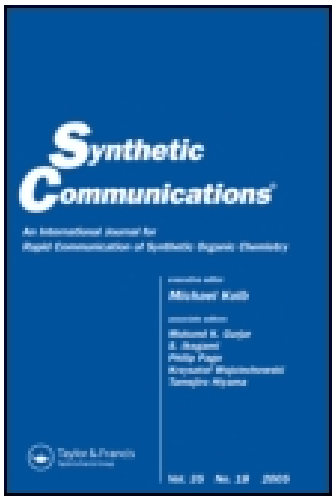

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STUDY ON THE FUNCTIONALIZATION AND REACTIVITY OF BICYCLIC ACETAL COMPOUNDS

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STUDY ON THE FUNCTIONALIZATION AND REACTIVITY OF BICYCLIC ACETAL COMPOUNDS

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ABSTRACT

Bicyclic acetal was known as a versatile reagent for the structural transformation reactions. Bicyclic acetal was functionalized to the acetal-lactol and halo-lactol, and applied for the new rearrangement reactions. The structural identification and rearrangement mechanism were discussed herein.

A versatile transformation utility of bicyclic acetals in the 6,8-dioxabicyclo[3.2.1]octane structure have been reported for the direct synthesis of 1,5-diketone,[1] *cis*-1,2-cyclopentanediol,[2] 2,6-disubstituted pyridine,[3] 2,3,6-trisubstituted pyridine,[4] cyclohexenone,[5] and allylic acetate derivatives.[6] In the continuous study of developing new chemistry utilizing bicyclic acetals, the acetal-lactol and halo-lactol were prepared and reacted with base to give the new rearrangement reactions.

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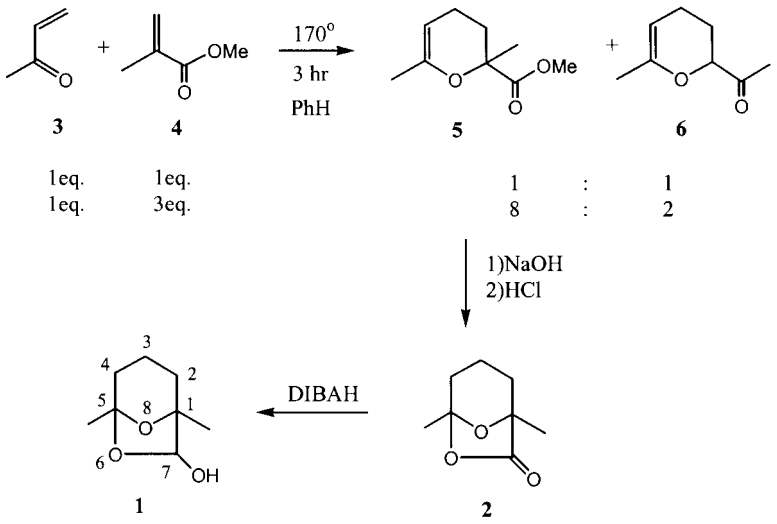
The bicyclic acetal-lactol **1** was obtained in 80% yield by using DIBAH reduction[7] from the acetal-lactone **2** as shown in Scheme 1. Dilution technique was used for the hetero Diels-Alder reaction.[8] The reaction of 3 equiv. of MVK **3** and 1 equiv. of methyl metacrylate (**4**) gave 8 : 2 ratio of pyrans **5** and **6** respectively. The ester **5** was hydrolyzed with NaOH and cyclized with HCl to give acetal-lactone **2** in 94% yield.



Scheme 1.

The acetal-lactol **1** was refluxed with NaH/THF or *t*-BuONa/*t*-BuOH and found a novel rearrangement to give acetyl-cyclopentene **7** in 89% and 82% yield respectively. The reaction mechanism was proposed as shown in Scheme 2. The lactol proton was deprotonated by base and ring opening was followed to give ketone-aldehyde **8** which was recyclized via aldol condensation yielding the acetyl-cyclopentene **7**.

We applied this reaction with 4-iodolactol and 7-phenyllactol, but obtained no reaction. 4-Bromolactol **10**, however, which was prepared as a single isomer (equatorial)[9] via halolactonization[10] from the ester **5** or via direct bromination[11] from the lactone **2** gave debromonated-*t*-butoxide substituted product in 63% yield by using *t*-BuONa/*t*-BuOH as shown in Scheme 3. Spectroscopic analysis could not distinguish the product from the two possible debromonated products **11** and **12**.

