(Alpinum Isoflavone, 1). To a solution of 8 (250 mg) in dry, freshly distilled benzene (15 ml) was added DDQ (180 mg) and the resulting red solution was refluxed for 30 min, when the colorless hydroquinone separated out. The solid was filtered while hot and the residue was washed with hot, dry benzene. Removal of benzene gave a residue which was purified by column chromatography over silica gel. Elution with chloroform–ethyl acetate (9:1) and crystallization from the same solvent mixture gave 1 (160 mg) as colorless plates: mp 216° (lit.[2] mp 216°); intense green ferric reaction; R_f 0.56 (solvent B); nmr δ 1.48 [s, 6, $(CH_3)_2C<$], 5.64, 6.78 (2 d, J = 10 Hz, 2, 2 olefinic H of pyran ring), 6.36 (s, 1 H in position 8), 6.87 (d, J = 9 Hz, 2 H in positions 3′ and 5′), 7.38 (d, J = 9 Hz, 2 H in positions 2′ and 6′), and 7.85 (s, 1 H in position 2); mass spectrum m/e 336, 321, 295, 203, and 118.

Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.4; H, 4.8. Found: C, 70.9; H, 5.2.

The above data are completely identical with those reported[2] for natural alpinum isoflavone. This was confirmed by comparing the ir spectrum in detail with one, kindly supplied by Professor Scheinmann, for a natural sample. They were completely identical.

Further, the acetate prepared by the acetic anhydride–pyridine method has the same properties as reported for the natural sample. Thus it crystallized from ethyl acetate–light petroleum mixture as colorless needles: mp 219°; R_f 0.42 (solvent B); nmr δ 1.50 [s, 6, $(CH_3)_2C<$], 2.30, 2.44 (2 s, 6, $-OCOCH_3$), 5.73, 6.52 (2 d, J = 10 Hz, 1 H, 2 olefinic H of pyran ring), 7.50 (d, J = 9 Hz, 2 H in positions 2′ and 6′), and 7.80 (s, 1 H in position 2).

Anal. Calcd for $C_{24}H_{20}O_7$: C, 68.6; H, 4.8. Found: C, 68.1; H, 5.3.

5,4′-Dihydroxy-8-prenyl-6″,6″-dimethylpyrano[2″,3″:7,6]-isoflavone (Warangalone, 3) and 5,4′-Dihydroxy-6-*C*-prenyl-6″,6″-dimethylpyrano[2″,3″:7,8]isoflavone (Osajin, 2). 5,7,4′-Trihydroxy-6,8-diprenylisoflavone (**7**, 0.5 g) on similar treatment with DDQ gave a residue (0.3 g) which proved to be a mixture on tlc. It was purified by column chromatography over silica gel. Elution with benzene–chloroform (94:6) gave the first few fractions as a single entity which crystallized from methanol as cream needles (100 mg): mp 160–163° (lit.[4] mp 163–165°); intense green ferric reaction; R_f 0.56 (solvent B); mass spectrum m/e 404, 389, 351, 349, 231, 181, 121, 118, and 55; ir ν_{max} 3600, 3300, 1660, 1625, and 1595 cm^{-1}.

Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.2; H, 6.0. Found: C, 73.9; H, 6.4.

These data agree with those described for natural warangalone[4] (**3**), although direct comparison could not be made because of nonavailability of the sample.

The later fractions eluted by benzene–chloroform (9:1) were found by tlc to be a mixture of compounds. They were separated by fractional crystallization from light petroleum (bp 60–80°) when **2** was obtained as pale yellow crystals (50 mg): mp 190–192° (lit.[3] mp 190–192.5°); intense green ferric reaction; R_f 0.52 (solvent B); ir ν_{max} 3390, 1645, 1615, 1580 cm^{-1}; mass spectrum m/e 404, 389, 351, 348, 333, 231, 181, 121, and 56.

Anal. Calcd for $C_{25}H_{24}O_5$: C, 74.2; H, 6.0. Found: C, 73.9 H, 5.6.

These data were found identical with those described for natural osajin.[3] However, direct comparison could not be made because of nonavailability of the sample.

Acknowledgments. The authors thank Professor T. R. Seshadri for kindly supplying samples of 6,8-diprenylbiochanin A and 5-hydroxy-7,4′-dimethoxy-6-*C*-prenylisoflavone. Their thanks are also due to Dr. F. Scheinmann for supplying the ir spectrum of alpinum isoflavone.

Registry No.—**1**, 34086-50-5; **1** acetate, 51472-54-9; **2**, 482-53-1; **3**, 4449-55-2; **5**, 446-72-0; **6**, 51225-25-3; **7**, 51225-28-6; **7** acetate, 51225-26-4; **8**, 51225-30-0; **8** acetate, 51225-29-7; **9**, 51225-27-5; **10**, 27762-81-8; **11**, 27762-83-0; **12**, 27762-86-3.

References and Notes

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(9) All melting points were taken on a Büchi melting point apparatus and are uncorrected. Tlc was carried out on silica gel plates using one of the following solvent systems: (A) benzene; (B) benzene–ethyl acetate (75:25); (C) toluene–ethyl formate–formic acid (5:4:1); and (D) benzene–ethyl acetate (1:1). Spraying reagent was either 10% aqueous H_2SO_4 or 10% alcoholic $FeCl_3$. Column chromatography was carried out using silica gel supplied by NCL Poona. Ir spectra were measured in Nujol mulls using a Perkin-Elmer Infracord spectrophotometer. Nmr spectra were determined in $CDCl_3$ unless otherwise stated, using a 60-MHz spectrophotometer. Chemical shifts are mentioned in parts per million ppm downfield from TMS used as internal standard. Mass spectra were taken with a MS-72 spectrometer, 70 eV ionizing voltage, 900 × 10 trap current, and 2 kV accelerating voltage.

