A Novel Synthetic Approach to the Eudesmane Class of Sesquiterpenes

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Received November 23, 1971

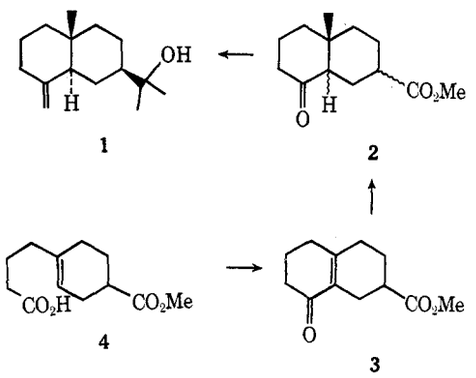
An efficient synthetic approach to the eudesmane class of sesquiterpenes is described. The key intermediate in the synthetic sequence is 7-carbomethoxy-$\Delta^{9,10}$-octal-1-one (**3**), which is prepared by an intramolecular acylation reaction. Addition of lithium dimethylcopper(I) to **3** produces a mixture of keto esters from which keto acid **14b** is readily obtained. This material has previously been converted to β-eudesmol.

Within the past two decades tremendous strides have been taken in the development of methods for the total synthesis of members of the decalin sesquiterpene class.[3] Indeed, the synthetic methodology currently available allows the synthesis of most compounds within this family of sesquiterpenes almost at will. Central to the preparation of the majority of these compounds has been the Robinson annelation reaction.[4] Although this is an extremely useful weapon in the arsenal available to the synthetic chemist, the yields for the sequence are often low and stereochemical complications arise when substituents are present on either the Michael donor or Michael acceptor. In connection with our interest in the development of general methods for the formation of carbocyclic ring systems[5] we have developed a synthetic approach to the eudesmane class of sesquiterpenes which is not dependent upon the traditional Robinson annelation sequence.[6,7]

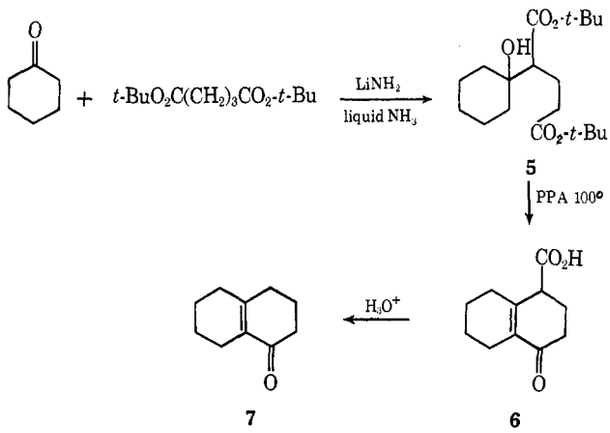
Our synthetic strategy, like that of other workers,[6c] centered on the development of an efficient synthesis of a keto ester of the type **2**. This compound is an extremely attractive synthetic goal because the ketone function at C-1 and ester function at C-7 allow epimerization at C-7 and C-9 and should permit the preparation of the stereoisomer required for conversion to β-eudesmol **1** (Scheme I). In contrast to other approaches to keto esters of the type **2**, we sought to prepare this key intermediate by the addition of lithium dimethylcopper(I)[8] to the unsaturated keto ester **3**. Although there are a number of possible routes to **3** from properly substituted naphthalene or tetralin derivatives, we chose to examine the intramolecular acylation of a cyclohexene derivative such as **4**. Compounds such as **4** are potentially available from the very useful, but seldom employed, Puterbaugh[9] extension of the Stobbe condensation.

