Synthesis of Fused-Ring α-Methylene-γ-butyrolactones

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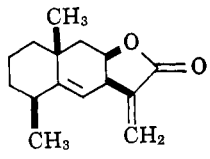
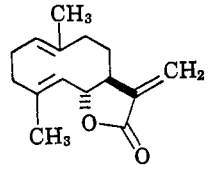
A new synthesis of α-methylene-γ-butyrolactones is described. The essential features involve reduction of α-carboalkoxy-γ-butyrolactone enolates with lithium aluminum hydride and oxidation of the resulting unsaturated diols with manganese dioxide. The fused-ring lactones **1–4** were prepared in order to examine the scope of the new method.

The α-methylene-γ-butyrolactone grouping characterizes a rapidly expanding group of sesquiterpenes.[2] The representative members presented below exemplify the structural diversity to be found within this class of natural products.



alantolactone



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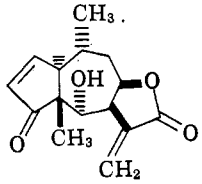

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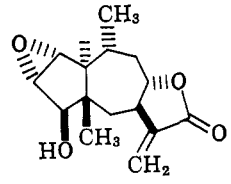
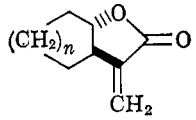
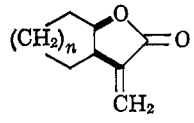


amaralin

From a synthetic viewpoint, these examples suggest a need for methods which will enable construction of the α-methylene-γ-butyrolactone moiety *cis* and *trans* fused to cyclohexane, cycloheptane, and cyclodecane rings. Anticipating these future requirements we chose as initial synthetic objectives structural prototypes **1–4** of naturally occurring sesquiterpene lactones.



1, $n = 2$
2, $n = 3$



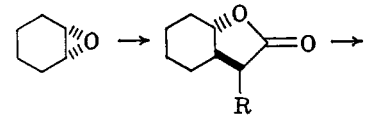
3, $n = 2$
4, $n = 3$

Two methods have previously been reported for the preparation of α-methylene-γ-butyrolactones. The first involves carbonylation of β-acetylenic carbinols and affords the methylene lactone directly in modest yield.[3] This straightforward approach has been successfully applied to the preparation of α-methylene-γ-butyrolactone itself and several of its homologs using readily available acetylenic alcohols. The acetylenic precursors required for lactones **1–4** were not available and, moreover, their preparation presented formidable synthetic obstacles. Furthermore, the relatively stringent acidic conditions used to effect the previously reported carbonylations cast serious doubts regarding the applicability of this method to intermediates which might be needed in a total synthesis of members belonging to the aforementioned class of natural products.

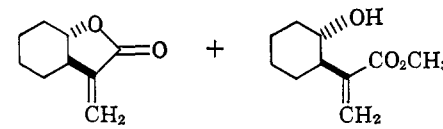
The second method originated with van Tamelen and Bach[4] and was employed by these workers in their total synthesis of *dl*-protolichesterinic acid. Since the essential features of this scheme appeared compatible with our present and projected needs, we investigated its applicability to the first of our synthetic objectives, the *trans*-cyclohexane-fused lactone **1**.

Lactone acid **6** was prepared along well-established lines[5] starting from cyclohexene oxide and diethyl sodiomalonate. The resulting lactone ester **5** was saponified and the diacid thus obtained was lactonized under acidic conditions.

A Mannich reaction was performed on lactone acid **6** and the amino lactone **7** anticipated by analogy with the findings of van Tamelen and Bach[4] was obtained,



5, R = $CO_2C_2H_5$
6, R = CO_2H
7, R = $CH_2N(C_2H_5)_2$



1 **8**

albeit in only 9% yield. Contrastingly, related monocyclic lactone acids afford the corresponding amino lactones in 40–50% yield under comparable reaction conditions.[6] In the hope that appropriate modifications might ultimately improve the yield of amino lactone, we decided to investigate the second phase of the van Tamelen–Bach method despite the unpromising nature of the first part. Accordingly, amino lactone **7** was converted to its methiodide and the quaternary salt was treated with methanolic sodium bicarbonate to effect the requisite elimination of diethylmethylamine. A mixture of the desired lactone **1** and hydroxy ester

(1) Fellow of the National Institute of General Medical Sciences, National Institutes of Health, 1964–1965.

(2) For leading references, see W. Herz, G. Högenauer, and A. Romo de Vivar, *J. Org. Chem.*, **29**, 1700 (1964); R. A. Lucas, S. Rovinski, R. J. Kiesel, L. Dorfman, and H. B. MacPhillamy, *ibid.*, **29**, 1549 (1964); M. T. Emerson, C. N. Caughlan, and W. Herz, *Tetrahedron Letters*, **No. 12**, 621 (1964).

(3) E. R. H. Jones, T. Y. Shen, and M. C. Whiting, *J. Chem. Soc.*, 230 (1950).

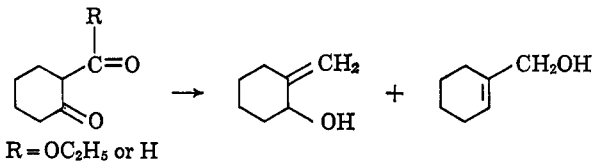
(4) E. E. van Tamelen and S. R. Bach, *J. Am. Chem. Soc.*, **77**, 4683 (1955); **80**, 3079 (1958).

(5) M. S. Newman and C. A. VanderWerf, *ibid.*, **67**, 233 (1945).

(6) Apparently the amino acid precursor of amino lactone **7** decarboxylates with difficulty because of the strain imposed in the requisite enol intermediate by the fused-ring system. Since such strain should be greatest in the *trans*-cyclohexane-fused lactone **1**, the method of van Tamelen and Bach[4] may prove more practical for the less strained lactones **2–4**.

