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Chiral linker 5: scope and limitations of arylsubstituted *m*-hydrobenzoins as solid supported open chain chiral auxiliaries for diastereoselective syntheses

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ABSTRACT

The applicability of five aryl substituted *m*-hydrobenzoin ethers already tested in the L-Selectride® mediated stereoselective reduction of phenylglyoxylates as open chain chiral auxiliaries was further investigated via the α-alkylation of propionates, the addition of *n*-BuZnCl to phenylglyoxylates and the Diels–Alder reaction of acrylates with cyclopentadiene as model reactions. As up to 90% de could be achieved in the solution phase, two optimized auxiliary structures were immobilized on commercially available Wang-resin and applied as a reusable solid supported chiral auxiliaries in the same type of reactions.

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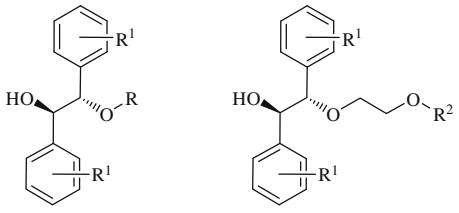
1. Introduction

In previous articles[1] we have already presented the synthesis of *m*-hydrobenzoin derived chiral auxiliaries **I** and **II** and their application either in solution phase chemistry or, after immobilization on solid support, as a chiral linker[2] for diastereoselective reactions on solid support.



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= H, 2-CH_3, 2-CF_3, 2-OCH_3, 4-OCH_3
R^2= CH_3, Wang-resin

The structures could be easily obtained starting from the corresponding *m*-hydrobenzoins, which were in the case of the aryl substituted derivatives, accessible via benzoin condensation of the substituted benzaldehydes or via TMS-protected cyanohydrins as an alternative strategy.[1d] The following synthetic pathway included the desymmetrization of the *m*-hydrobenzoins with commercially available NOE's anhydrolactol,[3] derivatization to build up the appropriate ether moieties or immobilization on solid support and subsequent cleavage of the chiral protecting group.[1]

During the primary investigations on the potential of the auxiliaries without aryl substituents to induce stereoselectivities in different model reactions, selectivities of up to 91% de (and 84% de for the solid bound auxiliary) in the L-Selectride® mediated reduction of α-keto esters[1b,c] and 36% de (or 28% de on solid support) in the α-alkylation of the corresponding propionates[1a] could be obtained. Apart from that it could be shown that after cleavage of the desired products, the solid bound auxiliaries could be reused at least three times without the loss of the stereoinducing ability,[1a,c] which is a benefit compared to other known chiral linkers, for example, those based on Evans oxazolidinones.[4] Finally solid bound *m*-hydrobenzoin, used as a chiral linker, was applied in the addition of *n*-BuZnCl to an α-ketoester as the stereoselective key step during the synthesis of frontalin.[1e]

Further investigations showed that the steric, electronic and coordinative properties of the auxiliaries could be easily varied not only via the ether moiety and the sublinking unit of the solid bound auxiliaries, but also to a large extent via the aryl substituents of the *m*-hydrobenzoin structure itself. Both a methoxyethyl ether moiety or an ethyleneglycol sublinking unit in the case of the solid phase experiments[1c] and *o*-methoxy substituents on the aryl moieties of the hydrobenzoin[1d] proved to have a positive impact on the stereoselectivities achievable in the L-Selectride® mediated reduction of α-keto esters.

However, as the aryl substituted structures have so far only been tested in one model reaction, the following experiments

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should determine their applicability in different stereoselective reactions such as the alkylation of propionates, the addition of Zn-organyls to phenyl glyoxylates and Diels–Alder reactions on acrylates. The results of these recent investigations will be presented herein.

2. Results and discussion

2.1. Evaluation of auxiliaries via model reactions in solution phase

As mentioned above, a set of arylsubstituted *m*-hydrobenzoins, as in the previous investigations including 2,2′-dimethyl, 2,2′-bistrifluoromethyl, 2,2′-dimethoxy and 4,4′-dimethoxy-*m*-hydrobenzoin, was accessible via benzoin-condensation[5] of the corresponding benzaldehydes or in case of the 2-trifluoromethyl- and 4-methoxysubstituted derivatives via an alternative route involving the corresponding TMS-protected cyanohydrins (Scheme 1).[6]

For the preliminary experiments in solution the corresponding *i*-butyl ethers bearing a sterically demanding moiety, as well as the methoxyethyl ether supplying further coordination sites, were chosen as appropriate test systems. These were, as already described,[1d] easily accessible via the selective protection of the (*R*)-carbon centre of the substituted *meso*-hydrobenzoins using *exo*-anhydrolactol **4** followed by etherification using NaH and 4-toluenesulfonic acid *i*-butyl esters **6a**–**6d** or via an alternative three-step procedure **6e** and cleavage of the chiral protecting group (Scheme 2).

As the α-alkylation of esters and amides is a reaction type that has been applied to a large variety of chiral auxiliaries in solution,[7] as well as enantiomerically pure linkers on the solid phase,[4a,4b,8] the α-benzylation of propanoic acid esters was chosen as the first alternative model reaction besides the already described L-Selectride® mediated reduction of phenyl glyoxylates. The results of the preliminary experiments using *m*-hydrobenzoin as a chiral linker for solid phase and using *m*-hydrobenzoin benzyl ether as a chiral auxiliary for the model reactions in solution have already been reported.[1a] It seemed obvious to apply this model reaction to the aryl substituted systems as well.

The auxiliary structures were esterified with propanoic acid according to the established procedure[1a] using DIC and catalytic amounts of DMAP to provide the desired test systems for the model reactions in solution. As during the preliminary investigations, the alkylation was carried out using LDA, as well as a combination of LDA and LiCl as a deprotonation agent followed by the addition of benzyl bromide. Additionally the influence of the electron density at the phenyl substituent of the alkylating agent was investigated using 4-nitrobenzylbromide for the alkylation step. The stereochemical outcome of the reactions was determined via ^{1}H NMR of the crude reaction mixtures as well as after saponification via specific rotation measurements of the acids obtained[8c,9] and HPLC-analysis of derivatives accessible by conversion with L-valine methyl ester (Scheme 3).[10]

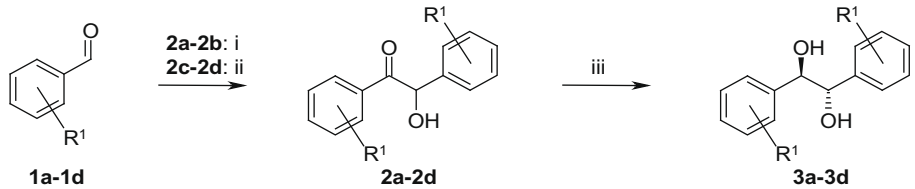
Table 1 shows the results of the diastereoselective alkylations of esters **8a**–**8e** in comparison to selected results of previous investigations already published. Additionally, the coupling constants of the two benzylic hydrobenzoin protons in the substrates **8a**–**8f** are shown as well, following the interpretation model stated in case of the stereoselective reduction of the corresponding phenyl glyoxylates.[1d,11]

As can be seen from Table 1 (entries 1 and 3–5), the application of an electron poor alkylating agent had a not very significant, but negative, effect on the achievable diastereoselectivities, a larger degree of racemization was observed during saponification of the obtained esters **9f**–**9g** due to the necessity for prolonged reaction times and higher reaction temperatures causing the nitro substituted acids **10b** to be obtained in only poor enantiomeric purities. However, especially in the case of the 2-methoxy substituted auxiliaries (see entries 1 and 8), satisfactory diastereomeric ratios were observed; looking at the correlation of de-values and the corresponding coupling constants determined for the benzylic protons of the substrates **8a**–**8e**, an interpretation based on the model proposed by Rosini et al.[11] seems obvious (Scheme 4).

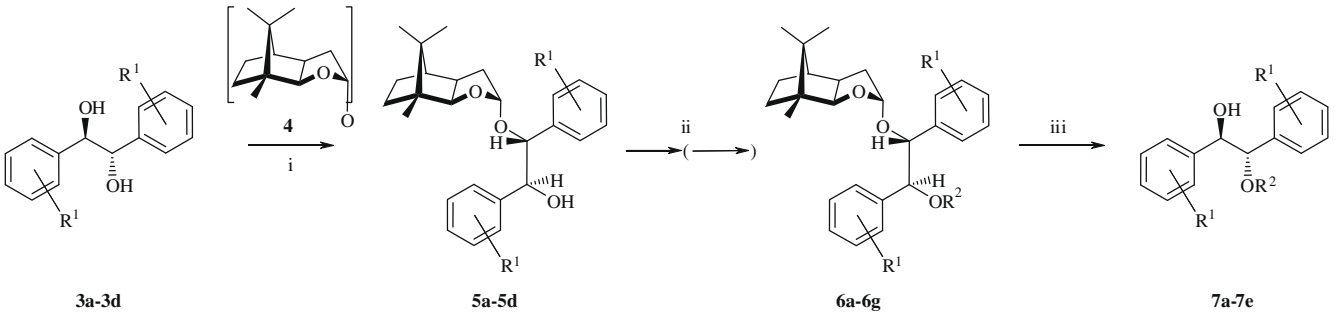
Only in case of the synclinal enolate conformations **A** and **B**, both of which should induce a coupling constant of 2–3 Hz, is an extensive shielding of the enolate by the ether moiety guaranteed. The less desirable conformation **C** should lead to a coupling constant of 10–15 Hz, therefore explaining the low diastereomeric ratios obtained with auxiliaries **8b**–**8d** and **8f**. As the coupling constants had so far only been determined for the **8,** the values of the enolate intermediates would be more useful, further deprotonation experiments with **8a** in THF-d_8 and in situ ^{1}H NMR measurements of the obtained enolates were carried out. However, a set of numerous signals was observed in the expected ppm-range most likely due to the different Li-enolate–diisopropylamine aggregates. Even after additional experiments with different diisopropylamine-concentrations and measurement of CH-correlation spectra, no reliable signal assignment was possible. However, since all relevant signals had coupling constants of 2.7–3.5 Hz which were similar to the observed values for the educt, the conformation of the educt and the intermediate seems to be very similar.

Finally, although no difference in the diastereomeric ratios was observed during the preliminary investigations, a significant enhancement of selectivities could be achieved for the 2-methoxy substituted derivatives **8a** and **8e** by the addition of 6 equiv LiCl before the deprotonation of the substrate (see Table 1, entries 1, 2 and 8–11). According to the literature,[12] this effect could, on the one hand be due to an enhanced polarity of the media and the more effective coordination of the Li-cation to the coordination sites of the substrate. On the other hand changed aggregation degrees of the base as well as the enolate have been published.

To gain further insight into the scope of aryl substituted auxiliaries, the methoxy substituted structures, which had allowed the highest selectivities during the model reactions carried out so

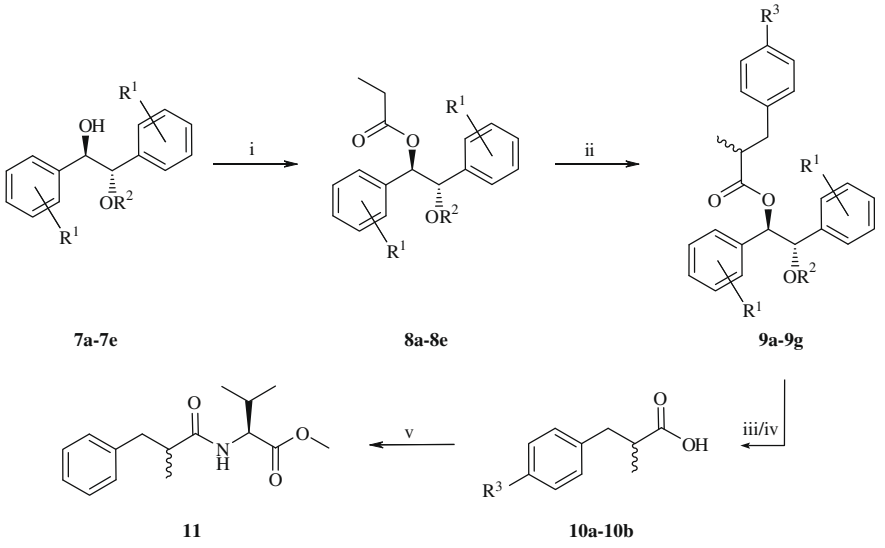


Scheme 1. Synthesis of hydrobenzoin derivatives; R^1 = 2-OCH_3 (**1a**–**3a**), 2-CH_3 (**1b**–**3b**), 4-OCH_3 (**1c**–**3c**), 2-CF_3 (**1d**–**3d**). Reagents and conditions: (i): KCN, EtOH/H_2O, 4 h reflux (**2a**: 50%, **2b**: 31%); (ii) (1) 1.1 equiv TMS-CN, cat. ZnI_2, 1 h 100 °**C**, (2) 1 equiv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



	R^1	R^2
a	2-OCH_3	$CH_2CH(CH_3)_2$
b	2-CH_3	$CH_2CH(CH_3)_2$
c	4-OCH_3	$CH_2CH(CH_3)_2$
d	2-CF_3	$CH_2CH(CH_3)_2$
e	2-OCH_3	$CH_2CH_2OCH_3$
f	2-OCH_3	CH_2COOt-Bu
g	2-OCH_3	CH_2CH_2OH

Scheme 2. Desymmetrization and etherification of hydrobenzoin derivatives **3a**–**3d**. Reagents and conditions: (i) 4-toluenesulfonic acid, CH_2Cl_2, 12 h rt (**5a**: 70%, **5b**: 63%, **5c**: 83%, **5d**: 57%); (ii) (for **5a**–**5d**): (1) NaH, (2) 4-toluenesulfonic acid *i*-butyl ester, DMF, 12 h rt (**6a**:76%, **6b**: 93%, **6c**: 77%, **6d**: 99%); (ii) (**5a**→**6f**): (1) NaH, (2) bromoacetic acid *t*-butyl ester, HMPT, THF, 12 h rt (72%); (**6f**→**6g**): $LiAlH_4$, Et_2O, 2 h rt (73%); (**6g**→**6e**): (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 alkylation of propionates, cleavage and derivatization; for R^1, R^2 and R^3 (**7a**–**9g**) see Scheme 2 and Table 1, R^3 = H (**10a**), NO_2 (**10b**); Reagents and conditions: (i) propanoic acid, DIC, DMAP, CH_2Cl_2, 12 h rt; (ii) (1) 3 equiv LDA, THF, 90 min −78 °C, (2) 8 equiv BnBr (for **9a**–**9e**) or 8 equiv 4-NO_2BnBr (for **9f**–**9g**), 1 h −78 °C; (iii) (for **9a**–**9e**→**10a**) 10 equiv LiOH, THF/MeOH/H_2O, 1.5 h rt; (iv) (for **9f**–**9g**→**10b**): 10 equiv LiOH, THF/MeOH/H_2O, 48 h rt; (v) L-Val-OMe, HOBt, DIC, CH_2Cl_2, 12 h −30 °C→rt.

far, were tested on additional model applications. As the addition of organometallics to phenylglyoxylic acid esters is a common method for the evaluation of chiral auxiliaries[13] and good results have been achieved with the already tested unsubstituted systems[1e], the addition of organo-Zn following the experiments of Borieau et al.[14] was carried out. Therefore **12a** and **12b** which were already in hand from previous investigations[1d] were converted into the corresponding 2-hydroxy-2-phenylhexanoic acid esters **13** using *n*-BuZnCl generated in situ from *n*-BuMgCl and $ZnCl_2$ at −78 °C in diethyl ether (Scheme 5).

