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HIGHLY ANTI-DIASTEREOSELECTIVE REDUCTION OF 2-ALKYL-3-OXO AMIDES BY POTASSIUM TRIETHYLBOROHYDRIDE

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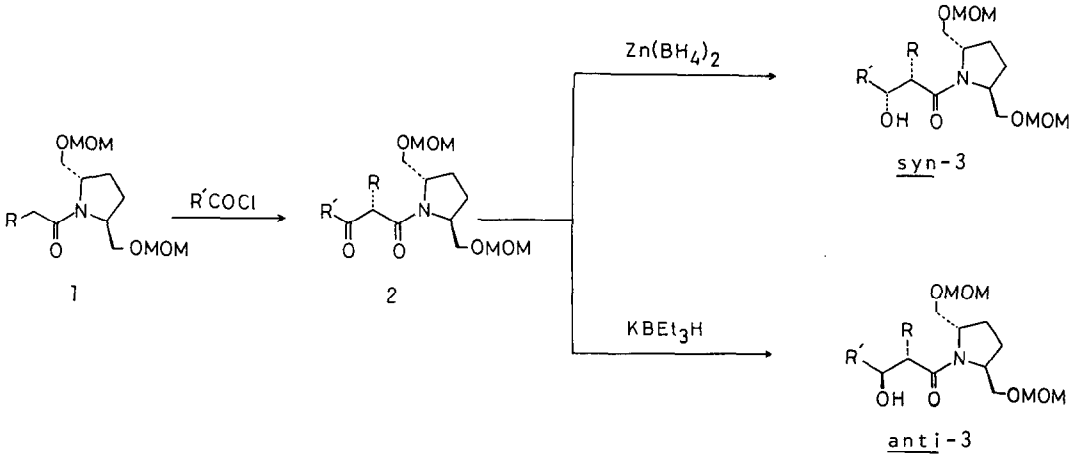
Summary: Potassium triethylborohydride was found to reduce 2-alkyl-3-oxo amides to the corresponding 3-hydroxy amides with excellent anti-diastereoselectivity (>99:1), and in combination with asymmetric acylation, a useful route to optically active anti-2-alkyl-3-hydroxy acids was developed.

We recently reported an asymmetric acylation of amide enolates[1] where trans-2,5-bis(methoxymethoxymethyl)pyrrolidine[2] served as an efficient chiral auxiliary, and established a highly enantio- and diastereoselective synthesis of syn-2-alkyl-3-hydroxy acids by subsequent syn-selective reduction of the acylated amides with zinc borohydride (**1**→**2**→syn-**3**), as an alternative to asymmetric aldol condensation.[3]

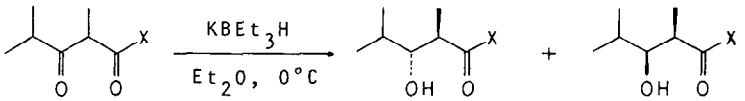
For the synthesis of the corresponding optically acitve anti-counterpart, the stereochemistry of which is also often encountered in natural products, however, few nice methods have so far been available. Anti-selective asymmetric aldol reaction has not been so successful,[3,4] and though the α-alkylation of optically active 3-hydroxy esters prepared by yeast reduction of the corresponding 3-oxo esters has recently been reported to proceed in highly anti-fashion, the diastereoselectivity of the reaction varied (84~96% de) depending on substrates and alkylating agents.[5]

The important factor in the syn-selective reduction was the intermediary formation of six-membered metal chelates.[1,6] Therefore, for the anti-



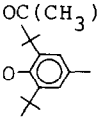
reduction, it was, at least, obvious that the use of metal hydride complexes having counter cations of high O-chelating ability were to be avoided. Furthermore, in order to eliminate complexity due to the disproportionation of the reducing species, those having complex hydride anions of less dissociative nature should have been the choice, and the anion should have had adequate bulkiness to discern the diastereomerically different environments. After examination of various types of metal hydride complexes which were thought to fit the above requirements, potassium trialkylborohydrides were found to be very profitable to the present purpose and potassium triethylborohydride was amongst the best. Thus, N-methyl-N-[2-(t-butyldimethylsiloxy)ethyl]-2,4-dimethyl-3-oxovaleramide was reduced to the corresponding anti-3-hydroxy amide with high diastereoselectivity (Table 1, entry 1). Mono- and non-substituted amides showed low selectivity. Though the corresponding ester substrates gave low selectivity it is noteworthy that the increased bulkiness in ester alkyls enhanced the anti-selectivity to a considerable extent (Table 1, entries 4, 5, and 6).

