A Stereoselective Synthesis of Cycloalkene-Fused Butyrolactones via Cyclopropylcarbinol Solvolysis

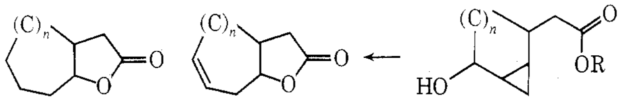
James A. Marshall* and Robert H. Ellison

Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received February 13, 1975

Various isomeric cyclohexanols and cyclopentanols bearing fused cyclopropane rings at the 2,3 position and acetic acid chains at the 4 position were synthesized by unambiguous routes. These cyclopropylcarbinols were then subjected to solvolysis in aqueous acid to give cycloheptene- and cyclohexene-fused γ-butyrolactones. These reactions proceeded in high yield with retention of C-3/C-4 stereochemistry and did not appear to be sensitive to the steric orientation of the carbinol grouping.

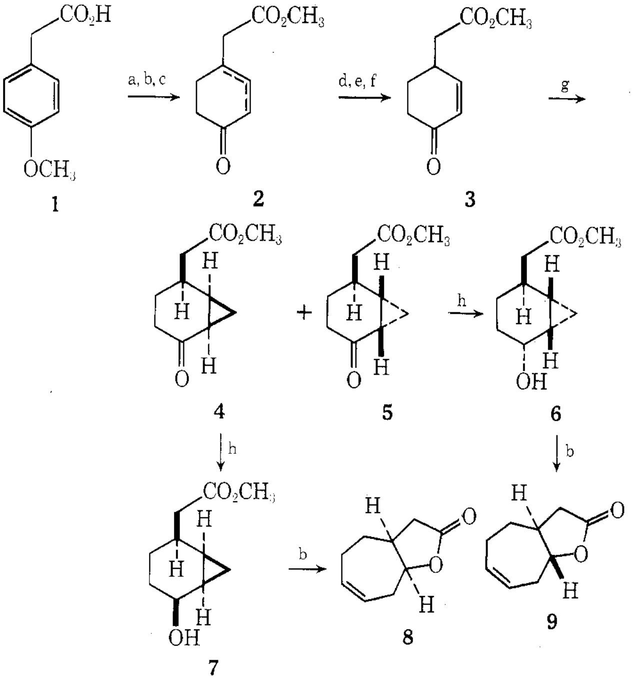
Fused ring γ-butyrolactones are widely distributed among natural products of plant origin, especially the sesquiterpene family.[1] The majority of these substances contain cis- or trans-fused lactones derived from 2-hydroxycyclohexyl- and 2-hydroxycycloheptylacetic acid moieties (part structure I). A reasonable route to (potentially more useful) unsaturated derivatives of such lactones (part structure II) can be envisioned as indicated (III → II) via solvolysis of a cyclopropylcarbinol (part structure III) with participation of an appropriately positioned acetic acid appendage.[2] In fact, preliminary work along these lines showed great promise.[3] However, before this methodology could be applied to natural product synthesis, additional studies were needed to probe the regio and stereo aspects of the solvolysis reaction. These studies are reported herein.



I ($n = 1$ or 2) II III

In our preliminary work we examined the solvolysis of the bicyclo[4.1.0]heptanol **6**.[3] This substance and an isomer (**7**) were obtained as an 85:15 mixture by the route outlined in Chart I. Birch reduction of p-methoxyphenylacetic acid (**1**) followed by acidic hydrolysis of the resulting enol ether and subsequent acidic esterification with methanol afforded the unsaturated keto ester **2** as a nearly 1:1 mixture of double bond isomers. The desired α,β isomer **3** was purified through the piperidine adduct.[4] Addition of dimethylsulfoxonium methylide[5] to enone **3** proceeded smoothly to give an 85:15 mixture of the cyclopropyl ketones **5** and **4**. This mixture could not be separated and was therefore used as such for the subsequent steps. Our stereochemical assignments are based on the expectation of favored attack by the methylide on the less hindered face of enone **3**.[6]

Chart I [a]



Reduction of the ketone mixture **5** and **4** with sodium borohydride led to the alcohols **6** and **7**. Again our stereochemical assignments presuppose favored attack by hydride on the less hindered face of the ketone carbonyl in a kinetically controlled process.[7] The alcohol mixture **6** and **7** upon treatment with aqueous perchloric acid in methanol at room temperature afforded an 85:15 mixture of the trans and cis lactones **9** and **8**. The identity of these products was ascertained by comparison of their dihydro derivatives, secured by catalytic hydrogenation, with authentic samples.[8]

