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Synthesis of novel chiral hydrobenzoin *mono-tert*-butyl ethers derived from *m*-hydrobenzoin and their application as chiral auxiliaries in the diastereoselective reduction of α-keto esters

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Dedicated to Prof. Dr. Fritz Sauter on the occasion of his 75th birthday

Abstract—Three *m*-hydrobenzoin derived chiral hydrobenzoin *mono-tert*-butyl ethers were synthesized by a new reaction pathway and tested as chiral auxiliaries in the L-selectride® mediated stereoselective reduction of their corresponding phenyl glyoxylates. As a result, improved stereoselectivities of up to a ratio of 92:8 compared to 84:16 with the initially examined analogous benzyl ether were achieved.

1. Introduction

Over the course of our recent studies on novel chiral auxiliaries, which could be attached onto a solid support to serve at the same time as polymer bound enantiomerically pure linkers and chiral auxiliaries,[1] we synthesized chiral hydrobenzoin *mono*-benzyl ethers **5a** and **b** as test systems.[2] These compounds were easily accessible by the desymmetrization of *m*-hydrobenzoin **1** with commercially available anhydro lactols **2a** and **b** as chiral protecting groups,[3] which finally lead to both (*R*)- and (*S*)-substituted hydrobenzoin auxiliaries **5a** and **b** with the benzyl ether moiety symbolizing the linkage of the auxiliary to a polystyrene resin such as Merrifield or Wang (Scheme 1).

Whereas these auxiliaries were only able to induce moderate diastereoselectivities up to 36% de in the alkylation of carboxylic esters,[2] we were surprised to find that when applying auxiliary **5a** in the L-selectride® mediated reduction of phenylglyoxylic acid to mandelic acid, in comparison with the analogous auxiliary derived from (*R*,*R*)-hydrobenzoin, which was reported by Rosini et al. to induce stereoselectivities up to 56% de in this type of reaction,[4] even a slightly increased diastereoselectivity of 68% de with the same (*S*)-absolute configuration on the transformed stereocentre could be achieved (Scheme 2, Table 1).

On the one hand, in the case of Rosini's (*R*,*R*)-auxiliary the resulting stereoselectivities were interpreted to be the result of intramolecular π,π-interactions which force the open chain auxiliary into a conformation where the benzyl ether moiety effectively shields away the *si*-face of the keto carbonyl from the attack of the reducing agent.[4] Thus, by strengthening these π,π-interactions by introducing various substituents into the benzyl ether moiety, Rosini was able to improve the resulting diastereo selectivities significantly[5] (Table 1). On the other hand, we surprisingly found that replacement of the benzyl ether moiety in our *m*-hydrobenzoin derived auxiliary **5a** by the sterically demanding, π,π-non-interacting *i*-butyl group leading to auxiliary **5c** increased the resulting stereoselectivity as well (Table 1). This fact suggested a different mechanistic influence on the auxiliary conformation and prompted us to look out for other sterically more demanding ether moieties such as *tert*-butyl ethers, which might lead to further improvements.

Herein, we report the synthesis of three novel *m*-hydrobenzoin derived chiral hydrobenzoin *mono-tert*-butyl ethers **5d–f** (Scheme 3) via a new synthetic pathway using exclusively basic reaction conditions in the key steps and their application as chiral auxiliaries in the diastereoselective reduction of benzoylformic acid.

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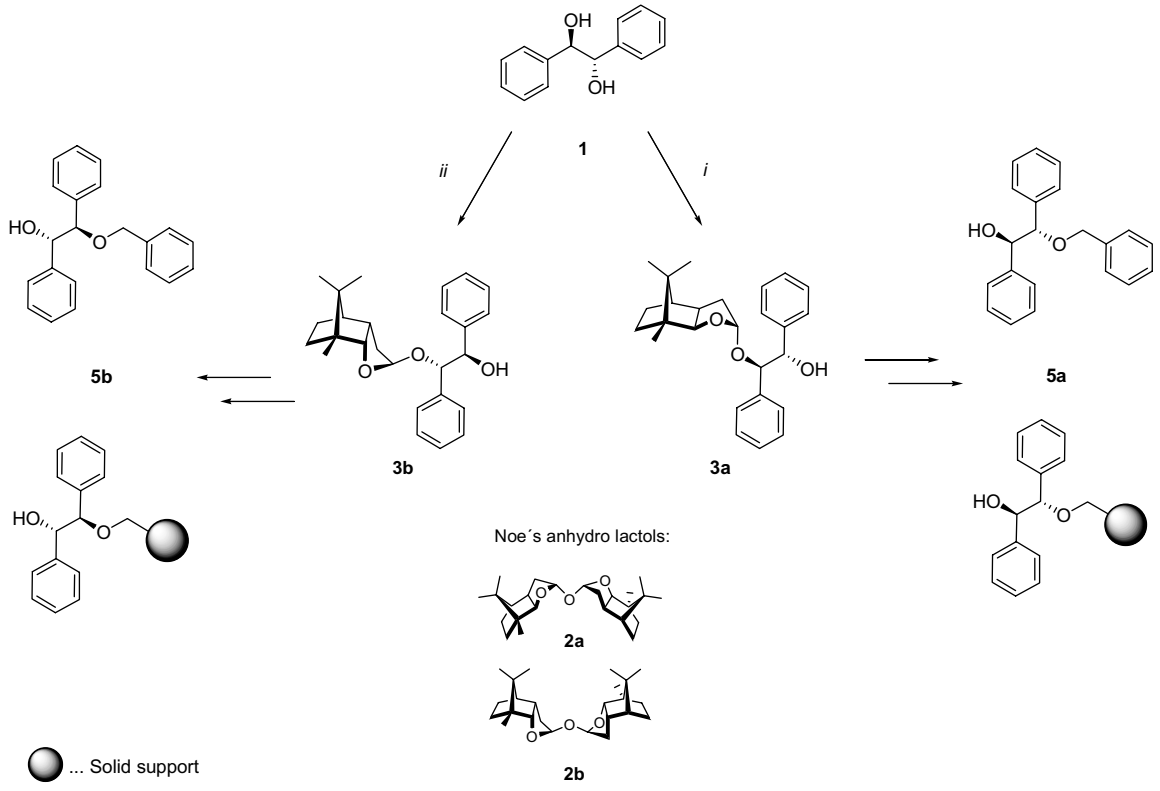
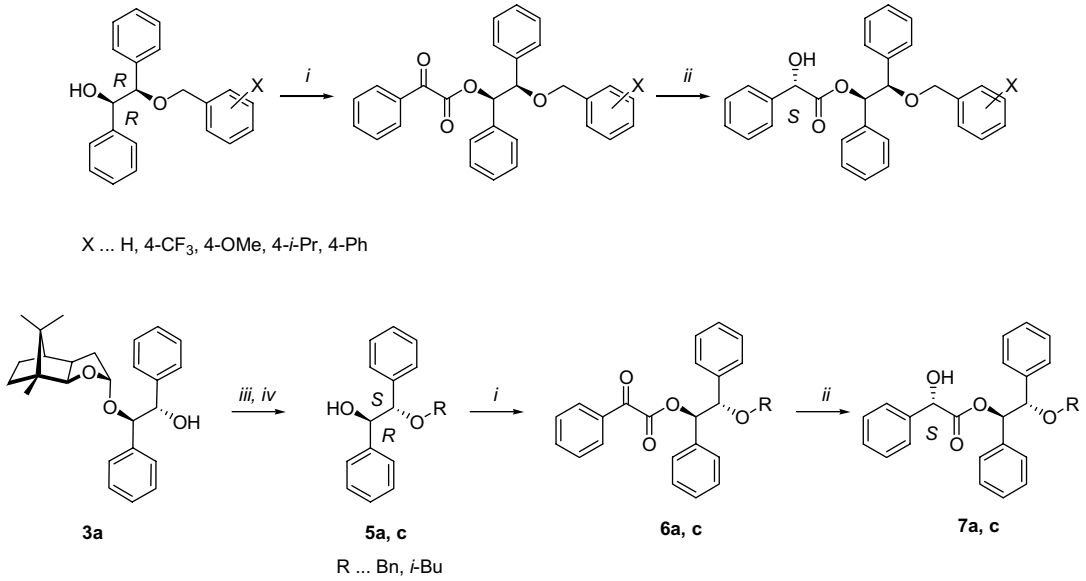


Scheme 1. Reagents and conditions: (i) *exo*-anhydro lactol **2a**, *p*-TsOH, CH_2Cl_2; (ii) *endo*-anhydro lactol **2b**, *p*-TsOH, CH_2Cl_2.



Scheme 2. Reagents and conditions: (i) PhCOCOOH, DIC, DMAP, CH_2Cl_2; (ii) L-selectride®, −78 °C, THF; (iii) NaH; BnBr or *i*-BuOTs, DMF; (iv) *p*-TsOH, MeOH.

2. Results and discussion

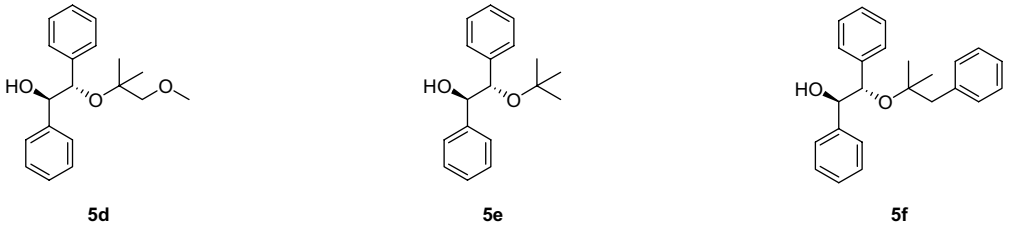
Bearing in mind that different kinds of analogous hydrobenzoin *mono-tert*-butyl ethers **5d–f** can be synthesized, we decided to derive these compounds from protected alkoxyacetic acid, *tert*-butyl ester **8** (Scheme 4), which was easily prepared in 98% yield by deprotonating protected, desymmetrized hydrobenzoin **3a** with NaH and refluxing the resulting alkoxide with bromoacetic acid, *tert*-butyl ester in THF in the presence of HMPA. Then ester **8** was methylated with 92% yield by deprotonation with LDA in THF and quenching of the enolate with CH_3I at −20 °C (Scheme 5).

The resulting ester **9** was an approximately 2:1 mixture of diastereoisomers. Trying to increase the stereoinduc-

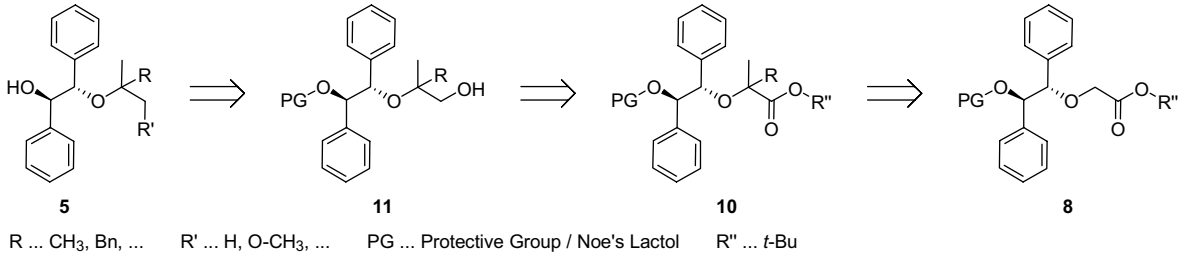
Table 1. Diastereoisomeric ratio of mandelates from the reduction of phenylglyoxylates using (*R*,*R*)-hydrobenzoin mono-benzyl ether auxiliaries and (*S*,*R*)-hydrobenzoin mono-benzyl/mono-*i*-butyl ether auxiliaries, respectively

Auxiliary	X	Ratio[a] (*R*,*R*,*S*)/(*R*,*R*,*R*)	Auxiliary	R	Ratio[a] (*S*,*R*,*S*)/(*S*,*R*,*R*)
(*R*,*R*)	H	78:22[b]	(*S*,*R*)	Bn	84:16
(*R*,*R*)	4-CF_3	87:13[c]	**5a**		
(*R*,*R*)	4-OMe	70:30[c]			
(*R*,*R*)	4-*i*-Pr	83:17[c]	(*S*,*R*)	*i*-Bu	89:11
(*R*,*R*)	4-Ph	80:20[c]	**5c**		

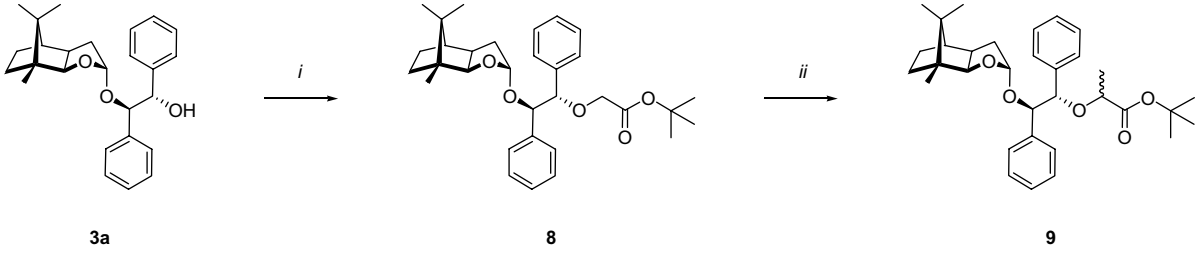
[a] Directly determined on crude by ^{1}H NMR spectroscopic analysis.
[b] Data from Ref. 4.
[c] Data from Ref. 5.



Scheme 3.



Scheme 4.



Scheme 5. Reagents and conditions: (i) NaH; $BrCH_2COO$-*t*-Bu, HMPA, THF; (ii) LDA; MeI, −20 °C, THF.

