β-Alkylalkanedioic Acids from Cycloalkenones via Michael Alkylation–Methoxycarbonylation

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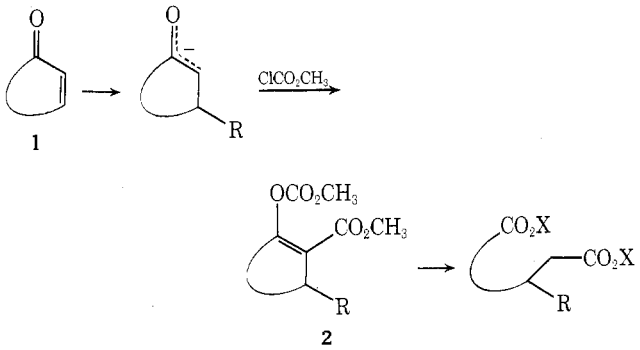
A synthesis of β-alkylalkanedioic acids is described which involves methoxycarbonylation of enolates produced by 1,4 addition of lithium dialkylcuprates to α,β-unsaturated ketones. Introduction of the methoxycarbonyl group serves both to complete the carbon skeleton and to activate an intermediate, the enol carbonate of a cyclic β-keto ester, toward further transformations. Thus, the enol carbonates are converted by a retro-Dieckmann cleavage into β-alkylalkanedioic acids or esters. The success of the method depends on the proclivity of the enolates toward acylation at carbon rather than oxygen, and upon the propensity of methyl chloroformate to acylate the carbonionic center of the ambident enolate ions. The new synthetic method is simple, convenient, and highly stereoselective. The method's scope is delineated by a study of the C- to O-acylation ratio for a series of substituted 2-cyclohexen-1-ones.

There is no short and convenient synthesis of β-alkylalkanedioic acids. Moreover, such compounds, in particular β-benzyladipic acid derivatives, are key intermediates for the synthesis of tetracyclines which are physiologically active and medicinally useful natural products.[1] We now report a new synthetic procedure for β-alkylalkanedioic acids which is not only simple and convenient, but which is also *highly stereoselective when applied to the synthesis of polysubstituted alkanedioic acids.* Our synthesis exploits Michael alkylation of α-enones coupled with reaction of the product enolates with a carbon electrophile in one combined step.[2] This procedure is particularly effective, since it allows rapid assembly of complex carbon networks in which new carbon–carbon bonds are created at both the α and β positions of the enone precursor. Use of a methoxycarbonyl group as electrophile serves both to complete the carbon skeleton and to activate the product toward further chemical modification.

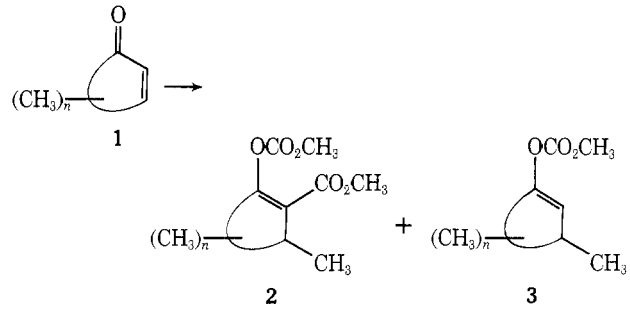
We find that methoxycarbonylation of enolates produced by 1,4 addition of lithium dialkylcuprates to 2-cycloalken-1-ones (**1**) yields enol carbonates (**2**) in a single combined step. The carbonates give alkanedioic acids or esters in high yields upon treatment with sodium hydroxide or sodium methoxide, respectively. In some cases, products



(**3**) resulting from O-acylation of the Michael enolates are also obtained. A study was made of the effect of enone structure on the ratio of C- to O-acylation in order to delineate the scope of our approach to α,ω-alkanedioic acids.

Results

Reaction of 2-cyclohepten-1-one, 2-cyclohexen-1-one, or 2-cyclopenten-1-one with a variety of lithium dialkylcuprates[3a] followed by treatment of the resulting Michael enolates with methyl chloroformate gives enol carbonates of β′-alkyl cyclic β-keto esters (**2**) in moderate yields (see Table I). Optimum conditions for a particular application depend on the relative expense of the organometallic reagent vs. the α,β-unsaturated ketone. We chose to limit the amount of organocuprate to 1.1 equiv. However, some improvement in yield based on α,β-unsaturated ketone is obtained in the one case examined by the use of a larger excess (2.2 equiv) of organocuprate. Application of the conjugate addition–methoxycarbonylation sequence to a series of methyl-substituted 2-cyclohexen-1-ones gives enol carbonates (**2**) and/or enol carbonates (**3**) of polymethylcyclo-



hexanones. Yields of **2** as well as the relative yields of **2** vs. **3** are also given in Table I.

