Medium-Ring Systems. 6.[1] Synthesis and Isomerizations of Medium-Ring 3-Methylenecycloalkanones and 3-Methylcycloalkenones

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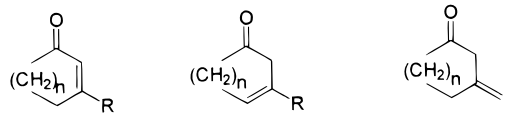
A series of 3-methylenecycloalkanones with ring sizes 7−10 has been prepared and subjected to base-catalyzed isomerization. Equilibrium between these exocyclic isomers and the corresponding 3-methyl-2-cycloalkenones and 3-methyl-3-cycloalkenones was reached in the 7- and 8-membered rings. The presence of the β-methyl shifts these equilibria toward the Δ^2 isomer in each ring relative to the unsubstituted compounds and to compounds containing electron-withdrawing groups at the β position. In the 9- and 10-membered rings, the Δ^2 isomers were isomerized to the Δ^3 isomers only with difficulty, and the reverse process could not be accomplished under the reaction conditions utilized. The ease of interconversion of the Δ^2 and Δ^3 isomers is directly related to the thermodynamic stability of planar conjugated dienes in medium ring carbocycles.

Previous work[1,2] studying the effect of electron-withdrawing substituents at carbon-3 on the equilibria of medium-ring (7−10-membered) 2-cycloalkenones (**1**) and 3-cycloalkenones (**2**) has shown that these substituents (R = CN, $COCH_3$, CH_2OAc) cause similar shifts in a given ring size toward the 3-cycloalkenones relative to the unsubstituted cases. As in the parent cycloalkenones,[3,4] the preference for the 3-cycloalkenone becomes more pronounced with increasing ring size. These results suggest that these substituents do not exert significant steric effects on these equilibria and that conjugative interactions in endocyclic dienolates and in 2-cycloalkenones become less effective as ring size increases.



1 **2** **3**

Since electron-withdrawing substituents might be expected to destabilize the enedione-type system in the 2-cycloalkenones,[1,2,5] it was desirable to prepare appropriate 3-alkylcycloalkenones. However, an additional complication in these systems is the possibility of an exocyclic enone isomer, the 3-methylenecycloalkanone **3**. Were the alkyl group to be substituted so that the 3-alkylidene isomer analogous to **3** would contain a trisubstituted double bond to match those found in the endocyclic isomers **1** and **2**, the exocyclic isomer could then exist as *E* and *Z* isomers. To avoid this complication, the decision was made to first study the system where the alkyl group is methyl, realizing that this would bias the equilibria in favor of the endocyclic isomers. Precedent from simple exocyclic and endocyclic double-bond isomers in medium ring systems[6,7] suggested a large preference would exist for the endocyclic systems. It therefore seemed necessary to synthesize the exocyclic isomers, the 3-methylenecycloalkanones (**3**), and to approach these equilibria from these isomers since they were predicted to be the least stable set.

Synthesis

The 8- and 9-membered 3-methylenecycloalkanones have been reported,[8] but only as minor byproducts of unrelated synthesis. We therefore embarked on a synthetic route whose key step would be an elimination reaction on an appropriately functionalized and protected derivative of a 3-(hydroxymethyl)cycloalkanol[9−11] or a 3-(hydroxymethyl)cycloalkanone.[12] After a wide variety[9−12] of leaving groups, protecting groups, and reaction conditions were probed with little success other than production of the desired protected alkene in moderate yield as part of a complex product mixture, elimination routes were abandoned.

The successful synthetic pathway (Scheme 1) was modeled on that of Harwood and Julia[13] for the conversion of α-pinene to β-pinene. Starting with the appropriate 3-carbomethoxycycloalkenone **4**,[1,9−11,14] the ketone was protected as the ethylene ketal **5** using PPTS[15] or p-TsOH.[16] The 9- and 10-membered rings could not be driven to completion (5−10% starting ketone) and were used without purification. Reduction of the unsaturated

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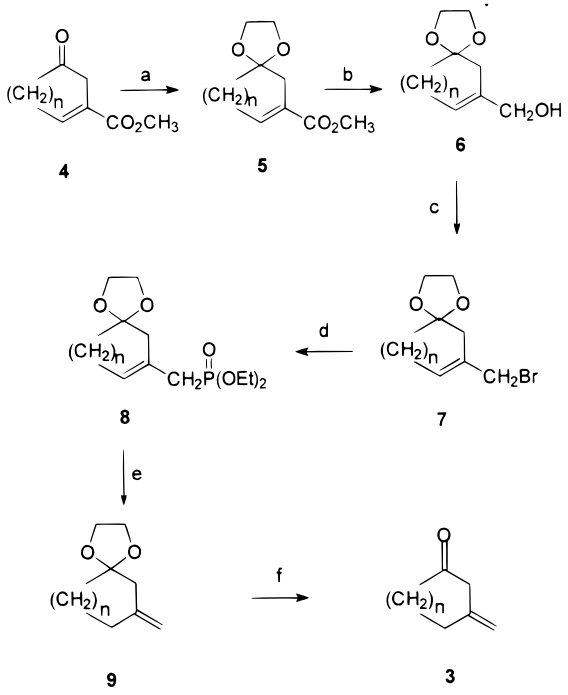
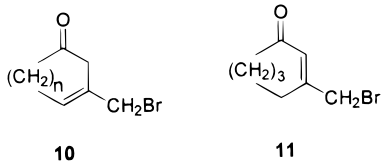
Scheme 1 [a]



[a] (a) $(HOCH_2)_2$, PPTS or p-TsOH, toluene; (b) DIBALH, CH_2Cl_2; (c) PBr_3, Et_2O; (d) $P(OEt)_3$, 85 °C; (e) $LiAlH_4$, Et_2O; (f) PPTS, wet acetone.

ester **5** to the allylic alcohol **6** was performed using alcoholic $LiAlH_4$[17] or, preferably, DIBALH[18] in CH_2Cl_2 or Et_2O. Bromination with PBr_3 in cold ether[19] afforded the apparently unstable allylic bromide **7** contaminated with the keto analog **10** (and, in the 7-membered ring, ketone **11**). Inconsistent yields and the apparent instability of the allylic bromides (**7**) were traced to overzealous cooling and the presence of phosphite ester intermediates.[20] Treatment of the reaction mixture with dry HBr gas until characteristic infrared P−O and P−H bands disappeared improved the yields and produced stable bromide products.



Allylic bromides **7** and **10** were subjected to the Arbuzov reaction[21] to produce allylic phosphonate ketals and ketones, which were chromatographed and reketalized to produce the desired phosphonates **8**. These phosphonates were then subjected to Harwood and Julia's[13] reductive fission/double-bond transposition conditions, producing high yields of crude ketals **9**. Careful hydrolysis of the ketal using PPTS in wet acetone[15] produced the desired 3-methylenecycloalkanones (**3**) after distillation or chromatography.

Table 1. Equilibrations of the 7- and 8-Membered Cycloalkenones[a]

ring size	starting isomer	temp (°C)	time (days)[b]	exo	Δ^2	Δ^3
7	exo (**3**, $n = 3$)	80	45 (7)		86	14
		80	25 (10)		86	14
7	Δ^2 (**1**, $n = 3$)	80	43 (14)		85	15
8	exo (**3**, $n = 4$)	35	55	1	66	33
8	Δ^2 (**1**, $n = 4$)	35	50		60	40
8	exo (**3**, $n = 4$)	80	24 (12)	2	36	63
		80	24 (12)	<2	36	63
		80	28 (21)	<2	33	66
		80	42 (19)	<2	34	65
8	Δ^2 (**1**, $n = 4$)	80	31 (20)	<1	37	63
8	1:1 Δ^2:Δ^3	80	27 (20)	<1	34	65
8	exo	100	28 (14)	<1	28	71
		100	34 (14)	1	29	70
8	exo	110	24 (11)	<1	29	70
		110	33 (14)	<3	29	68
		110	6[c]		33	67
8	Δ^3 (**2**, $n = 4$)	110	25 (10)	1	31	68

[a] Utilizing DBN in toluene. [b] Time of longest equilibration run and time at which product ratios approximately equal final results. [c] Excess DBN added to force fast isomerization to endo products.

When this synthetic scheme was virtually complete, a synthesis of 3-methylenecycloheptanone (**3**, $n = 3$) from 2-cycloheptenone was published.[22] This reported synthesis is attractive in the 7-membered ring where the starting enone is commercially available but is much less attractive in the larger ring sizes because of the problem[23−26] of obtaining the analogous enones in high yield.

Isomerizations

Equilibrations were performed as before[1] using DBN as the base catalyst in toluene. Equilibrations were performed at least in duplicate for each compound at each temperature and were approached from pure exocyclic isomer (**3**) and from at least one other isomer or mixture of isomers. Isomer ratios were obtained from gas chromatograph peak areas and by integration of vinylic hydrogen in the NMR. The thermal stability of the three cyclooctenone isomers (**1**, **2**, and **3**, $n = 4$, $R = CH_3$) was confirmed by heating each at 110 °C in deuterated toluene for 5−7 weeks. All showed no reaction after 5 weeks, but the exocyclic isomer **3** did begin to show conversion to the Δ^2 isomer **1** after 7 weeks. Equilibration data for the 7- and 8-membered systems are reported in Table 1 and compared to previous work with other substituents at carbon 3 in Table 2. Results for the 9-membered systems are reported in Table 3 and those for the 10-membered compounds in Table 4.

As can be seen from the data in Table 1, equilibrium was established at various temperatures in the 7- and 8-membered ring series ($n = 3$ and 4). In each ring size, the exo-methylene compounds **3** were less stable than the endocyclic isomers **1** and **2**, being converted to the endocyclic isomers in less than 3 days. As shown in Figure 1 and Table 5, the exocyclic isomer **3** is exclusively converted to the 2-cycloalkenone (**1**) via an exocyclic

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Table 2. Equilibrations of Substituted Cycloheptenones and Cyclooctenones[a]

ring size	3-substituent	% Δ^2 at 80 °C
7	H	77
	CO_2CH_3	17
	CN	15
	$COCH_3$	21
	CH_2OAc	17[b]
	CH_3	86[c]
8	H	20[3]
	CO_2CH_3	4
	CN	2
	$COCH_3$	3
	CH_3	35[c]

[a] Utilizing DBN in toluene, from ref 1 unless otherwise indicated. [b] At 33 °C. [c] This work.

Table 3. Isomerizations of 9-Membered Cycloalkenones[a]

starting isomer	temp (°C)	time (days)	exo	Δ^2	Δ^3
exo (**3**, $n = 5$)	35	48	3	94	3
exo (**3**, $n = 5$)	80	35	8	74	18
	80	35	10	78	12
	80	42	8	72	20
exo (**3**, $n = 5$)	100	28	8	59	33
exo (**3**, $n = 5$)	110	36	5	25	70
	110	46	5	38	57
Δ^3 (**2**, $n = 5$)	110	37			100
exo (**3**, $n = 5$)[b]	110	6		15	85

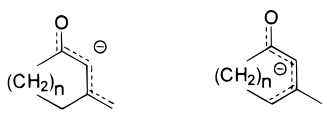
[a] Utilizing DBN in toluene. [b] Used excess DBN to accelerate kinetic formation of the Δ^3 isomer.

