Pergamon

Tetrahedron Vol. 50, No. 22, pp. 6505-6522, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)E0250-W

Unprecedented Stereochemical Control in the Intramolecular Ene-Reactions of δ,ε-Unsaturated Aldehydes Using Exceptionally Bulky Organoaluminum Reagents: Elucidation of the Transition State

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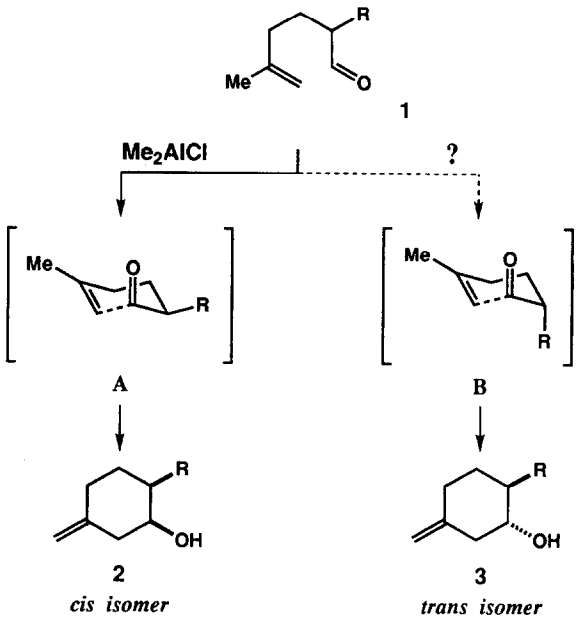
Abstract: Unprecedented stereochemical control has been achieved in the type II intramolecular ene reactions of δ,ε-unsaturated aldehydes leading to *trans*-cyclohexanols with excellent selectivity under very mild conditions, using exceptionally bulky methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR). Success of the stereocontrolled cyclization can be ascribable to the ability of this modified organoaluminum reagent, MABR, to change the conformation of the transition state. Examining the ene reactions of substrates **7**, **11**, **14** with MABR, the stereochemical outcome of the present organoaluminum-promoted intramolecular ene reactions is further elucidated.

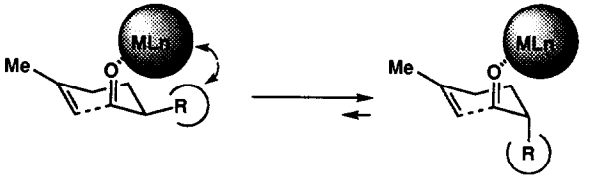
Extensive development during the last decade has demonstrated that Lewis acid promoted ene reactions of unsaturated carbonyl compounds are an attractive route to the regio- and stereoselective synthesis of highly functionalized carbocycles which are known to be valuable as important intermediates in organic synthesis.[1] Oppolzer and Snieckus have classified intramolecular ene reactions into three different types of cyclizations based on the connectivity of the ene and enophile.[1b] Among these, type-I and type-II reactions are conceivable for intramolecular ene reactions of unsaturated carbonyl compounds. The type-I ene reactions have been extensively and systematically investigated, and the possibilities, limitations and common features of this type of cyclizations illustrated. In contrast, type-II ene reactions have been much less studied and the stereochemical outcome remains elusive. Snider *et al.* recently reported the type-II intramolecular ene reactions of δ,ε-unsaturated aldehydes with α-substituents which gave a mixture of methylenecyclohexanols, **2** and **3**.[2]

As illustrated in Scheme 1, Me_2AlCl has been chosen as a very effective catalyst for the selective formation of *cis* isomer **2**, and it has been suggested that α–substituent (R) selectively adopted the equatorial conformation in the transition state **A**, since ene adduct **2** must be formed in the conformation with an axial hydroxy group.[2] However, there have been no promising Lewis acids to obtain *trans*-cyclohexanol **3** with high selectivity. In this context, we have been interested for some time in the possibility of changing the transition state structures of the intramolecular ene cyclizations by using certain bulky Lewis acids as shown in Scheme 2. This possibility is now beginning to become a reality with the use of exceptionally bulky organoaluminum reagents.

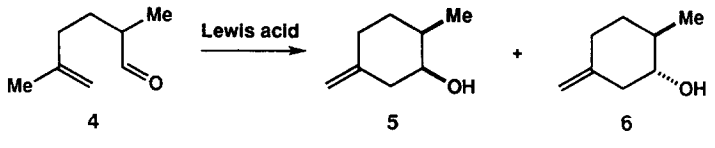
Scheme 1



Scheme 2



Initially, we studied the intramolecular ene reaction of 2,5-dimethyl-5-hexenal (**4**) (Table I). Attempted cyclization of **4** with several conventional Lewis acids (BF_3•OEt_2 and $SnCl_4$) afforded *cis*-6-methyl-3-methylenecyclohexanol (**5**) predominantly. Employing dimethylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide (DAD)[3] or methylaluminum bis(2,6-diphenylphenoxide) (MAPH)[4], ene reaction of **4** gave a mixture of **5** and **6** in a ratio of 3:2 or 2:1, respectively. When **4** was treated with exceptionally bulky methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)[5] in CH_2Cl_2 at -78 °C, the cyclization proceeded quite reluctantly. On warming up to -20 °C, the reaction was completed in 30 min to furnish methylenecyclohexanols **5** and **6** in 82% yield. The *cis*/*trans* ratio was determined to be 1:27 by capillary GLC. Although we were able to obtain unprecedented *trans* selectivity satisfactorily, it seemed that the Lewis acidity of MAD was not to be strong enough for activation of the unsaturated aldehyde **4**. Accordingly, more acidic methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR)[6] has been successfully applied to the intramolecular ene reaction of **4**, resulting in the clean generation of **5** and **6** at -78 °C~-40 °C in 82% yield in a ratio of 1:32.[7]



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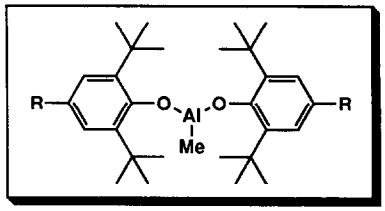


R = Me (MAD)
R = Br (MABR)

Table I. Stereocontrolled Ene Reactions of δ,ε-Unsaturated Aldehyde **4**[a]

entry	Lewis acid (equiv)	conditions (°C, h)	yield, % [b] (ratio of 5:6)
1	Me_2AlCl (1.2)	-78, 0.3	65 (9 : 1) [c]
2	$BF_3{\cdot}OEt_2$ (2)	-78, 0.3	58 (19 : 1)
3	$SnCl_4$ (2)	-78, 0.3	47 (9 : 1)
4	DAD (2)	-78, 3, -40, 1	92 (3 : 2)
5	MAPH (2)	-78, 3, -40, 2.5	76 (2 : 1)
6	MAD (2)	-78, 3, -40, 2, -20, 0.5	82 (1 : 27)
7	MABR (1.2)	-78, 2; -40, 1	85 (1 : 32)
8	MABR (2)	-78, 5, -40, 0.3	82 (1 : 32)

[a] The reaction was carried out in CH_2Cl_2 using 1.2~2 equiv of Lewis acids under the indicated conditions. [b] Determined by GLC analysis. [c] See ref 2.

