Study on the Novel Rearrangement Reaction of Bicyclic Acetal Compound by Using AcCl-NaI

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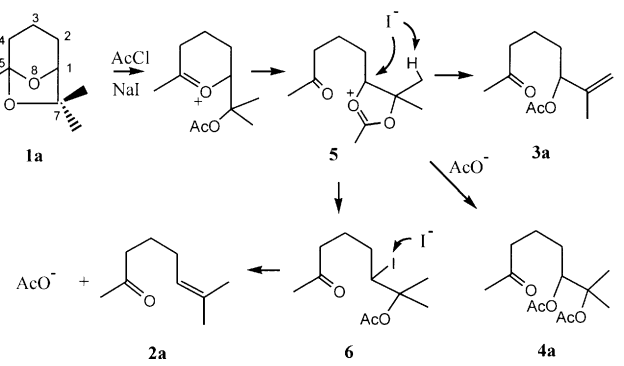
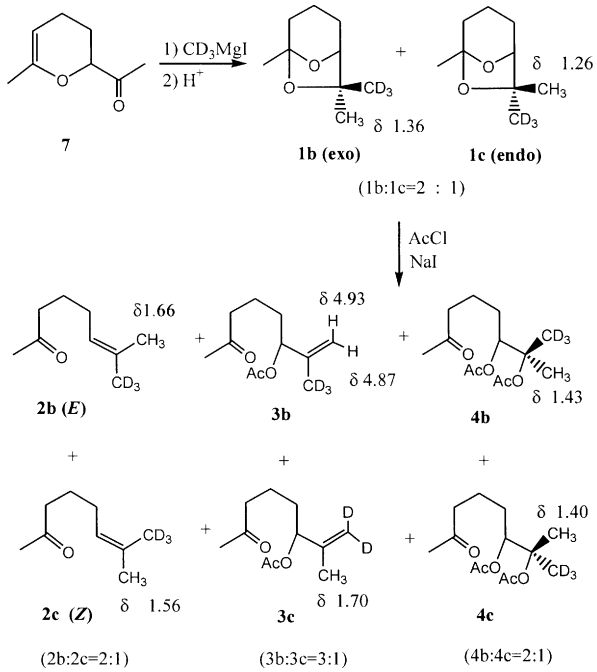
The selective C-O bond cleavage has been well documented[1] because it is not only important but also variable depending on the structure of starting materials. In the 6,8-dioxabicyclo[3.2.1]octane system, the preferable interaction of the O6 towards Lewis acid followed by the C5-O6 bond cleavage has been known by the lanthanide-induced shift studies.[2] Another reasonable explanation for the reaction preference may reside not in the site of initial attack, but rather in the notion that the anomeric effects of the O8 oxygen may help the displacement of the O6 oxygen considerably better than the O8.[3] This hypothesis for the preference of C5-O6 bond cleavage has been proved by the 1,2-hydride shift reaction.[4]

Recently, we found interesting results in the transformation reaction of bicyclic acetal compound by using AcCl-NaI.[5] 7-Methyl-6-octen-2-one (**2a**, 16%) 6-acetoxy-7-methyl-7-octen-2-one (**3a**, 37%), and 6,7-diacetoxy-7-methyl-2-octanone (**4a**, 16%) were prepared from the bicyclic acetal **1a** and the formation mechanisms similar to that used by Goldsmith[6] for ether cleavage were also proposed as shown in Scheme 1. The 5-membered acetoxonium intermediate **5**, which was formed through selective C5-O6 bond cleavage, was the key and common intermediate for the products **2a**, **3a** and **4a**. The enone **2a** was formed via regioselective nucleophilic attack of iodide ion (secondary vs tertiary carbon) followed by deiodo-olefination. The acetate anion was also produced during this process and used as a nucleophile on the intermediate **5** to make diacetate **4a**. The monoacetated ethylene **3a** was formed from the elimination reaction of the intermediate **5** by the iodide or acetate ion as a base.

For clear explanation for these transformation mechanisms, we introduced deuterated methyl at C7 as a 2 : 1 ratio of exo-



