Anal. Calcd for $C_{17}H_{14}F_9NO$: C, 48.69; H, 3.36. Found: C, 48.08; H, 3.40.

***cis-* and *trans-N*-Acetyl-3-methyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)pyrrolidine (17).**—**11** (14.5 g, 0.0300 mol), ether (50 ml), and acetic acid (glacial, 50 ml) were stirred by a magnet as zinc dust (5.0 g, 0.076 g-atom) was added in portions at 55°.[19] Exothermic reaction began immediately and continued for 0.5 hr; the cloudy white suspension was heated by means of a bath for 4 hr at reflux temperature (58°). The product was worked up by the literature procedure[19] and distilled, bp 102° (0.45 mm), $n^{25}D$ 1.3728, 9.2 g, 86%. A viscous oil residue, 1.0 g, remained: glpc analysis [8-ft FFAP column, 180° (30 psi)] gave 2.5% at 8.3 min, and 97.5% at 16.2 min; ir (KBr plates) ν_{CH} 2960, 2880, $\nu_{C=O}$ 1650, δ_{CH} 1470, 1440, 1420, 1380, 1350, ν_{CF} 1300–1200, 1140; bands at 1090, 1060, 1025, 985, 970, 930, 910, 885, 855, 730, 715, 690, 660, 620, 600, and 530 cm^{-1}; nmr (CCl_4) δ 1.00 (two doublets overlapped, three protons, J = 7 Hz, with 2-Hz additional splitting, CH_3CH, cis and trans), 1.9 (s, four protons, CH_3CO and $CHCH_2$), 2.25 (2.1–2.9) (t, three protons, J = 20 Hz, CH_2R_F and $CHCH_2$), 3.0–4.0 (4.5 protons, CH_2NCH_2); the methinyl protons were obscured by the other resonances.

Anal. Calcd for $C_{12}H_{14}F_9NO$: C, 40.11; H, 3.93. Found: C, 40.23; H, 3.96.

Hydrogenation of *N*-Acetyl-3-methylene-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)pyrrolidine (16) to *cis-* and *trans-N*-Acetyl-3-methyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)pyrrolidine (17).—**16** (7.14 g, 0.020 mol), 35 ml of 95% ethanol, and 0.10 g of 10% palladium on carbon were shaken in a Parr hydrogenator at 45 psi hydrogen pressure for 24 hr. **17** was recovered, bp 145–152° (12 mm), $n^{25}D$ 1.3913, 6.0 g, 84%. Spectra (nmr and ir) and glpc analysis showed that none of **16** remained in the sample of **17**.

Preparation of *N*-Trifluoroacetyl-3-methyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)pyrrolidine (18) by Zinc Reduction of *N*-Trifluoroacetyl-3-iodomethyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-pyrrolidine (12).—As with **17**, zinc reduction of **12** (10.8 g, 0.0200 mol) gave **18**, bp 89–92° (0.40 mm), $n^{25}D$ 1.3680, 76%, and a viscous residue (1.1 g): ir (KBr plates) ν_{CH} 2960, 2880, $\nu_{C=O}$ 1770, δ_{CH} 1460, 1440, 1385, 1350, ν_{CF} 1250–1140; bands at 1060, 1025, 985, 940, 932, 910, 882, 855, 760, 738, 730, 720, 595, and 530 cm^{-1}; nmr δ 1.1 (2 d, three protons, J = 7 Hz, CH_3C), 2.5–3.0 (m, four protons, CH_2R_F, CH), 3.0–4.2 [3.9 protons, m, $(CH_2)_2N$]; glpc analysis [8-ft FFAP column, 180° (20 psi)] gave two peaks at 5 min, not resolved.

Anal. Calcd for $C_{12}H_{11}F_{12}NO$: C, 34.56; H, 2.70. Found: C, 34.81; H, 2.71.

***cis-* and *trans-N*-Benzoyl-3-methyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)pyrrolidine (19).**—**13** (18.0 g, 0.0330 mol) by similar zinc reduction gave **19** (10.0 g, 86%), bp 138–139° (0.25 mm), $n^{25}D$ 1.4581, and a residue (2.6 g): ir $\nu_{CH=}$ 3080, 3050, ν_{CH} 2960, 2935, 2870, $\nu_{C=C(Ar)}$ 1710, $\nu_{C=O}$ 1640, δ_{CH} 1499, 1475, 1450, 1420, 1380, 1350; bands at 1140, 1075, 1055, 1025, 980, 930, 905, 880 (s), 850, 790, 730 (s), 720 (s), 670, 660, 650, 595, and 530 cm^{-1}; nmr (CCl_4) δ 0.9 (t, poorly resolved, 2.7 protons, J = 7 Hz, cis and trans (CH_3CH), 1.9–2.9 (t, 3.7 protons, J = 19 Hz, CH_2R_F and CH- ring), 2.9–3.9 [m, four protons, $(CH_2)_2N$], 5.2 (m, 0.2 protons, CH_2=CH impurity), 7.4 (s, five protons, C_6H_5). Some 4% of **13** appeared to be present in the sample.

Anal. Calcd for $C_{17}H_{16}F_9NO$: C, 53.26; H, 4.20. Found: C, 53.10; H, 4.25.

Registry No.—**5**, 124-02-7; **6**, 6296-61-3; **7**, 14618-49-6; **8**, 10283-70-2; **9**, 31164-08-6; **10**, 538-08-9; **11**, 31164-10-0; **12**, 31164-11-1; **14**, 31164-12-2; **16**, 31164-13-3; *cis*-**17**, 31164-14-4; *trans*-**17**, 31164-15-5; **18**, 31164-16-6; *cis*-**19**, 31164-17-7; *trans*-**19**, 31164-18-8; **21**, 31164-19-9; **22**, 31153-74-9.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(19) A. Hassner, R. P. Hoblitt, C. Heathcock, J. E. Kropp, and M. Lorber, *J. Amer. Chem. Soc.*, **92**, 1326 (1970).

