Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 16 (2005) 3211–3223

Chiral linker. Part 2: Synthesis and evaluation of a novel, reusable solid-supported open chain chiral auxiliary derived from *m*-hydrobenzoin for the diastereoselective reduction of α-keto esters

Christian Schuster, Max Knollmueller and Peter Gaertner*

Department of Applied Synthetic Chemistry, Vienna University of Technology, Getreidemarkt 9/163, A-1060 Vienna, Austria

Received 26 July 2005; accepted 17 August 2005

Abstract—Three novel *m*-hydrobenzoin derived chiral hydrobenzoin *mono*-alkyl ethers were synthesized and evaluated as open chain chiral auxiliaries in the L-selectride^R/$ZnCl_2$ mediated stereoselective reduction of their corresponding phenyl glyoxylates, resulting in des of up to 91%. The optimized auxiliary structure was immobilized on commercially available Wang-resin by using the ether substituent as a sublinking unit and applied as a reusable solid-supported chiral auxiliary in the same type of reaction with only little loss of stereofacial selectivity.

1. Introduction

Stereoselective solid phase synthesis methods employing solid-supported chiral reagents or catalysts have become a commonly used tool for combinatorial and parallel synthesis, and in recent years also a number of supported chiral auxiliaries have been developed,[1] mainly serine and tyrosine derived Evans oxazolidinones.[2] Such immobilized auxiliaries offer some advantages over their application in liquid phase, including an easy workup, simple separation, recovery and, thus, the possibility to recycle the expensive chiral material by simple filtration after cleavage of desired reaction products.

We have previously reported the synthesis and application of novel, *m*-hydrobenzoin derived chiral auxiliaries **I** and **II**, which are very similar to benzyl alcohol type linkers commonly used in solid phase organic synthesis (Scheme 1). These new auxiliaries were easily accessible by desymmetrization of *m*-hydrobenzoin **1** with Noe's commercially available chiral anhydro lactol protecting groups[3] and subsequent derivatization,[4] and induced moderate diastereoselectivities of up to 36% de in the α-alkylation of carboxylic acid esters in solution phase as well as on a solid support.[4]

Recently, we have found that replacing the benzyl ether moiety of auxiliaries **I** and **II** by sterically demanding *t*-alkyl ethers effected a substantial improvement in the stereoinducing ability of *m*-hydrobenzoin derived auxiliaries **III** in the L-selectride^R mediated reduction of phenyl glyoxylates up to 84% de[5] (Table 1, entries 1 and 2). These results were considerably superior to those previously reported with (*R*,*R*)-hydrobenzoin derived benzyl ether auxiliaries in this type of reaction.[6]

Herein, we report the synthesis and evaluation of a further modified *m*-hydrobenzoin derived chiral auxiliary for the stereoselective reduction of α-keto carboxylic acid esters and its immobilization and application on a solid support.

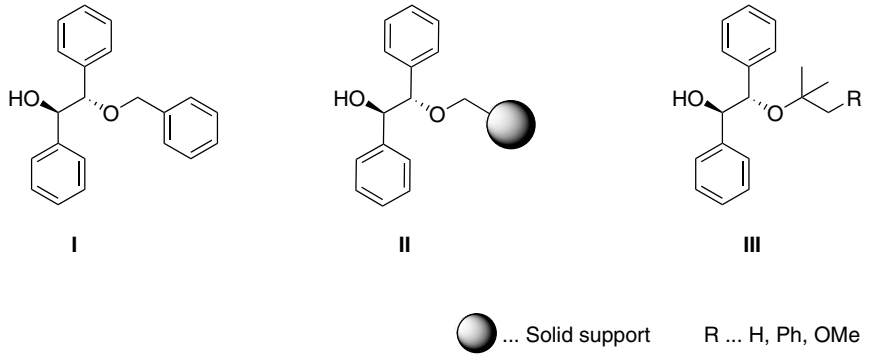
2. Results and discussion

2.1. Auxiliary evaluation using appropriate test systems in solution

In our preliminary studies, we had intended to modify the *t*-butyl moiety of auxiliary **III 6a** (Table 1, entries 1 and 2) such that it might serve as a sublinking unit between the auxiliary core and a polymer support by linking them together via a stable ether bond. However, disappointingly, it had turned out that introduction of the second oxygen in the *t*-alkyl moiety of **III 6b** decreased the diastereoselectivity significantly (Table 1, entries 3 and 4). This

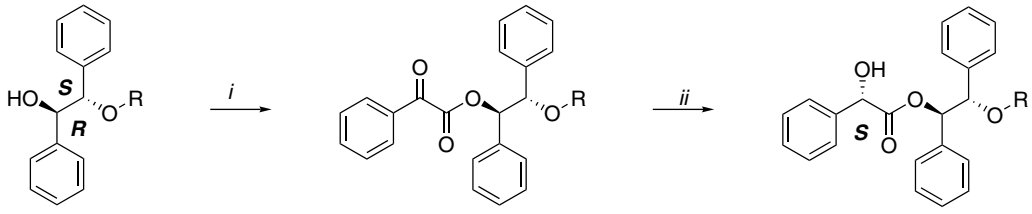
* Corresponding author. Tel.: +43 15880155421; fax: +43 15880115492; e-mail: peter.gaertner@tuwien.ac.at

0957-4166/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.08.030

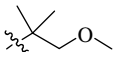
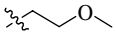
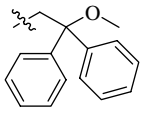
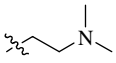


Scheme 1.

Table 1. Diastereoisomeric ratio of **8a**–**e** from reduction of α-keto esters **7a**–**e**[a]



6a-e **7a-e** **8a-e**

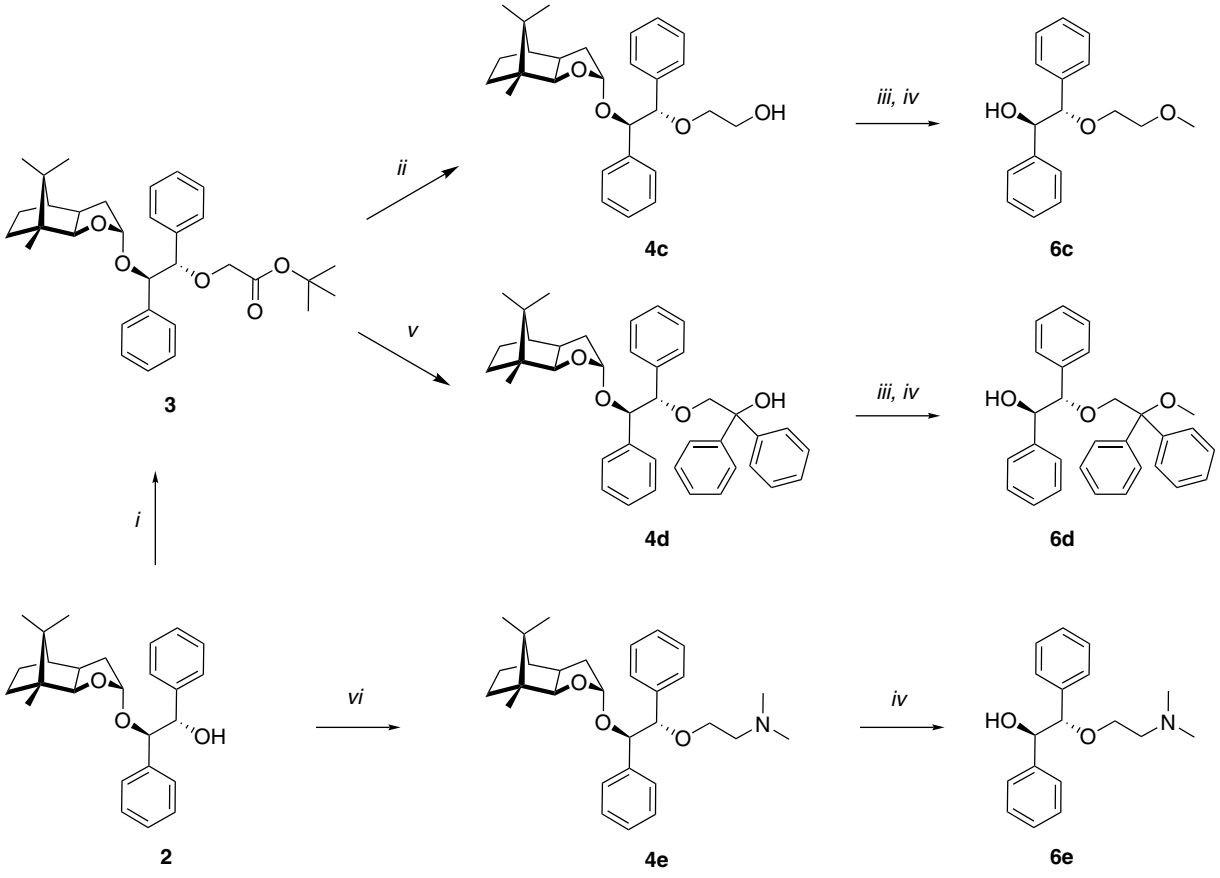
Entry	Ester	R	Additive	Ratio[c] (*S*,*R*,*S*)/(*S*,*R*,*R*)	Yield **8a**–**e**[d] (%)
1	**7a**[b]	*t*-Bu	—	92:8[b]	87
2	**7a**[b]		2 equiv $ZnCl_2$	92:8[b]	88
3	**7b**[b]		—	86:14[b]	80
4	**7b**[b]		2 equiv $ZnCl_2$	88:12[b]	80
5	**7c**		—	88.5:11.5	80
6	**7c**		2 equiv $ZnCl_2$	95.5:4.5	99
7	**7d**		—	75:25	85
8	**7d**		2 equiv $ZnCl_2$	95.5:4.5	86
9	**7e**		—	90.5:9.5	80
10	**7e**		2 equiv $ZnCl_2$	89.5:10.5	80

[a] Reagents and conditions: (i) PhCOCOOH, DIC, DMAP, CH_2Cl_2; (ii) L-selectride^R, −78 °C, THF.
[b] Data from Ref. 5.
[c] Diastereoisomeric ratios determined by ^{1}H NMR integration on crude reaction mixtures **8** and HPLC analysis of L-valine methyl ester derivatives **13** of cleaved mandelic acids **9**; absolute configuration of major diastereoisomers approved by optical rotation of **9**.
[d] Isolated yields by vacuum flash chromatography.

prompted us to assume that the oxygen having an additional—presumably coordinative—and therefore counterproductive influence on the preferred conformation of the open chain auxiliary.[5] Thus, as the *t*-butyl moiety had proved to be a residue only feasibly capable of sterical interactions, which had led to an optimum diastereoselectivity, one might have assumed that a sterically less demanding residue mainly capable for coordinating interactions might have also effected an optimization. Consequently, we decided to skip the two methyl groups and try out other ethylene glycol ether type sublinkers.

