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DRASTIC CONVERSION OF BICYCLO[m,n,0]ALKANE RINGS TO SPIROCYCLIC SKELETONS

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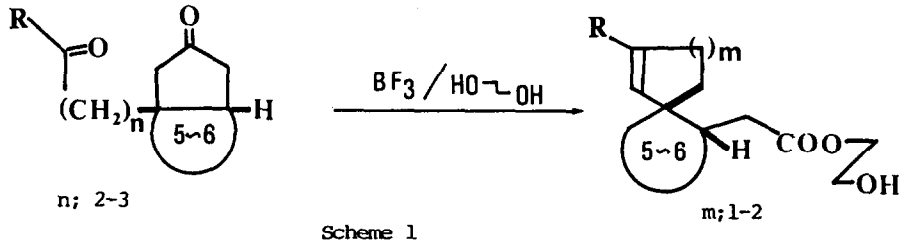
Summary: Under acetalization conditions (BF_3/ethylene glycol), bicyclo[m.n.0]alkanones with the carbonyl function at 3' or 4'-position of the C_1-side chain undergo the ring cleavage to build up the spirocyclic skeletons.

The characteristic framework of the spiro[4.5]decanes[1] with asymmetric centers such as β-vetivone, hinesol, and acoranes seems to be attractive target for synthetic chemists. One of the difficulties in the synthesis of spirocyclic compounds is how to create the pivotal quaternary carbon center.

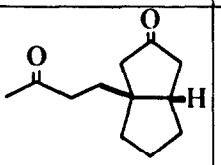
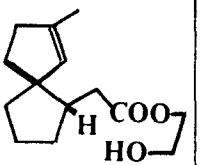
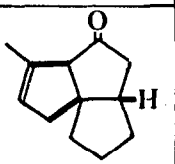
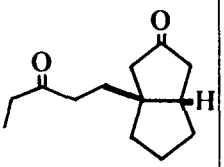
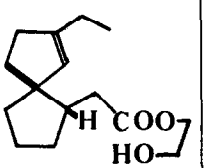
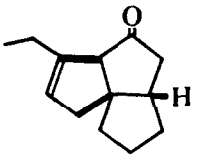
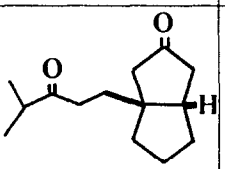
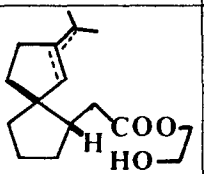
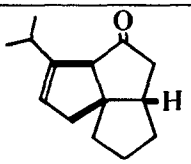
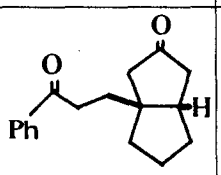
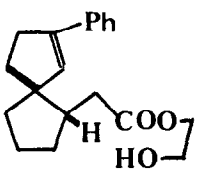
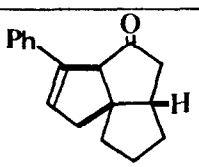
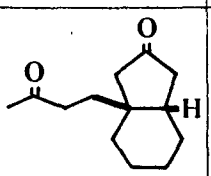
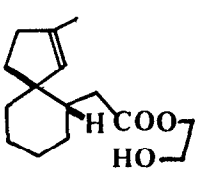
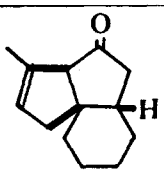
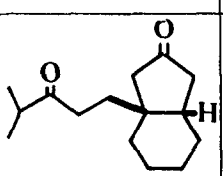
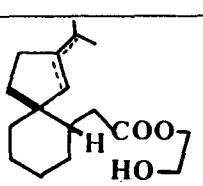
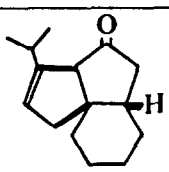
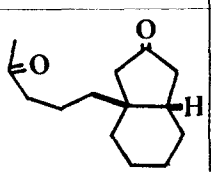
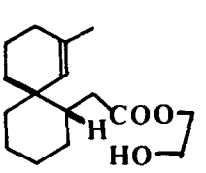
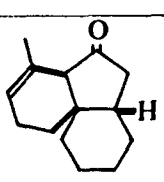
Previously, we reported the new type fragmentation reaction,[2] in which cyclopentanones and cyclohexanones with carbonyl function at the β-side chain undergo the facile ring cleavage under acetalization conditions[3] (BF_3/ethylene glycol) to reconstruct the five or six membered rings. In this communication, we wish to describe the first conversion of bicyclo[m.n.0]alkanones[4] with the carbonyl function at the 3' or 4'-position of the C_1-side chain to the spirocyclic compounds (Scheme 1).