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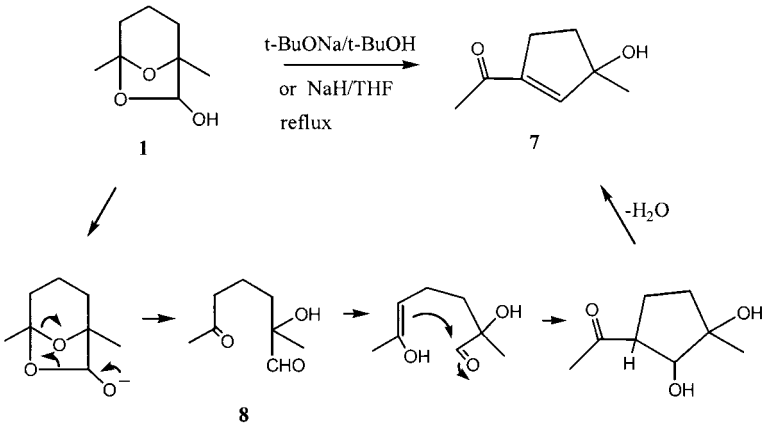
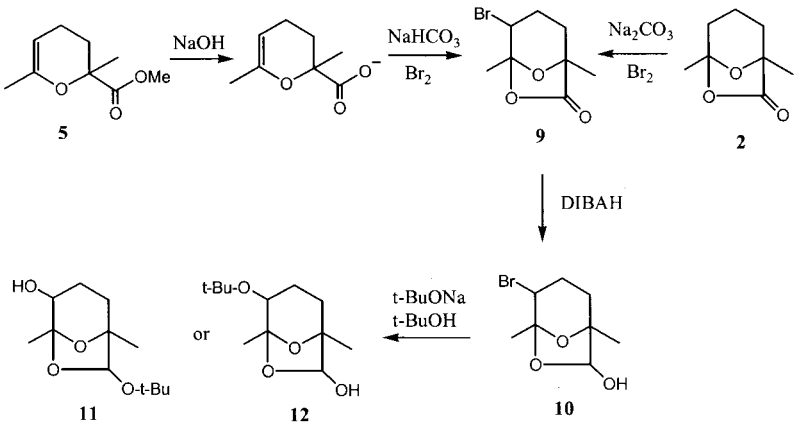


Scheme 2.



Scheme 3.

The plausible mechanisms for the two possible products **11** and **12** were showed in Scheme 4. The deprotonation of bromo-lactol **10** was same as acetal-lactol **1**, but epoxidation was followed in bromo-lactol instead of aldol condensation in acetal-lactol. The epoxide-aldehyde **13** was the intermediate for the two possible products. If *t*-butoxide attacks the aldehyde as a nucleophile followed by epoxide opening should give the

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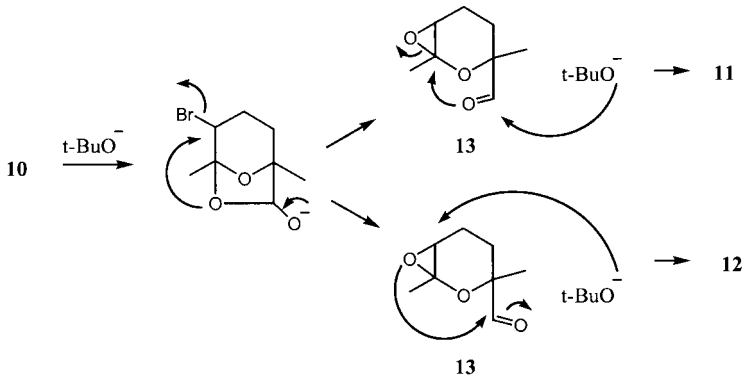
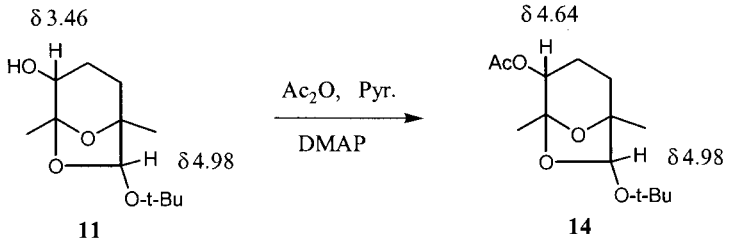


Scheme 4.

