# Ring Cleavage of Cyclohexane-1,3-diones in the Aldol Cyclization Step of Robinson Annelations: A Novel Mechanism via Oxa-Twistanes and δ-Lactones[1]

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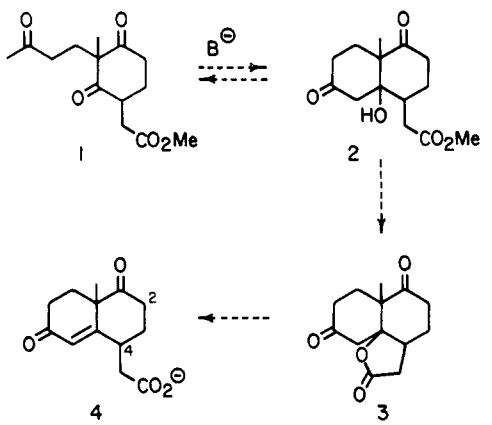
The pyrrolidine-induced aldol cyclization of methyl 2-methyl-2-(3-oxobutyl)-1,3-dioxocyclohexane-4-acetate (1) afforded methyl 1,2,3,4,6,7,8,8a-octahydro-8a-methyl-1,6-dioxonaphthalene-2-acetate (**13**) rather than undergoing lactonization-directed closure in the opposite sense. Mild base-induced cyclization of **1** with sodium methoxide in methanol or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in tetrahydrofuran (THF) effected cleavage of the cyclohexane-1,3-dione ring, giving mainly cyclohexenone acid **14a** (2-(1,4-dimethyl-3-oxo-1-cyclohexen-2-ylmethyl)butanedioic acid monomethyl ester) and δ-lactone **15** (methyl (4aβ,8aβ)-octahydro-6,8a-dimethyl-2,5-dioxo-2*H*-1-benzopyran-4a-acetate). Prolonged exposure of **15** to sodium methoxide in methanol yielded mixtures of acyclic diester **17** and the isomeric γ-lactone **18** presumably via lactone methanolysis to ketol diester **16** followed by retroaldol ring opening or relactonization onto the acetate ester. The structure and stereochemistry of **18** were established by X-ray crystallography (Figure 1). Similar aldol cyclizations of 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (**19**) and its 4-methyl analogue (**11**) with sodium methoxide in methanol or DBU in THF afforded cyclohexenone acids **20a** and **22a**, respectively, the latter accompanied by δ-lactone **23**. Bridged ketols **21** (from **19**) and **24** and **25** (from **11**) were also isolated from the reactions with DBU. A novel mechanism (Scheme I) involving bridging aldol cyclization to endo ketols (**27** and **30**), intramolecular hemiketal formation to oxa-twistanones (**28** and **31**), ring cleavage to δ-lactones (**29** and **32**), and β-elimination of the δ-lactones having an available α-hydrogen to cyclohexenone acids is proposed to explain the formal retro-Claisen transformations in the absence of an external nucleophile (DBU/THF) and the apparent hydrolyses under anhydrous conditions.

The application of the Robinson annelation to the synthesis of octalones bearing substituents at C-8 (C-4 in **4**, C-6 steroid numbering) has been rather limited.[2] Two examples are the annelations of 2-methylcyclohexanone (as the enamine)[3a] and 2,6-dimethylcyclohexanone[3b] with methyl vinyl ketone to give 8-methyl- and 4a,8-dimethyloctalones. However, the use of unsymmetrical α,α'-dialkylcyclohexanones would be expected to produce mixtures of regioisomeric 4a,8-dialkylated octalones. It occurred to us that a regiospecific annelation might be accomplished by a lactonization-directed aldol cyclization as depicted below (**1** → **4**). This process bears a formal resemblance to the Stobbe condensation.[4] Closer precedent for lactonization and elimination during Robinson annelations may be found in the literature.[5-7]




1 2 4 3

Although aldol cyclization to bridged bicyclo[3.3.1]decanols is generally kinetically favored,[2,8,9] this alternative reaction mode is also reversible under basic conditions. Thus, the opportunity to cyclize to the decalol (**2**) should be available, at which point lactonization and elimination may occur. This apparently reasonable and attractive scenario was unfortunately not to be. However, the present investigation led to the discovery of a remarkably facile rearrangement and has brought to light a new mechanism for the supposed retro-Claisen ring opening which often accompanies Robinson annelations with 1,3-cyclohexanediones.[2a]

## Results and Discussion

α-Alkylation of 2-methyl-1,3-cyclohexanedione was accomplished indirectly via its isobutyl enol ether **5**.[10,11] Formation of the enolate anion of **5** with lithium diisopropylamide in tetrahydrofuran (THF) followed by reaction with *tert*-butyl bromoacetate[11c] at −70 °C (30 min) and 25 °C (90 min) and purification of the product by flash chromatography afforded enone ester **6** of adequate purity in 66% yield. Further purification was achieved by crystallization of diketo ester **7** which was obtained in 70% yield after hydrolysis with aqueous hydrochloric acid in 1,2-dimethoxyethane.

Michael addition of **7** to methyl vinyl ketone in methanol with potassium hydroxide as catalyst gave triketo ester **8** in 93% yield. The *tert*-butyl ester was removed by exposure to trifluoroacetic acid at 0 °C for 1 h and the re-

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(2) (a) Jung, M. E. *Tetrahedron* **1976**, *32*, 3-31. (b) Gawley, R. E. *Synthesis* **1976**, 777-794.

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(4) For a review on the Stobbe condensation, see: Johnson, W. S.; Daub, G. H. *Org. React. (N.Y.)* **1951**, *6*, 1-73.

(5) Meyer, W. L.; Bielaski, B. S. *J. Org. Chem.* **1963**, *28*, 2896-2897.

(6) (a) Mander, L. N.; Hamilton, R. J. *Tetrahedron Lett.* **1981**, 4115-4118. (b) Mukherjee, D.; Mukhopadhyay, S. K.; Mahalanabis, K. K.; Gupta, A. D.; Dutta, P. C. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2083-2088.

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(8) (a) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; Chapters 9 and 10. (b) Hajos, Z. G. in "Carbon-Carbon Bond Formation"; Augustine, R. L., Ed.; Marcel Dekker: New York, 1979; Vol. 1, Chapter 1, pp 34-42.

(9) (a) Johnson, W. S.; Korst, J. J.; Clemens, R. A.; Dutta, J. *J. Am. Chem. Soc.* **1960**, *82*, 614-622. (b) Spencer, T. A.; Neel, H. S.; Ward, D. C.; Williamson, K. C. *J. Org. Chem.* **1966**, *31*, 434-436.

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(11) (a) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775-1776. (b) Heathcock, C. H.; Clark, R. D.; Wege, P. M. *J. Org. Chem.* **1976**, *41*, 3144-3148. (c) Alkylations attempted with methyl bromoacetate were unsuccessful.

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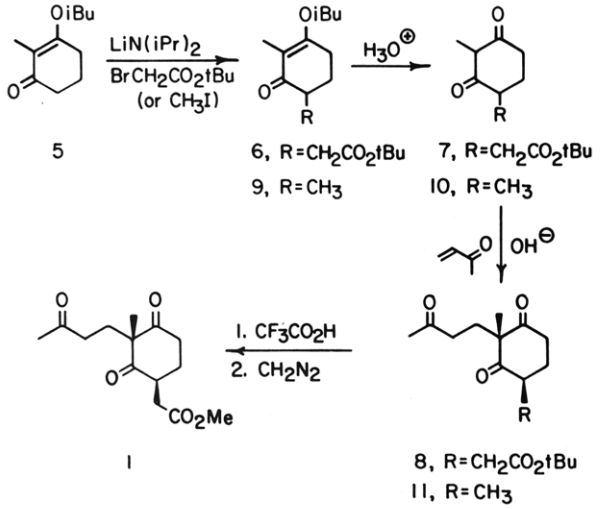
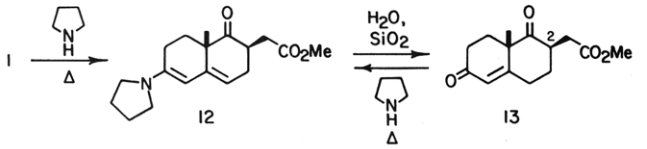
sulting acid was re-esterified with diazomethane to give the desired methyl ester **1** as a single diastereomer. Since equilibration of the acetic ester group would presumably produce both cis and trans isomers, the stereochemistry is tentatively assigned as shown in **1**, assuming the Michael addition occurred exclusively trans to the substituent. The analogous triketone (**11**) bearing an $\alpha'$-methyl group was prepared in the same way by methylation of the enolate anion of **5**. As in the case of **1** a single isomer was obtained which is assigned the stereochemistry shown with cis methyl groups.




