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Synthesis and Structures of Dilactones Related to Anemonin

Ioannis K. Stamos, Gary A. Howie, Peter E. Manni, Warren J. Haws, Stephen R. Byrn,* and John M. Cassady*

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

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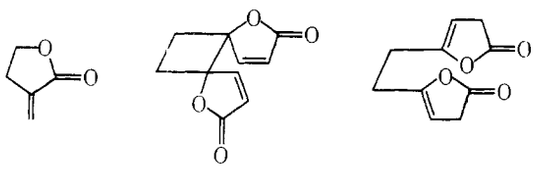
Reduction of anemonin (**2**) with H_2 over Pd/C gave tetrahydroanemonin (**3**) as reported in the literature, and reduction of anemonin with sodium borohydride in methanol gave keto ester **13** and dilactone **14**. However, reduction of anemonin (**2**) with sodium amalgam gave a compound with the properties of isotetrahydroanemonin which was assigned structure **6** in the literature. Spectroscopic evidence and single crystal x-ray analysis showed that isotetrahydroanemonin had structure **15** [2-oxa-3-oxo(*r*-1,*c*-5)bicyclo[3.3.0]octa-6-spiro[*t*-1′-oxa-2′-oxocyclopentane]] and not **6**. In addition, both the trans and cis di-α-methylenebutyrolactones **4a** and **4b** (1,7-dioxadispiro-[4.0.4.2]dodeca-3,9-dimethylene-2,8-dione) have been prepared by reaction of cyclobutane-1,2-dione with α-(bromomethyl)acrylate and zinc. The structure of the cis compound **4b** was established by single crystal x-ray techniques. Isotetrahydroanemonin (**15**) crystallized in space group $P2_1/c$ with a = 7.258 (4), b = 5.821 (1), and c = 22.285 (2) Å, β = 85.63 (1)°, and four molecules per unit cell. The structure was solved by direct methods and refined to an R factor of 0.061 on 1340 observed reflections. The di-α-methylene-γ-butyrolactone **4b** also crystallized in space group $P2_1/c$ with a = 11.300 (5), b = 7.915 (2), c = 11.903 (5) Å, β = 92.14 (5)°, and four molecules per unit cell. This structure was also solved by direct methods and refined to an R factor of 0.081 on 1545 independent reflections. The angle strain energy in lactones **4b** and **15** has been estimated using the Westheimer approach. A comparison of these strain energies with the strain energy in other lactones whose crystal structures have been published revealed the effect of ring fusion on the strain energy of these lactones. These comparisons indicated that the order of strain energy for both γ-butyrolactones and α-methylene-γ-butyrolactones was trans fused (to a six-membered ring) > cis fused ≃ spiro fused.

The isolation of anticancer drugs from natural sources has established a number of novel chemical templates which are valuable leads in the design of related synthetic antitumor agents. These compounds include a number of sesquiterpene lactones which have significant cytotoxic and antitumor activity. The biological activity of this class appears to be related to the presence of one or more highly electrophilic groups in the molecule including predominantly epoxides and conjugated carbonyl systems with the α-methylene-γ-butyrolactone group (**1**) appearing to play an especially important role.



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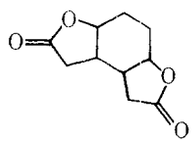

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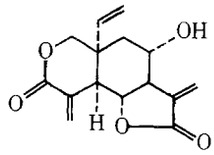

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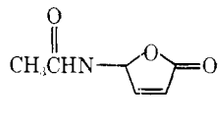

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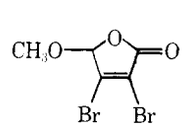
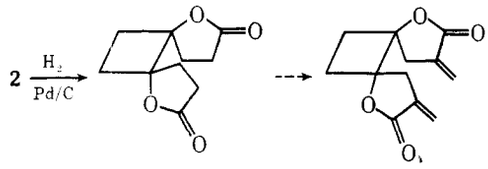


9

During the course of our studies aimed at the synthesis of potential tumor inhibitors containing the α-methylene-γ-butyrolactone moiety, we have explored the synthesis of several compounds related to anemonin (**2**).[2] Anemonin, which has received considerable attention in the literature, was an attractive synthetic intermediate based on the presence of two lactone rings in a fixed configuration which could potentially be modified to give an interesting series of related dilactones. For example, reduction of anemonin to tetrahydroanemonin (**3**)[3,4] followed by bis-α-methylenation was envisioned as a route to the bislactone **4a** (Scheme I). Other reported reduction products, including dihydroanemonin (**5**)[2,5,6] and isotetrahydroanemonin (**6**),[5-7] were promising precursors to open-chain dilactones and fused ring dilactones. For example, compound **6** was seen as a potential precursor to a close analogue of the tumor inhibitor vernolepin (**7**).[8] In addition the reported cytotoxic and antitumor activity of

Scheme I

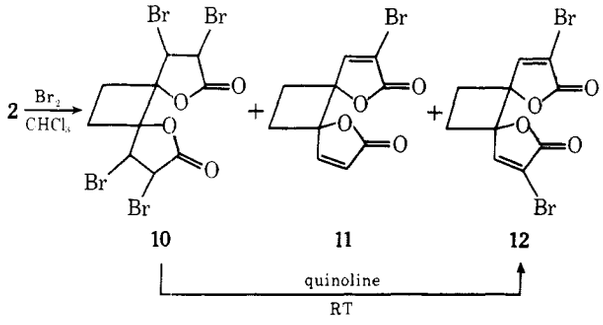


3 4a (trans)

simple substituted butenolides such as acetamido lactone 8[9] and bromo lactone 9[10] made attractive the synthesis of related bisbutenolides from anemonin.

Synthesis. Anemonin (2) was synthesized from α-angelicalactone in about 30% yield using a modification of the procedure reported by Grundmann and Kober.[11] Reaction of 2 with bromine in $CHCl_3$ gave the known tetrabromoanemonin (10)[12] in 55% yield. Chromatography of the mother liquor from this reaction gave two of the target butenolides, monobromoanemonin (11) in 20% yield and dibromoanemonin (12) in 6.6% yield. Compound 12 was also obtained by dehydrobromination of 10 using quinoline in benzene at room temperature (Scheme II).

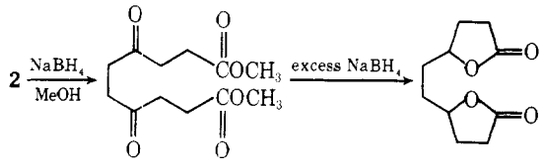
Scheme II



10 11 12

Whereas reduction of 2 with hydrogen in the presence of Pd/C gave the expected tetrahydroanemonin 3,[2,3] the products of the reactions with sodium borohydride and sodium amalgam were unusual. Reaction of 2 with sodium borohydride in methanol (Scheme III) gave the open-chain keto ester 13.