Cyclopentenone Synthesis by Directed Cyclization

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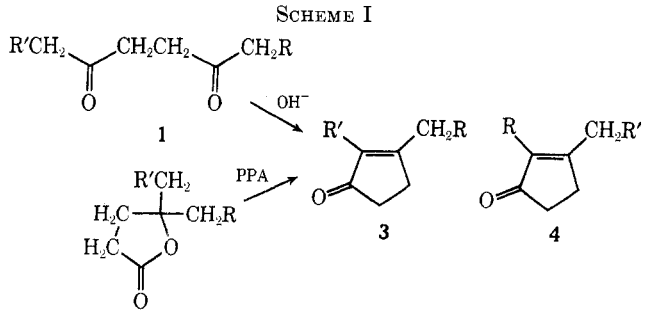
Received March 17, 1971

A procedure is described for the synthesis of 3-substituted 2-carbomethoxycyclopentenones **3** (R′ = CO_2CH_3). An attempt to prepare such a compound (**5**, R = CH_2CH_3) by the polyphosphoric acid catalyzed rearrangement of the γ lactone **9** was unsuccessful. A satisfactory route to **5** (R = CH_3) was the base-catalyzed cyclization of the appropriate diketone **17**, obtained by ring opening the 5-substituted 2-furanacetic ester **15**. Novel dimeric products were obtained on application of the procedure to 5-methyl-2-furanacetic ester.

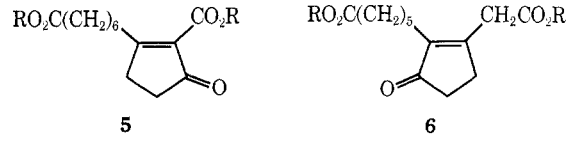
Two important methods of cyclopentenone synthesis, base-catalyzed cyclization of γ diketones[1] and polyphosphoric acid rearrangement of γ lactones[2] (Scheme I), suffer from the limitation that, except for the special

SCHEME I



cases of **1** (R = H) or (R = R′) and **2** (R = H) or (R = R′), the result is a difficultly separable mixture of cyclopentenones **3** and **4**.[3] That such difficulties are still encountered in the synthesis of a desired cyclopentenone was commented upon recently.[4]

We became interested in the synthesis of cyclopentenones, as they are intermediates in the route we have chosen to the prostaglandins.[5] More particularly we were desirous of obtaining access to **5** (R = CH_3), which would be a useful starting material.



5 6

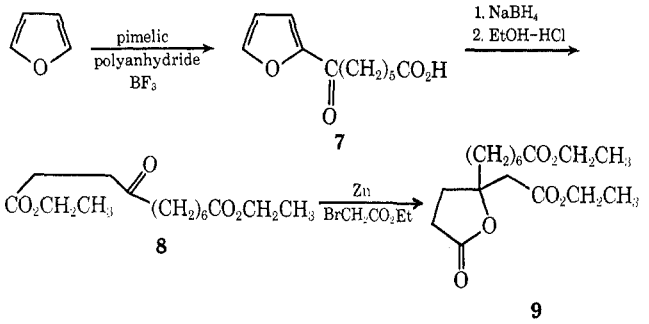
Allylic oxidation[5,6] would enable the additional oxygen function to be introduced, and the carbomethoxy

(1) H. Hunsdiecker, *Chem. Ber.*, **75**, 447, 455 (1942).
(2) C. Rai and S. Dev, *J. Indian Chem. Soc.*, **34**, 177 (1957).
(3) B. Samuelsson and G. Ställberg, *Acta Chem. Scand.*, **17**, 810 (1963).
(4) G. W. K. Cavill, B. S. Goodrich, and D. G. Laing, *Aust. J. Chem.*, **23**, 83 (1970).
(5) N. Finch and J. J. Fitt, *Tetrahedron Lett.*, 4639 (1969).
(6) N. Finch and E. Schlittler, *Tetrahedron*, **24**, 5421 (1968).

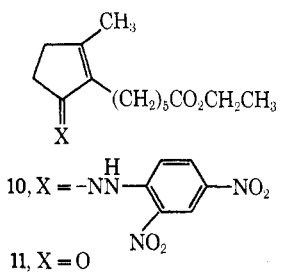
group is a useful handle by which the other prostaglandin side chain could be attached.[5] More importantly, though, we felt that the carbomethoxy group in the precursor might direct the cyclization step so that product **5** could be obtained uncontaminated by the isomer **6**.

The precursor **9** for the lactone rearrangement process[2] was readily obtained (Scheme II); however, on

SCHEME II



being subjected to the rearrangement conditions only a small yield of cyclopentenone was obtained. Apart from a trace of starting lactone **9** this material appeared to be homogeneous by tlc and gave a crystalline 2,4-dinitrophenylhydrazone in good yield. A 220-MHz nmr spectrum[7] of this 2,4-dinitrophenylhydrazone showed it to be **10**, and, therefore, the cyclopentenone



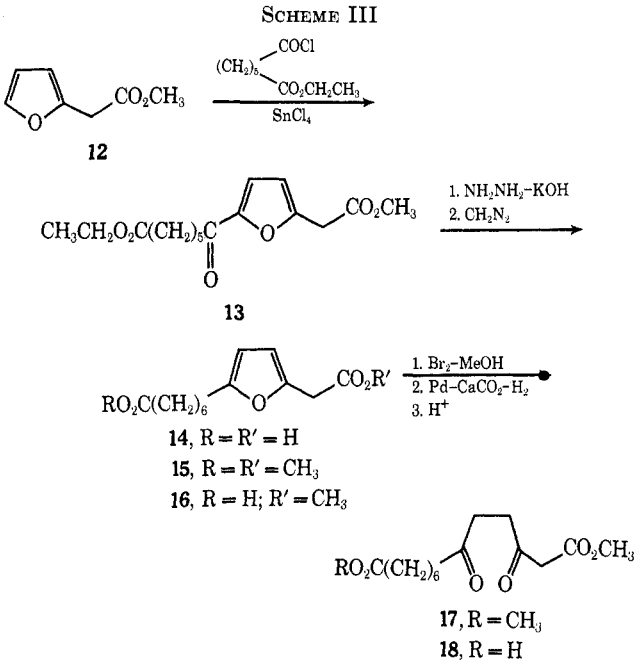
formed is presumably **11**. Thus while the carbomethoxy group in the lactone **9** has indeed had a directing influence, it is in the undesired sense.

We then turned our attention to the γ diketone cyclization procedure. The ready availability of 2-furanacetonitrile[8] made it an attractive starting material. This was converted *via* the acid into methyl 2-furanacetate **12** by the literature procedure,[9] or with diazomethane. Methyl 2-furanacetate **12** was then converted to the appropriate γ diketone **17** by standard procedures (Scheme III).

