Aldol Condensation *versus* Conjugate Addition: Intramolecular Cyclization Using a Combination of Lewis Acid and 1,2-Diol

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The reactivity of 3-substituted 4-methyl-4-(3-oxobutyl)-2-cyclohexen-1-ones (1) in the presence of a combination of a Lewis acid and a 1,2-diol was studied. The results suggest several factors that influence 6-membered ring formation, including two types of intramolecular aldol reaction and intramolecular 1,4-addition, due to the C3-substituent, Lewis acid, and the presence of diol. In this study, novel methodology to prepare two types of decalin skeleton could be developed.

Key words decalin skeleton; Lewis acid; 1,2-diol; intramolecular 1,4-addition

Previously, we reported novel reactions using a combination of a Lewis acid and a 1,2-diol. The first is ring transformation based on carbon–carbon bond formation (aldol-type reaction) and successive C–C bond cleavage (Grob fragmentation) in both intra- and inter-molecular systems. The other is intramolecular 1,4-addition to synthesize spirocyclic compounds (spirocyclization) (Chart 1). An asymmetric version of these reactions using optically active 1,2-diols has also been developed.[1,2]

In this paper we report structure–reactivity relationships using the above-mentioned reaction conditions by using 3-substituted 4-methyl-4-(3-oxobutyl)-2-cyclohexen-1-ones (**1**). The reasons for selection of this type of compound as a substrate were as follows. Several types of reactions to construct a C–C bond were expected such as intramolecular 1,4-addition (path A) to give bicyclo[4.4.0]decane derivatives (A), aldol-type reaction (path B) to give bicyclo[3.3.1]-nonane derivatives (B1 or B2) and a ring transformation product (B3) by subsequent C–C bond cleavage and aldol reaction (path C) to give hydronaphthalene derivatives (C1 or C2) if R is an active methylene substituent (Chart 2). According to Baldwin's rules,[3] the above reaction paths are allowed, thus cyclizations *via* paths A and C are 6-*enolendo-exo-Trig* and that of path B is 6-*enolexo-exo-Trig*. We were interested to determine which kind of reaction path might be preferable and what factors, such as Lewis acid, diol and substituent at the C3-position, might affect these reaction paths, in addition to elucidation of the basic role of diols in these reactions.

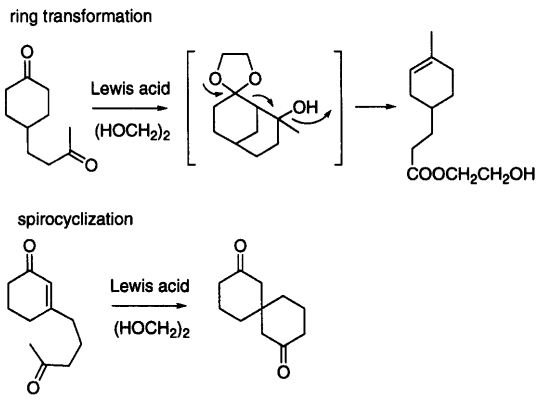

Chart 1. Reactions Using a Combination of Lewis Acid and 1,2-Diol

The designed substrates **1a**—**d** were prepared by a conventional method starting from 1,3-cyclohexanedione **2**. After conversion of **2** to the iso-butyl enol ether **3** (93%), subsequent monomethylation using lithium diisopropylamide (LDA) and MeI gave compound **4** (88%) accompanied a small amount of dimethylated product. Introduction of a 3-oxobutyl moiety into **4** was easily prepared by 1,4-addition with methyl vinyl ketone (MVK) to afford **5** (90%). Chemoselective protection of the carbonyl group as ethylene acetal was performed using pyridinium *p*-toluenesulfonate (PPTS) to give **6** (96%). Finally, reaction of **6** with $LiAlH_4$ and subsequent acid treatment gave **1a** (76%), and reaction with RLi (R=Me, Bu, Ph) followed by similar acid treatment gave **1b**—**d** in 88—91% yields (Chart 3).[4]

Initially, substrate **1a** was submitted to reaction with Lewis acids (3 eq. of $BF_3 \cdot Et_2O$ or trimethylsilyl trifluoromethanesulfonate (TMSOTf)) and diols (5 eq. of ethylene glycol **7** or