In order to test the feasibility of this route, the model study outlined in Scheme II was carried out. The di-

SCHEME I



SCHEME II



tert-butyl glutarate adduct of cyclohexanone **5** was readily obtained by the addition of the lithium salt of di-*tert*-butyl glutarate to cyclohexanone in liquid ammonia. The ready acid-catalyzed conversion of *tert*-butyl esters to the free acids suggested that the adduct **5** might undergo dehydration, deisobutylation, and cyclization to the octalone derivative **8** in a single step on treatment with polyphosphoric acid. When **5** was heated with polyphosphoric acid at 100° all of these transformations occurred and the keto acid **6** was obtained in 51% yield.[10] When **6** was heated at reflux in aqueous acid it underwent a smooth decarboxylation to give the octalone **7**.

This sequence of reactions was then applied to 4-carbomethoxycyclohexanone (**8**) as outlined in Scheme III. Condensation of di-*tert*-butyl glutarate with **8** gave the oily hydroxy triester **9**. Attempts to convert **9** directly to the unsaturated keto acid **11** by the method described above gave only a low (18%) yield of **11**. A

(1) Alfred P. Sloan Foundation Research Fellow, 1970–1972.

(2) Taken from the Ph.D. dissertation of E. G. Zey, University of Kansas, Sept 1968 [*Diss. Abstr. B*, **30**, 2623 (1969)].

(3) For a review see J. M. Mellor and S. Munavalli, *Quart. Rev., Chem. Soc.*, **18**, 270 (1964).

(4) E. C. du Feu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937); E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. React.*, **10**, 179 (1959).

(5) R. G. Carlson and R. G. Blecke, *Chem. Commun.*, 93 (1969).

(6) For previous syntheses of members of the eudesmane class see (a) J. A. Marshall, M. T. Pike, and R. D. Carroll, *J. Org. Chem.*, **31**, 2933 (1966); (b) D. C. Humber, A. R. Pinder, and R. A. Williams, *J. Org. Chem.*, **32**, 2335 (1967); (c) C. H. Heathcock and T. R. Kelly, *Tetrahedron*, **24**, 1801 (1968); (d) J. A. Marshall and M. T. Pike, *J. Org. Chem.*, **33**, 435 (1968).

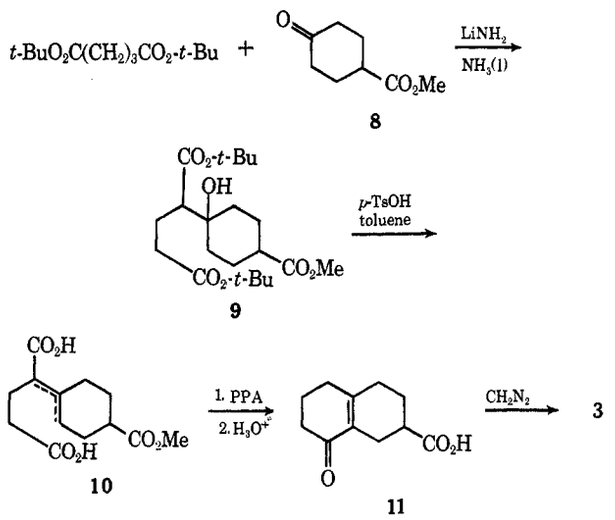
(7) Subsequent to the completion of this work[2] a report appeared of another route to **3**: J. W. Huffman and M. L. Mole, *Tetrahedron Lett.*, 501 (1971).

(8) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966); H. O. House and W. F. Fischer, Jr., *ibid.*, **33**, 949 (1968).

(9) W. H. Puterbaugh, *ibid.*, **27**, 4010 (1962).

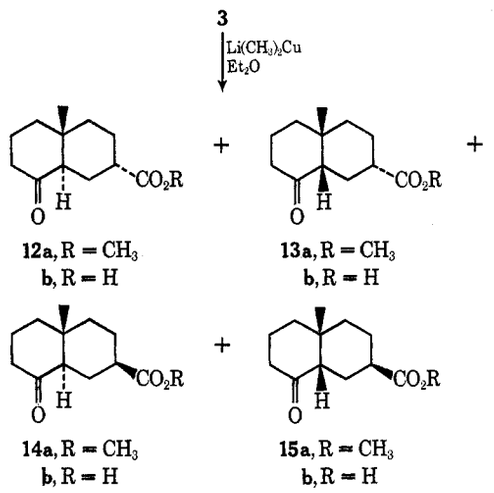
(10) No attempt was made to optimize the yields in this sequence.

