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Drastic Ring Transformation Reactions of Fused Bicyclic Rings to Bridged Bicyclic Rings

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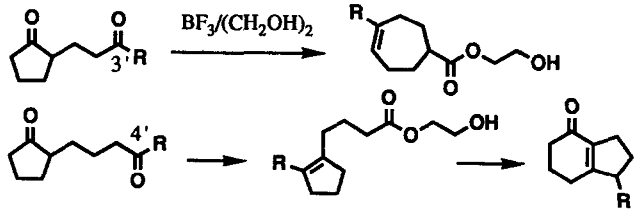
Abstract: *By treatment with BF_3-etherate/ethylene glycol, cyclohexanone with a carbonyl function at the 2'- (or 3'-) position of γ-side chain underwent novel ring transformation to afford five- (or six-) membered rings, and the fused bicyclic rings (bicyclo[3.3.0]octanone skeleton) were readily converted to bridged bicyclic rings (bicyclo[3.2.1]octene derivative).*

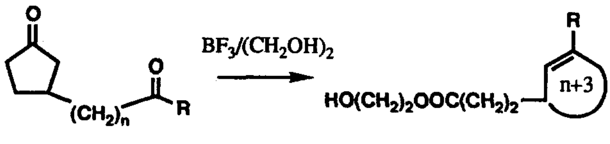
In the synthesis of natural products, the most difficult problem is how to build up the framework of the target compound. Ring transformations involving ring contraction, ring retention, and ring expansion seem to be one of the important strategies in synthetic chemistry, because this method suggests that synthetically difficult compounds are accessible by interconversion reactions from other readily prepared ring systems. Therefore, this indirect synthetic strategy is valid equally as the direct synthesis of the target compound.[1-5]

Previously, we[1, 6-8] reported that cyclic ketones with one carbonyl function at an appropriate position of the α- (or β-) side chain underwent facile ring cleavage to reconstruct the new ring by treatment with BF_3-etherate / ethylene glycol / CH_2Cl_2 at room temperature (acetalization conditions[9]) (Scheme 1), and no acetal was obtained. This novel ring transformation reaction seems to proceed *via* i) aldol condensation, ii) acetalization (or hemiacetalization), iii) Grob fragmentation[10]. Therefore, the two carbonyls in the molecule should be as close to each other as possible to facilitate the first aldol condensation.[11]

i) α-Side chain with a carbonyl function at the 3'- (or 4'-) position[1,6]



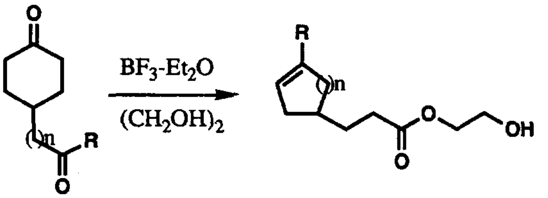
ii) β-Side chain with a carbonyl function at the 3'- (or 4'-) position[7,8]



Scheme 1. Novel ring transformation reaction

Examination using a Dreiding stereomodel suggested that cyclohexanone with a carbonyl function at the 2'- (or 3'-) position of γ-side chain, if it takes the axial orientation, may be transformed into the five- (or six-) membered ring with BF_3 / ethylene glycol. When the side chain occupies equatorial orientation, the two carbonyl functions are so far apart that the six-membered aldol cannot be formed. Ring transformation reaction was examined while stirring a mixture of substrate (1 eq.), ethylene glycol (5 eq.), and BF_3-etherate (7 eq.) in CH_2Cl_2 at room temperature for 1-2 h under an Ar atmosphere. The results are shown in Table 1. This reaction afforded the ring transformation products of the five- (or six-) membered ring in moderate yields, indicating that the ring transformation was effected *via* the axial side chain formed through the ring flip of cyclohexanone. The structure of each product was determined by the analysis of spectroscopic data. For example, the structure of the product in entry 1 was supported by ^{1}H-NMR spectrum ($CDCl_3$) [δ 5.23-5.34 (1H, m, olefinic H), 4.10-4.23 (2H, m, $COOCH_2$), 3.80-3.86 (2H, m, CH_2O), 1.66 (3H, s, CH_3)], ^{13}C-NMR ($CDCl_3$) [δ 174.4 (CO), 141.1 (=C-), 127.7 (=CH-)], in addition to IR spectrum (neat) [3450, 1730 cm^{-1}] and MS spectrum [*m/z* 198 (M^+)].