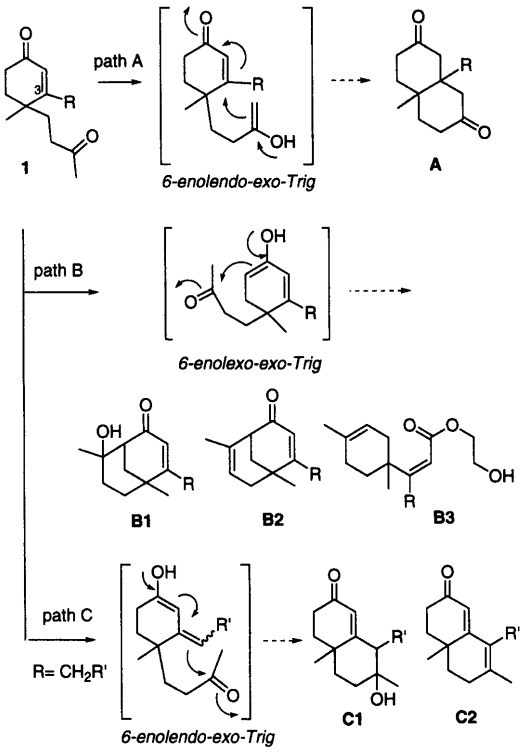

Chart 2. Possible Reaction Path from **1**

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(*dl*)-cyclohexane-1,2-diol **8**). The amount of Lewis acid and diol were set according to our previous studies.[1,2] Unexpectedly, all entries in Table 1, except for entry 2, resulted in a complex mixture of products which could not be isolated even in the cases without diols (entries 1, 4). Successive treatment of these mixtures with aqueous HCl gave the desired product **9** in low yields (12—42%). In entry 2, the tendency to give a complex mixture was clearly decreased and resulted in formation of an inseparable mixture of **9**, the corresponding monoacetal and diacetal, which was confirmed by the ^{1}H-NMR spectrum. Deacetalization of this mixture with aqueous HCl gave **9** in 75% yield from **1a**. The structure of **9** was determined by spectroscopic analysis.[5] The ^{13}C-NMR spectrum showed seven carbon signals and strongly supported the σ-symmetrical structure. The *cis*-fused stereochemistry was determined from the ^{1}H–^{1}H-nuclear Overhauser effect correlation spectroscopy (NOESY) NMR spectrum, in which a nuclear Overhauser effect (NOE) correlation between the signals at δ 1.38 (C6-Me) and δ 2.21 (C1-H) was observed. These results suggest that only the reaction conditions of entry 2 was suitable for intramolecular cyclization of **1a** to **9** (path A).

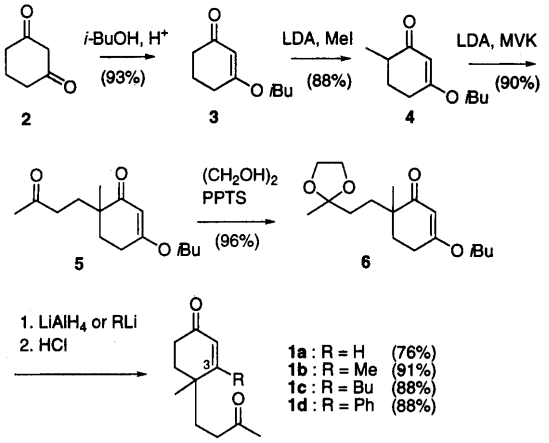
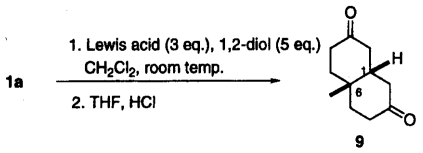


Chart 3. Preparation of Substrates **1a—d**

Table 1. Reaction of **1a** with Lewis Acid and 1,2-Diols



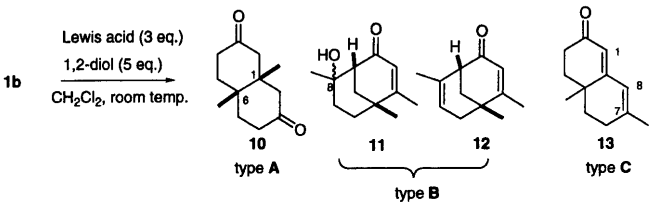
Entry	Lewis acid	1,2-Diol[a]	Time (d)	Yield (%) of **9**
1	$BF_3 \cdot Et_2O$	None	3	39
2	$BF_3 \cdot Et_2O$	**7**	1	75
3	$BF_3 \cdot Et_2O$	**8**	2	42
4	TMSOTf	None	2	29
5	TMSOTf	**7**	1	37
6	TMSOTf	**8**	2	12

a) **7**: ethylene glycol; **8**: (*dl*)-*trans*-cyclohexane-1,2-diol.

Next, similar reactions were performed using substrate **1b** and the results were quite different from those of **1a** (Table 2). In this case, three types of reaction (paths A—C) proceeded to afford the products **10—13**. The structures of these products were determined by spectroscopic analyses. For example, the ^{1}H- and ^{13}C-NMR spectra of **10** showed its σ-symmetry, similar to **9**, and the *cis*-fused stereochemistry of **10** was also determined by NOE correlation between C6-Me (δ 1.26) and C1-Me (δ 0.96) in the ^{1}H–^{1}H NOESY spectrum. For compound **13**, signals of two olefinic protons at δ 5.92 (C8-H) and δ 5.62 (C1-H), and for a methyl proton at δ 1.89 (C7-Me), and NOE correlations between C1-H and C8-H, C8-H and C7-Me were observed, which supported the structure depicted in Table 2.