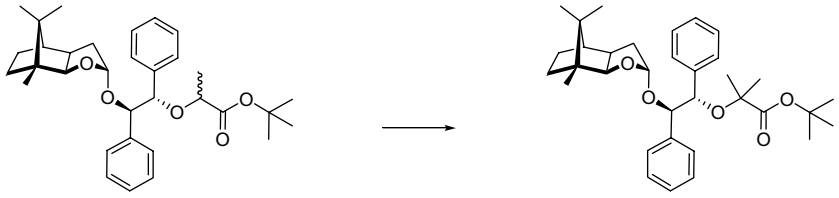
tion in this step by conducting the reaction at −78 °C resulted in no conversion and total recovery of ester **8**, which was interpreted as a dominance of the 'secondary amine effect' (vide infra) at lower temperatures.

In following another alkylation of *mono*-methylated ester **9** with different electrophiles, it should provide access to various α-*di*-alkylated alkoxyacetic acid esters **10**. After reduction to the corresponding alcohols **11**, these were thought to subsequently yield various *tert*-butyl ether derivatives **5** by further alkoxylation and reduction steps (Scheme 4).

2.1. Second alkylation step

Over the course of this strategy, it was surprising that subsequent methylation of ester **9** even when applying a higher excess of 2 equiv of LDA yielded only 15% of the desired ester **10a** while 63% of **9** were recovered. Therefore, we decided to try out some additives which are well known for this type of reaction. Whereas the use of HMPA[6] as a co-solvent resulted in almost total recovery of the starting ester **9**, employing LiCl[7] as deprotonation accelerating additive increased the yield of the second methylation step up to 57% (Table 2, entry 5).

Table 2. Second methylation step[a]—addition of additives



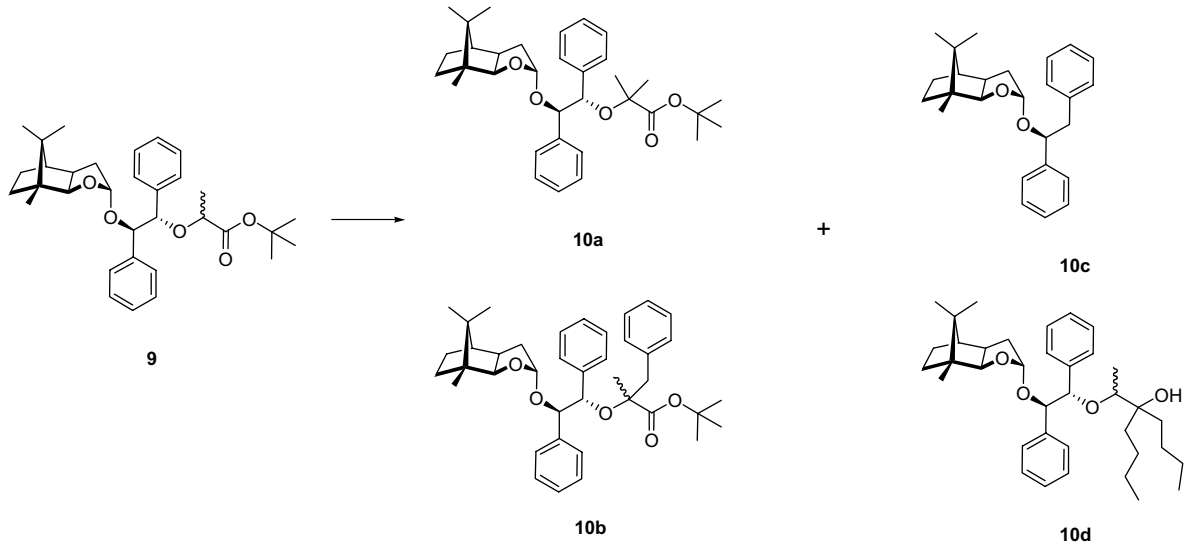
9 **10a**

Entry	Additive[a]	Yield[b] (%)
1	/	15[c]
2	6 equiv HMPA	00[d]
3	1 equiv LiCl	26
4	2 equiv LiCl	56
5	2.3 equiv LiCl	57
6	4 equiv LiCl	51

[a] Reaction conditions: LDA + **9** + additive, −15 °C, 20 min; +MeI, −15 °C → rt; solvent: THF.
[b] Isolated yields by vacuum flash chromatography.
[c] 63% of **9** recovered.
[d] 90% of **9** recovered.

Alternatively, we tried the addition of 1 equiv of BuLi after the deprotonation step, which is recommended to overcome the so-called 'secondary amine effect', that is known to be responsible for the reformation of the starting ester by a rapid, electrophile initiated proton transfer from *di-i*-propyl amine (DIPA), which is generated from LDA during the deprotonation, to the enolate.[8] Thereby, we achieved an increased methylation yield of 59% (Table 3, entry 1). Combining the deprotonation accelerating effect of adding LiCl to the reaction mixture

Table 3. Second alkylation step[a]—addition of BuLi



9 **10a** **10b** **10c** **10d**

Entry	LDA (2 equiv) deprot. time (min)	Add.	BuLi (1 equiv) deprot. time (min)	Temperature for BuLi addition	Electrophile	Yield[b]		
1	60	/	20	−20 °C	MeI	**10a** (59%)	**10c** (13%)	/
2	90	/	60	−60 °C	MeI	/	/	**10d** (26%)[c]
3	90	LiCl	60	−60 °C	MeI	/	/	**10d** (9%)[d]
4	90	LiCl	40	−20 °C	MeI	**10a** (60%)	**10c** (21%)	/
5	90	LiCl	40	−30 → −20 °C	MeI	**10a** (73%)	**10c** (21%)	**10d** (3%)
6	30	LiCl	20	−60 → −20 °C	MeI	**10a** (86%)	**10c** (2%)	**10d** (10%)
7	60	LiCl	30	−20 °C	BnBr	**10b** (60%)	**10c** (24%)	**10d** (6%)

[a] Reaction conditions: LDA + **9** + LiCl, −15 °C; +BuLi; +Electrophile, −20 °C → rt; solvent: THF.
[b] Isolated yields by vacuum flash chromatography.
[c] 68% **9** recovered.
[d] 84% **9** recovered.

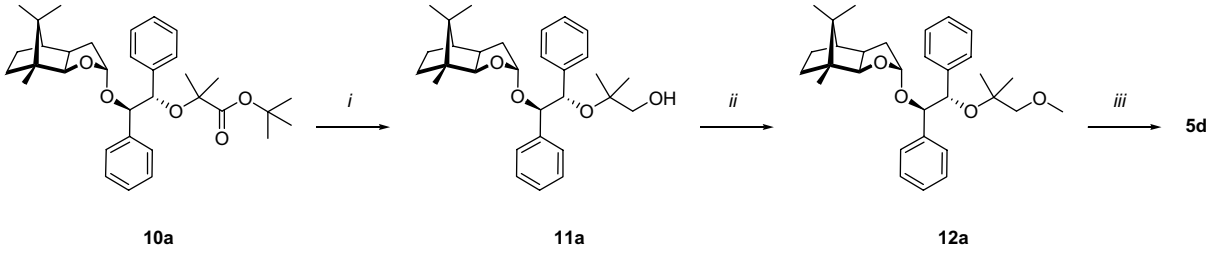
and destroying the enolate–DIPA complex by adding BuLi resulted in 86% of *di*-methylated ester **10a** in the best run (Table 3, entry 6). Benzylation of ester **9** similarly yielded 60% of ester **10b** (Table 3, entry 7). It is noteworthy, that on the one hand, deprotonation with LDA/LiCl needed to be carried out for a long enough time, otherwise the amount of by-product **10d** increased by addition of BuLi to unreacted ester **9** (Table 3, entry 6). On the other hand, an appropriate temperature was required for the decomposition of the enolate–DIPA complex. Thus, adding BuLi at too high a temperature caused the formation of by-product **10c** (Table 3, entries 4 and 5), which was thought to be generated by a Grignard-reduction type hydride attack on the ether bond of the enolate. Quenching with the electrophile at a too low temperature on the other side did not effect decomposition of the complex and resulted mainly in the recovery of ester **9** (Table 3, entries 2 and 3).

2.2. Transformation of alcohols 11a,b to *tert*-butyl ethers 5d–f

Di-alkylated esters **10a** and **b** were reduced to the corresponding alcohols **11a** and **b** with $LiAlH_4$ using standard conditions. Methylation of **11a** was then carried out by deprotonation with NaH and quenching of the alkoxide with CH_3I (Scheme 6). Finally, methyl ether **12a** was deprotected under acid catalyzed methanolysis affording auxiliary **5d** in 71% yield from **10a**. Noe's chiral protecting group[3] was isolated as its methyl acetal for recycling.

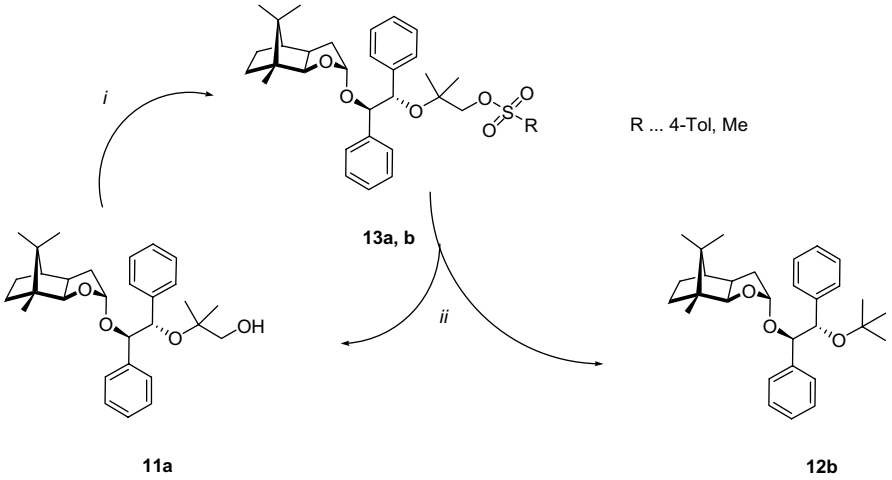
For the synthesis of *tert*-butyl ether **5e**, alcohol **11a** was first converted to tosylate **13a**, which we then tried to reduce with $LiAlH_4$ according to the procedure described by Collins and Jacobs.[9] This disappointingly yielded only 2% of the desired ether **12b**. Reduction of sulfonates **13a** and **b** with $LiBEt_3H$ (superhydride) instead of $LiAlH_4$, which was first recommended by Krishnamurthy,[10] resulted in an evident improvement of up to 21% yield. Nevertheless, the main product in all of these experiments was alcohol **11a**, a problem that is frequently reported to occur in the reduction of sterically hindered *n*-alkyl sulfonates[11] (Table 4).

Alternatively, we tried to reduce iodide **14a** with $LiAlH_4$, which unfortunately resulted only in traces of ether **12b** with alcohol **3a** as the main product. Taking into account, that Ashby has proved a single electron



Scheme 6. Reagents and conditions: (i) $LiAlH_4$, THF; (ii) NaH; MeI, HMPA, DMF; (iii) *p*-TsOH, MeOH.

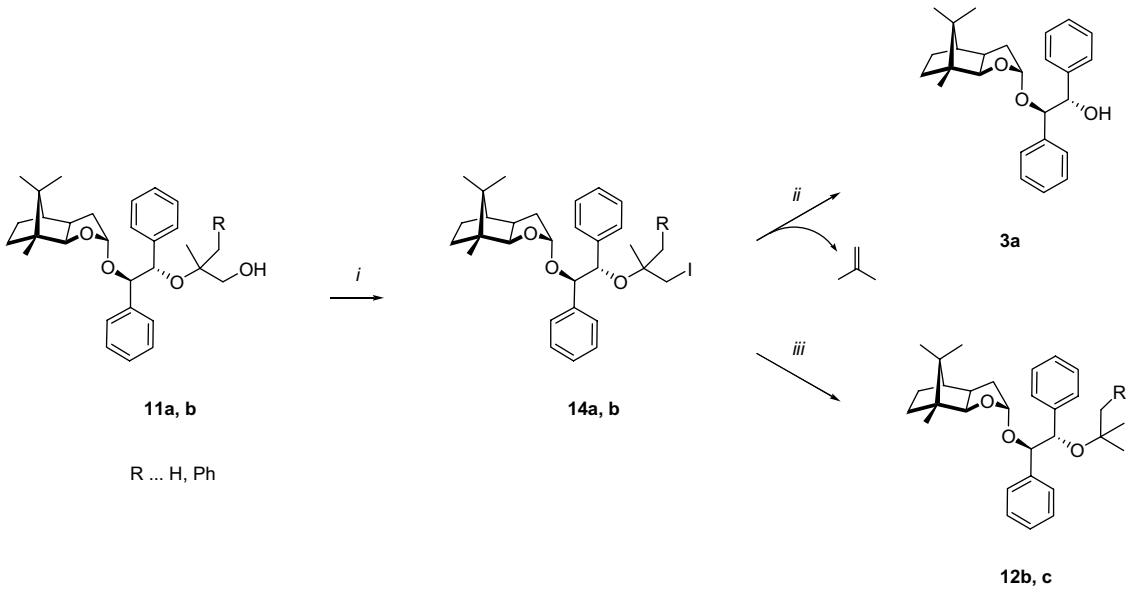
Table 4. Reduction of sulfonates **13a**,**b**[a]



Entry	R	Reducing agent	Yield **12b**[b] (%)	Yield **11a**[b] (%)
1	4-Tol **13a**	$LiAlH_4$	2	75
2	4-Tol **13a**	$LiBEt_3H$	21	65
3	CH_3 **13b**	$LiBEt_3H$	19	72

[a] Reagents and conditions: (i) TsCl, Py/MsCl, Et_3N, CH_2Cl_2; (ii) $LiAlH_4$/$LiBEt_3H$, THF.
[b] Isolated yields by vacuum flash chromatography.

