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Chemoselective Reduction of β-Keto-esters to β-Keto-alcohols

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Chemoselective reduction of the ester group in keto-esters was studied. Treatment of potassium (or lithium) enolate anions of β-keto-esters with aluminum hydride reduced the ester group chemoselectively to give β-keto-alcohols in moderate yield. Similar reactions of γ- and δ-keto-esters were not chemoselective, yielding a mixture of the diol and the keto-alcohol.

Keywords——chemoselective reduction; aluminum hydride; β-keto-ester; β-keto-alcohol; potassium hydride; enolate anion

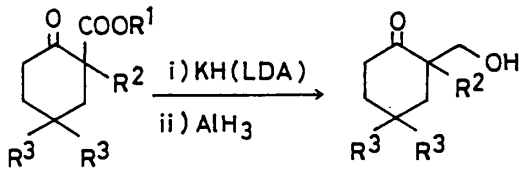
In 1968, Yoon and Brown[1] suggested that it should be possible to utilize aluminum hydride for selective reduction of the ester group in enolate salts of highly enolizable β-keto-esters without attack on the enolate anion. Based on the suggested method, Corey and Cane[2] converted the sodium enolate of 2-hydroxymethylene-4-*tert*-butylcyclohexanone to the 2-hydroxymethylcyclohexanone derivative in satisfactory yield by treatment with alminum hydride. However, neither of them tested its applicability to β-keto-esters. Since β-keto-esters are readily accessible by various methods and are frequently used as intermediates in organic syntheses, the above method, if it proceeds with considerable yield, would be a valuable alternative route for the preparation of α-hydroxymethyl ketones which are potential precursors of biologically active compounds such as α-methylene ketones. Here we report our results on aluminum hydride reduction of keto-esters.

The potassium (or lithium) salts of keto-esters were generated by reaction with KH or

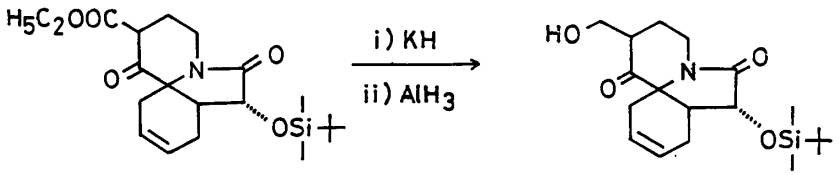
TABLE I. Reduction of Enolate Salts of Keto-esters with AlH_3 to Keto-alcohols

Keto-ester	Product (Keto-alcohol)	Yield (%)
2-Carbethoxycyclohexanone (**1**)	2-Hydroxymethylcyclohexanone (**2**)	59 (53)[a]
2-Carbomethoxycyclohexanone (**3**)	**2**	63
2-Carbethoxy-4,4-ethylenedioxy-cyclohexanone (**4**)	4,4-Ethylenedioxy-2-hydroxymethyl-cyclohexanone (**5**)	38 (36)[a]
$PhCOCH_2COOC_2H_5$ (**6**)	$PhCOCH_2CH_2OH$ (**7**)	38[b]
8	**9**	53
2-Carbethoxy-2-methylcyclo-hexanone (**10**)	2-Hydroxymethyl-2-methylcyclo-hexanone (**11**)	43
$PhCOCH_2CH_2COOCH_3$ (**12**)	$PhCOCH_2CH_2CH_2OH$ (**13**)	17[c]
$PhCOCH_2CH_2CH_2COOCH_3$ (**15**)	$PhCOCH_2CH_2CH_2CH_2OH$ (**16**)[d]	13[e]

a) Yields obtained by the LDA method are given in parentheses. *b*) Starting material (**8**) was recovered in *ca.* 45% yield. *c*) The diol (**14**) was obtained as a major product. *d*) Isolated as the 2,4-dinitrophenylhydrazone. *e*) The diol (**17**) was obtained as a major product.