In the reactions shown in Table 2, the distribution of the products was also found to be highly affected by the Lewis acid. In cases of employing $BF_3 \cdot Et_2O$, two kinds of aldol products, **11** and **13**, were obtained as major products *via* path B and C, respectively (entries 1—3). On the other hand, in cases using TMSOTf, conjugate addition products **10** and the corresponding acetals were obtained as major products (entries 4—6). In entry 6, the total yield of type A products was 70%. As a result, high selectivity to produce the decalin skeleton was observed in entries 2 and 6. These results suggest that chemoselective activation of the C1-carbonyl function by $BF_3 \cdot Et_2O$ might lead the reaction to paths B and C,

Table 2. Reaction of **1b** with Lewis Acid and 1,2-Diols



Entry	Lewis acid	1,2-Diol	Time (h)	Products (%)			
				1b	Type A (**10**)	Type B	Type C (**13**)
1	$BF_3 \cdot Et_2O$	None	12	55	—	27 (**11**)	8
2	$BF_3 \cdot Et_2O$	**7**	12	—	—	38 (**11**)	48
3	$BF_3 \cdot Et_2O$	**8**	12	—	7	52 (**11**)	39
4	TMSOTf	None	12	8	48	15 (**12**)	26
5	TMSOTf	**7**	1.5	—	41 (1 : 9 : 0)[a]	4 (**11**)	37
6	TMSOTf	**8**	1.5	—	70 (1 : 1 : 1.3)[a]	13 (**11**)	14

a) Ratio of products (**10** : corresponding monoacetal : diacetal) determined by ^{1}H-NMR.

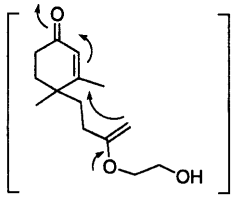


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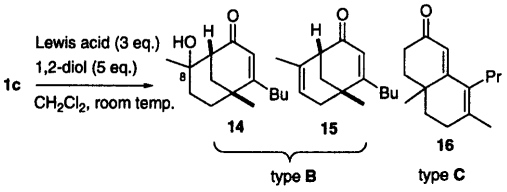
Fig. 1. Plausible Intermediate for Path A

Table 3. Reaction of **1c** with Lewis Acid and 1,2-Diols



Entry	Lewis acid	1,2-Diol	Time (h)	Products (%0			
				1c	**14**	**15**	**16**
1	$BF_3 \cdot Et_2O$	None	36	7	—	13	70
2	$BF_3 \cdot Et_2O$	**7**	16	—	45	—	41
3	TMSOTf	None	36	—	—	13	77
4	TMSOTf	**8**	2	—	37	—	61

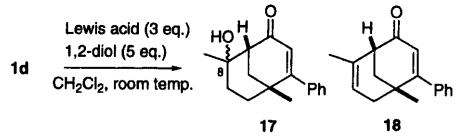
and of the C3′-carbonyl function of the C4-substituent by TMSOTf, to path A. This hypothesis is still unproven in spite of our spectroscopic studies.[6] In addition, it is noteworthy that this is the first example of the direct construction of compound **10**.[7]

In connection with reaction acceleration by addition of diols, moderate acceleration was observed in entries 2 and 3, in which the carbonyl function of the side-chain acts as an aldol acceptor to afford type B and C products. On the other hand, intramolecular 1,4-addition was highly accelerated to afford **10** (type A) and its acetals in entries 5 and 6. These results support our working hypothesis[1,2] that the enol ether intermediate (**I**) might play an important role in this type of intramolecular 1,4-addition (Fig. 1).

Further studies using compounds **1c, d** as substrates with bulky substituents such as butyl and phenyl groups at the C3-position were performed. The results are summarized in Tables 3 and 4. In these examples, no 1,4-addition product (type A) was obtained, probably because of steric hindrance around the C3-position. In Table 3, substrate **1c** gave the type B products **14**, **15** and **16** of type C. Reactions with only Lewis acids (entries 1, 3) required long reaction time (36 h) to consume the substrate **1c**, and gave product **16** (type C) in 70—77% yield as a major product with a small amount of **15** (13%). On the other hand, the combination of Lewis acid and 1,2-diol gave hydroxy ketone **14** in addition to **16** (entries 2, 4).

In Table 4, substrate **1d** gave only type B products **17**, an acetal of **17**, and a dehydrated product **18**. In these reactions, an obvious acceleration of reaction rate was not observed. However, the distribution of the products was found to be highly affected by the reagents used. Reactions without diol (entries 1, 4) gave **18**, and the combination of $BF_3 \cdot Et_2O$ and diols (entries 2, 3) gave β-hydroxy ketone **17** as major products. On the other hand, the combination of TMSOTf and **8** gave acetal of **17** (71%) as a major product (entry 6). The initially expected ring transformation *via* Grob reaction from the acetal of **17** to B3 did not take place at all.

Table 4. Reaction of **1d** with Lewis Acid and 1,2-Diols



Entry	Lewis acid	1,2-Diol	Time (h)	Products (%)		
				17	Acetal of **17**	**18**
1	$BF_3 \cdot Et_2O$	None	16	24	—	65
2	$BF_3 \cdot Et_2O$	**7**	16	80	—	—
3	$BF_3 \cdot Et_2O$	**8**	12	93	—	—
4	TMSOTf	None	12	4	—	73
5	TMSOTf	**7**	5	—	42	43
6	TMSOTf	**8**	5	—	71	15

The diastereomeric ratios at the C8-position of B1-type products (**11**, **14**, **17**) were in the range 2.5 : 1 to 10 : 1, and relative stereochemistry was not determined.