Table 5. Reduction of iodides **14a**,**b**[a]



Entry	Solvent	Reducing agent	Temp.	Reaction time (h)	Yield **11**[b]
1	THF	$LiAlH_4$	rt	12	**12b** (4%)[c]
2	THF	$LiBEt_3H$	rt	48	**12b** (0%)[d]
3	THF	$LiBEt_3H$	67 °C	16	**12b** (63%)[e]
4	THF/HMPA 4:1	$LiBEt_3H$	67 °C	16	**12b** (>98%)
5	THF/HMPA 4:1	$LiBEt_3H$	67 °C	16	**12c** (90%)

[a] Reagents and conditions: (i) I_2, PPh_3, imidazole, toluene; (ii) $LiAlH_4$, THF; (iii) $LiBEt_3H$, THF/HMPA 4:1.
[b] Isolated yields by vacuum flash chromatography.
[c] Total conversion of educt **14a**; 67% alcohol **3a** isolated.
[d] 98% **14a** recovered.
[e] 35% **14a** recovered.

mechanism (SET) for the reduction of sterically hindered alkyl iodides with numerous publications,[12] an SET seemed also to be responsible for the formation of **3a** due to the elimination of *i*-butene in our experiment. Consequently, we proposed superhydride as a solution for this problem as Ashby had found superhydride to be the only exception with a proposed ionic mechanism in the reduction of sterically hindered iodides.[12a] Therefore, when using HMPA as a co-solvent, iodide **14a** could be transformed to *tert*-butyl ether **12b**, quantitatively. Similarly, iodide **14b** was reduced to **12c** in 90% yield (Table 5).

Finally, *tert*-butyl ethers **12b** and **c** were deprotected under acid catalyzed methanolysis to afford auxiliaries **5e** and **f** with 82–84% yield. Noe's chiral protecting group[3] was isolated as its methyl acetal for recycling as mentioned above.

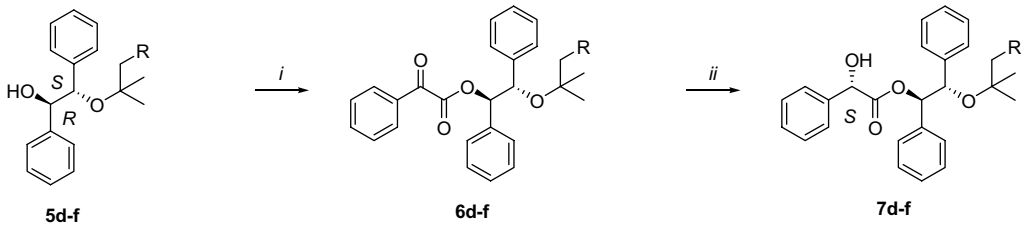
2.3. Selectivity test

Auxiliaries **5d**–**f** were esterified under mild conditions with benzoylformic acid and diisopropylcarbodiimide (DIC) in the presence of catalytic amounts of 4-(*N*,*N*-dimethylamino)pyridine (DMAP). The resulting esters **6d**–**f** were then reduced with L-selectride® in THF at −78 °C following the procedure described by Rosini and co-workers[4] (Table 6).

The diastereoisomeric ratios of the resulting α-hydroxy esters **7d**–**f** were directly analyzed by ^{1}H NMR analysis of the crude reaction mixtures by integration of the sufficiently resolved benzylic protons H_a in the two diastereoisomers (Fig. 1). The absolute configurations of the major diastereoisomers were determined by saponification of the hydroxy ester mixtures **7d**–**f** with LiOH in MeOH/THF/H_2O 5:4:1 at room temperature and comparing the specific rotations of the recovered mandelic acids with the literature values.[13] This, on the one hand, allowed us to assign all the major products as (*S*)-mandelic acid esters while on the other hand, to recover the auxiliaries quantitatively without any loss of enantiomeric purity. For further diastereoisomeric analysis, the mandelic acids were transformed into their L-valine methyl ester derivatives and analyzed by HPLC,[14] which resulted in diastereoisomeric ratios consistent with those obtained from the previous ^{1}H NMR spectroscopic analyses and therefore showed the ester saponifications to be free from racemization.

Rosini et al. proposed a conformational explanation in their work on the basis of the well-documented fact that in alkyl esters of secondary alcohols the hydrogen normally lies coplanar and *syn* to the ester carbonyl.[15] Therefore, conformation **A** was suggested to be predominant and responsible for the observed facial selectivity

Table 6. Diastereoisomeric ratio of **7d–f** from reduction of α-keto esters **6d–f**[a]



5d-f

R ... OMe, H, Ph

6d-f

7d-f

Entry	Ester	R	Additive	Ratio[b] (*S*,*R*,*S*)/(*S*,*R*,*R*)	Yield **7d–f**[c] (%)
1	**6d**	OMe	/	86:14	80
2	**6d**	OMe	2 equiv $ZnCl_2$	88:12	80
3	**6e**	H	/	92:8	87
4	**6e**	H	2 equiv $ZnCl_2$	92:8	88
5	**6f**	Ph	/	92:8	92

[a] Reagents and conditions: (i) PhCOCOOH, DIC, DMAP, CH_2Cl_2; (ii) L-selectride®, −78 °C, THF.

[b] Diastereoisomeric ratios determined by ^1H NMR integration on crude reaction mixtures and HPLC analysis of L-valine methyl ester derivatives of cleaved mandelic acids; absolute configuration of major diastereoisomers approved by specific rotation of cleaved mandelic acids.

[c] Isolated yields by vacuum flash chromatography.

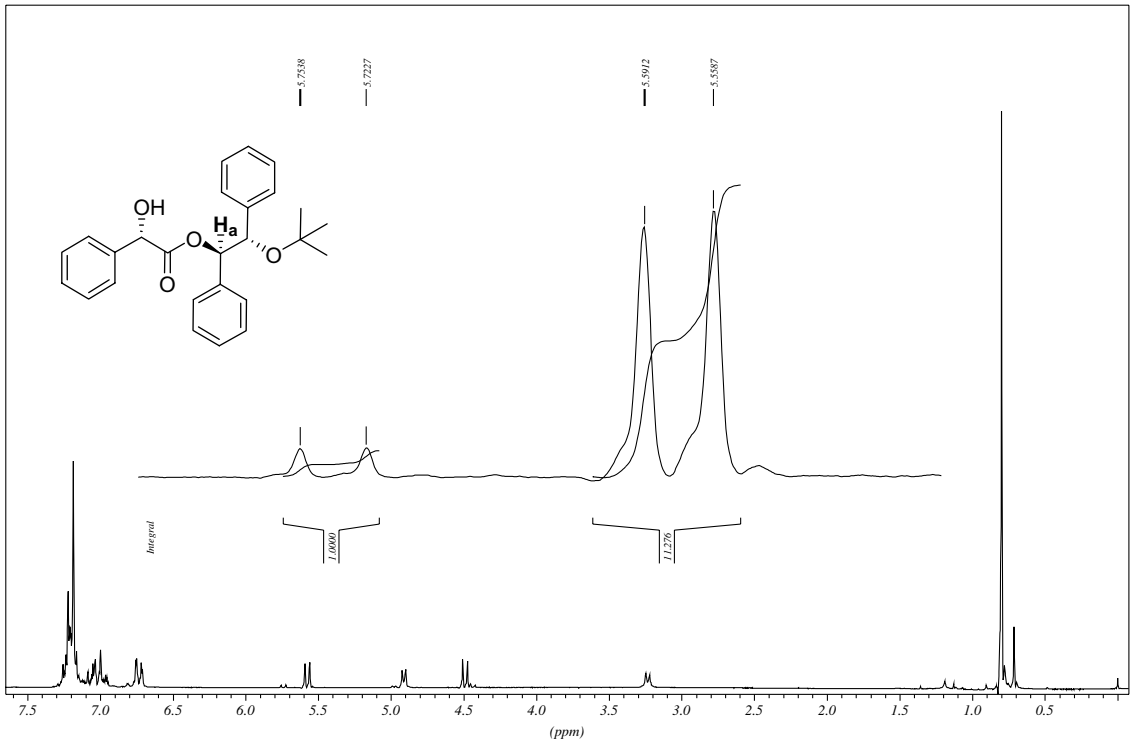
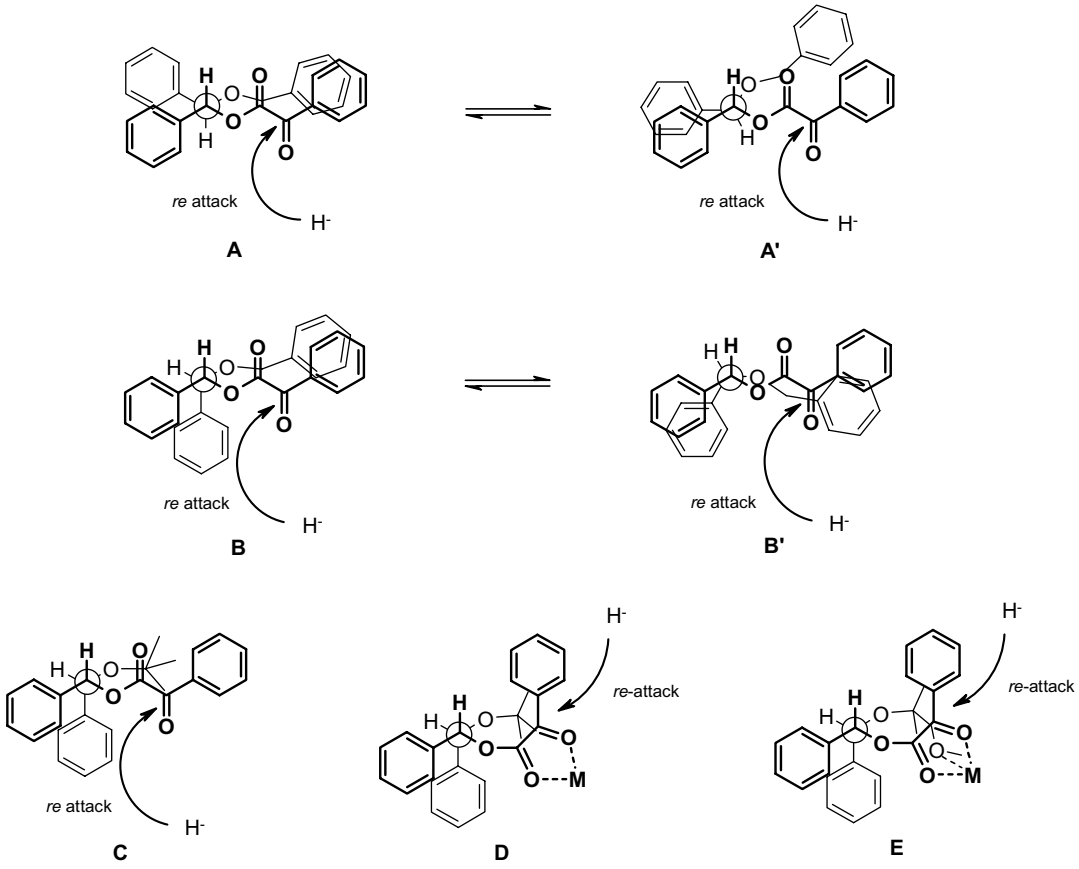


Figure 1. ^1H NMR spectrum of the mixture of diastereoisomers of mandelic acid ester **7e**.

with the (*R*,*R*)-hydrobenzoin derived benzyl ether auxiliaries (Scheme 7).[4,5] Therein the benzyl ether moiety had interacted via π–π stacking with the keto ester moiety and had consequently on the one hand forced the flexible molecule into conformation **A**, while on the other hand shielded away the *si*-face of the carbonyl from the hydride attack.[4]

Accordingly, our benzyl ether auxiliary test system **6a** might have adopted a conformation **B**, again with the benzyl ether moiety shielding away the *si*-face of the keto carbonyl. The fact that some additional π–π interactions between the two hydrobenzoin aryls might have forced the molecule out of the staggered into the more eclipsed conformation **B′** resulting in a more efficient covering of the keto carbonyl by the benzyl ether moiety, may therefore be an explanation for the slightly increased stereoinduction with our auxiliary compared to Rosini's (*R*,*R*)-auxiliary (Table 1). In contrast, the same effect might have moved the benzylether moiety away from the keto carbonyl **A′**.



Scheme 7. **A**: supposed mechanism for the stereoinduction with (*R*,*R*)-hydrobenzoin *mono*-benzyl ether auxiliaries from Refs. 4 and 5; **B**, **C**, **D** and **E**: adoptions from model **A** for the observed stereochemical outcomes with *m*-hydrobenzoin derived benzyl ether auxiliary **5a** and *tert*-butyl ether auxiliaries **5d**–**f**.

Consequently, conformation **C** with the sterically demanding *tert*-butyl ether moiety more effectively shielding away the *si*-face from the hydride attack might be responsible for the further improved stereoinduction with our *tert*-butyl ether auxiliary systems **5e** and **f**, although no π–π interactions between the ether moiety and the keto carbonyl are possible in the so far adopted model. At the moment, we have neither theoretical nor experimental evidence if this suggestion is correct or if other parameters are responsible for our unexpectedly good results. Though it is remarkable that use of the Lewis acidic additive $ZnCl_2$, which is well known to force the carbonyls of α-ketoesters from the normally known dipole–dipole interactions reducing *anti*[16] into a *syn* conformation by chelation,[17] did not have any effect at all, either on the diastereoisomeric excess or on the absolute configuration of hydroxy ester **7e** (Table 6, entry 4). Thus, another conformation **D** with the carbonyls *syn* oriented mediated by chelation even with the Li-cation of L-selectride[reg] seemed to be possible.

However, in the case of ester **6d** wherein the additional Lewis basic O-atom offers the possibility of further chelation a loss of stereofacial selectivity was observed (Table 6, entry 1) compared to **6e** and **f** (Table 6, entries 3 and 5) which could be slightly compensated by the addition of the more Lewis acidic Zn^{2+} (Table 6, entry 2). An explanation for this result may be that in the case of **6d** the two conformers **C** and **D** exhibit different stereoselectivities with **D** being more selective than **C**. With the addition of Zn^{2+}, the equilibrium between **C** and **D** is then shifted towards **D** which is stabilized by coordination to the O-atom (see **E**) and the selectivity is improved.

