Annulation of α-Formyl α,β-Unsaturated Ketones by a Michael Addition-Cyclization Sequence. A Versatile Synthesis of Alicyclic Six-Membered Rings[1]

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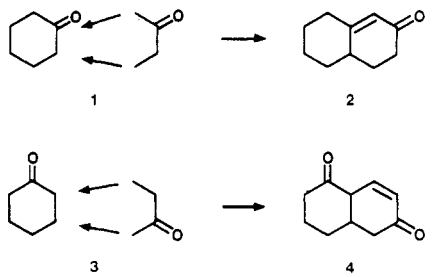
The potential generality of the annulation sequence shown in Scheme II (**10** → **11** → **12** → **13** → **14/15**) has been examined in model systems. Dehydrogenation of α-formylcyclohexanones **11a–d** with 1 equiv of DDQ rapidly produces α,β-unsaturated α-formyl ketones **12a–d**, even when the structures (**12a,b**) would permit over-oxidation to a benzenoid system. DDQ also converts 2-acetyl-4,4-dimethylcyclohexanone to its 2,3-dehydro derivative, but this reaction is much slower than that with the β-keto aldehydes. Enalones **12** are rapidly converted to their β,γ-unsaturated enolic isomers **16** by acid or base unless this transformation is blocked by geminate γ-substitution as in **12c** and **12d**. β-Keto ester sodium enolates also effect this isomerization, which precludes their Michael addition (**12** → **13**) to enalones bearing a γ-hydrogen (**12a**, **12b**, etc). 4,4-Dimethyl-2-formyl-2-cyclohexenone (**12c**) undergoes rapid Michael addition with sodium enolates of *tert*-butyl and benzyl β-keto esters **19a–d**. In addition to the normal adducts **13a–d**, a cyclic hemiketal tautomer **20** appears to be present in the adduct from **19a** and perhaps also that from **19c** but not in those from **19b** and **19d**. Treatment of the *tert*-butyl ester adducts with TFA or TsOH–AcOH transforms **13b** into the octalindione **14b** in high yield but produces neither **14a** nor **15a** from **13a**. Hydrogenolysis of the benzyl ester adducts is accompanied by decarboxylation to afford hydroxymethylene diketones **24a** and **24b**, which cyclize in acid to the octalindiones **14a/15a** (a tautomeric mixture) and **14b**, respectively. Structures of **14a** and **15a** were verified by conversion to *cis*- and *trans*-4,4-dimethyldecalin-1,6-diones (H_2/Pt and then Cr(VI)) and by aromatization and hydrogenolysis to 4,4-dimethyl-6-tetralol, which was independently prepared from 10-(ethoxycarbonyl)-8,8-dimethyl-$\Delta^{1(9)}$-2-octalone by SeO_2 dehydrogenation to the $\Delta^{1(9),3}$-2-hexalone, saponification, and decarboxylation.

The majority of synthetic sequences for adding a fused six-membered carbocyclic ring to a ketonic precursor essentially involve bridging two adjacent positions of the ketone by a new four-carbon segment.[2] The traditional Robinson annulation is a characteristic example. Like the Robinson process, most such annulations result in attachment of the new four-carbon unit to the carbonyl carbon and the α-carbon (**1** → **2**), these being the two readily reactive sites of the parent ketone. For elaboration of ring C in syntheses of several diterpenoids, we devised a new four-step sequence which utilizes the carbons α and β to the carbonyl to become part of the new ring (**3** → **4**),[3] a strategy which leaves the original carbonyl group intact and available for further manipulation. Since this sequence appears quite attractive as a general method for construction of substituted and functionalized six-membered rings, study of its versatility and limitations has been undertaken. The initial phase of this investigation is reported here.

The basic four-step sequence is illustrated in Scheme I with partial structures from our ferruginol synthesis.[3b] Ketone **5**, a *trans*-β-decalone in our diterpenoid work, is condensed with a formic ester and the hydroxymethylene derivative **6** is converted to an α-formyl α,β-unsaturated



ketone **7** by dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). At this stage the carbon β to the ketone has been converted to a highly electrophilic site, and Michael addition of a suitable enolate rapidly forms adduct **8**. If this adduct is a *tert*-butyl β-keto ester, as shown, exposure to acid brings about sequential de-*tert*-butylation, decarboxylation, and aldol cyclodehydration, completing formation of the new ring as an enedione (**9**). Yields in the individual reactions have generally been quite good, resulting in overall yields of 50–75% through the four-step sequence in ten related cases which differ only in substituents on the starting decalone and/or the new ring.[3] Furthermore, the sequence is convenient to conduct; reaction conditions are not cumbersome, reaction times are relatively short, and extensive purification of intermediates **6–8** is rarely necessary.

Projected to the more general case, part of the potential utility of this sequence and some of its possible limitations may be visualized from Scheme II. Step A poses the usual problem of regioselectivity in α-acylation of unsymmetrical ketones. In view of the relatively large body of existing literature on this subject,[4] we have not pursued it at this time. Step B provides several points of inquiry, including (a) whether dehydrogenation will also be satisfactory when one or both of R^1 and R^2 are hydrogen atoms (i.e., when

(1) Abstracted in part from Ph.D. dissertations of M.J.B., T.E.G., and R.W.H. and the M.S. thesis of C.G.B., University of Arkansas.

(2) For reviews and summaries of numerous annulation sequences, see inter alia: (a) Jung, M. E. *Tetrahedron* **1976**, *32*, 3. (b) Gawley, R. E. *Synthesis* **1976**, 777. (c) Mundy, B. P. "Concepts of Organic Synthesis"; Marcel Dekker: New York, 1979; pp 40–47. (d) Waring, A. J. In "Comprehensive Organic Chemistry"; Barton, D. H. R., Ollis, W. D., Stoddart, J. F., Eds.; Pergamon Press: Oxford, 1979; Vol. 1, pp 1049–1056.

(3) (a) Meyer, W. L.; Huffman, R. W.; Schroeder, P. G. *Tetrahedron* **1968**, *24*, 5959 (b) Meyer, W. L.; Clemans, G. B.; Manning, R. A. *J. Org. Chem.* **1975**, *40*, 3686. (c) Meyer, W. L.; Manning, R. A.; Schindler, E.; Schroeder, R. S.; Shew, D. C. *Ibid.* **1976**, *41*, 1005. (d) Meyer, W. L.; Manning, R. A.; Schroeder, P. G.; Shew, D. C. *Ibid.* **1977**, *42*, 2754. (e) Meyer, W. L.; Sigel, C. W. *Ibid.* **1977**, *42*, 2769. (f) Meyer, W. L.; Sigel, C. W.; Hoff, R. J.; Goodwin, T. E.; Manning, R. A.; Schroeder, P. G. *Ibid.* **1977**, *42*, 4131.

(4) Cf. Waring, A. J. In "Comprehensive Organic Chemistry"; Barton, D. H. R., Ollis, W. D., Stoddart, J. F., Eds.; Pergamon Press: Oxford, 1979; Vol. 1, pp 1027–1062 and references therein.

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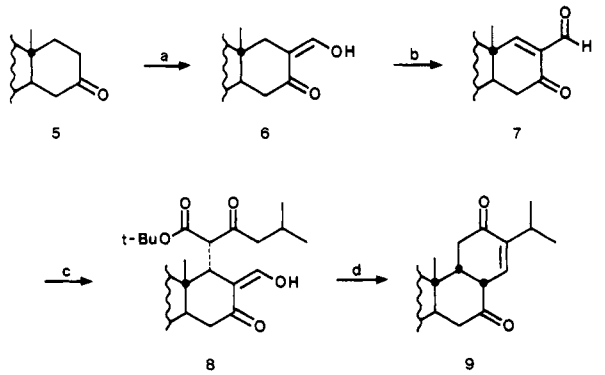
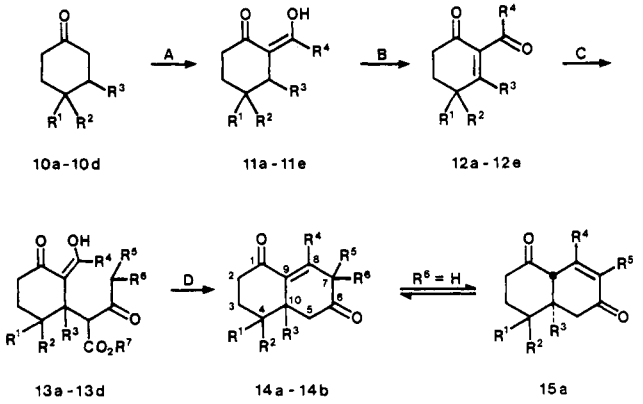
Scheme I[a]



[a] (a) HCO_2Et, NaH, 92%; (b) DDQ, 97%; (c) i-$BuCOCH_2CO_2$-t-Bu, NaH, 90%; (d) TsOH, HOAc, 75%.

Scheme II



10-12, a, R^1-R^4 = H
b, R^1 = t-Bu; R^2-R^4 = H
c, R^1 = R^2 = Me; R^3 = R^4 = H
d, R^1, R^2 = -S⁓S-; R^3 = R^4 = H
e, R^1 = R^2 = R^4 = Me; R^3 = H

13-15, a-d, R^1 = R^2 = Me; R^3 = R^4 = H
a, R^5 = R^6 = H; R^7 = t-Bu
b, R^5 = R^6 = Me; R^7 = t-Bu
c, R^5 = R^6 = H; R^7 = CH_2Ph
d, R^5 = R^6 = Me; R^7 = CH_2Ph

over-oxidation to an aromatic system is possible), (b) whether it will be as successful with β-diketones (R^4 = (alkyl or aryl) as it is with β-keto aldehydes (R^4 = H), and (c) whether it will be inhibited by a β′-substituent (R^3). The first two of these questions will be considered here. The major points regarding step C also focus on its applicability when one of R^1, R^2 is hydrogen or when either R^3 or R^4 is not, and the first of these cases will be described. Finally, in step D we will deal with the applicability of such cyclodehydrations not only in cases where one of R^5, R^6 is hydrogen but also where neither is hydrogen so that the resulting enedione is forced to have structure **14** rather than **15** (cf. **9**). we will also report some interesting differences in this reaction and its products when conformationally flexible systems are involved instead of the rigid *trans*-decalin derivatives.

Model Cyclohexanones (10) and α-Acylcyclohexanones (11). Step A. In order to probe the influence of γ-substitution on the course of events, four model ketones **10** were used for this study: cyclohexanone (**10a**) and its 4-*tert*-butyl (**10b**), 4,4-dimethyl (**10c**), and 4,4-ethylenedithio (**10d**) derivatives. Dimethyl ketone **10c** is readily available through the corresponding cyclohexenone[5] by hydrogenation over Pd, and thioketal **10d** can be prepared from 4-(benzoyloxy)cyclohexanone[6] by thioketalization, saponification, and Moffatt oxidation.

Each of ketones **10a-d** is converted to its α-hydroxymethylene derivative (**11a-d**) by condensation with ethyl formate using sodium hydride–ether,[7] sodium hydride–benzene,[3f] or potassium *tert*-butoxide–*tert*-butyl alcohols.[3e] Scrupulous purity of these derivatives is generally not required for their successful dehydrogenation. Thus, because considerable decomposition often occurs during their distillation, we have normally used crude products if the hydroxymethylene ketone is non-crystalline. These are obtained in over 90% yield, and from ^1H NMR spectra appear to be at least 95% pure.

So that the effect of replacing hydrogen by an alkyl group in the α-acyl substituent could be examined (R^4 in Scheme II), ketone **10c** was also converted to its α-acetyl derivative **11e** by reaction with acetic anhydride–boron trifluoride.[8]

DDQ Dehydrogenation of α-Acylcyclohexanones. Step B. Like their bicyclic and polycyclic analogues,[3,9] hydroxymethylene ketones **11a-d** all react rapidly with 1 equiv of DDQ in dioxane. Dehydrogenation is complete within 5 min even without acetic acid catalysis, which was beneficial with the decalone derivatives[3c] but is neither necessary nor desirable here. It appears that the α-formyl enone **12** is formed in good yield in each case and that further oxidation and aromatization of the enalones with C-4 hydrogen does not occur extensively, if at all, under these conditions.