1 : $R^1=C_2H_5$, $R^2=R^3=H$
2 : $R^2=R^3=H$
3 : $R^1=CH_3$, $R^2=R^3=H$
5 : $R^2=H$, $R^3+R^3=OCH_2CH_2O$
4 : $R^1=C_2H_5$, $R^2=H$, $R^3+R^3=OCH_2CH_2O$
11 : $R^2=CH_3$, $R^3=H$
10 : $R^1=C_2H_5$, $R^2=CH_3$, $R^3=H$



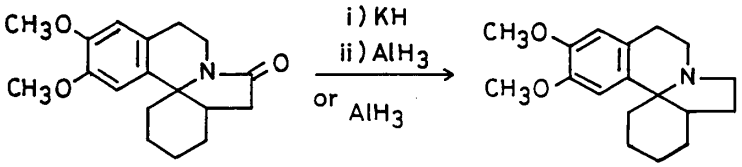
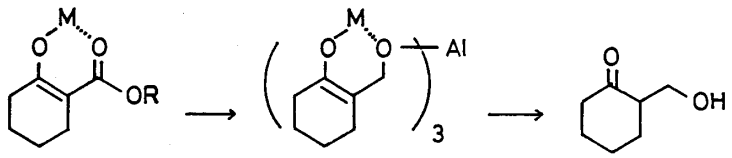
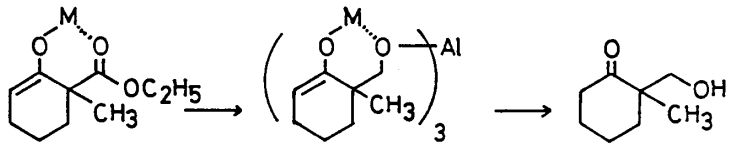


Chart 1



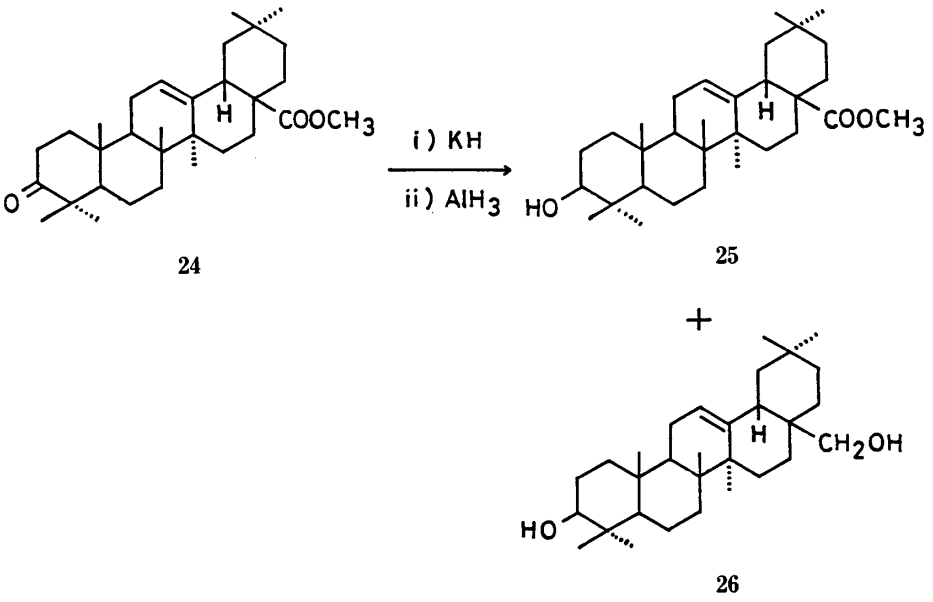


M=K or Li

Chart 2

lithium diisopropylamide (LDA) in tetrahydrofuran (THF), and, on treatment with a THF solution of AlH_3, furnished the keto-alcohols in the yields shown in Table I. The resultant keto-alcohols were purified by silica gel chromatography.