Scheme III

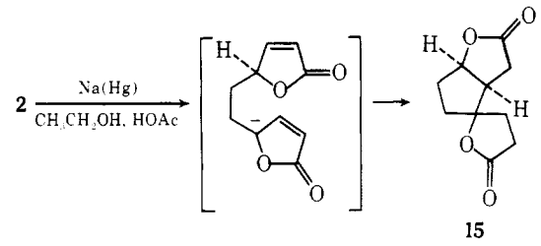


13 14

Further reaction with a large excess of sodium borohydride gave the open-chain dilactone (14) which was shown to be identical (IR, NMR, and MS) with an authentic reference compound.

The reduction of anemonin with sodium amalgam is reported to yield isotetrahydroanemonin (6).[6] Despite interest in the structures of anemonin[2] and some of its reduction products, the structure for isotetrahydroanemonin appeared secure and is reported as 6 in Beilstein[7] and Rodd.[5] However, we have found that the structure of isotetrahydroanemonin is not 6 but rather 15 as shown in Scheme IV. Reduction of anemonin with sodium amalgam in ethanol and acetic acid followed by chromatography gave a compound with the properties expected for 6. The melting point was consistent with that reported in the literature,[6,7] the infrared spectrum showed an absorption at 1775 cm^{-1} consistent with the γ-lactone function, and the expected molecular ion appeared in the mass spectrum at *m/e* 196.0730, consistent with a molecular formula of $C_{10}H_{12}O_4$. However, the NMR spectrum was inconsistent with structure 6 since only one proton absorption was observed in the region expected for a proton on carbon attached to lactone oxygen (HCO–). This evidence suggested that the reduction product was formed by an interesting rearrangement process and retained one spiro-linked lactone as in 15. In order to unequivocally establish the structure and stereochemistry of this rearrangement product, its structure was determined by the single crystal x-ray technique which is described later in detail.

Scheme IV

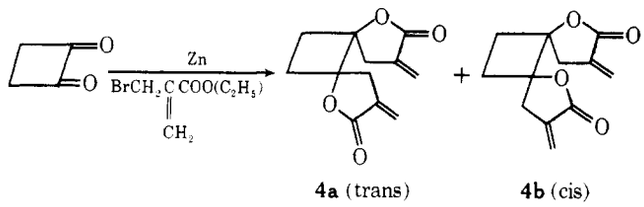


15

The formation of 15, 2-oxa-3-(*r*-1,*c*-5)bicyclo[3.3.0]octane-6-spiro[*t*-1′-oxa-2′-oxocyclopentane], from anemonin must derive via a 1,2 antarafacial shift of a spiro carbon atom, perhaps through an intermediate such as shown in Scheme IV or its free-radical equivalent. This reaction cannot be concerted as it requires 180° rotation of a γ-lactone group in order to form the cyclized product with the proper stereochemistry. The synthesis of isotetrahydroanemonin (15) from dihydroanemonin (5) by reduction with sodium amalgam[2b,6,7] may also proceed via a similar intermediate.

Although tetrahydroanemonin has not been converted to the target compound 4a, we have been able to isolate and characterize this compound and the related cis isomer, 4b, by a different approach. Reaction of cyclobutane-1,2-dione which was prepared by a literature route[13] with ethyl α-(bromomethyl)acrylate and zinc[14] gave a crude reaction mixture with

Scheme V



4a (trans) 4b (cis)

five major products. From this mixture, the trans product (4a) was obtained in 4.4% yield and the cis isomer (4b) in about 5% yield. The structure of 4b was determined unequivocally by the single crystal x-ray technique.

^1H NMR spectra provided further confirmation of the configuration of compounds 4a and 4b. The trans isomer 4a gave a singlet at δ 2.11 corresponding to the AA′BB′ system of the four cyclobutane ring protons (Figure 5, supplementary material), a pattern similar to that of anemonin which has the two lactone rings in a trans configuration.[4]

In contrast, in the cis isomer 4b, two of the hydrogens of the cyclobutane ring are in the environment of both of the lactone ring oxygen atoms. The other two cyclobutane ring protons are flanked by the α-methylene groups. In this case the patterns of the bands are relatively simple symmetrical multiplets of the A_2B_2 type (Figure 6, supplementary material).

Structure of Isotetrahydroanemonin (15). Figure 1 shows the structure of isotetrahydroanemonin (15) [2-oxa-3-oxo(*r*-1,*c*-5)bicyclo[3.3.0]octane-6-spiro[*t*-1′-oxa-2′-oxocyclopentane]] and the atomic numbering scheme used. Tables I and II show the bond lengths and angles in 15. Table III compares the bond lengths and angles in the cis and spiro

Table I. Bond Lengths for Isotetrahydroanemonin [a]

C(1)–C(2)	1.535 (8)	C(3)–C(5′)	1.533 (6)
C(2)–C(6)	1.518 (5)	C(5′)–C(4′)	1.516 (7)
C(6)–C(7)	1.504 (6)	C(4′)–C(3′)	1.511 (6)
C(7)–O(7)	1.198 (5)	C(3′)–O(3′)	1.191 (5)
C(7)–O(8)	1.358 (9)	C(3′)–O(2′)	1.351 (4)
O(8)–C(1)	1.468 (5)	O(2′)–C(3)	1.447 (5)
C(1)–C(5)	1.532 (8)		
C(5)–C(4)	1.519 (7)		
C(4)–C(3)	1.529 (9)		
C(3)–C(2)	1.516 (10)		

[a] The standard deviations are in parentheses.

Table II. Bond Angles in Isotetrahydroanemonin [a]

γ-Lactone		Spiro-γ-lactone	
O(8)–C(1)–C(2)	108.4 (3)	O(2′)–C(3)–C(5′)	103.9 (3)
C(1)–C(2)–C(6)	104.3 (3)	C(5′)–C(4′)–C(3′)	104.1 (3)
C(6)–C(7)–O(8)	110.3 (3)	C(4′)–C(3′)–O(2′)	109.5 (3)
C(6)–C(7)–O(7)	128.8 (4)	C(4′)–C(3′)–O(3′)	129.3 (3)
O(7)–C(7)–O(8)	120.9 (4)	O(3′)–C(3′)–O(2′)	121.2 (4)
C(7)–O(8)–C(1)	111.3 (3)	C(3′)–O(2′)–C(3)	111.5 (3)
C(1)–C(2)–C(3)	104.5 (3)	C(3)–C(4)–C(5)	103.5 (3)
C(3)–C(2)–C(6)	116.8 (3)	C(4)–C(5)–C(1)	105.4 (3)
C(2)–C(3)–C(4)	103.3 (3)	C(5)–C(1)–C(2)	106.8 (3)
C(2)–C(3)–C(5′)	123.0 (3)	C(5)–C(1)–O(8)	111.0 (3)
C(2)–C(3)–O(2′)	107.8 (3)		
O(2′)–C(3)–C(4)	106.9 (3)		
C(5′)–C(3)–C(4)	117.4 (3)		

[a] The standard deviations are in parentheses.

fused γ-lactone rings of isotetrahydroanemonin with those of other γ-lactones.