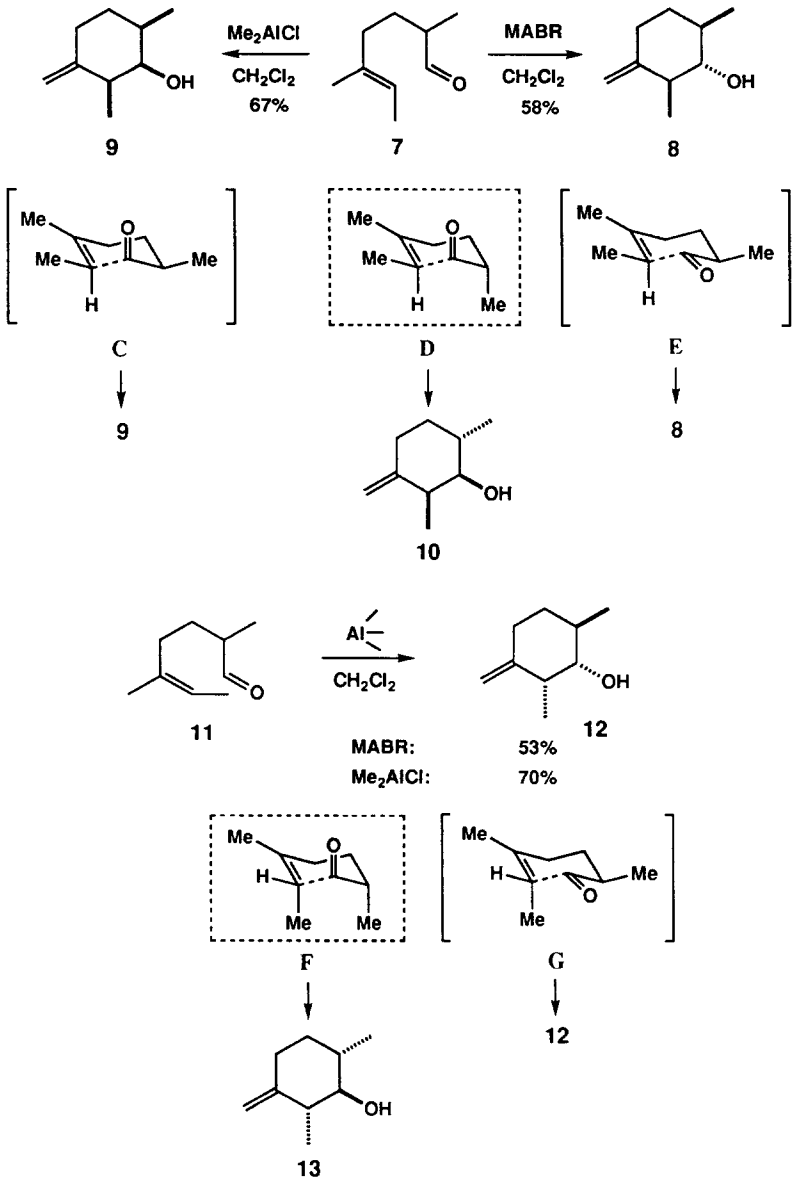
The generality of the present stereocontrolled intramolecular ene reaction is indicated in Table II. Several characteristic features of the reaction have been noted: (1) In general, MABR can be utilized to obtain the *trans* isomer, while the *cis* isomer can be produced with Me_2AlCl. (2) The cyclization proceeds under very mild conditions with very good *cis* and *trans* selectivity. The *p*-bromo substituent in MABR is indispensable for rate acceleration (Table I). (3) The bulkiness of α-substituents has no effect on the stereochemical course of this reaction. (entries 2 vs. 4) (4) The effect of phenylthio substituent leads to preferential formation of the *trans* isomer even with conventional Lewis acids (entries 9-13).[8]

Table II. Stereocontrolled Ene Reactions of δ,ε-Unsaturated Aldehydes **1**[a]

entry	aldehyde **1**	Lewis acid (equiv)	conditions (°C, h)	yield, % [b] (ratio of **2**:**3**)
1	R = Et	Me_2AlCl (1.2)	-78, 0.3	60 (19 : 1)
2		MABR (2)	-78, 2.5; -40, 0.5	89 (1 : 30)
3	R = *i*-Pr	Me_2AlCl (1.2)	-78, 0.3	70 (33 : 1)
4		MABR (2)	-78, 0.5; -40, 2	85 (1 : 17)
5	R = Allyl	Me_2AlCl (1.2)	-78, 0.7	59 (17 : 1)
6		MABR (2)	-78, 0.5; -40, 1	82 (1 : 62)
7	R = Ph	Me_2AlCl (1.2)	-78, 0.5	95 (26 : 1)
8		MABR (2)	-78, 0.5; -40, 2	98 (1 : 62)
9	R = SPh	Me_2AlCl (1.2)	-78, 0.3	95 (1 : 3)
10		$BF_3{\cdot}OEt_2$ (2)	-78, 0.2	86 (1 : 2)
11		$BF_3{\cdot}OEt_2$ (2)	-78, 0.2; -20, 2.5	63 (1 : 4) [c]
12		Camphorsulfonic acid (1.1)	-78, 0.5; -20, 1.5; 0, 1.5; 25, 1.5	40 (1 : 3.7)
13		$SnCl_4$ (2)	-78, 0.5	66 (1 : 3)
14		MABR (2)	-78, 1.5	75 (1 : 200)

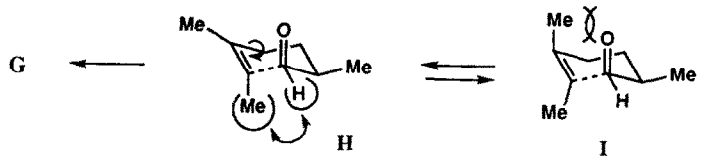
[a] The reaction was carried out in CH_2Cl_2 using 1.2~2 equiv of Lewis acids under the indicated conditions. [b] Determined by GLC analysis. [c] Use of Et_2O as solvent.

In a similar manner, the type II intramolecular ene reaction of (*E*)-2,5-dimethyl-5-heptenal (**7**), possessing trisubstituted double bond, was effected under the influence of MABR to furnish the desired alcohol **8** exclusively with excellent stereoselectivity (>95% pure), while treatment of **7** with Me_2AlCl afforded alcohol **9** as a sole product. The stereochemical outcome by the Me_2AlCl-promoted ene reaction of **7** leading to the alcohol **9** can be explained by way of the Snider's proposed transition state **C**. The transition state **D**, which Snider proposed to explain the *trans* selectivity, for the MABR-promoted ene reaction of **7**, however, leads to an isomeric alcohol **10**, and can not account for the stereochemistry of the MABR catalyzed cyclization of **7** leading to **8**. Therefore, the MABR-promoted ene reactions should be assumed to proceed through a different transition state, *i.e.* transition state **E** with both α-substituent (R) and the carbonyl group equatorial in accord with the experimental findings.

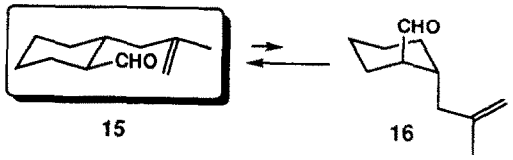


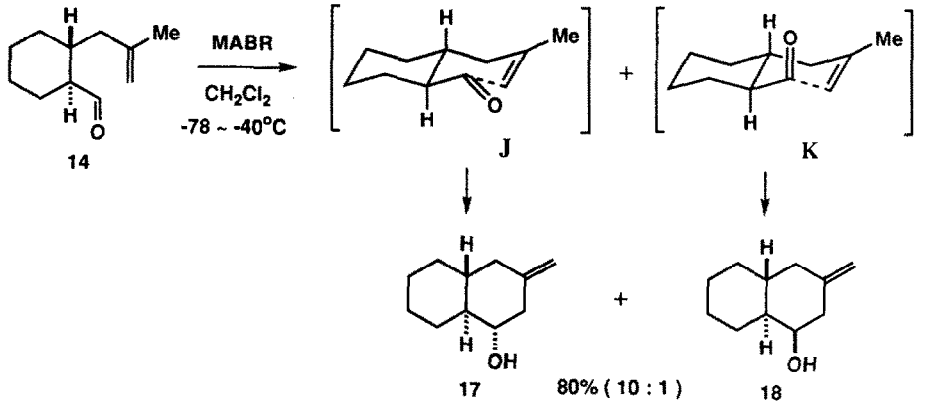
In contrast, the intramolecular ene reaction of (*Z*)-2,5-dimethyl-5-heptenal (**11**) using either MABR or Me_2AlCl gave the same alcohol **12** selectively. Here, again, the alcohol **12** was not formed by way of a Snider's proposed transition state **F** and a transition state **G** is reasonable rather than **F** to explain the product selectivity. With the creation of the new carbon-carbon bond in a transition state **H**, the internal methyl group of the Z-double bond in **11** would be forced closer to the aldehyde carbonyl due to the increasing 1,2 steric interaction between the terminal methyl group and the aldehyde hydrogen atom, which clearly induce 1,3-diaxial interaction between the internal methyl group and the carbonyl oxygen in **I** (Scheme 3). This is the reason even Me_2AlCl gave the alcohol **12** via the transition state **G**.

Scheme 3

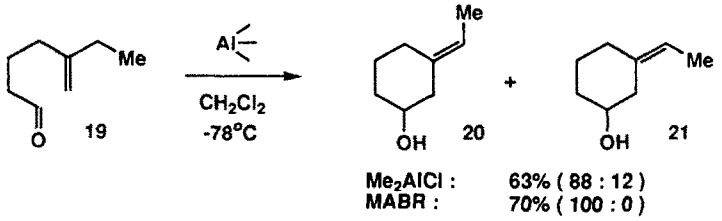


This finding led us to further examine the intramolecular ene reaction of a rigidly maintained cyclic substrate **14**. Although there are two possible conformations for this unsaturated aldehyde **14**, intramolecular ene cyclization could take place only from **15**. Indeed, treatment of **14** with MABR in CH_2Cl_2 at -78 °C for 2 h and at -40 °C for 1 h gave *trans* alcohol **17** predominantly. Consequently, in the type II intramolecular ene reaction of δ,ε-unsaturated aldehyde **14**, the *trans* selectivity is best accounted for by the transition state **J** with both α-alkenyl and the carbonyl groups equatorial, rather than by an alternative **K**.

