Tetrahedron Letters,Vol.29,No.14,pp 1733-1736,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

NOVEL RING EXPANSION OF CYCLOPENTANONES TO SEVEN MEMBERED RINGS

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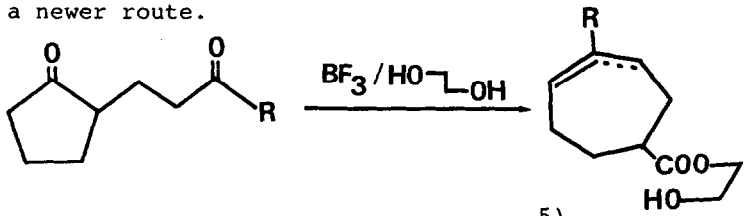
Summary: By treatment with BF_3/ethyleneglycol, cyclopentanones with the carbonyl function at the C_3-position of α-side chain undergo the ring cleavage to build up the seven membered rings, and this novel ring expansion was applied to the synthesis of bulnesol.

Recently, we have reported the new type fragmentation reaction,[1] in which 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 under acetalization conditions (BF_3-etherate/ethyleneglycol) to reconstruct the new five or six membered rings.

In this communication, we wish to describe that cyclopentanones with the carbonyl function at the C_3-position of α-side chain undergo the novel ring expansion[2] to afford the seven membered rings under acetalization conditions[3] (BF_3-etherate/ethyleneglycol) (scheme 1), and this ring enlargement method provides the synthesis of 5,7-fused rings[4] such as bulnesol with a newer route.

Scheme 1



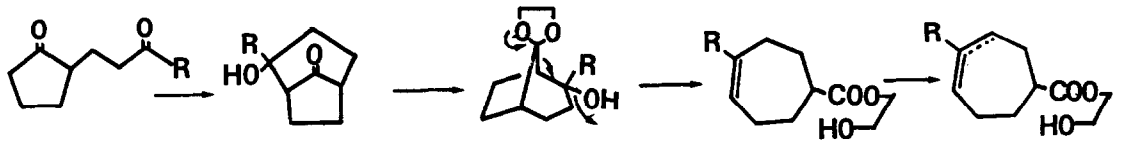
Treatment of the diketones (table 1, entry 1-5)[5] with BF_3-etherate/ethyleneglycol afforded the seven membered rings with ethyleneglycol half ester in fair to good yields. The structure[6] of these products was determined by ^{1}H-NMR, IR, and MS spectral data. For example, the ^{1}H-NMR spectrum of product in entry 5 revealed the presence of the olefinic proton (δ 6.00, 1H), aromatic proton (δ 7.10-7.30, 5H) and half ethyleneglycol ester [$-CH_2O$ (δ 3.78-3.86, 2H), $COOCH_2-$ (δ 4.15-4.27, 2H)], which could be converted to the corresponding methyl ester by treatment with K_2CO_3/MeOH. The IR spectrum [3425 (OH), 1710 cm^{-1} (ester)] and MS spectrum [m/z 260 (M^+), 208, 198] also supported the proposed structure. The ^{1}H-NMR of product in entry 3 indicated the presence of two olefinic protons (δ 5.16, 5.45), suggesting a mixture of positional isomers of double bond. Similar findings

were also observed in entry 4. In addition to olefinic proton (δ 5.50, 0.6H), the signal (δ 1.65, 2.4H) due to vinyl methyl appeared. The above findings suggest a facile rearrangement of the double bond under the employed reaction conditions. This ring expansion reaction seems to involve the following four steps; a) aldol condensation, b) acetalization, c) ring enlargement due to the cleavage of five membered ring, d) rearrangement of the double bond, as shown in scheme 2. Entry 5 in table 1 suggests that, if R-substituent (scheme 1) is quaternary carbon, the better yield may be obtained.

In cyclopentanones (entry 6,7) with the carbonyl function at C_4-position of the α-chain, an expected ring enlargement to eight membered ring was not observed, but the cyclopentene derivatives were obtained. In ^{1}H-NMR of each product, the olefinic proton was not observed, but the signal due to vinyl methyl (entry 6) appeared at δ 1.59 (3H, s), suggesting the presence of tetra-substituted double bond. Unequivocal evidence for this structure was obtained by the synthesis[7] of the corresponding methyl ester, starting with Wittig reaction of 2-(γ-methoxycarbonylpropyl)cyclopentanone with triphenylphosphinemethylene <u>via</u> rearrangement[8] of the double bond with $RhCl_3$. Reaction mechanism is tentatively proposed to be as shown in scheme 3.