Interestingly, by addition of 1 equiv of carefully titrated diazomethane, the diacid **14** could be converted into the half-ester acid **16**, which underwent ring opening to give the β keto ester **18**, thus establishing that the furanacetic acid had undergone esterification preferentially. This information enabled the appropriate nmr assignments of the OCH_3 signals to be made with related compounds.

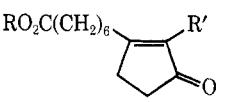
The furan diacid **14** could also be prepared more directly from 2-furanacetonitrile by Friedel–Crafts acyla-

SCHEME III



tion with pimelic half-ester acid chloride and Wolff–Kishner reduction of the product. The strong base in the reduction step causes hydrolysis of the nitrile function to the acid.

With the diketo diester **17** our expectations were fulfilled and cyclization was evident even under very mild conditions ($NaHCO_3$–MeOH). Preparatively it was more convenient to affect hydrolysis as well as cyclization by refluxing in aqueous methanolic K_2CO_3 to give a good (71%) yield of the diacid **19**. From the mother liquor was obtained a small amount of a second product readily identifiable as **20**.



19, R = H; R' = CO_2H
20, R = R' = H
21, R = CH_3; R' = CO_2CH_3
22, R = CH_3; R' = H

The structural relationship between **19** and **20** was confirmed by their hydrogenation to the same cyclopentanone acid **23** (spontaneous decarboxylation of the intermediate β keto acid occurring with **19**). This comparison was repeated with the semicarbazones **24**. The correctness of the assignment was further checked by catalytic reduction of **11** to the cyclopentanone, which was hydrolyzed to the keto acid and the isomeric semicarbazone **25** formed. This semicarbazone **25** differed from **24**, and both **25** and **24** differed from another isomeric semicarbazone **27** of the known keto acid[10] **26**, which we had prepared for other purposes (Scheme IV).

The structural assignment of the cyclization product **19** was further confirmed by catalytic reduction of the dimethyl ester **21** to the cyclopentanone diester **28**. This was clearly a β keto ester (uv shift with base, $FeCl_3$ test) and could be characterized as the copper(II) chelate.

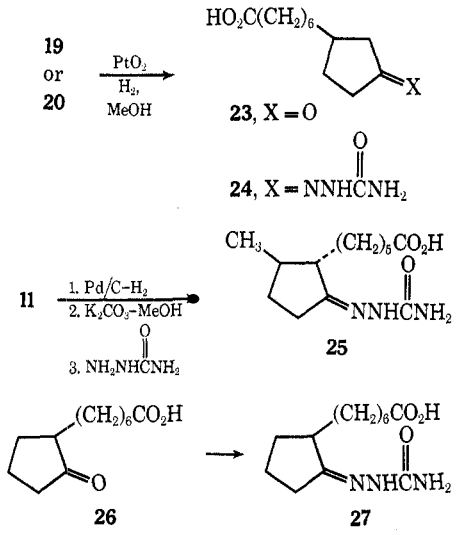
(7) We wish to acknowledge the kind help of Professor E. Wenkert, Indiana University, in obtaining this spectrum.

(8) Aldrich Chemical Co., Catalog No. 11, 822-2.

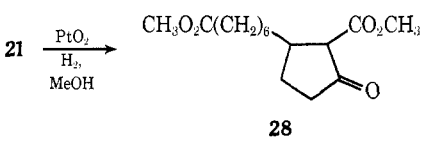
(9) J. F. Ryan, J. Plucker, and E. D. Amstutz, *J. Amer. Chem. Soc.*, **62**, 2037 (1940).

(10) J. F. Bagli, T. Bogri, R. Deghenghi, and K. Wiesner, *Tetrahedron Lett.*, 465 (1966).

SCHEME IV



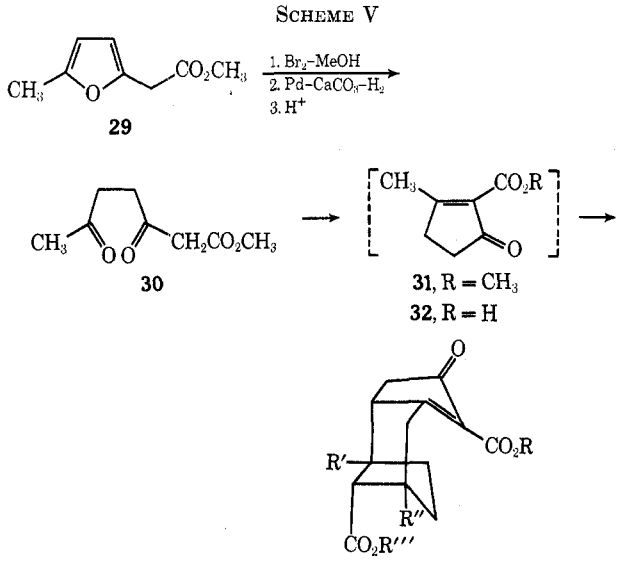
Despite the number of steps in our process and the lack of optimization work at each stage, the overall yield of compounds such as **21** and **28** is approximately



30% from methyl furanacetate **12**, and thus these compounds are relatively accessible. The cyclopentanone diester **28** is particularly useful, as the carbomethoxy group can be selectively operated upon[5] or a second side chain can be attached by alkylation of the β keto ester in a manner analogous to the preparation of **26**. Synthesis of specifically 2,3-disubstituted cyclopentanones by alternative processes is not an easy matter.[4]

To further explore the generality of our method we chose to examine the simplest case, by ring opening 5-methyl 2-furanacetic ester **29** (Scheme V).

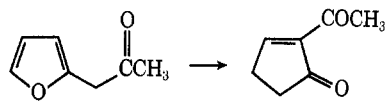
SCHEME V



33, R = R′ = R‴ = CH_3; R″ = OH
34, R = R″ = R‴ = CH_3; R′ = OH
35, R = H; R′ = R‴ = CH_3; R″ = OH
36, R = H; R″ = R‴ = CH_3; R′ = OH
37, R = R‴ = H; R′ = CH_3; R″ = OH
38, R = R‴ = H; R′ = OH; R″ = CH

This proved to be exceptional and none of the anticipated products **31** or **32** could be obtained. Instead crystalline dimers resulted to which the tentative structures **33** or **34**, **35** or **36**, and **37** or **38** have been assigned by analogy with base-catalyzed dimerization of other enone systems.[11,12]

Catalytic reduction of mother liquor material followed by hydrolysis and decarboxylation under conditions similar to that used for converting 2-carbomethoxy-3-methylcyclopentanone to 3-methylcyclopentanone[13] yielded only trace amounts of 3-methylcyclopentanone. Thus only small amounts of **31** were present in the mother liquors. The enhanced reactivity of these smaller molecules may account for the failure by Acheson[14] to achieve the analogous transformation of **39** into **40**.