The bond lengths in the spiro and cis fused γ-lactones of **15** are within two standard deviations of each other except for the C–OCO distance [O(8)–C(1)] which is 1.468 in the cis fused γ-lactone and 1.447 [O(2′)–C(3)] in the spiro fused γ-lactone. This shortening may be related to the spiro linkage at C(3); however, this bond length of 1.447 is not abnormally short compared to other γ-lactones (Table III).

The bond angles in **15** conform to previously observed patterns (Table III). The ring angles at C_A, C_B, and C_D are considerably less than tetrahedral. The bond angles about the carboxyl carbon atom C_C conform to a pattern previously noted for carboxylic acids.[18,25] In this pattern the $C_AC_CO_L$ angle is approximately tetrahedral while the $C_AC_CO_C$ and $O_LC_CO_C$ angles are considerably greater than 120°.

Analysis of the best planes through various groups of atoms in **15** (see Table IV of supplementary material) showed that

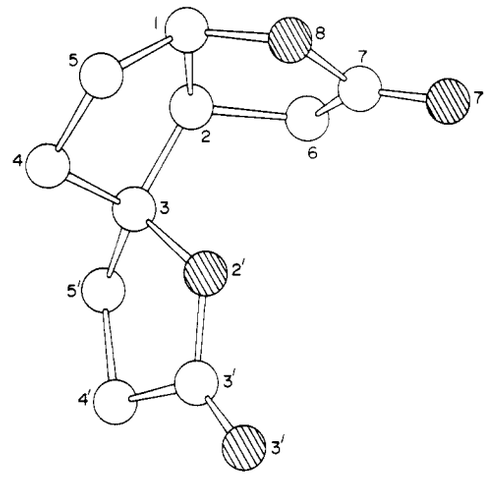


Figure 1. Isotetrahydroanemonin (**15**) with atomic numbering used in this paper. The open circles designate carbon atoms and the shaded circles designate oxygen atoms.

all three five-membered rings approximate an envelope conformation. The cis fused lactone ring adopts an approximate envelope conformation with C(2) deviating −0.330 Å from the best plane through atoms C(1), C(6), C(7), and O(8). The spiro fused γ-lactone is also in an approximate envelope conformation but C(5′) deviates only 0.210 Å from the best plane through C(3), C(4′), C(3′), and O(2′).

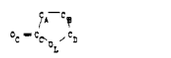
For the cyclopentane ring containing atoms C(1), C(2), C(3), C(4), and C(5) the equations of all possible planes containing three and four atoms were calculated. Only one of the best planes containing four atoms had the component atoms less than 0.1 Å from the plane. Atom C(3) deviates −0.590 Å from the best plane through C(1), C(2), C(4), and C(5) suggesting that this ring also adopts an envelope conformation.

For the three atom planes, the two atoms not included in the plane were usually on the same side of the plane ruling out a half-chair conformation. However, in one case atom C(3) was −0.413 Å below and C(4) was 0.230 Å above the plane through atoms C(1), C(2), and C(5). Therefore, this ring could also be considered to be in the half-chair conformation.

The observation that the γ-lactone rings in **15** approximate an envelope conformation is consistent with the conformation of the γ-lactone rings in dihydropulchellin,[27] the dimer of ascorbic acid and related compounds,[23] isophotosantonic lactone,[18] himbacine,[24] geigerin,[25] and α-santonin.[20]

Crystal Packing of Isotetrahydroanemonin (15). Figure 2 (supplementary material) shows a stereoscopic view of the crystal packing of I, and Table V (supplementary material) lists the important intermolecular contacts. The packing is

Table III. Comparison of bond lengths and angles in saturated γ-lactones.



	This work														
	cis fused γ-lactone	spiro fused γ-lactone	Rearr. prdt.[15] of androstane	Glucurono[16] lactone	Clactd[17] lactone	Isophotosantonic[18] lactone	Dihydrogaillardin[19]	α-Santonin[20]	butyrolactone[21]	Gulonolactone[22]	Ascorbic acid[23] Dimer	Himbacine[24]	Geigerin[25]	bromoisosteunli[26]	dihydropulchellin[27]
C_AC_B	1.518(5)	1.516(7)	1.56	1.526	1.519	1.44	1.50	1.51	1.51	1.531	1.554	1.56	1.54	1.51	1.54
C_BC_D	1.535(8)	1.533(6)	1.57	1.533	1.546	1.56	1.56	1.49	1.54	1.525	1.517	1.58	1.57	1.54	1.51
C_AC_C	1.504(6)	1.511(6)	1.54	1.511	1.522	1.55	1.51	1.45	1.44	1.503	1.499	1.50	1.54	1.51	1.51
C_CO_C	1.198(5)	1.191(5)	1.18	1.215	1.20	1.26	1.25	1.24	1.24	1.194	1.200	1.22	1.24	1.25	1.22
C_CO_L	1.358(9)	1.351(4)	1.32	1.340	1.36	1.37	1.38	1.34	1.36	1.346	1.338	1.38	1.35	1.32	1.36
C_DO_L	1.468(5)	1.447(5)	1.52	1.475	1.46	1.39	1.49	1.45	1.45	1.472	1.448	1.46	1.45	1.50	1.46
$C_AC_CO_L$	110.3(3)	109.5(3)	113.4	111.0	109.5	109	114	105	112	109.2	112.8	109.5	113	114.1	110.0
$C_AC_CO_C$	128.8(4)	129.3(3)	128.2	128.9	128.5	133	124	123	131	126.5	125.5	128.7	124	124.8	123.1
$O_LC_CO_C$	124.9(4)	121.2(4)	118.4	120.0	121.6	118	122	116	117	128.4	121.7	121.4	124	120.9	120.9
$C_AO_LC_D$	111.3(3)	111.5(3)	111.8	111.0	109.3	109	110	108	109	110.2	111.3	110.4	114	106.3	110.0
$O_LC_DC_B$	104.8(3)	103.9(3)	104.6	106.2	103.0	102	102	104	108	103.6	106.4	103.2	101	103.0	104.2
$C_DC_BC_A$	104.3(3)	103.6(3)	106.5	104.9	100.3	103	103	99	101	100.9	105.5	100.1	101	105.9	100.0
$C_BC_AC_C$	104.3(3)	104.1(3)	103.1	104.0	102.2	100	100	102	107	101.8	102.5	101.6	99	100.1	103.2
type of ring fusion	cis	spiro	cis	cis	cis	trans	trans	trans	none	none	cis	cis	cis	trans	cis
estimated angle strain energy (kcal/mole)	2.40	2.52	1.69	1.92	3.70	4.97 [b]	2.87	6.38 [c]	2.98	3.44	1.42	3.57	3.95	2.58	3.52

[a] Errors in these values are less than ± 1.0 kcal/mole unless noted.

