Tetrahedron Letters, Vol.32, No.10, pp 1335-1338, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

DIASTEREOSELECTIVE REDUCTION OF α-KETO ESTERS BEARING *CHIRO*-INOSITOL DERIVATIVES AS CHIRAL AUXILIARIES

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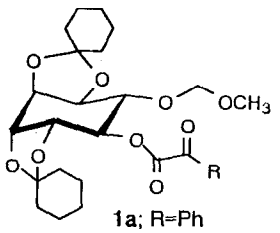
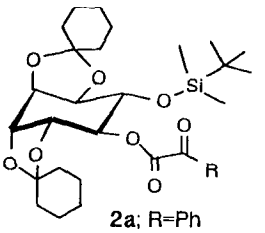
Summary: The reduction of α-keto esters derived from (1L)-1,2;5,6-biscyclohexylidene-3-*tert*-butyldimethysilyl-*chiro*-inositol with Selectride® proceeded with high diastereoselectivity to afford the corresponding α-hydroxy esters. Addition of 18-Crown-6 led to dramatic changeover in diastereofacial selectivity.

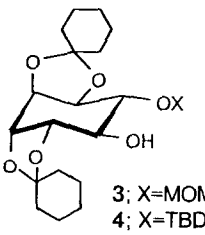
Chiral α-hydroxy acid derivatives are important and versatile synthetic intermediates for the construction of chiral organic framework,[1] and many useful methods have been reported for their preparation.[2] Diastereoselective reduction of chiral α-keto esters has been investigated, but has mostly resulted in moderate selectivity so far.[3] Highly diastereoselective reductions of α-keto amide derivatives were reported[4] but partial racemization took place during acidic hydrolysis of the chiral auxiliary groups. Various kinds of chiral auxiliary groups derived from sugar and amino acid have been developed, but little attention has been paid to chiral cyclitol derivatives. Recently L-quebrachitol (1L-(-)-2-*O*-methyl-*chiro*-inositol), a naturally occurring optically active inositol, has increasingly attracted attention as a chiral source in organic synthesis,[5,6] but has not been employed as a chiral auxiliary group. We have prepared new chiral auxiliaries **3** and **4** via a C_2-symmetric diol **5** starting from L-quebrachitol. We wish to describe here highly diastereofacial reduction of α-keto esters **1** and **2** by means of Selectride® to furnish α-hydroxy esters, in which dramatic changeover in diastereoselection was observed by addition of 18-Crown-6.



1a; R=Ph
1b; R=Me



2a; R=Ph
2b; R=Me



3; X=MOM
4; X=TBDMS
5; X=H

The α-keto ester **1a** was prepared via **3**, which was obtained from a diol **5**[7] (5.0 equiv of MOMCl / 3.0 equiv of i-Pr_2NEt / THF / 60 °C / 1 h) in 91% yield, by *O*-acylation with phenyl pyruvic acid chloride and triethylamine. The α-keto ester **1b** was prepared from **3** with pyruvic acid, dipyridyl disulfide, and triphenyl phosphine.[8] Chiral auxiliary group **4** was prepared by monosilylation of a diol **5** (1.8 equiv of TBDMSCl /

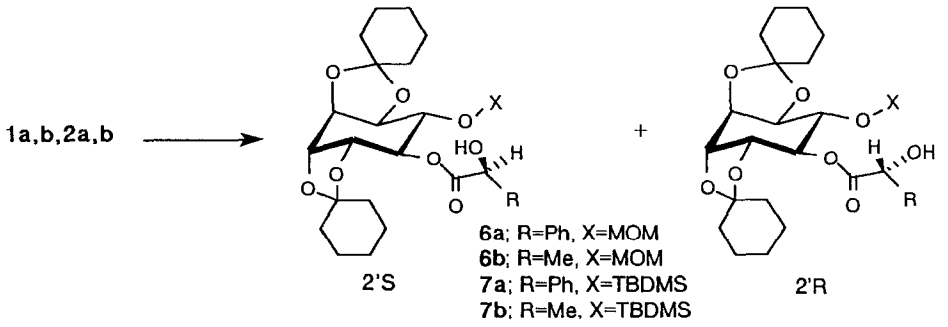


Table 1. Results of the reduction of **1a**.

Run	Reductant	equiv	Solvent	Temp/°C	Yield of **6a**	2'S : 2'R
1	$NaBH_4$	1.0	Ethanol	0	44	60 : 40
2	i-Bu_2AlH	1.0	Toluene	-72	46	50 : 50
3	Red-Al®	1.0	Toluene	-72	15	33 : 67
4	$LiBH_4$	1.0	THF	-72	83	52 : 48
5	$LiEt_3BH$	1.0	THF	-72	93	45 : 55
6	K-Selectride®	1.2	THF	-72	85	86 : 14

3.5 equiv of 1,8-diazabicylclo[5.4.0]undec-7-ene / CH_3CN / r.t. 3 h) in 83% yield. Esterification of **4** was carried out in the same manner as that of **3** to give **2a** and **2b**.

