 g (80%); dark violet crystals; mp 155–156 °C (benzene);[37,56] NMR (270 MHz) δ 3.08 (s, 3, 7-CH_3), 3.18 (s, 3, 12-CH_3), 6.37 (d, 1, H_2, $J_{1,2}$ = 10.7 Hz), 7.60 (m, 2, $H_{9,10}$), 7.99 (d, 1, H_6, $J_{5,6}$ = 9.07 Hz), 8.17 (d, 1, H_1), 8.27 (m, 2, $H_{8,11}$), 8.34 (d, 1, H_5).

Oxidation of 4-Hydroxy-7,12-dimethylbenz[*a*]anthracene. Oxidation of 4-hydroxy-7,12-dimethylbenz[*a*]anthracene, (0.55 g, 2 mmol) with PSA (3.6 g, 10 mmol) gave **11** [291 mg (60%), mp 196 °C] and **10** (0.069 g, 12%), eluted successively from the chromatography column with 1:1 benzene–CH_2Cl_2: NMR of **11** (270 MHz) δ 2.77 (s, 3, 12-CH_3), 3.03 (s, 3, 7-CH_3), 6.78 (d, 1, H_3,

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(56) The melting point of **10** reported earlier[37] (181–183 °C) has subsequently been found to be in error due to decomposition on standing.

$J_{2,3}$ = 10 Hz), 6.91 (d, 1, H_2), 7.48–8.51 (m, 6, aromatic).

General Procedure for Oxidation of Phenols with Fremy's Salt. Into a suspension of the phenol (10 mmol) in a solution of methanol (500 mL), water (500 mL), and potassium dihydrogen phosphate (12 mmol) was added Fremy's salt (6.75 g, 25 mmol). The mixture was stirred at 35 °C for 16 h, diluted with water (1 L), and filtered. Chromatography of the residue on silica gel gave, on elution with benzene (400 mL), recovered phenol (10–20%). Elution with methylene chloride (400 mL) and subsequently a mixture of methylene chloride and ethyl acetate (4:1, 300 mL) afforded the quinone (45–75%, 56–83% based on reacted phenol) which was further purified by crystallization from benzene or benzene–methylene chloride.

Oxidation of 3-Hydroxy-7,12-dimethylbenz[*a*]anthracene. Oxidation of 3-hydroxy-7,12-dimethylbenz[*a*]anthracene (1.9 g, 7 mmol) with Fremy's salt (5.4 g, 20 mmol) yielded 1.62 g (81%) of 7,12-dimethylbenz[*a*]anthracene-3,4-dione (**10**).

Oxidation of 3-Hydroxybenz[*a*]anthracene. Oxidation of 3-hydroxybenz[*a*]anthracene (0.25 g, 1 mmol) with Fremy's salt (1 g, 3.7 mmol) gave 0.18 g (68%) of benz[*a*]anthracene-3,4-dione (**8**).

Oxidation of 8-Hydroxybenzo[*a*]pyrene. 8-Hydroxybenzo[*a*]pyrene (0.26 g, 1 mmol) and Fremy's salt (0.8 g, 2.95 mmol) yielded 0.085 g (31%) of benzo[*a*]pyrene-7,8-dione (**9**).

General Procedure for the Reduction of Quinones with Lithium Aluminum Hydride. Ether (600 mL) was freshly distilled over $LiAlH_4$ into a flame-dried, 1-L, round-bottomed flask which formed part of a Soxhlet extraction assembly. $LiAlH_4$ (750 mg, 21 mmol) was stirred into this. Extraction of the quinone (1 mmol, dried at 50 °C under vacuum for 2 h prior to use) in a flame-dried, sintered-glass thimble was then carried out in refluxing ether. Reflux was maintained for 30 min after all the quinone had been extracted. Then the stirred reaction mixture was carefully treated with a mixture of water (2.5 mL), anhydrous sodium sulfate (20 g), and Celite (10 g), all ground together in a mortar. Stirring was continued for 20 min, and the mixture then filtered. The residue was stirred in a solution of ether and THF for 10 min and filtered. Removal of solvent from the combined filtrate and trituration with ether furnished the *trans*-dihydro diol (35–60%) as the only neutral product of reduction. The inorganic residue was stirred in THF (100 mL) containing 2.5 mL of glacial acetic acid for 20 min and filtered. The filtrate was partitioned between ether and water (200 mL each). The ether layer was washed with 50 mL of 5% sodium bicarbonate solution and dried ($MgSO_4$), and the solvent was evaporated to furnish the hydroquinone. The latter was acetylated with pyridine and acetic anhydride and purified by chromatography on Florisil.