In spite of their apparently efficient formation, formyl enones **12a** and **12b** are difficult to isolate without significant loss, for they are much more sensitive than their 4,4-disubstituted counterparts **12c** and **12d** and most of the α-formyl octalones we have prepared.[3] For example, attempted removal of residual dissolved $DDQH_2$ either by extraction with aqueous bicarbonate or by chromatography on Florisil or alumina of higher activity grades, methods which have generally been effective with the bicyclic compounds,[3] often affords relatively low yields of these products accompanied by additional substances which seem to be formed during isolation. Nonetheless, enalones **12a** and **12b** can be obtained in good purity by precipitating most of the $DDQH_2$ with pentane, removing dioxane at room temperature, and *rapidly* chromatographing the residue over neutral alumina of activity grade IV. This adsorbent holds not only $DDQH_2$ and residual DDQ but also polar byproducts from **11a** and **11b**, and the eluted material appears by ^1H NMR to consist of ca. 95% pure enalone in yields of about 75% for **12b** and up to 50% for **12a**. We believe that the low yield of **12a** is a consequence of its transformation to other substances during chromatography rather than during the reaction, because yields of both **12a** and **12b** are lower if chromatography is not completed quickly. Furthermore, rechromatography of the purified formyl enones gives poor material recovery, con-

(5) Chan, Y.; Epstein, W. W. *Org. Synth.* **1973**, *53*, 48.

(6) Jones, E. R. H.; Sondheimer, F. *J. Chem. Soc.* **1949**, 615.

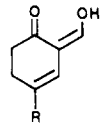
(7) Ainsworth, C. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 536, Method 2.

(8) (a) Manyik, R. M.; Frostick, F. C., Jr.; Sanderson, J. J.; Hauser, C. R. *J. Am. Chem. Soc.* **1953**, *75*, 5030. (b) Hussey, C. W. T.; Pinder, A. R. *J. Chem. Soc.* **1961**, 3525.

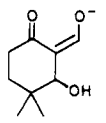
(9) (a) Edwards, J. A.; Calzada, M. C.; Ibanez, L. C.; Cabezas Rivera, M. E.; Urguiza, R.; Cardona, L.; Orr, J. C.; Bowers, A. *J. Org. Chem.* **1964**, *29*, 3481. (b) Caine, D.; DeBardeleben, J. F., Jr. *Tetrahedron Lett.* **1965**, 4585. (c) Ototani, N.; Kato, T.; Kitahara, Y. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1730. (d) Secor, H. V.; Bourlas, M.; DeBardeleben, J. F. *Experientia* **1971**, *27*, 18. (e) Piers, E.; Geraghty, M. B.; Smillie, R. D. *Chem. Commun.* **1971**, 614. (f) Peterse, A. J. G. M.; Roskam, J. H.; de Groot, Ae. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 277. (g) Kende, A. S.; Blacklock, T. J. *Tetrahedron Lett.* **1980**, *21*, 3119.

firming that even on this adsorbent they are converted to more polar substances, presumably their enolic Δ^3 isomers, which are retained on the column.

The sensitivity of **12a** and **12b** is at least partly due to the ease with which they enolize to the corresponding 2-hydroxymethylene 3-enones **16**. Distillation of samples which have IR and ^{1}H NMR spectra characteristic of almost pure **12a** or **12b** affords **12**:**16** mixtures, often with **16** preponderant. Mild bases also transform **12b** to **16b** and **12a** to unidentified products presumably through **16a**. The unsubstituted compound is much more labile than its 4-*tert*-butyl derivative, in which C-4 deprotonation is somewhat sterically hindered by the *tert*-butyl group. For example, with 0.01 M triethylamine in $CDCl_3$ ^{1}H NMR signals of 1 M **12a** are gone within 40 min whereas those of **12b** only completely disappear after 19 h. We believe that it is these changes, brought about by bicarbonate or alumina, which are responsible for the modest yield of **12a** and the poor recoveries in unsuccessful isolation procedures. We have confirmed that **16a** and **16b**, once formed, are completely retained by alumina.



16a, R = H
b, R = t-Bu



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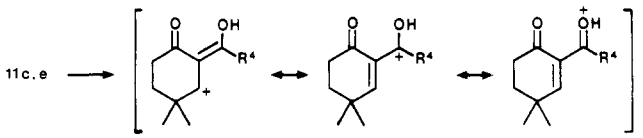
Many attempted syntheses of related cross-conjugated β-dicarbonyl compounds such as 2-acetyl-2-cyclohexenone and 2-carbethoxy-2-cyclohexenone have been frustrated by similar transformations, which have led to enolic Δ^3 isomers as the predominant products.[8b,10] Indeed, other than the DDQ method used here, only the recently developed elimination of α-selenoxy derivatives seems to have been very successful in creating these unusually sensitive structures by the direct introduction of an α,β double bond into the saturated dicarbonyl parent.[11,12] When it is applicable, the DDQ technique is preferable to the selenide methods in terms of experimental simplicity, rapidity, and freedom from obnoxious materials, as well as cost unless elemental selenium[11j] can be used.

4,4-Disubstituted enalones **12c** and **12d** are not nearly as sensitive as their 4-protio analogues. Thioketal **12d** cannot be isolated by the chromatographic technique because it is retained on grade IV alumina, but bicarbonate separation[3] affords it in 78% crude yield, ca. 90% pure. The 4,4-dimethyl compound is obtained in 75% yield by the chromatographic method; here the bicarbonate process is poor because some **12c** is transported into the aqueous phase by formation of hydroxy enolate **17**. The same type of nucleophilic addition is reflected in the shift of its UV absorption in basic solution.[3a,9a] If necessary, **12c** can even be further purified by distillation, but like all related enalones the crude product is adequate for synthetic use.

Dehydrogenation of diketone **11e** is several hundred times slower than the corresponding reaction of the keto aldehydes, but after 48 h with acetic acid catalysis α-acetyl enone **12e** is obtained in good yield. We are reluctant to ascribe the difference in rates to a difference in enol content between the diketone and the keto aldehydes, because all of **11a–e** are completely enolic in $CDCl_3$ so far as we can detect by ^{1}H NMR, and the keto:enol ratio should be about the same in dioxane as in chloroform.[13] In any event a substantial amount of the necessary[14] enol form should be present, and the keto:enol equilibrium should be maintained by acetic acid much faster than **11e** reacts with DDQ. It is also not apparent why a change in R^4 from H to CH_3 on the enolic system **11** should sterically or electronically have such a profound kinetic effect if the reaction involves hydride abstraction from the enol (**11c,e** → **18**) as the rate-determining step, the commonly invoked mechanism for DDQ dehydrogenation of monoketones.[14] Perhaps with these relatively acidic dicarbonyl compounds hydride abstraction (or electron and hydrogen atom transfer[14]) actually occurs from the small concentration of *enolate* which is present; the rate difference would be about right for the difference in pK_a between a keto aldehyde and a diketone.[15]



11c,e

18, R^4 = H, Me

In summary, DDQ dehydrogenation to form α-acyl enones **12** is successful with all of these systems, including those with a C-4 proton, although the latter products must be isolated and used rapidly. The problem which their base sensitivity poses to their use as Michael acceptors is discussed below.

Michael Addition of Enolates to α-Formyl Enones. Step C. For examination of the Michael addition and cyclodehydration steps of the synthesis, attention was focused on enalones **12b** and **12c** as typical examples of the sensitive 4-protio compounds and the more stable 4,4-disubstituted systems, respectively. Sodium enolates of β-keto esters **19a–d** were used as Michael nucleophiles. Enolates were prepared with sodium hydride in Me_2SO or benzene, the former often being preferable for the subsequent Michael addition. Products were usually isolated 1–5 min after addition of the enalone to the enolate, although longer reaction times are occasionally necessary, especially in benzene.

(10) McIntee, M. E.; Pinder, A. R. *J. Chem. Soc.* **1957**, 4419. Brenner, J. E. *J. Org. Chem.* **1961**, *26*, 22. Hussey, C. R. T.; Pinder, A. R. *J. Chem. Soc.* **1962**, 1517. Akhrem, A. A.; Moiseenkov, A. M.; Lakhvich, F. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1972**, 407.

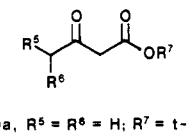
(11) (a) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Org. Chem.* **1974**, *39*, 2133. (b) Reich, H. J.; Renga, J. M. *Ibid.* **1975**, *40*, 3313. (c) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434. (d) Renga, J. M.; Reich, H. J. *Org. Synth.* **1979**, *59*, 58. (e) Bruhn, J.; Heimgartner, H.; Schmid, H. *Helv. Chim. Acta* **1979**, *62*, 2630. (f) Marx, J. N.; Minaskanian, G. *Tetrahedron Lett.* **1979**, 4175. (g) Goldsmith, D. J.; Kezar, H. S., III *Ibid.* **1980**, *21*, 3543. (h) Liotta, D.; Barnum, C.; Puleo, R.; Zima, G.; Bayer, C.; Kezar, H. S., III *J. Org. Chem.* **1981**, *46*, 2920. (i) Marx, J. N.; Minaskanian, G. *Ibid.* **1982**, *47*, 3306. (j) Liotta, D.; Saindane, M.; Barnum, C.; Ensley, H.; Balakrishnan, P. *Tetrahedron Lett.* **1981**, *22*, 3043. For other methods which have succeeded in isolated cases see: (k) Gorenstein, D.; Westheimer, F. H. *J. Am. Chem. Soc.* **1970**, *92*, 634. (l) Marx, J. N.; Cox, J. H.; Norman, L. R. *J. Org. Chem.* **1972**, *37*, 4489.

(12) For some other synthetic methods which have produced enolizable α,β'-unsaturated β-dicarbonyl compounds primarily in their keto forms see: Yates, P.; Jorgenson, N. J.; Singh, P. *J. Am. Chem. Soc.* **1969**, *91*, 4739. Finch, N.; Fitt, J. J.; Hsu, I. H. C. *J. Org. Chem.* **1971**, *36*, 3191. Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.* **1972**, *94*, 5109. Huckin, S. N.; Weiler, L. *Ibid.* **1974**, *96*, 1082. Guaciaro, M. A.; Wovkulich, P. M.; Smith, A. B., III *Tetrahedron Lett.* **1978**, 4661. Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1981**, *46*, 3696. Smith, A. B., III; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855.

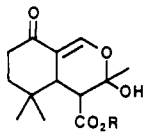
(13) Yoffe, S. T.; Petrovsky, P. V.; Goryunov, Ye. I.; Yershova, T. V.; Kabachnik, M. I. *Tetrahedron* **1972**, *28*, 2783.

(14) Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153. Becker, H.-D. In "The Chemistry of the Quinonoid Compounds"; Patai, S., Ed.; Wiley: New York, 1974; Part 1, pp 335–423 and references therein. The same difficulty applies if the reaction occurs by sequential electron and hydrogen atom transfers to form **18** from **11**, the alternative mechanism which has been suggested for related dehydrogenations.

(15) The pK_a of **11a** is 6.35 (H_2O, 25 °C) while that of 2-acetylcyclohexanone is 10.09; cf. Ebel, H. F. "Die Acidität der CH-Säuren"; Georg Thieme Verlag: Stuttgart, 1969. Schwarzenbach, G.; Felder, E. *Helv. Chim. Acta* **1944**, *27*, 1701.



