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Monobenzylethers of (*R*,*R*)-1,2-diphenylethane-1,2-diol as a possible alternative to cyclohexyl-based chiral auxiliaries in the stereoselective reduction of α-ketoesters

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Dedicated to Professor L. Lardicci on the occasion of his 75th birthday

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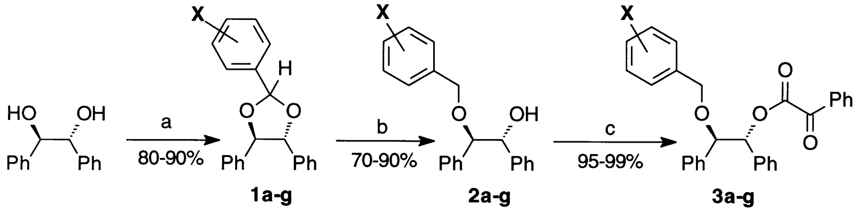
Abstract—The monobenzylethers of (*R*,*R*)-1,2-diphenylethane-1,2-diol have been used as chiral auxiliaries in the stereoselective reduction of the corresponding phenylglyoxylates. The diastereoselectivity of the reduction with either L-selectride or DIBAL was found to be strictly dependent on the nature of the substitution on the aromatic ring of the auxiliary and a maximum d.r. of 87:13 was obtained with the *p*-CF_3 substituted derivative. This investigation also shows that with open chain chiral auxiliaries diastereoselectivities of preparative interest can be achieved, suggesting that such auxiliaries can constitute a promising alternative to the commonest cyclohexyl-based ones. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Cyclohexyl-based chiral auxiliaries such as (−)-8-phenylmenthol[1] and *trans*-2-phenyl-1-cyclohexanol[2] are able to induce high levels of stereoselectivity in several asymmetric processes which involve the transformation of unsaturated moieties (usually dicarbonyls or activated double bonds). The high efficiency of these compounds results from a selective facial shielding of the functional group to be transformed,[2,3] due to a suitable face to face arrangement of the phenyl group of such auxiliaries and the unsaturated moiety. In these auxiliaries this arrangement is favored by the presence of a ring, which restricts the conformational mobility, and by the occurrence of π–π interactions[3,4] between these moieties. The main limitation of these auxiliaries is however their high cost and, for (−)-8-phenylmenthol, the commercial availability of only one antipode. For these reasons several efforts[5] have been devoted to find simpler and economic alternatives to them.

In order to achieve this task we also recently proposed[6] the use of the acyclic auxiliary **2a**, the monobenzylether of (*R*,*R*)-1,2-diphenylethane-1,2-diol, as chiral auxiliary for the diastereoselective reduction of α-keto esters. Compound **2a** shows the advantage that both enantiomers can be easily prepared from enantiopure 1,2-diphenylethane-1,2-diol,[7] as depicted in the Scheme 1. Significant diastereoselectivity (up to 60%) was obtained in the reduction of the



1a X=H
1b X=4-CF_3
1c X=4-OCH_3
1d X=4-*i*-Pr
1e X=4-Ph
1f X=2,3,4,5,6-F
1g X=3,4,5-OCH_3

Scheme 1. (a) ArCHO, TsOH, benzene, reflux, Dean–Stark; (b) DIBAL (2.5 equiv.), toluene, 0°C or $LiAlH_4/AlCl_3$ 1:2, Et_2O, 0°C; (c) PhCOCOOH (2.0 equiv.), DCC (2.0 equiv.), DMAP (0.5 equiv.), CH_2Cl_2, 25°C.

Keywords: chiral auxiliaries; a symmetric synthesis; α-hydroxyesters.

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corresponding ketoester **3a**,[6] thus demonstrating that in acyclic compounds like **3a** a substantial facial shielding of the dicarbonyl moiety can be achieved. Such shielding can, in principle, be improved either by increasing the strength of the π–π stacking interactions[4] between the carbonyl and the aryl groups, thus forcing their facial disposition, or by increasing the size of the aryl moiety. In auxiliaries like **2a** the nature of the shielding aryl group can be easily varied simply by changing the aldehyde used in the starting acetal (Scheme 1), and then an improvement of the efficiency of such an auxiliary seemed feasible. We therefore decided to carry out a systematic investigation on the effect of the nature of the shielding group upon the stereoselectivity of the reduction reaction with the aim to understand how the face to face disposition of the two unsaturated residues could be forced in order to improve the stereoselectivity.

We report herein the synthesis and characterization of compounds **2b–g**, their transformation into the corresponding phenylglyoxylates **3b–g**, and the outcome of their stereoselective reduction into the α-hydroxyesters **4b–g**. The aryl groups of compounds **2b–g** were chosen in order to test the effects on the stereoselectivity of both the electronic properties and the size of the aryl moieties. As a mater of fact, in the auxiliaries **2b** and **2c** we have a strong electron withdrawing group and electron donating group, respectively, which should affect the electron density on the benzene ring, and therefore the π-stacking. The auxiliary **2d**, by comparison with **2b** and **2c**, should allow us to understand the importance of simple steric effects, the *iso*-propyl group having almost the same size of a CF_3 moiety.[8] Compound **2e** was chosen since an extended aromatic system could increase the π-stacking and/or the shielding effect. The highly fluorinated benzene ring of **2f** displays[9] a reversed electrostatic charge distribution with respect to benzene, therefore should provide particularly efficient facial π–π interactions[10] with the phenylglyoxylate moiety. Finally, in **2g** the highly substituted and electron-rich aromatic residue should constitute a wide and efficient facial shield to the carbonyl group.

