= 6.5), 1.31 (s, 3), 3.24 (d, 1, J = 9.8), 3.65 (dd, 1, J = 4.0, 9.8), 4.17 (d, 1, J = 10.1), 8.22 (s, 1)]. Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.67; H, 10.20; N, 5.38.

(b) At 100 °C (Reflux Temperature). A solution of 104 mg (0.414 mmol) of **34** dissolved in 7 mL of 95% formic acid was heated at reflux under nitrogen for 12 h. The formic acid was removed with a rotary evaporator, and the residue was diluted with 50 mL of 10% aqueous $NaHCO_3$. The aqueous solution was extracted with 100 mL of CH_2Cl_2, and the organic phase was washed with brine, dried over Na_2SO_4, and concentrated to give 112 mg of a yellow oil. The crude product was purified by flash chromatography on 5 g of silica using a solvent gradient ranging from 1:4 to 1:1 EtOAc–hexane. The less polar fractions gave 23.3 mg (24%) of **38**. The more polar fractions yielded 63.2 mg (55%) of (1*RS*,4*SR*,7*RS*,8*RS*,10*SR*)-2-aza-8-(formyloxy)-7-methyl-10-(2-methylpropyl)tricyclo[5.2.1.$0^{4,10}$]decane-2-carboxaldehyde (**44**) as a colorless oil: IR ($CDCl_3$) 1722, 1640, 1380 cm^{-1}; ^1H NMR [for one rotational isomer] (250 MHz) 0.95 (complex, 9), 1.2–2.4 (complex, 9), 2.65 (m, 1), 3.02 (dd, 1, J = 6.1, 12.9), 4.11 (dd, 1, J = 9.3, 12.6), 4.53 (t, 1, J = 8.8), 5.23 (t, 1, J = 3.4), 8.07 (s, 1), 8.08 (s, 1) [the other rotational isomer showed additional signals at 3.23 (dd, 1, J = 6.8, 11.5), 3.92 (dd, 1, J = 9.1, 11.5), 4.24 (t, 1, J = 7.6), 8.13 (s, 1)]; mass spectrum, 279 (2.48), 264 (0.18), 250 (1.50), 234 (38.2), 223 (3.67), 204 (0.40), 190 (1.61), 177 (3.72), 163 (1.34), 151 (1.89), 132 (1.72). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.76; H, 8.82; N, 4.87.

(1*RS*,4*SR*,7*RS*,8*RS*,10*SR*)-2-Aza-2,7-dimethyl-10-(2-methylpropyl)tricyclo[5.2.1.$0^{4,10}$]decan-8-ol (45). To a suspension of $LiAlH_4$ (95%, 10.0 mg, 0.240 mmol) in 0.5 mL of ether under nitrogen at 0 °C was added, dropwise, a solution of 32.7 mg (0.117 mmol) of **44** in 0.5 mL of ether. The mixture was stirred for 15 min at 0 °C and was allowed to warm to room temperature. After 6 h, the suspension was diluted with 5 mL of ether; 1 drop of water, 1 drop of 15% aqueous NaOH, and 3 drops of water were added in succession. Sodium sulfate was added, and the mixture was stirred for 2 h. The solids were removed by suction filtration and were washed several times with ether. The filtrate was concentrated to give 24.1 mg (87%) of **45** as a white crystalline solid, which was judged to be pure by ^1H NMR spectroscopy: IR 3625, 2785, 1460, 1445, 1075, 1050 cm^{-1}; ^1H NMR (250 MHz) 0.88 (s, 3), 0.97 (d, 6, J = 6.6), 1.28 (d, 2, J = 4.8), 1.28 (m, 1), 1.50 (m, 3), 1.73 (m, 3), 1.92 (dd, 1, J = 5.7, 12.6), 2.25 (m, 1), 2.26 (s, 3), 2.44 (dd, 1, J = 6.0, 9.1), 2.52 (d, 1, J = 5.2), 2.63 (d, 1, J = 9.0), 4.09 (dd, 1, J = 5.7, 9.6); ^{13}C NMR (63 MHz) 15.7, 25.1, 25.9, 26.2, 30.3, 36.6, 38.7, 40.7, 44.4, 48.3, 55.1, 62.0, 65.0, 71.2, 77.9; mass spectrum, 237 (5.57), 222 (1.31), 204 (0.04), 194 (5.81), 180 (3.46), 164 (2.25), 150 (2.51), 136 (9.96), 122 (0.82), 108 (1.94), 94 (1.92), 86 (4.28), 70 (3.85). An analytical sample (mp 86–87.5 °C) was prepared by recrystallization from spectrophotometric grade pentane. Anal. Calcd for $C_{15}H_{27}NO$: C, 75.90; H, 11.46; N, 5.90. Found: C, 75.93; H, 11.50; N, 5.93.

Acknowledgment. This work was supported by grants from the National Science Foundation (CHE-79-06344 and CHE-81-20864). P.J.C. thanks the Regents of the University of California for financial assistance in the form of a Regents Fellowship.

Registry No. (±)-**1**, 30646-45-8; (±)-**8**, 97973-51-8; (±)-**9**, 97973-52-9; (±)-**10**, 97973-53-0; (±)-**11**, 97973-54-1; **12**, 97973-55-2; (4*RS*,7*RS*)-**13**, 97973-56-3; (4*RS*,7*SR*)-**13**, 97973-57-4; (4*RS*,7*RS*)-**14**, 97973-58-5; (4*RS*,7*SR*)-**14**, 97973-59-6; (±)-**15**, 97973-60-9; (±)-**16**, 97973-61-0; (±)-**18**, 89685-96-1; (±)-**19**, 97973-62-1; (±)-**20**, 97973-63-2; (±)-**21**, 97973-64-3; (±)-**23**, 97973-65-4; (±)-**24**, 97973-66-5; (±)-**26**, 97973-67-6; (±)-**29a**, 97973-68-7; (±)-**29b**, 98048-28-3; (±)-**30**, 97973-69-8; (±)-**31**, 97973-70-1; (±)-**32**, 97973-71-2; (±)-**33**, 97973-72-3; (±)-**34a**, 97973-73-4; (±)-**34b**, 98048-29-4; (±)-(*E*)-**38**, 97973-74-5; (±)-(*Z*)-**38**, 97973-75-6; (±)-**40** (isomer 1), 98087-64-0; (±)-**40** (isomer 2), 98168-17-3; (±)-**41** (isomer 1), 97973-76-7; (±)-**41** (isomer 2), 98048-30-7; (±)-**44**, 97973-77-8; (±)-**45**, 97973-78-9; 4-bromo-1-butene, 5162-44-7; *tert*-butyl acetoacetate, 1694-31-1; ethyl bromoacetate, 105-36-2.

Intramolecular Olefinic Aldehyde Prins Reactions for the Construction of Five-Membered Rings[1]

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Received August 29, 1983

Four catalysts ($Me_2AlCl \simeq SnCl_4 > EtAlCl_2 > Et_2AlCl$) for the cyclization of olefinic aldehydes by an internal Prins mechanism have been compared by using systems that afford five-membered rings by type I and type II ene processes. Stannic chloride and Me_2AlCl are clearly superior to the ethyl aluminum halides. Careful control of reaction conditions is required with Me_2AlCl in order to avoid byproducts that arise from competing ionic pathways. Chlorohydrin formation cannot be avoided with certain cyclopentane closures. These methods have been applied in the synthesis of a tricyclic trichothecane model in which the meta-fused five-membered C ring is generated by a net ene process (**4** → **5**). In this instance $SnCl_4$ effects a predominantly stepwise ionic cyclization. $TiCl_4$ is the best reagent for this transformation, affording essentially pure chloro alcohol **34**. Subsequent dehydrohalogenation completes the synthesis of **5** (86% overall yield from **4**). $TiCl_4$ has also been found to be a superior reagent for effecting cyclopentane closures in model systems; chlorohydrins are either isolated as such or deemed the likely intermediates for the resulting cyclopentenyl products. A means for controlling olefin regiochemistry in lactone eliminations (**32** → **31** or **33**, **24** → **26** or **27**) has been developed.

Meta-fused methylenecyclopentanol units are quite common in natural products. Homoallylic alcohols can generally be viewed as cyclization products of olefinic aldehydes; however, until Snider's work on R_xAlCl_{3-x}-"catalyzed" cyclizations[2] of olefinic carbonyl compounds, only a single example of five-membered ring formation (**1** → **2** + **3**) was recorded,[3] and to date only a single example of the formation of a meta-fused carbocycle by this means

(1) Reported in part in the thesis of Bacon, E. R. Ph.D. Thesis, University of Washington, 1981; *Diss. Abstr. Int. B* **1981**, *41*, 261013. Hadley, S. W.; Andersen, N. H. *Abstr. Pap—Chem. Congr. North Am. Cont., 2nd* **1980**, ORGN 112; *Abstr. Pap.—Am. Chem. Soc.* **1983**, *185th*, ORGN 220.

(2) (a) Karras, M.; Snider, B. B. *J. Am. Chem. Soc.* **1980**, *102*, 7951. (b) Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3957. (c) Snider, B. B.; Karras, M.; Price, R. T., Rodini, D. J. *J. Org. Chem.* **1982**, *47*, 4538–4545.

(3) Andersen, N. H.; Ladner, D. W. *Synth. Commun.* **1978**, *8*, 449–460.