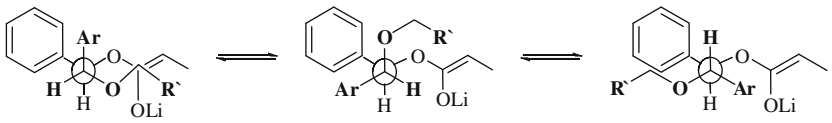
The stereoselectivities achieved were again determined via the ^{1}H NMR of the crude reaction mixtures as well as via HPLC- and NMR-analysis of the derivatives **15** obtained by conversion of the cleaved acids **14** with L-valine methyl ester following an already established procedure. Absolute configurations were assigned after the measurement of the specific rotations of the obtained acids **14**.[14] As Table 2 shows, the stereoselectivity obtained with the unsubstituted hydrobenzoin structure **12c**[1e] bearing coordination sites only at the methoxyethyl ether moiety could, however, not be reached with the methoxysubstituted compounds **12a** and **12b**. A possible explanation could be the competitive coordination of the organo-Zn with the methoxy substituents and the methoxyethyl ether leading to a reduced selectivity in the case of substrate **12e**. However, if coordination is only possible with the methoxy substituents, a better steric shielding of the reacting centre by the sterically demanding *i*-butyl moiety is observed.

Looking closer at the stereochemical outcome of the reaction, a mechanism based on the coordination posted in the literature[13a,14] does not seem very likely, as in case of a *syn*-arrangement of both carbonyl groups as well as in the benzylic α-hydrogen the steric

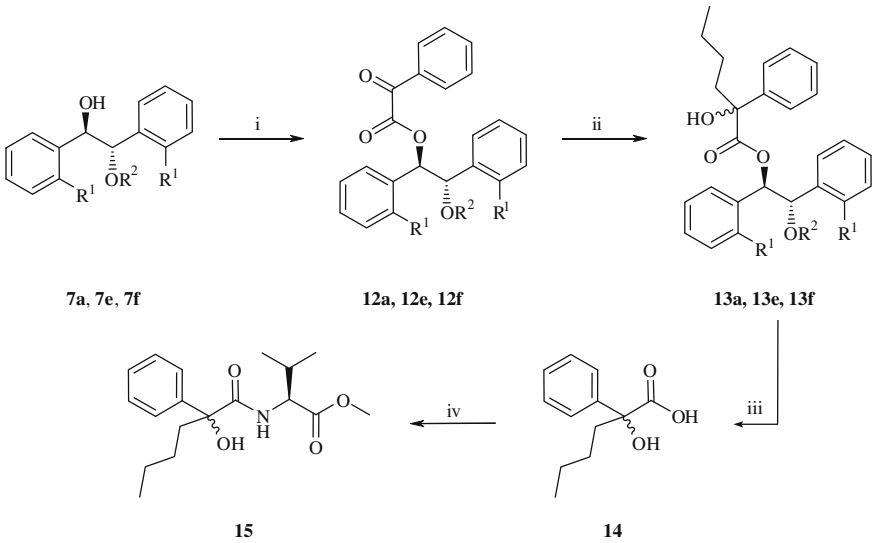
Table 1
Diastereoselective alkylation of propionates **8a**–**8e** compared to results from preceding investigations

Entry	Ester	R^1	R^2	R^3	$^3J_{(benz.)}$ **8** (Hz)	de[a] (*S*,*R*,*S*)-**9** (%)
1	**8a**	2-OCH_3	$CH_2CH(CH_3)_2$	H	3.7	59
2[b]	**8a**	2-OCH_3	$CH_2CH(CH_3)_2$	H	3.7	65
3	**8a**	2-OCH_3	$CH_2CH(CH_3)_2$	NO_2	3.7	57[c]
4	**8b**	2-CH_3	$CH_2CH(CH_3)_2$	H	6.7	44
5	**8b**	2-CH_3	$CH_2CH(CH_3)_2$	NO_2	6.7	30[c]
6	**8c**	4-OCH_3	$CH_2CH(CH_3)_2$	H	6.3	44
7	**8d**	2-CF_3	$CH_2CH(CH_3)_2$	H	7.4	29
8	**8e**	2-OCH_3	$CH_2CH_2OCH_3$	H	3.7	63
9[b]	**8e**	2-OCH_3	$CH_2CH_2OCH_3$	H	3.7	71
10[d]	**8f**	H	CH_2Ph	H	6.8	36
11[b,d]	**8f**	H	CH_2Ph	H	6.8	36

[a] Diastereoisomeric ratios determined by ^1H NMR integration of crude reaction mixtures **9** and HPLC analysis of L-valine methyl ester derivatives **11** of cleaved acids **10a**; absolute configuration of the major diastereoisomers approved by specific rotations of **10**.[9]
[b] 6 equiv of LiCl as additive.
[c] Only 14% ee (for **8a**) and 11% ee (for **8b**), respectively, by specific rotation of **10b** due to racemization during the course of the saponification.
[d] Data from Ref. 1a.



Scheme 4. Conformation analysis based on the model proposed by Rosini et al. [11]



Scheme 5. Application of the test systems on the addition of *n*-BuZnCl to phenylgyloxylates **12a**, **12e** and **12f**, cleavage and derivatization; R^1 = 2-OCH_3 (**7a**–**13a**, **7e**–**13e**), H (**7f**–**13f**); R^2 = $CH_2CH(CH_3)_2$ (**7a**–**13a**), $CH_2CH_2OCH_3$ (**7e**–**13e**), CH_2Ph (**7f**–**13f**). Reagents and conditions: (i) phenylglyoxylic acid, DIC, DMAP, CH_2Cl_2, 12 h rt; (ii) 8.8 equiv *n*-BuMgCl, 8 equiv $ZnCl_2$, Et_2O, 3 h −78 °C; (iii) 5 equiv LiOH, THF/MeOH/H_2O, 12 h rt; (iv) L-Val-OMe, HOBt, DIC, CH_2Cl_2, 12 h −30 °C→rt.

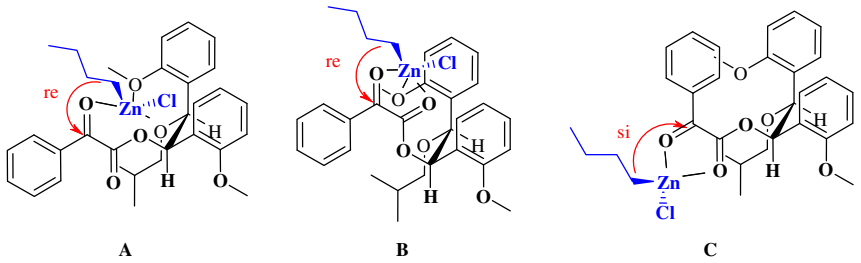
Table 2
Diastereoselective addition of *n*-BuZnCl to phenylglyoxylates **12a** and **12b** compared to the best result from preceding investigations

Entry	Ester	R^1	R^2	de[a] (*S*,*R*,*S*)-**13** (%)
1	**12a**	2-OCH_3	$CH_2CH(CH_3)_2$	90
2	**12e**	2-OCH_3	$CH_2CH_2OCH_3$	87
3[b]	**12f**	H	$CH_2CH_2OCH_3$	94

[a] Diastereoisomeric ratios determined by ^1H NMR integration on crude reaction mixtures **13** as well as by HPLC- and NMR-analysis of L-valine methyl ester derivatives **15** of cleaved acids **14**; absolute configuration of major diastereoisomers approved by specific rotations of **14**.[14]
[b] Data from Ref. 1e.

interactions would lead to a preferred *si*-attack of the alkyl moiety (see Scheme 6C). However, the substituted (*S*)-mandelates obtained in all reactions have to be formed by a *re*-side attack on the carbonyl, which could be explained either by a *syn*-orientation of the ester carbonyl and the α-hydrogen involving a coordination of the Zn-atom with the reacting carbonyl and two coordination sites of the auxiliary (see Scheme 6A) or via a coordination of the Zn-reagent with the *syn*-oriented carbonyls and one methoxy substituent of the auxiliary (see Scheme 6B).

Finally the stereoinductive properties of the most promising hydrobenzoin auxiliaries in the diastereoselective Diels–Alder reactions were also investigated. As the conversion of acrylates with cyclopentadiene on the one hand provides four diastereomeric norbornene esters allowing simple estimation of both the



Scheme 6. Possible mechanisms for the addition of *n*-BuZnCl to phenylglyoxylate **12a** compared to a mechanism based on a literature proposal.[13a,14]

endo/*exo* and the diastereomeric ratios, via NMR, and on the other hand this model reaction has already been applied to a large variety of auxiliary structures[15] and was chosen as a suitable test system for the applicability of the hydrobenzoin auxiliaries. Therefore the selected auxiliaries were esterified using acrylic acid chloride and NEt_3 in CH_2Cl_2, followed by conversion with cyclopentadiene under Lewis-acidic conditions in CH_2Cl_2.[16] The desired acids were obtained after saponification using LiOH in refluxing DME/H_2O (Scheme 7).[17]

The obtained *endo*/*exo*-selectivities and the enantiomeric purity of the *endo*-products were determined via ^{1}H NMR of the crude reaction mixtures, as well as after saponification via ^{1}H NMR of the obtained acids **18**[18] and GC analysis of the corresponding methyl esters **19**. The absolute configurations of the major products were assigned via the specific rotation of norbornene carboxylic acids **18**.[19]

Table 3 shows that although satisfactory *endo* selectivities were observed in the model reactions, only moderate enantiomeric purities of *endo*-**18** could be obtained even with the most suitable auxiliary **7a**. However, considering Oppolzer's model for the geometry of chiral secondary alcohol acrylates[20] under the influence of Lewis acids, the fact that in almost all experiments the (1*S*,2*S*,4*S*)-acid was isolated as the major product seems surprising.

Assuming the proposed *syn*-orientation of the carbonyl and the hydrogen at the stereogenic centre, the *anti*-directed coordination of the Lewis-acid regarding the ester oxygen and the therefore sterically favoured *s-trans* orientation of the acrylate as depicted in Scheme 8, the steric shielding of the *re*-face should cause an (*R*)-selectivity of the reaction.

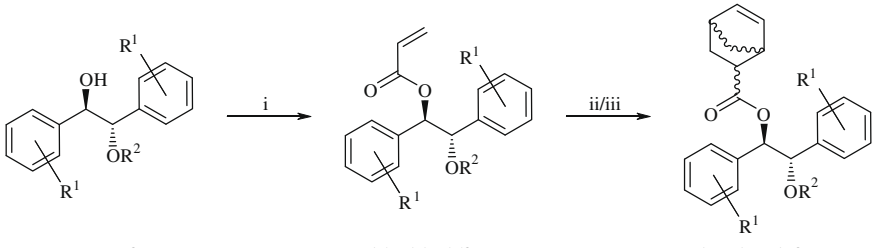
However, when considering the possible coordination of the Lewis acid with the methoxy substituents of the aryl moiety and the *i*-butyl ether–oxygen in **16a** as depicted in Scheme 9, an altered orientation of the carbonyl moiety seems conceivable.

Although the coordination of the Lewis acid with different oxygen atoms of the auxiliary would also be possible, assuming an acrylate geometry according to Oppolzer's model, a changed conformation of the hydrobenzoin structure would prevent possible $\pi\pi^*$-interactions of the aryl moieties of the auxiliary, therefore making this coordination model less likely (see Scheme 10). Similar conditions can be assumed for substrate **16f**. Although coordination of the Lewis acid with electron donors present in the auxiliary structure is possible, in the case of a *syn* orientation of the benzylic proton and the carbonyl moiety (see Scheme 10), the reduced extent of possible $\pi\pi^*$-interactions could favour an altered acrylate geometry in **16f**. On the other hand, as depicted in Scheme 10, in this case neither the ether nor the aryl substituents of the auxiliary would ensure a sufficient shielding of the *si*-face of the double bond. Therefore, the lowered selectivity observed for **16f** (see Table 3, entry 6) seems plausible.