Pyrrolidine-catalyzed aldol cyclization of 1,5-diketones to cyclohexenones via a dienamine intermediate has been used to complete a stepwise Robinson annelation.[12] Reaction of **1** with pyrrolidine in refluxing benzene followed by hydrolysis on silica gel[13] afforded enone **13** (58%) initially as a 5:1 mixture of C-6 epimers. The location of the acetic ester group at C-2 was clear from the UV ($\lambda_{max}$ 287)[14] and $^1$H NMR (2 vinyl H) spectra of the heteroannular dienamine **12** formed directly from **1** or via the purified enone **13**. The regioselectivity of this aldol cyclization of **1** to **13** is presumably attributable to steric hindrance at the ketone group flanked by the acetic ester substituent.




Attempted aldol cyclization of **1** with 2 equiv of sodium methoxide in methanol at 25 °C for 1.7 h produced a 40:60 mixture of enone acid **14a** and $\gamma$-lactone **18** along with about 5% of acyclic diester **17**. The enone acid was esterified with diazomethane and the two major products (**14b** and **18**) were separated by chromatography on silica gel. The structures of **14b** and **18** are based upon their IR, $^1$H NMR, $^{13}$C NMR, and mass spectra. Thus, a fully substituted $\alpha,\beta$-enone ($\delta_C$ 131.6 156.4, 201.0), two carbomethoxy groups ($\delta_C$ 172.5, 175.1, $\delta_H$ 3.648, 3.651), a vinyl methyl ($\delta_H$ 1.93, s), a secondary methyl ($\delta_H$ 1.12, d), and a fully substituted $\alpha,\beta$-enone (IR 1655 cm$^{-1}$; $^1$H NMR, no vinyl H) must be present in **14b**. The structure of **18** must contain a $\gamma$-lactone ($\nu_{max}$ 1775 cm$^{-1}$) having an $\alpha$-CH$_2$ ($\delta_H$ 2.29, 3.41 AB d) attached to a quaternary carbon, a carbomethoxy group ($\delta_H$ 3.66, $\delta_C$ 172.4 or 174.0), a methyl group ($\delta_H$ 1.44, s) on a fully substituted carbon, and a secondary methyl group ($\delta_H$ 1.04, d).

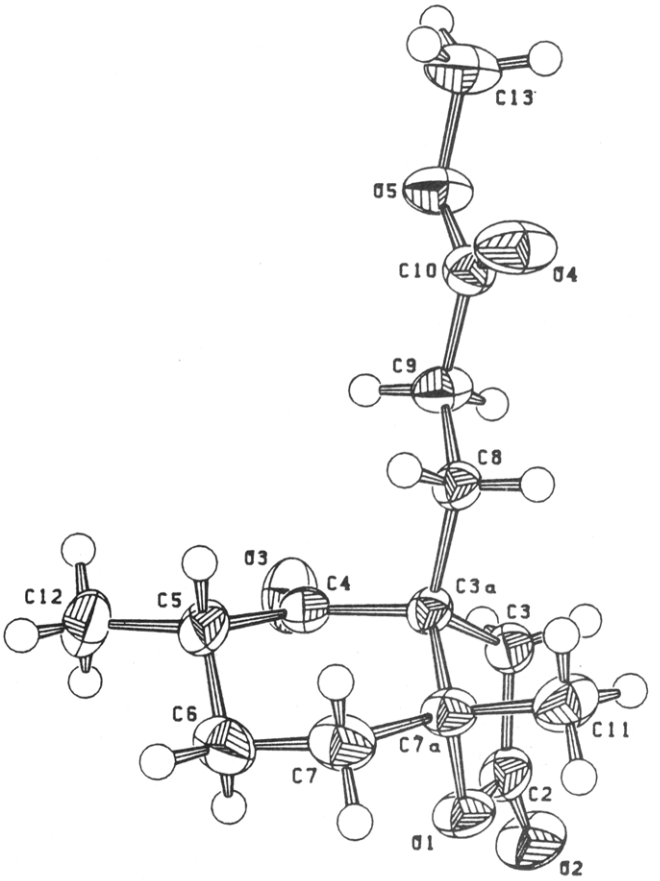



**Figure 1.** An ORTEP plot showing the structure of keto lactone **18** in the solid state from a single-crystal X-ray analysis.

The structure of keto lactone **18** was confirmed subsequently by a single-crystal X-ray diffraction analysis. An ORTEP drawing of the structure is shown in Figure 1. The $\gamma$-lactone is fused cis to the cyclohexanone ring and the methyl group adjacent to the ketone is trans to the angular propionate substituent. The conformation of the molecule in the crystal appears to be the thermodynamically more stable one with respect to the cyclohexanone ring—i.e., two axial substituents (lactone oxygen and propionate side chains) and three equatorial groups (lactone methylene, C-5 methyl, and C-7a methyl). Additional information on the X-ray analysis is given in the experimental section and the supplementary edition.

It was initially assumed that enone **14** resulted from a reverse Claisen ring opening of **1** followed by aldol cyclization. Enone acids similar to **14a** have been observed previously in the acid- or base-induced annelation of 1,3-cycloalkanediones with methyl vinyl ketone or related $\alpha,\beta$-enones under both anhydrous and hydrolytic conditions.[2,15,16] Reasonable pathways to **18** may also be readily formulated, e.g., bridging aldol cyclization, $\gamma$-lactone formation, and methoxide-induced retro-Claisen cleavage.

The progress of the reaction of **1** with 0.17–2.0 equiv of sodium methoxide at 0 and 25 °C was monitored closely by GC analyses to determine the sequence of reactions and

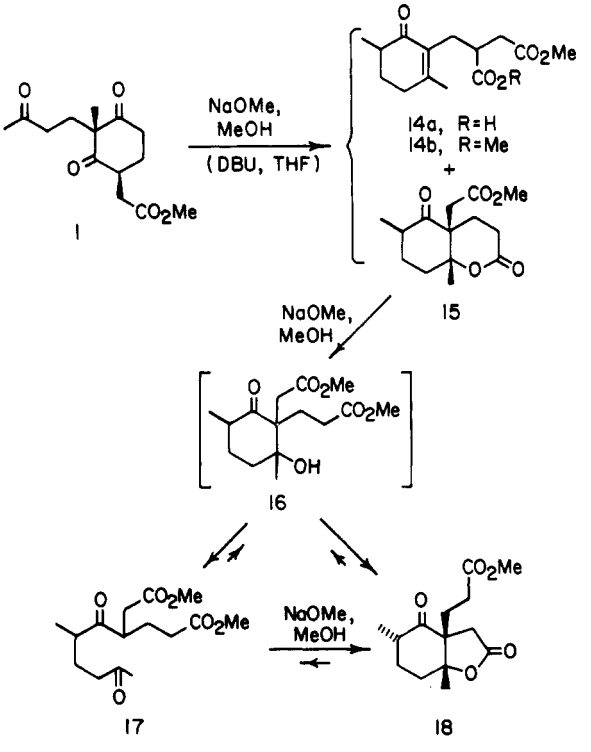
(12) Scanio, C. J. V.; Hill, L. P. *Synthesis* **1970**, 651–652.
(13) Heut, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63–65.
(14) Scott, A. I. "Interpretation of Ultraviolet Spectra of Natural Products"; Barton, D. H. R., Doering, W., Eds.; MacMillan: New York, 1964; Chapters 1 and 2.
(15) (a) Wendler, N. L.; Slates, H. L.; Tishler, M. *J. Am. Chem. Soc.* **1951**, *73*, 3816–3818. (b) Nazarov, I. N.; Zav'yalov, S. I. *Izvest. Akad. Nauk. SSSR Otd. Khim. Nauk.* **1952**, 300–313.
(16) (a) Balasubramanian, K.; John, J. P.; Swaminathan, S. *Synthesis* **1974**, 51–53. (b) Selvarajan, R.; John, J. P.; Narayanan, K. V.; Swaminathan, S. *Tetrahedron* **1966**, *22*, 949–954.