An unequivocal synthesis of the cyclopropylcarbinol **6** and its carbinyl epimer **12** (as the acid) is shown in Chart II. Oxidation of the tricyclic ketone **10** of known stereochemistry[9] with m-chloroperoxybenzoic acid in methylene chloride gave rise to the lactone **11**. Saponification followed by esterification of the acid **12** with diazomethane and oxidation with the chromium trioxide–pyridine reagent in methylene chloride[10] yielded the keto ester **5** identical with the major methylide adduct of enone **3**. Reduction either with sodium borohydride or K-Selectride afforded the previously obtained hydroxy ester **6**. Both this hydroxy ester and the epimeric hydroxy acid **12** were smoothly converted to the trans lactone **9** in aqueous perchloric acid. Lactone **11** could also be directly rearranged to lactone **9** under these reaction conditions.

Efforts at obtaining the *syn-cis-syn*-bicyclo[4.1.0]heptanol **16** along the lines described above were less rewarding owing to an unfavorable isomer distribution in the Baeyer–Villiger oxidation of the tricyclic ketone **13**. Despite numerous trials with a variety of peroxy acids we were able to realize only a 1:9 mixture of lactones **15** and **14**. Lactone **15**, however, could be purified by column chromatography, thereby permitting an examination of its solvolysis. Initial attempts at conversion of this lactone to hydroxy acid **16** by saponification and subsequent acidification gave mainly the cis-fused lactone **8**. Evidently the intermediate hydroxy acid **16** solvolyzes with exceptional ease. Lactone **8** was most efficiently prepared via acid-catalyzed rearrangement of lactone **15**. This rearranged lactone was identified by comparison of its hydrogenation product with an authentic sample.[8] It was also found to have gas chromatographic characteristics identical with those of the minor solvolysis

Chart II[a]

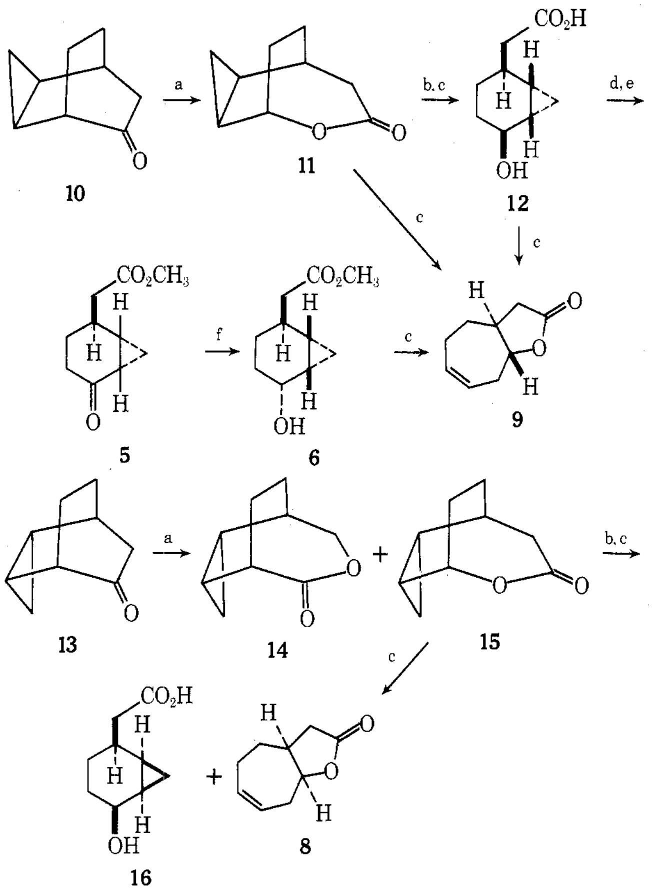
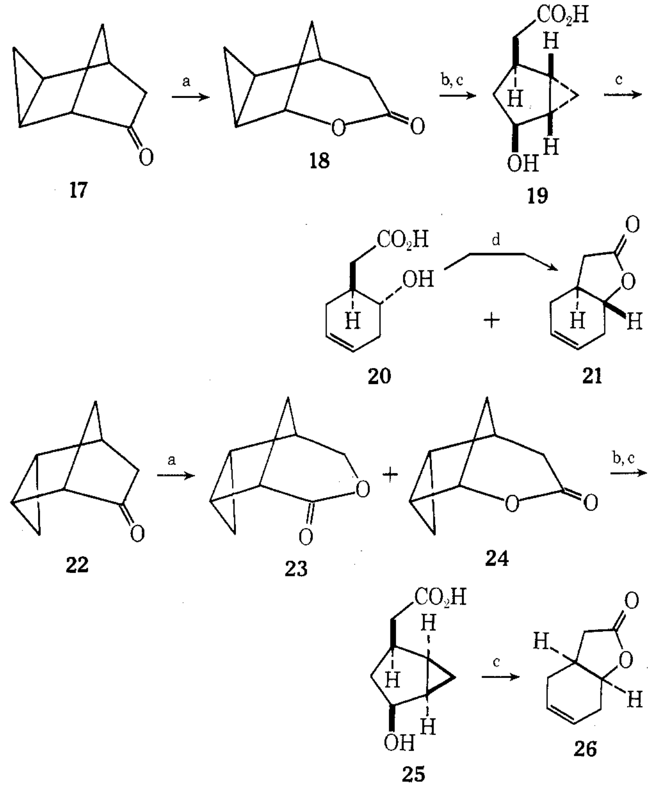