2. Results and discussion

Acetals **1b–g** were prepared in 80–90% yield by reacting (*R*,*R*)-1,2-diphenylethane-1,2-diol, a suitable arylaldehyde, and a catalytic amount of *p*-TsOH, in refluxing benzene under water removal using a Dean–Stark condenser. The monobenzylethers **2b–e** were obtained in 70–90% yield by reduction of the acetals **1b–e** with a three-fold excess of DIBAL in dry toluene at 0°C.[11] Unexpectedly, this procedure gave only poor yields in the case of **1f** and **1g**, even using a larger excess of DIBAL and employing either higher reaction temperatures or longer reaction times. We could not afford a satisfactorily explanation of this behavior, however we succeeded in this transformation by reducing the acetals **1f** and **1g** with a $LiAlH_4/AlCl_3$ (1:2) mixture in THF at 0°C.[12] This procedure afforded **2f** and **2g** in 68% yield. The auxiliaries **2b–g** were then esterified with phenylglyoxylic acid in the presence of DCC (2.0 equiv.) and DMAP (0.5 equiv.) in CH_2Cl_2 at 25°C, affording the required α-ketoesters **3b–g** in 95–99% yield (Scheme 1). Since all the reactions performed started from enantiopure (*R*,*R*)-1,2-diphenylethane-1,2-diol and did not involve the stereogenic centers, all the intermediate compounds can be safely considered enantiopure as well.

The reductions of α-ketoesters **3b–g** (Fig. 1) were performed in THF at −78°C with both L-selectride and DIBAL, the reducing agents which afforded the best results in our previous studies on **3a**.[6] The diastereoisomeric ratio of the α-hydroxy esters **4b–g** obtained (Table 1) was directly determined by ^1H NMR spectroscopic analysis of the crude reaction mixture by measuring the areas of the benzylic proton H_a (Fig. 2) in the two diastereoisomers (Table 2). The absolute configuration of the major diastereoisomer was determined by hydrolyzing the hydroxy ester mixture with K_2CO_3 in methanol and comparing the optical rotation of the recovered mandelic acid with literature values.[13] This assignment allowed us to establish that the lowest field doublet is related to the (*R*,*R*,*R*) stereoisomer. The basic hydrolysis also allowed quantitative recovery of the starting chiral auxiliary without loss of enantiomeric purity.

The results of the stereoselective reductions are collected in the Table 1. For clarity of comparison results for the α-ketoester **3a**, coming from our previous work,[6] are also

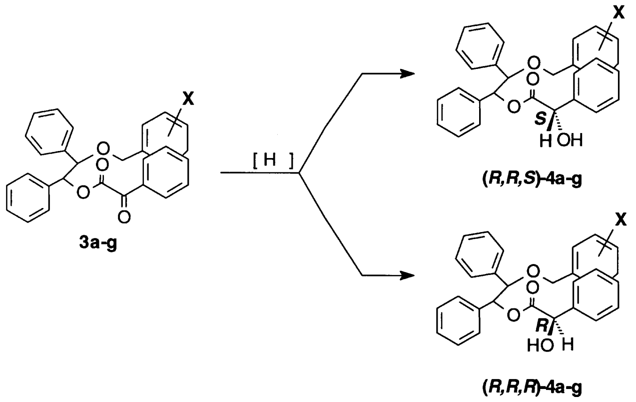


Figure 1.

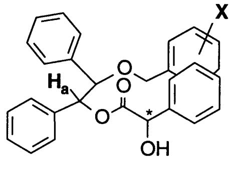
Table 1. Diastereoisomeric ratio of **4a–g** from reduction of α-ketoesters **3a–g**

Entry	Ester	X	Reducing agent	Ratio[a] (*R*,*R*,*S*)/(*R*,*R*,*R*)
1[b]	**3a**	H	L-Selectride	78:22
2[b]	**3a**	H	DIBAL	73:27
3	**3b**	4-CF_3	L-Selectride	87:13
4	**3b**	4-CF_3	DIBAL	57:43
5	**3c**	4-OCH_3	L-Selectride	70:30
6	**3c**	4-OCH_3	DIBAL	68:32
7	**3d**	4-*i*Pr	L-Selectride	83:17
8	**3d**	4-*i*Pr	DIBAL	70:30
9	**3e**	4-Ph	L-Selectride	80:20
10	**3f**	2,3,4,5,6-F	L-Selectride	75:25
11	**3f**	2,3,4,5,6-F	DIBAL	75:25
12	**3g**	3,4,5-OCH_3	L-Selectride	80:20
13	**3g**	3,4,5-OCH_3	DIBAL	30:70

Reductions performed in dry toluene, at −78°C under N_2 atmosphere (see Section 3).

[a] Directly determined on crude by ^1H NMR spectroscopic analysis.

[b] Data from Ref. 6.



4a-g

Figure 2.