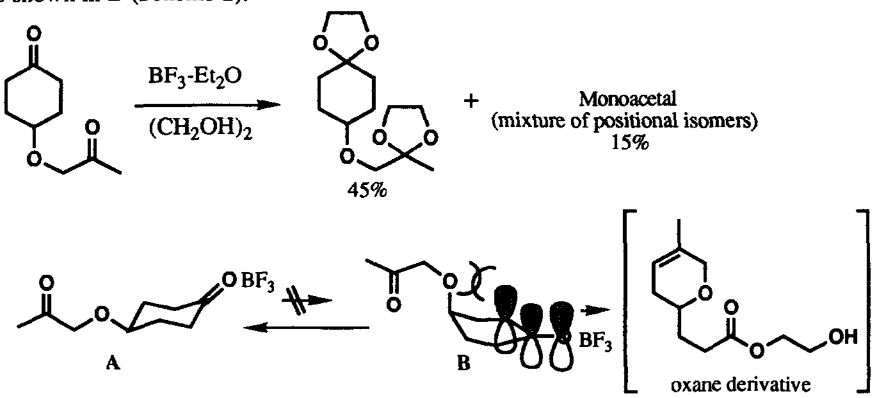
Table 1. Ring transformation of cyclohexanones with substituent at γ-position



Entry	Product n	Product R	Yield(%)
1	1	Me	62
2	1	Ph	51
3	1	Bu	53
4	2	Me	73

Reaction conditions: mixture of substrate (1eq.), ethylene glycol (5eq.) and BF_3-Et_2O (7eq.) in CH_2Cl_2(15-20ml) was stirred at room temp. for 1-2 h under an Ar atmosphere.

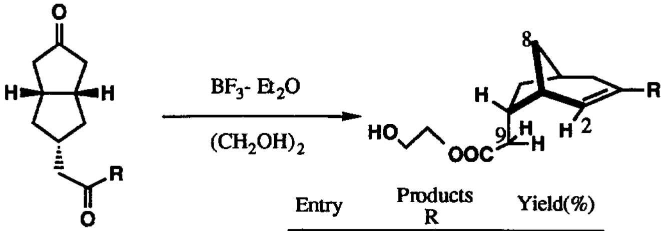
Ring transformation in Table 1 suggested a new method for construction of the oxane ring from carbocyclic ring with the ether linkage in side chain, as shown in Scheme 2. However, this reaction resulted in the formation of acetal, and the oxane derivative was not obtained. This may be explained by the following assumption. Namely, the γ-side chain cannot occupy the axial position required for this reaction, because of the electronic repulsion between the lone pair of ether oxygen in the pseudoaxial bond and enolate ion formed by BF_3, as shown in **B** (Scheme 2).



Scheme 2. Attempted construction of oxane ring

The success of ring transformation of cyclohexanone with the carbon chain at the γ-position prompted us to focus on the drastic, first ring transformation of the fused bicyclc ring into the bridged bicyclic ring.[12] In the examination of readily prepared 7α-(2-oxoalkyl)bicyclo[3.3.0]octan-3-one using a Dreiding stereomodel, the proximity of the two carbonyl functions was observed in the case of the *endo*-side chain. In accord with our expectation, this ring system was successfully converted to bicyclo[3.2.1]octene by treatment with BF_3 / ethylene glycol (the same conditions as the case of Table 1). The results are summarized in Table 2. The structure of each product was determined by the analysis of spectroscopic data, as exemplified by product in entry 1. The IR and ^{1}H-NMR spectra indicated the existence of OH (3450 cm^{-1}), ester (1735 cm^{-1}) functions, and CH_3 [δ 1.61 (3H, s)], $COOCH_2CH_2O$ [δ 3.80-3.86 (2H, m) and 4.19-4.23 (2H, m)], olefinic H [δ 5.42-5.45 (1H, m)], respectively. In addition, ^{13}C-NMR spectrum (one CH_3, six CH_2, three CH, one =CH-, one =C-, and one carbonyl), the observation of NOE between C_9-H (δ 2.43) and C_2-H (δ 5.43), and MS spectrum [*m/z* 224 (M^+), 206] also supported the correctness of this structure. In the case of entry 4, the ring transformation resulted in poor yield. This may be attributed to facile enolization of benzylcarbonyl function under the employed reaction conditions (Scheme 4), in which the carbonyl function remarkably reduces the function as the enolate acceptor.[13] The reaction process[14] involving three steps: i) aldol condensation, ii) acetalization, and iii) Grob fragmentation, is tentatively proposed as shown in Scheme 4. This facile ring transformation provides a new route for the construction of the bicyclo[3.2.1] ring system. Thus, this ring transformation may be further applied to the construction of different types of the bridged bicyclic ring system, by changing the fused bicyclic ring system.

