A New Approach to Remote Asymmetric Induction in the Diastereoselective Reduction of γ-Keto Esters by Use of a Chiral Podand as Chiral Auxiliary

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An efficient 1,7-asymmetric induction was achieved with up to 82% diastereoisomeric excess (d.e.) in the diastereoselective reduction of the γ-keto ester **4** and *o*-acetylbenzoate **6** using the chiral podand **2** as chiral auxiliary.

Diastereoselective reduction of chirally modified keto acids is a practical method for the synthesis of optically active hydroxy acid derivatives, which are important intermediates in the synthesis of optically active natural products. While several chiral auxiliaries have been reported for the efficient diastereoselective reduction of α- and β-keto acids,[1] those for γ-keto acids have not yet been found[2] presumably because of the difficulty in carrying out the remote asymmetric induction over at least the 1,6-positions required in these systems. We present here a preparation of 2′-[2-(2-methoxyethoxy)ethoxy]-1,1′-binaphthalen-2-ol **2**, a new chiral podand, and its application as a chiral auxiliary for the highly diastereoselective reduction of γ-keto acids. Our approach for such a remote asymmetric induction by use of **2** in conjunction with a Lewis acid is depicted in Fig. 1. Corey–Pauling–Koltun (CPK) molecular models indicate that the chelation of the oxygen atoms of the oxyethylene chain and the keto carbonyl function to the Lewis acid will fix the orientation of the carbonyl groups

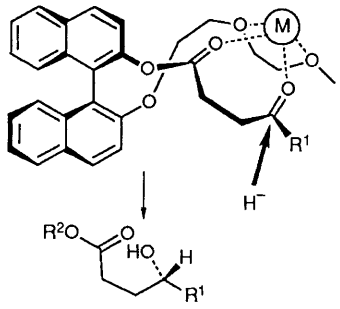


Fig. 1

Table 1 Diastereoselective reduction of **4**, **5** and **6**[a]

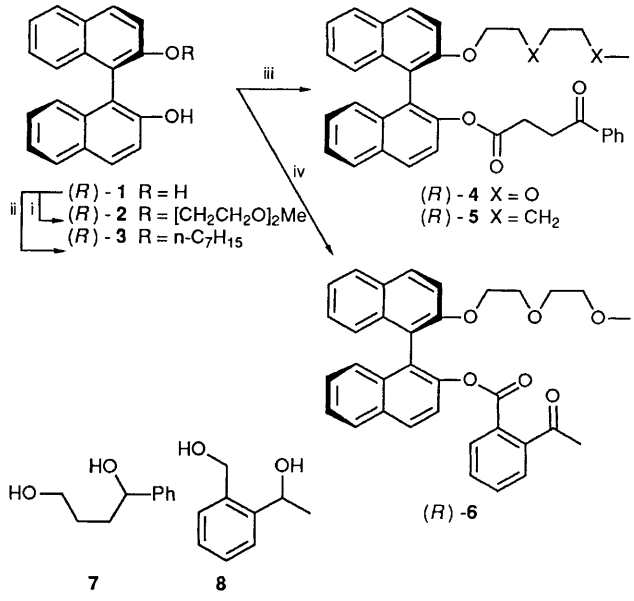
Run	Ester	Lewis acid	Product	Isolated yield (%)	E.e. (%)	Confign.
1	**4**	None	**7**	90	11	*R*
2	**4**	$ZnCl_2$	**7**	90	39	*R*
3	**4**	$MgBr_2$–OEt_2	**7**	82	82	*S*
4	**5**	None	**7**	99	4	*R*
5	**5**	$ZnCl_2$	**7**	92	5	*R*
6	**5**	$MgBr_2$–OEt_2	**7**	93	14	*R*
7	**6**	None	**8**	99	29	*S*
8	**6**	$ZnCl_2$	**8**	99	28	*S*
9	**6**	$MgBr_2$–OEt_2	**8**	61	83	*R*

[a] Unless otherwise noted, reactions were performed using Bu^i_2AlH (toluene; 1.0 mol dm^{-3}) in CH_2Cl_2 ([ester] = 0.02 mol dm^{-3}) in the presence of 3.0 equiv. of Lewis acid at −78 °C.

of the γ-keto esters. Consequently, one face of the ketocarbonyl π-bond is open while the other face is effectively blocked by the oxyethylene chain.