Table 2. ^{1}H NMR (CDCl$_3$, 300 MHz) chemical shift and coupling constant of doublet due to proton H$_a$ in α-hydroxyesters **4a–g**

Product	X	δ (ppm)	J (Hz)
(*R*,*R*,*R*)-**4a**	H	6.06	7.0
(*R*,*R*,*S*)-**4a**	H	5.92	7.5
(*R*,*R*,*R*)-**4b**	4-CF$_3$	6.09	7.1
(*R*,*R*,*S*)-**4b**	4-CF$_3$	5.95	7.3
(*R*,*R*,*R*)-**4c**	4-OCH$_3$	6.02	7.0
(*R*,*R*,*S*)-**4c**	4-OCH$_3$	5.89	7.5
(*R*,*R*,*R*)-**4d**	4-*i*Pr	6.04	6.5
(*R*,*R*,*S*)-**4d**	4-*i*Pr	5.88	6.9
(*R*,*R*,*R*)-**4e**	4-Ph	6.09	7.0
(*R*,*R*,*S*)-**4e**	4-Ph	5.95	7.5
(*R*,*R*,*R*)-**4f**	2,3,4,5,6-F	5.92	6.5
(*R*,*R*,*S*)-**4f**	2,3,4,5,6-F	5.83	7.5
(*R*,*R*,*R*)-**4g**	3,4,5-OCH$_3$	6.08	6.4
(*R*,*R*,*S*)-**4g**	3,4,5-OCH$_3$	5.97	7.0

reported. This ester, which derives from the simplest alcohol **2a**, afforded a diastereoisomeric ratio of ca 4:1, with both L-selectride and DIBAL (entries 1 and 2). With all the auxiliaries the reduction of the carbonyl group was quite fast, affording the corresponding α-hydroxy esters **4b–g** in 15–20 min, pointing out that the nature of the chiral auxiliary does not affect the rate of the reaction. As expected, however, a clear effect of the nature of the chiral auxiliary on the diastereoisomeric ratio was observed. In general, L-selectride provided higher stereoselectivity in the reduction, inducing the preferential formation of the (*R*,*R*,*S*) stereoisomer. With such a reducing agent, a significant improvement of the stereoselectivity was observed in the case of ester **3b** (entry 3), where the benzene ring of the shielding moiety is substituted with a strong electron withdrawing group like CF$_3$. On the contrary, introduction of the electron donating OCH$_3$ group on the benzyl moiety reduced the diastereoselectivity (entry 5). These results can be due to a major shield which occurs, thanks to a more significant π-stacking, in the ketoester **3b** with respect to **3c**. π-Stacking is in fact mainly due to electrostatic interactions and these should be more effective between a phenyl and an electron poor arene.[4] In order to determine if the higher diastereoselectivity in **3b** was due either to electronic or simple steric effects, a comparison with the sterically comparable ester **3d** was done. The result obtained (entry 7), displaying a slightly lower selectivity in **3d** with respect to **3b**, seems to point out that in the latter other effects than simple steric interactions are operative. The use of the extended aromatic ring in **3e** (entry 9) did not afford an increase of selectivity if compared with the previous ones. Interestingly, in the case of **3f**, where the π-stacking should be enhanced by favorable electrostatic interactions,[9] the d.r. is almost the same as in the simple benzyl derivative **3a**. Reductions with DIBAL afforded lower stereoselectivity and usually the same (*R*,*R*,*S*) major diastereoisomer as L-selectride. From this point of view the results obtained in the case of the α-ketoester **3g** appear however quite unexpected. With such an ester the use of L-selectride (entry 12) gave a 80:20 d.r. (*R*,*R*,*S*/*R*,*R*,*R*), whilst with DIBAL (entry 13) we observed an inversion of selectivity and a lower 30:70 d.r. Then in this case, starting from the same α-ketoester it is possible to obtain either the *R*,*R*,*R* or the *R*,*R*,*S* α-hydroxyester simply changing the reducing agent.[14] This result is quite important both from a preparative and mechanistic point of view. In fact two different stereoisomers can be obtained starting from the same α-ketoester, and the interpretation of this unexpected stereochemical outcome could be very useful in understanding the mechanism of the stereochemical induction of this reaction.

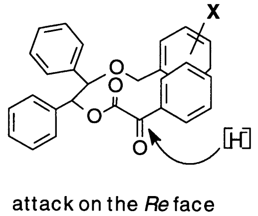


Figure 3.

The results reported in Table 1 can be qualitatively interpreted by the model we proposed[6] in the case of the parent α-ketoester **3a**, derived from **2a**, the simplest chiral auxiliary of the series. In this model the α-ketoesters **3b–g** assume the prevailing conformation depicted in Fig. 3. In this conformation the reducing agent can attack the carbonyl group only on the *Re* face, inducing the preferred formation of an (*S*) configured stereocenter. At present, we are not able to afford a clear interpretation of the unexpected result obtained with **3g** (entry 13), where an inversion of diastereoselectivity was observed in the reduction with DIBAL. This outcome could be determined by two different mechanisms: (a) a hydride attack from the inner *Si* face of the carbonyl group of the conformer depicted in Fig. 3, promoted by coordination of DIBAL to the oxygens of the trimethoxyphenyl group; (b) a *trans* to *cis* isomerization of the dicarbonyl moiety due to chelation of the Al atom[6,14] followed by hydride attack on the (in this conformation) outer *Si* face. We do not have neither experimental nor theoretical evidences to prefer one of these two possibilities over the other. This analysis of the stereochemical outcome of the reaction should prove instructive. Although we have tested several aryl moieties promoting, in principle, intramolecular π-stacking interactions, the diastereoselectivity was not improved so much with respect to the simple benzyl auxiliary **2a**. This result can be explained by arguing that the conformational freedom of such an auxiliary, related to the rotation around C*–C*, C*–O and OCH$_2$Ar bonds cannot be completely overcome by the relatively weak stabilizing effect of the intramolecular π-stacking. Working towards a reduction of molecular flexibility using, for instance, an aryl ether shielding moiety instead of a benzyl ether one could afford success in the diastereoselective induction.