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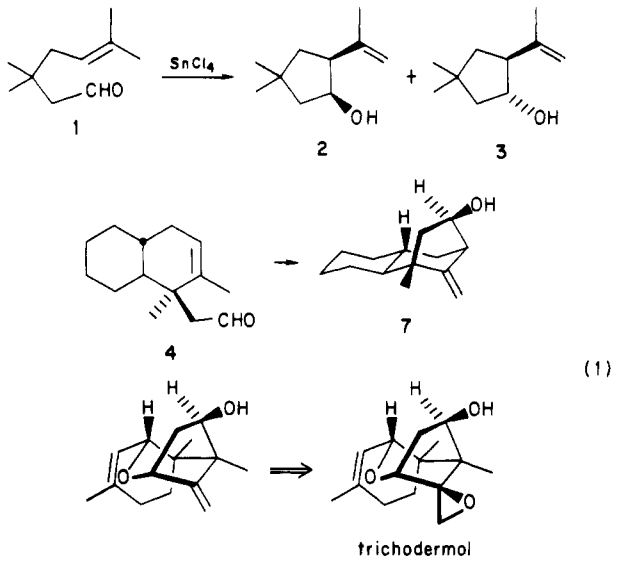
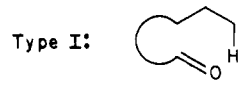


(1)

has appeared in the literature.[4] We now report further work on cyclopentanol formation which includes a successful cyclization (4 → **5**) that bears a resemblance to a synthetic precursor of trichodermol.

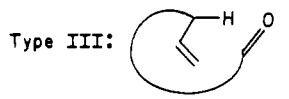
To the extent that the Lewis acid catalyzed cyclization of olefinic aldehydes can be viewed as a nearly concerted "ene" reaction, the possible modes of ring formation relative to the six-center transition state can be classified as follows for the formation of *n*-membered carbocyclic rings.

Type I: ortho-fused six-center transition state, two centers in both rings, loop size = $n - 2$.

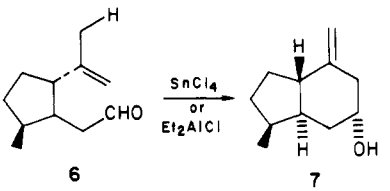


Type II: six-center transition state, meta-fused to carbocycle three centers shared, loop size = $n - 3$.

Type III: six-center transition state, para-fused, loop size = $n - 4$.



For type I processes the rate sequence for formation of various size cycloalkanols is $n = 6 > 5 \gg 7$. We have argued that this, together with the type II rate sequence ($n = 7 > 6 \gg 5$), is evidence for the concerted nature of the internal Prins reaction.[3,5] Net type III processes have been observed; however, ionic mechanisms seem more likely here, although several cases with $n = 7$ appear to be concerted.[5b] Snider's studies suggested that the ene process should not be viewed as general for five-membered rings. We therefore set out to compare a series of olefinic aldehydes yielding five- and six-membered rings using classical catalysts (e.g., $SnCl_4$) and proton-scavenging alkylaluminum halides.[2b]

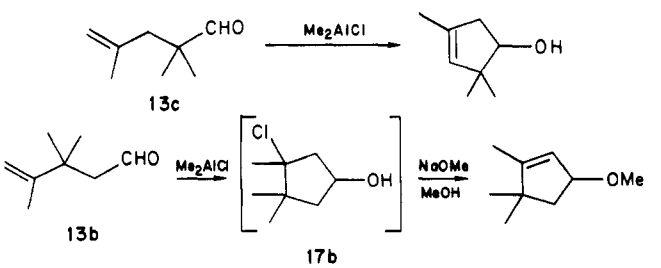


(2)

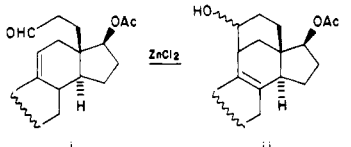
The systems (**8**, **13a–d**) for this study were selected to include tests of the influence of geminal dimethylation at the α-, β-, and γ-position relative to the aldehyde center. As an initial check on the suitability of R_xAlCl_{3-x} for cyclizations of olefinic aldehydes that display a strict stereospecificity due to the constraints associated with a concerted mechanism, we reexamined trans-hydrindanol formation (**6** → **7**). GC/MS analysis revealed that the axial isomer was the exclusive product (>98.5%) with both the Lewis acids illustrated.[6]

Comparison of Five- and Six-Membered Ring Formation. Table I gives the results for the isopropylidene-terminated aldehydes that cyclize by a type I process. All catalysts give excellent results for six-membered ring formation. Ethyl transfer is the major course of reaction between Et_2AlCl and **8b** under all conditions examined. The $SnCl_4$-catalyzed ene reaction of **8b** is confirmed under all conditions, but Me_2AlCl is a more convenient reagent for effecting this transformation since less stringent control (other than cooling) is required for high yields. At temperatures above −60 °C the cationic process leading to the trans chloro alcohol competes with the ene reaction. The α,α-dimethyl system **8c** reacts more slowly but also affords a ca. 85:15 mixture favoring the cis product. The cationic process, affording the trans-1,3-chlorohydrin, becomes the exclusive pathway when $TiCl_4$ is employed in place of Me_2AlCl (vide infra) and this new procedure gives superior yields (see entries 11 and 16). With $SnCl_4$, aldehyde **8c** affords the trans product, suggesting a nonconcerted mechanism.

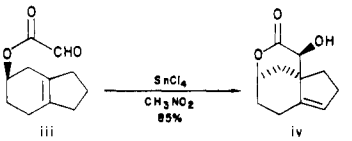
Five-member ring formation by a type II process proved more difficult (Table II): Et_2AlCl gave ethyl transfer; $EtAlCl_2$ served as a reducing agent (**13b** → **16b**). The latter side reaction cannot occur with Me_2AlCl. Aldehyde **13c** was cleanly cyclized by Me_2AlCl to the nonconcerted reaction product, a cyclopent-3-enol, as shown. However,



(4) A single example of the formation of a meta-fused six-membered carbocycle has come to our attention. This employed a 3-methoxy-activated A-ring aromatic steroid. A 16% yield of a mixture of epimers (i → ii) was realized.



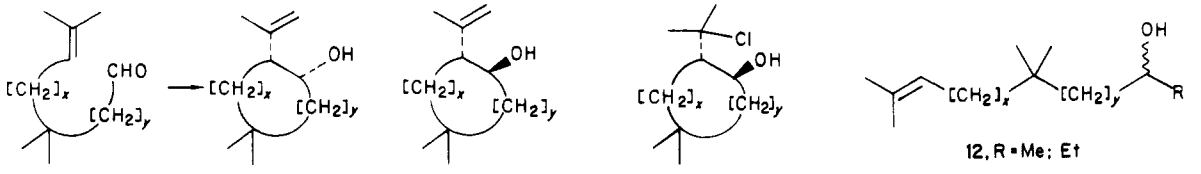
Pitt, C. G.; Rector, D. H.; Cook, C. E.; Wani, M. C. *J. Med. Chem.* **1979**, *22*, 966–970. This process is clearly not concerned. A related oxane formation (iii → iv) has been reported (Linder et al. *Tetrahedron Lett.* **1982**, *23*, 5111–5114.



(5) (a) Andersen, N. H.; Uh, H.-S.; Smith, S. E.; Wuts, P. G. M. *J. Chem. Soc., Chem. Commun.* **1972**, 955–957. (b) Andersen, N. H.; Ladner, D. W.; Moore, A. L. *Synth. Commun.* **1978**, *8*, 437–4448. Andersen, N. H.; Golec, F. A. *Tetrahedron Lett.* **1977**, 3783–3786.

(6) The equatorial hydroxy epimer was available from another study: Sarkar, T. K.; Andersen, N. H. *Tetrahedron Lett.* **1978**, 3513–3516.

Table I. Product Distributions of Type I Process



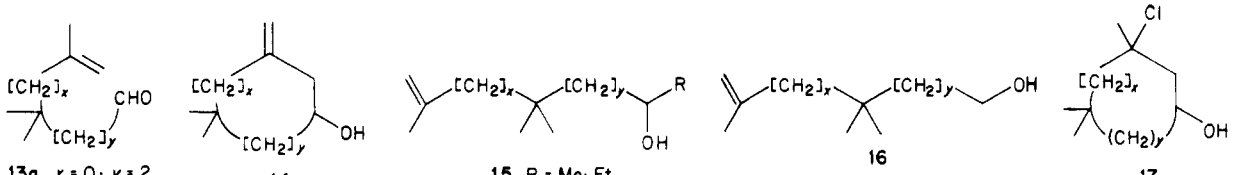
8a, $x = 2$, $y = 1$
b, $x = 1$, $y = 1$
c, $x = 2$, $y = 0$

9 10 11

entry	cyclization substrate [conc, M]	catalyst (equiv)	conditions time, h	conditions temp, °C	% product yield (distribution)[a] 9	10	11	12
1	**8a** [0.1]	$SnCl_4$ (0.15)	0.25	0	(8)	(92)		na
2	**8a** [0.2]	Et_2AlCl (1)	1.0	−72	(<2)	88 (100)		
3	**8b** [0.1]	$SnCl_4$ (0.1)	1.0	0	65 (77)	20 (23)		na
4	**8b** [0.05]	Et_2AlCl (1.1)	1.5	−72	(27)	(13)		(60)[b]
5	**8b** [0.04]	$EtAlCl_2$ (1)	0.8	−72	25 (45)	(<5)	30 (50)	(<5)
6	**8b** [0.05]	Me_2AlCl (1)	0.2	−72	(36)	(≈9)	*c*	
7	**8b** [0.05]	Me_2AlCl (1)	3	−72	(82)	(18)		
8	**8b** [0.05]	Me_2AlCl (1)	0.5	−50	41	10	43	
9	**8b** [0.05]	Me_2AlCl (2.2)	0.5	−45	(8)	(33)	(59)	*b*
10	**8b** [0.05]	$TiCl_4$ (0.1)	6.0	0	(<5)	(30)	(65)	na[b]
11	**8b** [0.1]	$TiCl_4$ (1)	0.33	0			85 (100)	na
12	**8c** [0.06]	$SnCl_4$ (0.17)	0.25	0	<5	31		na
13	**8c** [0.04]	Et_2AlCl (1)	1.0	−72	<3	<3		
14	**8c** [0.04]	$EtAlCl_2$ (1)	1.0	−72	10	<5	41 (65)	
15	**8c** [0.04]	Me_2AlCl (1)	10	−72	68	11	*d*	
16	**8c** [0.1]	$TiCl_4$ (1)	1.0	0			87 (100)	na

[a] Isolated yields of pure material are given. Parenthetic values are ratios of volatile products determined by NMR and/or GC after an initial chromatographic filtration. Na = not applicable. [b] Ratio by NMR. [c] 50% conversion. [d] 35% conversion.