Table 4. Isomerizations of 10-Membered Cycloalkenones[a]

starting isomer	temp (°C)	time (days)	exo	Δ^2 (*E* and *Z*)	Δ^3
exo (**3**, $n = 6$)	35	29		100 (*Z*)	
exo (**3**, $n = 6$)[b]	0° and rt	12	62	19.5 (*E*), 18.5 (*Z*)	
exo (**3**, $n = 6$)	80	44	1	99^+ (*Z*)	
	80	44	<2	98^+ (*Z*)	
exo (**3**, $n = 6$)	100	28	<2	93 (*Z*)	
	100	34	<1	88 (*Z*)	11
exo (**3**, $n = 6$)	110	33	<2	68 (*Z*)	30
	110	36	1	69 (*Z*)	30
	110	43	2	84 (*Z*)	14
Δ^3 (**2**, $n = 6$)	110	37			100
exo (**3**, $n = 6$)[c]	110	10		50	50

[a] Utilizing DBN in toluene. [b] Conducted at lower temperatures with less DBN and worked up early in order to isolate *E* for characterization. [c] Used excess DBN to accelerate kinetic formation of the Δ^3 isomer.

dienolate. Conversion of the 2-cycloalkenone (**1**) to the 3-cycloalkenone (**2**) via an endocyclic dienolate is a much slower process, requiring several weeks to reach equilibrium. This is consistent with the arguments previously presented[1,12] that exocyclic dienolates **12** are more stable than the corresponding endocyclic dienolates **13** in a given ring size. As expected, higher temperatures speed up both processes (Tables 5 and 6).



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13

In the isomerization of the 9-membered compounds (Table 3), isomerization times were so lengthy that the possibility of thermal processes and maintaining the integrity of the apparatus became problems, especially in the conversion of the 2-cyclononenone **1** ($n = 5$, R = CH_3) to the 3-cyclononenone **2** ($n = 5$, R = CH_3). Dark-brown insoluble residues began to appear, but were soluble in the acidic aqueous layer of the workup. Addition of excess DBN to the isomerization mixture did accelerate kinetic formation of the 3-cyclononenone isomer. However, quite surprisingly, the 3-methyl-3-cyclononenone (**2**, $n = 5$, R = CH_3) was totally resistant to conversion to the 2-cyclononenone isomer under any isomerization conditions used. This suggests that the 3-cycloalkenone isomer (**2**) faces a higher activation energy in going through the required endocyclic dienolate anion **13** than does the 2-cycloalkenone isomer (**1**) (see below). Equilibrium was therefore not attained in this 9-membered ring system.

A similar behavior was found in the 10-membered ring compounds (Table 4), which was further complicated by

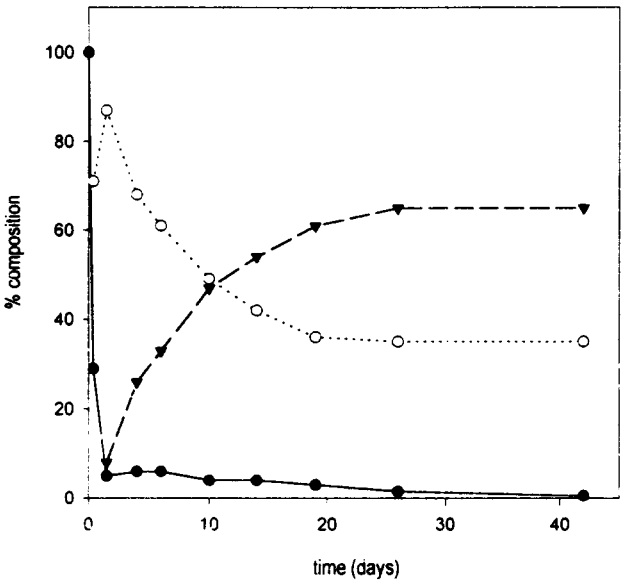

Figure 1. Equilibration of 3-methylenecyclooctanone (**3**, $n = 4$) at 80 °C: **3** (●), **1** (○), **2** (▼).

Table 5. Base-Catalyzed Isomerization of 3-Methylenecyclooctanone (3, $n = 4$) at 80 °C[a]

time (days)	exo	Δ^2	Δ^3
0	100		
0.4	29	71	
1.5	5	87	8
4	6	68	26
6	6	61	33
10	4	49	47
14	4	42	54
19	3	36	61
26	<2	35	65
42	<1	35	65

[a] Conducted by method 2 (NMR) and provided the data for Figure 1.

Table 6. Base-Catalyzed Isomerization of 3-Methylenecyclooctanone (3, $n = 4$) at 110 °C[a]

time (days)	exo	Δ^2	Δ^3
0	100		
0.05	61	39	
6	4	28	68
9	3	25	72
15	3	29	68
20	3	29	68
28	2	30	68
33	3	29	68
36	<2	31	67

[a] Conducted using method 2.

Table 7. Base-Catalyzed Isomerization of 3-Methylenecyclodecanone (3, $n = 6$) at 80 °C[a]

time (days)	exo	Δ^2 (*E*)	Δ^2 (*Z*)
0	100		
0.25	66	23	12
1.25	52	14	35
2.6	29	11	60
4	16	6	77
6	8	6	87
8	3	<1	97
12	<1	<<1	99
16			99
29			99
44			99

[a] This run showed no sign of any Δ^3 compound, so the data reflect the isomerization of the exo compound to the *E* and then the *Z* isomer of **1**. This run produced the data used in Figure 2 and was carried out using method 2.

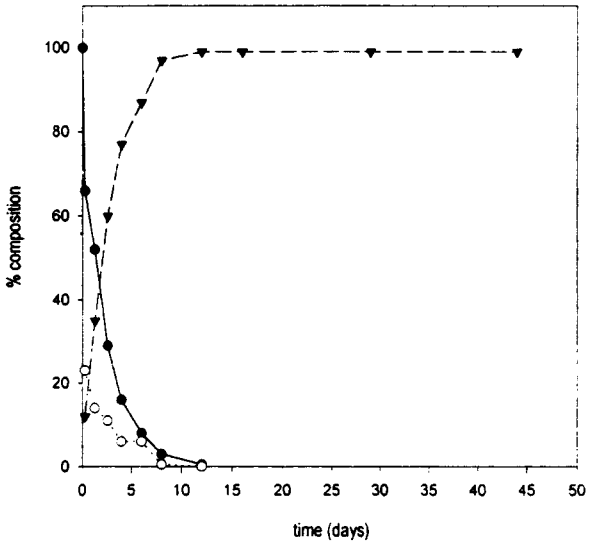

Figure 2. Isomerization of 3-methylenecyclodecanone (**3**, $n = 6$) at 80 °C: **3** (●), (*Z*)-**1** (○), (*Z*)-**2** (▼).

the involvement of *E* and *Z* isomers of both the Δ^2 and Δ^3 cyclodecenones. Equilibration of all exocyclic and endocyclic isomers was not attained since the 3-cyclodecenones again could not be converted to the 2-cyclodecenones under the isomerization conditions. Equilibrium studies by Cope[27] indicated that (*Z*)-cyclodecene was much more stable than (*E*)-cyclodecene. Starting from methylenecyclodecane, Cope[6] noted that both endo isomers were initially formed at the same rate but that the (*Z*)-methylcyclodecene greatly predominated at equilibrium. Whitham[4] equilibrated the unsubstituted (*E*)- and (*Z*)-2-cyclodecenones and observed 96% *Z*. In this study (Table 7), 3-methylenecyclodecanone (**3**, $n = 6$) isomerized to two 2-cyclodecenone isomers at similar rates (Figure 2), but only one of these isomers was present after 2 weeks under the isomerization conditions at 80 °C. This more stable product was assigned the *Z* structure on the basis of comparison with previous results and on spectral data (infrared comparison with the spectrum reported for the unsubstituted (*Z*)-2-cyclodecenone by Whitham[4] and by Hirano,[24] a more upfield shift in the NMR for the methyl hydrogens than in the other isomer,[28] comparison with the spectra of Still's 10-methyl-2-cyclodecenones,[25] and comparison with all spectral data for the 8- and 9-membered ring analogues, which must be *Z*). Only one 3-methyl-3-cyclodecenone was obtained in these isomerization studies, and it is assigned the *Z* configuration by spectral comparison with its smaller ring analogues.

The 7- and 8-membered rings do achieve equilibrium, while the 9- and 10-membered rings do not for the compounds and conditions employed herein. Previous work[1−4] in the 9- and 10-membered rings which did not result in demonstrable conversion of 3-cycloalkenones to 2-cycloalkenones with attainment of equilibrium must be viewed as isomerizations rather than as thermodynamic data, as previously discussed.[1] The difficulty in achieving equilibrium is directly related to the strain in the required endocyclic dienolate intermediates **13**. Conjugated dienes are not thermodynamically favored in rings of nine members and larger[29−31] because torsional and nonbonded transannular interactions force them out of coplanarity and, therefore, conjugation. Without the stability imparted by efficient electron delocalization, the dienes will rearrange under proper conditions to give that isomer which imparts the minimum strain on the molecule. Although the 7- and 8-membered conjugated dienes are strained, they can better attain coplanarity than the 9- or 10-membered rings. Endocyclic dienolate **13** is therefore more difficult to form as the ring size increases from seven to ten.

Additional evidence supporting these arguments has been provided by Majetich.[32] In a bicyclic 3-methyl-2-cyclooctenone fused at carbons 5 and 6 to a six-membered ring, photochemical deconjugation, reported by Pirrung and Webster[33] to convert 3-alkyl-2-cyclooctenones (**1**, $n = 4$, R = *n*-alkyl) to the exocyclic (**3**) and Δ^3 (**2**) double-bond systems, produced only the exocyclic isomer **3**. More importantly, treatment of Majetich's compound[32] with DBN in refluxing benzene for 5 days did not produce any isomeric material, while other attempts to generate the endocyclic dienolate and trap it as the silyl enol ether failed and attempts to utilize ketalization procedures to generate Δ^3 systems provided only exocyclic double-bond systems. Apparently the restricted mobility of the eight-membered ring in Majetich's system precluded formation of endocyclic dienols and dienolates at all.

Why then can dienolate **13** be formed from the 2-cycloalkenone (**1**) but not from the 3-cycloalkenone (**2**) in the larger medium ring sizes? The 2-cycloalkenones already contain an enone system with some tendency to be conjugated and coplanar. Removal of the γ-hydrogen more or less parallel to the cloud would give dienolate **13**, which could be protonated to give either a Δ^2- or a Δ^3-isomer. On the other hand, the nonconjugated enone of the 3-cycloalkenones does not necessarily possess a readily available conformation to permit abstraction of an α-hydrogen with formation of planar dienolate **13**. The hydrogen α to the carbonyl might be expected to be less acidic than in the 7- and 8-membered ring analogs and might lead to nonplanar/nonconjugated dienolate **14** with the same connectivity as in **13** but without any π-system overlap. Such a nonplanar dienolate would be rapidly reprotonated to regenerate the 3-cycloalkenone without

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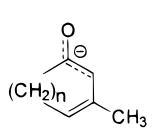
receiving enough energy to form the planar dienolate **13** necessary for isomerization to the 2-cycloalkenone. If the dienolate cannot be coplanar without assuming large amounts of strain, the nonconjugated dienolate **15** might be formed from the 3-cycloalkenone at a rate similar to that of **14**.[12,32]



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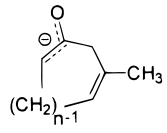

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As shown in Table 2, the methyl-substituted cycloalkenones at equilibrium exhibit more conjugated isomer (**1**) than the unsubstituted compounds or electron-withdrawing-substituted compounds in each ring size. The β-alkyl substituent could stabilize the conjugated enone system in **1** because of the presence of the electron-withdrawing carbonyl group at one end of the double bond and the electron-donating methyl group at the other end of the double bond.[34] This methyl effect could be inductive or could involve hyperconjugation. Other compounds containing better electron-donating substituents at the 3-position have been prepared[35] to verify this hypothesis and will be reported on separately.