From these results above, the following points are noted;

1. Regarding reaction paths A—C, compounds **1**, B1 and C1 may be in equilibrium, and intramolecular 1,4-addition from **1** to A and the dehydration process from B1 to B2 and from C1 to C2 should be irreversible. Treatment of **11** with $BF_3 \cdot Et_2O$ and ethylene glycol at room temperature for 19 h gave **13** in 23% yield with recovery of **11** (70%).

2. Several factors such as C3-substituent, species of Lewis acid and presence of diol affected the reaction path and reactivity. For the effect of C3-substituent, substrate **1a** preferentially undergoes intramolecular 1,4-addition rather than aldol reaction. Substrate **1b** has the possibility to access all reaction paths A—C. In the case of **1c** and **1d** with bulky substituents, intramolecular 1,4-addition was highly inhibited, probably due to steric hindrance around the C3-position.

3. The effect of the Lewis acid was typically observed in the case of using substrate **1b**; $BF_3 \cdot Et_2O$ led to path B and C, and TMSOTf to path A, which might be caused by chemoselective activation of carbonyl functions.

4. In reactions of substrate **1b**, the presence of diol (especially combination of TMSOTf and diol) accelerated the intramolecular 1,4-addition more than the aldol reaction.

Experimental

Melting points were measured on a Yanaco micro melting point apparatus without correction. ^{1}H-NMR spectra were taken on JEOL GX-270 (270 MHz) or JEOL JNM-GX-500 (500 MHz) spectrometers. ^{13}C-NMR were recorded on JEOL GX-270 (67.8 MHz). Chemical shifts are reported in δ units (part per million downfield from tetramethylsilane). IR spectra were measured on a JASCO IR A-100 IR spectrophotometer. Mass spectra (EI, FAB) were measured on JEOL JMS-D300 or JEOL JMS-SX102 spectrometers. The elemental analyses were performed on a Yanaco MT2 CHN recorder. Column chromatography was carried out on Kieselgel 60 (Merck, 70—230 mesh). Solvents were distilled and dried before use. All reactions were carried out under an Ar atmosphere.

3-(2-Methylpropoxy)cyclohex-2-en-1-one (3) A mixture of cyclohexane-1,3-dione **2** (52.4 g, 467 mmol), benzene (1.4 l), iso-BuOH (100 ml), and sulfuric acid (0.5 ml) was refluxed for 20 h using Dean–Stark apparatus. The resulting mixture was cooled to room temperature, and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine and dried over Na_2SO_4.

After removal of the solvent *in vacuo*, the residue was purified by distillation (bp 120—125 °C (3 mmHg)) to give **3** (71.2 g, 93%) as a colorless oil. IR (neat) cm^{-1}: 2960, 2875, 1650, 1605. ^{1}H-NMR ($CDCl_3$) δ: 5.34 (s, 1H), 3.59 (d, J=6.6 Hz, 2H), 2.38 (dt, J=18.8, 5.9 Hz, 4H), 2.08—1.93 (m, 3H), 0.98 (d, J=6.6 Hz, 6H). MS *m/z*: 168 (M^+, 100%).

6-Methyl-3-(2-methylpropoxy)cyclohex-2-en-1-one (4) A solution of **3** (10.3 g, 61.3 mmol) in tetrahydrofuran (THF) (100 ml) was added dropwise at −78 °C to a solution of LDA, prepared from diisopropylamine (10.3 ml, 73.6 mmol) and butyllithium (1.56 M solution in hexane, 47 ml, 73.6 mmol), and the whole was stirred for 45 min at −78 °C. Methyl iodide (5.3 ml, 85.3 mmol) was added to the mixture and the whole was warmed to room temperature over 4 h with stirring. The resulting mixture was washed with water, and the aqueous layer was extracted with ether (×2). The combined organic layers were washed with aqueous saturated NH_4Cl and brine, and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt, 5 : 1 to 2 : 1) to give **4** (9.82 g, 88%) as a pale yellow oil. IR (neat) cm^{-1}: 2960, 2940, 2875, 1650, 1610. ^{1}H-NMR ($CDCl_3$) δ: 5.31 (s, 1H), 3.58 (dd, J=6.6, 1.0 Hz, 2H), 2.49—2.41 (m, 2H), 2.30 (m, 1H), 2.10—1.97 (m, 2H), 1.71 (m, 1H), 1.16 (d, J=6.9 Hz, 3H), 0.97 (d, J=6.9 Hz, 6H). MS *m/z*: 182 (M^+, 100%).