Table II. Product Distribution of Type II Process



13a, $x = 0$; $y = 2$
b, $x = 0$; $y = 1$
c, $x = 1$; $y = 0$
d, $x = 2$; $y = 0$

14 15, R = Me; Et 16 17

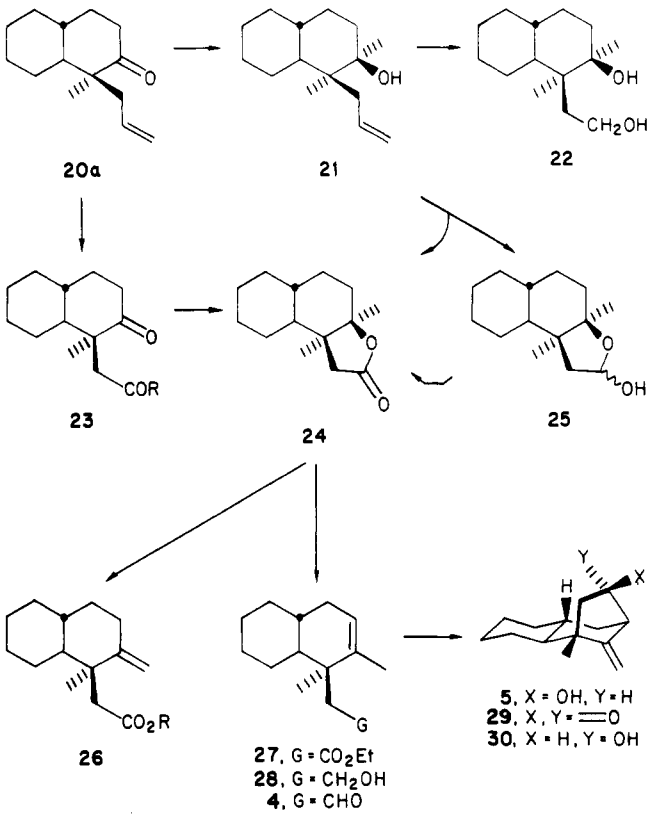
entry	cyclization substrate [conc, M]	catalyst (equiv)	conditions time, h	conditions temp, °C	% product yield (distribution)[a] 14	15	16	17
1	**13a** [0.09]	$SnCl_4$ (0.12)	0.5	0	88 (100)			
2	**13a** [0.04]	Et_2AlCl (1)	0.5	−72	92 (100)			
3	**13b** [0.1]	$SnCl_4$ (0.1)	1.0	0	nr[b]	nr[b]	nr[b]	nr[b]
4	**13b** [0.05]	Et_2AlCl (1)	3.0	−72		29 (100)		
5	**13b** [0.05]	Me_2AlCl (3.6)	0.25	0	*h*			
6	**13b** [0.04]	$EtAlCl_2$ (1)	0.8	−72	<5	<5	≈20[c]	
7	**13b** [0.05]	Me_2AlCl (1)	7.0	0	<5	10		≈60[e]
8	**13b** [0.1]	$TiCl_4$ (1)	0.10	0	<5			≲25[e,f]
9	**13c** [0.1]	$TiCl_4$ (1)	0.12	0				≲65[e]
10	**13c** [0.1]	$SnCl_4$ (0.1)	2.5	0	nr	nr	nr	nr
11	**13c** [0.05]	Et_2AlCl (1)	3.0	−72	nr	nr[b]	nr	nr
12	**13c** [0.04]	$EtAlCl_2$ (1)	0.2	−72[d]	<5	<5	≲5	
13	**13c** [0.05]	Me_2AlCl (1)	18	*g*				*i*
14	**13c** [0.05]	Me_2AlCl (3.8)	0.75	0				*i*
15	**13d** [0.1]	$SnCl_4$ (0.1)	0.1	0	95+ (100)			
16	**13d** [0.04]	Et_2AlCl (1)	1.0	−72	95 (100)			

[a] Isolated yields of pure material are given. Parenthetic values are ratios of volatile products determined by NMR and/or GC after an initial chromatographic filtration. Nr = no reaction. [b] Slow decomposition. [c] No aldehyde recovered. **16b** was the only volatile product detected. [d] Aldehyde **13c** recovered (≈40%). [e] From NMR of crude product. [f] Highly variable. [g] Room temperature. [h] Decomposition only. [i] Cyclopentenol, see text.

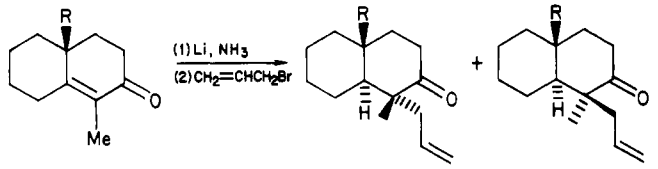
aldehyde **13b** upon treatment with Me_2AlCl gave a complex mixture. The crude NMR indicated the major product to be the cyclic tertiary chloride **17b** by virtue of a singlet at 1.53 ppm and a broad multiplet centered at 4.33 ppm. The yield was estimated at 60%. Also present was the 1,2-methyl adduct **15b** (~10%) and unidentified materials. Purification of this crude mixture led only to the decomposition of chlorohydrin **17b**. Attempts at the elimination of the crude chloride with DBN were unsuccessful; however, treatment with 0.5 N NaOMe/MeOH led to the cyclopent-2-enyl methyl ether as the major product. The results using $TiCl_4$ are discussed in a later section.

The Synthesis and Cyclization of Model Aldehyde 4. An axially oriented acetaldehyde side chain on a

Scheme I

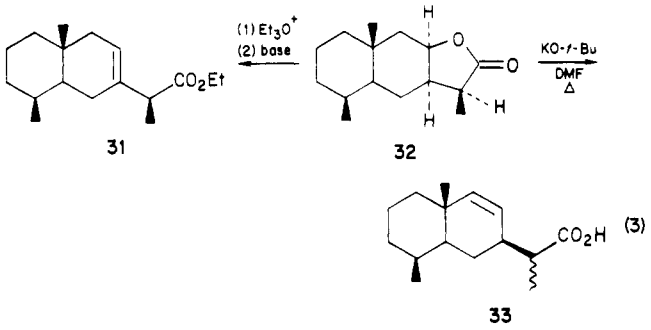


trans-fused octalin appeared to be a suitable test for the effect of conformational constraints in achieving the alignment of the reacting centers for the type II process. We chose an allyl unit as the acetaldehyde precursor and reductive allylation of an octalone as the means for ensuring the rigid trans fusion. The stereoselectivity of the ethylation of 1-methyl-1-octalin-2-olate with and without the added angular methyl has been determined by Matthews et al.[7] Our reduction–allylation results agree with respect to the exclusive equatorial (α) introduction in the presence of the β-oriented angular methyl. However, with **18a**, exclusive β-allylation was not observed.[8] Fortunately,

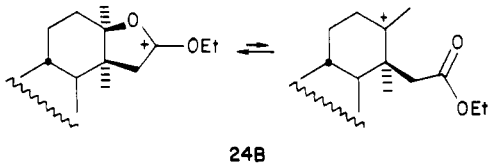


epimers **19a** and **20a** could be separated by either very careful spinning band distillation or by SiO_2 column chromatography. Their stereochemistry was assigned by using benzene solvent shifts for the NMR resonances of the methyl groups based on the literature analogies[7,9] and assuming that **19b** was a model for the behavior of an axial methyl α to the carbonyl. The further transformations that afforded octalins **4**, **27**, and **28** and the corresponding exomethylene isomers appear in Scheme I. Ozonolysis of allylated ketone **20a** afforded aldehyde **23** (R = H), which was converted to the methyl ester in order to set the stage for selective addition of a methyl at the ketone carbonyl. Keto ester **23** (R = OMe) reacted slowly with Me_3Al,[10] and even at low conversion the only product was lactone **24**, and this eventually became the intermediate of choice for production of both series of olefin isomers **26**, **27**.