A New Method for the Synthesis of Enones. Total Synthesis of (±)-Mayurone and (±)-Thujopsadiene

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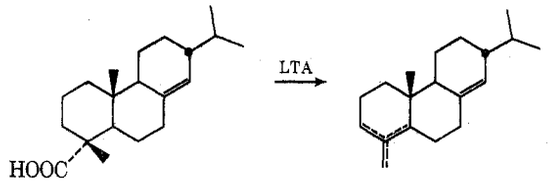
When a β-carboxy ketone is treated with lead tetraacetate, oxidative decarboxylation occurs, and the corresponding α,β-unsaturated ketone is produced in high yield. By use of this method, both *cis*- and *trans*-methyloctalones **10** and **8** are prepared. In addition, the method can be used to synthesize cross-conjugated dienones such as **6**, and phenols such as tetrahydro-β-naphthol (**17**) from the corresponding β-carboxy-α',β'-unsaturated ketones. Use of the method in natural product synthesis is illustrated in a total synthesis of (±)-mayurone (**18**). Mayurone is then further transformed into thujopsadiene (**20**) and thujopsene (**19**).

The oxidative decarboxylation of carboxylic acids is a well-known reaction.[1] It has, however, received little synthetic attention owing probably to the fact that a multiplicity of products usually result. Experimentally, the best method for effecting the reaction is due to Kochi,[2] who showed that good yields of olefins can be obtained by employing lead tetraacetate (LTA) as the oxidant in the presence of cupric ion. In the case of primary carboxylic acids. good yields of terminal olefins result. The reaction presumably proceeds *via* the following pathway.

$$RCH_2CH_2COOH \xrightarrow{LTA} RCH_2CH_2C(=O)Pb(OAc)_3 \xrightarrow{-CO_2}$$

$$RCH_2CH_2\cdot \xrightarrow{Cu^{2+}} RCH_2CH_2^+ \xrightarrow{-H^+} RCH{=}CH_2$$

When secondary or tertiary acids are used however, the carbonium ion intermediate can, and usually does, give mixtures of products. For example, in Johnson's synthesis of fichtelite from abietic acid,[3] oxidative decarboxylation of 1 with LTA in pyridine gave a mixture of all three possible olefinic products.



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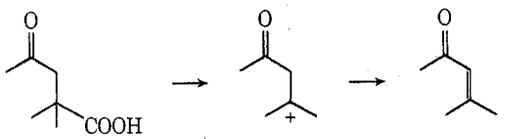
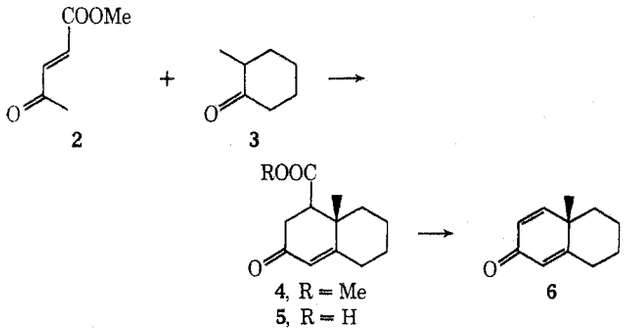
We felt that if the carboxy function were in a position γ to a second carbonyl group, then one of the possible olefinic products would be more stable than the others owing to conjugation, and should be the exclusive product formed.[4]



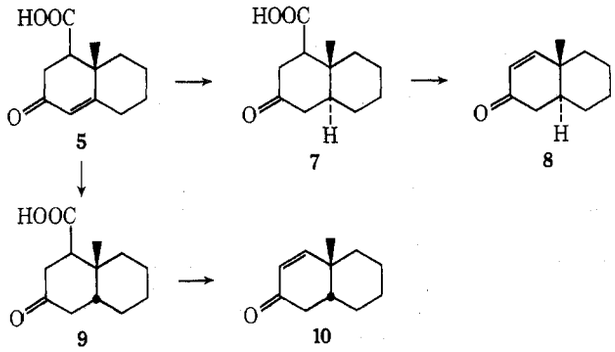
The product of such a sequence would be an α,β-unsaturated carbonyl compound, and synthesis by such means could provide an important route to some otherwise difficultly accessible molecules. In this paper, we wish to report that this sequence does in fact proceed in excellent yield, and to illustrate its utility in a total synthesis of (±)-mayurone (18).

Model Studies. We chose first to examine the reaction of 4-carboxy-10-methyloctalone (5) as a model compound. Ester 4 was readily prepared by Robinson annelation of 2-methylcyclohexanone with ethyl 4-oxo-2-pentenoate. Interestingly, we were completely unable to effect this reaction under a variety of basic conditions. Our recent acid-catalyzed modification of the Robinson reaction,[5] however, went smoothly and in one step to yield the desired octalone (4). Oxidative decarboxylation of 5 then gave the known[6] cross-conjugated cyclohexadienone 6 as the sole product in 78% yield. Thus not only does the key oxidative decarboxylation work well, this simple two-step annelation–decarboxylation sequence appears to be an attractive method for the synthesis of cross-conjugated cyclohexadienones. Such dienones have been prepared by dehydrohalogenation of dibromo ketones,[7] by dehydrogenation of a cyclohexenone with DDQ,[8] and by condensation of α-formylcyclohexanones with acetone.[6] This new method is certainly competitive in its simplicity.

