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# Monobenzylether of (*R,R*)-1,2-Diphenylethane-1,2-diol as Chiral Auxiliary in the Diastereoselective Reduction of α-Ketoesters†

Stefano Superchi, Michela Contursi and Carlo Rosini*

Dipartimento di Chimica, Università della Basilicata, via N. Sauro 85, 85100, Potenza, Italy.

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***Abstract:*** The α-ketoester **4a**, prepared in 3 steps from (*R,R*)-1,2-diphenylethane-1,2-diol can be reduced with several agents providing the corresponding α-hydroxyester **5** with diastereoselectivities up to 56%. This selectivity has been interpreted as due to carbonyl face-shielding by the stacked $OCH_2Ph$ moiety of **4a**. 

The preparation of chiral α-hydroxy acids is still an important goal in organic chemistry owing to their relevance as versatile chiral building blocks in the synthesis of biologically active compounds.[1] Since the seminal papers of Prelog,[2] the diastereoselective reduction of chiral α-keto esters has emerged as one of the most practical method in order to achieve this task. The earlier chiral auxiliaries used in the preparation of chiral α-keto esters for this purpose (i.e. (-)-8-phenylmenthol[3] and *trans*-2-phenyl-1-cyclohexanol[4]) although allowing good diastereoselectivities showed limitations in large scale use owing to their high cost. This fact has recently stimulated a great number of investigations aimed at disclosing new chiral auxiliaries with higher efficiency and availability.[5] All the chiral auxiliaries described so far show some common structural features: i) a large group is present which can shield one face of the ketone carbonyl by a nucleophilic attack; ii) the two stereogenic centres which bear, respectively, the ester moiety and the shielding group belong to a ring, in order to restrict the conformational mobility of the molecule. Moreover the shielding group is often an aromatic residue and in this case the occurrence of π–π (stacking) interaction[6] with the dicarbonyl is invoked[6b] in order to enforce the face to face arrangement of these two groups.

Reasoning that the presence of a ring is not strictly necessary if the molecule has other steric and electronic features which stabilize the required conformation, we started a study aimed at designing the new

† Dedicated with much respect to Professor S. F. Mason FRS on the occasion of his 75th birthday and in consideration of his fundamental contribution to the understanding of the chemical behaviour of chiral molecules.

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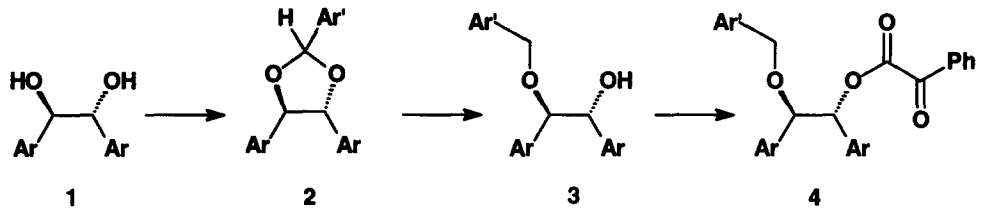
easily available class of auxiliaries **3** based on enantiomerically pure 1,2-diarylethan-1,2-diols **1**. Scheme 1 shows the simple and straightforward route followed to the auxiliaries **3** and to the chiral α-ketoesters **4**.

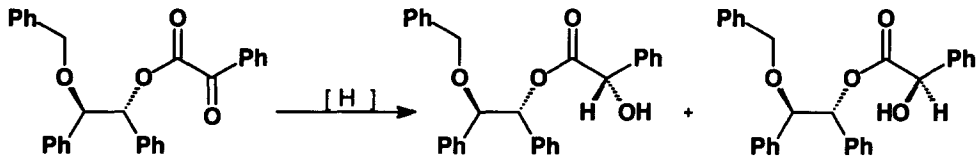
**Scheme 1**




Some aspects of the approach depicted are noteworthy: i) both enantiomers of **1** are easily available by catalytic asymmetric dihydroxylation of the corresponding (*E*)-olefins;[7] ii) the $C_2$-symmetric nature of **1** guarantees that only one product is afforded in the steps **1**→**2**→**3**; iii) a variety of Ar and Ar' groups (bearing EWG, EDG and sterically demanding substituents) can be used allowing a fine tuning of the stereoelectronic properties of **4**; iv) the ester moiety and the aryl group of the ether could give rise to a stabilizing π-stacking interaction allowing a selective blocking of one face of the ketone group.

