Tetrahedron Vol. 38, No. 19, pp. 2939 to 2947, 1982
Printed in Great Britain.

0040-4020/82/192939-09$03.00/0
Pergamon Press Ltd.

RULES FOR RING CLOSURE: APPLICATION TO INTRAMOLECULAR ALDOL CONDENSATIONS IN POLYKETONIC SUBSTRATES[1a]

JACK E. BALDWIN*
Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY

and

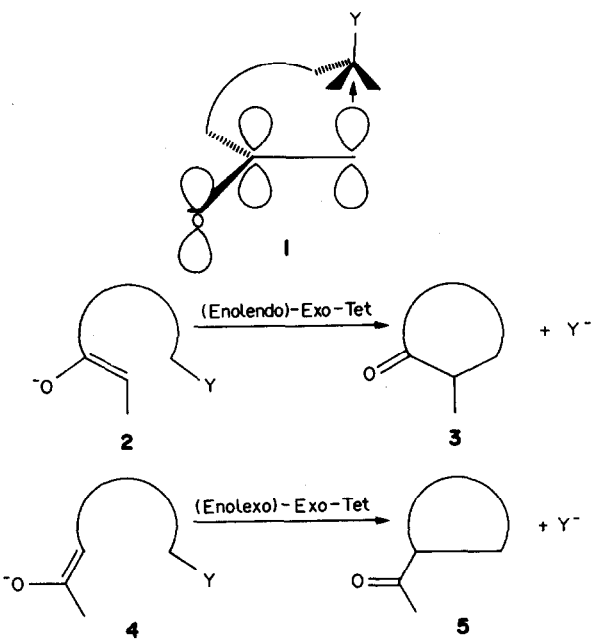
MICHAEL J. LUSCH[1b]
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, U.S.A.

(*Received in the U.K. 29 January* 1982)

Abstract—An extension of the nomenclature for classifying ring closures to include intramolecular reactions of enolate anions is described, and the rules governing such cyclizations are enumerated. The syntheses of the polyketonic substrates 4-acetyl-2,6-heptanedione (**11**), 4-acetyl-4-methyl-2,7-octanedione (**24**), and 3-acetyl-3-methyl-1,6-diphenyl-1,6-heptanedione (**33**) were carried out, and their base-induced intramolecular aldol condensations studied. With each substrate a favored 6-(enolendo)-exo-trig cyclization to produce cyclohexenone products was the only ring forming reaction observed, this process predominating in all instances over competing disfavored 5-(enolendo)-exo-trig closures, and also over other competing favored cyclizations. The identity of the cyclization product **12** derived from **11** was confirmed by aromatizing **12** to **17**, and alternately synthesizing **17** from 3-bromo-5-methylphenol.

In a recent general treatment of ring forming reactions[2] a classification system was described and a collection of rules were enumerated permitting the prediction of the relative facility with which ring closures occur. A number of examples illustrating the applicability of these rules have been published.[3] In searching for new reactions and substrates which would test the predictive power of these guidelines and the general validity of the steroelectronic concepts upon which they were based we turned to the intramolecular alkylation of ketone enolates.[4a] Especially when the enolate C–C bond is endocyclic to the ring being formed in the alkylation, the planarity of the enolate system curtails the freedom of movement of the chain of atoms between the reacting sites. This effect, in addition to the requirements of backside displacement of the leaving group and approach of the electrophilic halide carbon on a trajectory perpendicular to the enolate plane at the α-carbon atom, is an important factor in determining the ability of the reactive termini to meet the proper orientation (**1**). On the basis of these considerations the cyclization **2**→**3** was predicted to be favored for the formation of a cyclohexanone product but disfavored for the construction of a cyclopentanone ring. The validity of this prediction has been demonstrated experimentally.[4]

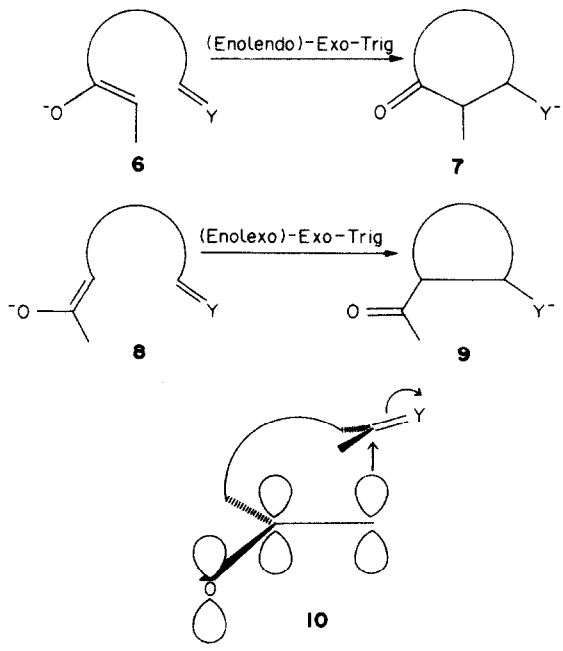
In our original investigation of intramolecular enolate alkylations,[4a] cyclizations such as **2**→**3** (exo-tet with respect to the C–Y terminus) were called "endocyclic alkylations" in referring to the orientation of the enolate C–C bond. We now wish to introduce a more precise and less ambiguous terminology[1a] that is an extension of our original nomenclature. "Endocyclic alkylations" such as **2**→**3** will now be designated (enolendo)-exo-tet cyclizations, with 6- and 7-membered ring formation being favored and 3-to 5-membered closures being disfavored. Intra-molecular enolate alkylations involving an enolate C–C bond exocyclic to the ring being formed (**4**→**5**) ("exocyclic alkylations") will now be referred to as (enolexo)-exo-tet closures, all 3- to 7-membered processes being favored.



Scheme 1.

When such terminology is extended to intramolecular aldol condensations (exo-trig with respect to the C = Y bond) we similarly identify the ring forming reactions as either (enolendo)-exo-trig (**6**→**7**) or (enolexo)-exo-trig (**8**→**9**). In these cyclizations once again the steroelectronic constraints presumably imposed (e.g. **10**) lead to the conclusion that the 3- to 7-(enolexo)- and 6- and 7-(enolendo)-exo-trig cases are favored, while 3- to 5-(enolendo)-exo-trig closures are disfavored.

It can be seen that intramolecular aldol condensations providing a competition between a 5-(enolendo)- and 6-(enolendo)-exo-trig ring closure, wherein there exists the dichotomy between a *disfavored* 5-membered and a *favored* 6-membered ring formation, will constitute a



Scheme 2.

crucial test of the solidity of these postulates. We therefore undertook to synthesize a number of polyketonic molecules having the option *within the same molecule* of *both* 5-(enolendo)- *and* 6-(enolendo)-exo-trig modes of ring formation (and perhaps other favored cyclizations as well) via aldol condensations. In this manner we sought to establish a direct kinetic competition between favored and disfavored modes of ring closure so that the ratio of products formed would be an indication of the relative facility of the competing processes. (In all cases the conditions were such that the observed products were enones resulting from subsequent dehydration of the initial β-hydroxy carbonyl adducts.)

RESULTS AND DISCUSSION

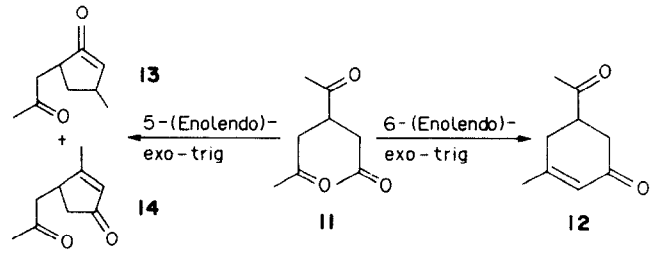
Cyclization of 4-acetyl-2,6-heptanedione (11)

This molecule was chosen for initial study because it has the desired competition between 5-(enolendo)- and 6-(enolendo)-exo-trig modes of intramolecular aldol condensation (Scheme 3). There are, however, *four* possible combinations of enolate and carbonyl which can produce a 5-membered aldol product, but only *two* such combinations leading to a 6-membered ring enone. Thus there is a *2:1 statistical advantage* in favor of the 5-(enolendo)-exo-trig reaction. In spite of this statistical bias, our prediction on the basis of stereoelectronic considerations (*vide supra*) was that the favored 6-(enolendo)-exo-trig condensation (to produce **12**) would be the predominant or exclusive process.