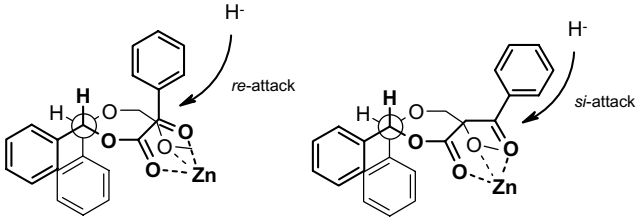
Therefore, desymmetrized hydrobenzoin **2**[3,5] was converted to alkoxyacetic acid ester **3**[5] and amine **4e**, respectively, which were further transformed to auxiliaries **6c**–**e** with good overall yields using standard reaction conditions (Scheme 2). Phenyl glyoxylates **7c**–**e**, which were prepared by DIC/DMAP mediated esterification under mild conditions, were finally reduced to mandelates **8c**–**e** according to the procedure described by Rosini et al.[6] (Table 1). The stereochemical outcomes of these reductions were analyzed by ^{1}H NMR integration on the mixtures of product diastereomers as well as after ester saponification by determination of the specific rotation of cleaved mandelic acids **9**[7] and by further derivatization with L-valine methyl ester and HPLC-analysis of resulting **13**[8] as described in our previous work.[5]

Thus, diastereoselectivities of 50–81% de were achieved employing auxiliaries **7c**–**e** (Table 1, entries 5, 7 and 9),



Scheme 2. Reagents and conditions: (i) NaH, $BrCH_2COO$–*t*-Bu, HMPA, THF; (ii) $LiAlH_4$, THF; (iii) NaH, MeI, DMF; (iv) *p*-TsOH, MeOH; (v) PhMgBr, THF; (vi) NaH, $ClCH_2CH_2N(CH_3)_2$, DMF.

which had no further improvement compared to our previous results.[5] However, when $ZnCl_2$ was used as an additive, diastereomeric excesses could be raised substantially up to 91% de with both 'methoxy' auxiliaries **7c** and **7d** (Table 1, entries 6 and 8). This was in accordance with our previous observation, that addition of the Lewis acid $ZnCl_2$ had improved the stereofacial selectivity of our hydrobenzoin derived chiral auxiliary **7b**, if an additional Lewis basic O-atom had been present in the ether residue (Table 1, entries 3 and 4). Therefore, we had suggested, that in this particular case the predominant auxiliary conformation had been stabilized by an additional coordination of the Lewis acidic Zn^{2+} to the O-atom of the ether residue, which thereby had shielded away the *si*-face of the keto carbonyl from the hydride attack[5] (Scheme 3). Further experiments with superhydride^R as reducing agent in the reduction of ester **7c** gave consistent results, whereas des were slightly decreased with this sterically less demanding reducing agent (Table 2, entries 3 and 4). By now, we still do not have neither theoretical nor experimental evidence to verify if our model is correct, but the complete loss of any stereoinduction in the reduction of ester **7c** (Table 2, entry 5) on addition of strongly coordinating HMPA as a co-solvent at least could support the suggestion of a coordination dependent explanation for the remarkable improvements with auxiliaries **7c** and **7d** on addition of $ZnCl_2$.



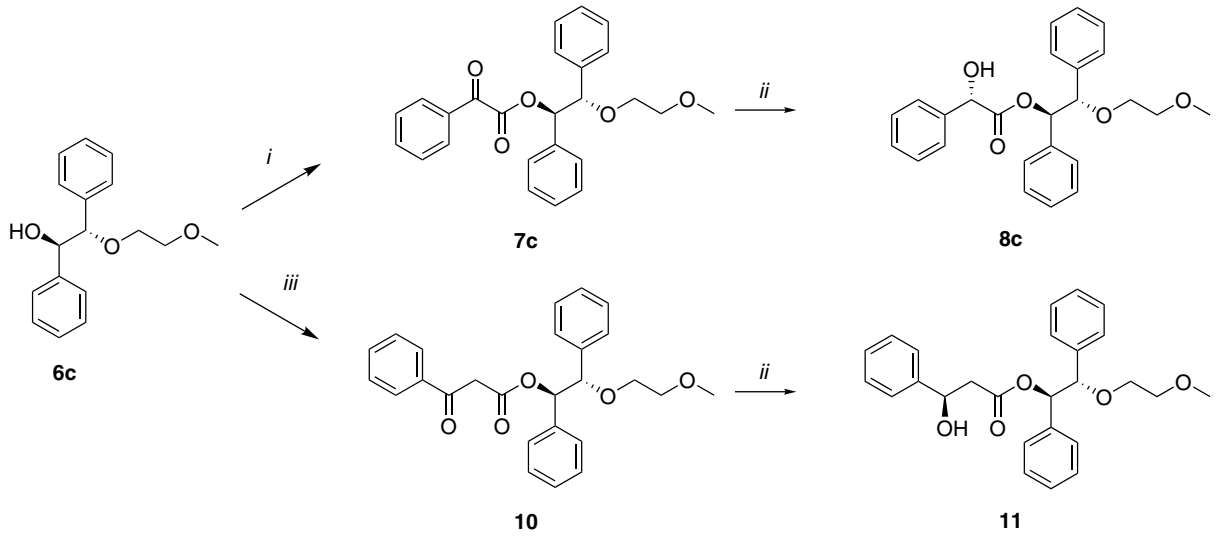
Scheme 3. Proposed model for the observed $ZnCl_2$ enhanced diastereoselection with auxiliary **7c**.

Furthermore, it is noteworthy, that our model could also be applied to predict correctly the stereochemical outcome of the analogous reduction of a β-keto acid attached to auxiliary **6c** (Scheme 3; Table 2, entry 6), although the diastereoisomeric excess was fairly moderate in this experiment, which might have been due to less favoured chelation as a matter of inappropriate molecular dimensions. The low yield of **11** was a result of β-keto esters' general tendency to easily enolize in the presence of any basic reagent and was consistent with known examples.[9]

2.2. Auxiliary immobilization and application on solid support

We finally chose auxiliary **6c** for the attachment onto a solid support, with regard to the above results and the expected ease of its immobilization. The latter was

Table 2. Diastereoisomeric ratio of **8c** and**11** from reduction of α-keto esters **7c** and **10**[a]



Entry	Ester	Red.	Additive	Ratio[b] (*S*,*R*,*S*)/(*S*,*R*,*R*)	Yield **8c**, **11**[c] (%)
1	**7c**	L-Sel.	—	88.5:11.5	80
2	**7c**	L-Sel.	2 equiv $ZnCl_2$	95.5:4.5	99
3	**7c**	$LiBEt_3H$	—	87.5:12.5	85
4	**7c**	$LiBEt_3H$	2 equiv $ZnCl_2$	90:10	93
5	**7c**	L-Sel.	2 equiv HMPA	50:50	90
6	**10**	L-Sel.	2 equiv $ZnCl_2$	23:77	33

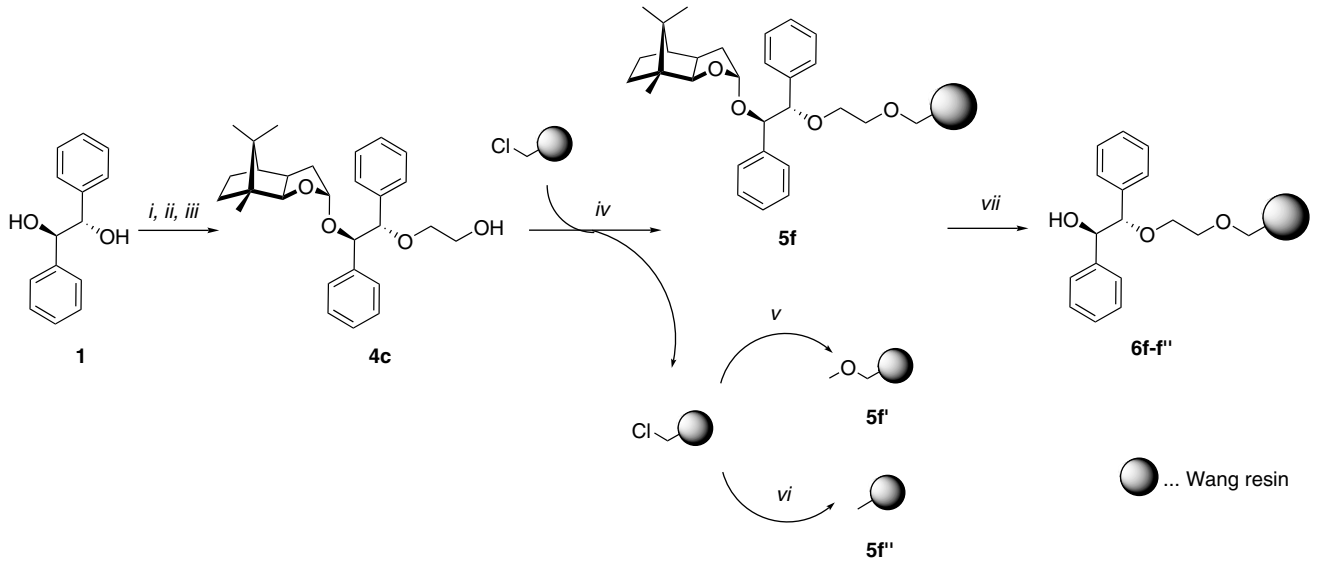
[a] Reagents and conditions: (i) PhCOCOOH, DIC, DMAP, CH_2Cl_2; (ii) L-selectride^R, −78 °C, THF; (iii) $PhCOCH_2COOEt$, DMAP, toluene, reflux.
[b] Diastereoisomeric ratios determined by ^1H NMR integration on crude reaction mixtures **8c** and **11** and HPLC analysis of L-valine methyl ester derivatives **13** of cleaved mandelic acids **9**; absolute configuration of major diastereoisomers approved by specific rotation of cleaved hydroxy acids **9** and **12**.
[c] Isolated yields by vacuum flash chromatography.

accomplished by attaching auxiliary precursor **4c**, which had easily been synthesized from desymmetrized hydrobenzoin **2**[5] in two steps with almost quantitative yield on a gram scale, onto a polymer support via a stable ether bond, thus using the ethylene glycol ether residue as a sublinking unit. Therefore an excess of alcohol **4c** was deprotonated with NaH and reacted with chloromethylated polystyrene/divinylbenzene type Wang-resin[10] employing analogous reaction conditions as for the methylation of **4c**. Commercially available Wang-resin (200–400 mesh, novabiochem) with an approx. 0.6 mmol/g loading was found to be best for a maximum auxiliary immobilization of up to 80%, whereas higher loaded resins of 1.0–1.5 mmol/g turned out to result in incomplete auxiliary attachment of only 30–60%. Neither employment of higher precursor excesses nor variation of solvent with regard to resin swelling abilities nor variation of base nor rerun of the auxiliary binding step could effect any further auxiliary binding, so that the auxiliary precursor was suggested to be sterically too demanding to achieve quantitative reaction especially with higher loaded resins. Kawana,[11] Worster[12] and Enders[13] have already reported the problem of incomplete transformation of all resin's active sites when attaching a chiral auxiliary onto a solid support, and especially in Worster's case dramatically decreased stereoselectivities had resulted. Therefore, Worster had deactivated any remaining active chloromethyl groups by a simple iodination/reduction protocol prior to substrate binding. As we had calculated only an 80% yield in the optimized auxiliary attachment step by gravimetric analysis and had further detected the presence of unreacted chloromethyl groups on our functionalized resin **5f** colorimetrically,[14] we also decided to inactivate those groups by a subsequent methoxylation **5f′** or reduction step[12] **5f″**, respectively.