Experimental Section

All NMR spectra were obtained in $CDCl_3$ solution unless otherwise noted. Ultraviolet spectra were taken using absolute ethanol. Gas chromatographic analysis were performed using 4 ft × $^1/_4$ in. 20% Carbowax 20M, 6 ft × $^1/_8$ in. 20% SE-30, 5 ft × $^1/_8$ in. 5% SE-30, 10 ft × $^1/_8$ in. 2% OV-17, or 10 ft × $^1/_8$ in. 1% OV-17 chromatography columns, as appropriate. Elemental analyses were performed by the Microanalytical Laboratory of Merck & Co., Rahway, NJ, or by Microanalytisches Laboratorium, Elbach, West Germany. Column chromatographic separations utilized E. Merck silica gel 60 (70−230 mesh) for gravity flow and E. Merck silica gel 60 (230−400 mesh) for flash[36] chromatography. Thin-layer chromatography was conducted on Analtech Uniplates with silica gel GF (indicating) and was visualized under 254 nm UV light and/or in an iodine tank or by charring with phosphomolybdic acid solution. Preparative thin-layer chromatography used the same plates in appropriate thickness.

Ethylene ketal of methyl 6-oxo-1-cycloheptenecarboxylate (5, *n* = 3) was prepared by a procedure similar to that of Sterzycki.[15] To a solution of 8.8 g (53 mmol) of the Δ^3 keto ester **4** ($n = 3$) dissolved in 100 mL of toluene were added 6 mL (108 mmol) of ethylene glycol and 800 mg (~3 mmol) of PPTS. The mixture was stirred well and heated to reflux, with the water being removed by a Dean−Stark trap. The heating was stopped after 90 min when GPC analysis of a probe showed no starting material remaining. After cooling, the reaction mixture was poured onto 100 mL of a 5% $NaHCO_3$ solution and extracted well with CH_2Cl_2; the organic layers were washed with water, dried ($MgSO_4$), and concentrated under reduced pressure to yield the desired ketal as 10.7 g (96%) of a slightly yellow oil. This oil crystallized at ~0 °C but remelted at room temperature: IR (neat) 1705, 1640, 1000−1300 (ketal) cm^{-1} (lit.[1] 1700, 1640 cm^{-1}); NMR δ 7.31 (br t, 1, $J = 6.5$ Hz), 4.00 (br s, 4), 3.74 (s, 3), 2.87 (br s, 2), 2.6−1.5 (m, 6) (lit.[1] δ 7.27 (t, 1), 4.00 (s, 4), 3.73 (s, 3), 2.87 (s, 2), 2.6−1.4 (m, 6)); bulb-to-bulb distillation of a small sample at 0.01 mmHg and 80−90 °C gave a sample with spectral data as above. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.20; H, 7.74.

Ethylene ketal of methyl 7-oxo-1-cyclooctenecarboxylate (5, *n* = 4) was prepared according to the procedure of House.[16] To a solution of 24 g (0.132 mol) of the unsaturated keto ester **4** ($n = 4$) in 70 mL of toluene were added 15 mL (0.26 mol) of ethylene glycol and 200 mg of p-TsOH. This mixture was stirred well and heated to reflux, with the water being removed by a Dean−Stark trap. When production of water had stopped (~3 h), the reaction mixture was cooled, poured onto a dilute $NaHCO_3$ solution, extracted well with CH_2Cl_2, washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. This yielded the desired ketal as 29.9 g (100%) of a slightly yellow oil which crystallized (low melting) upon standing: IR (neat) 1710, 1645, 1050−1150 (ketal) cm^{-1} (lit.[1] 1730, 1720, 1640 cm^{-1}); NMR δ 7.05 (t, 1, $J = 8$ Hz), 4.0 (m, 4), 3.77 (s, 3), 2.77 (s, 2), 2.6−2.1 (m, 2), 1.67 (br s, 6) (lit.[1] δ 6.97 (t, 1), 3.93 (m, 4), 3.7 (s, 3), 2.7 (s, 2), 2.23 (s, 2), 1.6 (s, 6)). Bulb-to-bulb distillation at 105 °C under 0.03 mmHg gave a small sample with spectral data as above. It crystallized upon standing (low melting). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.29; H, 7.99.

Ethylene Ketal of Methyl 8-Oxo-1-cyclononenecarboxylate (5, *n* = 5). Treatment of 60 g (0.306 mol) of the 9-membered keto ester **4** ($n = 5$) as above with 34 mL (0.6 mol) of ethylene glycol and 400 mg of p-TsOH in 200 mL of toluene could not be driven to completion. Even with additional refluxing (48 h total) and more ethylene glycol (7 mL), workup yielded 73.4 g (100%) of a light orange oil (crystallized upon standing) which contained 91% of ketal and 9% of starting ketone on the basis of GC and NMR comparisons. This was used without further treatment. Crystallization of a small probe from a pentane/benzene mixture produced a crystalline product with spectra in agreement with the ketal structure: mp 44.5−48.5 °C; IR (Nujol) 1710, 1640 cm^{-1} (lit.[1] 1725−1710, 1645 cm^{-1}); NMR δ 6.90 (t, 1, $J = 8.5$ Hz), 3.95 (m, 4), 3.75 (s, 3), 2.83 (s, 2H), 2.5−2.0 (m, 2), 1.9−1.3 (m, 10) (lit.[1] δ 6.88 (t, 1), 3.98 (m, 4), 3.73 (s, 3), 2.3 (s, 2), 1.6 (s, 8)). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.79; H, 8.50.

Ethylene ketal of methyl 9-oxo-1-cyclodecenecarboxylate (5, *n* = 6) (*all-E*) was prepared in a manner similar to that employed for the 8-membered homolog. To a solution containing 45 g (0.214 mol) of the (*all-E*) keto ester **4** ($n = 6$) and 24 mL (0.43 mol) of ethylene glycol in 120 mL of toluene was added 200 mg of p-TsOH. The water produced by the reaction was removed as above by refluxing under a Dean−Stark trap until evolution ceased. Analysis of probes by GC (20% SE-30 at 220 °C) indicated the presence of 5% starting material even after 18 h reflux. Usual workup provided 54.6 g (100%) of an off-white solid as a mixture of 95% ketal (*all-E* isomer) and 5% starting ketone (by spectral and GC comparison). This was used without further treatment. Recrystallization of a small probe from pentane/benzene removed the ketone and produced the solid white ketal (*all-E* isomer): mp 88−89 °C; IR (Nujol) 1710, 1640 cm^{-1}; NMR δ 6.66 (t, 1, $J =$ 8 Hz), 3.98 (m, 4), 3.76 (s, 3), 2.77 (s, 2), 2.6−2.1 (m, 2), 2.0−1.2 (m, 10) (lit.[1] δ 6.67 (t, 0.9), 6.3 (t, 0.1), 4.0 (m, 4), 3.8 (s) and 3.77 (s) (total of 3H), 2.8 (s, 2), 2.6−2.3 (m, 2), 1.9−1.2 (m, 10)). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.92; H, 8.79.

Ethylene Ketal of 6-Oxo-1-(hydroxymethyl)-1-cycloheptene (6, *n* = 3). A solution consisting of 10.5 g (.049 mol) of the unsaturated ester **5** ($n = 3$) in 120 mL of anhydrous ether was added dropwise over 45 min to 110 mL (0.11 mol) of 1 M DIBALH[18] in diethyl ether (Aldrich) which was being stirred under nitrogen and cooled to −10 °C. The reaction mixture was stirred for 30 min at 0 °C and worked up by the slow dropwise addition of 2 mL of a 30% KOH solution (copious bubbling). This was followed by 50 mL of this KOH solution, and the mixture was then stirred for 30 min after reaching room temperature. Another 50 mL of 30% KOH solution was added and the mixture extracted well with ether. The organic phase was washed with H_2O until neutral and once with brine, dried ($MgSO_4$), and concentrated under reduced pressure. This produced 6.5 g (71%) of the unsaturated alcohol as a slightly cloudy oil: IR (neat) 3460−3400 cm^{-1}, no C=O stretch; NMR

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(35) Thompson, G. S. Ph.D. Dissertation, Seton Hall University, 1995.

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δ 5.95 (t, 2, J = 6 Hz), 3.95 (br s, 6), 2.53 (s, 2), 2.5−1.4 (m, 7). Because of a less than desirable yield, the aqueous phase was salted with NaCl and extracted again with Et_2O, which gave another 2.7 g (29%) of the allylic alcohol as a clear oil with spectral characteristics as above. Both of these oils were used without further treatment.

Ethylene ketal of 7-oxo-1-(hydroxymethyl)-1-cyclooctene (6, *n* = 4) was produced by a method similar to the above. A solution of 23 g (0.1 mol) of the unsaturated ester **5** (n = 4) in 200 mL of CH_2Cl_2 (dried over 42 sieves) was added dropwise with stirring over 45 min to 220 mL (0.22 mol) of 1 M DIBALH in CH_2Cl_2 (Aldrich) cooled under N_2 at −10 °C. The reaction was quenched by the slow dropwise addition of 4 mL of H_2O (vigorous gas evolution) followed by 6 mL of a 10% NaOH solution. After being stirred well for a few minutes, the mixture gelled and required extensive extraction with EtOAc and filtration through Supercel in order to obtain a solution of the product. The resulting product was dried ($MgSO_4$) and concentrated under reduced pressure. The crude alcohol was obtained as 19.4 g (98%) of a clear oil. Column chromatography on silica gel eluted with 20% Et_2O in CH_2Cl_2 resulted in the isolation of 17 g (86%) of the desired unsaturated alcohol as a clear oil (later crystallized in flask as a low-melting solid): IR (neat) 3400 cm^{-1}, no C=O stretch; NMR δ 5.84 (br t, 1, J = 8 Hz), 4.0 with shoulder at 4.1 (br s, 6), 3.27 (br t, 1, J = 5 Hz, washed out by D_2O), 2.54 (s, 2), 2.4−2.0−1.4 (m, 8); bulb-to-bulb distillation (100−110 °C [0.1 mmHg]) gave a clear oil with spectral properties as above. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.24; H, 9.24.

Ethylene ketal of 8-oxo-1-(hydroxymethyl)-2-cyclononene (6, *n* = 5) was prepared in the same manner as that used for the 8-membered homolog. A solution of 24 g (0.1 mol) of the unsaturated ester **5** (n = 5) in 200 mL of CH_2Cl_2 (dried over 4A sieves) was added as above to 220 mL (0.22 mol) of 1 M DIBALH in CH_2Cl_2 (Aldrich). Workup of this reaction also produced gels which required repeated extraction with EtOAc and filtration in order to produce a solution which was then dried ($MgSO_4$) and concentrated under reduced pressure to yield 20.6 g (97%) of a cloudy oil. Column chromatography on 200 g of silica gel eluted with 20% Et_2O in CH_2Cl_2 gave 14.1 g (65%) of the desired alcohol as a clear oil: IR (neat) 3420, 1000−1150 (ketal) cm^{-1}; NMR δ 5.74 (t, 1, J = 8 Hz), 4.04 (s, 2), 3.98 (s, 4), 3.32 (br s, 1, washed out by D_2O), 2.60 (s, 2), 2.4−2.0 (m, 2), 1.9−1.4 (m, 8); bulb-to-bulb distillation of a small sample (115−120 °C [0.1 mmHg]) yielded a clear oil which crystallized (low melting) upon standing. Spectral properties were as above. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.64; H, 9.73.