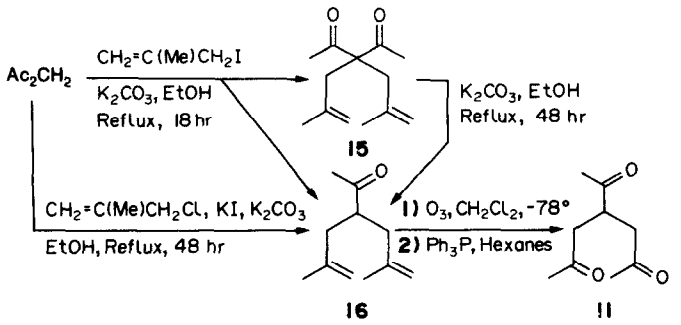
Although a known compound, **11** had previously been synthesized from precursors accessible only with much difficulty.[5] We therefore undertook to synthesize **11** by a much more convenient route (Scheme 4). An initial attempt to dialkylate 2,4-pentanedione with methallyl iodide[6] (a labile substance which must be prepared shortly before use) produced a mixture, easily separable by distillation, of the expected dione **15** and the penultimate synthetic objective, dienone **16**.[7] Dione **15** was found to be converted almost quantitatively into **16** by subjecting it to the conditions of the alkylation for a longer period of time (48 h instead of 18 h). The same net result was eventually achieved in a single step by utilizing methallyl *chloride* in combination with a catalytic quantity (10 mole %) of KI (thus generating methallyl *iodide* by exchange *in situ*), and by carrying out the reaction for the longer (48 h) period of time. In this fashion there was obtained directly a 50% distilled yield of dienone **16**. Ozonolysis followed by reductive work up and chromatography gave a 66% yield of purified trione **11**.

Mild basic treatment (1M methanolic KOH, room temperature) of **11** resulted in rapid (< 5 min) consumption of the starting trione and the direct formation of a *single* cyclization product, the predicted cyclohexenone **12**, in 77% yield. The complete absence of even small amounts of cyclopentenone products (whose enone carbonyl absorption would have appeared at approximately the same position in the IR spectrum as the acetyl absorption of **12** at 1710 cm^{-1}) was conclusively demonstrated by catalytic hydrogenation of the crude cyclization product. After thus transforming all enones into saturated ketones, the IR spectrum of the hydrogenation product showed carbonyl absorption at 1707 cm^{-1} due to acyclic and 6-membered ring ketones only (no cyclopentanone absorption in the 1740-50 cm^{-1} region). The favored 6-(enolendo)-exo-trig reaction in this case was thus so much more facile than the disfavored 5-(enolendo)-exo-trig closure that the formation of **12** totally dominated over even the statistically preferred production of cyclopentenones (**13** and **14**).

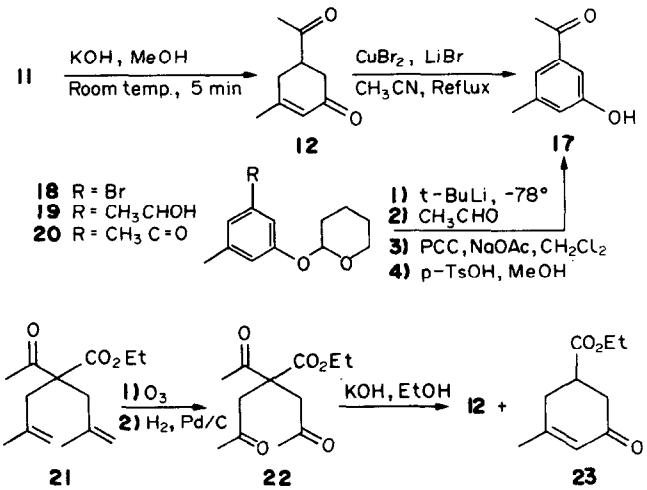
Although the formation of enone **12** has been described previously, and its reported spectral characteristics are in reasonable agreement with those of our cyclization product, the method by which it was obtained did not unambiguously establish its structure.[8] In order to unequivocally determine the identity of our cyclization product, we therefore proceeded to aromatize our



Scheme 3.



Scheme 4.



Scheme 5.

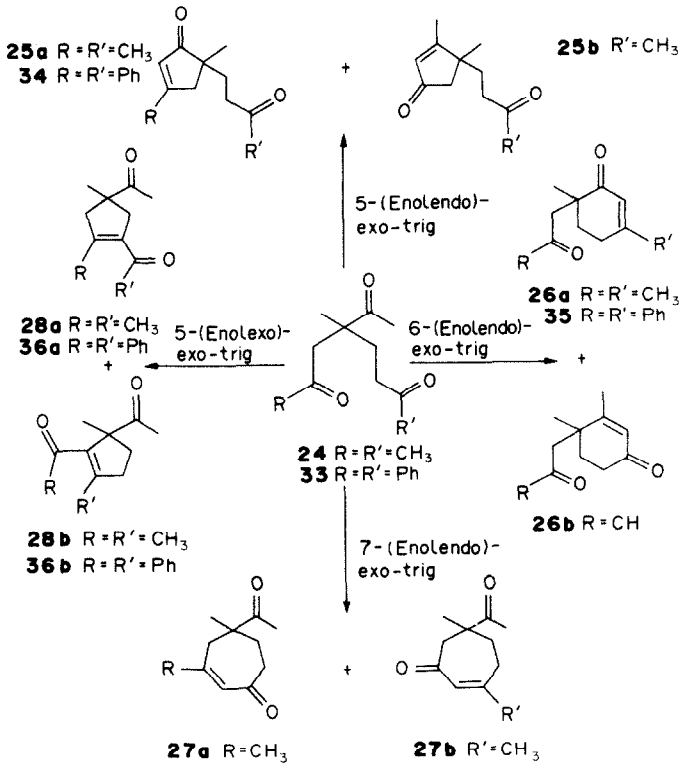
cyclohexenone, presumably to the substituted phenol **17**[8,9] and then alternately synthesize this phenol (Scheme 5). Aromatization was easily accomplished by treatment of the cyclohexenone with CuBr/LiBr in refluxing CH_3CN.[10] The alternate synthesis of **17** began with the tetrahydropyranyl ether **18** of the known 3-bromo-5-methylphenol.[11] Metal–halogen exchange,[12] reaction with acetaldehyde, and then oxidation of the resulting alcohol **19** with buffered pyridinium chlorochromate ($C_5H_5NHCrO_3Cl$, PCC)[13] gave the tetrahydropyranyl-protected phenol **20**. Mild acidic removal of the protecting group gave an acetylphenol **17** that was identical in every respect to the phenol obtained by aromatizing the cyclization product **12**.

In a further attempt to illustrate the favored nature of 6-(enolendo)-exo-trig ring closures, even in the face of a statistical advantage of the disfavored 5-(enolendo)-exo-trig process, carboethoxy trione **22** was prepared by ozonolysis of acetoacetate **21**.[14] Subsequent treatment of **22** with ethanolic KOH at reflux for 5 min (no reaction at room temperature as for **11**), however, gave a mixture of **12** and **23** along with a small amount of **17**. Although cyclohexenones (or phenols derived therefrom) were again the sole products, this experiment failed to reveal any additional information since it was not possible to ascertain conclusively whether cyclization occurred before or after the loss of the acetyl or carboethoxy groups. If loss of a carboethoxy group occurred *before* ring closure then the appearance of **12** in this case was due to the same cyclization of **11** as observed above. If the loss of an acetyl group occurred *before* the cyclization reaction then the formation of **23** by a 6-(enolendo)-exo-trig reaction took place without *any* competition from the 5-(enolendo)-exo-trig process. The results of this additional experiment unfortunately provide no additional confirmation of our hypotheses.

