The ether layer was washed with brine and dried over $MgSO_4$. Removal of the solvent at the water pump gave 1.91 g (86%) of **5**: mp 142–144° (lit.[11] mp 145–147°); $\lambda_{max}$ ($CHCl_3$) 4.43, 5.60, 5.81 $\mu$; $\delta$ $(CD_3)_2CO$ 1.65 (s, 4), 11.24 ppm (s, 1).

**B. From Malononitrile.** The reaction was carried out under conditions similar to those described above, except that the reaction time was reduced to 15 min. Thus 1.32 g (0.02 mol) of malononitrile gave 1.09 g (49%) of **5**, mp 142–144°.

**Preparation of Acetylcyclopropane-1-carboxylic Acid (6).** To 40 ml of a 50% solution of aqueous sodium hydroxide at 60° was added TEBA (2.27 g, 0.01 mol) following a solution of ethyl acetoacetate (2.60 g, 0.02 mol) and 1,2-dibromoethane (7.52 g, 0.04 mol). The resultant clear mixture was stirred for 1 hr, diluted with 100 ml of water, and extracted with ether. The aqueous layer was acidified with concentrated HCl and extracted with ether. The ether layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent at the water pump left a residue which was evaporatively distilled (bp ca. 110°, 0.3 mm) to give **6**:[12] 1.77 g (69%); $\lambda_{max}$ ($CHCl_3$) 5.71, 5.90 $\mu$; $\delta$ ($CDCl_3$) 1.69–1.78 (m, 4), 2.28 (s, 3), 12.07 ppm (s, 1).

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**Registry No.**—**1**, 5617-70-9; **2**, 598-10-7; **4**, 106-93-4; **5**, 6914-79-0; **6**, 56172-71-5; diethyl malonate, 105-53-3; isopropenyl acetate, 108-22-5; ethyl cyanoacetate, 105-56-6; malononitrile, 109-77-3; ethyl acetoacetate, 141-97-9.

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# Synthesis of δ-Lactones from Cyclohexenones. Preparation of a Vernolepin Analog

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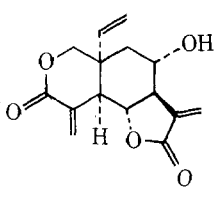
Lactone **2**, a prototype of the sesquiterpenoid antitumor agent vernolepin (**1**),[1] has been prepared by several workers[2] and has been found to show weak to moderate in vitro cytotoxicity in the CCNSC KB cell culture screen.[2f] The



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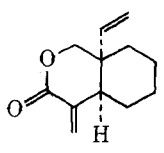

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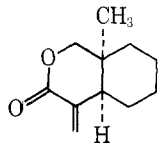
suggestion that the α-methylene δ-lactone moiety of vernolepin may contribute to this molecule's physiological activity is interesting and has prompted us to prepare other related α-methylene δ-lactones for evaluation. Since the angular vinyl group is apparently not crucial to activity (vernolepin and dihydrovernolepin have essentially the same activity),[3] lactones **3** and **4** have been selected for physio-



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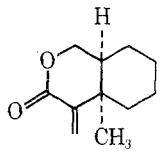

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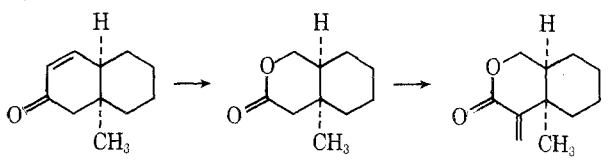
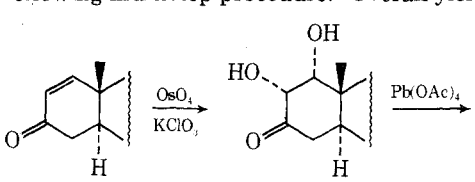
logical evaluation. Lactone **3** is available by a route involving ozonolytic cleavage of a silyloxyalkene.[2b] In this paper, we report the preparation of the isomeric lactone **4** by a route which shows some generality for the preparation of δ-lactones.

Ozonolysis of octalone **5**[4] in methanol solution at −60°, followed by the addition of excess sodium borohydride at 0°, afforded δ-lactone **6** in 45% yield. Introduction of the α-methylene unit by Grieco's two-step procedure[2a,5] (57% overall yield) afforded α-methylene δ-lactone **4**.