Lactone **24** is prepared in higher overall yield via tertiary alcohol **21**. Methyllithium adds to ketone **20a** to give greater than 95% of the equatorial methyl carbinol. In numerous attempts to prepare diol **22** via ozonolysis with a reductive workup, lactol **25** was the major product: the lactol survives methanolic borohydride. For the actual synthesis of lactone **24**, alcohol **21** is ozonized in CH_2Cl_2 at −78 °C and quenched by addition to excess $NaBH_4$ in isopropyl alcohol at 0 °C. An 8:1 mixture of lactol epimers **25** and lactone **24** is obtained is essentially quantitative yield. Direct oxidation (PCC/pyr) affords lactone **24** in 89% overall yield. A typical elimination reaction under basic conditions (1.15 equiv of KO-*t*-Bu/DMF, 140 °C 3 h)[11] affords exclusively **26** (R = H), 86% yield, when applied to lactone **24**. We therefore applied a novel lactone elimination sequence (eq 2) which we first developed during our effort to synthesize acetoxydiplophyllin.[12] As



observed with lactone **24**, *tert*-butoxide converts tetrahydroalantolactone (**32**) to the less substituted olefinic acid. However treatment with triethyloxonium fluoroborate followed by a hindered base, typically 1,8-bis(dimethylamino)naphthalene [Proton Sponge (Aldrich)], gives the trisubstituted isomer **31**. Application of this method to lactone **24** afforded an 87% yield of olefinic ester favoring **27** by a 20:1 ratio. The reaction presumably proceeds via the oxocarbenium ion (**24B**); however no elimination is



observed even after a 48-h treatment with excess Et_3O^+-

(7) Matthews, R. S.; Girgenti, S. J.; Folkers, E. A., *J. Chem. Soc., Chem. Commun.* **1970**, 708–709.

(8) In ref 7, it is reported that reductive ethylation of **18a** proceeds in 60% to afford only the β-ethyl compound. Numerous attempts to improve the regio- and stereochemistry and to reduce the degree of overallylation by capture of enol derivatives and subsequent specific generation of the enolate failed to effect a more practical overall conversion in our hands.

(9) (a) Bhacca, N.; Williams, D.; Tetrahedron *Lett.* **1964**, 3127–3130 *Tetrahedron* **1965**, *21*, 1641–1645, 2021–2028. (b) Mathews, R. S.; Hyder, P. K.; Folkers, E. A. *J. Chem. Soc., Chem. Commun.* **1970**, 38–39.

(10) Me_3Al has been reported as a particularly selective source of nucleophilic Me which reacts with ketones in preference to esters: Andersen, N. H.; Subramanian, N.; Imamoto, S.; Picker, D. H.; Ladner, D. W.; McCrae, D. A.; Lin, B.-S.; De, B. *Prostaglandins* **1981**, *22*, 809–830 and references cited therein.

(11) The KO-*t*-Bu/DMF elimination conditions were modeled after the work of Wolinsky and co-workers: Wolinsky, J.; Gibson, T.; Chan, D.; Wolf, H. *Tetrahedron* **1965**, *21*, 1247–52. Eustace, E.; Wolinsky, J. *J. Org. Chem.* **1972**, *37*, 3376–3382. Solas, D.; Wolinsky, J. *Ibid.* **1983**, *48*, 760–773.

(12) Ohta, Y.; Andersen, N. H.; Liu, C.-B. *Tetrahedron* **1977**, *33*, 617–628.

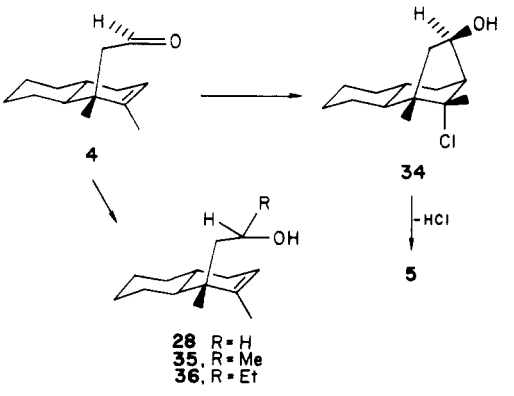
Table III. Cyclization Results for Aldehyde 4

Lewis acid (equiv)	conditions		% yield (product distribution)[c]				
	time, hr	temp	5	34	30	28	35/36
$SnCl_4$ (1.0)	3.5	−30	≈10[a]	≈50[a]	<5[a]		
$SnCl_4$ (1.0)	4.5	−20	42 (98+)[b]	12[b]	(0.5)[b]		
$TiCl_4$ (0.1)	3	−15	nr	nr	nr	nr	nr
$TiCl_4$ (1.0)	0.75	−20	<10 (98+)[a]	80–95+	(0)		
$TlCl_4$ (1.2)	0.75	−20	35–50[b]	10[b]			
Me_2AlCl (1.0)	26	−72	nr	nr	nr	nr	nr
Me_2AlCl (1.0)	4.5	0	≈5 (49)[a]	≈40	(0)		(50)[a]
Me_2AlCl (0.9)	2.0	24	≈17[d] (86)	≈47[d]	(0)		10[d] (11)
Et_2AlCl (0.9)	3.0	24	≈10 (30)	≈10	(0)	(54)	(16)
Me_3SiI (1.1)	0.25	−72	e	e	e	e	e

[a] Product analysis prior to SiO_2 column chromatography. [b] Isolated yields and GC composition data after column chromatography. [c] Parenthetic values are ratios of volatile products by GC analysis. When accompanied by an estimated yield, that estimate derives from an analysis of the NMR spectrum of the crude product. Chloride **34** is quantitatively converted to alcohol **5** during GC injection. Nr = no reaction. [d] % Yield based on unrecovered **4**. The reaction went to 80% completion. [e] Decomposition.

BF_4^-. Upon addition of Proton Sponge (Aldrich), the ester is produced at a modest rate—90+% completion of the reaction requires more than 16-h at ambient. Further applications of this lactone elimination method are under study.

The synthesis of aldehyde **4** was completed by $LiAlH_4$ reduction and PCC oxidation. The reactivity of aldehyde **4** toward a variety of Lewis acids—$SnCl_4$, $TiCl_4$, $SnBr_4$, ZnI_2, BF_3OEt_2, $EtAlCl_2$, and Et_2AlCl—was rapidly screened by adding 0.4 or 1.1 equiv of the catalyst to the CH_2Cl_2 solution of **4** at dry ice temperatures, monitoring by TLC as the temperature was raised in stepwise fashion to ambient. Of the catalysts listed, $SnCl_4$ proved to be the best behaved system in initial trials. The major alcoholic product (isolated in 20–35% yield after SiO_2 chromatography) was a single diastereomer [C*H*OH, 4.07 ppm (dd, J = 3.8 Hz)] bearing an exomethylene. When a stoichiometric quantity of $SnCl_4$ was employed the yield improved to 50%, GC/MS revealed ca. 2% of the other epimer (vide infra). Structure **5** correctly predicts the coupling pattern observed for the major product: coupling to the bridgehead methine should be minimal. PCC oxidation afforded cyclopentanone **29**—$\nu_{C=O}$ 1755 cm^{-1} ($CHCl_3$)—which displayed an otherwise unsplit AB pattern (J_{AB} = 17 Hz) for the α-methylene. The stereochemical assignment of the initial alcohol (**5**) was corroborated when ketone **29** was observed to produce **5** and its epimer (**30**) in a 1:3 ratio upon reduction with methanolic borohydride as expected based on approach hindrance. The exclusive production of epimer **5** in the cyclization is not viewed as an indication of a concerted pathway. In fact we favor the ionic pathway in all instances of type II cyclopentane formation (vide infra).



The ethylaluminum halides were much less effective for this transformation (Table III). With Et_2AlCl, the major products seen by GC/MS were alcohols **28** and **36**. The reduction product **28** presumably arises via a β-hydride transfer from an ethyl group of the Et_2AlCl–aldehyde complex. Likewise transfer of the ethyl group of the complex gives **36**. Aldehyde **4** proved relatively resistant to Me_2AlCl requiring several hours at −30 → 0 °C for complete disappearance. Methylene alcohols **5** and **30** were, at best, minor initial products.

Although the structure of product **5** isolated (after SiO_2 chromatography) or detected by direct GC/MS analysis of the $SnCl_4$ cyclization mixture was secure, NMR spectra of the material prior to chromatography suggested only a 10–20% yield of olefin **5**, and another C*H*OH resonance overlapped that due to **5** in the NMR. When $TiCl_4$ (0.75 h, <−25 °C) was used in place of $SnCl_4$, this new material was either the exclusive or dominant (>80%) product. Chlorohydrin structure **34** was assigned on the basis of the NMR spectrum, which displayed two methyl singlets at 1.08 and 1.65 ppm. The CHOH methine signal was centered at 4.00 ppm (dd, J = 4.8 Hz). Attempts to separate **5** from **34** by SiO_2 chromatography only resulted in the dehydrohalogenation of **34** (to **5**), which also occur upon GC/MS analysis. Both epimers (**5**, **30**) were stable to GC analysis with no evidence of a retro-ene process.

Our best overall yield of tricyclic alcohol **5** was realized when **34** was subjected to classical E1 elimination conditions. The crude $TiCl_4$ cyclization product affords **5** in 86% yield after a 12-treatment with 0.5 N NaOMe/MeOH at room temperature. Proton NMR at 500 MHz (see Figure 1 and Experimental Section) provides a structure confirmation for tricyclic products **34** and **5**, but the stereochemistry at the chloro center remains speculative.