4-hydroxy acetal **11**, but attacks the epoxide and following acetalization should gives the 4-*t*-butoxy acetal **12**.

The nmr chemical shift of H-4 shows at 3.46 ppm and H-7 shows at 4.98 ppm in the product. Acetylation of the product should change the chemical shift of the hydroxy attached proton and we found the chemical shift change from 3.46 ppm to 4.64 ppm after acetylation as shown in Scheme 5. This result indicates that the right structure of debromonated *t*-butoxide product is the 4-hydroxy acetal **11**. The stereostructure of the single isomer **11** could be an equatorial because of steric effect.[9]



Scheme 5.

The reaction of bromo-lactol **10** with NaH did not give the expected product **15**, but gave mostly starting material back with some decomposed products.

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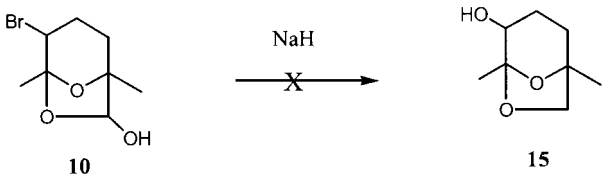

10 15

Scheme 6.

In conclusion, acetal-lactols were easily prepared and rearranged to cyclopentene or 4,7-dioxygenated acetal by using *t*-butoxide depend on substituent at C-4.

EXPERIMENTAL

The NMR spectra were recorded on a Varian Gemini-200 MHz FT-NMR, with the chemical shifts (δ) reported in parts per million (ppm) relative to TMS and the coupling constants (J) quoted in Hz. $CDCl_3$ was used as a solvent and an internal standard. Infrared spectra were recorded on a Shimadzu IR-435 spectrometer. GLC analyses were performed using a Shimadzu CG-7A equipped with a 11 ft × 1/4 in, 10% OV-17 column. Most of the chemicals were purchased from Aldrich and were used without further purification unless noted otherwise. Flash chromatography was carried out using silica gel Merck 60 (230–400 mesh). Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F_{254} (Merck, layer thickness 0.2 mm) plastic-backed silica gel plates with visualization by UV light (254 nm) or by treatment with *p*-anisaldehyde.

2-Methoxycarbonyl-2,6-dimethyl-3,4-dihydro-2H-pyran (5). A solution of methyl vinyl ketone **3** (12.0 mL, 0.14 mol), methyl metacrylate **4** (45.0 mL, 0.42 mol), hydroquinone (0.40 g, 3.63 mmol) in 150 mL of benzene was placed in a steel pressure bomb and heated at 170°C for 3 h. After cooling, the solvent was removed via a rotatory evaporator and the product was distilled to give 20.30 g of 2-methoxycarbonyl-2,6-dimethyl-3,4-dihydro-2H-pyran (**5**) and MVK dimer **6** as a 8 : 2 ratio. ^{1}H NMR ($CDCl_3$) δ 4.50 (1H, br s, =CH), 3.74 (3H, s, OCH_3), 2.15–1.93 (4H, m, CH_2CH_2), 1.79 (3H, br s, $=CCH_3$), 1.49 (3H, s, $OCCH_3$); ^{13}C NMR ($CDCl_3$) δ 172.8 (C=O), 148.2 (=C-O), 93.6 (C-O), 76.0 (C=), 50.6 (OCH_3), 28.4 (CH_3), 23.3 (CH_2), 18.4 (CH_2), 16.7 (CH_3); IR(neat): 1756 (C=O), 1687 (C=C-O), 1449, 1313, 1241, 1120, 1069 cm^{-1}.

