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An Insight into the Novel Ring Transformation Reactions Using Ethylene Glycol/BF_3

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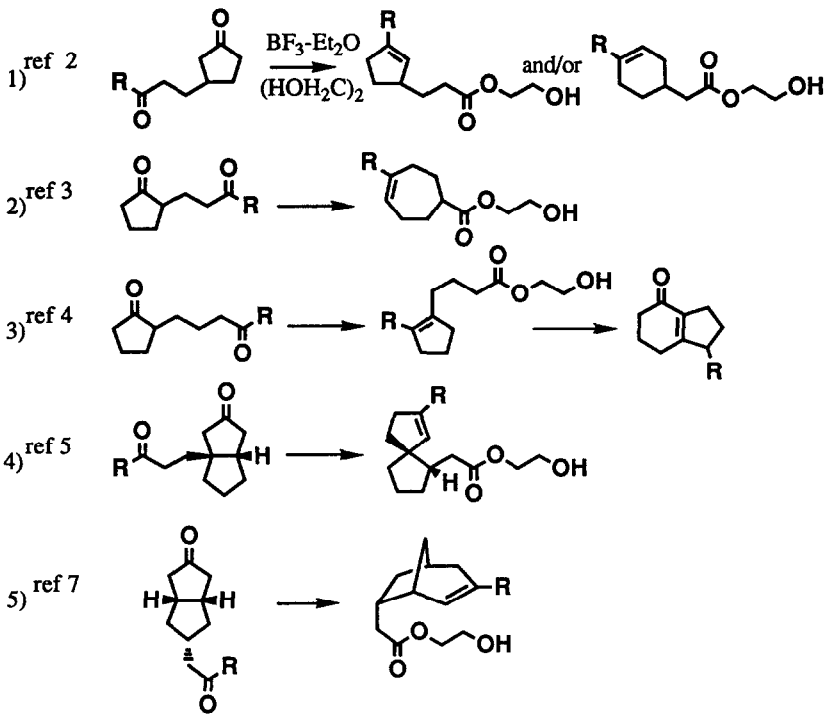
Abstract *The ring transformation of cyclic ketones with a carbonyl function at the side chain under acetalization conditions (BF_3/ethylene glycol) was studied The results suggested that this reaction proceeds via acetal pathway as a major course and hemiacetal pathway as a minor course cis-Cyclohexane-1,2-diol was found to be more effective than ethylene glycol for this ring transformation*

Ring transformation reaction seems to be one of the important strategies in synthetic chemistry, because it enables otherwise synthetically difficult compounds to be accessible by ring transformation from other, readily prepared ring systems Therefore, this indirect synthetic methodology is as useful as the direct synthesis of a target compound and provides a new synthetic route

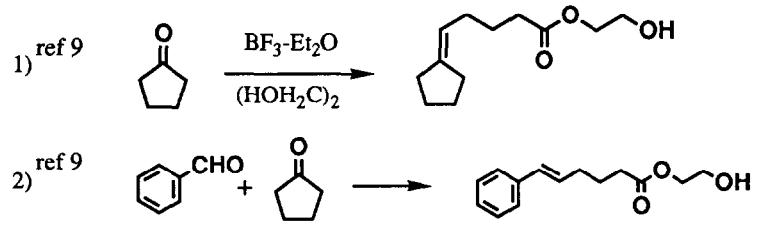
Recently, a novel ring transformation reaction based on aldol condensation followed by acetalization and subsequent Grob fragmentation[1] has been developed by our group [2-9] This reaction takes place when the cyclic ketones with a carbonyl function at the side chain are subjected to acetalization using BF_3/ethylene glycol in CH_2Cl_2 at room temperature This facile ring transformation can be classified into two types One is the intramolecular ring transformation (Scheme 1), and the other is the intermolecular ring transformation (Scheme 2) Our experimental results are summarized in Schemes 1 and 2 Intramolecular types in Scheme 1 can be further divided into several types, depending on the relative position of the two carbonyl functions Intermolecular types also were developed into the ring transformation based on a crossed intermolecular aldol condensation These reactions were successfully applied for the synthesis of natural products such as bulnesol,[3] acorenone B,[6] and trichodiene [8]

In this paper, we wish to describe an insight into this ring transformation It is well known that the reaction conditions using BF_3/ethylene glycol in the presence of carbonyl function afford acetals, similarly to the reaction conditions using *p*-toluenesulfonic acid/ethylene glycol This ring transformation using the same reaction conditions presumably involves the presumed three steps, that is to say, aldol condensation, acetalization, and Grob fragmentation However, whether an acetal is formed as a reaction intermediate is not clear To clarify this aspect, mono-ols, 1,3-diols, and cyclic-1,2-diols were examined instead of ethylene glycol