19a, $R^5 = R^6 = H$; R^7 = t-Bu
b, $R^5 = R^6$ = Me; R^7 = t-Bu
c, $R^5 = R^6 = H$; $R^7 = CH_2Ph$
d, $R^5 = R^6$ = Me; $R^7 = CH_2Ph$



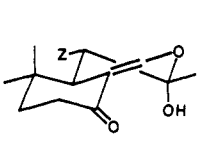
20a, R = t-Bu
c, $R = CH_2Ph$

As one might anticipate from its sensitivity to base-catalyzed isomerization, the only significant products from reaction of *tert*-butyl enalone **12b** with the enolate of either **19a** or **19b** were enol **16b** and recovered **19**. Even though the doubly conjugated double bond of **12b** should be an extremely reactive Michael acceptor, the compound is still more reactive as a carbon acid to these enolates. Thus, in its present form (i.e., with β-keto ester sodium enolates as Michael addends) the annulation sequence is probably inapplicable to α-acyl enones which have a γ hydrogen. Whether it can be induced to succeed by using less basic or softer Michael nucleophiles is under investigation.[16,17]

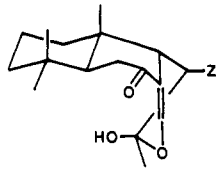
With C-4 substitution blocking isomerization of the enalone system, formyl enone **12c** smoothly undergoes Michael addition with all four enolates. As has been our practice with more complex systems,[3] the adducts have not been extensively purified unless they crystallize, as **13b** does in this case. However, ^{1}H NMR spectra of the crude products are quite diagnostic, structures **13** being readily recognized by characteristic resonances from =C*H*OH, $(CH_3)_3CO$ or $PhCH_2O$, and CH_3CO or $(CH_3)_2CHCO$ protons. Such spectra indicate that two diastereomers of adducts **13b** and **13d** are the only detectable products from **19b** and **19d**, and they are contaminated only by small amounts (15% or less) of residual enalone, excess β-keto ester, and/or oil from the hydride dispersion if it was not removed by washing prior to enolate formation or by extraction of the product into aqueous base.[18] These crude products are quite suitable for use in subsequent reactions.[19]

The product from reaction of **12c** with **19a** is more complex. Its ^{1}H NMR spectrum is best interpreted in terms of the presence of an internal hemiketal **20a** in addition to the usual two diastereomers of the normal adduct **13a**, the **13a:20a** ratio being about 3:1. In addition to two =C*H*OH singlets, two $CH_3C{=}O$ singlets, and two $(CH_3)_3CO$ singlets for **13a** (near δ 8.2, 2.1, and 1.4, respectively), there is a less intense =C*H*OR doublet at δ 7.22[21] and extra singlets at δ 1.53 and 1.42 which would correspond to the CH_3–C–OH and $(CH_3)_3C$–O groups of **20a**. A similar mixture is recovered after dissolution in aqueous base, removal of water-insoluble neutrals with ether, and acidification, strongly suggesting that the third substance is rapidly and reversibly formed from enols **13a**. Furthermore, conversion of the mixture to sodium enolates in benzene and quenching with acetic anhydride produces a 3:1 mixture of only the two diastereomeric enol acetates of **13a**, devoid of substances spectrally related to **20a** (resonance from only two =C*H*OAc, four $CH_3C{=}O$, and two $(CH_3)_3C$–O groups). This again indicates that **13a** and the additional substance revert to and react through common enolates, as is accommodated by structure **20a**. The benzyl acetoacetate adduct probably also contains such a hemiketal (**20c**) in addition to two diastereomers of **13c**. In this case its presence is less clear, however, because the phenyl resonance obscures any characteristic =C*H*OR absorption and the inference must be drawn solely from relative intensities of the =C*H*OH and various $PhCH_2O$ and CH_3 signals. Analogous hemiacetals have been encountered by Snider[16] in related structures.

We have not encountered tautomerization of adducts like **13** to hemiketals like **20** in any other system, including decalone derivatives in which an unsubstituted acetoacetic ester was the addend.[3d,f] Absence of such isomers in systems like **13b**, where there is γ substitution on the keto ester, can be ascribed simply to the greater steric congestion which would result from locating a larger alkyl group on the fully substituted hemiketal carbon of **20**. In the decalone derivatives, however, there is a more cogent factor. The carbocyclic ring of hemiketal **20** can be a chair with an exocyclic double bond only if the other exocyclic bond to the dihydropyran ring (the C–C bond formed in the Michael reaction) is equatorially located on it (cf. **21**). This is quite possible for cyclization of **13**, for even if the Michael addition involves a stereoselective axial attachment of the keto ester, as it is known to do in decalone systems,[3d] the ring is free to subsequently adopt the reverse chair form and thereby place the side chain in the necessary equatorial orientation. However, the trans ring fusion in decalin derivatives like **8** prevents such a ring inversion. Consequently, formation of an analogous tricyclic hemiketal would require the ketonic ring to adopt an unfavorable twist-boat conformation (**22**). This, of course, is also the reason that the trans-syn-cis tricyclic enediones have structures **9** rather than being double bond isomers related to **14**.[3d]



21, Z = CO_2R

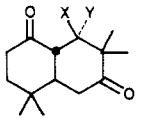


22, Z = CO_2R

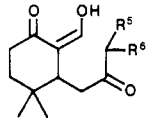
Decarboxylation and Cyclodehydration of Adducts 13. Step D. In previous work,[3] cyclization was brought about by treatment of *tert*-butyl ester adducts like **8** with *p*-toluenesulfonic acid in acetic acid, which induces sequential[3c] *tert*-butyl ester cleavage, decarboxylation, and cyclodehydration in a single synthetic step. This also

(16) See Snider, B. B. *Tetrahedron Lett.* **1980**, *21*, 1133.
(17) In principle such 4-protio annulation products are still accessible, of course, through the use of C-4 protected enalones like **12d** with later deprotection.
(18) Separation of adducts **13** from contaminants by extraction into aqueous base is often convenient but must be done rapidly at low temperature with immediate acidification to prevent loss by reversal of the Michael addition.
(19) The two diastereomers of **13** are considered to differ in the relative configurations of their chiral centers rather than the =CHOH double bond: (a) in analogy with decalone systems where this is certainly the case[3d] and (b) because their =C*H*OH protons differ little in chemical shift, which is unlikely for *E*/*Z* isomers.[13,20] In fact, of course, they are not just =CHOH compounds, but equilibrium mixtures of both intramolecularly hydrogen-bonded enolic forms.[20]
(20) Garbisch, E. W., Jr. *J. Am. Chem. Soc.* **1963**, *85*, 1696; **1965**, *87*, 505.
(21) In 64 α-(hydroxymethylene)cyclohexanone and -decalone derivatives we have examined, including adducts **8** and **13** with various β-keto ester and related side chains, all =C*H*OH resonances have been slightly broadened singlets between δ 8.07 and 8.66, reflecting the fact that they are rapidly equilibrating mixtures of hydroxymethylene ketone and aldehydoenol tautomers with the latter prdominant.[20,22] In 14 corresponding enol ethers, which are locked into the =CHOR form, this resonance falls between δ 7.02 and 7.60.
(22) The =C*H*OH resonance is significantly further upfield, δ 7.15–7.97, in **16a**, **16b**, several 3-hydroxymethylene-$\Delta^{1(9)}$-2-octalones (e.g., ref 3a), and the Δ^5 derivative of **11a**.[20] This suggests that conjugation of an additional endocyclic double bond with either the keto group or the hydroxymethylene system shifts the enolic equilibrium toward the =CHOH form. We doubt that the change in δ is simply due to the anisotropy of the additional C=C because that should deshield the =C*H*OH proton.

transforms adduct **13b** to enedione **14b** in good yield, and refluxing trifluoroacetic acid is even more efficient (73% overall from **12c**). Thus geminate C-7 substitution,[23] which forces the enedione double bond into the 8,9 location (**14** rather than **15**), is no deterrent to cyclodehydration. This is not unexpected. The system is designed so that after decarboxylation and aldol cyclization the hydroxyl group of intermediate ketol **23** is β to not only the C-6 carbonyl but also that at C-1, so that if dehydration toward C-7 is blocked the facile elimination mechanisms open to β-ketols can still occur to form a conjugated system. In fact, two diastereomers of ketol **23** could be isolated from reactions which were incomplete, and each is cleanly converted to **14b** by further acid treatment. This demonstrates that decarboxylation indeed precedes cyclodehydration.[3c,24]



23a, X = OH; Y = H
b, X = H; Y = OH

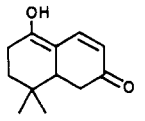


24a, $R^5 = R^6 = H$
b, $R^5 = R^6 = Me$

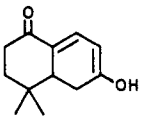
Surprisingly, treatment of the simple *tert*-butyl acetoacetate adduct **13a** with either *p*-toluenesulfonic acid or trifluoroacetic acid did not produce **14a**, **15a**, or any other isolable substance, and ^1H NMR spectra of the unidentified multicomponent product mixtures were devoid of the characteristic olefinic resonances of **14a** and **15a**. This is the only system we have encountered where the acid-catalyzed deesterification–decarboxylation–cyclodehydration sequence has failed. The difficulty clearly occurs before decarboxylation, because hydroxymethylene diketone **24a** can be prepared from the benzyl ester (see below), and it cyclizes normally. The problem also cannot be solely ascribed to the absence of γ substituents on the keto ester side chain, because several decalone analogues of **13a** (**8** without the isopropyl group) have been successfully used.[3d,f] We suggest that the problem originates in the rapid **13a**–**20a** equilibration which is unique to this system, hemiketal **20a** undergoing acid-catalyzed reactions (perhaps initiated by dehydration to pyran derivatives) more rapidly than it reacts at the *tert*-butyl ester moiety.

Problems which stem from unusual acid sensitivity of adducts **13** can be circumvented by use of benzyl β-keto esters, which allow separation of the decarboxylation and cyclization steps. In the presence of catalytic amounts of pyridine, hydrogenolysis of the benzyl group from crude **13c** or **13d** is accompanied by decarboxylation[3d] to cleanly afford hydroxymethylene diketone **24a** or **24b**. In acid these intermediates cyclize smoothly to the desired enediones.

The absence of geminate substitution at C-7 allows the enedione from **13c** to exist as either a Δ^7 or a Δ^8 structure, **15a** or **14a**. Tricyclic analogues have been exclusively of the former type. This is not at all the case in this bicyclic system. The cyclization product is invariably a mixture of three substances which we have not been able to separate and individually examine because every attempt to do so simply regenerates the three-component mixture. Nonetheless, from its ^1H NMR properties and chemical transformations it is clear that this product is a tautomeric mixture of the two enediones **14a** and **15a** together with enol **25**.



25



26

The relative amounts of **14a**, **15a**, and **25** vary from sample to sample, and we have not obtained a mixture which we can confidently demonstrate represents the true equilibrium composition. However, on the basis of relative intensities one can assign a δ 7.50 doublet of doublets (J = 2 and 10 Hz) and a δ 6.08 doublet of doublets (J = 3 and 10 Hz) to the vinyl protons of one component, a δ 7.04 doublet of triplets (J = 2 and 3 Hz) to the sole vinyl proton of the second, and a pair of 10-Hz doublets at δ 7.78 and 5.68 to the third. These assignments from relative intensities were confirmed by INDOR spectra,[25] which unequivocally show that the δ 7.50 resonance is spin coupled to the δ 6.08 resonance and to some peaks in the COC*H*C= multiplet between δ 3.0 and 2.8 but *not* to any other vinyl resonance and that the δ 7.04 resonance is coupled to other peaks in the δ 3.0–2.8 envelope but to *no* vinyl proton. That the three components are indeed interconvertibly related was not only inferred from the variable composition of their mixture but was demonstrated by their ^1H NMR spectrum in methanol containing a trace of sodium methoxide. In $CDCl_3$ interconversion is slow enough for the three compounds to show their individual spectra, but their base-catalyzed equilibration in methanol is fast on the NMR time scale so that only the time-average spectrum is seen. The vinyl region simplifies to a pair of 10-Hz doublets (δ 7.78 and 5.68) and the six C-methyl singlets are replaced by two (δ 1.02 and 0.86). Not only is equilibration fast, but also in methanol the equilibrium is shifted almost completely to enol **26**. That the base-induced change is not permanent is shown by reexamination of the same sample in $CDCl_3$, whereupon the original three-component spectrum is regenerated.

