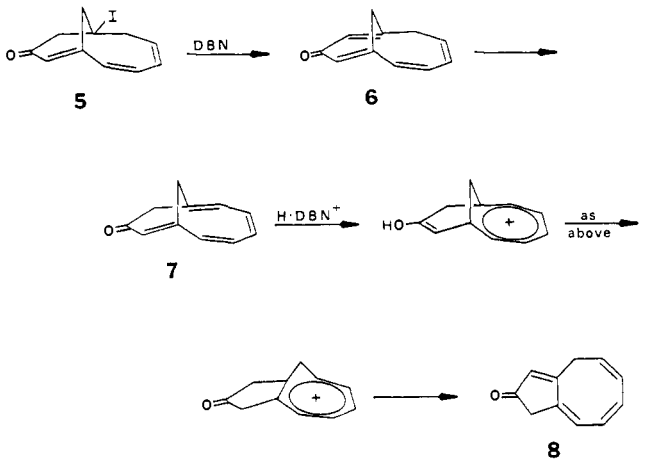
Scheme III



transfer from the conjugate acid of DBN generates a bridged homotropylium cation capable of circumambulatory rearrangement as in Schemes I and II. In agreement with this mechanism, it was found that rearrangement to **8** can be completely avoided by use of the stronger base (weaker conjugate acid) *i*-Pr_2NLi in THF. Under these conditions, however, only dimeric products could be isolated.

In sum, we have discovered two unexpected skeletal reorganizations which can reasonably be explained by circumambulatory rearrangements of homotropylium cations. Although lacking *direct* experimental evidence for the intermediates postulated in Schemes II and III, we believe our results strongly support the conclusions enumerated above.

Acknowledgments. Financial support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University of Nevada Research Advisory Board is gratefully acknowledged.

Supplementary Material Available: A more thorough discussion of the structural assignments for compounds **4** and **8**, including hydrogenation of **4** and Eu-shift studies on **8** (5 pages). Ordering information is given on any current masthead page.

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(9) 7-Iodobicyclo[5.3.1]undeca-1,3,5,9-tetraene (**3**) was prepared from tricyclo[5.3.1.$0^{1,7}$]undeca-2,4,9-triene[8] (I_2, $Cu(OAc)_2$, HOAc; then CF_3COOH, $CHCl_3$; 53% yield): ^1H NMR (CCL_4(Δ 2/5] (br d, J = 18 Hz, 1 H of $CH_2C{=}C$), 2.65 (d, J = 9 Hz, 1 bridging H), 2.92 (d, J = 9 Hz, 1 bridging H), 3.08 (d of t, J = 2, 18 Hz, 1 H of $CH_2C{=}C$), 5.3–5.6 (m, 1 vinyl H), 5.8–6.3 (m, 6 vinyl H's); IR (neat) 3070 (m), 2960 (m), 1625 (w), 1615 (w), 1405 (m), 1295 (m), 1129 (s), 962 (m), 906 (m), 868 (m), 786 (m), 740 (s), 722 (s), 696 (s, br) cm^{-1}; UV (hexane) λ_{max} 223 nm (ϵ 18 000), 319 (4600); mass spectrum parent peak, *m/e* 270.
(10) Bicyclo[6.3.0]undeca-1,3,5,8,10-pentaene (**4**):[15] NMR (CCl_4) δ 2.90 (d, J = 7 Hz, 2 H), 5.4–6.8 (m, 8 H); IR (neat) 3080 (m), 3000 (m), 1630 (m), 1495 (s), 1435 (m), 1340 (s), 1200 (s), 1110 (m), 782 (s), 765 (vs), 734 (s), and 694 cm^{-1} (m); UV (ethanol) λ_{max} 232 nm (ϵ 12 700), 255 (sh, 7200), 323 (6500), 420 (br sh, 270); mass spectrum parent peak, *m/e* 142. Of the seven possible double-bond isomers of this ring system, five have previously been reported: D. Schönleber, *Chem. Ber.*, **102**, 1789 (1969); H. Dürr and G. Scheppers, *ibid.*, **103**, 380 (1970).
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(12) Cyclopropane walk in the opposite direction would lead to the same product via a less fully conjugated tricyclic cation.
(13) 7-Iodobicyclo[5.3.1]undeca-2,4,10-trien-9-one (**5**) was prepared from tricyclo[5.3.1.$0^{1,7}$]undeca-2,4,9-triene[8] (I_2, $Cu(OAc)_2$, HOAc; then KOH, MeOH; then MnO_2, CH_2Cl_2; 41% overall yield): mp 85–87 °C; NMR (CCl_4) δ 2.04 (dd, J = 2, 17 Hz, 1 H), 2.5–2.8 (m, 3 H), 2.92 (d, J = 10 Hz, 1 bridging H), 3.42 (br d, J = 10 Hz, 1 bridging H), 5.76 (s, 1 H, H_{10}), 5.9–6.5 (m, 4 vinyl H's); IR (KBr) 1710 (m, sh), 1680 (vs), 1630 (m), 1570 (s), 1545 (m, sh), 1410 (m), 1305 (m), 1204 (m), 1180 (s), 874 (m), 851 (m) cm^{-1}; UV (hexane) λ_{max} 218, 304 (sh), 317, 332 (sh) nm; mass spectrum parent peak, *m/e* 286.
(14) Bicyclo[6.3.0]undeca-1,3,5,8-tetraen-10-one (**8**):[15] NMR (CCl_4) δ 2.92 (s, 2 H, $CH_2C{=}O$), 3.25 (d, J = 7 Hz, 2 H, $CH_2CH{=}C$, 5.5–6.25 (m, 6 vinyl H); IR (neat) 3040 (m), 2990 (w), 1670 (vs), 1560 (vs), 1425 (m), 1378 (m), 1220 (s), 1200 (s), 933 (m), 855 (m), 836 (m), 792 (m), 755 (vs), 719 (m) cm^{-1}; UV (hexane) λ_{max} 246, 303 nm; mass spectrum *m/e* (rel intensity) 158 (38), 157 (32), 131 (20), 130 (74), 129 (100), 128 (62), 127 (26), 117 (16), 116 (54), 115 (100), 103 (18), 91 (25), 77 (33).
(15) See paragraph at end of this paper regarding supplementary material.