In the case of substrate **16e**, a competition between coordination sites of the aryl substituents and the methoxyethyl ether could be a reason for the lowered selectivities compared to **16a** (see Table 3, entries 2 and 4). However, an obvious reason for the collapse and inversion of selectivity in the reaction of **16f** using Me_2AlCl (see Table 3, entry 5) could not be found.

2.2. Model reactions on solid support

The polymer supported auxiliaries **7h** and **7i** could be obtained by following procedures already described in previous articles[1d] providing conversions of up to 83% of the available active sites of the resin. As preliminary investigations have shown that the



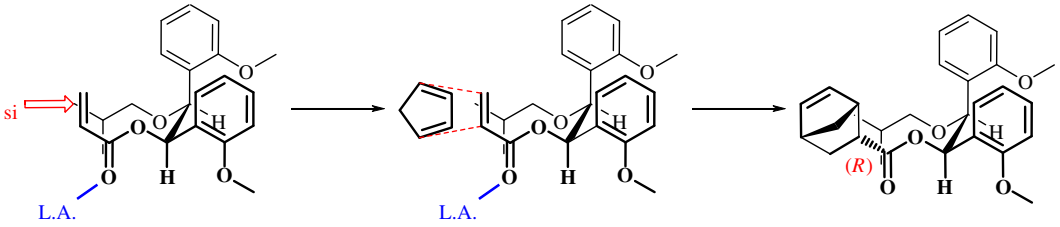
7, 16, 17	R^1	R^2
a	2-OCH_3	*i*-Bu
e	2-OCH_3	$CH_2CH_2OCH_3$
f	H	CH_2Ph

Scheme 7. Application of the test systems on the Diels–Alder reaction of acrylates **16a**, **16e** and **16f** with cyclopentadiene, cleavage and methylation. Reagents and conditions: (i) acrylic acid chloride, NEt_3, CH_2Cl_2, 12 h rt; (ii) 1.05 equiv Me_2AlCl, 10 equiv cyclopentadiene, 2 h −80 °C→−50 °C; (iii) 1.05 equiv $MgBr_2{\cdot}Et_2O$, 10 equiv cyclopentadiene, 2 h −80 °C→−30 °C; (iv) 50 equiv LiOH, DME/H_2O, 12–36 h rt; (v) 0.15 equiv 4toluenesulfonic acid, MeOH, 12 h rt.

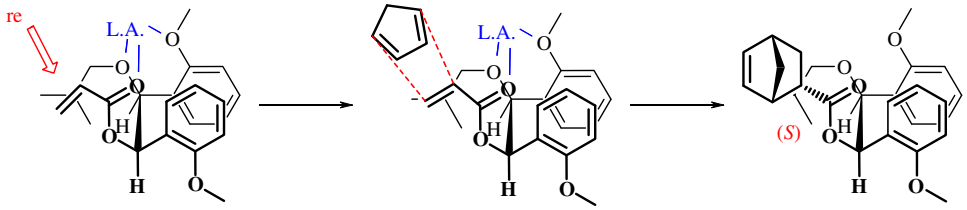
Table 3
Stereochemical outcome of the Diels–Alder reactions with acrylates **16a–16c**

Entry	Ester	R^1	R^2	Lewis-acid	*endo:exo*[a] **18**	ee[a] (1*S*,2*S*,4*S*)-**18** (%)
1	**16a**	2-OCH_3	$CH_2CH(CH_3)_2$	Me_2AlCl	21: 1	40
2[b]	**16a**	2-OCH_3	$CH_2CH(CH_3)_2$	Me_2AlCl	15: 1	42
3	**16a**	2-OCH_3	$CH_2CH(CH_3)_2$	$MgBr_2{\cdot}Et_2O$	9: 1	34
4[b]	**16e**	2-OCH_3	$CH_2CH_2OCH_3$	Me_2AlCl	18: 1	26
5	**16f**	H	$CH_2CH_2OCH_3$	Me_2AlCl	18: 1	6[c]
6	**16f**	H	$CH_2CH_2OCH_3$	$MgBr_2{\cdot}Et_2O$	11: 1	25

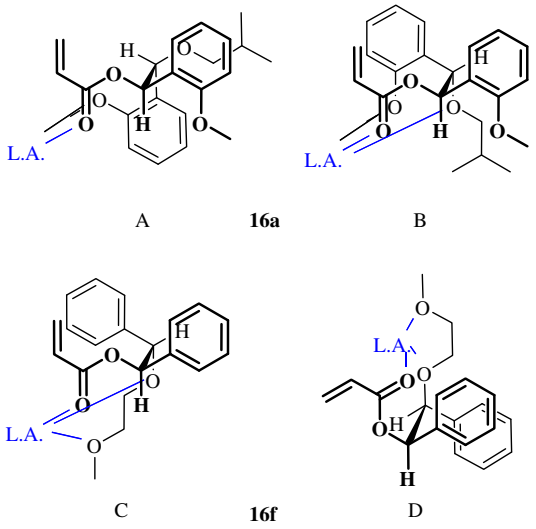
[a] *endo*-Selectivities and enantiomeric excesses were determined by GC analysis of methyl esters **19** and afterwards verified via comparison with values obtained from ^1H NMR integration on crude reaction mixtures **17** as well as acids **18**,[18] absolute configuration of major enantiomers was approved by optical rotations of **18**.[19]
[b] Reaction quenched at −80 °C.
[c] In this case (1*R*,2*R*,4*R*)-**18** was isolated as the major product.



Scheme 8. Selectivity considerations based on the acrylate geometry proposed by Oppolzer.[20]



Scheme 9. Selectivity considerations based on an alternative acrylate geometry.

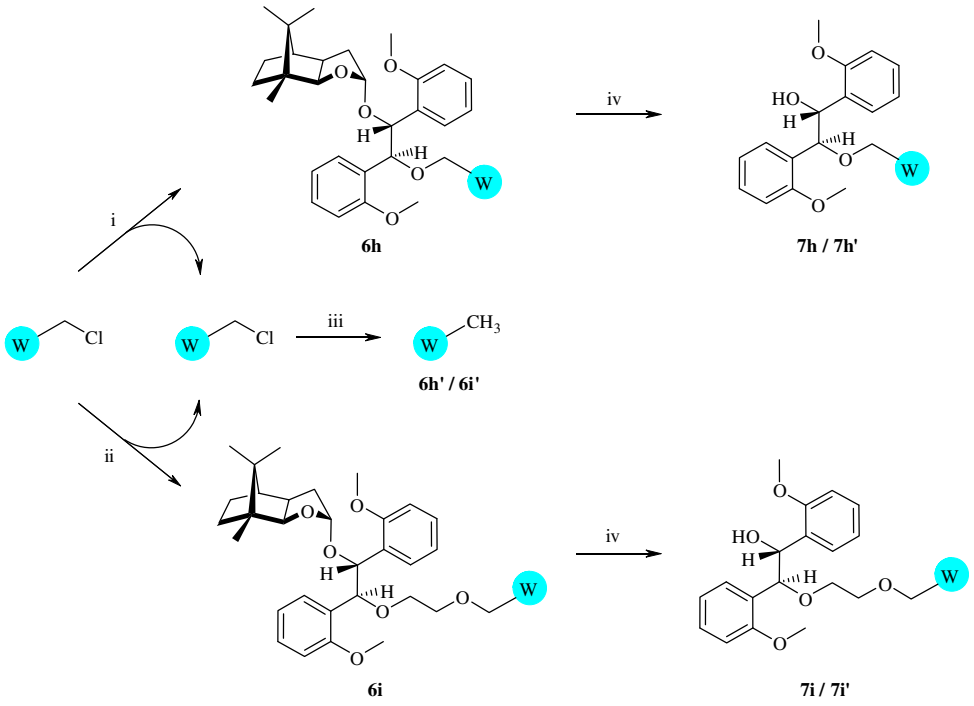


Scheme 10. Possible coordination of Lewis acids and electron donor sites of the auxiliary part in substrates **16a** and **16f**.

residual chloromethyl groups of the resin could cause a decrease in the achievable diastereoselectivities due to the direct attachment of the substrate acids to the resin, the remaining active sites were removed according to the literature procedures[1c,d,21] prior to the cleavage of the chiral protecting group providing **7h′** and **7i′** (Scheme 11).

The immobilization of the substrate acids on the chiral linker was carried out according to procedures similar to the ones used for the experiments in solution phase, in this case using longer reaction times and higher reagent excesses to allow usual conversions of 70–99%. For the benzylation of propionates on solid support, a larger excess of reagents, compared to the model reactions in solution was used as well, followed by cleavage of the chiral product using the usual amount of base, but longer reaction times to allow complete cleavage without loss of enantiomeric purity of the product. After recovery of the resin still carrying the chiral linker, the recyclability of the solid bound auxiliary was investigated via a second substrate attachment, benzylation and product cleavage cycle. The additions of *n*-BuZnCl to solid supported phenylglyoxylates as well as the following saponifications were carried out under almost the same reaction conditions as the model reactions in solution. However, in this case THF instead of Et_2O had to be used as the solvent for the selectivity reactions to ensure sufficient swelling of the resin and as no racemization had to be expected during the basic cleavage of the product, the amount of LiOH as well as the reaction times was increased compared to the reactions in solution phase. Although according to the literature,[4e] the reaction conditions used for the Diels–Alder reactions in solution should lead to the decomposition of the solid support in the case of a Wang resin the same Wang resin supported auxiliary as for the previous model reactions could be applied to the Diels–Alder reactions of acrylate **16h′** with cyclopentadiene. However, the solvent for the following saponification had to be slightly varied to provide sufficient swelling of the resin.

Over the course of previous investigations, all conversions on solid support could be monitored via FT-IR spectroscopy, and the extent of the conversions was in addition estimated gravimetrically. The enantiomeric purity of the products was determined via the same methodology as used for the products obtained from the selectivity experiments in solution. In the case of acids **10a** and



Scheme 11. Synthesis of solid phase test systems: Reagents and conditions: (i) **5a**, NaH, NaI, DMF; (ii) **6g**, NaH, NaI, DMF; (iii) (1) NaI, acetone, (2) *n*-Bu_3SnH, THF; (iv) PPh_3·HBr, MeOH, CH_2Cl_2.

14 via HPLC- and ^{1}H NMR-analysis of the derivatives **11** and **15** obtained after conversion with L-valine methyl ester and for acid **18** via ^{1}H NMR- and GC-analysis of the corresponding methyl ester **19** (Scheme 12).

As can be seen from Table 4, the correlations from the preliminary experiments in solution were confirmed; the advantages of almost complete conversion during the attachment step and deactivation of remaining active sites of the resin have already been presented in previous articles[1c,1d] and were again observed. Thus, a significant enhancement in the selectivities obtained was achieved by the application of immobilized auxiliaries showing a large extent of linker-attachment and not bearing residual chloromethyl moieties (see Table 4, entries 1/2 and 6/7). Furthermore in the case of the benzylation of propionates **8,** the presence of an ethyleneglycol sublinker unit as in **8i** and **9i** as well as the addition of LiCl as an additive could again increase the enantiomeric purity of the obtained products (see Table 4, entries 2/3 and 4/6), and the reapplication of the solid bound chiral auxiliary **7h** obtained from the first substrate attachment-alkylation-product cleavage cycle resulted in no significant change of stereoselective induction providing the chiral product in the same enantiomeric purity as from the first reaction cycle. On the other hand, as already observed during the experiments in the solution phase, additional coordination sites provided by the ethyleneglycol sublinker in substrate **12i**′ resulted in a slight decrease in enantiomeric purity in the α-alkylated α-hydroxy acid **14**. However, although quite similar *endo*/*exo*- and enantioselectivity-results were obtained from the Diels–Alder reactions in solution and on solid phase (see Table 3, entry 2 and Table 4, entry 10) the transfer of the diastereoselective model reactions to solid phase in all cases resulted in a drop in the achievable selectivities. These lowered selectivities were already observed in the L-Selectride® mediated reductions of phenylglyoxylates presented in a preceeding paper[1d] and may be explained by the changed steric environment and the thereby hindered coordinative interactions present in case of the resin bound auxiliaries compared to the surroundings of the *i*-butyl/methoxyethyl ethers **8a**/**8e**, **12a**/**12e** and **16a**/**16e** in solution phase.