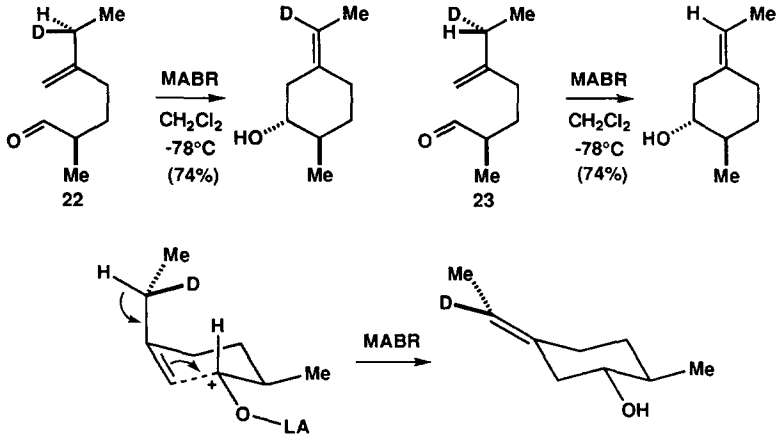




Another interesting feature of the MABR-promoted intramolecular ene reaction is the remote stereochemical control observed in the transformation of substrate **19** to *E*-olefinic alcohol **20** exclusively.



Marshall and Andersen recently reported the cyclization of diastereomerically deuterated aldehydes **22** and **23** and clearly demonstrated that the MABR promoted cyclization proceeds by external proton transfer.[9] This finding strongly supports the transition state we are proposing.



Experimental Section

General. Infrared (IR) spectra were recorded on a Hitachi 260-10 and Shimadzu FT-IR 8100 spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini-200 spectrometer. Analytical gas-liquid phase chromatography (GLC) was performed on Gasukuro Kogyo Model 370 and Shimadzu GC-8A instruments equipped with a flame ionization detector and a capillary column of PEG-HT (0.25 X 25,000 mm) using nitrogen as carrier gas. All experiments were carried out under an atmosphere of dry argon. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel E. Merck 9385. Microanalyses were accomplished at the Institute of Agriculture, Nagoya University.

In experiments requiring dry solvents, ether and tetrahydrofuran (THF) were freshly distilled from sodium metal using benzophenone ketyl as indicator. Benzene, hexane, and toluene were dried over sodium metal. Methylene chloride and DMF were stored over 4A molecular sieves. Pyridine and triethylamine were stored over KOH pellets. Trimethylaluminum, dimethylaluminum chloride, and triethylaluminum were obtained from Toso-Akzo Chem. Co. Ltd., Japan. Other simple chemicals were purchased and used as such.

Preparation of δ,ε-Unsaturated Aldehydes.

2,5-Dimethyl-5-hexenal (4).[2] To a solution of LDA (11 mmol) prepared from Pr^i_2NH (1.68 mL, 12 mmol) and a 1.6 M hexane solution of BuLi (6.88 mL, 11 mmol) in THF (15 mL) was added propionaldehyde *t*-butylimine (1.6 mL, 11 mmol) at 0 °C under Ar. After 30 min of stirring, 4-iodo-2-methyl-1-butene (2.1 g, 10 mmol) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred there for 1.5 h. The desired imine was hydrolyzed with an aqueous solution of oxalic acid (1.51 g, 12 mmol) and extracted with ether. The combined organic extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography (ether/pentane = 1:15 as eluant) gave 2,5-dimethyl-5-hexenal (915 mg, 7.3 mmol) in 73% yield: ^{1}H NMR ($CDCl_3$) δ 9.61 (1H, s, CHO), 4.72 (1H, s, CH=), 4.58 (1H, s, CH=), 2.32 (1H, sex, *J* = 3.7 Hz, CHC=O), 2.03 (2H, t, *J* = 4.5 Hz, CH_2C=) 1.87 (1H, m, CH_2) 1.70 (3H, s, CH_3C=) 1.46 (1H, m, CH_2) 1.09 (3H, d, *J* = 3.7 Hz, CH_3).

2-Ethyl-5-methyl-5-hexenal 1 (R = Et). To a solution of LDA (74 mmol) in ether (70 mL) was added acetaldehyde *t*-butylimine (9.26 mL, 70 mmol) at 0 °C under Ar. After stirring for 30 min, methallyl iodide (12.7 g, 70 mmol; prepared from methallyl chloride and NaI in acetone at room temperature for 3 h) in ether (5 mL) was added at 0 °C and the reaction mixture was stirred there for 1.5 h. Then hydrolysis of imine products with an aqueous solution of oxalic acid (9.3 g, 74 mmol) and extraction with ether were performed. The organic extracts were dried over $MgSO_4$ and concentrated. The residual crude aldehyde was directly used for the following reaction without any purification.

Ethyl diethylphosphonoacetate (12 mL, 60 mmol) was added dropwise at 0 °C to a suspension of NaH (2.88 g, 60 mmol) in THF (70 mL) under Ar and the resulting mixture was stirred at 0 °C for 30 min. The crude 4-methyl-4-pentenal in THF (5 mL) was added dropwise and stirring was continued at this temperature for 1.5 h. The solution was poured into saturated NH_4Cl and extracted with ether. The combined ethereal extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography (ether/hexane = 1:15 as eluant) gave ethyl 6-methyl-2,6-heptadienoate (6 g, 35.7 mmol) in 51% yield based on the *t*-butylimine: ^{1}H NMR ($CDCl_3$) δ 6.92 (1H, dt, *J* = 3.3, 7.5 Hz, CH=C-C=O), 5.80 (1H, d, *J* = 7.5 Hz, C=CH-C=O), 4.72 (1H, s, CH=), 4.67 (1H, s, CH=), 4.14 (2H, q, *J* = 3.5 Hz, O=C-O-CH_2-C), 2.07-2.40 (4H, m, 2(CH_2C=)), 1.69 (3H, s, CH_3C=), 1.24 (3H, t, *J* = 3.5 Hz, CH_3CC=O).

Reduction of ethyl 6-methyl-2,6-heptadienoate with AlH_3 and subsequent epoxidation with *t*-BuOOH in the presence of a catalytic amount of $VO(acac)_2$ afforded 2,3-epoxy-6-methyl-6-hepten-1-ol in 40% yield.

Introduction of the ethyl group was realized as follows: To a solution of Et_3Al (0.82 mL, 6 mmol) in hexane (5.2 mL) was added the epoxy alcohol (284 mg, 2 mmol) in hexane (3 mL) dropwise at 0 °C under Ar and the reaction mixture was stirred at 0 °C for 20 min. The resulting solution was diluted with CH_2Cl_2 (20 mL) and treated with NaF (2.5 g, 60 mmol) and water (1.1 mL, 60 mmol). Vigorous stirring was continued at room temperature for 1 h. The semi-solid was filtered and the remaining solid was washed with ether. The combined filtrates were concentrated. The residual oil was purified by column chromatography (ether/hexane = 9:1) to give 3-ethyl-6-methyl-6-heptene-1,2-diol (120 mg, 0.7 mmol) in 35% yield: ^1H NMR ($CDCl_3$) δ 4.66 (2H, s, CH_2=), 3.40-3.77 (3H, m, CH_2-O and CH-O), 2.34 (2H, br s, CH_2C=), 1.99 (2H, q, *J* = 3.3 Hz, CH_2), 1.69 (3H, s, CH_3C=), 1.10-2.20 (5H, m, CH_2, CH and 2OH), 0.87 (3H, t, *J* = 3.3 Hz, CH_3C).

The diol (120 mg, 0.7 mmol) in THF (6 mL) and water (2 mL) was treated with $NaIO_4$ (300 mg, 1.4 mmol) at 0 °C for 1 h and at room temperature for 2.5 h. The mixture was poured into water and extracted with ether. The combined extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography (ether/pentane = 1:20 as eluant) gave 2-ethyl-5-methyl-5-hexenal (76.4 mg, 0.54 mmol) in 77% yield: ^1H NMR ($CDCl_3$) δ 9.58 (1H, d, *J* = 1.5 Hz, CHO), 4.70 (1H, s, CH=), 4.66 (1H, s, CH=), 2.17 (1H, m, CHC=O), 1.98 (2H, t, *J* = 3.8 Hz, CH_2C=), 1.68 (3H, s, CH_3C=), 1.39-1.88 (4H, m, $2CH_2$), 0.88 (3H, t, *J* = 4 Hz, CH_3); IR (liquid film) 2930, 2878, 2708, 1728, 1651, 1456, 1375, 889, 770 cm^{-1}. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.97; H, 11.39.