The above ring expansion to seven membered ring was applied to the synthesis of bulnesol. As shown in scheme 4, the monoketal (2)[9] obtained from the diketone (1) was converted to the tertiary alcohol (3) by treatment with MeLi. Dehydration of 3 with TsOH in refluxing benzene, followed by treatment with aq.AcOH, afforded the ketone (4). By catalytic hydrogenation with H_2/Pt/MeOH, 4 was converted to the bicyclo[3.3.0]octanone (5) with β-methyl function. The configuration of methyl function in 5 was determined to be β by assuming the attack of hydrogen from the convex site. Introduction of the α-side chain with carbonyl function at the C_3 was accomplished by the alkylation (1-buten-3-one ethylene acetal, $TiCl_4$, $Ti(OisoPr)_4$)[10] of the silyl enol ether (6), which was prepared in kinetically controlled conditions (LDA/TMSCl/THF/-78°C).[11] Treatment of the diketone (7) with BF_3-etherate/ethyleneglycol afforded the expected ring expansion product (8), although total yield from 2 was unsatisfactory. Exhaustive methylation of 8 with MeLi gave (±)-bulnesol, which was identical with reported values[12] in ^{1}H-NMR spectrum and IR spectrum.

Scheme 2



Scheme 3

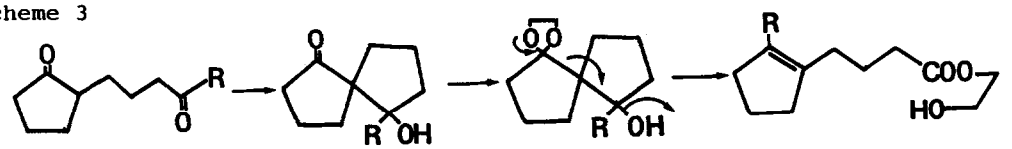
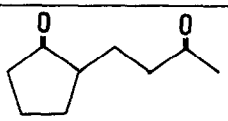
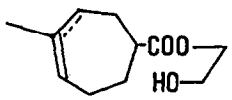
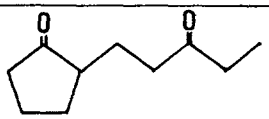
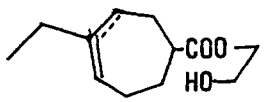
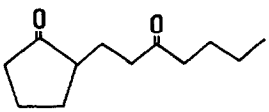
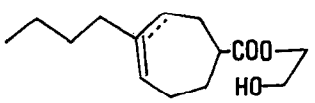
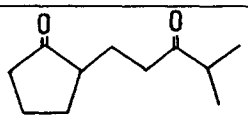
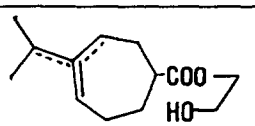
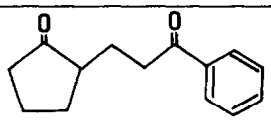
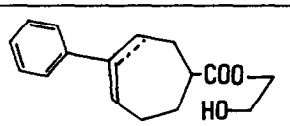
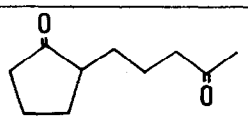
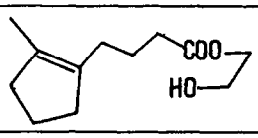
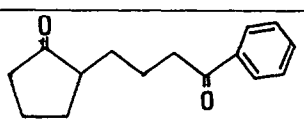
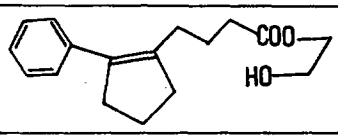
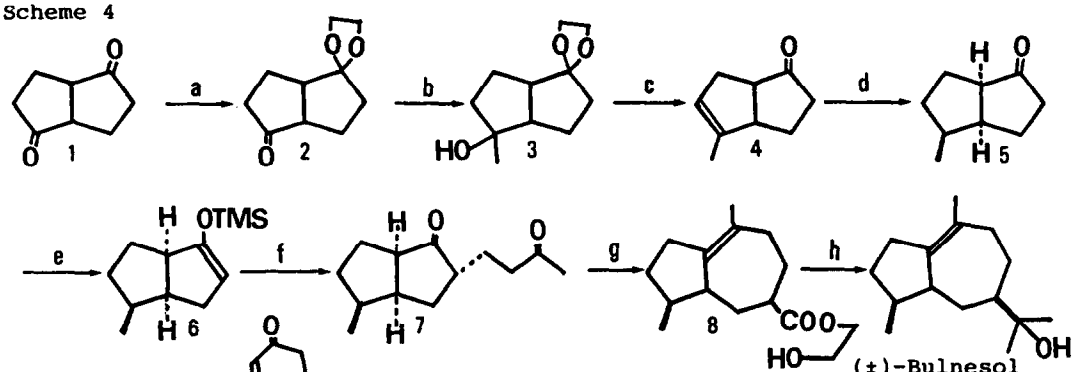


Table 1

Entry	Substrate	Product	Isolated Yield (%)
1			36
2			42
3			65
4			70
5			98
6			42
7			63

Reaction conditions: BF_3-etherate (7 eq), ethyleneglycol (5 eq), reaction times 2-3 h, room temperature. In entry 1, the enone (A) was also obtained in 35%yield. Unidentified products were isolated in entry 6 and 7.