In conclusion, the present investigation has clearly shown that an open chain chiral auxiliary can be satisfactorily used in the diastereoselective reduction of α-ketoesters, leading in some cases to stereoselectivities of preparative value. It has therefore pointed out that the alcohol **2b** could provide a practicable alternative to the cyclohexyl-based chiral auxiliaries. The mechanistic rationale formulated to analyze the stereochemical outcome has also indicated a possible way to further improve the stereoselectivity. Work is now in progress towards this end. As an important by-product, this investigation could provide a contribution to the understanding of weak bonding interactions, such as the π–π interactions, which play a fundamental role in chemistry, biology[15] and material science.[10,16]

3. Experimental

3.1. General procedures

Toluene, diethyl ether and THF were freshly distilled prior to their use on sodium benzophenone ketyl under nitrogen atmosphere. CH_2Cl_2 was distilled over P_2O_5 and stored over $CaCl_2$. Liquid aldehydes (Aldrich) were freshly distilled prior to their use under nitrogen atmosphere. Reductions were performed using syringe-septum cap techniques under nitrogen atmosphere. DIBAL (Aldrich) was a 1.5 M solution in toluene and L-selectride® (Aldrich) was a 1.0 M solution in THF. 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). 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 with TMS as internal standard. Infrared spectra were recorded on a Perkin–Elmer 883 instrument, using KBr disks.

3.2. Synthesis of (4*R*,5*R*)-2-aryl-4,5-diphenyl-1,3-dioxolanes 1b–g

A solution of arylaldehyde (11.2 mmol), (*R*,*R*)-1,2-diphenylethane-1,2-diol (9.33 mmol) and traces of *p*-toluensulfonic acid in benzene (150 mL) was heated at reflux in a Dean–Stark condenser. After removal of solvent the residue was purified by either recrystallization or column chromatography on silica gel.

3.2.1. (4*R*,5*R*)-2-(4-Trifluoromethylphenyl)-4,5-diphenyl-1,3-dioxolane (1b). The residue was purified by column chromatography (petroleum ether/Et_2O 3:1), recovering **1b** as a viscous colorless oil (77% yield). [Found: C, 71.5; H, 4.3. $C_{22}H_{17}F_3O_2$ requires C, 71.35; H, 4.63]; $[\alpha]_D^{20}=+6.3$ (*c* 1.0, $CHCl_3$); IR (KBr): 3040, 2900, 1330, 1170, 1120, 025, 1040, 760, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.90 (d, *J*=8.0 Hz, 1H), 4.99 (d, *J*=8.0 Hz, 1H), 6.45 (s, 1H), 7.27–7.40 (m, 10H), 7.71 (d, *J*=8.4 Hz, 2H), 7.80 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.3, 87.3, 103.6, 125.4, 125.5, 126.4, 126.9, 127.0, 127.1 (q, *J*=215.9 Hz), 128.4, 128.6, 131.4 (q, *J*=31.5 Hz), 136.1, 137.5, 142.3.

3.2.2. (4*R*,5*R*)-2-(4-Methoxyphenyl)-4,5-diphenyl-1,3-dioxolane (1c). The crude residue was purified by column chromatography (petroleum ether/Et_2O 3:1), obtaining **1c** as a viscous oil (57% yield). [Found: C, 79.2; H, 6.1. $C_{22}H_{20}O_3$ requires C, 79.50; H, 6.06]; $[\alpha]_D^{20}=+7.2$ (*c* 1.1, $CHCl_3$); IR (KBr): 3060, 3020, 2900, 1610, 1510, 1250, 1070, 1030, 760, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H), 4.95 (s, 2H), 6.36 (s, 1H), 6.98 (d, *J*=8.6 Hz, 2H), 7.27–7.35 (m, 10H), 7.61 (d, *J*=8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.3, 85.2, 87.1, 104.7, 113.8, 126.4, 126.9, 128.1, 128.4, 128.5, 128.6, 136.7.

3.2.3. (4*R*,5*R*)-2-(4-Isopropylphenyl)-4,5-diphenyl-1,3-dioxolane (1d). The residue was purified by column chromatography (petroleum ether/Et_2O 8:1), affording **1d** as a colorless oil (91% yield). [Found: C, 83.8; H, 7.5. $C_{24}H_{24}O_2$ requires C, 83.69; H, 7.02]; $[\alpha]_D^{20}=+10.1$ (*c* 0.7, $CHCl_3$); IR (KBr): 3030, 2960, 1450, 1390, 1090, 1020, 760, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (d, *J*=7.0 Hz, 6H), 2.96 (sept, *J*=7.0 Hz, 1H), 4.94 (d, *J*=9.3 Hz, 1H), 4.98 (d, *J*=9.3 Hz, 1H), 6.38 (s, 1H), 7.25–7.38 (m, 12H), 7.60 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 34.1, 85.2, 87.1, 104.7, 126.4, 126.6, 126.7, 126.9, 128.1, 128.5, 128.6, 135.7, 136.7, 138.4, 150.2.

