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Chiral linker. Part 3: Synthesis and evaluation of aryl substituted *m*-hydrobenzoins as solid supported open chain chiral auxiliaries for the diastereoselective reduction of α-keto esters

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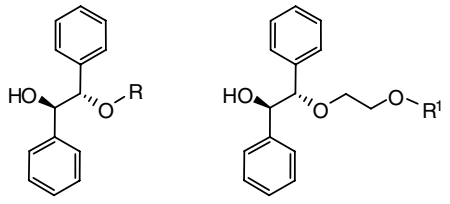
Abstract—Five partly novel aryl substituted *m*-hydrobenzoins were synthesized and the corresponding desymmetrized hydrobenzoin ethers evaluated as open chain chiral auxiliaries in the L-Selectride® mediated stereoselective reduction of phenylglyoxylates, resulting in de values of up to 91%. Two optimized auxiliary structures were immobilized on commercially available Wang-resin and applied as a reusable solid supported chiral auxiliary in the same type of reaction.

1. Introduction

In previous articles,[1] we have already described the benefits of novel *m*-hydrobenzoin derived chiral auxiliaries **I** and **II**, which can either be applied in solution phase chemistry or immobilized on solid support and used as a chiral linker.[2]



I **II**

R = Bn, *i*-Bu, *t*-Bu, $C(CH_3)_2CH_2Ph$, $C(CH_3)_2CH_2OCH_3$, $CH_2CPh_2OCH_3$, $CH_2CH_2N(CH_3)_2$, Wang-resin
$R^1 = CH_3$, Wang-resin

These structures are easily accessible via desymmetrization of *m*-hydrobenzoin with commercially available Noe's anhydrolactol,[3] followed by derivatization to build up the appropriate ether moieties or by immobilization on solid support and subsequent cleavage of the chiral protecting group.[1] Investigations on the potential of these auxiliaries to induce stereoselectivities in different model reactions resulted in selectivities of up to 91% de (and 84% de for the solid bound auxiliary, respectively) in the L-Selectride® mediated reduction of α-keto esters[1b,1c] and 36% de (or 28% de on solid support) in the α-alkylation of the corresponding propionates.[1a] Apart from that it could be shown that after cleavage of the desired products, the solid bound auxiliaries could be reused at least 3 times without the loss of stereoinducing ability,[1a,c] which is a remarkable benefit compared to other known chiral linkers for example, based on Evans oxazolidinones.[4]

Previous results indicated that the steric demand and coordinative properties of the ether moiety and the sublinking unit of the solid bound auxiliaries, respectively, had a large impact on the diastereoselectivities achievable in the different model reactions. However, the hydrobenzoin structure itself should allow the variation of the steric, electronic, and coordinative properties of the whole auxiliary via the introduction and variation of substituents into the hydrobenzoin aryl moieties. The results of our recent studies on the effect of such aryl substituents on the stereoinductive potential of *m*-hydrobenzoin derived chiral auxiliaries and solid phase linkers will be presented herein.

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2. Results and discussion

2.1. Evaluation of auxiliaries via model reactions in the solution phase

To gain a comprehensive insight into the possible impact of aryl substitution on the achievable stereoinduction, a set of five *m*-hydrobenzoins bearing substituents with different steric, electronic, and coordinative properties were synthesized as test systems.

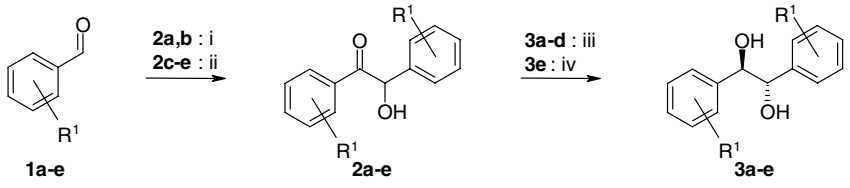
The *o*-methoxy- and *o*-methyl substituted compounds **3a** and **3b** could be obtained via benzoin condensation[5] and subsequent reduction with $NaBH_4$, but as the direct conversion of substituted benzaldehydes **1c–e** to the corresponding benzoins **2c–e** yielded only small amounts of the desired compounds, an alternative route[6] via the TMS-protected cyanohydrins was used for the synthesis of derivatives **2c–e**. Due to the low yield observed in the synthesis of benzoin **2e**, additional experiments for the optimization of the *meso*/*rac*-ratio of the following reduction were carried out. Thereby the *meso*-selectivity of the reaction could be improved (4.3:1 using $NaBH_4$ compared to 8.0:1 using $BH_3{\cdot}S(CH_3)_2{\cdot}THF$) allowing 89% yield for the pure *meso*-product **3e** (Scheme 1).

Due to previous investigations[1b] on the influence of the ether moiety on the stereoinductive properties of *m*-hydrobenzoin derived auxiliaries, the *i*-butylether proved to be an easily accessible test system allowing high selectivities in different model reactions, the aryl substituted *m*-hydrobenzoins were also converted to the corresponding *i*-butyl derivatives. After desymmetrization of the substituted *meso*-hydrobenzoins via selective protection of the (*R*)-carbon center using *exo*-anhydrolactol **4** in analogy to the literature procedures,[3] the desired ethers **6a–d** could be obtained using NaH and 4-toluenesulfonic acid *i*-butylester. However, even after variation of the reaction conditions and the base, it was not possible to convert the desymmetrized nitro substituted compound **5e** into the corresponding *i*-butylether (Scheme 2).

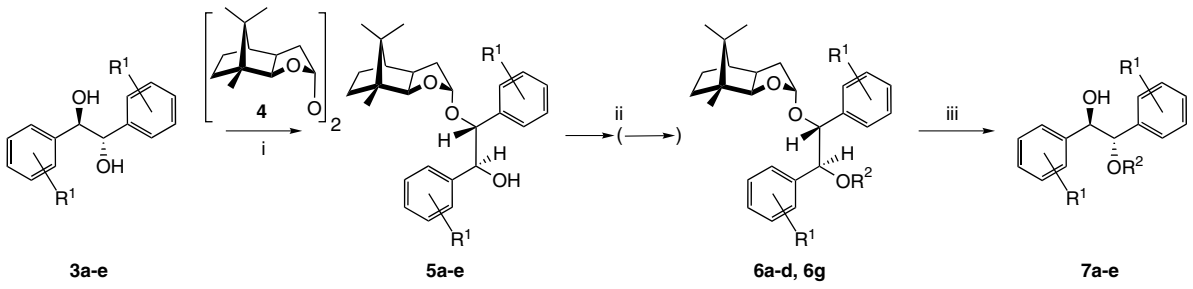
Over the course of our studies, a combination of the coordinative properties of the 2,2′-dimethoxy substituted system with the further coordination sites of the methoxyethyl ether structure became attractive; compound **6g** was synthesized following a four-step procedure already described previously.[1c]

Cleavage of the chiral protecting group allowed the recovery of the auxiliary via the corresponding methyl acetal and yielded the desired test systems **7a–e** for the following preliminary investigations in solution phase.

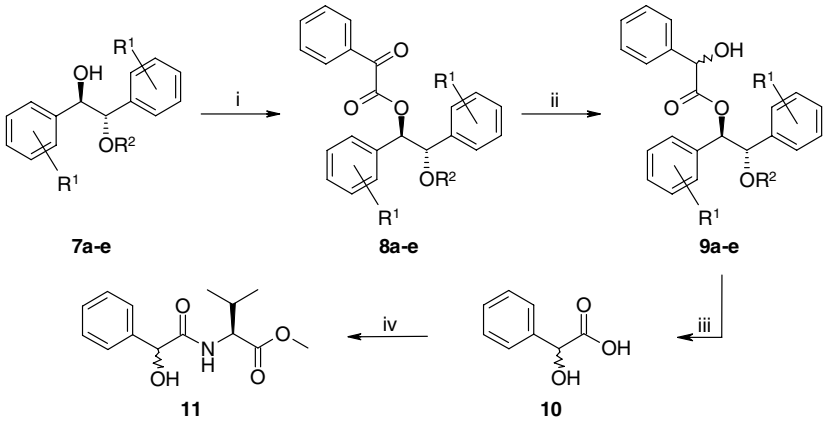
As in the previous investigations, the L-Selectride® mediated reduction of phenylglyoxylates was chosen as an appropriate model reaction for the auxiliaries. Therefore, the aryl substituted *m*-hydrobenzoin ethers **7a–e** were converted into the corresponding esters followed by reduction according to the procedure described by Rosini et al.[7] yielding mandelic acid esters **9a–e**.[8] The stereochemical outcome of these reactions was again determined via ^1H NMR of the crude reaction mixtures, as well as after saponification via the specific rotation values of the corresponding acids and via HPLC of their L-valine methylester derivatives **11**,[9] respectively (Scheme 3).



Scheme 1. Synthesis of hydrobenzoin derivatives; R^1 = 2-OCH_3 **1–3a**, 2-CH_3 **1–3b**, 4-OCH_3 **1–3c**, 2-CF_3 **1–3d**, 2-NO_2 (**1–3e**). Reagents and conditions: (i) KCN, EtOH/H_2O, 4 h reflux (**2a**: 50%, **2b**: 31%); (ii) (1) 1.1 equiv TMS–CN, cat. ZnI_2, 1 h 100 °C, (2) 1 equiv LDA, 1 equiv ArCHO, DME, −65 °C, (3) 2 M HCl, THF, 12 h rt (**2c**: 51%, **2d**: 79%, **2e**: 5%); (iii) $NaBH_4$, EtOH, 3 h rt (**3a**: 73%, **3b**: 63%, **3c**: 65%, **3d**: 21%); (iv) 1 equiv $BH_3{\cdot}S(CH_3)_2$, THF, −78 °C (89%).



Scheme 2. Desymmetrization and etherification of hydrobenzoin derivatives **3a–e**. Reagents and conditions: (i) 4-toluenesulfonic acid, CH_2Cl_2, 12 h rt (**5a**: 70%, **5b**: 63%, **5c**: 83%, **5d**: 57%, **5e**: 61%); (ii) (for **5a–d**) (1) NaH, (2) 4-toluenesulfonic acid *i*-butylester, DMF, 12 h rt (**6a**: 76%, **6b**: 93%, **6c**: 77%, **6d**: 99%); (ii) (**5a** → **6e**) (1) NaH, (2) bromoacetic acid *t*-butylester, HMPT, THF, 12 h rf (72%); (**6e** → **6f**) $LiAlH_4$, Et_2O, 2 h rt (73%); (**6f** → **6g**) (1) NaH, (2) CH_3I, DMF, 2 h rt (74%); (iii) 4-toluenesulfonic acid, CH_2Cl_2/MeOH, 12 h rt (**7a**: 96%, **7b**: 86%, **7c**: 80%, **7d**: 91%, **7e**: 85%).



Scheme 3. Application of the test systems on the L-Selectride® mediated reduction of phenylglyoxylates, cleavage, and derivatization. Reagents and conditions: (i) phenylglyoxylic acid, DIC, DMAP, CH_2Cl_2, 12 h rt; (ii) L-Selectride®, THF, 1 h −78 °C; (iii) 3 equiv LiOH, THF/MeOH/H_2O, 1.5 h rt; (iv) Val-OMe, HOBt, DIC, CH_2Cl_2, 12 h −30 °C → rt.

Table 1. Diastereoselective reduction of phenylglyoxylates **8a**–**e** compared to results from preceding investigations

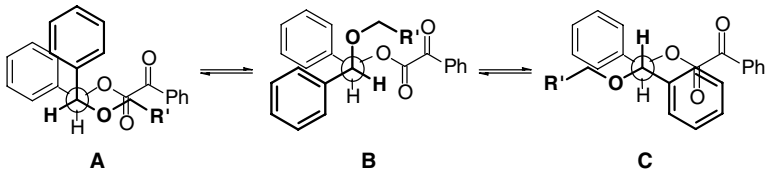
Entry	Ester	R^1	R^2	$^3J_{(benzyl)}$ (Hz) **8**	de[a] (%) (*S*,*R*,*S*)-9a
1	**8a**	2-OCH_3	$CH_2CH(CH_3)_2$	3.5	91
2[b]	**8a**	2-OCH_3	$CH_2CH(CH_3)_2$	3.5	72
3	**8b**	2-CH_3	$CH_2CH(CH_3)_2$	6.1	71
4	**8c**	4-OCH_3	$CH_2CH(CH_3)_2$	6.8	74
5	**8d**	2-CF_3	$CH_2CH(CH_3)_2$	6.6	39
6	**8e**	2-OCH_3	$CH_2CH_2OCH_3$	3.9	80
7[c]	**8f**	H	$CH_2CH(CH_3)_2$	5.8	78
8[c]	**8g**	H	$CH_2CH_2OCH_3$	6.7	77
9[b,c]	**8g**	H	$CH_2CH_2OCH_3$	6.7	91

[a] Diastereoisomeric ratios determined by ^{1}H NMR integration on crude reaction mixtures **9** and HPLC analysis of L-valine methyl ester derivatives **11** of cleaved mandelic acids **10**; absolute configuration of major diastereoisomers approved by optical rotation of **10**.
[b] 2 equiv of $ZnCl_2$ as additive.
[c] Data from Refs. 1b and 1c, respectively.

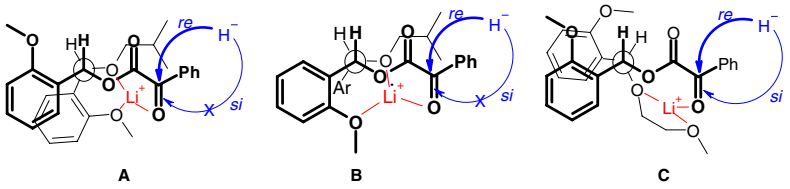
The results of the diastereoselective reductions of esters **8a**–**e** shown in Table 1 in comparison to the selected results of previous investigations[1b,c] make it clear that the aryl substituents allow a significant variation of the stereoinductive properties of the auxiliaries.

