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Diastereoselective Reduction of α-Keto Esters Derived From Functionalised Cholic Acid†

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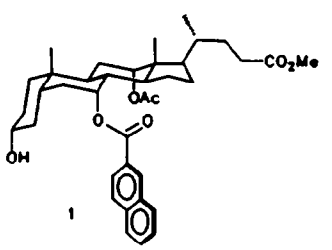
Abstract: The reduction of phenylglyoxalate **2a** and pyruvate **2b** with $LiBH_4$ in THF at -80°C yield the corresponding α-hydroxy esters with ca. 70% diastereoselectivity.

Optically active α-hydroxy carboxylic acid derivatives are versatile building blocks in the synthesis of chiral natural products.[1] As a result, considerable effort has been directed towards the development of viable synthetic methods for α-hydroxy acid derivatives either with covalently bound chiral auxiliaries[2,3] or with chiral promotors.[4] Most of the auxiliaries employed so far have been derived from amino acids, sugars and terpenes having 1,2 and 1,3 relationships between the reactive and the shielding sites. No attention, however, has been paid towards the use of readily available steroidal precursors as chiral auxiliaries to effect asymmetric reduction of α-keto esters.



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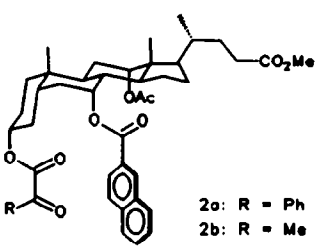
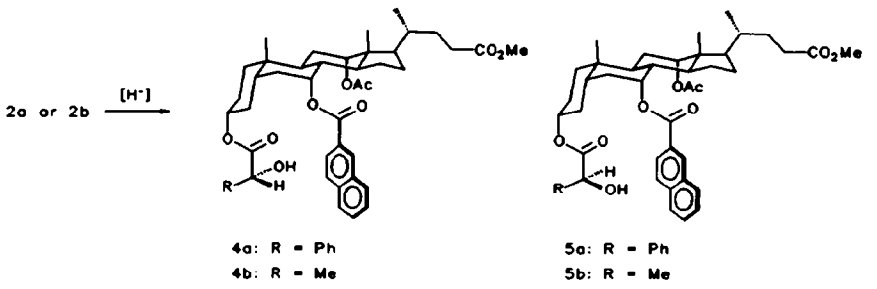


2a: R = Ph
2b: R = Me

We recently described the synthesis of a novel cholic acid derived chiral auxiliary which was used in asymmetric Diels-Alder reactions.[5] This new chiral auxiliary (**1**) has a *1,5 relationship* between the reactive centre and the shielding site. We present here our preliminary work on the diastereoselective reduction of α-keto acids using **1** as the chiral auxiliary.

Phenylglyoxalate ester **2a** was prepared by the esterification of alcohol **1** with phenylglyoxaloyl chloride in the presence of triethylamine and DMAP in CH_2Cl_2 at room temperature (95%), whereas

pyruvate ester **2b** was prepared using the mixed anhydride of pyruvic and pivalic acids according to a literature method (88%).[6] The reduction of phenylglyoxalate and pyruvate esters were examined with various reducing agents below room temperature. As a control, the 3α-phenylglyoxalate derivative of 7α,12α-diacetoxy methyl cholanate (**3**, *absence of the shielding naphthalene moiety*, structure not shown) was also synthesized. Reduction of these α-keto esters (8-25 mM) with various reducing agents are depicted in Scheme 1 and the results are summarized in Table 1.[7,8]



SCHEME 1

Table 1. Diastereoselective Reduction of Phenylglyoxalate (**2a**) and pyruvate ester (**2b**) of cholic acid derivatives.

Entry	Substrate	Reducing agent (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield[a] (%)	D.e. (config)
1	**2a**	$NaBH_4$ (4.8)	THF	0	1	60	22 (R)
2	**2a**	$LiBH_4$ (2.8)	THF	0	½	>98	34 (R)
3	**2a**	$LiBH_4$ (1.1)	THF	-80	4	>98	68 (R)
4	**2a**	KBH_4 (2.5)	THF	0	4½	>98	31 (R)
5	**2a**	DIBAL (1.4)	THF	-80	4	99[b]	42 (S)
6	**2a**	$Bn(Et)_3NBH_4$ (1.5)	CH_2Cl_2	0	6	>98	30 (S)
7	**2b**	$LiBH_4$ (1.6)	THF	-80	4	>98	70 (R)
8	**2b**	DIBAL (2.1)	THF	-80	7	90[b]	32 (S)

a Isolated yield. *b* Based on recovered starting material.

The reduction of phenylglyoxalate **2a** with $LiBH_4$ in THF at -80°C proceeded smoothly and a diastereomeric mixture of mandelate esters **4a** and **5a** were obtained in a 84:16 ratio; whereas with DIBAL in THF at the same temperature the ratio was 29:71. In an analogous manner the reduction

of pyruvate ester **2b** with $LiBH_4$ afforded diastereomeric lactate esters **4b** and **5b** in a 85:15 ratio. As expected, the absence of the shielding naphthalene unit at C-7 (**3**) did not result in any stereoselectivity.