Readily available homochiral (*R*)-1,1′-binaphthalen-2,2′-diol **1**[3] was converted to the keto esters **4**, **5** and **6** in good yields by conventional methods as shown in Scheme 1.† A typical asymmetric reduction procedure (Table 1, run 3) is as follows. Under a nitrogen atmosphere, **4** (0.91 mmol) was dissolved in dichloromethane (46 ml), to which was added $MgBr_2$–OEt_2 (2.73 mmol). The resulting dispersion was stirred at ambient temperature for 1 h, and then at −78 °C for 1 h. An excess of diisobutylaluminium hydride (5 mmol) in toluene (1.0 mol dm^{-3}) was added dropwise to the dispersion to complete the reduction of the ketocarbonyl group. The resulting hydroxy acid ester was treated with lithium aluminium hydride, and the usual work-up followed by preparative-scale TLC gave the diol (−)-**7** in 82% yield. Analysis of the bis-3,5-dinitrophenyl carbamate of **7** by chiral stationary phase HPLC[4] [ethanol–hexane (3:7) as eluent] showed the enantiomeric excess (e.e.) to be 82%. The absolute configuration of (−)-**7** was determined by converting‡ it to (*S*)-1-phenylbutan-1-ol.[5] Bu^i_2AlH reduction of the *o*-acetylbenzoate **6** gave 3-methylphthalide,[6] which was converted to diol **8** for HPLC determination of the e.e. by the same method as for **7**.

Table 1 shows the results of the reduction of the γ-keto acid esters **4**–**6**. The degree of asymmetric induction was found to be highly dependent on the kind of Lewis acid, the ratio of the Lewis acid to the keto esters, the solvent and the reducing agent used. A high level of 1,7-asymmetric induction (82% d.e.) was observed in the reduction of **4** (run 3) and **6** (run 9) by use of Bu^i_2AlH in dichloromethane in the presence of $MgBr_2$–Et_2O (3.0 equiv.). In these cases, the absolute configuration at the newly formed asymmetric centre may be explained by the addition of the hydride to the diastereoface opposite to the oxyethylene chain as depicted in Fig. 1. These results are in contrast with those obtained with $ZnCl_2$ as the Lewis acid (run 2 and 8). The origin of these discrepancies is not clear but the difference in coordination numbers between $MgBr_2$ and $ZnCl_2$ may be responsible. The levels of the asymmetric induction were dramatically decreased in the reduction of **5** (runs 4–6), in which the two dialkyl ether oxygen atoms were replaced for methylene groups. This result indicates that the cooperative chelation of the oxygen atoms of the oxyethylene chain and the carbonyl groups to the Lewis acid plays an important role for efficient remote asymmetric induction. Fig. 1 requires that the two carbonyl functions of the γ-keto acid residue should assume a rigid S-*cis*-conformation for highly stereoselective reduction. In this context, it should be noted that Bu^i_2AlH reduction of the *o*-acetylbenzoate **6** also proceeded with high stereoselectivity (run 9).



Scheme 1 *Reagents and conditions*: i, *p*-$MeC_6H_4SO_3[CH_2CH_2O]_2Me$ (1.0 equiv.), KOH (1.2 equiv.), tetrahydrofuran–H_2O (10:1), 43%; ii, n-$C_7H_{15}Br$ (1.1 equiv.), K_2CO_3 (1.1 equiv.), acetone, 45%; iii, $PhCOCH_2CH_2CO_2H$, 1,3-dicyclohexylcarbodiimide, 4-pyrrolidinopyridine, CH_2Cl_2, 94% (**4**), 90% (**5**); iv, *o*-$MeCOC_6H_4COCl$, Et_3N, 4-pyrrolidinopyridine, CH_2Cl_2, 80%

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† All new compounds gave satisfactory spectral data and elemental analyses. Yields are for the isolated pure products.

‡ *Reagents*: i, Al_2O_3, EtOAc, 56%; ii, Bu^tMe_2SiCl, imidazole, dimethylformamide (DMF), 89%; iii, $LiAlH_4$, Et_2O, 86%; iv, *p*-$MeC_6H_4SO_2Cl$, *N*,*N*-dimethylaminopyridine, pyridine, 52%; v, $LiAlH_4$, Et_2O, 91%; vi, 66% AcOH, 70%.