Chart III[a]



product of the hydroxy ester mixture (6 and 7) described above.

Parallel studies to those just detailed were next undertaken to examine the possible conversion of bicyclo[3.1.0]hexanols to cyclohexene-fused γ-butyrolactones (Chart III). Accordingly, the known tricyclic ketone **17**[11] was oxidized with *m*-chloroperoxybenzoic acid in methylene chloride to the lactone **18**. Saponification then gave the hydroxy acid **19**, which was converted to a mixture of hydroxy acid **20** and lactone **21** upon treatment with aqueous perchloric acid. Control experiments indicated that hydroxy acid **20** was formed via hydrolysis of lactone **21** rather than as a direct solvolysis product. Lactone **21** was identified through comparison of its hydrogenation product with an authentic sample.[12]

Oxidation of tricyclic ketone **22** with *m*-chloroperoxybenzoic acid in methylene chloride afforded the lactone **24**. Interestingly this oxidation, like its *endo*-bicyclo[2.2.2]octanone counterpart **13**, gave a significant amount of the isomeric lactone (**23**). However, this undesired isomer comprised a considerably smaller proportion of the product (20% vs. 90%) than in the aforementioned case. Lactone **24** could be purified by fractional crystallization, thus allowing for the preparation of pure hydroxy acid **25** by saponification. Solvolysis in aqueous perchloric acid led to the cis lactone **26**, identified by comparison of its hydrogenation product with an authentic sample.

Our findings indicate that the cyclopropylcarbinol solvolysis route to fused-ring γ-butyrolactones is efficient and highly stereoselective. It is tempting to speculate that the acetic acid (ester) side chain plays an important anchimeric part in the solvolysis reaction. The fact that both epimeric carbinols **6** and **12** afford the same lactone suggest that alcohol stereochemistry is not a critical factor. Thus an initial dissociative process followed by a carboxyl-assisted collapse of the intermediate ion would seem to best fit the results to date.

Experimental Section[13]

Methyl 2-(4-Oxo-2-cyclohexenyl)acetate (3). To a stirred solution of 101 g (0.61 mol) of *p*-methoxyphenylacetic acid in 200 ml of ethanol, 750 ml of ether, and 1.5 l. of liquid ammonia at −78° was added 27.3 g (3.9 g-atoms) of lithium wire in 2–3-cm pieces over a period of 3 hr. The ammonia was allowed to evaporate, water (500 ml) and concentrated hydrochloric acid (300 ml) were added, and the crude product was isolated by extraction with ether, affording 84 g of yellow oil (ca. 90% yield).

A 57.8-g portion of the above oil in 120 ml of 1,2-dichloroethane and 50 ml of methanol containing 3 ml of concentrated sulfuric acid was stirred at reflux for 6 hr. The cooled mixture was poured into water and the keto ester **2** (62.1 g), a 1:1 mixture of double bond isomers according to NMR analysis, was extracted with ether.