Because of the use of ethyl acetate under strongly basic conditions in the extraction of the crude alcohol, another compound was recovered during the column chromatography. Transesterification had produced 2.6 g of an acetoxy derivative of the alcohol function of **6** (n = 5): mass spectrum m/z 254 (M^+), 195, and 43 (base peak); IR (neat) no OH stretch, 1735, 1230 cm^{-1}; NMR δ 5.75 (br t, 1, J = 8 Hz), 4.65 (br s, 2), 3.94 (s, 4) 2.54 (s, 2), 2.07 (s) and 2.4−2.0 (m) (total 5H), 1.57 (m, 10). This material was hydrolyzed to give 1.92 g of the allylic alcohol **6** (n = 5) with spectral properties in agreement with those found above.

Ethylene Ketal of 9-Oxo-1-(hydroxymethyl)-2-cyclodecene (6, *n* = 6). This reduction of the *E* α,β-unsaturated ester **5** (n = 6) was carried out according to the method of Davidson.[17] A solution containing 25.4 g (0.1 mol) of the 100% *E* isomer of ester **5** (n = 6) in 300 mL of anhydrous ether was cooled to 0 °C under a N_2 atmosphere, and then 150 mL of an approximately 0.5 M solution of $LiAlH_4$−EtOH in diethyl ether was added dropwise with good stirring over 2 h. [The stock solution of $LiAlH_4$−EtOH was prepared by stirring 7.6 g (0.2 mol) $LiAlH_4$ in 300 mL of ethyl ether at room temperature for 20 min. The mixture was then cooled in an ice bath, and to it was added dropwise and carefully 100 mL of ether containing 12 mL (0.2 mol) of ethyl alcohol. The mixture was stirred at room temperature and then allowed to settle, with only the supernatant used as the reactant.] The workup of the reaction involved the dropwise addition of 2 mL of H_2O, 3 mL of 10% NaOH solution, and 6 mL of H_2O, followed by stirring at room temperature for 30 min. The salts were filtered and washed well with ether. The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure to yield 22 g of a clear oil which crystallized upon standing. Column chromatography on silica gel eluted with 7% ethyl acetate in CH_2Cl_2 produced 16.0 g (71%) of the allylic alcohol as a solid: IR (Nujol) 3400−3300 cm^{-1}, no C=O stretch; NMR δ 5.54 (t, 1, J = 8 Hz), 4.10 (s, 2), 4.0 (s, 4), 3.4−3.0 (m, 1, washed out by D_2O), 2.8−2.0 (m, 4), 1.9−1.2 (m, 10). Recrystallization of a small sample gave white crystals with spectral properties as above: mp 55−56.5 °C; mass spectrum m/z 226 (M^+), 99 (base peak). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.91; H, 9.77.

Ethylene Ketal of 6-Oxo-1-(bromomethyl)-1-cycloheptene (7, *n* = 3). The method of Ohloff[19] was used to convert alcohol **6** (n = 3) to the corresponding allyl bromide. A solution containing 8.9 g (48 mol) of the alcohol in 200 mL of anhydrous ether was cooled under N_2 to a temperature of −30 °C in a dry ice/acetone bath. A solution of 2.2 mL (5 g, 18.3 mmol or 15% excess Br) of phosphorus tribromide in 30 mL of anhydrous ether was added dropwise over 20 min with stirring. After addition the bath was allowed to come to 0 °C and the reaction mixture stirred at this temperature for 90 min. The reaction mixture, which contained some orange precipitate, was then carefully poured onto a vigorously stirred mixture of 10% sodium carbonate solution (excess) and ice, extracted well with Et_2O, washed with water and brine, and dried ($MgSO_4$). During concentration on the rotary evaporator, the liquors became cloudy with a brown immiscible oil before all of the solvent had been removed. Because of the results of this kind in earlier runs, the remaining solution was treated at room temperature with anhydrous hydrogen bromide gas bubbled through a sintered glass tube for 10 min according to Hutchins.[20] The treated ether solution was poured onto 10% sodium carbonate solution (excess), shaken and separated, washed well with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure. This yielded 7.2 g (72%) of an orange oil which became dark brown upon standing a short time at room temperature. Proton NMR seemed to indicate a mixture of Δ^3 keto compound **10** (n = 3) and Δ^2 keto compound **11** based upon the observation of a broad triplet at 6.0 and a broad singlet at 6.2 for the respective vinylic protons: IR (neat) 1700, 1660 cm^{-1}, no OH stretch; TLC (silica gel; CH_2Cl_2) showed two new fast spots which both absorbed UV light and I_2. The darkening mixture was used immediately in the following step without further purification. Another major impurity (25%) from this bromination was isolated after purification of the following reaction. It was not identified.

Ethylene Ketal of 7-Oxo-1-(bromomethyl)-1-cyclooctene (7, *n* = 4). The conversion of the allylic alcohol **6** (n = 4) into the corresponding allyl bromide was accomplished by a method similar to that of Ohloff.[19] A solution containing 2.76 g (13.5 mmol) of the allyl alcohol in 50 mL of anhydrous ether under N_2 was cooled to a temperature of −30 °C in a dry ice/acetone bath. A solution of 0.6 mL (1.36 g, 5 mmol or ∼10% excess Br) of phosphorus tribromide in 10 mL of anhydrous ether was added dropwise with stirring over 45 min. After addition, the bath was allowed to reach a temperature of 0 °C and this temperature was maintained for 90 min. The reaction mixture was then poured slowly onto a rapidly stirred, ice-cold 10% sodium carbonate solution (excess), extracted with Et_2O, washed with water three times and once with brine, dried ($MgSO_4$), and concentrated under reduced pressure. This workup gave 3.08 g (88%) of a slightly yellow oil (crystallized upon standing) which contained the desired bromo compound along with a small amount (15%) of the corresponding ketone **10** (n = 4): IR (Nujol) 1650, no OH stretch; NMR δ 5.93 (t, 1, J = 8 Hz), 4.13 (s, 2), 3.97 (s, 4), 3.27 (s, due to C2 protons from 15% of keto analog), 2.57 (s, 2), 2.02.4 (m, 2), 1.9−1.5 (m, 6). This mixture was utilized in the following step without further purification.

Ethylene Ketal of 8-Oxo-1-(bromomethyl)-1-cyclononene (7, *n* = 5). This bromination was carried out as above utilizing 300 mL of an anhydrous ether solution containing 15.6 g (74 mmol) of allylic alcohol **6** (n = 5). This solution was cooled to −30 °C under an N_2 atmosphere, and 3.2 mL (27 mmol) of phosphorus tribromide in 50 mL of anhydrous

ether was added dropwise over 30 min. After addition the reaction mixture was stirred at 0 °C for 90 min and worked up as above. This yielded 14.1 g (69%) of a light yellow oil as a mixture (~60/40) of the desired bromo compound and the analogous keto compound **10** (n = 5): TLC (silica gel, 1/1 methylene chloride/hexane) showed two spots which both absorbed UV light and I_2; IR (neat) no OH stretch, 1730, 1695 cm^{-1} (from ketone); NMR δ 5.92 and 5.80 (overlapping t, total 1H, J = 8 Hz for each), 4.22 (s, 0.6H, CH_2Br from ketal), 4.17 (s, 0.4H, CH_2Br from ketone), 3.97 (s, ketal), 3.25 and 2.67 (each s, total 2H, from ketone and ketal, respectively), 2.5−1.3 (m). This mixture was used as is in the following step.

Ethylene Ketal of 9-Oxo-1-(bromomethyl)-1-cyclodecene (7, *n* = 6). This bromination was accomplished using the procedure of Ohloff[19] and the suggestion of Hutchins[20] for the complete conversion of the intermediate phosphite esters. A solution containing 12.7 g (56.3 mmol) of the allylic alcohol **6** (n = 6) in 200 mL of anhydrous ether was cooled to −30 °C under N_2 in a dry ice/acetone bath. A solution of 5.7 g (21 mmol, 10% excess Br) of phosphorus tribromide in 30 mL of anhydrous ether was added dropwise over 30 min. The reaction mixture was then allowed to stir at 0 °C for 40 min and worked up as above. This produced 14 g (86%) of a yellow oil as a mixture (40/60) of the desired bromo compound and another compound which was determined to be a phosphite ester intermediate. This mixture was used without further purification in the following reaction.

A small portion of the mixture was filtered through silica gel as a solution in CH_2Cl_2 in order to obtain spectral data of the bromo compound free of interference by the intermediate phosphite ester: IR (neat) no OH stretch, no carbonyl, 740 cm^{-1}; NMR δ 5.71 (t, 1, J = 8 Hz), 4.28 (br s, 2), 4.0 (br s, 4), 2.65 (s, 2), 2.1−2.5 (m, 2), 1.3−1.9 (m, 10).

After the mixture had been used to make phosphonate **8** (n = 6), silica gel chromatography allowed recovery of 6.1 g of the phosphite ester intermediate: IR (neat) 2430, 1265, 1030−1055 cm^{-1} (lit.[20] 2400, 1250, 950−1000 cm^{-1}). Treatment of an ether solution of this intermediate with hydrogen bromide gas afforded 5 g of the allylic bromide **7** (n = 6) with spectral properties as above.

Ethylene Ketal of 6-Oxo-1-((*O*,*O*-diethylphosphono)-methyl)-1-cycloheptene (3, *n* = 3). The method of Harwood[13] was used to convert the crude bromo mixture, **7** (n = 3) and **10** (n = 3), to an allylic phosphonate isolated as the α,β-unsaturated ketone. A combination of 7.0 g of the mixture (with an additional unknown impurity) with 20 mL (0.12 mol) of triethyl phosphite was stirred at 85 °C under N_2 for 20 h in a hood. Excess triethyl phosphite was distilled off under reduced pressure to give 9.2 g of a brown oil. Column chromatography on silica gel eluted with 15% Et_2O/CH_2Cl_2 resulted in the isolation of 3 g (~40%) of a light yellow oil, which was assigned the structure of the α,β-unsaturated ketone on the basis of spectral properties: IR (neat) 1655 (C=O), 1250, 1050, 1030, 960 cm^{-1}; NMR δ 6.05 (br d, 1, J = 6 Hz, allylic coupling with P), 4.77 (m, 4), 2.8 (d, 2, J = 24 Hz, seen as s at 2.97 and 2.63), 2.4−2.8 (m), 1.6−2.1 (m), 1.13 (t, 3); mass spectrum m/z 260 (M^+), 122 (base peak), 232 (M^+ − 28); TLC (silica gel GF, 15% Et_2O/CH_2Cl_2) one spot (R_f 0.25) with strong UV absorbance.

This α,β-unsaturated keto product was reketalized in the usual manner with PPTS[15] to give 3.4 g of a ketal which appears to have rearranged to the desired β,γ-unsaturated ketal **8** (n = 3): IR (neat) no C=O stretch, 1250, 1055, 1025, 960 cm^{-1}; NMR δ 5.83 (q, 2), 4.1 (m, 4), 3.93 (s, 4), 2.63 (d, 2, J = 22 Hz, CH_2 coupled with P seen as 2 s at 2.80 and 2.43), 2.63 (d, 2, J = 3 Hz), 1.6−2.4 (m), 1.33 (t, 3); TLC (silica gel GF, 20% acetone/CH_2Cl_2) one spot, very little UV absorbance. This material was used without further purification.

