Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 2430–2441

# Chiral linker. Part 4: Diastereoselective addition of RZnX to α-keto esters using *m*-hydrobenzoin derived chiral auxiliaries in solution and on solid support and their application in the stereoselective synthesis of *frontalin*

Christian Schuster, Max Knollmueller and Peter Gaertner*

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

Received 18 August 2006; accepted 22 August 2006
Available online 26 September 2006

**Abstract**—Two recently reported, *m*-hydrobenzoin derived open chain chiral auxiliaries, which were developed for application in either solution or immobilized on a solid support, were tested in the diastereoselective addition of RZnX to their corresponding phenylglyoxylates and pyruvates, respectively, resulting in diastereoisomeric excesses of up to >98% de. The optimized procedure was applied in the stereoselective synthesis of *frontalin*, the aggregation pheromone of pine bark beetles of the *Dendroctonus* family, by the use of both the solution phase and the polymer supported chiral auxiliary.


## 1. Introduction

Chiral tertiary α-hydroxy carboxylic acids are important building blocks and intermediates in the synthesis of complex, biologically active molecules. For example, (*S*)-(+)-1-(4-{2-[bis(4-fluorophenyl)methoxy]ethyl}piperazin-1-yl)-2-phenylpropan-2-ol **A**, a potential cocaine abuse therapeutic,[1] (*S*)-oxybutynin (ditropan) **B**, a muscaronic receptor antagonist for the treatment of urinary incontinence[2] and even α-tocopherol[3] **C**, which is derived from the corresponding α-hydroxycarboxylic acid derivatives (Scheme 1).

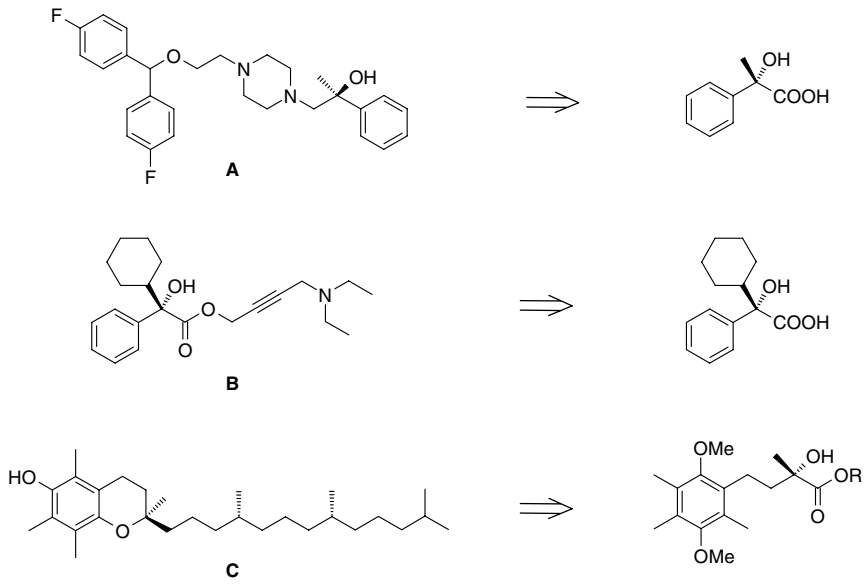
Diastereoselective addition of organometallic reagents to α-keto carboxylic acids by means of a chiral auxiliary is a proper methodology to obtain tertiary α-hydroxy carboxylic acids with high enantiomeric purities, with cyclohexyl based auxiliaries like menthol, Corey's 8-phenylmenthol[4] and Whitesell's *trans*-2-phenylcyclohexan-1-ol[5] being the gold standards[6] in the field. As these auxiliaries have to be isolated or synthesized expensively, a number of alternative auxiliaries have successfully been developed, in recent years for this type of reaction.[7]

We have recently reported a novel class of *m*-hydrobenzoin derived chiral auxiliaries **6** for the L-Selectride® mediated stereoselective reduction of phenylglyoxylates.[8] These auxiliaries were developed for the application in either solution or immobilized on a solid support and could easily be synthesized by desymmetrization of *m*-hydrobenzoin **1** using Noe's anhydro lactols[9] and subsequent derivatization steps.[8] Therefore, by utilizing each one of Noe's lactols, either stereoisomer of the resulting auxiliary could possibly be obtained, thus being a simple application of the so-called '*meso* trick'[10] (Scheme 2).