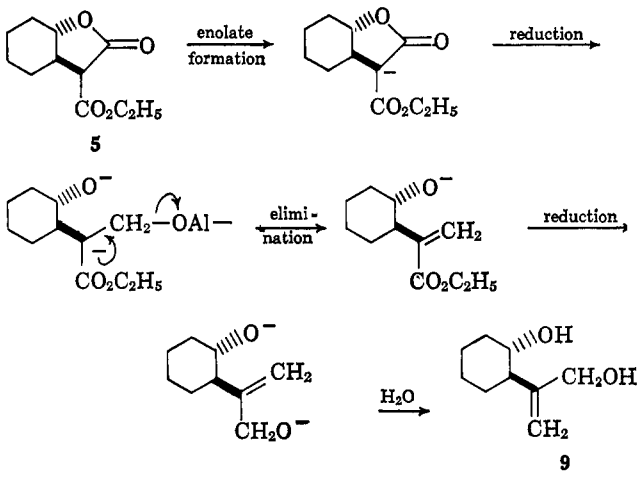
8 (5:1) was isolated in 60% yield. Hydroxy ester 8 was most likely formed by methanolysis of lactone 1. In view of these unpromising initial results, we provisionally abandoned the above route.

In our search for alternative routes to lactones 1–4 we noted the definitive paper by Dreiding and Hartman[7] describing the reduction of α-formyl and α-carbethoxy derivatives of cyclic ketones with lithium aluminum hydride. The products were shown to contain mixtures of isomeric allylic alcohols. The mechanism proposed by these workers involves an initial



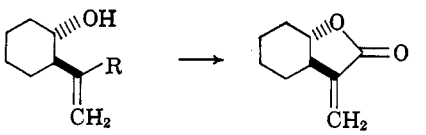
reaction of the enolic carbonyl compound with the hydride leading to an enolate which is subsequently reduced to a species which undergoes elimination and further reduction to the observed products. On this basis we anticipated the reductive elimination sequence shown in Scheme I for lactone ester 5. The essential correctness of this assumption was demonstrated experimentally, although the above sequence is an oversimplification of the actual mechanistic pathway.[8]

SCHEME I



Reduction of the sodioenolate of lactone ester 5 with ethereal lithium aluminum hydride afforded the desired diol 9, m.p. 66–67.5°, in 40% yield. This product was easily identified through elemental analysis and infrared and n.m.r. spectra. The relationship between diol 9 and methylene lactone 1 is apparent and we now consider the method by which this conversion was accomplished.

Numerous examples can be cited wherein allylic alcohols are selectively oxidized with manganese dioxide.[9] Most applications of this type utilized secondary alcohols but the reported oxidation of primary benzyl alcohols to benzaldehydes suggested that diol 9 might also be selectively oxidized by this reagent. Actually, the transformation was readily accomplished using a suspension of manganese dioxide in chloroform, and hydroxyaldehyde 10 was obtained in 85% yield. Silver oxide converted hydroxyaldehyde 10 to hydroxy acid 11 and this acid was subsequently cyclized using dicyclohexylcarbodiimide. The latter reagent has been used previously for the preparation of strained γ-lactones.[10] The methylene lactone 1 prepared previously according to the method of van Tamelen and Bach[4] and the sample obtained by the above route exhibited similar infrared and n.m.r. spectra except for the peaks due to hydroxy ester 8 which were absent in the latter material. In order to establish the potential utility of the above sequence as a synthetic method, we investigated the preparation of the remaining three methylene lactones 2–4 which serve as models for various sesquiterpenes.



9, R = CH_2OH
10, R = CHO
11, R = CO_2H

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Application of the reductive elimination route to *cis*-cyclohexane-fused α-methylene-γ-butyrolactone 2 required a supply of the corresponding lactone ester 13. This substance was prepared in high yield by acylation of the known lactone 12[11] with sodium hydride using dimethyl carbonate as the solvent according to the excellent procedure described for carbethoxylation of cyclic ketones by Rhoads and co-workers.[12] Our earlier efforts to effect this condensation using benzene as a solvent and a two- or threefold excess of dimethyl carbonate were unsuccessful owing to the ease with which lactone 12 self-condensed. Lactone ester 13 was converted to the enolate 14 with sodium hydride and the enolate was reduced using lithium aluminum hydride to give the expected diol 15, m.p. 59–60° (Scheme II).

Oxidation of diol 15 with manganese dioxide gave the hydroxyaldehyde 16, expected by analogy with diol 9, but only as a minor product. The major product was lactone 2, the ultimate objective of this sequence. Eventually, this lactone was obtained directly from diol 15 in over 60% yield. Evidently the initially formed aldehyde 16 undergoes facile cyclization to lactol 17 which is subsequently oxidized by virtue of its allylic alcohol grouping.

(7) A. S. Dreiding and J. A. Hartman, *J. Am. Chem. Soc.*, **75**, 939 (1953). Subsequent to our initial studies, reports appeared describing the reduction of malonic esters with lithium aluminum hydride [W. J. Bailey, M. E. Hermes, and W. A. Klein, *J. Org. Chem.*, **28**, 1724 (1963); W. F. Gannon and E. A. Steck, *ibid.*, **27**, 4137 (1962)]. Allylic alcohols were found in the products.

(8) A preliminary account summarizing part of this work has been published: J. A. Marshall and N. Cohen, *Tetrahedron Letters*, **No. 30**, 1997 (1964). Further studies (with Niels H. Andersen) of sodiomalonate reductions are in progress.

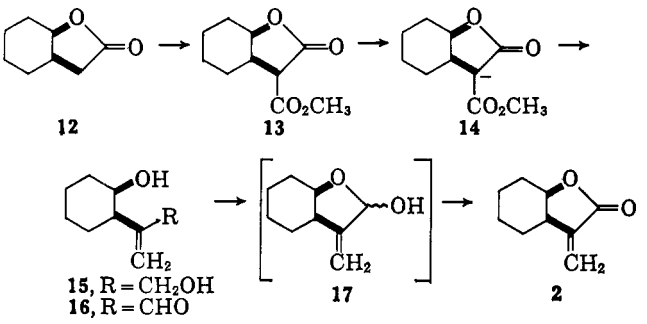
(9) *Cf.* (a) P. J. Neustaedter in "Steroid Reactions," C. Djerassi, Ed., Holden-Day, San Francisco, Calif., 1963, pp. 104–110; (b) E. F. Pratt and J. F. Van de Castle, *J. Org. Chem.*, **26**, 2973 (1961). See N. L. Wendler, H. L. Slates, N. R. Trenner, and M. Tishler, *J. Am. Chem. Soc.*, **73**, 719 (1951), for applications in the vitamin A field.