[b] Error estimated to be ± 1.3 kcal/mole.

[c] Error estimated to be ± 2.9 kcal/mole.

Table VII. Bond Lengths in Di-α-methylene Lactone 4b [a]

O(1)–C(2)	1.36 (1)	O(7)–C(8)	1.35 (2)
C(2)–O(15)	1.19 (2)	C(8)–O(16)	1.20 (3)
C(2)–C(3)	1.48 (1)	C(8)–C(9)	1.50 (1)
C(3)–C(13)	1.32 (2)	C(9)–C(14)	1.34 (3)
C(3)–C(4)	1.49 (2)	C(9)–C(10)	1.49 (2)
C(4)–C(5)	1.54 (1)	C(10)–C(6)	1.54 (4)
C(5)–O(1)	1.47 (2)	C(6)–O(7)	1.45 (3)
C(5)–C(12)	1.54 (1)		
C(12)–C(11)	1.55 (3)		
C(6)–C(11)	1.53 (1)		
C(5)–C(6)	1.54 (2)		

[a] Standard deviations are in parentheses.

Table VIII. Bond Angles in the Di-α-methylene Lactone 4b [a]

C(5)–O(1)–C(2)	111.3 (3)	C(6)–O(7)–C(8)	110.7 (3)
O(1)–C(2)–C(3)	108.7 (3)	O(7)–C(8)–C(9)	109.6 (4)
O(1)–C(2)–O(15)	121.4 (4)	O(7)–C(8)–O(16)	122.1 (4)
O(15)–C(2)–C(3)	129.9 (5)	O(16)–C(8)–C(9)	128.2 (5)
C(2)–C(3)–C(4)	107.7 (4)	C(8)–C(9)–C(10)	106.5 (4)
C(2)–C(3)–C(13)	121.2 (5)	C(8)–C(9)–C(14)	122.0 (4)
C(13)–C(3)–C(4)	131.1 (5)	C(14)–C(9)–C(10)	131.5 (4)
C(3)–C(4)–C(5)	102.7 (4)	C(9)–C(10)–C(6)	103.0 (4)
C(4)–C(5)–O(1)	105.2 (3)	C(10)–C(6)–O(7)	105.5 (3)
C(4)–C(5)–C(6)	123.0 (4)	C(10)–C(6)–C(5)	116.2 (4)
C(4)–C(5)–C(12)	121.0 (4)	C(10)–C(6)–C(11)	116.8 (4)
C(6)–C(5)–O(1)	108.7 (3)	C(5)–C(6)–O(7)	114.3 (4)
C(6)–C(5)–C(12)	88.1 (4)	C(5)–C(6)–C(11)	89.5 (4)
C(12)–C(5)–O(1)	109.8 (4)	C(11)–C(6)–O(7)	114.6 (4)
C(5)–C(12)–C(11)	89.0 (4)		
C(6)–C(11)–C(12)	87.9 (4)		

[a] Standard deviations are in parentheses.

controlled by O···C and O···O interactions with only two observed C···C intermolecular contacts of less than 3.70 Å; the second shortest intermolecular contact involves a C=O···C=O contact of 3.335 Å. Table VI (supplementary material) shows the parameters involved in these contacts according to the conventions of Burgi, Dunitz, and Shefter.[28] Our parameters are consistent with those tabulated by these workers who related these contacts to chemical reaction paths. The C=O···C=O distance of 3.335 is among the larger intermolecular distances tabulated by these workers.

Structure of 1,7-Dioxadispiro[4.0.4.2]dodeca-3,9-dimethylene-2,8-dione (4b). Tables VII and VIII show bond lengths and angles for **4b** and Figure 3 shows the structure and

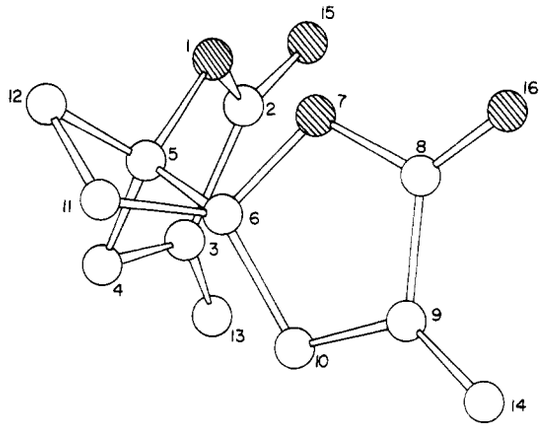


Figure 3. Di-α-methyleneanemonin (**4b**) with atomic numbering used in this paper. The open circles designate carbon atoms and the shaded circles designate oxygen atoms.

atomic numbering. The corresponding bond lengths in the two α-methylene-γ-lactones are the same within 2σ and the angles within 3σ. Table IX compares the bond lengths and angles in the spiro fused α-methylene-γ-lactones to cis and trans fused α-methylene-γ-lactones. The observed parameters for **4b** are consistent with these parameters.

The corresponding bond angles about the spiro carbon atoms C(5) and C(6) are quite different. The biggest differences are between C(4)–C(5)–C(6), 123.0°, and C(10)–C(6)–C(5), 116.2; between C(4)–C(5)–C(12), 121.0°, and C(10)–C(6)–C(11), 116.8°; between C(6)–C(5)–O(1), 108.7°, and C(5)–C(6)–O(7), 114.3°; and between C(12)–C(5)–O(1), 109.8°, and C(11)–C(6)–O(7), 114.6°. These differences serve to skew the cis lactone rings and apparently avoid close intramolecular ring–ring interactions. The only intramolecular ring–ring contact less than the sum of the van der Waals radii of the included atoms was O(1)···O(3) of 2.68 Å.

In contrast, the bond angles about the spiro carbon atom in the parent compound anemonin are much more alike with the biggest differences between corresponding angles being 3.6 and 2.4°.[38] These differences may be due, in part, to the fact that anemonin has trans rather than cis lactone rings.