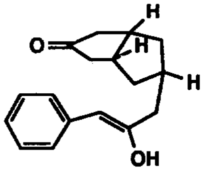
Table 2. Ring transformation of the bicyclic ring into bridged bicyclic ring

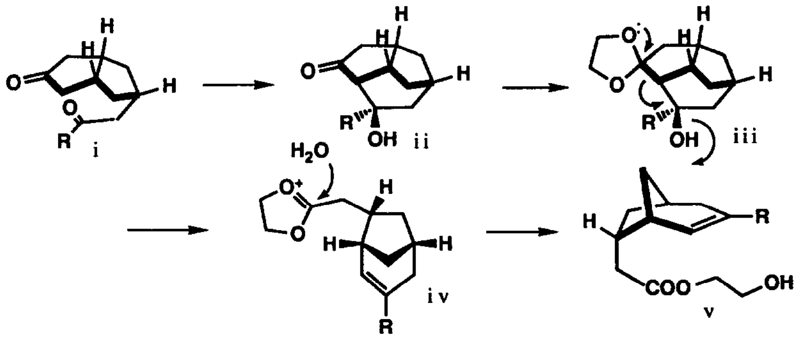


Entry	Products R	Yield(%)
1	Me	67
2	Et	48
3	Pentyl	51
4	CH_2Ph	10

Reaction conditions: see Table 1.

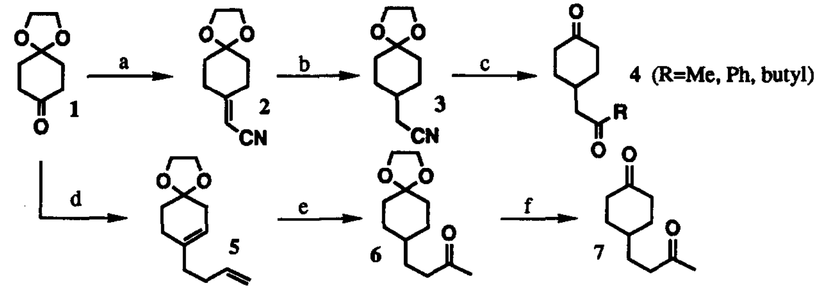
Scheme 3





Scheme 4. Reaction pathway

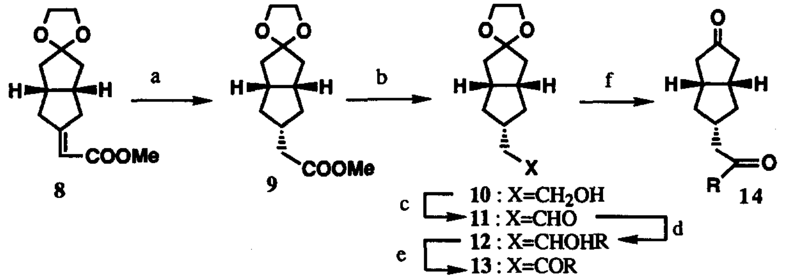
Substrates (n=1; R=Me, Bu, Ph) in Table 1 were prepared *via* the reaction sequences as shown in Scheme 5. Reaction of diethyl cyanomethylphosphonate sodium salt and the monoacetal (1) afforded the cyanomethylene derivative (2). By reduction with 5% Pd-C/H_2/MeOH, followed by alkylation with RLi and subsequent deprotection with 3% aq. H_2SO_4, 2 was converted to the ketone (4). Substrate (n=2, R=Me) was synthesized *via* i) introduction of butenyl function to 1 by Grignard reaction and subsequent dehydration by *p*-TsOH, ii) Wacker oxidation followed by reduction with 5% Pd-C/H_2/MeOH and subsequent deprotection with 3% aq. H_2SO_4.