(10) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958); W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frish, L. H. Dreger, and W. M. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).

(11) J. Klein, *ibid.*, **81**, 3611 (1959), and references cited therein.

(12) S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkit, *Tetrahedron*, **19**, 1625 (1963); J. A. Marshall, N. Cohen, and K. R. Arenson, *J. Org. Chem.*, **30**, 762 (1965).

SCHEME II



The contrasting oxidative fate of diol **9** *vs.* diol **15** constitutes a striking illustration of the relative stabilities of *cis* and *trans*-bicyclo[4.3.0]nonanes. Figure 1 presents Newman projections depicting the geometrical changes attending cyclization of hydroxyaldehydes **10** and **16**. Since the lactol ring is nearly planar, the bonds affixing the cyclohexane ring must be eclipsed. This requirement can be met by contiguous equatorial and axial bonds with the resulting compression strain in the cyclohexane ring being alleviated through a twist conformation. However, coplanarity of adjoined equatorial bonds causes expansion of the cyclohexane ring, thereby introducing an angle strain which cannot be relieved through bond rotation.[13] Lactol formation is thus rendered less favorable in hydroxyaldehyde **10** relative to hydroxyaldehyde **16**. Both of the isomeric homologous diols **19** and **22** are directly converted to corresponding methylene lactones **3** and **4** with manganese dioxide. Therefore, the conformational flexibility of the cycloheptane ring allows attainment of an eclipsed *trans*-1,2-diequatorial ring juncture which, unlike its cyclohexane counterpart, is free of angle strain. Similar conclusions are reflected in the stability relationships found by Herz and Glick[14] and Allinger and Zalkow[15] for bicyclo[5.3.0] ring systems. Our oxidation–cyclization results are summarized in Table I.

TABLE I

OXIDATIONS WITH MANGANESE DIOXIDE[a]

Diol	Aldehyde, %	Lactone, %	Yield, %	Time, hr.
9	10, 100	0	83	1.5
15	16, 40[b]	3, 60	80	2.0
19	0	2, 100	87	2.5
22	0	4, 100	60	2.5

[a] The ratio 2 g. of MnO_2/mmole of diol in 25 ml. of solvent was employed. [b] Oxidation to lactone **3** was complete when a larger ratio of MnO_2/diol was employed for a longer time.

The cycloheptane-fused model methylene lactones **3** and **4** were prepared along the lines employed for the cyclohexane-fused lactones **1** and **2**. Only two points relevant to these systems require comment. The first pertains to the *trans*-lactone ester **18**. We did not encounter the reported difficulties[14] in condensing cycloheptene oxide with diethyl sodiomalonate. Lactone ester **18** was thus obtained in nearly 50% yield when the reaction mixture was heated for 21 hr.

Our second noteworthy observation pertains to the *cis*-lactone ester **21**. Since the enolate required for the reductive elimination leading to diol **22** is the product from condensation between lactone **20** and dimethyl carbonate, it seemed unnecessary to isolate the lactone ester **21** provided the carbomethoxylation reaction proceeded in high yield. This proved to be the case, and the over-all conversion of lactone **20** to methylene diol **22** was easily performed by removing the excess dimethyl carbonate under reduced pressure and reducing the residual enolate with ethereal lithium aluminum hydride (Scheme III). Although the same reasoning might be applied to the *trans*-lactone esters **5** and **18**, we chose not to explore this possibility because the condensation reaction in these cases does not proceed in quantitative yield.

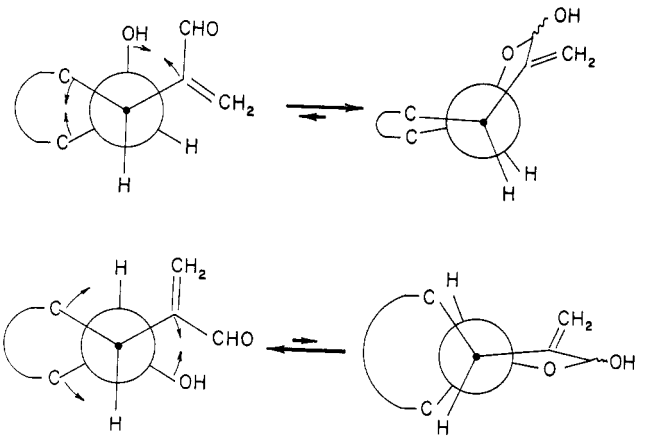
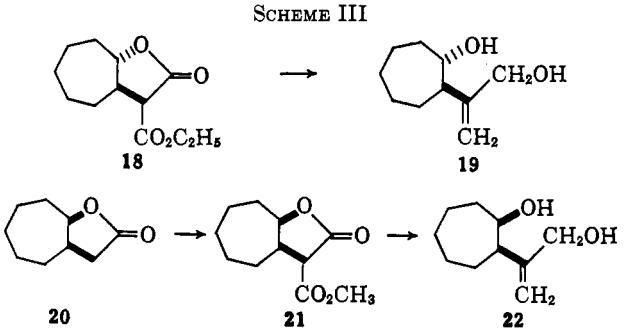


Figure 1.—Cyclization of *cis*- and *trans*-hydroxyaldehydes.