A correlation of the coupling constants of the two benzylic hydrobenzoin protons in substrates **8a**–**g** with the achievable selectivities based on a conformation dependent steric interaction of the ether moiety and the reacting carbonyl, as posted by Rosini et al.[7] for (*R*,*R*)-hydrobenzoin ethers, was not observed in case of the *meso*-derivatives. However, as steric shielding of the carbonyl group by the ether substituent or the aryl moiety is possible either in the case of a synclinal or antiperiplanar arrangement of the benzylic protons (see Scheme 4), on the basis of the Karplus relationship resulting in coupling constants of about 3 and 10 Hz, respectively, this does not seem surprising. Apart from this, the preferred conformation present in the substrate can be varied to a large extent by complexation effects involving the Lewis acidic metal cations of the reducing agent or an additive.

If coordinative interactions are considered in addition to steric effects, an explanation of the enhanced stereoselective induction of the *o*-methoxy substituted derivative **8a** (see Table 1, entries 1 and 7) based on the models depicted in Scheme 5 is plausible: because of the possible coordination of the Li cation with the α-carbonyl-O, the oxygen of the ether moiety, and either one of the *o*-methoxy substituents of substrate **8a** (see Scheme 5A/B), the conformation of the hydrobenzoin is fixed in a position allowing an extensive shielding of the *si*-face of the α-carbonyl. As a similar coordination is not possible in the case of substrates **8b** and **8c**, selectivities comparable to the value of the unsubstituted derivative **8f** were expected (see Table 1, entries 3, 4, and 7). Regarding Table 1, entries 1, 2, and 6, it appears that neither the addition of $ZnCl_2$ as a coordination agent nor the binding of an ether moiety bearing further coordination sites allows further enhancement of the stereoselective induction. In both cases, a competitive coordination model can serve as an explanation. The complexation of a Zn cation causes a *syn*-arrangement of the adjacent carbonyl groups, which leads, in case of an attack from the *si*-face of the α-carbonyl, to (*R*)-configuration of the corresponding mandelic acid ester. This *anti–syn* switch is only



Scheme 4. Conformation analysis based on the model proposed by Rosini et al.[7] (aryl substituents omitted for clarity reasons).



Scheme 5. Proposed model for the observed selectivities caused by the preferred *re*-attack on the α-carbonyl.

allowed if the energy gained in the complexation is greater than the steric repulsion and happens only in the case of Zn^{2+}, a stronger Lewis acid than Li^{+}.[7a] For substrate **8e** the coordination depicted in Scheme 5C is conceivable, also causing a fixed conformation of the hydrobenzoin but on the other hand a less distinctive shielding of the *si*-face of the α-carbonyl.

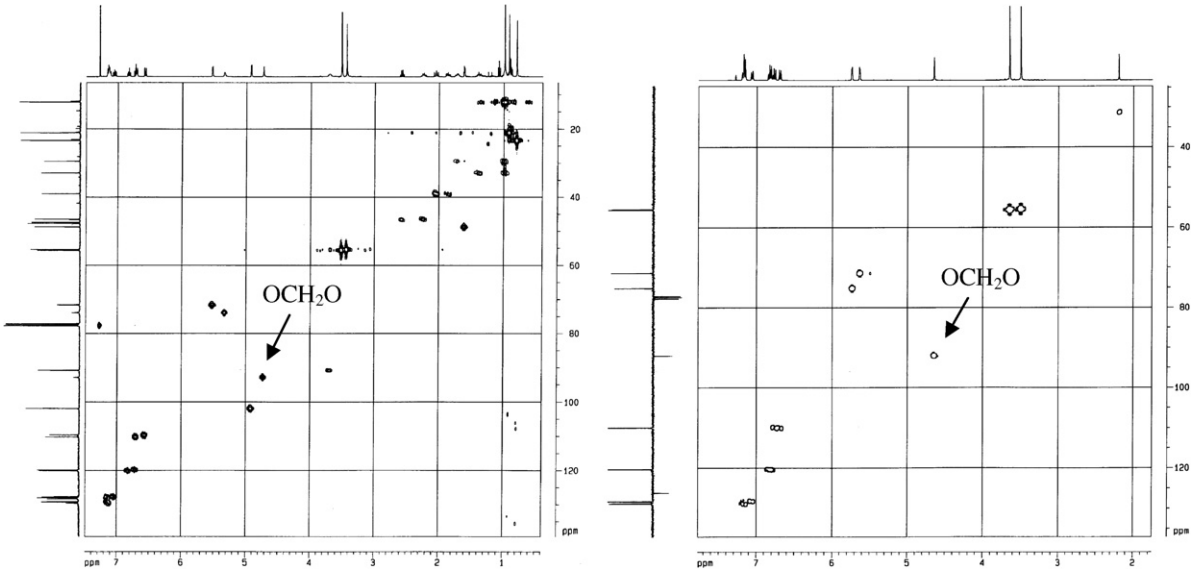
An explanation of the low selectivities obtained with auxiliary **8d** based on the results gained so far seems difficult as its steric and coordinative properties should be similar to **8b**. However, one reason could be the reduced electron density of the aromatic substituent of the hydrobenzoin causing a declined ππ-interaction with the carbonyl group. This could induce a less effective shielding of the *si*-face by the hydrobenzoin aryl residue compared to the model described in Scheme 4C.

2.2. Auxiliary immobilization and evaluation via model reactions on solid support

Similar to the initial experiments in the solution phase, the *o*-methoxy substituted auxiliaries **7a** and **7e** proved to be the most promising systems, further investigations were carried out to determine their applicability as chiral solid phase linkers. Therefore, the desymmetrized hydrobenzoin derivatives **5a** and **6f** were immobilized on solid support via deprotonation using NaH and subsequent conversion with chloromethylated Wang-resin,[10] in case of **6f** providing an ethyleneglycol spacer unit between the benzylic sublinker moiety of the Wang-resin and the hydrobenzoin structure. Over the course of previous investigations, presumably because of interactions of the sterically demanding auxiliary precursor, maximum auxiliary immobilization rates of 81% were observed using commercially available Wang-resins with about 0.6 mmol/g loading and a further drop of attachment rates occurred when resins with higher loadings were used. Even with higher reagent excesses, it was not possible to increase the conversion rate of the immobilization and when an excess of NaH compared to the amount of auxiliary precursor **5a** was used for the immobilization step, a surprising side reaction consuming **5a** and yielding by-product **12** was observed. After cleavage of the chiral protecting group under acidic conditions, which induced cyclization to [1,3,6]-trioxocan **13**, the structure of both by-products could be determined via CH-correlation spectra (Scheme 6).

Although the absolute configuration of trioxocan **13** could not be clearly determined so far, the following predictions can be stated on the basis of the observed specific rotation of **13**, the obtained NMR data and the mechanisms to be expected because of previous observations.

The observed specific rotation and the reduced set of signals in NMR spectra permit only C_2-symmetric relative

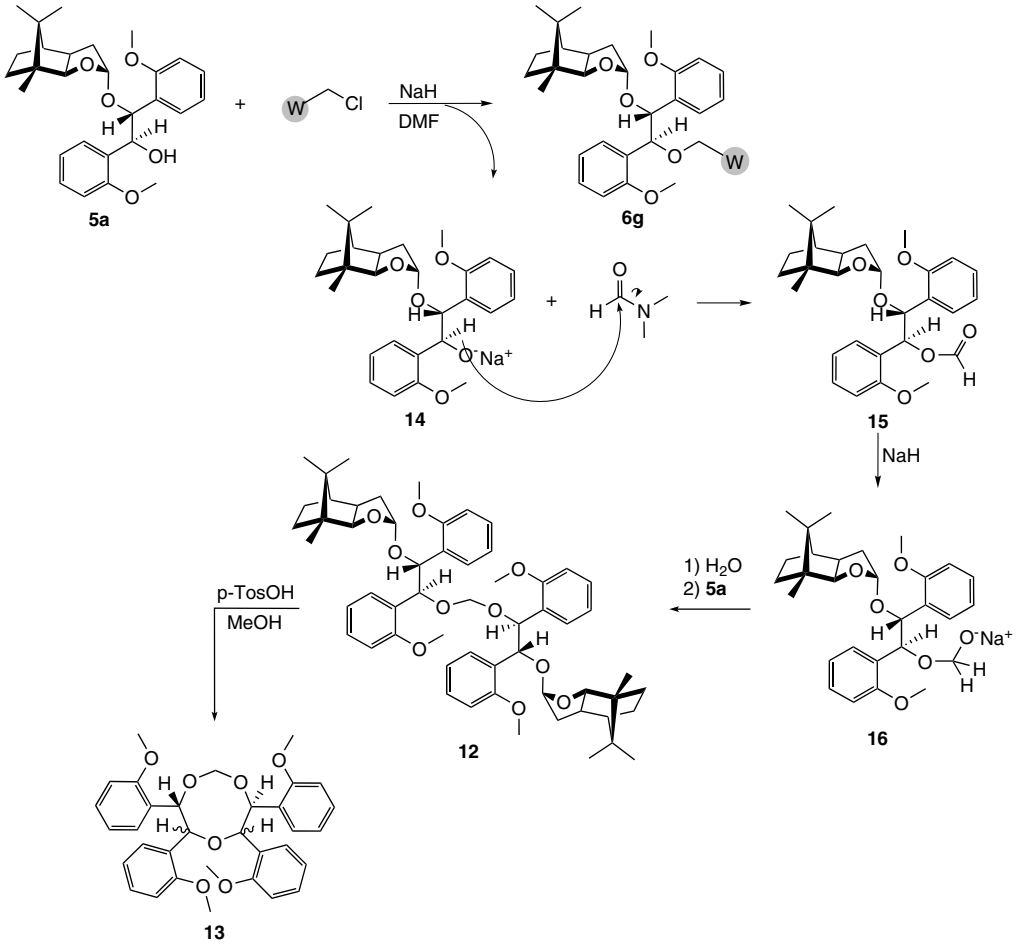


Scheme 6. CH-correlation spectra of by-products **12** and **13**.

configurations (4*R**,5*R**,7*R**,8*R**) and (4*R**,5*S**,7*S**,8*R**), respectively, which corresponds, presuming no change of configuration during the attack of alkoxide **14** on the solvent giving rise to **15**, to the absolute configurations (4*S*,5*S*,7*S*,8*S*) and (4*S*,5*R*,7*R*,8*S*). Therefore, retention of the configuration has to be assumed at the second unprotected carbon center during the formation of by-product **12** as well. Over the course of the following acid catalyzed cleavage of the chiral protecting group and the ring closure, an epimerization of both the remaining centers via the formation of the corresponding carbenium ions is possible. However, based on the fact that this reaction is an equilibrium reaction, the formation of the thermodynamically more stable product is more likely and retention of configuration of both the remaining stereogenic centers can be expected as well. Therefore—though not completely proven so far, (4*S*,5*R*,7*R*,8*S*) seems to be the most likely absolute configuration for trioxocane **13** (Scheme 7).

As already described,[1c,12] the incomplete conversion of the active sites of the resin can give rise to a direct attachment of the substrate to the resin, thus providing no possibility for the stereoselective induction from the chiral linker and therefore lowering the achievable selectivities drastically. To prevent the limitation of stereoselectivity caused by the attachment of the substrate on the residual active sites of the resin not provided with a chiral linker, the chloromethyl moieties remaining after the attachment step were converted to the corresponding iodides followed by Bu_3SnH mediated reduction to obtain a methyl residue using literature procedures.[12c,12d] Resins treated according to this deactivation procedure after the attachment of the linker are in the following labeled as **6g′/7g′** and **6h′/7h′**, respectively. The actual influence of the incomplete linker attachment was validated via comparison with resins not treated following the iodination/reduction procedure. As shown in Table 2, the achievable selectivities can be increased by deactivating the remaining chloromethyl residues (see entries 8 and 9). However, in the case of low attachment rates, even after conversion of the remaining active sites, only low stereoselectivities were achieved compared to the values obtained after almost complete linker attachment (see entries 2 and 6) (Scheme 8).

After acid catalyzed cleavage of the chiral protecting group, phenylglyoxylic acid was immobilized on the resin as the substrate for the following reduction step. As during previous investigations, model reactions were carried out using standard procedures and the immobilized products could be released via saponification using LiOH in



Scheme 7. Proposed mechanism of the formation of by-product **13** based on the lit.[11]

Table 2. Result of diastereoselective reductions of phenylglyoxylates **8g**, **8g′**, **8h**, and **8h′** including recyclability experiments

Entry	Ester	Attachment rate (%)	Recycling step	ee[a] (%) (*S*)-10
1	**8g**	51	—	33
2	**8g**	81	—	53
3			1	70
4			2	61
5			3	59
6	**8g′**	64	—	48
7			1	57
8	**8h**	76	—	31
9	**8h′**	75	—	55

[a] Enantiomeric excess determined by HPLC analysis of L-valine methyl ester derivatives **11**.

MeOH/THF/water yielding (*S*)-mandelic acids, which were derivatized for the following determination of their enantiomeric purity via HPLC. All conversions on solid support were again monitored via FT-IR spectroscopy and in addition conversion rates were estimated gravimetrically (Scheme 9).