The crude keto ester **2** (62.1 g) was dissolved in 105 ml of piperidine. After 32 hr, the mixture was poured into 500 ml of 20% aqueous hydrochloric acid. The acidic solution was extracted with ether, cooled, and made basic with cold 20% sodium hydroxide. Ether extraction afforded 31.9 g of an orange solid piperidine adduct of enone **3**. This material was combined with 4.5 g of adduct from another run and the whole was treated with 80 ml (ca. 1.3 mol) of methyl iodide added at a rate to maintain reflux. The mixture was stirred for 24 hr and the excess methyl iodide was removed under reduced pressure. Pyridine (40 ml) was added and the mixture was heated on a steam bath for 3 hr, cooled, and poured into water. The product was isolated with ether and distilled to give 12 g of keto ester **3**, bp 105–110° (0.02 mm), which crystallized on standing. Recrystallization from ether afforded material: mp 51.5–53°; λ_{max} ($CHCl_3$) 5.78, 5.98 μ; δ_{TMS} (CCl_4) 6.36 (doubled AB pattern, J_{AB} = 10 Hz, $\Delta\nu_{AB}$ = 54 Hz), 3.70 ppm (OCH_3). The analytical sample, mp 51.5–53°, was secured by recrystallization.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.15; H, 7.19.

Methyl 2-(5-Oxo-*r*-2-*H*,*c*-1-*H*,*c*-6-*H*-bicyclo[4.1.0]hept-2-yl)acetate (4) and Methyl 2-(5-Oxo-*r*-2-*H*,*t*-1-*H*,*t*-6-*H*-bicyclo[4.1.0]hept-2-yl)acetate (5). The ylide was prepared from 5.42 g (24.6 mmol) of trimethylsulfoxonium iodide[5] and 0.59 g (24.6 mmol) of pentane-washed sodium hydride (from 1.04 g of 57% oil dispersion) in 28 ml of dimethyl sulfoxide (DMSO). After stirring at 50° for 2 hr the milky suspension was cooled to room temperature and treated with a solution of 3.93 g (23.4 mmol) of keto ester **3** in 10 ml of DMSO. After stirring at room temperature for 3 hr and at 50° for 1 hr the mixture was treated with saturated brine and the product was isolated by extraction with ether to give 3.62 g (85%) of yellow oil. NMR and gas chromatographic analysis in conjunction with later synthetic work showed this to be a roughly 85:15 mixture of the anti (**5**) and syn (**4**) isomers, λ_{max} (film) 5.78, 5.92 μ; δ_{TMS} (CCl_4) 3.62 ppm (OCH_3).

Methyl 2-(5-Oxo-*r*-2-*H*,*t*-1-*H*,*t*-6-*H*-bicyclo[4.1.0]hept-2-yl)acetate (5). A solution of 1.63 g (9.6 mmol) of hydroxy acid **12** in 60 ml of ether was added to an ethereal solution of diazomethane generated from 3.2 g (30 mmol) of *N*-nitroso-*N*-methylurea.[14] After standing overnight the solution was washed with saturated aqueous sodium bicarbonate and dried over magnesium sulfate. Distillation afforded 1.71 g (96%) of hydroxy ester, bp 105° (bath temperature) (0.05 mm), which was 95% pure according to gas chromatography.

A 1.48-g sample of this material was oxidized with 4.83 g of CrO_3 and 7.75 ml of pyridine in 110 ml of methylene chloride (Collin's reagent)[10] at room temperature for 30 min. The product was isolated with ether and distilled to give 1.23 g (84%) of keto ester **5**: bp 105° (bath temperature) (0.05 mm); λ_{max} (film) 5.78, 5.92 μ; δ_{TMS} (CCl_4) 3.63 ppm (OCH_3). The analytical sample was secured by preparative layer chromatography (silica gel) and redistillation.

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 66.09; H, 7.90.

This material was found to coincide with the major dimethylsulfoxonium methylide adduct of enone **3** according to NMR and GC comparisons.