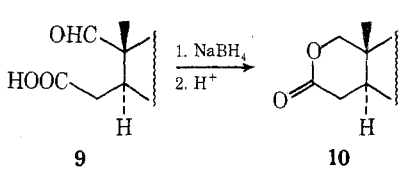


5 6 4

The conversion of **5** to **6** represents a convenient method for the synthesis of a δ-lactone when the corresponding cyclohexenone is available. While the yield in this case is only fair (although it has not been optimized), the conversion is a "one-flask" process, and may be generally useful in cases where the requisite cyclohexenone is not especially precious. Pappo has accomplished the same conversion by the following multistep procedure.[6] Overall yields in the Pappo



7 8



9 10

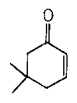
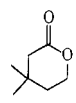
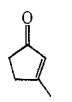
procedure are 50–60%, and the process requires use of the toxic and expensive reagent osmium tetroxide.[7] Consequently, we have examined the generality of our ozonolytic procedure with several other cyclic enones. The results obtained are shown in Table I.

As can be seen in Table I, modest yields of δ-lactones may be obtained by this process in some cases. The single cyclopentenone tested (compound **15**) gave only an insignificant amount of γ-lactone **20**.

## Experimental Section

**Synthesis of 8aα-Octahydro-4aα-methyl-3*H*-2-benzopyran-3-one (6).** A solution of octalone **5**[4] (1.074 g, 6.55 mmol) in methanol (15 ml) was ozonized at −60° with a Welsbach generator until 2 equiv of ozone had been added. After flushing with nitrogen, the solution was placed in an ice bath (0°) and sodium borohydride

**Table I**
**Lactones from α,β-Unsaturated Ketones**

| α,β-Unsaturated ketone | Lactone (yield, %) |
|---|---|
|  11 |  16 (58)[a] |
|  12 |  17 (47)[a] |
|  13 |  18 (42)[a,b] |
|  14 |  19 (<25)[c] |
|  15 |  20 (<10)[d] |

[a] Distilled yield. [b] Approximately a 1:1 mixture of cis and trans isomers as determined by $^1$H NMR. [c] Determined by spectral and elemental analyses and GLC. [d] Determined by spectral analysis and comparison with a known sample.

(244 mg, 6.5 mmol) was carefully added. The solution was stirred at 0° for 1 hr, sodium borohydride (244 mg) was again added, the solution was stirred at 0° for an additional 1 hr, and a final batch of sodium borohydride (244 mg) was added. The solution was then stirred at room temperature overnight. The methanol was evaporated off, 20 ml of 10% aqueous HCl was added, and the crude product was isolated by routine ether extraction. Column chromatography [40 g Silicar CC-7, 200–325 mesh, ether–hexanes (1:9)] afforded 490 mg (45%) of lactone **6**: $^1$H NMR ($CDCl_3$) δ 4.34 (AB q, 2, $J$ = 12 Hz, fine splitting for A and B, $\Delta\nu_{AB}$ = 26.1 Hz), 2.37 (AB q, 2, $J$ = 18 Hz, $\Delta\nu_{AB}$ = 34.9 Hz), 1.0–2.0 (m, 9), 1.17 (s, 3); ir (film) 1742, 1227, 1196, 1092 cm$^{-1}$; calcd $m/e$ 168.1150 ($M^+$), found 168.1187 ($C_{10}H_{16}O_2$).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.18; H, 9.73.

**Synthesis of 8aα-Octahydro-4aα-methyl-4-methylene-3*H*-2-benzopyran-3-one (4).** Lactone **6** (200 mg, 1.19 mmol) was α-methylenated by Grieco's α-hydroxymethylation procedure,[5] yielding 122 mg (57%) of the desired α-methylene lactone (**4**): $^1$H NMR ($CDCl_3$) δ 6.70 (d, 1, $J$ = 1 Hz), 5.70 (d, 1, $J$ = 1 Hz), 4.37 (AB q, 2, $J$ = 11 Hz, fine splitting for A and B, $\Delta\nu_{AB}$ = 32.2 Hz), 1.3–2.1 (m, 9), 1.30 (s, 3); ir (film) 1727, 1618, 1186, 810 cm$^{-1}$; calcd $m/e$ 180.1150 ($M^+$), found 180.1147 ($C_{11}H_{16}O_2$).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found C, 73.08; H, 9.02.

