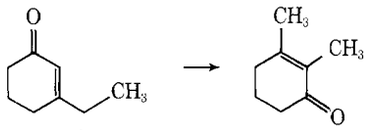
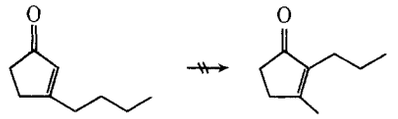


4

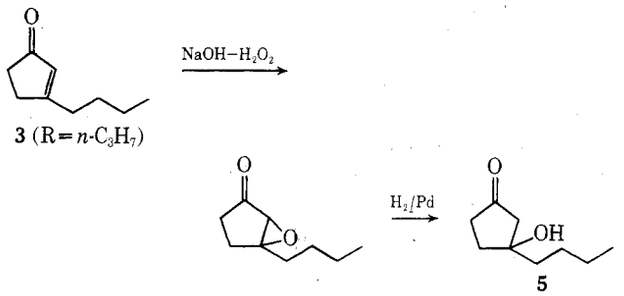
To test the degree of control over the reaction in the case of cyclopentenones, we have prepared 3-*n*-butylcyclopentenone[6] (**3**, R = *n*-C_3H_7) as a representative 3-*n*-alkylcyclopentenone and submitted it to reaction conditions (2% NaOH–EtOH–H_2O, reflux) which serve to convert **1** → **2** (R = *n*-C_3H_7).

Interestingly, the trisubstituted enone was recovered in high yield[7] (>95% distilled), and we were unable to detect the presence of the tetrasubstituted enone **2** which is



3 (R = *n*-propyl) **2** (R = *n*-propyl)

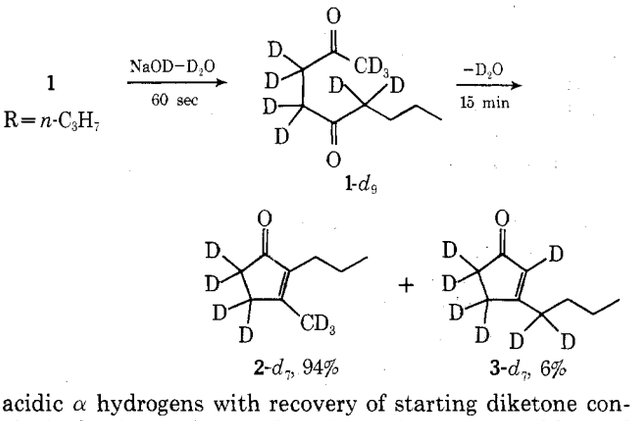
characterized by a sharp resonance (250-MHz nmr spectrum) at δ 2.040 for the vinyl methyl group. Lacey's conditions[5a] were also not useful[8] for the conversion of **3** → **2**. Aldol **5**, prepared in 93% yield by catalytic hydrogenation[9]



3 (R = *n*-C_3H_7)

5

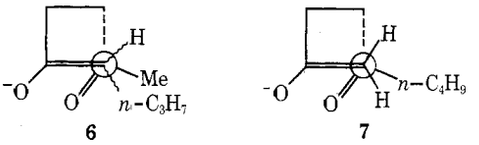
of the corresponding epoxy ketone derived from 3-*n*-butylcyclopentenone, was submitted to the cyclization conditions, and the sole detectable product was compound **3** (R = *n*-C_3H_7). Thus, at least in this case, to the extent that the aldolization of **1** → **5** had occurred, the trisubstituted product, **3**, would have been obtained. Under identical reaction conditions the corresponding 2,5 diketone (**1**, R = *n*-C_3H_7)[10] cyclized in excellent yield (15 min at 90°, 97%) to a 94:6 mixture of **2** and **3** (R = *n*-C_3H_7). This represents the first documented case in which a trisubstituted enone is formed as a minor product from the cyclodehydration of a compound of general formula **1**. When the same reaction was carried out in a deuterated solvent system and quenched after 1 min, **1**-d_9 (R = *n*-C_3H_7) was recovered in >95% yield. The exchangeability of all nine



1-d_9

2-d_7, 94% **3**-d_7, 6%

acidic α hydrogens with recovery of starting diketone convincingly shows that enolate formation is reversible, and cannot be construed as the product determining step. We are thus obliged to conclude that, under the reaction conditions thus far employed, the reaction in question is kinetically controlled at the level of aldol step and that the transition state for cyclization of enolate **6** is approximately 2.0 kcal/mol more stable than that for **7**.



6 **7**

Acknowledgments. We thank the Research Corporation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Chemistry Department of Carnegie-Mellon University for financial support of this work. The 250-MHz nmr of all compounds in this study were taken at the NIH Facility for Biomedical Studies (Grant No. RR20092), located at Carnegie-Mellon University.