Reaction conditions: a) $(EtO)_2P(O)CH_2CN$/NaH/DME. b) 5% Pd-C/H_2. c) RLi, then aq. H_3O^+.
d) CH_2=$CHCH_2CH_2MgBr$, then TsOH/benzene. e) Wacker oxid., then 5% Pd-C/H_2. f) 3% aq. H_2SO_4/acetone.

Scheme 5. Preparation of substrates in Table 1

Substrates (R= Me, Et, pentyl, Bn) in Table 2 were prepared according to the conventional method as shown in Scheme 6. The designed sequence starts with the α,β-unsaturated ester[15] (8) which was prepared from 3,3-ethylenedioxybicyclo[3.3.0]octan-7-one and dimethyl methoxycarbonylmethylphosphonate. Reduction of 8 with 5% Pd-C/MeOH/H_2 proceeded stereoselectively to afford the ester (9) with α-side chain. By reduction with $LiAlH_4$ and subsequent oxidation with PCC/CH_2Cl_2, 9 was converted to the aldehyde (11), which is the versatile intermediate in preparation of substrates. Compound 11 was converted to the substrates (14) *via* alkylation with RLi, PCC oxidation in CH_2Cl_2, and deacetalization with 3% aq. H_2SO_4 in acetone.



Reaction conditions: a) 5% Pd-C/MeOH. b) $LiAlH_4$. c) PDC/CH_2Cl_2. d) RLi. e) PCC/CH_2Cl_2. f) 3% aq. H_2SO_4/acetone.

Scheme 6. Preparation of substrates in Table 2

Experimental

Infrared (IR) spectra were measured with a JASCO A-202 spectrometer. ^{1}H- and ^{13}C-NMR spectra were measured on JEOL JNM-PS-100 and GX-270 spectrometers. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. Each reaction was carried out under an Ar atmosphere and monitored by TLC (Merck, silica gel 60F-254 plates). For column chromatography, silica gel (Merck, Kieselgel 60, 70-230 mesh) was used. All organic solvents were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Each product in Table 1 and 2 was obtained as a colorless oil.

General procedure

1) To a stirred solution of substrate (Table 1: entry 1; R=Me, 76 mg, 0.49 mmol) in CH_2Cl_2 (10 ml) were successively added BF_3-etherate (0.90 ml, 7 eq.) and ethylene glycol (0.14 ml, 5 eq.) at 0°C under an Ar atmosphere. After being stirred for 1 h at ambient temperature, the reaction mixture was diluted with ether. The organic layer was washed with sat. $NaHCO_3$ (aq.) and brine, then dried over $MgSO_4$. The solvent was removed *in vacuo* to leave an oily residue, which was purified by silica-gel column chromatography to afford the ring transformation product (60 mg, 62%).

2) In a similar manner to the case of procedure (1), substrate in Table 2 (entry 1; R=Me, 100 mg, 0.56 mmol) was transformed into the bridged bicyclic compound (84 mg), in 67% yield, by treatment with BF_3-etherate (1.03 ml, 7 eq.) and ethylene glycol (0.16 ml, 5 eq.).

Selected spectroscopic data of products in Table 1.