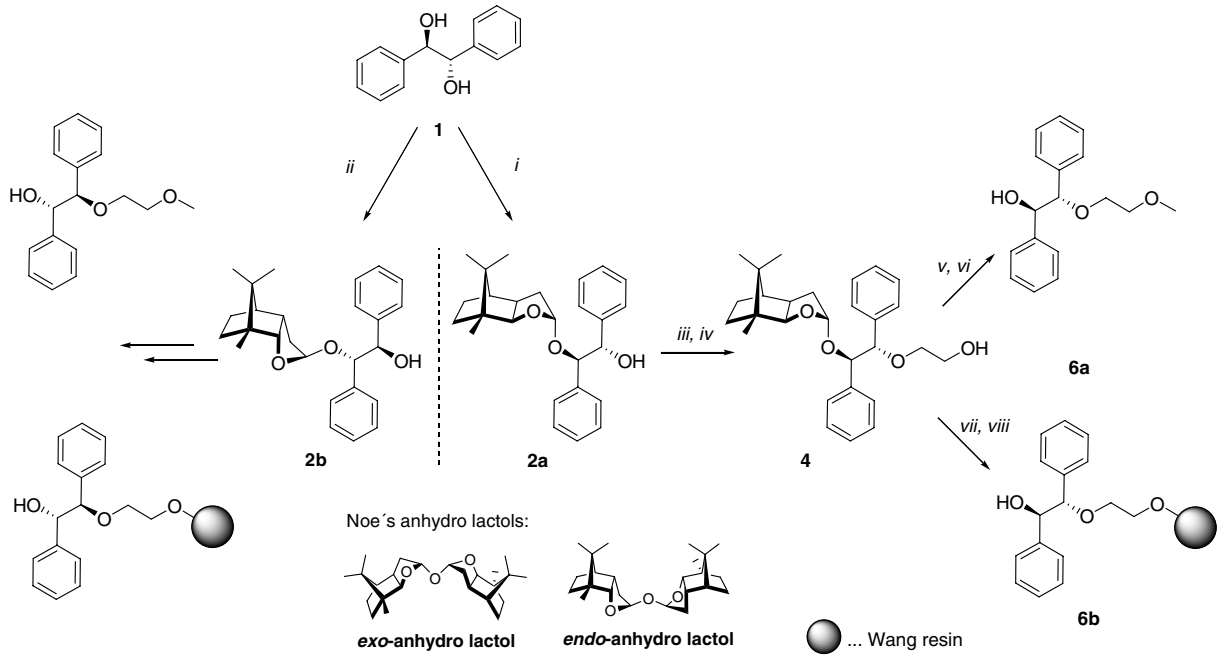
In our previous work, it became evident that the introduction of a second oxygen in the ether moieties of hydrobenzoin mono-ether auxiliaries **6a** and **6b**[8b] resulted in substantially improved diastereoselectivities in the L-Selectride® mediated reduction of their phenylglyoxylates **7a** and **7b**, especially when the Lewis acid $ZnCl_2$ was used as an additive, whereas this additive had no effect, when the analogous *tert*-butyl ether auxiliary **6c**[8a] was used in the same reduction of phenylglyoxylate **7c**. Therefore, based on the works of Rosini et al.,[11] we had proposed a conformational rationale for the stereochemical outcome of this reaction. Therein, we had supposed that the ether moiety had effectively shielded one face of the keto carbonyl from the hydride attack by chelation of the $Zn^{2+}$ cation, which itself had forced the two carbonyls of the keto carboxylic