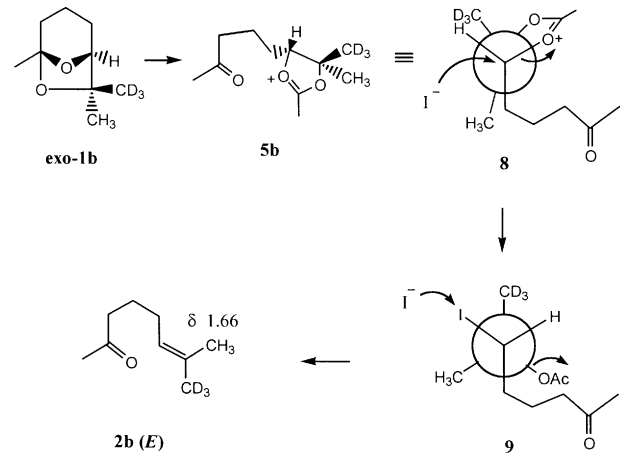
Scheme 1



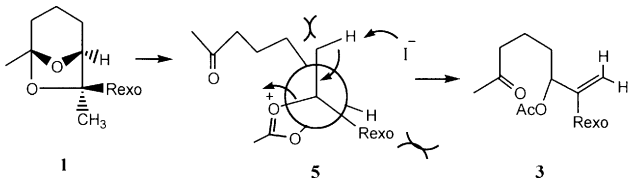
Scheme 2

acetal **1b** and endo-acetal **1c** from the methyl vinyl ketone (MVK) dimer **7** (Scheme 2). The exo-preference by using Grignard reagent in this system has been known.[3,7] The ratio of exo- and endo-acetal was determined by the integration of the chemical shift at 1.36 and 1.26 in ^{1}H NMR. The proton chemical shift of the endo-methyl in the bicyclic acetal system is known to show at more downfield than those of the exo-methyl by ~0.1 ppm.[8] The exo- and endo-acetal mixture were reacted with AcCl-NaI in acetonitrile to give the enones **2b** (*E*) and **2c** (*Z*) as a 2 : 1 ratio, the ethylenes **3b** and **3c** as a 3 : 1 ratio and the diacetates **4b** and **4c** as a 2 : 1 ratio.

The *E*-enone **2b** should be formed from the exo-acetal **1b** as known for the formal synthesis of Sirenin.[9] The transformation mechanism, which was proposed in the wrong concept before,[3] could be explained by the model structure using Newman projection as shown in Scheme 3. The model of the intermediate **5b** shows the eclipsed conformation **8** and the iodide ion attacks as S_N2 mode to give the staggered conformation **9**. Elimination (E2) reaction proceeded in anti-periplanar mode (I-C-C-OAc) of the conformation **9** and only gave the *E*-enone **2b**. The iodide ion is a key nucleo-



Scheme 3



Scheme 4

phile to make the double bond in this system and, therefore, the enone **2a** is not formed from **1a** without iodide ion.

The monoacetated ethylenes **3b** and **3c** were formed as a 3 : 1 ratio rather than the expected 2 : 1 ratio, but we could propose that **3b** was formed from **1b** and **3c** from **1c**, because that dedeuteration is much slower than dehydrogenation by isotope effect.[10] The stability of the intermediate **5** prefers the bulkier exo-substituent by steric reason and the elimination occurs at endo-proton *via* anti-periplanar conformation to give the allylic acetate[11] (Scheme 4). This hypothesis has been proved: the expected phenyl substituted ethylene **3** (R=Ph) was not obtained from the endo-acetal, but obtained from the exo-acetal **1** (R_{exo}=Ph).

The diacetates **4b** and **4c** were obtained from **1b** and **1c** respectively by the acetate ion reacting as a nucleophile in S_N2 process. The addition of the acetate ion in the reaction could improve the formation of the products **3** and **4** over **2** and the increased reaction temperature should prefer the eliminated product **3** over the diacetate **4**.

From this mechanistic studies for the formation of three products **2-4**, we could control the reaction condition to make the single product and are now under investigation which shows the promising result to make only the monoacetated ethylene **3** in high yield.

Experimental Section

The NMR spectra were recorded on a Bruker 250 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. Mass spectra were obtained using VG MM16 mass spectrometer and accurate mass data were obtained using a VG 7070 high resolution mass spectrometer. GLC analyses were performed using a Varian Aerograph series 2700 gas chromatograph 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.

exo/endo-7-Deuteriomethyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (1b)/(1c). Iodomethane-d_3 (2.50 g, 0.017 mol) was slowly added to 0.420 g (0.017 mol) of magnesium in 25 mL dry ether under nitrogen. After 2 h stirring at rt, the reaction was cooled to 0 °C and 1.820 g (0.013 mol) of MVK dimer **7** in 5 mL dry ether was added via syringe. The reaction mixture was allowed to warm to rt and was stirred for 16 h, after which the reaction was quenched with 25 mL of 5% aqueous HCl solution. The reaction mixture was extracted with three 30 mL portions of ether which were combined, washed with saturated brine, dried over anhydrous magnesium sulfate and reduced in volume *via* the rotatory evaporator. It was then chromatographed through a silica gel column using petroleum ether : ethyl acetate (7 : 3) as an eluent to give 1.480 g (71.6%) of exo/endo mixture as 2 : 1 ratio. ^{1}H NMR ($CDCl_3$): δ 3.87 (1H, br s, C1-H), 2.00-1.45 (6H, m), 1.40 (3H, s, C5-CH_3), 1.36 (2H, s, C7-endoCH_3), 1.26 (1H, s, C7-exoCH_3). MS m/z 159 (M^+), 117, 98, 89, 71, 43 (base). HRMS Found: 159.1339. $C_9H_{13}O_2D_3$ calcd.: 159.1338.