Aim of this paper is then to describe the results obtained in the stereoselective reduction of the ketoester **4a** (Ar=Ar'=Ph), i.e. the parent compound of the series **4** (see Scheme 2).

**Scheme 2**




## Results and discussion

**a.** Synthesis. (*R,R*)-1,2-Diphenylethane-1,2-diol (**1a**)[7] by reaction with benzaldehyde and traces of TsOH afforded, by water removal in a Dean-Stark condenser, the acetal **2a** which, after reduction with DIBAL (2.5 equiv.) in toluene at 0°C, gave the monobenzylether **3a**.[8] Esterification of **3a** with phenylglyoxylic acid in presence of DCC (2.0 equiv.) and DMAP (0.5 equiv.) in $CH_2Cl_2$ at 25°C afforded the α-ketoester **4a** in 70% overall yield. Alternatively, reaction of **3a** with phenylglyoxylic chloride (1.2 equiv.) and pyridine (2.0 equiv.) in $CH_2Cl_2$ afforded **4a** in similar yield.

**b.** Stereoselective reductions. Ester **4a** was reacted with several reducing agents and the results are collected in the Table. The reductions proceeded always quite rapidly, affording the alcohols **5a** and **5b** in about 15 minutes and in quantitative yields. The diastereoisomeric ratio of **5a** and **5b** was directly determined on crude by $^1$H NMR analysis. The chromatographic separation of this two α-hydroxyesters ($Et_2O$/Petroleum Ether 1:1), followed by basic hydrolysis ($K_2CO_3$/methanol) to mandelic acid and comparison of its optical rotation with literature values,[9] allowed the assignment of their absolute configuration. This basic hydrolysis also allowed recovery of the chiral auxiliary **3a** without loss of optical purity.

**Table.** Diastereoselective Reductions of the α-Ketoester **4a**.[a]

| run | reducing agent | additive (equiv.) | solvent | T(°C) | Ratio[b] (**5a** : **5b**) |
|---|---|---|---|---|---|
| 1 | $NaBH_4$ | - | EtOH/THF | 0 | 40 : 60 |
| 2 | $NaBH_4$ | - | EtOH/Toluene | -78 | 47 : 53 |
| 3 | $LiBEt_3H$ | - | THF | -78 | 67 : 33 |
| 4 | Li-Selectride | - | THF | -78 | 78 : 22 |
| 5 | K-Selectride | - | THF | -78 | 73 : 27 |
| 6 | Li-Selectride | - | $Et_2O$ | -78 | 75 : 25 |
| 7 | Li-Selectride | $ZnCl_2$ (2.0) | THF | -78 | 50 : 50 |
| 8 | DIBAL | - | THF | -78 | 73 : 27 |
| 9 | DIBAL | - | Toluene | -78 | 45 : 55 |
| 10 | DIBAL | - | $Et_2O$ | -78 | 50 : 50 |
| 11 | DIBAL | $ZnCl_2$ (2.0) | THF | -78 | 37 : 63 |
| 12 | DIBAL | LiCl (2.0) | THF | -78 | 55 : 45 |

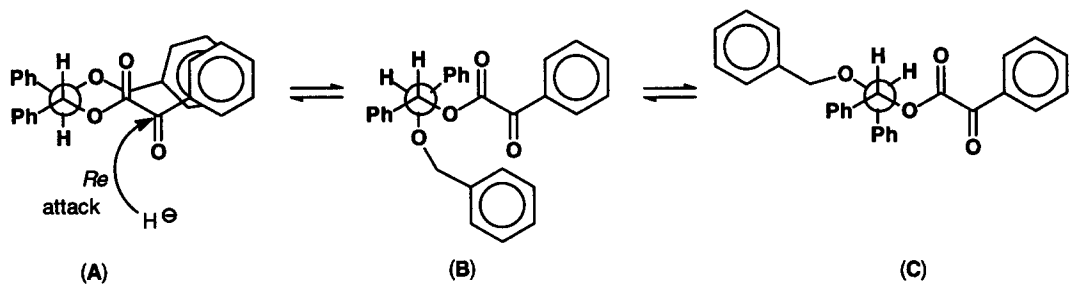
[a] For conditions see Experimental Section. [b] Directly determined on crude by $^1$H NMR analysis.