The enol carbonate structure assigned to the products **2** is consistent with their elemental analyses and proton magnetic resonance spectra. In addition, they all exhibit ultraviolet absorption at 234 ± 5 mμ (ε 3–6 × 10^3) due to an α,β-unsaturated ester chromophore.[3b] The enol carbonates **3** were characterized by elemental analyses and proton magnetic resonance spectra. A ^{1}H NMR resonance at δ 5.1–5.2 characteristic of the vinyl proton of an enol ester was observed.

Conversion of the enol carbonates (**2**) to the corresponding β-keto esters and subsequent retro-Dieckmann cleavage occurs in a single high-yield step upon treatment with sodium hydroxide in boiling ethanol or sodium methoxide in boiling methanol to give diacids or diesters,[4] respectively. The methoxide cleavage requires 1–6 days depending on keto ester structure, the more highly substituted keto es-

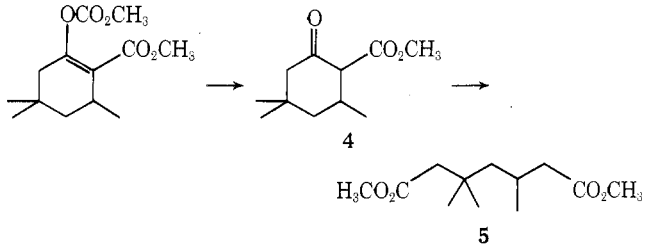


Table I
Michael Alkylation-Methoxycarbonylation of Cycloalkenones

Enone (1)	Cuprate[a]	Yield, %,[b] enol carbonate (2)	Mol %[c] enol carbonate (3)
2-Cyclopentenone (1a)	Me_2CuLi	46 (56)[d]	0
2-Cyclopentenone	n-Bu_2CuLi	71	0
2-Cyclopentenone	$Benzyl_2CuLi$	51[e]	0
2-Cyclohexenone (1b)	Me_2CuLi	58	0
2-Cyclohexenone	n-Bu_2CuLi	69	0
2-Cyclohexenone	$Benzyl_2CuLi$	43	0
2-Cycloheptenone (1c)	Me_2CuLi	47	0
5-Methyl-2-cyclohexenone (1d)	Me_2CuLi	54	0
5,5-Dimethyl-2-cyclohexenone (1e)	Me_2CuLi	20	68
3,5,5-Trimethyl-2-cyclohexenone (1f)	Me_2CuLi	0	100
4,4-Dimethyl-2-cyclohexenone (1g)	Me_2CuLi	51	9

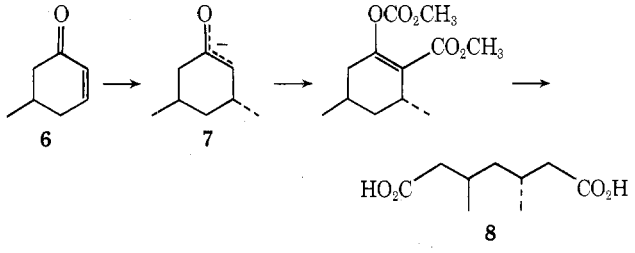
[a] 1.1 equiv. [b] Isolated by distillation. [c] Percent of enol carbonates (2 + 3) which is 3. [d] 2.2 equiv of Me_2CuLi used instead of 1.1 equiv. [e] Minimum yield (i.e., yield of diacid from retro-Dieckmann cleavage). See Experimental Section.

Table II

Diacid or diester	Yield, %	Cycloalkenone precursor
Dimethyl 3-methyladipate	99	Cyclopentenone (1a)
Dimethyl 3-methylpimelate	91	Cyclohexenone (1b)
Dimethyl 3-methylsuberate	89	Cycloheptenone (1c)
dl-3,5-Dimethylpimelic acid	85	5-Methylcyclohex-2-en-1-one (1d)
Dimethyl 3,3,5-trimethylpimelate	97	5,5-Dimethylcyclohex-2-en-1-one (1e)
Dimethyl 3,4,4-trimethylpimelate	90	4,4-Dimethylcyclohex-2-en-1-one (1g)
3-Benzyladipic acid	77	Cyclopentenone (1a)
Dimethyl 3-benzylpimelate	90	Cyclohexenone (1b)

ters requiring longer reaction periods. Thus the enol carbonate of 2-carbomethoxy-3,5,5-trimethylcyclohexanone gives a 4:6 mixture of 2-carbomethoxy-3,5,5-trimethylcyclohexanone (4) and dimethyl-3,3,5-trimethylheptanedioic acid (5), respectively, after boiling for 1 day in the presence of excess sodium methoxide in methanol. After 6 days 4 is converted completely to 5. (See Table II.)