3. Conclusion

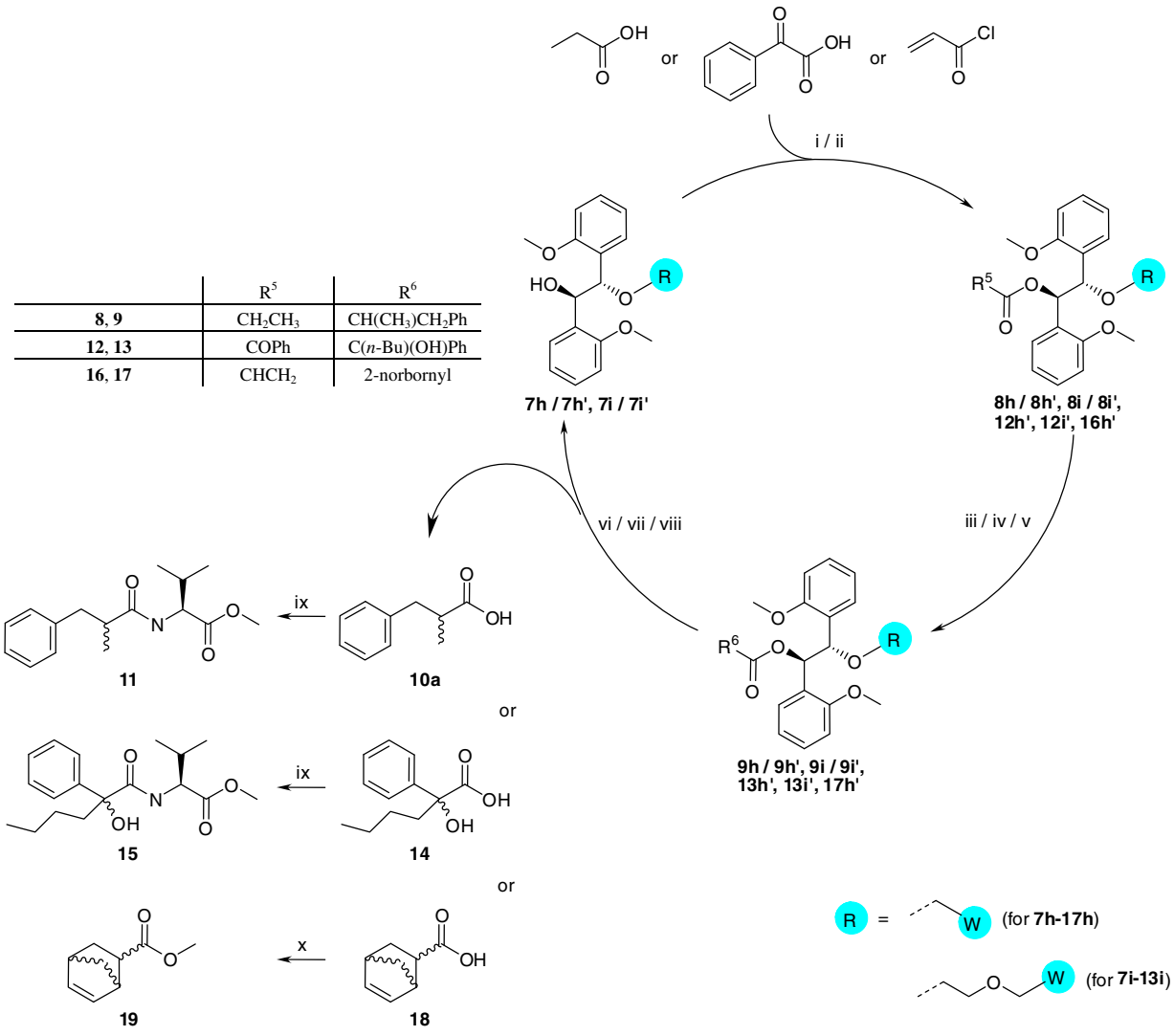
Encouraged by the results from our previous work on the stereoinductive potential of aryl substituted *meso*-hydrobenzoin ethers in the L-Selectride® mediated reduction of the corresponding glyoxylates,[1d] the effects of aryl substituents on the α-alkylation of propionates were investigated. Thereby, after having further outlined the benefits of 2,2′-dimethoxy substituted *meso*-hydrobenzoin ethers, these auxiliaries could be successfully applied to the diastereoselective addition of *n*-BuZnCl to the corresponding phenylglyoxylates as well as Diels–Alder reactions on the corresponding acrylates. After cleavage without the loss of the enantiomeric purity, the desired products were obtained in satisfactory yields and moderate to excellent enantiomeric purity.

Furthermore, the application of the methoxy substituted *meso*-hydrobenzoin auxiliary immobilized on a commercially available Wang resin, either directly or via an ethyleneglycol sublinker unit, even in case of a recyclization of the solid bound chiral auxiliary resulted in similar results as the experiments in solution. Thereby the applicability of the chiral linker on various types of conversions could be proved, and although only moderate selectivities were observed in this case, one of the first examples[22] of a diastereoselective conversion of an acrylate to a norbornenecarboxylic acid on solid support could be carried out.

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 pre-dried over KOH and distilled from Na/benzophenone. Dry dichloromethane was distilled from P_2O_5. Dry petroleum ether and dimethylformamide were dried and



	R^5	R^6
8, **9**	CH_2CH_3	$CH(CH_3)CH_2Ph$
12, **13**	COPh	C(*n*-Bu)(OH)Ph
16, **17**	$CHCH_2$	2-norbornyl

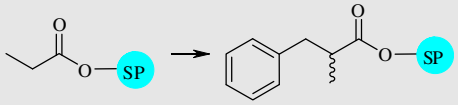
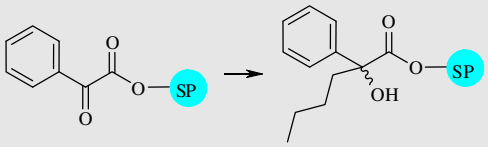
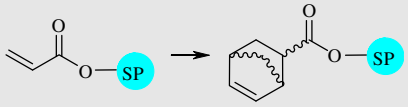
Scheme 12. Application of solid phase test systems: Reagents and conditions: (i) (for **8** and **12**): DIC, DMAP, CH_2Cl_2, 48 h rt; (ii) (for **16**): Et_3N, CH_2Cl_2, 72 h rt; (iii) (for **9**): (1) 5 equiv LDA, THF, 90 min −78 °C, (2) 10 equiv BnBr, 1 h −78 °C; (iv) (for **13**): 8.8 equiv *n*-BuMgCl, 8 equiv $ZnCl_2$, THF, 3 h −78 °C→−30 °C; (v) (for **17h**′): 1.05 equiv Me_2AlCl, 10 equiv cyclopentadiene, 5 h −80 °C then 1 h −50 °C; (vi) (for **9**→**10a**): 10 equiv LiOH, THF/MeOH/H_2O, 4 d rt; (vii) (for **13**→**14**): 10 equiv LiOH, THF/MeOH/H_2O, 24 h rt; (viii) (for **17h**′→18): 40 equiv LiOH, THF/DME/H_2O, 36 h rt; (ix) L-Val-OMe, HOBt, DIC, CH_2Cl_2, 12 h, −30 °C→rt; (x) 0.15 equiv 4-toluenesulfonic acid, MeOH, 12 h rt.

stored over molecular sieve 4 Å. *i*-Pr_2NH was distilled from CaH_2 and stored over molecular sieve 4 Å. Cyclopentadiene was distilled directly before use. 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 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. 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, CH-correlation spectra on a Bruker AC 400 at 400/100 MHz using TMS or the solvent peak as the reference. IR spectra were recorded on a BioRad FTS 135 FT-IR-spectrometer, using KBr disks. HPLC diastereoisomeric analysis of L-valine methyl ester derivatives **11** and **15** of acids **10a** and **14** was carried out with a Shimadzu LC-10AD (Shimadzu SPD-10AV UV–vis detector; Nucleosil 120 S C18; H_2O/MeOH (60/40). Enantiomeric analysis of methylester **19** was carried out via chiral GC on a HP 6890 Series Chromatograph (BGB175 30 m, 0.25 mm ID, 0.25 µm film, FID detector 230 °C, 80 °C→220 °C, carrier He 2 mL/min). Elemental analysis was carried out at Vienna University, Department of Physicochemistry—Laboratory for Microanalysis, Waehringer Str. 42, A-1090 Vienna.

4.2. Synthesis of auxiliaries 7a–7e and phenylglyoxylates 12a and 12b

For the synthesis and analytical data of auxiliaries **7a**–**7e** and phenylglyoxylates **12a** and **12b** see Ref. 1d.

Table 4
Results of model reactions on solid support including recyclability experiments

Entry	Model reaction[a]	Ester	Attachment rate[b] (%)	ee[c]
1		**8h→9h**	51	38%
2		**8h′→9h′**	83	49%
3[d]		**8h′→9h′**	83	55%
4		**8i→9i**	78	49%
5[e]		**8i→9i**	78	50%
6[d]		**8i→9i**	78	51%
7[d]		**8i′→9i′**	75	65%
8		**12h′→13h′**	64	62%
9		**12i′→13i′**	75	57%
10		**16h′→17h′**	73	*endo*/*exo*: 13.5:1 ee ((1*S*,2*S*,4*S*)-**18**): 35%

[a] SP = Solid phase.
[b] Extent of conversion during the attachment step.
[c] Enantiomeric excess determined by ^{1}H NMR and HPLC analyses of L-valine methyl ester derivatives **11** and **15** and ^{1}H NMR and GC analyses of acid **18** and methyl ester **19**.
[d] 6 equiv LiCl as additive.
[e] Re-application of recycled resin from entry 4.

4.3. Typical procedure for the esterification of auxiliaries 7a–7e with propanoic acid; propanoic acid (1*R*,2*S*)-1,2-bis(2-methoxyphenyl)-2-(2-methylpropoxy)-ethyl ester 8a

Alcohol **7a** (0.80 g, 2.42 mmol), propanoic acid (0.236 g, 3.19 mmol) and *N*,*N*-dimethyl-4-aminopyridine (DMAP) (0.029 g, 0.24 mmol) were dissolved in dry dichloromethane (12 mL) under a nitrogen atmosphere. *N*,*N*′-Diisopropylcarbodiimide (DIC) (0.403 g, 3.19 mmol) was added slowly and the mixture was stirred for 12 h at rt. The reaction mixture was diluted with dichloromethane, washed successively with $KHSO_4$ 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** (0.84 g, 90%) was obtained as a colourless oil {$[\alpha]_D^{20} = +38.9$ (*c* 0.70, CH_2Cl_2)}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.26–6.69 (m, 8H, Ph-H), 6.61/5.18 (2d, *J* = 3.7 Hz, 2H, OCHPh), 3.56/3.55 (2s, 6H, Ph-OC*H*$_3$), 3.21 (d, *J* = 6.4 Hz, 2H, O–C*H*$_2$CH(CH$_3$)$_2$), 2.39 (q, *J* = 7.4 Hz, 2H, OCO–C*H*$_2$CH$_3$), 2.01–1.76 (m, *J* = 6.7 Hz, 1H, OCH$_2$C*H*(CH$_3$)$_2$), 1.16 (t, *J* = 7.5 Hz, 3H, OCO–CH$_2$C*H*$_3$), 0.92/0.91 (2d, *J* = 6.7 Hz, 6H, OCH$_2$CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.0 (O–CO), 157.2/156.6 (Ph-*C*–OCH$_3$), 126.5/125.9 (Ph-C-1), 128.2/128.1/128.0/127.9/119.6/119.5/109.6/109.4 (Ph-C), 76.09/75.65 (O*C*HPh), 70.39 (O*C*H$_2$CH(CH$_3$)$_2$), 55.1/55.0 (Ph-OCH$_3$), 28.6 (O–CH$_2$*C*H(CH$_3$)$_2$), 27.8 (CO–*C*H$_2$CH$_3$), 19.3/19.2 (O–CH$_2$CH(*C*H$_3$)$_2$), 9.0 (CO–CH$_2$*C*H$_3$); *M* = 386.49. Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.47; H, 7.66).

4.4. Propanoic 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 4.3) using **7b** (0.450 g, 1.51 mmol). After chromatography (PE/E 20:1→PE/E 5:1) ester **8b** (0.485 g, 91%) was obtained as colourless crystals {F_p = 47–49 °C; $[\alpha]_D^{20} = +53.3$ (*c* 1.07, CH_2Cl_2)}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.47–7.06 (m, 8H, Ph-H), 6.19/4.84 (2d, *J* = 6.7 Hz, 2H, OCHPh), 3.10/2.90 (2dd, J_1 = 8.8 Hz, J_2 = 6.4 Hz/J_1 = 8.8 Hz, J_2 = 6.2 Hz, 2H, O–C*H*$_2$CH(CH$_3$)$_2$), 2.39/2.25 (2s, 6H, Ph-C*H*$_3$), 2.21 (q, *J* = 7.4 Hz, 2H, OCO–C*H*$_2$CH$_3$), 1.84/1.61 (m, *J* = 6.6 Hz, 1H, OCH$_2$C*H*(CH$_3$)$_2$), 1.01 (t, *J* = 7.6 Hz, 3H, OCO–CH$_2$C*H*$_3$), 0.78/0.78 (2d, *J* = 6.7 Hz, 6H, OCH$_2$CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.9 (O–CO), 136.9/136.8/136.6/136.5 (Ph-C-1, Ph-*C*–CH$_3$), 129.7/129.4/127.4/127.4/127.3/127.1/125.7/125.4 (Ph-C), 80.7/76.0 (O*C*HPh), 73.4 (O*C*H$_2$CH(CH$_3$)$_2$), 28.5 (O–CH$_2$*C*H(CH$_3$)$_2$), 27.5 (CO–*C*H$_2$CH$_3$), 19.1/19.0 (Ph-*C*H$_3$, O–CH$_2$CH(*C*H$_3$)$_2$), 8.7 (CO–CH$_2$*C*H$_3$); *M* = 354.49. Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.67; H, 8.61).

4.5. Propanoic 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 4.3) using **7c** (0.240 g, 0.73 mmol). After chromatography (PE/E 20:1→PE/E 5:1) ester **8c** (0.265 g, 94%) was obtained as a colourless oil {$[\alpha]_D^{20} = +14.4$ (*c* 0.65, CH_2Cl_2)}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.26–6.79 (m, 8H, Ph-H), 5.79/4.40 (2d, *J* = 6.3 Hz, 2H, OCHPh), 3.80/3.79 (2s, 6H, Ph-OCH$_3$), 3.08/2.91 (2dd, J_1 = 8.9 Hz, J_2 = 6.5 Hz, 2H, O–C*H*$_2$CH(CH$_3$)$_2$), 2.20 (q, *J* = 7.5 Hz, 2H, OCO–C*H*$_2$CH$_3$), 1.82–1.63 (m, 1H, O–CH$_2$C*H*(CH$_3$)$_2$), 1.00 (t, *J* = 7.5 Hz, 3H, OCO–CH$_2$C*H*$_3$), 0.76/0.75 (2d, *J* = 6.7 Hz, 6H, O–CH$_2$CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.0 (O–CO), 159.2 (Ph-*C*–OCH$_3$), 130.8/130.0 (Ph-C-1), 129.1/128.9/113.2/113.1 (Ph-C), 83.6/77.4 (O*C*HPh), 76.0 (O–*C*H$_2$–CH(CH$_3$)$_2$), 55.2 (Ph-OCH$_3$), 28.5 (O–CH$_2$–*C*H(CH$_3$)$_2$), 27.8 (CO–*C*H$_2$–CH$_3$), 19.2 (O–CH$_2$–CH(*C*H$_3$)$_2$), 9.0 (CO–CH$_2$–*C*H$_3$); *M* = 386.49. Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.23; H, 7.86).