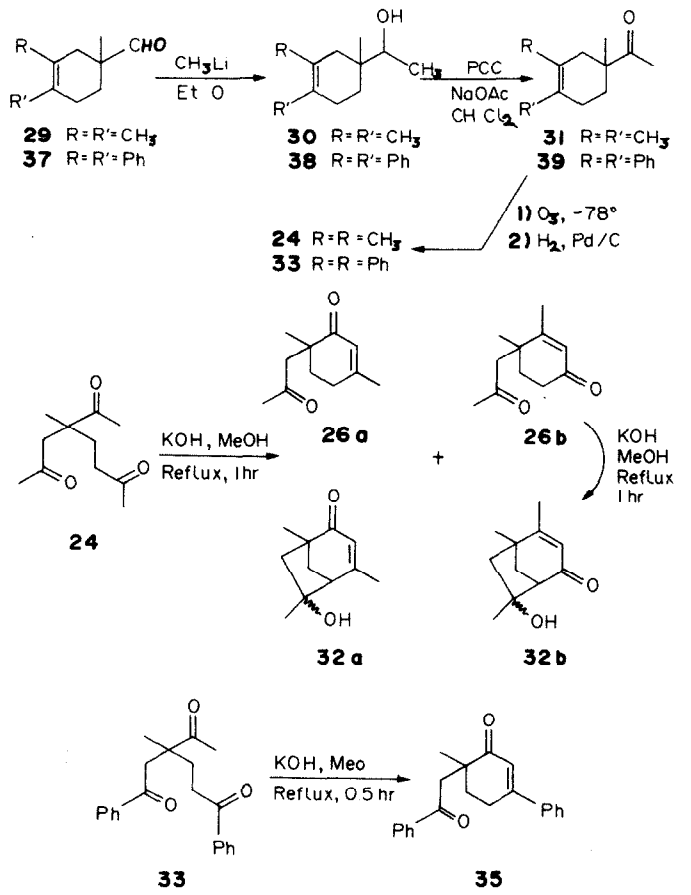
Cyclization of 4-acetyl-4-methyl-2,7-octanedione (**24**)

Emboldened by our initial predictive success, we next chose to examine the reactivity of a molecule with a much greater multiplicity of cyclization modes. Trione **24** is capable of producing 5-, 6-, or 7-membered aldol products in a total of eight ways (Scheme 6). Of these eight possibilities only two are produced via the disfavored 5-(enolendo)-exo-trig pathways (**25a** and **25b**), while the other six involve favored modes of ring closure: two cyclohexenones (**26a** and **26b**) via a 6-(enolendo)-exo-trig process, two cycloheptenones (**27a** and **27b**) via a 7-(enolendo)-exo-trig cyclization, and two cyclopentenyl ketones (**28a** and **28b**) capable of forming via a 5-(enolexo)-exo-trig pathway. Our judgement on the basis of stereo-electronic considerations was again that little or no 5-(enolendo) aldol product would be formed when base induced reaction was attempted, but we were unable to make any prognostication concerning the relative amounts that might be produced of the favored 6-(enolendo), 7-(enolendo), and 5-(enolexo) products.

The synthesis of trione **24** proceeded in straightforward fashion beginning with the thermal Diels–Alder adduct **29**[15,16] (Scheme 7). Addition of MeLi to form



Scheme 6.



Scheme 7.

alcohol **30**, followed by oxidation to ketone **31**,[17] ozonolysis, and reductive work up (H_2, Pd/C) gave the desired **24** in 68% overall yield.

Treatment of trione **24** with methanolic KOH at reflux for 1 h produced, much to our surprise and delight, only cyclohexenones **26a/26b** and **32a/32b** resulting from a 6-(enolendo)-exo-trig cyclization process. Once again the complete absence of 5-(enolendo)-exo-trig products (cyclopentenones **25a/25b**) was demonstrated by hydrogenation of the crude cyclization mixture. Examination of the mixture of saturated ketones thus produced by IR again revealed no evidence indicating the presence of cyclopentanones derived from **25a/25b**.

While the monocyclic enones **26** could be separated by preparative TLC from the bicyclic compounds **32**, these pairs could not be further resolved. It was subsequently demonstrated that **32** were secondary products derived [via a favored 5-(enolexo)-exo-trig closure] from the primary aldol products **26**, since **32a/32b** were produced when the separated **26a/26b** mixture was subjected to the same conditions used to cyclize **24** originally.

There was some evidence to suggest that **26a** was the major constituent of the 85:15 mixture (NMR integration of the vinylic protons) of monocylic enones. The mass spectrum of the **26a/26b** mixture displayed a base peak at *m/e* 82. This abundant fragment can be explained as having arisen via an initial McLafferty rearrangement fragmentation of **26a** (*m/e* 180) to form **26c** (*m/e* 122), followed by the loss of neutral propyne via a retro-Diels–Alder-like process[18] to generate the resonance stabilized ion **26e** (Scheme 8). Fragmentation of **26b** in a similar manner leads to ion **26d** which cannot as readily cleave via a retro-Diels–Alder type process, and which would produce a much less stabilized ion (**26f**) upon loss of propyne. The appearance of the *m/e* 82 base peak is therefore more readily accounted for if **26a** is the preponderant isomer in the **26a/26b** mixture.

Cyclization of 3-*acetyl*-1,6-*diphenyl*-3-*methyl*-1,6-*hexanedione* (**33**)

Insertion of phenyl groups in place of the two methyl groups at the ends of the main hydrocarbon chain in **24** markedly restricts the cyclization possibilities of the resulting trione **33** (Scheme 6). Although there are still two 5-(enolexo)-exo-trig products (**36a** and **36b**), there are now no 7-(enolendo) products possible, and only one 6-(enolendo) and one 5-(enolendo) product (**35** and **34**, respectively) capable of being formed. Our *a priori* conclusion on stereoelectronic grounds was that little if any disfavored 5-(enolendo) cyclization would occur, but we were reluctant to speculate on the relative amounts of the favored 6-(enolendo) and 5-(enolexo) products that might be generated. On a strictly statistical basis, however, we expected at least to observe the formation of *some* 5-(enolexo) product, since there are twice as many pathways to this type of product as to the 6-(enolendo) compound **35**.

Diphenyltrione **33** was synthesized in a manner completely analogous to that by which the similar trione **24** was obtained (Scheme 7). Cyclization of **33** in methanolic KOH at reflux for 0.5 h then resulted in the formation of a *single* product, the cyclohexenone **35** derived *exclusively* from a 6-(enolendo)-exo-trig aldol cyclization.

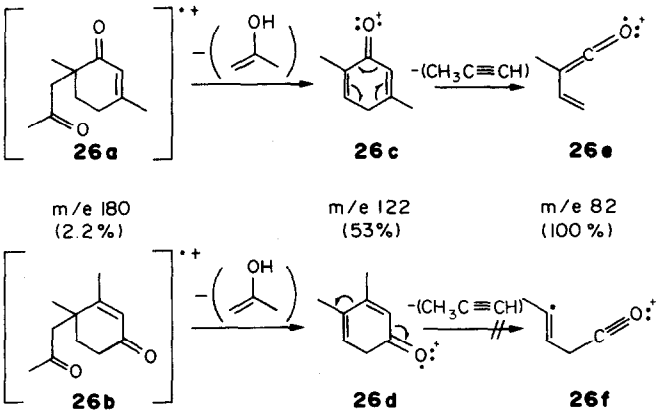
CONCLUSIONS

With all the polyketonic substrates studied it was found, in agreement with our predictions based on stereoelectronic considerations, that intramolecular aldol condensation via a *favored* 6-(enolendo)-exo-trig ring closure predominated to the exclusion of the *disfavored* 5-(enolendo)-exo-trig process, and also to the exclusion of all other *favored* ring forming pathways as well. This was especially curious in the case of the *favoured* 5-(enolexo)-exo-trig mode of reaction, which was apparently unable to compete effectively against the 6-(enolendo)-exo-trig closure, even when it also enjoyed a 2:1 statistical advantage. The explanation for this latter result is still uncertain. It is evident, however, that the formation of cyclohexenones via a 6-(enolendo)-exo-trig cyclization is by far the preferred mode of reaction in an intramolecular competition among several modes of aldol condensation, at least for the substrates in this study. Generalization of these observations to other polyketonic substrates should make it relatively simple to recognize transformations which stand little chance for success, and thus markedly facilitate the conceptualization of multistep synthetic schemes and the execution of the syntheses of complex organic molecules.

EXPERIMENTAL[19]

5-*Methyl*-3-(2-*methyl*-2-*propenyl*)-5-*hexen*-2-*one* (**16**)

A. Directly from 2,4-pentanedione. A mixture of 20.02 g (0.20 mol) of Ac_2CH_2, 45.28 g (0.50 mol) of $CH_2{=}C(Me)CH_2Cl$,



Scheme 8.

60.81 g (0.44 mol) of anhydrous K_2CO_3, and 7.30 g (44 mmol) of KI in 200 mL of absolute EtOH was refluxed under N_2 for 48 h. The resulting suspension was cooled, concentrated, and partitioned between H_2O and Et_2O. The combined ether layers were washed with brine, dried, and evaporated to leave 27.94 g (84%) of pale yellow liquid. Distillation separated 16.757 g (50%) of **16** as a colorless, fragrant liquid, b.p. 61–65° (3.4–3.5 mm). GC on a 6 ft × 0.125 in, 5% SE-30 on Chromasorb W column at 100° showed only one peak at 3.55 min. IR (neat) 1708 (C=O), 3075, 1645, 900 ($R_2C=CH_2$), 1445, 1380, 1358, 1165 cm^{-1}; NMR (90 MHz, CCl_4) δ 1.74 (d, J ≃ 2 Hz, 6H, $C=CCH_3$), 2.07 (s, 3H, CH_3CO), 2.18 (doublet of quartets, J = 14 and 8 Hz, 4H, $CH_AH_BCHC=O$), 2.87 (m, 1H, CHC=O), 4.73, 4.80 (broad singlets, 4H total, $C=CH_2$). MS *m/e* (rel intensity) 166 (M^+, 2), 43 (CH_3CO^+, 100), 151 (M-CH_3, 3), 123 (M-CH_3CO), 15), 111 (21), 108 (15), 95 (22), 81 (21), 67 (17), 55 (32), 41 (27), 39 (30). Calc. for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.16; H, 10.74%.