SCHEME III



more efficient route to **11** was developed which involved conversion of the hydroxy triester **9** to the unsaturated diacid **10** by reaction with *p*-toluenesulfonic acid in toluene. Treatment of **10** with polyphosphoric acid and subsequent decarboxylation of the cyclized product afforded the unsaturated keto acid **11** in 58% yield. Esterification with diazomethane gave **3**.

Treatment of **3** with lithium dimethylcopper(I) gave a high yield of the conjugate addition product as a mixture of isomers. Although the exact distribution of isomers varied somewhat from run to run, the approximate relative percentages of the esters **12a–15a** in the crude product were 24% **12a**, 48% **13a**, 11% **14a**, and 17% **15a**. The stereochemistry of these products was established in the following manner. Hydrolysis of the mixture of esters and chromatography of the resulting mixture of keto acids produced four acids, two of which were identical with authentic samples of **14b** and **15b**[6c,11] and two new acids, mp 131° and 159°.



Stereochemical assignments for the two new acids and the corresponding esters were based upon nuclear magnetic resonance (nmr) spectral data. The angular methyl groups in both the acid with mp 131° and its methyl ester appear in the nmr spectra at δ 0.82, whereas the angular methyl groups in the acid with mp 159° and its methyl ester appear at δ 0.95. Based upon the useful generalization[12] that the angular methyl group of a trans-fused decalin system appears at higher field than the corresponding cis isomer, the acid with mp 131° must be **12b** and the acid with mp 159° must be **13b**. Further confirmation of these stereochemical assignments was obtained by an examination of the $\Delta W_{1/2}$ values[13] for the angular methyl groups in the esters **12a–15a** (Table I). These values

TABLE I

NMR DATA FOR ANGULAR METHYL GROUPS IN ESTERS **12a–15a**

Ester	Chemical shift, ppm	$\Delta W_{1/2}$,[a] Hz
12a	0.82	0.64 ± 0.01[b]
13a	0.95	0.47 ± 0.01
14a	0.82	0.73 ± 0.01
15a	1.17	0.46 ± 0.03

[a] The $\Delta W_{1/2}$ values were determined[13a] by using the formula $\Delta W_{1/2} = CH_3\ W_{1/2} - TMS\ W_{1/2}$, where $CH_3\ W_{1/2}$ is the half band width of the angular methyl group and TMS $W_{1/2}$ is the half band width of the TMS signal. [b] Deviations are given as average deviations.

for $\Delta W_{1/2}$ are consistent with the stereochemical assignments made above.

It is clear, then, that there is a marked preference (~70%) for the introduction of the new angular methyl group from the side opposite the carbomethoxy group. The reason for this preference is not readily apparent from a conformational analysis of the various possible transition states in this reaction.

Because the keto ester **14a**, having the stereochemistry required for conversion to β-eudesmol (**1**), is not obtained in appreciable yield in the kinetically controlled methylation of **3**, we turned our attention to the equilibration of the esters **12a–15a**. When the mixture of esters obtained in the conjugate addition reaction was equilibrated with sodium methoxide in methanol, the equilibrium mixture consisted of 10% **12a**, 14% **13a**, 58% **14a**, and 18% **15a**. Saponification of the equilibrium mixture and chromatography of the resulting mixture of keto acids gave the pure keto acid **14b**. As this compound has been previously converted into β-eudesmol,[6c] this constitutes a formal total synthesis of this sesquiterpene.

