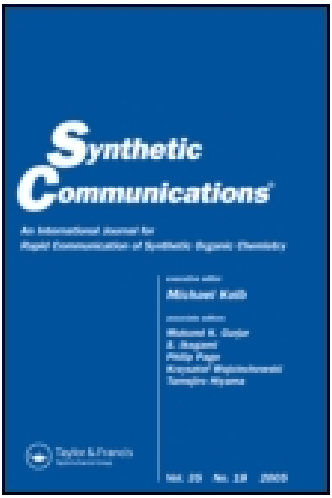

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TRANSKETALIZATION AND REGIOSELECTIVE ALDOL CONDENSATION IN BICYCLIC KETAL SYSTEM

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TRANSKETALIZATION AND REGIOSELECTIVE ALDOL CONDENSATION IN BICYCLIC KETAL SYSTEM

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ABSTRACT

A convenient one-pot transketalization reaction of bicyclic ketal compound was obtained by using NaI-AcCl in ketone, and a regioselective aldol condensation of bicyclic ketal compound was also made by using NaI-TMSCl in acetonitrile.

A versatile character and utility of bicyclic ketals in the 6,8-dioxabicyclo[3.2.1]octane structure have been reported forming into alkenone,[1] diketone,[2] cyclopentanediol,[3] pyridines,[4,5] cyclohexenone,[6] and allylic acetate derivatives.[7] In the continuous study of reagent/reactions that would provide new chemistry, we found new entries into transketalization by using NaI-AcCl-Acetone and regioselective aldol condensation by using NaI-TMSCl-CH_3CN.

The reagent system NaI-AcCl, has been used for the synthesis of δ, ε-unsaturated ketone[1] directly from the bicyclic ketal in ~20% yield and applied for the synthesis of the Douglas fir tussock moth pheromone.[8] An interesting result was found from the reaction study to improve the yield.

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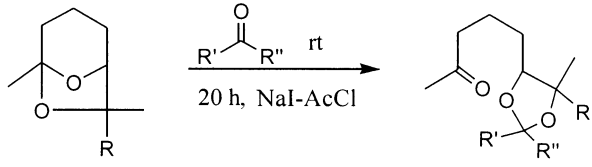
One-pot transketalization from the bicyclic ketal **1a** into **2a** in 75% yield was obtained in the reaction condition of NaI-AcCl in acetone at room temperature for 20 h (Scheme 1). The derivatives of ketal **1b–1d** also gave the expected results even though the yield of i-Pr (**1b**) and phenyl (**1d**) derivatives was low. 2-Butanone and cyclohexanone were used instead of acetone to give the expected acetals **2e** and **2f** in 28% and 8% yield, respectively. This result showed a convenient and mild transketalization reaction by using NaI-AcCl-ketone in bicyclic ketal system.



1 **2**

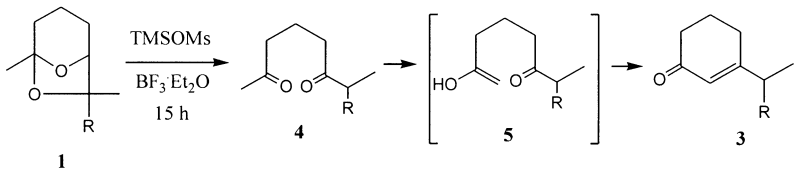
Entry	R	Ketone **1**	Yield (%)
a	Me	acetone	75
b	i-Pr	acetone	20
c	t-Bu	acetone	77
d	Ph	acetone	26
e	Me	2-butanone	28
f	Me	cyclohexanone	8

Scheme 1.

Conjugated cyclohexenones **3** were reported as the only products in a one-flask reaction from the ketal **1** through the aldol condensation of 1,5-diketone **4** via the terminal enol **5** by using TMSOMs-BF_3·Et_2O (Scheme 2).[6] The formation mechanism of the diketone **4** from the ketal **1** has been proposed, and proved by the deuterium labeled experiment in our lab.[9] The aldol condensation of the diketone **4** to give the cyclohexenone **3** was a well-known reaction, but the regioselective aldol condensation via the internal enol **6** to give the unconjugated cyclohexenone **7** was unusual (Scheme 3). We found that this unusual internal enol intermediate was favored in NaI-TMSCl reagent system.