Table I. Products, Product Ratios, and Yields from Base-Induced Reactions of Triketones 1, 11, and 19

| triketone | conditions: base,[a] equiv | conditions: temp, °C, time, h | products: structures | products: (ratios) | products: yield, % |
|---|---|---|---|---|---|
| 1 | A, 0.17 | 0, 1.5 | 14 + 15 + 17 + 18 | (32:24:20:2)[b] | c |
| 1 | A, 1.0 | 0, 1.5 | 14 + 17 + 18 | (1:1:1) | c |
| 1 | A, 2.0 | 25, 0.08 | 14 + 17 + 18 | (47:31:22) | c |
| 1 | A, 2.0 | 25, 1.7 | 14 + 17 + 18 | (38:5:57) | ~74 |
| 1 | B, 3.0 | 25, 9 | 14 + 15 | (18:82) | 60 |
| 11 | A, 1.15 | 25, 9 | 22 + 23 | (79:21) | 71 |
| 11 | B, 2.8 | 25, 9 | 22 + 23 + 24 + 25 | (27:42:18:18) | 84 |
| 19 | A, 1.15 | 25, 9 | 20 | (100) | 80 |
| 19 | B, 3.0 | 25, 10.5 | 20 + 21 | (76:24)[d] | 62 |

[a] (A) $NaOCH_3$, $CH_3OH$; (B) 1,8-diazabicyclo[5.4.0]undec-7-ene in tetrahydrofuran. [b] 22% of 1 was also present. [c] Not determined. [d] 15% of 2-methyl-1,3-cyclohexanedione was also present.

whether other intermediates might be detected. The appearance of two nonacidic intermediates **15** and **17** was observed when smaller amounts of methoxide, shorter times, and/or lower temperatures were used. δ-Lactone **15** was isolated in ca. 90% purity as an oil from a run conducted with 0.17 equiv of methoxide at 25 °C for 9 h. The structure of **15** is based upon spectral data which indicate the presence of a saturated ketone ($\delta_C$ 210.4, no vinyl H or vinyl C), a carbomethoxy group ($\delta^H$ 3.60, $\delta_C$ 169.7 or 170.7) with an α-methylene ($\delta_H$ 2.40 and 3.08, AB d) attached to a quaternary carbon, a δ-lactone ($\nu_{max}^{CHCl_3}$ 1725, $\delta_C$ 169.7 or 170.7), a methyl group on a fully substituted carbon ($\delta^H$ 1.48, s), and a secondary methyl group ($\delta_H$ 1.05, d). Lactone **15** was obtained as a single isomer although a 10% impurity present could have been a diastereomer. In contrast, acyclic diester **17** was isolated as a 1:1 mixture of two stereoisomers.




When purified samples of **15**, **17**, and **18** were treated with sodium methoxide in methanol, the same 10:90 "equilibrium" mixture of **17** and **18** was formed and none of the enone **14** was detected. GC analyses showed clearly that **14a**, **15**, and **17** arise concurrently in the early stages of the reaction whereas γ-lactone **18** appears later at the expense of **15** and **17**. It seems reasonable to suppose that **17** and **18** are formed from **15** via ketol diester **16** although this intermediate was not detected. Some of the acyclic diester **17** may also arise by irreversible retro-Claisen cleavage of **1**. If **18** were formed directly from **15** via **16** without epimerization, it should have a trans-fused γ-lactone, based on the cis stereochemistry proposed for **15** (see below). However, ketol diester **16** clearly has adequate opportunity to epimerize via retroaldol interconversion with **17**, allowing thermodynamic equilibration to produce the presumably more stable cis-fused γ-lactone (**18**) isolated (see Figure 1).

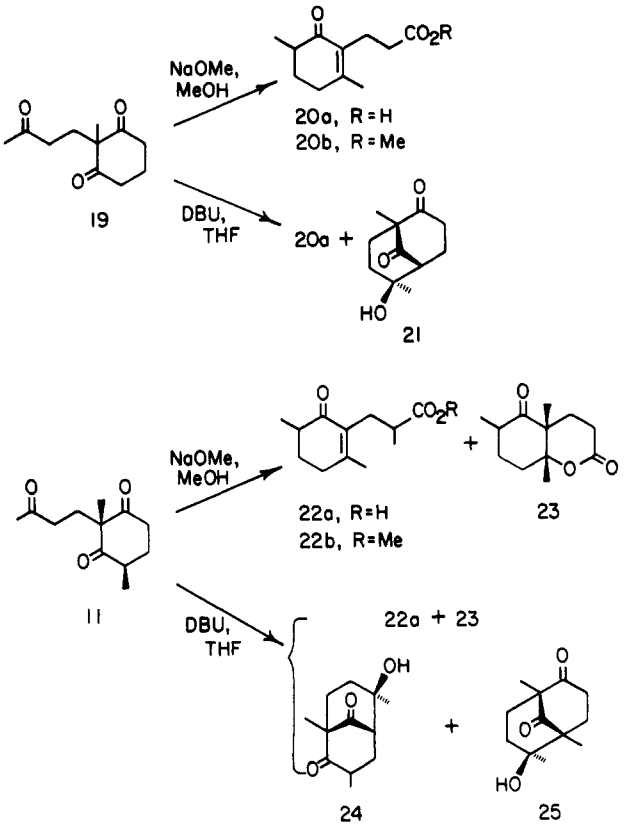
Since the production of **17** and **18** from **15** (or **1**) would seem to require the involvement of a nucleophile, the aldol cyclization was also attempted with a non-nucleophilic base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Reaction of **1** with 3 equiv of DBU in anhydrous THF at 15 °C for 9 h followed by diazomethane esterification afforded enone ester **14b** (11%) and lactone **15** (49%). The complete absence of **17** and **18** in the unpurified product was verified by GC analysis. The results of the various aldol cyclizations of **1** are summarized in Table I along with others to be discussed next.

Similar base-catalyzed reactions of triketones **11** and **19** were also carried out to determine the effect of an α′-substituent uncomplicated by the presence of the ester group. Treatment of **19** with 1.15 equiv of sodium methoxide in ostensibly dry methanol (25 °C, 9 h) gave rise to the known[15] enone acid **20a** which was purified as the ester (**20b**, 80%) following diazomethane esterification. A mixture of enone ester **20b** (46%), the known[9b] ketol **21** (15%), and 2-methyl-1,3-cyclohexanedione (15%) resulted from exposure of **19** to DBU/THF. Reaction of **11** with sodium methoxide in anhydrous methanol followed by esterification afforded enone ester **22b** (56%) and δ-lactone **23** (15%). A mixture of the same two products, **22b** (23%) and **23** (35%), accompanied by bridged ketols **24** (11%) and **25** (15%) was obtained when **11** was treated with DBU in THF.

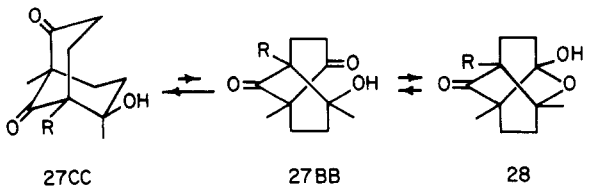
The formation of enone acids **14a**, **20a**, and **22a** under anhydrous, non-nucleophilic conditions[17] and in the presence of excess methanol seems to exclude mechanisms involving retro-Claisen reactions. An alternative explanation is that the three enone acids arise by rapid base-catalyzed β-elimination of δ-lactones isomeric to **15** and **23** with the substituent at the α′-position of the ketone. Thus, **15** and **23** are isolable simply because the substituent at the α-position prevents elimination.

We propose the four-step reaction pathway depicted in Scheme I to explain the formation of the δ-lactones and enone acids from **1**, **11**, and **19**. Base-catalyzed aldol cyclization of the triketones may occur adjacent to either of the carbonyl groups in the ring, giving two types of bridged

(17) There is of course no assurance that the DBU/THF conditions are absolutely anhydrous and free of trace amounts of nucleophiles. Thus, catalytic amounts of water could be released by aldol dehydration reactions and could possibly act as a nucleophile for retro-Claisen ring opening.

