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Synthesis of *both* enantiomers of 1-phenylethane-1,2-diol via chirality transfer from bile acid derivatives

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Abstract

Both enantiomers of 1-phenylethane-1,2-diol were synthesized with good to excellent enantioselectivities via selective reduction of the phenylglyoxalates derived from bile acids, followed by reductive cleavage.

Efficient synthesis of homochiral molecules is one of the important areas of organic synthesis. Among various methodologies available for the synthesis of chiral compounds, chirality transfer through a chiral auxiliary has been widely investigated and utilized. Derivatives of natural products from several classes such as terpenes, alkaloids, carbohydrates, amino acids etc., have been extensively used as chiral auxiliaries.[1] Bile acids have been successfully exploited as chiral auxiliaries and chiral templates by us[2,3] and others.[4] We demonstrated the induction of moderate to good stereoselectivities for Diels–Alder reactions and α-keto ester reductions using a bile acid-derived chiral auxiliary.[2] Herein, the versatility of bile acid-based auxiliaries is further demonstrated by synthesizing *both* enantiomers of 1-phenylethane-1,2-diol[5] with good to excellent enantioselectivities.

In the previously reported studies on the asymmetric reduction of bile acid derived α-keto esters, the relatively unhindered 3-OH group was used for attaching the substrate and up to 70% *de* was achieved.[6] Since the axial 7-OH and 12-OH groups are much more hindered, we planned to explore these sites for attaching a reactive site. We first synthesized α-keto esters **1** and **2** (Fig. 1 and Scheme 1) in order to establish the chiral influence of the bile acid backbone. These compounds were reacted with hydrides at low temperatures and the products obtained were analyzed by ^{1}H NMR and HPLC for estimating the diastereomeric ratio. Selected results are summarized in Table 1.

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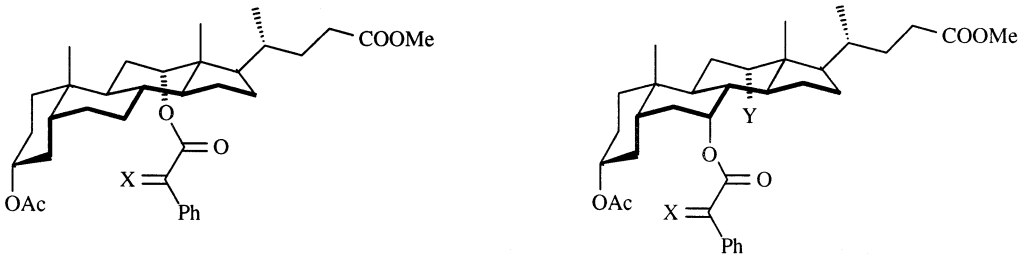
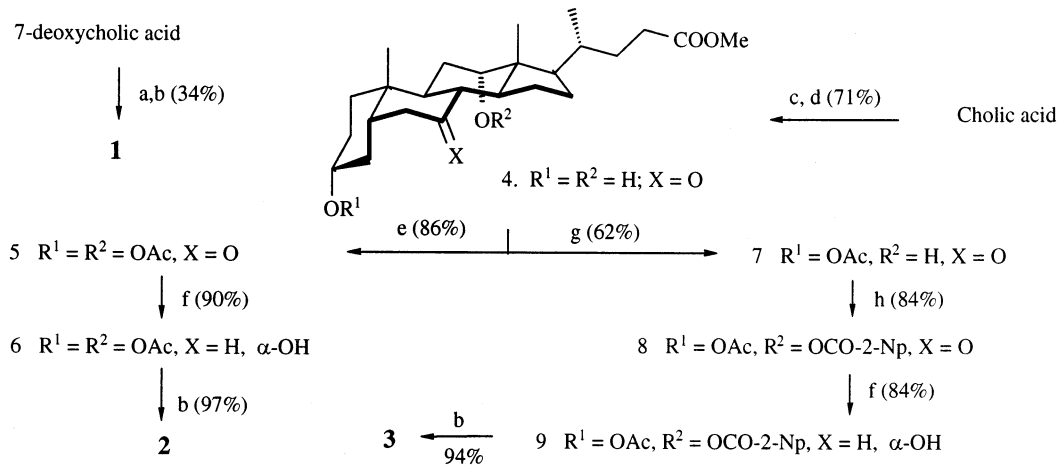


1. X = O
1a. X = H, OH

2. X = O; Y = OAc **3**. X = O; Y = OCO-2-Np
2a. X = H, OH; Y = OAc **3a**. X = H, OH; Y = OCO-2-Np

Figure 1.