2-Allyl-5-methyl-5-hexenal 1 (R = allyl). To a solution of LDA (12 mmol) in THF (15 mL) was added acetaldehyde *t*-butylimine (0.79 mL, 6 mmol) dropwise at 0 °C under Ar and the solution was stirred there for 20 min. Allyl bromide (0.52 mL, 6 mmol) was added at 0 °C and stirring was continued at this temperature for 1 h. Then 4-iodo-2-methyl-1-butene (980 mg, 5 mmol) was added and the resulting solution was stirred at 0 °C for additional 1 h. An aqueous solution of oxalic acid (882 mg, 7 mmol) was added and vigorous stirring was maintained at 0 °C for 40 min. After extraction with ether, the combined extracts were dried over $MgSO_4$. Evaporation of solvents and purification of the residue by column chromatography (ether/pentane = 1:20 to 1:15 as eluant) gave 2-allyl-5-methyl-5-hexenal (264 mg, 1.74 mmol) in 35% yield: ^1H NMR ($CDCl_3$) δ 9.61 (1H, d, *J* = 1.3 Hz, CHO), 5.70 (1H, m, C=CH-C), 5.03 (2H, m, CH_2=C-C), 4.71 (1H, s, CH=), 4.66 (1H, s, CH=), 2.15-2.50 (3H, m, $C=CCH_2$ and CHC=O), 2.00 (2H, t, *J* = 4 Hz, CH_2C=), 1.68 (3H, s, CH_3), 1.48-1.90 (2H, m, CH_2); IR (liquid film) 3079, 2936, 2859, 2714, 1728, 1449, 1375, 994, 918, 889 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.89; H, 10.73.

5-Methyl-2-phenyl-5-hexenal 1 (R = Ph). Phenylacetic acid (4.1 g, 30 mmol) in THF (7 mL) was added to a solution of LDA (62 mmol) in THF (50 mL) at -78 °C under Ar and the mixture was allowed to warm to room temperature, then heated at 50 °C for 2 h. After the yellow mixture was cooled to 0 °C, 4-iodo-2-methyl-1-butene (6.27 g, 32 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h. A little amount of ice and 1N HCl were added sequentially, and then extractive work up was performed with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (EtOAc/hexane = 1:1 to EtOAc only as eluant) to give 5-methyl-2-phenyl-5-hexenoic acid (6.2 g, 30 mmol) quantitatively: ^1H NMR ($CDCl_3$) δ 7.15-7.45 (5H, m, Ph), 4.72

(1H, s, CH=), 4.64 (1H, s, CH=), 3.53 (1H, t, J = 4 Hz, CHC=O), 1.76- 2.30 (4H, m, $2CH_2$), 1.68 (3H, s, CH_3C=).

Simple esterification of 5-methyl-2-phenyl-5-hexenoic acid with MeI/K_2CO_3 in DMF and subsequent reduction with $LiAlH_4$ in ether afforded 5-methyl-2-phenyl-5-hexenol in 65% yield.

Then the Swern oxidation was performed as follows: To a solution of oxalyl chloride (1.17 mL, 13.4 mmol) in CH_2Cl_2 (15 mL) precooled to -78 °C was added DMSO (1.89 mL, 26.7 mmol) and the resulting mixture was stirred there for 10 min. Then 5-methyl-2-phenyl-5-hexenol (1.7 g, 8.9 mmol) in CH_2Cl_2 (5 mL) was added at -78 °C and stirring was continued for 1.5 h at this temperature. Triethylamine (8.4 mL, 60.5 mmol) was added at -78 °C and the whole mixture was stirred at this temperature for 2 h. This mixture was poured into iced water and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography (ether/hexane = 1:15 to 1:10 as eluant) gave 5-methyl-2-phenyl-5-hexenal (1.45 g, 7.7 mmol) in 85% yield: ^{1}H NMR ($CDCl_3$) δ 9.66 (1H, d, J = 0.75 Hz, CHO), 7.12-7.41 (5H, m, Ph), 4.72 (1H, s, CH=), 4.65 (1H, s, CH=), 3.48 (1H, t, J = 3.5 Hz, CHC=O), 2.13-2.31 (1H, m, CH) 1.96 (2H, t, J = 3.75 Hz, CH_2C=), 1.72-1.91 (1H, m, CH), 1.68 (3H, s, CH_3C=); IR (liquid film) 3031, 2938, 2716, 1725, 1649, 1493, 1455, 891, 758, 700 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.96; H, 8.54.

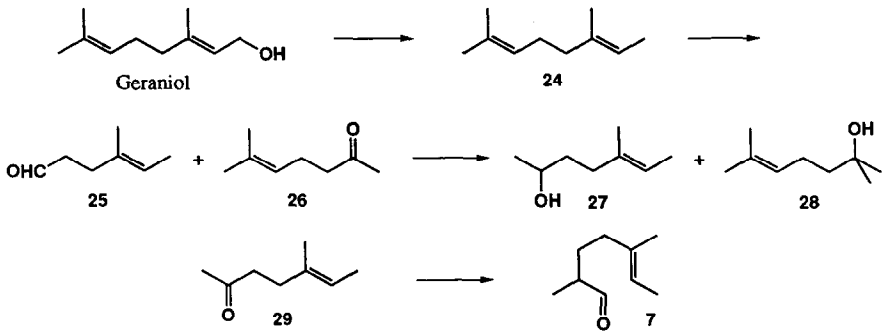
5-Methyl-2-isopropyl-5-hexenal 1 (R = *i*-Pr). This unsaturated aldehyde was prepared in a similar manner as described above, starting from isovaleric acid: ^{1}H NMR ($CDCl_3$) δ 9.61 (1H, d, J = 1.8 Hz, CHO), 4.70 (1H, s, CH=), 4.64 (1H, s, CH=), 1.68 (3H, s, CH_3C=), 1.42-2.13 (6H, m, $2CH_2$ amd 2CH), 0.94 (3H, d, J = 3.3 Hz, CH_3C), 0.93 (3H, d, J = 3.3 Hz, CH_3C); IR (liquid film) 2963, 2876, 2707, 1725, 1651, 1410, 1372, 889 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.85; H, 11.88.

5-Methyl-2-phenylthio-5-hexenal 1 (R = SPh). 2,3-Epoxy-6-methyl-6-heptene-1-ol was prepared in a manner as described for the synthesis of 2-ethyl-5-methyl-5-hexenal **1** (R = Et). To a solution of the epoxy alcohol (355 mg, 2.5 mmol) and thiophenol (0.41 mL, 4 mmol) in toluene (10 mL) was added $Ti(OPr^i)_4$ (1.12 mL, 3.75 mmol) dropwise at -78 °C under Ar. The reaction mixture was gradually allowed to warm to room temperature for 2 h with stirring. The resulting solution was diluted with ether and then 1N HCl was added. The whole mixture was stirred vigorously until two clear phases formed and extractive work up with ether was performed. The combined ethereal extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (ether/hexane = 3:1 as eluant) to afford a mixture of desired 6-methyl-3-phenylthio-6-heptene-1,2-diol and 6-methyl-2-phenylthio-6-heptene-1,3-diol (588 mg, 2.33 mmol) in 93% combined yield.

Treatment of these diols with $NaIO_4$ (1.01 g, 4.7 mmol) in THF (9 mL) and water (3 mL) at 0 °C for 1 h and room temperature for 2 h gave desired aldehyde, 5-methyl-2-thiophenyl-5-hexenal (312 mg, 1.42 mmol), in 57% yield based on the epoxy alcohol: ^{1}H NMR ($CDCl_3$) δ 9.40 (1H, d, J = 2.1 Hz, CHO), 7.20-7.42 (5H, m, SPh), 4.76 (1H, s, CH=), 4.71 (1H, s, CH=), 3.50 (1H, ddd, J = 2.1, 3.75, 7.25 Hz, CH-S), 2.20 (2H, t, J = 3.7 Hz, CH_2C=), 1.66-2.04 (2H, m, CH_2), 1.69 (3H, s, CH_3C=); IR (liquid film) 3075, 2938, 2824, 1721, 1649, 1482, 1439, 891, 749, 693 cm^{-1}. Anal. Calcd for $C_{13}H_{16}$ OS: C, 70.87; H, 7.32. Found: C, 70.89; H, 7.42.

Preparation of (*E*)-2,5-Dimethyl-5-heptenal (7). To a solution of geraniol (6.17 g, 40 mmol) in THF (160 mL) was added sulfur trioxide pyridine complex (9.55 g, 60 mmol) at 0 °C under Ar and stirring was continued there for 5 h.[10] The resulting mixture was treated with $LiAlH_4$ (9.1 g, 240 mmol) in THF

(130 mL) precooled to 0 °C slowly. It was then stirred there for 1 h and at room temperature overnight. After recooling to 0 °C, water (28 mL) was added carefully followed by addition of Na_2SO_4 (10.6 g) and the whole mixture was stirred at room temperature for 12 h. The white precipitate was removed by filtration through celite on a glass filter. Evaporation of solvents and purification of the residual oil by column chromatography (hexane as eluant) gave (6*E*)-2,6-dimethyl-2,6-octadiene **24** (3.98 g, 28.7 mmol) in 72% yield: ^{1}H NMR ($CDCl_3$) δ 5.18 (1H, q, *J* = 3.5 Hz, C=CHC), 5.07 (1H, t, *J* = 3.2 Hz, C=CHC-C), 1.86-2.12 (4H, m, 2(CH_2C=)), 1.65 (3H, s, CH_3C=), 1.57 (6H, s, 2(CH_3C=)), 1.53 (3H, d, *J* = 3.5 Hz, =CCH_3).