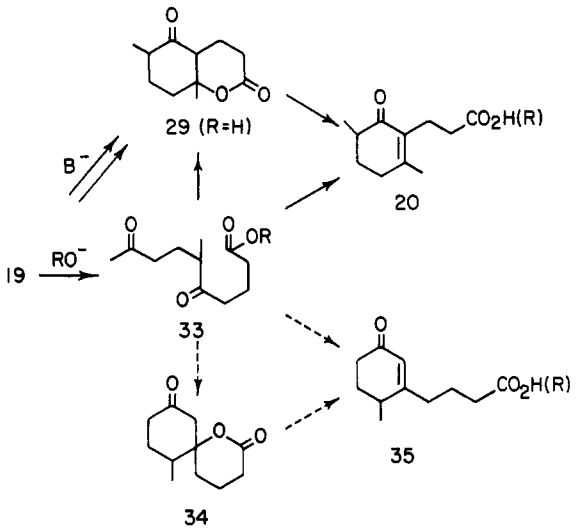



ketols presumably with both endo (**27** and **30**) and exo stereochemistry. When the hydroxyl group is endo, rearrangement to cis-fused δ-lactones **29** and **32** may occur via tricylic hemiketals **28** and **31**. Since these formal retro-Claisen transformations (**27** → **29** and **30** → **32**) involve an intramolecular nucleophilic addition, no external nucleophile is required. Although the cyclization of the *endo*-bicyclo[3.3.1]octane ketols **27** and **30** to oxa-twistanols **28** and **31** is accompanied by a substantial increase in strain energy,[18] similar aldol cyclizations of *cis*-decalindiones to twistane ketols have been realized.[19] The boat–boat conformer of bicyclo[3.3.1]octane is 8.23 kcal/mol higher in energy than the chair–chair form according to force-field calculations.[20] Since the presence of a ketone at the bridge position reduces the free energy difference between the chair–chair and boat–chair conformers by 1.1 kcal/mol,[20a] the energy difference between **27CC** and **27BB** may be as little as 6.0 kcal/mol.




The cis stereochemistry assigned to δ-lactones **15** and **23** is based solely on the proposed mechanism for their formation in Scheme I. Since **21**, **24**, and **25** proved to be stable to the DBU/THF conditions, the exo configuration has been assigned to these bridged ketols. Evidently the ratio of endo to exo ketols formed from **19** and **11** with DBU in THF is about 2–3:1.

It has generally been assumed that cyclohexanone acids such as **20a** arising from Robinson annelations of cyclic diketones, or from attempted aldol cyclizations of the corresponding Michael addition products, are formed via retro-Claisen ring opening followed by aldol cyclization of the resulting acyclic 1,5-diketones (e.g., **19** → **33** → **20**).[15,16b] A reasonable alternative under anhydrous basic conditions (e.g., $NaOCH_3/CH_3OH$) or with acidic catalysts would involve lactonization of the ketol intermediate (**19** → **33** → **29** → **20**).




The proposed acyclic diketone intermediates have not, however, been isolated or detected in reactions leading to the cyclohexenone acids. Furthermore, one might expect some aldol cyclization of **33** to occur in the opposite direction (**33** → **35** and/or **33** → **34** → **35**).[21] The NMR spectrum of **20** obtained from reaction of **19** with sodium methoxide in methanol does not show any evidence for the presence of the isomeric **35** although small amounts (<5–10%) might escape detection. It is also pertinent to note that the aldol cyclization of the acyclic diketone **17** to lactone **18** with sodium methoxide in methanol occurred considerably more slowly than the formation of cyclohexenone acid **14a** from **1**.[22a] It therefore seems likely that the cyclohexenone acids such as **20a** are usually formed more rapidly by the reaction sequence in Scheme I rather than the retro-Claisen alternatives, although there may well be exceptions to this generalization.[22b]

## Experimental Section

**General Aspects.** Proton nuclear magnetic resonance spectra ($^1H$ NMR) were recorded on a Varian Associates EM-390 (90 MHz, continuous wave mode) spectrometer, if unspecified, or Nicolet NT-360 (360 MHz, FT mode) spectrometer, as specified. The 90-MHz spectra were recorded with an internal lock on tetramethylsilane and the 360-MHz spectra were recorded with

(18) Engler, E. M.; Farcasiu, M.; Sevin, A.; Cense, J. M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 5769–5771.

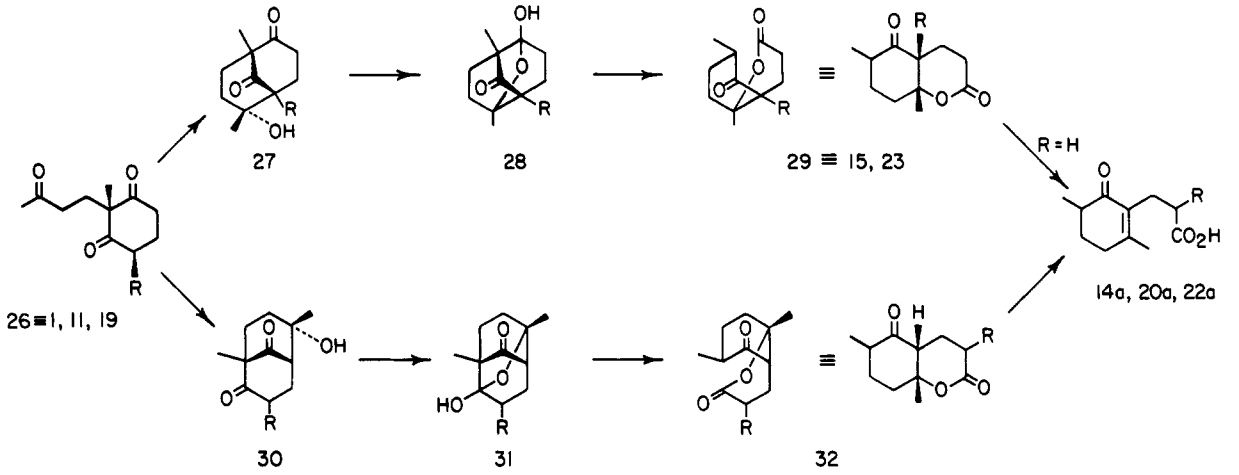
(19) (a) Deslongchamps, P.; Lambert, Y.; Bélanger, A. *Can. J. Chem.* **1969**, *47*, 795–802. (b) Yordi, J. D.; Reusch, W. *J. Org. Chem.* **1975**, *40*, 2086–2088.

(20) (a) Peters, J. A.; Baas, J. M. A.; Van de Graaf, B.; van der Toorn, J. M.; Bekkum, H. *Tetrahedron* **1978**, *34*, 3313–3323. (b) Engler, E. M.; Andose, J. D.; Schleyer, P. von R. *J. Am. Chem. Soc.* **1973**, *95*, 8005–8025.

(21) (a) Danishefsky, S.; Cain, P.; Nagel, A. *J. Am. Chem. Soc.* **1975**, *97*, 380–387. (b) Kobayashi, M.; Matsumoto, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2978–2990.

(22) (a) The regioselectivity of the aldol cyclization of acyclic diketone **17** leading to γ-lactone **18** is reasonably attributable to steric hindrance surrounding the midchain ketone which impedes nucleophilic addition at this site. (b) An alternative mechanism could be proposed to explain the regiospecific formation of enone acid **20a** to the exclusion of **35** under the DBU/THF conditions or in the presence of aqueous base. The three steps in the sequence are as follows: (1) base-catalyzed bridging aldol cyclization of **19** to **21** and/or its endo isomer **27** (R = H); (2) hydroxide-induced[17] retro-Claisen ring opening of **21** (and/or **27** (R = H); (3) dehydration to give **20a**. Regiospecific formation of **20a** would require dehydration to be faster than retroaldol ring opening of the ketol to **33**. Thus, a potential difficulty with the preceding mechanism is that retroaldol reactions in some cases are considerably faster than the dehdyration. See: Stiles, M.; Wolf, D.; Judson, G. V. *J. Am. Chem. Soc.* **1959**, *81*, 628.

**Scheme I**




an internal lock on the deuterium resonance of the solvent. Carbon-13 nuclear magnetic resonance ($^{13}C$ NMR) were recorded on a Nicolet NT-360 spectrometer (90.5 MHz). Infrared spectra were obtained with a Perkin-Elmer Model 137 spectrometer. Mass spectra were run on Varian-MAT CH-5, 311A (GC/MS), and 731 mass spectrometers by Carter Cook and associates. Elemental analyses were performed at the University of Illinois Microanalytical Laboratory by J. Nemeth and associates. Melting points were determined on a Reichert hot stages microscope, and are uncorrected.

Analytical gas chromatography (GC) was performed on a Varian Model 3700 instrument equipped with a flame-ionization detector and with helium as the carrier gas at the indicated column temperature. The following standard operating conditions were used: 230 °C injector temperature, 300 °C detector temperature, and a 40 mL/min carrier gas flow rate. Analyses were carried out with either column A, 1.8 m × 6 mm glass column packed with 3% OV-17 on 100/120 mesh Gas Chrom Q, or column B, 3.6 m × 6 mm glass column packed with 3% OV-17 on 100/120 mesh Gas Chrom Q.