3. Conclusion

In conclusion, we have confirmed the findings of Rosini et al. that an open chain chiral auxiliary derived from hydrobenzoin can be used satisfactorily in the diastereoselective reduction of α-keto esters.[4,5] Thereby it turned out that our benzylether auxiliary **5a** derived from *m*-hydrobenzoin was slightly superior to the one derived from (*R*,*R*)-hydrobenzoin.[4] Furthermore, it can be suggested that not only ether substituents, which are able to undergo π–π interactions, but also sterically demanding *tert*-alkyl substituents and alkyl substituents with additional chelating atoms, respectively, can force the flexible auxiliary into a conformation, so that one of the faces of the keto carbonyl is effectively shielded away from the hydride attack. Initial diastereoselectivities of about 56–68% de with benzyl ethers have thereby been improved up to 84% de with *tert*-alkyl ethers. Over the course of this work, we have developed a convenient

synthetic route towards *tert*-butyl ethers and analogous *tert*-alkyl ethers of chiral secondary alcohols exclusively under basic conditions. We have shown that homochiral *tert*-butyl ether **12b** can be synthesized from chiral alcohol **3a** in six steps with an overall yield of 58% by this method. This can be a useful alternative when acid sensitive functionalities make commonly used acid catalyzed methods for *tert*-butyl ether syntheses not applicable, for example, when applying the method described by Armstrong et al. using *tert*-butyl trichloroacetimidate under $BF_3{\cdot}Et_2O$ catalysis[18] had yielded only 5% of the desired ether **12b** from alcohol **3a**.

We have been encouraged by our present results to undertake further investigations on *m*-hydrobenzoin *mono*-ethers as chiral auxiliaries, especially by varying the ether substituent to such an extent, that it can not only serve as the stereoinduction optimizing moiety but also as a sublinking unit between the hydrobenzoin auxiliary and a polymer support. Additional introduction of substituents in the hydrobenzoin aryls could also be a possibility of changing steric and electronic properties of the auxiliary and thereby 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, petroleum ether (60–80 °C fraction), ethyl acetate 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 molecular sieves (4 Å). Diisopropylamine was distilled from CaH_2 and kept over molecular sieves (4 Å). Lithium diisopropyl amide was prepared according to procedures described in the literature.[19] *n*-Butyl lithium was purchased from Aldrich as a ~2.5 M solution in hexane and titrated following the literature procedures.[20] L-Selectride® and superhydride 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. Benzyl bromide was distilled prior to use. NaI, LiCl and $ZnCl_2$ were dried by heating to 150–300 °C in high vacuo for 30 min prior to use. *m*-Hydrobenzoin was prepared by *meso*-selective reduction of *rac*-benzoin with $NaBH_4$ or $LiAlH_4$ according to the literature procedures.[21] All moisture sensitive reactions were carried out under a nitrogen atmosphere. 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. Column chromatography and vacuum flash chromatography were 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 Et_3N. 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. HPLC diastereoisomeric analysis of L-valine methyl ester derivatives of mandelic acids[14] was carried out with a SHIMADZU LC-10AD (SHIMADZU SPD-10AV UV/vis detector; Nucleosil 120 5 C18; H_2O/MeOH 60:40; 0.16 mL/min; $t_{R1} = 17$ min. [*R*], $t_{R2} = 24$ min. [*S*]). Elemental analysis was carried out at Vienna University, Department of Physicochemistry, Laboratory for Microanalysis, Währinger Str. 42, A-1090 Vienna.

4.2. Desymmetrization of *m*-hydrobenzoin

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-diphenylethanol, 3a.** *m*-Hydrobenzoin **1** was desymmetrized by a modification of the method described in the literature—a 2-fold excess of **1** was used for achieving better selectivities.[3] A typical run was as follows: **1** (166 mmol/35.4 g) was dissolved in dry dichloromethane (1000 mL) with gentle heating. Then *exo*-anhydro lactol **2a** (42 mmol/15.5 g), *p*-toluenesulfonic acid (0.60 g) and triphenylphosphine hydrobromide (0.10 g) were added and the mixture stirred at ambient temperature until complete equilibration was monitored by TLC analysis. Then, a portion of Na_2SO_4 was added and stirring was continued for 15 min. Finally, $NaHCO_3$ was added and the solids were filtered off after additional 15 min stirring. The filtrate was evaporated and the crude product was taken up with diethyl ether (500 mL) and stirred thoroughly for 2 h at ambient temperature. The precipitated **1** was filtered off, washed with little portions of cold ether and recovered for the next desymmetrization batch. The filtrate was evaporated and the residue purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (20:1→0:100). As a result, 19.3 g (yield 59%) of the desired enantiopure (*R*)-monoacetal **3a** could be isolated. Further, enantiopure material could also be isolated by recrystallization of a mixed fraction containing only small amounts of undesired (*S*)-*mono*-acetal from petroleum ether/ether. All other fractions containing *di*-acetal, mixtures of (*R*)- and (*S*)-*mono*-acetal and unreacted **1** were combined and could be re-equilibrated by taking them up with dichloromethane and adding a catalytic amount of acid as described above.

4.3. Preparation of benzyl and isobutyl ethers

4.3.1. [2*S*-(2α(1*S,2*R**),3aα,4β,7β,7aα)]-2-(2-Benzyloxy-1,2-diphenylethoxy)octahydro-7,8,8-trimethyl-4,7-methanobenzofuran, 4a.** A solution of alcohol **3a** (12.74 mmol/5.00 g) in dry DMF (10 mL) was added slowly to a suspension of freshly washed NaH (21.60 mmol/0.52 g) in dry DMF (2 mL) and the mixture stirred for 1 h at room temperature. Then a catalytic amount of NaI and BnBr (19.11 mmol/2.3 mL)

were added slowly and stirring continued overnight. Unreacted NaH was carefully then hydrolyzed by adding portions of a mixture of water/THF (1:1) while cooling on an ice bath, until the reaction ceased. The resulting mixture was diluted with brine and 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 product was used in the next step without further purification. For product characterization a small amount was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (20:1→5:1). White solid, mp 124–127 °C, $R_f = 0.68$ (PE/E 9:1), 0.78 (PE/E 3:1), $[\alpha]_D^{20} = -54.0$ (*c* 1.10, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.40$–6.85 (m, 15H, aromatic), 4.83 (d, 1H, 2-H, $J = 3.9$ Hz), 4.70:4.28 (2d, 2H, Ph–C*H*–O, $J_{AB} = 8.0$ Hz), 4.41:4.10 (2d, 2H, O–CH_2–Ph, $J_{AB} = 12.0$ Hz), 2.40 (d, 1H, 7a-H, $J = 6.1$ Hz), 1.94–0.48 [m, 17H, 17MBE-aliphatic, therein 0.84:0.82:0.72 (3s, 9H, 3MBE-CH_3)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 140.7$:140.2:138.3 (3s, Ph–C-1), 128.4–127.0 (m, Ph–C), 100.8 (d, C-2), 89.9 (d, C-7a), 84.0:78.6 (2d, Ph–*C*H–O), 70.3 (t, O–*C*H_2–Ph), 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), 22.8:20.5:11.5 (3q, 3MBE-CH_3). Anal. Calcd for $C_{33}H_{38}O_3 \times 0.5\ H_2O$: C, 80.62; H, 8.00. Found: C, 80.51; H, 8.02.

4.3.2. [2*S*-(2α(1*S,2*R**),3aα,4β,7β,7aα)]-2-[2-(2-Methylpropoxy)-1,2-diphenylethoxy]octahydro-7,8,8-trimethyl-4,7-methanobenzofuran, 4c.** A solution of alcohol **3a** (1.019 mmol/0.40 g) in dry DMF (2 mL) was added slowly to a suspension of freshly washed NaH (4.076 mmol/0.10 g) in dry DMF (1 mL) and the mixture stirred for 1 h at room temperature. Then, a solution of *i*-BuOTs (4.076 mmol/0.94 g), which had been prepared by reaction of *i*-butyl alcohol with *p*-tosyl chloride and pyridine using standard conditions,[22] in DMF (2 mL) was added slowly and stirring continued overnight. Unreacted NaH was then carefully hydrolyzed 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 three times 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 (100:1 → 10:1). 0.323 g (yield 78%) colourless oil, $R_f = 0.85$ (PE/E 3:1), $[\alpha]_D^{20} = -66.9$ (*c* 0.98, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.46$–7.26 (m, 10H, aromatic), 4.86 (d, 1H, 2-H, $J = 4.1$ Hz), 4.65:4.16 (2d, 2H, Ph–C*H*–O, $J = 8.3$ Hz), 3.08:2.77 (2dd, 2H, O–CH_2–CH(CH_3)$_2$, $J_{1AB} = 9.0$ Hz, $J_2 = 6.4$ Hz), 2.42 (d, 1H, 7a-H, $J = 6.4$ Hz), 1.95–0.62 [m, 24H, 17MBE-aliphatic, therein 0.82:0.82:0.72 (3s, 9H, 3MBE-CH_3); 7 aliphatic, therein 0.68:0.66 (2d, 6H, O–CH_2–CH(CH_3)$_2$, $J = 6.6$ Hz)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 141.4$:1140.5 (2s, Ph–C-1), 128.3–127.3 (m, Ph–C), 100.8 (d, C-2), 89.8 (d, C-7a), 85.3:78.6 (2d, Ph–*C*H–O), 76.0 (t, O–*C*H_2–CH(CH_3)$_2$), 48.1 (d, C-4), 46.9 (s, C-7), 46.9 (s, C-8), 45.9 (d, C-3a), 38.3 (t, C-3), 32.2 (t, C-6), 28.9 (t, C-5), 28.4 (d, O–CH_2–*C*H(CH_3)$_2$), 22.8:20.5:11.5 (3q, 3MBE-CH_3), 19.1:19.1 (2q, O–CH_2–CH(*C*H_3)$_2$). Anal. Calcd for $C_{30}H_{40}O_3 \times 0.5\ H_2O$: C, 78.73; H, 9.03. Found: C, 78.81; H, 8.81.

4.4. Preparation of *tert*-butyl ethers

4.4.1. [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, 8.** A solution of alcohol **3a** (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, *tert*-butyl ester (15.32 mmol/2.3 mL) were added successively and the mixture refluxed overnight. After cooling to ambient temperature, unreacted NaH was carefully hydrolyzed 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. The remaining HMPA, bromoacetic acid and *tert*-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). 5.10 g (yield 98%) colourless oil, $R_f = 0.85$ (PE/E 3:1), $[\alpha]_D^{20} = -59.9$ (*c* 0.96, CH_2Cl_2). ^{1}H 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.

4.4.2. [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]propionic acid, 1,1-dimethylethyl ester, 9.** A solution of ester **8** (5.613 mmol, 2.844 g) in dry THF (30 mL) was slowly added to a solution of freshly prepared LDA (8.420 mmol) in THF (30 mL), precooled to −40 °C. After stirring for 20 min at −15 °C, CH_3I (28.065 mmol, 1.75 mL) was added and stirring continued for 20 min at −15 °C. Finally, the mixture was warmed to room temperature, poured into a saturated NH_4Cl solution 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 (50:1 → 20:1). 2.689 g (yield 92%) colourless oil with diastereomeric ratio ~1.5:1, $R_f = 0.79$ (PE/E 4:1). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.42$–7.23 (m, 10H, aromatic), 4.81 (m, 1H, 2-H), 4.70:4.43 (2d, 2H, Ph–C*H*–O, $J = 7.9$ Hz), 4.63*/4.22* (2d, 2H, Ph–C*H*–O, $J = 8.2$ Hz), 3.60 (q, 1H, O–C*H*(CH_3)–CO,

$J = 6.6$ Hz), 3.47* (q, 1H, O–C*H*(CH_3)–CO, $J = 6.6$ Hz), 2.49 (d, 1H, 7a-H, $J = 6.6$ Hz), 2.42* (d, 1H, 7a-H, $J = 6.6$ Hz), 1.92–0.58 [m; 29H, 17MBE-aliphatic, therein 0.80:0.78:0.68 (3s, 9H, 3MBE-CH_3), 1.26 (s, 9H, O–C(CH_3)$_3$), 1.18* (s, 9H, O–C(CH_3)$_3$), 1.14 (d, 3H, O–CH(C*H*$_3$)–CO, $J = 6.8$ Hz), 0.96* (d, 3H, O–CH(C*H*$_3$)–CO, $J = 6.8$ Hz)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 172.2$*:171.8 (s, CO), 141.0*:140.2*:139.9:139.9 (2s, Ph–C-1), 128.5–127.2 (m, Ph–C), 100.9*:100.8 (d, C-2), 89.9*:89.8 (d, C-7a), 85.6*:83.8:78.6:78.4* (2d, Ph–CH–O), 80.6*:80.5 (s, O–*C*(CH_3)$_3$), 76.2*:72.7 (d, O–*C*H(CH_3)–CO), 48.1 (d; C-4), 47.0 (s; C-7), 46.9*:46.8 (s, C-8), 45.8 (d, C-3a), 38.3*:38.2 (t, C-3), 32.2*:32.1 (t, C-6), 28.8 (t, C-5), 27.8:27.6* (q, O–C(*C*H_3)$_3$), 22.8:20.5 (2q, 2MBE-CH_3), 18.5:17.7* (q, O–CH(*C*H_3)–CO), 11.5:11.4* (q, 1MBE-CH_3). Anal. calcd for $C_{33}H_{44}O_5$: C, 76.12; H, 8.52. Found: C, 75.83; H, 8.51. (Values marked with * refer to the minor diastereomer.)