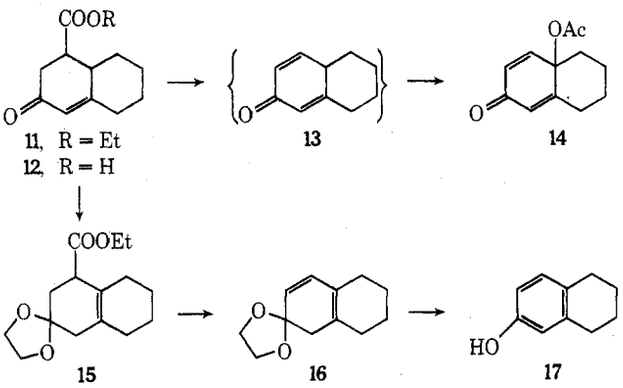


An important feature of this new enone synthesis is that the double bond is present in the precursor only in a protected, incipient form, thus allowing transformations to be carried out in other parts of the molecule which might not otherwise be possible. For example, if one wanted to obtain the simple Δ^1 enone, one could reduce the Δ^4 double bond of 5 and then generate the Δ^1 double bond by oxidative decarboxylation. In fact, we have been able to obtain both the trans-fused isomer 8 and the cis-fused isomer 10 by employing suitable methods of reduction. The trans-fused enone 8 is a known compound[9] and is generally obtained by a sequence involving lithium–ammonia reduction of the corresponding Δ^4 enone, bromination at C-2, and dehydrohalogenation. We found that enone acid 5 could be readily reduced with lithium in liquid ammonia in 97% yield, and that the resulting acid decarboxylated in 89% yield to give the known enone 8.

The cis-fused isomer 10 is currently available only with difficulty.[10] The problem in synthesizing it by conventional methods is that the corresponding saturated ketone cannot be selectively brominated at C-2, and a multistep alternative route must be employed. We encountered no difficulty in using our method, however. Acid 5 was reduced over a palladium on charcoal catalyst to cis acid 9 in 97% yield. Oxidative decarboxylation gave enone 10 in 92% yield.



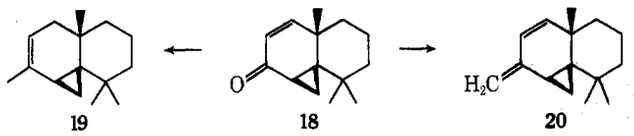
It would also be of potential synthetic interest to examine the reactions of the corresponding demethyl compound 12. One can imagine that decarboxylation of 12 should lead to a dienone, which would then tautomerize to a phenol. Thus the net overall effect of the annelation–decarboxylation sequence would be to build a new aromatic ring onto the existing system—a process which is difficult to effect at present. One potential difficulty with the scheme, however, is the fact that phenols themselves react rapidly with LTA[11] and might not survive reaction conditions. In fact, when acid 12 was treated with LTA, a mixture of products was obtained from which acetoxydienone 14 could be isolated (30%), but none of the desired phenol was obtained. When, however, keto ester 11 was first ketalized, followed by a saponification, oxidative decarboxylation, and acid treatment, the sensitive phenol 17 was isolated in 40% overall yield.



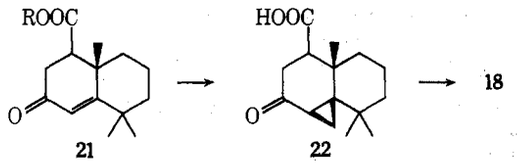
The value of the oxidative decarboxylation of γ-keto acids to enones had therefore been established, and we next sought to use the method in a synthetic scheme.

Synthesis of Mayurone. Mayurone (18) is a tricyclic, 14-carbon sesquiterpenoid whose structure was deter-

mined simultaneously by two groups[12] in 1965. Mayurone may be considered to occupy a central place in the thujopsane class of sesquiterpenes from a synthetic standpoint, because from it both of the other members of the class, thujopsene[13] (19) and thujopsadiene[14] (20), can be derived by simple transformations. Of the three sesquiterpenoids, however, only thujopsene itself has been synthesized,[15] neither mayurone nor thujopsadiene having been reported.

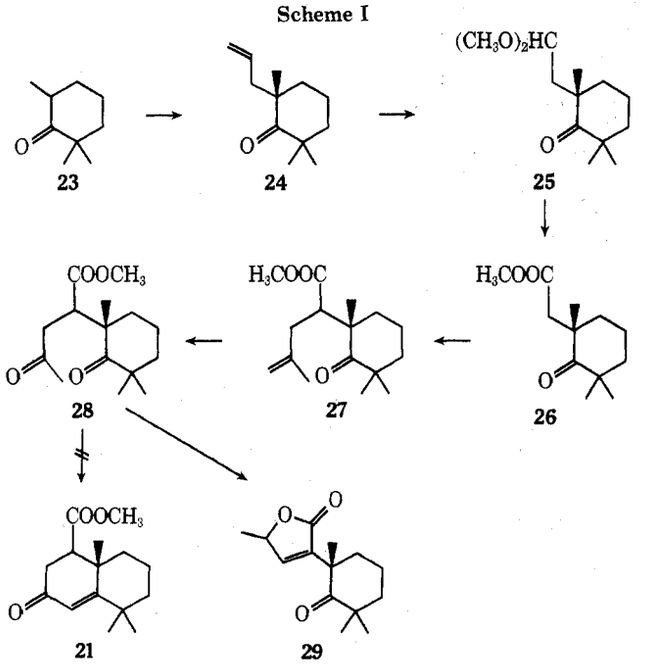


We anticipated that mayurone would make a particularly attractive demonstration of the new enone synthesis in that it may be considered a cross-conjugated cyclohexadienone derivative in which one of the double bonds has undergone further transformation. Thus one precursor might be an enone ester such as 21. One could imagine transforming the enone into the requisite cyclopropyl ketone, and then introducing the double bond by oxidative decarboxylation in the final synthetic step.