Experimental Section[15]

ζ-Oxo-2-furanheptanoic acid (7).—"Pimelic polyanhydride" was prepared by refluxing pimelic acid (250 g) in acetic anhydride (600 ml) for 7 hr and then removal of the excess acetic anhydride *in vacuo*. The resulting solid (250 g) was dissolved in tetrachloroethane, and furan (115 g) was added. The mixture was cooled to 0° (ice–salt) and boron trifluoride etherate (23 ml of freshly distilled) was added in one portion with stirring. The temperature rose to 20° rapidly then subsided to 0° during 30 min. Ice was added and the mixture was extracted by 10% potassium carbonate. The extracts were acidified and reextracted by methylene chloride. The resulting solid (116 g) was subjected to fractional crystallization (ether) to free it from pimelic acid. The lower melting material (47.2 g), mp 61–63°, was further crystallized from ether to give an analytical sample of compound **7**: mp 68–69°; uv λ_{max} (MeOH) 222 mμ (ε 2590), 270 (14,790); ir ($CHCl_3$) 1700 (s), 1670 (s), 1574 cm^{-1} (m); nmr ($CDCl_3$) 7.62 (d, 1), 7.22 (d, 1), 6.57 (q, 1), 2.96 (t, 2), 2.40 (t, 2).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 63.20; H, 6.77.

Ethyl 4-Oxo-1,11-undecanedioate (8).—6-(2-furoyl)hexanoic acid **7** (10 g) was dissolved in 3% aqueous potassium carbonate, and sodium borohydride solution was added dropwise with stirring and cooling (0–5°) for 1 hr. Completion of the reaction was estimated by uv, 10% oxalic acid solution was added to bring the pH to 3, and the aqueous solution was extracted (CH_2Cl_2). Removal of the solvent gave a clear oil (6.74 g). This oil was dissolved in 10 *N* ethanolic HCl and refluxed for 3 hr. The ethanol was removed and the residue was filtered through Florisil in methylene chloride. The eluted material (5.74 g) was an orange oil. This was distilled to remove a small amount of diethyl pimelate [bp 110° (3 mm)]. The main fraction was compound **8** [5.20 g, bp 178–180° (2 mm)]. It was characterized by hydrolysis (MeOH–KOH, room temperature overnight) to the keto diacid, mp 104° (benzene), ir 1700 cm^{-1} (s).

Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.57; H, 7.73.

Ethyl 4-Ethoxycarbonylmethyl-4-hydroxy-1,11-undecanedioate γ Lactone (9).—Diethyl 4-ketoundecanoate **8** (7.1 g) was mixed with ethyl bromoacetate (4.2 g) in dry benzene (100 ml). This was added slowly with stirring to a suspension of activated zinc

(11) G. Büchi, J. H. Hansen, D. Knutson, and E. Koller, *J. Amer. Chem. Soc.*, **80**, 5517 (1958).
(12) G. Kabas, *Chimia*, **21**, 260 (1967).
(13) G. Lukas, J. C. N. Ma, J. A. McCloskey, and R. E. Wolff, *Tetrahedron*, **20**, 1789 (1964).
(14) R. M. Acheson, *J. Chem. Soc.*, 4232 (1956).
(15) Melting points were obtained in a Thomas–Hoover melting point apparatus and are uncorrected. Nmr spectra were obtained on a Varian A-60 instrument. Chemical shifts are reported in δ units.

dust (2 g) in benzene (400 ml) containing a trace of iodine. The mixture was gently refluxed during the addition (15 min). After 1 hr the zinc was heavily coated and an additional 2 g was added. After a further hour ethyl bromoacetate (1.2 g) and more zinc (1 g) were added. Refluxing was continued for 3 hr. After the solution had stood overnight, ice–10 *N* H_2SO_4 was added and the mixture ether was extracted. The ether extract (7.21 g) was distilled. Compound **9** (2.71 g) had bp 154° (0.1 mm); ir (film) 1780 (s), 1732 cm^{-1} (s); nmr ($CDCl_3$) 4.20 (pair of quartets, 4), 2.72 (s, 2).

Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59. Found: C, 62.05; H, 8.57.

Ethyl 2-Methyl-5-oxo-1-cyclopentenehexanoate (11).—The γ lactone **9** (674 mg) was mixed with P_2O_5 (450 mg). The mixture blackened and became warm. It was heated for 0.5 hr on a steam bath and then distilled. A main fraction, 91 mg, bp 150–155° (0.05 mm), was collected, which contained some lactone **9** (tlc $CHCl_3$–silica gel), ir (film) 1730 (s), 1700 (s), 1650 cm^{-1} (m), but was principally compound **11**.

This oil was characterized as the 2,4-dinitrophenylhydrazone. Treatment with Brady's reagent gave a precipitate (80 mg), mp 100–106°. Recrystallization from ethanol gave crystals (35 mg), mp 111–112°. A further recrystallization gave the analytical sample of compound **10**: mp 111–112°; ir ($CHCl_3$) 1725 (m), 1613 cm^{-1} (s); uv λ_{max} (EtOH) 256 mμ (ε 17,000), 390 (25,200); nmr ($CDCl_3$) 2.54 (broad singlet, 4), 2.32 (overlapping triplets, 4), 1.92 (s, 3), 1.78–1.32 (m, 6), 1.23 (t, 3).

Anal. Calcd for $C_{20}H_{26}N_4O_6$: C, 57.41; H, 6.43. Found: C, 57.40; H, 6.26.

Hydrogenation and Hydrolysis of P_2O_5 Product (11).—The cyclopentenone **11** (440 mg) was dissolved in ethanol (10 ml) and 10% Pd/C (40 mg) was added. The mixture was stirred at room temperature in hydrogen. Uptake stopped at 28 ml (theory 40 ml). The catalyst was removed and the filtrate was concentrated to about one-quarter volume: 2 ml of 20% K_2CO_3 was added and the mixture was refluxed for 1 hr. The solution was diluted with salt solution and ether extracted. The basic solution was acidified and reextracted, yielding 190 mg. This gave a crystalline semicarbazone **25** (from MeOH), mp 138–140°, *not* identical with **24** or **27**.

