Bis-Heteroannulation. 16. A Synthetic Approach to Geigerin

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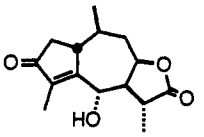
Furano alcohol **5**, the key intermediate in our proposed synthesis of the guaianolide sesquiterpene geigerin (**1**), was prepared by a novel sequence of reactions which includes a chemoselective oxy-Cope transformation of enynols of general structure **42**. Although **42** itself underwent oxy-Cope reaction with exclusive triple-bond participation, the corresponding *tert*-butyldimethylsilyl ether **46** gave the desired vinyl silyloxy Cope product **48** with 100% selectivity. The conversion of acetylenic oxazole **48** to **5** was then effected by a highly efficient (Diels–Alder)–(retro-Diels–Alder) transformation to generate the guaiane ketone **20**, followed by hydride reduction.

Introduction

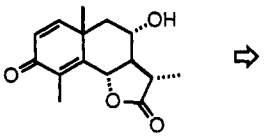
Geigerin (**1**) is a member of the guaiane class of sesquiterpenes which was initially isolated in 1936 from *G. aspera* Harv., a South African species of Geigeria known colloquially as the vermeerbos ("vomiting bush").[1a] In certain regions, ingestion of this shrub by grazing sheep resulted in devastating losses of livestock due to vermeersiekte ("vomiting disease"), the cause of which was of considerable interest to farmers.[1b] Geigerin (**1**) is one of several bitter principles associated with *G. aspera* Harv. and *G. africana* Gries., although it is not the active toxic component of vermeersiekte.[1a] The toxic component is known as vermeeric acid, and its precise composition is apparently still unknown.[1b,c]



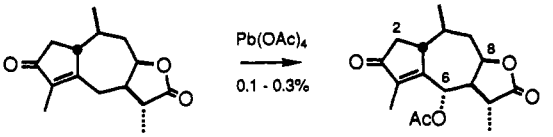
Geigerin (**1**)

The structure of **1** was first proposed in 1958 on the basis of an elegant series of degradation studies by Barton and Levisalles[2a] and confirmed in 1960 by X-ray analysis of the 1-bromo derivative of geigerin acetate (**4**).[3a] In 1964, Barton et al. reported a relay synthesis of **4** beginning with artemisin (**2**), which constituted a formal synthesis of **1** and remains the only successful preparation of this compound to date.[4,2a] Thus, **2** was converted by a lengthy, but remarkable, sequence of transformations to deoxygeigerin (**3**), which proved to be identical with the material derived by Zn/HOAc reduction of naturally occurring **1**. Finally, $Pb(OAc)_4$ oxidation of **3** afforded a mixture consisting mainly of the regioisomeric 2-acetoxy derivative (72%), but the presence of **4** (0.1–0.3%) was confirmed by isotopic dilution experiments.

In this paper we provide experimental details for our own synthetic efforts in this area, which although not yet complete have resulted in a number of interesting observations.



Artemisin (**2**)



Deoxygeigerin (**3**) Geigerin acetate (**4**)

Discussion and Results

The key intermediate for our proposed synthesis of geigerin (**1**) was the furano alcohol **5**, which incorporates the entire carbon skeleton of **1** and also has the proper relative stereochemistry at C-1 and C-10 for directing subsequent asymmetric induction (Scheme I). As the pivotal step in our strategy, we envisioned that the highly substituted furan ring in **5** might serve as an efficient precursor for the methyl lactone functionality of **1** by a sequence of steps which finds excellent precedent in the literature and also in our own model studies described below (vide infra). Thus, solvolytic ring opening of **5** was expected to proceed via the orthoester **6** to the methylene ester **7**,[5] which upon hydrolysis and subsequent intramolecular Michael addition might lead directly to the butenolide derivative **9** as the product of thermodynamic control. This last step would take advantage of the pseudoequatorial methyl group at C-10 as a conformational anchor for establishing the β-stereochemistry at C-8, which models indicate would be favored under equilibrating conditions. In particular, the α-configuration at C-8 not only requires an orthogonal relationship between the conjugated π-systems at C-6 and C-7, but it also leads to considerable steric crowding between the methyl groups at C-4 and C-11. Finally, **1** should be available from **9** by reduction, in situ epimerization, and deprotection (precedent indicates that the lactone methyl group at C-11 can be quantitatively epimerized to the thermodynamically most stable α-configuration[4]).

The viability of this strategy was initially tested in extensive model studies, which culminated in an extremely efficient synthesis of methyl lactone **15** from the acetylenic oxazole **10** (Scheme II).[6e] Thus, thermolysis of **10** at 134

(1) (a) Rimington, C.; Roets, G. C. S. *Onderstepoort J. Vet. Sci.* **1936**, *7*, 485. (b) Rimington, C.; Roets, G. C. S.; Steyn, D. G. *Ibid.* 507. (c) No further reference to vermeeric acid appears in Chemical Abstracts following the initial publication (ref 1b).

(2) (a) Barton, D. H. R.; Levisalles, J. E. D. *J. Chem. Soc.* **1958**, 4518 and references cited therein. For preliminary studies which established the structure of **1** as a guaianolide, see: (b) Perold, G. W. *J. S. African Chem Inst.* **1955**, *8*, 12. (c) Perold, G. W. *J. Chem. Soc.* **1957**, 47.

(3) (a) Hamilton, J. A.; McPhail, A. T.; Sim, G. A. *Proc. Chem. Soc.* **1960**, 278. See also: (b) Barton, D. H. R.; Pinhey, J. T. *Proc. Chem. Soc.* **1960**, 279.

(4) Barton, D. H. R.; Pinhey, J. T.; Wells, R. J. *J. Chem. Soc.* **1964**, 2518.

(5) Novotny, L.; Kotva, K. *Collect. Czech. Chem. Commun.* **1974**, *39*, 2949. See also ref 6e.

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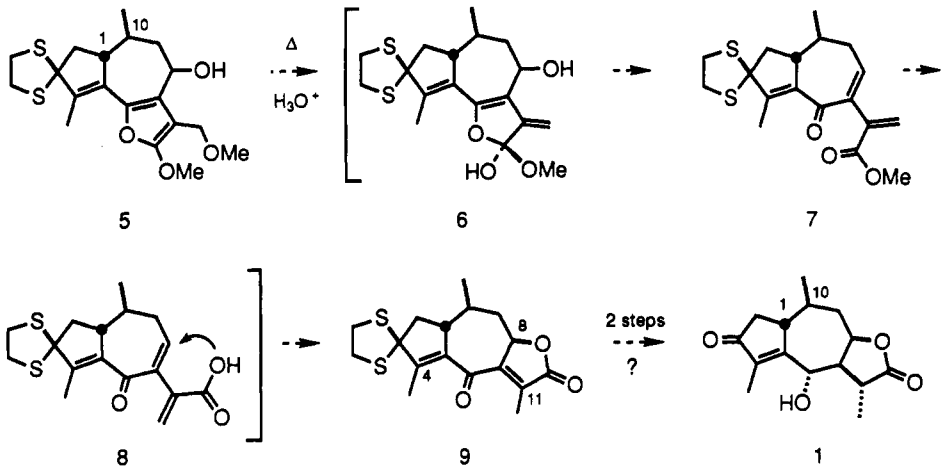
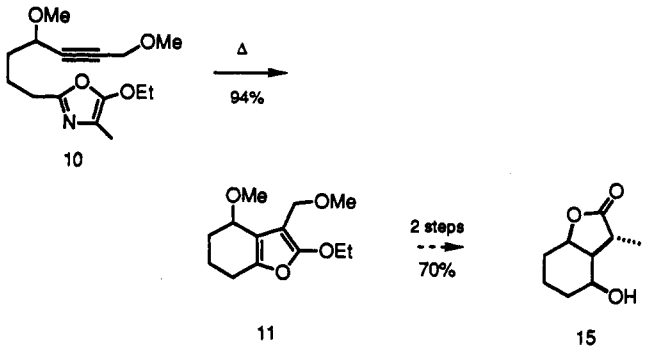
Scheme I



5 6 7 8 9 1

Scheme II



10 11 15

°C afforded a 94% yield of the ethoxyfuran **11**, making use of the (Diels–Alder)–(retro-Diels–Alder) methodology which we have employed for the synthesis of numerous furanosesquiterpenes and related materials.[6] Ethoxyfuran **11** then gave an ~70% overall yield of **15** by two-step sequence involving solvolytic ring opening, intramolecular Michael addition, and reduction of the resulting butenolide with $NaBH_4/NiCl_2$,[7] in exact analogy to the transformations outlined in Scheme I.[6]

Several approaches were considered for the preparation of **5**. However, we were particularly attracted to the possibility that stereochemical control at C-1 and C-10 might be achieved by the route diagrammed in Scheme III. This approach makes use of a chemoselective oxy-Cope rearrangement for introducing the crucial erythro stereochemistry at C-1 and C-10 in a stereospecific fashion, taking advantage of the fact that the (*Z*)-alkene **16** should rearrange to the acetylenic ketone **18** via the chair transition state **17**.[8] Once in hand, **18** was expected to lead directly to the furano ketone **20** by a (Diels–Alder)–(retro-Diels–Alder) transformation analogous to that described in Scheme II (cf. **10** → **11**).[6] Furano ketone **20** would then give the target compound **5** upon hydride reduction, thereby affording our projected starting material for **1** in two steps from the tertiary alcohol **16** (at this stage, stereochemistry at C-8 is immaterial).