The reduction of optically active N-2'-alkyl-3'-oxoacyl-trans-2,5-bis-(methoxymethoxymethyl)pyrrolidines (**2**) obtained by asymmetric acylation reported previously,[1] gave even better stereoselectivity (anti:syn=>99:1) and chemical



4 dl-anti dl-syn

Table 1. Reduction of 2,4-Dimethyl-3-oxovaleryl Amides and Esters with $KBEt_3H$[a] in Ether at 0°C

Entry	X in 4	Reduction Product anti : syn	Isolated Yield(%)
1	NCH_3 OTBDMS	80 : 1[b]	95
2	NH OTBDMS	20 : 1[b]	70
3	NH_2[c]	4 : 1[d]	93
4	OCH_3	2 : 1[e]	62
5	$OC(CH_3)_3$	5 : 1[e]	82
6		13 : 1[f]	38

a) A THF solution (1 mol dm^{-3}) was used. b) Ratio was deduced by GLPC of the corresponding methyl ester, after hydrolysis and esterification (CH_2N_2). c) The reaction was conducted in THF at 0°C. d) Ratio was determined by ^1H NMR. e) Ratio was determined by GLPC. f) Ratio was determined by HPLC.

yields. The reaction proceeded very rapidly and completed within a few min in ether at 0°C. The results are shown in Table 2, with the addition of examples by some other reducing agents for comparison. Hydrolysis of the hydroxy amides (**3**) to the corresponding hydroxy acids proceeded smoothly without appreciable epimerization under the conditions used for the syn-compounds[1] except for the N-3'-hydroxy-2'-methyl-3'-phenylpropionyl derivative (Table 2, entry 4) which gave low yield of the hydroxy acid (ca 50%) probably because of the presence of an acid-sensitive benzylic hydroxyl group.

Table 2. Reduction of The Optically Active 2'-Alkyl-3'-oxo Amides [(2S,5S,2'S)-**2**] in Ether at 0°C

Entry	3'-Oxo Amide **2**		Reducing Agent[a]	Reduction Product **3**[b]			
	R'	R		Yield(%)	anti:syn[c]	$[\alpha]_D$	($CHCl_3$)
1	C_2H_5	CH_3	$KBEt_3H$	94	>99:1	-74°[d]	c=1.03
2	$(CH_3)_2CH$	CH_3	$KBEt_3H$	99	>99:1	-19°[d]	c=1.86
3	c-C_6H_{11}	CH_3	$KBEt_3H$	99	>99:1	-10°	c=1.14
4	Ph	CH_3	$KBEt_3H$	98	>99:1	+27°	c=1.36
5	$(CH_3)_3C$	CH_3	$KBEt_3H$	97	>99:1	-25°	c=1.41
6	$(CH_3)_2CH$	C_2H_5	$KBEt_3H$	98	>99:1	-37°	c=0.37
7	$(CH_3)_2CH$	CH_2Ph	$KBEt_3H$	99	>99:1	-88°	c=0.69
8	$(CH_3)_2CH$	CH_3	KB^sBu_3H	77	32:1		
9	$(CH_3)_2CH$	CH_3	$KB(O^iPr)_3H$	72	13:1		
10	$(CH_3)_2CH$	CH_3	$LiBEt_3H$	99	3:2		
11	$(CH_3)_2CH$	CH_3	Al^iBu_2H[e]	90	11:9		

a) Solutions of the reducing agents in THF (1 mol dm^{-3}) were commercially available (Aldrich Chemical Co. Ltd.). b) All the products gave satisfactory ^1H NMR and elementary analyses. c) Diastereomeric ratios were determined from intensities of relevant ^1H NMR signals. d) Enantiomeric excess was determined to be 97% by ^1H NMR examination in C_6D_6 under the presence of a chiral shift reagent, $Eu(hfc)_3$ after hydrolysis and esterification (CH_2N_2). e) A hexane solution (1.35 mol dm^{-3}) was used.

The anti-selectivity may be explained by Felkin-Anh's model[7] where π^*-π^* and σ^*-π^* interactions stabilize the transition state, and such a conformation is considered to be particularly favored when substituents on the amide nitrogen are bulky, because $A^{1,3}$ interaction is minimized therein (Fig. 1.).[8] Thus, the hydride anion attacks the β-carbonyl at the opposite side to the bulky amide group exclusively. Reduced anti-selectivity in the reduction of mono- or non-substituted amide can also be explained by the steric factor. It is further

supported by the enhanced selectivity in the reduction of the 2,6-di-t-butyl-4-methylphenyl ester (Table 1, entry 6), the conformation of the ester being considered to be very similar to that of the disubstituted pyrrolidine amide.

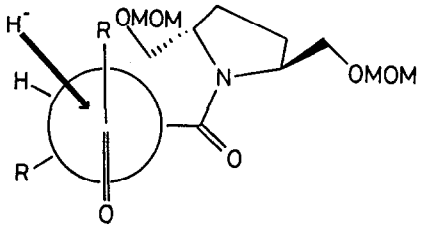


Fig. 1. A likely conformation in the transition state.

A typical example of the reduction is given below.

A solution of potassium triethylborohydride (1 mol dm^{-3}, 125 μl, 1.1 eq) in THF was added slowly to an ether solution (1.2 ml) of (2S,5S,2'S)-N-2',4'-dimethyl-3'-oxovaleryl-2,5-bis(methoxymethoxymethyl)pyrrolidine[1] (39.3 mg, 0.11 mmol) at 0°C. After stirring for a few min at the same temperature, aqueous phosphoric acid (3%, 0.2 ml) was added. Extraction (CH_2Cl_2), drying (Na_2SO_4), evaporation, and column chromatography (silica gel) gave (2S,5S,2'S,3'S)-N-2',4'-dimethyl-3'-hydroxyvaleryl-2,5-bis(methoxymethoxymethyl)pyrrolidine (39.1 mg, 99%).

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