B. Via isolation of 3,3-*Bis*(2-*methyl*-2-*propenyl*)-2,4-*pentanedione* (**15**). A mixture of 500 mL of Me_2CO, 83.00 g (0.50 mol) of KI, and 45.28 g (0.50 mol) of $CH_2=C(Me)CH_2Cl$ was refluxed under N_2 for 14 h. The resulting suspension was filtered, evaporated (≤ 25°), partitioned between H_2O and pentane. The pentane layers were washed successively with 10% $Na_2S_2O_3$ and H_2O, dried, and evaporated (≤ 25°) to leave 40.56 g (45%) of crude $CH_2=C(Me)CH_2I$[6] as a golden yellow light- and air-sensitive liquid. IR (neat) 3080, 1635, 910 ($R_2C=CH_2$), 1380, 1165 (CH_2I) cm^{-1}. A mixture of 39.68 g (0.218 mol) of this crude methallyl iodide, 10.01 g (0.10 mol) of Ac_2CH_2, and 30.01 g (0.22 mol) of K_2CO_3 in 100 mL of absolute EtOH was refluxed under N_2 for 18 h. The resulting suspension was cooled, concentrated, and partitioned between aqueous NH_4Cl and Et_2O. The combined ether layers were then washed with brine, dried, and evaporated to leave 17.801 g of yellow liquid. Distillation through a 16 cm Vigreux column separated 4.213 g (25%) of slightly impure **16**, b.p. 39–45° (0.29 mm), and then 10.475 g (50%) of **15** as a clear liquid, b.p. 71.5-75° (0.29-0.32 mm). IR (neat) 1695 (C=O), 3075, 1650, 908 ($R_2C=CH_2$), 1450, 1380, 1360, 1180, 1155 cm^{-1}; NMR (CCl_4) δ 1.65 (broad s, 6H, $C=CCH_3$), 2.09 (s, 6H, CH_3CO), 2.72 (s, 4H, $C=CCH_2$), 4.57, 4.80 (broad singlets, 4H total, $C=CH_2$); MS *m/e* (rel intensity) 208 (M^+, 0.2), 43 (CH_3CO^+, 100), 193 (M-CH_3, 1.3), 190 (M-H_2O, 0.7), 175 (M-CH_3, H_2O, 2.3), 165 (M-CH_3CO, 10), 151 (7), 137 (9), 123 (16), 109 (16), 107 (17), 93 (17), 81 (18), 67 (9), 55 (22), 49 (37), 42 (46), 41 (47), 39 (53). GC on a 10 ft × 0.125 in, 5% SE-30 on Chromasorb G column at 200° showed a single peak for **15** at 2.70 min (**16** came at 1.35 min under the same conditions). Calc. for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.14: H, 9.83%.

Refluxing a mixture of 9.214 g (44.2 mmol) of **15** and 7.602 g (55.0 mmol) of anhydrous K_2CO_3 in 50 mL of absolute EtOH under N_2 for 48 h gave, after work-up as above, 6.875 g (93%) of pure **16**, b.p. 49–53.5° (1.40 mm), showing a single peak at 1.30 min under the above GC conditions.

4-*Acetyl*-2,6-*heptanedione* (**11**)

A solution of 5.819 g (35.0 mmol) of **16** in 350 mL of CH_2Cl_2 was cooled in a dry ice/acetone bath and ozone was bubbled in until the blue-grey color of excess ozone was observed (*ca.* 80 min). After bubbling N_2 into the cold solution to remove excess O_3, the solution was warmed and diluted with 250 mL of hexanes. The CH_2Cl_2 was then evaporated (≤ 25°) and after adding 27.54 g (105 mmol) of Ph_3P and enough hexanes to give a total volume of *ca.* 600 ml the resulting solution was refluxed for 2 h. Cooling and evaporation gave a solid residue which was stirred with Et_2O and filtered (13.82 g solid collected), leaving a clear filtrate which gave 23.03 g of pale yellow semisolid upon evaporation. This was chromatographed on a 4.5 × 60 cm column of silica gel (*ca.* 400 g), eluting with Et_2O to separate early fractions containing 9.73 g of unreacted Ph_3P and later fractions containing first pure **11** and then **11** contaminated with small amounts of Ph_3PO. These later fractions were combined (5.771 g) and distilled to give 3.915 g (66%) of **11**[5] as a pale yellow liquid, b.p. 75–82° (0.09 mm). IR (neat (1710 C=O), 3010, 2920, 1415, 1370, 1280, 1240, 1171, 980 cm^{-1}; NMR (90 MHz, CCl_4) δ 2.13 (s, 6H, $CH_3C=O$), 2.20 (s, 3H, $CH_3C=O$) 2.65 (doublet of quartets, J = 18 and 7 Hz, 4H, CH_AH_B CHC=O), 3.26 (quintet, 1H, CHC=O); MS *m/e* (rel intensity) 171 (M + 1, 0.1), 170 (M^+, 0.03), 43 (CH_3CO^+, 100), 153 (M + 1 − H_2O, 2.2), 152 (M − H_2O, 1.1), 128 (M + 1 − CH_3CO, 18), 127 (M − CH_3CO), 110 (38), 95 (26), 85 (31), 71 (71), 58 ($C_3H_6O^+$, 33). Trione **11** darkened very rapidly upon standing even under N_2 in the cold. Careful rechromatography and redistillation gave **11** as a water-white liquid, b.p. 73–75.5° (0.07 mm), but did not prevent subsequent discoloration of this material.

5-*Acetyl*-3-*methyl*-2-*cyclohexen*-1-*one* (**12**)

A solution of 1.191 g (7.0 mmol) of **11** in 7.0 mL (7.0 mmol) of 1.0 M KOH in MeOH was stirred at room temperature for 5 min. Tlc (silica gel, 1:1 PhH/EtOAc) showed essentially no starting material (I_2 vapor) and only a *single* UV visualized product.

After quenching into saturated NH_4Cl and extracting with Et_2O, the combined ether layers were washed with brine, dried, and evaporated to leave 819 mg (77%) of **12** as a pale yellow oil. Preparative tlc (silica, gel, 1:1 PhH/EtOAc) of 156.3 mg of this material gave 137.7 mg (64%) of purified **12**.[8] IR (neat) 1710 (C=O), 1670 (cyclohexenone C=O), 1630 (enone C=C), 3040 (C=CH), 1440, 1389, 1365, 1310, 1260, 1180, 1030, 902, 825 cm^{-1}; NMR (90 MHz, CCl_4) δ 2.02 (s, 3H, $C=CCH_3$), 2.19 (s, 3H, $CH_3C=O$), 2.0 − 3.4 (m, 5H, aliphatic CH), 5.79 (broad s, 1H, C=CH); MS *m/e* (rel intensity) 153 (M + 1, 1.7), 152 (M^+, 0.7), 43 (CH_3CO^+, 100), 110 (3), 109 (M − CH_3CO, 20), 95 (7), 91 (1.6), 82 (21), 81 (22), 79 (13), 65 (4.6), 54 (14), 53 (21), 41 (29.5), 39 (51).

A solution of 152 mg (1.0 mmol) of crude **12** (from the above cyclization reaction) in 10 mL of MeOH containing 100 mg of 10% Pd on carbon was hydrogenated at room temperature and 1 atm until 26.8 mL of H_2 (22.4 mL = 100%) had been taken up (*ca.* 20 min). Filtration through Celite and evaporation gave 149 mg (97%) of pale yellow liquid. IR (neat) 1707 cm^{-1} (acyclic and/or cyclohexanone C=O), no cyclopentanone C=O in the 1740–1750 cm^{-1} region; NMR (CCl_4) δ 2.13 (s, CH_3CO), no C=CH in the 5.0–6.0 region.