SCHEME III



By-products from Reductive Eliminations.—Unsaturated diols **9, 15,** and **19** are crystalline compounds which were isolated and purified by crystallization. Chromatography of the mother liquors afforded materials eluted from silica gel ahead of the crystalline diols. These oily by-products displayed medium peaks at 2.9–3 μ in their infrared spectra indicative of an alcoholic grouping. Furthermore, n.m.r. peaks at 4.5–5.4 and 1.0–1.1 p.p.m. (doublets, J = 5–7 c.p.s.) suggested the presence of CHOH and $CHCH_3$ groupings. Unfortunately these compounds could not be purified sufficiently to give meaningful combustion analyses. However, their uptake of 1 equiv. of standard chromic acid reagent[16] to give the lactones **25, 26,** and **29**[14] coupled with the spectral evidence is best reconciled by formulating these by-products as lactols **23, 24,** and **27**. The analogous substance obtained from lactone ester **21** is a solid, m.p. 95.5–97°. The spectral properties of this material

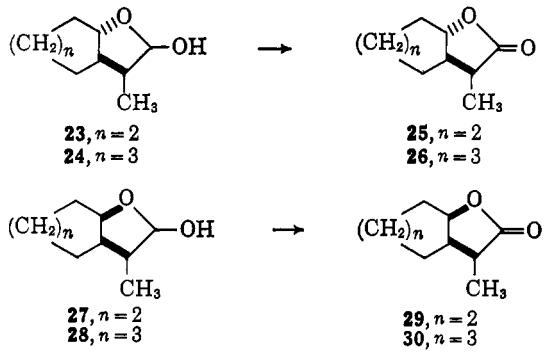
(13) *Cf.* E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 276.

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

(15) N. L. Allinger and V. B. Zalkow, *J. Am. Chem. Soc.*, **83**, 1144 (1961).

(16) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

coincided with those of the oily lactols and oxidation with chromic acid afforded the expected lactone **30**. Combustion analysis of this solid by-product is compatible with its formulation as lactol **28**. The observation that lactols are isolable reduction products of α-carboalkoxy-γ-butyrolactone enolates has mechanistic implications which will be discussed elsewhere.



Experimental Section[17]

2-(*trans*-2-Hydroxycyclohexyl)propenol (9).—The mineral oil was removed from 1.5 g. of 51.6% sodium hydride dispersion by washing with three 10-ml. portions of anhydrous ether. To a stirred suspension of the resulting sodium hydride in 50 ml. of 1,2-dimethoxyethane (DME) was added a solution of 4.24 g. of lactone ester **5** and 2 drops of ethanol in 50 ml. of anhydrous DME.[17c] The mixture was stirred at room temperature until hydrogen evolution ceased (5 hr.) and the resulting slurry was treated with 2.0 g. of lithium aluminum hydride and 150 ml. of anhydrous ether. After 3.5 hr., 7 ml. of water was cautiously added, and stirring was continued for 1 hr. to granulate the salts. The mixture was filtered, the filter cake was thoroughly washed with ether, and the solvent was removed from the filtrate under reduced pressure to give 3.1 g. of yellow oil which crystallized on standing. This oil was chromatographed on 150 g. of silica gel. The early ether fractions afforded 0.35 g. of oily lactol **23**: λ_{max}^{film} 2.95 (OH), 9.3, 9.75, 10.3–10.5, 10.75, 11.80, 11.95 μ; $\delta_{max}^{CCl_4}$ 5.4–4.5 [C*H*(O*H*)O–], 3.7–3.0 (C*H*O–), 1.05 p.p.m. (C*H*$_3$–CH; doublet, J = 6 c.p.s.).

The later fractions eluted with ether gave 1.35 g. (43%) of crystalline diol **9**. Two recrystallizations from hexane–ether afforded 0.65 g.: m.p. 64–66°; $\lambda_{max}^{CHCl_3}$ 2.97 (OH), 6.06 (C=C), 9.42, 10.9 μ; $\delta_{TMS}^{CCl_4}$ 5.01, 4.86 (C=CH$_2$), 4.4–4.0 (OH), 3.90 (C*H*$_2$O–), 3.6–3.1 p.p.m. (C*H*OH). The analytical sample, m.p. 66–67.5, was obtained after several recrystallizations from hexane.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.23; H, 10.26. Found: C, 69.1; H, 10.5.

2-(*trans*-2-Hydroxycyclohexyl)propenal (10).—The procedure of Herbst and Djerassi[18] was modified. A solution of 674 mg. of diol **9** in 120 ml. of chloroform was stirred with 8.3 g. of manganese dioxide for 1.5 hr. at room temperature. The mixture was filtered and the manganese dioxide was thoroughly washed with ether. The filtrate was concentrated, giving 554 mg. (83%) of oily aldehyde **10**. The analytical material, b.p. 50–60° (bath temperature) (0.03 mm.), was obtained by distillation: λ_{max}^{film} 2.94 (OH), 3.70 (aldehyde CH), 5.91 (aldehyde CO), 6.17, 9.36, 10.00, 10.59, 11.08, 11.40, 11.77, 12.00 μ; $\delta_{TMS}^{CCl_4}$ 9.50 (aldehyde H), 6.25, 6.01 (C=CH$_2$), 3.83–3.00 (C*H*OH), 2.91–2.75 (O*H*).

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.08; H, 9.17. Found: C, 70.0; H, 9.2.

The 2,4-dinitrophenylhydrazone had m.p. 191–192° after three recrystallizations from ethanol–chloroform.

Anal. Calcd. for $C_{15}H_{18}N_4O_5$: C, 53.88; H, 5.44; N, 16.76. Found: C, 54.0; H, 5.7; N, 16.7.

2-(*trans*-2-Hydroxycyclohexyl)propenoic Acid (11).—The procedure of Clark, *et al.*,[19] was employed. To a rapidly stirred solution containing 550 mg. of aldehyde **10** and 605 mg. of silver nitrate in 15 ml. of 1:1 ethanol–water was added dropwise over 1.2 hr. a solution of 590 mg. of sodium hydroxide in 26 ml. of water. After an additional 2 hr., the mixture was filtered and the filtrate was diluted with water and washed with ether. The alkaline solution was chilled in ice and acidified with cold 10% hydrochloric acid with stirring under a layer of benzene. The aqueous phase was saturated with salt and the product was isolated with benzene[17b] to give 567 mg. (93.5%) of crude acid which could be used without further purification: λ_{max}^{film} 2.9–4.0 (acid OH), 5.90 (CO), 6.15 (C=C), 7.80, 8.06, 8.59, 8.45, 9.98, 10.53, 11.51, 11.73, 12.13 μ.