3.2.4. (4*R*,5*R*)-2-(4-Biphenylyl)-4,5-diphenyl-1,3-dioxolane (1e). The residue was purified by column chromatography (petroleum ether/CH_2Cl_2 3:1) and then recrystallized by heptane, affording **3e** as white crystals (78% yield). Mp=84–86°C; [Found: C, 85.3; H, 6.2. $C_{27}H_{22}O_2$ requires C, 85.69; H, 5.86]; $[\alpha]_D^{20}=-13.0$ (*c* 1.0, $CHCl_3$); IR (KBr): 3080, 3040, 2900, 1500, 1460, 1100, 1080, 1010, 760, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.96 (d, *J*=10.0 Hz, 1H), 4.99 (d, *J*=10.0 Hz, 1H), 6.46 (s, 1H), 7.30–7.40 (m, 11H), 7.46 (t, *J*=7.6 Hz, 2H), 7.62 (d, *J*=7.2 Hz, 2H), 7.65 (d, *J*=8.3 Hz, 2H), 7.75 (d, *J*=8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.3, 87.2, 104.5, 126.4, 126.9, 127.1, 127.2, 127.3, 127.5, 128.2, 128.6, 128.8, 136.5, 140.8, 142.3.

3.2.5. (4*R*,5*R*)-2-(2,3,4,5,6-Pentafluorophenyl)-4,5-diphenyl-1,3-dioxolane (1f). The crude residue was purified by column chromatography (petroleum ether/Et_2O 4:1), recovering **1f** as a pale-yellow viscous oil (78% yield). [Found: C, 64.5; H, 3.7. $C_{21}H_{13}F_5O_2$ requires C, 64.29; H, 3.34]; $[\alpha]_D^{20}=+47.5$ (*c* 1.0, $CHCl_3$); IR (KBr): 3040, 2920, 1510, 1450, 1410, 1380, 1310, 1155, 1135, 1010, 935, 760, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (d, *J*=8.5 Hz, 1H), 5.02 (d, *J*=8.5 Hz, 1H), 6.76 (s, 1H), 7.23–7.38 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.4, 87.9, 97.0, 112.2 (m), 126.4, 127.0, 128.5, 128.6, 128.9, 134.8, 136.0 (m), 136.9, 139.4 (m), 140.42 (m), 144.2 (m), 147.6 (m).

3.2.6. (4*R*,5*R*)-2-(3,4,5-Trimethoxyphenyl)-4,5-diphenyl-1,3-dioxolane (1g). The residue was purified by column chromatography (petroleum ether/Et_2O 1:1), affording **1g** as viscous colorless oil (82% yield). [Found: C, 73.2; H, 6.3. $C_{24}H_{24}O_5$ requires C, 73.45; H, 6.16]; $[\alpha]_D^{20}=+0.5$ (*c* 1.0, $CHCl_3$); IR (KBr): 3020, 2950, 1600, 1510, 1470, 1240, 1130, 1010, 765, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 3.91 (s, 6H), 4.94 (d, *J*=7.9 Hz, 1H), 4.97 (d, *J*=7.9 Hz, 1H), 6.36 (s, 1H), 6.91 (s, 2H), 7.32–7.34 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.1, 60.7, 85.1, 87.0, 103.5, 104.4, 126.4, 126.8, 128.2, 128.5, 133.7, 136.4, 137.9.

3.3. Synthesis of monobenzylethers 2b–e

To a solution of the dioxolane **1** (4.96 mmol) in toluene (25 mL), under nitrogen, was slowly added at 0°C a solution of DIBAL (1.6 M, in toluene, 12.42 mmol) and the reaction was monitored by TLC. 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 on silica gel.

3.3.1. (1*R*,2*R*)-1,2-Diphenyl-2-(4-trifluoromethylbenzyloxy)ethanol (2b). The residue was purified by column chromatography (petroleum ether/CH_2Cl_2 4:1), affording **2b** as a colorless viscous oil (84% yield). [Found: C, 71.4; H, 5.7. $C_{22}H_{19}F_3O_2$ requires C, 70.96; H, 5.14]; $[\alpha]_D^{20}=-5.9$ (*c* 1.09, $CHCl_3$); IR (KBr): 3400 (OH), 3020, 2920, 1450, 1330, 1160, 1125, 1070, 760, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.41 (s, 1H), 4.37 (d, *J*=7.9 Hz, 1H), 4.41 (d, *J*=12.1 Hz, 1H), 4.57 (d, *J*=12.1 Hz, 1H), 4.77 (d, *J*=7.9 Hz, 1H), 7.04–7.26 (m, 10H), 7.41 (d, *J*=8.0 Hz, 2H), 7.60 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.0, 78.5, 87.2, 124.1 (q, *J*=269.6 Hz), 125.4, 127.1, 127.2, 127.8, 127.9, 128.3, 130.5 (q, *J*=31.4 Hz), 137.2, 139.2, 141.8.