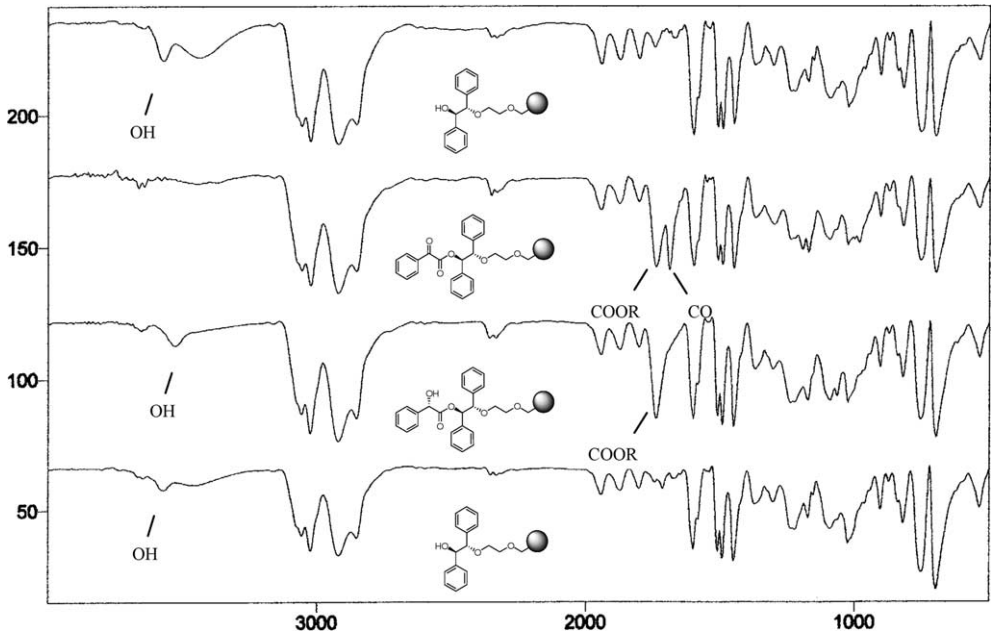
Release of Noe's chiral protecting group by acid catalyzed methanolysis then yielded resin bound hydrobenzoin auxiliaries **6f**–**f″**, which were to be tested in the reduction of their phenyl glyoxylates **7f**–**f″** according to the analogous experiments in solution (Scheme 4).

Therefore, auxiliaries **6f**–**f″** were esterified with benzoylformic acid as described above, and the resulting polymer bound phenyl glyoxylates **7f**–**f″** were reduced according to our pre-optimized L-selectride^R/$ZnCl_2$ protocol. All reactions on solid support were monitored qualitatively by FT-IR spectroscopy, employing KBr disks, as well as yields were estimated gravimetrically (Scheme 5).

As to date, we do not have an on-bead methodology[15] for the direct determination of diastereoisomeric ratios of the resulting polymer bound α-hydroxy esters **8f**–**f″**, this was accomplished only after saponification of **8f**–**f″** with LiOH in methanol/THF/water (5/4/1) at room temperature and recovery of the (*S*)-mandelic acids **9**,[7] which were then transformed to their L-valine methyl ester derivatives **13** and analyzed by HPLC.[8] This meth-



Scheme 4. Reagents and conditions: (i) Noe's *exo*-anhydro lactol, *p*-TsOH, CH_2Cl_2; (ii) NaH, $BrCH_2COO$–*t*-Bu, HMPA, THF; (iii) $LiAlH_4$, THF; (iv) NaH, NaI, Wang-Cl, DMF; (v) NaOMe, NaI, DMF; (vi) NaI, acetone; Bu_3SnH, THF; (vii) PPh_3·HBr, MeOH, CH_2Cl_2.



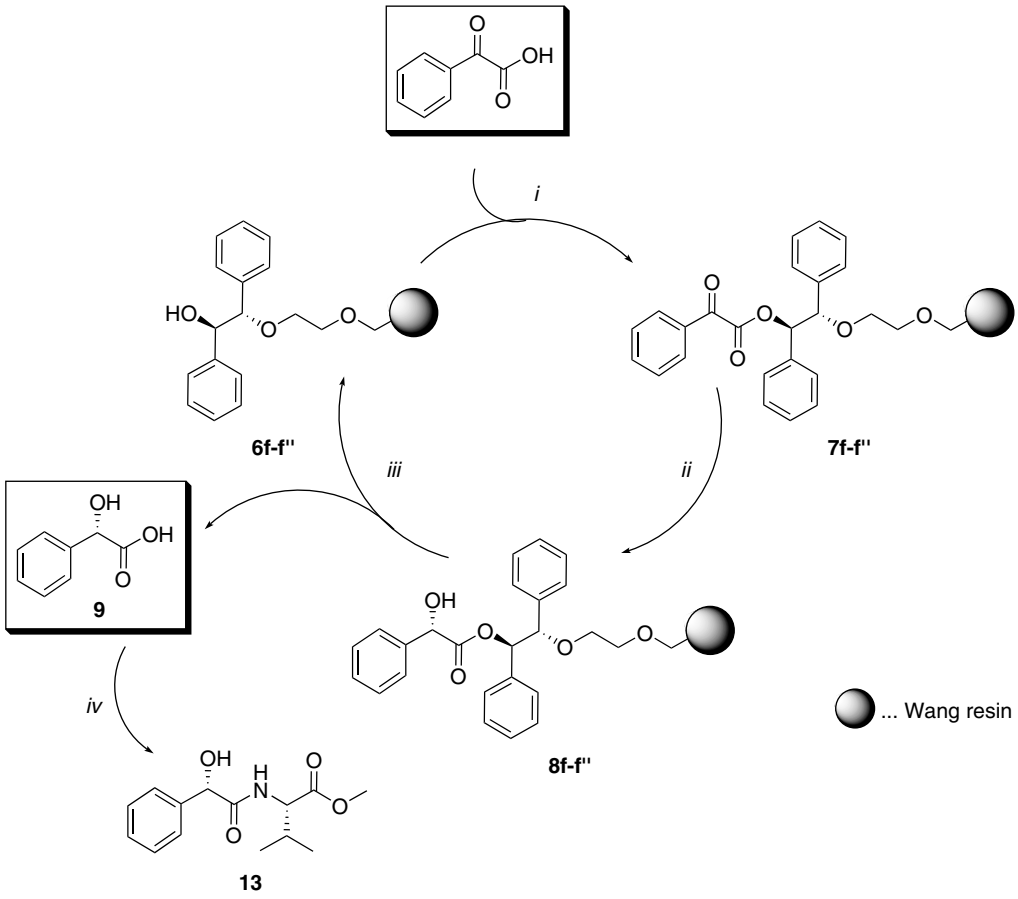
Scheme 5. Monitoring of selectivity test reactions on solid phase by FT-IR spectroscopy.

odology had resulted in diastereoisomeric ratios consistent with those obtained from the previous ^{1}H NMR spectroscopic analyses in all preceding solution phase experiments and had therefore proved the ester saponifications to be racemization free, and has thus given us a reliable tool for enantiomeric analysis in our solid phase experiments.

Diastereoselectivities of 80–86% de were obtained with solid-supported chiral auxiliaries **6f**–**f″**, depending on whether unreacted chloromethyl groups had been deactivated after the auxiliary attachment or not. This indicated, that our open chain chiral hydrobenzoin auxiliary was also suitable for a practicable application in the stereoselective reduction of phenyl glyoxylate on a solid support with only little loss of stereofacial selectivity compared to the analogous system in solution.

Despite the fact that simple and efficient recyclability is the main goal for attaching chiral auxiliaries onto a solid support, this feature is still left undescribed for many of the so far published polymer bound chiral auxiliaries.[1] Therefore, we next decided to have a closer look at auxiliary recycling. As we had been able to recover auxiliaries almost quantitatively without any loss of enantiomeric purity by ester saponification in our previous solution phase experiments, we analogously

Table 3. Auxiliary application and recycling on solid support[a]



Entry	Ester	Run	Ratio[b] (*S*,*R*,*S*)/(*S*,*R*,*R*)	Yield **9**[c]
1	**7f**	1	90:10	73
2	**7f′**	1	92:8	75
3	**7f″**	1	93:7	69
4	**7f″**	2	91:9	98
5	**7f″**	3	93:7	76
6	**7f″**	4	94:6	52
7	**7f″**	5	90:10	77

[a] Reagents and conditions: (i) PhCOCOOH, DIC, DMAP, CH_2Cl_2; (ii) L-selectride^R, −78 °C, THF; (iii) LiOH, THF/MeOH/H_2O; (iv) L-valine methyl ester, DIC, HOBt, CH_2Cl_2.
[b] Diastereoisomeric ratios determined by HPLC analysis of L-valine methyl ester derivatives **13** of cleaved mandelic acids **9**.
[c] Yields based on gravimetrically estimated amount of ketoacid bound in the esterification step.

recovered polymer bound auxiliary **6f″** by simple filtration and subsequent washing and drying steps and introduced the resin in the next esterification/reduction/saponification cycle immediately. Thus, auxiliary **6f″** could be reused at least three times without any loss of stereofacial selectivity (Table 3, entries 4–7).

3. Conclusion

Based on the suggestion of Rosini et al., that an open chain chiral auxiliary derived from hydrobenzoin can be satisfactorily used in the diastereoselective reduction of α-keto esters,[6] we have synthesized and evaluated a new class of *m*-hydrobenzoin derived chiral auxiliaries **6**. These were optimized by introducing an ether substituent bearing an additional heteroatom, which was capable of coordinating interactions with the keto acid to be reduced. By promoting these interactions through addition of the Lewis acid, $ZnCl_2$ diastereoselectivities could satisfactorily be raised up to 91% de with methoxyethyl ether auxiliaries **6c** and **6d**, which was a remarkable improvement compared to the results with our previously investigated hydrobenzoin *t*-butyl ethers **6a** and **6b**.[5] We were further able to immobilize our novel chiral auxiliary on commercially available Wang-resin by a simple modification of the ether substituent, so that it could serve as a sublinking unit between the auxiliary core and the polymer support. Thus, by applying the same '$ZnCl_2$ trick' we were able to induce almost equal stereoselectivities of 86% de with polymer bound, **6f″**, which could further be reused three times without any loss of its stereoinducing ability.