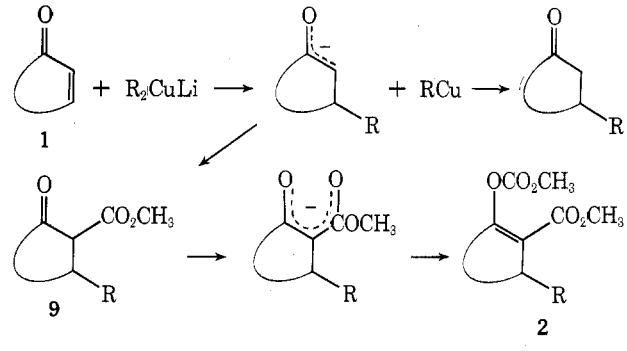
An important feature of the present approach to the synthesis of β-alkyl-α,ω-alkanedioic acids deserves comment. The method provides a *simple, highly stereoselective synthesis of polysubstituted alkanedioic acids*, since the conjugate addition of lithium diorganocuprates to substituted cycloalkenones is stereospecific.[5] For example, 5-methyl-2-cyclohexenone (6) reacts with lithium dimethylcuprate to give the Michael enolate (7) having a trans:cis ratio of 98:2.[6] We find that methoxycarbonylation of 7 followed by retro-Dieckmann cleavage gives *dl*-β,β′-dimethylpimelic acid (8).[7]



6 7 8

Discussion

The enol carbonates 2 presumably arise via C-acylation of the initial Michael enolate to give an intermediate β-keto ester, 9. Since this initial acylation product is an enolizable 1,3-dicarbonyl compound, a second equivalent of the original enolate might be expected to be consumed in the conversion of the 1,3-dicarbonyl compound to its enolate anion in the reaction mixture.[8] A maximum 50% theoretical yield of 2 based on 1 is anticipated in this event. The actual yields of 2 (see Table I) often exceed 50% and a larger excess of organocuprate increases the yield. These facts indicate that organocopper by-product and/or excess organocuprate compete with the original enolate in deprotonating the intermediate β-keto esters. Also butyl cuprate gives



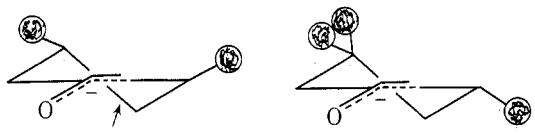
1 9 2

higher average yields (70%) than do methyl (49%) or benzyl (47%) cuprates. Thus butylcopper more effectively competes with the initial enolate in deprotonating the intermediate β-keto esters than do methyl- or benzylcopper.

The regioselectivity of acylation of the initial Michael enolates exhibits a dependence on the degree and position of substitution for the series of methyl-substituted 2-cyclohexen-1-ones examined. Generally O-acylation (3) increases relative to C-acylation (2) as the degree of substitution increases. For the series 2-cyclohexen-1-one, 5-methyl-2-cyclohexen-1-one, 5,5-dimethyl-2-cyclohexen-1-one, 3,5,5-trimethyl-2-cyclohexen-1-one the relative extent of O-acylation is 0, 0, 68, and 100%, respectively. The effect of disubstitution in the 5 position is more profound than of disubstitution in the 4 position in promoting O-acylation.

The sudden change from exclusive C-acylation of the enolate 7 (from Me_2CuLi + 5-methyl-2-cyclohexen-1-one) to predominant O-acylation of the enolate 10 (from Me_2CuLi + 5,5-dimethyl-2-cyclohexen-1-one) is readily explained in

terms of bimolecular nucleophilic substitution.[9] A transition state which involves axial attack of the methyl chloroformate on the enolate anion is expected.[3b] Axial attack on one face of **7** is not sterically hindered by a methyl group. In **10** both faces are shielded by methyl groups and acylation at the more accessible oxygen atom is favored. Predominant C-acylation (91%) of the enolate **11** (from Me_2CuLi + 4,4-dimethyl-2-cyclohexen-1-one) is expected for the conformer indicated (see figure) in which one face is sterically unencumbered. Other conformers (not pictured) favor O-acylation.



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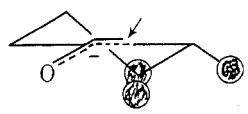