6-Methyl-3-(2-methylpropoxy)-6-(3-oxobutyl)cyclohex-2-en-1-one (5) A solution of **4** (9.82 g, 54.0 mmol) in THF (90 ml) was added at −78 °C to a solution of LDA, prepared from diisopropylamine (13.0 ml, 92.1 mmol) and butyllithium (1.56 M solution in hexane, 59 ml, 92.1 mmol), and the whole was stirred for 45 min at −78 °C. MVK (8.2 ml, 98.2 mmol) was added to the mixture and the whole was stirred for 1 h. The resulting mixture was washed with water and the aqueous layer was extracted with ether (×2). The combined organic layers were washed with aqueous saturated NH_4Cl and brine, and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt, 5 : 1 to 2 : 1) to give **5** (12.2 g, 90%) as a pale yellow oil. IR (neat) cm^{-1}: 2960, 2930, 2830, 1710, 1640, 1600. ^{1}H-NMR ($CDCl_3$) δ: 5.22 (s, 1H), 3.57 (d, J=6.6 Hz, 2H), 2.57—2.32 (m, 3H), 2.13 (s, 3H), 2.08—1.73 (m, 6H), 1.04 (s, 3H), 0.97 (d, J=6.6 Hz, 6H). MS *m/z*: 252 (M^+, 4%), 182 (100%).

6-Methyl-6-[2-(2-methyl(1,3-dioxolan-2-yl))ethyl]-3-(2-methylpropoxy)-cyclohex-2-en-1-one (6) Ethylene glycol (54 ml, 968 mmol) and PPTS (4.86 g, 19.4 mmol) were added to a solution of **5** (12.2 g, 48.4 mmol) in benzene (300 ml), and the whole was refluxed for 1.5 h using Dean–Stark apparatus. The resulting mixture was cooled to room temperature, and washed with water (100 ml). The aqueous layer was extracted with AcOEt, and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by short column chromatography (hexane–AcOEt, 3 : 1) to give **6** (13.5 g, 94%) as a colorless oil. IR (neat) cm^{-1}: 2960, 2930, 2870, 1650, 1610. ^{1}H-NMR ($CDCl_3$) δ: 5.23 (s, 1H), 4.00—3.87 (m, 4H), 3.57 (d, J=6.6 Hz, 2H), 2.53—2.32 (m, 2H), 2.09—1.85 (m, 2H), 1.79—1.55 (m, 5H), 1.31 (s, 3H), 1.09 (s, 3H), 0.97 (d, J=6.9 Hz, 6H). MS *m/z*: 297 (MH^+, 100%).

4-Methyl-4-(3-oxobutyl)cyclohex-2-en-1-one (1a) A solution of **6** (13.5 g, 45.6 mmol) in dry THF (50 ml) was added dropwise to a suspension of $LiAlH_4$ (1.38 g, 36.5 mmol) in dry THF (300 ml) at 0 °C, and the whole was stirred for 10 min. After quenching the reaction by addition of water, 10% aqueous HCl (150 ml) was added, and the whole was stirred for 30 min at room temperature. The resulting mixture was extracted with Et_2O (×3), and the combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt, 1 : 1) to give **1a** (6.24 g, 76%) as a colorless oil. IR (neat) cm^{-1}: 2950, 2925, 2850, 1705, 1670. ^{1}H-NMR ($CDCl_3$) δ: 6.63 (dd, J=10.2, 0.7 Hz, 1H), 5.90 (d, J=10.2 Hz, 1H), 2.55—2.38 (m, 4H), 2.18 (s, 3H), 1.93 (m, 1H), 1.87—1.73 (m, 3H), 1.21 (s, 3H). MS *m/z*: 181 (MH^+, 100%).

3,4-Dimethyl-4-(3-oxobutyl)cyclohex-2-en-1-one (1b) Methyllithium (1.14 M solution in Et_2O, 32.0 ml, 36.5 mmol) was added dropwise at 0 °C to a solution of **6** (5.41 g, 18.3 mmol) in dry THF (55 ml) and the whole was stirred for 10 min. After quenching the reaction by addition of water, 10% aqueous HCl (60 ml) was added, and the whole was stirred for 1 h at room temperature. The resulting mixture was washed with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with AcOEt (×5). The combined organic layers were dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt, 2 : 1) to give **1b** (3.28 g, 93%) as a colorless oil. IR (neat) cm^{-1}: 2950, 2850, 1705, 1660, 1605. ^{1}H-NMR ($CDCl_3$) δ: 5.83 (d, J=1.3 Hz, 1H), 2.55—2.23 (m, 4H), 2.17 (s, 3H), 1.96—1.67 (m, 4H), 1.90 (d, J=1.3 Hz, 3H), 1.17 (s, 3H). MS *m/z*: 195 (MH^+, 100%).

3-Butyl-4-methyl-4-(3-oxobutyl)cyclohex-2-en-1-one (1c) The compound **1c** was prepared from **6** by a similar manner to that described for **1b**: 88% yield; a colorless oil. IR (neat) cm^{-1}: 2950, 2925, 2860, 1710, 1660, 1600. ^{1}H-NMR ($CDCl_3$) δ: 5.87 (br s, 1H), 2.54—2.09 (m, 4H), 2.17 (s, 3H), 1.95—1.22 (m, 8H), 1.16 (s, 3H), 0.95 (q, J=10.9 Hz, 2H), 0.96—0.92 (m, 5H). MS *m/z*: 237 (MH^+, 100%).

4-Methyl-3-phenyl-4-(3-oxobutyl)cyclohex-2-en-1-one (1d) The compound **1d** was prepared from **6** by a similar manner to that described for **1b** in 88% yield as a colorless oil. IR (neat) cm^{-1}: 2950, 2870, 1710, 1670. ^{1}H-NMR ($CDCl_3$) δ: 7.39—7.32 (m, 3H), 7.28—7.17 (m, 2H), 5.91 (s, 1H), 2.04 (s, 3H), 1.33 (s, 3H). MS *m/z*: 257 (MH^+, 100%).