As precedent for this scheme, we had previously shown that gnididione ketal **23** could be prepared in 48% overall yield by brief thermolysis of the acetylenic oxazole **21** (Scheme IV).[6g,m] This work was of particular relevance in that it clearly demonstrated that conformational stabilities relating to the relative configuration at C-8 (*) could be utilized as a means of directing chemoselectivity. Thus, **21** reacted exclusively through conformation **21a**, even though acetylenes are normally much more reactive than alkenes in oxy-Cope rearrangements.[9] In this case, presumably, the transition state leading from **21b** to **25** is energetically unfavorable due to severe steric crowding involving the *cis*-propenyl group and the adjacent dioxolane ring. In contrast, conformation **21a** (and by inference the transition state leading from **21a** to **22**) not only avoids significant steric interactions, but it is also stabilized by hydrogen bonding as indicated (cf. also **24b**). In agreement with this hypothesis, the epimeric alcohol **24** reacted mainly through conformation **24b**, providing **25** as a mixture of (*E*)- and (*Z*)-isomers.[6g,m]

The starting point for our synthesis of **16** was the oxazole aldehyde **35**, which was readily prepared on gram scales and larger from the well-known diester **26** (Scheme V).[10] Thus, phenylselenation of **26** followed by oxidative elimination afforded the unstable cyclopentenone **28**, which generally was directly converted to the ketal derivative **29** by treatment with ethylene glycol (EC) under acid catalysis. As expected, dioxolane formation was accompanied by double-bond migration[11] to provide **29** as the only detectable isomer (32% overall yield from **26**). Next, diester **29** was selectively hydrolyzed to the monoacid derivative **30** (90%), which upon conversion to the acid chloride **31**, and subsequent coupling with methyl alaninate (MA), afforded the amino ester **32** in 60% yield from **30**. Finally, cyclodehydration of **32** with P_2O_5 (79%), followed by ketal

(6) (a) Jacobi, P. A.; Craig, T. *J. Am. Chem. Soc.* **1978**, *100*, 7748. (b) Jacobi, P. A.; Ueng, S. N.; Carr, D. *J. Org. Chem.* **1979**, *44*, 2042. (c) Jacobi, P. A.; Walker, D. G.; Odeh, I. M. A. *J. Org. Chem.* **1981**, *46*, 2065. (d) Jacobi, P. A.; Walker, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 4611. (e) Jacobi, P. A.; Frechette, R.; Arrick, B.; Walker, D.; Craig, T. *J. Am. Chem. Soc.* **1984**, *106*, 5585. (f) Jacobi, P. A.; Weiss, K.; Egbertson, M. *Heterocycles* **1984**, *22*, 281. (g) Jacobi, P. A.; Selnick, H. G. *J. Am. Chem. Soc.* **1984**, *106*, 3041. (h) Jacobi, P. A.; Zaczmarek, C. S. R.; Udodong, U. E. *Tetrahedron Lett.* **1984**, *25*, 4859. (i) Jacobi, P. A.; Frechette, R. F. *Tetrahedron Lett.* **1987**, *28*, 2937. (j) Jacobi, P. A.; Kaczmarek, C. S. R.; Udodong, U. E. *Tetrahedron* **1987**, *43*, 5475. (k) Jacobi, P. A.; Egbertson, M.; Frechette, R. F.; Miao, C. K.; Weiss, K. T. *Tetrahedron* **1988**, *44*, 3327. (l) Jacobi, P. A.; Blum, C. A.; DeSimone, R. W.; Udodong, U. E. S. *Tetrahedron Lett.* **1989**, *30*, 7173. (m) Jacobi, P. A.; Selnick, H. G. *J. Org. Chem.* **1990**, *55*, 202. (n) Jacobi, P. A.; Blum, C. A.; DeSimone, R. W.; Udodong, U. E. S. *J. Am. Chem. Soc.* **1991**, *113*, 5384. (o) Jacobi, P. A. *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press: Greenwich, CT, 1992; Vol. II.

(7) Kido, F.; Tsutsumi, K.; Maruta, R.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1979**, *101*, 6420 and references cited therein.

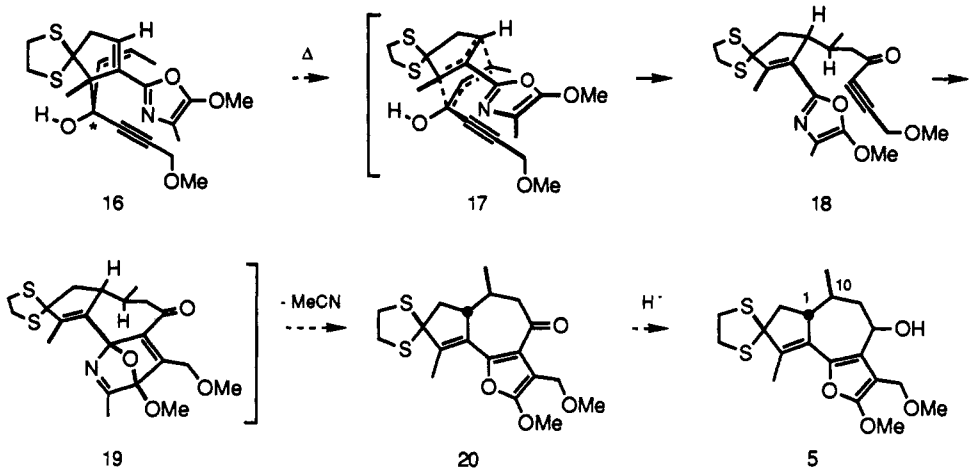
(8) (a) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765. (b) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774.

(9) Viola, A.; Collins, J. J.; Filipp, N. *Tetrahedron* **1981**, *37*, 3765.

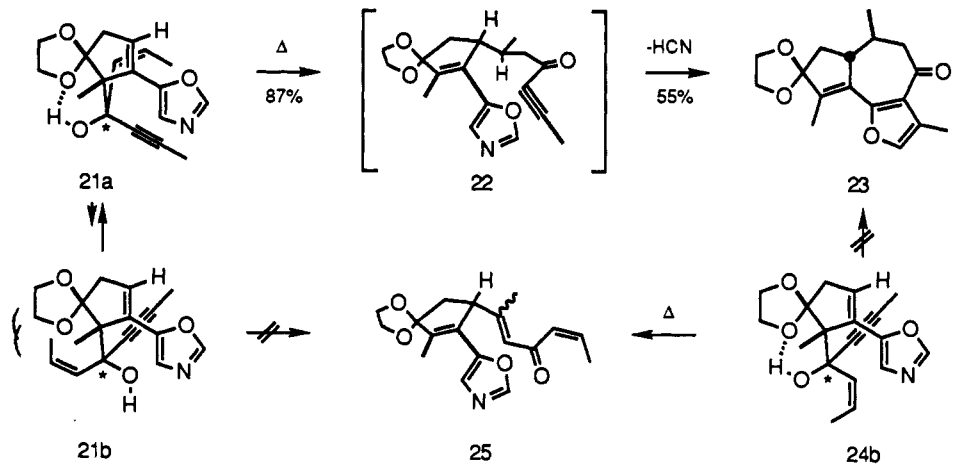
(10) (a) White, W. L.; Anzeveno, P. B.; Johnson, F. J. *J. Org. Chem.* **1982**, *47*, 2379. (b) Baker, J. W.; Burton, H. *J. Chem. Soc.* **1933**, 815.

(11) (a) Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734. (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *Ibid.* 736. (c) Baldwin, J. E. *Ibid.* 738.

Scheme III

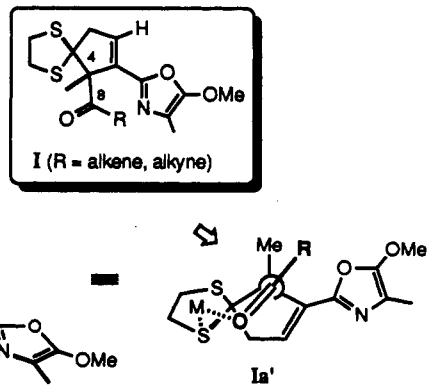


Scheme IV



exchange (73%), provided the dithiolane derivative **34**, which upon reduction with DIBAL-H at −78 °C gave a 75% yield of the desired aldehyde **35**.