3.3.2. (1*R*,2*R*)-1,2-Diphenyl-2-(4-methoxybenzyloxy)ethanol (2c). The residue was purified by column chromatography (petroleum ether/Et_2O 4:1), affording **2c** as an oil (68% yield). [Found: C, 79.2; H, 6.3. $C_{22}H_{22}O_3$ requires C, 79.02; H, 6.63]; $[\alpha]_D^{20}=-33.7$ (*c*1.1, $CHCl_3$); IR (KBr): 3400 (OH), 3030, 2860, 1620, 1510, 1380, 1240, 1060, 1020, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.53 (s, 1H), 3.81 (s, 3H), 4.26 (d, *J*=11.0 Hz, 1H), 4.32 (d, *J*=8.0 Hz, 1H), 4.45 (d, *J*=11.0 Hz, 1H), 4.70 (d, *J*=8.0 Hz, 1H), 6.90 (d, *J*=8.7 Hz, 2H), 7.02–7.24 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.3, 70.5, 78.6, 86.6, 113.3, 127.3, 127.6, 127.8, 127.9, 128.0, 128.1, 129.6, 129.8, 137.7.

3.3.3. (1*R*,2*R*)-1,2-Diphenyl-2-(4-isopropylbenzyloxy)ethanol (2d). The residue was purified by column chromatography (petroleum ether/Et_2O 3:1), recovering **2d** as white crystals (91% yield). Mp=75°C; [Found: C, 83.6; H, 7.3. $C_{24}H_{26}O_2$ requires C, 83.20; H, 7.56]; $[\alpha]_D^{20}=-15.3$ (*c* 1.0, $CHCl_3$); IR (KBr): 3400 (OH), 3070, 3040, 2970, 2870, 1460, 1390, 1200, 1090, 1045, 1020, 820, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, *J*=7.0 Hz, 6H), 2.92 (sept, *J*=7.0 Hz, 1H), 3.57 (s, 1H), 4.30 (d, *J*=11.0 Hz, 1H), 4.36 (d, *J*=8.3 Hz, 1H), 4.48 (d, *J*=11.0 Hz, 1H), 4.71 (d, *J*=8.3 Hz, 1H), 7.2–7.0 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.9, 33.9, 70.81, 78.6, 87.0, 126.5, 127.3, 127.6, 127.7, 127.8, 128.0, 128.1, 135.1, 137.7, 139.3, 148.6.

3.3.4. (1*R*,2*R*)-1,2-Diphenyl-2-(4-phenylbenzyloxy)ethanol (2e). The residue was purified by column chromatography (petroleum ether/Et_2O 4:1), recovering **2e** as white needles (81% yield). Mp=109–110°C; [Found: C, 85.7; H, 6.8. $C_{27}H_{24}O_2$ requires C, 85.23; H, 6.36]; $[\alpha]_D^{20}=-25.5$ (*c* 1.0, $CHCl_3$); IR (KBr): 3370 (OH) 3070, 3040, 2910, 2870, 1460, 1395, 1090, 1010, 770, 735, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.4 (bs, 1H), 4.41 (d, *J*=11.4 Hz, 1H), 4.42 (d, *J*=8.1 Hz, 1H), 4.59 (d, *J*=11.4 Hz, 1H), 4.78 (d, *J*=8.1 Hz, 1H), 7.1–7.7 (m, 19H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.6, 78.6, 87.0, 127.1, 127.2, 127.3, 127.7, 127.8, 127.9, 128.1, 128.2, 128.4, 128.7, 136.7, 137.6, 139.2, 140.8.

3.4. Synthesis of monobenzylethers 2f and 2g

To a solution of $AlCl_3$ (4.5 mmol) in 6 mL of Et_2O $LiAlH_4$ (2.25 mmol) was added at 0°C, under N_2. After 30 min of stirring, to the resulting mixture was slowly added a solution of the appropriate dioxolane **1** (1.5 mmol) in Et_2O (8 mL) and the reaction was monitored by TLC. After 24 h, the mixture was quenched with 10% aqueous H_2SO_4, and extracted with Et_2O. The combined ether layers were washed with brine and dried over Na_2SO_4. After removal of solvent, the recovered residue was purified by column chromatography on silica gel.

3.4.1. (1*R*,2*R*)-1,2-Diphenyl-2-(2,3,4,5,6-pentafluorobenzyloxy)ethanol (2f). The residue was purified by column chromatography (petroleum ether/Et_2O 4:1), recovering **2f** as white crystals (68% yield). Mp=96–97°C; [Found: C, 64.2; H, 3.5. $C_{21}H_{15}F_5O_2$ requires C, 63.96; H, 3.83]; $[\alpha]_D^{20}=-8.0$ (*c* 1.0, $CHCl_3$); IR (KBr): 3620 (OH), 3040, 2880, 1540, 1510, 1460, 1140, 1060, 980, 940, 780, 750, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.29 (s, 1H), 4.32 (d, *J*=8.0 Hz, 1H), 4.49 (d, *J*=11.0 Hz, 1H), 4.60 (d, *J*=11.0 Hz, 1H), 4.67 (d, *J*=8.0 Hz, 1H), 6.99–7.26 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.1, 78.4, 88.0, 111.2 (m), 127.1, 127.6, 127.8, 127.8, 128.2, 128.4, 135.8 (m), 136.7, 138.7 (m), 138.8, 143.1 (m), 144.0 (m), 147.3 (m).