Given the two regioisomeric epoxides by oxidation of the olefin with **24** m-CPBA, treatment of these epoxides with periodic acid in THF at 0 °C afforded each carbonyl compound **25** and **26**. Then these were alkylated together by MeLi in ether at 0 °C to give a mixture of desired 5-methyl-5-hepten-2-ol (**27**) and 2,6-dimethyl-5-hepten-2-ol (**28**).

These alcohols were directly applied to the Swern oxidation as follows: To a solution of oxalyl chloride (2.1 mL, 24 mmol) in CH_2Cl_2 (60 mL) was added at -78 °C DMSO (3.4 mL, 48 mmol) and the resulting mixture was stirred there for 15 min. Then the mixture of alcohols (1.65 g, 12.9 mmol) in CH_2Cl_2 (5 mL) was added at -78°C and stirring was continued at this temperature for 1.5 h. Triethylamine (15.1 mL, 108 mmol) was added and the whole mixture was stirred at -78 °C for 1 h, at 0 °C for 2 h and at room temperature for additional 2 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (ether/hexane = 1:5 as eluant) to give 5-methyl-5-hepten-2-one (**29**) (494 mg, 3.92 mmol) in ca. 14% overall yield based on the diene **24**: ^{1}H NMR ($CDCl_3$) δ 5.18 (1H, q, *J* = 3.3 Hz, C=CH-C), 2.30-2.57 (2H, m, CH_2C=O), 2.21 (2H, t, *J* = 4 Hz, CH_2C=), 2.10 (3H, s, CH_3C=O), 1.56 (3H, s, CH_3C=), 1.52 (3H, d, *J* = 3.3 Hz, =CCH_3).

A mixture of (methoxymethyl)triphenylphosphonium chloride (2.74 g, 8 mmol) in THF (10 mL) was treated with a 1.55 M hexane solution of BuLi (5.2 mL, 8 mmol) at 0 °C under Ar for 30 min. The ketone **29** in THF (2 mL) was added to the resulting deep red solution at 0 °C and stirring was continued at this temperature for 30 min. The reaction was quenched with water and extracted with hexane. The combined hexane phase was dried over $MgSO_4$. Evaporation of solvents and purification of the residue by column chromatography (ether/hexane = 1:50 to 1:40 as eluant) gave 2,5-dimethyl-1-methoxy-1,5-heptadiene (674 mg, inseparable PPh_3 was included)

This ether was dissolved in THF (20 mL) and water (2 mL) and then treated with $Hg(OAc)_2$ (2.55 g, 8 mmol) at room temperature for 1 h. The reaction was quenched with addition of aqueous solution of excess

KI and extracted with ether.[11] The organic layer was dried over $MgSO_4$. Evaporation of solvents and purification of the residual oil by column chromatography (ether/hexane = 1:19 as eluant) gave (*E*)-2,5-dimethyl-5-heptenal (**7**) (173 mg, 1.23 mmol) in 31% yield based on the alkenyl ketone **29** : ^{1}H NMR ($CDCl_3$) δ 5.19 (1H, q, *J* = 3.5 Hz, CH=C), 2.27 (1H, sep, *J* = 3.3 Hz, CHC=O), 1.98 (2H, t, *J* = 3 Hz, CH_2C=C), 1.67-1.90 (1H, m, CH), 1.55 (3H, s, CH_3C=C), 1.52 (3H, d, *J* = 3.5 Hz, C=CCH_3), 1.30-1.49 (1H, m, CH), 1.60 (3H, d, *J* = 3.5 Hz, CH_3C); IR (liquid film) 2970, 2810, 1728, 1460, 1032, 910, 819 cm^{-1}. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.01; H, 11.61.

(*Z*)-2,5-dimethyl-5-heptenal (**11**) was synthesized from nerol in a similar manner as described above: ^{1}H NMR ($CDCl_3$) δ 9.65 (1H, d, *J* = 1.9 Hz, CHO), 5.25 (1H, q, *J* = 6.6 Hz, CH=), 2.34 (1H, dsex, *J* = 1.9, 7 Hz, CHC=O), 2.08 (2H, t, *J* = 7.6 Hz, CH_2C=), 1.72-1.92 (1H, m, CH), 1.69 (3H, s, CH_3C=), 1.58 (3H, d, *J* = 6.3 Hz, =CCH_3), 1.32-1.55 (1H, m, CH), 1.13 (3H, d, *J* = 7 Hz, C-CH_3); IR (liquid film) 2967, 2932, 2863, 2708, 1728, 1458, 1377, 920, 810 cm^{-1}. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.12; H, 11.67.

Preparation of Cyclic Unsaturated Aldehyde 14. To a solution of methallylcyclohexanone (1.52 g, 10 mmol) and ICH_2Cl (0.8 mL, 11 mmol) in THF (20 mL) was added dropwise a 1.55 M hexane solution of BuLi (6.77 mL, 10.5 mmol) at -78 °C under Ar. The reaction mixture was allowed to warm to room temperature and stirred there for 3 h. The solution was poured into saturated NH_4Cl and extracted with ether. The combined extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography (ether/hexane = 1:10 as eluant) gave 1-oxa-4-methallylspiro[2.5]octane (1.16 g, 70% yield): ^{1}H NMR ($CDCl_3$) δ 4.72 (1H, s, CH=), 4.65 (1H, s, CH=), 2.73 (1H, d, *J* = 5 Hz, CH-O), 2.49 (1H, d, *J* = 5 Hz, CH-O), 1.95-2.05 (2H, m, CH_2-C=), 1.64 (3H, s, CH_3), 1.25-1.85 (9H, m, CH and $4CH_2$).

A 1 M hexane solution of DIBAH (10 mL, 10 mmol) was added to a solution of 4-bromo-2,6-di-*tert*-butylphenol (2.85 g, 10 mmol) in CH_2Cl_2 (15 mL) at room temperature. The resulting colorless solution was stirred at room temperature for 30 min to furnish diisobutylaluminum 4-bromo-2,6-di-*tert*-butylphenoxide.[12] This mixture was cooled to -78 °C and treated with 1-oxa-4-methallylspiro[2.5]octane (830 mg, 5 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C for 30 min. The solution was poured into diluted HCl and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography (ether/hexane = 2:3 to 1:1 as eluant) afforded a mixture of desired (2-methallylcyclohexyl)methanol and (6-methallyl-1-cyclohexenyl)methanol in 93% combined yield in a ratio of 73:27.

These alcohols were directly applied to the Swern oxidation as follows: To a solution of oxalyl chloride (0.6 mL, 6.9 mmol) in CH_2Cl_2 (20 mL) was added at -78 °C DMSO (0.98 mL, 13.8 mmol) in CH_2Cl_2 (2 mL) and the resulting mixture was stirred there for 20 min. Then the mixture of (2-methallylcyclohexyl)methanol and (6-methallyl-1-cyclohexenyl)methanol (785 mg, 4.7 mmol) in CH_2Cl_2 (5 mL) was added at -78 °C. Stirring was continued for 1 h at this temperature. Triethylamine (4.4 mL, 31.2 mmol) was added at -78 °C, and the whole mixture was stirred at this temperature for 1.5 h. The reaction mixture was poured into water and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residual oil by column chromatography (ether/hexane = 1:15 as eluant) gave cyclic unsaturated aldehyde **14** (415 mg, 2.5 mmol) in 73% yield based on the (2-methallylcyclohexyl)methanol: ^{1}H NMR ($CDCl_3$) δ 9.77 (1H, s, CHO), 4.73 (1H, s, CH=), 4.65 (1H, s, CH=), 2.38-2.48 (1H, m, CH-C=O), 1.93-2.20 (3H, m, CH-CH_2-C=), 1.67 (3H, s, CH_3), 1.15-

1.92 (8H, m, $4CH_2$);.IR (liquid film) 3075, 2932, 2857, 2705, 1725, 1647, 1449, 1375, 1242, 889 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.35; H, 10.89.

Preparation of Unsaturated Aldehyde 19.[2] To a solution of 5-hexyn-1-ol (982 mg, 10 mmol) and ethyl vinyl ether (1.15 mL, 12 mmol) in CH_2Cl_2 (10 mL) was added Py•TsOH (50 mg, 0.2 mmol) at 0 °C under Ar. The reaction solution was stirred at 0 °C for 1.5 h and at room temperature for additional 2 h. This mixture was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography (ether/hexane = 1:10 as eluant) gave ethoxyethyl ether of 5-hexyn-1-ol (1.7 g, 10 mmol) quantitatively.

The ether was alkylated as follows. A mixture of CuBr•Me_2S (1.44 g, 7 mmol) in ether (6.5 mL) and Me_2S (7.2 mL) was stirred until the mixture became homogeneous. The solution was treated with EtMgBr (2.33 mL, 7 mmol) at -45 °C over 10 min and stirred there for 2 h. Then the ethoxyethyl ether of 5-hexyn-1-ol (851 mg, 5 mmol) in ether (3 mL) was added at -45 °C and, after stirring for 2 h at this temperature, the reaction mixture was allowed to warm to 0 °C. The reaction was quenched by addition of saturated NH_4Cl and extracted with ether. The organic layer was dried over Na_2SO_4 and concentrated. The resulting crude product was dissolved in acetone (8 mL) and water (3.5 mL) and then conc. H_2SO_4 (2 drops) was added. The whole mixture was heated at reflux for 2 h and then cooled to room temperature. Acetone was evaporated and water (9 mL) was added. The aqueous phase was extracted with CH_2Cl_2 and the CH_2Cl_2 extracts were subsequently washed with saturated $NaHCO_3$. The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (ether/hexane = 1:1 to 3:2 as eluant) to give 5-ethyl-5-hexen-1-ol (355 mg, 2.77 mmol) in 55% yield.