Scheme 1 Intramolecular ring transformation

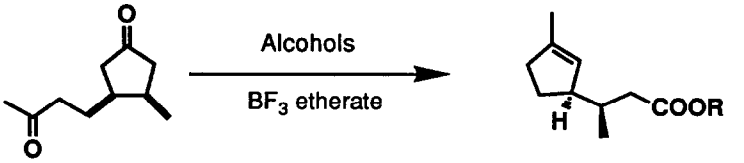


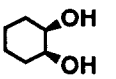
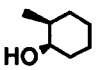
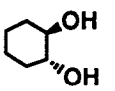
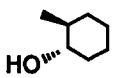
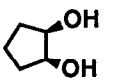
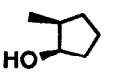
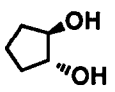
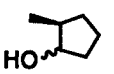
Scheme 2 Intermolecular ring transformation



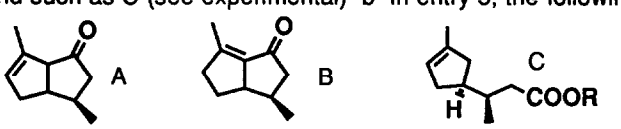
As shown in Table 1,[10] cyclic-1,2-diols such as *cis*- or *trans*-1,2-cyclohexanediol,[11] and *cis*- or *trans*-1,2-cyclopentanediol[12] were examined Among the tested cyclic diols, *cis*-1,2-cyclohexanediol afforded the better result than ethylene glycol *cis*-1,2-Cyclopentanediol and *trans*-1,2-cyclohexanediol also afforded the ring transformation products in good yield However, *trans*-1,2-cyclopentanediol, in which the acetal formation in the reaction pathway seems to be difficult, resulted in poor yield Therefore, this finding suggests that this ring transformation favors the acetal pathway, although it may partially proceed *via* the hemiacetal pathway (*vide supra*) In the ring transformation using *trans*-1,2-cyclopentanediol, the aldol condensation products followed by the dehydration reaction (mixture of conjugated and deconjugated enones) were mainly obtained This indicates

Table 1 Ring transformation using 1,2-diols/BF_3 etherate [a)]



Entry	Alcohols	R	Reaction times(h)	Yield(%)
1		$-CH_2CH_2OH$	2	69
2			3	95
3			4	74
4			4	83
5			4	24

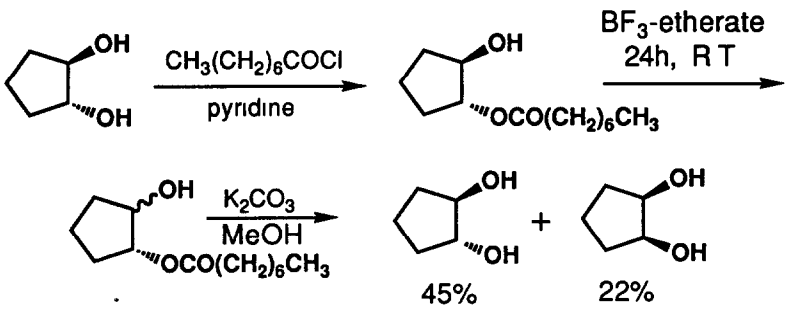
a Reaction conditions, substrates (1 eq), alcohols (5 eq) and BF_3-ether (7 eq) in CH_2Cl_2 were stirred at room temperature Each product contains a small amount of positional isomers of double bond such as C (see experimental) b In entry 5, the following enones (A,B) were obtained



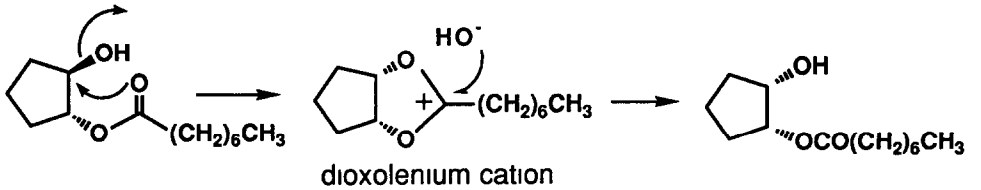
that the aldol reaction which should be the first step in ring transformation proceeds independently of the kind of diol In entries 2, 3, and 4, the configuration of the diols in ring transformation products was retained intact, because treatment of each product with K_2CO_3/MeOH afforded the corresponding methyl esters and the original diols However, in entry 5 using *trans*-1,2-cyclopentanediol, similar treatment of the products with K_2CO_3/MeOH afforded a mixture (3 1) of *cis*- and *trans*-1,2-cyclopentanediols, which could be separated by column chromatography on silica gel, in addition to the corresponding methyl ester The following experiment using a simple ester indicated that the inversion of *trans*-diol to *cis*-diol took place after completion of the ring transformation reaction (Scheme 3)