***cis*-6-Methylbicyclo[4.4.0]decane-3,9-dione (9)** Lewis acid (3.50 mmol) and 1,2-diol (5.84 mmol) was successively added to a solution of **1a** (211 mg, 1.17 mmol) in dry CH_2Cl_2 (10 ml), and the whole was stirred. The resulting mixtrure was washed with saturated aqueous $NaHCO_3$ and the aqueous layers were extracted with CH_2Cl_2 (×2). The combined organic layers were washed with brine, and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was dissolved in THF (3 ml) and 10% HCl (1 ml), and the whole was stirred for 1 d. The resulting mixture was extracted with Et_2O (×3) and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt, 2 : 1) to give **9** as colorless needles; mp 81—85 °C (hexane). IR (KBr) cm^{-1}: 2950, 1700. ^{1}H-NMR ($CDCl_3$) δ: 2.51 (ddd, J=15.0, 5.0, 1.0 Hz, 2H), 2.49—2.40 (m, 4H), 2.22 (m, 1H), 1.70 (dt, J=14.0, 7.0 Hz, 2H), 1.34 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 210.1 (s), 44.6 (d), 43.9 (t), 37.4 (t), 34.4 (t), 32.1 (s), 25.9 (q). MS *m/z*: 180 (M^+, 100%). *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.37; H, 9.00.

General Procedure for the Reaction of 1b—d with Lewis Acid and 1,2-Diol 1,2-Diol (5.84 mmol) and Lewis acid (3.50 mmol) was successively added to a solution of **1b—d** (1.17 mmol) in dry CH_2Cl_2 (10 ml), and the whole was stiirred. The reaction mixtrure was washed with saturated aqueous $NaHCO_3$, and the aqueous layers were extracted with CH_2Cl_2 (×2). The combined organic layers were washed with brine, and dried over Na_2SO_4. After removal of solvent *in vacuo*, the residue was purified by column chromatography (hexane–AcOEt).

***cis*-1,6-Dimethylbicyclo[4.4.0]decane-3,9-dione (10)** Colorless needles; mp 120—123 °C (hexane–ether); IR (KBr) cm^{-1}: 2930, 2860, 1700. ^{1}H-NMR ($CDCl_3$) δ: 2.54—2.37 (m, 5H), 2.28—2.05 (m, 7H), 1.74 (ddd, J=14.2, 7.1, 7.1 Hz, 2H), 1.26 (s, 3H), 0.96 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 210.0 (s), 50.8 (t), 44.6 (s), 37.8 (t), 34.9 (s), 34.3 (t), 23.6 (q), 22.1 (q). MS *m/z*: 195 (MH^+, 100%). *Anal.* Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.16; H, 9.38.

(1*RS*,5*RS*,8*S*)-8-Hydroxy-4,5,8-trimethylbicyclo[3.3.1]non-3-en-2-one (11) Colorless solid; mp 137—139 °C (hexane). IR (KBr) cm^{-1}: 3375, 2900, 1640, 1600. ^{1}H-NMR ($CDCl_3$) δ: 6.03 (d, J=1.0 Hz, 1H), 2.45 (br s, 1H), 2.31 (br s, 1H), 2.10 (dt, J=10.9, 2.6 Hz, 1H), 1.90 (d, J=1.3 Hz, 3H), 1.77 (dd, J=13.4, 2.6 Hz, 1H), 1.66—1.47 (m, 4H), 1.36 (s, 3H), 1.15 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 201.4 (s), 166.9 (s), 128.7 (127.7) (d), 68.9 (67.5) (s), 54.7 (55.6) (d), 39.8 (38.2) (t), 36.3 (37.7) (s), 34.1 (36.0) (t), 32.9 (33.4) (t), 26.0 (29.6) (q), 25.7 (29.0) (q), 19.8 (q). Chemical shifts in parentheses are those of the minor diastereomer at C8-position. MS *m/z*: 195 (MH^+, 5.5%), 177 (100%). *Anal.* Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.22; H, 9.37.

(1*RS*,5*RS*)-4,5,8-Trimethylbicyclo[3.3.1]nona-3,7-dien-2-one (12) Pale yellow oil. IR (neat) cm^{-1}: 2950, 2900, 2860, 1670, 1610. ^{1}H-NMR ($CDCl_3$) δ: 5.71 (s, 1H), 5.36 (br q, J=1.3 Hz, 1H), 2.72 (s, 1H), 2.19—2.04 (m, 3H), 1.89 (d, J=1.3 Hz, 3H), 1.19 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 199.7 (s), 164.6 (s), 132.4 (s), 124.4 (d), 121.4 (d), 50.1 (q), 39.0 (t), 35.9 (t), 34.2 (s), 26.7 (q), 21.7 (q), 19.9 (q). MS *m/z*: 177 (MH^+, 100%). FAB-MS *m/z*: 176.1182 (Calcd for $C_{12}H_{16}O$ $(M)^+$: 176.1201).