Flash chromatography was performed as described by Still,[23] on Woelm 32–63 micron silica gel supplied by Universal Scientific, Atlanta, GA. Preparative medium-pressure liquid chromatography (MPLC) was performed with a system developed in this laboratory by Dr. William Baker, as previously described.[24] The column was packed with Woelm 32–63 micron silica gel. Analytical thin-layer chromatography (TLC) was conducted on either Brinkmann Polygram plastic plates precoated with 0.25 mm of silica gel GF-254 or on Merck glass plates precoated with 0.25 mm of silica gel GF-254. Thin-layer chromatograms were visualized with 5% phosphomolybdic acid reagent in 95% ethanol, iodine vapors, and/or UV light.

All reactions, except those performed in aqueous solvents, were carried out in a dry nitrogen or argon atmosphere by using standard techniques for the exclusion of moisture. Glassware used in water-sensitive reactions was dried in a circulating oven at 130 °C for at least 1 h.

Tetrahydrofuran (THF) was purified by distillation from sodium-benzophenone ketyl. Diisopropylamine was distilled from calcium hydride. Absolute methanol was prepared by distillation from sodium. Ethereal diazomethane was generated from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald), supplied by Aldrich Chemical Company, by using the procedure provided on the container.

**2-Methyl-3-(2-methylpropoxy)-2-cyclohexenone (5)** was prepared from 9.07 g (72.0 mmol) of 2-methyl-1,3-cyclohexandione[25] according to the procedure of Eschenmoser.[10] Distillation of the crude product furnished 10.6 g (81%) of the enol ether **5**: bp 89–96 °C (0.2 mm) [lit.[10] bp 98–106 °C (0.1 mm)].

**1,1-Dimethylethyl 3-Methyl-4-(2-methylpropoxy)-2-oxo-3-cyclohexene-1-acetate (6).** The alkylation of ketone **5** was carried out according to the procedure of Heathcock and coworkers.[11b] A solution of 26.4 mmol of lithium diisopropylamide in hexane–THF [prepared from 2.67 g (26.4 mmol, 3.73 mL) of diisopropylamine in 2.2 mL of THF and 14.0 mL (27 mmol) of 1.93 M *n*-butyllithium in hexane] was stirred at −78 °C as a solution of 4.00 g (22.0 mmol) of ketone **5** in 5.5 mL of THF was added dropwise over 3 min. The solution was stirred at −70 °C for 1 h, at which time a solution of 5.15 g (26.4 mmol) of *tert*-butyl bromoacetate[26] in 2.2 mL of THF was added dropwise over 35 min. After 30 min at −70 °C and 90 min at room temperature, the dark solution was mixed with 20 mL of saturated sodium chloride. The aqueous layer was extracted twice with ether and the combined organic layers were washed several times with water and were dried ($Na_2SO_4$). Evaporation of the solvent and purification of the residue by flash chromatography on 155 g of silica gel with 50% ether in pentane as eluant, afforded 4.32 g (66%) of ester **6**. Although GC analysis (column B; temperature program; 150 °C for 1 min increased to 220 °C at 60 °C/min) indicated that the product was contaminated with 5% starting material, it was suitable for use in the next step. Additional purification by MPLC on 480 g of silica gel with 50% ether in hexane furnished 2.1 g (32%) of keto ester **6**: IR (film) $\nu_{max}$ 2942, 1725 (C=O), 1625 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.99 (d, 6 H, $J$ = 6 Hz, $CHCH_3$), 1.43 (s, 9 H, $OC(CH_3)_3$), 1.68 (br s, 3 H, $CH_3$), 1.7–3.0 (m, 8 H), 3.7 (d, 2 H, $J$ = 7 Hz, $OCH_2CH$).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.16. Found: C, 69.00; H, 9.51.

**1,1-Dimethylethyl 2-Methyl-1,3-dioxocyclohexane-4-acetate (7).** A solution of 1.10 g (3.70 mmol) of enol ether **6**, 12 drops of concentrated hydrochloric acid, and 12 mL of dimethoxyethane in 15 mL of water was stirred at room temperature for 12 h. After the reaction cooled at 0 °C for 1.5 h, a solid precipitated, which was collected and dried (25 °C, 0.01 mm) yielding 0.62 g (70%) of the diketone **7** (mp 117–119 °C). Recrystallization from water–ethanol furnished an analytical sample: mp 119–120.5 °C; IR (nujol) $\nu_{max}$ 1725 (C=O), 1560, 1351 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.27 (m, 2 H), 1.50 (s, 9 H, $OC(CH_3)_3$), 1.78 (s, 3 H, $CH_3$), 1.78–3.00 (m, 6 H, C(O)CH).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.76; H, 8.44.

**1,1-Dimethylethyl 2-Methyl-2-(3-oxobutyl)-1,3-dioxocyclohexane-4-acetate (8).** A solution of 1.60 g (22.8 mmol) of methyl vinyl ketone, 3.59 g (14.9 mmol) of dione **7**, and 8 mg (0.14 mmol) of powdered potassium hydroxide in 12 mL of methanol was stirred at reflux for 4 h. Evaporation of the solvent afforded 4.26 g (93%) of crude **8**, which was suitable for use in the next step. Purification of the crude product by MPLC with 30%

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(26) (a) Hauser, C. R.; Hudson, B. E.; Abramovitch, B.; Shivers, J. C. "Organic Syntheses"; Wiley: New York, 1955; Collect. Vol. III, pp 142–144. (b) McCloskey, A.; Fonken, G. S.; Kluiber, R. W.; Johnson, W. S. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, pp 261–263.

hexane in ether as eluant furnished an analytical sample as an oil: IR (film) $\nu_{max}$ 2974, 1757 (C=O), 1741 (C=O), 1724 (C=O), 1379, 1170 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.17 (s, 3 H, $CH_3$), 1.43 (s, 9 H, $C(CH_3)_3$), 1.2–3.2 (m, ~11 H).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 66.08; H, 8.44.

**Methyl 2-Methyl-2-(3-oxobutyl)-1,3-dioxocyclohexane-4-acetate (1).** A solution of 2.83 g (9.13 mmol) of crude ester 8 in 26 mL of trifluoroacetic acid was stirred at 0 °C for 1 h.[27] The volatile components were removed by rotary evaporation and the residual acid (1.66 g) was esterified with excess diazomethane in ether/THF. Evaporation of the solvent and purification of the residue by flash chromatography on 100 g of silica gel, with ether as eluant, afforded 1.44 g (59%) of 1 as a colorless oil: IR (film) $\nu_{max}$ 2950, 1724 (C=O), 1695 (C=O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.15 (s, 3 H, $CH_3$), 1.27–1.81 (8-line m, ~1 H), 2.13 (s, ~3 H, $C(O)CH_3$), 1.92–3.05 (m, ~9 H), 3.05–3.52 (9-line m, 1 H, C(O)CH), 3.68 (s, 3 H, $OCH_3$).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.77; H, 7.38.

**2,4-Dimethyl-1,3-cyclohexanedione (10).** Ketone 5 was alkylated with methyl iodide by using the procedure described in the preparation of keto ester 6. A solution of the crude product in 20 mL of 10% hydrochloric acid was stirred at 20 °C for 1 h. Solid sodium chloride was added and the layers were separated. The aqueous layer was extracted twice with ether and the combined organic layers were washed with saturated sodium chloride and were dried ($MgSO_4$). The dione precipitated as the solvent was evaporated. The crystals were collected and washed with ice-cold ether yielding 0.75 g (49%) of 10: mp 112–117 °C (lit.[28] mp 117–118 °C).

**2,4-Dimethyl-2-(3-oxobutyl)-1,3-cyclohexanedione (11)** was prepared with the method described for the preparation of trione 8. Purification of the crude product by flash chromatography on 70 g of silica gel afforded ~0.8 g of colorless product. Kugelrohr distillation (oven temperature 130 °C, 0.1 mm) of this material furnished 0.75 g (70%) of 11 as an analytical sample: IR (film $\nu_{max}$ 2900, 1720 (C=O), 1690 (C=O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.17 (d, 3 H, $CHCH_3$), 1.20 (s, 3 H, $CH_3$), 1.93–2.5 (m, ~4 H), 2.13 (s, 3 H, $C(O)CH_3$), 2.6–3.0 (m, ~4 H).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.72; H, 8.66.