2-Oxocyclopentaneheptanoic Acid (26).—Sodium hydride (5 g, 0.21 *M* as a 50% slurry in mineral oil) was added to 1,2-dimethoxyethane (DME) (500 ml, dried through neutral activity I Al_2O_3). 2-Carbethoxycyclopentanone (30 g, 0.19 mol) was added in DME (100 ml) slowly. A vigorous reaction ensued causing reflux. The suspension of enolate was stirred for 1 hr to complete reaction. Ethyl 7-bromoheptanoate (47 g, 0.20 mol) was added slowly in DME (50 ml). The mixture was refluxed for 12 hr. The DME was removed; the residue was dissolved in salt solution and ether extracted. The ether extract was distilled and the main fraction [41.10 g, 65%, bp 160–180° (0.2 mm)] was refluxed in concentrated HCl (200 ml) for 24 hr. This was ether extracted and the ether extract was washed with 10% K_2CO_3. The carbonate washings were acidified and reextracted (ether). The yellow oil (30 g) was distilled and a center cut, bp 155° (0.08 mm), was a water white oil (12.35 g, 29% overall) which crystallized to give compound **26**: mp 25°; ir (film) 1730 (s), 1705 m^{-1} (s).[10]

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.53; H, 9.12.

The semicarbazone **27** had mp 183–184° (MeOH); ir (Nujol) 1700 (s), 1644 (m), 1582 cm^{-1} (m).

Anal. Calcd for $C_{13}H_{23}N_3O_3$: C, 57.97; H, 8.61; N, 15.60. Found: C, 58.21; H, 8.44; N, 15.78.

Ethyl 5-Methoxycarbonylmethyl-ζ-oxo-2-furanheptanoate (13).—Pimelic half ethyl ester acid chloride (130 g, 0.63 mol) was dissolved in methylene chloride (125 ml, dried by passage through neutral activity I Al_2O_3) and stannic chloride (125 ml) was added dropwise to the well-stirred, cooled solution (ice–salt cooling), not permitting a temperature rise above 0°. After addition the mixture was stirred for a further hour at 0°. Methyl 2-furanacetate **12** (79.8 g, 0.57 mol) in $MeCl_2$ (150 ml) was added dropwise with stirring and cooling (0–2°). After addition was completed the mixture was stirred for 0.5 hr and then poured onto ice–water. The $MeCl_2$ layer separated after decomposition of the complex and was washed with 10% $KHCO_3$ and water and dried ($MgSO_4$). The $MeCl_2$ was removed and the residue was distilled. The product **13** (101.8 g, 58%) had bp 185–190° (0.35 mm); uv λ_{max} (MeOH) 278 mμ (ε 17,090); ir (film) 1735 (s), 1680 (s), 1524 cm^{-1} (s).

Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 62.02; H, 7.20.

5-Carboxymethyl-ζ-oxo-2-furanheptanoic Acid (14).—The diester **13** (54 g, 0.22 mol) was dissolved in ethylene glycol (600 ml), and KOH (190 g) and hydrazine hydrate (90 ml) were added. The mixture was refluxed for 2 hr, then the condenser was removed and slow evaporation was permitted for 8 hr. Then additional ethylene glycol (100 ml) and hydrazine hydrate (95 ml) were added. The mixture was refluxed for a further 3 hr. The ethylene glycol was removed and the residue was dissolved in water (3 l.) and cooled. The pH was adjusted to 2 and the precipitate was collected. This was well washed (water) and recrystallized (aqueous MeOH) to give compound **14** (36.4 g, 81%): mp 108–110°; ir (Nujol) 1705 (s), 1576 cm^{-1} (m).

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.68; H, 7.38.

The diacid was further characterized as the bisdimethyl amide: mp 34–5° (ether); ir (melt) 1650 (s), 1570 cm^{-1}; nmr ($CDCl_3$) 5.96 (q, 2), 3.67 (s, 2).

Anal. Calcd for $C_{17}H_{28}N_2O_3$: C, 66.20; H, 9.15; N, 9.08. Found: C, 66.45; H, 9.04; N, 9.16.

The dimethyl ester **15** was prepared in almost quantitative yield by reaction of an ethereal solution of the diacid with excess ethereal diazomethane: bp 142–144° (0.25 mm); ir (film) 1740 (s), 1570 cm^{-1} (m); nmr ($CDCl_3$) 6.02 (q, 2), 3.72 (s, 3), 3.68 (s, 3).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.69; H, 7.72.

5-Carboxymethyl-ζ-oxo-2-furanheptanoic Acid (14) (Directly from 2-Furanacetonitrile).—Pimelic half ethyl ester acid chloride (45.5 g, 0.22 mol) was dissolved in CH_2Cl_2 (250 ml, dried by passage through neutral activity I Al_2O_3) and cooled to −5° (ice–salt bath). With vigorous stirring stannic chloride (35 ml) was added dropwise, cooling to keep the temperature below 0° (45 min additional time). 2-Furanacetonitrile[8] (21.4 g, 0.20 mol) in dried CH_2Cl_2 (175 ml) was added dropwise during 2 hr, stirring and cooling to keep below 0°. After an additional 30 min the mixture was poured onto ice and stirred for 30 min, and the CH_2Cl_2 layer separated. The CH_2Cl_2 layer was washed with water and 10% $KHCO_3$, the solvent was removed, and the residue was distilled. The main fraction [24.62 g (45%)] had bp 195–199° (0.09 mm); nmr ($CDCl_3$) 7.18 (d, 1), 6.53 (d, 1), 4.13 (q, 2), 3.93 (s, 2).

A portion (7.6 g, 0.027 mol) of this main fraction was mixed with ethylene glycol (150 ml), and sodium hydroxide (20 g) and hydrazine hydrate (11 ml) were added. The mixture was heated for 1 hr at 150°. The condenser was removed, further hydrazine hydrate (11 ml) was added, and the mixture was heated at 170° for 3 hr and then concentrated to dryness *in vacuo*. The residue dissolved in water and adjusted to pH 4 (2 *N* HCl). The precipitate was collected, washed, and dried, and recrystallized from aqueous MeOH to give **14** (3.69 g, 53%), mp 99–105°, spectrally (ir, nmr) identical with the material derived from furanacetic ester.