Titanium tetrachloride has been commonly used for catalyzing the addition of electrophiles to allylmetalloids but has found less use with olefinic aldehyde cyclizations. Because of the particularly clean cyclization effected on aldehyde **4**, the use of $TiCl_4$ with other systems (**8**, **13**, and hydrindanol formation, eq 2) was examined. *trans*-Hydrindanol formation with 0.1 equiv of $TiCl_4$ gives a poorer yield than observed with either $SnCl_4$ or Et_2AlCl, approximately 65%, and appreciable quantities of unidentified byproducts. However, aldehydes **8b** and **8c** afford the corresponding tertiary chlorides **11b** and **11c** cleanly and in high yield with 1.0 equiv of $TiCl_4$. Aldehydes **13b** and **13c**, which are type II systems like model **4**, however, gave at best modest yield of unstable tertiary chlorides. Cyclopentenol formation with these latter systems was best effected with Me_2AlCl (vide supra), but we were unable to elucidate the factors that determine the double bond regiochemistry in the products. Our results suggest that $TiCl_4$ and $SnCl_4$ should be considered as alternatives to Me_2AlCl in the formation of five-membered rings from

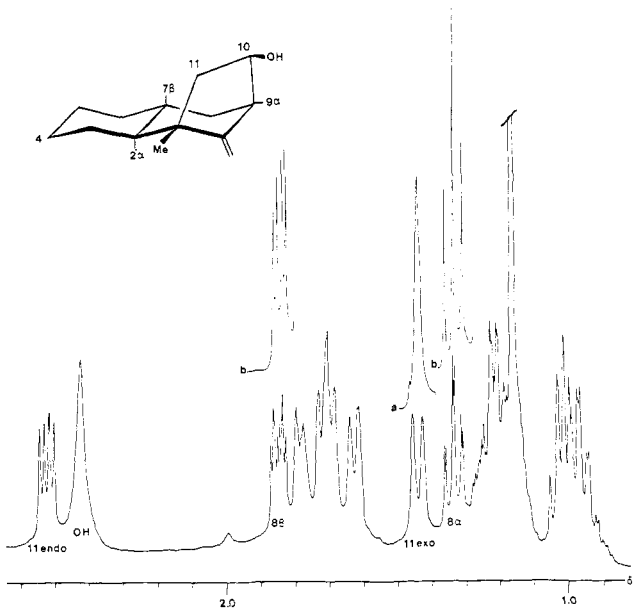


Figure 1. The upfield portion of the 500-MHz NMR spectrum of compound **5** with 3.89×10^{-2} equiv of $Eu(fod)_3$ added; a and b show the results of decoupling at protons 11-endo and 9α (δ 2.789), respectively. The assignments of 11-endo and 11-exo are based on decoupling irradiation of resonance 10-endo (δ 4.518) and the greater lanthanide-induced shift of 11-exo relative to 11-endo. Other downfield resonances are the vinyl protons at δ 4.902 and 4.971.

olefinic aldehydes. In the case of the tricyclic system, $TiCl_4$ was clearly superior.

Experimental Section

General Methods. All reactions performed in nonaqueous media were conducted in flame-dried glassware, with a septum seal, under an atmosphere of prepurified argon (or nitrogen) with syringes used for transfers. Unless otherwise specified products were obtained by an extractive isolation after the addition of water. The combined extracts, dried with $MgSO_4$, were concentrated at aspirator pressures on a rotary evaporator. The resulting crude products was further purified by distillation, column chromatography (on neutral SiO_2, 70–140 mesh Machery-Nagel, using a hexane/EtOAc gradient unless otherwise indicated), or HPLC. Analytical and semipreparative HPLC was accomplished with SiO_2-type phases and a Water Associates ALC-100 instrument equipped with a differential refractor and a UK-6 injector system (2-mL loop). Semipreparative runs employed a 4.6 mm × 25 cm Excalibur Spherisorb column at 0.7 mL/min; retention times are reported in minutes from injection. TLC was performed on commercial 0.25-mm layer SiO_2 plates containing F-254 indicator (E. Merck) with visualization by iodine vapor or aqueous copper acetate/phosphoric acid spray followed by heating at 120 °C.

Infrared spectra were recorded in CCl_4 solutions. NMR spectra are for $CDCl_3$ solution at 60 MHz unless otherwise specified and δ values are relative to internal Me_4Si as 0.00 ppm. High-resolution mass spectra (±0.1 mamu) were obtained by direct insertion on a AEI MS-9. Medium (±1 mamu) and low (±0.2 amu)-resolution GC/MS employed respectively V. G. Micromass 7070 and Hewlett-Packard 5985A instruments. Other GC analyses were performed on a HP 5830-A instrument equipped with a flame-ionization detector using packed 0.125 in. columns of 12–50 ft length. Relative area percentages and retention times (t_R, min) are uncorrected and are reported as printed by the computer.

Starting Materials and Cyclization Substrates. Aldehydes **8a** and **8b**[13] were prepared as previously described.[3] Aldehyde **8c**[14] was prepared from isobutyric acid. Isobutyrate dianion was generated by the addition of isobutyric acid to 2.1 equiv of LDA of THF at 0 °C. Reduction of the acid with $LiAlH_4$ followed by PCC oxidation afforded the aldehyde.

Aldehydes **13a** and **13b** were prepared as follows. Conjugate addition of 2-propenylmagnesium bromide (6 mol % CuCl) to diethyl isopropylidenemalonate in ether gave the 1,4 adduct. This malonate was hydrolyzed in 40% KOH/H_2O to afford the diacid, which was not purified but directly decarboxylated in refluxing toluene. Reduction of the acid with $LiAlH_4$ gave 3,3,4-trimethyl-4-penten-1-ol. Oxidation of the alcohol with PCC afforded aldehyde **13b**: NMR δ 9.72 (1 H, t, J = 3 Hz), 4.80 (2 H, brs), 2.38 (2 H, d, J = 3 Hz), 1.80 (3 H, brs), 1.20 (6 H, s). Aldehyde **13a** was prepared by homologation of 3,3,4-trimethyl-4-penten-1-ol. Conversion of the alcohol to the tosylate with *p*-toluenesulfonyl chloride in pyridine/CH_2Cl_2 followed by cyanide displacement (NaCN in HMPA, 75 °C) afforded the nitrile. Hydrolysis of the nitrile with KOH in ethylene glycol and reduction of the acid by $LiAlH_4$ gave 4,4,5-trimethyl-5-hexen-1-ol.[15] PCC oxidation gave aldehyde **13a**: NMR δ 9.90 (1 H, t, J = 2 Hz), 4.82, 4.75 (2 H, m), 2.30 (2 H, m), 1.70 (5 H, m), 1.05 (6 H, s). Aldehyde **13c** was prepared as previously reported.[16] Ladehyde **13d**[17] was prepared in an analogous manner to **8c**. Alkylation of isobutyrate dianion with 4-iodo-2-methylbut-1-ene was achieved only after the diisopropylamine had been removed prior to alkylation in THF.

Octalone **18a** was prepared in 76% yield from the pyrolidine enamine of cyclohexanone by the reported two-step procedure.[18] The Heathcock–McMurry H_2SO_4/C_6H_6 Robinson procedure[19] afforded **18a** in an unsatisfactory 26% yield. In contrast, octalone **18b**[20] [bp 85–88 °C (1 torr); MS, m/e 178.1388 amu (100%, = $C_{12}H_{18}O$ + 3 mamu)] could be obtained in 46–50% yield by the acid-catalyzed one-step sequence.

Lewis Acid Facilitated Aldehyde Cyclization Method. Unless otherwise stated (in Tables I or II or specific experimental descriptions) these reactions were performed in dry CH_2Cl_2 under argon with reaction volume adjusted to produce a solution 0.04–0.05 M in the aldehyde. The solutions were cooled to the desired temperatures, and the Lewis acid[21] was added dropwise. After the appropriate reaction time the reactions were quenched at the reaction temperature unless otherwise stated. $SnCl_4$ and $TiCl_4$ reactions were quenched by the addition of an equal volume of saturated aqueous NH_4Cl solution, while the alkyl aluminum chloride reactions were quenched with an equal volume of 10% aqueous NaOH. The resulting solutions were allowed to come to room temperature. Extractive workup into pentane afforded the crude products. Entry 3 of Table I is taken from our previous study[3] and was quantitatively confirmed in the present work. Alcohols **9a,b** and **10a,b** were identified by NMR comparison.[3,22]

Table I, Entry 4. Aldehyde **8b** (81.8 mg, 0.530 mmol) was treated with 1.0 equiv of Et_2AlCl (0.35 mL, 1.51 M) at −72 °C for

(13) See also: Gaoni, Y.; Wenkert, E. *J. Org. Chem.* **1966**, *31*, 3809–3814.

(14) House, H.; Liang, W.; Welks, P. *J. Org. Chem.* **1974**, *39*, 3102–3107.

(15) The product displayed the previously reported NMR spectral characteristics: Beckwith, A. L. J.; Moad, G. *Aust. J. Chem.* **1977**, *30*, 2733–2739.

(16) Hayashi, Y.; Nishizawa, Sakan, T. *Tetrahedron* **1977**, *33*, 2513–2519. See also: Dillenberger, Z.; Schmid, H.; Hansen, H. J. *Helv. Chim. Acta* **1978**, *61*, 1856–1902.

(17) The corresponding alcohol has been prepared previously by a circuitous route: Beckwith, A. L. J.; Lawrence, T. *J. Chem. Soc. Perkin Trans. 2* **1979**, *11*, 1535–1539.

(18) Marshall, J. A.; Andersen, N. H. *J. Org. Chem.* **1966**, *31*, 667–673.

(19) Heathcock, C. H.; Ellis, J. E.; McMurray, J. E.; Coppolino, A. *Tetrahedron Lett.* **1971**, 4995–4996.

(20) Marshall, J. A.; Hochstetler, A. R. *J. Org. Chem.* **1966**, *31*, 1020–1025.