To a solution of the alcohol obtained above (318 mg, 2.5 mmol) in CH_2Cl_2 (10 mL) was added PDC (1.88 g, 5 mmol) at room temperature under Ar and the reaction mixture was stirred there overnight. After filtration, evaporation of solvents and purification of the residue by column chromatography (ether/pentane = 1:10 as eluant) afforded 5-ethyl-5-hexenal (**19**) (174 mg, 1.38 mmol) in 55% yield: ^1H NMR ($CDCl_3$) δ 9.75 (1H, s, CHO), 4.73 (1H, s, CH=), 4.69 (1H, s, CH=), 2.40 (2H, t, J = 6.5 Hz, CH_2C=O), 1.89-2.11 (4H, m, =C-CH_2-C and C-CH_2C=), 1.68-1.84 (2H, m, CH_2), 0.99 (3H, t, J = 6 Hz, CH_3).

Preparation of Methylaluminum Bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR). To a solution of 4-bromo-2,6-di-*tert*-butylphenol (2 mmol) in CH_2Cl_2 (5 mL) was added at room temperature a 2 M hexane solution of Me_3Al (0.5 mL, 1 mmol). The methane gas evolved immediately. The resulting colorless solution was stirred at room temperature for 1 h and used as a solution of MABR in CH_2Cl_2 without any purification. Other modified organoaluminum reagents such as DAD, MAPH and MAD were prepared *in situ* from Me_3Al and the corresponding phenols in CH_2Cl_2 at room temperature for 1 h.

General Method for the Intramolecular Ene-Reaction of δ,ε-Unsaturated Aldehyde 1. To a solution of MABR (1 mmol) in CH_2Cl_2 (5 mL) was added δ,ε-unsaturated aldehyde **1** (0.5 mmol) at -78 °C. The resulting mixture was stirred at -78 ~ -40 °C for several hours. The solution was poured into diluted HCl and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography (ether/hexane as eluant) gave *trans*-6-alkyl-3-methylenecyclohexanol **3** with high stereoselectivity in the yields as shown in Tables I and II. The *cis*/*trans* ratio of ene-products **2** and **3** was determined by ^1H NMR and capillary GLC analysis.

General Method for the Intramolecular Ene-Reaction with Conventional Lewis Acids. To a solution of unsaturated aldehyde in CH_2Cl_2 was added 1.2~2 equiv of a Lewis acid at -78 °C under Ar and

the reaction solution was stirred at -78 °C for several hours. Usual work up and purification gave ene-products. The stereoselectivity was determined as mentioned above.

***cis*-2,5-Dimethylcyclohexanol (5):**[2] ^{1}H NMR ($CDCl_3$) δ 4.80 (1H, s, CH=), 4.71 (1H, s, CH=), 3.77 (1H, br s, CH-O), 2.20-2.37 (2H, m, O-C-CH_2-C=), 1.87-2.10 (2H, m, CH_2C=), 0.90-1.80 (4H, m, CH_2, CH and OH), 0.92 (3H, d, J = 6.5 Hz, CH_3).

***trans*-2,5-Dimethylcyclohexanol (6):**[2] ^{1}H NMR ($CDCl_3$) δ 4.66 (2H, s, CH_2=), 3.15 (1H, ddd, J = 4.5, 10, 14 Hz, CH-O), 2.53 (1H, dd, J = 4.5, 12 Hz, O-C-CH-C=), 2.18 (1H, dt, J = 4.5, 14 Hz, C-CH-C=), 1.87-2.09 (2H, m, CH_2C=), 1.74 (1H, dq, J = 4.5, 14 Hz, CH), 1.42 (1H, m, CH), 0.99 (3H, d, J = 6.5 Hz, CH_3), 0.82-1.24 (2H, m, CH_2).

***cis*-2-Ethyl-5-methylenecyclohexanol 2 (R = Et):** ^{1}H NMR ($CDCl_3$) δ 4.80 (1H, s, CH=), 4.72 (1H, s, CH=), 3.91 (1H, br s, CH-O), 1.87-2.42 (4H, m, 2(CH_2=)), 1.09-1.70.(6H, m, 2CH_2, CH and OH), 0.88 (3H, t, J = 3.8 Hz, CH_3); IR (liquid film) 3440, 2961, 2936, 1653, 1460, 1198, 1017, 889, 868 cm^{-1}. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.20; H, 11.68.

***trans*-2-Ethyl-5-methylenecyclohexanol 3 (R = Et):** ^{1}H NMR ($CDCl_3$) δ 4.70 (2H, br s, CH_2=), 3.32 (1H, ddd, J = 5, 9, 14 Hz, CH-O), 2.59 (1H, dd, J = 5, 12.5 Hz, O-C-CH-C=), 2.25 (1H, m, O-C-CH-C=), 1.67-2.12 (4H, m, C-CH_2-C= and C-CH_2-C-C=), 0.98-1.41 (3H, m, C-CH_2-C and CH), 0.92 (3H, t, J = 7.5 Hz, CH_3C); IR (liquid film) 3300, 2968, 1655, 1449, 1045, 955, 889, 855 cm^{-1}. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.11; H, 11.56.

***cis*-2-Isopropyl-5-methylenecyclohexanol 2 (R = *i*-Pr):** ^{1}H NMR ($CDCl_3$) δ 4.81 (1H, s, CH=), 4.72 (1H, s, CH=), 4.10 (1H, br s, CH-O), 2.30 (3H, m, CH_2C-O and CHC=), 1.97 (1H, ddd, J = 2.5, 6.6, 9.0 Hz, CHC=), 1.78 (1H, m, CH), 1.53 (1H, oct, J = 3Hz, CH), 1.01-1.37 (3H, m, CH_2 and OH), 0.95 (3H, d, J = 3 Hz, CH_3C), 0.88 (3H, d, J = 3 Hz, CH_3C); IR (liquid film) 3460, 2942, 2870, 1655, 1475, 1385, 1197, 993, 967, 889, 874 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.87; H, 11.91.

***trans*-2-Isopropyl-5-methylenecyclohexanol 3 (R = *i*-Pr):** ^{1}H NMR ($CDCl_3$) δ 4.66 (2H, s CH_2=), 3.44 (1H, br, CH-O), 2.58 (1H, dd, J = 2.5, 6.0 Hz, CHC=), 0.96-2.33 (8H, m, 2CH_2, 3CH and OH), 0.92 (3H, d, J = 3.3 Hz, CH_3C), 0.79 (3H, d, J = 3.3 Hz, CH_3C); IR (liquid film) 3310, 2957, 2872, 1655, 1466, 1387, 1370, 1051, 1032, 980, 891 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.80; H, 11.86.

Stereochemical Assignment of 3 (R = *i*-Pr). To a solution of **3** (R = i-Pr) (17.1 mg, 0.11 mmol) was added 10% Pd/C (11 mg) and this mixture was stirred at room temperature under H_2 for 1 h. After filtration, solvents were evaporated and purification of the residual oil by column chromatography (ether/hexane = 1:2 as eluant) gave 2-isopropyl-5-methylcyclohexanol (9.3 mg, 0.06 mmol) in 55% yield. The stereochemistry was confirmed in comparison with a retention time of *l*-menthol by GLC analysis: t_R (*l*-menthol) = 8.03 min at the column temperature of 120 °C.

***cis*-2-Allyl-5-methylenecyclohexanol 2 (R = allyl):** ^{1}H NMR ($CDCl_3$) δ 5.79 (1H, m, C=CH-C), 5.01 (2H, m, CH_2=C-C), 4.80 (1H, s, CH=), 4.72 (1H, s, CH=), 3.90 (1H, br s, CH-O), 1.05-2.35 (10H, m, 4CH_2, CH, and OH); IR(liquid film) 3340, 3075, 2936, 1653, 1642, 1445, 1186, 1065, 980, 910, 887, 758 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.91; H, 10.87.

***trans*-2-Allyl-5-methylenecyclohexanol 3 (R = allyl):** ^{1}H NMR ($CDCl_3$) δ 5.82 (1H, m, C=CH-C), 5.02 (2H, m, CH_2=C-C), 4.66 (2H, s, CH_2=), 3.31 (1H, m, CH-O), 2.53 (1H, dd, J = 2.5, 6.5 Hz, CHC=), 0.97-2.48 (9H, m, 3CH_2, 2CH and OH); IR (liquid film) 3350, 3075, 2938, 1655, 1642,

1445, 1043, 994, 911, 891 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.80; H, 10.75.