The dimethyl ester **15** was prepared by dissolving the acid (62.1 g, 0.24 mol) in anhydrous methanolic HCl (500 ml) and stirring overnight. After work-up and distillation the dimethyl ester **15** (58.3 g, 85%) obtained was identical (ir, mass spectrum, tlc) with that obtained by diazomethane.

The furan diacid **14** (26.89 g, 106 mmol) was dissolved in ether (2.5 l.) and ethereal diazomethane (128 mol) which had been standardized against benzoic acid was added with vigorous stirring. The mixture stood overnight at 4° and then was washed with aqueous 10% $KHCO_3$. The oil (24.5 g), resulting from removal of the ether, was extracted with petroleum ether (bp 30–60°). On cooling the petroleum ether deposited compound **16**, mp 32–37° (5.8 g, 20%). Recrystallization from ether–petroleum ether gave the analytical sample: mp 36–37°; ir (melt) 1750 (s), 1710 cm^{-1} (s); nmr ($CDCl_3$) 6.02 (q, 2), 3.72 (s, 3).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51. Found: C, 62.82; H, 7.67.

Methyl 3,6-Dioxotridecane-1,13-dioate (17).—The furan diester (12.35 g, 44 mmol) was dissolved in methanol (100 ml) and cooled (ice–salt bath). With vigorous stirring Na_2CO_3 (13 g) was added. Bromine (2.4 ml) in methanol (24 ml) was added dropwise. After addition was complete, the almost colorless solution was filtered, 5% Pd on $CaCO_3$ (2.55 g) was added to the filtrate, and the mixture was stirred under hydrogen. Hydrogen was rapidly taken up (940 ml in 2.5 hr, 986 ml theory). The mixture stirred overnight under hydrogen (an additional 174-

ml uptake), and the catalyst and methanol were removed. Water was added to the residue and this was acidified with dilute HCl. The water was salted and extracted with ether. The extract yielded an oil (12.72 g) which crystallized slowly. Recrystallization (ether) gave the product **17**: mp 38–39°; ir ($CHCl_3$) 1720 cm^{-1} (broad and strong); nmr ($CDCl_3$) 3.75 (s, 3), 3.68 (s, 3), 3.54 (s, 2), 2.78 (s, 4).

Anal. Calcd for $C_{15}H_{24}O_6$: C, 59.98; H, 8.05. Found: C, 59.81; H, 8.17.

12-Methoxycarbonyl-8,11-dioxolauric Acid (18).—The furan ester acid **16** (1 g) dissolved in methanol (50 ml) was cooled to −5° (ice–salt bath). Sodium carbonate (5 g) was added, and, with stirring, bromine (0.2 ml) in methanol (5 ml) was added dropwise. The color of the bromine was discharged rapidly and at completion of addition the solution was colorless. It is important for a rapid and complete hydrogen uptake that there be no excess bromine. A slow and incomplete uptake leads to a poorer yield. Then 5% Pd on $CaCO_3$ (100 mg) was added and the mixture was stirred overnight in a hydrogen atmosphere (80 ml uptake, theory 89 ml). The catalyst was removed and the filtrate was concentrated to dryness. The residue was dissolved in water and cooled in ice, and the pH adjusted to 2–3 (2 *N* HCl). The solution was extracted with ether. Removal of the ether gave an oil (986 mg) which slowly crystallized, mp 59–64°, and gave a positive $FeCl_3$ test. Recrystallization (ether) gave compound **18**: 380 mg; mp 70–71°; ir ($CHCl_3$) 1740 (s), 1710 cm^{-1} (s); nmr ($CDCl_3$) 3.75 (s, 3), 3.54 (s, 2), 2.78 (s, 4).

Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 59.15; H, 7.92.

2-Carboxy-3-oxo-1-cyclopenteneheptanoic Acid (19).—The diketo diester **18** (24.84 g, 82.8 mmol) was dissolved in methanol (125 ml) and 20% aqueous K_2CO_3 solution (250 ml) was added. The mixture was refluxed for 1 hr. The solution was concentrated (to one-third), cooled, and acidified with 2 *N* HCl. A crystalline precipitate (15.5 g) separated. The filtrate was extracted. The extract (2.1 g) was added to the crystals and recrystallized from ether to give compound **19**: mp 60–62° (15 g, 71%); uv λ_{max} (MeOH) 236 mμ (ε 12,800); ir ($CHCl_3$) 1740 (s), 1710 (s), 1680 (s), 1620 cm^{-1} (m); nmr ($CDCl_3$) 3.3–2.1 (m, 8), 1.5 (broad singlet, 8).

Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.04; H, 7.20.

Evaporation of the ethereal mother liquor gave an oil (2.4 g) which on trituration with ether gave a small amount (240 mg) of a crystalline substance melting higher than the main product **19**. Further recrystallizations (ether) gave a compound **20**: mp 100–101°; uv λ_{max} (MeOH) 227 mμ (ε 17,800); ir ($CHCl_3$) 1710 (s), 1680 (s), 1620 cm^{-1} (m); nmr 5.98 (t, 1).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.54; H, 8.73.

Treatment with diazomethane gave the methyl ester **22**: mp 37–38° (from petroleum ether); uv λ_{max} (MeOH) 228 mμ (ε 16,610); ir (melt) 1736 (s), 1706 (s), 1680 (m), 1620 cm^{-1} (m); nmr ($CDCl_3$) 5.97 (t, 1), 3.68 (s, 3).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.81; H, 8.99. Found: C, 70.08; H, 9.07;

3-Oxocyclopentaneheptanoic Acid (23).—The cyclopentenone diacid **19** (1 g) was dissolved in methanol and stirred in a hydrogen atmosphere with PtO_2 (100 mg) for 2 hr (uptake stopped at 1 molar equiv). The catalyst and methanol were removed. The residue crystallized slowly; recrystallization from ether gave crystals (384 mg, mp 68–70°). Recrystallization from ether gave the acid **23**: mp 69–70°; ir ($CHCl_3$) 1735 (s), 1710 cm^{-1} (s); uv, end absorption.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.18; H, 9.54.

This keto acid **23** was further characterized as the semicarbazone **24**, mp 175–177° (from methanol), uv λ_{max} (MeOH) 228 mμ (ε 13,620).

Anal. Calcd for $C_{13}H_{23}N_3O_3$: C, 57.97; H, 8.61. Found: C, 57.65; H, 8.84.