Accepting for the moment that all three components have the 1,6-dioxodecalin skeleton, evidence for which is presented below, the number and multiplicity of vinyl proton resonances requires that the first component is either the trans Δ^7 compound **15a** or its cis isomer, the second can only be the Δ^8 dione **14a**, and the third must be one of the two possible enols **25** or **26**. The decision between the cis and trans Δ^7 structures is straightforward from the H-8–H-9 and H-7–H-9 coupling constants; 2 Hz (vicinal) and 3 Hz (allylic) are in good accord with the ca. 90° dihedral angle in the trans compound **15a**, but not for the ca. 25° angle in its cis relative (Dreiding models), for which couplings of 6 Hz and less than 1 Hz, respectively, are expected.[26-28] For the enolic component we choose

(23) For convenience all hydronaphthalene derivatives in this paper are named by the decalin–tetralin convention, with numbering as shown in **14**. All substances were prepared only in racemic form, although the prefix (±) is omitted and only one enantiomer is depicted.

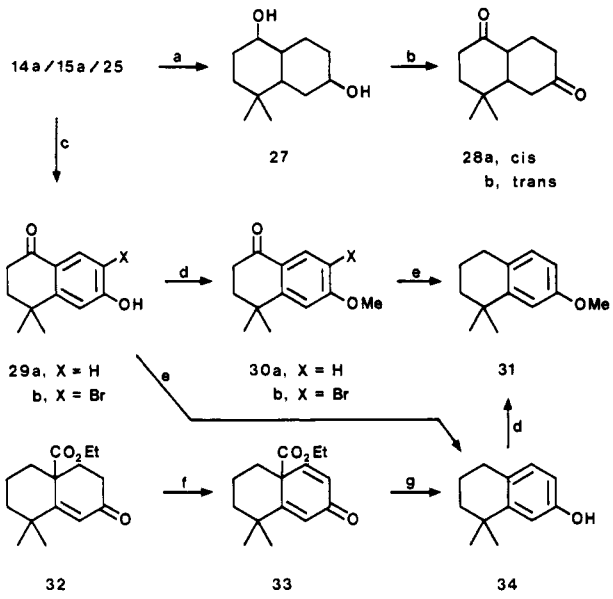
(24) The alcohols are tentatively assigned stereo structures **23a** and **23b** as shown, based on (a) the assumption that acid has equilibrated the α-decalone system to the trans ring fusion (cis isomers have serious nonbonded interactions in either chair–chair form), (b) the coupling constants between H-8 and H-9 (9.5 and 2 Hz, respectively), and (c) the presence of intramolecular H bonding in **23a** ($\nu_{C=O}$ 3540 cm^{-1}) but not **23b** ($\nu_{C=O}$ 3580 cm^{-1}) where the C-1 carbonyl is too far from the axial OH. In this system the peculiar juxtaposition of methyls and carbonyls makes the axial alcohol the less hindered of the two, so later chromatographic elution of **23b** is not discordant with these assignments. The relative adsorption of **23a** may also be diminished by its intramolecular H bonding.

(25) Baker, E. B. *J. Chem. Phys.* **1962**, *37*, 911. Cf. von Phillipsborn, W. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 472.

(26) Garbisch, E. W., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 5561.

(27) These dihedral angles and J's would be about the same in the reversed chair–half-chain conformer of the cis isomer as in **15a**, but that conformer is not a realistic possibility owing to serious nonbonded interactions of its axial methyl group.

Scheme III[a]



[a] (a) H_2, PtO_2, HOAc, 87%; (b) CrO_3, H_2SO_4, Me_2CO, 80%; (c) $PyHBr_3$, HOAc, 75%; (d) Me_2SO_4, K_2CO_3, 70% (29 → 30), 76% (34 → 31); (e) H_2, Pd/C, 80% (29a → 34), 92% (30a → 31); (f) SeO_2, 80%; (g) KOH, 45%.

25 over **26** from the absence of any detectable allylic coupling in its vinyl resonances; such long-range splittings would be expected in **26** (H-8 with H-10 and/or H-7 with H-5) but not in **25**.

Chemical confirmation of the 1,6-dioxodecalin skeleton in **14a**, **15a**, and **25** was obtained in two ways (Scheme III). Hydrogenation over platinum gives a mixture of saturated diols **27**, which is oxidized by the Jones method[29] to a ca. 1:1 mixture of only the *cis*- and *trans*-4,4-dimethyldecalin-1,6-diones **28**.[30] Alternatively, the enedione mixture was converted by pyridinium hydrobromide perbromide to a mixture of keto phenol **29a** and its bromo derivative **29b**,[3f] and hydrogenolysis of the former produced 4,4-dimethyl-6-tetralol (**34**). This phenol was also synthesized from the known[32] 10-(ethoxycarbonyl)-8,8-dimethyl-$\Delta^{1(9)}$-2-octalone (**32**) by selenium dioxide oxidation to dienone **33** and saponification–decarboxylation. The two samples of **34** and its methyl ether **31**, prepared as shown in Scheme III, were identical.

Thus, in this octalindione the Δ^8 and Δ^7 double-bond tautomers **14a** and **15a** are of about equal energy, while in its trans-syn-cis tricyclic relatives **9** the isomer corresponding to **14a** is substantially disfavored. This difference strikingly illustrates the influence of C-5 conformation on the $\Delta^8 \rightleftarrows \Delta^7$ equilibrium.[23] The Δ^8 compound is only noncompetitive when C-5 cannot be an equatorial substituent on the nonolefinic ring because only then is that ring forced into a twist-boat conformation. This result predicts, of course, that when trans-anti-trans epimers of tricyclic enediones **9** are encountered they should also exist as labile tautomeric mixtures.

In summary, the annulation sequence in Scheme II provides a convenient means for fusing a six-membered enone ring onto C-2 and C-3 of a 4,4-disubstituted cyclohexanone. The new ring can include one or two C-7 substituents (R^5, R^6) if desired. The sequence fails with 4-mono- or unsubstituted cyclohexanones when β-keto ester sodium enolates are used as Michael addends in step C, because C-4 deprotonation takes precedence over Michael addition.[17] Alternative Michael nucleophiles which will remove this limitation are currently under investigation, as are several other points regarding the generality of the sequence and the utility of the bicyclic products.

Experimental Section

Spectroscopic instrumentation and methods were the same as described earlier,[3] except that some ^1H NMR spectra were obtained with a Varian EM-360 or a Bruker HFX-90 spectrometer (CW mode), with the latter being used for all INDOR and spin-decoupling work. ^1H NMR spectra are for $CDCl_3$ solutions unless specified otherwise, with chemical shifts given in parts per million downfield from $SiMe_4$ and coupling constants in hertz. UV spectra indicated "base" were obtained by adding 1–2 drops of 5–10% aqueous NaOH or KOH to the EtOH solution in the cell. Relative intensities of mass spectral peaks are shown in parenthesis as percent of base peak intensity, with the molecular ion identified as M^+.

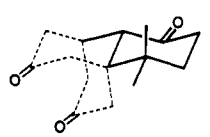
Unless otherwise specified, HCl, H_2SO_4, NaOH, KOH, NH_4OH, Na_2CO_3, K_2CO_3, and $NaHCO_3$ solutions were aqueous and HOAc was glacial. EtOH indicates 95% ethanol unless specified absolute. Petroleum ether refers to the fraction of bp 30–60 °C. Brine refers to saturated aqueous NaCl. General isolation procedures are abbreviated: (A) the specified organic solution was washed with the indicated sequence of aqueous solutions followed by H_2O or brine and dried (Na_2SO_4 or $MgSO_4$), and solvent was removed with moderate heating either in vacuo or in a stream of dry N_2; (B) the indicated aqueous mixture was extracted with the specified organic solvent followed by the steps in procedure A; (C) the reaction mixture was added to H_2O or brine followed sequentially by the steps in procedures B and A. When no temperature is specified, operations were conducted at room temperature, ca. 23 °C. Unless indicated, usually by "(no N_2)", reactions were conducted in a dry N_2 atmosphere. Hydrogenations were conducted at atmospheric pressure. Melting points (open capillary) are corrected for stem exposure. Microanalyses are by Alfred Bernhardt Mikroanalytisches Laboratorium, 5251 Elbach über Engelskirchen, BRD. Dioxane and tetrahydrofuran (THF) were freshly distilled from $LiAlH_4$, dimethyl sulfoxide (Me_2SO), and *t*-BuOH from CaH_2, and PhH from P_4O_{10}.

4,4-Dimethylcyclohexanone (10c). A mixture of 47.7 g (0.385 mol) of 4,4-dimethyl-2-cyclohexenone,[5] bp 46–48 °C (0.5 torr), and 1.0 g of 5% Pd/C in 350 mL of pentane was hydrogenated at ca. 5 °C until absorption ceased, filtered, and concentrated to 150 mL. Chilling in dry ice–*i*-PrOH and filtration gave 39.8 g (82%) of **10c**: mp 43.5–44 °C (lit.[33] mp 43–44.5 °C; lit.[34] mp 40.5–43.5 °C; IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR δ 2.37 (t, J = 7 Hz,

(28) The magnitudes of $J_{7,8}$ and $J_{8,10}$ in **14a** are also in good accord with the Garbisch predictions.[26]

(29) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548. See also: Djerassi, C.; Engle, R. R.; Bowers, A. *J. Org. Chem.* **1956**, *21*, 1547.

(30) Assignment of relative configurations to **28a** and **28b** is *very* tentative, being based only on the chemical shifts of the methyl groups (δ 0.97 and 1.15 vs. 0.96 and 1.36). Consideration of nonbonded interactions indicates that the cis compound should adopt the conformation in which C-4 is equatorial on the unmethylated ring. The equatorial methyl should therefore have the same shift in both isomers, because it is similarly located with respect to other parts of the molecules (cf. composite structure i). The δ 1.15 and 1.36 signals are thus ascribed to the axial methyls. Comparison with various bicyclic and tricyclic compounds from our own work and with steroid systems[31] suggests that such a methyl in the cis isomer should resonate 0.1–0.2 ppm downfield of its trans relative.



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(31) Zürcher, R. F. *Helv. Chim. Acta* **1963**, *46*, 2054.

(32) Meyer, W. L.; Levinson, A. S. *J. Org. Chem.* **1963**, *28*, 2184.

(33) Benkeser, R. A.; Bennett, R. W. *J. Am. Chem. Soc.* **1958**, *80*, 5414.

(34) Talaty, E. R.; Russell, G. A. *J. Am. Chem. Soc.* **1965**, *87*, 4867.

4 H), 1.65 (t, J = 7 Hz, 4 H), 1.09 (s, 6 H).

4,4-[1,2-Ethanediylbis(thio)]cyclohexyl Benzoate. A related procedure was adapted.[35] A solution of 3.72 g (17.1 mmol) of 4-oxocyclohexyl benzoate,[6] mp 59–60 °C, in 4 mL of $(CH_2SH)_2$ (practical grade) at ca. 0 °C was treated with 4 mL of freshly distilled $Et_2O{\cdot}BF_3$, stirred for 10 min, diluted with 20 mL of MeOH, and held at −10 °C overnight. Filtration and washing with cold MeOH afforded 4.38 g (87%) of the thioketal, mp 79–80 °C, which recrystallized from MeOH: mp 81.0–81.2 °C; IR (KBr) 1702 cm^{-1}; ^1H NMR δ 7.92 (m, 2 H), ca. 7.38 (m, 3 H), 5.03 (m, 1 H), 3.28 (s, 4 H), 2.3–1.9 (m, 8 H); MS, m/z (relative intensity) 294 (M^+, 4), 172 (44), 132 (4), 131 (32), 118 (14), 105 (100), 71 (35), 45 (34), 41 (65). Anal. Calcd for $C_{15}H_{18}O_2S_2$: C, 61.19; H, 6.16; S, 21.78. Found: C, 61.17; H, 6.26; S, 21.56.