4.4.3. [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]-2-methylpropionic acid, 1,1-dimethylethyl ester, 10a.** A solution of ester **9** (6.068 mmol, 3.160 g) and LiCl (24.28 mmol, 1.029 g) in dry THF (70 mL) was slowly added to a solution of freshly prepared LDA (12.10 mmol) in THF (30 mL), precooled to −40 °C. After stirring for 30 min at −15 °C, the bright yellow solution was cooled to −60 °C and 2.14 M *n*-BuLi (6.068 mmol, 2.84 mL) slowly added. The mixture was warmed to −20 °C over a period of 20 min. Then CH_3I (30.34 mmol, 1.89 mL) was added and stirring continued for 30 min at −15 °C. Finally, the mixture was warmed to room temperature, poured into a saturated NH_4Cl solution 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 (50:1 → 20:1). 2.806 g (yield 86%) colourless oil, $R_f = 0.81$ (PE/E 4:1), $[\alpha]_D^{20} = -57.6$ (*c* 1.66, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.37$–7.22 (m, 10H, aromatic), 4.82 (d, 1H, 2-H, $J = 4.1$ Hz), 4.63:4.43 (2d, 2H, Ph–C*H*–O, $J = 7.5$ Hz), 2.58 (d, 1H, 7a-H, $J = 6.5$ Hz), 2.00–0.64 [m, 32H, 17MBE-aliphatic, therein 0.82:0.80:0.70 (3s, 9H, 3MBE-CH_3), 1.14 (s, 9H, O–C(CH_3)$_3$), 1.04:0.89 (2s, 6H, O–C(C*H*$_3$)$_2$–CO)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 172.7$ (s, CO), 142.4:140.0 (2s, Ph–C-1), 128.5–126.8 (m, Ph–C), 100.8 (d, C-2), 89.8 (d, C-7a), 80.3 (s, O–*C*(CH_3)$_2$–CO), 79.1:78.9 (2d, Ph–*C*H–O), 77.9 (s, O–*C*(CH_3)$_3$), 48.1 (d, C-4), 46.9 (s, C-7), 46.8 (s, C-8), 45.9 (d, C-3a), 38.3 (t, C-3), 32.2 (t, C-6), 28.9 (t, C-5), 27.4 (q, O–C(*C*H_3)$_3$), 25.6:23.1 (2q, O–C(*C*H_3)$_2$–CO), 22.8:20.5:11.5 (3q, 3MBE-CH_3). Anal. Calcd for $C_{34}H_{46}O_5$: C, 76.37; H, 8.67. Found: C, 76.06; H, 8.90.

4.4.4. [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]-2-benzylpropionic acid, 1,1-dimethylethyl ester, 10b.** A solution of ester **9** (0.755 mmol, 0.393 g) and LiCl (3.02 mmol, 0.128 g) in dry THF (40 mL) was slowly added to a solution of freshly prepared LDA (2.265 mmol) in THF (15 mL), precooled to −40 °C. After stirring for 60 min at −15 °C the bright yellow solution was cooled to −30 °C and 2.14 M *n*-BuLi (0.793 mmol, 0.32 mL) slowly added. The mixture was warmed to −20 °C over a period of 20 min. Then BnBr (3.775 mmol, 0.45 mL) was added and stirring continued for 30 min at −15 °C. Finally, the mixture was warmed to room temperature, poured into a saturated NH_4Cl solution 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 (50:1 → 20:1). 0.278 g (yield 60%) colourless oil with diastereomeric ratio ~2:1, $R_f = 0.81$ (PE/E 4:1). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.32$–7.01 (m, 15H, aromatic), 4.79* (d, 1H, 2-H, $J = 4.8$ Hz), 4.70 (d, 1H, 2-H, $J = 4.7$ Hz), 4.79*:4.53* (2d, 2H, Ph–C*H*–O, $J = 6.4$ Hz), 4.45:4.40 (2d, 2H, Ph–C*H*–O, $J_{AB} = 7.6$ Hz), 2.94–2.88* (m, 2H, Ph–CH_2), 2.79:2.72 (2d, 2H, Ph–CH_2, $J_{AB} = 13.5$ Hz), 2.42 (d, 1H, 7a-H, $J = 6.9$ Hz), 2.39* (d, 1H, 7a-H, $J = 8.1$ Hz), 1.97–0.62 [m; 29H, 17MBE-aliphatic, therein 0.70:0.64:0.62 (3s; 9H, 3MBE-CH_3), 1.19* (s, 9H, O–C(CH_3)$_3$), 0.89 (s, 9H, O–C(CH_3)$_3$), 0.74 (s; 3H, O–C(Bn)(C*H*$_3$)–CO)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 171.9$*:171.8 (s, CO), 142.1:142.0*:139.8*:139.6:136.8*:136.6 (3s, Ph–C-1), 131.0–126.3 (m; Ph–C), 101.0*:100.9 (d, C-2), 90.1*:89.9 (d, C-7a), 81.4*:81.0 (s, O–*C*(Bn)(CH_3)–CO), 80.9*:80.8 (s, O–*C*(CH_3)$_3$), 80.0*:79.3:79.3:78.8* (2d, Ph–*C*H–O), 48.2*:48.1 (d, C-4), 47.1*:47.0 (s, C-7), 47.0*:46.9 (s, C-8), 46.0*:45.9 (d, C-3a), 45.9:44.6* (t, *C*H_2–Ph), 38.4*:38.3 (t, C-3), 32.3*:32.2 (t, C-6), 29.0*:28.9 (t, C-5), 27.7*:27.2 (q, O–C(*C*H_3)$_3$), 19.3:19.2* (q, O–C(Bn)(*C*H_3)–CO), 22.8*: 22.7:20.5*:20.4:11.6*:11.5 (3q, 3MBE-CH_3). Anal. Calcd for $C_{40}H_{50}O_5 \times 1.4\ H_2O$: C, 75.53; H, 8.37. Found: C, 75.44; H, 8.95. (Values marked with * refer to the minor diastereomer.)

4.4.5. General procedure for the reduction of *tert*-butylesters 10a and b. To an ice cooled solution of $LiAlH_4$ (1.286 mmol/48 mg) in dry ether (20 mL) was added a solution of the appropriate ester (0.643 mmol) **10a** or **b** in dry ether (10 mL) and the reaction mixture stirred for 1 h at ambient temperature. Water (0.5 mL) and 40% NaOH (0.1 mL) were added while cooling in an ice bath and the mixture stirred at ambient temperature until a white solid had precipitated. A small portion of Na_2SO_4 was added and the mixture filtered over a pad of Hyflo. Finally, the solvent was evaporated and the crude product was purified by vacuum flash chromatography on silica gel treated with Et_3N, eluting with petroleum ether/ether (20:1 → 5:1).

4.4.5.1. [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]-2-methylpropan-1-ol, 11a.** 0.281 g (yield 94%) white solid, mp 44–46 °C, $R_f = 0.47$ (PE/E 4:1), $[\alpha]_D^{20} = -49.4$ (*c* 2.28, CH_2Cl_2,). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.24$ (m, 10H, aromatic), 4.87 (d, 1H, 2-H, $J = 4.6$ Hz), 4.62:4.57 (2d, 2H, Ph–C*H*–O, $J_{AB} = 6.3$ Hz), 3.41 (dd, 1H, CH_2–OH,

$J_1 = 11.7$ Hz, $J_2 = 5.4$ Hz), 3.14 (dd, 1H, CH_2–OH, $J_1 = 11.7$ Hz, $J_2 = 8.0$ Hz), 2.98 (m, 1H, 7a-H), 2.62 (dd, 1H, OH, $J_1 = 8.0$ Hz, $J_2 = 5.4$ Hz), 2.14–0.64 [m, 23H, 17MBE-aliphatic, therein 0.87:0.75:0.72 (3s, 9H, 3MBE-CH_3), 0.97:0.80 (2s, 6H, O–C(CH_3)$_2$–CH_2–OH)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 142.9$:138.5 (2s, Ph–C-1), 128.8–127.1 (m, Ph–C), 101.5 (d, C-2), 90.6 (d, C-7a), 79.9:76.8 (2d, Ph–*C*H–O), 76.9 (s, O–*C*(CH$_3$)$_2$–CH_2–OH), 68.3 (t, O–C(CH$_3$)$_2$–*C*H_2–OH), 48.2 (d, C-4), 47.2 (s, C-7), 46.9 (s, C-8), 45.8 (d, C-3a), 38.4 (t, C-3), 32.3 (t, C-6), 28.8 (t, C-5), 24.5:22.0 (2q, O–C(*C*H$_3$)$_2$–CH_2–OH), 22.8:20.5:11.6 (3q, 3MBE-CH_3). Anal. Calcd for $C_{30}H_{40}O_4$: C, 77.55; H, 8.86. Found: C, 77.26; H, 8.84.

4.4.5.2. [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]-2-benzylpropan-1-ol, 11b.** 0.350 g (yield 73%) colourless oil with diastereomeric ratio ~2:1, $R_f = 0.36$ (PE/E 3:1). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.42$–6.88 (m; 15H, aromatic), 4.97* (d, 1H, 2-H, $J = 4.6$ Hz), 4.83 (d, 1H, 2-H, $J = 4.1$ Hz), 4.81*:4.71* (2d, 2H, Ph–C*H*–O, $J = 4.4$ Hz), 4.63:4.61 (2d, 2H, Ph–C*H*–O, $J_{AB} = 4.8$Hz), 3.74–0.57 [m, 26H, 18MBE-aliphatic, therein 0.80:0.72:0.62 (3s, 9H, 3MBE-CH_3); OH; 7 aliphatic, therein 0.85 (s, 3H, O–C-CH_3)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C =$ 143.2:141.8*:139.1:137.7*: 137.6:136.8* (3s, Ph–C-1), 131.1–126.0 (m, Ph–C), 102.0*:101.3 (d, C-2), 91.3*: 90.3 (d, C-7a), 80.4*:79.7: 77.0:76.6* (2d, Ph–*C*H–O), 79.6:79.3* (s, O–*C*(CH$_3$)- (CH$_2$Ph)–CH_2–OH), 65.8: 64.4* (t, O–C(CH$_3$)(CH$_2$Ph)–*C*H_2–OH), 48.3*:48.1 (d, C-4), 47.5*:47.1 (s, C-7), 46.9 (s, C-8), 45.8 (d, C-3a), 43.7*:42.2 (t, O–C(CH$_3$)- (*C*H$_2$Ph)–CH_2–OH), 38.5*: 38.3 (t, C-3), 32.4*:32.2 (t, C-6), 28.8 (t, C-5), 22.8*: 22.7:20.5*:20.4:11.6*:11.5 (3q, 3MBE-CH_3), 19.9:19.4* (O–C(*C*H$_3$)(CH$_2$Ph)–CH_2–OH). Anal. Calcd for $C_{36}H_{44}O_4$: C, 79.96; H, 8.20. Found: C, 79.72; H, 8.35. (Values marked with * refer to the minor diastereomer.)

4.4.6. [2*S*-(2α(1*S,2*R**),3aα,4β,7β,7aα)]-2-[2-(2-Methoxy-1,1-dimethylethoxy)-1,2-diphenyl-ethoxy]octahydro-7,8,8-trimethyl-4,7-methanobenzofuran, 12a.** A solution of alcohol **11a** (0.777 mmol/0.361 g) and HMPA (4.76 mmol/0.83 mL) in dry DMF (10 mL) was added slowly to a suspension of 60% NaH (1.583 mmol/ 0.063 g) in dry DMF (2 mL) and the mixture stirred for 1 h at room temperature. Then, CH_3I (1.583 mmol/0.1 mL) was added and stirring continued overnight. Unreacted NaH was carefully hydrolyzed 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. The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (20:1 → 5:1). 0.314 g (yield 84%) colourless oil, $R_f = 0.72$ (PE/E 3:1), $[\alpha]_D^{20} = -77.4$ (*c* 1.26, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.46$–7.22 (m, 10H, aromatic), 4.80 (d, 1H, 2-H, $J = 3.9$ Hz), 4.49:4.44 (2d, 2H, Ph–C*H*–O, $J_{AB} = 8.7$ Hz), 3.04 (s, 3H, CH_2–O–CH_3), 2.82 (s, 2H, CH_2–O–CH_3), 2.23 (d, 1H, 7a-H, $J = 6.1$ Hz), 1.92–0.55 [m, 23H, 17MBE-aliphatic, therein 0.73:0.72:0.68 (3s, 9H, 3MBE-CH_3), 0.78:0.76 (2s, 6H, O–C(CH_3)$_2$–CH_2)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 144.3$:140.6 (2s, Ph–C-1), 128.5–126.5 (m, Ph–C), 100.6 (d, C-2), 89.5 (d, C-7a), 79.9:77.6 (2d, Ph–*C*H–O), 78.9 (s, O–*C*(CH$_3$)$_2$–CH_2), 75.8 (q, CH_2–O–*C*H_3), 58.8 (t, *C*H_2–O–CH_3), 47.9 (d, C-4), 47.5 (s, C-7), 46.7 (s, C-8), 45.7 (d, C-3a), 38.2 (t, C-3), 32.0 (t, C-6), 28.7 (t, C-5), 23.4:23.3 (2q, O–C(*C*H$_3$)$_2$–CH_2), 22.6:20.3:11.3 (3q, 3MBE-CH_3). Anal. Calcd for $C_{31}H_{42}O_4$: C, 77.79; H, 8.84. Found: C, 77.57; H, 8.98.