3.4.2. (1*R*,2*R*)-1,2-Diphenyl-2-(3,4,5-trimethoxybenzyloxy) ethanol (2g). The residue was purified by column chromatography (petroleum ether/EtOAc 1:1), affording **2g** as colorless viscous liquid (68% yield). [Found: C, 73.5; H, 6.7. $C_{24}H_{26}O_5$ requires C, 73.08; H, 6.64]; $[\alpha]_D^{20}=-20.8$ (*c* 1.0, $CHCl_3$); IR(KBr): 3500 (OH), 3010, 2940, 1590, 1505, 1465, 1455, 1420, 1235, 1130, 755, 705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.60 (bs, 1H), 3.80 (s, 6H), 3.83 (s, 3H), 4.27 (d, *J*=11.0 Hz, 1H), 4.37 (d, *J*=7.8 Hz, 1H), 4.46 (d, *J*=11.0 Hz, 1H), 4.74 (d, *J*=7.8 Hz, 1H), 6.49 (s, 2H), 7.03–7.23 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.8, 60.5, 70.8, 78.2, 86.4, 104.8, 127.0, 127.4, 127.6, 127.7, 127.9, 133.2, 137.5, 139.2.

3.5. Synthesis of phenylglyoxylates 3b–g

To a mixture of the appropriate monobenzylether **2** (3.29 mmol), benzoylformic acid (6.58 mmol) and *N*,*N*-dimethylaminopyridine (1.15 mmol) in CH_2Cl_2 (15 mL) a solution of DCC (6.58 mmol) in CH_2Cl_2 (5 mL) was slowly added at 0°C. The resulting mixture was stirred overnight then quenched by addition of EtOH (1 mL). The mixture was then filtered under vacuum and the recovered solid carefully washed with petroleum ether. The collected filtrate was treated with 10% HCl, saturated aqueous $NaHCO_3$, brine and dried over Na_2SO_4. After evaporation of solvent the residue was purified by column chromatography on silica gel.

3.5.1. (1*R*,2*R*)-1,2-Diphenyl-2-(4-trifluoromethylbenzyloxy)-ethylphenylglyoxylate (3b). The residue was purified by column chromatography (petroleum ether/Et_2O 4:1), obtaining **3b** as a yellow viscous liquid, in 99% yield. [Found: C, 71.7; H, 4.3. $C_{30}H_{23}F_3O_4$ requires C, 71.42; H, 4.60]; $[\alpha]_D^{20}=-31.1$ (*c* 1.1, $CHCl_3$); IR (KBr): 2960, 2920, 2860, 1790 (CO), 1690 (CO), 1450, 1330, 1120, 1070, 760, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.40 (d, *J*=12.6 Hz, 1H), 4.58 (d, *J*=12.6 Hz, 1H), 4.70 (d, *J*=7.9 Hz, 1H), 6.30 (d, *J*=7.9 Hz, 1H), 7.12–7.38 (m, 14H), 7.52 (d, *J*=8.1 Hz, 2H), 7.60 (t, *J*=7.5 Hz, 1H), 7.92 (d, *J*=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.0, 80.3, 84.1, 125.2, 126.6 (q, *J*=211.2 Hz), 127.4, 127.6, 127.9, 128.2, 128.4, 128.4, 128.5, 128.6, 128.7, 128.8, 130.0, 132.3, 134.8, 135.4, 136.8 (q, *J*=57.7 Hz), 141.9, 163.1, 186.3.

3.5.2. (1*R*,2*R*)-1,2-Diphenyl-2-(4-methoxybenzyloxy)-ethylphenylglyoxylate (3c). The residue was purified by column chromatography (petroleum ether/Et_2O 1:1), obtaining **3c** as a white solid (65% yield). Mp=88–90°C; [Found: C, 77.5; H, 6.5. $C_{30}H_{26}O_5$ requires C, 77.24; H, 6.62]; $[\alpha]_D^{20}=-56.0$ (*c* 1.0, $CHCl_3$); IR (KBr): 3060, 3020, 2940, 1740 (CO), 1690 (CO), 1510, 1250, 1200, 1180, 990, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (s, 3H), 4.26 (d, *J*=11.5 Hz, 1H), 4.47 (d, *J*=11.5 Hz, 1H), 4.67 (d, *J*=7.8 Hz, 1H), 6.28 (d, *J*=7.8 Hz, 1H), 6.78 (d, *J*=12.7 Hz, 2H), 7.11–7.23 (m, 12H), 7.34 (t, *J*=7.5 Hz, 2H), 7.58 (t, *J*=7.5 Hz, 1H), 7.92 (d, *J*=7.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.2, 70.3, 80.4, 83.2, 113.7, 127.2, 127.6, 127.8, 128.0, 128.1, 128.2, 128.3, 128.7, 129.1, 129.6, 129.8, 129.9, 130.1, 132.4, 134.7, 135.7, 136.9, 163.2, 186.5.

3.5.3. (1*R*,2*R*)-1,2-Diphenyl-2-(4-isopropylbenzyloxy)-ethylphenylglyoxylate (3d). The residue was purified by column chromatography (petroleum ether/$CHCl_3$ 1:1), affording **3d** as a colorless viscous liquid (98% yield). [Found: C, 80.5; H, 6.2. $C_{32}H_{30}O_4$ requires C, 80.31; H, 6.32]; $[\alpha]_D^{20}=-55.8$ (*c* 1.0, $CHCl_3$); IR (KBr): 3060, 3030, 2960, 1740 (CO), 1690 (CO), 1600, 1450, 1380, 1200, 1175, 990, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (d, *J*=6.9 Hz, 6H), 2.90 (sept, *J*=6.9 Hz, 1H), 4.30 (d, *J*=11.6 Hz, 1H), 4.50 (d, *J*=11.6 Hz, 1H), 4.71 (d, *J*=7.9 Hz, 1H), 6.30 (d, *J*=7.9 Hz, 1H), 7.12–7.23 (m, 14H), 7.31 (t, *J*=8.2 Hz, 2H), 7.46 (t, *J*=7.5 Hz, 1H), 7.93 (d, *J*=8.2, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.00, 33.9, 70.7, 80.4, 83.7, 126.4, 127.6, 127.7, 128.0, 128.3, 128.4, 128.7, 128.8, 130.2, 132.5, 134.6, 135.3, 135.7, 137.0, 140.2 164.1, 186.5.