We next turned our attention to the conversion of aldehyde **35** to the enynol derivative **16**, in which stereochemical control at C-8 (*) would be crucial to the success of the desired chemoselective oxy-Cope transformation leading from **16** to the acetylenic ketone **18** (cf. Scheme III). Based upon our earlier studies (cf. gnididione ketal **23**, Scheme IV),[6g,m] we expected that the relative configurations at C-4 and C-8 could be controlled via a chelation mediated addition of a suitable organometallic reagent to ketones of general structure **I** (R = alkene, alkyne). Thus,

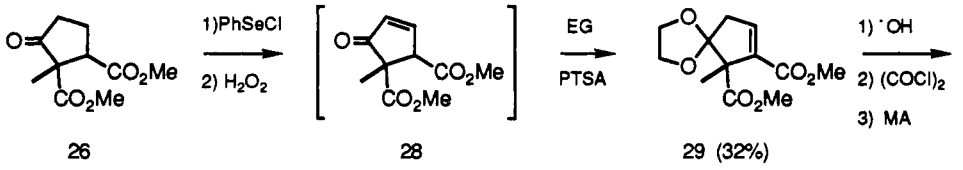


we had previously observed that reactive intermediates closely related to **Ia** undergo nucleophilic addition from the *Re* face (arrows), since the *Si* face is shielded by the oxazole ring (see also Newman projection **Ia'**). As a consequence, stereochemistry at C-8 in these systems ultimately depends upon the order of addition of organometallic reagents to aldehyde **35**: The second group added invariably approaches from the Re face, which in the case of **16** requires the addition of a methylpropargyl ether derivative to enone **I**, where R = *cis*-propenyl (cf. **37**, below).

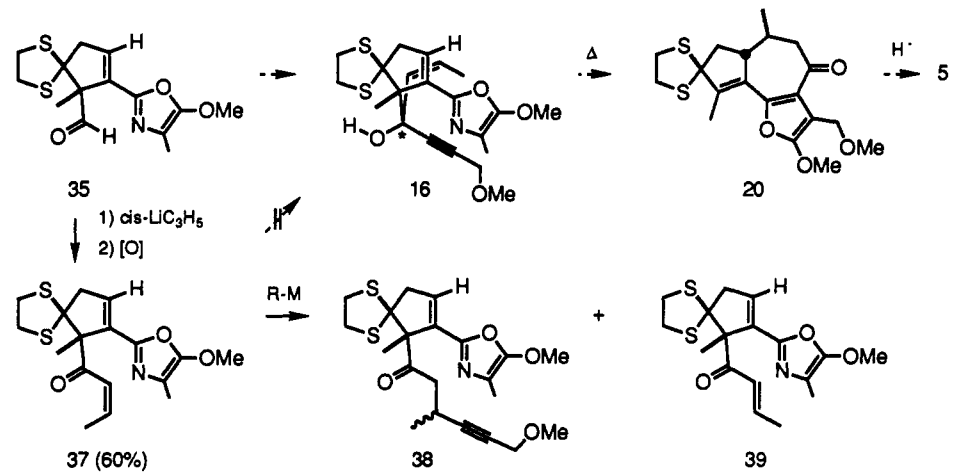
In practice, aldehyde **35** was readily converted to the enone derivative **37** by sequential addition of *cis*-lithiopropene (86%) followed by oxidation (70%) (Scheme VI). Unfortunately, however, all attempts at adding various metallo derivatives of methylpropargyl ether to **37** resulted in either 1,4-addition to afford **38** or simple proton abstraction and equilibration to give **39** (**M** = Li, Mg, Ce, etc.). The reasons for this failure remain unclear, especially in view of our earlier success in preparing the closely related tertiary alcohol **21** (Scheme IV).[6g,m] In any event, our inability to prepare **16** necessitated a reevaluation of our synthetic strategy.

As one alternative, it was of interest to explore the preparation of the isomeric acetylenic alcohol **42**, even though we had little hope that **42** would afford the desired vinylic oxy-Cope product **18** upon thermolysis (Scheme VII, see also **24b** in Scheme IV). In contrast to the difficulties encountered in the synthesis of **16** (Scheme VI), **42** was readily prepared by initial conversion of aldehyde **35** to the acetylenic ketone **41** (52% overall yield), followed by addition of *cis*-lithiopropene (74%). In this case there were no complications due to 1,4-addition or proton abstraction, and **42** was formed with virtually 100% stereo-

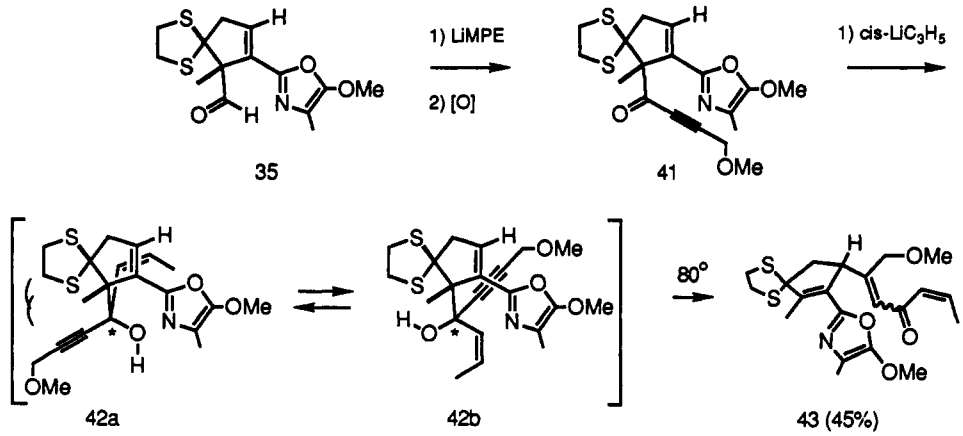
Scheme V



Scheme VI



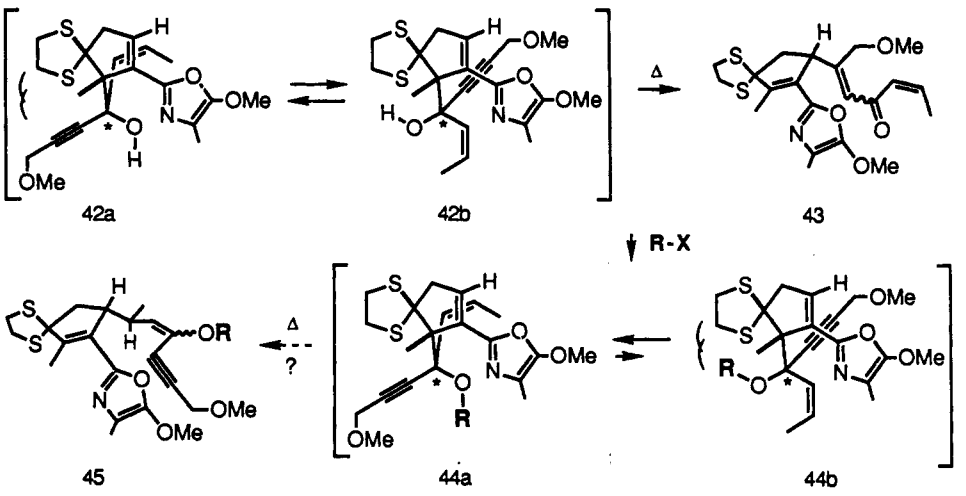
Scheme VII



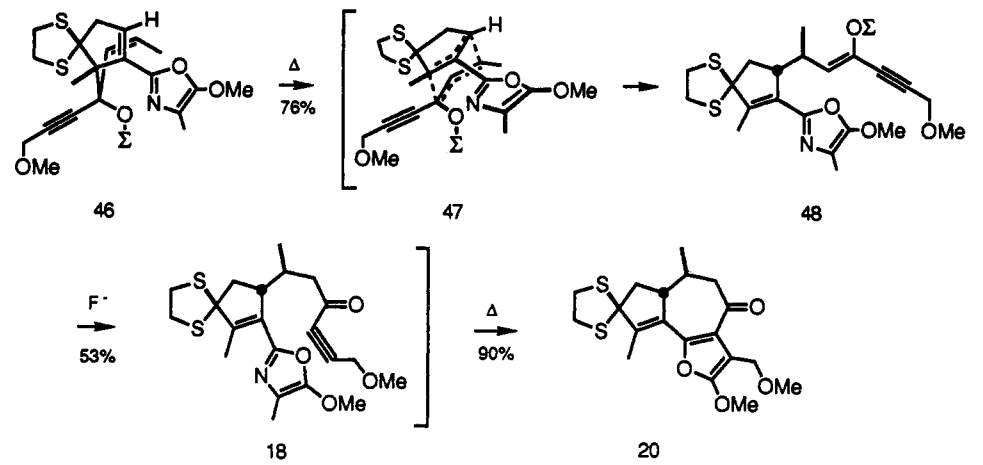
specificity. However, our doubts regarding the suitability of **42** as a precursor to **18** turned out to be well founded, since **42** gave the acetylenic oxy-Cope product **43** as the only characterizable product upon thermolysis at 80 °C (45%, **43***Z*/**43***E* = 2:1). In accordance with our previous analysis (Scheme IV), this result may be due to differing steric effects in the transition states corresponding to **42a** and **42b** or, more likely, it may simply reflect the inherently greater reactivity of acetylenic bonds *in the absence of destabilizing steric factors*.[9]