Procedure using AcCl-NaI. Acetyl chloride (0.46 mL, 6.4 mmol) in 10 mL of clean, dry acetonitrile was slowly added dropwise, via an additional funnel, to a solution of sodium iodide (0.96 g, 6.4 mmol) and bicyclic acetal **1b/1c** (0.50 g, 3.2 mmol) stirring at 0 °C in 20 mL of acetonitrile. The resulting solution was stirred at rt for 24 h and quenched by adding 15 mL of aqueous sodium bisulfite. The reaction mixture was then extracted with ether (50 mL×3), washed with aqueous sodium thiosulfate, aqueous sodium bicarbonate, brine and water, dried over anhydrous magnesium sulfate and reduced in volume. The crude dark black material was then passed through a Buchner funnel containing silica gel topped with Florisil under water aspirator until the color changed to pale brown, when it was then chromatographed through a silica gel column using petroleum ether:ethyl acetate (7 : 3) as an eluent to give **2b/2c** (0.072 g, 15.9%), **3b/3c** (0.24 g, 37.3%) and **4b/4c** (0.13 g, 16%).

(*E*/*Z*)-7-Deuteriomethyl-6-octen-2-one (2b/2c). ^{1}H NMR ($CDCl_3$): δ 5.06 (1H, br t, *J*=7.5 Hz, H-6), 2.39 (2H, t, *J*=7.5 Hz, $COCH_2$), 2.11 (3H, s, CH_3CO), 2.00-1.95 (2H, m, CH_2C=C), 1.66 (2H, s, (*Z*)-CH_3C=C), 1.56 (1H, s, (*E*)-CH_3C=C), 1.60-1.50 (2H, m, CH_2). IR (neat): 1700 (C=O), 1650 (C=C), 1420, 1360, 1160 cm^{-1}. MS m/z 143 (M^+), 85 (base), 69, 43.

6-Acetoxy-7-deuteriomethyl-7-octen-2-one(3b)/6-Acetoxy-8,8-dideuterio-7-methyl-7-octen-2-one (3c). ^{1}H NMR ($CDCl_3$):

δ 5.14 (1H, t, *J*=5.5 Hz, H-6), 4.93 (0.75H, br s, C=CH), 4.87 (0.75H, br s, C=CH), 2.43 (2H, t, *J*=7 Hz, $COCH_2$), 2.12 (3H, s, CH_3CO), 2.04 (3H, s, $OCOCH_3$), 1.70 (0.75H, br s, CH_3C=C), 1.7-1.5 (4H, m, CH_2CH_2). MS m/z 159 (M^+-CH_2CO), 141, 98, 43 (base).

7-Deuteriomethyl-6,7-Diacetoxy-2-octanone (4b/4c). ^1H NMR ($CDCl_3$): δ 5.15 (1H, m, H-6), 2.43 (2H, m, $COCH_2$), 2.12 (3H, s, CH_3CO), 2.08 (3H, s, $OCOCH_3$), 1.94 (3H, s, $OCOCH_3$), 1.7-1.5 (4H, m, CH_2CH_2), 1.43 (2H, s, endo-CH_3), 1.40 (1H, s, exo-CH_3). MS m/z 159 (M^+-$2CH_2CO$-H_2O), 141, 115, 97, 62, 43 (base).

6-Acetoxy-7-phenyl-7-octen-2-one (3). ^1H NMR ($CDCl_3$): δ 7.45-7.18 (5H, m), 5.69 (1H, br s, H-6), 5.30 (1H, s, C=CH), 5.28 (1H, s, C=CH), 2.37 (2H, br s, $COCH_2$), 2.13 (3H, s, CH_3CO), 2.08 (3H, s, $OCOCH_3$), 1.60 (4H, br s, CH_2CH_2). ^{13}C NMR ($CDCl_3$): 206.8 (C=O), 168.7 (ester C=O), 146.4 (=C), 137.7 (=C), 126.8 (2 =CH), 126.2 (=CH), 125.3 (2 = CH), 112.3 (=CH_2), 73.3 (C-OAc), 41.4, 31.3, 28.1, 19.6, 17.8. IR(neat): 3082 (=C-H), 1743 (ester C=O), 1720 (C=O), 1655 (C=C), 1494, 1371, 1244, 1162, 1024, 912 cm^{-1}.

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