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RING CLEAVAGE AND RECONSTRUCTION OF FIVE AND SIX MEMBERED RING

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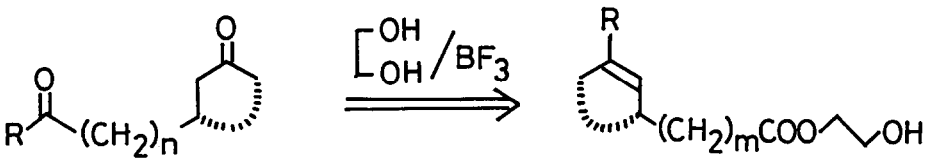
Summary: Under the acetalization conditions using BF_3-etherate/ethylene glycol, cyclopentanones and cyclohexanones with the carbonyl function at the C_3- or C_4-position of the β-side chain undergo the facile ring cleavage to reconstruct the new ring.

In many synthetic processes, carbonyl functions have to be protected against attack by various reagents. The most widely used protective forms for carbonyl compounds are ethylene acetals and ethylene thioacetals, which are introduced by treating the carbonyl compounds in the presence of strong acid (e.g., p-TsOH) with ethylene glycol or ethylene thioglycol. The use of BF_3-etherate in the place of strong acid is well known to proceed faster and with better yield than p-TsOH.[1)]

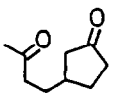
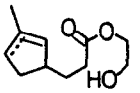
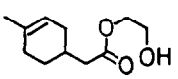
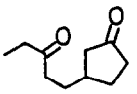
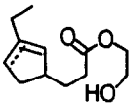
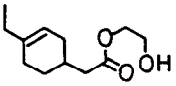
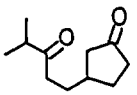
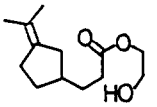
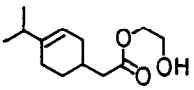
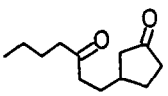
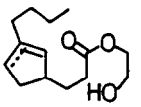
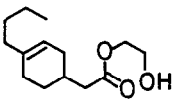
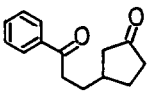
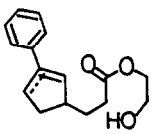
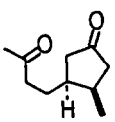
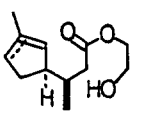
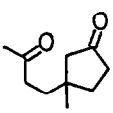
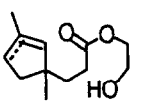
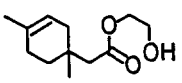
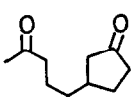
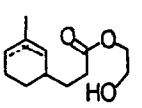
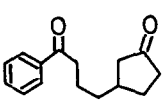
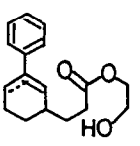
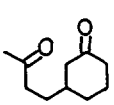
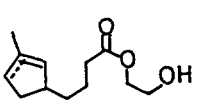
We now wish to describe that the five and six membered ring ketones with the carbonyl function at the C_3- or the C_4-position of β-side chain



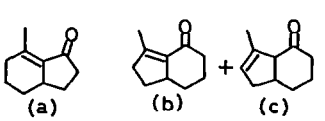
undergo the facile ring cleavage to reconstruct the new rings under the acetalization conditions using BF_3-etherate/ethylene glycol. Reaction proceeded smoothly in fair to good yield at room temperature, and the usual protection for the carbonyl function was not observed at all. The generality of this reaction is summarized in Table 1.

Typical example (entry 1 in Table 1) is as follows. BF_3-etherate (0.93 ml, 7.4 mmol) and then $HOCH_2CH_2OH$ (0.30 ml, 5.4 mmol)*1 were successively added dropwise to a stirred solution of the diketone (162 mg, 1.05 mmol) in CH_2Cl_2 (3 ml) at room temperature. After 2 h, the reaction was quenched by addition of 5% aq.$NaHCO_3$ (5 ml) at 0°C. The reaction products were extracted with ether, and purified by column chromatography on silica gel to afford the ethylene glycol half ester (124 mg, 60%).