4.6. Propanoic acid (1*R*,2*S*)-2-(2-methylpropoxy)-1,2-bis[2-(trifluoromethyl)phenyl]ethyl ester 8d

The synthesis was carried out as described above (Section 4.3) using **7d** (0.300 g, 0.74 mmol). After chromatography (PE/E

20:1→PE/E 5:1) ester **8d** (0.335 g, 98%) was obtained as colourless crystals {F_p = 54 °C; $[\alpha]_D^{20} = +13.9$ (*c* 0.70, CH_2Cl_2)}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.73–7.35 (m, 8H, Ph-H), 6.44/4.97 (2d, *J* = 7.4 Hz, 2H, OCHPh), 2.94/2.85 (2dd, J_1 = 8.8 Hz, J_2 = 6.3 Hz, 2H, O–CH_2CH(CH_3)$_2$), 2.13 (q, *J* = 7.5 Hz, 2H, OCO–$CH_2$$CH_3$), 1.71–1.51 (m, 1H, O–$CH_2$$CH$($CH_3$)$_2$), 0.91 (t, *J* = 7.6 Hz, 3H, OCO–$CH_2$$CH_3$), 0.65/0.64 (2d, *J* = 6.8 Hz, 6H, O–CH_2CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 172.2 (O–CO), 138.2/137.4 (q, *J*(C,F) = 1.4 Hz, Ph-C-1), 132.0/131.6 (q, *J*(C,F) = 0.9 Hz, Ph-C-4), 129.5/128.6/128.1/128.1 (Ph-C-5, Ph-C-6), 129.45/129.18 (q, *J*(C,F) = 30.5 Hz, Ph-C-2), 125.7/125.0 (q, *J*(C,F) = 5.8 Hz, Ph-C-3), 124.3/124.1 (2q, *J*(C,F) = 274.1/274.5 Hz, CF_3), 79.0/72.8 (q, *J* = 0.9/2.2 Hz, OCHPh), 75.9 (O–CH_2CH(CH_3)$_2$); 28.2 (O–CH_2–CH(CH_3)$_2$), 27.3 (CO–CH_2–CH_3), 18.9/18.9 (O–CH_2–CH(CH_3)$_2$), 8.7 (CO–CH_2–CH_3); *M* = 462.44. Anal. Calcd for $C_{23}H_{24}F_6O_3$: C, 59.74; H, 5.23; F, 24.65. Found: C, 59.87; H, 5.05; F, 24.83).

4.7. Propanoic 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 4.3) using **7e** (0.200 g, 0.60 mmol). After chromatography (PE/E 20:1→PE/E 5:1) ester **8e** (0.229 g, 98%) was obtained as a colourless oil ($[\alpha]_D^{20} = +17.8$ (*c* 1.00, CH_2Cl_2)};^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.26–6.60 (m, 9H, incl. 6.61 (d, *J* = 3.7 Hz, 1H, OC*H*Ph), Ph-H), 5.22 (d, *J* = 3.7 Hz, 2H, OC*H*Ph), 3.64–3.33 (m, 13H, incl. 3.60/3.47/3.35 (3s, 9H, OCH_3), OCH_2CH_2O), 2.36 (q, *J* = 7.5 Hz, 2H, OCO–$CH_2$$CH_3$), 1.12 (t, *J* = 7.6 Hz, 3H, OCO–$CH_2$$CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.1 (O–*C*O), 157.2/156.6 (Ph-C–OCH_3), 128.4/128.2/128.2/127.7/126.0/125.9/119.8/119.64/109.6/109.4 (Ph-*C*), 75.8/71.8/70.3/68.9 (O*C*HPh, OCH_2CH_2O), 58.9/55.2/54.9 (OCH_3), 27.8 (CO–CH_2–CH_3), 9.0 (CO–CH_2–CH_3); *M* = 388.46. Anal. Calcd for $C_{22}H_{28}O_6$: C, 71.48; H, 7.82. Found: C, 71.23; H, 7.86).

4.8. Typical procedure for the α-alkylation of esters 8a–8e; 2-methyl-3-phenylpropanoic acid (1*R*,2*S*)-1,2-bis(2-methoxyphenyl)-2-(2-methylpropoxy) ethyl ester 9a

Under a nitrogen atmosphere, diisopropylamine (0.052 g, 0.518 mmol) was dissolved in dry THF (0.5 mL), *n*-BuLi (0.205 mL, 0.510 mmol) was slowly added at −30 °C and the reaction mixture was stirred for 30 min at −5 °C. At −70 °C ester **8a** (100 mg, 0.259 mmol) dissolved in THF (2.5 mL) was added and after 90 min benzyl bromide (354 mg, 2.07 mmol) was added dropwise and the mixture was stirred for 1 h at −70 °C. The mixture was allowed to reach rt, stirred for 1 h and quenched with water. The aqueous phase was separated, extracted with ether, and the combined ether phases were washed with $KHSO_4$ solution (5%) and saturated $NaHCO_3$ solution, dried, filtered and evaporated to dryness. After chromatography (PE/E 50:1→E) **9a** (119 mg, 97%) was obtained as a colourless oil (^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.30–6.71 (m, 13H, Ph-H), 6.57 (d, *J* = 3.9 Hz, 1H, Ph-C*H*–OCO), 5.18/5.13 (2d(diast.), *J* = 3.9 Hz, 1H, OC*H*Ph), 3.59/3.58 (2s(diast.), 3H, Ph-OCH_3), 3.55/3.57 (2s(diast.), 3H, Ph-OCH_3), 3.22–3.08 (m, 3H, O–CH_2CH(CH_3)$_2$,CO–C*H*(CH_3)–CH_2Ph), 2.86–2.58 (m, 2H, CO–CH(CH_3)–CH_2Ph), 1.99–1.76 (m, *J* = 6.6 Hz, 1H, OCH_2C*H*(CH_3)$_2$), 1.16/1.13 (2d(diast.), *J* = 6.6 Hz, 3H, CO–CH(C*H*$_3$)–CH_2Ph), 0.92/0.90 (2d(diast.), *J* = 6.7 Hz, 6H, OCH$_2$CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.6 (O–CO), 157.3/156.7 (Ph-*C*–OCH_3), 139.5/139.4 (Ph-C-1(diast.)), 128.9–126.0 (Ph-C), 126.0/126.0 (Ph-C-1), 119.7/119.6/109.6/109.4 (Ph-C) 76.1/75.7 (OCHPh), 70.7/70.7 (OCH$_2$CH(CH_3)$_2$(diast.)), 55.2/55.0 (Ph-OCH_3), 41.6/41.4 (CO–*C*H(CH_3)–CH_2Ph(diast.)), 39.4/39.3 (CO–CH(CH_3)–*C*H$_2$Ph(diast.)), 28.6 (O–CH_2*C*H(CH_3)$_2$), 19.28/19.26 (O–CH_2CH(*C*H$_3$)$_2$), 16.4/16.3 (CO–CH(*C*H$_3$)–CH_2Ph(diast.)); *M* = 476.62. Anal. Calcd for $C_{30}H_{36}O_5$: C, 75.60; H, 7.61. Found: C, 75.62; H, 7.73.

4.9. 2-Methyl-3-phenylpropanoic acid (1*R*,2*S*)-1,2-bis(2-methylphenyl)-2-(2-methylpropoxy)ethyl ester 9b

The synthesis was carried out as described above (Section 4.8) using **8b** (0.100 g, 0.282 mmol). After chromatography (PE/E 50:1→E) **9b** (0.114 g, 99%) was obtained as a yellow oil (^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.45–6.99 (m, 13H, Ph-H), 6.17/6.16 (2d(diast.), *J* = 6.8/6.5 Hz, 1H, Ph-C*H*–OCO), 4.85/4.81 (2d(diast.), *J* = 6.8/6.5 Hz, 1H, Ph-C*H*-O), 3.14–2.82 (m, 3H, O–CH_2CH(CH_3)$_2$, CO–C*H*(CH_3)–CH_2Ph), 2.74–2.47 (m, 2H, CO–CH(CH_3)–CH_2Ph), 2.42 (s, 3H, Ph-CH_3), 2.30/2.26 (2s(diast.), 3H, Ph-CH_3), 1.84–1.65 (m, *J* = 6.6 Hz, 1H, OCH$_2$C*H*(CH_3)$_2$), 1.00/0.98 (2d(diast.), *J* = 6.7 Hz, 3H, CO–CH(C*H*$_3$)–CH_2Ph), 0.79 (d, *J* = 6.7 Hz, 6H, OCH$_2$CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.5/174.4 (O–CO(diast.)), 139.1/139.1 (Ph-C-1(diast.)), 137.0/136.9/136.9/136.7/136.6/136.5/136.4 (Ph-C-1, Ph-*C*–CH_3(diast.)), 129.8–125.4 (Ph-C), 80.8/75.9 (OCHPh), 73.7/73.6 (OCH$_2$CH(CH_3)$_2$(diast.)), 41.4/41.1 (CO–*C*H(CH_3)–CH_2Ph(diast.)), 39.2/39.1 (CO–CH(CH_3)–*C*H$_2$Ph(diast.)), 28.5 (O–CH_2*C*H(CH_3)$_2$), 19.2/19.1 (O–CH_2CH(*C*H$_3$)$_2$), 19.1/19.2 (Ph-CH_3), 16.1/15.9 (CO–CH(*C*H$_3$)–CH_2Ph(diast.)); *M* = 444.62. Anal. Calcd for $C_{30}H_{36}O_3$: C, 81.04; H, 8.16. Found: C, 80.83; H, 8.19.

4.10. 2-Methyl-3-phenylpropanoic acid (1*R*,2*S*)-1,2-bis(4-methoxyphenyl)-2-(2-methylpropoxy)ethyl ester 9c

The synthesis was carried out as described above (Section 4.8) using **8c** (0.100 g, 0.26 mmol). After chromatography (PE/E 50:1→E) **9c** (0.098 g, 79%) was obtained as a yellow oil (^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.24–6.78 (m, 13H, Ph-H), 5.81/4.41 (2d(diast.), *J* = 6.5 Hz, 2H, OCHPh), 3.80 (s, 6H, Ph-OCH_3), 3.14–2.84 (m, 3H, O–CH_2CH(CH_3)$_2$, CO–C*H*(CH_3)–CH_2–Ph), 2.71–2.45 (m, 2H, CH_2–Ph), 1.85–1.65 (m, 1H, O–CH_2C*H*(CH_3)$_2$), 1.00/0.97 (2d(diast.), *J* = 6.8 Hz, 3H, CO–CH(C*H*$_3$)–CH_2–Ph), 0.79/0.78 (2d, *J* = 6.7 Hz, 6H, O–CH_2CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.6/174.5 (CO(-diast.)), 159.2/159.1/159.1 (Ph-*C*-OCH_3(diast.)), 139.3/130.8/130.0/129.9 (Ph-C-1(diast.)), 129.1/129.0/128.9/128.2/126.1/113.3/113.1 (Ph-C), 83.6/77.4 (CH-Ph), 75.9 (O–*C*H$_2$–CH(CH_3)$_2$), 55.1 (Ph-OCH_3), 41.4/41.3 (CO–*C*H(CH_3)–CH_2-Ph(diast.)), 39.3/39.2 (CH_2-Ph(diast.)), 28.5 (O–CH_2–*C*H(CH_3)$_2$), 19.2 (O–CH_2–CH(*C*H$_3$)$_2$), 16.4/16.2 (CO–CH(*C*H$_3$)–CH_2-Ph(diast.)); *M* = 476.62. Anal. Calcd for $C_{30}H_{36}O_5$: C, 75.60; H, 7.61. Found: C, 75.30; H, 7.56.

