Pergamon

Tetrahedron Letters, Vol. 38, No. 47, pp. 8207-8210, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10196-4

Ketal-Lactone Compounds and their Stereoselective Cleavage to Cyclic Ethers

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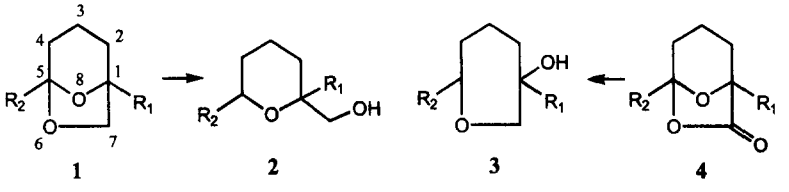
Summary: The easy preparation of ketal-lactone compounds via Diels-Alder reaction, followed by hydrolysis and cyclization and excellent stereoselective ring opening of the ketal-lactone to 6-membered and 7-membered cyclic ethers are described. © 1997 Elsevier Science Ltd.

Since the report of preparation of 6-membered and 7-membered cyclic ethers as mixture from the 6,8-dioxabicyclo[3.2.1]octane system by Utaka et. al.,[1] there was no successful investigation for the regioselective reductive ring opening of bicyclic ketal system. Mundy has suggested that the O_6-C_5 bond cleavage is more preferred than O_8-C_5 bond in bicyclic ketal **1** due to the O_6 preference of lanthanide interaction during lanthanide-induced shift studies.[2] This hypothesis has been proved with the experimental results, which showed all O_6-C_5 bond cleavage giving the single product **2**, by Mundy,[3] Kotsuki,[4] and Yamamoto.[5]

In every efforts to find a reagent that would specifically cleave the O_8-C_5 bond, with the expectation of creating a new approach to oxepane derivatives, we could not found one directly from the bicyclic ketal **1**, but we found an excellent result from the ketal-lactone **4**. The synthesis of ketal-lactone **4** in 6,8-dioxabicyclo[3.2.1]octan-7-one structure which was known to utilize for the synthesis of frontalin, cinenic acid, linaloyl oxide and cyclic oligoester, has been reported in low yield from 2,6-dimethyl-2,6-dibromocyclohexanone[1] or acrolein.[6] We report herein the easy preparation of ketal-lactone **4** and the regioselective C-O bond cleavage of **4** to the cyclic ether compounds **2** and **3** respectively.



1 2 3 4

a) R_1=R_2=Me
b) R_1=Me, R_2=H

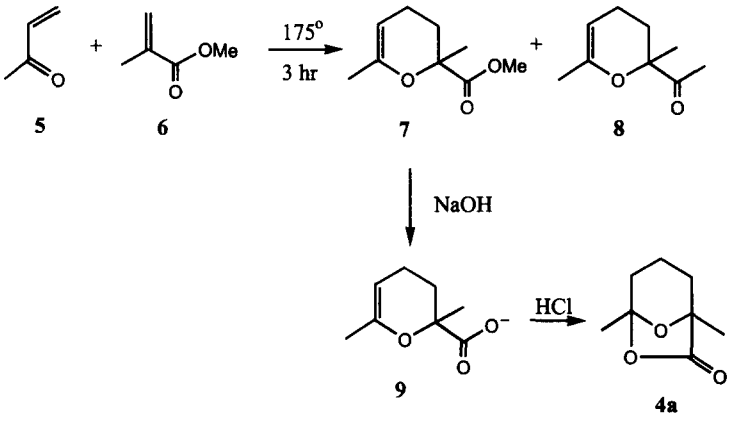
Scheme 1

In order to prepare the 1,5-dimethyl-6,8-dioxabicyclo[3.2.1]octan-7-one **4a**, we used the

Diels-Alder reaction of methyl vinyl ketone **5** and methyl methacrylate **6** to make 2-(carboxymethyl)-2,6-dimethyl-3,4-dihydro-2H-pyran **7** as an intermediate.[7] But equimolar Diels-Alder reaction of **5** and **6** gave the 1:1 ratio of expected pyran **7** and methyl vinyl ketone dimer **8** (Scheme 2). These mixture were hard to separate by chromatography.