The cis lactone rings in **4b** are also skewed by ring puckering in the cyclobutane ring. The plane through C(6), C(5), C(12) makes an angle of 152.9° with the plane through C(6), C(11), C(12). This angle is quite similar to that in anemonin (152°) and related compounds.[38]

Least-squares best planes calculations (Table X, supple-

Table IX. Comparison of bond lengths and angles in α-methylene-γ-lactones

	gaillardin[29]	vernolepin[30]	bromomexicanin[30]	bromohelenalin[31]	artesunin[32]	helenalin oxide[33]	berlandin[34]	parthenolin[35]	miscandenin[36]	autumnolide	methylene anemonin (this work) Mol I	methylene anemonin (this work) Mol II
C_A–C_D	1.51	1.54	1.51	1.51	1.50	1.500	1.508	1.481	1.491	1.511	1.49	1.49
C_B–C_E	1.51	1.56	1.56	1.54	1.52	1.530	1.547	1.563	1.514	1.564	1.54	1.537
C_A–C_C	1.45	1.40	1.55	1.52	1.48	1.486	1.503	1.491	1.484	1.479	1.50	1.48
C_C–O_C	1.22	1.21	1.22	1.21	1.21	1.211	1.201	1.167	1.193	1.198	1.20	1.19
O_C–O_L	1.30	1.38	1.33	1.33	1.38	1.349	1.372	1.351	1.363	1.345	1.35	1.358
O_D–O_L	1.52	1.44	1.47	1.50	1.48	1.475	1.480	1.447	1.459	1.458	1.45	1.47
C_A–C_E	1.40	1.10	1.34	1.31	1.31,	1.346	1.308	1.324	1.32-	1.317	1.34	1.32
$C_AC_DO_L$	112.3	116	109.3	110.1	108.6	109.0	108.4	106.7	108.3	109.3	109.6	108.7
$C_AC_CO_C$	129.0	128	126.3	126.8	131.2	129.2	129.7	129.6	130.6	128.9	128.2	129.9
$O_LC_CO_C$	118.6	116	124.3	122.9	120.1	121.8	121.8	123.6	121.1	121.8	122.1	121.4
$C_DO_LC_D$	106.6	103	110.5	110.0	108.3	110.4	108.6	NA	108.4	112.6	110.9	111.3
$O_LC_DC_B$	103.5	105	105.0	100.5	100.2	105.5	100.8	105.4	102.8	105.8	104.5	105.2
$C_DC_BC_A$	102.4	97	101.7	102.3	101.4	102.4	100.2	102.7	99.6	102.8	103.0	102.9
$C_BC_AC_C$	106.9	105	105.8	102.7	103.4	107.8	104.1	110.1	104.1	106.9	106.5	107.7
$C_BC_AC_E$	131.6	129	134.0	134.8	133.8	129.8	133.0	128.7	132.7	129.9	131.5	131.1
$C_CC_AC_E$	122.2	109	120.5	123.0	123.0	122.4	122.8	120.9	123.2	121.2	122.0	121.2
type of ring fusion	trans	trans	cis	cis	spiro-trans	cis	trans	cis	trans	cis	spiro	spiro
estimated angle strain[a] (kcal/mole)	4.72	8.8[b]	4.95	6.71	7.61	3.85	6.99	---	6.89	3.15	3.97	4.04

[a] Errors in these values are less than ± 1.0 kcal/mole unless noted.

[b] Error estimated to be ± 2.0 kcal/mole.

mentary material) indicated that one of the spiro fused α-methylene-γ-lactone rings of **4b** was in an approximate envelope conformation and one in a half-chair conformation. The γ-lactone ring incorporating O(1), C(2), C(3), C(4), and C(5) approximated an envelope conformation with C(4) deviating 0.310 Å from the best plane through C(2), C(3), O(1) while C(5) only deviated −0.05 Å from this plane. There is a small probability that the atoms O(1), C(2), C(3), C(5), and O(15) form a plane. An envelope conformation was also found for the α-methylene-γ-lactone ring in gaillardin,[19] bromomexicanin,[30] and miscandenin.[36]

The α-methylene-γ-lactone ring incorporating C(6), O(7), C(8), C(9), and C(10) was in a half-chair conformation with C(9) −0.184 Å and C(6) 0.164 Å from the plane through O(7), C(8), and C(9). Similar half-chair conformations were found for the α-methylene-γ-lactone rings in vernolepin,[29] berlandin,[34] and helenalin oxide.[33]

The dihedral angles about the C=C–C=O group are 13.1 and 8.1° in the two α-methylene-γ-lactone rings of **4b** (Table XI, supplementary material). These are consistent with the corresponding dihedral angle in the other α-methylene-γ-lactones including bromomexicanin (−9°),[30] vernolepin (−10°),[29] berlandin (−19°),[34] helenalin oxide (−7°),[33] parthemollin (0°),[35] and miscandenin (23°).[36]

The angles C(14)–C(9)–C(8)–O(16) and C(9)–C(10)–C(6)–O(7) differ by a factor of 2.62 while the corresponding angles C(13)–C(3)–C(2)–O(15) and C(3)–C(4)–C(5)–O(1) in the other ring differ by a factor of 1.5. Both of these factors loosely fit the suggestion of Sim and Cox[36] that these angles should differ by a factor of 2.

Crystal Packing of the Di-α-methylene Lactone 4b. The packing of **4b** is controlled by C···O and O···O interactions (see Table XII and Figure 4, supplementary material). There is a short C=O···C=O contact of 3.08 Å. Dunitz and co-workers have tabulated the structural parameters for short C=O··· C=O intermolecular contacts[28] and Table VI (supplementary material) defines these parameters and shows their value for **4b.** The observed parameters for **4b** are consistent with those reported for other compounds. The small displacement of C(2) from the R_X, R_Y, O plane is probably due to the interaction of this atom with an oxygen atom on each side of the plane.

Strain Energy in γ-Lactones. γ-Lactones possess angle strain energy due to the small bond angles at the sp^2 carbon atom and sp^3 carbon atoms required by the five-membered ring. In order to estimate this angle strain energy the parameters in Table XIII (supplementary material) were applied to the equation

$$\text{angle strain energy (kcal/mol)} = \frac{k}{2}(\theta - \theta_0)^2$$

where θ_0 = equilibrium bond angle

θ = bond angle observed in the crystal

$\frac{k}{2}$ = force constant in kcal/mol deg^2

The errors in the calculated strain energies depend on the estimated standard deviations of the bond angles and these vary from study to study. However, using representative compounds we found that the approximate error in strain energies was ±2.9 kcal/mol for esd's of 3°, ±1.3 kcal/mol for esd's of 2°, and ±0.9 kcal/mol for esd's of 1.5°. The errors in the calculated strain energies (Tables III and IX) should be assumed to be less than 1.0 kcal/mol unless otherwise noted.