The most straightforward synthesis of 21 would involve Robinson annelation of 2,2,6-trimethylcyclohexanone with ethyl 4-oxo-2-pentenoate. Although trimethylcyclohexanone is a strongly hindered ketone, there is some precedent for the desired reaction in the report that cyanoethylation of 23 is successful.[15c] Nevertheless, the annelation failed under a variety of both acidic and basic conditions. After considerable experimentation, a precursor to 21 was synthesized by the route shown in Scheme I. Thus, alkyl-

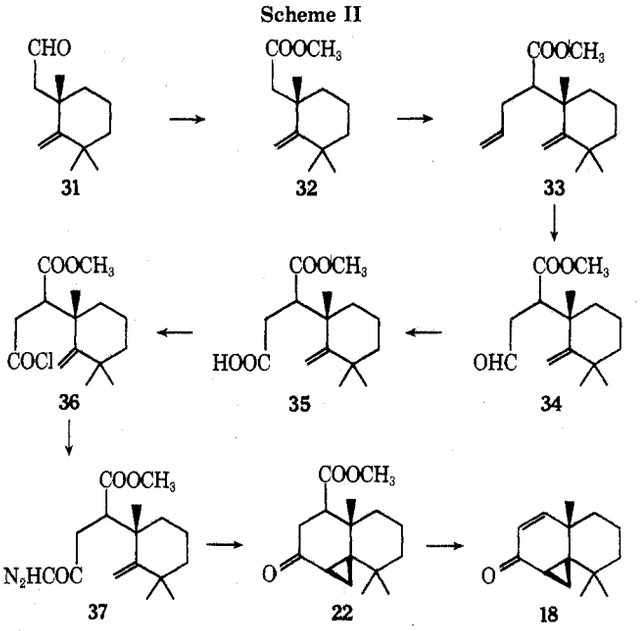
Scheme I



ation of trimethylcyclohexanone with allyl bromide followed by ozonolysis in methanol gave ketone acetal 25. Further ozonolysis[16] of 25 gave keto ester 26. Alkylation of the ester enolate of 26 with methallyl chloride and subsequent ozonolysis led to diketo ester 28, the immediate aldol precursor of 21. All attempts to cyclize 25 under both acidic and basic conditions led only to butenolide 29, however, and so a different route to mayurone was sought.

In their recent synthesis of thujopsene, Mori and Matsui[15b] effected an intramolecular α-ketocarbene–olefin insertion to generate dihydromayurone. By analogy, we felt that cyclization of diazo ketone 37 should lead directly to the mayurone precursor 22. The successful synthesis is shown in Scheme II.

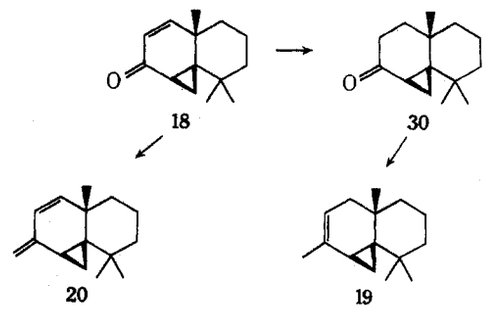
Scheme II



The known aldehyde 31, prepared by Buchi's method,[15b] was oxidized with silver oxide[17] to the corresponding acid, which was converted (K_2CO_3–CH_3I) to the methyl ester 32 (75%). Allylation of the ester enolate[18] of 32 then gave 33 (95%), which was selectively cleaved at the less hindered double bond by the $NaIO_4$–OsO_4 procedure of Pappo and Lemieux.[19] Although direct oxidation of 33 to acid 35 was attempted by the Lemieux–von Rudloff procedure,[20] no selectivity was observed. Aldehyde 34 was oxidized with silver oxide to succinic half ester 35, which was converted by standard methods to diazo ketone 37. This diazo ketone, when refluxed with Cu–$CuSO_4$ catalyst in cyclohexane, smoothly decomposed to give the desired tricyclic keto ester 22, the immediate precursor of mayurone.

Saponification of 22 followed by oxidative decarboxylation with LTA gave pure (±)-mayurone in 92% yield (13% overall from 31). The synthetic material was identical with natural mayurone[21] by direct comparison of spectral properties and gas chromatographic behavior.

We were now in a position to synthesize the remaining members of the thujopsane class. (±)-Mayurone was converted by catalytic hydrogenation over a palladium on charcoal catalyst to dihydromayurone (30), identified by comparison with an authentic sample.[22] Dihydromayu-



rone has been transformed into thujopsene by three different workers.[15a-c] Treatment of mayurone with methyllithium followed by mildly acidic work-up gave (±)-thujopsadiene[23] (20), whose ir and nmr spectra were identical with those of the natural material.

Summary. We believe that we have demonstrated by this work that the oxidative decarboxylation of γ-keto acids is a useful procedure, both for the synthesis of α,β-unsaturated ketones and for the construction of phenol rings onto existing frameworks. By using the new method, two previously unsynthesized natural products, mayurone and thujopsadiene, have become accessible. We are continuing this work on other γ-carbonyl acid systems which might be of synthetic use.

Experimental Section

Ethyl 4-Oxo-2-pentenoate (2). Ethyl levulinate (39 ml, 0.27 mol) was dissolved in 200 ml of $CHCl_3$ under nitrogen at room temperature, and a solution of bromine (16.5 ml, 0.30 mol) in 35 ml of $CHCl_3$ was slowly added over a 1-hr period while the reaction was stirred magnetically. The reaction mixture was then cooled in an ice bath, and triethylamine (120 ml) was added over a 1-hr period. After further stirring for 1 hr at 0°, the dark reaction mixture was transferred to a separatory funnel and washed sequentially with water, 1 *N* HCl, and brine. The organic layer was dried ($MgSO_4$), concentrated, and distilled to give 19 g (55%) of product: bp 65° (0.2 mm); ir (film) 1720, 1675 cm^{-1}; nmr (CCl_4) δ 1.43 (3 H, t, J = 6 Hz), 2.29 (3 H, s), 4.12 (2 H, q, J = 6 Hz), 6.61 (2 H, d of d, J = 15 Hz).