The highly enolizable β-keto-esters (**1**), (**3**), (**4**), and (**6**) gave the desired β-keto-alcohols in moderate yields. The β-keto-ester (**8**)[3] was also reduced smoothly to the β-keto-alcohol (**9**) by this method; interestingly, the amide group remained intact. This is in contrast to a report that an amide group is smoothly reduced to the amine by aluminum hydride.[1] This inertness of the amide group in **8** is presumably due to the presence of the adjacent bulky *tert*-butyldimethylsilyloxy group. In fact, the non-hindered tertiary amide (**18**) was smoothly



24 25 + 26

Chart 3

reduced to the amine (**19**) by the same reagent. It is noteworthy that 2-carbomethoxy-2-methylcyclohexanone (**10**), which is not as highly enolizable as the compounds mentioned above, also gave 2-hydroxymethyl-2-methylcyclohexanone (**11**) in moderate yield (43%). The yields of keto-alcohols from the γ- and δ-keto-esters (**12**) and (**15**) were low, as expected. The major product was the diol in each case. Therefore the above results suggest that this chemoselective reduction proceeds smoothly only when a stable enolate, (**21**) or (**23**), is formed as an intermediate. The 3-keto-triterpenoid (**24**) did not give the keto-alcohol, but instead gave methyl oleanolate (**25**) and erythrodiol (**26**) in 47% and 41% yields, respectively.

Experimental

Melting points were determined on a Yanaco model MP apparatus, and are uncorrected. The infrared (IR) spectra were taken with a Jasco IR-810 spectrophotometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Hitachi R-600 spectrometer or a JEOL FX-100 spectrometer, in $CDCl_3$ with tetramethylsilane as an internal standard, and mass spectra (MS) were determined with a JEOL JMS D-300 spectrometer.

Aluminum Hydride Reduction of β-Keto-esters (General Procedure)——Potassium Hydride Method: 2-Carbomethoxycyclohexanone (**3**) (312 mg, 2.0 mmol) and KH (100 mg, 2.5 mmol, Alfa) in THF (30 ml) were stirred for 30 min at 0 °C. AlH_3 (3 mmol) (prepared from 2 eq mol of $LiAlH_4$ and 1 eq mol of H_2SO_4 in THF according to Yoon and Brown[1]) in THF was added. After being stirred for 1 h at room temperature, the mixture was quenched with 10% KF solution, acidified with 10% HCl, and extracted with CH_2Cl_2. The organic extract was washed with water, dried, and concentrated to leave an oil, which was purified by passing it through a short column of silica gel, eluting with *n*-hexane followed by ethyl acetate. The ethyl acetate eluate gave 2-hydroxymethylcyclohexanone (**2**) (160 mg, 63%), as a colorless oil. Spectral data of **2** were identical with those of an authentic sample.[4]

By this method the β-keto-esters (**3**), (**4**), (**6**), (**8**), and (**10**) were reduced to the corresponding β-keto-alcohol (**2**), (**5**), (**7**), (**9**), and (**11**),[4] respectively. Similarly, methyl 3-benzoylpropionate (**12**) gave the keto-alcohol (**13**) and the diol (**14**) in 17% and 30%, yields, respectively, and methyl 4-benzoylbutyrate (**15**) gave the keto-alcohol (**16**) (isolated as the 2,4-dinitrophenylhydrazone) and the diol (**17**) in 13% and 25% yields, respectively.

LDA Method: 2-Carbetoxycyclohexanone (**1**) (368 mg, 2.0 mmol) was added to LDA–THF solution (2.4 mmol), and the mixture was stirred for 30 min at 0 °C. AlH_3–THF solution (3 mmol) was added and the whole was stirred for 1 h at room temperature. After work-up as above, the oily residue was purified by chromatography on a short silica gel column eluting with ethyl acetate to give 2-hydroxymethylcyclohexanone (**2**) (150 mg, 53%).

The products **5**, **7**, **9**, **13**, **14**, **16**, and **17** had the following physical properties.

4,4-Ethylenedioxy-2-hydroxymethylcyclohexanone (5)——Oil. IR ($CHCl_3$) cm^{-1}: 3575, 1710. ^{1}H-NMR δ: 3.70 (2H, d, J=7.5 Hz, $-CH_2OH$), 4.05 (4H, s, $-OCH_2CH_2O-$). MS *m/z*: 186 (M^+).