1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octan-7-one (2). The mixture (2.0 g, 9.4 mmol) of 2-methoxycarbonyl-2,6-dimethyl-3,4-dihydro-2H-pyran (**5**)

and MVK dimer **6** as a 8 : 2 ratio was added slowly to a solution of NaOH (1.5 g, 37.5 mmol) in water (25 mL), stirred for 12 h and extracted with ether (50 mL × 3). After the ether layer which contains MVK dimer **6** was removed, the water layer was acidified with 6N HCl (20 mL) and was extracted with ether (30 mL × 4). The combined organic layer was washed with $NaHCO_3$, brine, dried over $MgSO_4$, concentrated and chromatographed (ether : hexane = 1:1) to give a yellow oil (1.4 g, 94%). ^{1}H NMR ($CDCl_3$) δ 1.85–1.60 (6H, m, $CH_2CH_2CH_2$), 1.58 (3H, s, C5-methyl), 1.42 (3H, s, C1-methyl); ^{13}C NMR ($CDCl_3$) δ 175.6 (s, C=O), 109.4 (s, O-C-O), 80.3 (s, C-O), 30.7 (t), 30.3 (t), 23.5 (q), 20.4 (q), 17.4 (t); IR (neat): 1790, 1745, 1463, 1393, 1361, 1283, 1254, 1225, 1121, 1040, 947, 897, 871, 827 cm^{-1}.

7-Hydroxy-1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (1). To a stirred solution of acetal-lactone **2** (0.1 g, 0.64 mmol) in dry THF (3 mL) at − 20°C was added DIBAH (1.50 mmol) slowly and stirred for 1 h at − 20°C. Water (30 mL) was added to the reaction bottle and extracted with ethyl acetate (30 mL × 4). The combined organic layer was washed with $NaHCO_3$, brine, dried over $MgSO_4$, concentrated and chromatographed (ethyl acetate : hexane = 2 : 1) to give a yellow oil (0.08 g, 80%). ^{1}H NMR ($CDCl_3$) δ 5.14 (1H, s), 2.61 (1H, s), 1.80–1.45 (6H, m), 1.58 (3H, s), 1.29 (3H, s); IR (neat): 3424, 1460, 1385, 1250, 1214, 1118, 999, 848, 732 cm^{-1}.

1-Acetyl-3-hydroxy-3-methylcyclopentene (7). (Method A) To a stirred solution of *t*-BuONa (0.02 g, 0.22 mmol) in *t*-BuOH (3 mL) under N_2 atmosphere was added acetal-lactol **1** (0.01 g, 0.06 mmol) and refluxed for 20 min. After evaporation of *t*-BuOH, ether (15 mL), water (2 mL) and 3N HCl (15 mL) were added to the reaction mixture and extracted with ethyl acetate (20 mL × 4). The combined organic layer was washed with $NaHCO_3$, brine, dried over $MgSO_4$, concentrated and chromatographed (ethyl acetate : hexane = 2 : 1) to give a yellow oil (0.007 g, 82%).

(Method B) To a stirred solution of NaH (0.004 g, 0.15 mmol) in dry THF (1 mL) under N_2 atmosphere at 0°C was added acetal-lactone **1** (0.02 g, 0.13 mmol) and refluxed for 30 min. Water (2 mL) was added to the reaction mixture and extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with $NaHCO_3$, brine, dried over $MgSO_4$, concentrated and chromatographed (ethyl acetate : hexane = 2:1) to give a yellow oil (0.016 g, 89%). ^{1}H NMR ($CDCl_3$) δ 6.51 (1H, br s, = CH), 2.70–2.45 (2H, m), 2.34 (3H, s, $COCH_3$), 2.05–1.95 (2H, m), 1.67 (1H, br s, OH), 1.44 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 198.1 (C = O), 147.6 (= CH), 145.2 (= C), 84.0 (COH), 40.0 (CH_2), 29.3 (CH_2), 27.3 (CH_3), 27.2 (CH_3); IR (neat): 3453 (OH), 1663 (C = O), 1376, 1294, 1102, 1086, 930 cm^{-1}. Ms *m*/*z* 140 (M^+), 125, 122 (base), 107, 97, 84, 79, 61.