Experimental Section[14]

2-(1-Hydroxycyclohexyl)di-*tert*-butyl Glutarate (5).—Following the procedure of Puterbaugh,[9] 74.6 mmol of lithium amide was generated and used to condense 10.0 g (56.8 mmol) of di-*tert*-butyl glutarate with 5.58 g (56.8 mmol) of cyclohexanone. Work-up afforded 13.6 g (87%) of the crude hydroxy diester **5**, ir 3500 (OH), 1730 cm^{-1} (ester C=O).

$\Delta^{9,10}$-Octal-1-one (7).—Polyphosphoric acid (PPA) (150 g) and 10.0 g (36.5 mmol) of the hydroxy diester **5** were blended by

(11) We are indebted to Professor Heathcock for kindly providing us with authentic samples of **14b** and **15b**.

(12) R. F. Zurcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

(13) (a) K. L. Williamson, T. Howell, and T. A. Spencer, *J. Amer. Chem. Soc.*, **88**, 325 (1966); (b) M. J. T. Robinson, *Tetrahedron Lett.*, 1685 (1965); (c) C. W. Shoppee, F. P. Johnson, R. E. Lack, and S. Sternhell, *Chem. Commun.*, 347 (1965).

(14) All boiling points are uncorrected and all melting points are corrected. The infrared spectra were recorded on a Beckman IR-8 spectrophotometer and the nuclear magnetic resonance spectra were recorded on a Varian A-60, A-60A, or HA-100 instrument using tetramethylsilane as an internal standard. Gas chromatography studies utilized an Aerograph A-90P or F & M Model 700 gas chromatograph and a Beckman 10-in. recorder equipped with a Disc Integrator. Unless otherwise stated, magnesium sulfate was employed as the drying agent.

hand with a stirring rod. The mixture was heated for 1.5 hr on the steam bath, which effected immediate evolution of carbon dioxide. Ice (37 g) and 11 ml of water were added. The aqueous mixture was extracted with four 15-ml portions of ether, which were combined and washed with two 10-ml portions of saturated sodium bicarbonate solution. The combined aqueous fractions were acidified, extracted with ether, dried, and concentrated to afford 2.54 g (51%) of the crude keto acid **6**, ir ($CHCl_3$) 3550 (COOH), 1700 (acid C=O), and 1660 cm^{-1} (conjugated C=O). The crude sample of keto acid **6** (2.54 g, 13.1 mmol) was refluxed in a mixture of 15 ml of PPA, 18.5 ml of acetic acid, and 125 ml of water for 5 hr. After addition of 37 g of ammonium sulfate and enough sodium chloride to saturate the solution, the mixture was extracted with four 15-ml portions of ether. The combined ether layers were washed with three 10-ml portions of saturated sodium bicarbonate solution and brine, dried, concentrated, and distilled to afford 1.21 g (62%) of the ketone **7**: bp 130–145° (9 mm); $n^{10}D$ 1.5322; ir 1670 (conjugated C=O), 1640 cm^{-1} (C=C); uv max (95% EtOH) 248 mμ (ε 12,500) [lit.[15] uv max (95% EtOH) 246 mμ (ε 12,400)]; nmr δ 2.2 (m, 8, CH adjacent to unsaturated). A 2,4-dinitrophenylhydrazone derivative was prepared in 68% yield, mp 266.5–267° [lit.[15] mp 266–266.5°]; vpc analysis (6 ft × 0.25 in., 15% DEGS on 60–80 mesh Chromosorb W, 170°) indicated the presence of only one component.

4-Carbomethoxycyclohexanone (8).—A mixture of 50.0 g (0.329 mol) of methyl *p*-hydroxybenzoate,[16] 2.0 g of 5% rhodium on alumina, and 100 ml of freshly distilled ethanol was shaken in an atmosphere of hydrogen (60 psi) until the hydrogen uptake ceased. The catalyst was removed by filtration, the solvent was removed under reduced pressure, and the residue was distilled to afford 50.1 g (96%) of 4-carbomethoxycyclohexanol (stereochemistry not determined), bp 80–85° (0.06 mm) [lit.[16] bp 96–98° (0.35 mm)].