At this stage of the synthesis we faced a seemingly intractable dilemma: We were unable to prepare the tertiary alcohol **16** which we felt certain would lead directly to the key acetylenic ketone **18**, and the isomeric tertiary alcohol **42** behaved exactly as predicted and afforded exclusively the product **43** of acetylenic oxy-Cope rearrangement. Fortunately, however, a solution to the problem of chemoselectivity was in principle at hand. Thus, models clearly indicate that the hydroxyl group in conformation **42b** occupies the sterically most crowded position in the molecule, while that in rotamer **42a** is relatively unhindered (Scheme VIII). Due to the small size of the hydroxyl functionality neither of these conformations suffers from significant van der Waals' interactions. Upon O-alkylation, however, this situation would be expected to change, and with increasing size of R **44b** should become considerably more strained than **44a**. Experiments proved that this was indeed the case. Thus, with R = trimethylsilyl the major product isolated upon thermolysis at 80 °C was the desired vinylic silyloxy Cope product **45***Z* (R = TMS) arising from the sterically least hindered conformation **44a** (33% yield after hydrolysis to **18**).

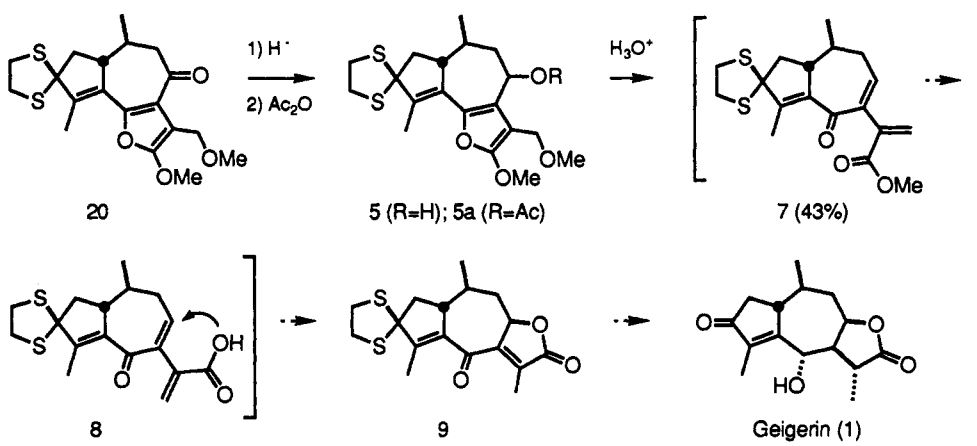
Scheme VIII



Scheme IX



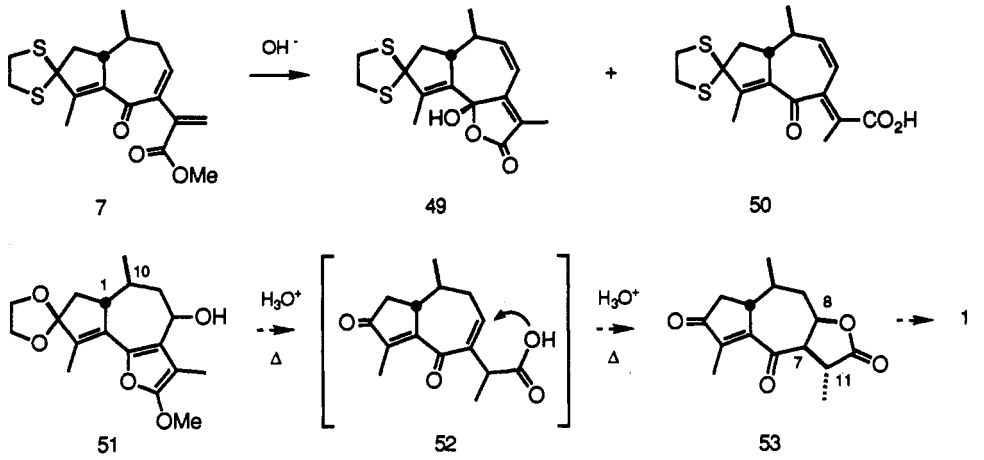
Scheme X



Several other compounds, although not fully characterized, appeared to be rearrangement products derived from the acetylenic silyloxy Cope pathway via conformation **44b**. With R = *tert*-butyldimethylsilyl (Σ), however, the only product formed was that corresponding to the desired vinylic silyloxy Cope reaction pathway. Thus, as indicated in Scheme IX, **46** gave a 76% yield of the acetylenic oxazole **48** upon warming for 30 min in refluxing benzene. This last material was then routinely cleaved to the acetylenic ketone **18** (53%, tetra-*n*-butylammonium fluoride), which gave a 90% yield of the expected furano ketone **20** upon heating for 4.5 h in refluxing toluene. To the best of our knowledge, the experiments summarized in Schemes VIII and IX represent the first examples where *chemo*selectivity in a 3,3-sigmatropic shift has been completely reversed by an appropriate choice of protecting groups.

With ample quantities of furano ketone **20** thus secured, attention was focused on the subsequent conversion of **20** to the key furano alcohol **5** and ultimately to geigerin (**1**) by the route originally proposed in Scheme I. Along these lines, we were pleased to find that $NaBH_4$ reduction of **20** provided a 92% yield of the target alcohol **5** as an ~3:1 inseparable mixture of epimers (Scheme X). However, in contrast to the results obtained with the model system

Scheme XI



11 (Scheme II), **5** gave a complex mixture of products upon attempted solvolytic ring opening. Eventually this difficulty was surmounted when it was discovered that the corresponding acetate derivative **5a**, prepared in 95% yield from **5**, afforded the desired methylene ester **7** in 43% yield (unoptimized) upon brief treatment with 1 N H_2SO_4.

In principle, we were now close to achieving the total synthesis of geigerin (**1**). However, an unexpected difficulty arose in the hydrolytic conversion of **7** to **8**. Thus, under acid conditions **7** suffered extensive decomposition to intractable materials at the temperatures required for hydrolysis (>80 °C), while under basic conditions double-bond migration intervened, leading to the formation of products tentatively identified as **49** and **50** (Scheme XI). This difficulty may be circumvented through the use of reagents such as trimethylsilyl iodide or bis(tributyltin)oxide, which are known to cleave esters under very mild conditions and without affecting dithiolane rings.[12a,b] This possibility is currently under investigation.

In addition, we are also investigating a modification of our strategy in which irreversible double-bond migration would be unlikely. By way of summary, we expect that furano alcohol **51** will undergo a solvolytic ring opening, concomitant with ketal hydrolysis, to afford the methyl acid **52**. Intramolecular Michael addition might then lead directly to dehydrogeigerin (**53**), a compound which has previously been derived from **1** by oxidation under acidic conditions[2a] and in which the stereogenic centers at C-7, C-8, and C-11 appear to be in their most stable configurations. Since each of these centers is epimerizable, it is possible that the proper diastereomer **53** might be obtained under equilibrating conditions. The conversion of **53** to **1** should then follow by selective protection of the C-3 carbonyl group, followed by reduction and deprotection. The results of this study will be the subject of a future paper.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. ^1H NMR spectra were recorded at either 200 or 400 MHz and are expressed as ppm downfield from tetramethylsilane.

Dimethyl 2-Methyl-3-oxo-4-(phenylseleno)cyclopentane-1,2-dicarboxylate (27). A solution of 15.3 g (71.5 mmol) of ketone **26**[10] in 500 mL of distilled EtOAc was treated with 7.0 g (~0.5 equiv) of dry Dowex 50W-X4. The mixture was stirred at rt under an inert atmosphere for 30 min and was then treated with 15.7 g (82.0 mmol, 1.2 equiv) of phenylselenenyl chloride added in one portion. The resulting dark orange suspension was then stirred under an inert atmosphere, with protection from light, for a total of 24 h. The resulting reaction mixture, now light orange, was diluted with 100 mL of EtOAc and washed with 3 × 250 mL of water. The organic layer was then dried (Na_2SO_4) and concentrated under reduced pressure to afford 27.6 g of selenide **27** as a viscous yellow oil. The crude product was usually used without further purification, but could be chromatographed (silica gel, 3:1 hexanes–Et_2O) to give pure selenide **27** (82%) as a viscous pale yellow oil: R_f 0.55 (silica gel, 1:1 hexanes–Et_2O); MS *m/e* 370 (M^+); IR (neat) 2988, 2953, 1740, 1578, 1453, 1437 cm^{-1}; ^1H NMR ($CDCl_3$) (major isomer) δ 1.60 (s, 3 H), 2.26 (dd, J = 7.0, 14.5 Hz, 1 H), 2.84 (ddd, J = 7.3, 12.0, 14.3 Hz, 1 H), 3.17 (dd, J = 7.0, 12.0 Hz, 1 H), 3.61 (s, 3 H), 3.68 (s, 3 H), 4.10 (d, J = 7.3 Hz, 1 H), 7.25–7.66 (m, 5 H).