3-*Acetyl*-5-*methylphenol* (**17**)

A. *From* **12**. A solution of 66.0 mg (0.43 mmol) of **2**, 192 mg (0.86 mmol) of $CuBr_2$, and 37.3 mg (0.43 mmol) of anhydrous LiBr in 5.0 mL of dry $MeCN$[10] was refluxed under N_2 for 1.0 h (dark green → pale yellow). The resulting solution was partitioned between H_2O and Et_2O and the combined ether layers washed with brine, dried, and evaporated to leave 75 mg (116%) of crude **17** as a pale brown solid. Recrystallization from PhH gave 30 mg (46%) of **17**, m.p. 118–120.5° (lit. m.p. 118–121°,[8] 122–123°[9]). IR ($CHCl_3$) 3560 (free OH), 3300 (associated OH), 1674 (ArC=O), 1590, 1445, 1360, 1325, 1163, 960, 880, 855 cm^{-1}; NMR ($CDCl_3$) δ 2.35 (s, 3H, CH_3Ar), 2.60 (s, 3H, CH_3COAr), 6.98 (broad s, 1H, ArH), 7.23 (broad s, 1H, OH; position variable), 7.35 (broad s, 2H, ArH); MS *m/e* (rel intensity) 150 (M^+, 60), 135 (M-CH_3, 100) 107 (M-CH_3CO, 57), 79 (12), 78 (9), 77 (39), 63 (8), 53 (14), 51 (19), 43 (CH_3CO^+, 53), 39 (27).

B. Alternate synthesis of **17**. A solution of 996 mg (5.3 mmol) of 3-bromo-5-methylphenol[11] and 1.632 g (19.4 mmol) of dihydropyran in 6.0 mL of EtOAc was stirred at room temperature with 0.4 mL of HCl-saturated EtOAc for 24 h.[20] The resulting solution was washed successively with 2% NaOH, H_2O, and brine, dried, and evaporated to leave 1.839 g (127%) of yellow liquid. Distillation gave 1.373 g (95%) of clear viscous liquid, b.p. 95–109° (0.125 mm), which proved to be the desired THP ether **18**, contaminated with what is probably oligomeric dihydropyran. IR (neat) 2950, 2875, 1600, 1575, 1450, 1360, 1270, 1210, 1165, 1130, 1035, 990, 920, 840 cm^{-1}; NMR (CCl_4) δ 1.0-2.0 (broad m, >6H, aliphatic CH), 2.27 (s, 3H, CH_3COAr), 3.1-4.1 (m, >2H, CH_2OR), 5.28 [broad *s*, 1H, $CH(OR)_2$], 6.68 (m, 1H, ArH), 6.84, 6.93 (m, 2H, ArH). Distillation of impure **18** through an 11 cm Vigreux column failed to remove the impurity, giving material, b.p. 91.5–96.5° (0.04 mm), that was essentially identical to that from simple distillation. Using less dihydropyran (only 2 equiv) also failed to prevent contamination by this impurity. Rather than attempt further purification, impure **18** was used in the next steps and any

impurities then removed in the final purification (yields given are therefore only approximate and probably lower than in reality).

A solution of 1.095 g ($\leq$4.04 mmol) of impure **18** in 10 mL of dry THF was treated at $\leq -65°$ with 4.70 mL (8.08 mmol) of 1.72 M t-BuLi in pentane,[12] added dropwise over *ca.* 15 min. The resulting bright yellow solution was stirred at $\leq -65°$ for 2.0 h and then treated with 360 mg (8.16 mmol) of MeCHO in 5.0 mL of THF added over *ca.* 20 min. After stirring at $\leq -65°$ for another 15 min the resulting almost colorless solution was warmed to room temperature and partitioned between ice water and Et_2O. Washing of the combined ether layers with brine, drying, and evaporation gave 1.087 g(114%) of impure **19** as a viscous yellow oil also containing some MeCCH(OH)Me. IR (neat) 3400 cm^{-1} (OH); NMR (CCl_4) δ 1.33 (d, J = 6.5 Hz, 3H, $\underline{CH_3}CHOH$), 1.2–2.2 (broad m, >6H, aliphatic CH), 2.27 (s, 3H, $Ar\underline{CH_3}$), 2.5–3.1 (broad m, 1H, OH), 3.1–4.1 (broad m, *ca.* 2H, CH_2OR), 4.95 (q, J = 6.5 Hz, 1H, $CH_3\underline{CH}OH$), 5.29 [broad s, 1H, $CH(OR)_2$], 6.62 (broad s, 3H, ArH). A mixture of 566 mg ($\leq$2.02 mmol) of this impure **19**, 871 mg (4.04 mmol) of $C_5H_5NHCrO_3Cl$[13] and 66.4 mg (0.81 mmol) of anhydrous NaOAc in 9.0 mL of CH_2Cl_2 was stirred at room temperature for 4.0 h under N_2. The resulting dark mixture was diluted with Et_2O, filtered through Florisil (residue washed with Et_2O and also filtered), dried, and evaporated to leave 440 mg ($\leq$93%) of crude **20**. IR (neat) 1688 cm^{-1} (ArC=O), little if any OH. Solvolysis of this THP ether in MeOH with 19.2 mg (0.1 mmol) of p-$MeC_6H_4SO_3H \cdot H_2O$ at room temperature for 25 h gave, after Et_2O extraction, drying, and evaporation, 221 mg ($\leq$73%) of dark brown solid. Recrystallization from PhH/hexanes (decolorized with carbon) gave 111 mg ($\leq$36%) of phenol **17** as pale yellow needles, m.p. 113–117.5°. The IR, NMR, and mass spectra of this material were identical to those of **17** obtained from cyclohexenone **12**. The melting point was also undepressed upon admixture with previously obtained **17**.

4-Acetyl-4-ethocycarbonyl-2,6-heptanedione (**22**)

A solution of 477 mg (2.0 mmol) of **21**[14] in 20 mL of EtOAc was ozonized at dry ice temperature until the color of excess O_3 was observed. After bubbling N_2 through the solution and warming to room temperature 200 mg of 10% Pd on carbon was added and the mixture was hydrogenated at room temperature and 1 atm until no more H_2 was taken up (5.7 h, 69 mL, 77% of theoretical). Filtration through Celite, drying, and evaporation gave 514 mg (106%) of clear liquid. A 398 mg sample of this material was chromatographed on a 2.2 × 30.5 cm column of silica gel (*ca.* 25 g), eluting with Et_2O, to give fractions containing 254 mg (68%) of **22** as a pale yellow liquid. IR (neat) 1715 (C=O), *ca* 1735 (shoulder, CO_2R), 2970, 2930, 1410, 1370, 1215, 1175, 1105, 1030 cm^{-1}; NMR (CCl_4) δ 1.22 (t, J = 7 Hz, 3H, $\underline{CH_3}CH_2$), 2.10, 2.12 (overlapping singlets, 9H total, CH_3C=O), 3.19 (s, 4H, CH_2C=O), 4.08 (q, J = 7 Hz, 2 H, $CH_3\underline{CH_2}$); MS *m/e* (*rel intensity*) 243 (M + 1, 0.09), 242 (M^+, 0.05), 43 (CH_3CO^+, 100), 225 (0.25), 199 (M-CH_3CO, 5.6), 157 (8), 139 (4), 111 (40), 83 (3.2). Calc. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.67; H, 7.51%.

Attempted base-induced cyclization of **22**

To a solution of 96.9 mg (0.40 mmol) of **22** in 1.6 mL of absolute EtOH was added 0.4 mL (0.40 mmol) of 1.0 M KOH in EtOH and the resulting bright yellow solution refluxed for 5 min under N_2. After cooling in an ice bath the reaction solution was partitioned between saturated NH_4Cl and Et_2O and the ether layers dried and evaporated to leave 50.5 mg of brown liquid. Tlc (silica gel, Et_2O) showed no starting **22** (R_f 0.37) and three product components, R_f 0.23, 0.46, and 0.52. The most mobile spot corresponds in retention time to phenol **17**. Preparative tlc (silica gel, Et_2O) of 49.5 mg of this product mixture separated 6.6 mg of material corresponding to the R_f 0.23 component, identified as cyclohexenone **12** by IR, NMR, and mass spectra. Another 12.2 mg of material was isolated corresponding to the R_f 0.37 component that is believed to be cyclohexenone **23** on the basis of spectral evidence: IR (neat) 1670 (enone C=O), 1635 (enone C=C), 1725 (ester C=O), 2980, 1442, 1385, 1255, 1195, 1043, 905, 868 cm^{-1}; NMR (CCl_4) δ 1.27 (t, J = 7 Hz, 3 H, $\underline{CH_3}CH_2O$–), 1.99 (broad s, 3H, CH_3C=C), 2.1–3.4 (m, 5H, aliphatic CH), 4.09 (q, J = 7 Hz, 2H, $CH_3\underline{CH_2}O$–), 5.75 (broad s, 1 H, C=CH); MS *m/e* (rel intensity) 182 (M^+, 3.3), 109 (M-CO_2Et, 100), 137 (7), 95 (2.5), 82 (60), 81 (20), 54 (16), 53 (13), 43 (6), 41 (13), 39 (18). A third fraction of 6.5 mg, corresponding to the R_f 0.52 component, appeared to be a mixture of phenol **17** and cyclohexenone **23**. An earlier experiment involving a longer reflux period (2.0h) and apparently producing a greater proportion of this more mobile component in addition to **12** and **23** gave a purified R_f 0.52 fraction whose IR spectrum was essentially identical to that of phenol **17**.