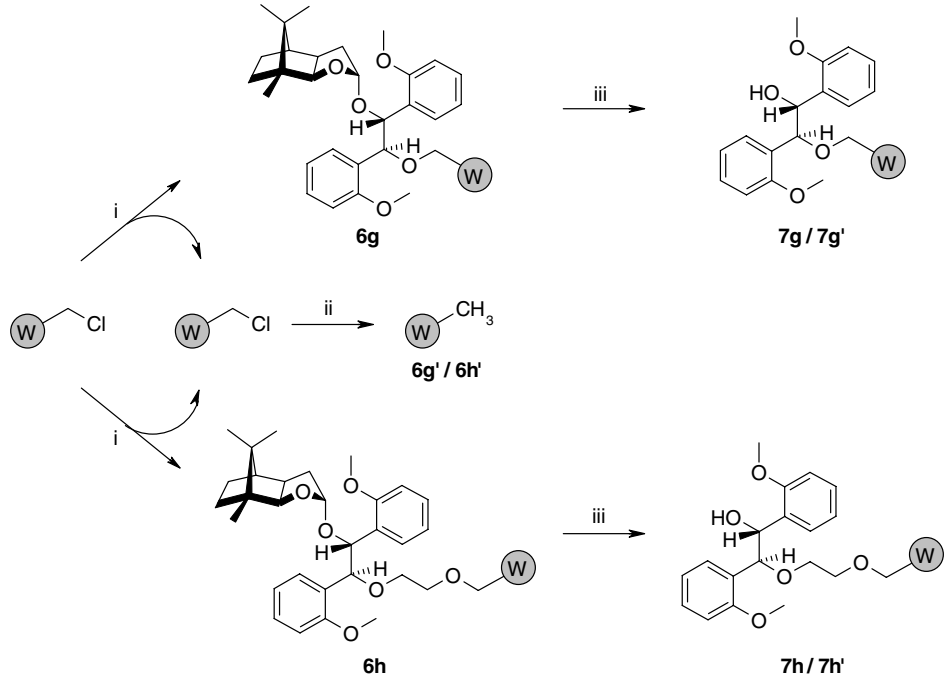
As in the case of previously investigated auxiliary systems, the results shown in Table 2 clearly prove the recyclability of the tested hydrobenzoin derived linkers. However, the selectivities observed in the solid phase experiments did not reach the values of the corresponding auxiliaries in solution with no dependence on whether the linker was attached via ethyleneglycol spacer unit or not (see Table 1, entries 1 and 6 and Table 2, entries 2 and 8). Although no clear explanation for this fact has been provided so far, a possible interpretation could be the changed steric environment present in case of the resin bound auxiliaries compared to the surroundings of the *i*-butyl **6a** or methoxyethyl **6g** ethers in solution phase. This could complicate the coordinative interactions, which were posted above as a conceivable reason for the enhanced selectivities related to the introduction of *o*-methoxy substituents onto the aryl residues of the hydrobenzoin structure.

3. Conclusion

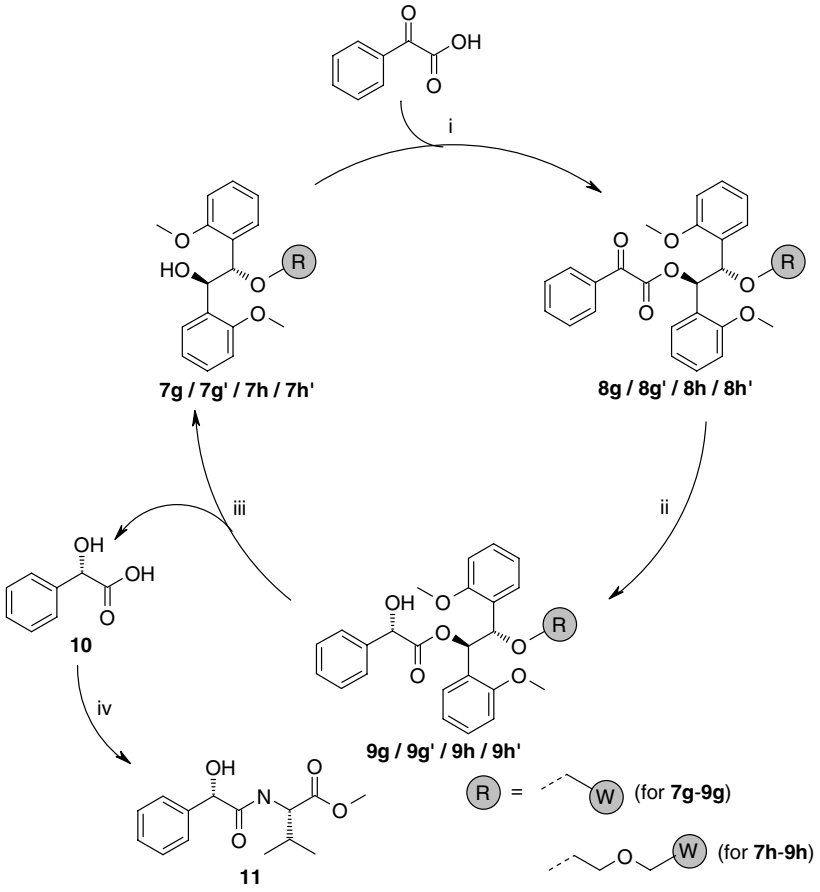
Herein, we have reported that conditions for the synthesis of partly aryl substituted hydrobenzoins were found. After desymmetrization of the obtained derivatives, the influence of different substituents on the aryl residues of the *m*-hydrobenzoin structure on the stereoselective induction during the reduction of the corresponding phenylgloxylates could be investigated. In the case of the *o*-methoxy derivative, an enhancement of the achievable stereoselectivities up to 91% de was observed; however, neither the introduction of an altered ether residue bearing additional coordinative options nor the addition of $ZnCl_2$ as a complexing agent led to further improvements of the induction rate.

Although the applicability and recyclability of the aryl substituted *m*-hydrobenzoins as asymmetric solid phase linkers could be proved, as in previous investigations, a slight drop of the stereoselective induction was observed when the *o*-methoxy substituted system was transferred to a solid support.

However, the investigations proved that the stereoselective induction potential of *m*-hydrobenzoins can be varied to a great extent via the introduction of different aryl substituents. In some cases, a significant improvement in the obtained results was possible; however this seems to be highly dependent on additional factors, for example, fur-



Scheme 8. Synthesis of solid phase test systems. Reagents and conditions: (i) **5a**, NaH/**6f**, NaH; NaI, DMF; (ii) (1) NaI, acetone, (2) Bu_3SnH, THF; (iii) $PPh_3{\cdot}HBr$, MeOH, CH_2Cl_2.



Scheme 9. Application of solid phase test systems. Reagents and conditions: (i) PhCOCOOH, DIC, DMAP, CH_2Cl_2; (ii) L-Selectride®, −78 °C, THF; (iii) LiOH, THF/MeOH/H_2O; (iv) Val-OMe, HOBt, DIC, CH_2Cl_2, 12 h −30 °C → rt.

ther substituents and reaction conditions. Therefore, we are encouraged to carry out further experiments to evaluate the potential of the differentially substituted derivatives via other model reactions as the α-alkylation of propionates, which was already applied to similar auxiliary systems[1a] in solution phase as well as on solid support.

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 molecular sieves (4 Å). L-Selectride® was 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 the 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 by 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 at 200 and 50 MHz, respectively, CH-correlation spectra were recorded on a Bruker AC 400 at 400/100 Hz using TMS or the solvent peak as the reference. IR spectra were recorded on a Bio-Rad *FTS 135* FT-IR-spectrometer, using KBr disks. HPLC diastereoisomeric analysis of L-valine methyl ester derivatives **13**[9] 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, Waehringer Str. 42, A-1090, Vienna.

4.2. 2-Hydroxy-1,2-bis-(2-methoxyphenyl)-ethanone 2a

2-Methoxybenzaldehyde **1a** (36.0 g, 264 mmol) was dissolved in ethanol (100 mL) and an aqueous solution (20 mL) of potassium cyanide (8.6 g, 132 mmol) was added. The mixture was refluxed for 4 h and afterwards concentrated under reduced pressure and cooled to −10 °C. The precipitated yellow crystals were separated and washed with small amounts of 50% ethanol and ether, yielding **2a** (18.0 g, 50%) (F_p = 96–98 °C, lit.:[5] 108–111 °C).

4.3. 2-Hydroxy-1,2-bis-(2-methylphenyl)-ethanone 2b

2-Tolylaldehyde **1b** (20.0 g, 166 mmol) was dissolved in ethanol (60 mL) and an aqueous solution (10 mL) of potassiumcyanide (3 g, 46 mmol) was added. The mixture was stirred at 70 °C for 6 h, and afterwards concentrated under reduced pressure and extracted with ether. The extracts were washed with brine, dried, filtered, and evaporated under reduced pressure. The resulting oil was purified via vacuum flash chromatography yielding **2b** (6.1 g, 31%) as white crystals (F_p = 76–78 °C, lit.:[13] 79 °C), as well as 12.2 g (61%) of the recovered aldehyde.

4.4. Typical procedure for the synthesis of benzoins 2c–e (method ii)

2-Hydroxy-1,2-bis-(4-methoxy-phenyl)-ethanone **2c**: Zinc iodide (0.2 g, 0.59 mmol) was added to 4-methoxybenzaldehyde **1c** (9.0 g, 66.1 mmol) and trimethylsilylcyanide (7.2 g, 72.5 mmol) under a nitrogen atmosphere and the mixture was stirred for 1 h at 100 °C. The reaction mixture was cooled to rt, dissolved in PE and insoluble salts were filtered off. The solution was evaporated to dryness yielding 14.15 g of crude α-[(trimethylsilyl)oxy]-4-methoxyphenylacetonitrile, which was used in the next step without further purification.

Lithiumdiisopropylamide (LDA) was prepared by adding butyllithium-solution (2.2 M in hexane) (27.3 mL, 60.1 mmol) to a solution of diisopropylamine (6.08 g, 60.1 mmol) in dry DME at −30 °C under a nitrogen atmosphere and stirred for 30 min at −10 °C. The solution was cooled to −65 °C and crude α-[(trimethylsilyl)oxy]-4-methoxyphenylacetonitrile (14.15 g, 60.1 mmol) in dry DME (80 mL) was added dropwise. After stirring for 30 min at −65 °C, 4-methoxybenzaldehyde (8.18 g, 60.1 mmol) solved in DME (30 mL) was added and the mixture stirred for 1 h. The reaction was slowly warmed to rt and hydrolyzed with saturated $NaHCO_3$-solution (100 mL). The mixture was extracted with ether, the extracts were washed with brine, dried, filtered, and evaporated to dryness under reduced pressure and a nitrogen atmosphere. Crude 1,2-bis-(4-methoxyphenyl)-2-[(trimethylsilyl)oxy]-1-ethanone (18.22 g) was isolated and used in the next step without further purification.

Crude 1,2-bis(4-methoxyphenyl)-2-[(trimethylsilyl)oxy]-1-ethanone (18.22 g) was solved in THF (150 mL) under nitrogen atmosphere. HCl (2 M, 3 mL) was added and the mixture was stirred at rt overnight. The solution was evaporated to dryness under reduced pressure and nitrogen atmosphere and the crude product was recrystallized from 95% ethanol yielding 2-hydroxy-1,2-bis-(4-methoxyphenyl)-ethanone **2c** (9.27 g, 51%) as yellow crystals (spectral data according to the literature[14]).

4.5. 2-Hydroxy-1,2-bis-(2-trifluoromethylphenyl)-ethanone 2d

The synthesis was carried out according to method ii described above (see Section 4.4) yielding 79% of the benzoin derivative **2d** as light yellow crystals (F_p = 117–125 °C; ^{1}H NMR δ 7.72–7.35 (m, 7H, Ph–H), 6.93 (d, J = 7.60 Hz, 1H, Ph–H), 6.11 (s, 1H, OCHPh) 4.35 (s, 1H, OH); ^{13}C NMR δ 201.67 (C=O), 135.24/134.98 (2q, J(C,F) = 1.4 Hz/2.0 Hz, Ph–C-1), 132.34/131.18/129.26/127.86 (4q, J(C,F) = 0.9 Hz, Ph–C-4/Ph–C-6), 130.88/128.88 (Ph–C-5), 128.77/127.91 (2q, J(C,F) = 30.6 Hz/32.4 Hz, Ph–C-2), 126.94/126.08 (2q, J(C,F) = 5.0 Hz/5.7 Hz, Ph–C-3), 123.66/123.17 (2q, J(C,F) = 274.2 Hz/273.6 Hz, Ph–CF_3), 74.30 (q, J(C,F) = 1.8 Hz, Ph–*C*H–OH); M = 348.25. Anal. Calcd for $C_{16}H_{10}F_6O_2$: C, 55.18; H, 2.89; F, 32.73. Found: C, 55.29; H, 3.09; F, 32.72).

4.6. 2-Hydroxy-1,2-bis-(2-nitrophenyl)-ethanone 2e

The synthesis was carried out according to method ii described above (see Section 4.4) yielding 5% of the benzoin derivative **2e** as orange crystals. In this case, the product was purified via chromatography (PE/E 20:1 → E/MeOH 3:1). (F_p = 142–144 °C; ^{1}H NMR δ 8.20–7.00 (m, 8H, Ph), 6.39 (s, 1H, C*H*OH), 4.19 (s, 1H, OH); ^{13}C NMR δ 200.61 (CO), 147.91/146.25 (Ph–*C*–NO_2), 135.10/132.83 (Ph–C-1), 134.09/134.03/131.16/130.21/129.64/128.45/125.05/124.23 (Ph–C), 75.41 (*C*HOH); M = 302.08. Anal. Calc. for $C_{14}H_{10}N_2O_6 \cdot 0.3C_2H_4 \cdot 0.1C_6H_{15}N$: C, 56.91; H, 3.99; N, 9.17. Found: C, 57.15; H, 3.78; N, 9.27).

4.7. Typical procedure for the reduction of benzoins 2a–d (method iii)

meso-1,2-Bis-(2-methoxyphenyl)-1,2-ethanediol **3a**: Sodiumborohydride (2.47 g, 65.31 mmol) was added to a solution of benzoin **2a** (17 g, 62.3 mmol) in dry ethanol (1 L) at 0 °C. The reaction mixture was allowed to reach rt and stirred for 2 h while the reaction was monitored via TLC. The reaction mixture was concentrated to 300 mL, acidified to pH 4 using concd HCl, neutralized with $NaHCO_3$, and extracted with CH_2Cl_2. The combined organic phases were washed with water and brine, dried, filtered, and evaporated under reduced pressure yielding 14.1 g of crude product. After recrystallization from toluene/ethanol, **3a** (12.52 g, 73%) was obtained as colorless needles (F_p = 146–149 °C, lit.[15] 152–153 °C, ^{1}H NMR according to the lit.[15]).