Dimethyl 2-Methyl-3-oxocyclopent-4-ene-1,2-dicarboxylate (28). A solution of 14.0 g (~38 mmol) of crude selenide **27** in 350 mL of CH_2Cl_2 was cooled to −15 °C under an inert atmosphere. A total of 11.5 mL (113 mmol, 3 equiv) of 15% aqueous H_2O_2 was then added dropwise to the vigorously stirred reaction mixture while a temperature of 10–15 °C was maintained (Caution: an initial induction period is followed by a strong exotherm). After addition was complete, the reaction mixture was allowed to warm slowly to rt. The light yellow reaction mixture was then transferred to a separatory funnel, washed thoroughly with 3 × 125 mL of water, dried (Na_2SO_4), and concentrated under reduced pressure to afford 5.25 g of crude cyclopentenone **28** as an unstable yellow oil which was used without further purification: R_f 0.39 (1:1 Et_2O–hexanes); MS *m/e* 212 (M^+), IR (neat) 2957, 1742, 1715, 1597, 1437 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56 (s, 3 H), 3.60 (s, 3 H), 3.65 (d, J = 2.0 Hz, 1 H), 3.71 (s, 3 H), 6.28 (dd, J = 2.0, 5.6 Hz, 1 H), 7.87 (dd, J = 2.0, 5.6 Hz, 1 H).

Dimethyl 6-Methyl-1,4-dioxaspiro[4.4]non-7-ene-6,7-dicarboxylate (29). A solution of 10.5 g of crude cyclopentenone **28** in 300 mL of dry benzene was treated with 35 mL (0.63 mol) of ethylene glycol and 1.2 g (6.3 mmol) of *p*-toluenesulfonic acid. The resulting mixture was heated at reflux with stirring for 48 h, using a Dean-Stark trap to remove water. After being cooled to rt the reaction mixture was diluted with 150 mL of Et_2O and 150 mL of water. The layers were separated, and the organic layer was washed in sequence with 150 mL of water, 75 mL of saturated aqueous $NaHCO_3$, 100 mL of water, and 100 mL of brine. The organic layer was then dried (Na_2SO_4), the solvent was removed under reduced pressure, and the product was chromatographed (silica gel, 20–40% Et_2O/hexanes) to afford 5.20 g (32% from saturated ketone **26**) of **29** as a light yellow oil: R_f 0.36 (1:1 Et_2O–hexanes); MS *m/e* 256 (M^+); IR (neat) 2953, 1732, 1632, 1437 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 3 H), 2.75 (d, J = 2.2 Hz, 2 H), 3.66 (s, 3 H), 3.71 (s, 3 H), 3.91–4.13 (m, 4 H), 6.78 (t, J = 2.2 Hz, 1 H). Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.16; H, 6.26.

6-Carbomethoxy-6-methyl-1,4-dioxaspiro[4.4]non-7-ene-7-carboxylic Acid (30). Ninety mL of a 1.5 N aqueous NaOH solution was added to 5.20 g (20.3 mmol) of diester **29**, and the resulting heterogeneous mixture was stirred vigorously at rt for

(12) (a) Jung, M. E.; Lyster, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 968. (b) Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1991**, *32*, 4239 and references cited therein.

1 h to produce a light yellow solution. The reaction mixture was then diluted with 90 mL of water and extracted with 2 × 30 mL of CH_2Cl_2 to remove any unreacted starting material. The aqueous phase was acidified to pH 2 with dilute aqueous HCl and extracted with 5 × 50 mL of EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford 4.42 g (90%) of **30** as a colorless solid. Recrystallization from EtOAc afforded **30** as colorless plates, mp 159–160 °C: R_f 0.54 (silica gel, 1:1:0.1 EtOAc–hexanes–AcOH); MS m/e 224 (M^+ – 18 [$-H_2O$]); IR (KBr) 3436, 2998, 1730, 1688, 1622 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, 3 H), 2.78 (d, J = 2.8 Hz, 2 H), 3.67 (s, 3 H), 3.84–4.04 (m, 4 H), 6.94 (t, J = 2.8 Hz, 1 H). Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.46; H, 5.86.

6-Carbomethoxy-6-methyl-1,4-dioxaspiro[4.4]non-7-ene-7-carbonyl Chloride (31). A solution of 3.60 g (14.9 mmol) of **30** in 150 mL of dry benzene containing a few drops of DMF was cooled to 5 °C and treated with 1.55 g of K_2CO_3. Freshly distilled oxalyl chloride (1.7 mL, 19 mmol, 1.3 equiv) was then added dropwise to the vigorously stirred reaction mixture over a 15-min period. After addition was complete the reaction was stirred at ~5 °C for an additional 30 min before being allowed to warm to rt. The reaction mixture was then diluted with 50 mL of benzene and washed with 50 mL of cold 5% aqueous Na_2CO_3. The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to afford **31** as a yellow oil which was used without further purification: R_f 0.71 (silica gel; 1:1:0.1 EtOAc–hexanes–AcOH); MS m/e 224 (M^+ – 36 [–HCl]); IR (neat) 2953, 2899, 1736, 1618, 1458 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 2.76 (d, J = 2.2 Hz, 2 H), 3.57 (s, 3 H), 3.75–3.96 (m, 4 H), 7.12 (t, J = 2.2 Hz, 1 H).

Amide 32. A solution of 3.14 g (22.5 mmol, 1.5 equiv) of methyl alaninate hydrochloride in 75 mL of dry pyridine was cooled to 0 °C under an inert atmosphere and was treated dropwise, with vigorous stirring, with a solution of crude acid chloride **31** (prepared from 3.60 g of **30** as described above) in 25 mL of dry CH_2Cl_2. After addition was complete, the resulting brown solution was allowed to warm slowly to rt and stirring was continued overnight. The reaction was then concentrated under reduced pressure to afford a dark residue which was taken up in 150 mL of CH_2Cl_2. The CH_2Cl_2 solution was then washed with 2 × 50 mL of water followed by 100 mL of saturated aqueous $NaHCO_3$. The aqueous layers were back-extracted with CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford a dark viscous oil. Chromatography (silica gel, 1:1 Et_2O–hexanes) then gave 2.91 g (60% from **30**) of amide **32** as a white crystalline solid. Recrystallization from Et_2O afforded **32** as colorless plates, mp 124–125 °C: R_f 0.43 (silica gel, Et_2O); MS m/e 268 (M^+ – 59 [$-CO_2Me$]); IR (KBr) 3389, 2957, 1755, 1715, 1663, 1618, 1530, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (dd, 4J = 1.6, 7.2 Hz, 3 H), 1.52 (d, J = 2.4 Hz, 3 H), 2.72 (dd, J = 2.4, 4.0 Hz, 2 H), 3.67 (d, J = 2.0 Hz, 3 H), 3.74 (s, 3 H), 3.83–4.04 (m, 4 H), 4.61 (m, 1 H), 6.32 (t, J = 2.4 Hz, 1 H), 6.38 (m, 1 H). Anal. Calcd for $C_{15}H_{21}O_7N$: C, 55.04; H, 6.47; N, 4.28. Found: C, 54.87; H, 6.89; N, 4.47.

Methyl 6-Methyl-7-(4-methyl-5-methoxy-2-oxazolyl)-1,4-dioxaspiro[4.4]non-7-ene-6-carboxylate (33). A solution of 2.91 g (8.90 mmol) of amide **32** and 2.9 mL (11 mmol, 1.2 equiv) of tributyl phosphate in 35 mL of dry CH_2Cl_2 at rt was treated with 480 mg of $NaHCO_3$ (buffer) and 2.9 g (20 mmol, 2.3 equiv) of P_2O_5. The resulting suspension was stirred vigorously under an inert atmosphere for 4.5 h. The reaction mixture was then poured carefully into a mixture of 225 mL of saturated aqueous $NaHCO_3$, 150 mL of brine, and 150 mL of Et_2O. After the excess P_2O_5 had been neutralized, the layers were separated and the aqueous phase was extracted with 3 × 125 mL of EtOAc. The combined organic extracts were dried (Na_2SO_4) and concentrated at reduced pressure. The crude product was chromatographed (silica gel, 25–50% EtOAc–hexanes) to give 2.15 g (79%) of oxazole **33** as a viscous pale orange oil: R_f 0.61 (1:1 EtOAc–hexanes); MS m/e 309 (M^+); IR (neat) 2950, 1734, 1663, 1532, 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 3 H), 1.99 (s, 3 H), 2.78 (dd, J = 2.8, 18 Hz, 1 H), 2.80 (dd, J = 2.8, 18 Hz, 1 H), 3.65 (s, 3 H), 3.87 (s, 3 H), 3.88–4.07 (m, 4 H), 6.42 (t, J = 2.8 Hz, 1 H).