Reduction of 1,2-Naphthoquinone. Reduction of 1,2-naphthoquinone (320 mg, 2 mmol) with $LiAlH_4$ (1.3 g, 34.2 mmol) in ether (800 mL) furnished 240 mg (61%) of *trans*-1,2-dihydroxy-1,2-dihydronaphthalene. Crystallization from 3:1 hexane–benzene gave the pure dihydro diol: mp 101 °C (lit.[30] mp 103 °C); NMR (270 MHz, acetone-d_6) δ 4.14 (d, 1, OH_2), 4.24 (m, 1, H_2), 4.43 (d, 1, OH_1), 4.57 (dd, 1, H_1), 5.76 (dd, 1, H_3), 6.26 (dd, 1, H_4); $J_{3,4}$ = 9.77 Hz, $J_{2,4}$ = 2.27 Hz, $J_{2,3}$ = 2.17 Hz, $J_{1,2}$ = 11.1 Hz.

Similar reaction of 1,2-naphthoquinone (250 mg, 1.6 mmol) with $LiAlH_4$ (450 mg) was carried out for 16 h after extraction of the quinone was complete to afford 135 mg of a 1:1 mixture of the dihydro and tetrahydro diols by NMR analysis. For 1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene: NMR (270 MHz) δ 2.01 (m, 2, H_3), 3.14 (m, 2, H_4), 3.66 (m, 2, OH), 4.37 (dd, 1, H_2), 4.71 (d, 1, H_1), 7.20–7.80 (m, 4, aromatic).

Reduction of 1,2-Anthraquinone. Reduction of 1,2-anthraquinone (250 mg, 1 mmol) with $LiAlH_4$ (800 mg, 21 mmol) gave 91 mg (36%) of *trans*-1,2-dihydroxy-1,2-dihydroanthracene: NMR (60 MHz, acetone-d_6 + D_2O) δ 4.35 (m, 1, H_2), 4.95 (d, 1, H_1, $J_{1,2}$ = 9.5 Hz), 6.01 (dd, 1, H_3), 6.65 (d, 1, H_4), 7.4–8.1 (m, 6, aromatic). Also obtained was 1,2-diacetoxyanthracene: 108 mg (31%); mp 155–157 °C (lit.[57] mp 157 °C).

Reduction of Phenanthrene-1,2-dione. Reduction of phenanthrene-1,2-dione (210 mg, 1 mmol) with $LiAlH_4$ (700 mg, 18 mmol) over 2 h gave 0.105 g (46%) of *trans*-1,2-dihydroxy-1,2-dihydrophenanthrene: NMR (270 MHz acetone-d_6 + D_2O) δ 4.51 (dt, 1, H_2), 4.85 (d, 1, H_1, $J_{1,2}$ = 11.3 Hz), 6.17 (dd, 1, H_3, $J_{3,4}$ = 10.05 Hz, $J_{2,3}$ = 2.17 Hz), 7.20 (dd, 1, H_4, $J_{2,4}$ = 2.35 Hz), 7.45–8.13 (m, 6, aromatic); this agrees with the 100-MHz NMR spectrum reported.[18] 1,2-Dihydroxyphenanthrene was also isolated as the diacetate: 95 mg (33%); mp 145–147 °C (lit.[58] mp 147 °C); NMR (60 MHz) δ 2.35 (s, 3, 2-OAc), 2.5 (s, 3, 1-OAc), 7.30–8.5 (m, 8, aromatic).