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

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.08.016



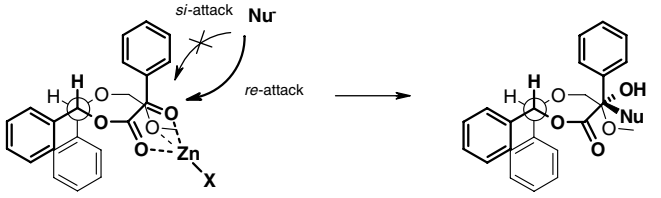

**Scheme 1.**




**Scheme 2.** Reagents and conditions: (i) Noe's *exo*-anhydro lactol, *p*-TsOH, $CH_2Cl_2$; (ii) Noe's *endo*-anhydro lactol, *p*-TsOH, $CH_2Cl_2$; (iii) NaH; $BrCH_2COO$–*t*-Bu, HMPA, THF; (iv) $LiAlH_4$, THF; (v) NaH; $CH_3I$, DMF; (vi) *p*-TsOH, MeOH, $CH_2Cl_2$; (vii) NaH; NaI, Wang-Cl, DMF; NaI, acetone; $Bu_3SnH$, THF; (viii) $PPh_3 \cdot HBr$, MeOH, $CH_2Cl_2$.

ester into a *syn*-conformation by chelation[8] (Scheme 3). This in consequence resulted in an improved diastereoselection of 91% de compared to 77% de without $ZnCl_2$ in the L-Selectride® mediated reduction of phenylglyoxylate **7a**.

Based on this model, we suggested that the addition of organozinc reagents to α-keto carboxylic esters might proceed in a similar manner with auxiliaries **6a** and **6b**, especially since there have been numerous examples of




**Scheme 3.** Proposed model for $Zn^{2+}$ enhanced diastereoselection with auxiliary **6a**.

auxiliary mediated stereoselective organozinc additions to α-keto esters reported in the literature,[6,7] even with improved stereoselections by using zinc instead of magnesium as the metal cation.[7d]

Herein, we report the stereoselective addition of several organozinc reagents to α-keto esters using *m*-hydrobenzoin derived chiral auxiliaries **6a** and **6b** in solution as well as on solid support, and the application of this type of reaction as the key step in the stereoselective synthesis of (+)-*frontalin*.

## 2. Results and discussion

### 2.1. RZnX addition in solution

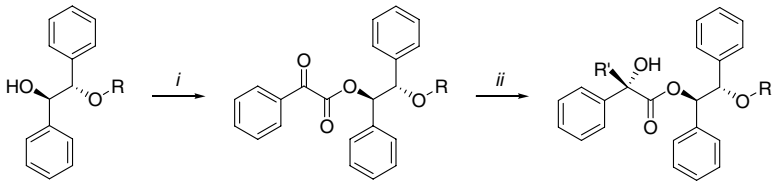
We chose the addition of *n*-BuZnCl, which had simply been prepared in situ by reaction of *n*-BuMgCl with dry $ZnCl_2$, to phenylglyoxylate **7a**[8b] at −78 °C in THF, according to the procedure described by Boireau et al.,[6e] for the evaluation of the stereoinducing ability of our chiral auxiliary **6a** in this type of reaction. Thereby, we initially found that all of the $ZnCl_2$ had to be consumed by using an equal amount of Grignard reagent for the formation of the organozinc reagent, otherwise only incomplete addition would result as a matter of competing coordination of unreacted $ZnCl_2$ by the ketoester[6e] (Table 1, entries 3 and 4). On the other hand, we were pleased to find that a diastereomeric excess of >98% de resulted in this experiment (Table 1, entries 3 and 4), with the absolute configuration at the new stereocenter being (*S*), as correctly predicted by our model (Scheme 3). The stereochemical outcome of this reaction was analyzed by $^1H$ NMR integration on the mixture of product diastereomers **9a**, as well as after ester saponification and further derivatization with L-valine methyl ester[12] by $^1H$ and $^{13}C$ NMR analysis of resulting **15a**, as described in our previous work,[8] resulting in consistent de values. The absolute configuration was approved by means of the specific rotation of the cleaved hydroxy acid **14a**.