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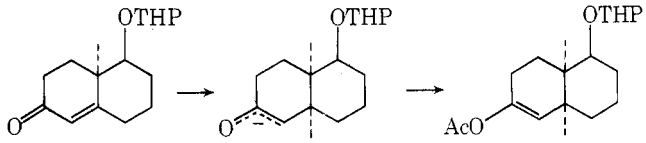
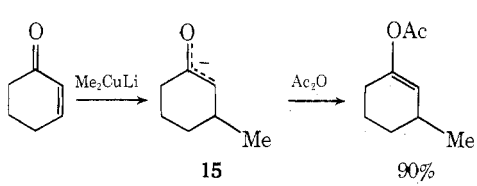
It is both interesting and significant that acylation of the initial enolate occurs on carbon rather than oxygen in most cases examined. Others have noted that when enolate anions of ketones are treated with excess acid chloride, the acyl group is introduced predominantly at oxygen rather than at carbon.[6] Our contrary results may arise from the sensitivity of acylation regioselectivity to the identity of the enolate counterion.[10] That is, the presence of copper salts in the reaction mixture may influence the regioselectivity of the acylation of enolates produced by Michael alkylation of enones with organocuprates. However, comparison of an acylation with, for example, acetyl chloride and acylations with methyl chloroformate is beclouded by the greater reactivity and proclivity toward O-acylation of the former.[10] Thus O-acylation is observed upon conjugate addition of lithium dimethylcuprate to enone **12**, followed by rapid quenching of the reaction mixture with excess acetyl chloride to give **14** in 88% yield.[11] The regioselectivity of acylation of the Michael enolate **13** may be due to steric factors. However, the regiospecific O-acylation observed in reaction of the Michael enolate **15** with acetic anhydride[12] contrasts with the C-acylation of **15** with methyl chloroformate observed by us under otherwise identical reaction conditions.



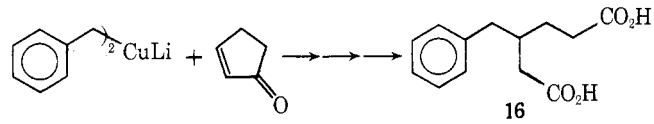
12 **13** **14**



15 90%

Conclusions

Michael alkylation–methoxycarbonylation–retro-Dieckmann cleavage is a simple and convenient new synthetic procedure for β-alkylalkanedioic acids starting from readily available cycloalkenones. Thus, for example, β-benzyladipic acid (**16**) is readily obtained (51%) in essentially one combined step (i.e., without isolation of pure intermediates) from lithium dibenzylcopper, cyclopentanone, and methyl chloroformate. Since Michael alkylation of substituted cycloalkenones is stereospecific, the procedure provides a highly stereoselective synthesis of polysubstituted alkanedioic acids. The applicability of the method is limited by the proclivity of highly substituted sterically congested enolates toward acylation at oxygen.



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Experimental Section

General. Ethyl ether (Baker Analyzed anhydrous) was used without further drying. Methyllithium (1.7 *M* in ethyl ether), vinyllithium (1.8 *M* in tetrahydrofuran), and *n*-butyllithium (1.65 *M* in *n*-hexane) were from Lithium Corp. of America. Ventron Corp. 98% copper(I) iodide was used without further purification. All reactions involving organometallics were conducted under a blanket of dry nitrogen in flame-dried reaction vessels. NMR spectra were obtained on a Varian A-60A instrument on solutions in CCl_4. Ultraviolet spectra were measured with a Beckman Model DU spectrophotometer on solutions in anhydrous methanol. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz., and by Par-Alexander Labs, South Daytona, Fla.

Michael Methylation–Methoxycarbonylation. A solution of methyllithium in ether (88 mmol) was added to a mechanically stirred suspension of CuI (8.4 g, 44 mmol) in ether (400 ml) cooled to 0° with an ice–water bath. After stirring for 0.5 hr, 2-cycloalkenone (40 mmol) was added over 3 min. After stirring for an additional 1 hr, methyl chloroformate (11 ml) was added in one portion. The resulting mixture was stirred for 1 hr and then allowed to warm to room temperature and stand for 10 hr. Cold aqueous 5% HCl (300 ml) was added. The aqueous layer was separated and washed with ether (3 × 150 ml). The combined ether extracts were washed with saturated aqueous NaCl (150 ml) and dried (Na_2SO_4). Solvent was removed by rotary evaporation, and the residue was distilled under reduced pressure. The distillations in cases A, B, D, F, and G were performed with a short-path distillation head (Kontes). In cases C and E, a vacuum-jacketed, 130-mm Vigreux column was included to improve fractionation.

A. Cyclohexenone (1b). Besides 3-methylcyclohexanone (1.2 g, 27%), the enol carbonate of 2-carbomethoxy-3-methylcyclohexanone, bp 98–102° (0.6 mm), was obtained (58%): NMR δ 1.07 (3 H, d, J = 7 Hz, C-3 methyl), 1.4–2.0 (4 H, C-4 and C-5), 2.0–2.4 (2 H, C-6), 2.6–3.0 (1 H, C-3), 3.70 (3 H, s, ester methyl), 3.80 (3 H, s, ester methyl); uv λ_{max} 238 mμ (ε 3600).

Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 57.83; H, 7.00.

B. 5-Methyl-2-cyclohexenone (1d). The title enone, prepared by the method of Blanchard and Goering,[13] gave the enol carbonate of 2-carbomethoxy-*trans*-3,5-dimethylcyclohexanone: bp 97–99° (0.3 mm) (54%); NMR δ 0.9–1.2 (6 H, m, methyls), 1.3–1.6 (2 H, m, C-4), 1.7–2.4 (3 H, C-5 and C-6), 2.6–3.1 (1 H, C-3), 3.65 (3 H, s, ester methyl), 3.75 (3 H, s, ester methyl); uv λ_{max} 230 mμ (ε 4550).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.25; H, 7.42.