4a,7-Dimethyl-3,4,4a,5,6-pentahydronaphthalen-2-one (13) Colorless oil. IR (neat) cm^{-1}: 2925, 1660, 1620, 1580. ^{1}H-NMR ($CDCl_3$) δ: 5.95 (s, 1H), 5.62 (s, 1H), 2.63 (ddd, J=18.0, 14.4, 5.6 Hz, 1H), 2.44—2.35 (m, 2H), 2.14 (dd, J=18.0, 5.0 Hz, 1H), 1.89 (s, 3H), 1.84 (dd, J=16.5, 5.0 Hz, 1H), 1.78 (ddd, J=13.3, 6.0, 2.0 Hz, 1H), 1.62 (ddd, J=13.3, 6.0, 2.0 Hz, 1H), 1.56 (ddd, 13.3, 12.0, 5.6 Hz, 1H), 1.15 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 199.7 (s), 163.1 (s), 148.1 (s), 123.9 (d), 121.8 (d), 36.8 (t), 36.3 (t), 34.1 (t), 32.7 (s), 28.4 (t), 24.1 (q), 21.4 (q). MS *m/z*: 177 (MH^+, 100%). FAB-MS *m/z*: 177.1285 (Calcd for $C_{12}H_{17}O$ (MH^+): 177.1279).

(1*RS*,5*RS*,8*S*)-4-Butyl-8-hydroxy-5,8-dimethylbicyclo[3.3.1]non-3-en-2-one (14) Colorless plates; mp 74—76 °C (hexane). IR (KBr) cm^{-1}: 3700, 2930, 2875, 1650, 1615. ^{1}H-NMR ($CDCl_3$) δ: 6.05 (d, J=1.0 Hz, 1H), 2.53 (br s, 1H), 2.34—2.07 (m, 6H), 1.76 (dd, J=13.4, 2.6 Hz, 1H), 1.37 (s, 3H), 1.16 (s, 3H), 0.93 (t, J=7.1 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ: 201.7 (s),

170.6 (s), 127.0 (126.0) (d), 69.0 (s), 54.6 (55.6) (d), 40.3 (38.8) (t), 36.7 (s), 34.3 (t), 33.7 (33.6) (t), 31.9 (31.7) (t), 29.3 (29.2) (t), 26.0 (26.1) (q), 25.9 (q), 22.6 (t), 13.9 (q). Chemical shifts in parentheses are those of the minor diastereomers at C-8 position. MS *m/z*: 237 (MH^+, 33%), 219 (100). *Anal.* Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.20; H; 10.28.

(1*RS*,5*RS*)-4-Butyl-5,8-dimethylbicyclo[3.3.1]nona-3,7-dien-2-one (15) Colorless oil. IR (neat) cm^{-1}: 2980, 2950, 2880, 1680, 1620. ^{1}H-NMR ($CDCl_3$) δ: 5.73 (d, J=1.0 Hz, 1H), 5.35 (br s, 1H), 2.72 (s, 1H), 2.36—2.12 (m, 2H), 2.06 (br s, 1H), 1.71—1.69 (m, 3H), 1.60—1.26 (m, 6H), 1.20 (s, 3H), 0.94—0.89 (m, 3H). ^{13}C-NMR ($CDCl_3$) δ: 199.8 (s), 168.3 (s), 132.3 (s), 122.7 (d), 121.4 (d), 49.9 (d), 39.3 (t), 36.3 (t), 34.5 (s), 31.8 (t), 29.7 (t), 26.7 (q), 22.5 (t), 21.7 (q), 13.9 (q). MS *m/z*: 219 (MH^+, 100%). FAB-MS *m/z*: 219.1735 (Calcd for $C_{15}H_{23}O$ (MH^+): 219.1749).

4a,7-Dimethyl-8-propyl-3,4,4a,5,6-pentahydronaphthalen-2-one (16) Colorless oil. IR (neat) cm^{-1}: 2900, 1650, 1600, 1560. ^{1}H-NMR ($CDCl_3$) δ: 5.92 (s, 1H), 2.67—2.12 (m, 6H), 1.94—1.72 (m, 1H), 1.88 (s, 3H), 1.64—1.52 (m, 3H), 1.48—1.22 (m, 2H), 1.11 (s, 3H), 0.91 (t, J=7.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$) δ: 200.6 (s), 163.0 (s), 142.5 (s), 130.2 (s), 119.7 (d), 37.4 (t), 36.2 (t), 33.5 (t), 30.1 (t), 22.0 (t), 21.32 (q), 21.26 (s), 14.1 (q). MS *m/z*: 219 (MH^+, 100%). FAB-MS *m/z*: 219.1782 (Calcd for $C_{15}H_{23}O$ (MH^+): 219.1749).