4.11. 2-Methyl-3-phenylpropanoic acid (1*R*,2*S*)-2-(2-methylpropoxy)-1,2-bis[2-(trifluoromethyl)phenyl]ethyl ester 9d

The synthesis was carried out as described above (Section 4.8) using **8d** (0.100 g, 0.216 mmol). After chromatography (PE/E 50:1→E) **9d** (0.057 g, 48%) was obtained as a colourless oil (^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.76–6.92 (m, 13H, Ph-H), 6.42/6.140 (2d(diast.), *J* = 7.3/7.5 Hz, 1H, Ph-C*H*–OCO), 4.98 (d, *J* = 7.6 Hz, 1H, Ph-C*H*–O), 3.00–2.35 (m, 5H, O–CH_2CH(CH_3)$_2$, CO–C*H*(CH_3)–CH_2Ph, CO–CH(CH_3)–*C*H$_2$Ph), 1.74–1.52 (m, *J* = 6.6 Hz, 1H, OCH$_2$C*H*(CH_3)$_2$), 0.90/0.86 (2d(diast.), *J* = 6.2/6.8 Hz, 3H, CO–CH(C*H*$_3$)–CH_2Ph), 0.65/0.64 (2d(diast.), *J* = 6.8/0.7 Hz, 6H, OCH$_2$CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.9/173.8 (CO(-diast.)), 139.0/138.9 (benzyl.Ph-C-1(diast.)), 138.4/138.2/137.3/137.3 (q, *J*(C,F) = 1.3/0.9/1.4/1.4 Hz, Ph-C-1(diast.)), 132.1/131.7 (Ph-C-4), 129.4/129.3/128.8/128.7/128.5/128.4/128.3/128.29/128.1/128.1/128.0 (benzyl. Ph-C, Ph-C-5, Ph-C-6(diast.)), 129.5/129.4 (q, *J*(C,F) = 29.9/30.1 Hz, Ph-C-2), 125.6/125.0/125.0 (q, *J*(C,F) = 5.6/5.7/5.9 Hz, Ph-C-3(diast.)), 124.3/124.1 (q, *J*(C,F) = 274.4/274.3 Hz, CF_3), 79.1/72.9/72.9 (OCHPh(diast.)), 75.9 (O–CH_2CH(CH_3)$_2$), 41.3/41.0 (CO–*C*H(CH_3)–CH_2-Ph(diast.)), 39.4/38.9 (CH_2-Ph(diast.)), 28.2 (O–CH_2–*C*H(CH_3)$_2$), 18.9/18.8 (O–CH_2–CH(*C*H$_3$)$_2$), 16.1/16.0 (CO–CH(*C*H$_3$)–CH_2-Ph(diast.)); *M* = 552.56. Anal. Calcd for $C_{30}H_{30}F_6O_3$: C, 65.21; H, 5.47. Found: C, 65.04; H, 5.58.

4.12. 2-Methyl-3-phenylpropanoic acid (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-bis(2-methoxyphenyl)ethyl ester 9e

The synthesis was carried out as described above (Section 4.8) using **8e** (0.100 g, 0.257 mmol). After chromatography (PE/E 50:1→E) **9e** (0.109 g, 89%) was obtained as a yellow oil (^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.43–6.67 (m, 13H, Ph-H), 6.57(d, J = 3.9 Hz, 1H, Ph-C*H*–OCO), 5.23/5.18 (2d(diast.), J = 3.9/3.8 Hz, 1H, Ph-C*H*–O), 3.67–2.54 (m, 16H, incl. 3.64/3.47/3.34 (3s, OCH_3), CO–C*H*(CH_3)–CH_2Ph, OCH_2CH_2O, CO–CH(CH_3)–CH_2Ph), 1.13/1.10 (2d(diast.), J = 6.7/6.8 Hz, 3H, CO–CH(C*H*$_3$)–CH_2Ph); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.7 (O–CO), 157.3/157.2/156.8 (Ph-*C*–OCH_3(-diast.)), 139.6/139.5 (Ph-C-1(diast.)), 129.1/129.0/128.6/128.5/128.3/128.3/127.7/127.6/126.1/126.1/126.0/119.9/119.8/119.7/109.7/109.5 (Ph-C(diast.)), 76.0/75.9/−71.8/71.8/70.7/70.6/68.9 (O*C*HPh, OCH_2(diast.)), 59.0/55.4/55.0(OCH_3), 41.6/41.4 (CO–*C*H(CH_3)–CH_2Ph(diast.)), 39.5/39.4 (CO–CH(CH_3)–*C*H_2Ph(diast.)), 16.5/16.4 (CO–CH(*C*H_3)–CH_2Ph(diast.)); M = 478.59. Anal. Calcd for $C_{29}H_{34}O_6$: C, 81.04; H, 8.16. Found: C, 80.83; H, 8.19.

4.13. 2-Methyl-3-(4-nitrophenyl)propanoic acid (1*R*,2*S*)-1,2-bis(2-methoxyphenyl)-2-(2-methylpropoxy)ethyl ester 9f

The synthesis was carried out as described above (Section 4.8) using **8a** (0.100 g, 0.259 mmol) and 4-nitrobenzylbromide (0.447 g, 2.07 mmol) instead of benzylbromide. After chromatography (PE/E 50:1→E) **9f** (0.083 g, 61%) was obtained as a yellow oil (^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.09/8.01 (2d(diast.), J = 8.7 Hz, 2H, C*H*=C-NO_2), 7.31–6.64 (m, 10H, Ph-H), 6.51/6.49 (2d(diast.), J = 4.1 Hz, 1H, Ph-C*H*–OCO), 5.12/5.08 (2d(diast.), J = 4.1 Hz, 1H, Ph-C*H*-O), 3.58/3.52 (2s, 6H, Ph-OCH_3), 3.18–3.02 (m, 3H, O–CH_2CH(CH_3)$_2$, CO–C*H*(CH_3)–CH_2Ph), 2.84–2.71 (m, 2H, CO–CH(CH_3)–C*H*$_2$Ph), 1.93–1.73 (m, J = 6.7 Hz, 1H, OCH_2C*H*(CH_3)$_2$), 1.20/1.15 (2d(diast.), J = 6.6 Hz, 3H, CO–CH(C*H*$_3$)–CH_2Ph), 0.87/0.84 (2d(diast.), J = 6.7 Hz, 6H, OCH_2CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz): 173.8 (O–CO), 157.3/156.6 (Ph-*C*–OCH_3), 147.2/147.1 (Ph-NO_2(C1)(diast.)), 146.5/146.4 (Ph-NO_2(C4) (diast.)), 126.3/125.6 (Ph-C-1), 129.7–123.4 (Ph-C), 119.7/119.5/109.6/109.4 (Ph-C); 76.0/75.5 (O*C*HPh), 71.0/71.0(OCH_2CH(CH_3)$_2$(diast.)), 55.2/54.9 (Ph-OCH_3), 41.4/41.0 (CO–*C*H(CH_3)–CH_2Ph(diast.)), 39.4/39.0 (CO–CH(CH_3)–CH_2Ph(diast.)), 28.6/28.5 (O–CH_2CH(CH_3)$_2$(diast.)), 19.2/19.2 (O–CH_2CH(*C*H_3)$_2$), 16.9/16.6 (CO–CH(*C*H_3)–CH_2Ph(diast.)); M = 521.62. Anal. Calcd for $C_{30}H_{35}NO_7$: C, 69.08; H, 6.76; N, 2.69. Found: C, 68.79; H, 6.82; N, 2.90).

4.14. 2-Methyl-3-(4-nitrophenyl)propanoic acid (1*R*,2*S*)-1,2-bis(2-methylphenyl)-2-(2-methylpropoxy)ethyl ester 9g

The synthesis was carried out as described above (Section 4.8) using **8b** (0.100 g, 0.282 mmol) and 4-nitrobenzylbromide (0.488 g, 2.26 mmol) instead of benzylbromide. After chromatography (PE/E 50:1→E) **9g** (0.082 g, 65%) was obtained as a yellow oil (^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.01/7.93 (2d(diast), J = 8.7 Hz, 2H, C*H*=C–NO_2), 7.34–6.99 (m,10H, Ph-H), 6.09/6.06 (2d(diast), J = 7.0/6.7 Hz, 1H, Ph-C*H*–OCO), 4.76/4.74 (2d(diast), J = 7.0/6.7 Hz, 1H, Ph-C*H*–O), 3.11–2.53 (m, 5H, O–CH_2CH(CH_3)$_2$, CO–C*H*(CH_3)–CH_2Ph, CO–CH(CH_3)–C*H*$_2$Ph), 2.37/2.35 (2s(diast), 3H, Ph-C*H*$_3$), 2.29/2.27 (2s(diast), 3H, Ph-C*H*$_3$), 1.85–1.52 (m, J = 6.7 Hz, 1H, OCH_2C*H*(CH_3)$_2$), 1.00/0.99 (2d(diast), J = 6.7 Hz, 3H, CO–CH(C*H*$_3$)–CH_2Ph), 0.71 (d, J = 6.7 Hz, 6H, OCH_2CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.6/173.5 (O–CO(diast.)), 146.7/146.7 (Ph-NO_2(C1) (diast.)), 146.4 (Ph-NO_2(C4)), 136.9/136.9/136.8/136.6/136.5/136.5/136.4 (Ph-C-1, Ph-*C*-CH_3(diast.)), 129.8–125.4 (Ph-C), 80.8/75.9 (O*C*HPh), 73.9/73.8 (OCH_2CH(CH_3)$_2$(diast.)), 41.3/40.7 (CO-*C*H(CH_3)-CH_2Ph(diast.)), 39.2/38.7 (CO–CH(CH_3)–*C*H_2Ph(diast.)), 28.5/28.4 (O–CH_2*C*H(CH_3)$_2$(diast.)), 19.1 (O–CH_2CH(*C*H_3)$_2$), 19.0 (Ph-CH_3), 16.6/16.3 (CO–CH(*C*H_3)–CH_2Ph(diast.)); M = 489.62. Anal. Calcd for $C_{30}H_{35}NO_5$: C, 73.59; H, 7.20; N, 2.86. Found: C, 74.14; H, 7.51; N, 2.39.

4.15. Typical procedure for the saponification of esters 9a–9g

Ester **9a** (0.092 g, 0.193 mmol) and LiOH (0.046 g, 1.93 mmol) were suspended in THF/H_2O/MeOH 3:3:1 (2.5 mL) and stirred for 12 h at rt. The mixture was concentrated under reduced pressure and the residue was diluted with saturated $NaHCO_3$ solution, washed with ether, acidified with 2 M HCl and extracted several times with ether. The combined extracts were dried, filtered and evaporated to dryness yielding 1-methyl-2-phenylpropanoic acid **10a** (0.026 g, 82%) (^{1}H NMR data according to Ref. 23).

The saponification of esters **9b**–**9e** was carried out following the same procedure yielding 82–97% of acid **10a**.

In the case of esters **9f** and **9g**, the same procedure was used but the reaction was additionally refluxed for 48 h to yield 76–81% of acid **10b** (^{1}H NMR-data according to Ref. 8c).

4.16. Derivatization of acids 10a for HPLC analysis; 3-methyl-2-(2-methyl-3-phenyl-propionylamino)butyric acid methyl ester 11

Acid **10a** (0.022 g, 0.134 mmol), L-valine methyl ester[10] (0.021 g, 0.161 mmol) and 1-hydroxybenzotriazole (0.020 g, 0.148 mmol) were dissolved in dry dichloromethane (1.5 mL) under nitrogen atmosphere. DIC (0.020 g, 0.161 mmol) dissolved in dry dichloromethane (0.5 mL) was added dropwise at −30 °C, the reaction was stirred at −30 °C for 30 min and afterwards for 12 h at rt. The mixture was filtered, diluted with dichloromethane, washed with $KHSO_4$ solution (5%), saturated $NaHCO_3$ solution and brine, dried, filtered and evaporated to dryness. The residue was dissolved in 0.5 mL of acetone, cooled to −10 °C, remaining diisopropylurea was filtered off and the filtrate was evaporated to dryness yielding derivative **11** (0.034 g, 92%) as a colourless oil, which could be used for HPLC-analysis without further purification (HPLC: Supelcosil LC-18; eluents water/methanol (45/55); flow 0.2 mL/min; sample volume 2 μL (c = 4 mg/mL); UV 214 nm, 254 nm. t_{R1} = 29.5 min; t_{R2} = 37.2 min; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.28–7.02 (m, 5H, Ph-H), 5.81(major)/5.77(minor) (2d, J = 9.4 Hz, 1H, NH), 4.44 (major)/4.40(minor) (2dd, J_1 = 6.6 Hz, J_2 = 5.0 Hz, 1H, C*H*–NH), 3.63(minor)/3.60(major) (2s, 3H, OCH_3), 2.97–2.39 (m, 3H, Ph-C*H*$_2$-C*H*), 2.10–1.82 (m, 1H, C*H*(CH_3)$_2$), 1.12 (minor)/1.05(major) (2d, J = 6.7/6.5 Hz, 3H, CH-C*H*$_3$), 0.81/0.78 (major)/0.62/0.60(minor) (4d, J = 6.5/6.9 Hz, 6H, CH(C*H*$_3$)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 175.5(major)/175.2(minor)/172.5(minor)/172.2(major) (CON, COO), 139.6(minor)/139.5(major)/128.9/128.3 (major)/128.3(minor)/126.2(major)/126.2(minor) (Ph-C), 56.7 (minor)/56.7(major) (NH*C*HCO), 52.0(major)/51.9 (minor) (O*C*H$_3$), 43.8(minor)/43.3(major) (*C*HCON), 40.5(minor)/39.9(major) (Ph*C*H$_2$), 31.3(major)/31.0(minor) (NH–*C*H–COO), 18.7(major)/18.5(minor) (*C*H(CH_3)$_2$), 17.7/17.7(major)/17.7/17.6(minor) (CH(*C*H$_3$)$_2$)).

In all other cases, the derivatization was carried out following the same procedure to yield 92–99% of derivative **11**.