In a similar run, the crude product (208 mg.) solidified on standing. This material was triturated with hexane–ether to give 168 mg. (75% yield) of white solid, m.p. 78–80°. The analytical specimen, m.p. 84.5–85.5°, was obtained after three recrystallizations from benzene–hexane.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.50; H, 8.30. Found: C, 63.6; H, 8.2.

2-(*trans*-2-Hydroxycyclohexyl)propenoic Acid Lactone (1). A. From Lactone Acid 6.—The method of van Tamelen and Bach[4] was employed. A mixture containing 6.0 g. of lactone acid **6**[5], 15.6 g. of diethylamine, and 7.7 g. of 37% aqueous formaldehyde initially at 0° was stirred for 48 hr. at room temperature.[17c] An additional 5 g. of aqueous formaldehyde was added, and stirring was continued for 40 hr. The mixture was saturated with potassium carbonate and extracted with ether. The combined extracts were washed with 10% aqueous hydrochloric acid, the acidic washings were neutralized with sodium bicarbonate, and the basic organic product was isolated with ether[17b] to give 0.93 g. (13%) of yellow oil. Amino lactone **7** (0.70 g., 9% yield), b.p. 100° (bath temperature) (0.07 mm.), was obtained by distillation: λ_{max}^{film} 5.62 (lactone CO), 7.21, 7.71, 8.25, 8.90, 9.13, 9.33, 9.80, 10.30, 10.61 μ.

Anal. Calcd. for $C_{13}H_{23}NO_2$: C, 69.28; H, 10.31; N, 6.22. Found: C, 68.5; H, 10.3; N, 7.1.

In view of the difficulty encountered in obtaining a satisfactory elemental analysis, amino lactone **7** was converted to its picrate, m.p. 147°, after two recrystallizations from ethanol.

Anal. Calcd. for $C_{19}H_{26}N_4O_9$: C, 50.21; H, 5.78; N, 12.33. Found: C, 50.3; H, 5.9; N, 12.1.

A solution of 485 mg. of amino lactone **7** in 5 ml. of methanol was stirred at 0° and 0.2 ml. of methyl iodide was added. The solution was stirred at room temperature for 5 min., 10 ml. of 5% aqueous sodium bicarbonate was added, and the oily mixture was stirred for 10 min. Saturated brine was added, and the mixture was extracted thoroughly with ether. The combined extracts were washed with aqueous hydrochloric acid, saturated brine, and dried over anhydrous sodium sulfate. Distillation yielded 0.20 g. (61%) of colorless oil, b.p. 50° (bath temperature) (0.05 mm.). The n.m.r. spectrum revealed peaks at 3.69 (OCH$_3$), 6.13, and 5.58 p.p.m. (C=CH$_2$) due to hydroxy ester **8** in addition to the peaks which are characteristic of the methylene lactone **1** (see part B below). A 5:1 ratio of lactone **1** to ester **8** could be estimated from the integrated spectrum.

B. From Hydroxy Acid 11.—This procedure is based on the method of Johnson and co-workers.[10] A solution containing 0.45 g. of crude hydroxy acid **11** and 0.55 g. of N,N-dicyclohexylcarbodiimide in 25 ml. of anhydrous pyridine was stirred at room temperature for 42 hr.[17c] The mixture was concentrated at room temperature under reduced pressure, and the residue was treated with chloroform and filtered. The filtrate was distilled giving 0.24 g. (59%) of methylene lactone **1**: b.p. 70° (bath temperature) (0.1 mm.); λ_{max}^{film} 5.65 (lactone CO), 5.99 (C=CH$_2$), 7.11, 7.40, 7.98, 8.16, 8.28, 8.71, 8.80, 8.91, 9.12, 9.71, 10.00, 10.69, 10.84, 11.27, 11.77, 11.98, 12.23, 14.68 μ; $\delta_{TMS}^{CCl_4}$ 5.91 (C=CH$_2$; doublet, J = 3 c.p.s.), 5.34 (C=CH$_2$; doublet, J = 3 c.p.s.), 3.9–3.4 (broad, C*H*O–).

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.01; H, 7.96. Found: C, 71.1; H, 8.1.

(17) (a) Melting points were determined on a Fisher-Johns hot stage. (b) The isolation procedure consisted of thorough extraction and back extraction with the specified solvent, washing the combined extracts with saturated brine, and drying the extracts over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a steam bath. (c) The apparatus described by W. S. Johnson and W. P. Schneider [*Org. Syn.*, **30**, 18 (1950)] was used to maintain a nitrogen atmosphere over reaction mixtures. (d) Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. (e) The prefix *dl*- is omitted from the names of racemic materials.

(18) D. Herbst and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 4337 (1960).

(19) K. J. Clark, G. I. Fray, R. H. Jaeger, and R. Robinson, *Tetrahedron*, **6**, 217 (1959).

Methyl (*cis*-2-Hydroxycyclohexyl)malonate Lactone (13).—The procedure of Rhoads and co-workers[12] was employed. To a suspension of 3.3 g. of 51.6% sodium hydride dispersion[20] in 50 ml. of anhydrous dimethyl carbonate was added 4.74 g. of lactone **12** in 25 ml. of dimethyl carbonate.[17c] The reaction mixture was stirred under reflux for 1 hr., at 70° for 2 hr., and at room temperature for 16 hr. The resulting slurry was cooled to 0° and 3 ml. of methanol was added followed by 4.5 ml. of acetic acid and 60 ml. of water. The product was isolated with ether[17b] and distilled, b.p. 95–98° (0.05 mm.). The distillate was chromatographed on 300 g. of silica gel to remove mineral oil which had codistilled. Elution with 1:1 ether in benzene gave 5.68 g. (85%) of lactone ester **13**: m.p. 35–40°; λ_{max}^{film} 5.61 (lactone CO), 5.77 (ester CO), 8.52, 8.89, 9.80, 10.12; $\delta_{TMS}^{CCl_4}$ 4.69 (C*H*O–; quartet, J = 5 c.p.s.), 3.76 (CH_3O), 3.26 (α-H; doublet, J = 6 c.p.s.). The analytical sample was obtained by distillation of chromatographed material.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.58; H, 7.13. Found: C, 60.6; H, 7.2.