4,4-[1,2-Ethanediylbis(thio)]cyclohexanol. A mixture of 2.94 g (10.0 mmol) of the thioketal benzoate, mp 79–80 °C, and 3.00 g (53.6 mmol) of KOH in 30 mL of MeOH was stirred under reflux for 3 h. Isolation C ($CHCl_3$; 10% $NaHCO_3$ wash) gave 1.90 g (100%) of the hydroxy thioketal, mp 82.0–82.5 °C, which recrystallized from Et_2O–petroleum ether: mp 84.2–84.4 °C; IR ($CHCl_3$) 3610, 3450, 1050 cm^{-1}; ^1H NMR δ 3.63 (m, 1 H), 3.24 (s, 4 H), 2.2–1.7 (m, 8 H), 2.03 (s, 1 H); MS, m/z (relative intensity) 190 (M^+, 56), 132 (89), 131 (100), 118 (9), 105 (5), 71 (34), 45 (23). Anal. Calcd for $C_8H_{14}OS_2$: C, 50.49; H, 7.42; S, 33.69. Found: C, 50.45; H, 7.32; S, 33.55.

4,4-[1,2-Ethanediylbis(thio)]cyclohexanone (10d). A related procedure was adapted.[36] A solution of 950 mg (5.00 mmol) of hydroxy thioketal, mp 82–83 °C, and 3.09 g (15.0 mmol) of 99% dicyclohexylcarbodiimide in 7.5 mL of 2:1 Me_2SO–PhH was treated with two drops of anhydrous H_3PO_4, stirred for 3 h, and filtered. The filtrate was added to 1.0 g of oxalic acid in 20 mL of 1:1 MeOH–EtOAc, stirred for 30 min, and filtered. Isolation A (10% $NaHCO_3$ wash), dissolution of crude **10d** in 2 mL of CH_2Cl_2, chilling, filtration of residual dicyclohexylurea (DCU), and evaporation afforded 982 mg of an oily 9:1 mixture of **10d** and the starting alcohol (^1H NMR CH_2S intensities) containing some DCU. Chromatography in $CHCl_3$ on 50 g of silica gel gave 613 mg (65%) of the DCU-free mixture in the first 175 mL and 122 mg (13%) of the mixture containing a little DCU in the next 150 mL.

Residual hydroxy thioketal was removed by conversion of **10d** to its (2,4-dinitrophenyl)hydrazone. A solution of 445 mg (2.37 mmol) of the DCU-free mixture and 445 mg (2.25 mmol) of (2,4-dinitrophenyl)hydrazine in 2.5 mL of Me_2SO was treated with two drops of 12 M HCl.[37] Precipitation began at once. Dilution with 1% HCl, filtration, and washing with 1% HCl, H_2O, and MeOH afforded 1.18 g of the derivative, which was hydrolyzed with 25 mL of 2:1 HOAc–H_2O and 2 mL of 99% pyruvic acid at reflux for 4 h. This mixture was added to 100 mL of 5% Na_2CO_3 and brought to pH 9 with solid Na_2CO_3. Isolation B ($CHCl_3$; 10% Na_2CO_3 wash) gave 437 mg (100%) of **10d** as a yellowish oil indistinguishable by ^1H NMR from a distilled sample: bp 170–190 °C (bath) (3 torr); IR (film) 1710 cm^{-1}; ^1H NMR δ 3.33 (s, 4 H), 2.46 (br s, 8 H); MS, m/z (relative intensity) 188 (M^+, 46), 132 (24), 131 (100), 118 (21), 71 (31), 55 (15), 45 (42). Anal. Calcd for $C_8H_{12}OS_2$: C, 51.03; H, 6.42; S, 34.05. Found: C, 50.91; H, 6.43; S, 34.06.

4-*tert*-Butyl-2-(hydroxymethylene)cyclohexanone (11b). A related procedure was adapted.[7] A solution of 15.4 g (100 mmol) of **10b** (mp 49–50 °C; prepared by oxidizing the alcohol by the general method of Brown[38]) in 11.1 g (150 mmol) of HCO_2Et, bp 53–54 °C, was added over 0.5 h to 7.2 g (150 mmol) of 50% NaH–mineral oil in 200 mL of Et_2O at 0 °C. After 6 h at 0 °C and 6 h at ca. 23 °C, the mixture was treated with 2 mL of EtOH, stirred for 1 h, and extracted with 1 × 100 mL and 2 × 50 mL of H_2O which was then neutralized with 6 N HCl. Isolation B (Et_2O) gave 17.4 g (96%) of pale yellow **11b**, mp 29–31 °C, which had no extraneous ^1H NMR absorption and recrystallized from pentane to afford 14.0 g (77%) of colorless **11b**; mp 38.5–40.5 °C.[39] The analytical sample had the following: mp 44.2–45.0 °C; IR (CCl_4) 1648, 1585, 1365 cm^{-1}; UV λ_{max} (EtOH) 281 nm (ϵ 13 900), (base) 313 nm (ϵ 22 200); ^1H NMR δ 8.45 (s, 1 H), 2.5–1.1 (m, 7 H), 0.90 (s, 9 H); MS, m/z (relative intensity) 182 (M^+, 54), 167 (17), 125 (96), 111 (69), 98 (56), 70 (32), 57 (71), 41 (100). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.34; H, 9.72.

4,4-Dimethyl-2-(hydroxymethylene)cyclohexanone (11c). Reaction of 8.63 g (68.5 mmol) of **10c**, mp 44.5–45.0 °C, in 40 mL of *t*-BuOH with the KO-*t*-Bu from 9.7 g (250 mmol) of K in 250 mL of *t*-BuOH followed by 18.4 g (250 mmol) of HCO_2Et in 20 mL of *t*-BuOH was conducted as described for preparation of compound **5a** in ref 3c (8 h reaction time at 45 °C) to afford 9.77 g (93%) of crude **11c** which was suitable for use and indistinguishable by ^1H NMR from distilled samples. Considerable decomposition accompanied distillation, which afforded 4.27 g (40%) of **11c**[11h] as a colorless oil: bp 36 °C (0.05 torr; bath temperature 47 °C); 63–66 °C (3.5 torr); IR ($CHCl_3$) 1648, 1583, 1365 cm^{-1}; UV λ_{max} (EtOH) 280 nm (ϵ 8200), (base) 313 nm (ϵ 19 100); ^1H NMR δ 14.17 (br s, 1 H), 8.39 (s, 1 H), 2.33 (t, J = 6.5 Hz, 2 H), 2.08 (s, 2 H), 1.44 (t, J = 6.5 Hz, 2 H), 0.98 ppm (s, 6 H); MS m/z 154 (M^+, 39), 111 (20), 98 (59), 70 (65), 43 (100). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.95; H, 9.30.

4,4-[1,2-Ethanediylbis(thio)]-2-(hydroxymethylene)-cyclohexanone (11d). Reaction of 96 mg (0.51 mmol) of undistilled **10d** (spectrally pure) in 5 mL of *t*-BuOH with the KO-*t*-Bu from 39 mg (1.0 mmol) of K in 5 mL of *t*-BuOH followed by 74 mg (1.0 mmol) of HCO_2Et in 5 mL of *t*-BuOH was conducted as described for **10c** (11.5-h reaction time, $CHCl_3$ for isolation) to afford 106 mg (96%) of crude **11d** as a yellow oil. It was dissolved in 20 mL of Et_2O and rapidly extracted with cold 1% NaOH which was immediately neutralized with cold 1% HCl. Isolation B ($CHCl_3$) gave 75 mg (68%) of **11d** as light yellow crystals, mp 60–65 °C, which recrystallized from Et_2O–petroleum ether to mp 71.5–71.8 °C: IR ($CHCl_3$) 1645, 1590, 1370 cm^{-1}; UV λ_{max} (EtOH) 282 nm (ϵ 5100), (base) 312 nm (ϵ 16 200); ^1H NMR δ 8.44 (s, 1 H), 3.33 (s, 4 H), 2.90 (s, 2 H), 2.58 (t, J = 6 Hz, 2 H), 2.20 (t, J = 6 Hz, 2 H); MS, m/z (relative intensity) 216 (M^+, 19), 132 (14), 131 (9), 118 (100), 111 (3), 105 (4), 98 (3), 71 (24), 70 (7), 58 (37), 45 (44). Anal. Calcd for $C_9H_{12}O_2S_2$: C, 49.97; H, 5.59; S, 29.64. Found: C, 49.87; H, 5.52; S, 29.64.

General Procedure for DDQ Dehydrogenation of 11a–c. A solution of **11** in dioxane (3–4 mL/mmol) was treated with recrystallized DDQ (mp 213–214 °C; 1.0–1.05 mmol/mmol), stirred for 5 min, diluted with 2–3.5 volumes of pentane, filtered, and evaporated. The residue was rapidly chromatographed through activity IV neutral Al_2O_3 (5–6 g/mmol) with $CHCl_3$. Evaporation left crude **12**, suitable for use. Yields, purities estimated by ^1H NMR, and properties are as follows.

6-Oxo-1-cyclohexene-1-carboxaldehyde (12a) and 2-(Hydroxymethylene)-3-cyclohexen-1-one (16a). Reaction of 378 mg (3.00 mmol) of distilled **11a** gave 108 mg (29%) of oily **12a**,[11h] ca. 95% pure and free of **11a** and **16a**: IR (film) 1705, 1685, 1585 cm^{-1}; ^1H NMR δ 9.93 (s, 1 H), 7.72 (t, J = 4.0 Hz, 1 H), ca. 2.5 (m, 4 H), ca. 2.1 (m, 2 H). Distillation isomerized it partially or completely to **16a**: bp 30–35 °C (2 torr); ^1H NMR δ 7.32 (s, 1 H), 6.08 (d, J = 10 Hz, 1 H), 5.62 (dt, J = 10 and 4 Hz, 1 H), 2.8–2.2 (m, 4 H).

3-*tert*-Butyl-6-oxo-1-cyclohexene-1-carboxaldehyde (12b). Reaction of 182 mg (1.00 mmol) of **11b**, mp 43.5–45 °C, gave 134 mg (74%) of colorless oily **12b**, ca. 98% pure: IR (film) 1715 (w), 1695, 1680, 1595 cm^{-1}; UV λ_{max} (EtOH) 235 nm (ϵ 8800); ^1H NMR δ 9.83 (s, 1 H), 7.71 (t, J = 2.0 Hz, 1 H), 2.6–1.7 (m, 5 H), 1.03 (s, 9 H); MS, m/z (relative intensity) 180 (M^+, 29), 165 (100), 123 (5), 57 (7), 41 (9). Distillation afforded a 1:2 mixture of **12b** and **16b**.

3,3-Dimethyl-6-oxo-1-cyclohexene-1-carboxaldehyde (12c). Reaction of 800 mg (5.19 mmol) of crude **11c** gave 593 mg (75%) of yellowish **12c**[11h] with the same IR and ^1H NMR spectra as a distilled sample: bp 85 °C (0.7 torr); IR (CCl_4) 1720 (w), 1705, 1690, 1600 cm^{-1}; UV λ_{max} (EtOH) 237 nm (ϵ 3900), (base) 305 nm (8400); ^1H NMR δ 9.82 (s, 1 H), 7.30 (s, 1 H), 2.53 (t, J = 6.5 Hz, 2 H), 1.88 (t, J = 6.5 Hz, 2 H), 1.25 (s, 6 H); MS, m/z (relative intensity) 152 (M^+, 11), 85 (69), 83 (100), 47 (33). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.86; H, 8.03.

3,3-[1,2-Ethanediylbis(thio)]-6-oxo-1-cyclohexene-1-carboxaldehyde (12d). Reaction of 59 mg (0.27 mmol) of **11d**,

(35) Sondheimer, F.; Rosenthal, D. *J. Am. Chem. Soc.* **1958**, *80*, 3995.
(36) Fenselau, A. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 1962.
(37) Parrick, J.; Rasburn, J. W. *Can. J. Chem.* **1965**, *43*, 3453.
(38) Brown, H. C. *J. Org. Chem.* **1971**, *36*, 387.
(39) Corey, E. J.; Cane, D. E. *J. Org. Chem.* **1971**, *36*, 3070.

mp 69–70 °C, with 93 mg (0.41 mmol) of DDQ in 3 mL of dioxane for 5 min was followed by dilution with 15 mL of $CHCl_3$ and isolation A (water, 1% $NaHCO_3$ washes) to give 45 mg (78%) of ca. 90% pure **12d** as a yellow oil (^1H NMR estimate): IR ($CHCl_3$) 1725 (w), 1700, 1685, 1595 cm^{-1}; ^1H NMR δ 9.78 (s, 1 H), 7.26 (s, 1 H), 3.34 (s, 4 H), 2.54 (s, 4 H).