An acetone solution of the hydroxy ester (50.0 g, 0.316 mol) was treated at 15° with 77 ml of a 2.67 *M* solution of chromium trioxide in aqueous sulfuric acid.[17] After 1 hr, 2.5 ml of isopropyl alcohol was added, the acetone solution was decanted, and the chromium salts were dissolved in brine. The aqueous layer was extracted with ether and the ether extracts were combined with the acetone solution. The organic layers were dried and concentrated, and the residue was distilled to afford 38.1 g (76%) of keto ester: bp 94–95° (0.65 mm) [lit.[16] bp 80–81° (0.40 mm)]; ir 1730 (ester C=O) and 1715 cm^{-1} (ketone C=O); nmr δ 3.7 (s, 3, OCH_3) and unresolved absorption in the region 2.5–1.2 (9 H).

2-(1-Hydroxy-4-carbomethoxycyclohexyl)di-*tert*-butyl Glutarate (9).—The lithium salt of 86.2 g (0.352 mol) of di-*tert*-butyl glutarate was prepared from 0.410 mol of lithium amide in 2 l. of anhydrous ammonia in a flask fitted with a Vibromixer. A solution of 48.2 g (0.308 mol) of keto ester **8** was added over a 30-min period with agitation. After an additional 1 hr, a mixture of 22.1 g of ammonium chloride and 400 ml of ether was added and the solution was brought to reflux to expel excess ammonia. The mixture was cooled to 0° and treated with 206 ml of water. The aqueous phase was separated, acidified (pH 2), saturated with sodium chloride, and extracted with ether. The combined ether layers were washed with 5% hydrochloric acid, saturated sodium carbonate solution, and brine. The ether solution was dried and concentrated, and the unreacted starting materials were removed by distillation (70–85°, 0.06 mm). The residue consisted of 78 g (64%) of the hydroxy triester **9** as a thick, viscous oil: ir 3500 (OH), 1730 (ester C=O), and 1385 and 1365 cm^{-1} (*gem*-dimethyl); nmr δ 3.65 (s, 3, OCH_3), 1.51 [s, 9, $-C(CH_3)_3$], 1.53 [s, 9, $-C(CH_3)_3$], and unresolved absorption in the region 1.1–2.8 (15 H).

Anal. Calcd for $C_{21}H_{36}O_7$: C, 62.98; H, 9.06. Found: C, 62.87; H, 9.16.

2-(4-Carbomethoxy-1-cyclohexenyl)glutaric Acid (10).—A solution of 78 g (0.194 mol) of the hydroxy triester **9**, 292 ml of toluene, and 3.9 g of *p*-toluenesulfonic acid in a flask fitted with a Dean–Stark apparatus was refluxed for 3 hr. The solution was concentrated, diluted with 292 ml of ether, and extracted with three 30-ml portions of saturated sodium carbonate solution. The combined sodium carbonate solutions were acidified, saturated with sodium chloride, and extracted with ether. The combined ethereal extracts were dried and concentrated to afford 50.2 g (95%) of the diacids **10** as a viscous oil: ir ($CHCl_3$) 3600–2500 (acid –OH), 1735 (ester C=O), 1710 (acid C=O), and 1620 cm^{-1} (C=C); nmr δ 8.56 (s, 2 H, $-CO_2H$), 5.75 (m, –C=CH), and 3.74 (s, 3 H, $-OCH_3$).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.77. Found: C, 57.79; H, 6.97.