Octalone (4). Ethyl 4-oxo-2-pentenoate (14.2 g, 0.1 mol), 2-methylcyclohexanone (11.2 g, 0.1 mol) and *p*-toluenesulfonic acid (0.57 g, 0.003 mol) were dissolved in 200 ml of benzene and placed in a 500-ml flask fitted with a Dean-Stark water separator. The reaction was refluxed vigorously for 48 hr, then cooled and washed with saturated $NaHCO_3$. After drying ($MgSO_4$), the benzene solution was concentrated and distilled through an oil-jacketed still to give 4.83 g (21%) of octalone (4): bp 120° (10^{-3} mm); ir (film) 1730, 1665, 1630 cm^{-1}; nmr (CCl_4) δ 1.21 (3 H, s), 1.25 (3 H, t, J = 6 Hz), 4.14 (2 H, q, J = 6 Hz), 5.64 (1 H, s); 2,4-DNP mp 131°. *Anal.* Calcd for $C_{19}H_{22}N_4O_6$: C, 57.69; H, 5.81. Found: C, 57.62; H, 5.64.

Enone Acid 5. Ester 4 (2.36 g, 0.01 mol) was dissolved in 50 ml of methanol under nitrogen, and 20% aqueous NaOH (10 ml) was added. After refluxing for 3 hr, the solution was poured into a separatory funnel and extracted with ether. The aqueous layer was acidified and further extracted with methylene chloride. These extracts were combined, dried ($MgSO_4$), and concentrated to yield acid 5 (2.00 g, 96%), mp 198–201° dec.

Representative Procedure for Oxidative Decarboxylation. Dienone 6. Acid 5 (210 mg, 1.0 mmol), pyridine (300 μl), cupric acetate (50 mg), and benzene (8 ml) were stirred at room temperature until the mixture became a homogeneous green solution. LTA (1.3 g, 3.0 mmol) was added and the reaction mixture was stirred for 2 hr in the dark under a nitrogen atmosphere. The reaction mixture was then heated to 80°, at which point vigorous gas evolution occurred. After 1 hr, the reaction mixture was cooled and filtered through a small mat of alumina to remove inorganic residues. A small amount of hot methanol was used to aid the transfer. After the alumina was washed with 50 ml of ether, the organic filtrates were combined, washed with water, 1 *N* HCl, and saturated $NaHCO_3$, then dried ($MgSO_4$) and concentrated. Distillation of the residue gave 143 mg (88%) of dienone 6: ir (film) 1655, 1630, 1590 cm^{-1}; nmr (CCl_4) δ 1.25 (3 H, s), 6.30 (3 H, m).

Dienone 6 was further identified by rearrangement by known procedure[6] to 1-acetoxy-4-methyl-5,6,7,8-tetrahydronaphthalene, mp 80–81° (lit.[6] mp 82°).

Trans-Fused Octalone 8. Unsaturated keto acid 5 (233 mg, 1.11 mmol) was dissolved in 50 ml of dry liquid ammonia, and lithium wire (0.2 g, 30 mmol) was added in small pieces. After stirring for 1 hr, the ammonia was allowed to evaporate, and the residue was partitioned between 2 *N* HCl and chloroform. The chloroform extracts were dried ($MgSO_4$) and concentrated to give 211 mg of crude acid 7.

This acid was subjected to the usual LTA oxidative decarboxylation as described above to give, after distillation, 158 mg (86% overall) of octalone 8: ir (film) 1670 cm^{-1}; nmr (CCl_4) δ 1.23 (3 H, s), 6.26 (2 H, dd, J = 10 Hz); 2,4-DNP mp 161–162° (lit.[9] mp 161–162°).

Cis-Fused Octalone 10. Keto acid 5 (220 mg, 1.06 mmol) was dissolved in 15 ml of ethanol and hydrogenated at atmospheric pressure over a 10% palladium on charcoal catalyst (50 mg). Reaction was complete after 2 hr, and the reaction mixture was filtered and concentrated to give 210 mg of crude solid product. This crude material was subjected to LTA decarboxylation as described above to give, after distillation, 154 mg (89% overall) of enone 10: ir (film) 1680, 1605 cm^{-1}; nmr (CCl_4) δ 1.08 (3 H, s), 6.30 (2 H, dd, J = 11 Hz).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.82. Found: C, 80.41; H, 9.85.

Acetoxydienone 14. Keto acid 12[24] (194 mg, 1.0 mmol) was subjected to the usual LTA oxidative decarboxylation as described above (45°, 15 min). After work-up, the reaction product consisted of 58 mg (30%) of material identified spectrally as 14: ir (film) 1725, 1660 cm^{-1}; nmr (CCl_4) δ 2.03 (3 H, s), 5.85 (1 H, s), 6.27 (2 H, dd, J = 8 Hz).

Tetrahydronaphthol 17. Keto ester 11[24] (10 g, 0.045 mol), ethylene glycol (4 mol), and *p*-toluenesulfonic acid (100 mg) were dissolved in 200 ml of benzene and refluxed for 16 hr in a flask fitted with a Dean-Stark water separator. The benzene solution was then cooled and washed with saturated $NaHCO_3$. After drying ($MgSO_4$), the solution was concentrated to give crude ketal. Without purification, this ketal was dissolved in 100 ml of ethanol. Aqueous NaOH (10% solution, 20 ml) was added, and the reaction mixture was refluxed for 3 hr under nitrogen. The solution was diluted with water and washed with ether. The aqueous layer was acidified and extracted with methylene chloride. These extracts were combined, dried ($MgSO_4$), and concentrated to give 10.2 g (95% overall) of crude waxy ketal acid: ir (film) 1710 cm^{-1}; nmr ($CDCl_3$) δ 4.11 (4 H, s), 10.12 (1 H, s), no vinyl protons.

This ketal acid (957 mg, 4.0 mmol) was submitted to LTA decarboxylation by the procedure previously described to give a dark oil which was immediately dissolved in 30 ml of THF and 4 ml of 6 *N* HCl. After 2 hr at 65°, the reaction mixture was cooled, diluted with water, and extracted with ether. These combined ether extracts were extracted with 5% NaOH. The basic extracts were acidified to pH 1 and extracted with chloroform. After drying ($MgSO_4$) the chloroform solution was concentrated to give the air-sensitive tetrahydronaphthol 17.