Reduction of Phenanthrene-3,4-dione. Reaction of phenanthrene-3,4-dione (210 mg, 1 mmol) with $LiAlH_4$ (0.5 g, 13 mmol) gave a mixture (2:3) of 141 mg (66%) of *trans*-3,4-dihydroxy-3,4-dihydrophenanthrene and *trans*-3,4-dihydroxy-1,2,3,4-tetrahydrophenanthrene. For *trans*-3,4-dihydroxy-3,4-dihydrophenanthrene: NMR (270 MHz, acetone-d_6 + D_2O) δ 4.35 (dd, 1, H_3, $J_{3,4}$ = 2 Hz, $J_{2,3}$ = 6 Hz), 5.34 (br s, 1, H_4), 6.21 (dd, 1, H_2), 6.68 (d, 1, H_1, $J_{1,2}$ = 9.5 Hz), 7.25–8.20 (m, 6, aromatic). For *trans*-3,4-dihydroxy-1,2,3,4-tetrahydrophenanthrene: NMR (270 MHz, acetone-d_6 + D_2O) δ 2.25 (m, 2, H_2), 2.81 (dd, apparent t, 2, H_1), 6.22 (m, 2, $H_{3,4}$), 7.20–8.25 (m, 6, aromatic).

Reduction of 7,12-Dimethylbenz[*a*]anthracene-3,4-dione. Reduction of 7,12-dimethylbenz[*a*]anthracene-3,4-dione (300 mg, 1.05 mmol) with $LiAlH_4$ (500 mg, 13.7 mmol) gave 130 mg (43%) of *trans*-3,4-dihydroxy-3,4-dihydro-7,12-dimethylbenz[*a*]anthracene (mp 182–184 °C after crystallization from 1:1 acetone–hexane) and 3,4-dihydroxy-7,12-dimethylbenz[*a*]anthracene (75 mg, 21%, isolated as 97 mg of diacetate). For *trans*-dihydro diol: NMR (270 MHz, acetone-d_6 + D_2O) δ 3.07 (s, 3, 12-CH_3), 3.14 (s, 3, 7-CH_3), 4.67 (dt, 1, H_3), 4.74 (d, 1, H_4), 6.16 (dd, 1, H_2), 7.05 (dd, 1, H_1), 7.30–8.37 (m, 6, aromatic); $J_{1,2}$ = 10.1 Hz, $J_{1,3}$ = 2.06 Hz, $J_{2,3}$ = 1.5 Hz, $J_{3,4}$ = 11.5 Hz. For 3,4-diacetoxy-7,12-dimethylbenz[*a*]anthracene: mp 165 °C; NMR (270 MHz, acetone-d_6) δ 2.41 (s, 3, 2-OAc), 2.52 (s, 3, 1-OAc), 3.07 (s, 3, 7-CH_3), 3.36 (s, 3, 12-CH_3), 7.27–8.44 (m, 8, aromatic).

Reduction of Benz[*a*]anthracene-3,4-dione. Reaction of benz[*a*]anthracene-3,4-dione (260 mg, 1 mmol) with $LiAlH_4$ (100 mg, 18 mmol) required more than 16 h for complete extraction. The product (127 mg, 49%) was shown by reverse-phase high-performance LC on a Waters Bondapak C18 column eluted with 70% methanol–water to consist of a mixture of the tetrahydro diol and dihydro diol products (3:1). The NMR spectrum and retention time of the latter were in agreement with those of an authentic sample.[17,18] For *trans*-3,4-dihydroxy-1,2,3,4-tetrahydrobenz[*a*]anthracene: NMR (60 MHz, acetone-d_6) δ 2.0 (m, 2, H_2), 2.6 (m, 2, H_1), 4.20 (m, 1, H_3), 4.40 (dd, 1, H_4), 7.20–8.20 (m, 8, aromatic).