Examination of the Table reveals that only low diastereoselectivities can be achieved with $NaBH_4$ and $LiBEt_3H$ either at 0°C and -78°C (runs 1-3), while better results were obtained with DIBAL as well as with Li- and K-Selectride in THF at -78°C (runs 4, 5). Moreover, except for $NaBH_4$, all the reducing agents employed afforded in THF and in absence of added salts the (*R,R,S*) diastereoisomer **5a** as the major one. In the reductions with DIBAL a clear solvent effect was observed: while in THF the diastereoselection was good (run 8), in $Et_2O$ there was not selection at all (run 10) and an inversion of facial selectivity in hydride attack was obtained changing from THF to toluene (run 9). Li-Selectride provides, on the contrary, almost the same extent of stereoselection either in THF and $Et_2O$. Also the presence of added salts influenced the stereoselectivity of the reductions: addition of 2 equivalents of $ZnCl_2$ and LiCl in the reduction with DIBAL

caused an inversion (run 11) and a reduction of selectivity (run 12). The same addition of $ZnCl_2$ to Li-Selectride decreased the extent of facial selectivity as well.

Even if at the moment we are not able to provide a detailed explanation for all these results, we can interpret the sense of the asymmetric induction observed as follows. It is well known[10] that in simple alkyl esters having a secondary alcoholic residue, the hydrogen lies nearly coplanar and *syn* to the ester carbonyl. Moreover in **4a** the *anti* disposition of carbonyls is preferred[11] to reduce their dipole-dipole interactions. With these structural restrictions in mind we can depict the three conformations A, B and C for **4a** (see Figure)[12] where only in A the *Si* face of the carbonyl is shielded by the benzyl ether moiety. If we assume an equal concentration of the three conformers A, B and C, in the $^1H$ NMR spectrum a mean $J_{HC^*\text{-}C^*H}$ of about 7 Hz will result[13] and a maximum selectivity of about 33% is to be expected. As a matter of fact only in conformer A we can have face selection with hydride attack on the *Re* face of carbonyl and obtain **5a** with complete stereoselectivity while in B and C the same attack can occur on both carbonyl faces, with the same probability. As we experimentally measured a larger $J_{HC^*\text{-}C^*H}$($\approx$ 8 Hz) and obtained significantly larger stereoselectivity (about 60%), we can then conclude that the conformer A prevails on both B and C.

**Figure**




The inversion of configuration or the decreasing of selectivity noticed by addition of $ZnCl_2$ can be explained[5] admitting that this Lewis acid, by complexing the two carbonyls changes the conformation of the dicarbonyl moiety in A from *anti* to *syn*, allowing the attack of [$H^-$] onto the *Si* face and so providing the **5b** diastereoisomer in excess. Even if it is reported that Selectrides as well often determine[5] the attack of the hydride to a *syn* dicarbonyl moiety, owing to the complexation of the $Li^+$ or $K^+$ cation to the dicarbonyl, we did not observe a similar trend as in **4a** the *anti-syn* transformation put the phenyl group of the ester close to a phenyl coming from the diol, giving rise to steric hindrance. This *anti-syn* switch is allowed only if the energy gained in the complexation is greater than the steric repulsion and happens only in the case of $Zn^{++}$, a stronger Lewis acid than $Li^+$. Another evidence of this statement is that the addition of LiCl (entry 12) lead only to a loss of diastereoselectivity, but not to an inversion as $ZnCl_2$ did. With this simple considerations we can also

attempt at explaining the solvent effect observed in the DIBAL reductions. When the reaction is carried out in THF it proceeds as described before while, in a non coordinating solvent like toluene, the aluminum atom of DIBAL can be coordinated by the carbonyls. In this way the hydride attack can be explained as above by a Cram chelate model[14] with attack on the more exposed *Si* face leading to the **5b** isomer.

The significant (although moderate, 56 % as a maximum) de's observed can be explained as the result of the prevalence of conformation A with stacked $OCH_2Ph$ and ketoester moieties. The facile tuning of the stereoelectronic effects, as discussed in the Introduction, by a suitable choice of the substituents on the diol and the ether moiety should allow the synthesis of a taylor-made **4** where the conformation A is the only present and then higher selectivities can be obtained. In other words could then be designed a new chiral auxiliary which guarantees high stereoselectivities without the intervention of a ring linking the ester moiety and the shielding group.

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## EXPERIMENTAL SECTION

**General Procedures.** Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. $^1H$ NMR (300 MHz) and $^{13}C$ NMR (75 MHz) spectra were recorded in $CDCl_3$ on a Bruker Aspect 300 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 883 instrument, using KBr disks. Reductions were performed using syringe-septum cap techniques under nitrogen atmosphere. DIBAL was a 1.5 M solution in toluene, L-Selectride®, K-Selectride® and $LiBEt_3H$ (Super-Hydride®) were 1.0 M solutions in THF. Toluene, $Et_2O$ and THF were freshly distilled prior their use on sodium benzophenone ketyl under nitrogen atmosphere. $CH_2Cl_2$ was distilled over $P_2O_5$ and stored over $CaCl_2$. Analytical TLC was performed on 0.2 mm silica gel plate Merck 60 F-254 and column chromatography was carried out with silica gel Merck 60 (80-230 mesh).