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(4) Such is not always the case when *n* = 3; see S. Danishefsky, A. Nagel, and D. Peterson, *J. Chem. Soc., Chem. Commun.*, 374 (1972).
(5) (a) R. N. Lacey, *J. Chem. Soc.*, 1639; (1960); (b) A. A. Nagel, Ph.D. Thesis, University of Pittsburgh, 1971.
(6) The synthesis of this and related 3-alkylcyclopentenones is reported in the following communication.
(7) The tetrasubstituted cyclopentenone **2** (R = *n*-C_3H_7) was also stable to these conditions.
(8) We never observed more than 5% conversion under Lacey's conditions. These reactions always led to significant loss of material.
(9) *Cf.* D. P. Strike and H. Smith, *Tetrahedron Lett.*, 4393 (1970).
(10) Prepared by the low temperature (−78°) addition of butyllithium to the ethylene ketal of ethyl levulinate, followed by acid hydrolysis.

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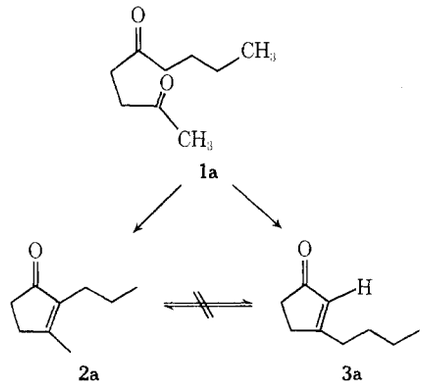
Cyclenones. VI.[1] The Retroaldol-Aldol Route to *cis*-Jasmone and Related Compounds

Summary: When 3-alkylmethylcyclopent-2-enones (**3**) synthesized in two steps from cyclopentenone are heated with *aqueous* base, they are converted to 2-alkyl-3-methylcyclopent-2-enones.

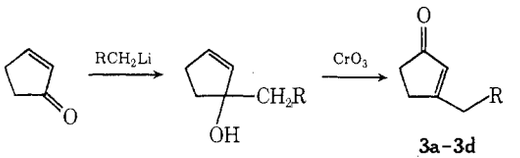
Sir: In the preceding communication,[1] we have demonstrated that the cyclization of 2,5-nonanedione (**1a**) in aqueous alcoholic base is irreversible; *i.e.*, the products **2a** and **3a** are stable to the conditions of their formation. We now wish to report a two-step synthesis of **3a** and related 3-alkylmethylcyclopentenones **3b–3d.** Concurrently we wish to report conditions which are successful in effecting their isomerizations to the tetrasubstituted enones **2a** (**2**, R = *n*-C_3H_7), **2b** (dihydrocinerone), **2c** (dihydrojasmone), and **2d** (*cis*-jasmone), respectively.

Table I

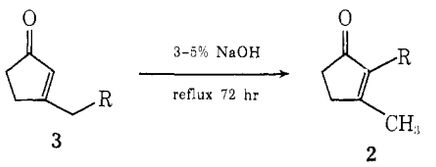
Organometallic reagent	3-Alkylcyclopentenone	Boiling point, °C (mm)	Overall yield, %
n-C_4H_9Li	3-n-Butylcyclopentenone (**3a**, R = n-C_3H_7)	98–100 (1)	27
n-$C_5H_{11}Li$	3-n-Pentylcyclopentenone (**3b**, R = n-C_4H_9)	100–105 (1)	54
n-$C_6H_{13}Li$	3-n-Hexylcyclopentenone (**3c**, R = n-C_5H_{11})	100–105 (0.05)	47
(Z)-3-Hexenyllithium	3-[(Z)-3-Hexenyl]-cyclopentenone (**3d**)	94–96 (0.03)	29



The required trisubstituted enones were synthesized by alkyllithium addition to cyclopentenone,[2] followed by chromium trioxide oxidation[3] of the intermediate cyclopentenols. The overall yields and boiling points of **2a–2d** are shown in Table I.



When the 3-alkylmethylcyclopentenones **3a–3d** were heated under reflux with dilute aqueous sodium hydroxide, they were converted to the thermodynamically more stable cyclopentenones **2a–2d.**



a, R = $CH_2CH_2CH_3$
b, R = $CH_2(CH_2)_2CH_3$
c, R = $CH_2(CH_2)_3CH_3$
d, R = $CH_2CH{=}CHCH_2CH_3$

The details[4] are given for the synthesis of *cis*-jasmone.[5] Thus, when a heterogeneous mixture of 0.160 g of compound **3d** was refluxed under argon with 160 ml of 0.75 N NaOH for 72 hr, *cis*-jasmone, identical with an authentic sample,[6] was obtained in 80% yield, after preparative glc (220°, 10-ft 20% Carbowax on 60–80 Chrom W, retention time, 9.6 min). The 250-MHz nmr spectra (1% in CCl_4) of **3d** and synthetic *cis*-jasmone (**2d**) are shown in Figure 1.