A small probe was purified by bulb-to-bulb distillation at 150 °C (0.05 mmHg) and gave spectral properties as above: mass spectrum m/z 304 (M^+), 99 (base peak), 167. One peak in gas chromatography (2% OV-17 at 200 °C). HRMS: calcd for $C_{14}H_{25}O_5P$ 304.14396. Found: 304.14396.

Ethylene Ketal of 7-Oxo-1-((*O*,*O*-diethylphosphono)-methyl)-1-cyclooctene (8, *n* = 4). The desired allylic phosphonate was prepared according to the method of Harwood.[13] A combination of 22 g (0.084 mol) of the allylic bromide (as an 85:15 mixture of ketal **7** (n = 4) and ketone **10** (n = 4)) and 25 mL (0.146 mol) of triethyl phosphite was stirred at 85 °C under N_2 for 16 h in a good hood. Excess triethyl phosphite was removed by distillation under reduced pressure to give 29.4 g of a golden brown oil. Column chromatography on silica gel utilizing 10% acetone/CH_2Cl_2 resulted in the recovery of 23 g (86%) of the phosphonate as a mixture of the ketal and ketone forms.

The entire mixture was reketalized[15] by refluxing in 250 mL of toluene with 6 mL (0.1 mol) of ethylene glycol and 300 mg of PPTS under a Dean−Stark trap. When evolution of water had ceased (2 h), the reaction mixture was cooled, poured onto a dilute $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with water and brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 22.5 g (84% overall) of phosphonate **8** (n = 4) as a yellow oil: IR (neat) no C=O stretch, 1250, 1060, 1030, 960 cm^{-1}; NMR δ 5.73 (broad d of t, 1, J = 6 and 8 Hz), 4.10 (d of q, J = 7 and 7 Hz) and 3.97 (s) total 8H, 2.75 (d, 2, J = 22 Hz), 2.62 (d, 2, J = 2 Hz), 2.4−2.0 (m, 2), 1.6 (m) and 1.47 (t, J = 7 Hz) total 12 H; TLC (silica gel GF) with several eluents (Et_2O; 10% acetone/CH_2Cl_2; 20% acetone/hexane) showed one spot.

A small sample was further purified by bulb-to-bulb distillation at 140−150 °C (0.1 mmHg) to give a clear oil with spectral characteristics identical to those given above. Anal. Calcd for $C_{15}H_{27}O_5P$: C, 56.59; H, 8.55; P, 9.73. Found: C, 56.96; H, 8.61; P, 9.95.

Ethylene Ketal of 8-Oxo-1-((*O*,*O*-diethyl)phosphono)-methyl)-1-cyclononene (8, *n* = 5). Following the same procedure as shown above,[13] 15.2 g (0.055 mol) of the allylic bromide (as a 60:40 mixture of ketal **7** (n = 5) and ketone **10** (n = 5) was stirred at 85−90 °C with 20 mL (0.12 mol) of triethyl phosphite for 18 h under N_2. Excess triethyl phosphite was then distilled off at reduced pressure to give 19.8 g of residual yellow oil. Column chromatography on silica gel eluted with 10% acetone/CH_2Cl_2 produced 17.3 g (94%) of the allylic phosphonate as a mixture of the ketal and ketone forms.

This mixture was reketalized by refluxing in 200 mL of toluene with 6 mL (0.11 mol) of ethylene glycol and 300 mg of PPTS with azeotropic removal of water using a Dean−Stark trap. After 5 h, the reaction mixture was cooled, poured onto 200 mL of a dilute $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with water and saturated NaCl solution, dried ($MgSO_4$), and concentrated under reduced pressure. This yielded 16.8 g (91%) of the desired allylic phosphonate **8** (n = 5) as a light yellow oil. This crude oil contained a small amount of toluene (according to the NMR spectrum) but exhibited spectra otherwise identical to those of a small distilled sample. Bulb-to-bulb distillation of a sample at 170−185 °C (0.3 mmHg) produced a clear yellow oil: IR (neat) no C=O stretch, 1250, 1055, 1030, 960 cm^{-1}; NMR δ 5.69 (d of t, 1, J = 8 and 6 Hz), 4.14 (d of q, J = 7 and 7 Hz) and 4.0 (s) total 8H, 2.82 (d, 2, J = 22 Hz), 2.72 (d, 2, J = 2 Hz), 2.4−2.1 (m), 1.8−1.4 (m), and 1.32 (t, J = 7 Hz) total 16H; mass spectrum m/z 332 (M^+), 99 (base peak), 289 (M^+ − 43), 287 (M^+ − 45). Anal. Calcd for $C_{16}H_{29}O_5P$: C, 57.82; H, 8.79; P, 9.32. Found: C, 57.58; H, 8.83; P, 9.67.

Ethylene Ketal of 9-Oxo-1-((*O*,*O*-diethyl)phosphono)-methyl)-1-cyclodecene (8, *n* = 6). The above procedure[13] was used to convert the allylic bromide to the desired allylic phosphonate. A solution of 4.7 g (16.2 mmol) of the bromo compound **7** (n = 6) in 6 mL (36 mmol) of triethyl phosphite was heated at 85 °C for 15 h, and the excess reagent then was removed at reduced pressure. The yellow oil (5.4 g) was purified by column chromatography on silica gel eluted with 10% acetone in methylene chloride to yield 3.4 g (61%) of the desired phosphonate as an orange oil: IR (neat) 1250, 1055, 1025, 965 cm^{-1}; NMR δ 5.44 (m, 1), 3.8−4.4 (m, 8), 2.0−3.1 (m, 6), 1.6 (m, 10), 1.30 (t, 6); mass spectrum m/z 346 (M^+), 301 (M^+ − 45), 99.

A small probe was further purified by bulb-to-bulb distillation at 180 °C (0.4 mmHg) to give a clear oil with spectral characteristics above. Anal. Calcd for $C_{17}H_{31}O_5P$: C, 58.94; H, 9.02; P, 8.94. Found: C, 59.30; H, 9.21; P, 9.15.

Ethylene Ketal of 3-Methylenecycloheptanone (9, n = 3). The allylic phosphonate **8** (n = 3) was converted to the ethylene ketal of 3-methylenecycloheptanone according to the procedure of Harwood and Julia.[13] A *well-ventilated* hood is required for the entire procedure because of the evolution of objectionable fumes. The fumes were scrubbed by constantly passing N_2 through the closed reaction apparatus and bubbling the effluent through an aqueous solution containing 5% $KMnO_4$ and 0.5% H_2SO_4. A solution containing 1.6 g (5.2 mmol) of the phosphonate in 15 mL of anhydrous ether was stirred under the N_2 purge and cooled to 0 °C. A commercially prepared (Aldrich) solution of 1 M lithium aluminum hydride in ether (5 mL = 5 mmol) was added via syringe over 3 min, and the reaction mixture was stirred for another 30 min in the ice bath. The reaction was quenched by the careful addition of 2 drops of water with vigorous stirring, followed by 6 drops of 2.5 N NaOH, and then 10 drops of water. The ice bath was removed, and the heterogeneous mixture was stirred at room temperature for 30 min. The mixture was filtered, the solids were washed well with ether, and the filtrate was dried ($MgSO_4$). The ether was carefully removed by distillation, and the distillate was trapped in a dry ice condenser to minimize the evolution of obnoxious odors. Column chromatography of the residue on silica gel eluted with 2% ether in methylene chloride gave 500 mg (60%) of the desired methylene compound after careful removal of solvent: IR (neat) 3065, 1640, 890 cm^{-1}; NMR δ 4.89 (br d, 2, J = 8, 1 Hz), 3.98 (br s, 4), 2.54 (s, 2), 2.34 (m, 2, J = 6.5 Hz), 1.8 (m, 2, J = 6.5, 4 Hz), 1.66 (m, 4); mass spectrum m/z 168 (M^+), 99 (base peak). GC (2% OV-17 at 120 °C) and TLC (silica gel, CH_2Cl_2) both indicate one component. HRMS: calcd for $C_{10}H_{16}O_2$ 168.1150. Found: 168.1120.

Ethylene Ketal of 3-Methylenecyclooctanone (9, n = 4). Reductive fission of the allylic phosphonate **8** (n = 4) to give the exocyclic methylene ketal was accomplished according to the procedure of Harwood and Julia[13] as above. A solution containing 22 g (0.069 mol) of the allylic phosphonate in 300 mL of anhydrous ether was stirred under a nitrogen purge and cooled in an ice bath. Lithium aluminum hydride (2.6 g, 0.069 mol) was added in portions over 20 min, and the reaction was stirred for a total of 2 h in the ice bath. Thin-layer chromatography (silica gel, 20% acetone in CH_2Cl_2) showed no starting material. The reaction was quenched by the careful, dropwise addition of 2.6 mL of water, 2 mL of 20% NaOH, and finally 7 mL of water. This heterogeneous mixture was stirred at room temperature for 30 min, the solids were filtered and washed well with anhydrous ether, and the combined filtrate was dried ($MgSO_4$). Most of the ether was slowly removed by distillation and the residue concentrated further under reduced pressure to yield 12.5 g (99%) of the exocyclic methylene compound as a slightly yellow oil contaminated with a little diethyl ether. Gas chromatography (20% SE-30 at 190 °C) showed one peak at 4.9 min, while TLC (silica gel, 8% acetone in hexane) showed one spot at R_f 0.65 and a spot at the origin when visualized with iodine: IR (neat) no C=O stretch, 3080, 1635, 895 cm^{-1}; NMR δ 4.96 (br s, 2), 3.99 (s, 4), 2.44 (s) and 2.45−2.1 (m) total 4 protons, 2.0−1.4 (m, 8).

Preparative-layer TLC (Analtech silica gel GF, 1000 μm) of a small sample developed with 12% ether in hexane followed by bulb-to-bulb distillation of the fast-moving band produced a clear oil which crystallized at <−20 °C; bp 90−95 °C (2.5 mmHg) (bulb-to-bulb). Spectral characteristics were the same as above. Mass spectrum: m/z 182 (M^+), 99 (base peak), 125. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.69; H, 10.08.

Ethylene Ketal of 3-Methylenecyclononanone (9, n = 5). The reductive fission of the 9-membered allylic phosphonate **8** (n = 5) was carried out as above.[13] A solution containing 16 g (0.048 mol) of the phosphonate in 250 mL of anhydrous ether was cooled under a N_2 purge (vented into scrubber as above) to 0 °C in an ice bath, and 2.2 g (0.058 mol) of lithium aluminum hydride was added in portions over 20 min. The reaction was quenched after 20 min and worked up as above to yield 10.7 g (100%+) of the desired methylene compound as a clear oil contaminated with solvent. Thin-layer chromatography (silica gel, 8% acetone in hexane) shows a spot at R_f 0.7 and at the origin (visualized with I_2). Spectral data are in agreement with those of a small probe which was further purified by preparative TLC (Analtech silica GF, 1000 μm, 12% ether in hexane) and bulb-to-bulb distillation (bp 70−75 °C [0.25 mmHg]) to give a clear oil (crystallization at <−20 °C): IR (neat) no C=O stretch, 3080, 1640, 910, 890, 825 cm^{-1}; NMR δ 5.26 (br d, 1, J = 2 Hz), 5.04 (m, 1, J = 1.5 Hz), 3.97 (s, 4), 2.42 (s, 2), 2.4−2.0 (m, 2), 1.9−1.3 (m, 10); GPC (20% SE-30 at 190) and TLC (silica gel, 8% acetone in hexane) both indicate one material; mass spectrum m/z 196 (M^+), 43 (base peak), 99, 125. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.42; H, 10.27. Found: C, 73.42; H, 10.27.