Thus, we have developed a simple, easily accessible and reusable polymer bound open chain chiral auxiliary, which seems to be a viable tool for stereoselective solid phase organic synthesis, especially when bearing in mind that by desymmetrization of *m*-hydrobenzoin with both of Noe's chiral anhydro lactols[3] both possible enantiomers of polymer bound **6f″** can easily be synthesized.

Further investigations are underway to evaluate applications of our novel, polymer bound chiral auxiliary **6f″**, especially in reactions involving Lewis acidic reagents and additives, which can be supposed to result in chelation mediated enhancements of stereoselectivities as described above. We are also encouraged to undertake additional investigations on further auxiliary improvements, on the one hand by trying out other polymer supports with regard to minimize differences between the solution phase and solid phase auxiliary, and on the other hand, for example, by introducing substituents in the hydrobenzoin aryls, which by changing steric and electronic properties of the auxiliary could probably increase stereoselectivities as well.

4. Experimental

4.1. General

Commercially available reagents and solvents were used as received from the supplier unless otherwise specified. Diethyl ether (E), petroleum ether (PE, 60–80 °C fraction), ethyl acetate (EE) and dichloromethane were distilled prior to use. Dry toluene, ether and tetrahydrofuran were predried over KOH and distilled from Na/benzophenone. Dry dichloromethane was distilled from P_2O_5. Dry petroleum ether and dimethylformamide were dried and stored over mole sieve 4 Å. L-Selectride^R and superhydride^R were purchased from Aldrich as 1 M solutions in THF. NaH was purchased from Aldrich as a 55–65% oil moistened powder and washed with dry petroleum ether directly before use unless otherwise stated. NaI and $ZnCl_2$ were dried by heating to 150–300 °C in high vacuo for 30 min prior to use. Hydroxymethylated Wang-resin (200–400 mesh; 0.64 mmol/g) was purchased from *novabiochem* and was thoroughly washed successively with DMF, methanol, dichloromethane, methanol, and dried overnight in high vacuo prior to use. All moisture sensitive reactions were carried out under a nitrogen atmosphere. Reactions on solid phase were shaken on a laboratory shaker unless otherwise stated. For TLC-analysis, precoated aluminium-backed plates (silica gel 60 F_{254}, Merck) were used. Compounds were visualized by spraying with 5% phosphomolybdic acid hydrate in ethanol and heating. Vacuum flash chromatography was carried out with silica gel Merck 60. All fractions of products containing Noe's acetal protecting group together with a free hydroxy group were concentrated immediately after chromatography together with a few drops of NEt_3. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Specific rotations were measured on a Perkin–Elmer 241 polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 in $CDCl_3$ at 200 and 50 MHz, respectively, using TMS or the solvent peak as the reference. IR spectra were recorded on a BioRad *FTS 135* FT-IR-spectrometer, using KBr disks. HPLC diastereoisomeric analysis of L-valine methyl ester derivatives **13**[8] of mandelic acids **9** was carried out with a SHIMADZU LC-10AD (SHIMADZU SPD-10AV UV/VIS detector; Nucleosil 120 S C18; H_2O/MeOH 60/40). Elemental analysis was carried out at Vienna University, Department of Physicochemistry—Laboratory for Microanalysis, Währinger Str. 42, A-1090 Vienna.

4.2. Preparation of auxiliary precursors

4.2.1. [2*S*-(2α(1*R,2*S**),3aα,4β,7β,7aα)]-[2-[(Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)oxy]-1,2-diphenylethoxy]acetic acid, 1,1-dimethylethyl ester, 3.** A solution of alcohol **2** (10.22 mmol/4.01 g) in dry THF (250 mL) was slowly added to a suspension of 60% NaH (21.5 mmol/0.86 g) in dry THF (50 mL). Then HMPA (61.296 mmol/10.8 mL) and bromoacetic acid, *t*-butyl ester (15.32 mmol/2.3 mL) were added successively and the mixture was refluxed overnight. After cooling to ambient temperature unreacted NaH was carefully hydrolized by adding portions of a mixture of water/THF (1/1) until the reaction ceased. The resulting mixture was diluted with brine and extracted three times with ether. The combined ethereal extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated. Remainings of HMPA and bromoacetic acid, *t*-butyl ester were evaporated in high vacuo overnight. The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (100/1→10/1). A colourless oil (5.10 g, yield 98%), $R_f = 0.85$ (PE/E 3/1), $[\alpha]_D^{20} = -59.9$ (*c* 0.96, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.44$–7.26 (m, 10H, aromatic), 4.83 (d, 1H, 2-H, $J = 3.9$ Hz), 4.74/4.41 (2d, 2H, Ph–C*H*–O, $J = 7.7$ Hz), 3.76/3.63 (2d, 2H, O–CH_2–CO, $J_{AB} = 15.7$ Hz), 2.55 (d, 1H, 7a-H, $J = 4.6$ Hz), 1.97–0.57 [m, 26H, 17MBE-aliphatic, therein 0.81/0.80/0.70 (3s, 9H, 3MBE–CH_3), 1.34 (s, 9H, O–C(CH_3)$_3$)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 169.1$ (s, CO), 139.7/139.6 (2s, Ph–C-1), 128.4–127.8 (m, Ph–C), 100.9 (d, C-2), 90.0 (d, C-7a), 85.2/78.4 (2d, Ph–*C*H–O), 67.3 (t, O–*C*H_2–CO), 48.1 (d, C-4), 47.0 (s, C-7), 46.9 (s, C-8), 45.8 (d, C-3a), 38.3 (t, C-3), 32.2 (t, C-6), 28.8 (t, C-5), 28.0 (q, O–C(*C*H_3)$_3$), 22.8/20.5/11.5 (3q, 3MBE–CH_3). Anal. Calcd for $C_{32}H_{42}O_5$: C, 75.86; H, 8.36. Found: C, 75.56; H, 8.58.

4.2.2. [2*S*-(2α(1*R,2*S**),3aα,4β,7β,7aα)]-2-[2-[(Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)oxy]-1,2-diphenylethoxy]ethanol, 4c.** To an ice cooled solution of $LiAlH_4$ (13.4 mmol/0.500 g) in dry ether (40 mL), a solution of ester (6.7 mmol/3.395 g) **3** in dry ether (100 mL) was added, and the reaction mixture was stirred for 1 h at ambient temperature. Water (5 mL) and 40% NaOH (3 mL) were added while cooling on an ice bath and the mixture was stirred at ambient temperature until a white solid had precipitated. A small portion of Na_2SO_4 was added and the mixture was filtered over a pad of hyflo. Finally the solvent

was evaporated and the crude product was purified by vacuum flash chromatography on silica gel pretreated with NEt_3, eluting with petroleum ether/ether (20/1→5/1). A colourless oil (2.920 g, yield 99.6%), $R_f = 0.45$ (PE/E 1/1), $[\alpha]_D^{20} = -73.1$ (*c* 1.08, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.35–7.19$ (m, 10H, aromatic), 4.78 (d, 1H, 2-H, $J = 4.3$ Hz), 4.59/4.20 (2d, 2H, Ph–C*H*–O, $J = 7.9$ Hz), 3.47–3.02 (m, 4H, O–CH_2–CH_2–OH), 2.46 (d, 1H, 7a-H, $J = 6.7$ Hz), 1.93–0.42 [m, 17H, 17MBE-aliphatic, therein 0.74/0.72/0.63 (3s, 9H, 3MBE–CH_3)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 140.3/139.9$ (2s, Ph–C-1), 128.1–127.7 (m, Ph–C), 101.1 (d, C-2), 90.2 (d, C-7a), 85.4/78.8 (2d, Ph–*C*H–O), 70.6/61.5 (2t, O–*C*H_2–*C*H_2–OH), 48.1 (d, C-4), 47.0 (s, C-7), 46.9 (s, C-8), 45.8 (d, C-3a), 38.4 (t, C-3), 32.2 (t, C-6), 28.8 (t, C-5), 22.8/20.5/11.5 (3q, 3MBE–CH_3). Anal. Calcd for $C_{28}H_{36}O_4 \times 0.7H_2O$: C, 74.87; H, 8.39. Found: C, 74.79; H, 8.49.

4.2.3. [2*S*-(2α(1*R,2*S**),3aα,4β,7β,7aα)]-2-[2-[(Octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)oxy]-1,2-diphenylethoxy]-1,1-diphenylethanol, 4d.** A freshly prepared 0.7 M solution of PhMgBr (18.0 mmol/25.7 mL) in THF was added to a solution of ester **3** (4.5 mmol/2.281 g) in dry THF (80 mL) and the resulting mixture was refluxed for 24 h. After cooling to ambient temperature, the mixture was poured into a saturated solution of NH_4Cl (200 mL) and extracted four times with ether. The combined ethereal extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (50/1→10/1). A white solid (1.97 g, yield 74%), mp 63–65 °C, $R_f = 0.62$ (PE/E 3/1), $[\alpha]_D^{20} = -77.2$ (*c* 1.00, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.38–7.16$ (m, 20H, aromatic), 4.83 (d, 1H, 2-H, $J = 4.2$ Hz), 4.62/4.37 (2d, 2H, Ph–C*H*–O, $J = 7.6$ Hz), 4.12/3.45 (2d, 2H, O–CH_2–C(Ph)$_2$–OH, $J = 10.0$ Hz), 3.22 (s, 1H, OH), 2.54 (d, 1H, 7a-H, $J = 6.5$ Hz), 2.02–0.56 [m, 17H, 17MBE-aliphatic, therein 0.81/0.79/0.71 (3s, 9H, 3MBE–CH_3)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 144.8/144.0/139.9/139.4$ (4s, Ph–C-1), 128.2–126.1 (m, Ph–C), 101.1 (d, C-2), 90.1 (d, C-7a), 86.5/78.8 (2d, Ph–*C*H–O), 77.9 (s, O–CH$_2$–*C*(Ph)$_2$–OH), 76.1 (t, O–*C*H$_2$–C(Ph)$_2$–OH), 48.1 (d, C-4), 47.0 (s, C-7), 46.8 (s, C-8), 45.7 (d, C-3a), 38.3 (t, C-3), 32.2 (t, C-6), 28.8 (t, C-5), 22.8/20.4/11.5 (3q, 3MBE–CH_3). Anal. Calcd for $C_{40}H_{44}O_4 \times 0.3H_2O$: C, 80.86; H, 7.57. Found: C, 80.96; H, 7.77.