The reaction is sensitive[7] to (a) air oxidation, (b) the volume of the aqueous phase, and (c) the concentration of

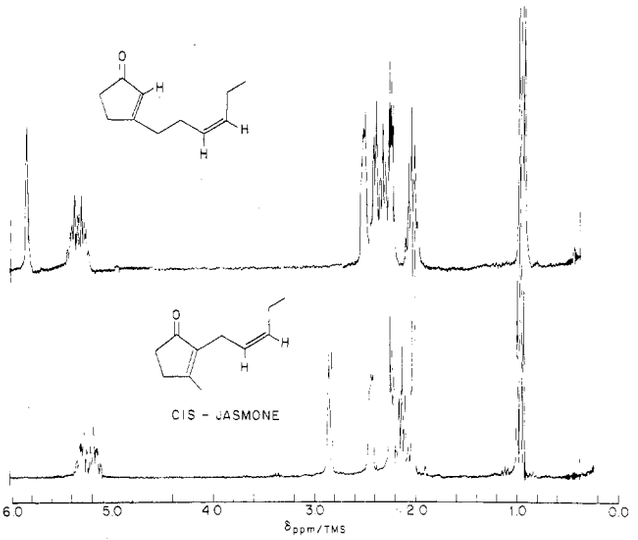
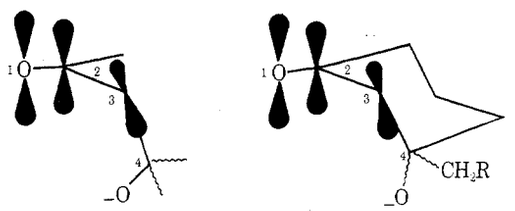


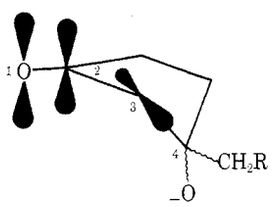
Figure 1. 250-MHz nmr spectra (2% in CCl_4) of **3d** (top) and synthetic *cis*-jasmone (bottom).

hydroxide ion. The reaction at 100° is not quite complete even after 72 hr, and, although the material recovery is excellent (95–100%), we have only obtained conversions of **3a–3d** → **2a–2d** of 65–95% under these conditions. We are presently investigating conditions which will increase the rate of conversion **3** → **2.**

An interesting parenthetical observation was the greater propensity for dealdolization of the β-aldol in acyclic ketones[8] (2 hr, room temperature) and cyclohexenones[9] (3 hr, reflux) relative to cyclopentenones (days, reflux).



acyclic β-alkoxycyclohexanone



β-alkoxycyclopentanone

For cleaving the α–β C–C (C_3–C_4 bond in above diagrams) bond of an aldol, there must be significant overlap of this bond with the π bond of the carbonyl moiety; *i.e.*, the dihedral angle between atoms 2 and 3 should approach 90°. Any deviation from this idealized situation, as would be the case in a *nearly* planar cyclopentanone ($\angle 1234 \simeq 0°$) would require significant distortion in the conformation of the reacting molecule to obtain overlap. To the extent that this effect would raise the energy of the transition state, it retards the rate of the reaction.

More detailed studies concerning the factors affecting the rates of dealdolization of β-hydroxycycloalkanones are currently in progress.

Acknowledgment. We thank the Research Corporation and the Chemistry Department of Carnegie-Mellon University for financial support of this work. The 250-MHz nmr spectra of all compounds in this study were taken at

the NIH Facility for Biomedical Studies (Grant No. RR20092), located at Carnegie-Mellon University.

Supplementary Material Available. Full experimental details of this work will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2317.