Methyl 2-(*c*-5-Hydroxy-*r*-2-*H*,*t*-1-*H*,*t*-6-*H*-bicyclo[4.1.0]-hept-2-yl)acetate (6). A solution of 0.22 g (1.2 mmol) of keto ester **5** in 20 ml of THF at 0° was treated with 4 ml of 0.5 *M* K-Selectride[15] in THF. After 1 hr, 1.5 ml of 20% aqueous sodium hydroxide and 1.5 ml of 30% hydrogen peroxide were added and stirring was continued for 15 min. The product was isolated by extraction with ether and distillation, which gave 0.22 g (98%) of hydroxy ester **6**: bp 105° (bath temperature) (0.05 mm); λ_{max} (film) 2.96, 5.76 μ; δ_{TMS} (CCl_4) 4.05 (H-5, m), 3.63 (OCH_3), 3.45 ppm (OH). The analytical sample was secured by preparative layer chromatography (silica gel) and redistillation.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.97; H, 8.97.

Methyl 2-(*c*-5-Hydroxy-*r*-2-*H*,*t*-1-*H*,*t*-6-*H*-bicyclo[4.1.0]-hept-2-yl)acetate (6) and Methyl 2-(*t*-5-Hydroxy-*r*-2-*H*,*c*-1-*H*,*c*-6-*H*-bicyclo[4.1.0]hept-2-yl)acetate (7). The crude 85:15 mixture of keto esters **5** and **4** described above (3.62 g, 19.9 mmol) in 30 ml of methanol at 0° was treated with 0.75 g (20 mmol) of solid sodium borohydride. The mixture was stirred for 15 min, poured into brine, and extracted with ether to give 2.87 g (66.5% based on enone **3**) of hydroxy esters **6** and **7**, bp 120° (bath temperature) (0.05 mm), a roughly 85:15 mixture. The spectral properties attributable to the major component matched those of an authentic sample of the anti-cis-syn isomer **6** prepared as described above.

***cis*-2-(2-Hydroxy-4-cycloheptenyl)acetic Acid Lactone (8).** A solution of 54 mg (0.35 mmol) of lactone **15** (98% pure according to gas chromatography) in 5 ml of 7% aqueous perchloric acid and 0.5 ml of acetone was stirred for 24 hr at room temperature. The product was isolated with ether and distilled, affording 47 mg (87%) of lactone **8**: bp 130° (bath temperature) (0.05 mm); λ_{max} (film) 5.59 μ; δ_{TMS} (CCl_4) 5.48–5.68 (H-4, H-5, m), 4.50–4.87 ppm (H-2, m). The analytical sample was secured by preparative layer chromatography (silica gel) and redistillation.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.05; H, 8.14.

Hydrogenation of a 40-mg sample over 20 mg of 5% platinum on carbon in 10 ml of ethanol afforded material with identical spectral (infrared, NMR) and chromatographic properties with those of an authentic sample.[8]

***trans*-2-(2-Hydroxy-4-cycloheptenyl)acetic Acid Lactone (9). A. From Hydroxy Ester 6.** A solution of 0.21 g (1.1 mmol) of hydroxy ester **6** in 10 ml of 7% aqueous perchloric acid and 3 ml of acetone was stirred at room temperature for 24 hr. The product was isolated with ether and distilled, affording 0.15 g (85%) of white solid, mp 44–46.5° after recrystallization from ether.

Solvolysis of the 85:15 mixture of hydroxy esters **6** and **7** under similar conditions afforded an 85:15 mixture of lactones **9** and **8** according to gas chromatographic analysis.

B. From Hydroxy Acid 12. A solution of 0.30 g (1.76 mmol) of hydroxy acid **12** in 8 ml of 7% aqueous perchloric acid and 1 ml of methanol was stirred for 24 hr at room temperature. The product was isolated with ether and distilled, affording 0.251 g (94%) of white solid: mp 41–43°; λ_{max} (KBr) 5.62 μ; δ_{TMS} (CCl_4) 5.63–5.96 (H-4, H-5, m), 3.61–4.09 ppm (H-2, m). The analytical sample, mp 44–46°, was obtained after several recrystallizations from ether–hexane.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.91; H, 8.00.

Hydrogenation of this material over 5% platinum on carbon in ethyl acetate afforded *trans*-2-(2-hydroxycycloheptyl)acetic acid lactone, identified by comparison with an authentic sample.[8]

C. From Lactone 11. A solution of 0.20 g (1.31 mmol) of lactone **11** in 10 ml of 7% aqueous perchloric acid and 1 ml of acetone was stirred for 24 hr at room temperature. The product was isolated with ether and distilled, affording 150 mg (75%) of lactone **9**, mp 43–45° after recrystallization from ether.

