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STEREOSELECTIVE REDUCTION OF α-HYDROXY KETONES

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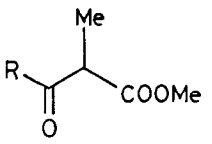
Summary: Reduction of α-hydroxy ketones with zinc borohydride afforded the erythro-glycols in high stereoselectivity, while reduction of their α-(t-butyldiphenylsilyl)oxy derivatives with sodium bis(2-methoxyethoxy)aluminum hydride gave the isomeric threo-glycols. The structure-stereoselectivity relationship has been discussed.

In the previous paper, we reported that the reduction of α-methyl-β-keto esters 1[1] and α,β-epoxy ketones 2[2] with zinc borohydride [$Zn(BH_4)_2$] afforded the corresponding erythro compounds in high stereoselectivity. In order to extend the scope of the stereoselective reduction mediated by $Zn(BH_4)_2$, we then focused our attention on the reduction of α-hydroxy ketones 3.



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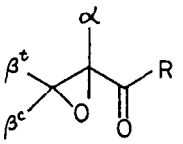

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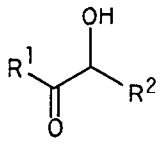
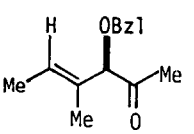


3

The stereochemistry of the reduction of 3 with various aluminum hydride reagents has been extensively studied by Katzenellenbogen and Bowlus.[3] In their studies, however, the stereoselectivity leading to erythro compounds was not satisfactory except when R^2 was t-butyl group and the reagent was triisobutylaluminum. Quite recently, the highly erythro-selective reductions of 4 ($LiAlH_4$ or $NaBH_4$; erythro/threo ratio, 90-95/10-5), 5 ($LiAlH_4$; ratio, 98/2), and 6 ($LiAlH_4$; ratio, >20/1) were reported by Tokuyama,[4a] Overman,[4b] and Stork,[4c] respectively. Independent of these works,[5] we carried out the reduction of various α-hydroxy ketones 3 by means of $Zn(BH_4)_2$ and examined a relationship between the substitution pattern of the α-hydroxy ketones and the stereoselectivity of the reduction in general. The results were shown in Table 1.



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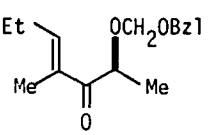

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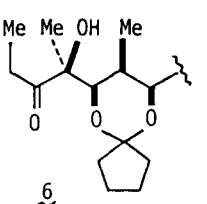

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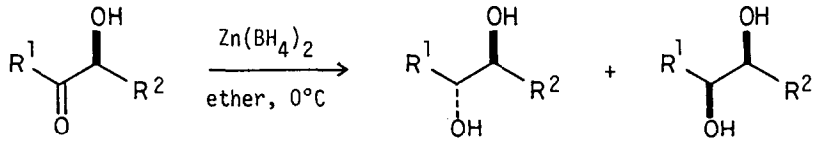


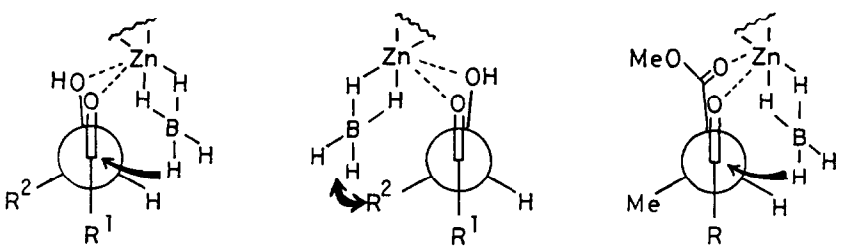
3 erythro-7 threo-8

Table 1. Reduction of α-Hydroxy Ketones 3 with $Zn(BH_4)_2$

Entry	Compounds	R^1	R^2	$Zn(BH_4)_2$ erythro-7 : threo-8	$LiAlH_4$[3] erythro-7 : threo-8
1	3a	n-C_5H_{11}	CH_3	77 : 23*	64 : 36
2	3b	n-C_4H_9	C_2H_5	89 : 11*	
3	3c	n-C_3H_7	n-C_3H_7	>99 : <1*	
4	3d	C_2H_5	n-C_4H_9	87 : 13*	
5	3e	CH_3	n-C_5H_{11}	85 : 15*	70 : 30
6	3f	i-C_3H_7	CH_3	85 : 15*	58 : 42
7	3g	CH_3	i-C_3H_7	96 : 4**	73 : 27
8	3h	Ph	CH_3	98 : 2*	87 : 13
9	3i	CH_3	Ph	90 : 10*	80 : 20