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Stereospecific Total Synthesis of *dl*-Pentalenolactone

Sir:

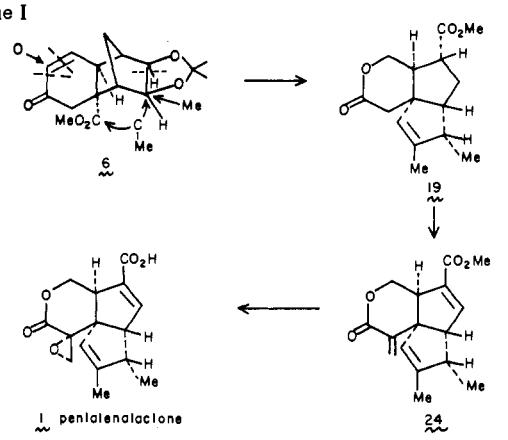
The sesquiterpene antibiotic, tumor inhibitory agent, pentalenolactone (**1**) is a member of a growing class of pentalenopyranones which includes pentalenolactone G[1a] and quadrone.[1b] It may also be perceived as bearing a structural similarity to the hirsutanes[1c] and to coriolin.[1d] The structure of pentalenolactone was deduced, by an Upjohn group[2a] by crystallographic analysis of its tetrahydrobromohydrin derivative, whose relationship to the natural product was ascertained by spectroscopic methods.[2b]

The challenges inherent in an enterprise of total synthesis directed at pentalenolactone are apparent on inspection of its compactly housed functionality, and recognition of its five centers of chirality. A stereospecific total synthesis of *dl*-pentalenolactone (**1**) is described herein.

Our operating strategy, rested on the assumption that prototropically dependent transformations of an intermediate such as **19** might be differentiable, so as to allow for its conversion to **24**, and that, in some way, the properly configured epoxymethylene group could be obtained from **24** (Scheme I). We thus sought an intermediate bearing, implicitly, the essential stereochemical information for reaching **19** through a variety of possibilities. We envisioned that compound **6** would fulfill these criteria and it was with the synthesis of this substance that we were first concerned.