2-Acetyl-4,4-dimethyl-2-cyclohexen-1-one (12e). Dehydrogenation of 584 mg (3.48 mmol) of **11e**,[8b] bp 82–85 °C (2.25 torr), by 790 mg (3.48 mmol) of DDQ in 12 mL of dioxane was conducted as described for **11a**, except that 0.3 mL of HOAc was added before DDQ and reaction time was 48 h, with filtration of precipitated $DDQH_2$ and addition of another 790 mg (3.48 mmol) of DDQ after 24 h. Isolation used 20 mL of pentane for precipitation and 10 g of Al_2O_3 with 200 mL of $CHCl_3$ for chromatography, to afford 385 mg (67%) of **12e** with the same ^1H NMR spectrum as a pure colorless sample from Hickman microdistillation: bp 88–98 °C (bath temperature; 1.75 torr); IR (film) 1685, 1585 cm^{-1}; UV λ_{max} (EtOH) 230 nm (ε 6100); ^1H NMR δ 7.16 (t, J = 0.75 Hz, 1 H), 2.50 (t, J = 6.5 Hz, 2 H), 2.39 (s, 3 H), 1.85 (t, J = 6.5 Hz, 2 H), 1.22 (s, 6 H); MS, m/z (relative intensity) 166 (M^+, 82), 151 (67), 85 (32), 83 (49), 43 (100). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.32; H, 8.48.

Base-Catalyzed Isomerization of Formyl Enones 12a and 12b. 4-*tert*-Butyl-2-(hydroxymethylene)-3-cyclohexen-1-one (16b). Solutions of **12a** (54 mg, 0.44 mmol) and **12b** (102 mg, 0.57 mmol), each ca. 95% pure and in 0.4 mL of $CDCl_3$, were treated with 6.0 μL (4.3 μmol) and 7.7 μL (5.5 μmol) of Et_3N, respectively, and their ^1H NMR spectra were taken periodically. The –C*H*=O and –C*H*=C resonances of **12a** disappeared in 40 min and those of **12b** disappeared after 19 h. At those times the solutions were diluted with Et_2O and processed by isolation A (10% HCl wash). From **12a** there resulted 54 mg (100%) of an oil with ^1H NMR properties indicative of some **11a**, very little **16a**, and an unidentified olefinic substance. From **12b** there resulted 87 mg (85%) of an oil which ^1H NMR showed to be mostly **16b**. Distillation afforded ca. 98% pure **16b**: bp 110–130 °C (bath temperature; 2 torr); IR (film) 3050 (v br), 1650, 1625, 1580 cm^{-1}; ^1H NMR δ 7.15 (s, 1 H), 5.72 (t, J = 1 Hz, 1 H), 2.6–2.3 (m, 4 H), 1.07 (s, 9 H); MS, m/z (relative intensity) 180 (M^+, 22), 165 (100), 138 (25), 123 (6), 57 (36), 41 (22).

***tert*-Butyl 4-Methyl-3-oxopentanoate (19b).** Procedures for synthesis of a homologue were modified.[3b] A solution of 134 g (0.848 mol) of **19a**, bp 106–108 °C (22 torr), in 480 mL of PhH was added over 1 h to 61.2 g (1.28 mol) of 50% NaH–mineral oil in 1.2 L of stirred PhH and 1.5 h later 90.4 g (0.849 mol) of *i*-PrCOCl, bp 90–93 °C, in 480 mL of PhH was added over 0.5 h. The mixture was stirred for 25 h, treated with 78 g (1.3 mol) of HOAc, and washed with 1.4 L of brine which was then acidified with 30 mL of HOAc and backwashed with 600 mL of Et_2O. Removal of PhH and Et_2O left 162 g (84%) of crude *i*-PrCOCH(Ac)CO_2-*t*-Bu. Distillation gave 143 g (74%) of colorless diketo ester, free of the *O*-acylation product:[3b] bp 104–106 °C (0.75 torr); ^1H NMR δ 3.12 (sp, J = 6.5 Hz, 1 H), 2.22 (s, 3 H), 1.52 (s, 9 H), 1.12 ppm (d, J = 6.5 Hz, 6 H).

Reaction of 10.0 g (43.9 mmol) of this ester with 17.2 g of 1% NaOH (4.30 mmol) in 115 mL of MeOH for 2.5 h, acidification with 5% HCl, concentration, addition of Et_2O, and isolation A gave 5.77 g (71%) of crude **19b**. Distillation afforded 5.10 g (62%) of colorless **19b**: bp 55 °C (0.1 torr), 64–65 °C (1.5 torr); IR ($CHCl_3$) 1735, 1710, 1375 cm^{-1}; ^1H NMR δ 3.30 (s, 2 H), 2.67 (sp, J = 7 Hz, 1 H), 1.43 (s, 9 H), 1.08 (d, J = 7 Hz, 6 H); MS, m/z (relative intensity) 186 (M^+, 0.2), 130 (9), 113 (10), 87 (18), 71 (40), 57 (100), 43 (81), 41 (49), 29 (31). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 63.87; H, 9.88.

Benzyl 4-Methyl-3-oxopentanoate (19d). A related procedure was adapted.[40] A mixture of 1.27 g (8.04 mmol) of *i*-$PrCOCH_2CO_2Et$[41] and 0.871 g (8.06 mmol) of $PhCH_2OH$ was heated at 160 °C under a short Vigreaux column and still head until EtOH distillation ceased. Hickman distillation of the residue (150 °C bath; 1.75 torr) gave 0.844 g (48%) of colorless **19d**: IR (film) 1740, 1710, 1635 (w), 1613 cm^{-1} (w); ^1H NMR δ 7.19 (s, 5 H), 5.06 (s, 2 H), 3.45 (s, 2 H), 2.62 (sp, J = 7 Hz, 1 H), 1.06 (d, J = 7 Hz, 6 H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.02; H, 7.14.

General Procedure for Michael Addition of Keto Esters 19a–d to Enalone 12c. A mixture of distilled **19** and 50% NaH–mineral oil (0.9–1.1 mmol/mmol) in Me_2SO (1.5–3.0 mL/mmol) was stirred for 15 min, rapidly treated with a solution of crude **12c** (0.7–1.1 mmol/mmol of **19**) in Me_2SO (1.5–2.0 mL/mmol of **12c**), stirred for 1–5 min, and treated with HOAc (0.1 mL/mmol of NaH). Crude **13** was obtained either by isolation C (Et_2O) (**13a,b**) or by dilution with H_2O, extraction with Et_2O, extraction into 10% K_2CO_3 at 10 °C with immediate neutralization in Et_2O–5% HCl, and isolation B (Et_2O) (**13c,d**).[18] Further purification, if any, and properties of the adducts are as follows.

3-(1-(*tert*-Butoxycarbonyl)-2-oxopropyl)-4,4-dimethyl-2-(hydroxymethylene)cyclohexanone (13a). Crude **13a** (324 mg) from 186 mg (1.18 mmol) of **19a**, 53 mg (1.10 mmol) of NaH–mineral oil, and 166 mg (1.09 mmol) of **12c** was separated into mineral oil and two other fractions by preparative TLC on silica gel (Merck F-254) with 9:1 $CHCl_3$–Et_2O. The major fraction (R_f 0.2–0.5) was 227 mg (67%) of an oily mixture of two diastereomers of **13a**, hemiketal **20a**, and a trace of **12c** (^1H NMR assay). This was extracted repeatedly from Et_2O with cold 1% NaOH which was immediately acidified in 1:1 Et_2O–1% HCl.[18] Isolation A gave 170 mg (50%) of an oil which was also *ca.* 75% **13a** and 25% **20a**: IR (film) 3350 (br), 1735, 1715, 1665, 1580 cm^{-1}. ^1H NMR: **13a** isomer A, δ 8.27 (br s, 1 H), 2.17 (s, 3 H), 1.35 (s, 9 H), 0.97 (s, 3 H), 0.85 (s, 3 H); **13a**, isomer B, δ 8.23 (br s, 1 H), 2.01 (s, 3 H), 1.50 (s, 9 H), 1.03 (s, 3 H), 0.97 (s, 3 H); **20a**, δ 7.22 (d, J = 2 Hz, 1 H), 1.53 (s, 3 H), 1.42 (s, 9 H), 0.96 (s, 3 H), 0.92 (s, 3 H). A similar product was obtained in 69% yield by conducting the reaction in PhH and omitting the TLC step.

A 913-mg (2.95-mmol) sample of the 3:1 **13a–20a** mixture in 20 mL of PhH was added to 96 mg (4.00 mmol) of NaH (192 mg of 50% NaH–mineral oil washed with PhH), stirred for 10 min, treated with 719 mg (7.05 mmol) of Ac_2O, stirred for 10 min, and poured into Et_2O–H_2O. Isolation B (Et_2O) gave 810 mg (78%) of a 3:1 mixture of two diastereomers of the **enol acetate of 13a**: IR (film) 1770, 1730, 1700, 1620 cm^{-1}. ^1H NMR: minor isomer, δ 8.06 (s, 1 H), 3.60 and 3.31 (AB, J = 6.0 Hz, 2 H), 2.22 (s, 3 H), 2.19 (s, 3 H), 1.37 (s, 9 H), 1.08 (s, 3 H), 0.87 (s, 3 H); major isomer, δ 7.92 (s, 1 H), 3.75 and 3.55 (AB, J = 8.5 Hz, 2 H), 2.25 (s, 3 H), 2.03 (s, 3 H), 1.47 (s, 9 H), 1.08 (s, 3 H), 0.98 (s, 3 H).

3-(1-(*tert*-Butoxycarbonyl)-3-methyl-2-oxobutyl)-4,4-dimethyl-2-(hydroxymethylene)cyclohexanone (13b). Crude **13b** (388 mg) from 279 mg (1.50 mmol) of **19b**, 72 mg (1.5 mmol) of NaH–mineral oil, and 163 mg (1.07 mmol) of **12c** was stirred in 10 mL of 40% TFA–Et_2O for 8 h to cleave excess **19b**. Isolation C (Et_2O) left 322 mg (89%) of an oily mixture of **13b** (3:1 diastereomers A:B) and a little mineral oil (^1H NMR assay): IR ($CHCl_3$) 1740, 1705, 1630, 1580, 1370 cm^{-1}. ^1H NMR: isomer A δ 8.32 (br s, 1 H), 3.71 (d, J = 4.5 Hz, 1 H), 3.19 (dd, J = 4.5 and 1.5 Hz, 1 H), 1.33 (s, 9 H), 1.10 (d, J = 7 Hz, 6 H), 0.96 (s, 3 H), 0.84 (s, 3 H); isomer B, δ 8.23 (br s, 1 H), 3.67 (d, J = 8.5 Hz, 1 H), 3.05 (dd, J = 8.5 and 1.2 Hz, 1 H), 1.40 (s, 9 H), 1.08 (d, J = 7 Hz, 3 H), 0.95 (s, 6 H), 0.88 (d, J = 7 Hz, 3 H).

Similar reaction of **19b** (89 mg, 0.48 mmol) and **12c** (49 mg, 0.32 mmol) in PhH (13 mL) with 2-h reaction time and without the TFA step gave 138 mg of a **13b–19b**–mineral oil mixture in which the A:B ratio was 1:3. Diastereomer B precipitated from hexanes at –15 °C. Reprecipitation from hexanes at –15 °C followed by precipitation from pentane at –78 °C afforded it as a colorless powder: mp 85.5–86.5 °C; IR and ^1H NMR above. Anal. Calcd for $C_{19}H_{30}O_5$: C, 67.41; H, 8.94. Found: C, 67.03; H, 8.87.