Scheme 1

As shown in Table 1, treatment of the diketones (entry 1-7) with BF_3/ethylene glycol afforded the corresponding spirocyclic compounds with ethylene glycol half ester as a major product in described yields. Typical example (entry 1) is as follows. Ethylene glycol (0.12 ml, 2.17 mmol) and then BF_3-etherate (0.35 ml, 2.86 mmol) were successively added to a stirred solution of the diketone (77 mg, 0.398 mmol) in CH_2Cl_2 (5 ml) at room temperature. After 1 h, the reaction mixture was diluted with 5% aq.$NaHCO_3$ (5 ml) at 0°C, and

Table 1

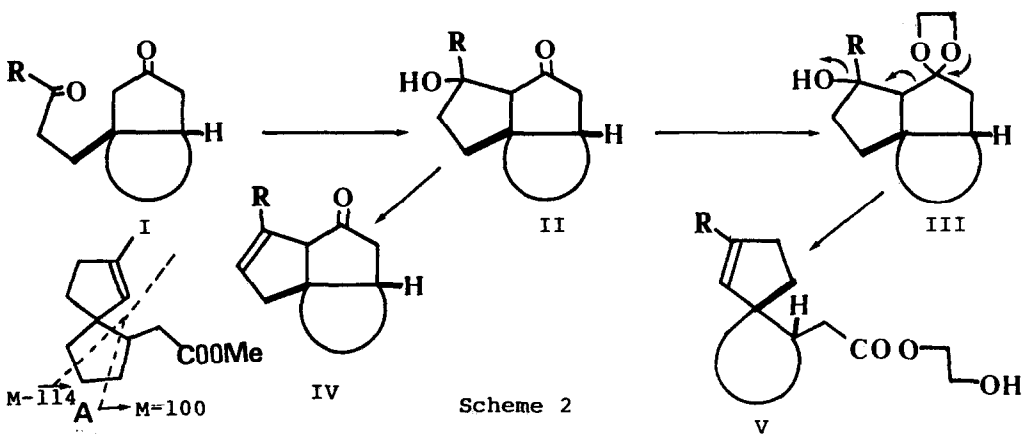
Entry	Substrate	Spirocyclic compound	Isolated yield (%)	Tricyclic compound	Isolated yield (%)
1			75		15
2			87		trace
3			40		14
4			84		trace
5			53		4
6			35		17
7			65		12

Reaction conditions; BF_3-etherate (7 eq); ethylene glycol (5 eq); reaction times 1h, except for entry 3 and 6 (24 h); room temperature

extracted with AcOEt, then purified by silica-gel column chromatography to afford the spirocyclic compound (72 mg, 75%) and the tricyclic compound (11 mg, 15%). In this reaction, the acetal compound was not detected. The structure of each product was determined by examination of ^{1}H-NMR, IR, and MS spectra.[5] For example, the ^{1}H-NMR spectrum of spiro product in entry 1 reavealed the presence of olefinic proton (δ 5.13, 1H), half ethylene glycol ester [$-CH_2O$ (δ 3.77-3.86, 2H)], $COOCH_2-$ (δ 4.15-4.27, 2H), and vinyl methyl (δ 1.70, 3H). The IR spectrum [3400 (OH), 1700 cm^{-1} (ester)] also supported the proposed structure. By treatment with K_2CO_3/MeOH, the half ethylene glycol ester was converted to the corresponding methyl ester. In EIMS of the methyl ester, fragmentation peaks of M^+ (208), M-(100+1), and M-114 (A) were compatible with the proposed spirocyclic structure. The structure of tricyclic compound was also consistent with the IR, MS, and ^{1}H-NMR spectra. In ^{1}H-NMR, vinyl methyl (δ 1.71, 3H), olefinic proton (δ 5.40, 1H), and COCHC=C (δ 2.79, 1H) were observed, in addition to the absorption bands of 1715 and 1645 cm^{-1} in IR spectrum and fragmentation peaks [176(M^+), 148, 133] in EIMS spectrum. In substrates (entry 3 and 6) with the isopropyl function at the terminal of side chain, the spirocyclic compounds were obtained in unsatisfactory yields. This may be attributed to the steric hindrance due to a bulky isopropyl function.

The reaction mechanism is tentatively proposed as shown in Scheme 2. The aldol (II) formed by BF_3-catalyzed aldol condensation undergoes the unusual Grob fragmentation[6] via the acetal (III) to yield the spirocyclic compound (V). It is noteworthy that in independent treatment of the tricyclic compound (IV) or the spirocyclic compound (V) under the employed acetalization conditions, partial interconversion was observed by monitoring with TLC.