C. 5,5-Dimethyl-2-cyclohexenone (1e). The title enone, prepared by the method of Hiegel and Burk,[14] gave 1-methoxycarbonyloxy-3,5,5-trimethylcyclohexene: bp 118–124° (10 mm) (42%); NMR δ 0.9–1.1 (9 H, m, methyls), 1.1–1.6 (2 H, m, C-4), 1.8–1.9 (1 H, C-6), 1.9–2.1 (1 H, C-6), 2.1–2.6 (1 H, C-3), 3.70 (3 H, s, ester methyl), 5.1–5.3 (1 H, C-2, vinyl).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.66; H, 9.17.

Also the enol carbonate of 2-carbomethoxy-3,5,5-trimethylcyclohexanone, methyl 2-methoxycarbonyloxy-4,4,6-trimethylcyclohexenecarboxylate, was obtained: bp 100–106° (0.5–0.6 mm) (20%); NMR δ 0.9–1.2 (9 H, m, methyls), 1.2–1.8 (2 H, C-4), 1.8–2.0 (1 H, C-6), 2.1–2.3 (1 H, C-6), 2.4–2.8 (1 H, C-3), 3.69 (3 H, s, ester methyl), 3.77 (3 H, s, ester methyl), uv λ_{max} 229 mμ (ε 3100).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.71; H, 7.96.

Finally, 3,3,5-trimethylcyclohexanone (9%) was isolated from the distillation forerun (bp 80–118, 10 mm) by preparative gas–liquid chromatography on a 5 ft × 0.25 in. column filled with 20% FFAP on 60/80 Chromosorb P at 110°: NMR δ 0.9–1.1 (9 H, m, methyls), 1.2–1.6 (2 H, C-4), 1.7–2.5 (5 H, C-2, C-5, and C-6).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.98; H, 11.49.

D. 3,5,5-Trimethyl-2-cyclohexenone (Isophorone, 1f). The title enone gave 3,3,5,5-tetramethyl-1-methoxycarbonyloxycyclohexene-1, the enol carbonate of 3,3,5,5-tetramethylcyclohexanone: bp 52–62° (0.6–0.8 mm) (93%); NMR δ 1.03 (6 H, s, methyls), 1.07 (6 H, s, methyls), 1.33 (2 H, s, C-4), 1.91 (2 H, d, J = 1.2 Hz, C-6), 3.72 (3 H, s, ester methyl) 5.17 (1 H, t, J = 1.2 Hz, C-2 vinyl).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.00; H, 9.34.

E. 4,4-Dimethyl-2-cyclohexenone (1g). The title enone, prepared by the method of Eliel and Lurach,[15] gave the enol carbonate of 2-carbomethoxy-3,4,4-trimethylcyclohexanone, methyl 2-methoxycarbonyloxy-5,5,6-trimethylcyclohexenecarboxylate: bp 100–102° (0.25 mm) (51%); NMR δ 0.95 (3 H, s, methyl), 0.97 (3 H, d, J = 7 Hz, C-3 methyl), 0.99 (1 H, s, methyl), 1.1–2.0 (2 H, m, C-5), 2.0–2.6 (3 H, m, C-3 and C-6), 3.67 (3 H, s, ester methyl), 3.77 (3 H, s, ester methyl).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 61.11; H, 8.18.

Also 1-methoxycarbonyloxy-3,4,4-trimethylcyclohexene was obtained from the distillation forerun by preparative gas–liquid phase chromatography on a 5 ft × 0.25 in. column filled with 20% FFAP on 60/80 Chromosorb P at 180° (5%): NMR δ 0.8–1.0 [9 H, d (apparent), methyls], 1.1–1.7 (2 H, C-5), 1.8–2.3 (3 H, C-3 and C-6), 3.73 (3 H, s, ester methyl), 5.05–5.20 (1 H, m, C-2 vinyl).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.68; H, 9.33.

F. 2-Cyclopentenone (1a). The title enone gave the enol carbonate of 2-carbomethoxy-3-methylcyclopentanone, bp 125–135° (10–15 mm) (46%). The use of 2.2 equiv of Me_2CuLi instead of the usual 1.1 equiv gave an improved yield (56%): NMR δ 1.19 (3 H, d, J = 6 Hz, methyl), 1.3–3.3 (5 H, C-3, C-4, and C-5), 3.67 (3 H, s, ester methyl), 3.82 (3 H, s, ester methyl); uv λ_{max} 238 mμ (ε 5850).

Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.96; H, 6.60.