Similarly, 94% de could be achieved in the analogous addition reaction of *i*-PrZnCl to phenylglyoxylate **7a** (Table 1, entry 5), whereas the reaction with the small nucleophile MeZnCl resulted in only 45% de (Table 1, entry 6), thus revealing the limitation of auxiliary **6a** in this type of reaction. Furthermore, the application of *tert*-butyl auxiliary **6c**[8a] in the addition of *n*-BuZnCl to phenylglyoxylate **7c** resulted in a diminished diastereoisomeric excess of only 89% de (Table 1, entry 9). This was in accordance with our previous results from the L-Selectride®/$ZnCl_2$ mediated reduction of phenylglyoxylates **7a** and **7c**,[8] respectively (Table 1, entries 2 and 8) and obviously underlined the benefit of the additional Lewis basic O-atom in the ether moiety of auxiliary **6a**.

### 2.2. RZnX addition on solid support

Polymer supported chiral auxiliary **6b**[8b] was tested analogously in the addition of several organozinc reagents to α-keto esters. Thus, by employing identical reaction conditions, we obtained results very similar to the ones mentioned above, with the larger nucleophiles added to phenylglyoxylate **7b** yielding good to excellent diastereoselectivities (Table 2, entries 1–3), whereas the small ones MeZnCl and EtZnCl, respectively, gave only poor results (Table 2, entries 4–5). Furthermore, it could be shown that even the addition to enolizable keto esters such as pyruvate

**Table 1.** Diastereoisomeric ratio of **8a**–**11a** from addition of H- and C-nucleophiles, respectively, to α-keto esters **7a**,**c**[a]

