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Selective transformation reaction of 6,8-dioxabicyclo[3.2.1]octane structure to δ,ε-enone and application to the synthesis of Douglas-fir tussock moth pheromone

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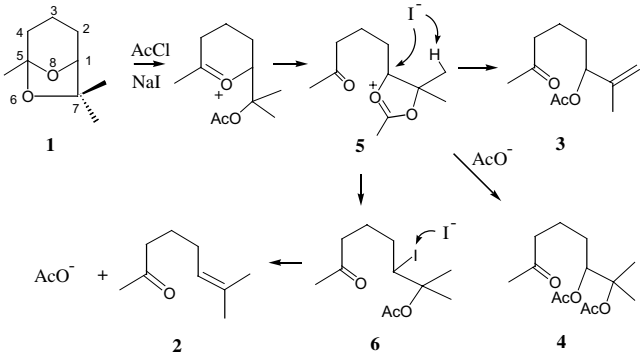
Abstract—Lewis acid induced C–O bond cleavage of a bicyclic ketal compound using AcCl–NaI produced a mixture of δ,ε-enone, allylic acetate and diacetate derivatives via a common 5-membered acetoxonium intermediate. A selective method to the synthesis of δ,ε-enone in high yield was introduced and applied to the synthesis of Douglas-fir tussock moth pheromone.

The selective C–O bond cleavage of the 6,8-dioxabicyclo[3.2.1]octane (**1**) system using many Lewis acids has been known.[1] The preferable interaction of the O6 toward most Lewis acids followed by the C5–O6 bond cleavage was favored.[2] The lanthanide-induced shift studies[3] and the anomeric effects of the O8 oxygen may help understanding of this preference.[4]

The selective C–O bond cleavage of a bicyclic ketal **1** followed by rearrangement reaction in different conditions produced so many interesting results.[1,5] One of the results showed a mixture of 7-methyl-6-octen-2-one (**2**, 16%), 6-acetoxy-7-methyl-7-octen-2-one (**3**, 37%), and 6,7-diacetoxy-7-methyl-2-octanone (**4**, 16%) by using AcCl–NaI as shown in Scheme 1.[6] We proposed the mechanism of this rearrangement reaction as follows; the 5-membered acetoxonium intermediate **5**, which was formed through selective C5–O6 bond cleavage, was the key and common intermediate for the products **2**, **3**, and **4**. The δ,ε-enone **2** was formed via a 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 in the intermediate **5** to make diacetate **4**. The allylic acetate **3** was formed from the elimination reaction of the intermediate **5** by the iodide ion as a base.



Scheme 1. Transformation mechanism of bicyclic ketal.

From these mechanistic studies for the formation of three products **2**–**4**, we could control the reaction condition to make the single product in high yield. The acetate anion using as a nucleophile in the acetoxonium intermediate could produce the diacetate **4**, but as a base to eliminate the terminal methyl proton followed by acetoxonium ring opening produce the allylic acetate **3**. The reaction conditions for the selective synthesis of the allylic acetate **3** and the diacetate **4** were found by using $MgBr_2$–Ac_2O–NaOAc[7] and $FeCl_3$–Ac_2O,[8] respectively (Table 1).

We focused our efforts on the selective synthesis of δ,ε-enone **2**, which had demonstrated to be a useful structure for the natural product synthesis such as sirenin[9] and Douglas-fir tussock moth pheromone[10] etc. for

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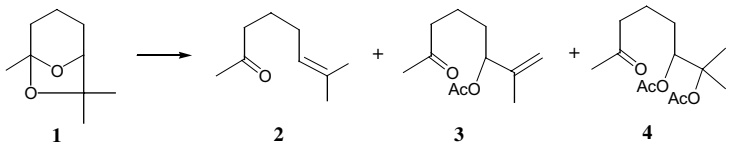
Table 1. Synthesis of enone, allylic acetate, and diacetate