4.4.7. 4-Methylbenzene-1-sulfonic acid, [2S-(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]-2-methylpropyl ester, 13a.** A solution of *p*-tosyl chloride (0.462 mmol/0.088 g) in pyridine (2 mL) was added dropwise to a solution of alcohol **11a** (0.308 mmol/0.143 g) in pyridine (4 mL) while cooling on an ice bath. After stirring for 4 days at room temperature the mixture was taken up with a 10% aqueous solution of $KHSO_4$ and extracted three times with ether. The combined ethereal extracts were washed twice with $KHSO_4$ solution and 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). 0.151 g (yield 79%) white solid, mp 121–123 °C, $R_f = 0.50$ (PE/E 2:1), $[\alpha]_D^{20} = -66.2$ (*c* 0.84, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.63$:7.28 (2d, 4H, Ts-aromatic, $J = 8.3$ Hz), 7.31–7.26 (m, 10H, aromatic), 4.77 (d, 1H, 2-H, $J = 3.8$ Hz), 4.41:4.27 (2d, 2H, Ph–C*H*–O, $J = 8.4$ Hz), 3.44:3.36 (2d, 2H, CH_2–OTs, $J_{AB} = 9.4$ Hz), 2.46 (s, 3H, Ph–CH_3), 2.21 (d, 1H, 7a-H, $J = 6.4$ Hz), 1.91–0.48 [m, 23H, 17MBE-aliphatic, therein 0.73:0.67:0.63 (3s, 9H, 3MBE-CH_3), 0.76 (2s, 6H, O–C(CH_3)$_2$–CH_2–OTs)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 144.5$ (s, Ts-C-1), 143.6:140.2 (2s, Ph–C-1), 132.9 (s, Ts-C-4), 129.7–127.0 (m, Ph–C), 100.8 (d, C-2), 89.7 (d, C-7a), 78.8:77.9 (2d, Ph–*C*H–O), 75.6 (t, O–C(CH$_3$)$_2$–*C*H_2–OTs), 48.1 (d, C-4), 46.9 (s, C-7), 46.9 (s, C-8), 45.8 (d, C-3a), 38.3 (t, C-3), 32.1 (t, C-6), 28.8 (t, C-5), 23.3:21.6 (2q, O–C(*C*H$_3$)$_2$–CH_2–OTs), 22.4 (q, Ph–CH_3), 22.8:20.5:11.4 (3q, 3MBE-CH_3). Anal. Calcd for $C_{37}H_{46}O_6S \times 0.3$ hexane: C, 72.29; H, 7.85; S, 4.97. Found: C, 71.99; H, 8.02; S, 4.77. 0.015 g (yield 10%) of alcohol **11a** were recovered.

4.4.8. Methanesulfonic acid, [2*S*-(2α(1*R,2*S**),3aα,4β,7-β,7aα)]-2-[2-[(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)oxy]-1,2-diphenylethoxy]-2-methylpropylester, 13b.** Methanesulfonyl chloride (1.661 mmol/ 0.13 mL) was added dropwise to a solution of alcohol **11a** (0.923 mmol/0.429 g) in dichloromethane (20 mL) while cooling on an ice bath. After stirring for 3 h at room temperature the mixture was extracted successively with a 10% aqueous $KHSO_4$ solution, a saturated aqueous $NaHCO_3$ solution and 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 (10:1 → 5:1).

0.492 g (yield 98%) colourless oil, $R_f = 0.24$ (PE/E 3:1), $[\alpha]_D^{20} = -68.9$ (c 1.15, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.45$–7.20 (m, 10H, aromatic), 4.79 (d, 1H, 2-H, $J = 3.9$ Hz), 4.49:4.37 (2d, 2H, Ph–C*H*–O, $J = 8.3$ Hz), 3.66:3.59 (2d, 2H, O–C(CH_3)$_2$–C*H*$_2$–OMs, $J_{AB} = 9.6$ Hz), 2.71 (s, 3H, O–SO_2–C*H*$_3$), 2.23 (d, 1H, 7a-H, $J = 6.6$ Hz), 1.93–0.45 [m, 23H, 17MBE-aliphatic, therein 0.77:0.76:0.68 (3s, 9H, 3MBE-CH_3), 0.77:0.76 (2s, 6H, O–C(C*H*$_3$)$_2$–CH_2–OMs)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 143.6$:140.2 (2s, Ph–C-1), 128.6–127.1 (m, Ph–C), 100.8 (d, C-2), 89.8 (d, C-7a), 78.9:78.0 (2d, Ph–*C*H–O), 75.12 (t, O–C(CH_3)$_2$–*C*H$_2$–OMs), 74.7 (s, O–*C*(CH_3)$_2$–CH_2–OMs), 48.0 (d, C-4), 46.9 (s, C-7), 46.8 (s, C-8), 45.8 (d, C-3a), 38.3 (t, C-3), 36.6 (q, O–SO_2–*C*H$_3$), 32.1 (t, C-6), 28.8 (t, C-5), 22.9:22.6 (2q, O–C(*C*H$_3$)$_2$–CH_2–OMs), 22.7:20.4:11.4 (3q, 3MBE-CH_3). Anal. Calcd for $C_{31}H_{42}O_6S \times 1.1\ H_2O$: C, 66.19; H, 7.92; S, 5.70. Found: C, 66.44; H, 7.92; S, 5.53.

4.4.9. General procedure for the preparation of iodides 14a and b. Iodine (0.994 mmol/0.250 g) was added to a solution of alcohols **11a** and **b** (0.497 mmol), PPh_3 (0.994 mmol/0.260 g) and imidazole (1.989 mmol/0.140 g) in dry toluene (40 mL) and the resulting mixture was refluxed overnight. After cooling to ambient temperature, the residue was filtered off and the filtrate extracted successively twice with a 10% aqueous $KHSO_4$ solution, once with a 10% aqueous $Na_2S_2O_3$ solution and then with brine, dried over Na_2SO_4, filtered and evaporated. The crude product was purified by column chromatography on silica gel, eluting with petroleum ether/ether (100:1). Since iodides **14a** and **b** turned out to be rather unstable when being stored for more than 48 h at room temperature, they were reacted in the next step almost immediately.

4.4.9.1. [2*S*-(2α(1*S,2*R**),3aα,4β,7β,7aα)]-2-[2-(2-Iodo-1,1-dimethylethoxy)-1,2-diphenyl-ethoxy]octahydro-7,8,8-trimethyl-4,7-methanobenzofuran, 14a.** 0.232 g (yield 81%) colourless oil, $R_f = 0.67$ (PE/E 10:1), $[\alpha]_D^{20} = -54.6$ (c 1.00, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.47$–7.22 (m, 10H, aromatic), 4.81 (d, 1H, 2-H, $J = 3.8$ Hz), 4.53:4.32 (2d, 2H, Ph–C*H*–O, $J = 8.3$ Hz), 2.92:2.85 (2d, 2H, O–C(CH_3)$_2$–C*H*$_2$–I, $J_{AB} = 10.0$ Hz), 2.27 (d, 1H, 7a-H, $J = 6.6$ Hz), 2.00–0.47 [m, 23H, 17MBE-aliphatic, therein 0.78:0.78:0.69 (3s, 9H, 3MBE-CH_3), 0.91:0.82 (2s, 6H, O–C(C*H*$_3$)$_2$–CH_2–I)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 143.7$:140.3 (2s, Ph–C-1), 128.6:127.8:127.5:127.5:127.4:127.0 (6d, Ph–C), 100.8 (d, C-2), 89.7 (d, C-7a), 78.9:78.3 (2d, Ph–*C*H–O), 74.7 (s, O–*C*(CH_3)$_2$–CH_2–I), 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), 25.8:24.7 (2q, O–C(*C*H$_3$)$_2$–CH_2–I), 22.8:20.5:11.4 (3q, 3MBE-CH_3), 18.6 (t, O–C(CH_3)$_2$–*C*H$_2$–I).

4.4.9.2. [2*S*-(2α(1*S,2*R**),3aα,4β,7β,7aα)]-2-[2-(1-Benzyl-2-iodo-1-methylethoxy)-1,2-diphenyl-ethoxy]octahydro-7,8,8-trimethyl-4,7-methanobenzofuran, 14b.** 0.302 g (yield 93%) yellowish oil with diastereomeric ratio ~2:1, $R_f = 0.65$ (PE/E 10:1). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.43$–7.17 (m; 15H, aromatic), 4.83:4.80* (d, 1H, 2-H, $J = 3.9$ Hz), 4.56:4.52*:4.41:4.35* (2d, 2H, Ph–C*H*–O, $J = 8.2$ Hz), 2.92–2.41 (m, 4H, C*H*$_2$–I, C*H*$_2$–Ph), 2.28*:2.26 (d, 1H, 7a-H, $J = 6.2$ Hz), 1.95–0.48 [m, 20H, 17MBE-aliphatic, therein 0.80:0.80:0.70 (3s, 9H, 3MBE-CH_3), 0.80 (s, 3H, O–C(CH_2Ph)-(CH_2I)–C*H*$_3$)]. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 143.7$:143.5*:140.1:139.9*:137.2:137.1* (3s, Ph–C-1), 133.9–126.3 (m, Ph–C), 100.9 (d, C-2), 89.8 (d, C-7a), 79.1:79.0*:78.2*:78.1 (2d, Ph–*C*H–O), 77.1:76.7* (s, O–*C*(CH_2Ph)(CH_2I)-CH_3), 48.1 (d, C-4), 46.9 (s, C-7), 46.8 (s, C-8), 45.8 (d, C-3a), 45.6*:44.9 (t, CH_2-I), 39.0*:38.3 (t, C-3), 32.1:31.9* (t, C-6), 29.5*:29.9 (t, C-5), 22.3 (q, O–C(CH_2Ph)(CH_2I)–*C*H$_3$), 22.9:20.1:11.5 (3q, 3MBE-CH_3), 16.4:14.1* (2t, *C*H$_2$–Ph). (Values marked with * refer to the minor diastereomer.)

4.4.10. General procedure for the reduction of sulfonates 13a,b. A 1 M solution of $LiBEt_3H$ in THF (10 equiv) was added to a solution of sulfonate **13a** and **b** (1 equiv/~0.100 g) in dry THF (10 mL) and the resulting mixture refluxed overnight. 5 mL of water, 5 mL of 2 M NaOH and 5 mL of 35% H_2O_2 were added successively while cooling on an ice bath and stirring continued at ambient temperature until gas evolution had ceased. Finally, the mixture was diluted with brine and extracted three times with ether. The combined ethereal extracts were washed with an aqueous $FeSO_4$ solution and 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).

Starting with tosylate **13a**, 21% of the desired *tert*-butyl ether **12b**, as well as 65% of alcohol **11a**, were isolated. Reduction of mesylate **13b** yielded 19% of *tert*-butyl ether **12b** and 72% of alcohol **11a**.

4.4.11. General procedure for the reduction of iodides 14a,b. A 1 M solution of $LiBEt_3H$ in THF (7.64 mmol/7.6 mL) was added to a solution of iodide **14a** (0.764 mmol/0.439 g) in dry THF (33 mL) and HMPA (10 mL) and the resulting mixture refluxed for 16 h. After cooling to ambient temperature, 2 M NaOH (30 mL) was added in portions and stirring continued until the gas evolution had ceased. 35% of H_2O_2 (30 mL) was added and stirring continued again until gas evolution had ceased. Finally, the mixture was diluted with brine and extracted three times with ether. The combined ethereal extracts were washed with an aqueous $FeSO_4$ solution and two times 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 (100:1).

4.4.11.1. [2*S*-(2α(1*S,2*R**),3aα,4β,7β,7aα)]-2-[2-(1,1-Dimethylethoxy)-1,2-diphenylethoxy]octahydro-7,8,8-trimethyl-4,7-methanobenzofuran, 12b.** 0.335 g (yield 98%) colourless oil, $R_f = 0.84$ (PE/E 4:1), $R_f = 0.70$ (PE/E 10:1), $[\alpha]_D^{20} = -80.5$ (c 1.10, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.46$–7.18 (m, 10H, aromatic), 4.80 (d, 1H, 2-H, $J = 4.1$ Hz), 4.47:4.28 (2d, 2H, Ph–C*H*–O, $J = 8.6$ Hz), 2.22 (d, 1H, 7a-H,

$J = 6.6$ Hz), 1.92–0.67 [m, 26H, 17MBE-aliphatic, therein 0.77:0.75:0.67 (3s 9H, 3MBE-CH_3), 0.73 (s, 9H, O–C(CH_3)$_3$)]. ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 144.9:140.8 (2s, Ph–C-1), 128.6:127.8:127.3:127.2: 127.1:126.6 (6d, Ph–C), 100.7 (d, C-2), 89.6 (d, C-7a), 79.0:77.6 (2d, Ph–*C*H–O), 74.1 (s, O–*C*(CH_3)$_3$), 48.1 (d, C-4), 46.8 (s, C-7), 46.8 (s, C-8), 45.9 (d, C-3a), 38.3 (t, C-3), 32.1 (t, C-6), 29.0 (t, C-5), 28.1 (q, O–C(*C*H_3)$_3$), 22.8:20.5:11.4 (3q, 3MBE-CH_3). Anal. Calcd for $C_{30}H_{40}O_3 \times 0.1$ H_2O: C, 79.99; H, 9.00. Found: C, 80.02; H, 9.19.

4.4.11.2. [2*S*-(2α(1*S,2*R**),3aα,4β,7β,7aα)]-2-[2-(1,1-Dimethyl-2-phenylethoxy)-1,2-diphenyl-ethoxy]octahydro-7,8,8-trimethyl-4,7-methanobenzofuran, 12c.** 0.240 g (yield 90%) colourless oil, $R_f = 0.69$ (PE/E 10:1), $[\alpha]_D^{20} = -65.8$ (*c* 1.00, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.44$–7.12 (m, 15H, aromatic), 4.85 (d, 1H, 2-H, $J = 3.7$ Hz), 4.52:4.38 (2d, 2H, Ph–C*H*–O, $J = 8.3$ Hz), 2.56:2.47 (2d, 2H, O–C(CH_3)$_2$–C*H*$_2$–Ph, $J_{AB} = 18.6$ Hz), 2.24 (d, 1H, 7a-H, $J = 6.6$ Hz), 1.97–0.87 (m, 14H, MBE-aliphatic), 0.82 (s, 6H, O–C(C*H*$_3$)$_2$–CH_2–Ph), 0.73 (s, 6H, 2MBE-CH_3), 0.56 (s, 3H, 1MBE-CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 144.8:140.6:138.4 (3s, Ph–C-1), 130.9–125.8 (m, Ph–C), 100.9 (d, C-2), 89.7 (d, C-7a), 79.2:77.5 (2d, Ph–*C*H–O), 76.5 (s, O–*C*(CH_3)$_2$–CH_2–Ph), 49.2 (t, O–C(CH_3)$_2$–*C*H_2–Ph), 48.1 (d, C-4), 46.9 (s, C-8), 45.9 (d, C-3a), 38.3 (t, C-3), 32.1 (t, C-6), 28.9 (t, C-5), 25.9:24.2 (2q, O–C(*C*H_3)$_2$–CH_2–Ph), 22.8:20.5:11.5 (3q, 3MBE-*C*H_3). Anal. Calcd for $C_{36}H_{44}O_3 \times 0.1$ H_2O: C, 82.12; H, 8.46. Found: C, 82.26; H, 8.60.