Iodotrimethylsilane has been reported as a useful ether-cleaving agent.[10–13] An important feature of the reagent is its cleavage pattern with dialkyl ethers, which is somewhat different from that of boron halides. However, its hydrolytic susceptibility, sensitivity in air, and decomposition on prolonged storage are undesirable. Due to these difficulties, in situ generation of iodotrimethylsilane from NaI-TMSCl was developed.[14,15]

Interestingly, unconjugated cyclohexenone **7a** was produced directly from the bicyclic ketal **1a** in 80% yield by using NaI-TMSCl in acetonitrile at reflux for 20 h. But the ketal derivatives **1b** (R=i-Pr), **1c** (R=t-Bu), and **1d** (R=phenyl) yielded only the 1,5-diketones, **4b** (68%), **4c** (67%), and **4d** (40%), respectively instead of the expected unconjugated cyclohexenones, **7b–d**. No further reaction resulted after 48 h reflux in this reagent system, but the conjugated cyclohexenones, **3b** (83%), **3c** (88%), and **3d** (72%) were easily obtained within 15 h reflux by using TMSOMs-$BF_3{\cdot}Et_2O$. This result indicates that the internal enols **6b–d** were favored in NaI-TMSCl reagent system, even though the steric congestion of the internal enols did not allow the aldol condensation that would give the unconjugated cyclohexenones. In conclusion, the different behavior of NaI-TMSCl reagent from that of boron halides shows not only in ether cleavage reaction, but also in the formation of enolate.

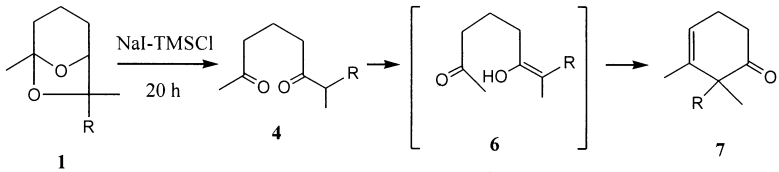


		Yield (%)	
Entry	R	**3**	**4**
a	Me	80	0
b	i-Pr	83	0
c	t-Bu	88	0
d	Ph	72	0

Scheme 2.

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 GC-7A equipped with a 11-ft×1/4-inch, 10% OV-17 column. Most of the chemicals were purchased from Aldrich and were used without further purification unless noted otherwise. Flash chromatography was



		Yield (%)	
Entry	R	7	4
a	Me	80	0
b	i-Pr	0	68
c	t-Bu	0	67
d	Ph	0	40

Scheme 3.

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.

Typical Procedure for the Preparation of Dioxolane 2 from Bicyclic Ketal 1

To a solution of dry sodium iodide (0.10 g, 0.67 mmol) in acetone (15 mL) under nitrogen atmosphere at 0°C was added slowly acetyl chloride (0.02 mL, 0.29 mmol) and stirred for 10 m. Bicyclic ketal **1a** (0.03 g, 0.19 mmol) was added to the solution and stirred for 20 h at room temperature. The reaction was quenched by the addition of 10% aqueous sodium bisulfite solution (10 mL). The organic product was extracted with ethyl acetate (3 × mL) and washed with saturated sodium bicarbonate (30 mL) and saturated brine (30 mL). The solvent was dried over magnesium sulfate and removed via a rotary evaporator. Flash chromatography (ether:hexane=1:1) yielded the dioxolane **2a** (0.03 g, 75% yield).