**Methyl 1,2,3,4,6,7,8,8a-Octahydro-8a-methyl-1,6-dioxo-2-naphthaleneacetate (13).** A solution of 168 mg (0.627 mmol) of keto ester 1 and 68 mg (1.0 mmol, 80 $\mu$L) of pyrrolidine in 12 mL of benzene was stirred at reflux for 6 h. A Dean–Stark trap containing 4 Å molecular sieves was used to remove the water formed during the reaction. The solution was cooled and the solvent was evaporated. A mixture of the residue, 1.6 g of silica gel, and 150 $\mu$L of water in 10 mL of dichloromethane was stirred at room temperature for 1 h.[13] The silica gel was removed by filtration and the filtrate was evaporated. Purification of the residue by flash chromatography on 8 g of silica gel, with ether as eluant, afforded 93 mg (59%) of enone 13 as a white solid. Recrystallization of a portion from ether afforded an analytical sample: mp 205–208 °C; IR ($CHCl_3$) $\nu_{max}$ 2900, 1736 (C=O), 1713 (C=O), 1668 (C=O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.13–1.72 (m, 1 H), 1.50 (s, 3 H, $CH_3$), 1.90–3.07 (m, 9 H), 3.07–3.48 (6-line m, 1 H, C(O)CH), 3.68 (s, 3 H, $OCH_3$), 5.81 (d, 1 H, $J$ = 1, C=CH); mass spectrum, $m/e$ (relative intensity) 250 ($M^+$, 33), 219 (16), 218 (17), 190 (100), 175 (13), 127 (19), 91 (30), 79 (38); exact mass calcd for $C_{14}H_{18}O_4$ $m/e$ 250.1205, found $m/e$ 250.1212.

The $^1H$ NMR and UV spectra of the crude dienamine 12 as a 1:5 mixture of C-2 epimers were as follows: $^1H$ NMR ($CDCl_3$, unlocked) $\delta$ 1.10 (s, 0.5 H, $CH_3$), 1.32 (s, 2.5 H, $CH_3$), 1.63–1.93 (6-line m, ~4 H, $NCH_2CH_2$), 1.3–2.87 (m, ~10 H), 2.90–3.17 (3-line m, ~4 H, $NCH_2$), 3.52 (s, 3 H, $OCH_3$), 4.57 (s, 0.83 H, C=CH), 4.63 (s, 0.17 H, C=CH), 4.77 (t, 0.83 H, $J$ = 3 Hz, $C=CHCH_2$), 5.27 (t, 0.17 H, $J$ = 3 Hz, $C=CHCH_2$); UV $\lambda_{max}$ (ether) 287 ($\epsilon$ 27 000).

The crude dienamine 12 was also obtained when a solution of 100 mg (0.40 mmol) of enone 13 and 47 mg (0.66 mmol, 55 $\mu$L) of pyrrolidine in 2 mL of benzene was stirred and heated at reflux for 18 h. Evaporation of the solvent afforded 12 as a red oil. The $^1H$ NMR spectrum was similar to that obtained previously, although the ratio of the C-2 epimers was 1.4:1 compared to the original 5:1 ratio.

**Methyl 3-((3a$\alpha$,5$\beta$,7a$\alpha$)-Octahydro-5,7a-dimethyl-2,4-dioxobenzofuran-3a-yl)propionate (18) and Dimethyl 2-(1,4-Dimethyl-3-oxo-1-cyclohexen-2-ylmethyl)butanedioate (14b).** A solution of 94.1 mg (0.35 mmol) of ketone 1 in 0.4 mL of methanol was stirred at 25 °C as 1.56 mL (0.7 mmol) of 0.45 M sodium methoxide in methanol was added in one portion. The progress of the reaction was monitored by GC analysis (column A, 200 °C) of aliquots withdrawn from the reaction mixture. Each aliquot was treated with 10% hydrochloric acid and excess ethereal diazomethane before dilution to a standard volume. After 5 min at 25 °C, GC analysis indicated a 31:22:47 ratio of ketones 17, 18, and 14b. After 100 min the ratio was found to be 5:60:40 and the sodium methoxide was quenched by the addition of 1 mL of 10% hydrochloric acid. The solution was extracted once with ether and twice with dichloromethane and the organic layers were washed with saturated sodium chloride. The combined organic extracts were dried ($MgSO_4$) and evaporated, affording a mixture (86 mg) of lactone 18 and acid 14a. The residue was treated with excess diazomethane in ether and the solution was evaporated under a stream of nitrogen. Purification of the residue by flash chromatography on 8 g of silica gel, with 100-mL portions of 20% and 40% ethyl acetate in hexane as eluants, afforded 25 mg (25%) of enone 14b and 57 mg (49%) of lactone 18 that was contaminated with 5% of diester 17 as indicated by GC analysis (column A, 220 °C). Ester 14b had the following spectral properties: IR ($CHCl_3$) $\nu_{max}$ 2900, 1728 (C=O), 1655 (C=O), 1430, 1200, 1160 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 1.12 (d, 3 H, $J$ = 7 Hz, $CHCH_3$), 1.57–1.70 (m, 1 H), 1.93 (s, 3 H, $C=CCH_3$), 2.00 (dq, 1 H, $J$ = 4 and 13 Hz), 2.25–2.78 (m, ~7 H, C(O)CH and C=CCH), 2.89–2.99 (m, ~1 H, C(O)CH), 3.648 and 3.651 (2s, 6 H, $OCH_3$); $^{13}C$ NMR ($CDCl_3$) 15.5, 21.3, 27.9, 30.0, 32.2, 35.6, 40.66, 40.74, 51.7, 51.8, 131.6 (C=CC(O)), 156.4 (C=CC(O)), 172.5 (ester C=O), 175.1 (ester C=O), 201.0 (C=CC(O)); GC mass spectrum (10 eV), $m/e$ (relative intensity) 282 ($M^+$, 12), 251 (39), 250 (45), 222 (100), 167 (20), 163 (55), 162 (69), 149 (79), 145 (18); exact mass calcd for $C_{15}H_{22}O_5$ $m/e$ 282.1467, found $m/e$ 282.1450.

Recrystallization of impure 18 from ether provided 41 mg (44%) of 18 as colorless rods: mp 130.5–131 °C; IR ($CHCl_3$) $\nu_{max}$ 2900, 1775 (C=O), 1725 (C=O) $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 1.04 (d, 3 H, $J$ = 6 Hz, $CHCH_3$), 1.44 (s, 3 H, $CH_3$), 1.63 (dq, 1 H, $J$ = 7 and 14 Hz), 1.85–2.25 (m, ~9 H), 2.29 and 3.41 (ABd, 2 H, $J$ = 17 Hz, $C(O)CH_2$), 2.62–2.70 (5-line m, 1 H, $J$ = 6 Hz, $C(O)CHCH_3$), 3.66 (s, 3 H, $OCH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.3, 24.1, 27.0, 28.8, 29.7, 32.3, 34.9, 41.4, 51.8, 58.8, 90.6 (CO), 172.4 and 174.0 (ester and lactone C=O), 210.9 (ketone C=O); mass spectrum (70 eV), $m/e$ (relative intensity) 268 ($M^+$, 10).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.92; H, 7.28.

A solution of 10 mg (0.037 mmol) of lactone 18 in 0.20 mL of methanol was stirred at 25 °C as 0.2 mL (0.09 mmol) of 0.4 M sodium methoxide in methanol was added. After 1 h, GC analysis indicated a 90:10 mixture of lactone 18 and keto diester 17.

**Isolation of Dimethyl 3-(2-Methyl-1,5-dioxohexan-1-yl)-hexanedioate (17).** A solution of 253 mg (0.944 mmol) of ketone (1) in 1.1 mL of methanol was stirred at 0 °C as 1.89 mL (0.944 mmol) of ice-cold 0.5 M sodium methoxide in methanol was added. The reaction progress was monitored by GC in the same manner as described previously in the preparation of lactone 18. After 90 min the reaction was a 1:1:1 mixture enone acid 14a, ketone 17, and lactone 18. A 0.30-mL aliquot was withdrawn from the reaction solution and added to 1 mL of 10% hydrochloric acid. The resulting mixture was extracted three times with ether. The combined organic layers were washed with saturated sodium bicarbonate in order to remove acid 14a and were dried ($MgSO_4$). Evaporation of the solvent afforded a residue (20 mg) that was indicated by GC analysis to be a 1:1 mixture of lactone 18 and the desired ketone 17. The majority of the lactone was removed by recrystallization from ether/pentane. Evaporation of the mother liquor and purification of the residue by flash chromatography on 6 g of silica gel, with 10% pentane in ether as eluant, afforded 5 mg of 17 that was homogeneous by GC analysis and

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7 mg of a 4:1 mixture of **17** and **18**. Ketone **17**, as a 1:1 mixture of methyl epimers, had the following spectral properties: IR ($CHCl_3$) $\nu_{max}$ 2900, 1728 (C=O), 1430, 1200 $cm^{-1}$; $^1H$ NMR (220 MHz, $CDCl_3$) $\delta$ 1.09 (d, 1.5 H, $J$ = 7 Hz, $CHCH_3$), 1.15 (d, 1.5 H, $J$ = 7 Hz, $CHCH_3$), 2.13 (s, 1.5 H, $C(O)CH_3$), 2.14 (s, 1.5 H, $C(O)CH_3$), 1.0–2.0 (m, ~4 H), 2.20–2.50 (m, ~6 H, CHC(O)), 3.64, 3.65, 3.68, 3.69 (4s, 6 H, $OCH_3$); GC mass spectrum (10 eV), $m/e$ (relative intensity) 300 ($M^+$, 0.25), 269 (0.8), 251 (2.5), 201 (30), 127 (50), 99 (50), 43 (100).