3.5.4. (1*R*,2*R*)-1,2-Diphenyl-2-(4-phenylbenzyloxy)-ethylphenylglyoxylate (3e). The crude residue was purified by column chromatography (petroleum ether/Et_2O 8:1), recovering **3e** as a pale-yellow viscous liquid (74% yield). [Found: C, 82.3; H, 5.4. $C_{35}H_{28}O_4$ requires C, 82.01; H, 5.51]; $[\alpha]_D^{20}=-58.0$ (*c* 1.0, $CHCl_3$); IR (KBr): 3060, 3040, 2920, 2880, 1740 (CO), 1690 (CO), 1600, 1490, 1450, 1200, 1180, 990, 760, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (d, *J*=11.9 Hz, 1H), 4.59 (d, *J*=11.9 Hz, 1H), 4.74 (d, *J*=8.0 Hz, 1H), 6.32 (d, *J*=8.0 Hz, 1H), 7.16–7.59 (m, 22H), 7.94 (d, *J*=7.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.4, 80.4, 83.7, 127.1, 127.2, 127.7, 127.9, 128.0, 128.2, 128.3, 128.4, 128.7, 130.1, 132.4, 134.7, 135.8, 136.9, 140.4, 140.9, 163.3, 186.5.

3.5.5. (1*R*,2*R*)-1,2-Diphenyl-2-(2,3,4,5,6-pentafluorobenzyloxy)-ethylphenylglyoxylate (3f). The residue was purified by column chromatography (petroleum ether/$CHCl_3$ 1:2), affording **3f** as a white solid (95% yield). Mp=107–108°C; [Found: C, 66.5; H, 3.9. $C_{29}H_{19}F_5O_4$ requires C, 66.16; H, 3.64]; $[\alpha]_D^{20}=-43.0$ (*c* 1.0, $CHCl_3$); IR (KBr): 3060, 3040, 2960, 2920, 2880, 1740 (CO), 1690 (CO), 1505, 1200, 1180, 990, 940, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$), 4.44 (d, *J*=9.9 Hz, 1H), 4.57 (d, *J*=9.9 Hz, 1H), 4.67 (d, *J*=7.6 Hz, 1H), 6.16 (d, *J*=7.6 Hz, 1H), 7.10–7.26 (m, 10H), 7.43 (t, *J*=7.2 Hz, 2H), 7.64 (t, *J*=7.2 Hz, 1H), 7.89 (d, *J*=7.9 Hz, 2H); ^{1}C NMR (75 MHz, $CDCl_3$) 58.3, 80.6, 84.8, 111.0 (m), 127.5, 127.8, 128.2, 128.4, 128.5, 128.6, 128.7, 130.0, 132.4, 134.7, 135.4, 139.0 (m), 139.7 (m), 143.0 (m), 143.9 (m), 147.3 (m), 162.8, 185.9.

3.5.6. (1*R*,2*R*)-1,2-Diphenyl-2-(3,4,5-trimethoxybenzyloxy)-ethylphenylglyoxylate (3g). The crude residue was purified by column chromatography (petroleum ether/AcOEt 3:1), affording **3g** as a colorless viscous liquid (79% yield). [Found: C, 73.3; H, 6.1. $C_{32}H_{30}O_7$ requires C, 72.99; H, 5.74]; $[\alpha]_D^{20}=-52.4$ (*c* 1.2, $CHCl_3$); IR (KBr): 3060, 3010, 2940, 1740 (CO), 1690 (CO), 1595, 1455, 1330, 1240, 1200, 1130, 990, 760, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 6H), 3.83 (s, 3H), 4.28 (d, *J*=12.0 Hz, 1H), 4.52 (d, *J*=12.0 Hz, 1H), 4.71 (d, *J*=8.1 Hz, 1H), 6.31 (d, *J*=8.1 Hz, 1H), 6.48 (s, 2H), 7.13–7.26 (m, 10H), 7.38 (t, *J*=7.9 Hz, 2H), 7.61 (t *J*=7.9 Hz, 1H), 7.94 (d, *J*=8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.0, 60.7, 70.7, 80.4, 83.3, 104.5, 127.8, 128.0, 128.1, 128.3, 128.4, 128.5, 128.8, 130.1, 132.4, 133.4, 134.8, 135.7, 136.7, 153.2, 186.4.

3.6. General procedure of reduction of phenylglyoxylates 3b–g

A solution of DIBAL (1.5 M in toluene, 0.23 mmol) was slowly added by syringe to a solution of the phenylglyoxylate **3** (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 α-hydroxyesters **4b–g** was analyzed by ^{1}H NMR spectroscopy in order to measure the diastereoisomeric ratio.

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