Table 1

Entry	Substrate	Reaction time	Compound I	Compound II	Yield	Ratio (I:II)
1		2 hr			60%	65 : 35
2		1 hr			77%	74 : 26
3		2 hr			78%	80 : 20
4		2 hr			82%	72 : 28
5		1 hr			87%	
6		2 hr			69%	
7		1 hr			81%	69 : 31
8		2 hr			27%	
9		20 hr			73%	
10		2.5hr			36%	

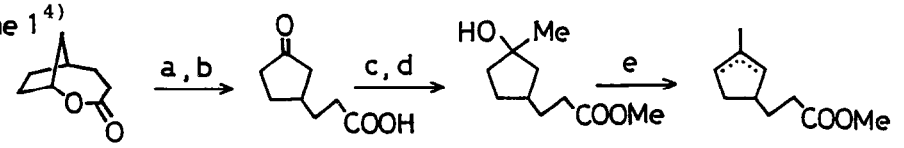
a) BF_3-etherate (7 eq) and ethylene glycol (5 eq) were used.
b) In entry (8,9,10), the formation of seven membered rings was excluded by comparison of the ^{1}H-NMR spectra with 1-methyl-1-cycloheptene.
c) In compound I of entry 3, no olefinic protons were observed in ^{1}H-NMR.
d) Entry 8 and 9 resulted exceptionally in poor yield, because of the formation of the enone (a in entry 8 and b+c in entry 10).



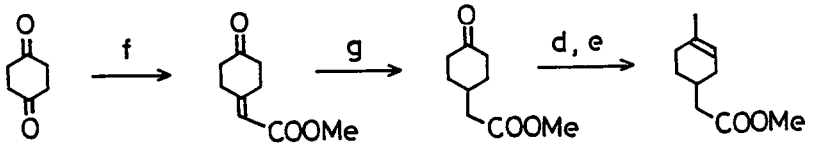
In this reaction of the ring cleavage and reconstruction, reaction products were usually obtained as ethylene glycol half esters. The presence of this ester function was supported by the signals of C-CH_2OH (2H, m) at δ 3.76-3.85 and COOCH_2-C (2H, m) at δ 4.16-4.26 in ^{1}H-NMR spectrum, in addition to the absorption band at 3450(OH) and 1730(ester) cm^{-1} in IR spectrum. By treatment with K_2CO_3 in MeOH, the half esters were converted to the corresponding methyl esters in good yield. Methyl esters in entry (1,2,3,4, and 7) were observed as one spot on TLC. However, the fragmentation pattern in GC-EIMS suggested that each methyl ester consists of two compounds (compound I and II in Table 1). Compound I and II showed similar fragmentation patterns. However, among the common fragmentation peaks (M-74 and M-87) in compound I, the peak of M-87 was not observed in compound II, and instead, only the peak of M-74 was detected as common fragmentation peak in compound II. These fragmentation peaks were rationalized by assuming the presence of cyclopentene-CH_2-CH_2-COOMe (M-(73+1) and M-87) in compound I and cyclohexene-CH_2COOMe (M-(73+1)) in compound II. In EIMS of entry (5,6,8,9, and 10 methyl esters) also, typical peaks of M-74 and M-87 (M-74 and M-101 in entry 6 and 10) were observed as common fragmentation patterns. These peaks were compatible with the structure as shown in Table 1. Furthermore, the detailed examination of compound I using GC-EIMS and ^{1}H-NMR (or ^{13}C-NMR) suggested that compound I is a mixture of the positional isomers of the double bond (see Table 1). Unequivocal evidence for the structure of compound I and II was obtained by the synthesis of typical compounds (compound I and II in entry 1) as shown in Scheme 1 and 2. The ratio of compound I to II in entry (1,2,3,4, and 7) was determined to be ca.3:1 by gas chromatography.

This reaction involving 4 steps, a) aldol condensation, b) acetalization, c) fragmentation, d) rearrangement of the double bond, may be considered as one of the unusual case[2] of Grob's fragmentation.[3] The reaction mechanism*2 is tentatively proposed as shown in Scheme 3. This reaction may be applied for the ring transformation of five to six membered ring and six to five membered ring, as well as the synthesis of enantiomer (see entry 3).