Entry 1: IR (neat) 3450, 1730, 1650 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 1.66 (3H, s, CH_3), 3.80-3.86 (2H, m, CH_2O), 4.19-4.23 (2H, m, $COOCH_2$), 5.23-5.34 (1H, m, =CH-); ^{13}C-NMR δ ($CDCl_3$) 174.4 (s), 141.1 (s), 127.7 (d), 66.0 (t), 61.0 (t), 38.0 (d), 16.6 (q); MS *m/z* 198 (M^+), 137, 94; HRMS for $C_{11}H_{18}O_3$ (M^+): Calcd *m/z* 198.1256; Found 198.1239. **Entry 2**: IR(neat) 3450, 1740, 1650 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 3.79-3.86 (2H, m, CH_2O), 4.20-4.24 (2H, m, $COOCH_2$), 6.09-6.11 (1H, m, =CH-), 7.19-7.45 (5H, m, aromatic H); ^{13}C-NMR δ ($CDCl_3$) 174.1(s), 142.7 (s), 128.3 (x2, d), 127.1 (d), 126.0 (x2, d), 125.4 (d), 66.0 (t), 61.1(t), 37.4 (d); MS *m/z* 261 (M^++1), 260 (M^+), 199, 156; HRMS for $C_{16}H_{20}O_3$ (M^+): Calcd *m/z* 260.1413; Found 260.1445. **Entry 3**: IR (neat) 3450, 1740, 1650 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.90 (3H, t, *J*=7.1 Hz, CH_3), 3.82-3.84 (2H, m, CH_2O), 4.20-4.23 (2H, m, CH_2O), 5.24-5.25 (1H, m, =CH-); ^{13}C-NMR δ ($CDCl_3$) 174.4 (s), 144.0 (s), 126.5(d), 65.9 (t), 61.1 (t), 37.6 (d), 14.2 (q); MS *m/z* 241 (M^++1), 240 (M^+), 179, 136; HRMS for $C_{14}H_{26}O_3$ (M^+): Calcd *m/z* 240.1726; Found 240.1733. **Entry 4**: IR (neat) 3450, 1740, 1670 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 1.64 (3H, s, CH_3), 3.80-3.86 (2H, m, CH_2O), 4.20-4.24 (2H, m, $COOCH_2$), 5.34 (1H, m, =CH-); ^{13}C-NMR δ ($CDCl_3$) 174.4 (s), 134.0 (s), 120.2 (d), 65.2 (t), 61.2 (t), 33.0 (d), 23.5 (q); MS *m/z* 212 (M^+), 150, 132; HRMS for $C_{12}H_{20}O_3$ (M^+): Calcd *m/z* 212.1413; Found 212.1429.

^{13}C-NMR spectra of each product indicated that products are a mixture of positional isomers (2-13%) of double bond.

Selected spectroscopic data of products in Table 2.

Entry 1: IR (neat) 3450, 1735, 1660 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 1.61 (3H, s, CH_3), 2.43 (2H, dd, J=16.0, 10.2 Hz, CH_2CO), 3.80-3.86 (2H, m, CH_2O), 4.19-4.23 (2H, m, $COOCH_2$), 5.42-5.45 (1H, m, =CH-); ^{13}C-NMR δ ($CDCl_3$) 174.2 (s), 133.8 (s), 124.5 (d), 65.8 (t), 61.4 (t), 44.9 (d), 38.3 (d), 33.3 (d), 22.9 (q); MS *m/z* 224 (M^+), 206, 162, 118; HRMS for $C_{13}H_{20}O_3$ (M^+): Calcd *m/z* 224.1413; Found 224.1433.

Entry 2: IR (neat) 3450, 1730, 1650 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.97 (3H, t, *J*=7.5 Hz, CH_3), 3.81-3.85 (2H, m, CH_2O), 4.19-4.24 (2H, m, CH_2O), 5.44 (1H, d, *J*=6.6 Hz, =CH-); ^{13}C-NMR δ ($CDCl_3$) 174.2 (s), 139.3

(s),122.7 (d), 65.8 (t), 61.4 (t), 44.9 (d), 38.1 (d), 33.3 (d), 12.5 (q); MS *m/z* 238 (M^+), 220, 176; HRMS for $C_{14}H_{22}O_3$ (M^+): Calcd *m/z* 238.1569; Found 238.1590.