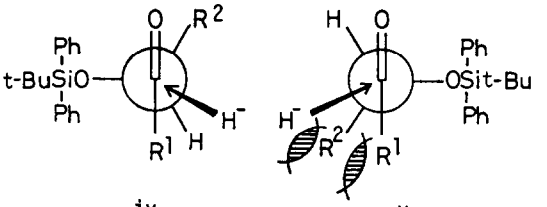
* Ratio determined by GLC on 2 m column packed with 1.5% OV-17/chromosorb W after acetylation.
** Ratio determined by 400 MHz NMR data.

Reduction is presumed to proceed through the transition state i, contribution of the same type of transition state being discussed in the reduction of 1 and 2 with $Zn(BH_4)_2$.[1,2] The high erythro-selectivity was obtained when R^1 was phenyl[6] as expected from the previous data.[1] Moreover, when R^2 was bulky isopropyl group, the erythro-selectivity was excellent (96 : 4, entry 7) even if R^1 was methyl. This result is not unexpected because the stereochemistry of the reduction is presumed to be governed mainly by the stability of the chelated transition state[2] and when R^2 is bulky, the transition state i leading to erythro compounds is apparently much favoured over ii leading to threo compounds.[7] It should be recalled here that in the reduction of β-keto ester 1, when R was normal alkyl group, selectivity was almost lost.[1] In the present reduction, however, fair to excellent selectivity was obtained even in these cases (see, particularly entry 3). These results suggest that the five-membered transition state i from 3 would be much rigid than the six-membered transition state iii from 1.



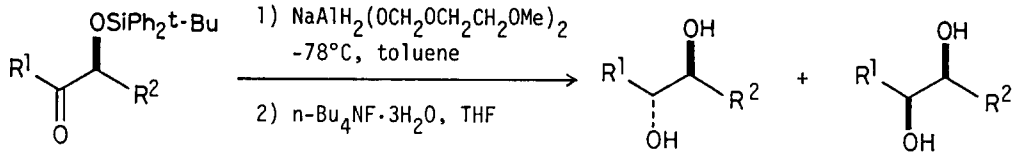
i ii iii

Then, we examined the reduction of the α-(t-butyldiphenylsilyl)oxy derivatives 9 of 3. This bulky alcohol protecting group was chosen so that the reduction should proceed through open-chain model iv or v proposed by Felkin[8] and Anh[9]. Furthermore, the reduction was carried out at low temperature (-78°C) so that the ketone should hold their most stable conformer (iv or v) during the reaction. Several metal hydrides having low coordinating ability were tested.



iv v

Among them, sodium bis(2-methoxyethoxy)aluminum hydride (Vitride) was found to give the most excellent selectivity. The results were shown in Table 2.



9 erythro-7 threo-8

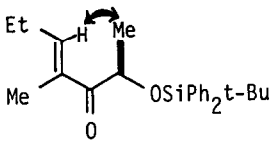
Table 2. Reduction of α-(t-Butyldiphenylsilyl)oxy Ketones 9 with Sodium Bis(2-methoxyethoxy)aluminum Hydride (Vitride)

Entry	Compounds	R^1	R^2	Products erythro-7 : threo-8
10	9a	n-C_5H_{11}	CH_3	39 : 61*
11	9b	n-C_4H_9	C_2H_5	14 : 86*
12	9c	n-C_3H_7	n-C_3H_7	14 : 86*
13	9d	C_2H_5	n-C_4H_9	7 : 93*
14	9e	CH_3	n-C_5H_{11}	2 : 98**
15	9f	i-C_3H_7	CH_3	54 : 46**
16	9g	CH_3	i-C_3H_7	4 : 96**
17	9h	Ph	CH_3	9 : 91*
18	9i	CH_3	Ph	24 : 76*

* Ratio determined by GLC on 2 m column packed with 1.5% OV-17/chromosorb W after acetylation.
** Ratio determined by 400 MHz NMR data after acetylation.