4.8. *meso*-1,2-Bis-(2-methylphenyl)-1,2-ethanediol 3b

The synthesis was carried out according to method iii described above (see Section 4.7) using 2-hydroxy-1,2-bis-

(2-methylphenyl)-ethanone **2b** (5.5 g, 22.89 mmol). The crude product (6.38 g, *meso*/*dl*-ratio 8:1) was purified via chromatography (PE/E 10:1 → E/MeOH 5:1) yielding **3b** (3.52 g, 63%) as a colorless solid (F_p = 111–116 °C, lit.[15] 104–105 °C, ^{1}H NMR according to the lit.[15]).

4.9. *meso*-1,2-Bis-(4-methoxyphenyl)-1,2-ethanediol 3c

The synthesis was carried out according to method iii described above (see Section 4.7) using 2-hydroxy-1,2-bis-(4-methoxy-phenyl)-ethanone **2c** (1.0 g, 3.67 mmol). The crude product (0.95 g, *meso*/*dl*-ratio 4:1) was recrystallized from toluene yielding **3c** (0.65 g, 65%) as a colorless solid (F_p = 174 °C, lit.[16] 169 °C, ^{1}H NMR according to the lit.[17]).

4.10. *meso*-1,2-Bis-(2-trifluoromethylphenyl)-1,2-ethanediol 3d

The synthesis was carried out according to method iii described above (see Section 4.7) using 2-hydroxy-1,2-bis-(2-trifluoromethylphenyl)-ethanone **2d** (17.50 g, 50.3 mmol). In this case, $CeCl_3{\cdot}7H_2O$ (1.86 g, 5.0 mmol) was added to the reaction mixture to achieve a higher *meso*/*dl*-ratio. The crude product (15.7 g, *meso*/*dl*-ratio 4.6:1) was purified via chromatography (PE/E 10:1 → E/MeOH 5:1) yielding **3d** (3.76 g, 21%) as yellow needles (F_p = 65–73 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.64–7.34 (m, 8H, Ph), 5.44 (s, 2H, OCHPh), 2.39 (s, 2H, OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.22 (Ph–C-1), 131.60/128.85/127.97 (Ph–C-4, Ph–C-5, Ph–C-6), 128.32 (q, J(C,F) = 30.0 Hz, Ph–C-2), 125.19 (q, J(C,F) = 6.0 Hz, Ph–C-3), 123.93 (q, J(C,F) = 274.2 Hz, Ph–*C*F$_3$), 71.97 (Ph–*C*H–OH); M = 350.26. Anal. Calcd for $C_{16}H_{12}F_6O_2$: C, 54.87; H, 3.45. Found: C, 54.72; H, 3.22) besides 6.22 g (36%) of hydrobenzoin as a *meso*/*dl*-mixture.

4.11. *meso*-1,2-Bis-(2-nitrophenyl)-1,2-ethanediol 3e

Borane dimethylsulfide complex (2 M solution in THF) (0.12 mL, 0.24 mmol) was added to a solution of 2-hydroxy-1,2-bis-(2-nitrophenyl)-ethanone **2e** (0.10 g, 0.33 mmol) in dry THF (5 mL) at −78 °C under a nitrogen atmosphere and the reaction stirred for 2 h at −78 °C and then afterwards for 1 h at rt while being monitored via TLC. The mixture was hydrolyzed with 2 M HCl (5 mL), extracted with ether, and the extracts were dried, filtered, and evaporated under reduced pressure yielding 0.107 g of crude product (*meso*/*dl*-ratio 8:1). After recrystallization from toluene, **3e** (0.089 g, 89%) was obtained as light brown crystals (F_p = 218–222 °C; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 7.83–7.45 (m, 8H, Ph), 5.87 (s, 2H, OH), 5.19 (s, 2H, C*H*OH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 149.62 (Ph–*C*–NO$_2$), 137.67 (Ph–C-1), 132.83/128.60/128.28/123.51 (Ph–C), 71.14 (Ph*C*HOH); M = 304.08. Anal. Calcd for $C_{14}H_{12}N_2O_6$: C, 55.27; H, 3.98; N, 9.21. Found: C, 55.29; H, 3.85; N, 8.91).

4.12. Typical procedure for the desymmetrization of hydrobenzoins 3a–e

[(2*S*)-(2α(1*R**,2*S**),3aα,4β,7β,7aα)]-1,2-Bis-(2-methoxyphenyl)-2-[(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)oxy]-ethanol **5a**: Diol **3a** (12.0 g, 43.75 mmol) and dilactol **4** (4.1 g, 10.94 mmol) were dissolved in dichloromethane (450 mL). *p*-Toluenesulfonic acid monohydrate (0.55 g, 2.89 mmol) was added and the mixture stirred for 2 h at rt. Na_2SO_4 and after 1 h $NaHCO_3$ were added, the mixture was filtered and then evaporated under reduced pressure to yield 16.6 g of crude product, which was purified via chromatography (PE/E 50:1 → E). Compound **5a** (6.93 g, 70%) was obtained as a colorless foam ($[\alpha]_D^{20}$ = −77.9 (*c* 1.49, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.22–7.13 (m, 4H, Ph), 6.93–6.76 (m, 4H, Ph), 5.51 (d, J = 6.2 Hz, 1H, OCHPh), 4.98–4.93 (m, 2H, OCHPh/OCHO), 3.71/3.70 (2s, 6H, OCH_3), 3.18 (d, J = 7.2 Hz, 1H, 7a′-H), 2.11–0.75 (m, 17H, aliph. incl. 0.91/0.86/0.75 (3s, 9H, CH_3)); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.13/157.73 (Ph–*C*–OCH_3), 130.43/129.48/128.61/128.47/120.66/120.46/110.76/110.16 (Ph–C), 128.18/128.02 (Ph–C-1), 102.94 (O*C*HO), 90.95 (C-7a), 74.34/73.39 (O*C*HPh), 55.82/55.68 (O*C*H$_3$), 48.74 (C-4), 47.73 (C-7), 47.33 (C-8), 46.37 (C-3a), 38.91 (C-3), 32.72 (C-6), 29.33 (C-5), 23.29/20.94/12.06 (3MBE–CH_3); M = 452.60. Anal. Calcd for $C_{28}H_{36}O_5$: C, 74.31; H, 8.02. Found: C, 74.26; H, 7.64).

4.13. [(2*S*)-(2α(1*R**,2*S**),3aα,4β,7β,7aα)]-1,2-Bis-(2-methylphenyl)-2-[(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)oxy]-ethanol 5b

The synthesis was carried out as described above (see Section 4.12) using *meso*-1,2-bis-(2-methylphenyl)-ethan-1,2-diol **3b** (3.5 g, 14.44 mmol). Compound **5b** (1.91 g, 63%) was obtained as a colorless oil ($[\alpha]_D^{20}$ = −95.7 (*c* 0.90, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.42–7.06 (m, 8H, Ph), 5.13/5.07 (2d, J = 6.8/6.7 Hz, 2H, OCHPh), 4.83 (d, J = 4.3 Hz, 1H, OCHO), 2.99 (d, J = 5.7 Hz, 1H, 7a′-H), 2.33/2.26 (2s, 6H, Ph–C*H*$_3$), 2.03–0.75 (m, 17H, aliph. incl. 0.89/0.85/0.75 (3s, 9H, CH_3)); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.92/137.62/136.68/136.05 (Ph–*C*–CH_3/Ph–C-1), 129.90/129.38/127.81/127.46/127.03/126.45/125.71/125.57 (Ph–C), 101.37 (O*C*HO), 90.31 (C-7a), 76.04/72.87 (O*C*HPh), 48.14 (C-4), 47.07 (C-7), 46.70 (C-8), 45.83 (C-3a), 38.38 (C-3), 32.08 (C-6), 28.78 (C-5), 22.72/20.39/11.27 (3CH_3), 19.27/19.24 (Ph–*C*H_3); M = 420.59. Anal. Calcd for $C_{28}H_{36}O_3{\cdot}0.7H_2O$: C, 77.63; H, 8.70. Found: C, 77.66; H, 8.68).

4.14. [(2*S*)-(2α(1*R**,2*S**),3aα,4β,7β,7aα)]-1,2-Bis-(4-methoxyphenyl)-2-[(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)oxy]-ethanol 5c

The synthesis was carried out as described above (see Section 4.12) using *meso*-1,2-bis-(4-methoxyphenyl)-ethan-1,2-diol **3c** (1.0 g, 3.65 mmol). In this case, the reaction was carried out under an argon atmosphere and degassed solvents were used for chromatography. Compound **5c** (0.667 g, 83%) was obtained as a yellow oil ($[\alpha]_D^{20}$ = −72.95 (*c* 0.95, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.20/7.19/6.84/6.83 (4d, J = 8.7 Hz, 8H, Ph), 4.91 (d, J = 4.3 Hz, 1H, OCHO), 4.65 (s, 2H, OCHPh), 3.79 (s, 6H, OCH_3), 2.99 (d, J = 7.1 Hz, 1H, 7a′-H), 2.29 (s, 1H, OH), 2.13–0.67 (m, 17H, aliph. incl. 0.74/0.84/0.88 (3s, 9H, CH_3)); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.33/159.00 (Ph–*C*–OCH_3), 133.53/130.50 (Ph–C-1), 129.30/128.44/

113.55/113.06 (Ph–C), 101.80 (O*C*HO), 90.55 (C-7a), 80.11/76.78 (O*C*HPh), 55.18 (O*C*H$_3$), 48.24 (C-4), 47.23 (C-7), 46.89 (C-8), 45.89 (C-3a), 38.43 (C-3), 32.25 (C-6), 28.90 (C-5), 22.81/20.43/11.52 (3MBE–CH$_3$); $M = 452.60$. Anal. Calcd for $C_{28}H_{36}O_5 \cdot 0.3H_2O$: C, 73.43; H, 8.05. Found: C, 73.38; H, 8.07).

4.15. [(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-bis-(2-trifluoromethylphenyl)-ethanol 5d

The synthesis was carried out as described above (see Section 4.12) using *meso*-1,2-bis-(2-trifluoromethylphenyl)-ethan-1,2-diol **3d** (3.30 g, 9.4 mmol). Compound **5d** (1.50 g, 57%) was obtained as a colorless oil ($[\alpha]_D^{20} = -85.6$ (*c* 1.95, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.65–7.46 (m, 6H, Ph–H), $\delta = 7.42$–7.32 (m, 2H, Ph–H), 5.37–5.28 (m, 2H, OCHPh), 4.84 (d, $J = 4.2$ Hz, 1H, OCHO), 3.03 (d, $J = 7.1$ Hz, 1H, 7a′-H), 2.65 (s, 1H, OH), 2.10–0.65 (m, 17H, aliph. incl. 0.87/0.82/0.73 (3s, 9H, CH_3)); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.94/137.80 (q, J(C,F) = 1.4 Hz, Ph–C-1), 131.54/131.46/129.66/128.84 (2q, J(C,F) = 1.1 Hz, Ph–C-4/Ph–C-6), 129.58/128.54 (q, J(C,F) = 30.0 Hz, Ph–C-2), 127.78/127.50 (Ph–C-5), 125.10/124.90 (q, J(C,F) = 5.7 Hz/5.9 Hz, Ph–C-3), 124.06/123.89 (q, J(C,F) = 274.4 Hz, Ph–*C*F$_3$), 102.13 (O*C*HO), 90.61 (C-7a), 72.03/71.99 (O*C*HPh), 48.17 (C-4), 47.19 (C-7), 46.60 (C-8), 45.52 (C-3a), 38.35 (C-3), 32.04 (C-6), 28.69 (C-5), 22.67/20.24/11.07 (3CH$_3$); $M = 528.54$. Anal. Calcd for $C_{28}H_{30}F_6O_3$: C, 63.63; H, 5.72. Found: C, 63.34; H, 5.43).

4.16. [(2*S*)-(2α(1*R**,2*S**),3aα,4β,7β,7aα)]-1,2-Bis-(2-nitrophenyl)-2-[(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)oxy]-ethanol 5e

The synthesis was carried out as described above (see Section 4.12) using *meso*-1,2-bis-(2-nitrophenyl)-ethan-1,2-diol **3e** (0.49 g, 1.16 mmol). Compound **5e** (0.241 g, 61%) was obtained as colorless crystals ($F_p = 140$–144 °C, $[\alpha]_D^{20} = -16.4$ (*c* 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.88–7.38 (m, 8H, Ph); 5.70 (dd, $J_1 = 7.8$ Hz, $J_2 = 5.8$ Hz, 1H, PhCHOH); 5.47 (d, $J = 7.8$ Hz, 1H, OCHPh); 4.76 (d, $J = 4.5$ Hz, 1H, OCHO); 3.09 (d, $J = 5.8$ Hz, 1H, OH); 2.61 (d, $J = 7.1$ Hz, 1H, 7a′-H); 2.16–0.53 (m, 17H, aliph. incl. 0.79/0.76/0.70 (3s, 9H, CH_3)); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 150.75/149.71 (Ph–*C*–NO$_2$), 137.68/134.71 (Ph–C-1), 132.79/132.69/128.89/128.67/128.35/127.83/123.98/123.48 (Ph–C), 101.73 (O*C*HO), 90.74 (C-7a), 73.86/71.17 (O*C*HPh), 48.17 (C-4), 47.19 (C-7), 46.69 (C-8), 45.46 (C-3a), 38.23 (C-3), 32.20 (C-6), 28.77 (C-5), 22.71/20.37/11.28 (3CH$_3$); $M = 482.54$. Anal. Calcd for $C_{26}H_{30}N_2O_7 \cdot 0.15C_6H_{14}$: C, 65.21; H, 6.53; N, 5.65. Found: C, 65.48; H, 6.20; N, 5.95).