4 Acetyl-1,2,4-Trimethyl cyclohexene (**31**)

A solution of 40.0 mL (78.1 mmol) of 1.952 M MeLi in Et_2O under N_2 was diluted with another 40 mL of Et_2O and cooled in an ice/salt bath to *ca.* -5°. To it was added, dropwise over *ca.* 15 min while keeping the temperature below 10°, a solution of 9.357 g (61.5 mmol) of **29**[15,16] in 40 mL of Et_2O. After washing in the last traces of **29** with another 10 mL of Et_2O the reaction solution was stirred at ice bath temperature for 0.5 h and was then transferred via canula into a mixture of 100 mL of saturated aqueous NH_4Cl and 100 mL of ice. After separating the ether layer the aqueous layer was extracted with Et_2O and the combined ether layers were then washed with brine and dried. Removal of the solvent left 10.196 g (98.5%) of reasonably pure **30** as a viscous pale yellow liquid. IR (neat) 3360 (OH), 1095 (C–O), 1380, 930 cm^{-1}; NMR (CCl_4) δ 0.78 (s, 3H, CH_3), 1.08 (d, J = 7 Hz, 3H, $\underline{CH_3}CHOH$), 1.0–2.7 [m, 13H, aliphatic CH, including a broad singlet at 1.58 (CH_3C = C) and a broad singlet at *ca.* 2.45 (OH, Exchangeable with D_2O)], 3.42 (q, J = 7 Hz, 1H, $CH_3\underline{CH}OH$); MS *m/e* (rel intensity) 168 (M^+, 9), 107 (100), 150 (M-H_2O, 17), 135 (M-H_2O, CH_3, 50), 123 (M-CH_3CHOH, 56), 93 (39), 81 (75), 67 (44), 49 (87), 48 (66), 45 (CH_3CHOH^+, 49), 43 (89), 41 (82), 39 (47).

A solution of 10.196 g (60.6 mmol) of this crude **30** in 30 mL of dry CH_2CL_2 was added to a suspension of 19.885 g (92.25 mmol) of $C_5H_5NHCrO_3Cl$[13] and 1.513 g (18.45 mmol) of anhydrous NaOAc in 125 mL of dry CH_2Cl_2. After washing in the last traces of **30** with 15 mL of CH_2Cl_2 the resulting black mixture was stirred under N_2 for 2.0 h at room temperature. The reaction mixture was then poured into 150 mL of Et_2O and the black residue remaining in the reaction flask was washed thoroughly with Et_2O. The combined solutions were filtered through Florisil and concentrated to leave a green liquid. A small amount of CCl_4 was added, depositing a green solid, and the mixture was filtered through Celite and concentrated again to leave 9.761 g (97%) of reasonably pure **31** as a yellow liquid. Distillation gave 7.830 g (78%) of purified **31** as a pale yellow liquid, b.p. 72–77.5° (3.7–3.8 mm) [lit[17] b.p. 111° (26 mm)]. IR (neat) 1704 (C = 0), 1380, 1360, 1185, 1140, 1115 cm^{-1}; NMR (CCl_4) δ 1.07 (s, 3H, CH_3), 1.1–2.8 [m, 15H, aliphatic CH, including a broad singlet at 1.60 (CH_3C=C) and a sharp singlet at 2.03 (CH_3C=O)]; MS *m/e* (rel intensity) 166 (M^+, 25), 43 (CH_3CO^+, 100), 81 (100), 151 (M-CH_3, 63), 133 (17), 123 (M-CH_3CO, 85), 107 (48), 91 (57), 67 (63), 55 (30), 41 (54), 39 (74).

4-Acetyl-4-methyl-2,7-octanedione (**24**)

A solution of 332 mg (2.0 mmol) of **31** in 10 mL of 1:1 MeOH/EtOAc was ozonized at dry ice temperature until the blue color of excess ozone was detected. Nitrogen was bubbled through the resulting cold solution to remove excess O_3 and after warming to room temperature 10 mg of 10% Pd on carbon was added. Hydrogenation was carried out at ice bath temperature under 1 atm pressure until *ca.* 45 mL (*ca.* 2 mmol) of H_2 had been taken up (2.5 h). The resulting suspension was then filtered through Celite and evaporated to leave 347 mg (88%) of **24** as a pale yellow liquid. Tlc (silica gel, 1:1 EtOAc/hexanes) showed essentially one component, R_f 0.23. Preparative tlc (silica gel, EtOAc) gave analytically pure **24**; although **24** is not exceedingly unstable when thus purified, attempted distillation gave material which rapidly decomposed, even in the cold. IR (neat) 1709 (C=O), 2975, 2940, 1425, 1370, 1180, 1120 cm^{-1}; NMR (90 MHz, CCl_4) δ 1.19 (s, 3H, CH_3), 1.70 (m, 2H, $CH_2\underline{CH_2}C$=O), 2.09 (s, 9H, CH_3C=O), 2.0–2.7 (m, 3H, $CH_2\underline{CH_2}C$=O and H_A of CH_AH_BC=O), 2.96 (d, J = 18 Hz, 1H, H_B of CH_AH_BC=O AB quartet); Ms *m/e* (rel intensity) 199 (M + 1, 3.1, 198 (M^+, 0.6), 43

(CH_3CO^+, 100), 181 ($M+1-H_2O$, 15), 180 ($M-H_2O$, 3.6), 155 ($M-CH_3CO$, 2.5), 138 (11), 98 (28), 95 (34), 85 (14), 71 (8), 58 (17), 57 (15), 42 (75), 39 (15). Calc. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.49; H, 9.06%.

Cyclization of **24**

A solution of 595 mg (3.0 mmol) of **24** in 12 mL of MeOH was treated with 3.0 mL (3.0 mmol) of 1.0 M KOH in MeOH and then refluxed for 1.0 h under N_2, at which time all of the **24** had been consumed (tlc). Saturated NH_4Cl was added and the resultant mixture extracted with Et_2O. Washing the combined ether layers with brine, drying, and evaporation gave 470 mg (87%) of a dark orange liquid. Tlc (silica gel, EtOAc) showed UV-visualized components at R_f 0.44 and 0.56, 0.58 (possibly two overlapping components). Preparative tlc (silica gel, EtOAc) of 67.8 mg of a similar material obtained in another reaction separated 28.2 mg of higher R_f material (Fraction A) and 18.1 mg of lower R_f material (Fraction B). Fraction A (R_f 0.56–0.58), the major product of the cyclization, is believed to be a mixture of cyclohexenones **26a** and **26b**, in a ratio of *ca.* 85:15 (NMR integration of vinyl protons). Repeated preparative tlc (silica gel, 3:1 hexanes/EtOAc) finally gave analytically pure **26**. IR (neat) 1665 (enone C=O), 1710 cm^{-1} (ketone C=O); NMR (90 MHz, CCl_4, predominantly of one isomer) δ 1.08 (s, 3H, CH_3), 1.96 (s, 3H, $C=CCH_3$), 2.08 (s, 3H, $CH_3C=O$), 2.0–2.5 (m, 5H, aliphatic CH), 2.82 (d, J = 16.5 Hz, 1H, H_A of $CH_AH_BC=O$ AB quartet), 5.56, 5.71 (broad singlets, total 1H, C = CH of minor and major isomers, respectively, in *ca.* a 15:85 ratio); MS *m/e* (rel intensity) 180 (M^+, 2.2), 82 ($C_5H_6O^+$, 100), 162 (2.6), 137 ($M-CH_3CO$, 14), 122 [$M-CH_2=C(CH_3)OH$, 53)], 110 (7), 95 (15), 67 ($82-CH_3$, 9), 54 ($82-CO$, 16), 43 (CH_3CO^+, 77), 41 (18.5), 39 (29). Calc. for $C_{11}H_{16}O_2$: *m/e* 180.11503. Found: *m/e* 180.11356. Fraction B (R_f 0.44), the minor product of the cyclization, is believed to be two of the four possible alcohols **32a** and **32b** in *ca.* a 2:1 ratio (NMR integration of vinyl and methyl protons). Repeated preparative tlc (silica gel, 3:1 hexanes/EtOAc) finally gave analytically pure **32**. IR (neat) 3400 (OH), 1660 cm^{-1} (enone C=O); NMR (90 MHz, CCl_4) δ 1.11, 1.17 (two singlets, *ca.* 1:2 ratio, 3H total, bridgehead CH_3), 1.34, 1.52 (two singlets, *ca.* 2:1 ratio, 3H total, carbinol CH_3), 1.73 (broad s, $CH_3C=C$ of minor isomer), 2.06 (narrow doublet, $J \approx 1.5$ Hz, $CH_3C=$ of major isomer), 2.5-3.2 (variable, broad s, OH), 1.65–2.8 (m, 9H total, including $CH_3C=C$ and OH protons, aliphatic CH), 5.60, 5.73 (two broad singlets, *ca.* 2:1 ratio, 1H, C=CH); MS *m/e* (rel intensity) 181 ($M+1$, 1.5), 180 (M^+, 0.6), 122 [$M-CH_3C(OH)=CH_2$, 100], 165 ($M-CH_3$, 0.7), 147 ($M-H_2O$, CH_3, 2.2), 137 (2.3), 123 (31), 121 (24), 107 ($122-CH_3$, 41), 91 (12), 82 (8), 79 (18), 77 (16), 67 (15), 55 (10), 53 (14), 43 (79), 41 (39), 39 (41). Calc. for $C_{11}H_{16}O_2$: *m/e* 180.11503. Found: *m/e* 180.11559. A solution of 21.2 mg (0.12 mmol) of isolated **26a/26b** mixture in 0.94 mL of MeOH was treated with 0.12 mL (0.12 mmol) of 1.0 M KOH in MeOH and refluxed for 1.0 h under N_2. Work-up as above gave 20.4 mg (96%) of yellow liquid which was shown by tlc, IR, and NMR analysis to be a mixture of starting **26a/26b** and roughly the same 2:1 mixture of bicylic alcohols **32a/32b** as was produced in the original cyclization reaction, the alcohols being the major component now.