For compound **1** the highest diastereoselectivity (78%) was obtained with $LiBH_4$ at −78°C in THF, while $NaBH_4$ reduction in 1:3 MeOH/THF at −78°C gave a *de* of 63%. On the contrary, substrate **2** gave a diastereoselectivity of 76% with $NaBH_4$ and 68% with $LiBH_4$ under similar



Scheme 1. Reagents and conditions: (a) MeOAc, TsOH; (b) PhCOCOCl, DMAP, CH_2Cl_2; (c) NBS, $NaHCO_3$, H_2O; (d) MeOH, AcCl; (e) Ac_2O, Et_3N, DMAP, Δ; (f) $NaBH_4$, MeOH–THF; (g) Ac_2O, Py, rt; (h) 2-NpCOCl, CaH_2, $BnEt_3N^+Cl^-$, PhMe, Δ (Np: naphthyl)

Table 1
Product diastereomer excess upon reduction of bile acid derived α-keto esters with hydride reagents

Substrate	*T* (°C)	Reagent	Solvent	*de* HPLC (NMR)	Major stereoisomer	Yield (%)[b]
1	−78	$NaBH_4$	MeOH/THF[a]	63 (64)	*R*	96
1	−78	$LiBH_4$	THF	78 (77)	*R*	96
2	−78	$NaBH_4$	MeOH/THF[a]	76 (75)	*S*	95
2	−78	$LiBH_4$	THF	68 (68)	*S*	94
3	−20	$NaBH_4$	MeOH	>99	*S*	93
3	−78	$LiBH_4$	THF	96	*S*	88

[a] 1:3 ratio.
[b] Isolated yields of **1a**, **2a** and **3a**.

conditions used for the reduction of **1**. The use of additives such as LiBr, HMPA, TMEDA etc.,[7] had no significant effect on the diastereoselectivities. The stereochemistry of the newly formed stereocentre for **1a** was found to be *R*, while that for **2a** was *S*.[8] These results suggested that the hydride addition took place from the less hindered side of the prochiral keto group of the keto ester in the predominant anti conformation of the two carbonyl groups (Fig. 2).

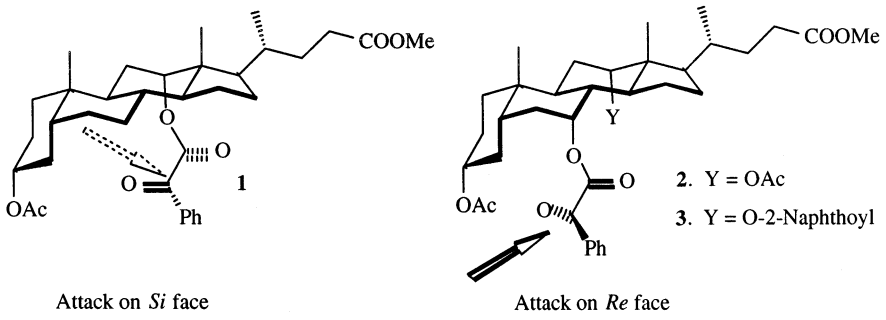


Figure 2. Proposed model to explain observed selectivities

We subsequently designed chiral auxiliary **3** with 2-naphthoate as the shielding group at 12-OH to shield one of the faces of the keto group and hence enhance the chiral induction. This indeed gave a diastereoselectivity of >99% at −20°C with $NaBH_4$, but somewhat reduced *de* with $LiBH_4$ (Table 1).

Selective hydrolytic cleavage of the α-hydroxy ester linkage in **1a**–**3a** in the presence of multiple ester linkages using a variety of reagents was unsuccessful in removing the chiral auxiliary to yield chiral mandelic acid. However, the chiral auxiliary could be removed by selective reductive cleavage of the mandelate ester with $LiBH_4$ in dry THF at rt to regenerate the chiral auxiliary and produce 1-phenylethane-1,2-diol. The enantiomeric excess and the configuration of the product were determined by comparison of the specific rotation values with the literature value.[9] The enantiomeric excesses were in good agreement with the observed diastereomeric ratios of **1a**, **2a** and **3a** (Table 2).

Table 2
Enantiomeric excesses after reductive cleavage of the α-hydroxy esters

Mandelate ester	Recovered auxiliary	1-Phenylethane-1,2-diol			
	Yield (%)	Yield (%)	$[\alpha]_D^{24}$ [a]	*ee*	Configuration of the major isomer
1a	57	53	−30.5	77	*R*
2a	50	65	+30.0	76	*S*
3a	52	44	+38.3	97	*S*

[a] Measured in ethanol (see Ref. 9).

In conclusion, we have demonstrated the utility of derivatives of readily available bile acids as chiral auxiliaries by synthesizing both enantiomers of 1-phenylethane-1,2-diol with good to excellent enantiomeric excess. Further work to optimize some of the reactions described here are in progress and these results will be reported elsewhere.

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