$\Delta^{9,10}$-Octal-1-one-7-carboxylic Acid (11).—The mixture of diacid **10** (33 g, 0.12 mol) and 400 g of PPA was blended by hand with a glass rod and heated for 2.5 hr at 65°. After cooling, the mixture was treated with 600 ml of crushed ice and diluted with water to 700 ml. The aqueous solution was refluxed for 1.25 hr, cooled to room temperature, saturated with sodium chloride, and continuously extracted with ether for 48 hr. Saturated sodium carbonate solution was added to the ethereal extract until the aqueous phase had pH 8. This solution was cooled and the precipitated inorganic salts were removed by filtration. The aqueous phase was acidified (pH 2) and extracted with five 100-ml portions of ether. The combined ethereal extract was dried and concentrated and the residue (23 g) was subjected to chromatography (Mallinckrodt Silic AR, CC-4, 230 g) using hexane–ether and 400-ml fractions were collected. Fractions 9–17 (hexane–ether, 1:1) afforded 8.02 g (34%) of the keto acid **11**. Fractions 19–24 (ether, 400-ml fractions) afforded 12.8 g of a material believed to be a mixture of uncyclized triacids. Recycling this material by the above procedure afforded an additional 5.90 g of **11** (total yield 58%). Although this material was pure enough (mp 140–145°) for subsequent reactions, a sample was recrystallized from aqueous acetonitrile to give the pure keto acid **11** as white needles: mp 146–147°; ir ($CHCl_3$) 3600–2300 (COOH), 1700 (acid C=O), 1660 (conjugated C=O), and 1640 cm^{-1} (C=C); uv max (95% EtOH) 244 mμ (ε 10,520); nmr ($CDCl_3$) δ 11.2 (s, 1, COOH) and unresolved absorption in the region 2.7–1.7 (13 H).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.75; H, 7.08.

7-Carbomethoxy-$\Delta^{9,10}$-octal-1-one (3).—An ethereal solution of keto acid **11** (6.74 mmol) was treated with excess diazomethane for 1 hr at 0°. The resulting ether solution was washed with sodium carbonate solution and brine, dried, and concentrated to afford 1.29 g (93%) of the crude keto ester **3**: ir 1730 (ester C=O), 1660 (conjugated C=O), and 1640 cm^{-1} (C=C); nmr δ 3.68 (s, 3 H, OCH_3) and unresolved absorption in the region 2.5–1.7 (13 H); uv max (95% EtOH) 243 mμ (ε 14,500). A sample of this material was distilled, bp 119–122° (0.11 mm), for elemental analysis.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.29; H, 7.82.

Isomeric Mixture of 7-Carbomethoxy-10-methyl-1-decalones (12a–15a).—A mixture of 0.25 g (37.4 mmol) of lithium wire and 20 ml of dry ether was treated with 1.07 ml (2.45 g, 17 mmol) of methyl iodide. This mixture was refluxed for 1 hr and transferred to a second flask under anhydrous conditions. After 1.11 g (5.75 mmol) of cuprous iodide had been added and the mixture had been cooled to 0°, 1.06 g (5.05 mmol) of ketone **3** in 2.5 ml of anhydrous ether was added with stirring over a 10-min period. The mixture was stirred for 1.5 hr at 0° and treated with 33 ml of saturated ammonium chloride solution. The solid material was removed by filtration and the aqueous layer was separated and extracted with two 25-ml portions of ether. The combined ether layers were washed with saturated ammonium chloride solution, saturated sodium carbonate solution, and brine. The ethereal extract was dried and concentrated to afford 0.880 g (78%) of the crude isomeric keto esters: ir 1735 (ester C=O) and 1710 cm^{-1} (ketone C=O); nmr δ 3.63 (s, OCH_3), 1.17 (s, CH_3), 0.95 (s, CH_3), and 0.82 (s, CH_3). Vpc analysis (6 ft × 0.25 in. 10% C6-DEGS on Chromosorb W, 195°) revealed the presence of four components later shown to be the four isomeric keto esters (see below) in relative proportions as follows: 26% **12a**, 43% **13a**, 11% **14a**, and 20% **15a**. Approximately 1% starting material was found to be present.