A solution of 180 mg (1.0 mmol) of the crude mixture of **26a/26b** and **32a/32b** (obtained from the above cyclization reaction) in 10 mL of MeOH containing 50 mg of 10% Pd on carbon was hydrogeneated at room temperature and 1 atm until *ca.* 32 mL of H_2 (22.4 mL = 100%) had been taken up (3.0 h). Filtration through Celite and evaporation gave 172 mg (95%) of golden yellow liquid. IR (neat) 1705 cm^{-1} (acyclic and/or cyclohexanone C=O), no cyclopentanone C=O in the 1710–1750 cm^{-1} region; NMR (CCl_4) δ 2.09 (broad s, $CH_3C=O$), no C=CH in the 5.2–6.2 region.

4-Acetyl-4-methyl-1,2-diphenyl-cyclohexene (**39**)

To an ice-cold solution of 1.70 mL of 1.952 M ethereal MeLi (3.32 mmol) in another 12.0 mL of Et_2O was added, dropwise over *ca.* 5 min, a solution of 829 mg (3.0 mmol) of **37**[16] in 6.0 mL of Et_2O. After washing in traces of **37** with 2.0 mL of Et_2O and stirring at ice temperature for 0.5 h the resulting solution was transferred via cannula into 25 mL of cold saturated aqueous NH_4Cl. Extraction with Et_2O, washing with brine, drying, and concentration gave 1.055 g of crude **38** as a pale yellow viscous liquid IR (neat) 3360 (OH), 3060, 3025, 1595, 1493, 773, 712 (Ph-) 1100 cm^{-1} (C–O); NMR (CCl_4) δ 1.00 (s, 3H, CH_3), 1.17 (d, J = 6.5 Hz, 3H, $\underline{CH_3}CHOH$), 1.4-2.8 (m, 7H, aliphatic CH, including a broad singlet at 1.85, exchangeable with D_2O, due to alcohol OH), 3.50 (m, 1H, $CH_3\underline{CH}OH$), 6.97 (s, 10H, ArH); MS *m/e* (rel intensity) 292 (M^+, 11), 91 ($C_7H_7^+$, 100), 274 ($M-H_2O$, 4), 259 ($M-H_2O$, CH_3, 5), 247 ($M-CH_3CHOH$, 10), 231 (18), 129 (16), 128 (17), 115 (24), 105 (20), 77 ($C_6H_5^+$, 27), 65 (12), 45 (CH_3CHOH^+ 34.6), 44 (20), 43 (33).

Without further purification crude **38** was stirred at room temperature in 15 mL of CH_2Cl_2 with 970 mg (4.5 mmol) of $C_5H_5NHCrO_3Cl$[13] and 74 mg (0.9 mmol) of NaOAc for 2.0 h (some alcohol remaining), and then with another 485 mg of $C_5H_5NHCrO_3Cl$ and 37 mg of NaOAc for another 2.0 h. The resulting dark brown mixture was diluted with *ca.* 4 volumes of Et_2O and filtered through Florisil. The residue in the reaction flask was washed several times with Et_2O and the washings also filtered. Evaporation of the combined solutions left 977 mg of reasonably pure **39** as a viscous yellow liquid, that solidified slowly upon standing. This was dissolved in 10 mL of hexanes and cooled in a dry ice bath to give 560 mg (64%) of pale yellow powder, m.p. 73.5–76.5°. Concentration and cooling of the mother liquor gave another 197 mg (23%) of yellow solid, m.p. 65–72°. Several recrystallizations from hexanes gave analytically pure **39**, m.p. 76.5–78.5°. IR (melt) 1700 (C=O), 3050, 3025, 1595, 1495, 772, 712 (Ph-), 1445, 1360 cm^{-1}; NMR (CCl_4) δ 1.23 (s, 3H, CH_3), 2.13 (s, 3H, $CH_3C=O$), 1.4–3.2 (m, 6H, aliphatic CH), 7.0 (m, 10H, ArH); MS *m/e* (rel intensity) 290 (M^+, 30), 247 ($M-CH_3CO$, 100), 275 ($M-CH_3$, 9), 205 (19), 191 (17), 169 (17), 144 (16), 129 (17), 128 (13), 115 (15), 105 (13), 91 (53), 77 (14), 43 (CH_3CO^+, 76). Calc for $C_{21}H_{22}O$: C, 86.85; H, 7.64. Found: C, 86.64; H. 7.80%.

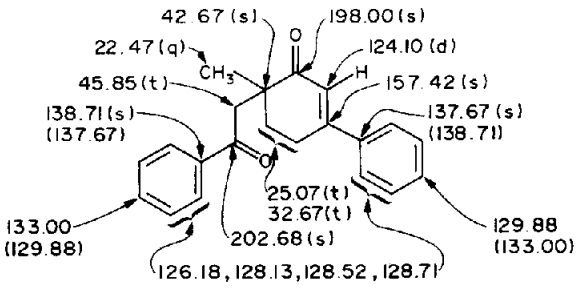
3-Acetyl-3-methyl-1,6-diphenyl-1,6-hexanedione (**33**)

Ozonolysis of 145 mg (0.5 mmol) of **39** in 10 mL of EtOAc was performed at -78° until the purple color of excess O_3 became visible. Excess O_3 was removed by bubbling N_2 into the cold solution, and after warming to room temperature 25 mg of 10% Pd on carbon was added. The mixture was cooled in an ice bath and hydrogenated at 1 atm pressure until 11.6 mL of H_2 (11.2 mL = 100%) had been taken up (0.5 h). Filtration through Celite and evaporation left 173.6 mg (108%) of crude **33** as a viscous pale yellow oil. Tlc (silica gel, 5% EtOAc in CH_2Cl_2) showed one major component, R_f 0.405, contaminated by small amounts of other substances. Preparative tlc (silica gel, 5% EtOAc in CH_2Cl_2) gave 126.3 mg (77%) of purified **33**. A second ptlc (silica gel, 3:1 hexanes/EtOAc) gave analytically pure **33** as a viscous pale yellow liquid. IR (neat) 1685 (ArC=O), 1700 (C=O), 3070, 1599, 1580, 767, 705, (Ph-), 1455, 1360, 1226, 1015 cm^{-1}; NMR (CCl_4) δ 1.31 (s, 3H, CH_3), 1.7–2.1 (pseudotriplet, 2H, $\underline{CH_2}CH_2C=O$), 2.16 (s, 3H, $CH_3=O$), 2.6–3.0 (pseudotriplet, 2H, $\underline{CH_2}CH_2C=O$), partially overlaps AB quartet: 2.99, 3.50 (doublets, J = 18 Hz, 2H total, $CH_2C=O$), 7.0–7.5 (m, 6H, ArH), 7.6–8.2 (m, 4H, ortho-ArH); MS *m/e* (rel intensity) 323 ($M+1$, 0.06), 105 ($PhCO^+$, 100), 305 (0.24), 279 ($M-CH_3CO$, 2.7), 203 [$M+1-PhC(OH)=CH_2$, 2.8], 158 (11), 120 [$PhC(OH)=CH_2^+$, 24], 77 ($C_6H_5^+$, 64), 51 (17), 43 (28). Calc. for $C_{21}H_{22}O_3$: C, 78.23: H, 6.88. Found: C, 78.04; H, 6.70%.