4,4-Dimethyl-2-(hydroxymethylene)-3-[2-oxo-1-((phenylmethoxy)carbonyl)propyl]cyclohexanone (13c). Crude **13c** (932 mg, 76%) from 979 mg (5.10 mmol) of **19c**,[40] 244 mg (5.08 mmol) of NaH–mineral oil, and 541 mg (3.56 mmol) of **12c** was a 1:2 mixture of two diastereomers containing ca. 15% of **12c**: IR ($CHCl_3$) 1740, 1715, 1680, 1630, 1580 cm^{-1}. ^1H NMR: minor isomer, δ 8.22 (br s, 1 H), 7.18 (br s, 5 H), 4.87 (s, 2 H), 2.18 (s, 3 H), 0.90 (s, 3 H), 0.82 (s, 3 H); major isomer, δ 8.22 (br s, 1 H), 7.18 (br s, 5 H), 5.05 (s, 2 H), 2.12 (s, 3 H), 1.12 (s, 3 H), 0.90 (s, 3 H.

4,4-Dimethyl-2-(hydroxymethylene)-3-[3-methyl-2-oxo-1-((phenylmethoxy)carbonyl)butyl]cyclohexanone (13d).

(40) Baker, B. R.; Schaub, R. E.; Querry, M. V.; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 77.
(41) Krocker, E. H.; McElvain, S. M. *J. Am. Chem. Soc.* **1934**, *56*, 1171.

Crude **13d** (153 mg, 38%[42]) from 240 mg (1.09 mmol) of **19d**, 60 mg (1.25 mmol) of NaH–mineral oil, and 177 mg (1.16 mmol) of **12c** was an oily 2:1 mixture of two diastereomers. ^{1}H NMR: major isomer, δ 8.23 (s, 1 H), 7.17 (s, 5 H), 5.03 (s, 2 H), 3.83 (d, J = 9 Hz, 1 H), 3.12 (dd, J = 9 and 1.5 Hz, 1 H), 1.07 (d, J = 7 Hz, 3 H), 0.96 (s, 6 H), 0.86 (d, J = 7 Hz, 3 H); minor isomer, δ 8.25 (s, 1 H), 7.17 (s, 5 H), 4.85 (s, 2 H), 3.79 (d, J = 4.5 Hz, 1 H), 3.22 (dd, J = 4.5 and 1.5 Hz, 1 H), 1.10 (d, J = 7 Hz, 6 H), 0.95 (s, 3 H), 0.87 (s, 3 H).

4,4-Dimethyl-2-(hydroxymethylene)-3-(2-oxopropyl)-cyclohexanone (24a). A mixture of 932 mg (2.71 mmol) of crude **13c**, 271 mg of 30% Pd/C, and 9 drops of pyridine in 150 mL of EtOAc was stirred under H_2 until absorption ceased (3 h), filtered through Celite, and evaporated. The residue was taken up in $CHCl_3$. Isolation A (1% HCl wash) gave 510 mg (90%) of crude solid **24a** which recrystallized from $CHCl_3$–pentane: mp 106–107 °C; IR ($CHCl_3$) 1715, 1630, 1580, 1360 cm^{-1}; UV λ_{max} (EtOH) 272 nm (ϵ 16 500), (base) 310 nm (ϵ 23 000); ^{1}H NMR δ 8.28 (br s, 1 H), 2.6–2.0 (m, 5 H), 2.09 (s, 3 H), 1.50 (m, 2 H), 0.96 (s, 3 H), 0.91 (s, 3 H). The analytical sample decomposed during postal transmittal, so **24a** was characterized as its enol acetate.

A solution of 46 mg (0.22 mmol) of pure **24a** in 3 mL of pyridine and 1.1 mL of Ac_2O was stirred for 15 h. Isolation C (Et_2O) gave 55 mg (99%) of crude **enol acetate** which recrystallized from Et_2O–pentane: mp 54–56 °C; IR ($CHCl_3$) 1770, 1715, 1685, 1605, 1365 cm^{-1}; UV λ_{max} (EtOH) 252 nm (ϵ 14 500); ^{1}H NMR δ 7.81 (s, 1 H), 2.7–2.2 (m, 5 H), 2.16 (s, 3 H), 2.09 (s, 3 H), 1.65 (m, 2 H), 1.06 (s, 3 H), 0.96 (s, 3 H). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.82; H, 7.95.

4,4-Dimethyl-2-(hydroxymethylene)-3-(3-methyl-2-oxobutyl)cyclohexanone (24b). Hydrogenolysis of 150 mg (0.403 mmol) of crude **13d** was conducted as described for **13c** (15 mg of Pd/C, 2 drops of pyridine, 10 mL of EtOAc) to afford 98 mg (102%) of crude semicrystalline **24b**. Trituration with pentane left 45 mg (47%) of colorless **24b**, mp 78–82 °C, which recrystallized from Et_2O: mp 95–95.5 °C; IR ($CHCl_3$) 1710, 1625, 1580, 1365 cm^{-1}; UV λ_{max} (EtOH) 285 nm (ϵ 6450), (base) 313 nm (ϵ 12 500); ^{1}H NMR δ 8.24 (s, 1 H), 2.9–2.3 (m, 6 H), 1.6 (m, 2 H), 1.05 (d, J = 7 Hz, 3 H), 1.02 (d, J = 7 Hz, 3 H), 0.97 (s, 3 H), 0.94 (s, 3 H); MS, m/z (relative intensity) 238 (M$^+$, 7), 220 (12), 205 (26), 195 (13), 177 (45), 153 (47), 71 (71), 43 (100), 41 (44). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.61; H, 9.35.

4,4-Dimethyl-Δ^8-octalin-1,6-dione (14a) and 4,4-Dimethyl-*trans*-Δ^7-octalin-1,6-dione (15a). A solution of 269 mg (1.28 mmol) of **24a**, mp 106–107 °C, and 40 mg (0.21 mmol) of TsOH·H_2O in 17 mL of HOAc was stirred at reflux for 80 min, treated with 150 mg of NaOAc, and concentrated to a small volume. Addition of H_2O and $CHCl_3$ followed by isolation B ($CHCl_3$) left 174 mg (71%) of an oily mixture of **14a**, **15a**, and **25**. Filtration through a short column of Florisil with PhH afforded 134 mg of the same mixture as a yellowish oil which could not be separated into its components or further purified: IR ($CHCl_3$) 1710, 1680 cm^{-1}. ^{1}H NMR: **14a**, δ 7.04 (dt, J = 2 and 3 Hz, 1 H), 2.95 (m, 2 H), 1.06 (s, 3 H), 1.00 (s, 3 H); **15a**, δ 7.50 (dd, J = 10 and 2 Hz, 1 H), 6.08 (dd, J = 10 and 3 Hz, 1 H), 2.85 (m, 1 H), 1.20 (s, 3 H), 1.04 (s, 3 H); **25**, δ 7.78 (d, J = 10 Hz, 1 H), 5.68 (d, J = 10 Hz, 1 H), 1.02 (s, 3 H), 0.86 (s, 3 H).

4,4,7,7-Tetramethyl-Δ^8-octalin-1,6-dione (14b). A. From 13b. A solution of 321 mg (0.950 mmol) of crude **13b** in 10 mL of TFA was refluxed for 45 min. Isolation C (Et_2O; 10% K_2CO_3 wash) left 172 mg (82%; 73% from **12c**) of crude **14b** as a pale yellow oil indistinguishable by ^{1}H NMR from a pure sample. Filtration through Florisil with 19:1 PhH–Et_2O gave crystalline **14b**, mp 50–60 °C, which was recrystallized from hexanes and then from Et_2O at −15 °C to mp 61.5–62 °C: IR ($CHCl_3$) 1720, 1685, 1615 cm^{-1}; UV λ_{max} (EtOH) 240 nm (ϵ 3000); ^{1}H NMR δ 6.63 (d, J = 2.1 Hz, 1 H), 2.48 (m, 5 H), 1.72 (t, J = 7 Hz, 2 H), 1.24 (s, 3 H), 1.15 (s, 3 H), 1.03 (s, 3 H), 0.94 ppm (s, 3 H); MS, m/z (relative intensity) 220 (M$^+$, 0.3), 136 (24), 79 (43), 77 (41), 55 (42), 53 (36), 43 (37), 41 (100), 39 (62), 27 (52). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.39; H, 9.33.

Cyclization of 138 mg of crude **13b** with 17 mg of TsOH in 7 mL of HOAc as described for preparation of **14a–15a** (30 min reaction time) also afforded **14b** (54% from **12c**).

B. From 24b. A solution of 45 mg (0.19 mmol) of **24b**, mp 78–82 °C, in 2 mL of TFA was refluxed for 30 min. Isolation C (Et_2O; 10% K_2CO_3 wash) gave 39 mg (93%) of crude **14b** spectrally identical with the pure sample.

4,4,7,7-Tetramethyl-8-hydroxy-*trans*-decalin-1,6-diones (23a and 23b).[24] Florisil chromatography of the crude product from cyclization of **13b** with TsOH–HOAc for a shorter time gave in early 1:1 Et_2O–hexanes fractions a mixture of **14b** and **23a**, from which **14b** was removed by washing with hexanes to leave colorless **23a**, mp 144.5–148 °C, which recrystallized from Et_2O at −15 °C: mp 148–150 °C; IR ($CHCl_3$) 3540, 1700 cm^{-1}; ^{1}H NMR δ 3.77 (br s, O*H*), 3.62 (d, J = 9.5 Hz, C-8-H_{ax}), 1.17 (s, 6 H), 1.12 (s, 3 H), 0.95 (s, 3 H); MS, m/z (relative intensity) 238 (M$^+$, 7), 220 (8), 153 (100), 55 (21), 43 (27), 41 (37).

A later 1:1 Et_2O–hexanes fraction afforded **23b**, mp 100–106 °C after trituration with PhH. Recrystallization from Et_2O (−15 °C) gave colorless needles: mp 127.2–129.2 °C; IR ($CHCl_3$) 3580, 1710 cm^{-1}; ^{1}H NMR δ 4.13 (d, J = 2 Hz, C-8-H_{eq}), 2.77 (br s, O*H*), 1.17 (s, 6 H), 1.12 (s, 3 H), 0.98 (s, 3 H); MS, m/z (relative intensity) 238 (M$^+$, 13), 220 (5), 153 (100), 55 (26), 43 (33), 41 (43).

Treatment of **23a** or **23b** with TsOH–HOAc for 1.5 h gave **14b**.

***cis*- and *trans*-4,4-Dimethyldecalin-1,6-diones (28a and 28b).** A mixture of 202 mg (1.05 mmol) of crude **14a/15a/25** and 82 mg of PtO_2 in 25 mL of EtOH was hydrogenated for 16 h, filtered through Celite which was washed with $CHCl_3$, and taken to dryness. Dissolution in $CHCl_3$ and isolation A left 180 mg (87%) of an oily mixture of several diastereomers of **27**: IR ($CHCl_3$) 3630 cm^{-1}; ^{1}H NMR δ 4.1 (br), 7 or more sharp singlets 1.45–1.07 ppm.

A solution of 214 mg (1.08 mmol) of crude **27** in 36 mL of Me_2CO at 10 °C was treated with 0.70 mL of Jones reagent[29] (1.87 mmol of Cr(VI)). The cold bath was removed, and after 2 h isolation C ($CHCl_3$; 5% $NaHCO_3$ wash) afforded 168 mg (80%) of an oily ca. 1:1 mixture of **28a** and **28b** (^{1}H NMR CH_3 intensities). The ratio was unchanged after 1 h in MeOH:NaOMe. Chromatography over 5.25 g of Florisil with Et_2O–hexane afforded in early 1:1 fractions 30 mg of pure **28a**, an oil which could not be crystallized, and in late 1:1 fractions 27 mg of pure **28b**, a solid. Intermediate fractions were mixtures.

Oily cis-diketone **28a**[30] had: IR ($CHCl_3$) 1710 cm^{-1}; ^{1}H NMR δ 3.0–1.6 (m, 12 H), 1.36 (s, 3 H), 0.96 (s, 3 H).

trans-Diketone **28b**[30] recrystallized from Et_2O–hexane as colorless prisms: mp 77–78 °C; IR ($CHCl_3$) 1710 cm^{-1}; ^{1}H NMR δ 2.6–2.2 (m, 7 H), 2.1–1.6 (m, 5 H), 1.15 (s, 3 H), 0.97 (s, 3 H). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.20; H, 9.33. Found: C, 74.06; H, 9.23.