Reduction of Benzo[*a*]pyrene-7,8-dione. Reaction of benzo[*a*]pyrene-7,8-dione (180 mg, 0.64 mmol) with $LiAlH_4$ (100 mg) in 200 mL of ether was terminated at the end of 16 h while 95 mg of the quinone remained in the extraction thimble. Workup yielded 36 mg (42% based on quinone extracted) of 7,8-dihydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene: NMR (60 MHz, acetone-d_6 + D_2O) δ 2.20 (m, 2, H_9), 3.00 (m, 2, H_{10}), 4.45 (dd, 1, H_7), 5.0 (d, 1, H_8), 8.2–8.6 (m, 8, aromatic).

3-Methoxybenz[*a*]anthracene-7,12-dione (15). A solution of 3-methoxy-BA[37,43] (700 mg, 2.7 mmol) and sodium dichromate (1.19 g) in acetic acid (25 mL) was heated at reflux for 25 min, allowed to cool, and poured into 200 mL of cold 30% sulfuric acid. The precipitate was filtered, washed free of acid with water, and chromatographed on a short column of silica gel. Elution with benzene–chloroform (1:1) gave **15**: 526 mg (67%); mp 162–164 °C (lit. mp 162–163 °C,[45] 145 °C[46]); NMR (60 MHz) δ 3.95 (s, 3, OCH_3), 9.6 (d, 1, H_1, $J_{1,2}$ = 9.5 Hz), 7.10–8.40 (m, 8, aromatic); while the NMR data are consistent with those reported by Rosen et al.,[46] the melting point was significantly higher, in agreement with that reported by Newman et al.[45]

7-Chloromethyl-3-methoxy-12-methylbenz[*a*]anthracene (16). Reaction of **15** with methyllithium followed by treatment of the resulting dimethyldihydro diol with gaseous HCl, essentially according to the method of Newman,[45] afforded **16**: mp 148 °C (lit.[45] mp 149–150 °C); NMR (60 MHz) δ 3.35 (s, 3, H_{12}), 4.00 (s, 3, OCH_3), 5.60 (s, 2, H_7), 7.20–8.40 (m, 9, aromatic).

3-Methoxy-7,12-dimethylbenz[*a*]anthracene (17a). To a solution of **16** (400 mg, 1.25 mmol) in anhydrous Me_2SO (20 mL)

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was added $NaBH_4$ (0.50 g, 13.5 mmol), and the suspension was stirred at ambient temperature for 5 h. The product was poured into ice–water, stirred for 10 min, and worked up conventionally to provide the crude product which was purified by chromatography on silica gel. Elution with benzene provided **17a**: 340 mg (95%); mp 130 °C (lit.[45] mp 131–132 °C); NMR (60 MHz) δ 3.05 (s, 3, H_7), 3.25 (s, 3, H_{12}), 3.90 (s, 3, OCH_3), 7.05–8.50 (m, 9, aromatic).

3-Hydroxy-7,12-dimethylbenz[*a*]anthracene (17b). Treatment of **17a** (1.5 g, 5.24 mmol) with lithium thiomethoxide (1 g, 18.5 mmol) in dry dimethylformamide (50 mL) at reflux for 4 h afforded **17b** (1.35 g, 95%) which was purified by passage through a short column of Florisil. A sample crystallized from benzene–hexane (1:1) melted at 169 °C (lit.[45] mp 167–168 °C): NMR (60 MHz) δ 3.05 (s, 3, H_7), 3.30 (s, 3, H_{12}), 7.00–8.50 (m, 9, aromatic).

Oxidation of 1,2-Dihydroxyphenanthrene. A solution of 1,2-diacetoxyphenanthrene (294 mg, 1 mmol) in THF (5 mL) was added to a solution of sodium methoxide (180 mg, 3.3 mmol) in methanol (10 mL), and heated at reflux for 10 min. Workup gave 1,2-dihydroxyphenanthrene which was oxidized directly with $FeCl_3$·$6H_2O$ (2 g, 8 mmol) in dilute (5%) hydrochloric acid (10 mL). The product which separated was immediately washed with water, dried, and chromatographed on silica gel to provide phenanthrene-1,2-dione: 135 mg (63%); mp 207–212 °C (lit.[55] mp 216 °C).