A sample (490 mg) of the crude mixture of isomeric keto esters was chromatographed on silica gel (Mallinckrodt, Silic AR, CC-7, 49 g) collecting 65-ml fractions. Fractions 18 and 19 (ether–hexane, 1:1) contained 64 mg of a mixture. Fraction 20 (ether–hexane, 1:1) contained 137 mg (28%) of keto ester **13a** having essentially the same spectral and physical properties as

(15) H. O. House and H. W. Thompson, *J. Org. Chem.*, **26**, 3729 (1961).
(16) H. O. House, H. Babad, R. B. Toothill, and A. W. Noltes, *ibid.*, **27**, 4141 (1962).
(17) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

those of a sample prepared below. Fractions 21–23 (ether–hexane, 1:1) contained 96 mg of a mixture. Fractions 25–27 (ether–hexane, 1:1, 65-ml fractions) contained 6 mg of unreacted keto ester 3.

Equilibration of Keto Esters.—A sample of a mixture of the keto esters (1.33 g, 5.9 mmol) was refluxed in 50 ml of 0.24 *M* sodium methoxide in methanol. Aliquots were withdrawn from the reaction mixture, worked up, and subjected to vpc analysis. Equilibrium was reached after 46 hr. The mixture was added to 300 ml of ether and washed with 25 ml of saturated sodium carbonate solution. The basic solution was acidified to pH 2 and extracted with ether. The combined ether fractions were washed with brine and dried. After the solvent was removed, 477 mg of a dark yellow viscous mass was obtained which cystallized on standing. This material was shown by nmr and tlc analysis to consist mainly of the corresponding isomeric keto acids. The original ethereal extracts were washed with brine, dried, and concentrated to afford 732 mg (55%) of the equilibrated mixture of the keto esters. Vpc analysis (6 ft × 0.25 in. 10% DEGS on 60–80 mesh Chromosorb W, 194°) showed the presence of four isomers in the relative ratio of 10% **12a**, 14% **13a**, 58% **14a**, and 18% **15a**.

Saponification of Keto Esters. A. Unequilibrated Mixture.—A sample of the unequilibrated mixture of the keto esters (871 mg, 3.88 mmol) was refluxed with 3.30 g (59 mmol) of potassium hydroxide and 21 ml of water in 43 ml of methanol for 3 hr. The mixture was diluted with 30 ml of water, saturated with sodium chloride, and extracted with 20 ml of ether. After acidification (pH 2) the mixture was extracted with four 50-ml portions of ether. The combined extracts wre dried and concentrated to afford 572 mg (70%) of the crude mixture of isomeric keto acids as a yellow solid mass. This material was recrystallized from ether–hexane to afford 209 mg of white needles, mp 150–157°, which was shown by nmr to consist mainly of keto acid **13b**. The mother liquor was concentrated and the residue (355 mg) was subjected to chromatography on silca gel (Mallinckrodt, Silic AR, CC-4, 18 g).

Fractions 24 and 25 (ether–hexane, 1:1) afforded 94 mg of crude keto acid **12b** which, after two recrystallizations from 5% acetronitrile in water, afforded 25 mg of pure **12b** as white needles: mp 130.5–132°; ir ($CHCl_3$) 3600–2250 (COOH) and 1710 cm^{-1} (ketone and acid C=O); nmr ($CDCl_3$) δ 9.3 (s, 1, COOH), 0.82 (s, 3, CH_3) and unresolved absorption in the region 2.4–1.2 (14 H). A sample for elemental analysis was prepared by sublimation, mp 131.5–132.5°.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.71; H, 8.57.

Fraction 26 (ether–hexane, 1:1) contained 67 mg which, after two recrystallizations from 5% acetonitrile–water, afforded 36 mg of keto acid **13b** as white needles: mp 159–160°; ir ($CHCl_3$) 3600–2300 (COOH) and 1710 cm^{-1} (acid and ketone C=O); nmr ($CDCl_3$) δ 8.9 (s, 1, COOH), 0.95 (s, 3, CH_3) and unresolved absorption in the region 2.5–1.1 (14 H). A sample for elemental analysis was prepared by sublimation, mp 159.5–160°.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.65; H, 8.55.