When R^2 is bulky, the conformer v leading to the erythro-glycol 7 should be destabilized due to the interaction with R^1. Moreover, since an attack of nucleophiles to carbonyl carbon is claimed to take place non-perpendicularly,[9] an approach of reducing reagents is heavily influenced by R^2 in v, but not so much by R^1. Therefore, when R^2 is bulky, reduction is expected to proceed through conformer iv leading to threo-glycol 8. In fact, when R^2 is isopropyl group, the high threo-selectivity was obtained (entry 16). Even when R^2 is normal alkyl group, a remarkably high selectivity was obtained provided that it had more than four carbon chains (entry 13, 14). On the other hand, almost no selectivity was obtained when R^1 was branched or long normal alkyl group (entry 10, 15). These results suggest that Felkin-Anh model, iv and v, no longer shows the favourable conformer since the interaction of R^1 with the

t-butyldiphenylsilyloxy group is expected to be increased in these cases. However, when R^1 is phenyl (9h, entry 17), a reasonably high threo-selectivity was obtained. Furthermore, after the present work had been completed,[5] Overman and McCready reported that reduction of 10 structurally corresponding to 9h with $LiAlH_4$ or triisobutylaluminum afforded the threo-glycol in high selectivity (94-95/6-5).[4b] Since phenyl or olefins conjugated with carbonyl group are flat and spatially fixed and thence the interaction with silyloxy group is presumed to be much less than when R^1 are bulky alkyl groups, Felkin-Anh model again becomes valid in these cases. Because of a severe interaction of olefinic proton with R^2 in v (9h, 10), the prefered conformer should be iv giving threo-isomer. Further studies are being continued to verify the above assumption.



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References and Notes

1. T. Nakata and T. Oishi, Tetrahedron Lett., 21, 1641 (1980).
2. T. Nakata, T. Tanaka, and T. Oishi, Tetrahedron Lett., 22, 4723 (1981).
3. J. A. Katzenellenbogen and S. B. Bowlus, J. Org. Chem., 38, 627 (1973); S. B. Wowlus and J. A. Katzenellenbogen, ibid., 39, 3309 (1974).
4. a) T. Tokuyama, K. Shimada, M. Uemura, and J. W. Daly, Tetrahedron Lett., 23, 2121 (1982); b) L. E. Overman and R. J. McCready, ibid., 23, 2355 (1982); c) G. Stork, I. Paterson, and F. K. C. Lee, J. Am. Chem. Soc., 104, 4686 (1982).
5. This work was presented at the 102th Annual Meeting of the Pharmaceutical Society of Japan at Osaka, April, 1982. Abstracts of Papers, p. 405. This work was also presented at the 41th Symposium on the Synthetic Organic Chemistry at Tokyo, June, 1982. Proceeding, p. 29.
6. Coordinating ability of the carbonyl oxygen to Zn^{++} is expected to be increased when olefins are conjugated with carbonyl group, which should make the transition state i more stable. High erythro-selectivity observed in the reduction of 5 will be rationallized by the same arguments.
7. The present assumption that when R^2 is bulky, branched alkyl group, the erythro-selectivity would be excellent was proved to be valid in general from the subsequent experiments (see the accompaning paper). The reported experiments[4] that 4 and 6 gave the erythro-glycol in high selectivity should be involved in this categoly. However, the fact that high selectivity was obtained even by $NaBH_4$ reduction of 4 is quite noteworthy.
8. M. Cherest, H. Felkin, and N. Prudent, Tetrahedron Lett., 2199 (1968).
9. N. T. Anh and O. Eisenstein, Nouv. J. Chem., 61 (1977); N. T. Anh, Topics Current Chem., 88, 145 (1980).

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