Table III tabulates the bond angles and strain energies in saturated γ-lactones. In general, the strain energies of the trans fused γ-lactones are greater than those of their cis fused counterparts. This is consistent with White and Sim's detailed study of the santonins.[39] However, there are some notable exceptions to this generalization. The trans fused γ-lactone rings in dihydrogallardin (2.87 kcal/mol) and bromoisotenulin (2.58) have lower calculated strain energies than the cis fused lactone rings of dihydropulchellin (3.62), gulonolactone (3.44), himbicaine (3.57), geigerin (3.28), and galactolactone (3.70). Nevertheless, in this series, the two γ-lactone rings with the highest calculated strain energy were trans fused. The spiro fused γ-lactone ring in **15** had about the same strain energy as the cis fused lactones.

The case is more clear-cut among the α-methylene-γ-lactones where of the ten compounds (five trans fused and five cis fused) studied (Table IX) the four most strained rings all had trans fusion. The only trans fused α-methylene-γ-lactone ring less strained than all of the cis fused lactones was that in gaillardin. The spiro fused α-methylene-γ-lactone ring had about the same angle strain energy as the cis fused lactones.

It is striking that the order of estimated angle strain energies (Table IX) for the four lactones vernolepin (8.89 kcal/mol), bromohelenalin (6.71), bromomexicanin (4.95), and gaillardin (4.72) parallels their rate of reaction with cysteine (vernolepin, 15 000 L M^{-1} min^{-1}; helenalin, 1375; mexicanin, 417; gaillardin, 280).[1] Unfortunately, there are no crystallographic data for any of the other lactones for which rates of cysteine addition are known. Research is underway in our laboratory to further explore this relationship.

Experimental Section

Melting points were taken in a capillary tube and are uncorrected. UV spectra were determined in 95% EtOH using a Cary Model 17 spectrophotometer. IR spectra were determined in KBr using a Beckman Model 33 recording spectrophotometer. NMR spectra were recorded either on a Varian Model EM-360 or A-60 or JEOL PFT-100 spectrometer; chemical shifts were recorded in parts per million downfield from Me_4Si. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU 6-A or a Consolidated Model 21-110-B mass spectrometer. High-resolution mass spectral data were obtained on the CEC 21-110.

Anemonin (2). A solution of α-angelicalactone (9.8 g, 0.1 mol) in 50 mL of dry CS_2 was cooled to a slurry with dry ice–acetone. Bromine in CS_2 (1 mL of Br_2 per 10 mL of CS_2) was added dropwise with efficient stirring until the orange color persisted. The mixture was allowed to warm to room temperature and stirred until the orange color disappeared. The solvent was evaporated under vacuum at room temperature, and the residue was dissolved in dry toluene (250 mL). The solution was cooled with an ice–H_2O bath, dry quinoline (19.35 g, 0.15 mol) and a little methylhydroquinone were added, and the solution was stirred at room temperature for 35 h.

The formed salt was filtered under anhydrous conditions, 7.75 g (0.06 mol) of quinoline added, and the mixture refluxed gently for 1 h. After cooling to room temperature the mixture was filtered, and the solid was combined with the previous salt and treated with CH_2Cl_2. The CH_2Cl_2 extracts were washed well with dilute HCl and H_2O, dried (Na_2SO_4), and concentrated. The toluene filtrate was also washed well with dilute HCl and H_2O, dried (Na_2SO_4), and without concentration was applied to a silica gel column followed by the CH_2Cl_2 extracts. The column was washed first with C_6H_6 and then eluted with CH_2Cl_2 to give 3 g (31%) of anemonin.

***cis*- and *trans*-1,7-Dioxadispiro[4.0.4.2]dodeca-3,9-dimethylene-2,8-dione (4a, 4b).** About 1 mL of a solution of cyclobutane-1,2-dione[13] (2 g, 0.024 mol), purified by sublimation, and ethyl α-(bromomethyl)acrylate[14] (11.6 g, 0.06 mol) in 40 mL of dry THF was added to activated Zn (3.3 g, 0.05 g-atom, 20 mesh) under dry N_2. The reaction was started by warming the flask, and the solution was added dropwise to keep the temperature of the reaction at about 45 °C. Stirring was continued for another 2.5 h at 45 °C (H_2O bath), and the mixture was poured into ice-cold dilute H_2SO_4 solution (1–2%) and extracted with EtOAc. The ethyl acetate layer was washed with a cold, dilute solution of aqueous $NaHCO_3$, dried (Na_2SO_4), concentrated, and filtered through Florisil.

The obtained syrup consisted of five major products (TLC, silica gel, EtOAc–Et_2O–hexane, 1:1:1). The trans product (**4a**) (second highest in R_f) was purified by TLC on silica gel, F-254 (EtOAc–Et_2O–hexane, 1:2:2; three to four runs), extraction with EtOAc to give

230 mg (4.4%): mp 105–115 °C; IR 1755 (C=O), 1655 cm^{-1} (C=C); NMR (JEOL PFT-100, $CDCl_3$) δ 6.24 (t, 2 H, J = 1.5 Hz), 5.72 (t, 2 H, J = 1.5 H), quartet of triplets, centered at 3.22 (4 H, t's, J = 1.5 Hz), 2.11 (s, 4 H); UV λ_{max} 210 nm (ε 18 985); high-resolution mass spectrum m/e 192.046 (calcd for $C_{12}H_{12}O_4$–C_2H_4, 192.042).

The cis product (**4b**) (lowest R_f) was purified as above with a mixture of EtOAc–Et_2O–hexane in 1:1:1 ratio to give 250 mg (4.8%): mp 102 °C (from EtOAc) with polymerization; IR 1760 (C=O), 1670 cm^{-1} (C=C); NMR (JEOL PFT-100, $CDCl_3$) δ 6.23 (t, 2 H, J = 1.5 Hz), 5.69 (t, 2 H, J = 1.5 Hz), quartet of triplets, centered at 3.00 (4 H, t's, J = 1.5 Hz), symmetrical multiplet centered at 2.32 (4 H); UV λ_{max} 210 nm (ε 16 194); high-resolution mass spectrum m/e 192.039 (calcd for $C_{12}H_{12}O_4$–C_2H_4, 192.042).

Monobromoanemonin (11). Tetrabromoanemonin was prepared as described in the literature.[12] It was obtained as powdery white crystals (55%) by the addition of ether to the filtered reaction solution.