4.17. Typical procedure for the etherification of hydrobenzoin-acetals 5a–d

2-[[(2*S*)-(2α(1*R**,2*S**),3aα,4β,7β,7aα)]-1,2-Bis-(2-methoxyphenyl)-2-(2-methylpropoxy)-ethoxy]-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran **6a**: Under a nitrogen atmosphere, hydrobenzoin acetal **5a** (2.0 g, 4.42 mmol) dissolved in dry DMF (10 mL) was added to a suspension of NaH (0.2 g, 8.64 mmol) in dry DMF (5 mL) and the mixture stirred for 1 h at rt. *p*-Toluenesulfonic acid *i*-butylester (1.51 g, 6.63 mmol), which was prepared according to the literature,[18] was added and the reaction mixture stirred for 12 h at rt. The reaction was quenched with water, the aqueous layer separated, and then extracted with ether. The combined organic phases were washed with brine, dried, filtered, and evaporated to dryness yielding 2.48 g of crude product. After chromatography (PE/E 20:1 → E), **6a** (1.71 g, 76%) was obtained as a colorless oil ($[\alpha]_D^{20} = -51.9$ (*c* 1.08, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.27–6.60 (m, 8H, Ph), 5.34 (d, $J = 4.7$ Hz, 1H, OCHO), 4.91/4.82 (2d, $J = 4.7$ Hz, 2H, OCHPh), 3.57 (d, $J = 5.9$ Hz, 1H, 7a′-H), 3.56/3.41 (2s, 6H, Ph–O*C*H$_3$), 3.06/3.02 (2dd, $J_1 = 8.9$ Hz, $J_2 = 6.3$ Hz/$J_1 = 9.1$ Hz, $J_2 = 6.7$ Hz, 2H, O–C*H*$_2$CH(CH$_3$)$_2$), 2.16–0.69 (m, 1H, OCH$_2$C*H*(CH$_3$)$_2$, 6H, OCH$_2$CH(C*H*$_3$)$_2$, 17H, aliph.); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.24/157.10 (Ph–*C*–OCH$_3$), 129.40/129.05/128.84/128.73/120.30/120.12/110.18/110.05 (Ph–C), 128.08/128.03 (Ph–C-1), 102.03 (O*C*HO), 90.66 (C-7a), 77.31/72.12 (O*C*HPh), 76.41 (O*C*H$_2$CH(CH$_3$)$_2$), 55.72/55.71 (Ph–O*C*H$_3$), 48.69 (C-4), 47.67 (C-7), 47.44 (C-8), 46.56 (C-3a), 38.93 (C-3), 32.95 (C-6), 29.51 (C-5), 29.16 (O–CH$_2$*C*H(CH$_3$)$_2$), 23.36/21.08/12.18 (3MBE–CH$_3$), 19.88/19.77 (O–CH$_2$CH-(*C*H$_3$)$_2$); $M = 508.70$. Anal. Calcd for $C_{32}H_{44}O_5 \cdot 0.5H_2O$: C, 74.24; H, 8.76. Found: C, 74.17; H, 8.49).

4.18. 2-[[(2*S*)-(2α(1*R**,2*S**),3aα,4β,7β,7aα)]-1,2-Bis-(2-methylphenyl)-2-(2-methylpropoxy)-ethoxy]-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran 6b

The synthesis was carried out as described above (see Section 4.17) using **5b** (1.77 g, 4.21 mmol). Compound **6b** (1.87 g, 93%) was obtained as a colorless oil ($[\alpha]_D^{20} = -67.4$ (*c* 0.80, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.49–7.09 (m, 8H, Ph), 4.95/4.53 (2d, $J = 8.4$ Hz, 2H, OCHPh), 4.71 (d, $J = 3.9$ Hz, 1H, OCHO), 3.00/2.70 (2dd, $J_1 = 8.7$ Hz, $J_2 = 6.4$ Hz/$J_1 = 8.8$ Hz, $J_2 = 6.2$ Hz, 2H, O–C*H*$_2$CH(CH$_3$)$_2$), 2.43 (s, 6H, Ph–C*H*$_3$), 2.38 (d, $J = 6.5$ Hz, 1H, 7a′-H), 1.88–0.69 (m, 1H, OCH$_2$-C*H*(CH$_3$)$_2$, 17H, aliph.), 0.65/0.62 (2d, $J = 6.8$ Hz/6.7 Hz; 6H, OCH$_2$CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 140.02/139.26/137.93/137.42 (Ph–C-1, Ph–*C*–CH$_3$), 129.35/129.29/127.00/126.73/126.69/125.44/125.29 (Ph–C), 100.36 (O*C*HO), 89.52 (C-7a), 82.29/77.06 (O*C*HPh), 75.82 (O–*C*H$_2$CH(CH$_3$)$_2$), 47.99 (C-4), 46.74 (C-7), 46.64 (C-8), 45.77 (C-3a), 41.21 (C-3), 31.98 (C-6), 28.76 (C-5), 28.38 (O–CH$_2$*C*H(CH$_3$)$_2$) 22.67/20.40/11.21 (3CH$_3$) 19.64/19.46/18.96/18.92 (O–CH$_2$CH(*C*H$_3$)$_2$, 2Ph–*C*H$_3$); $M = 476.71$. Anal. Calcd for $C_{32}H_{44}O_5 \cdot 0.5H_2O$: C, 79.43; H, 9.33. Found: C, 79.59; H, 9.36).

4.19. 2-[[(2*S*)-(2α(1*R**,2*S**),3aα,4β,7β,7aα)]-1,2-Bis-(4-methoxyphenyl)-2-(2-methylpropoxy)-ethoxy]-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran 6c

The synthesis was carried out as described above (see Section 4.17) using **5c** (1.34 g, 2.95 mmol). Compound **6c** (1.15 g, 77%) was obtained as a colorless oil ($[\alpha]_D^{20} = -66.9$ (*c* 4.70, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ

7.30/7.28/6.87/6.85 (4d, $J = 8.7$ Hz, 8H, Ph), 4.82 (d, $J = 4.2$ Hz, 1H, OCHO), 4.52/4.06 (2d, $J = 8.2$ Hz, 2H, OCHPh), 3.81 (s, 6H, Ph–OCH_3), 3.03/2.75 (2dd, $J_1 = 8.9$ Hz, $J_2 = 6.5$ Hz, 2H, O–CH_2CH(CH$_3$)$_2$), 2.45 (d, $J = 6.5$ Hz, 1H, 7a′-H), 1.96–0.51 (m, 23H, aliph. incl. 0.81/0.80/0.69 3s, 9H, CH$_3$, 0.67/0.64 2d, $J = 3.5$/$J = 3.4$ Hz, 6H, OCH$_2$CH(CH_3)$_2$); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 158.95/158.86 (Ph–*C*–OCH$_3$), 133.51/132.72 (Ph–C-1), 129.33/129.15/113.00/112.92 (Ph–C), 100.67 (O*C*HO), 89.79 (C-7a), 84.81/78.27 (O*C*HPh), 75.79 (O*C*H$_2$CH(CH$_3$)$_2$), 55.21/55.13 (Ph–O*C*H$_3$), 48.09 (C-4), 46.91 (C-7), 46.87 (C-8), 45.91 (C-3a), 38.29 (C-3), 32.19 (C-6), 28.95 (C-5), 28.40 (O–CH$_2$*C*H(CH$_3$)$_2$), 22.81/20.49/11.51 (3CH$_3$), 19.18 (O–CH$_2$CH(*C*H$_3$)$_2$); $M = 508.70$. Anal. Calcd for $C_{32}H_{44}O_5 \cdot 0.6C_2H_4$: C, 75.88; H, 8.90. Found: C, 75.81; H, 9.02).

4.20. 2-[[(2*S*)-(2α(1*R**,2*S**),3aα,4β,7β,7aα)]-2-(2-Methylpropoxy)-1,2-bis-(2-trifluoromethylphenyl)-ethoxy]-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran 6d

The synthesis was carried out as described above (see Section 4.17) using **5d** (1.00 g, 1.89 mmol). Compound **6d** (1.09 g, 99%) was obtained as a colorless oil ($[\alpha]_D^{20} = -53.7$ (*c* 1.80, CH_2Cl_2); ^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.83–7.72 (m, 2H, Ph–H), 7.64–7.52 (m, 4H, Ph–H), 7.44–7.33 (m, 2H, Ph–H), 5.21/4.74 (2d, $J = 8.0$ Hz, 2H, OCHPh), 4.70 (d, $J = 4.2$ Hz, 1H, OCHO), 2.89/2.73 (2dd, $J_1 = 8.8$ Hz, $J_2 = 6.3$ Hz/$J_1 = 8.7$ Hz, $J_2 = 6.1$ Hz, 2H, O–CH_2CH(CH$_3$)$_2$), 2.29 (s, $J = 7.1$ Hz, 1H, 7a′-H), 1.84–0.53 (m, 18H, aliph., OCH$_2$C*H*(CH$_3$)$_2$), 0.65/0.62 (2d, $J = 6.8$/6.7 Hz, 6H, OCH$_2$CH(CH_3)$_2$); ^{13}C NMR (CDCl$_3$, 50 MHz) δ 131.69/131.47 (q, J(C,F) = 1.0/1.3 Hz, Ph–C-1), 129.14/128.58/127.57/126.86 (Ph–C-4, Ph–C-2, Ph–C-6), 127.27/127.22 (Ph–C-5), 124.64/124.52 (Ph–C-3), 124.12 (q, ^1J(C,F) = 273.3 Hz, Ph–*C*F$_3$), 100.87 (O*C*HO), 89.69 (C-7a), 80.27/74.24 (O*C*HPh), 75.69 (O–*C*H$_2$CH(CH$_3$)$_2$), 47.98 (C-4), 46.81 (C-7), 46.50 (C-8), 45.44 (C-3a), 38.16 (C-3), 31.98 (C-6), 28.69 (C-5), 28.07 (O–CH$_2$*C*H(CH$_3$)$_2$), 22.66/20.26/11.07 (3CH$_3$), 18.71/18.63 (O–CH$_2$CH(*C*H$_3$)$_2$); $M = 584.65$. Anal. Calcd for $C_{32}H_{38}F_6O_3$: C, 65.74; H, 6.55. Found: C, 65.56; H, 6.61).

4.21. Three-step synthesis of 2-[[(2*S*)-(2α(1*R**,2*S**),3aα,4β,7β,7aα)]-(2-(2-methoxyethoxy)-1,2-bis-(2-methoxyphenyl)-ethoxy)]-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran 6g

[[(2*S*)-(2α(1*R**,2*S**),3aα,4β,7β,7aα)]-1,2-Bis-(2-methoxyphenyl)-2-(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl-oxy)ethoxy]acetic acid, 1,1-dimethylethylester **6e**: Acetal **5a** (3.0 g, 6,6 mmol) dissolved in dry THF (25 mL) was added under a nitrogen atmosphere to a suspension of NaH (0.36 g, 15 mmol) in THF (5 mL) and the mixture stirred for 1 h at rt. Bromoacetic acid, *t*-butylester (2.85 g, 14.6 mmol), and HMPT (11.35 g, 63.36 mmol) dissolved in dry THF (30 mL) were added and the mixture was heated at reflux for 12 h. The mixture was quenched with water, the aqueous layer was separated, and extracted several times with ether. The combined organic phases were washed with brine, dried, filtered, and evaporated to dryness yielding 5.7 g of crude product. After chromatography (PE/E 100:1 → E), **6e** (2.70 g, 72%) was obtained as a colorless oil ($[\alpha]_D^{20} = -66.5$ (*c* 1.03, CH_2Cl_2); ^{1}H NMR (CDCl$_3$) δ 7.34–6.64 (m, 8H, Ph), 5.50/5.17 (2d, $J = 3.9$ Hz, 2H, OCHPh), 4.92 (d, $J = 4.5$ Hz, 1H, OCHO), 4.03 (s, 3H, OCH$_2$CO), 3.82 (d, $J = 7.5$ Hz, 1H, 7a-H), 3.61/3.45 (2s, 6H, OCH$_3$), 2.33–0.75 (m, 26H, aliph. incl. 1.40/0.98/0.90/0.77 (4s, 12H, CH$_3$)); ^{13}C NMR (CDCl$_3$) δ 170.2 (O–CO), 157.97/157.58 (Ph–*C*–OCH$_3$), 129.52/128.93/128.32/128.27/120.33/120.24/110.03 (Ph–C), 127.74/127.47 (Ph–C-1), 102.4 (O–CH–O), 90.99 (C-7a), 81.22 (*C*(CH$_3$)$_3$), 77.25/71.22 (CH–Ph), 67.91 (O–CH$_2$–CO), 55.67/55.57 (O–CH$_3$), 48.76 (C-4), 47.76 (C-7), 47.45 (C-8), 46.42 (C-3a), 38.89 (C-3), 32.85 (C-6), 29.41 (C-5), 28.43 (C(*C*H$_3$)$_3$), 23.34/21.03/12.17 (C-9, C-10, C-11); $M = 566.74$. Anal. Calcd for $C_{34}H_{46}O_7 \cdot 0.6H_2O$: C, 70.71; H, 8.24. Found: C, 70.81; H, 8.35).

4.21.1. [[(2*S*)-(2α(1*R,2*S**),3aα,4β,7β,7aα)]-1,2-Bis-(2-methoxyphenyl)-2-[(octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl)-oxy]-2-ethoxy]-ethanol 6f.** Compound **6e** (2.58 g, 4.55 mmol) dissolved in dry ether (70 mL) was added to a suspension of $LiAlH_4$ (0.518 g, 13.7 mmol) in dry ether (100 mL) at 0 °C under a nitrogen atmosphere and the mixture stirred for 2 h at rt. The reaction was quenched with 2 M NaOH (6 mL), diluted with brine and extracted several times with ether. The combined organic phases were washed with brine, dried, filtered, and evaporated to dryness yielding 1.94 g of crude product. After chromatography (PE/E 10:1 → E/MeOH 1:1), **6f** (1.649 g, 73%) was obtained as a colorless oil ($[\alpha]_D^{20} = -61.9$ (*c* 1.40, CH_2Cl_2); ^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.32–6.65 (m, 8H, Ph), 5.52 (d, $J = 4.1$ Hz, 1H, OC*H*O), 5.09/4.95 (2d, $J = 4.4$ Hz, 2H, OC*H*Ph), 3.87–3.24 (m, 12H, incl. 3.70/3.41 (2s, 6H, OCH_3) OCH_2CH_2O*H*, 7a′-*H*), 2.35–0.78 (m, 17H, aliph.); ^{13}C NMR (CDCl$_3$, 50 MHz) 157.55/157.27 (Ph–*C*–OCH$_3$), 128.89/128.09/127.98/126.82/119.97/119.90/109.74/109.68 (Ph–C/Ph–C-1), 102.18 (O*C*HO), 90.85 (C-7a), 78.36/71.67 (O*C*HPh), 77.20/70.99 (O*C*H$_2$*C*H$_2$OH), 55.39/55.04 (Ph–O*C*H$_3$), 48.33 (C-4), 47.44 (C-7), 46.99 (C-8), 45.91 (C-3a), 38.56 (C-3), 32.53 (C-6), 28.92 (C-5), 22.91/20.57/11.72 (CH$_3$); $M = 496.65$. Anal. Calcd for $C_{30}H_{40}O_6$: C, 72.55; H, 8.12. Found: C, 72.33; H, 8.36).