. Reduction of **1a** was studied by use of various metal hydrides and the results are shown in Table 1. The diastereomeric mixture of alcohols (**2'S-6a** and **2'R-6a**) were inseparable by column chromatography and the diastereomeric ratio was determined by integral of 270 MHz ^1H NMR of the methylene signal. When potassium tri-s-butylborohydride (K-Selectride®) was employed, highly diastereoselective reduction took place to give **2'S-6a** in 72% de. (Run 6)

Next we examined the effect of the solvent system on the reduction by use of K- and L-selectrides® and the results are shown in Table 2. When K-Selectride was used in Et_2O, 2'S isomer was obtained highly diastereoselectively in 94% de. (Run 1) Addition of 18-Crown-6 led to dramatic changeover in diastereoselection and 2'R isomer was obtained in 80% de. (Run 2) The reduction with L-Selectride® in THF showed low selectivity, and reversal of stereoselection was attained in the presence of HMPA. (Run 3) Further we investigated the reduction of **2a**, bearing bulky substituent vicinal to the ester moiety in the hope of improving the diastereoselectivity. In this case, the diastereomer of the obtained alcohols (**2's-7a** and **2'R-7a**) could be readily separated by column chromatography and the diastereomeric ratio was determined by the amount of the separated isomer as well as 270 MHz ^1H NMR analysis. When K-Selectride® was used in THF, highly diastereoselective reduction took place in the same stereofacial manner to give **2'S-7a** in 92% de. (Run 4) Reversal of diastereoselection in the presence of 18-Crown-6 in THF was enhanced to 92% de. (Run 5)

Table 2. Reduction of α-keto esters with Selectride.[a]

Run	Comp.	Reductant[b]	Equiv	Solvent	Additive[c]	Yield	2'S :2'R
1	**1a**	K	1.5	Et_2O	-	79	97 : 3
2	**1a**	K	1.7	THF	18-Crown-6	78	10 : 90
3	**1a**	L	1.3	THF	HMPA	79	10 : 90
4	**2a**	K	1.0	THF	-	75	96 : 4
5	**2a**	K	1.2	THF	18-Crown-6	66	4 : 96
6	**2a**	L	1.3	Et_2O	-	63	96 : 4
7	**2a**	L	1.3	THF	HMPA	68	9 : 91
8	**1b**	K	1.0	THF	-	62	88 : 12
9	**2b**	K	1.0	THF	-	61	98 >2
10	**2b**	K	1.2	THF	18-Crown-6	61	34 : 66
11	**2b**	L	1.3	THF	HMPA	68	27 : 73

a) The reactios were carried out at -72 °C for 10-20 min, b) K: K-Selectride®, L: L-Selectride®, c) 1.3-1.6 Equiv of additives were employed.

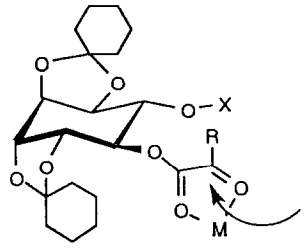
When L-Selectride® was employed, high diastereoselectivity was observed in Et_2O (Run 6) and high reversal of diastereoselection also took place on addition of HMPA. (Run 7)

Consequently, selectrides reduced **1a** and **1b** highly diastereoselectively to give 2'S isomer exclusively. The changeover in diastereoselection was attained either with K-Selectride in the presence of 18-Crown-6 in THF or L-Selectride in the presence of HMPA in Et_2O. t-Butyldimethylsilyl group has proved to be more effective than methoxymethyl group as a stereodirecting group.

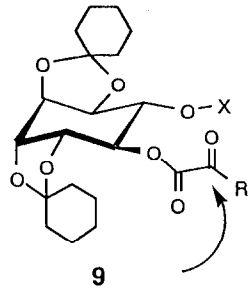
Diastereoselective reduction of **1b** and **2b** also proceeded in a high stereoselective manner although the reversal of diastereoselection was modest.

The absolute configurations of **6a** and **7a** were determined by the optical rotation of the mandelic acid obtained by saponification of them. An optically pure alcohol **7a-2'S** purified by column chromatography was treated with KOH in THF at room temperature to obtain chiral mandelic acid without concurrent racemization. The absolute configurations of **6b** and **7b** were determined by comparing ^1H NMR of the acetylated compound with the one obtained from acetyl lactic acid and **3** and **4** respectively.

Although the detailed mechanism of the present reaction remains to be studied, the stereoselection might be explained as follows. The reduction of α-keto ester with Selectrides in Et_2O proceeds via s-cis conformation **8**, thereby the hydride attacks from the opposite side of the MOM or silyl ether to produce 2'S isomer predominantly. In contrast, in the presence of 18-Crown-6 or HMPA, which traps metal cation strongly, hydride attacks via s-trans conformation **9** to give 2'R isomer favorably. Reversal of the diastereoselection in the reduction of ketone by changing reducing agents has been reported,[4c,9] and in many instances Selectrides®



8 M = Li or K



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are classified as a reagent of choice in non-chelation controlled reduction. Our results, however, strongly suggests that the chelation of the metal cation, Li^+ or K^+, plays a crucial role on the diastereoselection in Selectrides® reduction.

These results led us to conclude that cyclitols 3 and 4 have proved to be effective as chiral auxiliaries, and that both diastereomers of α-hydroxy esters 6 and 7 were obtained stereoselectively by use of K-Selectride® as the sole reducing agent either with or without 18-Crown-6.

Acknowledgments: The authors wish to express our gratitude to Dr. Yutaka Watanabe of this department for his helpful discussions and to Yokohama Rubber Co. for the kind gift of L-quebrachitol.

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(Received in Japan 7 December 1990)