The monooctanoate of *trans*-1,2-cyclopentanediol was subjected to the same reaction conditions as ring transformation reactions, and subsequent treatment with K_2CO_3/MeOH afforded a mixture of *cis*- and *trans*-diols This unexpected conversion of *trans*-diol to *cis*-diol is considered to pass through the dioxolenium cation, which is formed in the SNi reaction, as shown in Scheme 4 The formation of *cis*-diol in entry 5 also may be rationalized by the above finding

Scheme 3. Conversion of *trans*-1,2-cyclopentanediol monooctanoate to *cis*-isomer by BF_3 etherate

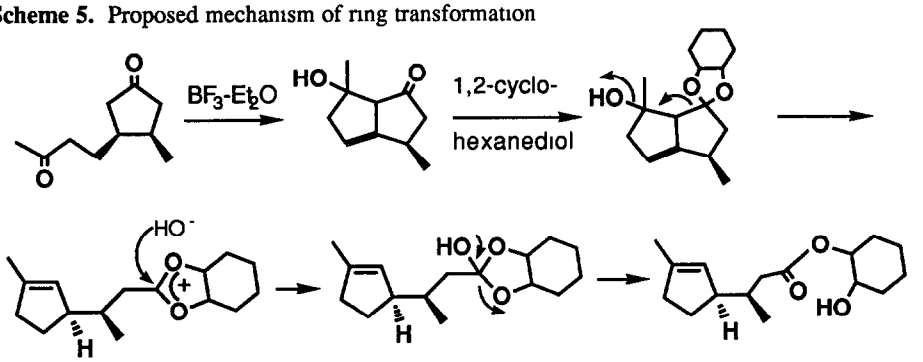


Scheme 4 The dioxolenium cation intermediate



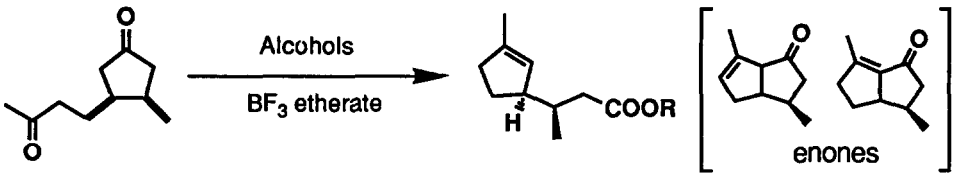
The reaction pathway of this ring transformation is proposed as shown in Scheme 5 Retention of the configuration of the diol in entries 2, 3, and 4 suggests that the dioxolenium cation formed as an intermediate undergoes the cleavage in a manner to retain the configuration of 1,2-cyclohexanediol

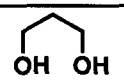
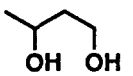
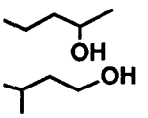
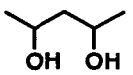
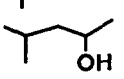
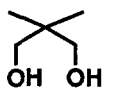
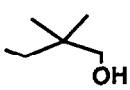
Scheme 5. Proposed mechanism of ring transformation



1,3-Diols also were examined In all cases, ring transformation reaction was observed, but the yields were not so good as those of 1,2-diols (Table 2) Also, a considerable amount of the enones was obtained In conclusion, 1,3-diols such as 1,3-propanediol, 1,3-butanediol, 2,4-pentanediol, and 2,2-dimethyl-1,3-propanediol are less efficacious than 1,2-diols Monoalcohols such as MeOH, EtOH, cyclohexanol, and 2-methoxyethanol, were also examined In all cases, an inseparable complex mixtures and the enones derived from aldols were obtained, but the ring transformation product was not obtained Only 2-methoxyethanol afforded the ring formation product in 13% yield This finding provides additional proof that the ring transformation proceeds in part *via* the hemiacetal pathway, as described in *trans*-1,2-cyclopentanediol (Table 1, entry 5), in addition to the main acetal pathway