The observed diastereoselectivity in the case of **2a** and **2b** may be explained by the co-ordination of the metal ion (Li^+) to the two carbonyl oxygens of the α-keto ester (Fig. 1) thereby allowing the hydride species to preferentially attack the accessible *si*-face of the carbonyl group.[9] Interestingly, addition of LiBr did not significantly alter the stereoselectivity of $LiBH_4$ reduction product of **2a** (de 64%).

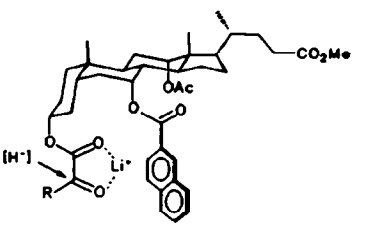
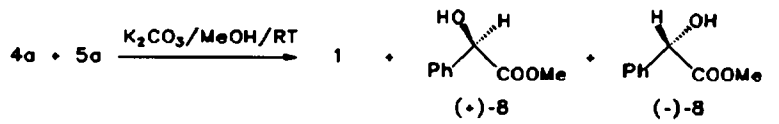


Fig. 1

The mandelate ester was removed from the steroidal backbone under mild conditions (Scheme 2). Treatment of the diastereomeric mixture of **4a** and **5a** with anhydrous K_2CO_3 in MeOH at room temperature yielded chiral alcohol **1** (87%) and enantiomeric methyl mandelate (+)-**8**/(-)-**8** (84%). The enantiomeric excess of (+)-**8**/(-)-**8** ($[\alpha]_D^{23}$ = -107.6 (*c* 0.38, $CHCl_3$, ee = 65%)) was found to be in good agreement with the observed de of **4a**/**5a** (entry 3).[10]



SCHEME 2

In conclusion, we have demonstrated the versatility of a new chiral auxilary derived from inexpensive cholic acid for the reduction of α-keto esters to the corresponding α-hydroxy esters. Further work on the application of bile acid based chiral auxiliaries to other areas of asymmetric synthesis is in progress. We believe that future research in this hitherto unexplored facet of bile acid chemistry will eventually lead to the practical synthesis of a variety of chiral molecules.

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References and Notes

† This paper is dedicated to Professor Subramania Ranganathan on the occasion of his 60th birthday.

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7. Authentic samples were synthesized from racemic as well as scalemic samples of O-acetylated mandelic and lactic acids, and alcohol **1**. NMR spectra (400 MHz) and HPLC traces of (2R) O-acetyl mandelate **6a** and (2S) O-acetyl lactate ester **7b** were compared with those of the acetylated reduction products. HPLC analysis was carried out using a Shimadzu ODS column (250 mm X 4.6 mm) with CH_3CN/H_2O (85:15 v/v) as the mobile phase. The configuration refers to the stereochemistry of C-2 of the α-hydroxy ester.
8. All the compounds gave satisfactory analytical and spectroscopic data. Selected data: **2a** mp 124°C; $[\alpha]_D^{22}$ = +53.6 (*c* 4.31, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 5.313 (d, *J* 2.6 Hz, 1H), 5.159 (s, 1H), 4.92 (m, 1H), 3.593 (s, 3H), 2.152 (s, 3H), 1.035 (s, 3H), 0.805 (d, *J* 6.5 Hz, 3H), and 0.77 (s, 3H); *IR* (thin film) 1725 (*COO*), 1680 (*CO*) cm^{-1}. **2b** mp 107°C; $[\alpha]_D^{23}$ = +64.9 (*c* 1.57, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 8.60 (s, 1H), 5.286 (br. s, 1H), 5.16 (s, 1H), 3.607 (s, 3H), 2.215 (s, 3H), 2.206 (s, 3H), 1.02 (s, 3H), 0.812 (d, *J* 6.1 Hz, 3H), and 0.763 (s, 3H). **6a** mp 99°C; $[\alpha]_D^{24}$ = +50.6 (*c* 1.19, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.582 (s, 1H), 5.695 (s, 1H), 5.21 (br. s, 1H), 5.197 (s, 1H), 4.62 (m, 1H), 3.605 (s, 3H), 2.24 (s, 3H), 1.94 (s, 3H), 0.982 (s, 3H), 0.821 (d, *J* 6.5 Hz, 3H), and 0.763 (s, 3H). **7b** mp 135°C; $[\alpha]_D^{22}$ = +53.5 (*c* 1.03, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 5.28 (d, *J* = 2.5 Hz, 1H), 5.17 (s, 1H), 4.85 (q, J = 21.3 Hz, 1H), 4.64 (m, 1H), 3.607 (s, 3H), 2.198 (s, 3H), 1.91 (s, 3H), 1.259 (d, *J* 6.9 Hz, 3H), 1.04 (s, 3H), 0.824 (d, *J* 6.4 Hz, 3H), and 0.775 (s, 3H).
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