Functionalization at C-4 of Heterocyclic Ketal Compound; 6,8-Dioxabicyclo[3.2.1]octane

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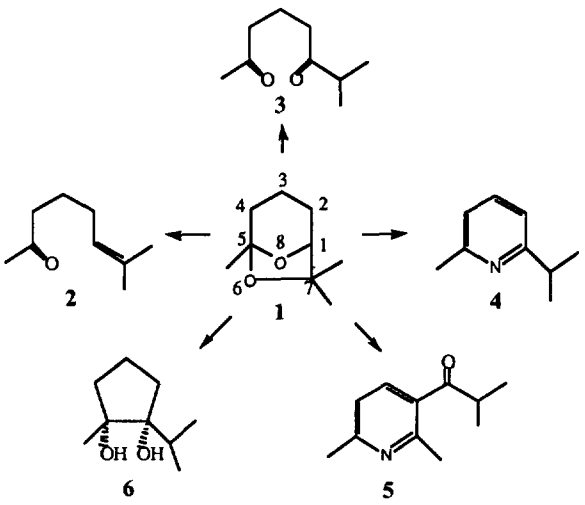
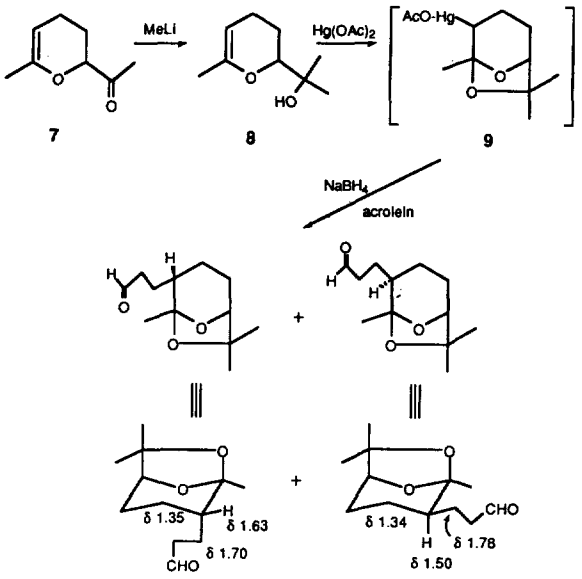
The functionalization of heterocyclic ketal **1** in the 6,8-dioxabicyclo[3.2.1]octane series is essential since the application of this ketal system to the direct syntheses of δ,ε-unsaturated ketone (**2**)[1], 1,5-diketone (**3**)[2], 2,6-disubstituted pyridine (**4**)[3], 2,3,6-trisubstituted pyridine (**5**)[4] and *cis*-1,2-cyclopentanediol derivatives (**6**)[5] are developed (Scheme 1).

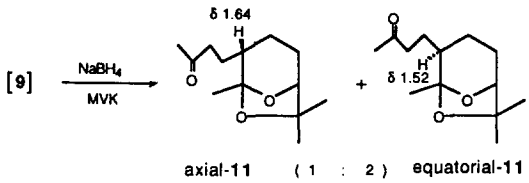
The position at C-4 of bicyclic ketal **1** is important to the synthesis of multistriation **6**[6] and α′-substituted cyclohexenone.[7] I report herein the facile functionalization at C-4 of bicyclic ketal compound.

There are two possible ways to introduce functional groups at C-4 of bicyclic ketal compound. Scheme 2 shows the introduction of acrolein or methyl vinyl ketone (MVK) at C-4 of bicyclic ketal during the cyclization of alcohol **8**. MVK dimer **7** was methylated with MeLi to the carbinol **8** (98% yield). $Hg(OAc)_2$ was used for the formation of C_4-Hg bond of bicyclic ketal **9** which was reacted with $NaBH_4$ and acrolein to give Michael adduct **10** in 1 : 2 ratio of axial and equatorial isomers (42% yield).[8] MVK was also used instead of acrolein to give the ketal **11** which shows 1 : 2 mixture of axial and equatorial isomers (58% yield). The configurational assignments of isomers of **10** and **11** are based on the chemical shift of the proton at C-4. The chemical shift of equatorial proton is more deshieled than axial proton.[9] Irradiation of the 1.50 ppm signals for major-**10** gave triplet at 1.78 and 1.34 from multiplet. Also, irradiation of the 1.63 ppm signals of minor-**10** gave triplet at 1.70 and 1.35. This indicates that major-**10** have axial proton and minor-**10** have equatorial proton at C-4. Thus, major-**10** can be assigned as equatorial-**10** and minor-**10** as axial-**10** which is sterically unfavorable because of 1,3-synaxial interaction. The chemical shift of 1.64 and 1.52 ppm signals at C-4 of isomers **11** indicate axial-**11** (minor) and equatorial-**11** (major) respectively.