Ethylene Ketal of 3-Methylenecyclodecanone (9, n = 6). The desired ethylene ketal of 3-methylenecyclodecanone was prepared from 3.4 g (10 mol) of the phosphonate **8** (n = 6) in 170 mL of anhydrous ether by the addition of 380 mg (10 mmol) of lithium aluminum hydride as described above.[13] This reaction was quenched by the dropwise addition of 1 mL of H_2O to the vigorously stirred reaction, stirring at room temperature for 15 min and drying ($MgSO_4$). The reaction mixture was then filtered through E. Merck silica gel 60 (70−230 mesh) followed by a thorough washing of the cake with diethyl ether and careful distillation of the solvent at atmospheric and reduced pressures to yield 1.63 g (78%) of a clear oil. Column chromatography on silica gel eluted with CH_2Cl_2 gave 1.1 g (52%) of a clear oil which crystallized at 0 °C but melts at room temperature. TLC (silica gel, 8% acetone in hexane, R_f 0.7) and GC (20% SE-30 at 190 °C) indicated one material: IR (neat) 3080, 1635, 905 cm^{-1}; NMR δ 5.23 (br s, 1), 5.05 (br s, 1), 3.95 (s, 4), 2.45 (s, 2), 2.4−2.1 (m, 2), 2.0−1.4 (m, 12). Bulb-to-bulb distillation of a small sample produced a clear oil with spectral properties identical to the above: bp 80−85 °C (0.15 mmHg); mass spectrum m/z 210 (M^+), 155, 99 (base peak).

3-Methylenecycloheptanone (3, n = 3). The hydrolysis of the ethylene ketal **9** (n = 3) was carried out according to the method of Sterzycki.[15] A solution containing 100 mg (0.6 mmol) of the ethylene ketal in 1.5 mL of acetone was prepared, and water was added dropwise until the solution became slightly turbid (0.5 mL). A small amount (10 mg) of PPTS was added and the reaction mixture maintained at 50 °C in a warm water bath. After 90 min, GC (2% OV-17 at 80−120 °C, 6°/min) still showed considerable starting material. Another 10 mg of PPTS and 3 drops of water were added, and heating was continued until GC showed no starting material and only one faster new material (3.5 h total time). The reaction mixture was cooled, added to 10 mL water, and extracted with 10 mL portions of ether three times. The extracts were combined, washed with water, and dried ($MgSO_4$). The ether was carefully removed at atmospheric pressure and the residue transferred to a bulb-to-bulb distillation apparatus. The 3-methylenecycloheptanone distilled at 100 °C bath temperature (9 mmHg); 45 mg (61%) were collected. Both GC (2% OV-17, 80−120 °C, 6°/min) and TLC (silica gel, CH_2Cl_2 or 10% ether in hexane, visualized with I_2) showed a one-component material: IR ($CDCl_3$) 3075, 1695, 1640, 850 cm^{-1} (lit.[22] (neat) 3090, 1720, 1648 cm^{-1}); UV (absolute ethanol) λ_{max} 289 nm (ϵ = 69); 200 MHz NMR δ 4.99 (br s, 1), 4.93 (t, 1, J = 1 Hz), 3.24 (s, 2), 2.52 (m, 2), 2.30 (m, 2), 1.8 (m, 4) (lit.[22] δ 4.97 (br s, 2), 3.23 (s, 2), 2.16−2.67 (m, 4), 1.67−2.0 (m, 4); 4.94 (s, 1), 4.88 (s, 1), 3.19 (s, 2), 2.40−2.50 (m, 2), 2.19−2.32 (m, 2), 1.58−1.94 (m, 4)[8b]); 200 MHz NMR (d_8-toluene) δ 4.70 (br s, 1), 4.66 (br s, 1), 2.90 (s, 2), 2.2 (m, 2), 1.90 (m, 2), 1.30 (m, 4); ^{13}C NMR 211.4, 143.1, 115.7, 52.6, 43.5, 38.3, 30.9, 24.6.

3-Methyl-2-cycloheptenone (1, n = 3, R = CH_3) and 3-Methyl-3-cycloheptenone (2, n = 3, R = CH_3). These materials were isolated as hydrolysis products of the ethylene ketal **9** (n = 3) that was standing on the bench for several weeks. A mixture containing 100 mg of the two endo isomers of the 7-membered ketone (with a small amount of ketal still intact) was completely hydrolyzed by the Sterzycki PPTS method.[15] Workup by dilution with water, extraction with ether, careful removal of solvent, and preparative-layer chromatography (silica gel, CH_2Cl_2) gave two bands. The faster

(non-UV absorbing) and slower (strong UV) bands were extracted with ether and carefully reduced in volume.

3-Methyl-3-cycloheptenone (**2**, $n = 3$, R = CH_3) was isolated from the faster band as a mixture with some (19%) exocyclic isomer **3** ($n = 3$) after bulb-to-bulb distillation at approximately 100 °C (8 mmHg) as a film (less than 10 mg). Thin-layer chromatography (silica gel, CH_2Cl_2, I_2) showed one spot, while GC (2% OV-17, 80−120 °C, 6°/min) exhibited 19% at the retention time of the exo isomer and 81% at a slightly slower retention time. 200 MHz NMR shows <20% of the exo isomer. For the Δ^3 isomer **2** ($n = 3$, R = CH_3): 200 MHz NMR δ 5.53 (br t, 1, $J = 5$ Hz), 3.19 (br s, 2), 2.55 (m, 2), 2.3 (m, 2), 1.78 (s, 3), 1.61 (m, 2) (lit.[37] δ 5.53 (t, 1, $J = 5.1$), 3.19 (s, 2), 2.55 (t, 2, $J = 6.4$), 2.25 (m, 2), 1.94 (m, 2), 1.78 (s, 3)); 200 MHz NMR (d_8-toluene) δ 5.22 (5, 1, $J = 3$ Hz), 2.83 (s, 2), 2.19 (m, 2), 1.86 (m, 2), 1.54 (s, 3), 1.3 (m, 2).

3-Methyl-2-cycloheptenone (**1**, $n = 3$, R = CH_3) was isolated by extraction of the slower (UV absorbing) band with ether and bulb-to-bulb distillation of the residue at 120 °C (10 mmHg) to give 25 mg of the Δ^2 isomer as a clear oil. Thin-layer chromatography and GC (as above) showed one component: IR (neat) 1680−1630, 955, 875−855, 740 cm^{-1} (lit. 1650 cm^{-1},[26] (CCl_4) 1661 cm^{-1} [22]); 200 MHz NMR δ 5.94 (br s, 1), 2.58 (m, 2), 2.42 (m, 2), 1.96 (d, 3, $J = 1.6$ Hz), 1.8 (m, 4) (lit. (CCl_4) 5.85 (br s, 1), 2.3−2.7 (m, 4), 1.7−2.0 (m, 4), 1.97 (s, 3)[26]; ($CDCl_3$) 5.93 (s, 1), 2.51−2.62 (m, 2), 2.37−2.46 (m, 2), 1.96 (s, 3), 1.70−1.84 (m, 4)[8b]); 200 MHz NMR (d_8-toluene) δ 5.89 (br s, 1), 2.32 (m, 2), 1.78 (m, 2), 1.46 (br s, 3), 1.2−1.4 (m, 4); ^{13}C NMR δ 203.5, 158.2, 129.9, 42.5, 34.6, 27.5, 25.2, 21.5; UV (absolute ethanol) λ_{max} 236.5 nm ($\epsilon = 11\,400$), 314 nm ($\epsilon = 68$) (lit.[38] (EtOH) λ_{max} 238 nm ($\epsilon = 13\,600$)). HRMS: calcd for $C_8H_{12}O$: 124.0888. Found: 124.0888.

3-Methylenecyclooctanone (3, *n* = 4). The ethylene ketal **9** ($n = 4$) was hydrolyzed according to the method of Sterzycki.[15] A solution of 12.2 g (0.067 mol) of the ethylene ketal in 55 mL of acetone plus 15 mL of H_2O was prepared. To this solution was added 750 mg (0.0030 mol) of PPTS, and the solution was stirred in an oil bath heated at 65 °C. When gas chromatography (20% SE-30 at 190 °C) showed no remaining starting material (~2 h), the reaction mixture was cooled, poured onto 200 mL of H_2O, and extracted with 50 mL portions of diethyl ether five times. These extracts were combined, washed well with water and once with saturated brine, dried ($MgSO_4$), and concentrated carefully under reduced pressure to yield 7.4 g (80%) of a clear oil: IR (neat) 3070, 1700, 1630, 905 cm^{-1}; NMR indicated that this material contained some solvent peaks and a trace of the Δ^2 isomer (tiny peak at δ 6.05).

The entire sample was chromatographed on 200 g of silica gel utilizing 8% acetone in hexanes as eluent. The fractions were checked by TLC (silica gel, 8% acetone/hexanes), combined as appropriate, and concentrated carefully under reduced pressure to yield 5.86 g (63.4%) of the desired exocyclic methylenecyclooctanone (contaminated with solvent residues) along with 700 mg (7.6%) of a mixture consisting mainly of the Δ^2 isomer **1** ($n = 4$, R = CH_3).

Because the desired exocyclic methylene compound was still not totally pure, 5 g of the mixture was subjected to vacuum distillation in a Firestone still, giving 2.1 g (23% overall) of the desired methylene compound as a clear oil: bp 97−98 °C (12 mmHg); TLC (silica gel, 10% ether in hexanes) shows one non-UV spot at R_f 0.4 (I_2); gas chromatography shows only one peak in two different systems (20% SE-30 at 170 °C and 1% OV-17 at 100 °C); IR (neat) 3070, 1700, 1640, 905 cm^{-1} (lit. 3075, 1700, 1640, 900 cm^{-1})[8a], 200 MHz NMR δ 5.10 (q, 1, $J = 1.5$ Hz), 5.02 (br s, 1), 3.08 (d, 2, $J = 1$ Hz), 2.50 (dd, 2, $J = 4$ and 4.5 Hz), 2.26 (t, 2, $J = 4$ Hz), 1.74 (m, 2), 1.52 (m, 4); 200 MHz NMR (d_8-toluene) δ 4.79 (m, 1), 4.66 (br s, 1), 2.76 (s, 2), 2.17 (m, 2), 1.91 (m, 2), 1.48 (m, 2), 1.25 (m, 4); 200 MHz NMR in d_6-benzene is essentially identical (lit.[8a] (CCl_4) δ 5.00 (br s, 2), 2.97 (s, 2), 2.30 and 1.55 (m, total of 6 and 4 H)); ^{13}C NMR δ 213.5, 143.1, 117.1, 52.6, 39.3, 37.9, 27.7, 25.9, 25.0; UV (absolute ethanol) λ_{max} 293 nm ($\epsilon = 57$) (lit.[8a] (isooctane) λ_{max} 285 (34.5), 293 (38), 301 (37), 312 (27), 323 (12.5)); mass spectrum *m/z* 138 (M^+), 110, 109, 95, 81. Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.41; H, 10.15.