Cyclization of **33** *to 6-methyl-3-phenyl-6-(2-oxo-2-phenylethyl)-2-cyclohexen-1-one* (**35**)

To a solution of 75.2 mg (0.23 mmol) of **33** in 4.0 mL of MeOH was added 0.23 mL (0.23 mmol) of 1.0 M KOH in MeOH, and the resulting yellow solution was then refluxed under N_2 for 0.5 h. After cooling in an ice bath the reaction mixture was partitioned between H_2O and Et_2O, and the combined ether layers washed with brine, dried, and evaporated to leave 69.0 mg (97%) of viscous golden yellow liquid. Tlc (silica gel, 5% EtOAc in CH_2Cl_2) showed only one component, R_f 0.57, except for a trace of starting material (R_f 0.30). Preparative tlc (silica gel, 5% EtOAc in CH_2Cl_2) gave analytically pure **35**. IR (CCl_4) 1690 (ArC=O), 1665 (enone C=O), 3060, 1610, 1595, 1495, 700 (Ph-), 2930, 1450, 1353, 1220, 898 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 1.14 (s, 3H, CH_3), 1.7–2.98 (m, 4H, aliphatic CH), 3.10, 3.36 [two

doublets, AB quartet, J = 17.5 Hz, 2H total, $CH_AH_BC(Ar)=O$], 6.36 (broad s, 1H, C=CH), 7.2–7.8 (m, 8H, ArH), 7.8–8.3 (m, 2H, ortho-$C_6H_5C=O$); ^{13}C NMR (CCl_4) ppm (off-resonance multiplicity:



MS *m/e* (rel intensity 305 (M + 1, 1.03), 304 (M^+, 0.44), 77 ($C_6H_5^+$, 100), 199 (M-PhCO, 1.5), 184 [M-PhC(OH)=CH_2, 60], 144 (184–$CH_3C{\equiv}CH$, 59), 128 (7), 116 (144–CO, 33), 115 (144–CHO, 48), 105 ($PhCO^+$, 60), 91 ($C_7H_7^+$, 17), 65 (8), 63 (8), 55 (16), 51 (40.6), 50 (28), 43 (10), 41 (16), 39 (29). (Calc. for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.57; H, 6.47%.

Acknowledgements—We thank the National Institutes of Health and the National Science Foundation for financial support.

REFERENCES AND NOTES

[1a]Presented in part at the American Chemical Society National Meeting, Chicago, Illinois, 28 August–2 September 1977; Abstract ORGN 169; [b]National Cancer Institute Postdoctoral Trainee, 1 April 1977–30 September 1978.

[2]J. E. Baldwin, *J. Chem. Soc. Chem. Commun.* 734 (1976).

[3a]J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman and R. C. Thomas, Ibid., 736 (1976); [b]J. E. Baldwin, Ibid., 738 (1976); [c]J. E. Baldwin and J. A. Reiss, Ibid., 77 (1977); [d] J. E. Baldwin, R. C. Thomas, L. I. Kruse and L. Silberman, *J. Org. Chem.* **42** 3846 (1977).

[4a] J. E. Baldwin and L. I. Kruse, *J. Chem. Soc. Chem. Commun.*, 233 (1977); [b]H. O. House, W. V. Phillips, T. S. B. Sayer, and C. -C. Yau, *J. Org. Chem.* **43**, 700 (1978).

[5]R. Criegee, A. Banciu and H. Keul, *Chem. Ber.* **108**, 1642 (1975), and references cited therein.

[6]M. Tamele, C. J. Ott, K. E. Marple and G. Hearne, *Ind. Eng Chem.* **33**, 116 (1941).

[7]The formation of small amounts of diketone **15** and monoketone **16** as by-products in a similar *mono*alkylation-cleavage procedure has been suggested: [a]S. Boatman, T. M. Harris and C. R. Hauser, *J. Org. Chem.* **30**, 3321 (1965); [b]*Org. Synth. Coll. Vol. V*, 767 (1963).

[8]G. Casini, M. Ferappi and D. Giardina, *Ann. Chim. (Rome)* **62**, 814 (1972).

[9]A. Butenandt, E. Biekert, M. Däuble and K. H. Körhmann, *Chem. Ber* **92**, 2172 (1959).

[10]D. Bondon, Y. Pietrasanta and B. Pucci, *Tetrehedron Letters* 821 (1977).

[11]M. Kohn and M. Weissberg, *Monatsh.* **45**, 295 (1924).

[12a]D. Seebach and H. Neumann, *Chem. Ber.* **107**, 847 (1974); [b]H. Neumann and D. Seebach, *Tetrehedron Letters* 4839 (1976).

[13]E. J. Corey and J. W. Suggs, *Ibid.* 2647 (1975).

[14]C. Weizmann, E. Bergmann and M. Sulzbacher, *J. Org. Chem.* **15**, 918 (1950).

[15]A. V. Gurevich, N. I. Skvortsova, N. Ya. Zyryanova, G. V. Kostyuk and S. A. Prikhod'ko, *Tr. Vses. Nauch. -Issled. Inst. Sin. Natur. Dushist. Veschest*, 60 (1971); *Chem. Abs.* **78**, 110657n.

[16]J. E. Baldwin and M. J. Lusch, *J. Org. Chem.* **44**, 1923 (1979).

[17]J. Dreux, *Bull. Soc. Chim. Fr.* 521 (1955).

[18]A similar formal retro-Diels–Alder type process with loss of an *alkene* rather than an *alkyne* was invoked to explain the appearance of base peak (*m/e* 82) in the mass spectra of piperitone and carvone: H. Budzikiewicz, C. Djerassi and D. H. Williams, *Mass Spectrometry of Organic Compounds*, p. 203. Holden-Day, San Francisco (1967).

[19]Reactions involving air or moisture sensitive substances were conducted in a static, slightly positive-pressure nitrogen atmosphere. Reactions involving aqueous work-up usually employed a final wash of the combined organic extracts with a saturated aqueous NaCl solution (brine). Drying was then carried out over anhydrous $MgSO_4$ unless otherwise stated, and the solvent removed at ≤40° on a rotary evaporator at water aspirator pressure. Traces of solvent were removed with a vacuum pump when feasible in light of product volatility.

Analytical thin-layer chromatography (tlc) was performed on precoated Merck Silica Gel 60F-254 plates (2 × 10 cm) with UV or I_2vapor visualization. Preparative thin-layer chromatography (PTLC) was carried out on 20 × 20 cm plates with a 1.25 mm thick layer prepared from Merck Silica Gel 60F-254, or with a commercially prepared 2.0 mm layer of Silica Gel GF-254 (Analabs). Column chromatographies utilized Merck Silica Gel 60 adsorbent (70–230 mesh). Gas chromatographic analyses (GC) were performed on a Varian Aerograph Model 700 thermal conductivity instrument or a Varian Model 1200 flame ionization instrument. Ozonolyses were conducted with a Welsbach Model T-23 ozonator producing *ca.* 1.4 mmol O_3/min. Melting points were taken on a Thomas-Hoover apparatus in sealed, evacuated capillary tubes, and melting points and boiling points are uncorrected.

Ir spectra were recorded on a Perkin–Elmer Model 700 infrared spectrophotometer and were calibrated against polysterene. Proton NMR spectra were obtained at 60 MHz unless otherwise stated, on a Varian Associates T-60, or a Perkin–Elmer R-20B or R-24B spectrometer; 90 MHz spectra were recorded on a Perkin–Elmer R-22 spectrometer. Chemical shifts are reported in δ values, parts per million (ppm) relative to Me_4Si as an internal standard. The notations given in parentheses are the multiplicity of the signal (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), the coupling constants if applicable, the number of protons, and the assignment (if made). Carbon-13 NMR spectra were recorded on a JEOL FX 60Q FT-NMR instrument at 15 MHz with complete proton decoupling. Mass spectra were determined on a Varian MAT 44 quadrupole mass spectrometer at 70 ev.

[20]H. N. Grant, V. Prelog and R. P. A. Sneeden, *Helv. Chim. Acta* **47** 415 (1963).