4.5. Deprotection of auxiliary precursors 4a,c, 12a–c

4.5.1. General procedure. Ethers **4a**,**c**, **12a**–**c** (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 continued for 10 min. The organic solvents were evaporated and the aqueous remains diluted with water 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 → 1:1). Methyl acetal was recovered as an additional product fraction for recyclation of Noe's chiral protecting group.[3]

4.5.1.1. (1*R*,2*S*)-2-Benzyloxy-1,2-diphenylethanol, 5a. 3.43 g (yield 88% over two steps from **3a**) white solid, mp 77–79 °C, $R_f = 0.30$ (PE/E 3:1), $[\alpha]_D^{20} = +31.1$ (*c* 1.00, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.38$–7.07 (m, 15H, aromatic), 4.91 (dd, 1H, Ph–C*H*–O, $J_1 = 4.0$ Hz, $J_2 = 4.0$ Hz), 4.51:4.24 (2d, 2H, O–C*H*$_2$–Ph, $J = 12.0$ Hz), 4.49 (d, 1H, Ph–C*H*–O, $J = 4.0$ Hz), 2.32 (d, 1H, OH, $J = 4.0$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 140.4:137.9:137.6 (3s, Ph–C-1), 128.3–127.1 (m, Ph–C), 85.0:77.0 (2d, Ph–*C*H–O), 70.6 (t, O–*C*H_2–Ph). Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.86; H, 6.89.

4.5.1.2. (1*R*,2*S*)-2-(2-Methylpropoxy)-1,2-diphenylethanol, 5c. 0.22 g (yield 77% over two steps from **3a**) white solid, mp 57–60 °C, $R_f = 0.51$ (PE/E 3:1), $[\alpha]_D^{20} = +43.7$ (*c* 0.90, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.33$–7.14 (m, 10H, aromatic), 4.86 (dd, 1H, Ph–C*H*–O, $J_1 = 5.6$ Hz, $J_2 = 4.1$ Hz), 4.41 (d, 1H, Ph–C*H*–O, $J = 5.6$ Hz), 3.17:3.02 (2dd, 2H, O–C*H*$_2$–CH(CH_3)$_2$, $J_{1AB} = 9.0$ Hz, $J_2 = 6.7$ Hz), 2.54 (d, 1H, OH, $J = 4.1$ Hz), 1.84 (m, 1H, O–CH_2–C*H*(CH_3)$_2$), 0.85:0.84 (2d, 6H, O–CH_2–CH(C*H*$_3$)$_2$, $J = 6.7$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 140.4:138.1 (2s, Ph–C-1), 127.9:127.8:127.7:127.6: 127.3:127.1 (6d, Ph–C), 86.0:77.1 (2d, Ph–*C*H–O), 76.0 (t, O–*C*H_2–CH(CH_3)$_2$), 28.5 (d, O–CH_2-*C*H(CH_3)$_2$), 19.3:19.2 (2q, O–CH_2–CH(*C*H_3)$_2$). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.37; H, 8.48.

4.5.1.3. (1*R*,2*S*)-2-(2-Methoxy-1,1-dimethylethoxy)-1,2-diphenylethanol, 5d. 0.171 g (yield 91%) colourless oil, $R_f = 0.18$ (PE/E 4:1), $[\alpha]_D^{20} = +123.2$ (*c* 0.56, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.19$–7.04 (m, 10H, aromatic), 4.86:4.68 (2d, 2H, Ph–C*H*–O, $J =$ 4.6 Hz), 3.82 (s, 1H, OH), 3.34 (s, 3H, O–CH_3), 3.42:3.09 (2d, 2H, C*H*$_2$–O–CH_3, $J = 9.8$ Hz), 1.15:0.94 (2s, 6H, O–C(C*H*$_3$)$_2$–CH_2–OH). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 141.1$:140.1 (2s, Ph–C-1), 127.5–126.9 (m, Ph–C), 78.0 (t, CH_2–O), 78.0 (s, O–*C*(CH_3)$_2$), 77.9:75.8 (2d, Ph–*C*H–O), 58.9 (q, O–CH_3), 25.0:23.0 (2q, O–C(*C*H_3)$_2$). Anal. Calcd for $C_{19}H_{24}O_3 \times 0.2$ H_2O: C, 75.07; H, 8.09. Found: C, 75.06; H, 8.13.

4.5.1.4. (1*R*,2*S*)-2-(1,1-Dimethylethoxy)-1,2-diphenylethanol, 5e. 0.152 g (yield 84%) white solid, mp 73–75 °C, $R_f = 0.43$ (PE/E 3:1), $[\alpha]_D^{20} = +55.8$ (*c* 0.64, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.32$–7.10 (m, 10H, aromatic), 4.70 (dd, 1H, Ph–C*H*–O, $J_1 = 6.0$ Hz, $J_2 = 3.7$ Hz), 4.54 (d, 1H, Ph–C*H*–O, $J = 6.0$ Hz), 2.36 (d, 1H, OH, $J = 3.7$ Hz), 0.99 (s, 9H, O–C(C*H*$_3$)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 141.5$:140.9 (2s, Ph–C-1), 127.7:127.5:127.5:127.3: 127.3:127.2 (6d, Ph–C), 78.3:78.0 (2d, Ph–*C*H–O), 74.9 (s, O–*C*(CH_3)$_3$), 28.4 (q, O–C(*C*H_3)$_3$). Anal. Calcd for $C_{18}H_{22}O_2 \times 0.1$ H_2O: C, 79.43; H, 8.22. Found: C, 79.67; H, 8.23.

4.5.1.5. (1*R*,2*S*)-2-(1,1-Dimethyl-2-phenylethoxy)-1,2-diphenylethanol, 5f. 0.125 g (yield 82%) colourless oil, $R_f = 0.39$ (PE/E 3:1), $[\alpha]_D^{20} = +1.4$ (*c* 1.00, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.37$–7.13 (m, 15H, aromatic), 4.71 (dd, 1H, Ph–C*H*–O, $J_1 =$ 5.8 Hz, $J_2 = 3.4$ Hz), 4.63 (d, 1H, Ph–C*H*–O, $J =$ 5.8 Hz), 2.77:2.69 (2d, 2H, O–C(CH_3)$_2$–C*H*$_2$–Ph, $J = 13.2$ Hz), 2.39 (d, 1H, OH, $J = 3.4$ Hz), 0.96:0.89 (2s, 6H, O–C(C*H*$_3$)$_2$–CH_2–Ph). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C = 141.3:140.6:138.1 (3s, Ph–C-1), 130.8–126.1 (m, Ph–C), 78.2:77.9 (2d, Ph–*C*H–O), 77.1 (s, O–*C*(CH_3)$_2$–CH_2–Ph), 49.2 (t, O–C(CH_3)$_2$–*C*H_2–Ph), 26.1:24.7 (2q, O–C(*C*H_3)$_2$–CH_2–Ph). Anal. Calcd for

$C_{24}H_{26}O_2 \times 0.05\ H_2O$: C, 82.98; H, 7.57. Found: C, 83.01; H, 7.73.

4.6. Preparation of benzoylformic acid esters 6a, c–f

4.6.1. General procedure. DIC (1.1 equiv) was added dropwise to a solution of auxiliary **5a**, **c–f** (1.0 equiv), benzoylformic acid (1.1 equiv) and DMAP (0.2 equiv) in dry dichloromethane while cooling on an ice bath. The mixture was stirred for 1–20 h at room temperature until TLC control indicated total conversion. Then the white precipitate was filtered off and the filtrate diluted with dichloromethane and washed successively with a saturated aqueous $NaHCO_3$ solution, 5% $KHSO_4$ solution and then 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).

4.6.1.1. Oxophenylacetic acid, (1*R*,2*S*)-2-benzyloxy-1,2-diphenylethyl ester, 6a. 0.217 g (yield 79%) white solid, mp 130–134 °C, $R_f = 0.41$ (PE/E 3:1), $[\alpha]_D^{20} = +28.9$ (*c* 1.04, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.62$–7.02 (m, 20H, aromatic), 6.30:4.68 (2d, 2H, Ph–C*H*–O, $J = 7.0$ Hz), 4.50:4.24 (2d, 2H, O–CH_2–Ph, $J_{AB} = 12.0$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 186.0$ (s, CO), 162.7 (s, O–CO), 137.6:137.3:136.3:134.7 (4s, Ph–C-1), 132.2:129.9:128.7:128.5:128.4:128.4:128.3:128.2:128.1:127.9:127.5:126.1 (12d, Ph–C), 82.4:79.1 (2d, Ph–*C*H–O), 70.7 (t, O–*C*H_2–Ph). Anal. Calcd for $C_{29}H_{24}O_4$: C, 79.80; H, 5.54. Found: C, 79.60; H, 5.84.

4.6.1.2. Oxophenylacetic acid, (1*R*,2*S*)-2-(2-methylpropoxy)-1,2-diphenylethyl ester, 6c. 0.726 g (yield 98%) white solid, mp 70–73 °C, $R_f = 0.62$ (PE/E 3:1), $[\alpha]_D^{20} = +26.0$ (*c* 1.05, CH_2Cl_2,). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.68$–7.32 (m, 15H, aromatic), 6.27:4.61 (2d, 2H, Ph–C*H*–O, $J = 6.8$ Hz), 3.16:3.00 (2dd, 2H, O–CH_2–CH(CH_3)$_2$, $J_1 = 8.8$ Hz, $J_2 = 6.5$), 1.88–1.68 (m, 1H, O–CH_2–C*H*(CH_3)$_2$), 0.79:0.78 (2d, 6H, O–CH_2–CH(CH_3)$_2$, $J = 6.7$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 186.1$ (s, CO), 162.7 (s, O–CO), 137.9:136.4:134.6 (3s, Ph–C-1), 132.1–127.7 (m, Ph–C), 83.7:79.2 (2d, Ph–*C*H–O), 76.1 (t, O–*C*H_2–CH(CH_3)$_2$), 28.4 (d, O–CH_2–*C*H(CH_3)$_2$), 19.1:19.0 (2q, O–CH_2–CH(*C*H_3)$_2$). Anal. Calcd for $C_{26}H_{26}O_4 \times 0.3\ H_2O$: C, 76.56; H, 6.57. Found: C, 76.96; H, 6.56.

4.6.1.3. Oxophenylacetic acid, [1*R*,2*S*]-2-(2-methoxy-1,1-dimethylethoxy)-1,2-diphenylethyl ester, 6d. 0.187 g (yield 81%) white solid, mp 58–61 °C, $R_f = 0.56$ (PE/E 4:1), $[\alpha]_D^{20} = +12.9$ (*c* 1.06, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.67$–7.22 (m, 15H, aromatic), 6.10:4.98 (2d, 2H, Ph–C*H*–O, $J = 6.8$ Hz), 3.08 (s, 3H, O–CH_3), 3.03:2.97 (2d, 2H, O–C(CH_3)$_2$–CH_2–O, $J_{AB} = 9.7$ Hz), 0.95:0.91 (2s, 6H, O–C(CH_3)$_2$–CH_2–O). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 186.2$ (s, CO), 162.8 (s, O–CO), 140.9:136.8:134.6 (3s, Ph–C-1), 132.2–127.5 (m, Ph–C), 80.1:76.7 (2d, Ph–*C*H–O), 80.0 (t, CH_2–O), 76.6 (s, O–*C*(CH_3)$_2$), 58.9 (q, O–CH_3), 23.7:23.6 (2q, O–C(*C*H_3)$_2$). Anal. Calcd for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 74.83; H, 6.48.

4.6.1.4. Oxophenylacetic acid, (1*R*,2*S*)-2-(1,1-dimethylethoxy)-1,2-diphenylethyl ester, 6e. 0.206 g (yield 99%) white solid, mp 53–55 °C, $R_f = 0.53$ (PE/E 3:1), $[\alpha]_D^{20} = +14.1$ (*c* 0.71, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.58$–7.14 (m, 15H, aromatic), 5.98:4.66 (2d, 2H, Ph–C*H*–O, $J = 6.9$ Hz), 0.85 (s, 9H, O–C(CH_3)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 186.2$ (s, CO), 162.8 (s, O–CO), 141.3:136.8:132.2 (3s, Ph–C-1), 134.6:130.0:128.7:128.2:127.9:127.9:127.8:127.7:127.5 (9d, Ph–C), 80.2:76.3 (2d, Ph–*C*H–O), 75.1 (s, O–*C*(CH_3)$_3$), 28.2 (q, O–C(*C*H_3)$_3$). Anal. Calcd for $C_{26}H_{26}O_4 \times 0.3\ H_2O$: C, 76.56; H, 6.57. Found: C, 76.47; H, 6.52.