2,2,4,4-Tetramethyl-5-(4-petanoyl)-1,3-dioxolane (**2a**)

^{1}H NMR ($CDCl_3$) δ 3.66 (1H, dd, J=9 and 4 Hz, C5-H), 2.50 (2H, m, C3′-H), 2.15 (3H, s, C5′-H), 1.90–1.40 (4H, m, C1′ and C2′-H), 1.44 (3H, s,

C2-methyl), 1.33 (3H, s, C2-methyl), 1.24 (3H, s, C4-methyl), 1.08 (3H, s, C4-methyl); ^{13}C NMR ($CDCl_3$) δ 209.9 (C=O), 106.9 (C2), 83.6 (C5), 80.5 (C4), 43.8 (C3′), 30.3 (C5′), 29.1 (C1′), 28.9 (C2-methyl), 27.2 (C2-methyl), 26.3(C4-methyl), 23.2 (C4-methyl), 21.7 (C2′); IR(neat): 2942, 1714 (C=O), 1371, 1235, 1201, 1115, 1007, 912, 733 cm^{-1}.

4-Isopropyl-2,2,4-trimethyl-5-(4-pentanoyl)-1,3-dioxolane (**2b**)

^{1}H NMR ($CDCl_3$) δ 3.79 (1H, dd, J=8 and 4 Hz, C5-H), 2.50 (2H, br t, J=7 Hz, C3′-H), 2.15 (3H, s, C5′-H), 1.90–1.40 (5H, m, C1′, C2′ and C4-isopropyl H), 1.41 (3H, s, C2-methyl), 1.30 (3H, s, C2-methyl), 1.00 (3H, s, C4-methyl), 0.94 (3H, d, J=14 Hz, C4-isopropyl-methyl), 0.91 (3H, d, J=14 Hz, C4-isopropyl-methyl); ^{13}C NMR ($CDCl_3$) δ 208.9 (C=O), 106.4 (C2), 84.7 (C5), 81.2 (C4), 43.4 (C3′), 36.4 (isopropyl C), 30.2 (C5′), 29.9 (C1′), 28.9 (C2-methyl), 26.9 (C2-methyl), 21.8 (C2′), 18.0 (C4-methyl), 17.8 (isopropyl-methyl), 17.5 (isopropyl-methyl); IR(neat): 2981, 1716 (C=O), 1373, 1273, 1215, 1093, 920, 912, 732 cm^{-1}.

4-t-Butyl-2,2,4-trimethyl-5-(4-pentanoyl)-1,3-dioxolane (**2c**)

^{1}H NMR ($CDCl_3$) δ 3.94 (1H, m, C5-H), 2.52 (2H, m, C3′-H), 2.16 (3H, s, C5′-H), 1.90–1.40 (4H, m, C1′ and C2′-H), 1.47 (3H, s, C2-methyl), 1.37 (3H, s, C2-methyl), 1.27 (3H, s, C4-methyl), 0.98 (9H, s, *t*-butyl); ^{13}C NMR ($CDCl_3$) δ 207.4 (C=O), 104.5, (C2), 84.7 (C5), 76.9 (C4), 41.8 (C3′), 34.1 (*t*-butyl-C), 29.1 (C5′), 28.2 (C1′), 27.4 (C2-methyl), 25.1 (C2-methyl), 24.5 (3×C, *t*-butyl), 20.4 (C4-methyl), 15.7 (C2′); IR(neat): 2980, 1719 (C=O), 1371, 1257, 1218, 1091, 1012 cm^{-1}.

4-Phenyl-2,2,4-trimethyl-5-(4-pentanoyl)-1,3-dioxolane (**2d**)

^{1}H NMR ($CDCl_3$) δ 7.50–7.25 (5H, m, phenyl), 3.81 (1H, t, J=6 Hz, C5-H), 2.46 (2H, br t, J=6 Hz, C3′-H), 2.11 (3H, s, C5′-H), 1.90–1.40 (4H, m, C1′ and C2′-H), 1.54 (3H, s, C4-methyl), 1.45 (3H, s, C2-methyl), 1.43 (3H, s, C2-methyl); ^{13}C NMR ($CDCl_3$) δ 207.1 (C=O), 142.7 (C1′-phenyl), 126.7 (2×C3′-phenyl), 125.5 (C4′-phenyl), 123.3 (2×C2′-phenyl), 105.8 (C2), 82.4 (C5), 82.1 (C4), 41.6 (C3′), 28.2 (C5′), 27.0 (C2-methyl), 26.6 (C2-methyl), 24.7 (C1′), 20.6 (C4-methyl), 19.8 (C2′); IR(neat): 3061, 2938, 1718 (C=O), 1622, 1495, 1447, 1372, 1241, 1218, 1108, 1116, 1067, 1004, 762, 700 cm^{-1}.