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Registry No. 1, 655-04-9; 2, 573-12-6; 3, 4733-11-3; 4, 4841-37-6; 5, 60917-41-1; 6, 569-20-0; 7, 74877-24-0; 8, 74877-25-1; 9, 65199-11-3; 10, 70092-13-6; 11, 71964-73-3; 12, 68162-13-0; 13, 60968-10-7; 14, 37994-80-2; 15, 63216-11-5; 16, 66240-01-5; 17a, 66240-02-6; 17b, 57266-83-8; 1-naphthol, 90-15-3; 2-naphthol, 135-19-3; naphthalene-1,2-dione, 524-42-5; naphthalene-1,4-dione, 130-15-4; 2-hydroxyanthracene, 613-14-9; 2-hydroxyphenanthrene, 605-55-0; 3-hydroxyphenanthrene, 605-87-8; 3-hydroxybenz[*a*]anthracene, 4834-35-9; 8-hydroxybenzo[*a*]pyrene, 13345-26-1; 4-hydroxy-7,12-dimethylbenz[*a*]anthracene, 14760-53-3; *trans*-1,2-dihydroxy-1,2-dihydronaphthalene, 771-16-4; *trans*-1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene, 14211-53-1; 1,2-diacetoxyanthracene, 74877-26-2; 1,2-diacetoxyphenanthrene, 19551-05-4; *trans*-3,4-dihydroxy-1,2,3,4-tetrahydrophenanthrene, 60967-97-7; 3,4-diacetoxy-7,12-dimethylbenz[*a*]anthracene, 74893-01-9; 3-methoxy-BA, 69847-25-2.

An Approach to Angularly Functionalized Methylhydrindane Systems[1]

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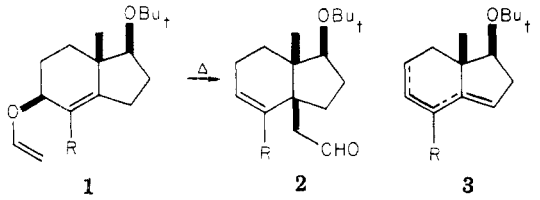
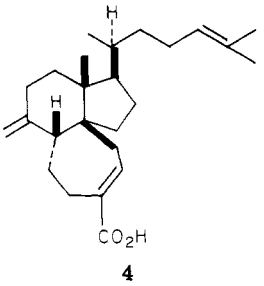
A new version of the Claisen rearrangement utilizing a diosphenol has been developed. This modification attaches an allyl group to the ring juncture of the methylhydrindane system, and other hindered centers, with the retention of the oxygen function on the ring itself.

In recent years a wide variety of natural products have been reported which possess a tricyclic, fused-ring system with a quaternary carbon common to all three rings and approaches toward the preparation of this ring system have been reported by this laboratory.[3,4] In connection with studies directed toward control of the stereochemistry of the quaternary center, the utility of the stereospecific Claisen rearrangement to introduce a functionalized angular group was evaluated.[3] For example, the stereospecific attachment of an acetaldehyde unit to a ring juncture with cis stereochemistry, i.e., 1 to 2, was achieved, and subsequently this reaction sequence was utilized by Boeckman and co-workers[5a] to prepare the natural product gascardic acid (4).[5b,6] The general utility of this thermal rearrangement reaction appears to be limited, however, by irreproducible yields (dienes such as 3 are always found



1 2 3



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(2) (a) Postdoctoral Fellow, National Research Service Award, National Institute of Health. (b) Postdoctoral Fellow, Swiss National Science Foundation.

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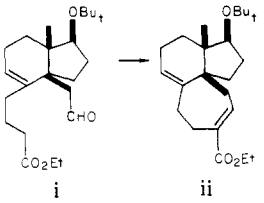
(6) The cyclization of i to ii has been carried out in these laboratories (Dietsche, T. J. Ph.D. Thesis, University of California, Berkeley, 1973).



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