The mother liquor was then concentrated and chromatographed on silica gel plates (F-254) (Et_2O–hexane–EtOAc, 1:1:2) to give dibromoanemonin (**12**), 6.6% (for analytical data, see the following experiment), and monobromoanemonin (**11**), 20%: mp 117–118 °C from $CHCl_3$–Et_2O; IR 1780 (C=O), 1600 cm^{-1} (C=C); NMR (Varian EM 360, $CDCl_3$) δ 7.90 (s, 1 H), 7.80 (d, 1 H, J = 4 Hz), 6.16 (d, 1 H, J = 4 Hz), 2.50 (s, 4 H); UV λ_{max} 220 nm (ε 17 030). Anal. Calcd for $C_{10}H_7BrO_4$: C, 44.28; H, 2.58; Br, 29.52. Found: C, 44.10; H, 2.82; Br, 29.30.

Dibromoanemonin (12). To a solution of tetrabromoanemonin (2.56 g, 0.005 mol) in 200 mL of dry benzene, dry quinoline (1.5 g, 0.0116 mol) was added, and the reaction mixture was stirred overnight. After dilution with an equal volume of C_6H_6, the mixture was washed well with dilute HCl solution and H_2O and dried (Na_2SO_4), and the solvent was evaporated. Crystallization from $CHCl_3$–Et_2O gave 1.485 g (86%) of dibromoanemonin: mp 130–132 °C; IR 1780 (C=O), 1600 cm^{-1} (C=C); NMR (Varian EM 360, $CDCl_3$) δ 7.92 (s, 2 H), 2.56 (s, 4 H); UV λ_{max} 230 nm (ε 22 115). Anal. Calcd for $C_{10}H_6Br_2O_4$: C, 34.28; H, 1.71; Br, 45.71. Found: C, 34.41; H, 1.92; Br, 45.70.

Decane-4,7-dione-1,10-dioic Acid Dimethyl Ester (13). A mixture of 378 mg (1.97 mmol) of anemonin and 41.2 mg (1.09 mmol) of sodium borohydride was stirred at room temperature for 65 min in 50 mL of methanol. Methanol was then removed at reduced pressure, 50 mL of water was added, and the solution was extracted with 5 × 30 mL of ethyl acetate. Drying over anhydrous sodium sulfate, filtration, and removal of solvent from the filtrate gave 211 mg of solid shown by TLC to contain unreacted anemonin and one other major component. Trituration with 2 × 5 mL of carbon tetrachloride and preparative chromatography (silica gel precoat) of 16 mg of the resulting solid gave 7.7 mg of pure ester: mp 95.0–95.8 °C;[40] NMR ($CDCl_3$) δ 3.55 (s, 6 H, $-OCH_3$), 2.6 (m, 12 H, $-CH_2-$); IR ($CHCl_3$) 1750 and 1730 cm^{-1} (ester and ketone C=O).

Synthesis of 4,7-Dihydroxy-1,10-decanedioic Acid γ-Dilactone (14). To a stirred solution of 501 mg (2.6 mmol) of anemonin in 50 mL of absolute methanol at room temperature was added five 100-mg portions of sodium borohydride at 20-min intervals. After addition of 50 mL of water the pH was adjusted to ≈3 by dropwise addition of concentrated hydrochloric acid, the methanol was removed at reduced pressure, and the aqueous solution was extracted with 2 × 75 mL plus 2 × 50 mL of ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous sodium sulfate and filtered, and the ethyl acetate was removed at reduced pressure. The 544 mg of material so obtained was adsorbed with chloroform on 2.5 g of silica gel (Woelm dry column grade; activity III/30 mm) and placed on a 0.625 × 13.5 in. nylon column prepared from the same material. After eluting with chloroform until 50 mL of chloroform was collected, the column was cut into three portions. Each portion was eluted with 200 proof ethanol, filtered, and concentrated. This material yielded 74 mg of stationary material, 51 mg of low R_f material (first 1.5 in. of column), and 2.50 mg of crude product (remainder of column). The crude product was triturated with ether and the white solid obtained was recrystallized twice from benzene to give 26 mg of white solid: mp 103–104 °C; mp of an authentic sample (supplied by Rohm and Haas Co.)[41] 109–111 °C; mmp 106–108 °C. The IR, NMR, and mass spectral data of the recrystallized sample were identical with those of the authentic sample: IR ($CHCl_3$), 1790 cm^{-1} (γ-lactone C=O); NMR ($CDCl_3$) δ 4.5 (m, 2 H, $-OCH_2-$), 1.6–2.8 (m, 12 H, $-CH_2-$); MS m/e 198 (M^+, 0.001), 170 (0.2), 114 (0.6), 98 (0.2), 88 (1.0), 55 (0.2), 54 (0.2).

7-Oxo-8-oxabicyclo[3.3.0]octane-3-spiro[2-oxa-3′-oxocyclopentane] (15). To 500 mg (2.6 mmol) of anemonin was added 20 mL of a 1:1 mixture of water and 200 proof ethanol. The stirred solution was heated to reflux and acidified by addition of concentrated acetic acid. At 10-min intervals, 2.5-g portions of 3% sodium amalgam[42] and 0.2 mL of concentrated acetic acid were added to the refluxing solution. After a total of 250 g (0.33 mol) of 3% sodium amalgam had been added, 50 mL of distilled water was poured into the solution and concentrated hydrochloric acid was added to pH ≈3. Ethanol was removed at reduced pressure, and the remaining aqueous solution was extracted with 4 × 75 mL of ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous sodium sulfate, the sodium sulfate was removed by filtration, and the ethyl acetate was removed at reduced pressure to give 421 mg of oil.

The oil was adsorbed with chloroform on 2 g of silica gel (Woelm dry column grade; activity III/30 mm) which was placed on a 0.625 × 14.5 in. nylon column of the same material. After eluting with chloroform until 15 mL of chloroform was collected, the column was cut into four portions. Each portion was eluted with 200 proof ethanol, filtered, and concentrated. From the second portion of the column (first 2 in. after stationary phase) was obtained 133 mg of crude **15**. Recrystallization from benzene gave 25 mg of clear, colorless crystals: mp 146–148 °C; NMR ($CDCl_3$) δ 5.0 (m, 1 H, –OCH–), 1.5–3.0 (m, 11 H, $-CH_2-$ and –CH–); IR ($CHCl_3$) 1775 cm^{-1} (γ-lactone C=O); MS 196 (m/e of M^+ 196.0730 obsd, 196.0736 calcd).

Crystal Data for Isotetrahydroanemonin (15). Least-squares analysis[45] of the position of 15 independent hand centered reflections gave a = 7.258 (4) Å, b = 5.821 (1), c = 22.285 (2), β = 85.63 (1)°, V = 938.78 Å^3, Z = 4, ρ_{calcd} = 1.39 g/cm^3, mol wt for $C_{10}H_{12}O_4$ 196.07, $F(000)$ = 416, μ = 6.61 (Cu Kα, λ = 1.5418), space group $P2_1/c$.