3-Methyl-2-cyclooctenone (1, *n* = 4, R = CH_3). The 700 mg mixture containing the Δ^2 isomer (above) was also purified further by preparative layer chromatography on Analtech plates (silica gel GF, 1000 μm) eluted with 10% acetone in hexanes followed by bulb-to-bulb distillation at 135−140 °C (14 mmHg) to give a clear oil: TLC (silica gel GF, 8% acetone/hexanes) R_f 0.3, strong UV absorbance; gas chromatography (20% SE-30 at 170 °C and 2% OV-17 at 120 °C) shows one peak: IR (neat) 3020, 2930, 2860, broad 1650, 1450, 1265, 885, 845 cm^{-1} (lit.[39] 2940, 1650, 1450, 1380, 1340, 1265, 1145, 885, 845 cm^{-1}); 200 MHz NMR δ 6.06 (br s, 1), 2.73 (t, 2, $J = 7$ Hz), 2.59 (dd, 2, $J = 6$ and 7 Hz), 1.94 (d, 3, $J = 1.5$ Hz), 1.8−1.5 (m, 6) (lit.[39] (CCl_4) 5.78 (br m, 1), 2.8−2.2 (br m, 4), 1.84 (d, 3, $J = 1.5$ Hz), 2.1−1.35 (br m, 4)); 200 MHz NMR (d_8-toluene) δ 5.98 (br s, 1), 2.44 (m, 2), 2.02 (m, 2), 1.48 (s, 3), 1.43 (m, 2), 1.23 (m, 4); 200 MHz NMR in d_6-benzene is almost identical; ^{13}C NMR δ 203.9, 153.0, 130.3, 42.1, 33.4, 27.6, 24.3, 23.5, 22.8; UV (absolute ethanol) λ_{max} 237.5 nm ($\epsilon = 11\,400$), 308 nm ($\epsilon = 100$) (lit.[39] (95% EtOH) λ_{max} 245 nm ($\epsilon = 7500$)); mass spectrum *m/z* 138 (M^+), 123, 109, 95, 85, 83 (base), 67 (lit.[39] 138, 123, 109, 95 (base), 82, 67). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.59; H, 10.58.

This isomer is identical in all respects to that observed and isolated as the α,β-unsaturated ketone in all of the base-catalyzed isomerizations of this study.

3-Methyl-3-cyclooctenone (2, *n* = 4, R = CH_3). This isomer in the 8-membered series was prepared by a large scale base-catalyzed isomerization of 3-methylenecyclooctanone (**3**, $n = 4$) which was "pushed" by using an excess of base. A solution of 440 mg (3.2 mmol) of the exocyclic methylene compound in 13 mL of toluene was refluxed for 6 days together with 0.6 mL (4.8 mmol) of DBN. The reaction was monitored by GC and 200 MHz NMR analysis of small probes which had been quenched in the usual way (see below). It was stopped when a ratio of 67% of the Δ^3 isomer **2** ($n = 4$, R = CH_3) and 33% of the Δ^2 isomer **1** ($n = 4$, R = CH_3) had been obtained. The reaction mixture was added to 30 mL of 5% sulfuric acid and extracted well with pentane. The organic phase was washed with water until neutral and dried ($MgSO_4$), and the solvent was carefully removed by distillation. The crude product was chromatographed by preparative TLC (Analtech, silica gel GF, CH_2Cl_2), with the faster (non-UV absorbing) band assigned structure **2** and the slower (strongly UV absorbing) band assigned structure **1**.

The faster band was further purified by bulb-to-bulb distillation at 85−90 °C (7 mmHg) to give 160 mg of 3-methyl-3-cyclooctenone (**2**, $n = 4$, R = CH_3) shown to be one component by GPC (2% OV-17 at 120 °C) and TLC (silica gel, CH_2Cl_2, I_2); IR (neat) 3030, 1700, 1665, 890, 840, 825 cm^{-1}; 200 MHz NMR δ 5.44 (dt, 1, $J = 1.3$ and 7.6 Hz), 3.05 (s, 2), 2.40 (m, 2, $J = 5.5$ Hz), 2.05 (m, 2), 1.6−1.8 (m with s at 1.72, 5), 1.55 (m, 2); 200 MHz NMR (d_8-toluene) δ 5.17 (dt plus, 1, $J = 8$ and 2.5 Hz), 2.77 (s, 2), 2.14 (m, 2), 1.82 (m, 2), 1.51 (s, 3), 1.48 (m, 2), 1.25 (m, 2); ^{13}C NMR δ 212.7, 131.8, 125.7, 48.3, 42.3, 27.8, 26.3, 25.0, 24.5; UV (absolute ethanol) λ_{max} 291 nm ($\epsilon = 94$). Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.01; H, 10.00. Although referred to in the literature,[40] no physical data were reported.

The slower band, which was highly absorbing under ultraviolet light, was isolated as 80 mg of a clear oil after bulb-to-bulb distillation at 95 °C (5.5 mmHg) and was assigned structure **1** ($n = 4$, R = CH_3). Spectral characteristics were identical with those already described.

3-Methylenecyclononanone (3, *n* = 5). The above method[15] was used to hydrolyze 9.1 g (0.046 mol) of the 9-membered ethylene ketal **9** ($n = 5$) in 55 mL of acetone with 15−20 mL of H_2O and 650 mg (0.003 mol) of PPTS at 65 °C. The reaction was followed by GC (20% SE30 at 190 °C) and showed completion after 1 h. Workup as above yielded 7 g (100%) of a clear oil which still contained some solvents.

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(40) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.

Column chromatography on 200 g of silica gel in 1% Et_2O/CH_2Cl_2 gave 4.48 g (64%) of the desired 3-methylenecyclononanone (contaminated with solvent residues) along with 30 mg of the Δ^2 isomer 3-methyl-2-cyclononenone (**1**, $n = 5$, R $= CH_3$). Spectral data for the Δ^2 isomer: IR (neat) no 3070, broad 1670−1610 (λ_{max} 1640), no 900 cm^{-1}; NMR (C_6D_6) δ 6.08 (br s, 1), 2.7−2.4 (m, 2), 2.42.0 (m, 2), 1.52 (d, $J = 1.5$ Hz) and 1.8−1.1 (m); TLC (silica gel, 1% Et_2O/CH_2Cl_2) R_f 0.3 with strong UV absorbance; gas chromatography (20% SE-30 at 170 °C) 95% at 8.2 min plus 5% at 5.3 min (exo-methylene **3**). These are in agreement with the more complete data cited later.

The entire sample of 4.48 g was distilled under reduced pressure to give 3.15 g (45%) of pure **3** ($n = 5$) as a clear oil which would crystallize at less than 0 °C; bp 115−118 °C at 12 mmHg; TLC (silica gel GF, either 1% Et_2O/CH_2Cl_2 or 8% acetone/hexanes) R_f 0.65 (I_2, no UV); gas chromatography (20% SE-30 at 170 °C or 1% OV-17 at 100 °C) 99% clean; IR (neat) 3075, 2930, 2870, 1703, 1640, 1440, 1200, 900 cm^{-1} (lit.[8a] 3080, 2930, 2870, 1702, 1635, 1440, 1200, 895 cm^{-1}); ($CDCl_3$ solution) 3075, 1690, 1635, 850 cm^{-1}; 200 MHz NMR δ 5.12 (d, 2, $J =$ 1.2 Hz), 3.15 (s, 2), 2.52 (dd, 2, $J = 6$ and 6.5 Hz), 2.25 (dd, 2, $J = 4.5$ and 6 Hz), 1.76 (m, 2), 1.6−1.35 (m, 6) (lit.[8] (CCl_4) δ 5.03 (s, 2), 3.03 (s, 2), two large multiplets centered at 2.33 and 1.45 (12 H)); 200 MHz NMR (d_6-benzene) δ 4.90 (m, 2, $J =$ 1 Hz), 2.87 (d, 2, $J = 0.8$ Hz), 2.19 (dd, 2, $J = 6$ and 6.5 Hz), 1.98 (m, 2), 1.56 (m, 2), 1.34 (m, 6); ^{13}C NMR δ 213.4, 143.3, 116.7, 54.6, 40.9, 35.6, 25.8, 25.6, 25.1, 24.7; UV (absolute ethanol) λ_{max} 294 nm ($\epsilon = 79$) (lit.[8a] (isooctane) λ_{max} 285 nm ($\epsilon =$ 45), 293.5 nm ($\epsilon = 45.5$), 303 nm ($\epsilon = 42$), 312.5 nm ($\epsilon =$ 29)); mass spectrum m/z 152 (M^+), 109, 95, 81, 67, 55, 41. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.91; H, 10.63.

3-Methyl-2-cyclononenone (1, $n = 5$, R $= CH_3$) and 3-methyl-3-cyclononenone (2, $n = 5$, R $= CH_3$) were prepared in the same way as the 8-membered analogs. A solution of 430 mg (2.8 mmol) of 3-methylenecyclononanone (**3**, $n = 5$) and 0.6 mL (4.8 mmol) of DBN in 13 mL of toluene was refluxed for 6 days. During this time some solvent was lost through a bad seal. Analysis by 200 MHz NMR and GC (2% OV-17, 120 °C) showed a ratio of 85% of the Δ^3 isomer **2** and 15% of the Δ^2 isomer **1**. Acid quench in 5% H_2SO_4, extraction with pentane, and careful distillation of the solvent gave 900 mg of the crude mixture contaminated with toluene. Chromatography on preparative layer plates (silica gel, CH_2Cl_2) produced a non-UV absorbing fast band, **2**, and a strongly absorbing slower band, **1**.

Bulb-to-bulb distillation of the fast band at 95−100 °C (7.6 mmHg) gave 275 mg of the Δ^3 isomer as a clear oil. This material showed one component by TLC (silica gel, CH_2Cl_2, I_2) and GC (2% OV-17, 120 °C): IR (neat) 3010, 1700, 1663, 885, 853 cm^{-1}; 200 MHz NMR δ 5.31 (dt, 1, $J = 8.3$ and 1.3 Hz), 3.08 (s, 2), 2.44 (m, 2), 2.13 (m, 2), 1.87 (s, 3), 1.7 (m, 2), 1.44 (m, 4); 200 MHz NMR (d_8-toluene) δ 5.06 (br t, 1, $J =$ 8-9 Hz), 2.74 (s, 2), 2.10 (m, 2), 1.93 (m, 2), 1.76 (s, 3), 1.40 (m, 2), 1.2 (m, 4); ^{13}C NMR δ 211.7, 129.9, 126.6 (=CH, C4), 46.6, 44.1, 26.7, 25.7, 25.6 (CH_3), 24.5, 22.8; mass spectrum m/z 152 (M^+), 109 (base, $M^+ - 43$); UV (absolute ethanol) λ_{max} 293 nm ($\epsilon = 118$). Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.53; H, 10.19. Although described in the literature,[41] no physical data were reported.

The slower moving band of the chromatography was further purified by bulb-to-bulb distillation at 115−120 °C (6.4 mmHg) to give 61 mg of the Δ^2 isomer as a clear oil. The one-spot material absorbed UV light strongly on indicating TLC plates (silica gel, CH_2Cl_2) and did not strongly absorb I_2. Gas chromatography (2% OV-17, 120 °C) also showed only one component: IR (neat) 3010, 1685, 1640, 880 cm^{-1}; 200 MHz NMR δ 6.02 (br s, 1), 2.7 (m, 2, $J = 5.5$ and 6.5 Hz), 2.6 (m, 2, $J = 5.5$ and 6.5 Hz), 1.94 (d, 3, $J = 1.3$ Hz), 1.82 (m, 2), 1.6 (m, 4), 1.44 (m, 2); 200 MHz NMR (d_8-toluene) δ 6.0 (br s, 1), 2.44 (m, 2, $J = 5.6$ and 6 Hz), 2.1 (m, 2, $J = 4$ and 6.5 Hz), 1.66 (m, 2), 1.5 (s, 3), 1.2−1.4 (m, 6); ^{13}C NMR δ 205.8, 153.5, 130.8, 41.1, 31.1, 28.9, 28.6, 27.4, 26.8, 24.4; UV (absolute ethanol) λ_{max} 239.5 nm ($\epsilon = 11\,200$), 315 nm ($\epsilon = 91$). HRMS: calcd for $C_{10}H_{16}O$ 152.1201. Found: 152.1203.