Entry 3: IR (neat) 3450, 1730, 1650 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.89 (3H, t, *J*=6.5 Hz, CH_3), 3.78-3.87 (2H, m, CH_2O), 4.17-4.26 (2H, m, $COOCH_2$), 5.46 (1H, m, =CH-); ^{13}C-NMR δ ($CDCl_3$) 174.2 (s), 137.8 (s), 123.9 (d), 65.8 (t), 61.4 (t), 44.9 (d), 38.2 (d), 33.3 (d), 14.1 (q); MS *m/z* 280 (M^+), 262, 71; HRMS for $C_{17}H_{28}O_3$ (M^+): Calcd *m/z* 280.2039; Found 280.2045. **Entry 4:** IR (neat) 3450, 1730, 1650 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 3.22 (2H, s, CH_2Ph), 3.80-3.85 (2H, m, CH_2O), 4.19-4.23 (2H, m, $COOCH_2$), 5.53 (1H, m, =CH), 7.14-7.25 (3H, m, aromatic H), 7.25-7.33 (2H, m, aromatic H); ^{13}C-NMR δ ($CDCl_3$) 174.1 (s), 140.2 (s), 137.2 (s), 128.9 (x2, d), 128.2 (x2, d), 126.2 (d), 125.9 (d), 65.9 (t), 61.4 (t), 45.0 (d), 38.3 (d), 33.2 (d); MS *m/z* 300 (M^+), 282, 238; HRMS for $C_{19}H_{24}O_3$ (M^+): Calcd *m/z* 300.1726; Found 300.1711.

^{13}C-NMR spectra of each product indicated that products contain a small amount of positional isomers (1-4%) of double bond.

Preparation of substrates in Table 1.

4-Cyanomethylene-1,1-ethylenedioxycyclohexane (2). To a stirred suspension of NaH (60% oil suspension, 384 mg, 9.6 mmol) in DME (5 ml) was added dropwise diethyl cyanomethylphosphonate (1.70 g, 9.6 mmol) in DME (10 ml) at 0°C. After being stirred for 1 h, the monoacetal (**1**)(1.00g, 6.41 mmol) in DME (7 ml) was added dropwise at 0°C. The whole was stirred for 3 h at room temperature, and diluted with ether, then water. The ether extract was washed with 5% $NaHCO_3$, and brine, then dried. The solvent was removed *in vacuo* to leave an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with 5% AcOEt in hexane (v/v) afforded **2** (1.02 g, 89%) as a colorless oil. IR (neat) 2220, 1630 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 3.99 (4H, s, OCH_2CH_2O), 5.12-5.14 (1H, t, *J*=1.0 Hz, =CH-); MS *m/z* 180 (M^++1), 179 (M^+), 150, 99.

4-Cyanomethyl-1,1-ethylenedioxycyclohexane (3). Hydrogenation of **2** (958 mg) over 5% Pd-C in MeOH and subsequent purification by column chromatography on silica gel afforded **3** (885 mg, 91%) as a colorless oil. IR (neat) 2240 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 1.19-1.99 (9H, m), 2.26-2.32 (2H, dd, *J*=5.9, 0.5 Hz, CH_2CN), 3.94 (4H, s, OCH_2CH_2O).

4-(2-Oxopropyl)cyclohexanone (entry 1 (R=Me), Table 1) (4). MeLi (1.11M in ether, 3.0 ml) was added dropwise to a stirred solution of **3** (408 mg, 2.26 mmol) in THF (5 ml) at 0°C, and the whole was stirred for 1 h, diluted with sat. NH_4Cl (aq.), then extracted with AcOEt. The crude product was subjected to deacetalization reaction using 3% aq. H_2SO_4 in acetone. After usual work-up and purification by silica-gel column chromatography, the diketone (**4**)(R=Me, 77 mg, 22% from **3**) was obtained. In a similar manner, substrates in entry 2 (R=Ph) and 3 (R=Bu) were prepared. **R=Me** : IR (neat) 1720, 1700 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 1.26-2.14 (5H, m), 2.22-2.50 (6H, m, $COCH_2$), 2.17 (3H, s, CH_3); MS *m/z* 154 (M^+), 111, 99; HRMS for $C_9H_{14}O_2$ (M^+): Calcd *m/z* 154.0994; Found 154.1025. **R=Ph** (20% from **3**): IR (neat) 1710, 1670, 1590, 1570 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 1.20-2.89 (9H, m), 2.98 (2H, d, *J*=7.0 Hz, CH_2COPh), 7.21-7.87 (3H, m, aromatic H), 7.92-8.02 (2H, m, aromatic H); MS *m/z* 216 (M^+), 120, 105; HRMS for $C_{14}H_{16}O_2$ (M^+): Calcd *m/z* 216.1151; Found 216.1135. **R=Bu** (14% from **3**) : IR (neat) 1710 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.79-0.99 (3H, m, CH_3), 1.14-2.15 (9H, m), 2.20-2.61 (8H, m, $COCH_2$); MS *m/z* 196 (M^+), 139, 96; HRMS for $C_{12}H_{20}O_2$ (M^+): Calcd *m/z* 196.1464; Found 196.1483.