2-(*cis*-2-Hydroxycyclohexyl)propenol (15).—The procedure described for the *trans* isomer **9** was employed using 1.98 g. of lactone ester **13**. The crude product was chromatographed on 85 g. of silica gel. Elution with 20% ether in benzene gave 0.07 g. of lactone **29**. The fractions eluted with 50% ether in benzene gave 0.12 g. of lactol **27**: λ_{max}^{film} 2.95 (OH), 8.62, 9.3, 9.8–10.2, 10.40, 11.55, 12.40 μ; $\delta_{TMS}^{CCl_4}$ 5.4–4.5 [C*H*(O*H*)O–], 4.5–3.7 (C*H*O–), 1.01 p.p.m. (CHC*H*$_3$; doublet, J = 7 c.p.s.). Elution with ether afforded 0.99 g. (63.5%) of crystalline diol **15**. Recrystallization from ether–hexane gave 0.53 g. of material, m.p. 52–55°. Two additional recrystallizations gave white prisms, m.p. 59–60°, which were sublimed (50° at 0.03 mm.) prior to combustion analysis: $\lambda_{max}^{CHCl_3}$ 2.8, 3.0 (OH), 6.09 (C=CH$_2$), 8.05, 8.45, 8.96, 9.37, 10.29, 11.43 μ; $\delta_{TMS}^{CCl_4}$ 4.89 (C=CH$_2$; doublet, J = 2 c.p.s.), 5.04 (C=CH$_2$; doublet, J = 2 c.p.s.), 4.69–4.09 (–OH–, C*H*O–, multiplet), 3.94 p.p.m. (CH_2O–).

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.23; H, 10.26. Found: C, 69.0; H, 10.3.

2-(*cis*-2-Hydroxycyclohexyl)propenoic Acid Lactone (3).—A solution containing 202 mg. of diol **15** in 50 ml. of dry benzene was stirred with 3 g. of manganese dioxide at room temperature for 9 hr. The infrared spectrum of a small aliquot revealed incomplete reaction and therefore an additional 1 g. of manganese dioxide and 10 ml. of benzene was added and stirring was continued for 2 hr. Work-up as described for the cycloheptyl analog **2** afforded 120 mg. (61.5%) of essentially pure lactone **3**. The analytical sample, b.p. 60° (bath temperature) (0.06 mm.), was obtained by distillation: λ_{max}^{film} 5.66 (lactone CO), 6.00 (C=CH$_2$), 7.61, 7.71, 7.91, 8.10, 8.40, 8.60, 8.85, 9.05, 9.85, 10.20, 10.32, 11.24, 12.20; $\delta_{TMS}^{CCl_4}$ 6.05 (C=CH$_2$; doublet, J = 2.5 c.p.s.), 5.44 (C=CH$_2$; doublet, J = 2.5 c.p.s.), 4.46 (C*H*O–; quartet, J = 6 c.p.s.).

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.01; H, 7.96. Found: C, 71.2; H, 8.2.

Ethyl *trans*-2-Hydroxycycloheptylmalonate Lactone (18).—The procedure of Herz and Glick[14] was used with slight modification. A solution of sodium ethoxide (from 12.3 g. of sodium) in 400 ml. of ethanol containing 85.5 g. of diethyl malonate was stirred at 0° for 15 min. and 55 g. of cycloheptene oxide[21] was added over a 20-min. period.[17c] The mixture was stirred at reflux for 21 hr., cooled in an ice bath, and neutralized with 33 g. of acetic acid. Most of the solvent was removed under reduced pressure, the residue was mixed with water, and the product was isolated with ether.[17b] The lactone ester **18** (54.2 g., 48.8% yield), b.p. 136–138° (0.5 mm.), was obtained by distillation: λ_{max}^{film} 5.61 (lactone CO), 5.78 (ester CO), 7.29, 7.45, 7.85, 8.52, 8.67, 9.25, 9.90 μ.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.7; H, 7.9.

2-(*trans*-2-Hydroxycycloheptyl)propenol (19).—The procedure described for the cyclohexyl analog **9** was employed on 4.5 g. of lactone ester **18**. The crude product distilled at 70–100° (bath temperature) (0.03 mm.) giving 2.14 g. of colorless oil which crystallized. Recrystallization from hexane gave a total of 0.95 g. (28% yield) of material in various crops, m.p. 56–57° (0.42 g.), 55–57° (0.11 g.), and 53–56° (0.42 g.). The combined mother liquors were treated with ethanolic sodium hydroxide to remove a small amount of unreduced lactone ester **18** and the neutral material was chromatographed on 60 g. of silica gel. The fractions eluted with ether and ether–ethyl acetate gave 0.62 g. (18% yield) of crystalline diol **19**. The analytical sample, m.p. 58–58.5°, was obtained by recrystallization from hexane–ether and sublimation (70° at 0.05 mm.): $\lambda_{max}^{CHCl_3}$ 3.0 (OH), 6.06 (C=CH$_2$), 11.10 μ; $\delta_{TMS}^{CCl_4}$ 4.88, 5.03 (C=C*H*$_2$), 4.4–4.1 (OH), 3.97 (C*H*$_2$O–), 3.8–3.4 p.p.m. (C*H*O–).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.53; H, 10.68. Found: C, 70.7; H, 10.6.

The fractions eluted with 50% ether in benzene afforded 0.48 g. of lactol **24**: λ_{max}^{film} 2.95 (OH), 8.42, 8.65, 8.91, 9.6–10.5, 10.67, 11.16 μ; $\delta_{TMS}^{CCl_4}$ 5.2–4.8 [C*H*(O*H*)O–], 4.2–3.3 (C*H*O–), 1.04 p.p.m. (CHC*H*$_3$; doublet, J = 6 c.p.s.).