This novel ring conversion of bicyclo[m.n.0]alkanones to the spirocyclic rings may provide a newer method for the synthesis of natural products consisting of spirocyclic rings.



Scheme 2

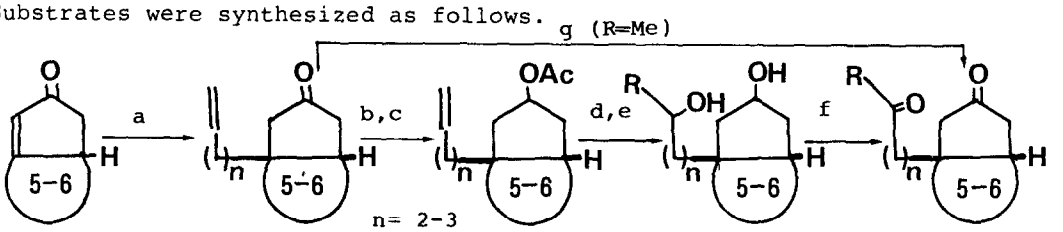
References and Notes

1) J.Apsimon, "The Total Synthesis of Natural Products Vol. 5" J.Wiley and Sons: New York, 1982, p. 264.

2) H.Suemune, K.Oda, and K.Sakai, Tetrahedron Lett., 28, 3373, 1987. M.Tanaka, H.Suemune, and K.Sakai, ibid., 29, 1783, 1988.

3) T.W.Greene, "Protective Groups in Organic Synthesis" J.Wiley and Sons: New York, 1981, Chapter 4.

4) Substrates were synthesized as follows.



Reagents; a=≡-$(CH_2)_n$MgBr/CuBr,Me_2S, b=$NaBH_4$, c=Ac_2O/Py., d=O_3, e=RMgBr(R=Et, Ph, Isopropyl), f=Jones oxid., g=$PdCl_2$,O_2,CuCl

For cis-1,4-addition, see Ref. 1, p 421 and 427.

5) Spectroscopic data of spirocyclic compounds in Table 1.

Entry 1: see the text. ^{1}H-NMR spectrum was measured on JEOLJNM-GX 270.

Entry 2: IR (neat); 3450, 1735, 1650, 1150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.80-3.83 (2H, m, CH_2O), 4.17-4.21 (2H, m, CH_2OCO), 5.24 (1H, brs, =CH). MS m/z: 252 (M^+), 234, 121, 108.

Entry 3: spectroscopic data of the methyl ester. IR (neat): 1740, 1645, 1155 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3.6H, d, J=7 Hz, $(Me)_2CH$), 1.65 (2.4H, s, =-Me), 3.64 (3H, s, COOMe), 5.13 (0.6H, m, =CH). MS m/z: 236 (M^+), 135, 122. The ^{1}H-NMR spectrum suggests that this spirocyclic compound is a mixture of positional isomers of double bond.[2)]

Entry 4: IR (neat); 3450, 1730, 1600 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 3.72-3.78 (2H, m, CH_2O), 4.10-4.18 (2H, m, CH_2OCO), 6.01 (1H, m, =CH), 7.18-7.33 (3H, m, aromatic-H), 7.38-7.44 (2H, m, aromatic-H). MS m/z: 300 (M^+), 282, 169, 156.

Entry 5: IR(neat); 3440, 1730, 1660, 1075 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.70 (3H, brs, =-Me), 3.79-3.83 (2H, m, CH_2O), 4.17-4.21 (2H, m, CH_2OCO), 5.33 (1H, brs, =CH). MS m/z: 252 (M^+), 234, 148, 107.

Entry 6: IR(neat); 3440, 1730, 1665 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 0.95 (3.6H, d, J=7Hz, $(Me)_2CH$), 1.67 (2.4H, s, =-Me), 3.80-3.84 (2H, m, CH_2O), 4.18-4.23 (2H, m, CH_2OCO), 5.37 (0.6H, brs, =CH). A mixture of positional isomers of double bond, similarly to the case of entry 3.

Entry 7: IR(neat): 3450, 1735, 1160, 1080 cm^{-1}. ^{1}H-NMR($CDCl_3$) δ: 1.68 (3H, brs, =-Me), 3.80-3.94 (2H, m, CH_2O), 4.18-4.23 (2H, m, CH_2OCO), 5.41 (1H, brs, =CH). MS m/z: 266 (M^+), 248, 204, 137.

6) C.A.Grob, Angew. Chem. Int. Ed., 6, 1 (1967), and 8, 535 (1969).

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