Data Collection for Isotetrahydroanemonin (15). Data were collected on a Picker four-circle diffractometer (card-driven) using Ni-filtered Cu Kα radiation and a scintillation detector. A θ–2θ scan of 2.4° was applied with a scan speed of 60 s/deg. Backgrounds were counted for 20 s at each end of the scan range. The reciprocal region $\bar{h}\bar{k}l$ and $\bar{h}k\bar{l}$ was explored to a 2θ maximum of 130°. Three standards were measured after each group of 60 reflections. The intensity of the standards remained essentially constant during the data collection. There were 1595 reflections out of which 1340 satisfied the condition $F_o \geq 3\sigma(F_o)$ and were considered observed. No absorption or extinction correction was made.

Structure Determination of 15. The structure was determined by direct methods. An E map based on the phases obtained from the programs Singen and Phase[43] revealed the positions of all nonhydrogen atoms. Refinement of these positions first with isotropic and then with ansiotropic temperature factors proceeded smoothly to an R factor of 0.109. A difference Fourier map revealed the position of all hydrogen atoms. Further refinement of these atomic positions using anisotropic temperature factors for the nonhydrogen atoms and isotropic temperature factors for the hydrogen atoms proceeded smoothly to a final R factor of 0.061 after three reflections (0,0,−6; −1,0,2; and 0,−1,−1) were omitted because they apparently suffered from extinction.

Crystal Data for the Di-α-methylenelactone 4b. Least-squares analysis[43] of the positions of 15 hand centered reflections gave a = 11.300(5) Å, b = 7.915 (2), c = 11.903 (5), β = 92.14 (5), V = 1063.86 Å^3, Z = 4, ρ_{calcd} = 1.37 g/cm^3, mol wt for $C_{12}H_{12}O_4$ 220.2, $F(000)$ = 464, μ = 6.38 (Cu Kα, λ = 1.5418), space group $P2_1/c$.

Data Collection for 4b. Data were collected as before except that a θ–2θ scan speed of 30 s/deg was used. Backgrounds were counted for 10 s at each end of the scan range. The reciprocal region $\bar{h}\bar{k}l$ and $\bar{h}kl$ was explored to a 2θ maximum of 130°. Three standards were measured after each group of 60 reflections. The intensity of two of these standards remained essentially constant during the data collection while the intensity of the third dropped more or less linearly to approximately 80% of its original value. There were 1952 reflections out of which 1545 satisfied the condition $F \geq 3\sigma(F_o)$ and were considered observed. No absorption or extinction correction was made.

Structure Determination of 4b. The structure was determined as before and an E map revealed the positions of all nonhydrogen atoms except for one carbon atom. Refinement of these atomic positions proceeded smoothly to a final R factor of 0.081 after six reflections (−1,−2,0; −3,−2,−1; 0,−2,0; 0,0,−2; −1,0,−2; and −3,0,0) were omitted because they apparently suffered from extinction.

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Registry No.—**2,** 508-44-1; **4a,** 61597-44-2; **4b,** 61597-45-3; **10,** 61597-46-4; **11,** 61597-47-5; **12,** 61597-48-6; **13,** 61597-49-7; **14,** 58936-17-7; **15,** 61597-50-0; cyclobutane-1,2-dione, 33689-28-0; ethyl α-(bromomethyl)acrylate, 17435-72-2.

Supplementary Material Available. (1) The final atomic positions and temperature factors for isotetrahydroanemonin (**15**), and the final atomic positions and temperature factors for di-α-methyleneanemonin (**4b**) (Tables 1–4); (2) supplements to Tables I, II, VII, and VIII, which list the bond lengths and angles involving hydrogen atoms in **15** and **4b**; (3) Tables IV, V, VI, VII, VIII, X, XI, XII, and XIII, which are mentioned in the text; and (4) Figures 2, 4, 5, and 6 mentioned in the text (15 pages). Ordering information is given on any current masthead page.

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Synthesis of ω-Bromo Ketones[1]

Herbert O. House,* Chia-Yeh Chu, William V. Phillips, Trevor S. B. Sayer, and Cheuk-Chung Yau

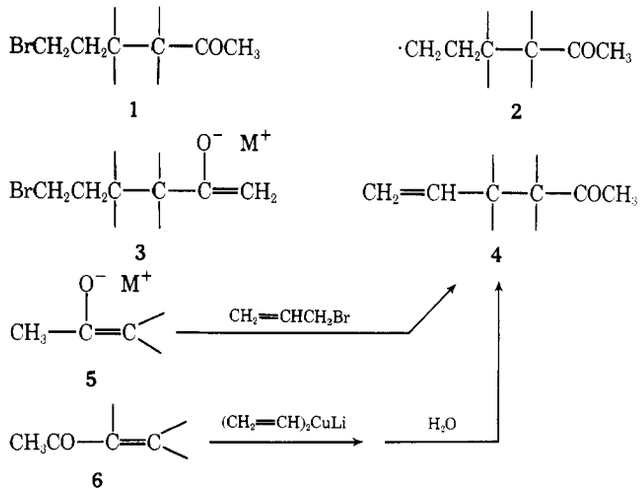
School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

Received October 20, 1976

Various methyl ketones **8**, **9**, **21**, **24**, **26**, **27**, **34**, and **54** containing terminal vinyl groups have been synthesized by regiospecific alkylations of metal enolates with allyl bromide, by the conjugate addition of $(CH_2{=}CH)_2CuLi$ or $CH_2{=}CHMgBr$ with Me_2SCuBr as a catalyst to enones, and by other procedures. The light-catalyzed radical-chain addition of HBr in pentane solution to these olefinic ketones constituted an efficient method for the synthesis of ω-bromo ketones **40–47** and **55**.

We were interested in preparing a group of ω-bromo ketones of the type **1** as substrates for use in studying the behavior of the related carbon radicals **2** and the enolate anions **3** (Scheme I). The vinyl ketones **4** appeared to be particularly attractive precursors for such bromo ketones **1** since these olefinic intermediates **4** were readily accessible either by regiospecific alkylation of a preformed lithium enolate **5** with an allyl halide[2] or by the conjugate addition of lithium divinylcuprate (or its equivalent) to an enone **6**.[3,4]

Scheme I



Preparation of the Olefinic Ketones. In the present study we utilized the ketone **7**, from a previously described[2a] regiospecific alkylation, and prepared the α-allyl ketones **8** and **9** by allylation of the enolates **9** and **10** (Scheme II). We also utilized a regiospecific alkylation of the enolate **10** to obtain precursors **16–18** of the bromo ketone **19**, a lower homologue of the bromo ketone system **1**. The precursor **21** for a second lower homologue of the bromo ketone **1** was obtained by the previously described[5] reaction of the acid **20** with MeLi. To obtain a precursor for a higher homologue of the