2-(*trans*-2-Hydroxycycloheptyl)propenoic Acid Lactone (2).—A solution of 200 mg. of diol **19** in 30 ml. of benzene[22] was stirred with 2.5 g. of manganese dioxide for 2.5 hr. at room temperature. The mixture was filtered, and the filter cake was thoroughly washed with ether. The solvent was removed from the filtrate under reduced pressure affording 170 mg. (87%) of essentially pure methylene lactone **2**. The crude sample was distilled for analysis: b.p. 60° (bath temperature) (0.03 mm.); λ_{max}^{film} 5.67 (lactone CO), 6.00 (C=CH$_2$), 7.15, 7.62, 7.91, 8.01, 8.68, 8.85, 9.98, 10.63, 11.12, 12.26 μ; $\delta_{TMS}^{CCl_4}$ 6.18 (C=CH$_2$; doublet, J = 3 c.p.s.), 5.45 (C=CH$_2$; doublet, J = 3 c.p.s.), 4.3–3.9 p.p.m. (C*H*O–).

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.24; H, 8.51. Found: C, 72.0; H, 8.6.

***cis*-2-Hydroxycycloheptylacetic acid lactone (20)** was prepared as described by Herz and Glick.[14] However, our application of their method afforded lactone **20** in substantially better yield and we therefore present the experimental procedure. Methyl cycloheptanone-2-carboxylate was prepared from cycloheptanone in 89% yield following the procedure of Rhoads and co-workers.[12] Ethyl 1-carbomethoxy-2-oxocycloheptane-1-acetate was prepared in 74% yield according to Plattner and co-workers.[23] A 33.7-g. sample of this material was refluxed with 150 ml. of concentrated hydrochloric acid for 12 hr. An additional 20 ml. of acid was added and heating was resumed for 24 hr. Most of the water was removed under reduced pressure, and the residue was dissolved in 120 ml. of 10% aqueous sodium hydroxide. The aqueous solution was washed with ether and acidified with concentrated hydrochloric acid, and the acid was isolated with ether giving 22 g. (99%) of crude acid. A 4.9-g. sample of the crude acid was refluxed for 17 hr. with 50 ml. of acetic anhydride containing 1 drop of acetyl chloride. Most of the acetic acid and acetic anhydride was distilled at atmospheric pressure and the residue was distilled under reduced pressure giving 3.8 g. (87%) of oil, b.p. 81–92° (0.15 mm.), which solidified. This material dissolved in 200 ml. of 95% ethanol was hydrogenated in a Parr apparatus over W-2 Raney nickel. The initial pressure was 46 p.s.i. and shaking was continued for 3.5 hr. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in ether and the solution was washed with saturated aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. Distillation gave 3.4 g. (89% based on crude cycloheptanone-2-acetic acid) of lactone **20**, b.p. 69–72° (0.07 mm.). The infrared spectrum of this revealed none of the bands characteristic of the *trans* isomer.

Methyl (*cis*-2-Hydroxycycloheptyl)malonate Lactone (21).—The procedure described for the cyclohexyl analog **13** was followed except the reaction time was diminished to 2 hr. at reflux. From 3.41 g. of lactone **20**, 3.9 g. (83.5%) of lactone ester **21**, b.p. 118° (0.02 mm.), was obtained which crystallized on standing. A sample of this material was chromatographed on silica gel, and the fractions eluted with 50% ether in benzene to pure ether were combined and recrystallized twice from ether–pentane at −10° giving white prisms: m.p. 37.5–38°; λ_{max}^{film} 5.61 (lactone CO), 5.77 (ester CO), 8.55, 8.70, 9.90, 10.21 μ; $\delta_{TMS}^{CCl_4}$ 4.96–4.42 (C*H*O–), 3.81 (CH_3O), 3.27 p.p.m. (α-H; doublet, J = 8 c.p.s.).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.24; H, 7.61. Found: C, 62.3; H, 7.7.

(20) The mineral oil dispersion was purchased from Metal Hydrides, Inc., Beverley, Mass.

(21) P. B. Talukdar and P. E. Fanta, *J. Org. Chem.*, **24**, 555 (1959).

(22) Chloroform was not used as the solvent because we found in our preliminary studies that the ethanol preservative prevented oxidation of the lactol intermediate owing to acetal formation. The acetal was not characterized beyond its infrared (which displayed only weak peaks in the 2.5–3- and 5.5–6-μ region) and n.m.r. spectra (the characteristic CH_3CH_2O quartet and triplet patterns were present at the expected chemical shifts).

(23) Pl. A. Plattner, A. Fürst, and K. Jirasek, *Helv. Chim. Acta*, **29**, 730 (1946).

2-(*cis*-2-Hydroxycycloheptyl)propenol (22).—The procedure described for the cyclohexyl analog **9** was employed except 1,2-dimethoxyethane was used as the solvent throughout, and the mineral oil was not washed from the sodium hydride. An equal volume of ether was added to aid granulation of the salts after the addition of aqueous sodium hydroxide. From 2.87 g. of lactone ester **21** and 2.0 g. of 50% sodium hydride in mineral oil was obtained 3.3 g. of crude product.

This material was chromatographed on 60 g. of silica gel. Elution with 50% ether in benzene gave 0.31 g. (14%) of crystalline lactol **28**. The analytical sample, m.p. 95.5–97°, was obtained after two recrystallizations from hexane followed by sublimation at 30° (0.05 mm.): $\lambda_{max}^{CHCl_3}$ 2.95 (OH), 8.15, 9.00, 9.17, 9.25, 10.15, 10.64 μ; $\delta_{TMS}^{CCl_4}$ 5.25 [CHC*H*(OH)O–; doublet, J = 4 c.p.s.], 5.0–3.8 (C*H*O–, OH), 0.97 p.p.m. (CHCH_3; doublet, J = 6 c.p.s.).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.53; H, 10.68. Found: C, 70.6; H, 10.7.

Elution with ether gave 0.73 g. (32%) of oily diol **22**: $\lambda_{max}^{CHCl_3}$ 3.0 (OH), 6.08 (C=CH_2), 10.9 μ; $\delta_{TMS}^{CCl_4}$ 5.02 (C=CH_2; doublet, J = 1.5 c.p.s.), 4.88 (C=CH_2; doublet, J = 1.5 c.p.s.), 5.4–4.7 (OH), 4.0 p.p.m. (CH_2OH). A sample of the oil was distilled, b.p. 80–90° (bath temperature) (0.2 mm.).