(21) Stock solutions of $SnCl_4$ (0.51 M in benzene) and $TiCl_4$ (0.98 M in CH_2Cl_2) were prepared and stored up to 1 month during use. Et_2AlCl and $EtAlCl_2$ were purchased from Alfa as 25% solutions in hexane. Me_2AlCl was purchased from Texas Alkyls as a 25% solution in hexane.

(22) The cis/trans assignments of **9c** and **10c** are based on the NMR spectra of **9b** and **10b**, reespectively. Since coupling constants are not a clear-cut guide to assigning cis/trans stereochemistry in cyclopentanes, compounds **9b** and **10b** were assigned on the basis of LIS studies.[3] Additionally, **9b** and **10b** could be quantitatively differentiated by their characteristic NMR spectra. Cis disposition of the hydroxyl and isopropenyl groups (**9b**) gives rise to two distinct broad singlets for the two vinyl hydrogens, while a trans relationship (**10b**) displays a single broad singlet corresponding to two vinyl hydrogens. Compounds **9c** and **10c** exhibited the same phenomenon and analogous TLC mobilities; the trans compounds (**10**) are more polar.

2 h. The reaction was quenched at 0 °C with an equal volume of 10% aqueous NaOH. Extraction into pentane followed by washing with H_2O and brine and drying over Na_2SO_4 afforded 82.8 mg of crude product. NMR showed this to be a mixture of 27% **9b**, 13% **10b**, and 60% **12b**: NMR (for **12b**) δ 5.20 (1 H, brt, J = 7 Hz), 3.68 (1 H, quintet, J = 6 Hz), 1.75 (3 H, brs), 1.62 (3 H, brs), 0.93 (6 H, s).

Table I, Entry 11. Aldehyde **8b** (28.1 mg, 0.182 mmol) was treated with 1.0 equiv of $TiCl_4$ (0.20 mL, 0.91 M) at 0 °C. The reaction was quenched after 0.33 h with an equal volume of saturated aqueous NH_4Cl. The resulting solution stirred with H_2O and brine and dried over Na_2SO_4 afforded 28.4 mg (82%) of **11b**: NMR δ 4.3 (1 H, m), 1.65, 1.53 (6 H, s), 1.12, 1.03 (6 H, s).

Table I, Entry 14. Aldehyde **8c** (49.0 mg, 0.318 mmol) was treated with 1.0 equiv of $EtAlCl_2$ (0.22 mL, 1.45 M) to afford after workup and chromatography (SiO_2, 15% EtOAc/hexanes) 25.0 mg (41%) of **11c**: NMR δ 3.67 (1 H, d, J = 7 Hz), 1.63, 1.57 (6 H, s), 1.02, 0.92 (6 H, s).

Table I, Entry 15. Aldehyde **8c** (57.8 mg, 0.375 mmol) was treated with 1.0 equiv of Me_2AlCl (0.20 mL, 1.93 mmol). The crude alcohols were isolated by chromatography (SiO_2, 5% Et_2O/pentane) to afford 33.5 mg (58%) of **9c**: NMR δ 5.0, 4.9 (2 H, brs), 3.52 (1 H, d, J = 4 Hz), 2.8 (1 H, m), 1.8 (3 H, brs), 1.05, 0.95 (6 H, s). Following was 5.0 mg (9%) of the more polar **10c**: NMR δ 4.8 (2 H, brs), 3.48 (1 H, d, J = 9 Hz), 2.4 (1 H, m), 1.7 (3 H, brs), 1.05, 0.93 (6 H, s).

Table II, Entry 2. Aldehyde **13a** (25.0 mg, 0.718 mmol) was treated with 1.0 equiv of Et_2AlCl to afford after workup 23.0 mg (92%) of **14a**: NMR δ 4.77 (2 H, brs), 3.73 (1 H, 7 lines), 2.35 (2 H, m), 1.08 (6 H, s); IR (neat) 3330, 3095, 1642, 1055, 905, 890 cm^{-1}; MS, m/e 122.1106 amu (8.5%, $C_9H_{14}O$–1.1 mamu).

Table II, Entry 4. Aldehyde **13b** (99.5 mg, 0.788 mmol) was treated with 1.0 equiv of Et_2AlCl to give after chromatography (SiO_2, 5% Et_2O/pentane) 36.0 mg (29%) of **15b**: NMR δ 4.87 (2 H, brs), 3.60 (1 H, m), 1.80 (3 H, brs), 1.13 (3 H, s), 1.08 (3 H, s).

Table II, Entry 7. Aldehyde **13b** (67.7 mg, 0.536 mmol) was treated with 1.0 equiv of Me_2AlCl to give, after workup, 64.8 mg of crude product (containing **17b**), which was immediately dissolved in 5 mL of 0.5 N NaOMe/MeOH. The solution was stirred for 12 h, at which time 10% aqueous HCl was added. The crude products were extracted into CH_2Cl_2 to give after chromatography (SiO_2, CH_2Cl_2), in order of elution, 14.4 mg (19%) of 3,3,4-trimethyl-4-cyclopentenyl methyl ether [NMR δ 5.38 (1 H, brs), 4.25 (1 H, m), 3.27 (3 H, s), 1.63 (3 H, brs), 1.07 (3 H, s), 0.98 (3 H, s); IR 3180, 1650, 1470, 1440, 1085 cm^{-1}; MS, m/e 140.2 (7.2%), 139.1 (10.0%), 125.1 (100%), 109.1 amu (22.4%)] and 7.1 mg of **15b** (9.3%) [NMR δ 4.83 (2 H, brs), 2.20 (1 H, m), 1.78 (3 H, brs), 1.12 (3 H, s), 1.12 (3 H, d, J = 6 Hz), 1.07 (3 H, s).

Table II, Entry 13. Aldehyde **13c** (77.4 mg, 0.613 mmol) was treated with 1.0 equiv of Me_2AlCl to give after chromatography (SiO_2, CH_2Cl_2) 47.8 mg (62%) of 2,2,4-trimethyl-3-cyclopentenol: NMR δ 5.08 (1 H, brs), 3.92 (1 H, t, J = 6 Hz), 2.32 (2 H, AB of ABX, $\Delta\nu_{AB}$ = 23.2 Hz, J_{AB} = 16.5 Hz, $J_{AX} = J_{BX}$ = 6 Hz), 1.60 (3 H, brs), 1.00 (3 H, s), 0.97 (3 H, s): IR 3380, 3025, 1650, 1460, 1450, 1080, 730 cm^{-1}: MS, m/e 126.1 (18.3%), 111.1 amu (100%). A small portion of the alcohol was oxidized (PCC/CH_2Cl_2) to the β,γ-unsaturated ketone: NMR δ 5.55 (1 H, brs), 2.83 (2 H, brs), 1.80 (3 H, brs), 1.08 (6 H, s): IR 1740 cm^{-1}. This unsaturated ketone could be cleanly isomerized to the conjugated enone by treatment with anhydrous p-toluenesulfonic acid in $CDCl_3$: NMR δ 5.96 (1 H, brs), 2.4 (2 H, brs), 2.1 (3 H, brs), 1.12 (6 H, s); MS, m/e 124.1 (24.0%), 109.1 (100%), 81.1 amu (50.7%).

Table II, Entry 14. Aldehyde **13d** (35.1 mg, 0.250 mmol) was treated with 0.1 equiv of $SnCl_4$ to afford 32.0 mg (95%) of **14d**: NMR δ 4.72 (2 H, brs), 3.37 (1 H, dd, J = 4, 8 Hz), 2.2 (4 H, m), 1.00 (3 H, s), 0.95 (3 H, s); IR 3390, 3065, 1650, 1455, 1050, 895 cm^{-1}. MS, m/e 122.1069 amu (10.3%, $C_9H_{14}O$–2.6 mamu).

Reductive Allylation of Enones 18a,b. A solution of enone **18a** (12.8 g, 78.0 mmol) and 0.8 equiv of i-PrOH in ether (80 mL) was added to 450 mL of freshly distilled (from Na) ammonia maintained at reflux. To this solution was added lithium (ca. 2.5 equiv) as necessary to produce a persistent blue coloration. After 30 min, a mixture of 47.2 g of allyl bromide and 20 mL of ether was added. The NH_3 was allowed to evaporate and saturated aqueous NH_4Cl was added carefully. An ether extractive workup afforded a crude product analyzed by GC (Carbowax 20M, 135 °C): t_R (%, compound); 2.84 (4, (5α,10β)-1α-methyl-2-decalone); 6.92 (34, epimer **19a**); 9.21 (38, epimer **20a**). In addition ca. 14% of diallylated material was present. Spinning-band distillation [110 °C (2 torr)] gave a forerun of **19a** and a main fraction of (5α,10β)-1β-allyl-1α-methyl-2-decalone NMR ($CDCl_3$) δ 5.66, 5.03, 5.00 (3 H, vinyl group), 2.0–2.85 (4 H, CH_2CO and $CH_2C{=}C$), 1.073 (3 H, s, 1α-Me); NMR (C_6D_6) δ 1.10 (1α-Me); IR 3080, 1740, 1650 cm^{-1}; MS, m/e 206.1670 (100%, $C_{14}H_{22}O$ + 0.0 mamu), 191.1442 amu (41%, $C_{13}H_{19}O$ + 0.4 mamu). Epimer **19a** displayed the following: NMR ($CDCl_3$) δ 1.04 (1β-CH_3), (C_6D_6) 0.82 (1β-CH_3); MS, m/e 206.1668 (62%, $C_{14}H_{22}O$ – 0.2 mamu), 191.1440 amu (100%, $C_{13}H_{19}O$ + 0.2 mamu).