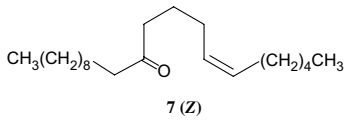
1 **2** **3** **4**

Reagents	**2** (%)	**3** (%)	**4** (%)
AcCl–NaI	16	37	16
$MgBr_2$–Ac_2O–NaOAc	0	85	0
$FeCl_3$–Ac_2O	0	0	84
AcCl–NaI–AcOH/CH_3CN	90	0	3

several years. In most experiments, we failed to make the enone as a single, high yield product and only found to get the mixture, low yield and other products. According to our previous experience and the proposed mechanism, the iodide anion was essential to produce the enone **2**. We examined various reaction conditions and finally found an effective condition for the selective synthesis of δ,ε-enone **2** from the bicyclic ketal in one-step.

The reaction of bicyclic ketal **1** and AcCl(2.5 equiv)-NaI (6 equiv)-AcOH(10 equiv) in acetonitrile at 40 °C for 24 h afforded the desired enone **2** in 90% yield with a trace amount of diacetate **4**.[11] The amount of AcOH used in this reaction was the most important. The small amount of AcOH (0–8 equiv) produced the low yield of enone with the mixture **3** and **4** and the large amount (more than 30 equiv) gave no completion of this reaction. We found that the 10–20 equiv of AcOH used in this reaction gave the best yield of enone **2**. We think that the AcOH in this reaction dramatically diminishes the deprotonation of intermediate **5** to give the allylic acetate **3** and also prevents the acetate ion from attacking intermediate **5** to produce the diacetate **4**.

The Douglas-fir tussock moth (*Orgyia pseudotsugata*) is a pernicious defoliator of the fir trees of the Northwestern United States.[12] The active pheromone constituent has been identified as (*Z*)-6-heneicosen-11-one **7** (Fig. 1). It has also been found that a 60:40 (*E*/*Z*) mixture of the 6-heneicosen-11-one was considerably more active



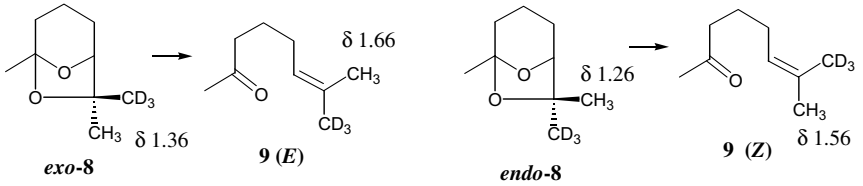
7 (*Z*)

Figure 1.

as a pheromone than pure material isolated from female tussock moths.[13]

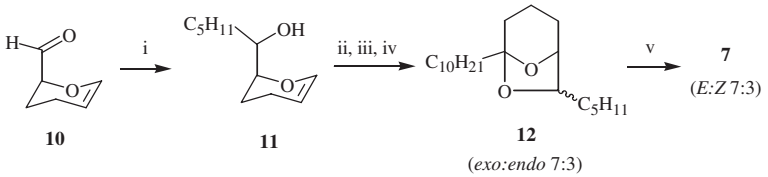
From the previous deuterium labeled experiment, we confirmed that the *exo*-ketal **8** produced *E*-enone **9** and the *endo*-ketal **8** did *Z*-enone **9** selectively (Scheme 2), and reported the mechanism of this stereospecific transformation reaction.[14] This previous result and a newly developed selective enone synthesis made us synthesize Douglas-fir tussock moth pheromone to prove the utility of this methodology.

The preparation of the requisite bicyclic ketal was achieved by a modification of the Cohen synthesis of brevicomin.[15] The dimer of acrolein **10** was treated with 2 equiv of *n*-pentylmagnesium bromide to yield **11** (76%, Scheme 3). Alkylation of the enol ether carbon was achieved by the method of Boeckman and Bruza,[16] where *tert*-butyllithium (2.5 equiv) was added to **11**, followed by a decyl iodide (2 equiv), and the reaction product was cyclized with 6 N HCl without purification to a 70:30 mixture of *exo*/*endo* **12** in 85% yield. Fragmentation of the bicyclic ketal **12** with AcCl(2.5 equiv)-NaI



exo*-8** **9** (E***) ***endo*-8** **9** (***Z***)

Scheme 2. Deuterium labeled experiment of bicyclic ketal to enone.