4.17. Typical procedure for the addition of *n*-BuZnCl to phenylglyoxylates 12a and 12e; 2-hydroxy-2-phenylhexanoic acid (1*R*,2*S*)-1,2-bis(2-methoxyphenyl)-2-(2-methylpropoxy) ethyl ester 13a

A freshly prepared and titrated[24] solution of *n*-BuMgX in THF (1.92 mL, 1.90 mmol) was slowly added to a thoroughly stirred solution of pre-dried $ZnCl_2$ (0.236 g, 1.73 mmol) in dry ether

(2 mL) while cooling on an ice bath, and stirring was continued for 2 h at 0 °C. The supernatant solution of the prepared *n*-BuZnCl reagent was slowly added, by means of a syringe, over 15 min to a solution of ester **12a** (0.100 g, 0.216 mmol) in dry ether (3 mL) which was pre-cooled to −90 °C and the resulting mixture was stirred for 2 h at −78 °C. A 10% aqueous NH_4Cl solution was added and stirring was continued for 15 min at room temperature. The mixture was taken up with a saturated aqueous NH_4Cl solution and extracted three times with ether. The combined ethereal extracts were successively washed with aqueous NH_4Cl and brine, dried over Na_2SO_4, filtered and evaporated. After chromatography (PE/E 4:1→E) **13a** (99 mg, 88%) was obtained as a yellow oil (^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.57–6.32 (m, 14H, Ph-H, OCHPh), 5.16/5.06 (2d(diast.), J = 4.1/3.7 Hz, 1H, OCHPh), 3.88 (s, 1H, OH), 3.61/3.46 (2s, 6H, Ph-OCH_3), 3.25–3.05 (m, 2H, O–CH_2CH(CH_3)$_2$), 2.36–0.81 (m, 16H, aliph. incl. 0.87 (d, J = 6.7 Hz, 6H, O–CH_2CH(CH_3)$_2$)); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.4 (CO), 157.3/156.7 (Ph-C-2), 141.7/126.1/125.2 (Ph-C-1), 128.5/128.4/128.3/127.9/127.3/127.1/125.9/120.0/119.7/109.7/109.6 (Ph-C), 78.1 (C–OH), 76.2 (CH_2O), 75.5/74.0(OCHPh), 55.3/54.9 (OCH_3), 39.2 ($CH_2CH_2CH_2CH_3$), 28.7 (O–CH_2–CH(CH_3)$_2$), 25.7/23.0 ($CH_2CH_2CH_2CH_3$), 19.4/19.3 (O–CH_2–CH(CH_3)$_2$), 14.0 ($CH_2CH_2CH_2CH_3$); M = 520.67. Anal. Calcd for $C_{32}H_{40}O_6$: C, 73.82; H, 7.74. Found: C, 73.58; H, 7.80).

4.18. 2-Hydroxy-2-phenylhexanoic acid (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-bis(2-methoxyphenyl)ethyl ester 13e

The synthesis was carried out as described above (Section 4.17) using **12e** (0.098 g, 0.211 mmol). After chromatography (PE/E 50:1→E) **13e** (0.093 g, 84%) was obtained as a colourless oil (^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.56–6.21 (m, 14H, Ph-H, OCHPh), 5.14/5.06 (2d(diast.), J = 4.1/3.9 Hz, 1H, OCHPh), 3.84 (br s, 1H, OH), 3.60/3.23 (m, 13H, incl. 3.55/3.33/3.24 (3s, 9H, OCH_3), OCH_2CH_2O), 2.26–1.86 (m, 2H, $CH_2CH_2CH_2CH_3$), 1.42–0.81 (m, 7H, $CH_2CH_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.3 (CO), 157.2/156.6 (Ph-C-2), 141.8/125.6/125.1 (Ph-C-1), 128.6/128.5/128.3/127.9/127.3/127.0/125.9/120.0/119.7/109.7/109.6 (Ph-C), 78.2 (C–OH), 75.7/73.7 (OCHPh), 71.8/68.9 (OCH_2CH_2O), 59.0/55.4/54.9 (OCH_3), 39.2 ($CH_2CH_2CH_2CH_3$), 25.6/22.9 ($CH_2CH_2CH_2CH_3$), 14.0 ($CH_2CH_2CH_2CH_3$)); M = 522.64. Anal. Calcd for $C_{31}H_{38}O_7$: C, 71.24; H, 7.33. Found: C, 71.03; H, 7.57).

4.19. Saponification of 13a and 13e and derivatization of 2-hydroxy-2-phenylhexanoic acid 14

The saponifications of esters **13a** and **13e** as well as the derivatization of acids **14** with L-valine methyl ester were carried out according to Ref. 1e.

4.20. Typical procedure for the synthesis of acrylates 16a, 16e and 16f; propenoic acid (1*R*,2*S*)-1,2-bis(2-methoxyphenyl)-2-(2-methylpropoxy)ethyl ester 16a

Alcohol **7a** (0.250 g, 0.76 mmol) and triethylamine (0.154 g, 1.52 mmol) were dissolved in dry dichloromethane (10 mL) under nitrogen atmosphere, acrylic acid chloride (0.137 g, 1.52 mmol) was slowly added and the mixture was stirred for 12 h at rt. The reaction mixture was diluted with dichloromethane, washed successively with $KHSO_4$ solution (5%), saturated $NaHCO_3$ solution and brine, dried, filtered and evaporated to dryness yielding 0.338 g of crude product, which was purified via chromatography (PE/E 6:1→E). **16a** (0.254 g, 87%) was obtained as colourless crystals {F_p = 53–55 °C; $[\alpha]_D^{20}$ = +58.3 (c 1.17, CH_2Cl_2)}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.16–7.01 (m, 4H, Ph-H), 6.78–6.59 (m, 4H, Ph-H), 6.55/5.10 (2d, J = 3.5 Hz, 2H, OCHPh), 6.34 (dd, J_1 = 17.2 Hz, J_2 = 1.8 Hz, 1H,CH=CH_2), 6.08 (dd, J_1 = 17.2 Hz, J_2 = 10.2 Hz, 1H, CH=CH_2), 5.73 (dd, J_1 = 10.2 Hz, J_2 = 1.8 Hz, 1H, CH=CH_2), 3.46/3.45 (2s, 6H, OCH_3), 3.12 (d, J = 6.3 Hz, 2H, O–CH_2CH(CH_3)$_2$), 1.89–1.69 (m, 1H, O–CH_2CH(CH_3)$_2$), 0.81 (d, J = 6.7 Hz, 6H, O–CH_2CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.0 (O–CO), 157.3/156.7 (Ph-C-2), 130.3 (CH=CH_2), 129.0/128.3/128.3/128.2/128.1/119.8/119.7/109.7/109.5 (Ph-C, CH=CH_2), 126.5/125.8 (Ph-C-1), 76.3 (O–CH_2–CH(CH_3)$_2$), 75.8/70.9 (OCHPh), 55.3/55.1 (OCH_3), 28.7 (O–CH_2–CH(CH_3)$_2$), 19.4/19.3 (O–CH_2–CH(CH_3)$_2$); M = 384.5. Anal. Calcd for $C_{23}H_{28}O_5{\cdot}0.2H_2O$: C, 71.19; H, 7.38. Found: C, 71.26; H, 7.47.

4.21. Propenoic acid (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-bis(2-methoxyphenyl)ethyl ester 16e

The synthesis was carried out as described above (Section 4.20) using **7e** (0.118 g, 0.355 mmol). After chromatography (PE/E 10:1→E) **16e** (0.102 g, 74%) was obtained as a colourless oil {$[\alpha]_D^{20}$ = +40.7 (c 0.95, CH_2Cl_2)}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.18–6.57 (m, 9H, Ph-H, OCHPh), 6.35 (dd, J_1 = 17.3 Hz, J_2 = 1.8 Hz, 1H, CH=CH_2), 6.09 (dd, J_1 = 17.3 Hz, J_2 = 10.3 Hz, 1H, CH=CH_2), 5.74 (dd, J_1 = 10.3 Hz, J_2 = 1.8 Hz, 1H, CH=CH_2), 5.19 (d, J = 3.5 Hz, 1H, OCHPh), 3.58–3.42 (m, 7H, incl. 3.54 (s, 3H, OCH_3), OCH_2CH_2O), 3.39/3.28 (2s, 6H, OCH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.0 (O–CO), 157.2/156.7 (Ph-C-2), 130.4 (CH=CH_2), 129.0/128.5/128.4/128.3/127.7/119.8/119.8/109.7/109.5 (Ph-C, CH=CH_2), 125.9/125.7 (Ph-C-1), 76.0/69.1 (OCH_2CH_2O), 76.0/70.9 (OCHPh), 59.0/55.3/55.0 (OCH_3); M = 386.45. Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.16; H, 6.83.

4.22. Propenoic acid (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-diphenylethyl ester 16f

The synthesis was carried out as described above (Section 4.20) using (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-diphenylethanol **7f**[1c] (0.300 g, 1.10 mmol). After chromatography (PE/E 10:1→E) **16f** (0.234 g, 65%) was obtained as a colourless oil ($[\alpha]_D^{20}$ = +27.2 (c 1.00, CH_2Cl_2)}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.28 (s, 10H, Ph-H), 6.33 (dd, J_1 = 17.2 Hz, J_2 = 1.6 Hz, 1H, CH=CH_2), 6.06 (dd, J_1 = 17.3 Hz, J_2 = 10.3 Hz, 1H, CH=CH_2), 6.02/4.67 (2d, J = 6.1 Hz, 2H, OCH-Ph), 5.78 (dd, J_1 = 10.3 Hz, J_2 = 1.7 Hz, 1H, CH=CH_2), 3.59–3.38 (m, 4H, OCH_2CH_2O), 3.26 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.7 (O–CO), 137.9/137.4 (Ph-C-1), 130.8 (CH=CH_2), 128.4 (CH=CH_2), 128.0/127.9/127.9/127.8/127.7 (Ph-C), 84.4/77.8 (OCHPh), 71.9/68.9 (O–CH_2–CH_2–O), 58.9 (OCH_3); M = 326.40. Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.34; H, 7.09.

4.23. Typical procedure for the Diels–Alder reaction of 16a, 16e and 16f with cyclopentadiene; bicyclo[2.2.1]hept-5-en-2-carboxylic acid (1*R*,2*S*)-1,2-bis(2-methoxyphenyl)-2-(2-methylpropoxy)ethyl ester 17a

To a stirred solution of Me_2AlCl (0.20 mL 1 M solution in THF, 0.202 mmol) or $MgBr_2{\cdot}Et_2O$ (0.035 g, 0.133 mmol) in dry dichloromethane (10 mL) at −80 °C under nitrogen atmosphere **16a** (0.074 g, 0.192 mmol in the case of Me_2AlCl; 0.049 g, 0.127 mmol in case of $MgBr_2{\cdot}Et_2O$) dissolved in dry dichloromethane (7 mL) was added slowly. After 1 min cyclopentadiene (0.127 g, 1.92 mmol or 0.084 g, 1.27 mmol) was added dropwise and the mixture was stirred for 2 h at −80 °C and for 30 min at −50 °C. Afterwards water (3 mL) was added and the mixture was allowed to reach rt. The mixture was extracted several times with dichloromethane, the combined extracts were washed with brine, dried, filtered and evaporated to dryness. After chromatography (PE/E 10:1→E) **17a** (0.062 g, 72% in case of Me_2AlCl; 0.053 g, 93% in case of $MgBr_2{\cdot}Et_2O$) was obtained as a colourless oil (^{1}H NMR ($CDCl_3$,

200 MHz) δ 7.36–6.57 (m, 8H, Ph-H), 6.40/6.37 (2d(diast.), J = 3.7/4.5 Hz, 1H, OCHPh), 6.05/5.99 (2dd(diast.), J_1 = 5.5 Hz, J_2 = 2.9 Hz/J_1 = 5.6 Hz, J_2 = 3.0 Hz, 1H, CH=CH), 5.72/5.66 (2dd(diast.), J_1 = 5.8 Hz, J_2 = 2.6 Hz/J_1 = 5.7 Hz, J_2 = 2.7 Hz, 1H, CH=CH), 5.05/5.03 (2d(diast.), J = 3.5 Hz, 1H, OCHPh), 3.53/3.44 (2s(diast.), 6H, OCH_3), 3.16/2.79 (2br s, 2H, C*H*–CH=CH–C*H*), 3.10/3.07 (2d(diast.), J = 6.5 Hz/6.7 Hz, 2H, $OCH_2CH(CH_3)_2$), 2.98/2.84 (m, 1H, CHCOO), 1.87–0.77 (m, 11H, incl. 0.82/0.79 (2d, J = 5.9 Hz, 6H, $OCH_2CH(CH_3)_2$), $OCH_2CH(CH_3)_2$, CH_2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.5/173.4 (CO(diast.)), 157.5/157.3/156.9/156.7 (Ph-C-2(diast.)), 137.4/132.6/132.5 (CH=CH(diast.)), 128.5/128.4/128.2/.128.1/128.1/127.8/119.9/119.8/119.7/119.5/109.8/109.7/109.6/109.5 (Ph-C(diast.)), 126.9/126.7/126.6/126.1 (Ph-C-1), 76.2 (OCH_2), 75.8/75.7/70.9/70.6 (OCHPh(diast.)), 55.4/55.2/55.1 (OCH_3(diast.)), 49.6/49.5/29.0/28.8 (CH_2(diast.)), 45.8/45.7/43.5/42.6/42.5 (aliph. CH(diast.)), 28.7 ($CH(CH_3)_2$), 19.4 ($CH(CH_3)_2$); M = 450.58. Anal. Calcd for $C_{28}H_{34}O_5 \cdot 0.3H_2O$: C, 73.76; H, 7.65. Found: C, 73.81; H, 7.63.