For product identification, naphthol 17 was dissolved in 40 ml of acetone. Anhydrous K_2CO_3 (2 g) and methyl iodide (5 ml) were added, and the reaction mixture was refluxed for 6 hr under nitrogen. The reaction mixture was diluted with water and extracted with hexane. The hexane extracts were dried (Na_2SO_4), concentrated, and distilled to give 308 mg (49%) of 2-methoxy-5,6,7,8-tetrahydronaphthalene: bp 105° (0.3 mm); ir (film) 1602, 1500, 1038 cm^{-1}; nmr (CCl_4) δ 1.70 (4 H, m), 2.62 (4 H, broad s), 3.60 (3 H, s), 6.64 (3 H, m); mass spectrum m/e 162 (P^+).

2-Allyl-2,6,6-trimethylcyclohexanone (24). Potassium metal (4.05 g, 0.104 mol) was dissolved in 70 ml of dry *t*-BuOH under a nitrogen atmosphere, and 2,2,6-trimethylcyclohexanone (10.8 ml, 0.070 mol) was added. After stirring for 10 min, allyl bromide (20 ml) was added, and stirring was continued for 1 hr at room temperature and 10 hr at reflux. After concentration at the rotary evaporator, the reaction mixture was partitioned between ether and water. The ether layer was dried ($MgSO_4$), concentrated, and distilled to yield 7.95 g (45%) of 24: ir (film) 3080, 1695, 1630, 910 cm^{-1}; nmr (CCl_4) δ 1.01 (6 H, s), 1.03 (3 H, s) 4.67–5.84 (3 H, m).

Methyl 2-(2,6,6-Trimethylcyclohexanone)acetate (26). Keto olefin 24 (6.85 g, 0.038 mol) was dissolved in 90 ml of 2:1 (v/v) methanol–methylene chloride. The solution was cooled to −78° and a stream of ozone was passed through until the solution turned blue. After removal of excess ozone, methyl sulfide (15 ml) was added and the resultant solution was allowed to warm to room temperature. After stirring for 12 hr, the solution was washed with water, dried ($MgSO_4$), and concentrated.

The residue was dissolved in 50 ml of methylene chloride and again ozonized at −78° for 13 hr. After removal of excess ozone, the reaction mixture was concentrated and distilled to give 5.74 g (70%) of keto ester 26; ir (film) 1735, 1695 cm^{-1}; nmr (CCl_4) δ 1.27 (9 H, s), 2.50 (2 H, dd, J = 16 Hz).

Keto Ester 27. Cyclohexylisopropylamine (4 ml) was dissolved in 25 ml of THF at 0°, and *n*-BuLi (12.5 ml, 1.85 *M* solution) was introduced *via* syringe. After stirring for 15 min under nitrogen atmosphere, keto ester 26 (1.37 g, 6.5 mmol) was added, and stirring was continued for 15 min. Methallyl chloride (10 ml) was added and the reaction mixture was stirred for 1 hr at 0°, then

poured into water and extracted with hexane. The extracts were washed with dilute HCl, then dried ($MgSO_4$) and concentrated. The residue (1.68 g, 97%) was found to be approximately 95% pure by vpc analysis, and was used without further purification: ir (film) 3075, 1735, 1695, 887 cm^{-1}; mass spectrum m/e 266 (P^+).

Diketo Ester 28. Keto ester **27** (2.16 g, 7.9 mmol) was dissolved in 50 ml of methylene chloride and ozonized at −78° until the solution turned blue. After removal of excess ozone, dimethyl sulfide (10 ml) was added and the mixture was allowed to stand for 12 hr at room temperature. The mixture was diluted with hexane, washed with water, dried (Na_2SO_4), and concentrated to give 2.14 g (98%) of **28**, pure by vpc analysis.

Attempted Cyclization of 28. Crude **28** (450 mg, 1.68 mmol) was dissolved in 10 ml of 0.1 *N* KO-*t*-Bu in *t*-BuOH, and the mixture was refluxed for 2 hr, then cooled and diluted with water. The solution was then extracted with ether, and the extracts were dried (Na_2SO_4) and concentrated. Spectral analysis of the product showed it to be butenolide **21**: ir (film) 1745, 1695, 1650 cm^{-1}; mass spectrum m/e 236 (P^+).

Ester 32. Aldehyde **31**[15d] (9.0 g, 0.05 mol) was dissolved in 250 ml of 95% ethanol under nitrogen, and a solution of 18.3 g of $AgNO_3$ in 25 ml of water was added. A solution of 21 g of KOH in 350 ml of H_2O was added over 45 min with cooling to keep the temperature below 30°. After 2 hr, the reaction mixture was filtered, and the filtrate was acidified and extracted with chloroform. The extracts were dried (Na_2SO_4) and concentrated to yield an orange oil which was immediately esterified.

The crude acid was dissolved in 300 ml of acetone under nitrogen. Anhydrous K_2CO_3 (10.5 g) and methyl iodide (25 ml) were added, and the solution was refluxed for 6 hr. The mixture was cooled, filtered, and concentrated. The residue was partitioned between hexane and saturated $NaHCO_3$, and the organic layer was then dried (Na_2SO_4) and concentrated to give a yellow oil (7.9 g, 75% overall). The analytical sample was prepared by preparative vpc: ir (film) 3120, 1735, 903 cm^{-1}; nmr (CCl_4) δ 1.18 (6 H, s), 1.28 (3 H, s), 2.50 (2 H, s), 3.60 (3 H, s), 5.00 (2 H, d, J = 5 Hz).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.15; H, 10.35.