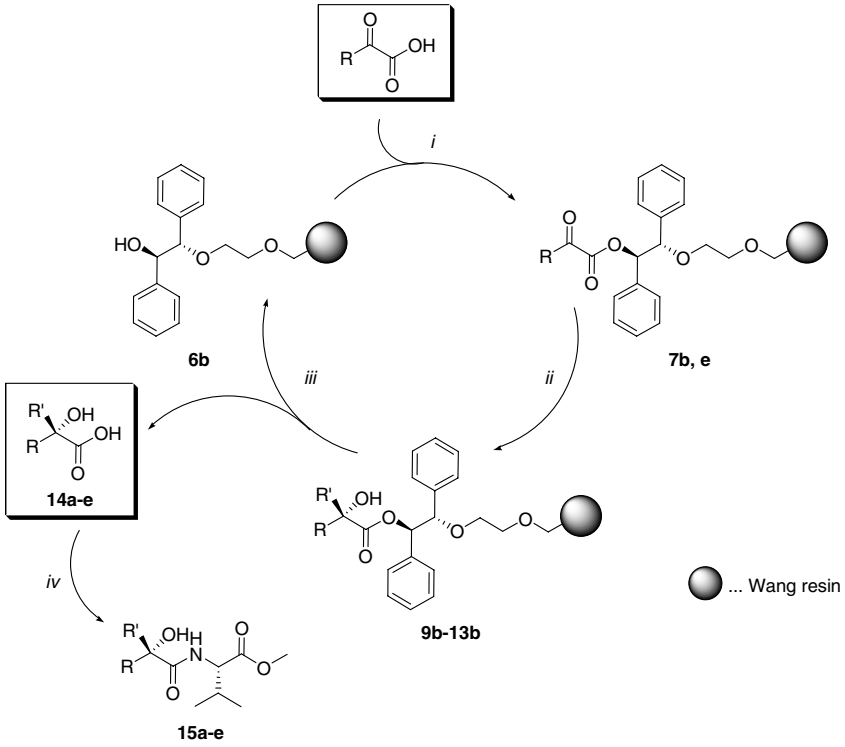



**6a-c** **7a-c** **8-11**

| Entry | Ester | R | Nucleophile R′ | $ZnCl_2$ (equiv) | Ratio[d] (*S*,*R*,*S*)/(*S*,*R*,*R*) | Product (yield, %)[e] |
|---|---|---|---|---|---|---|
| 1 | **7a**[b] | | H/1 equiv L-Selectride® | — | 88.5:11.5[b] | **8a** (80) |
| 2 | **7a**[b] | | H/1 equiv L-Selectride® | 2 | 95.5:4.5[b] | **8a** (99) |
| 3 | **7a** | | 4.5 equiv *n*-BuMgCl | 9 | >99:1 | **9a** (20) |
| 4 | **7a** | | 8 equiv *n*-BuMgCl | 7.5 | >99:1 | **9a** (98) |
| 5 | **7a** | | 8 equiv *i*-PrMgBr | 7.5 | 97:3 | **10a** (97) |
| 6 | **7a** | | 8 equiv MeMgBr | 7.5 | 72.5:27.5 | **11a** (82) |
| 7 | **7c**[c] | *t*-Bu | H/1 equiv L-Selectride® | — | 92:8[c] | **8c** (87) |
| 8 | **7c**[c] | | H/1 equiv L-Selectride® | 2 | 92:8[c] | **8c** (88) |
| 9 | **7c** | | 8 equiv *n*-BuMgCl | 7.5 | 94.5:5.5 | **9c** (92) |

[a] Reagents and conditions: (i) PhCOCOOH, DIC, DMAP, $CH_2Cl_2$; (ii) nucleophile R′, −78 °C, THF.
[b] Data from Ref. 8b.
[c] Data from Ref. 8a.
[d] Diastereoisomeric ratios determined by $^1H$ NMR integration on crude reaction mixtures **8**–**11** and L-valine methyl ester derivatives **15** of cleaved hydroxy acids **14**; absolute configuration of major diastereoisomers approved by optical rotation of **14**.
[e] Isolated yields by vacuum flash chromatography.

**Table 2.** Stereoisomeric ratio of **14a**–**e** from addition of R′ZnX to polymer supported α-keto esters **7b**,**e**[a]




| Entry | Ester | R | Run | Nucleophile R′ | Ratio[b] (*S*)/(*R*) | Product (yield, %)[c] |
|---|---|---|---|---|---|---|
| 1 | **7b** | Ph | **1a** | *n*-BuZnCl | 95:5 | **14a** (76) |
| 2 | **7b** | Ph | **1b** | *i*-PrZnCl | 92:8 | **14b** (95) |
| 3 | **7b** | Ph | **2a** | *c*-HexZnCl | 93:7 | **14c** (90) |
| 4 | **7b** | Ph | **2b** | EtZnCl | 75:25 | **14d** (95) |
| 5 | **7b** | Ph | **3a** | MeZnCl | 65:35 | **14e** (90) |
| 6 | **7e** | Me | **3b** | PhZnCl | 11:89 | **14f** (75) |

[a] Reagents and conditions: (i) RCOCOOH, DIC, DMAP, $CH_2Cl_2$; (ii) R′ZnX, −78 °C, THF; (iii) LiOH, THF/MeOH/$H_2O$; (iv) L-valine methyl ester, DIC, HOBt, $CH_2Cl_2$.

[b] Stereoisomeric ratios determined by $^1H$ and $^{13}C$ NMR analysis of L-valine methyl ester derivatives **15a**–**e** of cleaved hydroxy acids **14a**–**e**; absolute configuration of major enantiomers approved by optical rotation of **14a**–**e**.

[c] Yields over two steps, based on gravimetrically estimated amount of ketoacid bound in the esterification step.

**7e** could result in acceptable yields and stereoselectivities as well—a small amount of dry methanol had been added to the PhZnCl solution in the pyruvate experiment, as was recommended by Dosa and Fu for achieving higher yields and selectivities in the addition of $Ph_2Zn$ to enolizable ketones.[13] Thus, the addition of PhZnCl to pyruvate **7e** yielded hydroxy acid **14c** with a much more satisfying enantiomeric purity than the addition of MeZnCl to phenylglyoxylate **7b** had achieved, and, certainly, with the inverse absolute configuration (*R*) (Table 2, entry 6).