10 **11** **12** (*exo*:*endo* 7:3) **7** (*E*:*Z* 7:3)

Scheme 3. Reagents: (i) $C_5H_{11}MgBr$; (ii) *t*-BuLi; (iii) $C_{10}H_{21}I$; (iv) H^+; (v) AcCl, NaI, AcOH.

(8 equiv)-AcOH(20 equiv) in acetonitrile at 80 °C for 24 h gave the (*E*)/(*Z*) [70:30] mixture of 6-heneicosen-11-ones in 73% yield.[17]

In conclusion, the δ,ε-enone was selectively prepared from the bicyclic ketal directly by using AcCl–NaI–AcOH in acetonitrile, and this method was successfully applied to the synthesis of Douglas-fir tussock moth pheromone.

Acknowledgments

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11. *Typical experimental procedure*: to a solution of NaI (580 mg, 11.5 mmol) in acetonitrile (2 mL), AcOH (1.10 mL, 19.2 mmol), AcCl (0.11 mL, 1.60 mmol), and bicyclic ketal **1** (100 mg, 0.64 mmol) dissolved in acetonitrile (2 mL) were added successively at 0 °C under nitrogen atmosphere, and stirred for 24 h at 40 °C. The reaction mixture was cooled, diluted with aqueous $NaHSO_3$, extracted with ether, washed successively with $Na_2S_2O_3$, $NaHCO_3$, and brine, dried with $MgSO_4$, removal of solvent, and column chromatographic purification (hexane) afforded the desired enone **2** as a colorless oil, 80.7 mg (90%). R_f 0.72 (hexane/EtOAc, 9:1); IR (KBr) 1700 (C=O), 1650 (C=C), 1420, 1360, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 3H, *E* methyl), 1.58–1.68 (m, 2H, *C*4 methylene), 1.69 (s, 3H, *Z* methyl), 1.98 (q, $J = 7.2$ Hz, 2H, *C*5 methylene), 2.12 (s, 3H, methyl ketone), 2.40 (t, $J = 7.4$ Hz, 2H, *C*3 methylene), 5.60 (br t, $J = 7.2$ Hz, 1H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0 ($C8_E$), 24.3 (*C*4), 26.0 ($C8_Z$), 27.7 (*C*5), 30.2 (*C*1), 43.5 (*C*3), 123.9 (*C*6), 132.5 (*C*7), 209.5 (*C*2).
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17. The isomeric ratio of the bicyclic ketal **12** and the enone **7** was determined by the integration of ^1H NMR. The spectroscopic data of **12**: 85%, yellow liquid; R_f 0.60 (hexane/EtOAc, 9:1); ^1H NMR (300 MHz, $CDCl_3$) δ 0.80–0.98 (br t, 6H, strongly coupled methyls), 1.20–1.45 (br s, 26H), 1.50–1.60 (m, 4H), 1.70–1.95 (m, 2H), 3.98 (m, 1H, *C*1 methine), 4.05 (br s, 0.7H, *exo* methine), 4.10 (br s, 0.3H, *endo* methine). The spectroscopic data of **7**: 73%, colorless oil; R_f 0.62 (hexane/EtOAc, 9:1); IR (KBr) 1718 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80–0.98 (br t, 6H, strongly coupled methyls), 1.18–1.40 (br s, 22H), 1.50–1.70 (m, 4H), 1.90–2.10 (m, 4H), 2.35–2.45 (m, 2H), 5.08 (br s, 0.6H, *cis* HC=CH), 5.35 (br s, 1.4H, *trans* HC=CH).