2-Benzoylethanol (7)——Oil. The 2,4-dinitrophenylhydrazone had mp 187—189 °C (lit.[5] mp 187—189 °C). IR ($CHCl_3$) cm^{-1}: 3475, 1680. ^{1}H-NMR δ: 3.21 (2H, t, $-COCH_2-$), 4.04 (2H, t. $-CH_2OH$), 8.2—7.2 (5H, aromatic protons).

7-*tert*-Butyldimethylsilyloxy-2-hydroxymethyl-6*H*-pyrido[2,1-*i*]indole-1,6-dione (9)——Colorless prisms, mp 84—85.5 °C. IR(KBr) cm^{-1}: 3430, 1720, 1685. ^{1}H-NMR δ: 0.15 (6H, s, $Si(CH_3)_2$), 0.85 (9H, s, $C(CH_3)_3$), 3.70 (2H, m, $-CH_2OH$), 4.04 (1H, d, J=6 Hz, –CHOSi), 5.54 (1H, m, olefinic proton), 5.87 (1H, m, olefinic proton). MS *m/z* Calcd for $C_{19}H_{31}NO_4Si$: 365.2023. Found: 365.2035.

2-Benzoylpropanol (13)——mp 31—33 °C (lit.[5] mp 32—33 °C). The 2,4-dinitrophenylhydrazone had mp 176—178 °C. IR (CCl_4) cm^{-1}: 3460, 1690. ^{1}H-NMR δ: 1.99 (2H, quintet, J=6.6 Hz), 3.11 (2H, t, J=6.6 Hz), 3.72 (2H, t, J=6.6 Hz), 7.2—8.2 (5H, aromatic protons).

1-Phenylbutane-1,4-diol (14)——mp 73—75 °C (lit.[6] mp 75 °C). IR (CCl_4) cm^{-1}: 3450, 3615.

2-Benzoylbutanol (16)——The 2,4-dinitrophenylhydrazone had mp 142—144 °C (lit.[5] mp 142—144 °C). IR(KBr) cm^{-1}: 3430, 3310, 1620, 1595.

1-Phenylpentane-1,5-diol (17)——mp 53 °C (lit.[6] mp 53.5 °C). IR(CCl_4) cm^{-1}: 3490, 3615.

15,16-Dimethoxyerythrinan (19)——KH–AlH_3 Method: 15,16-Dimethoxy-8-oxoerythrinan (**18**) (301 mg. 1.0 mmol) was added to KH (48 mg, 1.2 mmol) in THF solution, and the mixture was stirred for 30 min at 0 °C. AlH_3–THF solution (1.2 mmol) was added with stirring. Stirring was continued for 1 h at room temperature, then the reaction mixture was quenched with 10% KF aqueous solution, and diluted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and concentrated *in vacuo* to give an oil, which was dissolved in ether and treated with a solution of picric acid in ethanol. The separated yellow crystals were collected and recrystallized from ethanol to give the picrate of **19**, 335 mg (65%) as yellow prisms, mp 188—189 °C (lit.[7] mp 180 °C).

AlH_3 Method: A mixture of the lactam (**18**) (301 mg, 1.0 mmol) and AlH_3–THF solution (1.2 mmol) in THF (15 ml) was stirred at room temperature for 1 h. The product, after work-up as above, was converted to the picrate, yielding 377 mg (73%) as yellow prisms, mp 187—189 °C.

KH–AlH_3 Reduction of Methyl 3-Oxoolean-12-en-28-oate (24)——A solution of the 3-keto-triterpenoid (**24**) (468 mg, 1.0 mmol) was reduced by the KH–AlH_3 method to give methyl 3-hydroxyolean-12-en-28-oate (**25**), 221 mg (47%), mp 196—198 °C (lit.[8] mp 197—199 °C), and erythrodiol (**26**), 180 mg (41%), mp 233—235 °C (lit.[8] mp 235—237 °C).

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