G. 2-Cycloheptenone (1c). The title enone gave the enol carbonate of 2-carbomethoxy-3-methylcycloheptanone: bp 98–101° (0.3 mm) (47%); NMR δ 1.14 (3 H, d, J = 7 Hz, methyl), 1.5–2.1 (6 H, C-4, C-5, and C-6), 2.2–2.6 (2 H, C-7), 2.6–3.1 (1 H, C-3), 3.66 (3 H, s, ester methyl), 3.78 (3 H, s, ester methyl); uv λ_{max} 229 mμ (ε 3000).

Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.32; H, 7.33.

Michael Butylation–Methoxycarbonylation. A solution of n-butyllithium in n-hexane (88 mmol) was added to a mechanically stirred suspension of CuI (8.4 g, 44 mmol) in ether (400 ml) cooled to −30°. After stirring for 30 min, cycloalkenone (40 mmol) was added over 3 min. The temperature of the reaction mixture was allowed to increase slowly to −10° over an additional 1 hr with continued stirring. Then methyl chloroformate (11 ml) was added in one portion. The resulting mixture was stirred for 1 hr at 0° and then allowed to warm to room temperature and stand for 10 hr. The rest of the procedure is the same as described above for methylation.

A. Cyclopentenone (1a). The title enone gave the enol carbonate of 3-butyl-2-carbomethoxycyclopentanone: bp 110–115° (0.7 mm) (71%); NMR δ 0.92 (3 H, t, J = 5 Hz, methyl), 1.1–3.2 (11 H), 3.68 (3 H, s, ester methyl), 3.82 (3 H, s, ester methyl); uv λ_{max} 234 mμ (ε 6100).

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.80; H, 7.94.

B. Cyclohexenone (1b). The title enone gave the enol carbonate of 3-butyl-2-carbomethoxycyclohexanone: bp 118–122° (0.8 mm) (69%); NMR δ 0.90 (3 H, t, J = 5 Hz, methyl), 1.1–2.4 (12 H), 2.4–2.9 (1 H, C-3), 3.67 (3 H, s, ester methyl), 3.78 (3 H, s, ester methyl); uv λ_{max} 229 mμ (ε 3890).

Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.08; H, 8.20.

Michael Benzylation–Methoxycarbonylation. A solution of benzyllithium in ether (88 mmol) was prepared from tribenzyltin(IV) chloride[16] (12.8 g, 30 mmol) and methyllithium (120 mmol) according to the procedure of Seyferth et al.[17] This solution was drawn off from the white precipitate of LiCl with a hypodermic syringe and added to a suspension of CuI (8.4 g, 44 mmol) at −25 to −20° with mechanical stirring. After 1 hr, cycloalkenone (40 mmol) was added dropwise over 5 min. The mixture was stirred at −25 to −10° for 1.5 hr. Then methyl chloroformate (11 ml) was added in one portion to the dark green solution. The resulting mixture was slowly warmed to room temperature and stirred for 10 hr. Then cold aqueous 5% HCl (300 ml) was added. The aqueous layer was separated and washed with ether (3 × 150 ml). The combined ether extracts were washed with saturated aqueous NaCl (150 ml) and dried (Na_2SO_4). Solvent was removed by rotary evaporation. Further purification is detailed for each example studied (see below).

A. Cyclopentenone (1a). The crude product was purified by removal of volatile impurities by distillation under reduced pressure (up to 83°, 0.3 mm). The residue weighed 7.66 g (66% assuming pure enol carbonate of 3-benzyl-2-carbomethoxycyclopentanone).

B. Cyclohexenone (1b). The enol carbonate of 3-benzyl-2-carbomethoxycyclohexanone was obtained from the crude reaction product as follows. Some enol carbonate crystallized from the crude oily product mixture. The crystalline product was isolated by filtration on a Buchner funnel, and volatile impurities were removed from the filtrate by distillation under reduced pressure (up to 90°, 0.25 mm). The remaining oily product was taken up in a minimum of methanol and the solution was placed in the refrigerator for several days. Crystals of enol carbonate which separated were collected on a Buchner funnel and all crystalline product was recrystallized from methanol to give product: mp 109–110° (43%); NMR δ 1.3–2.1 (4 H, C-4 and C-5), 2.2–2.5 (2 H, C-6), 2.82 [2 H, dd (apparent), J = 9, 14 Hz, benzylic CH_2], 2.9–3.3 (1 H, C-3), 3.70 (3 H, s, ester methyl), 3.87 (3 H, s, ester methyl); uv λ_{max} 229 mμ (ε 4800).

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.02; H, 6.75.