The regiochemistry and reactivity of hetero Diels-Alder reaction could be explained by FMO theory.[8] The heterodiene cycloaddition of methyl vinyl ketone **5** and methyl methacrylate **6** was proceeded that the HOMO of the methyl vinyl ketone joined to form the ring **7** with the LUMO of the methyl methacrylate. We thought that the competition reaction of the HOMO of the methyl vinyl ketone with the another LUMO of the methyl vinyl ketone to give the ring **8** could be minimized by dilution method. When we used 3 molar equivalent excess of methyl methacrylate to methyl vinyl ketone in equivolume of benzene, the product ratio was increased to 8:2 ratio of pyrans **7** and **8**.

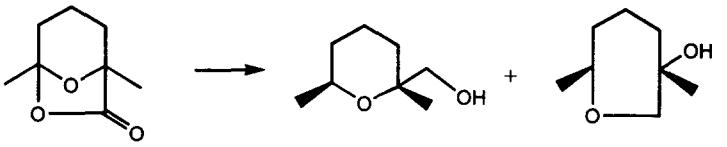
Since it is not practical to isolate the pyrans **7** and **8** by chromatography, the mixture was hydrolyzed with 2N NaOH and then the desired salt **9** was isolated in water layer after ether extraction. The salt **9** in water layer was finally acidified with 6N HCl to give the cyclized ketal-lactone **4a** which was extracted with ether in 72% yield.



5 **6** **7** **8** **9** **4a**

Scheme 2

Utaka[1] reported the C-O bond cleavage of ketal-lactone **4a** gave the mixture of cyclic ethers **2a** and **3a** in 36% and 26% yield respectively. But when we repeated this reaction, which condition was the reductive cleavage of **4a** with $NaBH_4$ (2 equiv.) in dry ether in the presence of 30 equiv. of BF_3Et_2O at 0 °C for 1 hr and then at reflux temperature for 2 hr, we could get only starting material back. It was necessary to change the solvent system from ether to THF. We tried several conditions to improve the yield and selectivity and found the novel system yielding only **2a** in $NaBH_4$ (4 equiv.) - BF_3Et_2O (30 equiv.) in THF or yielding only **3a** in $NaBH_4$ (6 equiv.) - $AlCl_3$ (30 equiv.) in THF (Scheme 3).[9]



4a **2a** **3a**

Hydride	Lewis Acid	Rxn Time (h)	Yield(%)	
			2a	**3a**
$NaBH_4$(4 eq.)	$BF_3{\cdot}Et_2O$(30 eq.)	15	93	0
$NaBH_4$(6 eq.)	$AlCl_3$(30 eq.)	2.5	0	94

Scheme 3

Surprisingly, the reductive cleavage of **4a** with $NaBH_4$ showed totally different selectivity in $BF_3{\cdot}Et_2O$ and $AlCl_3$. Especially, the reaction was quantitatively proceeded within 2.5h in $AlCl_3$ to give the single product **3a**, which was most difficult to get from ketal **1**, in 94% isolated yield. But the ether **3a** was totally decomposed in the longer reaction time. It was required more reaction time (15h) to make the ether **2a** in $BF_3{\cdot}Et_2O$, but also gave the single product in 93% yield. The mechanisms between these two reactions are surely depend on the character of Lewis acids. Most Lewis acids including $AlCl_3$ preferred to coordinate at O_6 in the ketal **1** system,[10] but the $AlCl_3$ containing vacant d-orbital compare to $BF_3{\cdot}Et_2O$ could discriminate the decreased electron density of O_6 by the resonance effect of the lactone **4a**, and preferred to coordinate at O_8. It is noteworthy that aluminum and boron Lewis acids show inverse reactivity in the C-O bond cleavage of 1-methoxy-2-phenoxy ethane.[11] Following hydride attack at C_5 from the less hindered side cleaves the O_8-C_5 bond yielding the ether **3a**. The chemical shifts of **2a** (δ 3.69) and **3a** (δ 3.63) for C5-H indicate that the both protons are in axial position which compare to equatorial proton at ~δ 4.2; the stereochemistry and the mechanism of C-O bond cleavage in bicyclic ketal system has been discussed in previous paper.[12]

We also used several other Lewis acids such as $TiCl_4$, $ZnCl_2$, TMSOMs-$BF_3{\cdot}Et_2O$[13] with $NaBH_4$ for the selective C-O bond cleavage of **4a**, and found that these conditions yielded only other products which were not identified. Other hydride sources such as DIBAH, $NaBH_3CN$, Et_3SiH, $LiAlH_4$ were used instead of $NaBH_4$, and also resulted other products.