4.6.1.5. Oxophenylacetic acid, (1*R*,2*S*)-2-(1,1-dimethyl-2-phenylethoxy)-1,2-diphenylethyl ester, 6f. 0.159 g (yield 75%) white solid, mp 85–88 °C, $R_f = 0.47$ (PE/E 3:1), $[\alpha]_D^{20} = +9.8$ (*c* 1.00, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.64$–7.05 (m, 15H, aromatic), 6.01:4.77 (2d, 2H, Ph–C*H*–O, $J = 6.9$ Hz), 2.60 (s, 2H, O–C(CH_3)$_2$–CH_2–Ph), 0.77 (s, 6H, O–C(CH_3)$_2$–CH_2–Ph). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 186.1$ (s, CO), 162.7 (s, O–CO), 141.3:138.0:136.7:132.2 (4s, Ph–C-1), 134.6–126.0 (m, Ph–C), 80.2:76.2 (2d, Ph–*C*H–O), 77.3 (s, O–*C*(CH_3)$_2$–CH_2–Ph), 49.1 (t, O–C(CH_3)$_2$–*C*H_2–Ph), 25.9:24.6 (2q, O–C(*C*H_3)$_2$–CH_2–Ph). Anal. Calcd for $C_{32}H_{30}O_4 \times 0.3\ H_2O$: C, 79.41; H, 6.37. Found: C, 79.40; H, 6.51.

4.7. Selectivity tests

4.7.1. General procedure for the reduction of keto esters 6a, c–f. A solution of ester **6a**, **c–f** (1 equiv/~100 mg) in dry THF (10 mL) and (optionally) $ZnCl_2$ was stirred for 10 min at −78 °C. A 1 M solution of L-selectride® in THF (1.1 equiv) was added dropwise and the resulting mixture stirred for 1 h at −78 °C. After TLC analysis had indicated total conversion, the reaction was quenched by the 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[13] and finally by HPLC-analysis of their L-valine methyl ester derivatives.[14] In the data, NMR values are given only for the main (*S*)-diastereoisomers; yields are given for the mixtures of diastereoisomers.

4.7.1.1. (*S*)-Hydroxyphenylacetic acid, (1*R*,2*S*)-2-benzyloxy-1,2-diphenylethyl ester, 7a. (Yield 88%) white solid, $R_f = 0.20$ (PE/E 3:1). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.37$–6.79 (m, 20H, aromatic), 5.95:4.54 (2d, 2H, Ph–C*H*–O, $J = 6.2$ Hz), 5.05 (s, 1H, Ph–C*H*(OH)–CO), 4.50:4.21 (2d, 2H, O–CH_2–Ph,

$J_{AB} = 12.3$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 172.1$ (s, CO), 137.8:137.2:136.8:136.4 (4s, Ph–C-1), 128.5–126.8 (m, Ph–C), 82.4:79.5 (2d, Ph–*C*H–O), 72.9 (d, Ph–*C*H(OH)–CO), 70.6 (t, O–*C*H_2–Ph). Anal. Calcd for $C_{29}H_{26}O_4$: C, 79.43; H, 5.98. Found: C, 79.14; H, 6.26.

4.7.1.2. (*S*)-Hydroxyphenylacetic acid, (1*R*,2*S*)-2-(2-methylpropoxy)-1,2-diphenylethyl ester, 7c. (Yield 73%) yellowish oil, $R_f = 0.27$ (PE/E 3:1). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.37$–6.80 (m, 15H, aromatic), 5.88:4.43 (2d, 2H, Ph–C*H*–O, $J = 5.8$ Hz), 5.08 (s, 1H, Ph–C*H*(OH)–CO), 3.13:2.94 (2dd, 2H, O–CH_2–CH(CH_3)$_2$, $J_1 = 8.8$ Hz, $J_2 = 6.3$ Hz), 1.86–1.66 (m, 1H, O–CH_2–C*H*(CH_3)$_2$), 0.90:0.79 (2d, 6H, O–CH_2–CH(CH_3)$_2$, $J = 6.7$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 172.1$ (s, CO), 137.8:137.3:136.4 (3s, Ph–C-1), 128.4–126.7 (m, Ph–C), 83.4:79.6 (2d, Ph–*C*H–O), 76.1 (t, O–*C*H_2–CH(CH_3)$_2$), 73.0 (d, Ph–*C*H(OH)–CO), 28.4 (d, O–CH_2-*C*H(CH_3)$_2$), 19.1 (q, O–CH_2–CH(*C*H_3)$_2$). Anal. Calcd for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98. Found: C, 77.00; H, 7.24.

4.7.1.3. (*S*)-Hydroxyphenylacetic acid, (1*R*,2*S*)-2-(2-methoxy-1,1-dimethylethoxy)-1,2-diphenylethyl ester, 7d. (Yield 80%) white solid, $R_f = 0.15$ (PE/E 3:1). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.25$–6.71 (m, 15H, aromatic), 5.60:4.70 (2d, 2H, Ph–C*H*–O, $J = 6.4$ Hz), 4.92 (s, 1H, Ph–C*H*(OH)–CO), 3.30 (s, 1H, OH), 3.14–2.65 [m, 5H, C(CH_3)$_2$–CH_2–O–CH_3, O–CH_3, therein 2.97 (s, 3H, O–CH_3)], 0.82:0.77 (2s, 6H, C(CH_3)$_2$–CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 172.1$ (s, CO), 141.0:138.0:137.0 (3s, Ph–C-1), 128.4–126.8 (m, Ph–C), 80.5:76.6 (2d, Ph–*C*H–O), 80.0 (t, CH_2–O), 76.5 (s, O–*C*(CH_3)$_2$), 73.0 (d, Ph–*C*H(OH)–CO), 58.9 (q, O–CH_3), 23.6 (q, O–C(*C*H_3)$_2$).

4.7.1.4. (*S*)-Hydroxyphenylacetic acid, (1*R*,2*S*)-2-(1,1-dimethylethoxy)-1,2-diphenylethyl ester, 7e. (Yield 87–88%) white solid, $R_f = 0.40$ (PE/E 2:1), ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.26$–6.71 (m, 15H, aromatic), 5.58:4.49 (2d, 2H, Ph–C*H*–O, $J = 6.1$ Hz), 4.91 (d, 1H, Ph–C*H*(OH)–CO, $J = 5.0$ Hz), 3.23 (d, 1H, OH, $J = 5.0$ Hz), 0.80 (s, 9H, O–C(CH_3)$_3$). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 172.2$ (s, O–CO), 141.5:138.0:137.0 (3s, Ph–C-1), 128.4–126.8 (m, Ph–C), 80.6:76.3 (2d, Ph–*C*H–O), 74.8 (s, O–*C*(CH_3)$_3$), 72.9 (d, Ph–*C*H(OH)–CO), 28.1 (q, O–C(*C*H_3)$_3$). Anal. Calcd for $C_{26}H_{28}O_4 \times 0.4\ H_2O$: C, 75.85; H, 7.05. Found: C, 75.90; H, 7.26.

4.7.1.5. (*S*)-Hydroxyphenylacetic acid, (1*R*,2*S*)-2-(1,1-dimethyl-2-phenylethoxy)-1,2-diphenylethyl ester, 7f. (Yield 92%) white solid, $R_f = 0.10$ (PE/E 3:1). ^{1}H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.24$–6.60 (m, 20H, aromatic), 5.57:4.55 (2d, 1H, Ph–C*H*–O, $J = 6.4$ Hz), 4.91 (s, 1H, Ph–C*H*(OH)–CO), 3.27 (s, 1H, OH), 2.55:2.48 (2d, 2H, O–C(CH_3)$_2$–CH_2–Ph, $J = 13.5$ Hz), 0.70:0.68 (2s, 6H, O–C(CH_3)$_2$–CH_2–Ph). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta_C = 172.2$ (s, O–CO), 141.2:137.9:137.9:136.6 (4s, Ph–C-1), 130.9:128.4–126.0 (m, Ph–C), 80.5:76.1 (2d, Ph–*C*H–O), 77.0 (s, O–*C*(CH_3)$_2$–CH_2–Ph), 72.9 (d, Ph–*C*H(OH)–CO), 49.1 (t, O–C(CH_3)$_2$–*C*H_2–Ph), 25.8:24.5 (2q, O–C(*C*H_3)$_2$–CH_2–Ph).

4.8. Saponification of (*S*)-mandelic acid esters 7a, c–f

4.8.1. General procedure. A solution of ester **7a**, **c**–**f** (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 **5a**, **c**–**f** the combined ethereal extracts were washed with brine, dried over Na_2SO_4, filtered, evaporated and the residue purified by vacuum flash chromatography (if necessary). Thereby all auxiliaries **5a**, **c**–**f** 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 organic extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated, to yield the free mandelic acids.

(Yield 90–98%) white solid. All $[\alpha]_D^{20}$ values were (+) assigning the absolute configurations to be [S].[13] ^{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).

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. Gaertner, P.; Schuster, C.; Knollmueller, M. *Lett. Org. Chem.* **2004**, *1*, 249–253.
3. (a) Noe, C. R. *Chem. Ber.* **1982**, *115*, 1576–1590; (b) Noe, C. R.; Knollmüller, M.; Wagner, E.; Völlenkle, H. *Chem. Ber.* **1985**, *118*, 1733–1745; (c) Noe, C. R.; Knollmüller, M.; Steinbauer, G.; Völlenkle, H. *Chem. Ber.* **1985**, *118*, 4453–4458; (d) Noe, C. R.; Knollmüller, M.; Steinbauer, G.; Jangg, E.; Völlenkle, H. *Chem. Ber.* **1988**, *121*, 1231–1239.
4. Superchi, S.; Contursi, M.; Rosini, C. *Tetrahedron* **1998**, *54*, 11247–11254.
5. Scafato, P.; Leo, L.; Superchi, S.; Rosini, C. *Tetrahedron* **2002**, *58*, 153–159.
6. (a) For the effects of HMPA on alkylation reactions of esters and amides see: Ireland, R. E.; Müller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877; (b) Ireland, R. E.; Wipf, P.; Armstrong, J. D. *J. Org. Chem.* **1991**, *56*, 650–657; (c) Seebach, D. *Angew. Chem.* **1988**, *100*, 1685–1715.
7. (a) For the effects of Li-halides on alkylation reactions of esters and amides see: Seebach, D. *Angew. Chem.* **1988**, *100*, 1685–1715; (b) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem.* **1996**, *108*, 2880–2921.
8. (a) For the 'Secondary Amine Effect' see: Pfeffer, P. E.; Silbert, L. S.; Chirinko, J. M. *J. Org. Chem.* **1972**, *37*, 451; (b) Seebach, D.; Laube, T.; Dunitz, J. D. *Helv. Chim. Acta* **1985**, *68*, 1373–1393; (c) Seebach, D.; Aebi, J. D. *Helv.*

Chim. Acta **1985**, *68*, 1507–1518; (d) Seebach, D.; Bossler, H.; Gründler, H.; Shoda, S.; Wenger, R. *Helv. Chim. Acta* **1991**, *74*, 197–224; (e) Seebach, D.; Miller, S. A.; Griffiths, S. L. *Helv. Chim. Acta* **1993**, *76*, 563–595; (f) Boons, G.-J.; Downham, R.; Kim, K. S.; Ley, S. V.; Woods, M. *Tetrahedron* **1994**, *50*, 7157–7176; (g) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem.* **1996**, *108*, 2880–2921.

9. Collins, D. J.; Jacobs, H. A. *Aust. J. Chem.* **1986**, *39*, 2095–2110.
10. Krishnamurthy, S. *J. Organomet. Chem.* **1978**, *156*, 171–181.
11. For example, see: (a) Wenkert, E.; Stenberg, V. I.; Beak, P. *J. Am. Chem. Soc.* **1961**, *83*, 2320–2325; (b) Buchbauer, G.; Heneis, V. M.; Krejci, V.; Talsky, C.; Wunderer, H. *Monatshefte f. Chemie.* **1985**, *116*, 1345–1358.
12. (a) Ashby, E. C.; Pham, T. N. *J. Org. Chem.* **1986**, *51*, 3598–3602; (b) Ashby, E. C.; DePriest, R. N.; Goel, A. B.; Wenderoth, B.; Pham, T. N. *J. Org. Chem.* **1984**, *49*, 3545–3556; (c) Ashby, E. C.; DePriest, R. N.; Goel, A. B. *Tetrahedron Lett.* **1981**, *22*, 1763–1766.
13. (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.
14. Cavelier, F.; Gomez, S.; Jacquier, R.; Llinares, M.; Mereadier, J.-L.; Petrus, C.; Verducci, J. *Tetrahedron: Asymmetry* **1993**, *4*, 2495–2500.
15. (a) Mathieson, A. McL. *Tetrahedron Lett.* **1965**, *46*, 4137–4144; (b) Whitesell, J. K.; Younathan, J. N.; Hurst, J. R.; Fox, M. A. *J. Org. Chem.* **1985**, *50*, 5499–5503.
16. Kawanami, Y.; Fujita, I.; Ogawa, S.; Katsuki, T. *Chem. Lett.* **1989**, 2063.
17. Ghosh, A. K.; Chen, Y. *Tetrahedron Lett.* **1995**, *36*, 6811–6814.
18. Armstrong, A.; Brackenridge, I.; Jackson, R. F. W.; Kirk, J. M. *Tetrahedron Lett.* **1988**, *29*, 2483–2486.
19. (a) Devant, R.; Mahler, U.; Braun, M. *Chem. Ber.* **1988**, *121*, 397–406; (b) Sacha, H.; Waldmüller, D.; Braun, M. *Chem. Ber.* **1994**, *127*, 1959–1968.
20. Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–168.
21. (a) Cullis, P. M.; Lowe, G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2317–2321; (b) Yamada, M.; Horie, T.; Kawai, M.; Yamamura, H.; Araki, S. *Tetrahedron* **1997**, *53*, 15685–15690.
22. (a) Butler, C. L.; Hostler, M.; Cretcher, L. H. *J. Am. Chem. Soc.* **1937**, *59*, 2354–2355; (b) Sekera, V. C.; Marvel, C. S. *J. Am. Chem. Soc.* **1933**, *55*, 345–349.