2-(*t*-5-Hydroxy-*r*-2-*H*,*t*-1-*H*,*t*-6-*H*-bicyclo[4.1.0]hept-2-yl)acetic Acid Lactone (11). A mixture containing 0.80 g (5.9 mmol) of ketone **10**,[9] 1.33 g (7.7 mmol) of *m*-chloroperoxybenzoic acid,[16] and 0.49 g (5.9 mmol) of sodium bicarbonate in 40 ml of methylene chloride was stirred at room temperature for 2 days. The solution was washed with 10% aqueous sodium hydroxide and saturated brine and dried over magnesium sulfate. After removal of solvent under reduced pressure the solid residue was distilled to give 0.55 g (62%) of waxy solid lactone **11**: bp 160° (bath temperature) (0.05 mm); λ_{max} (film) 5.84 μ; δ_{TMS} ($CDCl_3$) 4.67 (H-5, m), 2.98 ppm (H-2, m). The analytical sample, mp 96–100.5°, was secured by recrystallization from hexane and sublimation (70°, 0.05 mm).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.89; H, 8.05.

2-(*t*-5-Hydroxy-*r*-2-*H*,*t*-1-*H*,*t*-6-*H*-bicyclo[4.1.0]hept-2-yl)acetic Acid (12). A solution of 0.77 g (5.1 mmol) of lactone **11** and 0.85 g of potassium hydroxide in 25 ml of methanol was heated at reflux for 4 hr. Most of the methanol was distilled under reduced pressure, water was added, and the aqueous phase was washed with ether and acidified with cold 10% aqueous hydrochloric acid. The acidic product was isolated with ethyl acetate, affording 0.85 g (98%) of solid. Recrystallization from chloroform afforded 0.72 g (84%) of acid **12**: mp 113–116°; λ_{max} (KBr) 3.05, 3.8–4.0, 5.81 μ; δ_{TMS} (acetone-d_6) 5.52–6.58 (OH), 4.13 ppm (H-5, m). The analytical sample, mp 115–116.5°, was secured after an additional recrystallization and sublimation (80°, 0.05 mm).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.50; H, 8.23.

***t*-5-Hydroxymethyl-*r*-2-*H*,*c*-1-*H*,*c*-6-*H*-bicyclo[4.1.0]heptane-2-carboxylic Acid Lactone (14) and 2-(*t*-5-Hydroxy-*r*-2-*H*,*c*-1-*H*,*c*-6-*H*-bicyclo[4.1.0]hept-2-yl)acetic Acid Lactone (15).** A mixture containing 1.72 g (12.7 mmol) of ketone **13**,[9] 4.38 g (25.4 mmol) of *m*-chloroperoxybenzoic acid,[16] and 1.09 g (13 mmol) of sodium bicarbonate in 150 ml of methylene chloride was stirred at room temperature for 5 days. The mixture was diluted with ether, washed with 20% aqueous sodium hydroxide, dried over magnesium sulfate, and concentrated under reduced pressure to give 1.87 g of yellow solid. Analysis by gas chromatography indicated a 90:10 mixture of lactones **14** and **15**. This mixture could be partially separated by chromatography on silica gel. Lactone **14** was eluted in the earlier fractions. Material thus obtained was recrystallized from ether–petroleum ether to give a white solid: mp 190–192°; λ_{max} (KBr) 5.82 μ; δ_{TMS} ($CDCl_3$) 4.08 ($-CH_2O-$, d, $J = 2$ Hz), 3.3 (H-2), 2.46 (H-5), 1.84 ppm ($-CH_2CH_2-$).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.12; H, 8.00.

The later fractions were further purified by high-pressure liquid chromatography on a Corasil-2 column using 15% ethyl acetate–hexane as eluent. Lactone **15** was thus secured as a white solid, mp 124–127°, after recrystallization from ether–petroleum ether: λ_{max} (KBr) 5.74 μ; δ_{TMS} ($CDCl_3$) 4.77 ppm (H-5, m).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.16; H, 8.02.