The cyclopentenone acid **20** (100 mg) was dissolved in methanol (10 ml) and hydrogenated over platinum oxide (15 mg). There was a rapid uptake (30 ml) of hydrogen but the reaction was allowed to stir for 1 hr. The catalyst and methanol were removed. Crystallization from ether gave a material whose melting point, mixture melting point, and spectra were identical with those of compound **23**. This material was converted to the semicarbazone **24** and the comparison was repeated.

Methyl 2-Methoxycarbonyl-3-oxocyclopentanoneheptanoate (28).—The cyclopentenone diacid **19** (400 mg) was dissolved in methanol and treated with excess ethereal diazomethane. The solvents were removed and the oily residue **21** (410 mg) was redissolved in methanol (25 ml), PtO_2 (50 mg) was added, and the mixture was stirred at room temperature under hydrogen (uptake 48 ml). The catalyst and solvent were removed and the oily residue **28** (409 mg) was treated with aqueous methanolic cupric sulfate. The green precipitate (402 mg, mp 105–107°) was recrystallized from methanol: mp 105–107°; uv λ_{max} (MeOH) 232 mμ (ε 6240), 286 (13,850); ir ($CHCl_3$) 1730 (s), 1494 cm^{-1} (s).

Anal. Calcd for $C_{30}H_{46}CuO_{10}$: C, 57.18; H, 7.36. Found: C, 57.06; H, 7.62.

Methyl 3-6 Dioxoheptanoate (30).—5-Methyl-2-furanacetic acid[16,17] was esterified to give the methyl ester **29**.[18] The methyl-5-methyl-2-furanacetate **29** (24.0 g) was dissolved in methanol (150 ml), and sodium carbonate (36 g) was added. The slurry was cooled to −5° (ice–salt) and 85 ml of a 10% v/v solution of bromine in methanol was added dropwise with stirring during 1 hr. The reaction was rapidly filtered, catalyst (2 g, 5% Pd–$CaCO_3$) was added, and the mixture was stirred at room temperature in hydrogen. There was a rapid uptake (3.6 l.). The reaction stirred overnight, the catalyst was removed, and the filtrate was acidified with 2 *N* HCl. The methanol was removed *in vacuo* without heating above 40°. The residue was diluted with salt solution and ether extracted. The ether extract was vacuum distilled. A forerun [2.14 g, bp 50–95° (1 mm)] was principally acetonylacetone (vpc) and the main fraction (17.0 g) was compound **30**, bp 110–114° (1 mm). A satisfactory elemental analysis could not be obtained on this unstable substance: ir (film) 1740 (s), 1714 (s), 1630 cm^{-1} (w); nmr ($CDCl_3$) 3.74 (s, 3), 3.54 (s, 2), 2.80 (s, 4), 2.18 (s, 3).

Dimer Diester 33 or 34.—The diketo ester **30** (4.29 g) was dissolved in 20% K_2CO_3 (25 ml). The clear yellow solution became cloudy on standing and an oil separated. After 0.75 hr at room temperature the mixture was extracted (ethyl acetate). The extract (3.5 g) was allowed to stand in ether. Crystals separated (590 mg) which were recrystallized (H_2O) to give compound **33** or **34** (276 mg, mp 145–147°): negative $FeCl_3$ test; uv λ_{max} (MeOH) 234 mμ (ε 12,000); ir ($CHCl_3$) 3550 (m), 1735 (s), 1710 (s), 1630 cm^{-1} (m); nmr ($CDCl_3$) 3.86 (s, 3), 3.78 (s, 3), 1.17 (s, 3); mass spectrum *m/e* 308 (M), 290 (M − H_2O), 277 (M − OCH_3).

Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.65; H, 6.67.

A portion of the material from the mother liquors (750 mg) was dissolved in methanol and hydrogenated over 10% Pd/C until uptake ceased (6 hr). The product was refluxed overnight in concentrated HCl (5 ml). The acid solution was extracted by ether (much resin remained undissolved) and washed with 10% $KHCO_3$. The ether was removed on a steam bath, yielding a small amount of oil having the odor of 3-methylcyclopentanone. This was dissolved in methanol and treated with Brady's reagent. The crystalline product, 14 mg, mp 116–117°, was collected. The melting point was undepressed on admixture with an authentic sample of (±)-3-methylcyclopentanone 2,4-dinitrophenylhydrazone.[19]

Dimer Half-Ester Acid 35 or 36.—The diketo ester **30** (2 g) was dissolved in 10% K_2CO_3 (20 ml) and stirred at room temperature for 3 hr. The solution was ether extracted several times. The aqueous solution was poured through a Dowex 50W X12 (H^+ form) column (35-cm diameter, 11 cm long). The eluate (500 ml) was freeze dried, and the lyophilisate (1.1 g) was allowed to stand in ethyl acetate. Crystals (158 mg, mp 170–180°) were deposited which were recrystallized (EtAc) to give compound **35** or **36**: mp 176–177° dec; negative $FeCl_3$; uv λ_{max} (MeOH) 240 mμ (ε 10,900); ir (Nujol) 3475 (m), 1740 (s), 1724 (s), 1670 (s), 1632 cm^{-1} (m); nmr (DMSO) 3.70 (s, 3), 1.06 (s, 3); mass spectrum *m/e* 294 (M), 276 (M − H_2O), 263 (M − OCH_3).

Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.67; H, 6.27. Found: C, 61.21; H, 6.17.

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(17) E. W. Scott and J. R. Johnson, *J. Amer. Chem. Soc.*, **54**, 2549 (1932).

(18) K. Y. Novitskii, Y. K. Yurev, V. N. Zhingareva, and M. S. Yunusov, *Zh. Obshch. Khim.*, **33**, 2164 (1963).

(19) D. H. R. Barton, O. C. Brockman, and P. deMayo, *J. Chem. Soc.*, 2263 (1960).

The dimer half-ester acid **35** or **36** (68 mg) was dissolved in methanol (5 ml) and hydrogenated over PtO_2 (10 mg) for 3 hr. The catalyst and solvent were removed, and the oily residue (68 mg) was crystallized. Recrystallization from ether–petroleum ether gave 22 mg, mp 105–107°. This substance gave an intense dark green color with $FeCl_3$. On heating at the melting point gas was evolved, and after cessation of bubbling, the $FeCl_3$ test was redetermined and was negative.