4.2.4. [2*S*-(2α(1*S,2*R**),3aα,4β,7β,7aα)]-2-[2-(2-Methoxyethoxy)-1,2-diphenylethoxy]octahydro-7,8,8-trimethyl-4,7-methanobenzofuran, 5c.** A solution of alcohol **4c** (6.642 mmol/2.900 g) in dry DMF (40 mL) was added slowly to a suspension of 60% NaH (13.284 mmol/0.319 g) in dry DMF (5 mL) and the mixture was stirred for 1 h at room temperature. Then CH_3I (13.284 mmol/0.84 mL) was added and stirring was continued overnight. Unreacted NaH was carefully hydrolized then by adding portions of a mixture of water/THF (1/1) until the reaction ceased. The resulting mixture was diluted with brine and extracted three times with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (20/1→5/1). A colourless oil (2.574 g, yield 86%), $R_f = 0.54$ (PE/E 1/1), $[\alpha]_D^{20} = -67.8$ (*c* 0.90, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.43–7.22$ (m, 10H, aromatic), 4.81 (d, 1H, 2-H, $J = 4.1$ Hz), 4.64/4.25 (2d, 2H, Ph–C*H*–O, $J = 8.2$ Hz), 3.50–3.17 (m, 4H, O–CH_2–CH_2–O), 3.13 (s, 3H, O–CH_3), 2.43 (d, 1H, 7a-H, $J = 6.4$ Hz), 1.98–0.48 [m, 17H, 17MBE-aliphatic, therein 0.79/0.79/0.69 (3s, 9H, 3MBE–CH_3)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 140.8/140.3$ (2s, Ph–C-1), 128.3/128.2/127.7/127.6/127.4/127.3 (6d, Ph–C), 100.8 (d, C-2), 89.9 (d, C-7a), 85.7/78.3 (2d, Ph–*C*H–O), 71.7/68.7 (2t, O–*C*H_2–*C*H_2–O), 58.7 (q, O–CH_3), 48.1 (d, C-4), 46.9 (s, C-7), 46.8 (s, C-8), 45.8 (d, C-3a), 38.3 (t, C-3), 32.2 (t, C-6), 28.8 (t, C-5), 22.8/20.5/11.4 (3q, 3MBE–CH_3). Anal. Calcd for $C_{29}H_{38}O_4$: C, 77.30; H, 8.50. Found: C, 77.10; H, 8.68.

4.2.5. [2*S*-(2α(1*S,2*R**),3aα,4β,7β,7aα)]-2-[2-(2-Methoxy-2,2-diphenylethoxy)-1,2-diphenylethoxy]octahydro-7,8,8-trimethyl-4,7-methanobenzofuran, 5d.** Alcohol **4d** was methylated analogously. Ten equivalents of 18-crown-6 was added to the reaction mixture for yield optimization. A white solid (yield 91%), mp 52–54 °C, $R_f = 0.75$ (PE/E 3/1), $[\alpha]_D^{20} = -42.6$ (*c* 1.23, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.29–7.03$ (m, 20H, aromatic), 4.79 (d, 1H, 2-H, $J = 4.1$ Hz), 4.53/4.22 (2d, 2H, Ph–C*H*–O, $J = 8.1$ Hz), 3.78 (s, 2H, O–CH_2–C(Ph)$_2$–O), 2.92 (s, 3H, O–CH_3), 2.34 (d, 1H, 7a-H, $J = 6.4$ Hz), 1.97–0.38 [m, 17H, 17MBE-aliphatic, therein 0.78/0.77/0.69 (3s, 9H, 3MBE–CH_3)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 143.4/143.3/140.0/140.0$ (4s, Ph–C-1), 128.4–126.7 (m, Ph–C), 100.9 (d, C-2), 89.8 (d, C-7a), 86.0/78.7 (2d, Ph–*C*H–O), 82.2 (s, O–CH$_2$–*C*(Ph)$_2$–O), 72.9 (t, O–*C*H$_2$–C(Ph)$_2$–O), 51.5 (q, O–CH_3), 48.1 (d, C-4), 46.9 (s, C-7), 46.8 (s, C-8), 45.8 (d, C-3a), 38.3 (t, C-3), 32.1 (t, C-6), 28.8 (t, C-5), 22.6/20.4/11.5 (3q, 3MBE–CH_3). Anal. Calcd for $C_{41}H_{46}O_4$: C, 81.69; H, 7.69. Found: C, 81.53; H, 7.89.

4.2.6. [2*S*-(2α(1*R,2*S**),3aα,4β,7β,7aα)]-Dimethyl-*N*-[(2-(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)-oxy-1,2-diphenylethoxy)ethyl]amine, 4e.** A solution of alcohol **2** (2.548 mmol/1.006 g) in dry DMF (20 mL) was added slowly to a suspension of NaH (5.095 mmol/0.122 g) in dry DMF (3 mL) and the mixture was stirred for 1 h at room temperature. Then a solution of (2-chloroethyl)-dimethylamine (3.932 mmol/0.423 g) and a catalytic amount of NaI in DMF (4 mL) was added and stirring was continued for 2 h at room temperature. Unreacted NaH was carefully hydrolized then by adding portions of a mixture of water/THF (1/1) until the reaction ceased. The resulting mixture was diluted with brine and extracted three times with ether. The combined ether extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ethyl acetate (20/1→EE). A colourless oil (0.376 g, yield

32%), $R_f = 0.63$ ($CHCl_3$/MeOH 9/1 + 2 drops $NH_{3(aq)}$), $[\alpha]_D^{20} = -82.5$ (*c* 0.79, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.33–7.19$ (m, 10H, aromatic), 4.73 (d, 1H, 2-H, $J = 4.0$ Hz), 4.56/4.14 (2d, 2H, Ph–C*H*–O, $J = 8.2$ Hz), 3.31/3.06 (2td, 2H, O–CH_2–CH_2–$N(CH_3)_2$, $J_1 = 10.0$ Hz, $J_2 = 5.7$ Hz), 2.36 (d, 1H, 7a-H, $J = 6.7$ Hz), 2.20 (dt, 2H, O–CH_2–CH_2–$N(CH_3)_2$, $J_1 = 5.7$ Hz, $J_2 = 1.3$ Hz), 1.96 (s, 6H, $N(CH_3)_2$), 1.85–0.45 [m, 17H, 17MBE-aliphatic, therein 0.71/0.71/0.61 (3s, 9H, 3MBE–CH_3)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 140.9/140.2$ (2s, Ph–C-1), 128.4/128.2/127.7/127.6/127.4/127.3 (6d, Ph–C), 100.8 (d, C-2), 89.9 (d, C-7a), 85.7/78.4 (2d, Ph–*C*H–O), 68.0/58.6 (2t, O–*C*H_2–*C*H_2–N), 48.1 (d, C-4), 46.9 (s, C-7), 46.8 (s, C-8), 45.8 (d, C-3a), 45.7 (q, $N(CH_3)_2$), 38.3 (t, C-3), 32.2 (t, C-6), 28.8 (t, C-5), 22.8/20.5/11.4 (3q, 3MBE–CH_3). Anal. Calcd for $C_{30}H_{41}NO_3 \times 0.3H_2O$: C, 76.82; H, 8.94; N, 2.99. Found: C, 76.77; H, 9.05; N, 2.66.

4.3. Deprotection of auxiliary precursors 4e, 5c,d

4.3.1. General procedure. Ether **5c**,**d** (1 equiv) and a catalytic amount of *p*-TsOH were dissolved in a 10-fold amount of a mixture of methanol/dichloromethane (1/1) and stirred overnight at room temperature. After TLC analysis had shown total conversion, a saturated aqueous $NaHCO_3$ solution was added and stirring was continued for 10 min. The organic solvents were evaporated and the aqueous remainings were diluted with water and extracted three times with ether. The combined ethereal extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (20/1→1/1). Methyl acetal was recovered as an additional product fraction for recyclation of Noe's chiral protecting group.[3]

4.3.1.1. (1*R*,2*S*)-2-(2-Methoxyethoxy)-1,2-diphenylethanol, 6c. A colourless oil (yield 93%), $R_f = 0.29$ (PE/E 1/1), $[\alpha]_D^{20} = 22.9$ (*c* 1.04, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.27–7.10$ (m, 10H, aromatic), 4.94/4.53 (2d, 2H, Ph–C*H*–O, $J = 4.8$ Hz), 3.67–3.31 (m, 4H, O–CH_2–CH_2–O), 3.31 (s, 3H, O–CH_3), 3.04 (s, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C =$ 140.1/137.5 (2s, Ph–C-1), 127.8–127.0 (m, Ph–C), 86.3/76.7 (2d, Ph–*C*H–O), 71.8/68.5 (2t, O–*C*H_2–*C*H_2–O), 58.8 (q, O–CH_3). Anal. Calcd for $C_{17}H_{20}O_3 \times 0.1H_2O$: C, 74.48; H, 7.43. Found: C, 74.67; H, 7.70.

4.3.1.2. (1*R*,2*S*)-2-(2-Methoxy-2,2-diphenylethoxy)-1,2-diphenylethanol, 6d. A colourless oil (yield 99%), $R_f = 0.38$ (PE/E 2/1), $[\alpha]_D^{20} = 42.6$ (*c* 1.00, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.39–6.82$ (m, 20H, aromatic), 4.68/4.44 (2d, 2H, Ph–C*H*–O, $J = 5.4$ Hz), 4.05/3.95 (2d, 2H, O–CH_2–C$(Ph)_2$O, $J_{AB} = 9.9$ Hz), 3.09 (s, 3H, O–CH_3), 2.46 (s, 1H, –OH). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 143.0/142.9/139.8/137.3$ (4s, Ph–C-1), 128.0–127.1 (m, Ph–C), 86.8/82.6 (2d, Ph–CH–O), 77.2 (s, CH_2–*C*$(Ph)_2$O), 72.4 (t, O–*C*H_2–C$(Ph)_2$O), 51.4 (q, O–CH_3). Anal. Calcd for $C_{29}H_{28}O_3 \times 0.2H_2O$: C, 81.36; H, 6.69. Found: C, 81.43; H, 6.93.