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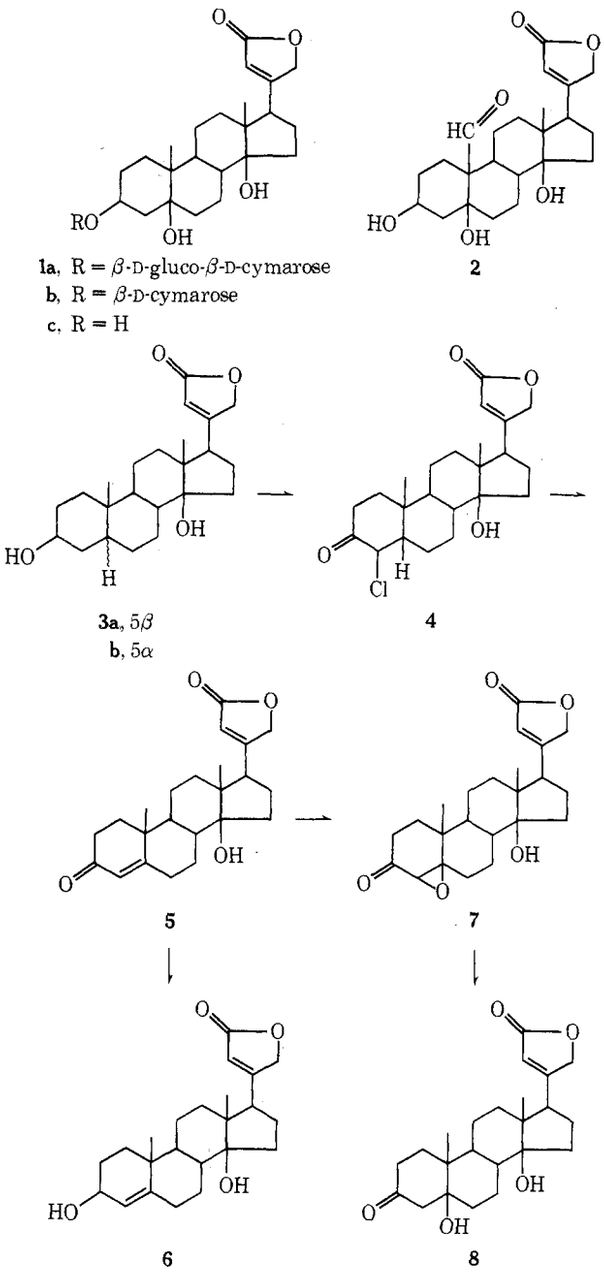
Steroids and Related Natural Products. 88. Synthesis of Periplogenin[1,2]

Summary: Digitoxigenin (**3a**) was converted to canarigenin (**6**), periplogenin (**1c**), and uzarigenin (**3b**); the use of *tert*-butyl hypochlorite for oxidation of digitoxigenin (**3a**) to chloro ketone **4** and application of chromium(II) acetate for reduction of epoxy ketone **7** to hydroxy ketone **8** represented particularly convenient aspects of these synthetic transformations.

Sir: The digitalis-like cardiac activity of periplocin (**1a**)[3] was first reported in 1896 (in Russia) and isolation of this cardenolide in pure form was described the following year.[4] Some 30 years later Jacobs[5] began the careful structural studies of periplocymarin (**1b**) and periplogenin (**1c**) which were continued by Stoll[6] and brought by Reichstein[7] to a partial synthesis of periplogenin from strophanthidin (**2**). By 1960 periplogenin (**1c**) and its glycoside derivatives had been isolated from a number of plants of the *Asclepiadaceae* family and their structures were well established.[8] We now wish to report a formal total synthesis of periplogenin employing digitoxigenin (**3a**)[9] as relay. One of the synthetic intermediates (**5**) also formed the basis for completing convenient syntheses of canarigenin (**6**)[10] and uzarigenin (**3b**).[11]



Digitoxigenin (**3a**, 0.70 g) was simultaneously oxidized and chlorinated with *tert*-butyl hypochlorite[12] (in *tert*-butyl alcohol–hydrochloric acid, room temperature, 8 hr) to provide ketone **4** (0.50 g, mp 131–133°).[13] Dehydrohalogenation of ketone **4** (0.20 g) with lithium chloride in dimethylformamide (reflux 8 hr) led to canarigenone (**5**, 90 mg, mp 257–263°).[10] Careful reduction of α,β-unsaturated ketone **5** (0.10 g in THF) with lithium tri-*tert*-butoxyaluminum hydride (ice bath, 2 hr) gave (after silica gel chromatography and recrystallization from acetone–hexane) canarigenin (**6**, 71 mg, mp 259–261°, lit.[10] mp 260–262°). Further reduction of canarigenone (**5**, 0.16 g) with lithium borohydride in pyridine (ice bath, 5 hr) afforded a route to uzarigenin (**3b**, 0.12 g, mp 246–249° from methylene chloride–methanol, lit.[14] mp 230–246°).[11]

Oxidation of canarigenone (**5**, 40 mg) employing *m*-chloroperbenzoic acid in chloroform provided epoxy ketone **7** (10 mg, prisms from acetone–hexane, mp 229–