Table 2. Ring transformation using 1,3-diols/BF_3 etherate [a)]



Entry	Alcohols	Products (R)	Reaction times(h)	Yield(%)	Enones (%)
1		$(CH_2)_3OH$	14	26	37
2		 1 2	40	29	17
3			6	36	21
4			6	50	29

a Reaction conditions, the same as the case of table 1

The reason why *cis*-1,2-cyclohexanediol affords good yield in this ring transformation may be attributed to the fixed dioxolane ring formed by the acetalization In the fixed dioxolane ring, as shown in Fig 1, a lone pair of oxygen in the dioxolane ring can take the desired position of antiperiplaner to the orbital of C-C bond to undergo the cleavage This favorable orientation causes the ring transformation reaction to afford a good yield The reaction seems to start with the formation of carbocation which should be formed by BF3-catalyzed elimination of aldol In contrast, a lone pair of unfixed oxygen in mono-ols can not take the desired antiperiplaner orientation for ring transformation Although other Lewis acids such as $TiCl_4$, $AlCl_3$, and $ZnCl_2$ were also examined, BF3-etherate was found to be the most effective for the novel ring transformation reaction under study

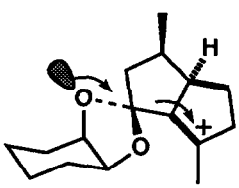


Fig. 1

Experimental

Infrared (IR) spectra were measured with a JASCO A-202 spectrometer ^1H- 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, and positional isomer (2-13% depending on reaction times) of double bond was observed by ^1H-NMR spectra

General procedure

To a stirred solution of substrate (see Table 1, Entry 2)(150 mg, 0 89 mmol) in CH_2Cl_2 (10 ml) were successively added BF3-etherate (1 6 ml, 7 eq) and *cis*-1,2-cyclohexanediol (500 mg, 5 eq) at 0°C under an Ar atmosphere After being stirred for 3 h at room temperature, the reaction mixture was diluted with ether, washed with sat $NaHCO_3$, and brine, then dried 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 (225 mg, 95%)

Selected spectroscopic data of each product in Table 1

Entry 1 IR (neat) 3450, 2970, 1740, 1660 cm^{-1}, ^1H-NMR δ ($CDCl_3$) 5 22 (2H, m, -C=CH-), 4 19 (2H, m, $COOCH_2$-), 3 80 (2H, m, -CH_2OH), 1 71 (3H, m, =C-CH_3), 2 70-1 40 (8H, m), 0 91 (3H, d, *J*=6 5 Hz, CH_3), MS *m/z* 212 (M^+), 151, 108, 81, HRMS for $C_{12}H_{20}O_3$ (M^+) Calcd *m/z* 212 1412, Found 212 1445

Entry 2 IR (neat) 3450, 2950, 1720, 1650 cm^{-1}, ^1H-NMR δ ($CDCl_3$) 5 24 (1H, m, =CH-), 4 95 (1H, m, CHOCO), 3 86 (1H, m, -CHOH), 2 64-2 58 (20H, m), 0 92 (3H, d, *J*=6 5 Hz,-CH_3), MS *m/z* 266 (M^+), 167, 108, 81, HRMS for $C_{16}H_{26}O_3$ (M^+) Calcd *m/z* 266 1882, Found 266 1871

Entry 3 IR (neat) 3450, 2950, 1720, 1660 cm^{-1}, ^1H-NMR δ ($CDCl_3$) 5 25 (1H, m, =CH-), 4 95 (1H, m, CHOCO), 3.85 (1H, brs, -CHOH), 2 66-0 99 (20H, m), 0 94 (3H, m,-CH_3), MS *m/z* 266 (M^+), 186, 167, 81, HRMS for $C_{16}H_{26}O_3$ (M^+) Calcd *m/z* 266 1882, Found 266 1897

Entry 4 IR (neat) 3450, 2950, 1720, 1650 cm^{-1}, ^1H-NMR δ ($CDCl_3$) 5 24 (1H, m, =CH-), 4,98 (1H, m, CHOCO), 4 15 (1H, m, -CHOH), 2 65-1 24 (18H, m), 0 92 (3H, d, *J*=6 5 Hz, -CH_3), MS *m/z* 252 (M^+), 234, 81, HRMS for $C_{15}H_{24}O_3$ (M^+) Calcd *m/z* 252 1725, Found 252 1756