B. Equilibrated Mixture.—In the same manner, 732 mg (3.26 mmol) of the equilibrated mixture of the keto esters was saponified to afford 551 mg (80%) of a crude mixture of isomeric keto acids. This material was subjected to chromatography on silica gel (Mallinckrodt, Silic AR, CC-4, 50 g), whereby fractions 32–36 (ether–hexane, 1:1) afforded 235 mg (34%) of the keto acid **14b** in a high state of purity (tlc analysis). A sample of this material was recrystallized from 5% acetonitrile–water, which afforded a sample of **14b** as white needles: mp 123.8–125° (lit.[13] mp 124–125.8°); ir ($CHCl_3$) 3600–2300 (COOH) and 1710 cm^{-1} (acid and ketone C=O); nmr ($CDCl_3$) δ 9.3 (s, 1, COOH), 0.82 (s, 3, CH_3), and unresolved absorption in the region 2.5–1.2 (14 H). This material was identical with an authentic sample.[11]

Conversion of Keto Acids to Keto Esters.—Authentic samples[11] of keto acids **14b** and **15b** and keto acids **12b** and **13b**, isolated above, were treated with ethereal diazomethane and the corresponding four keto esters were obtained. Each ester was subjected to vpc analysis (6 ft × 0.25 in. 10% C6-DEGS on 60–80 mesh Chromosorb W, 193°) and correlated with the four isomeric keto esters obtained in the reaction mixture of 3 with lithium dimethylcopper(I).

Keto ester **12a** had bp 130–150° (pot temperature, 0.05 mm); ir (CCl_4) 1735 (ester C=O) and 1710 cm^{-1} (ketone C=O); nmr (CCl_4) δ 3.63 (s, 3, OCH_3), 0.82 (s, 3, CH_3), and unresolved absorption in the region 2.8–1.2 (14 H); $\Delta W_{1/2} = 0.64 \pm 0.01$ Hz.

Keto ester **13a** had bp 120–130° (pot temperature, 0.04 mm); ir (CCl_4) 1735 (ester C=O) and 1710 cm^{-1} (ketone C=O); nmr (CCl_4) δ 3.63 (s, 3, OCH_3) and 0.95 ppm (s, 3, CH_3), and unresolved absorption in the region 2.4–1.1 (14 H); $\Delta W_{1/2} = 0.47 \pm 0.03$ Hz.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.42; H, 9.20.

Keto ester **14a** had bp 130–150° (pot temperature, 0.05 mm); ir (CCl_4) 1735 (ester C=O) and 1710 cm^{-1} (ketone C=O); nmr (CCl_4) δ 3.63 (s, 3, OCH_3) and 0.82 ppm (s, 3, CH_3) and unresolved absorption in the region 2.4–1.1 (14 H); $\Delta W_{1/2} = 0.73 \pm 0.01$ Hz.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.45; H, 9.27.

Keto ester **15a** had bp 130–150° (pot temperature, 0.05 mm); ir (CCl_4) 1735 (ester C=O) and 1710 cm^{-1} (ketone C=O); nmr (CCl_4) δ 3.63 (s, 3, OCH_3), 1.17 (s, 3, CH_3), and unresolved absorption in the region 2.4–1.3 (14 H); $\Delta W_{1/2} = 0.46 \pm 0.03$ Hz.

Registry No.—**3**, 34407-92-6; **7**, 18631-96-4; **9**, 34407-94-8; **10**, 34407-95-9; **11**, 32178-64-6; **12a**, 34407-97-1; **12b**, 34407-98-2; **13a**, 34407-99-3; **13b**, 32298-30-9; **14a**, 2450-96-6; **14b**, 2450-97-7; **15a**, 34408-02-1.