(1*RS*,5*RS*,8*S*)-8-Hydroxy-5,8-dimethyl-4-phenylbicyclo[3.3.1]non-3-en-2-one (17) Colorless plates; mp 128—129 °C (hexane–ether). IR (KBr) cm^{-1}: 3400, 2910, 2850, 1640, 1580. ^{1}H-NMR ($CDCl_3$) δ: 7.40—7.33 (m, 3H), 7.22—7.17 (m, 2H), 6.13 (d, J=0.7 Hz, 1H), 2.81 (s, 1H), 2.45—2.43 (br s, 1H), 2.28 (dt, J=13.5, 3.3 Hz, 1H), 1.45 (s, 3H), 1.03 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 201.5 (200.8) (s), 167.4 (166.5) (s), 139.3 (139.6) (s), 130.1 (129.4) (d), 128.2 (d), 128.1 (d), 126.9 (d), 69.5 (68.0) (s), 54.8 (55.6) (d), 41.3 (39.8) (t), 36.7 (36.4) (s), 34.2 (33.6) (t), 34.0 (30.7) (t), 27.1 (29.1) (q), 26.2 (27.4) (q). Chemical shifts in parentheses are those of the minor diastereomer at C8-position. MS *m/z*: 257 (MH^+, 34%), 239 (100). *Anal.* Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.50; H, 7.96.

Ethylene Acetal of 17 Pale yellow oil. IR (neat) cm^{-1}: 3400, 2920, 2850, 2220, 1650. ^{1}H-NMR ($CDCl_3$) δ: 7.39—7.32 (m, 3H), 7.21—7.16 (m, 2H), 6.08 (s, 1H), 3.85—3.75 (m, 1H), 3.70 (br s, 2H), 3.61—3.55 (m, 1H), 3.26 (br s, 1H), 2.77 (br s, 1H), 2.26 (dt, J=13.2, 3.3 Hz, 1H), 1.99—1.81 (m, 2H), 1.77—1.60 (m, 3H), 1.42 (s, 3H), 1.02 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 200.8 (s), 166.2 (s), 139.3 (s), 130.2 (d), 128.1 (d), 128.0 (d), 127.0 (d), 73.8 (s), 63.1 (t), 62.2 (t), 51.0 (d), 41.1 (t), 36.7 (s), 33.2 (t), 32.8 (t), 27.0 (q), 21.4 (q). MS *m/z*: 301 (MH^+, 28%), 239 (100). FAB-MS *m/z*: 301.1817 (Calcd for $C_{19}H_{25}O_3$ (MH^+): 301.1804).

Acetal of 17 with (*dl*)-Cyclohexane-1,2-diol Reaction in Table 4, entry 6 gave four possible diastereomers, which could be devided into two groups, consisting of two diastereomers. A pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 7.37—7.33 (m, 3H), 7.28—7.15 (m, 2H), 6.13 (6.11) (s, 1H), 3.41 (m, 1H), 2.68 (br s, 1H), 2.43 (br s, 1H), 2.38 (m, 1H), 1.50 (1.44) (s, 3H), 1.03 (1.01) (s, 3H). Chemical shifts in parentheses are those of the minor diastereomer. A pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 7.39—7.33 (m, 3H), 7.28—7.15 (m, 2H), 6.10 (6.02) (s, 1H), 3.49—3.32 (m, 2H), 2.57 (m, 1H), 2.27 (m, 1H), 2.38 (m, 1H), 1.47 (s, 3H), 1.08 (1.02) (s, 3H). Chemical shifts in parentheses are those of the minor diastereomer.

(1*RS*,5*RS*)-5,8-Dimethyl-4-phenylbicyclo[3.3.1]non-3,7-dien-2-one (18) Colorless plates; mp 118—120 °C (hexane). IR (KBr) cm^{-1}: 2950, 2900, 1650, 1580. ^{1}H-NMR ($CDCl_3$) δ: 7.36—7.31 (m, 3H), 7.23—7.18 (m, 2H), 5.86 (d, J=0.7 Hz, 1H), 5.51 (br s, 1H), 2.83 (s, 1H), 2.49 (m, 1H), 2.21 (m, 1H), 1.83 (dd, J=12.5, 3.3 Hz, 1H), 1.76 (dt, J=2.3, 1.7 Hz, 3H), 1.06 (s, 3H). ^{13}C-NMR ($CDCl_3$) δ: 199.1 (s), 166.0 (s), 139.8 (s), 132.3 (s), 127.9 (d), 127.9 (d), 127.6 (d), 126.6 (d), 121.6 (d), 50.0 (d), 40.1 (t), 36.7 (t), 34.4 (s), 28.1 (q), 21.8 (q). MS *m/z*: 239 (MH^+, 100%). *Anal.* Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.68; H, 7.59.

References and Notes

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6) By comparing the chemical shifts of C2-H, C3-Me and the terminal methyl group of 3-oxobutyl substituent of **1b** with those in the presence of $BF_3 \cdot Et_2O$ (1 eq.) at 20 °C, $\Delta\delta$ values (δ (in presence of Lewis acid) − δ (original)) showed 0.64 (C2-H), 0.30 (C3-Me) and 0.03 (C4′-3H) ppm. In the case of using TMSOTf instead of $BF_3 \cdot Et_2O$ at −20 °C gave the similar results; $\Delta\delta$ values were 0.51 (C2-H), 0.27 (C3-Me) and 0.02 (C4′-3H) ppm.
7) Flemming S., Kabbara J., Nickisch K., Westermann J., *Synthesis*, **1995**, 317—320.