4-Bromo-1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octan-7-one (9). (Halolactonization Method); The mixture[8] (0.5 g, 2.94 mmol) of 2-methoxycarbonyl-2,6-dimethyl-3,4-dihydro-2H-pyran (**5**) and MVK dimer **6** as a

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8 : 2 ratio was added slowly to a solution of NaOH (0.47 g, 11.75 mmol) in water (15 mL), stirred for12 h and extracted with ether (30 mL × 3). After the ether layer which contains MVK dimer **4** was removed, the water layer was evaporated to dryness and mixed with aqueous $NaHCO_3$ (0.75 g, 8.82 mmol). After 30 min stirring, Br_2 (0.15 mL, 2.94 mmol) was added to the aqueous layer and stirred for 3 h at rt and extracted with methylene chloride (30 mL × 4). The combined organic layer was washed with 10% aqueous $Na_2S_2O_3$, brine, dried over $MgSO_4$, concentrated and chromatographed (ether : hexane = 1:1) to give a pale yellow solid (0.42 g, 71%).

(Direct Bromination); To a stirred solution of Na_2CO_3 (0.24 g, 2.24 mmol) in CCl_4 (10 mL) under N_2 atmosphere were slowly added acetal-lactone **2** (0.10 g, 0.64 mmol) and Br_2 (0.04 mL, 0.7 mmol), and stirred for 3 h at rt. Water (13 mL) was added to the reaction mixture and extracted with methylene chloride (30 mL × 4). The combined organic layer was washed with 10% aqueous $Na_2S_2O_3$, brine, dried over $MgSO_4$, concentrated and chromatographed (ether : hexane = 1:1) to give a pale yellow solid (0.11 g, 73%). mp 72–75°C, ^{1}H NMR ($CDCl_3$) δ 4.13 (1H, br d, BrCH), 2.4–1.6 (4H, m), 1.77 (3H, s, C5-Me), 1.50 (3H, s, C1-Me); IR (KBr): 1808 (C = O), 1449, 1411, 1278, 1252, 1164, 1127, 1079, 1037, 890, 860, 823, 767 cm^{-1}.

4-Bromo-7-hydroxy-1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (10). To a stirred solution of bromo-lactone **9** (0.1 g, 0.43 mmol) in dry THF (2.5 mL) at −20°C was added DIBAH (1.06 mmol) slowly and stirred for 1 h at −20°C. Water (30 mL) was added to the reaction bottle and extracted with ether (30 mL × 4). The combined organic layer was washed with $NaHCO_3$, brine, dried over $MgSO_4$, concentrated and chromatographed (ethyl acetate : hexane = 2 :1) to give a white solid (0.075 g, 75%). mp 120–122°C, ^{1}H NMR ($CDCl_3$) δ 5.03 (1H, br d, HOCH), 3.93 (1H, br d, BrCH), 2.61 (1H, br d, OH), 2.4–2.3 (2H, m), 2.1–1.9 (2H, m), 1.66 (3H, s, C5-Me), 1.35 (3H, C1-Me); IR (KBr): 3361 (OH), 1467, 1383, 1262, 1196, 1125, 982, 856 cm^{-1}.

7-*t*-Butoxy-4-hydroxy-1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octane (11). To a stirred solution of *t*-BuONa (0.28 g, 2.95 mmol) in *t*-BuOH (20 mL) under N_2 atmosphere was added bromo-lactol **10** (0.20 g, 0.84 mmol) and refluxed for 5 h. After evaporation of *t*-BuOH, 3N HCl (15 mL) were added to the reaction mixture and extracted with ethyl acetate (20 mL × 4). The combined organic layer was washed with $NaHCO_3$, brine, dried over $MgSO_4$, concentrated and chromatographed (ethyl acetate : hexane = 2 :1) to give a yellow oil (0.12 g, 63%). ^{1}H NMR ($CDCl_3$) δ 4.98 (1H, s, C7-H), 3.46 (1H, dd, J = 9 and 7 Hz, C4-H), 1.9–1.75 (3H, m, CH_2 and OH), 1.6–1.4 (2H, m), 1.45 (3H, s, C5-Me), 1.25 (9H, s, *t*-butyl), 1.19 (3H, s, C1-Me); ^{13}C NMR ($CDCl_3$) δ 107.8 (5-C), 102.4 (7-CH), 80.2 (1-C), 75.3 (O-*t*-butyl C), 71.6 (4-CH), 31.1 (3-CH_2), 28.7 (*t*-butyl Me_3), 28.2 (2-CH_2), 22.0

(5-CH_3), 21.9 (1-CH_3); IR (neat): 3436 (OH), 1451, 1391, 1368, 1207, 1134, 1075, 994, 882 cm^{-1}. CIMs (NH_3) *m*/*z* 248.

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