**General Procedure for the Preparation of δ-Lactones from Cyclohexenones.** A solution of 16.1 mmol of enone in 25 ml of methanol was ozonized at −60° until 1.1 equiv of ozone had been added. After nitrogen flushing, 3 × 600 mg (16 mmol) of sodium borohydride was carefully added over 1-hr intervals at 0°, and the mixture was then stirred at room temperature overnight. The methanol was evaporated off, 40 ml of 10% aqueous HCl was added, and the product was isolated by routine ether extraction (three times). The following compounds were prepared in this manner.

**5-Hydroxy-3,3-dimethylpentanoic acid δ-lactone (16)** was obtained in 58% yield by bulb-to-bulb distillation [oven temperature 85–95° (0.3 mm)]: $^1$H NMR ($CDCl_3$) δ 4.40 (t, 2, $J$ = 6 Hz), 2.33 (s, 2), 1.72 (t, 2, $J$ = 6 Hz), 1.13 (s, 6); ir ($CHCl_3$) 1739, 1250, 1078 cm$^{-1}$; $m/e$ 128 ($M^+$).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.33; H, 9.50.

**5-Hydroxy-3,3-dimethylhexanoic acid δ-lactone (17)** was obtained in 47% yield after bulb-to-bulb distillation [oven temperature 85–95° (0.5 mm)]: $^1$H NMR ($CDCl_3$) δ 4.50 (m, 1), 2.27 (m, 2), 1.6 (m, 2), 1.37 (d, 3, $J$ = 6 Hz), 1.10 (s, 3), 1.07 (s, 3); ir (film) 1736, 1235, 1042, 805 cm$^{-1}$.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.42; H, 9.76.

**5-Hydroxy-3-methylhexanoic acid δ-lactone (18)** was obtained in 42% yield after bulb-to-bulb distillation [oven temperature 85–95° (0.5 mm)]: $^1$H NMR ($CDCl_3$) δ 4.47 (m, 1), 1.40–2.80 (m, 5), 1.40 (d, 3, $J$ = 6 Hz), 1.07 (m, 3); ir (film) 1736, 1244, 1092 cm$^{-1}$.

Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.27; H, 9.17.

**5-Hydroxy-3-methylpentanoic acid δ-lactone (19)** was obtained in less than 25% overall yield, as determined by $^1$H NMR and GLC (crude recovery was only 50%): $^1$H NMR ($CDCl_3$) δ 4.33 (m, 2), 1.2–3.0 (m, 5), 1.08 (d, 3, $J$ = 6 Hz); ir (film) 1733, 1227, 1092 cm$^{-1}$; $m/e$ 114 ($M^+$).

Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.21; H, 8.84.

**4-Hydroxypentanoic acid γ-lactone (20)** was obtained in less than 10% overall yield, as determined by $^1$H NMR and GLC (crude recovery was 36%). $^1$H NMR and ir revealed absorptions identical with those for commercially available γ-valerolactone (Aldrich); $m/e$ 100 ($M^+$), 85 ($M^+ - CH_3$).

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**Registry No.**—**4**, 56247-19-9; **5**, 32980-06-6; **6**, 56247-20-2; **11**, 4694-17-1; **12**, 78-59-1; **13**, 1123-09-7; **14**, 7214-50-8; **15**, 2758-18-1; **16**, 22791-80-6; **17**, 10603-06-2; *cis*-**18**, 24405-13-8; *trans*-**18**, 24405-14-9; **19**, 1121-84-2; **20**, 108-29-2.

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## A Facile Synthesis of 1-β-D-Arabinofuranosyl-2-seleno- and -4-selenouracil and Related Compounds

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2-Thiouridine and 4-thiouridine have been characterized as minor nucleoside components of transfer ribonucleic acid (t-RNA).[1,2] Later several thiopyrimidine nucleosides have been isolated or prepared by multistep syntheses.[3–12] Recently, a facile method was reported by Ueda et al.[13] for the synthesis of 4-thiopyrimidine or 6-thiopurine nucleosides. The seleno analogs, 4-selenouridine and 2-selenouridine, were also synthesized through a coupling method.[14] We have described in recent articles a one-step synthesis of