***cis*-2-Phenyl-5-methylenecyclohexanol 2 (R = Ph):** ^1H NMR ($CDCl_3$) δ 7.17-7.38 (5H, m, Ph), 4.90 (1H, s, CH=), 4.79 (1H, s, CH=), 4.07 (1H, br s, CH-O), 2.86 (1H, m, PhCH), 2.40-2.53 (3H, m, O-C-CH_2-C= and O-C-CH-C=), 1.90-2.29 (2H, m, O-C-CH-C= and C-CH-C), 1.69-1.73 (1H, m, C-CH-C), 1.40 (1H, d, J = 5 Hz, OH); IR (KBr) 3330, 3061, 2914, 2898, 1647, 1495, 1443, 1306, 1194, 1086, 982, 895, 760 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.90; H, 8.35.

***trans*-2-Phenyl-5-methylenecyclohexanol 3 (R = Ph):** ^1H NMR ($CDCl_3$) δ 7.22-7.39 (5H, m, Ph), 4.70 (2H, s, CH_2=), 3.68 (1H, dt, J = 2.8, 11.5 Hz, CH-O), 2.73 (1H, m, PhCH), 2.57 (1H, m, O-C-CH-C=), 2.38 (1H, m, O-C-CH-C=), 1.87-2.28 (3H, m, C-CH_2-C= and C-CH-C), 1.50-1.71 (2H, m, CH and OH); IR (liquid film) 3551, 3028, 2936, 2840, 1653, 1495, 1454, 1342, 1065, 1048, 957, 893, 758, 700 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 82.92; H, 8.50.

Stereochemical Assignment of 3 (R = Ph). The authentic hydrogenated sample of **3** (R = Ph) was independently synthesized as follows. To a solution of 4-methylcyclohexanone (245 μl, 2 mmol) in ether (5 mL) was added 2M cyclohexane/diethylether solution of PhLi (1.1 mL, 2.2 mmol) at 0 °C under Ar and the reaction solution was stirred at 0 °C for 30 min. The solution was poured into water and extracted with ether. The combined ethereal extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography (ether/hexane = 1:2 as eluant) gave 4-methyl-1-phenyl-1-cyclohexanol quantitatively. The alcohol was dissolved in CH_2Cl_2 (5 mL) and triethylamine (606 mg, 6 mmol) and methanesulfonyl chloride (232 μl, 3 mmol) were added sequentially at 0 °C. Stirring was continued at room temperature for several hours. The mixture was poured into saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (hexane as eluant) to give 2-phenyl-5-methyl-1-cyclohexene (156 mg, 0.91 mmol) in 46% yield based on 4-methylcyclohexanone. The 2M THF solution of BH_3•SMe_2 (0.69 mL, 1.37 mmol) was added to a solution of the olefin in THF (5 mL) at 0 °C under Ar and the mixture was stirred at 0 °C for 1 h and at room temperature for 4 h. The excess borane reagent was decomposed by the careful addition of water. Then this mixture was treated with 3N aqueous solution of NaOH (0.55 mL) and 30% aqueous solution of H_2O_2 (0.3 mL) at room temperature for 15 h. After usual work up, purification by column chromatography (ether/hexane = 1:2 as eluant) gave *rel*-(1*S*,2*R*,5*S*)- and *rel*-(1*S*,2*R*,5*R*)-2-phenyl-5-methyl-1-cyclohexanol (136 mg, 0.72 mmol) in a ratio of 1:1.3 in 78% yield: ^1H NMR ($CDCl_3$) δ 7.18-7.42 (5H, m, Ph), 3.91 (0.43H, ddd, J = 4, 10, 15 Hz, CH-O), 3.68 (0.57H, ddd, J = 4, 10, 14 Hz, CH-O), 0.86-2.47 (8H, m, 3CH_2 and 2CH), 1.08 (1.7H, d, J = 7.5 Hz, CH_3), 0.98 (1.3H, d, J = 6 Hz, CH_3). GLC analysis of these products revealed corresponding two peaks: t_R = 16.36 min, 19.13 min at the column temperature of 160 °C.

Hydrogenation of **3** (R = Ph) with Pd/C in THF at room temperature gave stereoisomeric mixtures of *rel*-(1*S*,2*R*,5*S*)- and *rel*-(1*S*,2*R*,5*R*)-2-phenyl-5-methyl-1-cyclohexanol in a ratio of 1:3.6 and the stereochemistry was confirmed by correlation to the authentic sample prepared above by GLC analysis.

***trans*-2-Phenylthio-5-methylenecyclohexanol 3 (R = SPh):** ^1H NMR ($CDCl_3$) δ 7.45-7.53 (2H, m, Ph), 7.27-7.36 (3H, m, Ph), 4.73 (2H, s, CH_2=), 3.41 (1H, ddd, J = 4, 10, 15 Hz, CH-O), 2.84-3.01 (2H, m, PhSCH and OH), 2.76 (1H, ddd, J = 1.4, 4.5, 13 Hz, CH-C-SPh), 1.98-2.36 (4H, m,

2(CH_2C=)), 1.27-1.53 (1H, m, CH); IR (liquid film) 3430, 2940, 1655, 1479, 1439, 1053, 895, 741, 693 cm^{-1}. Anal. Calcd for $C_{13}H_{16}OS$: C, 70.87; H, 7.32. Found: C, 70.89; H, 7.40.

Stereochemical Assignment of 3 (R = SPh). Treatment of 4-methylcyclohexanone with PhSH and P_2O_5 in benzene afforded 4-methyl-1-phenylthio-1-cyclohexene which was subsequently exposed to the hydroboration condition to give an authentic sample *rel*-(1*S*,2*S*,5*S*)-2-phenylthio-5-methyl-1-cyclohexanol: ^1H NMR ($CDCl_3$) δ 3.32 (1H, ddd, *J* = 4.5 11, 15 Hz, CH-O), 2.92 (1H, s, OH), 2.70 (1H, ddd, *J* = 4, 11, 16 Hz, CH-SPh), 1.98-2.13 (2H, m, CH_2), 1.56-1.70 (1H, m, CH), 0.88 (3H, d, *J* = 7 Hz, CH_3), 0.80-1.55 (4H, m, CH_2 and 2CH).

Hydrogenation of **3** (R = SPh) with $(Ph_3P)_3RhCl$ and H_2 in benzene at room temperature gave stereoisomeric mixtures of *rel*-(1*S*,2*S*,5*S*)- and *rel*-(1*S*,2*S*,5*R*)-2-phenylthio-5-methyl-1-cyclohexanol. GLC analysis revealed two peaks; t_R = 14.63 min, 21.32 min at the column temperature of 200 °C, which were identical with an authentic sample prepared above.

Ene Reaction of Unsaturated Aldehydes 7 and 11. Lewis acid promoted ene reactions of **7** and **11** were carried out in a similar manner as described for the intramolecular cyclization of **1**.

2,6-Dimethyl-5-methylenecyclohexanol (8): ^1H NMR ($CDCl_3$) δ 4.69 (1H, s, CH=), 4.64 (1H, s, CH=), 3.31 (1H, q, *J* = 6 Hz, CH-O), 2.54 (1H, quint, *J* = 7 Hz, O-C-CH-C=) 1.97-2.23 (2H, m, CH_2C=), 1.60-1.87 (2H, m, 2CH), 1.51 (1H, d, *J* = 6 Hz, OH), 1.02 (3H, d, *J* = 7 Hz, =C-C-CH_3), 1.00-1.24 (1H, m, CH), 0.96 (3H, d, *J* = 6 Hz, CH_3); IR (liquid film) 3400, 2928, 1653, 1456, 1360, 1075, 1036, 984, 891 cm^{-1}. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.12; H, 11.50.

2,6-Dimethyl-5-methylenecyclohexanol (9): ^1H NMR ($CDCl_3$) δ 4.90 (1H, s, CH=), 4.68 (1H, s, CH=), 3.53 (1H, d, *J* = 8.8 Hz, CH-O), 2.20-2.36 (2H, m, 2CH=), 2.01 (1H, ddd, *J* = 5, 13, 17 Hz, CH-C=), 1.46-1.80 (2H, m, CH_2), 1.28 (1H, ddd, *J* = 5, 13, 17 Hz, CH), 1.09 (3H, d, *J* = 7 Hz, CH_3-C-C=), 0.96 (3H, d, *J* = 6.5 Hz, CH_3); IR (liquid film) 3390, 2980, 2925, 1645, 1460, 1380, 1140, 1040, 984, 891 cm^{-1}. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.07; H, 11.62.

2,6-Dimethyl-5-methylenecyclohexanol (12): ^1H NMR ($CDCl_3$) δ 4.77 (1H, s, CH=), 4.73 (1H, s, CH=), 3.44 (1H, br s, CH-O), 2.42 (1H, dq, *J* = 4, 7 Hz, O-C-CH-C=), 2.00-2.30 (2H, m, CH_2C=), 1.88 (1H, m, CH), 1.10-1.60 (3H, m, CH_2 and CH), 1.09 (3H, d, *J* = 7.5 Hz, CH_3-C-C=), 0.94 (3H, d, J = 7 Hz, CH_3); IR (liquid film) 3420, 2963, 2930, 1647, 1456, 1379, 1035, 983, 891 cm^{-1}. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.98; H, 11.55.