It had been shown in our previous phenylglyoxylate reduction series that auxiliary **6b** could be reused several times, without any loss of its stereoinducing ability.[8b] Consequently, the current set of experiments was also carried out in three runs, starting with a freshly prepared sample of auxiliary **6b**,[8b] which was first esterified with phenyl glyoxylic acid, then divided into two parts and used in the first two RZnX addition experiments (run 1). After cleavage of the resulting hydroxy esters **9b** and **10b** by LiOH mediated ester saponification, both resins were recovered, recombined, and introduced in the next reaction cycle (run 2), as far as IR spectroscopic analysis had indicated quantitative ester cleavage by the complete disappearance of the CO band at 1740 $cm^{-1}$. The third run finally started with the esterification of the recovered, recombined and then divided resin **6b** from run 2 with phenyl glyoxylic acid and pyruvic acid, respectively (run 3).

All reactions on solid support were monitored qualitatively by FT-IR spectroscopy, employing KBr disks, as well as yields, which were estimated gravimetrically.[8b] The stereochemical outcomes were analyzed after cleavage of hydroxy esters **9b**–**13b** from the resin and further derivatization of recovered hydroxy acids **14a**–**e** with L-valine methyl ester.[12] While the absolute configurations of **14a**–**e** were determined by their specific rotations and comparison with literature values, their stereoisomeric ratios were quantified by $^1H$ and $^{13}C$ NMR integration on the mixtures of product diastereoisomers of L-valine methyl ester derivatives **15a**–**e**.

### 2.3. Preparation of *frontalin*

1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octane, *frontalin*, is part of the aggregation pheromone of pine beetles of the *Dendroctonus* family, with the (1*S*,5*R*)-(−) enantiomer being the much more active stereoisomer.[14] *Frontalin* has also been isolated from the temporal gland secretion of male Asian elephant bulls during the period of musth,[15] as well as from the bark of several angiosperm trees.[16] As the molecule consists of only two stereocenters, of which the one at *C*5 is dictated by that at *C*1 through the formation of the bicyclic, ketal structure, it has frequently been used from the 1970s on[17] as a valuable simple target to test diverse stereoselective synthetic methods.[18] In 1986, Whitesell published the diastereoselective addition of Grignard reagents to keto esters by the use of 8-phenylmenthol as the key step in the syntheses of each of the enantiomers of *frontalin* with high enantiomeric purities.[19]

Based on Whitesell's findings, we suggested our *m*-hydrobenzoin derived chiral auxiliaries **6a** and **6b** to be equally applicable in this synthetic pathway, especially since we had supposed organozinc reagent **21** to be big enough for achieving good diastereoisomeric selectivities in addition to pyruvates **7d** and **7e** with regards to the above mentioned results. Therefore, **7d** and **7e** were reacted with **21**, which had been prepared from the corresponding Grignard reagent **20** and $ZnCl_2$, according to the procedure used in our preceding experiments. Compound **20** had been synthesized directly before from bromide **19**, which had been prepared from ethyl laevulinate **16** in three steps by a modification of known procedures.[20,21]

Thus, according to the above mentioned solution phase series, the diastereoselective addition reaction of **21** to pyruvate **7d** yielded hydroxy ester **22a** with 81% yield. It is noteworthy that in contrast to Whitesell's findings with RMgBr, in our hands, no Grignard reduction based lactate could be detected at all. The diastereoisomeric ratio of α-hydroxy ester **22a** was again directly evaluated by $^1H$ NMR analysis of the crude reaction mixture by integration of the sufficiently resolved benzylic protons $H_a$ in the two diastereoisomers,[8a] which indicated a high enantiomeric excess of 92% de. The absolute configuration of the major diastereoisomer was determined after the reduction of **22a** with $LiAlH_4$ to be (*R*) by comparing the specific rotation of liberated 1,2-diol **23** with the value reported by Whitesell and Buchanan.[19] For test purposes, **23** was finally converted by ozonolysis, as described by Whitesell and Buchanan,[19] to *frontalin* **24**, which proved to be the expected (+)-enantiomer with an enantiomeric excess of about 98% ee as indicated by chiral GC. On the other hand, the analogous synthesis using polymer supported chiral auxiliary **6b** yielded 1,2-diol **23** with an isolated yield of 50% over two steps, which resulted in (+)-*frontalin* **24** with 86% ee analyzed by GC (Scheme 4).