2-Ethyl-2,4,4-trimethyl-5-(4-pentanoyl)-1,3-dioxolane (**2e**)

^{1}H NMR ($CDCl_3$) δ 3.67 (1H, m, C5-H), 2.51 (2H, t, J=8 Hz, C3′-H), 2.16 (3H, s, C5′-H), 2.00–1.40 (6H, m, C1′, C2′-H and C2-ethyl), 1.35 (3H, s, C2-methyl), 1.26 (3H, s, C4-methyl), 1.10 (3H, s, C4-methyl), 0.91 (3H, t, J=8 Hz, C2-ethyl-methyl); ^{13}C NMR ($CDCl_3$) δ 209.0 (C=O), 108.8 (C2), 83.6 (C5), 80.1 (C4), 43.5, 34.1, 32.9, 28.9, 26.7, 26.0, 25.6, 24.2, 21.5; IR(neat): 2975, 1713 (C=O), 1372, 1245, 1189, 1113, 1045, 1006, 914, 730 cm^{-1}.

4,4-Dimethyl-2,2-pentamethylene-5-(4-pentanoyl)-1,3-dioxolane (**2f**)

^{1}H NMR ($CDCl_3$) δ 3.65 (1H, m, C5-H), 2.53 (2H, t, J=8 Hz, C3′-H), 2.16 (3H, s, C5′-H), 1.90–1.40 (14H), 1.24 (3H, s, C4-methyl), 1.06 (3H, s, C4-methyl); ^{13}C NMR ($CDCl_3$) δ 209.5 (C=O), 109.2 (C2), 83.2 (C5), 81.1 (C4), 43.7, 34.6, 33.9, 31.5, 29.2, 28.2, 27.9, 26.2, 24.3, 23.5, 21.3; IR(neat): 2969, 1715 (C=O), 1376, 1235, 1209, 1091, 920 cm^{-1}.

The typical procedure for the preparation of cyclohexenone **3** from bicyclic ketal **1** was reported.[6]

Typical Procedure for the Preparation of Cyclohexenone 7 from Bicyclic Ketal 1

To a solution of dry sodium iodide (1.92 g, 12.80 mmol) in acetonitrile (25 mL) under nitrogen atmosphere at −20°C was added slowly trimethylsilyl chloride (0.81 mL, 6.40 mmol) and stirred until the color change to yellow. Bicyclic ketal **1a** (0.50 g, 3.20 mmol) was added to the solution and refluxed for 20 h. After being cooled to room temperature, saturated sodium bicarbonate (30 mL) was added. The organic product was extracted with diethyl ether (3 × 30 mL). The ether layer was washed with saturated brine (30 mL), dried over magnesium sulfate, and the solvent was removed via a rotary evaporator. Flash chromatography (ether:hexane = 1:1) gave the unsaturated cyclohexenone **7a** (0.35 g, 80% yield).

2,2,3-Trimethyl-3-cyclohexen-1-one (**7a**)

^{1}H NMR ($CDCl_3$) δ 5.53 (1H, brs, C4-H), 2.56 (2H, t, J=7 Hz, C6-H), 2.36 (2H, m, C5-H), 1.72 (3H, br s, C3-methyl), 1.19 (6H, s, C2-dimethyl); ^{13}C NMR ($CDCl_3$) δ 215.4 (C=O), 140.5 (C3), 121.0 (C4), 47.7 (C2), 35.7

(C6), 25.0 (C5), 23.9 (2×C2-methyl), 18.3 (C3-methyl); IR(neat): 2971, 1714 (C=O), 1463, 1379, 1237, 1190 cm^{-1}.

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