Dimer Diacid 37 or 38.—The diketo ester **30** (4.0 g) was dissolved in water and 40 drops of 45% aqueous KOH was added until the pH rose to 10.5. The solution was stirred for 1 hr at room temperature and then passed through Dowex 50W X12 (H^+ form) column. The eluates (1 l.) were freeze dried, and the lyophilisate (2.7 g) was allowed to stand in ethyl acetate; crystals (740 mg, mp 192–195°) were deposited. Recrystallization (MeOH) gave compound **37** or **38**: mp 194–195°; ir (Nujol) 3500 (m), 1735 (s), 1710 (s), 1685 (m), 1628 cm^{-1} (m).

Anal. Calcd for $C_{14}H_{16}O_6$: C, 59.56; H, 6.43. Found: C, 59.60; H, 6.11.

Registry No.—**7**, 31235-77-5; **8**, 31281-12-6; **8** diacid, 31235-94-6; **9**, 32777-42-7; **10**, 31235-78-6; **11**, 31235-79-7; **13**, 23131-62-6; **14**, 23029-38-1; **14** bisdimethyl amide, 31235-81-1; **15**, 23029-39-2; **16**, 31235-83-3; **17**, 23029-40-5; **18**, 31281-14-8; **19**, 23029-36-9; **20**, 23029-37-0; **22**, 31281-15-9; **23**, 31235-87-7; **24**, 31235-88-8; **25**, 31235-89-9; **26**, 3288-67-5; **27**, 31235-91-3; **28** Cu complex, 31235-92-4; **30**, 31235-93-5; **33–34**, 31228-76-9; **35–36**, 31228-77-0; **37–38**, 31228-78-1.

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Studies on Terpenes. IV.[1] The Synthesis of a Bridged Tricyclic Ketone Embodying the BCD Ring System of Diterpenes of the Kaurene Class[2]

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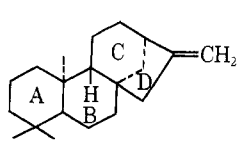
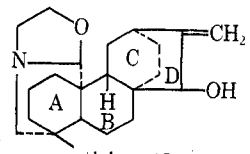
A stereoselective synthesis of *dl*-12-oxo-7,9-ethano-*cis*-$\Delta^{1,2}$-octalin (**4**) is described. This unsaturated tricyclic ketone comprises the BCD ring skeleton present in the kaurene (**1**) class of diterpenes and is a potentially suitable intermediate for the total synthesis of several natural products. Of particular interest is the successful application of the Nagata reagent (Et_2Al/HCN) for effecting the 1,6 addition of HCN to conjugated dienone **24**.

We have previously[1] outlined our concern for the total synthesis of diterpenes which contain, for rings C and D, a bicyclo[3.2.1]- or -[2.2.2]octane moiety. The hydrocarbon (−)-kaurene (**1**) and the alkaloid atisine (**2**) are typical of those members of this class which possess a *trans–anti–cis* fusion of rings ABC. Although a fair number of CD-bridged diterpenes have yielded to total synthesis,[4] the number of suitable synthetic targets remains large and grows rapidly.[5]

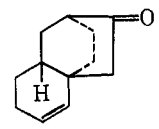


(−)-kaurene (**1**)



atisine (**2**)

Our work in this field has been based on a ring construction sequence BCDA in contrast to the more commonly employed ABCD sequence[4a,c,d] and has focused on the preparation of compounds **3**, **4**, and **5** as BCD models.[6] In the synthesis of **3**, which has been reported in detail,[1] 6-carbethoxyoctalone (**6**) served as



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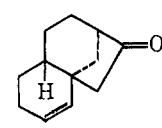

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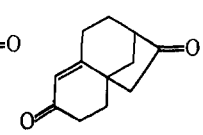

5

a convenient starting material. As we intended to make use of a parallel series of reactions for the preparation of **4**, our attention turned to the obtention of isomeric octalone **7**. Although **6** was readily available from the condensation of methyl vinyl ketone with ethyl 4-ketocyclohexanecarboxylate, we anticipated that the analogous reaction with the 3-keto ester **8** would lead to a mixture of octalones (**7** and **9**) (Scheme I) and, accordingly, we embarked initially on an unambiguous, though lengthier, preparation of **7**.

The sequence of reactions which led to **7** is outlined in Scheme II and requires only brief comment. That the cyclization of **11** to **12** occurred in the expected direction was shown by the conversion of the derived tetralin, **13**, to a series of known 2,7-disubstituted naphthalene der vatives, **16**, **16a**, and **16b**, whose physical properties distinguished them from their 1,6 isomers. Lithium–ammonia reduction of **13**, followed by hydrolysis of the resultant enol ether, provided only poor yields of **7**, probably owing to complicating ammonolysis reactions. However, when the corresponding acid, **13a**, was reduced, and the crude enol ether was hydrolyzed under conditions which simultaneously effected reesterification, a satisfactory yield of a mix-

(1) Previous paper in this series: R. A. Finnegan and P. L. Bachman, *J. Org. Chem.*, **30**, 4145 (1965).

(2) This work was supported in part by Research Grants GM-11412 and RG-8004 from the Division of General Medical Sciences, National Institutes of Health, U. S. Public Health Service, Bethesda, Md. Preliminary announcement of this work has been made before the Organic Division at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, Abstracts, p 25S.

(3) Public Health Service Predoctoral Fellow, 1962–1965. This paper is based on a portion of a thesis submitted by P. L. Bachman to the Department of Chemistry, The Ohio State University, in partial fulfillment of the requirements for the Doctor of Philosophy degree, June 1965.

(4) For example, kaurene: (a) R. A. Bell, R. E. Ireland, and R. A. Partyka, *J. Org. Chem.*, **31**, 2530 (1966); (b) S. Masamune, *J. Amer. Chem. Soc.*, **86**, 289 (1964). Atisine: (c) W. Nagata, *et al.*, *J. Amer. Chem. Soc.*, **89**, 1483 (1967); (d) R. W. Guthrie, Z. Valenta, and K. Wiesner, *Tetrahedron Lett.*, 4645 (1966); (e) S. Mansamune, *J. Amer. Chem. Soc.*, **86**, 291 (1964).

(5) J. R. Hanson, *Progr. Phytochem.*, **1**, 161 (1968); E. Fujita, *Bull. Inst. Chem. Res., Kyoto Univ.*, **48**, 111 (1970), and previous papers in this series.

(6) Compound **5** has been reported recently by D. J. Beames and L. N. Mander, *J. Chem. Soc. D*, 498 (1969).