Entry 5 IR (neat) 3450, 2950, 1730, 1660 cm^{-1}, ^1H-NMR δ ($CDCl_3$) 5 22 (1H, m, =CH-), 4 79 (1H, m, CHOCO), 4 06 (1H, brs, -CHOH), 2 63-1 48 (18H, m), 0 94-0 90 (3H, m, -CH_3), MS *m/z* 252 (M^+), 234, 151, 81, HRMS for $C_{15}H_{24}O_3$(M^+) Calcd *m/z* 252 1725, Found 252 1742

Selected spectroscopic data of each product in Table 2

Entry 1 IR (neat) 3400, 2900, 1720, 1640 cm^{-1}, ^1H-NMR δ ($CDCl_3$) 5 23 (1H, m, =CH-), 4 23 (2H, d, *J*=6 1 Hz, $COOCH_2$), 3 70 (2H, dt, *J*=5 6, 5 6 Hz, CH_2OH), 1 71 (3H, m, =CH-Me), 0 92 (3H, d, *J*=6 6Hz, -CH_3), 2 66-1 45 (9H, m), MS *m/z* 226 (M^+), 151, 108, 81, HRMS for $C_{13}H_{22}O_3$(M^+) Calcd *m/z* 226 1569, Found 226 1593

Entry 2 IR (neat) 3450, 2950, 1730, 1660 cm^{-1}, ^1H-NMR δ ($CDCl_3$) 5 23 (1H, m, =CH-), 5 18-4 07 & 3 87-3 53 (3H, m, COOCH & CHOH), 1 72-1 69 (3H, m, =C-CH_3), 1 29-1 21 (3H, m, OCH-CH_3), 0 95-0 94 (3H, m, -CH_3), 2 62-1 45 (11H, m), MS *m/z* 240 (M^+), 151, 108, 81, HRMS for $C_{14}H_{24}O_3$(M^+) Calcd *m/z* 240 1725, Found 240 1737

Entry 3 IR (neat) 3450, 2950, 1730, 1660 cm^{-1}, ^1H-NMR δ ($CDCl_3$) 5 23 (1H, m, =CH-), 5 17 (1H, m, COOCH), 3 72 (1H, m, CHOH), 2 84 (1H, m, -OH), 1 73-1 69 (3H, m, =C-CH_3), 1 28-1 25 (3H, d, *J*=6 3 Hz, COOCH-CH_3), 1 18 (3H, d, *J*=6 3 Hz, OCH-CH_3), 0 93 (3H, d, *J*=6 6 Hz, -CH_3), 2 64-1 43 (10H, m), MS *m/z* 254 (M^+), 236, 173, 108, 81, HRMS for $C_{15}H_{26}O_3$(M^+) Calcd *m/z* 254 1882, Found 254 1847

Entry 4 IR (neat) 3450, 2950, 1730, 1660 cm^{-1}, ^1H-NMR δ ($CDCl_3$) 5 23 (1H, m =CH-), 3 93 (2H, s, $COOCH_2$), 3 30 (2H, d, *J*=6 6 Hz, CH_2OH), 1 72 (3H, s, =CH-CH_3), 2 64-1 43 (9H, m), 0 95-0 88 (9H, m, other-Me), MS *m/z* 254 (M^+), 168, 108, 81, HRMS for $C_{15}H_{26}O_3$(M^+) Calcd *m/z* 254 1882, Found 254 1854

***trans*-2-Capryloyloxycyclopentanol**

IR (neat) 3450, 2950, 1730 cm^{-1}, ^1H-NMR δ ($CDCl_3$) 4 73 (1H, m, CHCOR), 4 12 (1H, m, CHOH), 3 84 (1H, m, -OH), 2 32 (2H, t, *J*=7 1 Hz, $COOCH_2R$), 2 17-1 47 (8H, m), 1 29 (8H, s, (-$(CH_2)_4$-Me), 0 90 (3H, t, *J*=7 2 Hz, -CH_3), MS *m/z* 229 (M^++1), 228, 127

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9 Nagumo, S , Matsukuma, A , Inoue, F , Yamamoto, T , Suemune, H , Sakai, K *J Chem Soc , Chem Commun* **1990**, 1538
10 For the preparation of substrate, see Suemune, H , Oda, K , Saeki, S , Sakai, K *Chem Pharm Bull* **1988**, 36, 172
11 Both compounds are commercially available (Aldrich)
12 For *cis*-1,2-cyclopentanediol, see Van Rheenen, V , Kelly, R C , Cha, D Y *Tetrahedron Lett* **1976**, 23, 1973 For *trans*-1,2-cyclopentanediol, see Pascul, J , Castellis, J *J Am Chem Soc* **1953**, 74, 2899