4.21.2. 2-[[(2*S*)-(2α(1*R,2*S**),3aα,4β,7β,7aα)]-2-(2-Methoxyethoxy)-1,2-bis-(2-methoxyphenyl)-ethoxy]-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran 6g.** Compound **6f** (0.688 g, 1.39 mmol) dissolved in dry DMF (5 mL) was added to a suspension of NaH (0.100 g, 4.17 mmol) in dry DMF (5 mL) under a nitrogen atmosphere and the mixture stirred for 1 h. MeI (1.02 g, 7.20 mmol) was added and the solution was stirred for 2 h at rt. The reaction was quenched with water, extracted several times with ether, and the combined organic phases were washed with brine, dried, filtered, and evaporated to dryness yielding 0.648 g of crude product. After chromatography (PE/E 30:1 → E/MeOH 5:1), **6g** (0.525 g, 74%) was obtained as a colorless oil ($[\alpha]_D^{20} = -85.4$ (*c* 1.05, CH_2Cl_2); ^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.34–6.68 (m, 8H, Ph), 5.46 (d, $J = 4.3$ Hz, 1H, OC*H*O), 5.06/4.90 (2d, $J = 4.5$ Hz, 2H, OC*H*Ph), 3.72–3.46 (m, 11H, incl. 3.62/3.51 (2s, 6H, OCH_3) OCH_2CH_2O, 7a′-*H*), 3.32 (s, 3H, OCH$_2$CH$_2$OCH_3),

2.29–0.77 (m, 17H, aliph.); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.77/157.47 (Ph–*C*–OCH_3), 128.95/128.51/128.06/127.95/127.75/119.91/119.78/109.75 (Ph–C/Ph–C-1), 101.77 (O*C*HO), 90.40 (C-7a), 77.28/71.37 (O*C*HPh), 72.18/68.88 ($OCH_2CH_2OCH_3$), 58.99 ($OCH_2CH_2OCH_3$) 55.30/55.27 (Ph–OCH_3), 48.32 (C-4), 47.29 (C-7), 46.99 (C-8), 46.09 (C-3a), 38.49 (C-3), 32.52 (C-6), 29.04 (C-5), 22.92/20.61/11.72 (CH_3); $M = 510.68$. Anal. Calcd for $C_{31}H_{42}O_6 \cdot 0.1H_2O$: C, 72.66; H, 8.30. Found: C, 72.63; H, 8.20).

4.22. Typical procedure for the deprotection of acetals 6a–d and 6g

(1*R*,2*S*)-1,2-Bis-(2-methoxyphenyl)-2-(2-methylpropoxy)-ethanol **7a**: Acetal **6a** (1.6 g, 3.15 mmol) was dissolved in methanol (15 mL), *p*-toluenesulfonic acid monohydrate (0.11 g, 0.58 mmol) was added and the reaction stirred for 12 h. Saturated $NaHCO_3$-solution (5 mL) was added to the mixture, methanol evaporated under reduced pressure, and the residue dissolved in water and extracted several times with ether. The combined extracts were washed with brine, dried, filtered, and evaporated to dryness, yielding 1.56 g of crude product that was purified via chromatography (PE/E 20:1 → E). Compound **7a** (1.01 g, 96%) was obtained as a colorless oil ($[\alpha]_D^{20} = +29.8$ (*c* 0.84, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.34–6.70 (m, 8H, Ph), 5.32/5.16 (2d, $J = 4.6$Hz, 2H, OCHPh), 3.67/3.54 (2s, 6H, Ph–O*C*H_3), 3.20/3.11 (2dd, $J_1 = 9.0$ Hz, $J_2 = 6.9$ Hz/$J_1 = 8.9$ Hz, $J_2 = 6.4$ Hz, 2H, O–CH_2–CH(CH_3)$_2$), 1.98–1.70 (m, 1H, $OCH_2CH(CH_3)_2$), 0.88/0.89 (2d, $J = 6.5$/6.7 Hz, 6H, $OCH_2CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.46/156.72 (Ph–*C*–OCH_3), 127.75/127.69 (Ph–C-1), 130.45/128.60/127.96/127.88/119.91/119.76/109.56/109.55 (Ph–C), 77.38/75.96 (O*C*HPh), 71.47 ($OCH_2CH(CH_3)_2$), 55.07/54.94 (Ph–O*C*H_3), 28.53 (O–$CH_2CH(CH_3)_2$), 19.29/19.20 (O–CH_2-CH(*C*H_3)$_2$); $M = 330.42$. Anal. Calcd for $C_{21}H_{24}O_4 \cdot 0.9C_4H_{10}O$: C, 72.57; H, 8.17. Found: C, 72.47; H, 7.79).

4.23. (1*R*,2*S*)-1,2-Bis-(2-methylphenyl)-2-(2-methylpropoxy)-ethanol 7b

The synthesis was carried out as described above (see Section 4.22) using **6b** (1.73 g, 3.63 mmol). In this case dichloromethane (10 mL) was added because of the poor solubility of the educt in methanol. Crude product (1.74 g) was purified via chromatography (PE/E 50:1 → E) yielding **7b** (0.93 g, 86%) as a colorless oil ($[\alpha]_D^{20} = +37.3$ (*c* 1.26, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.33–7.03 (m, 8H, Ph), 5.18/4.76 (2d, $J = 5.6$ Hz, 2H, OCHPh), 3.10/2.96 (2dd, $J_1 = 8.8$ Hz, $J_2 = 6.8$ Hz/$J_1 = 8.8$ Hz, $J_2 = 6.1$ Hz, 2H, O–CH_2CH(CH_3)$_2$), 2.37 (s, 1H, OH), 2.21/2.17 (2s, 6H, Ph–CH_3), 1.90–1.71 (m, $J = 6.6$ Hz, 1H, $OCH_2CH(CH_3)_2$), 0.84/0.82 (2d, $J = 6.6$ Hz, 6H, $OCH_2CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.01/136.99/136.46/135.84 (Ph–*C*–CH_3, Ph–C-1), 129.91/129.51/127.44/127.11/126.58/125.78/125.58 (Ph–C), 81.62 (O*C*H_2CH(CH_3)$_2$), 75.84/72.57 (O*C*HPh), 28.59 (O–$CH_2CH(CH_3)_2$), 19.30/19.21/19.14/19.05 (O–CH_2CH-(*C*H_3)$_2$, Ph–*C*H_3); $M = 298.43$. Anal. Calcd for $C_{20}H_{26}O_2 \cdot 0.2H_2O$: C, 79.54; H, 8.81. Found: C, 79.56; H, 8.71).

4.24. (1*R*,2*S*)-1,2-Bis-(4-methoxyphenyl)-2-(2-methylpropoxy)-ethanol 7c

The synthesis was carried out as described above (see Section 4.22) using **6c** (1.15 g, 2.26 mmol). Crude product (1.40 g) was purified via chromatography (PE/E 20:1 → 2:1) yielding **7c** (0.595 g, 80%) as a yellow oil ($[\alpha]_D^{20} = +25.4$ (*c* 0.90, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.13–6.77 (m, 8H, Ph–H), 4.75/4.29 (2d, $J = 5.5$ Hz, 2H, CH–Ph), 3.79/3.78 (2s, 6H, Ph–OCH_3), 3.10/2.96 (2dd, $J_1 = 8.9$ Hz, $J_2 = 6.5$ Hz, 2H, O–CH_2–CH(CH_3)$_2$), 1.89–1.69 (m, 1H, O–CH_2–C*H*(CH_3)$_2$), 0.81/0.80 (2d, $J = 6.7$ Hz, 6H, O–CH_2–CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ 159.23/158.87 (Ph–*C*–OCH_3), 132.81/130.20 (Ph–C 1), 129.02/128.26/113.28/113.08 (Ph–C), 85.62/76.76 (*C*H–Ph), 75.83 (O–*C*H_2–CH(CH_3)$_2$), 55.17 (Ph–O*C*H_3), 28.52 (O–CH_2–*C*H(CH_3)$_2$), 19.34/19.27 (O–CH_2–CH(*C*H_3)$_2$); $M = 330.43$. Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.99; H, 8.22).

4.25. (1*R*,2*S*)-2-(2-Methylpropoxy)-1,2-bis-(2-trifluoromethylphenyl)-ethanol 7d

The synthesis was carried out as described above (see Section 4.22) using **6d** (1.07 g, 1.84 mmol). Crude product (1.08 g) was purified via chromatography (PE/E 50:1 → E) yielding **7d** (0.679 g, 91%) as a colorless oil ($[\alpha]_D^{20} = +34.3$ (*c* 0.40, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.60–7.30 (m, 8H, Ph–H), 5.37 (br s, 1H, Ph–C*H*–OH), 5.00 (d, $J = 5.3$ Hz, 1H, Ph–C*H*–OR), 3.09–2.95 (m, 2H, O–CH_2–CH(CH_3)$_2$), 2.61 (br s, 1H, OH), 1.86–1.66 (m, $J = 6.6$ Hz, 1H, O–CH_2–C*H*(CH_3)$_2$), 0.78/0.77 (2d, $J = 6.7$ Hz, 6H, O–CH_2–CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 139.14/137.55 (q, J(C,F) = 1.2 Hz, Ph–C-1), 131.65/131.46 (q, J(C,F) = 0.8 Hz, Ph–C-4), 129.04 (q, J(C,F) = 29.5, Ph–C-2) 128.00/127.73 (Ph–C-5, Ph–C-6), 125.20/125.16 (q, J(C,F) = 5.9 Hz, 2 × Ph–C-3), 124.17/124.12 (q, J(C,F) = 274.2/274.1 Hz, 2 × *C*F_3), 79.65/72.11 (2q, $J = 1.7$/2.3 Hz, O*C*HPh), 75.88 (O–*C*H_2CH(*C*H_3)$_2$); 28.40 (O–CH_2*C*H(CH_3)$_2$), 19.19/19.04 (O–CH_2CH(*C*H_3)$_2$); $M = 406.37$. Anal. Calcd for $C_{20}H_{20}F_6O_2$: C, 59.11; H, 4.96. Found: C, 59.00; H, 5.22).

4.26. (1*R*,2*S*)-2-(2-Methoxyethoxy)-1,2-bis-(2-methoxyphenyl)-ethanol 7e

The synthesis was carried out as described above (see Section 4.22) using **6g** (0.475 g, 0.93 mmol). Crude product (0.422 g) was purified via chromatography (PE/E 30:1 → E/MeOH 5:1) yielding **7e** (0.264 g, 85%) as a yellow oil ($[\alpha]_D^{20} = +17.3$ (*c* 1.00, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.25–6.66 (m, 8H, Ph), 5.39/5.20 (2d, $J = 3.9$ Hz, 2H, OC*H*Ph), 3.72–3.46 (m, 11H, incl. 3.62/3.47 (2s, 6H, O*C*H_3), O*C*H_2*C*H_2O, Ph–CH–O*H*), 3.36 (s, 3H, OCH_2CH_2O *C*H_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.41/156.70 (2s, Ph–*C*–OCH_3), 128.62/126.30 (2s, Ph–C-1), 128.17/127.97/127.86/127.77/120.02/119.90/109.59/109.55 (8d, Ph–C), 77.81/70.85 (2d, O*C*HPh), 71.91/68.56 (2t, O*C*H_2*C*H_2OCH$_3$), 58.91 (q, $OCH_2CH_2OCH_3$) 55.16/55.01 (2q, Ph–O*C*H_3); $M = 332.40$. Anal. Calcd for $C_{19}H_{24}O_5 \cdot 0.1H_2O$: C, 68.29; H, 7.30. Found: C, 68.23; H, 7.40).

4.27. Typical procedure for the esterification of auxiliaries 7a–e

Oxophenylacetic acid, (1*R*,2*S*)-1,2-bis-(2-methoxyphenyl)-2-(2-methylpropoxy)ethyl ester **8a**:

Alcohol **7a** (0.50 g, 1.51 mmol), benzoylformic acid (0.453 g, 3.02 mmol), and *N*,*N*-dimethyl-4-aminopyridine (DMAP) (0.092 g, 0.755 mmol) were dissolved in dry dichloromethane (12 mL) under a nitrogen atmosphere. *N*,*N*′-Diisopropylcarbodiimide (DIC) (0.378 g, 3.02 mmol) was slowly added and the mixture stirred for 12 h at rt.

The reaction mixture was diluted with dichloromethane, washed successively with a $KHSO_4$-solution (5%), saturated $NaHCO_3$-solution, and brine, dried, filtered, and evaporated to dryness yielding 0.90 g of crude product, which was purified via chromatography (PE/E 20:1 → PE/E 5:1). Compound **8a** (0.636 g, 91%) was obtained as a colorless oil ($[\alpha]_D^{20} = +51.8$ (*c* 1.10, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.98–6.68 (m, 13H, Ph–H), 6.90/5.30 (2d, $J = 3.9$ Hz, 2H, OCHPh), 3.66/3.49 (2s, 6H, Ph–OCH_3), 3.22 (d, $J = 6.5$ Hz, 2H, O–CH_2CH(CH_3)$_2$), 1.99–1.79 (m, $J = 6.7$ Hz, 1H, OCH$_2$CH(CH_3)$_2$), 0.89 (d, $J = 6.7$ Hz, 6H, OCH$_2$CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 186.62 (CO), 163.14 (O–CO), 157.28/156.70 (Ph–*C*–OCH$_3$), 134.51/125.65/124.52 (Ph–C-1), 132.45/129.94/128.72/128.63/128.31/128.27/128.03/119.92/119.78/109.68/109.51 (Ph–C), 76.23/75.26 (O*C*HPh), 72.77 (O*C*H$_2$CH(CH_3)$_2$), 55.29/54.91 (Ph–OCH$_3$), 28.61 (O–CH$_2$*C*H(CH_3)$_2$), 19.24/19.17 (O–CH$_2$CH(*C*H$_3$)$_2$); $M =$ 462.55. Anal. Calcd for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 72.58; H, 6.81).