Compound **2**,[3] itself readily available through the Diels–Alder reaction of dimethyl acetylenedicarboxylate with cyclopentadiene, was transformed into **3**[4,5] by the indicated steps[6–8] in 46% overall yield. Compound **3** now served as a dienophile toward the diene, **4**, in whose development our

Scheme I



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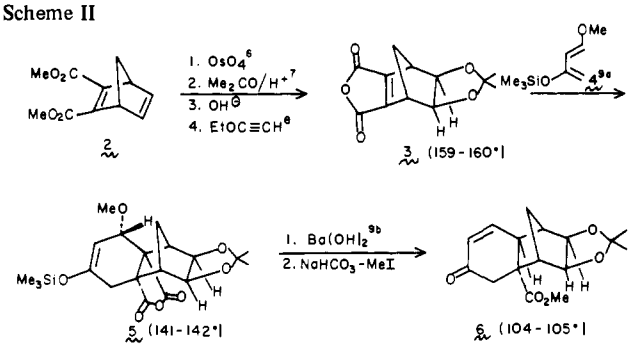
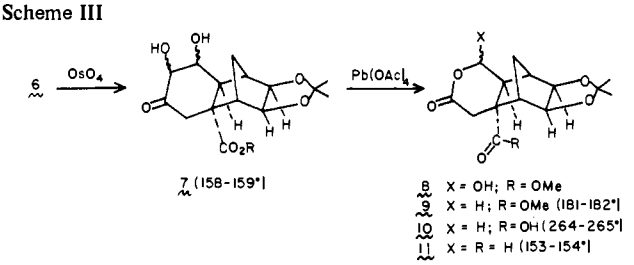
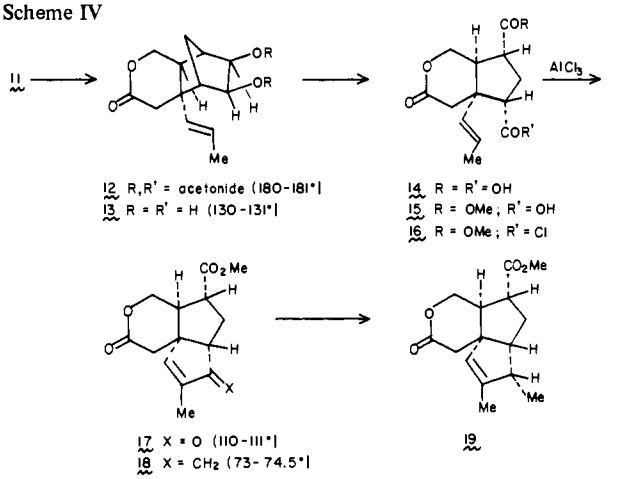
Scheme II



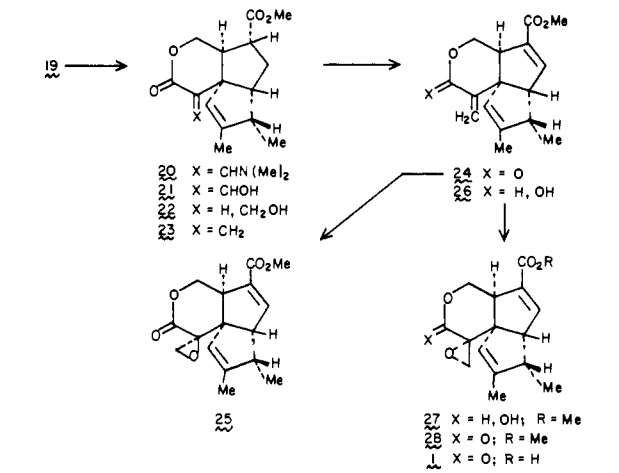
Scheme III



Scheme IV



Scheme V



laboratory had played some role in the past.[9a] Reaction of **3** + **4** was carried out in benzene under reflux, or at room temperature for 20 h. There was thus obtained a nearly quantitative yield of adduct **5**.[4] Treatment of **5** with barium hydroxide brought about its desired (and expected) unraveling to an enone, hydrolysis to a dicarboxylate, decarboxylation[9b] of the vinylogous (β-ketocarboxylate), and ketonization of the mechanistically likely homoannular dienolate intermediate, to a cis-fused, bridged hydrindenone. The resultant acid was converted, by methylation of its sodium salt, to ester **6**[4] in 80% overall yield from **3**. These transformations are summarized in Scheme II.