***(4R,5R)*-2,4,5-Triphenyl-1,3-dioxolane (2a).** A solution of benzaldehyde (1.2 g, 11.2 mmol), **1a** (2.0 g, 9.33 mmol) and traces of *p*-toluensulfonic acid in benzene (150 mL) was refluxed for 3 h in a Dean-Stark condenser. After removal of solvent the residue was recrystallized from heptane recovering 2.35 g (83%) of **2a** as white crystals. mp 71-72°C (for (±) **2a** lit.[15] mp 100-101°C) ; $[\alpha]^{20}_D$ = + 16.1 (*c* 1.02, $CHCl_3$); IR (KBr)

3020, 2880, 1500, 1470, 1460, 1410, 1375, 1225, 1095, 1070, 1010, 975, 920, 765, 700 $cm^{-1}$; *$^1$H-NMR* $\delta$ 4.94 (d, *J*= 8.0 Hz, 1H), 4.98 (d, *J*= 8.0 Hz, 1H), 6.41 (s, 1H), 7.2-7.6 (m, 13H), 7.68 (dd, *J'*= 7.3 Hz, *J"*= 1.6 Hz, 2H); *$^{13}$C-NMR* $\delta$ 85.26, 87.18, 104.69, 124.42, 126.64, 126.91, 128.20, 128.45, 128.51, 128.56, 129.35, 136.54, 138.16, 138.26; Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.46; H, 6.10.

***(1R,2R)*-1,2-Diphenyl-2-benzyloxyethanol (3a).** To a solution of **2a** (1.5 g, 4.96 mmol) in toluene (25 mL), under $N_2$, was slowly added at 0°C a solution of DIBAL (1.5 M in toluene, 8.3 mL, 12.42 mmol). After 2h the mixture was quenched with methanol (1 mL), diluted with $Et_2O$, washed with 10% aqueous NaOH, brine and dried over $Na_2SO_4$. After evaporation of solvent the recovered residue was purified by column chromatography (petroleum ether/$Et_2O$ 3:1) affording 1.38 g (92%) of **3a** as white needles. mp 55 °C; $[\alpha]^{20}_D$ = -11.4° (*c* 1.1, $CHCl_3$); IR (KBr) 3540 (OH), 3025, 2860, 1500, 1455, 1200, 1075, 765, 700 $cm^{-1}$; *$^1$H-NMR* $\delta$ 3.54 (d, *J*= 1.4 Hz, 1H), 4.34 (d, *J*= 11.4 Hz, 1H), 4.36 (d, *J*= 8.2 Hz, 1H), 4.53(d, *J*= 11.4 Hz, 1H), 4.73 (d, *J*= 8.2 Hz, 1H), 6.9-7.5 (m, 15H); *$^{13}$C-NMR* $\delta$ 70.75, 78.53, 86.87, 127.23, 127.62, 127.76, 127.81, 127.90, 128.04, 128.09, 128.42, 137.52, 137.68, 139.15; Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.88; H, 6.55.