Alkylation of 32. Isopropylcyclohexylamine (4 ml) was dissolved in 30 ml of THF at 0° under N_2, and *n*-BuLi (9.5 ml of 2.1 *M* solution) was added with stirring. After 15 min, ester **32** (4.2 g, 20 mmol) in 5 ml of THF was added. After stirring for 30 min at 0°, allyl bromide (8 ml) in 12 ml of HMPA was added and the reaction mixture was stirred for 1 hr at room temperature. The reaction mixture was diluted with hexane and washed with dilute HCl, then dried (Na_2SO_4) and concentrated to give 4.7 g (95%) of product **33**. An analytical sample was prepared by preparative vpc: ir (film) 3100, 1735, 903, 840 cm^{-1}.

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.80; H, 10.23.

Oxidation of 33 to Acid 35. Olefin **33** (9.3 g, 0.037 mol) was dissolved in a mixture of 375 ml of dioxane and 125 ml of water under nitrogen, and a solution of OsO_4 in benzene (1.5 ml of 1 *M* solution) was added. After 25 min of stirring at room temperature, powdered $NaIO_4$ (61 g, 7.5 equiv) was added in small portions. Stirring was continued for a further 2.5 hr. The mixture was then filtered and washed with brine. After the brine was back extracted with ether, the organic layers were combined, dried (Na_2SO_4), and concentrated to give an orange oil which was oxidized without further purification: ir (film) 2730, 1725, 1615 cm^{-1}.

This crude aldehyde (**34**) was dissolved in 150 ml of ethanol under a nitrogen atmosphere. To this was added a solution of $AgNO_3$ (11 g, 0.070 mol) in 15 ml of water. A solution of KOH (9 g) in 150 ml of water was slowly added over 1 hr, and after an additional 2 hr of stirring, the reaction mixture was filtered free of inorganic salts and diluted with 200 ml of water. After two washes with ether, the basic aqueous layer was acidified with HCl and extracted several times with chloroform. These extracts were combined, dried (Na_2SO_4), and concentrated to give 7.63 g (74% overall) of a colorless, semicrystalline mixture of diastereomers of **35**: ir ($CHCl_3$) 2950, 1735, 1705, 1615 cm^{-1}; nmr ($CDCl_3$) δ 1.16 and 1.22 (two singlets, 9 H), 3.67 (3 H, s), 5.10 (2 H, d, J = 12 Hz); mass spectrum m/e 268 (P^+, weak).

Cyclization of Acid 35 to Cyclopropyl Ketone 22. Acid **35** (1.6 g, 0.006 mol) was dissolved in 50 ml of dry benzene under nitrogen, and 2.7 ml of oxalyl chloride was added. After stirring for 1 hr at room temperature, volatile material was removed at the rotary evaporator to give crude acid chloride **36**: ir (film) 1790, 1735, 1620 cm^{-1}.

This crude acid chloride was dissolved in 10 ml of ether and added to a cold solution of 0.06 mol of diazomethane in 50 ml of ether. After stirring for 1 hr at ice temperature, excess diazomethane was removed by bubbling nitrogen through the solution. Concentration at the rotary evaporator then gave crude diazo ketone **37**: ir (film) 2100, 1735, 1640, 903 cm^{-1}.

This crude diazo ketone was dissolved in 100 ml of cyclohexane under nitrogen. Copper powder (2 g) and anhydrous $CuSO_4$ (0.5 g) were added as catalysts, and the mixture was refluxed for 1.5 hr. After filtration through Celite and concentration at the rotary evaporator, the residue (1.47 g) was chromatographed on neutral alumina. Elution with 3% ether in benzene gave 385 mg (25% overall) of cyclopropyl ketone **22**. Recrystallization from cyclohexane gave the analytical sample: mp 133–135°; ir ($CHCl_3$) 2950, 1730, 1680 cm^{-1}; nmr ($CDCl_3$) δ 0.67 (3 H, s), 0.88 (2 H, d), 1.17 (3 H, s), 1.33 (3 H, s), 3.59 (3 H, s); mass spectrum m/e 264 (P^+).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.45; H, 8.90.

(±)-Mayurone (18). Tricyclic keto ester **22** (265 mg, 1.0 mmol) was dissolved in 10 ml of ethanol under nitrogen, and 2 ml of 10% aqueous NaOH was added. After 1 hr of reflux, the alkaline solution was diluted with water and extracted with ether. The alkaline layer was then acidified and extracted with chloroform. These extracts were dried (Na_2SO_4) and concentrated to give 248 mg (98%) of acid which was decarboxylated in the manner described above. After distillation, 180 mg (91%) of (±)-mayurone (**18**) was isolated. An analytical sample was prepared by preparative vpc: mp 59.5–61°; ir (film), 3075, 1665 cm^{-1}; nmr (CCl_4) δ 0.67 (3 H, s), 0.86 (2 H, m), 1.15 (3 H, s), 1.31 (3 H, s), 5.74 (2 H, dd, J = 10.5 Hz); mass spectrum m/e 206 (P^+).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.42; H, 10.11.

(±)-Mayurone was spectroscopically and chromatographically identical with a sample of natural mayurone supplied by Professor Dev.

(±)-Thujopsadiene (20). (±)-Mayurone (40 mg, 0.19 mmol) in 5 ml of ether was added to a solution of methyllithium (5 ml of 1.2 *M* solution), and the reaction mixture was gently refluxed for 3 hr. The solution was then cooled to 0°, and 20 ml of saturated NH_4Cl was added. The pasty mixture was then partitioned between hexane–water. The organic layer was drawn off, dried ($MgSO_4$), concentrated, and microdistilled to give 31 mg (77%) of pure (±)-thujopsadiene whose ir and nmr spectra were identical with those of the natural material as supplied by Professor Hirose.

(±)-Dihydromayurone (30). (±)-Mayurone (40 mg, 0.19 mmol) was dissolved in 5 ml of ethanol and hydrogenated at atmospheric pressure over 10 mg of Adams catalyst. After 5 hr, reaction was complete, and the solution was filtered and concentrated to give 40 mg (100%) of semisolid product. Recrystallization from isopropyl ether gave colorless needles, mp 100–101° (lit.[15a] mp 100.5–101.5°). There was no depression on admixture with an authentic sample of (±)-dihydromayurone provided by Professor Dauben.