4,4-Dimethyl-6-hydroxy-1-tetralone (29a). A stirred solution of 774 mg (4.03 mmol) of chromatographed **14a/15a/25** in 125 mL of HOAc was treated with 1.52 g (4.75 mmol) of $PyHBr_3$,[3b,f] mp 132–135 °C. After 30 min isolation C ($CHCl_3$; 5% $NaHCO_3$ wash) gave 649 mg of a 2:1 mixture (H-8 ^{1}H NMR intensities) of **29a** (50% yield) and its 7-bromo derivative **29b** (25% yield) as a brown semisolid. Fractional crystallization from EtOAc gave pure **29a**: mp 142.0–142.3 °C; IR ($CHCl_3$) 3600, 1680 cm^{-1}; UV λ_{max} (EtOH) 280 nm (ϵ 12 300); (base) 340 nm (ϵ 20 400); ^{1}H NMR δ 7.84 (d, J = 8 Hz, 1 H), 7.48 (br s, 1 H), 6.73 (s, 1 H), 6.63 (dd, J = 2.5 and 8 Hz, 1 H), 2.72 (t, J = 7 Hz, 2 H), 1.97 (t, J = 7 Hz, 2 H), 1.36 (s, 6 H). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.41. Found: C, 75.41; H, 7.56.

^{1}H NMR of the **29a–29b** mixture also had δ 8.02 (s, 1 H), 6.92 (s, 1 H), and 1.34 (s, 6 H) from **29b**.

4,4-Dimethyl-6-methoxy-1-tetralone (30a) and 7-Bromo-4,4-dimethyl-6-methoxy-1-tetralone (30b). A mixture of 120 mg of crude **29a–29b**, 2.0 g of K_2CO_3, and 0.3 mL of Me_2SO_4 in 15 mL of dry Me_2CO was refluxed for 13 h, filtered, and taken to dryness.[3c] Dissolution in Et_2O and isolation A (5% NH_4OH wash) followed by filtration in 1:1 petroleum ether–$CHCl_3$ through 9 g of activity III Al_2O_3 afforded 86 mg (70%) of a mixture of **30a** and **30b** from which samples of each were obtained by fractional crystallization from petroleum ether. **30b**, a yellowish solid, had: mp 103–110 °C; IR ($CHCl_3$) 1680 cm^{-1}; ^{1}H NMR δ 8.19 (s, 1 H), 6.85 (s, 1 H), 3.96 (s, 3 H), 2.68 (t, J = 7 Hz, 2 H), 1.98 (t, J = 7 Hz, 2 H), 1.35 (s, 6 H). **30a**, a yellowish oil, had: IR ($CHCl_3$) 1680 cm^{-1}; ^{1}H NMR δ 8.00 (d, J = 8.5 Hz, 1 H), 6.85 (s, 1 H), 6.78 (dd, J = 2.5 and 8.5 Hz, 1 H), 3.86 (s, 3 H), 2.68 (t, J = 7 Hz, 2

(42) Conditions for preparation of **13d** have not been optimized.

H), 1.98 (t, J = 7 Hz, 2 H), 1.37 (s, 6 H).

8,8-Dimethyl-10-(ethoxycarbonyl)-$\Delta^{1(9),3}$-2-hexalone (33).[43] A related procedure was adapted.[44] A solution of 1.50 g (6.00 mmol) of **32**,[32] 1.60 g (14.4 mmol) of SeO_2, and 6 drops of pyridine in 120 mL of t-BuOH was stirred at reflux for 31 h, filtered, and evaporated to afford 3.15 g of a reddish oil which slowly solidified. This was refluxed with two 15-mL portions of cyclohexane which were filtered and evaporated to leave 1.19 g (80%) of crude **33** as a yellowish solid which was used without further purification. It had: IR (KBr) 1725, 1640 (br) cm^{-1}; UV λ_{max} (EtOH) 250 nm (ϵ 10 900); ^1H NMR δ 6.64 and 6.28 (AB, J = 9 Hz, 2 H), 6.38 (s, 1 H), 4.09 (q, J = 7 Hz, 2 H), 1.23 (s, 3 H), 1.17 (t, J = 7 Hz, 3 H), 1.07 (s, 3 H).

4,4-Dimethyl-6-tetralol (34). A. Hydrogenolysis of 29a. A mixture of 176 mg (0.926 mmol) of pure **29a**, 47 mg of 5% Pd/C, and 3 drops of conc. H_2SO_4 in 25 mL of absolute EtOH was hydrogenated for 36 h, filtered through Celite which was washed with Et_2O, and evaporated. Dissolution in Et_2O, washing with H_2O, extraction into 5% NaOH, and acidification with HCl followed by isolation B ($CHCl_3$) gave 130 mg (80%) of crude **34** as an oil which was crystallized from hexane to mp 103.5–104.5 °C. It was identical by IR, ^1H NMR, and mixture melting point with the product from route B.

B. Saponification of 33. A solution of 566 mg (2.28 mmol) of crude **33** and 1.76 g (31.4 mmol) of KOH in 115 mL of 2:1 H_2O–MeOH was refluxed for 90 h and extracted with Et_2O which was extracted with 5% NaOH. Acidification (HCl) and isolation B (Et_2O) gave 181 mg (45%) of crude **34** which recrystallized from hexane: mp 104–105 °C; IR ($CHCl_3$) 3610, 1603, 1575 cm^{-1}; UV λ_{max} (EtOH) 279 nm (ϵ 1470), (base) 294 nm (ϵ 1800); ^1H NMR δ 6.75 (d, J = 9 Hz, 1 H), 6.66 (d, J = 3 Hz, 1 H), 6.41 (dd, J = 9 and 3 Hz, 1 H), 4.82 (br s, 1 H), 2.63 (br t, J = 6 Hz, 2 H), 1.8–1.6 (m, 4 H), 1.26 (s, 6 H). Anal. Calcd for $C_{12}H_{16}O$: C, 81.78; H, 9.14. Found: C, 81.88; H, 9.28.

4,4-Dimethyl-6-methoxytetralin (31). A. Hydrogenolysis of 30a. A mixture of 119 mg (0.583 mmol) of **30a** and 21 mg of 5% Pd/C in 10 mL of absolute EtOH was hydrogenated until absorption ceased (20 h), filtered, and taken to dryness. Dissolution in Et_2O and isolation A (5% $NaHCO_3$ wash) gave 102 mg (92%) of **31** as a yellowish oil: IR ($CHCl_3$) 1595, 1555 cm^{-1}; ^1H NMR δ 6.82 (d, J = 8 Hz, 1 H), 6.73 (d, J = 2.5 Hz, 1 H), 6.50 (dd, J = 8 and 2.5 Hz, 1 H), 3.70 (s, 3 H), 2.65 (br t, J = 5.5 Hz, 2 H), 1.8–1.6 (m, 4 H), 1.27 (s, 6 H).

B. Methylation of 34. Methylation of **34** (85 mg, 0.48 mmol, prepared from **33**) was conducted like methylation of **29a**, using 1.8 g of K_2CO_3 and 0.2 mL of Me_2SO_4 in 10 mL of Me_2CO. Isolation A (5% NH_4OH wash) gave 85 mg (77%) of crude **31** which was chromatographed on 6 g of activity III Al_2O_3 with 1:1 petroleum ether–$CHCl_3$ to provide 84 mg (76%) of **31** as an oil with the same IR and ^1H NMR spectra as the product from route A.

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Registry No. **10b**, 98-53-3; **10c**, 4255-62-3; **10d**, 54531-74-7; **10d** (2,4-dinitrophenylhydrazone), 94250-45-0; **11a**, 823-45-0; **11b**, 22252-96-6; **11c**, 64230-02-0; **11d**, 94250-46-1; **11e**, 94250-53-0; **12a**, 94250-47-2; **12b**, 94250-49-4; **12c**, 77630-12-7; **12d**, 94250-51-8; **12e**, 94250-52-9; **13a** (diastereomer 1), 94250-57-4; **13a** (diastereomer 2), 94250-58-5; **13a** (enol acetate diastereomer 1), 94250-60-9; **13a** (enol acetate diastereomer 2), 94250-61-0; **13b** (diastereomer 1), 94250-62-1; **13b** (diastereomer 2), 94250-63-2; **13c** (diastereomer 1), 94250-64-3; **13c** (diastereomer 2), 94250-65-4; **13d** (diastereomer 1), 94250-66-5; **13d** (diastereomer 2), 94250-67-6; **14a**, 94250-71-2; **14b**, 94250-74-5; **15a**, 94250-72-3; **16a**, 94250-48-3; **16b**, 94250-50-7; **19a**, 1694-31-1; **19b**, 94250-54-1; **19c**, 5396-89-4; **19d**, 94250-56-3; **20a**, 94250-59-6; **23a**, 94250-75-6; **23b**, 94250-76-7; **24a**, 94250-68-7; **24a** (enol acetate), 94250-69-8; **24b**, 94250-70-1; **25**, 94250-73-4; **27**, 94250-83-6; **28a**, 94250-77-8; **28b**, 94250-78-9; **29a**, 28204-62-8; **29b**, 94250-79-0; **30a**, 23203-51-2; **30b**, 94250-80-3; **31**, 23203-50-1; **32**, 1146-13-0; **33**, 94250-81-4; **34**, 94250-82-5; $(CH_2SH)_2$, 540-63-6; HCO_2Et, 109-94-4; i-PrCOCl, 79-30-1; i-PrCOCH(Ac)CO_2-t-Bu, 94250-55-2; i-PrCOCH$_2$CO$_2$Et, 7152-15-0; $PhCH_2OH$, 100-51-6; 4,4-dimethyl-2-cyclohexenone, 1073-13-8; 4,4-[1,2-ethanediylbis(thio)]cyclohexyl benzoate, 54531-77-0; 4-oxocyclohexyl benzoate, 23510-95-4; 4,4-[1,2-ethanediylbis(thio)]cyclohexanol, 22428-86-0; 2,4-dinitrophenylhydrazine, 119-26-6; 4-*tert*-butylcyclohexanol, 98-52-2.

(43) This preparation was carried out by Dr. A. S. Levinson.
(44) Ringold, H. J.; Ruelas, J. P.; Batres, E.; Djerassi, C. *J. Am. Chem. Soc.* **1959**, *81*, 3712.

Synthesis and Interconversion of the Four Isomeric 6-Oxo-2,4-heptadienoic Acids[1]

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The synthesis of the structural isomers of 6-oxo-2,4-heptadienoic acid was undertaken as a means of providing analogues to investigate the structural requirements of maleylacetone cis–trans isomerase. 6-Oxo-2(Z),4(E)-heptadienoic acid and the methyl esters of 6-oxo-2(E),4(Z)-, 6-oxo-2(Z),4(Z)-, and 6-oxo-2(E),4(E)-heptadienoic acid were synthesized. Base-catalyzed hyrolysis of these esters furnished the corresponding acids except in the case of the 2Z,4Z isomer, which yielded instead the 2Z,4E acid. A mechanism for isomerization is suggested. Photocatalyzed isomerization of the acids and esters as a possible way of generating the ZZ acid was studied. The properties of the acids, their interaction with the enzyme, and what this suggests about the interaction of substrate maleylacetone with the enzyme is discussed.

Studies in this laboratory have been concerned with the mechanism of the enzyme-catalyzed cis–trans isomerization of maleylacetone (1) to fumarylacetone (4-hydroxy-6-oxo-2(E),4-heptadienoic acid, **2**; eq 1).[2] The enzyme requires glutathione as a coenzyme for this reaction. Maleylacetone has been shown to be an approximately 1:1 mixture of diketo (4,6-dioxo-2(Z)-heptenoic, **1b**) and ketoenol (4-hydroxy-6-oxo-2(Z),4(E)-heptadienoic, **1a**, and/or

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(2) Seltzer, S. *J. Biol. Chem.* **1973**, *248*, 215–222. Seltzer, S.; Lin, M. *J. Am. Chem. Soc.* **1979**, *101*, 3091–3097. Morrison, W. S.; Wong, G.; Seltzer, S. *Biochemistry* **1976**, *15*, 4228–4233.

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