Asymmetric Reduction of Prochiral 3-Aryl-3-oxoesters with Lithium Borohydride using *N,N'*-Dibenzoylcystine as a Chiral Auxiliary

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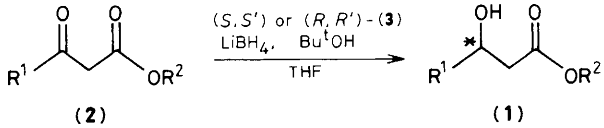
Optically active 3-aryl-3-hydroxyesters of high enantiomeric excess (80—92% e.e.) are obtained by the reduction of 3-aryl-3-oxoesters with lithium borohydride which has been chirally modified with *N,N'*-dibenzoylcystine and t-butyl alcohol.

Optically active 3-hydroxyesters (**1**) form an important class of compounds.[1] Asymmetric reductions of 3-oxoesters (**2**) to (**1**) by microbial[2] or chemical (modified Raney nickel[3]) methods are known. However, very few examples of the reduction of (**2**; R^1 = aryl) have been reported.[2a]

During our continuing study on chemoselective[4] and asymmetric[5] reduction with complex borohydrides, we observed a highly enantioselective reduction of (**2**; R^1 = aryl) by $LiBH_4$ partially decomposed with *N,N'*-dibenzoylcystine (**3**) and Bu^tOH. When ethyl benzoylacetate (**2b**) was reduced in the presence of (*R,R'*)-(**3**), (*R*)-(+)-(**1b**) was obtained in 94% yield and in 87% enantiomeric excess (%e.e., Table 1, entry 2).† The chiral auxiliary was recovered in over 70% yield. Esters of sec-, tert-alcohols (**2c, e**), and ethyl 1-naphthoylacetate (**2i**) were found to be slightly more effectively reduced, thus the %e.e.'s of (**1c, e, i**) reached 90% (entries 4, 6, and 10).



(**2**) (**1**)

a; R^1 = Ph, R^2 = Me
b; R^1 = Ph, R^2 = Et
c; R^1 = Ph, R^2 = Pr^i
d; R^1 = Ph, R^2 = Bu^n
e; R^1 = Ph, R^2 = Bu^t
f; R^1 = Ph, R^2 = n-Hexyl
g; R^1 = *p*-Tolyl, R^2 = Et
h; R^1 = 4-MeO-C_6H_4, R^2 = Et
i; R^1 = 1-Naphthyl, R^2 = Et

(**3**) = *N,N'*-Dibenzoylcystine, THF = tetrahydrofuran

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† (*S*)-(−)-(**1b**), produced *via* yeast reduction {$[\alpha]_D^{20}$ −25.8° (*c* 1.3, $CHCl_3$)}, ref. 2a, is claimed to be optically pure based on the lit. value of $[\alpha]_D^{20}$ +19.2° (*c* 1.0, $CHCl_3$) (J. Kenyon, H. Phillips, and G. R. Schutt, *J. Chem. Soc.*, 1935, 1663). However, the specific rotation of our (*S*)-(−)-(**1b**) had a larger value: $[\alpha]_D^{22}$ −40.8° (*c* 1.03, $CHCl_3$) (Table 1, entry 3).

Table 1. Asymmetric reduction of (**2**) to (**1**).[a]

		(**1**)			
Entry	(**2**)	Yield (%)	$[\alpha]_D^{22}$ (*c*, solvent)	Enantiomeric excess (%e.e.)[b]	Configuration
1	**a**	78	+16.0° (4.80, EtOH)	84(87[c])	*R*[c]
2	**b**	94	+43.1° (3.11, $CHCl_3$)	87(79[d])	*R*[d]
3[e]	**b**	93	−41.5° (3.40, $CHCl_3$) −40.8° (1.03, $CHCl_3$)[f]	86(76[d])	*S*[d]
4	**c**	83	+38.7° (2.61, $CHCl_3$)	91	
5	**d**	83	+35.2° (3.78, $CHCl_3$)	80	
6	**e**	88	+9.6° (3.03, EtOH)	90	
7	**f**	66	+31.6° (4.87, $CHCl_3$)	86	
8	**g**	88	+38.6° (4.59, $CHCl_3$)	85	
9	**h**	85	+35.7° (5.26, $CHCl_3$)	84	
10	**i**	90	+62.3° (3.55, $CHCl_3$)	92	

[a] Molar ratio of (**2**) : $LiBH_4$: (**3**) : Bu^tOH = 1.0 : 3.6 : 1.2 : 1.6. Temperature (−78 → −30°C). Unless otherwise noted, (*R,R'*)-(**3**) was used. [b] Determined by ^1H n.m.r. spectroscopic analyses of the corresponding (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid esters, J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, 1969, **34**, 2543. [c] Based on the reported value of (*R*)-(**1a**) $[\alpha]_D^{24}$ +18.3° (*c* 4.78, EtOH), C. Schoepf and W. Wuest, *Ann.*, 1959, **626**, 150. [d] Based on the reported value of (*S*)-(**1b**) $[\alpha]_D^{22}$ −54.9° (*c* 3.5, $CHCl_3$), S. G. Cohen and S. Y. Weinstein, *J. Am. Chem. Soc.*, 1964, **86**, 725. [e] (*S,S'*)-(**3**) was used. [f] Data measured in different concentration. See footnote†.

One of the advantages of the present procedure over microbial methods is its easy access to either enantiomer of (**1**). The reduction of (**2b**) using either (*R,R'*)-(**3**) or (*S,S'*)-(**3**) afforded the corresponding enantiomer of (**1b**) in almost the same yield and %e.e. (entries 2 and 3).

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