Stereochemical Assignment of 8, 9 and 12. The stereochemistries of ene products **8**, **9**, and **12** were ascertained in comparison with the retention time of independently synthesized authentic samples by GLC analysis after hydrogenation of their acetates. The authentic samples were prepared from 2,3,6-trimethyl-2-cyclohexenone.[13] To a solution of 1M hexane solution of DIBAH (5 mL, 5 mmol) in CH_2Cl_2 (10 mL) was added 2,3,6-trimethyl-2-cyclohexenone[13] (591 μl, 4 mmol) at -78 °C under Ar and the reaction solution was stirred at this temperature for 30 min. This reaction was quenched with diluted HCl aqueous solution and extracted with CH_2Cl_2. The organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by column chromatography (ether/hexane = 1:9 to 1:2.5 as eluant) afforded pure *cis*-2,3,6-trimethyl-2-cyclohexen-1-ol (273 mg, 1.98 mmol) and 2:1 isomeric mixture of *cis*- and *trans*-2,3,6-trimethyl-2-cyclohexen-1-ol (78 mg, 0.57 mmol) in 64% combined yield. These alcohols were further converted to their acetates with Ac_2O-Py.

Hydrogenation of *cis*-1-acetoxy-2,3,6-trimethyl-2-cyclohexene with Pt/C in THF at room temperature for several hours gave *rel*-(1*S*,2*R*,3*R*,6*S*)- and *rel*-(1*S*,2*S*,3*S*,6*S*)-1-acetoxy-2,3,6-trimethylcyclohexane. GLC analysis revealed corresponding two peaks at the column temperature of 80 °C: t_R = 13.44 min, 14.03 min.

The mixture of *cis*- and *trans*-1-acetoxy-2,3,6-trimethyl-2-cyclohexene (*cis*/*trans* = 2:1) was also hydrogenated in a similar manner to give four possible stereoisomeric mixtures. GLC analysis revealed four peaks and the retention times corresponded to *rel*-(1*R*,2*R*,3*R*,6*S*)- and *rel*-(1*R*,2*S*,3*S*,6*S*)-1-acetoxy-2,3,6-trimethylcyclohexane were identified in comparison with the retention times obtained above: t_R = 14.97 min, 15.53 min at the column temperature of 80 °C.

Acetylation of **8** and subsequent hydrogenation with Pt/C afforded *rel*-(1*R*,2*R*,3*S*,6*S*)- and *rel*-(1*R*,2*R*,3*R*,6*S*)-1-acetoxy-2,3,6-trimethylcyclohexane and the stereochemistry was confirmed by correlation to authentic sample by GLC analysis: t_R = 12.64 min, 15.53 min (identical with the retention time of authentic sample) at the column temperature of 80 °C. The same transformations on **9** afforded *rel*-(1*S*,2*R*,3*R*,6*S*)- and *rel*-(1*S*,2*R*,3*S*,6*S*)-1-acetoxy-2,3,6-trimethylcyclohexane: t_R = 11.81 min, 14.03 min (identical with authentic sample), and on **12** gave *rel*-(1*R*,2*S*,3*R*,6*S*)- and *rel*-(1*R*,2*S*,3*S*,6*S*)-1-acetoxy-2,3,6-trimethylcyclohexane: t_R = 13.67 min, 14.98 min (identical with authentic sample).

Ene Reaction of Aldehyde 14. To a solution of MABR (1 mmol) in CH_2Cl_2 (5 mL) was added cyclic unsaturated aldehyde **14** (83 mg, 0.5 mmol) in CH_2Cl_2 (0.5 mL) at -78 °C and the resulting mixture was stirred there for 1 h and at -40 °C for 1 h. The solution was then poured into diluted HCl and extracted with CH_2Cl_2. Evaporation of solvents and purification of the residue by column chromatography on silica gel (ether/hexane = 2:3 as eluant) gave a mixture of *trans* and *cis* alcohols **17** and **18** (66.4 mg, 80% yield), the ratio of which was determined to be 10:1 by GLC at the column temperature of 130 °C. **17**: ^{1}H NMR ($CDCl_3$) δ 4.70 (2H, s, CH_2=), 3.70-3.85 (1H, s, CH-O), 2.51 (1H, dd, *J* = 4, 13 Hz, OC-CH-C=); IR (liquid film) 3550, 2924, 2859, 1653, 1449, 1339, 1043, 991, 887 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O$: C, 79.47; H, 10.91. Found: C, 79.49; H, 10.90. **18**: ^{1}H NMR ($CDCl_3$) δ 4.80 (1H, s, CH=), 4.71 (1H, s, CH=), 3.69-3.81 (1H, m, CH-O), 2.06-2.45 (4H, m, CH_2-C= and OC-CH_2-C=).

Determination of the Stereochemistry of 17.[14] The structure of **17** was confirmed by conversion to the known *trans*-decaline-1,3-diol[14] as follows. To a solution of **17** (47.8 mg, 0.29 mmol) in CH_2Cl_2 (5 mL) was added m-CPBA (75.5 mg, 0.35 mmol) at 0 °C under Ar and stirring was continued there for 1 h. The mixture was poured into saturated $NaHCO_3$ and extracted with EtOAc. The combined EtOAc extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography (EtOAc/hexane = 1:1 to 2:3 as eluant) gave epoxide (35.1 mg, 0.19 mmol) in 66% yield: ^{1}H NMR ($CDCl_3$) δ 3.85 (1H, q, *J* = 2.3 Hz, CH-O), 2.56 (2H, s CH_2-O-C), 0.9-2.5 (15H, m, 6CH_2, 2CH and OH).

The epoxide was dissolved in THF (3 mL) and then treated with periodic acid (48 mg, 0.21 mmol) at 0 °C for 30 min. The reaction was quenched with satureted $NaHCO_3$ and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (EtOAc/hexane = 3:2 to 2:1 as eluant) to give cyclic ketone (19.1 mg, 0.11 mmol) in 58% yield: ^{1}H NMR ($CDCl_3$) δ 4.12 (1H, q, *J* = 2.1 Hz, CH-O), 2.61 (1H, dd, *J* = 2.1, 7 Hz, CHC=O), 1.0-2.5 (14H, m, 5CH_2, 3CH and OH).

$LiAlH_4$ (5 mg, 0.13 mmol) was added to a solution of the cyclic ketone in THF (3 mL) at 0 °C under Ar. After 15 min, the reaction was quenched by careful addition of MeOH, 1N HCl and extracted with EtOAc. The combined extracts were dried over Na_2SO_4. Evaporation of solvents and purification of the residue by column chromatography (EtOAc/hexane = 5:1 to 7:1 as eluant) afforded *trans*-decaline-*cis*-1,3-diol and *trans*-

decaline-*trans*-1,3-diol. *trans*-decaline-*cis*-1,3-diol: R*f* = 0.21 (EtOAc/hexane = 5:1); ^{1}H NMR (DMSO) δ 4.41 (2H, t, *J* = 5.5 Hz, 2OH), 3.68 (2H, m, 2(CH-O)), 2.48 (2H, s, CH_2), 0.95-2.11 (12H, m, $5CH_2$ and 2CH). *trans*-decaline-*trans*-1,3-diol: R*f* = 0.16 (EtOAc/hexane = 5:1); 1H NMR (DMSO) δ 4.31 (2H, d, *J* = 4.5 Hz, 2OH), 3.74 (1H, oct, *J* = 5 Hz, CH-O), 3.67 (1H, br s, CH-O), 2.49 (2H, s, CH_2), 0.90-2.12 (12H, m, $5CH_2$ and 2CH).

Ene Reaction of Unsaturated Aldehyde 19. Intramolecular ene cyclization of **16** was also performed in a similar manner described for the ene reaction of unsaturated aldehyde **1**.

(*E*)-3-Ethylidenecyclohexanol (20):[2] ^{1}H NMR ($CDCl_3$) δ 5.23 (1H, q, *J* = 6.7 Hz, CH=), 3.70 (1H, m, CH-O), 2.42 (1H, dd, *J* = 3.4, 12.7 Hz, O-C-CH-C=), 2.24 (1H, m, O-C-CH-C=), 1.70-2.10 (4H, m, $2CH_2$), 1.50 (3H, d, *J* = 6.7 Hz, CH_3), 1.30-1.60 (2H, m, CH_2).

(*Z*)-3-Ethylidenecyclohexanol (21):[2] ^{1}H NMR ($CDCl_3$) δ 5.30 (1H, q, *J* = 6.7 Hz, CH=), 2.65 (1H, dd, *J* = 3.6, 12.7 Hz, O-C-CH-C=).

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(*Received in Japan* 16 *February* 1994; *accepted* 16 *March* 1994)