When the procedure above (using t-BuOH in place of i-PrOH) was applied to enone **18b**, silica chromatographed (eluting with benzene) afforded a 73% yield of ketone **19b**: NMR ($CDCl_3$) δ 5.69, 5.05, 4.90 (3 H, vinyl group), 1.10 (3 H, s, 1β-CH_3), 1.018 (3 H, s, 10β-CH_3), (C_6D_6) 0.87 (1β-CH_3), 0.77 (10β-CH_3); IR 3080, 1710, 1650 cm^{-1}; MS, m/e 220.1836 (30%, $C_{15}H_{24}O$ + 1.0 mamu), 205.1610 amu (100%, $C_{14}H_{21}O$ + 1.8 mamu).

Synthesis of Alcohol 21. To a solution of ketone **20a** (467 mg, 2.26 mmol) in 10 mL of ether at –30 °C was added 2.8 equiv of ethereal MeLi. The reaction proceeded for 30 min at –30 °C and 2 h at room temperature and was quenched with saturated aqueous NH_4Cl, and chromatography (CH_2Cl_2) afforded 35 mg of recovered ketone and 436 mg (94%) of alcohol **21**: homogeneous by GC; NMR δ 6.23, 5.1, 5.0 (3 H, vinyl group), 1.88 (1 H, s, OH), 1.15 (3 H, s, 2α-CH_3), 1.00 (3 H, s, 1α-CH_3); IR 3540, 3080, 1640, 1155 cm^{-1}.

[(5α,10β)-1α,2α-Dimethyl-2β-hydroxydecal-2β-yl]acetic Acid Lactone (24). A. Preferred Route via Alcohol 21. A solution of the alcohol **21** (454.2 mg, 2.04 mmol) in dry CH_2Cl_2 (25 mL), to which 10 drops of pyridine had been added, was ozonized at –78 °C. The resulting blue solution was poured into a 0 °C suspension of $NaBH_4$ (523 mg, 13.8 mmol) in isopropyl alcohol (40 mL). After this solution was stirred for 30 min, the excess borohydride was destroyed with acetic acid. Extractive workup afforded a crude mixture of lactone **24** and lactol **25**, which was directly oxidized with PCC (820 mg, 3.80 mmol) in CH_2Cl_2 (50 mL) at room temperature. After 4.5 h the reaction mixture was diluted with five volumes of ether. This residue was passed through a Florisil column, affording, after further column chromatography (10% EtOAc/hex) 411 mg (91%) of lactone **24**: mp 46–47 °C; NMR δ 2.35 (2 H, AB, $\Delta\nu$ = 46.5 Hz, J = 17 Hz), 1.36 (3 H, s), 1.06 (3 H, s); IR 1755, 1470, 1235 cm^{-1}; MS, m/e 222.1612 (18.6%, $C_{14}H_{22}O_2$ – 0.6 mmu), 194.1670 amu (100%, $C_{13}H_{22}O$ + 0.0 mmu).

B. Via Keto Ester 23 (R = OMe). A 405-mg portion of α-allyl ketone **20a** was ozonized as described for **21**, above. The oxonide was destroyed by adding 3 equiv of Me_2S. SiO_2 chromatography afforded **23** (R = H) [NMR δ 9.72 (1 H, t, 2.5 Hz), 1.23 (3 H, s)] and 230 mg of its trioxane. Aldehyde **23** (R = H) was quantitatively oxidized (50% ethanolic $AgNO_3$ + aqueous NaOH) and then esterified with excess ethereal CH_2N_2, affording ester **23** (R = OMe): IR ν_{max} ($CDCl_3$) 1740 cm^{-1}; NMR δ 3.63. Upon stirring with excess Me_3Al in benzene at 30 °C for 2 h keto ester **23** afforded lactone **24** (by TLC, mmp, NMR) in ca. 50% yield along with recovered ketone **23**.

Lactone Elimination Reactions. A. Synthesis of Ester 27. To a solution of lactone **24** (416.1 mg, 1.87 mmol) in anhydrous CH_2Cl_2 (35 mL) at room temperature under argon was added $Et_3O^+BF_4^-$ (1.60 g, 8.4 mmol). The solution was stirred for 12 h, and then 1,8-bis(dimethylamino)naphthalene (789 mg, 3.7 mmol) was added. After an additional 22 h, TLC (CH_2Cl_2) indicated complete conversion to product: R_f 0.57. Concentration and SiO_2 chromatography (10% EtOAc/hexanes) afforded 434.8 mg (93%) of ester **27** (contaminated with 2–5% of the exo isomer by NMR: IR (neat) 3080, 1750, 1460, 1380, 1225, 1050 cm^{-1}; NMR δ 5.45 (1 H, brs), 4.05 (2 H, q, J = 7 Hz), 2.29 (2 H, s), 1.7 (3 H, brs; vinyl CH_3), 1.23 (3 H, t, J = 7 Hz), 1.10 (3 H, s); MS, m/e 250.1932 (34%, $C_{16}H_{26}O_2$ – 0.2 mmu), 163.1446 (100%, $C_{12}H_{19}$ – 4.2 mmu), 119.0824 amu (89%, C_9H_{11} – 3.8 mmu).

B. Ester 26 (R = CH_3). A solution of lactone **24** (81 mg, 0.39 (mmol) and 50 mg of freshly sublimed KO-t-Bu in 5 mL of DMF was stirred at 140 °C for 3 h under argon. The rapidly cooled

mixture was diluted with 15 mL of ice–water, and an ether extractive workup afforded, after acidification (10% aqueous H_2SO_4), 70 mg (86%) of acid **26** (R = H). Ethereal CH_2N_2 treatment gave the ester **26** (R = CH_3), which contained <10% of the endo product by NMR analysis: R_f 0.44 (CH_2Cl_2); IR ($CDCl_3$) 3160, 1760, 1645, 1255, 1100, 1000 cm^{-1}; NMR δ 4.67 (2 H, m), 3.53 (3 H, s), 2.36 (AB, $\Delta\nu_{AB}$ = 31.8 Hz, J_{AB} = 13 Hz), 1.18 (3 H, s).

[(5α,10β)-1α,2-Dimethyldecal-2β-yl]acetaldehyde (4). Ester **27** (434.8 mg, 1.74 mmol) in 25 mL of ether was reduced with 216 mg of $LiAlH_4$ for 2 h. The usual aqueous NaOH hydroxide quench afforded 360 mg of alcohol **28** from the ethereal layer: IR (neat) 3330, 3020, 1460, 1070, 1050 cm^{-1}; NMR δ 5.42 (1 H, brd), 3.52 (3 H, m, CH_2OH), 1.68 (3 H, brs), 1.01 (3 H, s); MS, *m/e* 208.3 (0.5%), 164.2 (67.9%), 163.2 (100%), 149.2 (26.0%), 107.2 (37.0%), 95.2 (48.1%), 93.1 (38.8%), 91.1 (33.0%), 81.2 (38.7%), 79.1 (36.3%), 67.1 amu (30.3%).

The entire alcohol sample above, in 20 mL of CH_2Cl_2, was oxidized by stirring with 689 mg (3.2 mmol, 1.9 equiv) of PCC for 2 h. The reaction mixture was diluted 5-fold with ether and filtered through Florisil, affording 304 mg (85%) of aldehyde **4**: NMR δ 9.70 (1 H, t, J = 3.5 Hz), 5.48 (1 H, brd), 2.31 (2 H, d, J = 3.5 Hz), 1.72 (3 H, brs), 1.06 (3 H, s); IR (neat) 3025, 2970, 2930, 2860, 2740, 1730, 1455, 815 cm^{-1}; MS, *m/e* 206.2 (1.6%), 164.3 (21.6%), 163.2 (30.6%), 162.2 (100%), 147.1 (30.5%), 120.1 (32.2%), 119.1 (56.3%), 105.1 (34.0%, 95.1 (37.3%, 91.1 (30.9%), 79.1 amu (27.3%).

Illustrative Cyclizations of Aldehyde 4. A. Syntheses of Alcohol 5 via Stannic Chloride Cyclization/Chromatography. To a solution of the aldehyde **4** (52.0 mg, 0.252 mmol) in CH_2Cl_2 (5.0 mL) at −45 °C was added 1.0 equiv of $SnCl_4$. The reaction mixture was warmed to −15 °C over 4.5 h, at which time an equal volume of saturated aqueous NH_4Cl was added. The crude products were extracted into CH_2Cl_2, washed with saturated aqueous $NaHCO_3$, H_2O, brine and dried over Na_2SO_4 to afford 52.2 mg of an 80:20 (by NMR) mixture of **34/5**. The crude mixture was flash chromatographed (SiO_2, CH_2Cl_2) to afford 21.6 mg (42%) of **5** (mp 69–71 °C) and 7.5 mg (12%) of **34**. Spectral data for alcohol **5** are as follows: NMR δ 4.75 (1 H, brs), 4.67 (1 H, brs), 3.98 (1 H, dd, J = 2.5, 7 Hz), 1.03 (3 H, s); IR (neat) 3375, 3070, 1660, 1445, 1025, 1010, 880 cm^{-1}; MS, *m/e* 206.1687 (9.5%, $C_{14}H_{22}O$ − 1.6 mmu), 189.1608 amu (100%, $C_{14}H_{20}$ − 0.9 mmu).