4-(3-Buten-1-yl)-1,1-ethylenedioxy-3-cyclohexene (5). The alcohol (800 mg, 3.77 mmol) prepared from **1** and 3-butenylmagnesium bromide according to conventional method was subjected to dehydration reaction in refluxing benzene in the presence of *p*-TsOH. After 8 h, the reaction mixture was successively washed with sat. $NaHCO_3$ and brine, then dried. Compound **5** was obtained as an inseparable mixture of *exo*- and *endo*-double bond (550 mg, 75%). IR (neat) 1670, 1640 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 3.98 (4H, s, OCH_2CH_2O), 4.88-5.12 (2H, m, olefinic H), 5.32-5.97 (2H, m, olefinic H).

4-(3-Oxobutyl)-1,1-ethylenedioxycyclohexane (6) and 4-(3-Oxobutyl)cyclohexanone (7) (entry 4, Table 1). A mixture of $PdCl_2$ (320 mg, 1.8 mmol) and $CuCl_2$ (2.5 g, 25 mmol) in DME (12 ml)/H_2O(0.2ml) was stirred at room temperature under an oxygen atmosphere. After 2 h, **5** (580 mg, 2.99 mmol) in DME (3 ml) was added, and the whole was stirred for 3 h. The reaction mixture was diluted with water, then extracted with ether. Hydrogenation of the crude product with standard method (5% Pd-C/MeOH) and subsequent purification by silica-gel column chromatography afforded **6** (365 mg, 63% from **5**). IR (neat) 1710, 1370 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 2.14 (3H, s, CH_3) 2.44 (2H, t, *J*=7.6 Hz, $COCH_2$), 3.93 (4H, s, OCH_2CH_2O); Ms *m/z* 212(M^+), 141, 99. Deacetalization of **6** with 3% aq. H_2SO_4 in acetone afforded **7** (70%) as a colorless oil, which was purified by column chromatography on silica gel. IR (neat) 1710, 1360 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 1.19-1.79 (7H, m), 1.82-2.59 (6H, m, $COCH_2$), 2.17 (3H, s, CH_3); MS *m/z* 168 (M^+), 150, 122, 111; HRMS for $C_{10}H_{16}O_2$ (M^+): Calcd *m/z* 168.1151; Found 168.1177.

Preparation of substrates in Table 2.

3,3-Ethylenedioxy-7α-methoxycarbonylmethyl-1βH,5βH-bicyclo[3.3.0]octane (9), and 3,3-Ethylenedioxy-7α-(2-hydroxyethyl)-1βH,5βH-bicyclo[3.3.0]octane (10). Hydrogenation of **8** over 5% Pd-C in MeOH followed by reduction using $LiAlH_4$/ether was carried out in standard manner. Compound **10** was obtained in 76% yield from **8** *via* **9**. **9**: IR (neat) 1740, 1430, 1370 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 3.66 (3H, s, CH_3) , 3.89 (4H, s, OCH_2CH_2O); MS *m/z* 240 (M^+), 209, 197, 169. **10**: IR (neat) 3400, 1460, 1440, 1320 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 3.65 (2H, t, J=6.6 Hz, CH_2O), 3.89 (4H, s, OCH_2CH_2O); MS *m/z* 212 (M^+), 181, 169.

3,3-Ethylenedioxy-7α-(2-formylmethyl)-1βH,5βH-bicyclo[3.3.0]octane(11). Standard oxidation of **10** with PDC/CH_2Cl_2 afforded the unstable aldehyde (**11**), which was subjected to the next alkylation reaction without being purified. **11**: IR (neat) 2700, 1720, 1460, 1430 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 3.90 (4H, s, OCH_2CH_2O), 9.92 (1H, m, CHO).