2-(*t*-4-Hydroxy-*r*-2-*H*,*t*-1-*H*,*t*-5-*H*-bicyclo[3.1.0]hex-2-yl)-acetic Acid Lactone (18). A 3.37-g (27.6 mmol) sample of ketone **17**[11] was oxidized with 7.1 g (41.5 mmol) of *m*-chloroperoxybenzoic acid[16] as described above to give 3.04 g (80%) of waxy solid, bp 110° (bath temperature) (0.05 mm). The analytical sample was secured by preparative layer chromatography (silica gel) and short-path distillation: λ_{max} (film) 5.80 μ; δ_{TMS} (CCl_4) 4.63 ppm (H-4).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.30; H, 7.46.

2-(*t*-4-Hydroxy-*r*-2-*H*,*t*-1-*H*,*t*-5-*H*-bicyclo[3.1.0]hex-2-yl)acetic Acid (19). A solution of 1.16 g (8.40 mmol) of lactone **18** and 1.4 g of potassium hydroxide in 40 ml of methanol was stirred at reflux for 4 hr. Most of the methanol was removed under reduced pressure and the aqueous residue was washed with ether and acidified with cold 10% hydrochloric acid. Extraction with ethyl acetate afforded 1.14 g (87%) of solid acid. Recrystallization from ether afforded 0.93 g: mp 107.5–109°; λ_{max} (KBr) 2.99, 3.2–3.8, 5.83 μ; δ_{TMS} (acetone-d_6) 5.25–7.1 (OH), 4.17 ppm (H-4). The analytical sample, mp 108–109°, was secured by recrystallization from ether.

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.59; H, 7.86.

***trans*-2-(2-Hydroxy-4-cyclohexenyl)acetic Acid Lactone (21).** A solution of 200 mg of hydroxy acid **19** in 10 ml of 7% aqueous perchloric acid and 0.5 ml of acetone was stirred at room temperature for 24 hr. The product was extracted with ethyl acetate and separated into acidic material (**20**, 140 mg) and neutral material (**21**, 60 mg) by base washing (10% sodium hydroxide) and acidification. The acidic material was stirred at reflux for 4 hr with 10 mg of *p*-toluenesulfonic acid in 10 ml of benzene to give 90 mg of lactone **21**. The combined material (150 mg) was distilled to give 136 mg (77%) of waxy solid: bp 100° (bath temperature) (0.05 mm); λ_{max} (KBr) 5.62 μ; δ_{TMS} (CCl_4) 5.58–5.79 (H-4, H-5), 3.75–4.22 ppm (H-2). The analytical sample, mp 54–55.5°, was secured by recrystallization from hexane.

Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.51; H, 7.13.

Hydrogenation of this material over 5% platinum on carbon in ethyl acetate afforded the known *trans*-2-(2-hydroxycyclohexyl)acetic acid lactone.[12]

2-(*t*-4-Hydroxy-*r*-2-*H*,*c*-1-*H*,*c*-5-*H*-bicyclo[3.1.0]hex-2-yl)acetic Acid Lactone (24). The oxidation of 1.87 g (15.3 mmol) of ketone **22**[11] was carried out with 3.98 g of *m*-chloroperoxybenzoic acid[16] for 60 hr as described above to give 1.76 g (83%) of solid lactone **24** contaminated with ca. 20% of the isomeric hydroxymethylcyclopentanecarboxylic acid lactone **23** according to NMR spectral analysis. Purification was effected by five successive recrystallizations from ether–hexane to give material with mp 77–80°: λ_{max} (KBr) 5.80 μ; δ_{TMS} ($CDCl_3$) 4.90 ppm (H-4, m).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.56; H, 7.42.

2-(*t*-4-Hydroxy-*r*-2-*H*,*c*-1-*H*,*c*-5-*H*-bicyclo[3.1.0]hex-2-yl)acetic Acid (25). Saponification of 1.20 g (8.70 mmol) of lactone **24** was effected with 2.9 g of potassium hydroxide in 50 ml of methanol as described above to give 1.37 g of solid acid **25**. Recrystallization from ethyl acetate afforded 1.1 g (81%) of material: mp 133–135°; λ_{max} (KBr) 3.08, 3.6–4.1, 5.90 μ.

The analytical sample, mp 134–135°, was secured after three additional recrystallizations from ethyl acetate.

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.51; H, 7.91.