Methyl 6-Methyl-7-(4-methyl-5-methoxy-2-oxazolyl)-1,4-dithiaspiro[4.4]non-7-ene-6-carboxylate (34). A solution of 2.06 g (6.67 mmol) of oxazole **33** in 11.2 mL of ethanedithiol was treated with 3.3 mL (27 mmol, 4 equiv) of BF_3·Et_2O, and the reaction was kept at rt under an inert atmosphere for 18 h. After this period, the reaction mixture was diluted with 85 mL of CH_2Cl_2 and then poured carefully into 300 mL of saturated aqueous $NaHCO_3$. After being stirred 30 min the layers were separated and the aqueous phase was extracted with 3 × 50 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure (first at 30 mmHg and then at 1 mmHg). Chromatography (silica gel, 3:1 hexanes–Et_2O) then afforded 1.66 g (73%) of dithiolane oxazole ester **34** as a viscous pale yellow oil: R_f 0.36 (1:1 Et_2O–hexanes); MS m/e 341 (M^+); IR (neat) 2950, 2928, 2859, 1736, 1663, 1524, 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 3 H), 1.99 (s, 3 H), 3.18 (dd, J = 2.8, 18.2 Hz, 1 H), 3.28 (s, 4 H), 3.40 (dd, J = 2.8, 18.2 Hz, 1 H), 3.66 (s, 3 H), 3.87 (s, 3 H), 6.49 (t, J = 2.8 Hz, 1 H). The peaks at δ 3.18 and 3.40 collapse to doublets, J = 18.2 Hz, upon irradiation at δ 6.49.

6-Methyl-7-(4-methyl-5-methoxy-2-oxazolyl)-1,4-dithiaspiro[4.4]non-7-ene-6-carboxaldehyde (35). A solution of 780 mg (2.29 mmol) of dithiolane ester **34** in 30 mL of dry CH_2Cl_2 was cooled to –78 °C under an inert atmosphere and treated in a dropwise fashion, with vigorous stirring, with 3.0 mL (1.3 equiv) of a 1 N DIBAL-H solution in CH_2Cl_2. After addition was complete, stirring was continued for 1 h at –78 °C, and then excess DIBAL-H was destroyed with 5 mL of MeOH. The reaction mixture was then poured into a 1:1 mixture of Et_2O and saturated aqueous sodium potassium tartrate. After being stirring vigorously for 1 h, the layers were separated and the aqueous phase was extracted with 3 × 30 mL of Et_2O. The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed (silica gel, 1:5 Et_2O–hexanes) to give 530 mg (75%) of aldehyde **35** as a colorless solid. Recrystallization from Et_2O/hexanes afforded **35** as a colorless solid, mp 85–86 °C: R_f 0.47 (1:1 Et_2O–hexanes); MS m/e 311 (M^+); IR (KBr) 2924, 2859, 1717, 1665, 1524, 1453 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 3 H), 2.00 (s, 3 H), 3.07–3.31 (m, 6 H), 3.91 (s, 3 H), 6.69 (t, J = 2.8 Hz, 1 H), 9.90 (s, 1 H). Anal. Calcd for $C_{14}H_{17}NO_3S_2$: C, 54.00; H, 5.50; N, 4.50; S, 20.59. Found: C, 54.20; H, 5.80; N, 4.05; S, 20.90.

6-Methyl-7-(4-methyl-5-methoxy-2-oxazolyl)-α-1(*Z*)-propenyl-1,4-dithiaspiro[4.4]non-7-ene-6-methanol (36). This material was prepared in 86% yield as a 9:1 diastereomeric mixture from 126 mg (0.41 mmol) of aldehyde **35** by a similar procedure as that described below for the conversion of **35** to **40**.[13] Analytical data for the major (more polar) isomer: R_f 0.25 (1:1 Et_2O–hexanes); IR (neat) 3296, 2008, 2964, 1740, 1665 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.41 (s, 3 H), 1.66 (dd, J = 2.0, 7.0 Hz, 3 H), 2.02 (s, 3 H), 3.00–3.35 (m, 6 H), 3.20 (s, 3 H), 3.82–3.90 (m, 1 H), 3.92 (s, 3 H), 4.84 (d, J = 10 Hz, 1 H), 5.52 (dq, J = 7.0, 10 Hz, 1 H), 5.85 (m, 1 H), 6.56 (t, J = 3.0 Hz, 1 H).

1-[6-Methyl-7-(4-methyl-5-methoxy-2-oxazolyl)-1,4-dithiaspiro[4.4]non-7-en-6-yl]-(*Z*)-2-buten-1-one (37). This material was prepared in 70% yield from 219 mg (0.62 mmol) of dithiolane alcohol **36** by a procedure similar to that described below for the conversion of **40** to **41**.[13] Purification by chromatography gave 157 mg of **37** as a viscous pale yellow oil: R_f 0.53 (1:1 Et_2O–hexanes); IR (neat) 3005, 2961, 1736, 1682, 1662, 1615 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.68 (s, 3 H), 1.97 (s, 3 H), 2.06 (dd, J = 2.0, 7.0 Hz, 3 H), 3.04–3.31 (m, 6 H), 3.85 (s, 3 H), 6.10 (dq, J = 7.0, 11 Hz, 1 H), 6.43 (dq, J = 2.0, 11 Hz, 1 H), 6.57 (t, J = 3.0 Hz, 1 H).

6-Methyl-7-(4-methyl-5-methoxy-2-oxazolyl)-α-(3-methoxy-1-propynyl)-1,4-dithiaspiro[4.4]non-7-ene-6-methanol (40). A solution of 0.40 mL (4.8 mmol, 2.8 equiv) of methyl propargyl ether in 15 mL of dry THF was cooled to –78 °C under an inert atmosphere and treated dropwise, with vigorous stirring, with 1.64 mL (4.1 mmol, 2.4 equiv) of 2.5 M *n*-butyllithium in hexanes. After addition was complete, stirring was continued for 20 min at –78 °C, and the resulting solution of 1-lithiomethylpropargyl ether was then treated dropwise with a solution of 530 mg (1.70 mmol) of aldehyde **35** in 15 mL of dry THF. The light yellow reaction mixture was stirred at –78 °C for an additional 30 min and was then allowed to warm slowly to –20 °C. The

(13) Selnick, H. G. Ph.D. Thesis, Wesleyan University, 1985.

reaction mixture was then poured into 115 mL of pH 7 phosphate buffer, and the aqueous phase was extracted with 4 × 35 mL of CH_2Cl_2. After drying (Na_2SO_4), the organic extracts were concentrated under reduced pressure and then chromatographed (silica gel, 2:3 Et_2O–hexanes) to afford 467 mg (72%) of **40** as a 5:1 diastereomeric mixture. Recrystallization from Et_2O–hexanes afforded the ynols **40** as pale yellow solids.

Analytical data for the major (more polar) isomer: mp 103 °C; R_f 0.26 (3:1 Et_2O–hexanes); MS m/e 381 (M^+); IR (KBr) 3403, 3169, 2923, 2858, 1667, 1618, 1543, 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 3 H), 2.00 (s, 3 H), 3.19–3.42 (m, 7 H), 3.37 (s, 3 H), 3.92 (s, 3 H), 4.12 (d, J = 1.6 Hz, 2 H), 4.96 (t, J = 1.6 Hz, 1 H), 6.60 (t, J = 2.8 Hz, 1 H). Anal. Calcd for $C_{18}H_{23}NO_4S_2$: C, 56.67; H, 6.08; N, 3.67. Found: C, 56.53; H, 6.09; N, 3.59.

Analytical data for the minor (less polar) isomer: mp 74–75 °C; R_f 0.47 (3:1 Et_2O–hexanes); MS m/e 381 (M^+); IR (KBr) 3295, 2928, 1667, 1524, 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 3 H), 2.01 (s, 3 H), 3.21 (s, 3 H), 3.11–3.37 (m, 7 H), 3.92 (s, 3 H), 4.02 (br s, 2 H), 4.54 (s, 1 H), 6.48 (t, J = 2.8 Hz, 1 H).