7α-(2-Oxopropyl)-1βH,5βH-bicyclo[3.3.0]octan-3-one (14, R=Me), 7α-(2-Oxobutyl)-1βH, 5βH-bicyclo[3.3.0]octan-3-one (14, R=Et), 7α-(2-Oxoheptyl)-1βH,5βH-bicyclo[3.3.0]octan-3-one (14, R=pentyl), and 7α-(2-Oxo-3-phenylpropyl)-1βH,5βH-bicyclo[3.3.0]octan-3-one (14, R=Bn). To a stirred solution of **11** (558 mg) in THF (30 ml) was added dropwise MeLi (1.15 M in ether, 4 ml) at 0°C, and the whole was stirred for 0.5 h at room temperature. Usual work-up and purification by silica-gel column chromatography afforded **12** (R=Me, 321 mg, 58%) as a colorless oil, which was subjected to conventional oxidation with PCC in CH_2Cl_2 and deacetalization using 3% aq. H_2SO_4 in acetone. In this manner, **14** (R=Me) was obtained in 72% yield (183 mg) from **12** (R=Me)(321 mg). **R=Me**: IR (neat) 1730, 1705, 1450, 1350 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.90-0.98 (2H, m), 1.99-2.07 (2H, m), 2.14 (3H, s, CH_3), 2.21-2.42 (3H, m), 2.45-2.56 (4H, m), 2.67-2.74 (2H, m); ^{13}C-NMR δ ($CDCl_3$) 220.7 (s), 208.3 (s), 49.3 (t), 44.7 (x2, t) , 40.6 (x2, t), 39.1 (x2, d), 36.8 (d), 30.2 (q); MS *m/z* 180 (M^+), 162, 123; HRMS for $C_{11}H_{16}O_2$ (M^+): Calcd *m/z* 180.1151; Found 180.1169. In a similar manner, **14** (R=Et, pentyl, Bn) were prepared. **R=Et** (35% from **11**) : IR (neat) 1730, 1710, 1450, 1370 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.89-1.01 (2H, m), 1.05 (3H, t, *J*=7.3 Hz, CH_3), 1.99-2.07 (2H, m), 2.33-2.58 (5H, m), 2.23-2.34 (2H, m), 2.41 (2H, q, *J*=7.3 Hz,

CH_2CH_3), 2.67-2.76 (2H, m); ^{13}C-NMR δ ($CDCl_3$) 220.6 (s), 210.9 (s), 47.9 (t), 44.7 (x2, t), 40.7 (x2, t), 39.1 (x2, d), 36.9 (d), 39.3 (t), 7.8 (q); MS *m/z* 194 (M^+), 176, 165, 137; HRMS for $C_{12}H_{18}O_2$ (M^+): Calcd *m/z* 194.1307; Found 194.1325. **R=pentyl** (29% from **11**): IR(neat) 1730, 1700, 1450, 1370 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.89 (3H, t, *J*=6.4 Hz, CH_3) 0.80-1.15 (2H, m), 1.19-1.67 (6H, m), 1.89-2.12 (2H, m), 2.14-2.89 (11H, m); ^{13}C-NMR δ ($CDCl_3$) 220.4 (s), 210.6 (s), 48.4 (t), 44.8 (x2, t), 43.2 (t), 40.7 (x2, t), 39.1 (x2, d), 36.9 (x2, d), 22,5-31.4 (x3, t), 13.9 (q); MS *m/z* 236 (M^+), 218, 137; HRMS for $C_{15}H_{24}O_2$ (M^+): Calcd *m/z* 236.1777; Found 236.1799. **R=Bn** (35% from **11**): IR (neat) 1730, 1710, 1490, 1400 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 0.83-0.88 (2H, m), 1.89-2.95 (11H, m), 3.66 (2H, s, CH_2Ph), 7.13-7.44 (5H, m, aromatic H); ^{13}C-NMR δ ($CDCl_3$) 220.5 (s), 207.6 (s), 134.1 (d), 129.1 (x2, d), 128.8 (x2, d), 127.1 (d), 50.5 (t), 47.4 (t), 44.7 (x2, t), 40.5 (x2, t), 39.0 (x2, d), 36.7 (d); MS *m/z* 256 (M^+), 238, 165, 137; HRMS for $C_{17}H_{20}O_2$ (M^+): Calcd *m/z* 256.1464; Found 256.1459.

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