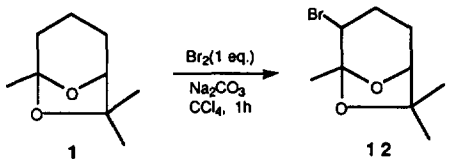


Scheme 1.





Scheme 2.



Scheme 3.

Scheme 3 shows the introduction of bromine at C-4 of bicyclic ketal from the bicyclic ketal **1** directly. Bromination of acyclic acetals is shown to occur on the carbon atom α to the functional group.[10] Accordingly, **1** was brominated with one equiv. of bromine in carbon tetrachloride for 7 hrs stirring at room temperature to obtain mono-brominated ketal **12** in 88% yield. With the addition of Na_2CO_3, the reaction was completed within 1 hr in quantitative yield. The product showed single peak on the capillary gas-liquid chromatogram. The chemical shift of 4.01 ppm signals at C-4 of this single isomer **12** could not indicate the exact configuration. But the single isomer **12** could be an equatorial-**12** because of steric effect.

All of the functionalized ketals (**10**, **11** and **12**) are useful intermediate for the C-C bond formation and other transformation reactions such as the synthesis of mouse Mus musculus pheromone.[11]

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8. Spectral data for axial-**10**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 9.73 (1H, br s, CHO) 4.02 (1H, br s, C_1-H), 2.42 (2H, t, J=7 Hz, CH_2CO), 1.92 (2H, m, CH_2), 1.70 (2H, m, CH_2), 1.63 (1H, m, equatorial C_4-H), 1.39 (3H, s, $OCCH_3O$), 1.35 (2H, m, CH_2), 1.30 (3H, s, *endo*-CH_3), 1.18 (3H, s, *exo*-CH_3); IR: 1725 cm^{-1}.
   Spectral data for equatorial-**10**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 9.75 (1H, br s, CHO) 3.99 (1H, br s, C_1-H), 2.48 (2H, t, J=7 Hz, CH_2CO), 1.95 (2H, m, CH_2), 1.78 (2H, m, CH_2), 1.50 (1H, m, axial C_4-H), 1.40 (3H, s, $OCCH_3O$), 1.34 (2H, br, t, CH_2), 1.31 (3H, s, *endo*-CH_3), 1.19 (3H, s, *exo*-CH_3); IR: 1727 cm^{-1}.
   Spectral data for axial-**11**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.87 (1H, br s, C_1-H), 2.44 (2H, t, J=7 Hz, CH_2CO), 2.12 (3H, s, CH_3CO), 1.90 (2H, m, CH_2), 1.72 (2H, m, CH_2), 1.52 (1H, m, axial C_4-H), 1.42 (3H, s, $OCCH_3O$), O), 1.37 (3H, s, *endo*-CH_3), 1.35 (2H, m, CH_2), 1.22 (3H, s, *exo*-CH_3; IR: 1711 cm^{-1}.
   Spectral data for equatorial-**11**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.86 (1H, br s, C_1-H), 2.46 (2H, t, J=7 Hz, CH_2CO), 2.13 (3H, s, CH_3CO), 1.90 (2H, m, CH_2), 1.80 (2H, m, CH_2), 1.52 (1H, m, axial C_4-H), 1.42 (3H, s, $OCCH_3O$), 1.35 (3H, s, *endo*-CH_3), 1.35 (2H, m, CH_2), 1.19 (3H, s, *exo*-CH_3); IR: 1715 cm^{-1}.
   Spectral data for **12**: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.01 (1H, dd, C_4-H), 3.95 (1H, br d, C_1-H), 2.30 (2H, m, CH_2), 1.89 (2H, m, CH_2), 1.59 (3H, s, $OCCH_3O$) 1.41 (3H, s, *endo*-CH_3), 1.30 (3H, s, *exo*-CH_3); ^{13}C-NMR (200 MHz, $CDCl_3$) δ 107.3, 82.2, 80.6, 54.2, 30.1, 28.7, 27.4, 24.6, 20.9; MS: 154 (M^+-HBr), 111, 93, 83, 77, 67, 55 (base), 41.
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