Scheme 1[4]

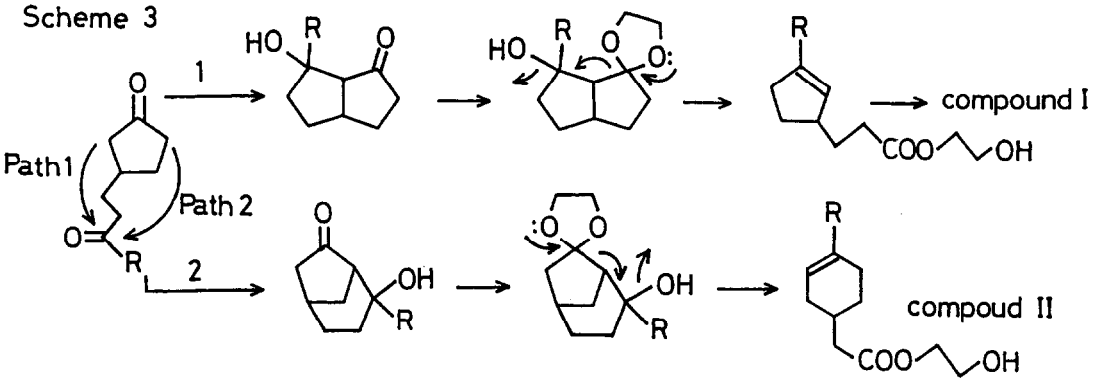


Scheme 2



a) NaOH/MeOH. b) Jones oxid. c) CH_2N_2. d) MeMgBr. e) TsOH.
f) Ph_3P=CHCOOMe. g) Pd-C/H_2.

Scheme 3



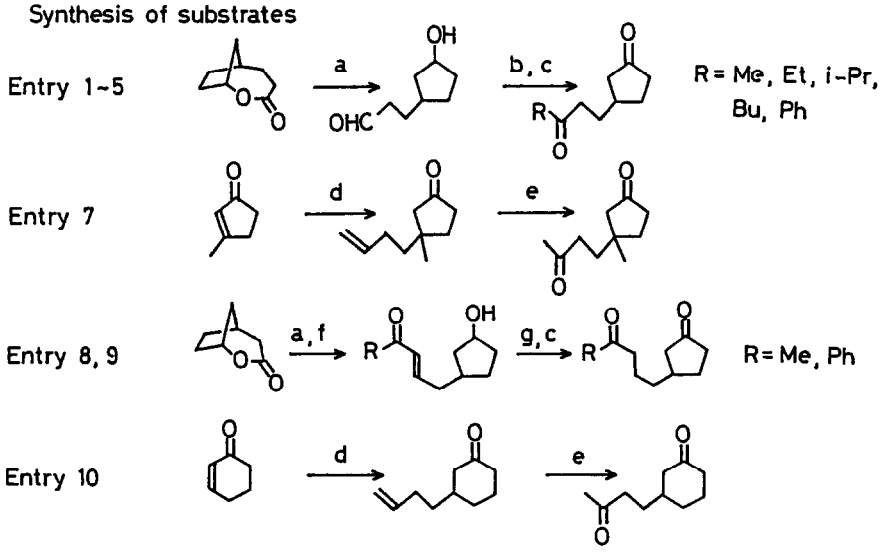
References and Notes

1) T.W.Green,"Protective Groups in Organic Synthesis"; p.114, John Wily & Sons. Inc. 1981, Canada.
2) R.O.Duthaler and P.Maienfisch, Helv. Chim. Acta, 67, 842 (1982). J.H.Hutchinson, T.Money, and S.E.Piper, Can. J. Chem., 64, 854 (1986). J.W.Blunt, M.P.Hartshorn, and D.N.Kirk, J. Chem. Soc., Chem. Commun., 1965, 545.
3) C.A.Grob, Angew. Chem. Int. Ed., 6, 1 (1967), and 8, 535 (1969).
4) P.E.Eaton, R.H.Mueller, G.R.Carlson, D.A.Cullison, G.F.Cooper, T.C.Chon, and E.P.Krebs, J. Am. Chem. Soc., 91, 5527 (1969).
5) K.Sakai, Y.Ishiguro, K.Funakoshi, K.Ueno, and H.Suemune, Tetrahedron Lett., 25, 961 (1984).

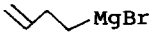
*1 Even addition of ethylene glycol and then BF_3-etherate, the same result was obtained.

*2 When MeOH was used instead of ethylene glycol, the ring cleavage was not observed at all. The reason remains unclear. However, one reason may be connected to the free rotation of dimethyl acetal, in contrast to the rigid ethylenedioxy structure. Thus, it is likely that the lone pair of oxygen in methoxy function occupies unfavorable position for fragmentation.

Synthesis of substrates



See ref. 5) for entry 6.

a) DIBAL-H. b) RMgX. c) Jones oxid. d)  MgBr/CuBr·Me_2S.

e) O_2, CuCl, $PdCl_2$/DMF. f) Ph_3P=CHCOR. g) Pd-C/H_2.

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