3-Methylenecyclodecanone (3, $n = 6$). The method of Sterzycki[15] was used to hydrolyze 1.1 g (5.25 mmol) of ethylene ketal **9** ($n = 6$) in 30 mL of acetone with 2 mL of H_2O and 200 mg (0.8 mmol) PPTS at 65 °C. Gas chromatography (20% SE-30, 190 °C) indicated complete reaction after 3 h. Workup as above yielded 860 mg (99%) of 3-methylenecyclodecanone as a clear oil which crystallized upon standing at room temperature: mp < 30 °C. Both thin-layer (silica gel, 10% Et_2O/hexane) and gas chromatography (20% SE-30, 190 °C or 2% OV-17, 100 °C) showed >95% clean material: IR (Nujol) 3070, 2690, 1810, 1700, 1635, 905, 925 (shld) cm^{-1}; 200 MHz NMR δ 5.07 (s, 2), 3.14 (s, 2), 2.64 (dd, 2, $J = 6.2$ and 6.6 Hz), 2.20 (m, 2), 1.78 (m, 2), 1.40 (narrow m, 8); 200 MHz NMR (d_8-toluene) δ 4.84 (br s, 1), 4.81 (br s, 1), 2.82 (s, 2), 2.24 (m, 2, $J =$ 6.2 and 6.4 Hz), 1.97 (m, 2), 1.65 (m, 2), 1.33 (m) and 1.23 (m) (total 8 H); this NMR is almost identical with that run in d_6-benzene; ^{13}C NMR δ 211.5, 143.9, 117.6, 54.0, 37.6, 36.1, 25.5, 25.3, 23.2, 23.0; UV (absolute ethanol) λ_{max} 290 nm ($\epsilon =$ 72); mass spectrum m/z 166 (M^+), 123, 98, 67, 55 (base). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.54; H, 10.74.

3-Methyl-2(*Z*)-cyclodecenone (1Z, $n = 6$, R $= CH_3$) and 3-Methyl-3(*Z*)-cyclodecenone (2Z, $n = 6$, R $= CH_3$). These endocyclic isomers were prepared as in the other ring sizes. A solution of 340 mg (2 mmol) of 3-methylenecyclodecanone (**2**, $n = 6$) and 0.6 mL (4.8 mmol) of DBN in 13 mL of toluene was heated to reflux. Small probes were removed, quenched in the usual way, and analyzed by 200 MHz NMR and GC. Heating for 10 days under these conditions, followed by the usual acid workup, resulted in the recovery of 800 mg of a toluene solution containing the *Z* Δ^2 and *Z* Δ^3 isomers in a 47:53 percent ratio, respectively. Preparative layer chromatography on silica gel plates eluted with 20% hexane in CH_2Cl_2 produced two closely eluting bands, a faster non-UV absorbing spot (strong I_2) and a slightly slower strong UV spot (weak I_2).

The faster spot was extracted (ether), carefully concentrated, and isolated by bulb-to-bulb distillation at 105−100 °C (5 mmHg) to give 120 mg of **2Z** ($n = 6$, R $= CH_3$) as a clear oil. Both TLC (silica gel, 2/1 CH_2Cl_2/hexane, I_2) and GC (2% OV-17, 120 °C) indicated one component: IR (neat) 3010, 1700, 1665 (shld), 870, 853 cm^{-1}; 200 MHz NMR δ 5.34 (br t, l, $J =$ 8 Hz), 3.10 (s, 2), 2.46 (m, 2, $J = 6.5$ Hz), 2.1 (m, 2), 1.86 (s, 3), 1.7 (m, 2), 1.3−1.6 (m, 6); 200 MHz NMR (d_8-toluene) δ 5.07 (br t, 1, $J = 8$ Hz), 2.80 (s, 2), 2.13 (m, 2), 1.87 (m, 2), 1.70 (s, 3), 1.5 (m, 2), 1.2−1.4 (m, 6); ^{13}C NMR δ 214.4, 131.2, 128.4, 47.9, 37.7, 26.7, 25.8, 25.4, 25.3, 23.5, 22.1; UV (absolute ethanol) λ_{max} 293 nm ($\epsilon = 57$); mass spectrum m/z 166 (M^+), 151, 123, 109, 95, 96 (base). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.30; H, 10.57.

Assignment of the *Z* configuration is based upon stability considerations, comparison of spectral data with the smaller rings in the series (*all-Z*), and with a similar dehydromuscone[42] and related materials.[4,24,25]

The UV-absorbing TLC spot was extracted (ether), concentrated, and isolated by bulb-to-bulb distillation at 110−115 °C (5.5 mmHg) to give 120 mg of a clear oil assigned structure **1Z** ($n = 6$, R $= CH_3$). Both TLC (silica gel, 2/1 CH_2Cl_2/hexane) and GPC (2% OV17, 120 °C) indicated one component: IR (neat) 3350, 1675, 1630, 825 cm^{-1}; 200 MHz NMR δ 6.12 (s, 1), 2.3−2.5 (m, 4), 1.9 (m, 2), 1.79 (d, 3, $J = 1.3$ Hz), 1.5 (m, 4), 1.2 (m, 4); 200 MHz NMR (d_8-toluene) δ 5.71 (br s, 1), 2.40 (t, 2, $J = 7.5$ Hz), 2.1 (m, 2, under methyl peak in d_8-toluene), 1.6 (m, 2), 1.44 (d, 3, $J = 1$ Hz), 1−1.4 (m, 8); ^{13}C NMR δ 208.7, 147.1, 128.7, 44.8, 28.4, 27.6, 23.0, 22.6 (CH_3), 22.0, 21.3, 21.2; UV (absolute ethanol) λ_{max} 237 nm ($\epsilon = 5600$), 301 ($\epsilon = 78$); mass spectrum m/z 166 (M^+), 151, 123, 109, 95 (base). Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; 10.91. Found: C, 79.51; H, 10.54.

Assignment of the *Z* configuration is based upon NMR data, comparison with spectra in the other ring sizes and the unsubstituted analog (**1Z**, $n = 6$, R = H),[24] and stability considerations.

(41) Damiano, J.-C.; Luche, J.-L.; Crabbe, R. *Tetrahedron Lett.* **1976**, 779.

(42) Shono, T.; Hayashi, J.; Onoto, H.; Matsumura, Y. *Tetrahedron Lett.* **1977**, 2667.

3-Methyl-2(*E*)-cyclodecenone (1E, $n = 6$, R = CH_3) is only briefly present during isomerization procedures and required mild isomerization conditions in order to be isolated. A solution of 130 mg (0.78 mmol) of 3-methylenecyclodecanone (**3**, $n = 6$) and 0.05 mL (0.4 mmol) of DBN in 3 mL of toluene was stirred at room temperature during the day and stored in the freezer overnight (to prevent over-reaction) for 12 days. Comparison of TLC and GC probes (quenched as usual) with starting material (fast) and the *Z* isomer **1Z** ($n = 6$, R = CH_3) (slightly faster than *E*) indicated that quenching the reaction while starting material **3** was still present was required to prevent complete conversion to **1Z**. Usual workup and very careful preparative layer chromatography (silica gel, 8% ether in hexane; eluted, dried, and eluted again), extraction of the slower UV active band with ether, and rechromatography as above produced one isomer. Bulb-to-bulb distillation at 90 °C (0.9 mmHg) produced only a few milligrams of the 3-methyl-2(*E*)-cyclodecenone as a clear oil. Thin-layer chromatography (silica gel, 10% ether in hexane; eluted, dried, and eluted again) showed a UV active material just slightly slower than **1Z** ($n = 6$, R = CH_3) and GC (2% OV-17, 120 °C) showed >95% of the trans isomer **1E** ($n = 6$, R = CH_3) at t_R 7.8 min (relative to the cis **1Z** at 6.3 min): IR (neat) 3360, 1680−1695, 1620, 1465, 1220, 900, 870, 775, 720 cm^{-1}; 200 MHz NMR δ 6.45 (d, 1, $J = 2.5$ Hz), 2.34 (m, 2), 2.13 (m, 2), 1.89 (d, 3, $J = 2.5$ Hz), 1.79 (m, 2), 1.5 (m, 4), 1.34 (m, 2), 1.16 (m, 2); 200 MHz NMR (d_8-toluene) δ 6.05 (br s, 1), 2.1 (m, 2), 1.79 (d, 3, $J = 1$ Hz), 1.76 (m, 2), 1.4 (m, 2), 1.19 (m, 4), 1−1.2 (m, 4); UV (absolute ethanol) λ_{max} 238.5 nm ($\epsilon = 6940$). HRMS: calcd for $C_{11}H_{18}O$ 166.13573. Found: 166.13573.

Base-Catalyzed Isomerizations of Cycloalkenones. Two methods were generally employed to conduct these experiments: large-scale (generally 100−200 mg of olefin) or NMR-scale (using 5−15 mg of olefin).

Method 1, Large-Scale.[2] A typical isomerization was conducted in the following manner: A sample of 200 mg of the starting isomer was dissolved in 8 mL of toluene (distilled under N_2), and 0.1 mL (approximately $^2/_3$ of an equivalent) of DBN was added. (All glassware was oven-dried and the DBN periodically distilled and stored under N_2.) A condenser was fitted and the system purged of air with a Firestone valve. The reaction mixture was stirred at the appropriate temperature under a N_2 atmosphere. Temperature was maintained in an oil bath controlled by a Therm-O-Watch apparatus. The isomerization was continued until no further change in the product ratio was observed by gas chromatography. The reaction mixture was then quenched by pouring onto 5% aqueous H_2SO_4 solution and extracting repeatedly (at least 5 times) with 20 mL portions of Gold Label (Aldrich) pentane. The organic layers were combined, washed with water until neutral and once with saturated brine, and dried ($MgSO_4$). The final isomer ratio was then determined by the average of at least three chromatograms. The area of the chromatography peaks was determined by the height multiplied by the width at one-half the peak height. (This method was verified by running a control experiment with weighed amounts of isomers.) The solution was concentrated by slow and careful distillation at atmospheric pressure. Product ratios were often confirmed by integration of the vinylic ^{1}H NMR peaks.

Method 2, NMR-Scale. All NMR tubes were of a special thick-wall type which were oven-dried and sealed during reaction by a special high-pressure triple-seal cap and wrapped with Parafilm. A typical experiment involved dissolving 15 mg of the starting isomer in 0.5 mL of d_8-toluene (Aldrich 99 + % D atom) and adding 7.5 μL (approximately $^2/_3$ of an equivalent) of distilled DBN. The tube was flushed with argon and preheated a short time in the oil bath and the triple-seal cap applied. The ^{1}H NMR at zero time was recorded and the tube immersed in the oil bath at an appropriate temperature maintained as above. Periodic ^{1}H NMR spectra were taken at 200 MHz (at room temperature) until no further change in product ratio was observed (vinylic protons) or until decomposition (thought to be due to DBN) prevented continuation. Occasionally some NMR tubes were opened so that a confirming gas chromatography sample could be withdrawn for analysis (these were resealed as above). Not all samples were quenched and extracted. Those that were quenched followed the procedure as above on a smaller scale and were reanalyzed by both ^{1}H NMR and GC.

Typical Base-Catalyzed Isomerizations. See Tables 5−7.

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