4.28. Oxophenylacetic acid, (1*R*,2*S*)-1,2-bis-(2-methylphenyl)-2-(2-methylpropoxy)ethyl ester 8b

The synthesis was carried out as described above (Section 4.27) using **7b** (0.150 g, 0.50 mmol). After chromatography, ester **8b** (0.206 g, 95%) was obtained as a colorless oil ($[\alpha]_D^{20} = +46.9$ (*c* 1.13, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.63–7.06 (m, 13H, Ph–H), 6.48/4.90 (2d, $J = 7.1$ Hz, 2H, OCHPh), 3.09/2.90 (2dd, $J_1 = 8.7$ Hz, $J_2 = 6.4$ Hz/$J_1 = 8.7$ Hz, $J_2 = 6.2$ Hz, 2H, O–CH_2CH(CH_3)$_2$), 2.39/2.30 (2s, 6H, Ph–CH_3), 1.83/1.63 (m, $J = 6.6$ Hz, 1H, OCH$_2$CH(CH_3)$_2$), 0.75/0.74 (2d, $J =$ 6.7 Hz, 6H, OCH$_2$CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 186.06 (CO), 162.65 (O–CO), 136.88/136.85/136.34/135.35/134.49 (Ph–C-1, Ph–*C*–CH$_3$), 132.12/130.10/129.73/129.66/128.61/127.98/127.66/127.08/126.00/125.72 (Ph–C), 80.26/76.01 (O*C*HPh), 75.56 (O*C*H$_2$CH(CH_3)$_2$), 28.43 (O–CH$_2$*C*H(CH_3)$_2$), 19.18/19.02/18.97 (Ph–*C*H$_3$, O–CH$_2$CH(*C*H$_3$)$_2$); $M = 430.55$. Anal. Calcd for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02. Found: C, 77.83; H, 7.17).

4.29. Oxophenylacetic acid, (1*R*,2*S*)-1,2-bis-(4-methoxyphenyl)-2-(2-methylpropoxy)ethyl ester 8c

The synthesis was carried out as described above (Section 4.27) using **7c** (0.30 g, 0.90 mmol). After chromatography, **8c** (0.288 g, 89%) was obtained as a colorless solid ($F_p = 102$–106 °C; $[\alpha]_D^{20} = +17.1$ (*c* 0.55, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.63–6.79 (m, 13H, Ph–H), 6.13/4.48 (2d, $J = 6.8$ Hz, 2H, OCHPh), 3.81/3.79 (2s, 6H, OCH$_3$), 3.08/2.94 (2dd, $J_1 = 8.8$ Hz, $J_2 = 6.5$ Hz, 2H, O–CH_2CH(CH_3)$_2$), 1.85–1.64 (m, 1H, O–CH$_2$CH(CH_3)$_2$), 0.75/0.74 (2d, $J = 6.7$ Hz, 6H, O–CH$_2$CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ 186.34 (CO), 162.99 (O–CO), 159.60/159.48 (Ph–C-4), 134.66/128.72/128.69 (Ph–C-1), 132.25/130.11/129.94/129.24/113.57/113.41 (Ph–C), 83.31/79.18 (OCHPh), 76.01 (O–*C*H$_2$–CH(CH_3)$_2$), 55.25/55.17 (OCH$_3$), 28.48 (O–CH$_2$–*C*H(CH_3)$_2$), 19.20 (O–CH$_2$–CH(*C*H$_3$)$_2$); $M = 462.55$. Anal. Calcd for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 73.01; H, 6.73).

4.30. Oxophenylacetic acid, (1*R*,2*S*)-2-(2-methylpropoxy)-1,2-bis-(2-trifluoromethylphenyl)-ethyl ester 8d

The synthesis was carried out as described above (Section 4.27) using **7d** (0.30 g, 0.74 mmol). After chromatography, **8d** (0.362 g, 91%) was obtained as a colorless oil ($[\alpha]_D^{20} = +10.8$ (*c* 1.15, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.81–7.35 (m, 13H, Ph–H), 6.81/5.10 (2d, $J = 6.5$ Hz, 2H, OCHPh), 2.98 (d, $J = 6.4$ Hz, 2H, O–CH_2CH(CH_3)$_2$), 1.79–1.59 (m, 1H, O–CH$_2$CH(CH_3)$_2$), 0.70 (d, $J = 6.7$ Hz, 6H, O–CH$_2$CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$) δ 185.42 (CO), 161.71 (O–CO), 136.85/135.06 (2q, J(C,F) = 1.4 Hz/1.5 Hz, Ph–C-1), 134.64 (Ph–C-1), 131.97/129.66/129.63/128.88/128.61/128.53/128.25 (Ph–C), 131.69 (q, J(C,F) = 0.8 Hz, Ph–C-4), 129.54/128.95 (2q, J(C,F) = 30.3 Hz/30.6 Hz, Ph–C-2), 125.56/125.12 (2q, J(C,F) = 5.7 Hz, Ph–C-3), 123.87/123.79 (2q, J(C,F) = 274.3 Hz, CF_3), 78.31/73.99 (2q, J(C,F) = 1.3 Hz/2.0 Hz, OCHPh), 75.94 (O–*C*H$_2$CH(CH_3)$_2$), 28.16 (O–CH$_2$–*C*H(CH_3)$_2$), 18.85/18.74 (O–CH$_2$–CH(*C*H$_3$)$_2$); $M = 538.49$. Anal. Calcd for $C_{28}H_{24}F_6O_4$: C, 62.45; H, 4.49. Found: C, 62.22; H, 4.56).

4.31. Oxophenylacetic acid, (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-bis-(2-methoxyphenyl)-ethyl ester 8e

The synthesis was carried out as described above (Section 4.27) using **7e** (0.43 g, 1.29 mmol). After chromatography, **8e** (0.593 g, 99%) was obtained as a colorless oil ($[\alpha]_D^{20} = +34.9$ (*c* 0.80, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.91–7.87 (m, 2H, Ph–H), 7.61–6.95 (m, 7H, Ph–H), 6.84/5.29 (2d, $J = 4.1$ Hz, 2H, OCHPh), 6.77–6.57 (m, 4H, Ph–H), 3.65–3.42 (m, 7H, incl. 3.61 (s, 3H, OCH$_3$), OCH$_2$-CH$_2$O), 3.36/3.26 (2s, 6H, OCH$_3$); ^{13}C NMR ($CDCl_3$) δ 186.61 (CO), 163.09 (O–CO), 157.20/156.66 (Ph–C-2), 134.55 (Ph–C-1), 132.42/130.01/128.77/128.65/128.46/128.39/127.84/119.98/119.83/109.67/109.51 (Ph–C), 125.07/124.34 (Ph–C-1), 75.40/72.58 (OCHPh), 71.71/68.82 (OCH$_2$CH$_2$O), 58.84/55.32/55.86 (OCH$_3$); $M = 464.52$. Anal. Calcd for $C_{27}H_{28}O_7$: C, 69.81; H, 6.08. Found: C, 69.54; H, 6.09).

4.32. Typical procedure for the reduction of esters 8a–e

Hydroxyphenylacetic acid, (1*R*,2*S*)-1,2-bis-(2-methoxyphenyl)-2-(2-methylpropoxy) ethylester **9a**:

To a stirred solution of ester **8a** (0.100 g, 0.216 mmol) at −78 °C under a nitrogen atmosphere, a 1 M solution of

L-Selectride® in THF (0.24 mL, 0.24 mmol) 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 ether extracts were washed with brine, dried over Na_2SO_4, filtered, and evaporated. After chromatography (PE/E 20:1 → E), **9a** (0.070 g, 94%, 12 mg of starting material recovered) was obtained as a colorless oil (^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.38–6.15 (m, 13H, Ph–H), 6.51 (d, $J = 3.5$ Hz, 1H, Ph–C*H*–OCO), 5.27 (s, 1H, C*H*(OH)), 5.15/4.99 (2d(diast.), $J = 3.5$ Hz, 1H, Ph–C*H*–O), 3.52/3.47 (2s, 6H, Ph–OCH_3), 3.18 (d, $J = 6.4$ Hz, 2H, O–CH_2CH(CH_3)$_2$), 1.95–1.75 (m, $J = 6.7$ Hz, 1H, $OCH_2CH(CH_3)_2$), 0.89 (d, $J = 6.7$ Hz, 6H, $OCH_2CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.39 (O–CO), 157.04/156.34 (Ph–*C*–OCH_3), 138.10/126.68/124.56 (Ph–C-1), 128.22–126.67 (Ph–C), 119.73/119.40/109.40/109.34 (Ph–C) 76.13/75.23 (O*C*HPh), 73.20 (*C*H(OH)), 72.83 (O*C*H_2CH(CH_3)$_2$), 55.08/54.85 (Ph–OCH_3), 28.53 (O–CH_2*C*H(CH_3)$_2$), 19.22/19.20 (O–CH_2CH(*C*H_3)$_2$); $M = 464.56$. Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.14; H, 7.05).

4.33. Hydroxyphenylacetic acid, (1*R*,2*S*)-1,2-bis-(2-methylphenyl)-2-(2-methylpropoxy)ethyl ester 9b

The synthesis was carried out as described above (see Section 4.32) using ester **8b** (0.100 g, 0.231 mmol). After chromatography, **9b** (0.082 g, 82%) was obtained as a yellow oil (^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.33–6.54 (m, 13H, Ph–H), 6.26/6.10 (2d(diast.), $J = 6.1$ Hz, 1H, Ph–C*H*–OCO), 5.06/5.03 (2s(diast.), 1H, C*H*(OH)), 4.74/4.65 (2d(diast.), $J = 6.1$ Hz, 1H, Ph–C*H*–O), 3.06/2.85 (2dd, $J_1 = 8.7$ Hz, $J_2 = 6.3$ Hz, 2H, O–CH_2CH(CH_3)$_2$), 2.25/2.23 (2s, 6H, Ph–CH_3), 1.80–1.58 (m, $J = 6.6$ Hz, 1H, $OCH_2CH(CH_3)_2$), 0.75/0.69 (2d(diast.), $J = 6.7$ Hz, 6H, $OCH_2CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.61/172.11 (O–CO-(diast.)), 137.94/137.73/136.95/136.40/136.27/136.24/135.74/135.32 (Ph–C-1, Ph–*C*–CH_3(diast.)), 129.83–125.26 (Ph–C (diast.)), 80.05/79.59/75.95/75.74 (O*C*HPh(diast.)), 75.91/75.36 (O*C*H_2CH(CH_3)$_2$(diast.)), 73.04/72.83 (*C*H(OH)(diast.)), 28.39 (O–CH_2*C*H(CH_3)$_2$), 19.02/19.01/18.95/18.71 (O–CH_2CH(*C*H_3)$_2$, Ph–CH_3),; $M = 432.56$. Anal. Calcd for $C_{28}H_{32}O_4 \cdot 0.2\ H_2O$: C, 77.11; H, 7.49. Found: C, 77.14; H, 7.64).

4.34. Hydroxyphenylacetic acid, (1*R*,2*S*)-1,2-bis-(4-methoxyphenyl)-2-(2-methylpropoxy)ethyl ester 9c

The synthesis was carried out as described above (see Section 4.32) using ester **8c** (0.053 g, 0.115 mmol). Crude **9c** (0.071 g) was isolated as a yellow oil and used for the following saponification without further purification due to the poor stability of the product. (^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.31–6.57 (m, 13H, Ph–H), 5.69 (d, $J = 6.2$ Hz, 1H, OCHPh), 5.04 (s, 1H, C*H*–OH), 4.26 (d, $J = 5.9$ Hz, 1H, OCHPh), 3.79/3.71 (2s, 6H, OCH_3), 3.00/2.83 (2dd, $J_1 = 8.9$ Hz, $J_2 = 6.4$ Hz, 2H, O–CH_2CH(CH_3)$_2$), 1.83–1.59 (m, 1H, $OCH_2CH(CH_3)_2$), 0.69/0.68 (2d, $J = 6.7$ Hz, 6H, $OCH_2CH(CH_3)_2$)).

4.35. Hydroxyphenylacetic acid, (1*R*,2*S*)-2-(2-methylpropoxy)-1,2-bis-(2-trifluoromethylphenyl)-ethyl ester 9d

The synthesis was carried out as described above (see Section 4.32) using ester **8d** (0.100 g, 0.186 mmol). After chromatography, **9d** (0.094 g, 94%) was obtained as a colorless oil (^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.67–6.60 (m, 13H, Ph–H), 6.54/6.36 (2d(diast.), $J = 6.4$ Hz/6.8 Hz, 1H, OCHPh), 5.02/4.98 (2s(diast.), 1H, C*H*–OH), 4.91/4.84 (2d(diast.), $J = 6.5$ Hz/6.9 Hz, 1H, OCHPh), 3.25 (br s, 1H, OH), 2.96–2.76 (m, 2H, O–CH_2CH(CH_3)$_2$), 1.67–1.37 (m, 1H, $OCH_2CH(CH_3)_2$), 0.63/0.61 (3d(diast.), $J = 6.6$/6.7 Hz, 6H, $OCH_2CH(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.90/171.53 (O–CO(diast.)), 137.59/137.45 (Ph–C-1(diast.)), 137.33/136.62/135.76/135.40 (4q(diast.), J(C,F) = 1.4/1.3/1.3/1.3 Hz, Ph–C-1), 131.96/131.54/131.17/129.24/128.99/128.62/128.46/128.37/128.45/128. 02/127.88/127.51/126.69/126.60 (Ph–C(diast.)), 129.21/128.99 (2q, J(C,F) = 30.3 Hz, Ph–C-2), 125.61/125.42/125.08/124.94 (4q(diast.), J(C,F) = 5.7/5.6/5.7/6.1 Hz, Ph–C-3), 123.85/123.75 (2q, J(C,F) = 274.4 Hz, CF_3), 78.20 (q, J(C,F) = 0.9 Hz, CHOH), 75.78/75.66 (O–*C*H_2CH(CH_3)$_2$(diast.)), 74.98/74.13 (2q(diast.), J(C,F) = 2.3 Hz/1.9 Hz, OCHPh), 73.06/72.64 (OCHPh(diast.)), 28.05 (d, O–CH_2–*C*H-(CH_3)$_2$), 18.79/18.70 (2q, O–CH_2–CH(*C*H_3)$_2$); $M =$ 574.52. Anal. Calcd for $C_{31}H_{26}F_6O_4 \cdot 1.1H_2O$: C, 62.65; H, 4.44. Found: C, 62.61; H, 4.76).