The carbomethoxylation experiment described for lactone ester **21** was repeated using 1.54 g. of lactone **20**. The dimethyl carbonate was removed under reduced pressure after carbomethoxylation was complete and the residual enolate was reduced using 1.7 g. of lithium aluminum hydride according to the procedure described for lactone ester **9**. Chromatography on silica gel gave 0.25 g. of lactol **28** and 0.81 g. of diol **22**.

2-(*cis*-2-Hydroxycycloheptyl)propenoic Acid Lactone (4).—The procedure described for diol **19** was followed using 0.26 g. of chromatographed diol **22**. The resulting lactone (0.15 g., 58% yield) was distilled and the distillate, b.p. 60–70° (bath temperature) (0.05 mm.), was chromatographed on 6 g. of silica gel. Elution with 5% ether in benzene afforded 0.1 g. of material which was distilled for analysis: λ_{max}^{film} 5.68 (lactone CO), 6.00 (C=CH_2), 7.87, 8.62, 8.87, 9.99, 12.26 μ; $\delta_{TMS}^{CCl_4}$ 6.27 (C=CH_2; doublet, J = 3 c.p.s.), 5.56 (C=CH_2; doublet, J = 3 c.p.s.), 4.72 p.p.m. [C*H*O–; triplet of doublets, J (triplet) = 9 c.p.s., J (doublet) = 4 c.p.s.].

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.24; H, 8.51. Found: C, 72.8; H, 8.7.

2-(*trans*-2-Hydroxycyclohexyl)propanoic Acid Lactone (25).—A stirred solution containing 341 mg. of crude lactol **23** in 5 ml. of acetone at 0° was treated dropwise with 8 M chromic acid reagent until the red color was no longer dissipated (0.55 ml. required). The mixture was diluted with aqueous sodium bicarbonate and the product was isolated with ether.[17b] The crude material was treated with 10 ml. of 10% ethanolic potassium hydroxide, and the solution was warmed briefly on a steam bath and allowed to stand at room temperature for 3 hr. Water was added, and the mixture was washed with ether. The alkaline solution was acidified with concentrated hydrochloric acid and saturated with salt, and the product was isolated with ether. The crude hydroxy acid was dissolved in 40 ml. of benzene, 10 mg. of *p*-toluenesulfonic acid was added, and the solution was stirred under reflux with continuous removal of water *via* a Dean–Stark trap. The cooled solution was washed with saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate, and the product was distilled giving 195 mg. (58%), b.p. 55–70° (bath temperature) (0.05 mm.).

This compound was identical with the lactone **25** previously prepared by Herz and Glick[14] as evidenced by infrared and n.m.r. spectral comparison.[24]

2-(*cis*-2-Hydroxycyclohexyl)propanoic Acid Lactone (29).—A solution containing 103 mg. of crude lactol **27** in 2 ml. of acetone was oxidized using 0.16 ml. of standard chromic acid reagent. The material was processed according to the procedure described for the *trans* isomer **25** except the benzene azeotrope procedure was unnecessary. Distillation afforded 57 mg. (56%) of lactone **29**,[14] b.p. 70–80° (bath temperature) (0.2 mm.). The identity of this material was ascertained by comparison of the infrared and n.m.r. spectra with those of authentic lactone **29**.[24]

2-(*trans*-2-Hydroxycycloheptyl)propanoic Acid Lactone (26).—A solution containing 205 mg. of crude lactol **24** in 3 ml. of acetone was oxidized with 0.3 ml. of standard chromic acid reagent. The material was processed according to the procedure described above for lactone **29**, and the crude lactone was chromatographed on 10 g. of silica gel. Elution with 10% ether in benzene gave 100 mg. (50%) of lactone **26**[14] identified by comparison of the infrared and n.m.r. spectra with those of authentic material.[24]

2-(*cis*-2-Hydroxycycloheptyl)propanoic Acid Lactone (30).—The procedure described above for the *trans* isomer **26** was followed using 33 mg. of crystalline lactol **28** and 0.05 ml. of standard chromic acid solution. The product was isolated with ether and distilled giving 33 mg. (100%) of lactone **30**,[14] b.p. 70–80° (bath temperature) (0.15 mm.).

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(24) The infrared and n.m.r. spectra of this material were kindly provided by Professor Herz.

Acid-Catalyzed Reactions of 4,5-Epoxy-2,2,4-trimethylpentyl Isobutyrate[1]

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4,5-Epoxy-2,2,4-trimethylpentyl isobutyrate was found to rearrange to tetrahydro-2,4,4-trimethylfurfuryl isobutyrate and 2,2,4-trimethyl-5-oxopentyl isobutyrate in the presence of boron fluoride. In reactions catalyzed by other acids, this epoxy ester isomerized to the aldehydic ester, 2,2,4-trimethyl-5-oxopentyl isobutyrate, but did not give the tetrahydrofurfuryl ester. The greatest emphasis was placed on the boron fluoride catalyzed rearrangement of the 4,5-epoxyalkyl ester to the tetrahydrofurfuryl ester, since this reaction has not been previously reported. The reactions could be directed to give either the tetrahydrofurfuryl ester or the aldehydic ester as the major product by varying the medium and temperature used for the reaction.

A 4,5-epoxypentyl ester, 4,5-epoxy-2,2,4-trimethylpentyl isobutyrate (**1**), has been found to undergo an unexpected rearrangement in the presence of boron fluoride. The authors previously disclosed an acid-catalyzed rearrangement of 3,4-epoxyalkyl esters to substituted tetrahydro-3-furyl esters and briefly mentioned the above 4,5-epoxyalkyl ester in the earlier publication.[2]

In considering the chemistry of epoxides, reactions of the epoxy group generally involve an attack by an external nucleophilic group. However, it has been recognized that an attack on an epoxy group can be initiated by a nucleophilic site on the epoxide molecule

(1) Presented at the 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964.

(2) W. V. McConnell and W. H. Moore, *J. Org. Chem.*, **28**, 822 (1963).