Registry No.—**2**, 4188-88-9; **4**, 51417-17-5; 4 DNP, 51417-18-6; **5**, 51417-19-7; **6**, 51417-20-0; **8**, 51417-21-1; **10**, 51446-89-0; **11**, 51417-22-2; **12**, 51417-23-3; **14**, 51417-24-4; **17**, 1125-78-6; **18**, 51446-90-3; **20**, 51446-91-4; **22**, 51417-25-5; **24**, 51417-26-6; **26**, 51417-27-7; **27**, 51417-28-8; **28**, 51417-29-9; **31**, 51417-30-2; **32**, 51417-31-3; **33**, 51464-51-8; **34**, 51417-32-4; **35** *R*,R** isomer, 51417-33-5; **35** *R*,S** isomer, 51417-34-6; **36**, 51417-35-7; **37**, 51417-36-8; ethyl levulinate, 539-88-8; 2-methylcyclohexanone, 583-60-8; *p*-toluenesulfonic acid, 104-15-4; 2-methoxy-5,6,7,8-tetrahydronaphthalene, 1730-48-9; 2,2,6-trimethylcyclohexanone, 2408-37-9; cyclohexylisopropylamine 1195-42-2.

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(21) We thank Professor Dev (Poona, India) for a sample of natural mayurone.
(22) We thank Professor W. G. Dauben (Berkeley, Calif.) for a sample of (±)-dihydromayurone.
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Synthesis and Some Reactions of 3-Thiabicyclo[3.2.0]hepta-1,4-diene. A Case for Revival of the Mills–Nixon Effect?[1]

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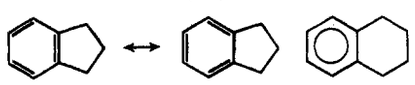
3-Thiabicyclo[3.2.0]hepta-1,4-diene (**10**) has been synthesized by a Wittig reaction between cyclobuta-1,2-dione (**8**) and the bisylide **9**, derived from dimethyl thioether α,α'-bis(triphenylphosphonium) dichloride. The compound **10** was oxidized to the sulfone **11**. Compound **10** underwent electrophilic substitution with benzoyl chloride to give the ketone **12**, but it added bromine to give the tetrabromide **13**. It is suggested that the addition, rather than the substitution, of bromine to **10** indicates that delocalization of the electrons in the thiophene ring of **10** has been decreased by annelation.

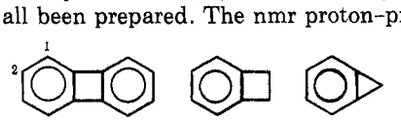
The fusion of a three- or four-membered ring onto a benzene ring might be expected to drastically alter its aromatic character. Many years ago Mills and Nixon[3,4] suggested that some differences in chemical properties which they observed between indan (**1**) and tetralin (**2**) derivatives arose from the destabilization of the aromatic ring in the indan systems.[5] This destabilization they supposed to be due to the strain induced by the five-membered ring, and the Kekulé structure (**1b**) was considered to be the



1a **1b** **2**

predominant resonance contributor. Although the basis for their conclusions was later shown to be unfounded,[6] Longuet-Higgins and Coulson[7] deduced from a theoretical study of the effects of strain that there would be some disruption of the aromatic system on annelation. However, these authors concluded that the Kekulé form **1a** would be favored.

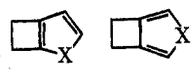
At the time the Mills–Nixon proposal was made, compounds containing three- or four-membered rings fused to a benzene ring were thought to be unknown,[8] despite many attempts to prepare them. Subsequently, biphenylene (**3**),[9] benzocyclobutene (**4**),[10] and benzocyclopropene (**5**)[11] have all been prepared. The nmr proton–proton cou-



3 **4** **5**

pling constants indicate that there is an increase in ring strain on passing from **4** to **5**,[12,13] and subsequent ^{13}C nmr studies can also be interpreted in the same way.[14,15] It was also suggested that the proton nmr spectrum supported the view that in **5** the Kekulé structure with the central double bond (*cf.* **1a**) was preferred,[12,13] but an X-ray crystallographic structural analysis of a derivative showed that the bond lengths do not alternate in the way expected if this form predominated.[16] It has also been observed that the chemical reactivities of aryl positions adjacent to the fused ring are affected and, for example, the kinetic acidity of position 1 in biphenylene (**3**) is greater than that expected from model systems.[17,18] Taylor[17] has attributed this difference to the strain effects due to the four-membered ring which favor those transition states with least double-bond character between the carbon atoms at the ring junctions.[19] Finnegan[20] and Streitweiser and his coworkers[18] have suggested that these effects can be accounted for by a model in which the σ bonds of the small ring have more p character, with the consequence that the adjacent aryl σ bonds have more s character. Riecke and his coworkers[21] have presented evidence in support of the Finnegan–Streitweiser model, and it has also been suggested that both models may be operative.[22] It can thus be seen that changes in both the chemical and physical properties of the aromatic ring occur when it is annelated by a small ring, but it does not appear at present that any of these changes imply a measurable degree of double-bond localization.[23]

Although these results tend to discredit the operation of a Mills–Nixon effect based on bond localization in benzenoid systems, it seemed possible that such an effect might be more pronounced, and therefore more readily observed, in heterocyclic systems. In particular the five-atom 6-π heterocycles, such as pyrrole, have only one uncharged Kekulé structure, and offer two modes of annelation. Thus fusion of the small ring at the 2,3 position forms a system (**6**) with a formal double bond in the annelating ring (**4**), whereas fusion at the 3,4 position forms a system (**7**) with



6 **7**

a formal single bond in the annelating ring. A synthesis of these types of systems would then be expected to give