4.3.2. (1*R*,2*S*)-2-(2-Dimethylaminoethoxy)-1,2-diphenylethanol, 6e. Aminoether **4e** (0.727 mmol/0.337 g) and *p*-TsOH (1.454 mmol/0.250 g) were dissolved in a mixture of methanol/dichloromethane (1/1) (20 mL) and stirred for 2 h at room temperature. After TLC analysis had shown total conversion, an equal amount of a saturated aqueous $NaHCO_3$ solution was added and stirring was continued for 10 min. The organic solvents were evaporated and the aqueous remainings were extracted three times with ether. The combined ethereal extracts were extracted three times with 2 N HCl. The combined acidic aqueous extracts were washed with ether and all combined ethereal extracts were dried over Na_2SO_4, filtered and evaporated to yield Noe's chiral protecting group as methyl acetal for recycling.[3] The acidic aqueous phase was carefully made basic by addition of a saturated aqueous $NaHCO_3$ solution and extracted three times with ether. The combined ethereal extracts were dried over Na_2SO_4, filtered and evaporated. A white solid (0.184 g, yield 89%), mp 48–50 °C, $R_f = 0.50$ ($CHCl_3$/MeOH 9/1 + 2 drops $NH_{3(aq)}$), $[\alpha]_D^{20} = 134.7$ (*c* 0.49, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.19–6.92$ (m, 10H, aromatic), 4.82/4.59 (2d, 2H, Ph–C*H*–O, $J = 3.9$ Hz), 3.64 (ddd, 1H, O–CH_2–CH_2–$N(CH_3)_2$, $J_1 = 11.6$ Hz, $J_2 = 7.3$ Hz, $J_3 = 4.3$ Hz), 3.36 (ddd, 1H, O–CH_2–CH_2–$N(CH_3)_2$, $J_1 = 11.6$ Hz, $J_2 =$ 5.9 Hz, $J_3 = 4.4$ Hz), 2.63 (ddd, 1H, O–CH_2–CH_2–$N(CH_3)_2$, $J_1 = 13.0$ Hz, $J_2 = 7.4$ Hz, $J_3 = 4.4$ Hz), 2.37 (ddd, 1H, O–CH_2–CH_2–$N(CH_3)_2$, $J_1 = 13.1$ Hz, $J_2 =$ 5.8 Hz, $J_3 = 4.5$ Hz), 2.26 (s, 6H, $N(CH_3)_2$). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 140.1/138.5$ (2s, Ph–C-1), 127.8/127.5/127.3/127.3/127.2/127.0 (6d, Ph–C), 85.6/77.4 (2d, Ph–*C*H–O), 66.1/58.4 (2t, O–*C*H_2–*C*H_2–N), 45.1 (q, $N(CH_3)_2$). Anal. Calcd for $C_{18}H_{23}NO_2 \times 0.9H_2O$: C, 71.68; H, 8.29; N, 4.64. Found: C, 71.65; H, 8.30; N, 4.64.

4.4. Preparation of ketoacid esters 7c–e, 10

4.4.1. General procedure for the preparation of benzoylformic acid esters 7c–e. DIC (1.1 equiv) was added dropwise to a solution of auxiliary **6c–e** (1.0 equiv), benzoylformic acid (1.1 equiv) and DMAP (0.2 equiv) in dichloromethane while cooling on an ice bath. The mixture was stirred for 1–20 h at room temperature until TLC control had indicated total conversion. Then the white precipitate was filtered off and the filtrate was diluted with dichloromethane and washed successively with a saturated aqueous $NaHCO_3$ solution, 5% $KHSO_4$ solution and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated. The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (20/1→5/1).

4.4.1.1. Oxophenylacetic acid, (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-diphenylethyl ester, 7c. A white solid (yield 91%), mp 79–81 °C, $R_f = 0.65$ (PE/E 4/1), $[\alpha]_D^{20} = 18.6$ (*c* 0.71, CH_2Cl_2). ^1H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.67–7.26$ (m, 15H, aromatic), 6.29/4.70 (2d, 2H, Ph–C*H*–O, $J = 6.7$ Hz), 3.59–3.38 (m, 4H, O–CH_2–CH_2–O), 3.23 (s, 3H, O–CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 186.1$ (s, CO), 162.7 (s, O–CO), 137.4/136.3/132.2 (3s, Ph–C-1), 134.7/129.9–127.7 (m,

Ph–C), 84.0/78.9 (2d, Ph–*C*H–O), 71.8/68.7 (2t, O–*C*H_2–*C*H_2–O), 58.8 (q, O–CH_3). Anal. Calcd for $C_{25}H_{24}O_5 \times 0.4H_2O$: C, 72.94; H, 6.07. Found: C, 72.99; H, 5.87.

4.4.1.2. Oxophenylacetic acid, (1*R*,2*S*)-2-(2-methoxy-2,2-diphenylethoxy)-1,2-diphenylethyl ester, 7d. A colourless oil (yield 91%), $R_f = 0.37$ (PE/E 4/1), $[\alpha]_D^{20} = 19.3$ (*c* 1.21, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.48$–6.84 (m, 25H, aromatic), 5.95/4.51 (2d, 2H, Ph–C*H*–O, $J = 6.8$ Hz), 3.86/3.76 (2d, 2H, O–CH_2–C(Ph)$_2$O, $J_{AB} = 9.7$ Hz), 2.88 (s, 3H, O–CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 186.0$ (s, CO), 162.6 (s, O–CO), 143.0/142.9/137.0/136.0/132.1 (5s, Ph–C-1), 134.7/133.7/130.2–126.9 (m, Ph–C), 84.3/79.3 (2d, Ph–*C*H–O), 82.3 (s, O–CH_2–*C*(Ph)$_2$–O), 72.8 (t, O–*C*H_2–C(Ph)$_2$–O), 51.5 (q, O–CH_3). Anal. Calcd for $C_{37}H_{32}O_5 \times 1.4H_2O$: C, 76.37; H, 6.03. Found: C, 76.45; H, 6.35.

4.4.1.3. Oxophenylacetic acid, (1*R*,2*S*)-2-(2-dimethylaminoethoxy)-1,2-diphenylethyl ester, 7e. The crude product was purified by vacuum flash chromatography on silica gel, eluting with chloroform/methanol (100/1→1/1). A white solid (yield 80%), mp 96–98 °C, $R_f = 0.61$ ($CHCl_3$/MeOH 9/1 + 2 drops $NH_{3(aq)}$), $[\alpha]_D^{20} = -2.4$ (*c* 0.95, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.54$–7.17 (m, 15H, aromatic), 6.17/4.55 (2d, 2H, Ph–C*H*–O, $J = 6.9$ Hz), 3.43–3.18 (m, 2H, O–CH_2–CH_2–N), 2.33–2.25 (m, 2H, O–CH_2–CH_2–N), 2.02 (s, 6H, N(CH_3)$_2$). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 186.0$ (s, CO), 162.6 (s, O–CO), 137.5/136.4/132.1 (3s, Ph–C-1), 134.6/129.8/128.7/128.4/128.3/128.2/128.0/128.0/127.8 (9d, Ph–C), 84.0/78.9 (2d, Ph–*C*H–O), 67.9/58.5 (2t, O–*C*H_2–*C*H_2–N), 45.6 (q, N(CH_3)$_2$). Anal. Calcd for $C_{26}H_{27}NO_4 \times 1.57H_2O$: C, 70.05; H, 6.81; N, 3.14. Found: C, 70.05; H, 7.11; N, 3.41.

4.4.2. 3-Oxo-3-phenylpropionic acid, (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-diphenylethyl ester, 10. A solution of auxiliary **6c** (1.131 mmol/0.308 g), 3-oxo-3-phenylpropionic acid, ethyl ester (3.393 mmol/0.652 g) and DMAP (0.566 mmol/0.069 g) in toluene (20 mL) was refluxed for 48 h. After cooling to ambient temperature, the mixture was poured into a saturated aqueous solution of NH_4Cl and extracted two times with ether. The combined ethereal extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (20/1→1/1). A white solid (0.402 g, yield 85%), mp 70–78 °C, $R_f = 0.41$ (PE/E 1/1), $[\alpha]_D^{20} = 31.7$ (*c* 0.73, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): Keto form: $\delta_H = 7.75$–7.05 (m, 15H, aromatic), 5.87/4.49 (2d, 2H, Ph–C*H*–O, $J = 5.9$ Hz), 3.82/3.73 (2d, 2H, Ph–CO–CH_2–COO, $J_{AB} = 15.4$ Hz), 3.47–3.23 (m, 4H, O–CH_2–CH_2–O), 3.13 (s, 3H, O–CH_3). Enol form: $\delta_H = 7.68$–7.05 (m, 15H, aromatic), 5.97/4.61 (2d, 2H, Ph–C*H*–O, $J = 5.8$ Hz), 5.57 (s, 1H, Ph–C(OH)=C*H*–COO), 3.47–3.23 (m, 4H, O–CH_2–CH_2–O), 3.17 (s, 3H, O–CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): Keto form: $\delta_C = 191.8$ (s, CO), 166.0 (s, O–CO), 137.7/136.7/136.0 (3s, Ph–C-1), 133.5/128.7–126.1 (m, Ph–C), 84.0/78.8 (2d, Ph–*C*H–O), 71.8/68.8 (2t, O–*C*H_2–*C*H_2–O), 58.8 (q, O–CH_3), 45.9 (t, Ph–CO–*C*H_2–COO). Enol form: $\delta_C = 171.7$ (s, O–CO), 137.8/137.3/133.3 (3s, Ph–C-1), 131.2/128.7–127.7 (m, Ph–C, Ph–*C*(OH)=CH–COO), 87.3 (d, Ph–C(OH)=*C*H–COO), 84.3/77.7 (2d, Ph–*C*H–O), 71.9/68.9 (2t, O–*C*H_2–*C*H_2–O), 58.9 (q, O–CH_3). Anal. Calcd for $C_{26}H_{26}O_5 \times 0.1H_2O$: C, 74.30; H, 6.28. Found: C, 74.39; H, 6.54.

4.5. Selectivity tests

4.5.1. General procedure for the reduction of keto esters 7c–e, 10. A solution of ester **6c**–**e**, **10** (1 equiv/~100 mg) in dry THF (10 mL) and $ZnCl_2$ was stirred for 10 min at −78 °C. A 1 M solution of L-selectride^R in THF (1.1 equiv) was added dropwise and the resulting mixture was stirred for 1 h at −78 °C. After TLC analysis had indicated total conversion (otherwise another 1.1 equiv of L-selectride^R was added and stirring was continued for 15 min at −78 °C) the reaction was quenched by addition of a 10% aqueous solution of $KHSO_4$ and warmed to ambient temperature. The mixture was diluted with water and extracted three times with ether. The combined ethereal extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (5/1→1/5).

The diastereoisomeric ratios were determined by integration of appropriate signals of the ^{1}H NMR spectra of the crude reaction mixtures as well as after saponification with LiOH by measuring the optical rotation of the resulting mandelic acids[7] and finally by HPLC-analysis of their L-valine methyl ester derivatives.[8] The following NMR-values are given only for the main diastereoisomers; yields are given for the mixtures of diastereoisomers.