Attention was now directed to the A ring lactone. Osmylation[10] of **6** afforded, in nearly quantitative yield, the ketodiol **7**.[4] Reaction of **7** with lead tetraacetate in aqueous acetic acid[11] provided the pseudolactone **8**.[4] This was treated with 1 equiv of aqueous sodium hydroxide containing 6 equiv of sodium borohydride. Acidification gave lactone ester **9**[4] in 85% yield from **7**.

Saponification of **9** with 4.5 equiv of aqueous sodium hydroxide was accompanied by opening of the δ-lactone. Acidification afforded lactone acid **10**,[4] which was converted (thionyl chloride, benzene) to its acid chloride and, thence, by Rosenmund reduction[12] to aldehyde **11**[4] (94% yield from **10**). The δ-lactone was thus in hand, as shown in Scheme III.

Wittig olefination of **11** was carried out with 1.2 equiv of triphenylethylidenephosphorane in dimethoxyethane to afford (88%) **12**.[4] The stage was now set for disconnection of the two-carbon bridge. The acetonide was cleaved with aqueous HCl in dimethoxyethane under reflux, to afford a 96% yield of diol **13**.[4] Treatment of **13** with 1.5 equiv of Jones reagent afforded diacid **14**[4] which was selectively esterified (MeOH H_2SO_4) to provide **15**.[4] Treatment of **15** with thionyl chloride afforded **16**, which underwent Darzens-type acylation,[13] through reaction with aluminum chloride in CH_2Cl_2 at room temperature for 40 h. Enone **17**,[4] thus obtained in 44% from **13**, was converted (43%) by Wittig olefination[14a] to the methylenecyclopentene, **18**.[4] Catalytic reduction of **18** in the presence of the homogeneous Wilkinson catalyst, $(Ph_3P)_3RhCl$,[14b] afforded **19**[4] as the only detectable[15] product (see Scheme IV).

Treatment of **19** with bis(dimethylamino)-*tert*-butoxymethane (neat, 95 °C, 20 h)[16] afforded **20**[4] which, on exposure to moist silica gel, suffered conversion to **21**.[4] This was reduced ($NaBH_4$) to **22**,[4] which was transformed in the usual way[17] to the desired **23**[4] in 63% yield from **19**. The α-methylenelactone survived, reasonably well, the conditions ((i) LDA-THF, 76 °C; (ii) PhSeCl, 76 °C; (iii) $NaIO_4$-aqueous methanol) of Reich[18a] and Sharpless,[18b] which afforded **24** in 50% overall yield.

Treatment of **24**[19] with alkaline hydrogen peroxide[20] afforded only traces of pentalenolactone methyl ester (**28**). The major product (~5:1) was the epimeric β-epoxide **25**.[4,19] *We reasoned that the more stable anomer of a lactol derivable from* **24**, *might well have the hydroxyl group disposed on the convex* (α) *face of the oxahydrindanone system. So stationed, the hydroxyl might provide guidance for the introduction of the required* α*-epoxy linkage.*

Treatment of **24** with Dibah in toluene afforded allylic hemiacetal **26**.[4,21] Epoxidation according to Sharpless[22] (*t*-BuOOH; $VO(acac)_2$) followed by Jones oxidation yielded (45% from **26**) *dl*-**28**, whose chromatographic properties and solution infrared, mass, and 250-MHz NMR spectra were the same as those of authentic **28**. TLC and NMR analysis[15] of the crude reaction mixture indicated the possible presence of traces of **25**, inadequate for isolation. Hydrolysis (2.5 equiv of KOH, aqueous THF, room temperature, 20 h) of fully synthetic **28** afforded *dl*-pentalenolactone (**1**) whose chromatographic and spectral (infrared, NMR and mass) properties were the same as those of authentic pentalenolactone. The stereospecific total synthesis was thus complete (Scheme V).

Acknowledgments. This research was begun under Public Health Service Grant CA-12107-13 and completed under Public Health Service Grant AI-13939-02. NMR spectral facilities were supported by RR-00297-07. Authentic samples

of pentalenolactone as its benzylamine salt (see ref 19) were provided by the Pfizer Laboratories through the courtesy of Drs. Arthur Nagel and Robert Volkmann and by Professor David Cane of Brown University. The authors also acknowledge the help and advice of Dr. Milan Uskokovic of the Hoffmann-La Roche Laboratories in dealing with the Brederick reagent.