Scheme 4



a) $HOCH_2CH_2OH$/p-TsOH. b) MeLi. c) p-TsOH/benzene. d) H_2/Pt/MeOH. e) LDA/TMSCl/-78°C. f) 1-Buten-3-one ethylene acetal, $TiCl_4$/Ti(OisoPr)$_4$. g) Ring expansion h) MeLi.

References and Notes

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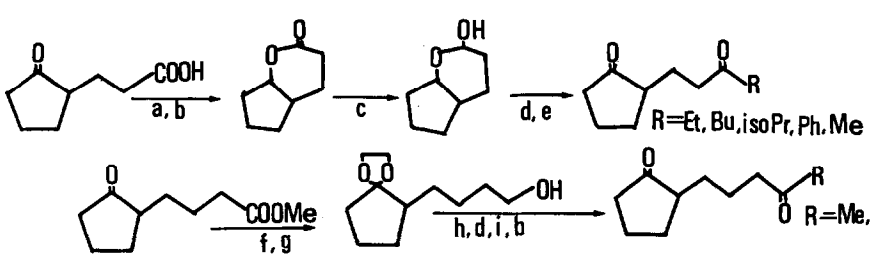
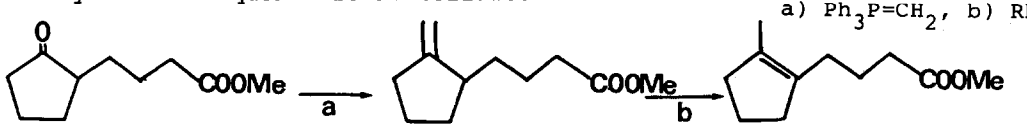
5) Substrates were synthesized as follows.



6) Spectroscopic data of products in entry 1-7.
Entry 1: IR; 3425, 1720, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.51 (1H, m, olefinic H), 4.16-4.25 (2H, m, $COOCH_2$), 3.77-3.86 (2H, m, CH_2O), 1.71 (3H, s, vinyl Me). MS m/z: 198 (M^+), 180, 136.
Entry 2: IR; 3400, 1710, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.23-5.32 (1H, m, olefinic H), 4.16-4.25 (2H, m, $COOCH_2$), 3.77-3.86 (2H, m, CH_2O), 0.96 (3H, t, J=7.6 Hz, Me). MS m/z: 212 (M^+), 194, 150, 122.
Entry 3: IR; 3425, 1710, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.45 (0.8H, m, olefinic H), 5.16 (0.2H, m, olefinic H), 4.15-4.25 (2H, m, $COOCH_2$), 3.81-3.85 (2H, m, CH_2O), 0.83 (3H, t, J=5.7 Hz, Me). MS m/z: 240 (M^+), 222, 178.
Entry 4: IR; 3400, 1710, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.50 (0.6H, m, olefinic H), 4.15-4.25 (2H, m, $COOCH_2$), 3.72-3.86 (2H, m, CH_2O), 1.65 (2.4H, s, =-Me), 0.96 (3.6H, d, J=6.9 Hz, $(Me)_2CH$). MS m/z: 226 (M^+), 208, 164.
Entry 5: IR; 3425, 1710, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.10-7.30 (5H, m, aromatic H), 6.00 (1H, olefinic H), 4.15-4.27 (2H, m, $COOCH_2$), 3.78-3.86 (2H, m, CH_2O). MS m/z: 260 (M^+), 242, 198.
Entry 6: IR; 3400, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.14-4.26 (2H, m, $COOCH_2$), 3.78-3.87 (2H, m, CH_2O), 1.60 (3H, s, Me). MS m/z: 212 (M^+), 194, 150, 108.
Entry 7: IR; 3370, 1705, 1165 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.12-7.42 (5H, m, aromatic H), 4.10-4.19 (2H, m, $COOCH_2$), 3.70-3.80 (2H, m, CH_2O). MS m/z: 274 (M^+), 212, 170.
7) The synthetic sequence is as follows.



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(Received in Japan 25 January 1988)