The isolated keto diester was resubmitted to sodium methoxide in methanol in the manner described previously for lactone **18** and, after 9 h, was found to have rearranged to a 85:15 mixture of lactone **18** and diester **17**, as indicated by GC analysis.

**Methyl (4a$\beta$,8a$\beta$)-Octahydro-6,8a-dimethyl-2,5-dioxo-2*H*-1-benzopyran-4a-acetate (15). Method A. Sodium Methoxide.** A solution of 189.4 mg (0.707 mmol) of ketone **1** in 2.3 mL of methanol was stirred at 0 °C as 0.23 mL (0.12 mmol) of 0.5 M sodium methoxide in methanol was added in three portions over 1.5 h. The ice bath was removed and the solution was stirred at 25 °C for 9 h. Analysis of the reaction mixture by GC, with those conditions and techniques described in the preparation of lactone **18**, indicated a product distribution of 22% **1**, 2% **18**, 32% **14a**, 20% **17**, and 24% **15**. The reaction was terminated by the addition of 10% hydrochloric acid, and the water–methanol mixture was extracted three times with ether. Acid **14a** was removed by washing the extracts with 10% saturated sodium bicarbonate solution in water. The organic layer was dried ($MgSO_4$) and evaporated. Purification of the residue by flash chromatography on 6 g of silica gel, with 5% pentane in ether as eluant, provided 30 mg of a mixture of **1** and **17** and 36 mg (20%) of the polar lactone **15**. The spectral properties of **15** are as follows: IR ($CHCl_3$) $\nu_{max}$ 2950, 1725 (C=O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.05 (d, 3 H, $J$ = 6 Hz, $CHCH_3$), 1.48 (s, 3 H, $CH_3$), 1.6–2.07 (m, ~4 H), 2.40 and 3.08 (ABd, 2 H, $J$ = 13.5 Hz, $CH_2CO_2CH_3$), 2.20–3.0 (m, ~6 H), 3.60 (s, 3 H, $OCH_3$). Singlets at 1.23 and 3.67 indicate 10% of an impurity or diastereomer. $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.5, 23.0, 24.3, 26.4, 30.0, 33.7, 40.4, 41.6, 51.4, 52.2, 88.7 (COC(O)), 169.7 and 170.7 (ester or lactone), 210.4 (C=O). GC mass spectrum (10 eV), $m/e$ (relative intensity) 268 ($M^+$, 22), 237 (11), 209 (13), 195 (28), 177 (18), 157 (24), 125 (40), 121 (20), 112 (100), 93 (30); exact mass calcd for $C_{14}H_{20}O_5$ $m/e$ 268.1307, found $m/e$ 268.1309.

**Method B. DBU-Induced Condensation.** A solution of 50 mg (0.18 mmol) of keto ester **1** and 82 mg (0.54 mmol) of 1,8-diazabicyclo[5.4.0]undecen-7-ene (DBU) in 0.5 mL of THF was stirred at 25 °C. After 9 h the reaction was acidified with 1 mL of 10% hydrochloric acid in water and excess solid sodium chloride was added. The mixture was extracted three times with ether and the combined extracts were washed with saturated sodium chloride and dried ($MgSO_4$). The solution was treated with excess diazomethane in ether. Evaporation and purification of the residue by flash chromatography on 6 g of silica gel, with 70 mL of 20% ethyl acetate in hexane as eluant, afforded, in order of elution, 6 mg (11%) of enone **14b** and 24.4 mg (49%) of lactone **15**. Lactone **18** was not present as indicated by GC (column A, 200 °C) analysis. Lactone **15** was contaminated with 10% of an impurity, presumably bicyclic ketol as indicated by the GC retention time and the TLC $R_f$ value.

Pure lactone **15** was found to rearrange to an 85:15 mixture of lactone **18** and diester **17** when treated with sodium methanol as described previously for lactone **18**.

**GC Analysis of the Progress of the Reaction of Sodium Methoxide with Methyl 2-Methyl-2-(3-oxobutyl)-1,3-dioxocyclohexane-4-acetate (1).** A solution of 64 mg (0.24 mmol) of ketone **1** in 0.8 mL of methanol was stirred at 0 °C as 35 $\mu$L (0.018 mmol, 0.07 equiv) of 0.5 M sodium methoxide in methanol was added. At various intervals 10-$\mu$L aliquots were removed and processed in the manner described in the preparation of lactone **18**. After 1 h, 0.2 mL (0.1 mmol, 0.4 equiv) of 0.5 M sodium methoxide solution was added, and 1 h later 0.4 mL (0.2 mmol, 0.80 equiv) of the sodium methoxide solution was added. After 20 min, the ice bath was removed. The composition of each aliquot was determined by GC (column A, 200 °C) and the results are summarized in Table I in the text.

**2-Methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (19)** was prepared by using the method described for the preparation of trione **8**. Kugelrohr distillation of the crude product afforded 5.90 g (95%) of **19** as a colorless oil: bp 170 °C (1 mm) [lit.[29] bp 114 °C (0.1 mm)].

**Methyl 3-(1,4-Dimethyl-3-oxo-1-cyclohexen-2-yl)-propanoate (20b). Method A. Sodium Methoxide.** A solution of 102 mg (0.52 mmol) of trione **19** in 1.2 mL (0.6 mmol) of 0.5 M sodium methoxide in methanol was stirred at 25 °C for 9 h. The excess base was quenched by the addition of 1 mL of 10% hydrochloric acid and processed as described in the preparation of diester **18**. In a preliminary experiment the crude acid was purified by Kugelrohr distillation [bp 175–180 °C (1 mm)] [lit.[15] bp 105–110 °C (0.03 mm)] and had the following spectral properties: IR ($CHCl_3$) $\nu_{max}$ 3400–2400 (OH), 2900, 1705 (C=O), 1655 (C=O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.12 (d, 3 H, $J$ = 7 Hz, $CHCH_3$), 1.97 (s, 3 H, $CH_3$), 1.2–2.7 (m, ~9 H), 8.9–9.4 (br s, 1 H, $CO_2H$).

The crude acid was esterified with excess diazomethane in ether and the ester was purified by flash chromatography on 5 g of silica gel. Elution with 20% ethyl acetate afforded 87.2 mg (80%) of enone ester **20b**. Kugelrohr distillation (130 °C oven temperature, 0.2 mm) afforded an analytical sample: IR (neat) $\nu_{max}$ 2900, 1730 (C=O), 1660 (C=O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.17 (d, 3 H, $J$ = 2 Hz, $CHCH_3$), 1.93 (s, 3 H, $C=CCH_3$), 1.43–1.9 (m, ~1 H), 2.18–2.77 (m, ~7 H), 3.63 (s, 3 H, $OCH_3$).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.71; H, 8.86.

**Method B. DBU-Induced Cyclization.** A solution of 0.60 g (3.06 mmol) of trione **19** and 1.37 g (9.0 mmol, 1.35 mL) of DBU in 6 mL of THF was stirred at 25 °C for 10.5 h. The crude product was isolated and esterified in the manner previously described for the preparation of lactone **15**, Method B. The products were separated by flash chromatography on 30 g of silica gel, with 300-mL portions of 20% and 40% ethyl acetate in hexane as eluants. The three products isolated and identified were, in order of elution, 296 mg (46%) of enone **20b**, 83 mg (15%) of ketol **21**, and 57 mg (15%) of 2-methyl-1,3-cyclohexanedione. Enone **20b** had the identical GC retention time, TLC $R_f$ value, and $^1H$ NMR spectrum as that of the product isolated in the preceding procedure. Ketol **21** had the following physical and spectral properties: mp 117–118 °C (lit.[9b] 115–116 °C); IR ($CHCl_3$) $\nu_{max}$ 3350 (OH), 2900, 1690 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 1.17 and 1.39 (2s, 6 H, $CH_3$), 1.63–1.85 (m, 3 H), 1.96–2.15 (m, 3 H), 2.40 and 2.57 (t of ABd, 2 H, $J$ = 16.5 and 6.8 Hz, $C(O)CH_2CH_2$), 2.68 (d, 1 H, $J$ = 8.8 Hz, C(O)CH).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.12; H, 8.07.