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(15) When the sequence **6** → **19** is carried through on chromatographically homogeneous and crystalline intermediates, which had not been recrystallized at each stage, there can be seen, in the NMR spectrum of **19**, traces of a contaminant which may contain a secondary methyl group. We have not yet established the stage(s) at which this imperfect stereospecificity arises, if, indeed, this be the nature of the trace contaminant. This contaminant, which is not seen chromatographically, persists until the end of the synthesis.
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(19) The early experiments on the epoxidation of **24** were, in fact, conducted on material obtained ($CrCl_2$) from naturally derived **28**. It was with this material that we found that direct epoxidation gave largely, the optically active iso compound **25** and it was with this material that we first developed the stereospecific route leading back to **28**. These steps were then repeated on fully synthetic (dl) **24** to complete the total synthesis. The iso compound, **25**, has not yet been prepared in the racemic series.
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Thione *S*-Methylides as Quasi-Wittig Reagents

Sir:

Betaines (**1**) derived from reaction of carbonyl functions with alkylidenesulfuranes (**2**) undergo an intramolecular displacement reaction leading to oxiranes,[1] while alkylidenephosphoranes (Wittig reagents) select the alternate closure to a hypervalent phosphorus intermediate which is penultimate to the alkene product.[2] The partition of **1** between two potential surfaces whose maxima are described by transition states **3** or **4** electronically[3] depends upon the magnitude of the first-order frontier interaction[4] (E) between the overlapping oxygen p orbital (p_o) and the terminus of the high lying σ^* orbital involved (S in **4**, C in **3**; Figure 1). Sulfonium ylide derived betaines might be encouraged to undergo intramolecular closure to yield a "Wittig" reaction if a low-lying π^* orbital was available at sulfur (Figure 1). This requirement would be met by betaines (**6**) generated from thione methylides[5] and appropriate carbonyl substrates. We now report that thione methylides can undergo Wittig-type reactions and stereochemically complement the Wadsworth–Emmons phosphonate modification of the Wittig reaction in substituted acrylic ester syntheses.

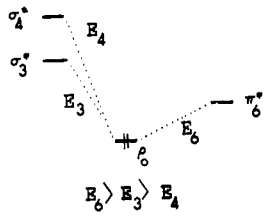
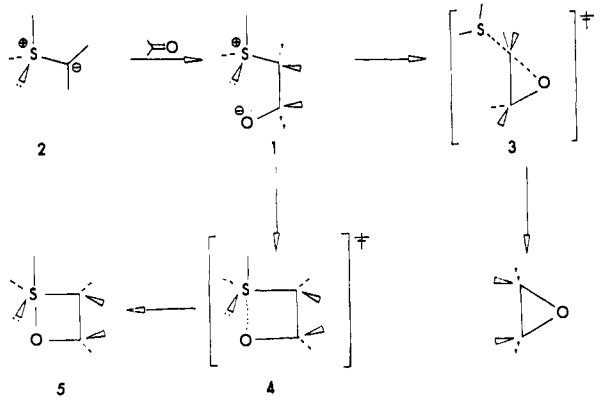
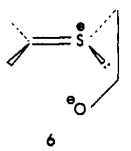
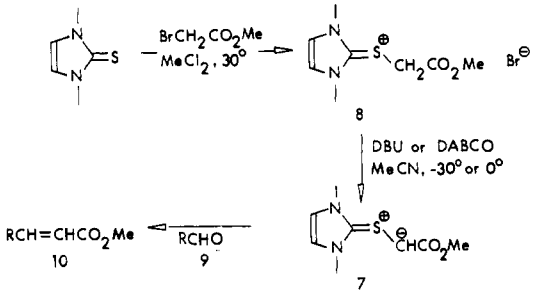


Figure 1. Frontier molecular orbitals involved in betaine decompositions.





The quasi-Wittig reagent, *N,N'*-dimethylimidazole-2-thione *S*-carbomethoxymethylide (**7**), is easily generated in situ from the corresponding salt **8**. Specifically, to a solution of 1 equiv of **8** in dry acetonitrile at 0 °C is added 1 equiv of base and after 5 min the carbonyl reagent is introduced. The resulting mixture is stirred for 10 min at 0 °C to complete the reaction. Table I summarizes the results including overall isolated yield of pure product and the isomer distribution for some representative



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