4.5.1.1. (*S*)-Hydroxyphenylacetic acid, (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-diphenylethyl ester, 8c. A white solid (yield 99%), $R_f = 0.35$ (PE/E 1/1). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.25$–6.66 (m, 15H, aromatic), 5.85/4.43 (2d, 2H, Ph–C*H*–O, $J = 5.6$ Hz), 4.98 (s, 1H, Ph–C*H*(OH)–CO), 3.45–3.24 (m, 5H, O–CH_2–CH_2–O, OH), 3.15 (s, 3H, O–CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 172.1$ (s, O–CO), 137.9/137.2/136.5 (3s, Ph–C-1), 128.3–126.7 (m, Ph–C), 84.3/79.3 (2d, Ph–*C*H–O), 72.9 (d, Ph–*C*H(OH)–CO), 71.8/68.8 (2t, O–*C*H_2–*C*H_2–O), 58.8 (q, O–CH_3). Anal. Calcd for $C_{25}H_{26}O_5$: C, 73.87; H, 6.45. Found: C, 73.63; H, 6.68.

4.5.1.2. (*S*)-Hydroxyphenylacetic acid, (1*R*,2*S*)-2-(2-methoxy-2,2-diphenylethoxy)-1,2-diphenylethyl ester, 8d. A white solid (yield 86%), $R_f = 0.54$ (PE/E 1/1). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.20$–6.60 (m, 25H, aromatic), 5.65/4.36 (2d, 2H, Ph–C*H*–O, $J = 6.0$ Hz), 4.88 (s, 1H, Ph–C*H*(OH)–CO), 3.82/3.76 (2d, 2H, O–CH_2–C(Ph)$_2$–O, $J_{AB} = 9.7$ Hz), 3.22 (s, 1H, OH), 2.91 (s, 3H, O–CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 172.0$ (s, O–CO), 142.9/142.9/137.8/

136.8/136.0 (5s, Ph–C-1), 128.4–126.7 (m, Ph–C), 84.4/79.5 (2d, Ph–*C*H–O), 82.2 (s, O–CH_2–*C*(Ph)$_2$–O), 72.8 (d, Ph–*C*H(OH)–CO), 72.5 (t, O–*C*H_2–C(PH)$_2$–O), 51.4 (q, O–CH_3). Anal. Calcd for $C_{37}H_{34}O_5 \times 0.4H_2O$: C, 78.53; H, 6.20. Found: C, 78.45; H, 6.45.

4.5.1.3. (*S*)-Hydroxyphenylacetic acid, (1*R*,2*S*)-2-(2-dimethylaminoethoxy)-1,2-diphenylethyl ester, 8e. After quenching with 10% aqueous $KHSO_4$, the mixture was further diluted with a 10% aqueous solution of $KHSO_4$ and extracted three times with ether. The aqueous phase was made basic with a saturated aqueous solution of $NaHCO_3$ and extracted three times with dichloromethane. The combined dichloromethane extracts were dried over Na_2SO_4, filtered and evaporated. A white solid (yield 85%), $R_f = 0.24$ ($CHCl_3$/MeOH 9/1 + 2 drops NH_3). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.23$–6.69 (m, 15H, aromatic), 5.82/4.36 (2d, 2H, Ph–C*H*–O, $J = 6.0$ Hz), 4.96 (s, 1H, Ph–C*H*(OH)–CO), 3.97 (s, 1H, OH), 3.34/3.18 (2td, 2H, O–CH_2–CH_2–N, $J_1 = 10.1$ Hz, $J_2 = 5.7$ Hz), 2.28 (dd, 2H, O–CH_2–CH_2–N, $J_1 = 5.7$ Hz, $J_2 = 5.7$ Hz), 2.01 (s, 6H, N(CH_3)$_2$). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 172.0$ (s, O–CO), 138.1/137.4/136.5 (3s, Ph–C-1), 128.3/128.2/128.1/127.9/127.8/127.8/127.6/127.0/126.8 (9d, Ph–C), 84.3/79.0 (2d, Ph–*C*H–O), 73.0 (d, Ph–*C*H(OH)–CO), 67.8/58.5 (2t, O–*C*H_2–*C*H_2–N), 45.6 (q, N(CH_3)$_2$).

4.5.1.4. (*R*)-3-Hydroxy-3-phenylpropionic acid, (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-diphenylethyl ester, 11. A white solid (yield 33%), $R_f = 0.29$ (PE/E 1/1). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.26$–7.09 (m, 15H, aromatic), 5.96/4.92 (2d, 2H, Ph–C*H*–O, $J = 5.9$ Hz), 4.92 (dd, 1H, Ph–C*H*(OH)–CH_2–COO, $J_1 = 7.1$ Hz, $J_2 = 5.6$ Hz), 3.47–3.28 (m, 5H, O–CH_2–CH_2–O, *OH*), 3.17 (s, 3H, O–CH_3), 2.59–2.55 (m, 2H, Ph–CH(OH)–CH_2–COO). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 171.0$ (s, O–CO), 142.4/137.5/136.9 (3s, Ph–C-1), 128.4–127.6/125.6 (m, Ph–C), 84.2/77.9 (2d, Ph–*C*H–O), 71.8/68.7 (2t, O–*C*H_2–*C*H_2–O), 70.1 (d, Ph–*C*H(OH)–CH_2–COO), 58.8 (q, O–CH_3), 43.7 (t, Ph–CH(OH)-*C*H_2–COO). Anal. Calcd for $C_{26}H_{28}O_5$: C, 74.26; H, 6.71. Found: C, 74.00; H, 6.92. 49% of educt ester **10** were recovered.

4.6. Saponification of hydroxy esters 8c–e, 11

4.6.1. General procedure. A solution of ester **8c–e, 11** (50–100 mg) and LiOH (3.0 equiv) in THF/methanol/water (5/4/1) (10 mL) was stirred for 3 h at ambient temperature. The mixture was diluted with a saturated aqueous $NaHCO_3$ solution and the organic solvents were evaporated carefully (bath temperature max. 40 °C). The aqueous remaining was extracted three times with ether. For recovery of the auxiliaries **6c–e**, the combined ethereal extracts were washed with brine, dried over Na_2SO_4, filtered, evaporated and the residue was purified by vacuum flash chromatography if necessary. Thereby all auxiliaries **6c–e** could be recovered almost quantitatively without any loss of enantiomeric purity. The combined aqueous phases were carefully acidified with HCl conc. while cooling on an ice bath and extracted three times with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated yielding the free hydroxy acids **9, 12**.

4.6.1.1. (*S*)-Mandelic acid, 9. A white solid (yield 90–98%). All $[\alpha]_D^{20}$ values were (+) assigning the absolute configurations to be (*S*).[7] ^{1}H NMR (200 MHz, d_6-acetone, TMS): $\delta_H = 7.40$–7.16 (m, 5H, aromatic), 5.08 (s, 1H, Ph–C*H*(OH)–COOH), 4.71 (s, 1H, OH).

4.6.1.2. (*R*)-3-Hydroxy-3-phenylpropionic acid, 12. A pale yellow solid (yield 97%), $[\alpha]_D^{22} = -9.7$ (*c* 1.34, EtOH).[16] ^{1}H NMR (200 MHz, d_6-acetone, TMS): $\delta_H = 7.30$–7.17 (m, 5H, aromatic), 5.07 (dd, 1H, Ph–C*H*(OH)–CH_2–COOH, $J_1 = 4.1$ Hz, $J_2 = 8.5$ Hz), 2.77 (dd, 1H, Ph–CH(OH)–CH_2–COOH, $J_1 = 16.4$ Hz, $J_2 = 8.5$ Hz), 2.66 (dd, 1H, Ph–CH(OH)–CH_2–COOH, $J_1 = 16.4$ Hz, $J_2 = 4.1$ Hz).

4.7. Derivatization of mandelic acids 9 with L-valine methyl ester and HPLC analysis of these derivatives 13[8] for determination of enantiomeric excess

4.7.1. General procedure. To a solution of mandelic acid **9** (10–30 mg) and HOBt (10–30 mg) in dry dichloromethane (3 mL), a solution of L-valine methyl ester (10–30 mg) in dry dichloromethane (~1 mL) was added and the resulting mixture was cooled to −30 °C. Then a solution of DIC (10–30 mg) in dry dichloromethane (~1 mL) was added and stirring was continued for 1 h at −30 °C and then overnight at ambient temperature. Finally the reaction mixture was diluted with dichloromethane, filtered, successively washed with 10% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered and evaporated. For removal of diisopropyl urea, the crude product was taken up with ~1 mL of acetone, cooled for 10 min on an ice bath, filtered and evaporated. The crude product was used for HPLC analysis without further purification. Nucleosil 120 S C18 (4); eluents water/methanol (60/40); flow 0.16 mL/min; sample volume 2 μL ($c = 4$ mg/mL); UV 214, 230, 254 nm. $t_R = 17$ min. [*R*]; $t_R = 24$ min. [*S*].

4.8. Reactions on solid support

4.8.1. Chlorination of hydroxymethylated Wang-resin.[10] Hydroxymethylated Wang-resin (3.14 mmol/4.90 g) was suspended in dry DMF (60 mL) and cooled to −10 °C. Diisopropylethylamine (31.6 mmol/5.5 mL) and methanesulfonyl chloride (31.1 mmol/2.4 mL) were added successively while maintaining the temperature below −10 °C and the resulting mixture was stirred for 4 days at ambient temperature. Finally the resin was filtered off and thoroughly washed successively with DMF, dichloromethane, methanol, dichloromethane, methanol, dichloromethane, methanol, and dried in vacuo overnight at 40 °C. The whole procedure was once repeated to assert quantitative chlorination. A colourless resin (4.984 g). IR ν (KBr) = 693 cm^{-1} (shoulder; C–Cl); no further changes. Anal.

Calcd for 0.63 mmol/g Cl: Cl, 2.24. Found: Cl, 2.33; N, <0.05.

4.8.2. Immobilization of auxiliary precursor 4c on the solid support 5f. A solution of alcohol **4c** (9.375 mmol/4.093 g) in dry DMF (25 mL) was added slowly to a suspension of 55% NaH (8.457 mmol/0.369 g) in dry DMF (5 mL) and the mixture was shaken for 1.5 h at room temperature. Then chloromethylated Wang resin[10] (1.875 mmol/2.702 g) and a catalytic amount of NaI were added in one portion and the resulting suspension was shaken for 24 h at room temperature. Unreacted NaH was carefully hydrolized by adding portions of a mixture of water/THF (1/1) until the reaction ceased. The resin was filtered off and thoroughly washed successively with water, methanol, dichloromethane, petroleum ether, methanol, dichloromethane, methanol, dichloromethane, methanol, and dried in vacuo overnight at 40 °C. A colourless resin (3.283 g, mass increase: 0.581 g ≈ yield 80%). IR ν (KBr) = 693 cm^{-1} (C–Cl: shoulder vanished); no further changes.