4.24. Bicyclo[2.2.1]hept-5-en-2-carboxylic acid (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-bis(2-methoxyphenyl)ethyl ester 17e

The synthesis was carried out as described above (Section 4.23) using **16e** (0.082 g, 0.212 mmol). After chromatography (PE/E 10:1→E) **17e** (0.062 g, 65%) was obtained as a colourless oil (^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.32–6.11 (m, 9H, Ph-H, OCHPh), 6.07/5.97 (m, 1H, CH=CH), 5.79/5.62 (m, 1H, CH=CH), 5.13/5.11 (2d(diast.), J = 5.1/3.9 Hz, 1H, OCHPh), 3.60–3.24 (m, 13 H, incl. 3.60/3.52/3.38/3.37/3.28/3.24 (6s/(diast.), 9H, OCH_3), OCH_2CH_2O), 3.16/2.80 (2br s, 2H, C*H*–CH=CH–C*H*), 3.00/2.85 (m, 1H, CHCOO), 1.89–1.14 (m, 4H, 2 × CH_2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.4/173.4 (CO), 157.4/157.2/156.9/156.7 (Ph-C-2(diast.)), 137.4/137.3/132.7/132.4 (CH=CH(diast.)), 128.7/128.6/128.5/128.3/128.2/127.8/127.6/120.0/119.8/119.8/119.6/109.9/109.7/109.6/109.5 (Ph-C(diast.)), 126.5/126.2/126.3/126.01 (Ph-C-1(diast.)), 75.9/75.8/70.7/70.5 (OCHPh(diast.)), 71.9/69.0/68.8 (OCH_2CH_2O(diast.)), 59.0/59.0/55.5/55.3/55.0 (OCH_3(diast.)), 49.6/49.5/29.0/28.8 (CH_2 (diast.)), 45.9/45.7/43.5/42.6/42.5 (aliph. CH(diast.)); M = 452.55. Anal. Calcd for $C_{27}H_{32}O_6 \cdot 0.3H_2O$: C, 70.81; H, 7.18. Found: C, 70.89; H, 7.23).

4.25. Bicyclo[2.2.1]hept-5-en-2-carboxylic acid (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-diphenylethyl ester 17f

The synthesis was carried out as described above (Section 4.23) using **16f** (0.076 g, 0.234 mmol in the case of Me_2AlCl; 0.077, 0.236 mmol in the case of $MgBr_2 \cdot Et_2O$). After chromatography (PE/E 10:1→E) **17f** (0.083 g, 90% in the case of Me_2AlCl; 0.070, 76% in the case of $MgBr_2 \cdot Et_2O$) was obtained as a colourless oil (^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.25–7.19 (m, 10H, Ph-H), 5.97–5.88 (m, 1H, CH=CH), 5.79/5.62 (m, 1H, CH=CH), 5.78/5.75 (2d(diast.), J = 6.9/7.6 Hz, 1H, OCHPh), 5.48/5.13 (2dd(diast.), J_1 = 5.7 Hz, J_2 = 2.7 Hz/J_1 = 5.5 Hz, J_2 = 2.7 Hz, 1H, CH=CH), 4.49 (d, J = 7.0 Hz, 1H, OCHPh), 3.44–3.22 (m, 4H, OCH_2CH_2O), 3.14/3.10 (2s(diast.), 3H, OCH_3), 3.06/2.87 (2br s, 2H, C*H*–CH=CH–C*H*), 2.78–1.07 (m, 5H, aliph.-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 173.2/173.1 (CO), 138.6/138.4/138.2/137.9 (Ph-C-1(diast.)), 137.5/137.4/132.2/132.0 (CH=CH(diast.)), 128.0/127.9/127.8/127.8/127.8/127.7/127.7 (Ph-C(diast.)), 84.6/84.5/77.3/77.3 (OCHPh(diast.)), 71.9/71.8/68.8/68.7 (OCH_2CH_2O(diast.)), 58.9/58.8 (OCH_3(diast.)), 49.6/49.4/29.0/28.6 (CH_2(diast.)), 46.0/45.6/43.3/43.1/42.7 (aliph. CH(diast.)); M = 392.50. Anal. Calcd for $C_{25}H_{28}O_4$: C, 76.50; H, 7.19. Found: C, 76.29; H, 7.26).

4.26. Saponification of esters 17a, 17e and 17f; bicyclo[2.2.1]hept-5-en-2-carboxylic acid 18

Esters **17a**, **17e** and **17f** (0.039–0.066 g, 0.09–0.17 mmol) and LiOH (0.179 g, 7.5 mmol) were suspended in DME/water 1:1 (5 mL) and stirred at reflux for 24 h. DME was evaporated and the residue was diluted with saturated $NaHCO_3$ solution, washed with ether, acidified with concd HCl to pH 2 and extracted several times with ee. The combined extracts were washed with brine, dried, filtered and evaporated to dryness yielding **18** (0.009–0.022 g, 75–97%) as a colourless oil (^{1}H NMR ($CDCl_3$, 200 MHz) according to Ref. 18).

4.27. Typical procedure for the synthesis of bicyclo[2.2.1]hept-5-en-2-carboxylic acid methyl ester 19

Acid **18** (0.018 g, 0.130 mmol) and 4-toluenesulfonic acid (4 mg, 0.02 mmol) were dissolved in methanol and stirred at reflux for 12 h. The mixture was concentrated, diluted with dichloromethane, washed with saturated $NaHCO_3$ solution and brine, dried, filtered and concentrated under reduced pressure (100 mbar) yielding **19** (0.030 g, 150% because of methanol traces) as a colourless liquid which was used directly for GC-analysis (^{1}H NMR ($CDCl_3$, 200 MHz) according to Ref. 25).

4.28. Reactions on solid support

4.28.1. Synthesis of immobilized auxiliaries 7h, 7h′, 7i and 7i′

The synthesis of auxiliaries **7h**, **7h′**, **7i** and **7i′** was carried out following the literature procedures.[1d]

4.28.2. Typical procedure for the esterification of auxiliaries 7h/7h′ and 7i/7i′ with propanoic acid 8h–8i′

At first, DIC (0.655 g, 5.2 mmol) was added dropwise to a mixture of resin **7i′** (0.908 g, 0.52 mmol), propanoic acid (0.385 g, 5.2 mmol) and DMAP (0.064 g, 0.52 mmol) in dry dichloromethane (15 mL) while cooling on an ice bath. The resulting 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. Therefore, 0.929 g of colourless resin **8i′** (mass increase: 0.021 g ≈ 96%) was isolated (IR ν (KBr) = 3570 cm^{-1} (OH: vanished), 1737 cm^{-1} (COOR); no further changes).

4.28.3. Typical procedure for the α-alkylation of propionates 8h–8i′ to 9h–9i′

A mixture of resin **8i′** (0.855 g, 0.38 mmol) and LiCl (0.097 g, 2.3 mmol) in dry THF (15 mL) was cooled to −85 °C and a solution of LDA in THF (5 mL) freshly prepared from BuLi (2.35 M in THF, 0.81 mL, 1.90 mmol) and diisopropylamine (0.202 g, 2.00 mmol) and cooled to −60 °C was added dropwise. The mixture was carefully stirred at −78 °C for 1.5 h, cooled to −90 °C and benzyl bromide (0.650 g, 3.8 mmol) was added. After stirring for 1 h at −78 °C the mixture was allowed to reach rt and quenched with saturated NH_4Cl solution. Then the resin was filtered off and thoroughly washed successively with dichloromethane, methanol, water, methanol, dichloromethane, methanol, dichloromethane, methanol and dried in vacuo overnight at 40 °C. Therefore, 0.888 g of a colourless resin **9i′** was obtained (IR ν (KBr) = 1736 cm^{-1} (COOR); no further changes).

4.28.4. Typical procedure for the saponification of esters 9h–9i′ to 10a

A mixture of resin **9i′** (0.839 g, 0.38 mmol) and LiOH (0.091 g, 3.8 mmol) in THF/methanol/water 10/4/1 (11 mL) was shaken for 96 h. After complete conversion had been indicated by IR spectroscopy, the resin was filtered off and thoroughly washed successively with saturated aqueous $NaHCO_3$, water, water/THF (1/1), methanol, THF, water, methanol, THF, methanol, THF, metanol and dried in vacuo overnight at 40 °C. Therefore, 0.751 g of a colourless resin

7i′ was obtained (IR *ν* (KBr) = 3560 cm^{-1} (OH), ~1736 cm^{-1} (COOR: vanished); no further changes). The recovered resin could be introduced in the next reaction cycle without any further purification.

The combined filtrates were diluted with saturated $NaHCO_3$ solution, and THF and methanol were evaporated. The aqueous that remained was extracted three times with ether, acidified carefully with concd HCl while cooling on an ice bath and then extracted three times with ee. The combined ethyl acetate extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated. Compound **10a** (0.027 g, 49%) was obtained as a yellow oil (^{1}H NMR ($CDCl_3$, 200 MHz) according to Ref. 23). The derivatization of **10a** was carried out according to the procedure described above (Section 4.16).

4.28.5. Synthesis of immobilized phenylglyoxylic acid esters 12h′ and 12i′

The synthesis of esters **12h′** and **12i′** was carried out following the literature procedures.[1d]

4.28.6. Typical procedure for the addition of *n*-BuZnCl to phenylglyoxylates 12h′ and 12i′ to 13h′ and 13i′

A freshly prepared and titrated[24] solution of *n*-BuMgCl (1.0 mL, 1.94 mmol) in THF was slowly added to a thoroughly stirred solution of pre-dried $ZnCl_2$ (0.240 g, 1.76 mmol) in dry THF (2 mL) while cooling on an ice bath, and stirring was continued for 2 h at 0 °C. The solution of thus prepared *n*-BuZnCl was slowly added, by means of a syringe, over 15 min to a suspension of ester **12i′** (0.594 g, 0.22 mmol) in dry THF (10 mL) which was pre-cooled to −90 °C and the resulting mixture was stirred for 1 h at −78 °C. Then the temperature was raised up to −30 °C over a period of 1 h, kept constant at −30 °C for 2 h and finally a 10% aqueous NH_4Cl solution (10 mL) was added and stirring was continued for 15 min at rt. The resin was filtered off and thoroughly washed successively with aqueous NH_4Cl, NH_4Cl/THF (1/1), water, water/THF (1/1), THF, methanol, dichloromethane, methanol, dichloromethane, methanol and dried in vacuo overnight at 40 °C. Therefore, 0.629 g of a colourless resin **13i′** was obtained (IR *ν* (KBr) = 3505 cm^{-1} (OH), 1728 cm^{-1} (COOR), 1690 cm^{-1} (C=O: vanished); no further changes).

4.28.7. Typical procedure for the saponification of esters 13h' and 13i′ to 14

A mixture of resin **13i′** (0.611 g, 0.31 mmol) and LiOH (0.075 g, 3.1 mmol) in THF/methanol/water 10/4/1 (11 mL) was refluxed for 24 h. After complete conversion had been indicated by IR spectroscopy, the resin was filtered off and thoroughly washed successively with saturated aqueous $NaHCO_3$, water, water/THF (1/1), methanol, THF, water, methanol, THF, methanol, THF, methanol and dried in vacuo overnight at 40 °C. Therefore, 0.561 g of a colourless resin **7i′** was obtained (IR *ν* (KBr) = 3567 cm^{-1} (OH), ~1728 cm^{-1} (COOR: vanished); no further changes).

The combined filtrates were diluted with saturated aqueous $NaHCO_3$, and THF and methanol were evaporated. The aqueous that remained was extracted three times with ether, acidified carefully with concd HCl while cooling on an ice bath and then extracted three times with ee. The combined ethyl acetate extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated. Compound **14** (0.039 g, 85%) was obtained as a colourless solid (^{1}H NMR (acetone-d_6, 200 MHz) and derivatized for HPLC-analysis according to Ref. 1e).

4.28.8. Synthesis of immobilized acrylate 16h′

Acrylic acid chloride (0.507 g, 5.6 mmol) was added dropwise to a mixture of resin **7h′** (0.967 g, 0.56 mmol) and Et_3N (0.565 g, 5.6 mmol) in dry dichloromethane (15 mL). The resulting mixture was shaken for 72 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. Therefore, 0.993 g of a colourless resin **16h′** (mass increase: 0.026 g ≈ 86%) was isolated (IR *ν* (KBr) = 3567 cm^{-1} (OH: vanished), 1726 cm^{-1} (COOR); no further changes.)

4.28.9. Diels–Alder reaction of immobilized acrylate 16h′ to 17h′

A suspension of resin **16h′** (0.964 g, 0.49 mmol) in dry dichloromethane (35 mL) was cooled to −100 °C °C and stirred for 15 min at this temperature. Me_2AlCl (1 M solution in THF, 0.51 mL, 0.51 mmol) was added dropwise followed after 1 min by cyclopentadiene (0.40 mL, 4.9 mmol). The mixture was stirred for 5 h at −80 °C and for 1 h at −50 °C and afterwards the resin was filtered off, and thoroughly washed successively with methanol, dichloromethane, methanol, dichloromethane, methanol, dichloromethane, methanol and dried in vacuo overnight at 40 °C. Therefore, 1.00 g of a colourless resin **17h′** was obtained (IR *ν* (KBr) = 3324 cm^{-1} (broad peak 3100–3700 cm^{-1}), 1727 cm^{-1} (COOR); no further changes).

4.28.10. Saponification of ester 17h′ to 18

A mixture of resin **17h′** (0.946 g, 0.51 mmol) and LiOH (0.500 g, 20.8 mmol) in DME/THF/water 1/2/1 (20 mL) was refluxed for 36 h. After complete conversion had been indicated by IR spectroscopy, the resin was filtered off and thoroughly washed successively with saturated aqueous $NaHCO_3$, water, water/THF (1/1), methanol, THF, water, methanol, THF, methanol, THF, methanol and dried in vacuo overnight at 40 °C. Therefore, 0.927 g of a colourless resin **7h′** was isolated (IR *ν* (KBr) = 3567 cm^{-1} (OH), ~1727 cm^{-1} (COOR: vanished); no further changes).

The combined filtrates were diluted with saturated aqueous $NaHCO_3$, and THF and DME were evaporated. The aqueous that remained was extracted three times with ether, acidified carefully with concd HCl while cooling on an ice bath and then extracted three times with ee. The combined ethyl acetate extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated. Compound **18** (0.015 g, 22%) was obtained as a colourless oil (^{1}H NMR ($CDCl_3$, 200 MHz) according to the literature[18]). The derivatization of **18** was carried out according to the procedure described above (Section 4.27).

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