Michael Vinylation–Methoxycarbonylation of 2-Cyclopentenone (1a). A solution of vinyllithium in tetrahydrofuran (22 mmol) was added to a mechanically stirred suspension of CuI (2.1 g, 11 mmol) in ether (100 ml) at −50°. The resulting mixture was stirred for 1 hr at −55 to −35°. Then 2-cyclopentenone (10 mmol) was added and the resulting mixture was stirred at −40 to −35° for 10 min and then at 0° for 30 min. Then methyl chloroformate (2.8 ml) was added in one portion and the resulting mixture was stirred for 1 hr at 0° and then allowed to warm slowly to room temperature and stirred for 10 hr. An aqueous work-up analogous to those described above for methylation, etc., gave the enol carbonate of 2-carbomethoxy-3-vinylcyclopentanone: bp 98–100° (0.6 mm) (31%); NMR δ 3.67 (3 H, s, ester methyl), 3.84 (3 H, s, ester methyl), 4.8–5.3 (2 H, m, vinyl CH_2), 5.6–6.2 (1 H, m, vinyl CH).

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.65; H, 6.23.

Dimethyl Alkanedioates via Retro-Dieckmann Cleavage with Sodium Methoxide.[4] Sodium (0.93 g, 41 mmol) was dissolved in anhydrous methanol (60 ml) and then the enol carbonate was added (15 mmol). The resulting mixture was boiled under reflux for 1–8 days, longer periods being required for more highly substituted enol carbonates. After cooling to 0° (ice–water bath), dry HCl was bubbled through the reaction mixture until it was acidic. Methanol was then removed by rotary evaporation and the residue was partitioned between water (20 ml) and ether (30 ml). The aqueous fraction was extracted with additional ether (30 ml), and the combined organic extracts were washed with saturated aqueous NaCl (30 ml) and dried (Na_2SO_4). Solvent was removed by rotary evaporation. In most cases the crude product which remained was almost pure diester, and an analytical sample was obtained by preparative gas–liquid phase chromatography on a 5 ft × 0.25 in. column of 20% FFAP on Chromosorb P (60/80). In some cases the residual oil was fractionally distilled under reduced pressure.

Dimethyl 3-Methyladipate. The enol carbonate of 2-carbomethoxy-3-methylcyclopentanone was cleaved in 1 day by boiling methanolic sodium methoxide. The crude product was pure dimethyl 3-methyladipate (99%), which had an identical NMR spectrum and gas–liquid chromatographic retention time with those of authentic diester prepared by methylation of the diacid (Aldrich) with diazomethane.

Dimethyl 3-Methylpimelate. The enol carbonate of 2-carbomethoxy-3-methylcyclohexanone was cleaved in 1 day by boiling methanolic sodium methoxide. The crude product was pure diester (91%): NMR δ 0.94 (3 H, d, J = 7 Hz, methyl), 1.1–2.0 (5 H, C-3, C-4, and C-5), 2.0–2.4 (4 H, C-2 and C-6), 3.61 (6 H, s, ester methyls).

Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.27; H, 9.26.

Dimethyl 3-Methylsuberate. The enol carbonate of 2-carbomethoxy-3-methylcycloheptanone was cleaved in 1 day by boiling methanolic sodium methoxide. The crude product was pure diester (89%): NMR δ 0.93 (3 H, d, J = 6 Hz, methyl), 1.1–2.0 (7 H, C-3,

C-4, C-5, and C-6), 2.0–2.5 (4 H, C-2 and C-7), 3.62 (6 H, s, ester methyls).

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.01; H, 9.37.

***dl*-3,5-Dimethylpimelic Acid.** The enol carbonate of 2-carbomethoxy-*trans*-3,5-dimethylcyclohexanone was cleaved in 8 days by boiling methanolic sodium methoxide to give crude diester, NMR δ 3.62 (6 H, s, ester methyls), which was saponified with boiling aqueous methanolic KOH to give diacid (85%), mp 138–140° (reported[7] mp 139.9–140.5°), after crystallization from ethyl acetate. The alternative isomeric meso diacid has a reported melting point of 99.3–99.6°.

Dimethyl 3,3,5-Trimethylpimelate. The enol carbonate of 2-carbomethoxy-3,5,5-trimethylcyclohexanone gave a 6:4 mixture of 2-carbomethoxy-3,5,5-trimethylcyclohexanone and dimethyl 3,3,5-trimethylpimelate, respectively, upon boiling in methanolic sodium methoxide for 1 day. These products were separated by preparative gas–liquid phase chromatography on a 5 ft × 0.25 in. column of SE-30 on Chromosorb P (60/80) at 180°. Dimethyl 3,3,5-trimethylpimelate: NMR δ 1.00 [9 H, broad s (apparent), methyls], 1.2–1.4 (2 H, C-4), 1.5–2.5 (5 H, C-2, C-5 and C-6), 3.60 (6 H, s, ester methyls).

Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.72; H, 9.43.