For recovery of excess auxiliary precursor **4c**, the combined filtrates were diluted with brine. Dichloromethane and methanol were evaporated and the aqueous remaining was extracted three times with ether. The combined ethereal extracts were washed three times with brine, dried over Na_2SO_4, filtered and evaporated. The crude oil was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (4/1→2/1). A colourless oil (3.276 g), which was re-introduced in another auxiliary immobilization step without any loss of stereoisomeric purity.

4.8.3. Deactivation of unreacted chloromethyl groups.

4.8.3.1. Method A: methoxylation 5f′. Dry methanol (0.44 mL) was added slowly to a suspension of 55% NaH (10.96 mmol/0.48 g) in dry DMF (20 mL) and the mixture was shaken for 30 min. at room temperature. Then resin **5f** (1.636 g) and a catalytic amount of NaI were added in one portion and the resulting suspension was shaken for 48 h at room temperature. Unreacted NaH was carefully hydrolized by adding portions of a mixture of water/THF (1/1) until the reaction ceased. The resin was filtered off and thoroughly washed successively with water, methanol, dichloromethane, petroleum ether, methanol, dichloromethane, methanol, dichloromethane, methanol, and dried in vacuo overnight at 40 °C. A colourless resin (1.617 g).

4.8.3.2. Method B: iodination/reduction[12] 5f″. A mixture of resin **5f** (1.732 g) and NaI (6.5 mmol/0.97 g) in dry acetone (20 mL) were refluxed for 48 h. After cooling to room temperature, the resin was filtered off and successively washed with acetone, THF, ethanol, methanol, methanol/water (1/1), THF, water, THF/water (1/1), methanol, dichloromethane, methanol, dichloromethane, methanol and dried in high vacuo for 3 h at room temperature. Then the resin was suspended in dry THF (25 mL). Bu_3SnH (0.67 mmol/0.18 mL) was added and the mixture was refluxed for 48 h. After cooling to room temperature, the resin was filtered off and thoroughly washed successively with THF, ethanol, methanol, methanol/water (2/1), water, methanol, dichloromethane, methanol, dichloromethane, methanol and dried in vacuo overnight at 40 °C. A colourless resin (1.694 g).

4.8.4. Deprotection of auxiliary precursors 5f–f″.

4.8.4.1. General procedure. Dry methanol (51.8 mmol/2.1 mL) and triphenylphosphine hydrobromide (0.968 mmol/0.332 g) were added to a suspension of resin **5f** (~0.880 mmol/1.601 g) in dry dichloromethane and the mixture was shaken for 24 h at room temperature. Then the resin was filtered off and thoroughly washed successively with dichloromethane, methanol, dichloromethane, methanol, dichloromethane, methanol, and dried in vacuo overnight at 40 °C. A pale yellow resin (1.367 g, mass decrease: 0.234 g ≈ 0.679 mmol auxiliary loading). IR ν (KBr) = 3576 cm^{-1} (O–H); no further changes.

4.8.5. Esterification of auxiliaries 6f–f″.

4.8.5.1. General procedure. DIC (7.21 mmol/1.13 mL) was added dropwise to a mixture of resin **6f″** (~0.721 mmol/1.452 g), benzoylformic acid (7.21 mmol/1.08 g) and DMAP (0.721 mmol/0.088 g) in dry dichloromethane (15 mL) while cooling on an ice bath. The resulting mixture, which had turned from pale yellow to orange, was shaken for 48 h at room temperature. Then the resin was filtered off and thoroughly washed successively with dichloromethane, methanol, dichloromethane, methanol, dichloromethane, methanol, and dried in vacuo overnight at 40 °C. A pale yellow resin (1.542 g, mass increase: 0.090 g = 0.681 mmol). IR ν (KBr) = 3576 cm^{-1} (OH: vanished), 1739 cm^{-1} (COOR), 1689 cm^{-1} (CO); no further changes.

4.8.6. Stereoselective reduction of keto esters 7f–f″.

4.8.6.1. General procedure. A mixture of resin **7f–f″** (~1 g) and $ZnCl_2$ (2 equiv) in dry THF (10 mL) was stirred for 5 min. at room temperature and subsequently cooled to −78 °C and stirred for another 15 min. at this temperature. Then L-selectride^R (1.15 equiv; calculated on the mass increase in the esterification step) was slowly added and stirring was continued for 3 h at −78 °C. After complete conversion had been detected by IR spectroscopy (otherwise another 0.1 equiv of L-selectride^R were added and stirring was continued for 30 min. at −78 °C), the reaction was quenched by addition of an equal volume of 10% aqueous $KHSO_4$ and the resulting mixture was allowed to warm to room temperature. The resin was filtered off, treated two times with a solution of triphenylphosphine hydrobromide in dichloromethane and thoroughly washed successively with dichloromethane, THF, water, THF/water (1/1), methanol, dichloromethane, methanol, dichloromethane, methanol, and dried in vacuo overnight at 40 °C. A pale yellow resin. IR ν (KBr) = 3528 cm^{-1} (OH), 1739 cm^{-1} (COOR), 1689 cm^{-1} (CO: vanished); no further changes.

4.8.7. Saponification of hydroxy esters 8f–f″.

4.8.7.1. General procedure. A mixture of resin **8f–f″** and LiOH (5 equiv) in THF/methanol/water (10/4/1) was shaken for 3 h at room temperature. After complete conversion had been detected by IR spectroscopy, the

resin was filtered off and thoroughly washed successively with saturated aqueous $NaHCO_3$, water, methanol, THF, water, methanol, THF, methanol, THF, methanol, and dried in vacuo overnight at 40 °C. The resin was introduced in the next reaction cycle without any further purification. A pale yellow resin. IR ν (KBr) = 3528 cm^{-1} (OH), 1739 cm^{-1} (COOR: vanished); no further changes.

The combined filtrates were diluted with saturated aqueous $NaHCO_3$, and THF and methanol were evaporated (bath temperature max. 40 °C). The aqueous remaining was extracted three times with ether, acidified with HCl and then extracted three times with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated. To obtain mandelic acids **9** with appropriate purities the extractive purification step was repeated once or twice if necessary. Mandelic acids **9** were dried in high vacuo and introduced directly in the derivatization step for enantiomeric analysis (vide supra). Yield 52–98%-based on gravimetrically estimated amounts of acid bound in the esterification steps; white solid.

References

1. For a recent review on polymer-supported chiral auxiliaries see: Chung, C. W. Y.; Toy, P. H. *Tetrahedron: Asymmetry* **2004**, *15*, 387–399.
2. (a) Burgess, K.; Lim, D. *Chem. Commun.* **1997**, 785–786; (b) Purandare, A. V.; Natarajan, S. *Tetrahedron Lett.* **1997**, *38*, 8777–8780; (c) Phoon, C. W.; Abell, C. *Tetrahedron Lett.* **1998**, *39*, 2655–2658; (d) Winkler, J. D.; McCoull, W. *Tetrahedron Lett.* **1998**, *39*, 4935–4936; (e) Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron Lett.* **2000**, *41*, 1265–1269; (f) Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron* **2001**, *57*, 8313–8322; (g) Desimoni, G.; Faita, G.; Galbiati, A.; Pasini, D.; Quadrelli, P.; Rancati, F. *Tetrahedron: Asymmetry* **2002**, *13*, 333–337; (h) Kotake, T.; Rajesh, S.; Hayashi, Y.; Mukai, Y.; Ueda, M.; Kimura, T.; Kiso, Y. *Tetrahedron Lett.* **2004**, *45*, 3651–3654.
3. (a) Noe, C. R. *Chem. Ber.* **1982**, *115*, 1576–1590; (b) Noe, C. R.; Knollmueller, M.; Wagner, E.; Völlenkle, H. *Chem. Ber.* **1985**, *118*, 1733–1745; (c) Noe, C. R.; Knollmueller, M.; Steinbauer, G.; Völlenkle, H. *Chem. Ber.* **1985**, *118*, 4453–4458; (d) Noe, C. R.; Knollmueller, M.; Steinbauer, G.; Jangg, E.; Völlenkle, H. *Chem. Ber.* **1988**, *121*, 1231–1239.
4. Gaertner, P.; Schuster, C.; Knollmueller, M. *Lett. Org. Chem.* **2004**, *1*, 249–253.
5. Schuster, C.; Broeker, J.; Knollmueller, M.; Gaertner, P. *Tetrahedron: Asymmetry* **2005**, *16*.
6. (a) Superchi, S.; Contursi, M.; Rosini, C. *Tetrahedron* **1998**, *54*, 11247–11254; (b) Scafato, P.; Leo, L.; Superchi, S.; Rosini, C. *Tetrahedron* **2002**, *58*, 153–159.
7. (a) Polavarapu, P. L.; Fontana, L. P.; Smith, H. E. *J. Am. Chem. Soc.* **1986**, *108*, 94–99; (b) *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, 1995; Vol. 5, pp 3219–3221.
8. Cavelier, F.; Gomez, S.; Jacquier, R.; Llinares, M.; Mereadier, J.-L.; Petrus, C.; Verducci, J. *Tetrahedron: Asymmetry* **1993**, *4*, 2495–2500.
9. Taber, D. F.; Deker, P. B.; Gaul, M. D. *J. Am. Chem. Soc.* **1987**, *109*, 7488–7494.
10. Nugiel, D. A.; Wacker, D. A.; Nemeth, G. A. *Tetrahedron Lett.* **1997**, *38*, 5789–5790.
11. (a) Kawana, M.; Emoto, S. *Tetrahedron Lett.* **1972**, *48*, 4855–4858; (b) Kawana, M.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 160–165.
12. (a) Worster, P. M.; McArthur, C. R.; Leznoff, C. C. *Angew. Chem.* **1979**, *91*, 255; (b) McArthur, C. R.; Worster, P. M.; Jiang, J.-L.; Leznoff, C. C. *Can. J. Chem.* **1982**, *60, 1836–1841.*
13. Enders, D.; Kirchhoff, J. H.; Köbberling, J.; Pfeiffer, T. H. *Org. Lett.* **2001**, *3*, 1241–1244.
14. Deegan, T. L.; Gooding, O. W.; Baudart, S.; Porco, J. A. *Tetrahedron Lett.* **1997**, *38*, 4973–4976.
15. For an example of a successful on-bead measurement of the enantiomeric excess of a polymer bound Sharpless asymmetric dihydroxylation product by HRMAS NMR of its Mosher's ester derivative see: Riedl, R.; Tappe, R.; Berkessel, A. *J. Am. Chem. Soc.* **1998**, *120*, 8994–9000.
16. Boaz, N. W. *J. Org. Chem.* **1992**, *57*, 4289–4292.