1-[6-Methyl-7-(4-methyl-5-methoxy-2-oxazolyl)-1,4-dithiaspiro[4.4]non-7-en-6-yl]-4-methoxy-2-butyn-1-one (41). A solution of 160 mL (232 mg, 1.81 mmol, 1.5 equiv) of oxalyl chloride in 20 mL of dry CH_2Cl_2 was cooled to −78 °C under an inert atmosphere and was treated dropwise, with vigorous stirring, with 244 mL (268 mg, 3 equiv) of DMSO. After being stirred for an additional 10 min at −78 °C, a solution of 460 mg (1.21 mmol) of ynols **40** in 10 mL of CH_2Cl_2 was added over a period of 20 min. The reaction mixture was then stirred at −78 °C for an additional 50 min, at which time 835 mL (5 equiv) of dry triethylamine was added dropwise followed by gradual warming to rt. The resulting golden-colored solution was poured into 100 mL of pH 7 phosphate buffer, and the aqueous phase was extracted with 3 × 40 mL of CH_2Cl_2. After drying (Na_2SO_4), the organic extracts were concentrated under reduced pressure and chromatographed (silica gel, 10:1 hexanes–acetone) to afford 330 mg (72%) of ynone **41** as a pale yellow oil: R_f 0.49 (3:1 Et_2O–hexanes); MS m/e 379 (M^+); IR (neat) 2930, 2216, 1736, 1663, 1512, 1445, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.78 (s, 3 H), 2.00 (s, 3 H), 3.33 (s, 3 H), 3.21–3.44 (m, 6 H), 3.88 (s, 3 H), 4.18 (s, 2 H), 6.61 (t, J = 2.8 Hz, 1 H). Anal. Calcd for $C_{18}H_{21}NO_4S_2$: C, 56.97; H, 5.58; N, 3.69. Found: C, 56.74; H, 5.65; N, 3.63.

(*R*,S)-6-Methyl-7-(4-methyl-5-methoxy-2-oxazolyl)-α-1-(*Z*)-propenyl-α-(3-methoxy-1-propynyl)-1,4-dithiaspiro[4.4]non-7-ene-6-methanol (42).** A solution of 315 mg (0.83 mmol) of dithiolane ynone **41** in 32 mL of dry Et_2O was cooled to −78 °C under an inert atmosphere and was treated dropwise, with vigorous stirring, with a total of 2.6 mL (2 equiv) of a 0.63 M Et_2O solution of *cis*-1-lithiopropene.[14] After addition was complete, the resulting cloudy yellow reaction mixture was stirred at −78 °C for an additional 10 min and was then poured into 75 mL of pH 7 phosphate buffer. After the layers were separated, the aqueous layer was extracted with 3 × 50 mL of CH_2Cl_2, and the combined extracts were dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed (silica gel, 1:10 acetone–hexanes) to afford 260 mg (74%) of enynol **42** as an unstable pale yellow oil: R_f 0.53 (3:1 Et_2O–hexanes); MS m/e 421 (M^+); IR (neat) 3202, 2928, 1736, 1669, 1532, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50 (s, 3 H), 2.02 (s, 3 H), 2.07 (dd, J = 1.6, 7.2 Hz, 3 H), 3.15 (s, 3 H), 3.11–3.41 (m, 7 H), 3.91 (s, 3 H), 4.00 (s, 2 H), 5.69 (dq, J = 7.2, 11.6 Hz, 1 H), 6.39 (d, J = 11.6 Hz, 1 H), 6.52 (t, J = 2.8 Hz, 1 H).

6-[9-Methyl-8-(4-methyl-5-methoxy-2-oxazolyl)-1,4-dithiaspiro[4.4]non-8-en-7-yl]-7-methoxy-2,5-heptadien-4-one (43). A solution of 40 mg (0.095 mmol) of enynol **42** in 7.5 mL of dry, degassed benzene was treated with 1 mg of $NaHCO_3$. The resulting suspension was heated to reflux with stirring for 75 min under an inert atmosphere. After being cooled to rt, the reaction mixture was diluted with 10 mL of Et_2O and washed with 10 mL of water. The organic phase was dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed (silica gel, 1:1 Et_2O–hexanes) to afford 18 mg (45%) of a 2:1 mixture of acetylenic oxy-Cope products **43** as a pale yellow oil. Analytical data for the major isomer (*Z*-enone): R_f 0.52 (1:3 acetone–hexanes); IR (neat) 2926, 1740, 1661, 1622, 1437 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.89 (dd, J = 1.6, 7.2 Hz, 3 H), 2.00 (s, 3 H), 2.27 (d, J = 2.0 Hz, 3 H), 2.44 (dd, J = 5.2, 14.8 Hz, 1 H), 3.23 (dd, J = 9.2, 14.8 Hz, 1 H), 3.29 (s, 3 H), 3.31–3.38 (m, 4 H), 3.71 (dd, J = 1.6, 16.4 Hz, 1 H), 3.82 (s, 3 H), 3.95 (dd, J = 1.6, 16.4 Hz, 1 H), 5.06 (m, 1 H), 6.22 (dd, J = 1.6, 15.6 Hz, 1 H), 6.53 (s, 1 H), 6.86–6.92 (m, 1 H); MS m/e 421 (M^+); exact mass calcd for $C_{21}H_{27}NO_4S_2$ 421.1381, found 421.1387.

(*R*,S)-6-Methyl-7-(4-methyl-5-methoxy-2-oxazolyl)-α-1-(*Z*)-propenyl-α-(3-methoxy-1-propynyl)-1,4-dithiaspiro[4.4]non-7-ene-6-methanol, *tert*-Butyldimethylsilyl Ether (46).** A solution of 492 mg (1.17 mmol) of enynol **42** in 12 mL of dry CH_2Cl_2 was cooled to 0 °C under an inert atmosphere and treated dropwise, with vigorous stirring, first with 355 mg (0.489 mL, 3 equiv) of dry triethylamine, followed by 619 mg (0.538 mL, 2 equiv) of *tert*-butyldimethylsilyl triflate. The resulting solution was stirred at 0 °C for 30 min and was then allowed to warm slowly to rt. After being stirred an additional 1 h at rt, the reaction mixture was diluted with 40 mL of CH_2Cl_2 and then poured into 150 mL of water. The layers were separated and the aqueous phase extracted with 3 × 40 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed (silica gel, 15% acetone/hexanes) to afford 449 mg (72%) of **46** as an unstable pale yellow oil: R_f 0.57 (3:1 Et_2O–hexanes); MS m/e 535 (M^+); IR (neat) 2928, 2857, 1736, 1663, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 3 H), 0.18 (s, 3 H), 0.89 (s, 9 H), 1.81 (s, 3 H), 1.85 (d, J = 6.0 Hz, 3 H), 2.05 (s, 3 H), 2.93 (dd, J = 3.6, 17.6 Hz, 1 H), 3.08–3.40 (m, 4 H), 3.31 (s, 3 H), 3.50 (dd, J = 2.0, 17.6 Hz, 1 H), 3.89 (s, 3 H), AB system 3.99, 4.03 (J_{AB} = 11.6 Hz, 2 H), 5.32–5.45 (m, 2 H), 6.65 (dd, J = 2.0, 3.6 Hz, 1 H).

(*Z*)-(*R*,S)-6-[9-Methyl-8-(4-methyl-5-methoxy-2-oxazolyl)-1,4-dithiaspiro[4.4]non-8-en-7-yl]-1-methoxy-4-[(*tert*-butyldimethylsilyl)oxy]hept-4-en-2-yne (48).** A solution of 430 mg (0.80 mmol) of TBDMS ether **46** in 70 mL of dry, degassed benzene was heated at reflux under an inert atmosphere for 30 min. After being cooled to rt, the solvent was evaporated under reduced pressure. The residue was then chromatographed (silica gel, 1:3 Et_2O–hexanes) to afford 326 mg (76%) of **48** as a colorless oil: R_f 0.57 (1:1 Et_2O–hexanes); MS m/e 535 (M^+); IR (neat) 2957, 2928, 2857, 1736, 1661, 1630, 1462 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.12 (s, 3 H), 0.13 (s, 3 H), 0.83 (d, J = 6.4 Hz, 3 H), 0.89 (s, 9 H), 2.03 (d, J = 2.4 Hz, 3 H), 2.18 (br s, 3 H), 2.48 (dd, J = 3.8, 13.8 Hz, 1 H), 2.67 (dd, J = 8.0, 13.8 Hz, 1 H), 3.10 (m, 1 H), 3.20 (m, 1 H), 3.30–3.43 (m, 4 H), 3.37 (s, 3 H), 3.91 (s, 3 H), AB system 4.24, 4.28 (J_{AB} = 11.6 Hz, 2 H), 5.12 (d, J = 10.0 Hz, 1 H).