***cis*-2-(2-Hydroxy-4-cyclohexenyl)acetic Acid Lactone (26).** A solution of 0.19 g (1.2 mmol) of hydroxy acid **25** in 10 ml of 7% aqueous perchloric acid and 1 ml of acetone was stirred at 80° for 24 hr. The product was isolated with ether and distilled, affording 0.14 g (81%) of lactone **26**: bp 85° (bath temperature) (0.05 mm); λ_{max} (film) 5.61 μ; δ_{TMS} (CCl_4) 5.57–5.80 (H-4, H-5, m), 4.54–4.77 ppm (H-2, m). The analytical sample was secured by preparative layer chromatography (silica gel) and redistillation.

Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.37; H, 7.31.

Hydrogenation of this material over 5% platinum on carbon in ethyl acetate afforded the known *cis*-2-(2-hydroxycyclohexyl)acetic acid lactone.[12]

Acknowledgment. We are indebted to the National Institutes of Health (Cancer Division) for support of this work through a research grant (5 RO1 CA 11089).

Registry No.—**1**, 104-01-8; **3**, 52294-81-2; **4**, 55156-65-5; **5**, 52294-82-3; **6**, 52294-83-4; **7**, 55177-23-6; **8**, 55156-66-6; **9**, 52294-84-5; **10**, 51260-37-8; **11**, 55156-67-7; **12**, 55156-68-8; **12** Me ester, 55177-24-7; **13**, 51260-38-9; **14**, 55156-69-9; **15**, 55177-25-8; **17**, 2443-85-8; **18**, 55156-70-2; **19**, 55156-71-3; **21**, 34905-87-8; **22**, 2443-86-9; **23**, 55156-72-4; **24**, 55177-26-9; **25**, 55177-27-0; **26**, 55156-73-5; dimethylsulfoxonium methylide, 5367-24-6; *m*-chloroperoxybenzoic acid, 937-14-4.

References and Notes

(1) For a recent review see H. Yoshioka, T. J. Mabry, and B. N. Timmermann, "Sesquiterpene Lactones", University of Tokyo Press, Tokyo, 1973.

(2) A scheme involving the synthesis of α-methylene-γ-butyrolactones from geminally substituted hydroxymethylcyclopropanecarboxylic esters has been reported: P. F. Hudrlik, L. R. Rudnick, and S. H. Korzeniowski, *J. Am. Chem. Soc.*, **95**, 6848 (1973).

(3) J. A. Marshall, F. N. Tuller, and R. Ellison, *Synth. Commun.*, **3**, 465 (1973).

(4) G. Stork and W. N. White, *J. Am. Chem. Soc.*, **78**, 4604 (1956).

(5) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1353 (1965).

(6) Cf. G. B. Payne, *J. Org. Chem.*, **32**, 3351 (1967).

(7) Cf. H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Menlo Park, Calif., 1972, pp 54–64.

(8) W. Herz and L. A. Glick, *J. Org. Chem.*, **28**, 2970 (1963).

(9) (a) G. R. Wenzinger and J. A. Ors, *J. Org. Chem.*, **39**, 2060 (1974); (b) P. E. Schueler and Y. E. Rhodes, *ibid.*, **39**, 2063 (1974).

(10) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(11) K. B. Wiberg and G. R. Wenzinger, *J. Org. Chem.*, **30**, 2278 (1965).

(12) J. Klein, *J. Am. Chem. Soc.*, **81**, 3611 (1959).

(13) The apparatus described by W. S. Johnson and W. P. Schneider ("Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 132) was used to maintain an argon atmosphere. The isolation procedure consisted of thorough extractions with the specified solvent, washing the combined extracts with water and saturated brine solution, and drying the extracts over anhydrous sodium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a rotary evaporator. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Infrared spectra were obtained with a Perkin-Elmer 137 spectrophotometer. Infrared absorptions are reported in wavelengths (μ) and are standardized with reference to the 6.24-μ peak of polystyrene. Nuclear magnetic resonance spectra were recorded with a Varian T-60 spectrometer. Signals are reported as the chemical shift downfield from tetramethylsilane (Me_4Si) in parts per million (ppm) of the applied field. The multiplicity of the peak is abbreviated: singlet, s; doublet, d; triplet, t; quartet, q; and multiplet, m. Coupling constants are reported in hertz. Melting points were determined on a calibrated Thomas capillary melting point apparatus. Melting points are not corrected.

(14) F. Arndt, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 165.

(15) Available from Aldrich Chemical Co., Milwaukee, Wis.

(16) Available from Wychem Ltd., Newmarket, Suffolk, England.