B. Synthesis of Chloro Alcohol 34. To a solution of **4** (21.9 mg, 0.106 mmol) in CH_2Cl_2 (2.1 mL) at −25 °C was added 1.0 equiv of $TiCl_4$. The reaction was stirred for 30 min and then quenched at −20 °C with an equal volume of saturated aqueous NH_4Cl. After the quenched solution was stirred for 1 h at room temperature, the mixture was separated and extracted into CH_2Cl_2 to afford 25.7 mg (98%) of **34** as a crystalline solid: mp 43–44 °C; IR ($CDCl_3$) 3580, 1445, 1025, 590 cm^{-1}; NMR (500 MHz) δ 4.010 (1 H, dd, J = 4.0, 8.3 Hz, 10-endo), 2.416 (1 H, brs, 9α), 2.292 (1 H, dd, J = 8.3, 14.7 Hz, 11-endo), 1.790 (2 H, m), 1.695 (1 H, m), 1.662 (3 H, s, 12-CH_3), 1.652 (1 H, dd, J = 4.0, 14.7 Hz, 11-exo), 1.573 (2 H, m, contains 8β), 1.434 (1 H, d of t, J = 3.0, 11.5 Hz; 8α), 1.28–1.10 (3 H, m), 1.101 (3 H, s, 1α-CH_3), 0.930 (3 H, m, contains 7β).

C. Synthesis of Alcohol 5 via Methoxide-Induced Elimination of Chloro Alcohol 34. Aldehyde **4** (24.7 mg, 0.20 mmol) was treated with 1.0 equiv of $TiCl_4$, as previously described, to give the crude **34**. This crude material was directly dissolved in 2.5 mL of 0.5 N NaOMe/MeOH and stirred at room temperature for 14 h. Extractive workup gave 21.2 mg (86%) of **5** (identity by co-TLC): NMR (500 MHz) δ 4.760 (1 H, s; vinyl H), 4.672 (1 H, s; vinyl H), 4.002 (1 H, dd, J = 2.2, 7.0 Hz, 10-endo), 2.441 (1 H, brs, 9α), 2.346 (1 H, dd, J = 7.0, 14.3 Hz, 11-endo), 1.753 (2 H, m, contains 8β as a d of t, J = 4.3, 12.2 Hz), 1.650 (2 H, m), 1.580 (2 H, m, contains OH), 1.245 (1 H, t of d, J = 3.0, 12.2 Hz, 8α), 1.185 (2 H, m), 1.060 (2 H, m, contains 11-exo as a brd, J = 14.3 Hz), 1.050 (3 H, s; 1α-CH_3), 0.923 (3 H, m, contains 7β).

Other Studies of the Cyclization of Aldehyde 4. These are summarized in Table III. In at least one case for each "catalyst" the crude product was directly assayed by capillary GC (10 m; methyl silicone SP-2100; temperature program, 80 °C for 2 min and the increased at a rate of 10 °C/min to 200 °C). The observed product retention times were as follows, t_R (min): 9.17 (**4**), 9.22 (**5**), 9.42 (**30**), 10.22 (**28**), 10.62 (**35**), 11.64 (**36**). Alcohol **28** was confirmed by coinjection with authentic material from the $LiAlH_4$ reduction of **27**. The identity of **35** and **36** was ascertained by separate GC/MS runs (30 m; DB-5; temperature program, 75 °C for 2 min and then increase at a rate of 15 °C/min to 250 °C). The observed retention time and mass spectrum for **35** was as follows: t_R, 11.70 min; MS, *m/e* 222.3 (27.6%), 207.3 (49.1%), 189.2 (78.5%), 163.2 (32.4%), 161.2 (31.7%), 149.2 (33.1%), 148.2 (34.1%), 147.2 (34.5%), 139.1 (29.7%), 135.2 (100%). 111.2 (72.0%), 109.2 (71.0%), 107.1 (52.9%), 81.2 (81.6%), 67.1 amu (78.2%). Compound **36**: t_R, 12.58 min; *m/e* 234.3 (30.4%), 205.2 (43.6%), 163.2 (84.5%), 149.2 (100%), 121.2 (40.1%), 107.2 (31.7%), 95.2 (37.2%), 81.2 (59.8%), 67.1 (45.4%), 55.1 (38.4%), 41.1 amu (37.6%).

Further Transformations of Alcohol 5. A mixture of 43 mg (0.208 mmol) of alcohol **5** and 112 mg of PCC in 5 mL of CH_2Cl_2 was stirred for 2.5 h, then diluted with 10 mL of Et_2O, and filtered through Florisil, affording ketone **29**: IR ($CDCl_3$) 3175, 3100, 1755, 1680, 980 cm^{-1}; NMR δ 4.72 (2 H, brs), 1.9–2.8 (3 H, m, includes CH_2CO AB pattern, $\Delta\nu_{AB}$ = 28.8 Hz, J_{AB} = 17 Hz), 1.05 (3 H, s). The ketone was used as is, for reduction. Excess methanolic $NaBH_4$ (0 °C, 3 h) gave two products, in a 3:1 ratio, which were separated by centrifugal preparative TLC on SiO_2 (4% EtOAc/CH_2Cl_2), affording as the more polar product 8 mg (19%) of alcohol **5** and, as the more mobile epimer, 21.3 mg (51%) of alcohol **30** as a white crystalline powder: mp 97–103 °C; NMR δ 4.60 and 4.50 (2 H, each brs), 4.30 (1 H, ≈q, J = 7 Hz), 2.55 (1 H, OH), 0.95 (3 H, s); IR ($CDCl_3$) 3620, 3160, 3080, 1670, 1000, 900 cm^{-1}; MS, *m/e* 206.2 (10.3%), 205.2 (7.9%), 188.2 (36.8%), 173.1 (41.1%), 162.2 (86.1%), 131.1 (37.6%), 119.1 (43.7%), 111.2 (61.6%), 105.1 (51.6%), 95.1 (96.5%), 93.1 (69.7%), 91.1 (100%), 81.2 (50.0%), 77.1 (53.8%) 67.1 amu (59.5%).

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Registry No. **4**, 97571-56-7; **5**, 97571-57-8; **8a**, 17920-90-0; **8b**, 13820-23-0; **8c**, 52279-00-2; **9a**, 68261-86-9; **9b**, 68261-84-7; **9c**, 97571-26-1; **10a**, 68261-87-0; **10b**, 68261-85-8; **10c**, 97571-27-2; **11b**, 97571-28-3; **11c**, 97571-29-4; **12b**, 97571-30-7; **13a**, 97571-24-9; **13b**, 97571-21-6; **13c**, 39482-50-3; **13d**, 81331-91-1; **14a**, 97571-31-8; **14b**, 97571-32-9; **14c**, 16626-38-3; **14d**, 97571-33-0; **15b**, 97571-34-1; **15c**, 97571-35-2; **16b**, 97571-20-5; **16c**, 53907-70-3; **17b**, 97591-98-5; **17c**, 97571-36-3; **18a**, 5164-37-4; **18b**, 878-55-7; **19a**, 97571-39-6; **19b**, 97591-99-6; **20a**, 97571-40-9; **20a** (ozonide), 97571-45-4; **21**, 97571-42-1; **23** (R = H), 97571-46-5; **23** (R = OMe), 97571-49-8; **23** (trioxane), 97571-47-6; **23** (acid), 97571-48-7; **24**, 97571-43-2; **25**, 97571-44-3; **21** (R = H), 97571-52-3; **26** (R = Me), 97571-53-4; **26** (R = Me) (endocyclic isomer), 97571-54-5; **27**, 97571-50-1; **27** (exocyclic isomer), 97571-51-2; **28**, 97571-55-6; **29**, 97571-60-3; **30**, 97643-13-5; **34**, 97592-00-2; **35**, 97571-58-9; **36**, 97571-59-0; $TsOCH_2CH_2(CH_3)_2C(CH_3)=CH_2$, 97571-22-7; Me_3Al, 75-24-1; $SnCl_4$, 7646-78-8; Et_2AlCl, 96-10-6; $EtAlCl_2$, 563-43-9; Me_2AlCl, 1184-58-3; $TiCl_4$, 7550-45-0; Me_3SiCl, 75-77-4; isobutyrate dianion, 40435-46-9; isobutyric acid, 79-31-2; 2,2,6-trimethyl-5-heptenoic acid, 97571-25-0; 2-propenylmagnesium bromide, 1730-25-2; diethyl isopropylidenemalonate, 6802-75-1; ethyl 4,3,3-trimethyl-2-(ethoxycarbonyl)-4-pentenoate, 758-65-6; 3,3,4-trimethyl-2-(hydroxycarbonyl)-4-pentenoic acid, 97571-19-2; 3,3,4-trimethyl-4-pentenoic acid, 90370-81-3; 3,3,4-trimethyl-4-penten-1-ol, 97571-20-5; 4,4,5-trimethyl-5-hexenenitrile, 6926-31-4; 4,4,5-trimethyl-5-hexenoic acid, 97571-23-8; 4,4,5-trimethyl-5-hexen-1-ol, 65502-56-9; 4-iodo-2-methybut-1-ene, 53750-52-0; 3,3,4-trimethyl-4-cyclopentenyl methyl ether, 97571-37-4; 2,2,4-trimethyl-3-cyclopentenol, 26308-77-0; 2,2,4-trimethyl-3-cyclopentenyl methyl ether, 97571-38-5; 2,2,4-trimethyl-4-cyclopentenyl methyl ether, 24156-95-4; allyl bromide, 106-95-6; 1-methyl-1,8A-diallyl-2-oxodecahydronaphthalene, 97571-41-0.