2-Carbomethoxy-3,5,5-trimethylcyclohexanone: NMR δ 1.00 [9 H, d (apparent), J = 7 Hz, methyls], 1.2–1.8 (2 H, broad d, J = 12 Hz, C-4), 2.12 [2 H, broad s (apparent), C-6], 2.2–2.8 (1 H, m, C-3), 2.84 (1 H, d, J = 12 Hz, C-2), 3.70 (3 H, s, ester methyl).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.68; H, 9.17.

The enol carbonate gave almost pure diester (97% crude) upon boiling in methanolic sodium methoxide for 7 days.

Dimethyl 3,4,4-Trimethylpimelate. The enol carbonate of 2-carbomethoxy-3,4,4-trimethylcyclohexanone gave the title diester upon boiling in methanolic sodium methoxide (90%): bp 84–86° (1.5 mm); NMR δ 0.95 (6 H, s, methyls), 0.97 (3 H, d, J = 6 Hz, methyl), 1.3–2.5 (7 H, C-2, C-3, C-4, and C-5), 3.61 (6 H, s, ester methyls).

Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.33; H, 9.62.

Alkanedioic Acids via Retro-Dieckmann Cleavage with Sodium Hydroxide. Sodium hydroxide (4.2 g, 105 mmol) was boiled under reflux with magnetic stirring in anhydrous ethanol (52 ml) until the hydroxide dissolved. Then the crude enol carbonate of 3-benzyl-2-carbomethoxycyclopentanone (see above) (7.66 g) was added to the solution at 30–50° together with 10 ml of additional ethanol. The resulting mixture was boiled under reflux for 6 hr. The reaction mixture was cooled to room temperature and then poured into an ice–water mixture (50 ml). The resulting mixture was washed with ether (2 × 50 ml) and then acidified with excess concentrated HCl (50 ml). The diacid was extracted into ether (2 × 50 ml). The ether solution was dried (Na_2SO_4). Solvent was removed by rotary evaporation to yield crude diacid (51% based on starting cyclopentenone). This was crystallized from chloroform–pentane (1:1 v/v, 40 ml). The product was collected on a Buchner funnel, washed with 1:1 chloroform–pentane (15 ml), and air dried to yield 3-benzyladipic acid (40% based on starting cyclopentenone) as a white powder: mp 108–109° (yields are overall from cyclopentanone); NMR ($CDCl_3$) δ 1.4–1.9 (2 H, C-4), 1.9–2.5 (5 H, C-2, C-3, and C-5), 2.5–2.9 (2 H, benzylic), 7.20 (5 H, s, aromatic), 11.5 (2 H, s, carboxyl).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 65.95; H, 6.85.

Similar treatment of the enol carbonate of 3-benzyl-2-carbomethoxycyclohexanone (see above) gave 3-benzylpimelic acid, mp 71–74°, which was methylated with ethereal diazomethane to give dimethyl 3-benzylpimelate (90%): NMR δ 0.9–1.9 (5 H, C-3, C-4, and C-5), 1.9–2.3 (4 H, C-2 and C-6), 2.3–2.6 (2 H, benzylic), 3.51 (6 H, s, ester methyls), 7.08 (5 H, s, aromatic).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.99; H, 8.03.

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Registry No.—**1a,** 930-30-3; **1b,** 930-68-7; **1c,** 1121-66-0; **1d,** 7214-50-8; **1e,** 4694-17-1; **1f,** 78-59-1; **1g,** 1073-13-8; **2a** (R = Me), 54575-96-1; **2a** (R = Bu), 54575-97-2; **2a** (R = CH_2Ph), 54575-98-3; **2a** (R = $CH{=}CH_2$), 54576-00-0; **2b** (R = Me), 54576-01-1; **2b** (R = Bu), 54576-02-2; **2b** (R = CH_2Ph), 54576-03-3; **2c** (R = Me), 54575-99-4; **2d** (R = Me), 54576-20-4; **2e** (R = Me), 54576-04-4; **2f** (R = Me), 54576-05-5; **2g** (R = Me), 54576-06-6; **3e,** 54576-07-7; **3f,** 54576-08-8; **3g,** 54576-09-9; **4,** 54576-10-2; **5,** 54576-11-3; **8,** 54576-21-5; **16,** 54576-12-4; dimethyl 3-methyladipate, 54576-13-5; dimethyl 3-methylpimelate, 54576-14-6; dimethyl 3-methylsuberate, 54576-15-7; dimethyl 3,4,4-trimethylpimelate, 54576-16-8; 3-benzylpimelic acid, 54576-17-9; dimethyl 3-benzylpimelate, 54576-18-0; Me_2CuLi, 15681-48-8; *n*-Bu_2CuLi, 24406-16-4; $benzyl_2CuLi$, 51467-05-1; methyl chloroformate, 79-22-1; sodium methoxide, 124-41-4; sodium hydroxide, 1310-73-2; 3,3,5-trimethylcyclohexanone, 873-94-9; 3,3,5,5-tetramethylcyclohexanone, 14376-79-5.

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