(*R*,S)-6-[9-Methyl-8-(4-methyl-5-methoxy-2-oxazolyl)-1,4-dithiaspiro[4.4]non-8-en-7-yl]-1-methoxyhept-2-yn-4-one (18).** A solution of 322 mg (0.60 mmol) of enol ether **48** in 30 mL of dry THF was cooled to −78 °C under an inert atmosphere and treated dropwise, with vigorous stirring, with 1.0 mL (1.7 equiv) of a 1.0 N THF solution of tetra-*n*-butylammonium fluoride. After addition was complete, the originally pale yellow reaction was stirred for an additional 20 min to give an amber solution, which was poured into 150 mL of pH 7 phosphate buffer. The aqueous phase was extracted with 3 × 50 mL of CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was chromatographed (silica gel, 30% Et_2O–hexanes) to afford 135 mg (53%) of **18** as a colorless oil: R_f 0.35 (1:1 Et_2O–hexanes); MS m/e 421 (M^+); IR (neat) 2926, 2211, 1746, 1663, 1512, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.72 (d, J = 6.8 Hz, 3 H), 2.04 (s, 3 H), 2.19 (d, J = 2.0 Hz, 3 H), 2.37–2.43 (m, 2 H), 2.54 (dd, J = 5.6, 15.6 Hz, 1 H), 2.66 (dd, J = 8.0, 14.4 Hz, 1 H), 3.04 (m, 1 H), 3.27 (m, 1 H), 3.36 (m, 4 H), 3.39 (s, 3 H), 3.92 (s, 3 H), 4.25 (s, 2 H); exact mass calcd for $C_{21}H_{27}NO_4S_2$ 421.1381, found 421.1360.

Dithiolane Furano Ketone 20. A solution of 112 mg (0.27 mmol) of **18** in 50 mL of dry, degassed toluene was treated with 5 mg of hydroquinone and 5 mg of $NaHCO_3$. The resulting suspension was heated at reflux with stirring for 4.5 h under an inert atmosphere. After being cooled to rt the reaction mixture was diluted with 50 mL of Et_2O and washed with 50 mL of water. The organic phase was then dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed (silica gel, 15% ace-

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tone–hexanes) to give 91 mg (90%) of furano ketone **20** as a pale yellow oil which solidified upon standing. Recrystallization from Et_2O afforded pale yellow needles of **20**, mp 115–116 °C: R_f 0.45 (3:1 hexanes–acetone); MS m/e 380 (M^+); IR (neat) 2963, 2921, 2834, 1746, 1657, 1644, 1609, 1528, 1420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, J = 6.8 Hz, 3 H), 1.93 (m, 1 H), 2.14 (m, 1 H), 2.22 (d, J = 2.0 Hz, 3 H), 2.63–2.79 (m, 4 H), 3.20–3.45 (m, 4 H), 3.33 (s, 3 H), 4.00 (s, 3 H), AB system 4.41, 4.45 (J_{AB} = 11.6 Hz, 2 H). Anal. Calcd for $C_{19}H_{24}O_4S_2$: C, 59.97; H, 6.36. Found: C, 59.75; H, 6.33.

Dithiolane Furano Alcohol 5. A solution of 42 mg (0.11 mmol) of furano ketone **20** in 10 mL of dry MeOH was treated with 23 mg (0.61 mmol) of $NaBH_4$. The reaction mixture was then stirred at rt under an inert atmosphere for 30 min, quenched with 25 mL of pH 7 phosphate buffer, and extracted with 3 × 15 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford 39 mg (92%) of **5** as a colorless oil (~3:1 inseparable diastereomeric mixture). Analytical data for the major isomer: R_f 0.46 (3:1 Et_2O–hexanes); MS m/e 382 (M^+); IR (neat) 3430, 2923, 2870, 1730, 1645, 1513, 1455, 1078 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, J = 6.8 Hz, 3 H), 1.46 (m, 1 H), 1.70 (m, 1 H), 2.04 (m, 2 H), 2.15 (d, J = 2.4 Hz, 3 H), 2.55 (m, 1 H), 2.55 (m, 1 H), 2.76 (dd, J = 6.0, 12.8 Hz, 1 H), 3.15–3.38 (m, 5 H), 3.32 (s, 3 H), 3.95 (s, 3 H), AB system 4.26, 4.33 (J_{AB} = 11.6 Hz, 2 H), 4.66 (m, 1 H).

Dithiolane Furano Acetate 5a. A solution of 36 mg (0.094 mmol) of furano alcohol **5** in 2 mL of dry pyridine was treated with 1 mL of acetic anhydride, and the reaction mixture was stirred at rt for 18 h with protection from moisture. The excess acetic anhydride and pyridine were then evaporated under reduced pressure, and the residue was partitioned between 20 mL of water and 20 mL of CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with 2 × 10 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford 38 mg (95%) of acetate **5a** as a pale yellow solid (~3:1 inseparable mixture of diastereomers). Recrystallization from Et_2O gave the major isomer as colorless needles, mp 140–141 °C: R_f 0.56 (3:1 Et_2O–hexanes); MS m/e 364 (M^+ – 76 [–CH_3COOH]); IR (neat) 2959, 2923, 2872, 1740, 1645, 1238, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 6.8 Hz, 3 H), 1.63 (m, 1 H), 1.75 (m, 1 H), 2.05 (s, 3 H), 2.09 (m, 2 H), 2.15 (d, J = 2.0 Hz, 3 H), 2.74 (m, 2 H), 3.23 (s, 3 H), 3.17–3.38 (m, 4 H), 3.96 (s, 3 H), AB system 4.08, 4.23 (J_{AB} = 11.6 Hz, 2 H), 5.88 (dd, J = 5.2, 8.4 Hz, 1 H).

Dithiolane Methylene Ester 7. A solution of 35 mg of furanoacetate **5a** in 3 mL of THF was treated with 3 mL of 1 N H_2SO_4, and the resulting solution was stirred at rt for 5 h. The reaction mixture was then diluted with 30 mL of water, neutralized with saturated aqueous $NaHCO_3$, and extracted with 4 × 10 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and chromatographed (silica gel, 1:1 Et_2O–hexanes) to afford 12 mg (43%) of methylene ester **7** as a viscous pale yellow oil that solidified on standing. Recrystallization from Et_2O–hexanes gave **7** as pale yellow needles, mp 107 °C: R_f 0.48 (1:1 Et_2O–hexanes); MS m/e 350 (M^+); IR (KBr) 2953, 2924, 2870, 1725, 1653, 1605, 1435, 1372, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, J = 6.4 Hz, 3 H), 2.08–2.20 (m, 2 H), 2.21 (s, 3 H), 2.39 (dd, J = 6.4, 16.8 Hz, 1 H), 2.47 (m, 1 H), 2.63 (dd, J = 7.6, 16.8 Hz, 2 H), 3.31–3.40 (m, 4 H), 3.69 (s, 3 H), 5.77 (d, J = 1.6 Hz, 1 H), 6.21 (d, J = 1.6 Hz, 1 H), 6.51 (t, J = 6.8 Hz, 1 H). Anal. Calcd for $C_{18}H_{22}O_3S_2$: C, 61.68; H, 6.33. Found: C, 61.64; H, 6.34.

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Supplementary Material Available: ^1H NMR spectra of **5**, **5a**, **7**, **27–37**, **40–43**, **46**, **48**, **18**, and **20** (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering formation.

Synthesis of Ketone and Alcohol Derivatives of Methylene-Bridged Polyarenes, Potentially New Classes of Active Metabolites of Carcinogenic Hydrocabons

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Methods for the syntheses of bridge ketone and alcohol derivatives of methylene-bridged polyarenes from the parent hydrocarbons are described. The polyarenes investigated include 4*H*-cyclopenta[*def*]phenanthrene (**1a**), fluorene (**2a**), 7*H*-benzo[*c*]fluorene (**3a**), 4*H*-cyclopenta[*def*]chrysene (**4a**), 11*H*-Benz[*bc*]aceanthrylene (**5a**), 10*H*-indeno[1,2,7,7a-*bcd*]pyrene (**6a**), 11*H*-dibenzo[*bc*,*l*]aceanthrylene (**7a**), 4*H*-fluoreno[4,4a,4b,5-*abc*]anthracene (**8a**), and 7*H*-dibenzo[*a*,*g*]fluorene (**9a**). The bridge ketone derivatives are most efficiently synthesized via treatment of the parent hydrocarbons with *n*-butyllithium and reaction of the resulting anionic intermediates with molecular oxygen. The direct formation of ketones rather than the expected hydroperoxides from reaction of the bridge anions with O_2 presumably involves intra- or intermolecular abstraction of a proton from the benzylic site of the intermediate by the peroxy anion leading to loss of hydroxide ion with formation of a carbonyl group. Yields are generally high except in the cases of **1a** and **4a**; the former affords as the principal product a dimeric alcohol arising from reaction of the anion of **1a** with the corresponding ketone **1b**. The related bridge alcohols are readily obtained in yields of 75–95% by reduction of the crude products from the preceding oxidations with $NaBH_4$.

Methylene-bridged polycyclic aromatic hydrocarbons (PAHs) are produced by combustion at moderate temperatures of PAHs that bear a bay region methyl group.[1,2] Relatively high ratios of bridged PAHs are present in crude petroleum,[1] and significant levels occur as environmental pollutants. Substantial levels of the ketone derivatives of bridged polyarenes are found in ambient urban air, in carbon black extracts, and in emissions from wood and coal combustion, municipal incineration, and diesel engines.[3,4]

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