4.36. Hydroxyphenylacetic acid, (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-bis-(2-methoxyphenyl)-ethyl ester 9e

The synthesis was carried out as described above (see Section 4.32) using ester **8e** (0.107 g, 0.230 mmol). Crude **9e** (0.167 g) was isolated as a yellow oil and used for the following saponification without further purification due to the poor stability of the product. (^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.38–5.94 (m, 13H, with 6.46 (d, $J = 3.4$ Hz, 1H, OCHPh), Ph–H), 5.20/5.07 (2s(diast.), 1H, C*H*–OH), 5.13/5.00 (2d(diast.), $J = 3.4$/3.8 Hz, 1H, OCHPh), 3.55–3.22 (m, 13H, incl. 3.52/3.30/3.28 (3s, 9H, OCH_3), OCH_2CH_2O)).

4.37. Reduction of ester 8a under addition of $ZnCl_2$

A solution of ester **8a** (0.100 g, 0.216 mmol) together with a 1 M $ZnCl_2$-solution in Et_2O (0.43 mL, 0.43 mmol) was stirred at −78 °C under a nitrogen atmosphere for 10 min. A 1 M solution of L-Selectride® in THF (0.24 mL, 0.24 mmol) was added dropwise and the resulting mixture stirred for 1 h at −78 °C. After TLC analysis had indicated total conversion, the reaction was allowed to reach −30 °C and quenched by the addition of 2 M NaOH (3 mL) and H_2O_2-solution (30%) (3 mL). The mixture was 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. After chromatography (PE/E 20:1 → E), pure **9a** (0.079 g, 79%) was obtained.

4.38. General procedure for the saponification of esters 9a–e

A solution of esters **9a**–**e** (50–150 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 evaporated carefully (bath temperature max 40 °C). The aqueous remaining was extracted three times with ether. For recovery of auxiliaries **6a**–**e**, the combined ether extracts were washed with brine, dried over Na_2SO_4, filtered, evaporated, and the residue was purified by vacuum flash chromatography when necessary. Thereby all auxiliaries **6a**–**e** could be recovered almost quantitatively without the loss of any enantiomeric purity. The combined aqueous phases were carefully acidified with concd HCl 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 mandelic acid **10** (77–92% yield, white solid). All $[\alpha]_D^{20}$ values were (+) assigning the absolute configurations to be (*S*).[19] ^{1}H NMR (200 MHz, acetone-d_6, TMS) δ 7.40–7.16 (m, 5H, Ph–H), 5.08 (s, 1H, Ph–C*H*-(OH)-COOH), 4.71 (s, 1H, OH).

4.39. Derivatization of mandelic acids 10 and diastereoisomeric HPLC analysis of L-valine methyl ester derivatives 11[9]

To a solution of mandelic acid **10** (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 cooled to −30 °C. A solution of DIC (10–30 mg) in dry dichloromethane (~1 mL) was added and stirring continued for 1 h at −30 °C and then overnight at ambient temperature. Finally, the reaction mixture was diluted with dichloromethane, filtered, washed successively with 10% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and evaporated. For the removal of diisopropyl urea, the crude product was dissolved in ~1 mL of acetone, cooled for 10 min on an ice bath, filtered, and evaporated. The crude product was used for diastereoisomeric HPLC analysis without further purification.

Nucleosil 120 S C18; 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*].

4.40. Reactions on solid support

4.40.1. Chlorination of hydroxymethylated Wang-resin.[10] Hydroxymethylated Wang-resin (4.90 g, 3.14 mmol) was suspended in dry DMF (60 mL) and cooled to −10 °C. Diisopropylethylamine (5.5 mL, 31.6 mmol) and methanesulfonyl chloride (2.4 mL, 31.6 mmol) were added successively while maintaining the temperature below −10 °C and the resulting mixture was stirred for four 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 repeated once to assert quantitative chlorination.

4.984 g of colorless resin. 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.

4.40.2. Immobilization of auxiliary precursor 5a on the solid support 6g. A solution of alcohol **5a** (1.099 g, 4.39 mmol) in dry DMF (25 mL) was added to a suspension of NaH (60%) (0.167 g, 4.17 mmol) in dry DMF (5 mL) and the mixture shaken for 15 min at rt. Then chloromethylated Wang-resin (1.099 g, 0.695 mmol) and a catalytic amount of NaI were added in one portion and the resulting suspension was shaken for 18 h at rt. Unreacted NaH was carefully hydrolyzed 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.

1.339 g of colorless resin (mass increase: 0.241 g ≈ yield 83%). IR ν (KBr) = 693 cm^{-1} (C–Cl: shoulder vanished); no further changes.

For the recovery of excess auxiliary precursor **5a**, the combined filtrates were diluted with brine. Dichloromethane and methanol were evaporated and the aqueous remaining extracted three times with ether. The combined ether 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 (PE/E 10:1 → E). 1.55 g (91%) of colorless oil was obtained, which was re-introduced in another auxiliary immobilization step without any loss of stereoisomeric purity.

The immobilization step was carried out as described above, but in this case using 5.2 equiv of **5a** (2.95 g, 6.52 mmol) and 14.4 equiv of NaH (0.438 g, 18.25 mmol) for 2.00 g of chlorinated Wang-resin (1.26 mmol) and the deprotonation time was increased up to 72 h. The recovery of the auxiliary precursor followed by chromatographic purification (PE/E 10:1 → E) resulted in 1.01 g (42%) of precursor **5a** and 0.66 g (27%) of 2,2′-[methylenebis(oxy)]-bis-[2-((2*S*-(2α(1*S**,2*R**),3aα,4β,7β,7aα))-1,2-bis-(2-methoxyphenyl)-ethoxy)-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran] **12** as a colorless oil ($[\alpha]_D^{20} = -95.5$ (*c* 1.04, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.19–7.02 (m, 8H, Ph–H), 6.87–6.57 (m, 8H, Ph–H), 5.55/5.35 (2d, $J = 4.1$ Hz/3.9 Hz, 4H, OCHPh), 4.94 (d, $J = 4.5$ Hz, 2H, OCHO), 4.74 (s, 2H, OCH_2O), 3.72 (d, $J = 7.2$ Hz, 2H, 7a′-H), 3.53/3.44 (2s, 12H, OCH_3), 2.32–0.80 (m, 34H, aliph., with 0.99/0.93/0.80 (3s, 18H, CH_3)); ^{13}C NMR ($CDCl_3$) δ 157.89/157.30 (2s, Ph–C-2), 129.18/129.79/127.60/127.30/119.65/119.39/109.76/109.23 (8d, Ph–C), 127.93/127.73 (2s, Ph–C-1), 101.45 (d, OCHO), 92.43 (t, OCH_2O), 90.41 (d, C-7a), 73.43/71.18 (2d, OCHPh), 55.21/54.99 (2q, OCH_3), 48.37 (d, C-4), 47.30 (s, C-7), 47.03 (s, C-8), 46.05 (d, C-3a), 38.56 (t, C-3), 32.46 (t, C-6), 29.02 (t, C-5), 22.95/20.66/11.79 (3q, C-9, C-10, C-11); $M =$ 917.20. Anal. Calcd for $C_{57}H_{72}O_{10}\cdot 1.2H_2O$: C, 72.92; H, 7.99. Found: C, 72.98; H, 7.86).

The chiral auxiliary was cleaved by dissolving **12** (0.171 g, 0.19 mmol) together with *p*-toluenesulfonic acid monohydrate (0.02 g, 0.10 mmol) in methanol/CH_2Cl_2 (1:1) (10 mL) and stirring the resulting mixture for 2 h at rt. Saturated $NaHCO_3$-solution (4 mL) was added, MeOH was

removed under reduced pressure, and the residue was diluted with water and extracted with CH_2Cl_2. The extracts were washed with brine, dried over Na_2SO_4, and evaporated to dryness yielding after recrystallization from CH_2Cl_2 0.088 g (85%) of (4*S*)-(4*R**,5*R**,7*R**,8*R**)- or (4*S*)-(4*R**,5*S**,7*S**,8*R**)-4,5,7,8-tetra(2-methoxyphenyl)-[1,3,6]-trioxocan **20** as a colorless solid ($F_p = 143$–145 °C; $[\alpha]_D^{20} = +58.1$ (*c* 1.10, acetone); ^{1}H NMR ($CDCl_3$) δ 7.11–6.94 (m, 8H, Ph–H), 6.77–6.58 (m, 8H, Ph–H), 5.64/5.54 (2d, $J = 3.5$ Hz, 4H, OCHPh), 4.55 (s, 2H, OCH_2O), 3.56/3.40 (2s, 12H, OCH_3); ^{13}C NMR ($CDCl_3$) δ 157.84/157.17 (2s, Ph–C-2), 128.80/128.71/128.29/128.22/120.30/109.96/109.91 (7d, Ph–C), 126.15 (s, Ph–C-1), 92.09 (t, OCH_2O), 75.18/71.40 (2d, OCHPh), 55.56/55.41 (2q, OCH_3); $M = 542.63$. Anal. Calcd for $C_{33}H_{34}O_7 \cdot 1.0H_2O$: C, 70.70; H, 6.47. Found: C, 70.62; H, 6.84).

4.40.3. Immobilization of auxiliary precursor 6f on the solid support 6h. The synthesis was carried out as described above (see Section 4.40.2) using auxiliary precursor **6f** (1.793 g, 3.61 mmol), NaH (60%) (0.14 g, 4.17 mmol), and chlorinated Wang-resin (1.045 g, 0.700 mmol). This gave 1.287 g of a colorless resin (mass increase: 0.242 g ≈ yield 75%). IR ν (KBr) = 693 cm^{-1} (C–Cl: shoulder vanished); no further changes. 1.40 g (92%) of excess auxiliary precursor **6f** was recovered in analogy to Section 4.40.2.

4.40.4. Typical procedure for the deactivation of unreacted chloromethyl groups in resins 6g and 6h (6g′/6h′). A mixture of resin **6g** (1.206 g) and NaI (0.752 g, 5.02 mmol) in dry acetone (10 mL) was refluxed for 48 h. After cooling to rt, 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 vacuo for 12 h at 40 °C. The resin was then suspended in dry THF (10 mL), Bu_3SnH (0.39 mL, 1.49 mmol) was added and the mixture was refluxed for 48 h. After cooling to rt, 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. 1.143 g of colorless resin.

4.40.5. Typical procedure for the deprotection of auxiliary precursors 6g/6g′/6h/6h′. Dry methanol (2.0 mL) and triphenylphosphine hydrobromide (0.209 g, 0.61 mmol) were added to a suspension of resin **6g′** (1.065 g, 0.554 mmol) in dry dichloromethane (10 mL) and the mixture was shaken for 48 h at rt. 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. 0.975 g of pale yellow resin (mass decrease: 0.090 g ≈ 94%). IR ν (KBr) = 3566 cm^{-1} (O–H); no further changes.

4.40.6. Typical procedure for the esterification of auxiliaries 7g/7g′/7h/7h′ (8g–h′). DIC (0.517 g, 4.1 mmol) was added dropwise to a mixture of resin **7h′** (0.714 g, 0.41 mmol), benzoylformic acid (0.616 g, 4.1 mmol), and DMAP (0.050 g, 0.41 mmol) 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 rt. The resin was filtered off and thoroughly washed successively with dichloromethane, methanol, dichloromethane, methanol, dichloromethane, methanol, and dried in vacuo overnight at 40 °C. 0.755 g of pale yellow resin (mass increase: 0.041 g ≈ 76%). IR ν (KBr) = 3570 cm^{-1} (OH: vanished), 1742 cm^{-1} (COOR), 1690 cm^{-1} (CO); no further changes.

4.40.7. Typical procedure for the stereoselective reduction of keto esters 8g–h′ (9g–h′). A suspension of resin **8h′** (0.697 g, 0.31 mmol, determined gravimetrically from the mass increase during the esterification) in dry THF (10 mL) was cooled to −78 °C and stirred for 15 min at this temperature. The L-Selectride® (0.34 mL, 0.34 mmol) was then slowly added and stirring was continued for 2 h at −78 °C. After complete conversion had been detected by IR spectroscopy (otherwise another 0.1 equiv of L-Selectride® was added and stirring was continued for 30 min at −78 °C), the reaction mixture was allowed to warm to 0 °C. 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. 0.703 g of pale yellow resin. IR ν (KBr) = 3524 cm^{-1}(OH), 1737 cm^{-1} (COOR), 1690 cm^{-1} (CO: vanished); no further changes.

4.40.8. Typical procedure for the saponification of hydroxy esters 9g–h′ (7g–7h′). A mixture of resin **9h′** (0.679 g, 0.35 mmol) and LiOH (0.025 g, 1.05 mmol) in THF/methanol/water (10/4/1) (10 mL) was shaken for 2 h at rt. 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.

0.649 g of pale yellow resin. IR ν (KBr) = 3567 cm^{-1}(OH), 1737 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, evaporated, and dried in high vacuo yielding mandelic acid **10** (0.029 g, 71%), which was dried in high vacuo and introduced directly in the derivatization step for enantiomeric analysis (vide supra).

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