Derivative of the ketal-lactone **4b** (R_1=Me, R_2=H) was prepared in 69% yield from acrolein with methyl methacrylate and applied for the selective cleavage using $NaBH_4$ (4 equiv.) - $BF_3{\cdot}Et_2O$ (30 equiv.) in THF and $NaBH_4$ (6 equiv.) - $AlCl_3$ (30 equiv.) in THF to give the expected cyclic ethers **2b** and **3b** in 92% and 91% yield respectively.[14]

In conclusion, we found an easy way to make 6,8-dioxabicyclo[3.2.1]octan-7-one derivatives via dilution method of hetero Diels-Alder reaction and developed its transformation utility to cyclic ethers in excellent regioselective yield by using $NaBH_4$-$AlCl_3$ and $NaBH_4$-$BF_3{\cdot}Et_2O$.

Acknowledgment This work was supported by the Basic Science Research Institute Program of

Ministry of Education(BSRI-96-3401) and by the Hallym Academy of Sciences, Hallym University.

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9. Typical Procedure for Compound **3a**; To a stirred solution of $NaBH_4$ (0.045 g, 1.17 mmole) with $AlCl_3$ (0.768 g, 5.76 mmole) in anhydrous THF (60 ml) the ketal-lactone **4a** (0.03 g, 0.192 mmole) was added slowly at 0 °C. After stirring for 1h at 0 °C, the reaction mixture was refluxed for 2.5h. Aqueous saturated $NaHCO_3$ (45 ml) was added, and the product was extracted with ether (3 x 60 ml). The combined ether layer was washed with brine (30 ml), dried over $MgSO_4$, filtered, concentrated, and chromatographed (ether:hexane=1:1) to give the clear liquid **3a** (0.026 g, 94% yield). Spectral data were similar with the reference.[1]
   Compound **2a**. ^1H NMR ($CDCl_3$) δ 1.12 (d, 3H, *J*=6Hz, C5-CH_3), 1.16 (s, 3H, C1-CH_3), 1.50-1.75 (m, 6H), 2.24 (br s, 1H, OH), 3.41 (br s, 2H, $\underline{CH_2}OH$), 3.69 (m, 1H, C5-H).
   Compound **3a**. ^1H NMR ($CDCl_3$) δ 1.16 (d, 3H, *J*=6Hz, C5-CH_3), 1.21 (s, 3H, C1-CH_3), 1.40-1.90 (m, 6H), 3.17 (br d, 1H, *J*=10Hz, C7-H_a), 3.42 (br s, 1H, OH), 3.63 (m, 1H, C5-H), 4.03 (d, 1H, *J*=10Hz, C7-H_b).
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14. Compound **2b**. ^1H NMR ($CDCl_3$) δ 1.18 (s, 3H, CH_3), 1.25-1.45 (m, 2H, C3-H_2), 1.50-1.75 (m, 4H), 2.52 (br s, 1H, OH), 3.46 (br s, 2H, $C\underline{H_2}OH$), 3.69 (t, 2H, *J*=6Hz, C5-H_2); ^{13}C NMR ($CDCl_3$) δ 19.6, 26.3, 26.9, 30.7, 62.2, 71.0, 73.8; IR (neat) 3418 cm^{-1}.
   Compound **3b**. ^1H NMR ($CDCl_3$) δ 1.18 (s, 3H, CH_3), 1.50-1.80 (m, 6H), 3.35-3.60 (m, 4H), 3.69 (br d, 1H); ^{13}C NMR ($CDCl_3$) δ 18.2, 19.4, 22.5, 29.9, 33.4, 66.6, 71.5, 73.9; IR (neat) 3448 cm^{-1}.

(*Received in Japan* 17 *July* 1997; *revised* 20 *August* 1997; *accepted* 16 *September* 1997)