***(1R,2R)*-1,2-Diphenyl-2-benzyloxyethyl phenylglyoxylate (4a).** To a mixture of **3a** (1.0 g, 3.29 mmol), benzoylformic acid (0.98 g, 6.58 mmol) and N,N-dimethylaminopyridine (0.140 g, 1.15 mmol) in $CH_2Cl_2$ (15 mL) was slowly added at 0°C a solution of DCC (1.36 g, 6.58 mmol) in $CH_2Cl_2$ (5 mL) and left stirring overnight. To the resulting mixture was then added EtOH (1 mL) and the formed solid filtered under vacuum and washed with petroleum ether. The filtrate was treated with 10% HCl, saturated aqueous $NaHCO_3$, brine and dried over $Na_2SO_4$. After evaporation of solvent the recovered residue was purified by column chromatography (petroleum ether/$Et_2O$ 3:1) affording 1.30 g of **4a** (91%) as white plates. mp 125 °C; $[\alpha]^{20}_D$ = -53.9° (*c* 1.1, $CHCl_3$); IR (KBr) 3025, 2860, 1750 (CO), 1680 (CO), 1590, 1495, 1450, 1285, 1200, 1090, 1070, 980, 760, 690, 605, 550 $cm^{-1}$; *$^1$H-NMR* $\delta$ 4.34 (d, *J*= 11.9 Hz, 1H), 4.56 (d, *J*= 11.9 Hz, 1H), 4.71 (d, *J*= 8.0 Hz, 1H), 6.32 (d, *J*= 8.0 Hz, 1H), 7.1-7.5 (m, 17H), 7.60 (dt, *J'*= 7.4 Hz, *J"*= 1.0 Hz, 1H), 7.94 (dd, *J'*= 8.1 Hz, *J"*= 1.0 Hz, 2H); *$^{13}$C-NMR* $\delta$ 70.62, 80.35, 83.64, 127.42, 127.47, 127.64, 127.98, 128.15, 128.29, 128.43, 128.76, 130.13, 132.36, 134.73, 135.59, 136.76, 137.82, 163.28, 186.51; Anal. Calcd for $C_{29}H_{24}O_4$: C, 79.80; H, 5.54. Found: C, 79.75; H, 5.50.

**Representative procedure of reduction:** A solution of DIBAL (1.5 M in toluene, 0.23 mmol) was slowly added by syringe to a solution of **4a** (0.23 mmol) in THF (5 mL) kept at -78°C under $N_2$ atmosphere. The reaction, monitored by TLC was quenched by addition of methanol (0.1 mL), diluted with $Et_2O$, extracted with NaOH 10%, brine and dried over $Na_2SO_4$. After evaporation of solvent the crude mixture of

**5a** and **5b** was analyzed by $^1$H NMR in order to determine the diastereoisomeric ratio. The two diastereoisomers could also be isolated by column chromatography ($Et_2O$/petroleum ether 1:1).

**(*1R,2R*)-1,2-Diphenyl-2-benzyloxyethyl (*S*)-mandelate (5a).** $[\alpha]^{20}_D$ = - 7.1° (*c* 0.8, $CHCl_3$); *$^1$H-NMR* $\delta$ 3.52 (d, *J*= 5.2 Hz, 1H), 4.26 (d, *J*= 12.4 Hz, 1H), 4.51 (d, *J*= 7.5 Hz, 1H), 4.56 (d, *J*= 12.4 Hz, 1H), 5.25 (d, *J*= 5.2 Hz, 1H), 5.92 (d, *J*= 7.5 Hz, 1H), 6.57 (d, *J*= 7.3 Hz, 2H), 6.94 (t, *J*= 7.3 Hz, 2H), 7.0-7.1 (m, 3H), 7.1-7.4 (m, 13H); *$^{13}$C-NMR* $\delta$ 70.48, 73.01, 80.49, 82.97, 126.84, 127.50, 127.56, 127.64, 127.86, 128.12, 128.20, 128.31, 128.40, 135.87, 136.87, 138.05, 172.54.

**(*1R,2R*)-1,2-Diphenyl-2-benzyloxyethyl (*R*)-mandelate (5b).** $[\alpha]^{20}_D$ = - 11.3° (*c* 1.3, $CHCl_3$); *$^1$H-NMR* $\delta$ 3.48 (d, *J*= 5.0 Hz, 1H), 4.03 (d, *J*= 12.0 Hz, 1H), 4.29 (d, *J*= 12.0 Hz, 1H), 4.44 (d, *J*= 7.0 Hz, 1H), 5.19 (d, *J*= 5.0 Hz, 1H), 6.06 (d, *J*= 7.0 Hz, 1H), 6.84 (d, *J*= 6.8 Hz, 2H), 6.9-7.6 (m, 18H); *$^{13}$C-NMR* $\delta$ 70.39, 73.18, 80.21, 83.03, 126.97, 127.18, 127.25, 127.48, 127.75, 127.99, 128.09, 128.23, 128.38, 128.51, 136.20, 136.74, 137.82, 138.21, 172.74.

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12. The structures depicted are simply the result of some $^1$H NMR and literature data, as discussed above. Work is now in progress in order to establish the minimum energy conformation both by a more detailed analysis of the NMR spectra and by molecular mechanics calculations.

13. The $J_{HC^*\text{-}C^*H}$ value can be obtained by the classical Karplus equation, assuming an equal molar ratio for the three conformers. (see for instance: Hesse, M.; Meier, H.; Zeeh, B. *Metodi Spettroscopici nella Chimica Organica*; EdiSES: Napoli, 1996)

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