Ketol **21** was resubmitted to the reaction conditions for 9 h and was found to be stable.

**Methyl 2-Methyl-3-(1,4-dimethyl-3-oxo-1-cyclohexen-2-yl)propanoate (22b) and 4a,6,8a-Trimethyl-4,4a,6,7,8,8a-hexahydro-2*H*-1-benzopyran-2,5(3*H*)-dione (23). Method A. DBU-Induced Cyclization.** A solution of 208 mg (1 mmol) of trione **11** and 427 mg (2.81 mmol) of DBU in 2 mL of THF was stirred at 25 °C. After 9 h, the reaction was processed in the manner described for lactone **15**. After treating the crude product with excess diazomethane in ether, the products were separated by flash chromatography on 6 g of silica gel. The column was eluted with 70-mL portions of 20%, 30%, and 40% ethyl acetate in hexane and 10-mL fractions were collected. Fractions 4–5 contained 50 mg (23%) of enone **22b**. Kugelrohr distillation (oven temperature 130 °C, 0.1 mm) afforded an analytical sample: IR (film) $\nu_{max}$ 2900, 1730 (C=O), 1660 (C=O), 1625 (C=C) $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 1.10–1.13 (7-line m, 6 H, $CHCH_3$), 1.6–1.71 (m, 2 H), 1.93 (s, 3 H, $C=CCH_3$), 2.00 (dq, 1 H, $J$ = 13.1 and 4.5 Hz), 2.25–2.36 (m,H), 2.40–2.50 (m, 2 H), 2.56–2.68 (m, 2 H), 3.62 (s, 3 H, $OCH_3$).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.63; H, 8.89.

Fraction 14 contained lactone **23** (24 mg) which had the following spectral properties: IR (film) $\nu_{max}$ 2900, 1715 (br, C=O) $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 1.03 (d, 3 H, $J$ = 6.4 Hz, $CHCH_3$), 1.24 and 1.46 (2s, 6 H, $CH_3$), 1.65–1.80 (m, 2 H), 1.89–1.96 (br dd, 2 H, $J$ = 14 and 3 Hz), 2.19–2.05 (6-line m, 1 H), 2.32–2.54 (8-line m, 2 H), 2.67–2.83 (9-line m, 2 H), singlets at 1.18 and 1.32

(29) Newman, M. S.; Ramachandran, S. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, pp 486–489.

suggest an 8% impurity or isomer.

Fractions 21–24 contained 13.1 mg (6%) of ketol **24**: IR ($CHCl_3$) $\nu_{max}$ 3300 (br, OH), 2900, 1705 (C=O), 1210 $cm^{-1}$; $^1H$ NMR (360 MHz, $CDCl_3$) $\delta$ 1.09 (d, 3 H, $J$ = 6 Hz, $CHCH_3$), 1.13 (s, 3 H, $CH_3$), 1.5–1.6 (m, 2 H), 1.9–2.0 (m, 2 H), 2.1–2.4 (m, 3 H), 2.55 (br d, 1 H, $J$ = 9 Hz, C(O)C*H*COH).

Fractins 15–20 were combined (86 mg) and examined by GC (column A, 170 °C) and $^1H$ NMR. GC analysis indicated that the oil was a 1:1 mixture of ketol(s) **24** and/or **25** and lactone **23**. The $^1H$ NMR spectrum indicated that the oil was primarily composed of 48% of lactone **23**, 14% of ketol **24**, and 39% of ketol **25**. The $^1H$ NMR chemical shifts of the methyl protons for ketol **25** were 1.17, 1.23, and 1.33 ppm.

**Method B. Sodium Methoxide.** Ketone **11** (210 mg, 1 mmol) was allowed to react with sodium methoxide in methanol with conditions identical with those described under Method A for preparation of enone **20b**. The yield, after flash chromatography, was 128 mg (56%) of enone **22b** and 32 mg (15%) of lactone **23**, each having identical TLC, GC, and spectral properties to those samples prepared in Method A.

**Single-Crystal X-ray Structure Determination of 18.** Crystals suitable for X-ray diffraction analysis were grown from dichloromethane–pentane.[30] The crystal used for data collection was a colorless, transparent prism measuring 0.05 × 0.08 × 0.22 mm. Lattice constants and intensity data were measured at 298 K and $\lambda$ 1.54178 Å (Cu $K_\alpha$) on a Syntex $P2_1$ automated four-circle diffractometer equipped with a graphite crystal monochromotor.

Data collection was attempted only to $2\theta < 120.0°$. A total of 2469 reflections were collected (one form, $\pm h,k,l$) yielding 2092 unique intensities and 1250 reflections with $I > 2.58\sigma(I)$. This set of reflections was used in the structure solution and refinement. Data reduction included corrections for background, extinction, Lorentz and polarization effects, and anomalous dispersion effects. No absorption correction was necessary. Systematic absences for $0k0$, $k = 2n + 1$, and $h0l$, $l = 2n + 1$, unambiguously indicated the space group to be $P2_1/c$ ($C^5_{2h}$). Cell data: monoclinic; $a$ = 14.072 (6) Å, $b$ = 13.395 (7) Å, $c$ = 7.803 (3) Å, $V$ = 1411 (1) Å$^3$, $\rho_c$ = 1.263 g $cm^{-3}$, $Z$ = 4.

The structure was solved by direct methods (MULTAN).[31] Calculations were performed on a DEC VAX 11/780 computer system. Correct positions for all of the non-hydrogen atoms were deduced from an $E$ map. Subsequent least-squares difference Fourier calculations revealed positions for all of the hydrogen atoms; however, owing to the paucity of data, the hydrogen positions were not refined. In the final cycle of least squares, all non-hydrogen atoms were refined independently with anisotropic thermal coefficients and the hydrogen atoms were fixed in "idealized" positions while an isotropic thermal parameter was refined for the group. Refinement converged at $R$ = 0.053 ($R_w$ = 0.060). The final difference Fourier map was featureless. An ORTEP drawing[32] of the molecule in the crystal is presented in Figure 1. The non-hydrogen atoms are depicted as 35% probability ellipsoids. The hydrogen atoms are shown as arbitrary spheres and are not labeled.

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**Registry No.** 1, 93350-19-7; **5**, 37457-15-1; **6**, 93350-16-4; **7**, 93350-17-5; **8**, 93350-18-6; **10**, 20990-14-1; **11**, 93350-20-0; *cis*-**12**, 93350-22-2; *trans*-**12**, 93350-23-3; **13**, 93350-21-1; **14a**, 93350-26-6; **14b**, 93350-25-5; **15**, 93350-27-7; (*R**,*R**)-**17**, 93350-24-4; (*R**,*S**)-**17**, 93350-28-8; **18**, 93382-93-5; **19**, 5073-65-4; **20a**, 52086-93-8; **20b**, 93350-29-9; **21**, 6134-90-3; **22b**, 93350-30-2; **23**, 93350-31-3; **24**, 93350-32-4; **25**, 93350-33-5; DBU, 6674-22-2; $BrCH_2CO_2Bu$-*t*, 5292-43-3; $CH_2$=$CHCOCH_3$, 78-94-4; pyrrolidine, 123-75-1.

**Supplementary Material Available:** Tables of bond distances, bond angles, atomic positional parameters, and atomic thermal parameters for keto lactone **18** (4 pages). Ordering information is given on any current masthead page.

(30) The crystal was grown by Sharbil Firsan. We are grateful for his assistance with this structure determination.

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# Reduction of Aromatic Carbonyl Compounds Promoted by Titanium Trichloride in Basic Media. Stereochemistry Studies

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Aromatic ketones, which are not affected by Ti(III) chloride in acidic medium, react smoothly in basic media to afford the reductively coupled products according to the increase of the reducing power of Ti(III) ion with increasing pH. Benzil, benzoin, and methoxybenzoin give the corresponding alcohols. The observed stereochemistry is discussed in terms of intermolecular Ti bridging control (*dl* > meso) when intramolecular Ti complexation is prevented and in terms of steric control (meso > *dl*) when two sites of potential Ti complexation are available in the molecule. The reagent, Ti(III) chloride, is selective in that many other functional groups are unaffected by it.

Within the past few years there have been a number of investigations that have used the McMurry reagents ($TiCl_3/LiAlH_4$ or $TiCl_3$/K, Li, Zn, and Cu) to affect the reduction of aldehydes and ketones.[1] These reductions

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