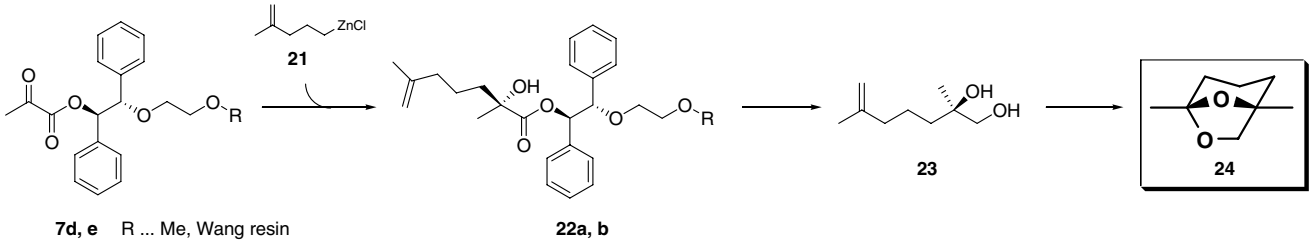
## 3. Conclusion

In conclusion, we have demonstrated the applicability of *m*-hydrobenzoin derived, open chain chiral auxiliaries **6a** and **6b** in the diastereoselective addition of RZnX to α-keto esters such as phenylglyoxylates **7a** and **7b** and pyruvates, respectively. Thereby, good to excellent diastereoisomeric excesses of up to >98% de could be achieved using solution phase auxiliary **6a**, provided that the nucleophiles were not too small. Similarly good results were achieved with polymer supported auxiliary **6b**, whereas diastereoisomeric excesses were diminished to some extent in all solid phase experiments compared to the ones employing solution phase auxiliary **6a**. In summary, it can be said that the reusable auxiliaries **6a** and **6b**, of which both enantiomers are easily accessible from *m*-hydrobenzoin by desymmetrization with Noe's anhydro lactols,[8,9] are within the best auxiliaries in their class[6,7] and therefore seem to be a viable alternative to cyclohexyl based chiral auxiliaries for accessing tertiary α-hydroxy acids from their corresponding keto acids by addition of RZnX with good yields and high enantiomeric purities. The applicability of this method was demonstrated in the stereoselective synthesis of 1,2-diol **23**, which is the key intermediate in the 8-phenylmenthol mediated stereoselective synthesis of *frontalin* reported by Whitesell and Buchanan.[19] Therein auxiliary **6a** proved to be equally useful resulting in (+)-*frontalin* **24** with high enantiomeric purities of 92–98% ee, whereas the result with polymer supported auxiliary **6b** was again slightly inferior. Nevertheless, to the best of our knowledge, the latter is the first reported application of a polymer supported chiral auxiliary in a stereoselective synthesis of *frontalin*. We were, therefore, encouraged to carry on our investigations on further auxiliary improvements, as well as to look out for other applications of our novel hydrobenzoin derived, reusable open chain chiral auxiliaries.

## 4. Experimental

### 4.1. General

Commercially available reagents and solvents were used as received from the supplier unless otherwise specified.




**Scheme 4.** Stereoselective preparation of *frontalin* by the application of hydrobenzoin mono-ether auxiliaries **6a**,**b**.

Diethyl ether (E), petroleum ether (PE, 60–80 °C fraction), ethyl acetate (EE) and dichloromethane were distilled prior to use. Dry ether and THF were pre-dried over KOH and distilled from Na/benzophenone. Dry dichloromethane was distilled from $P_2O_5$. $ZnCl_2$ was dried by heating to 150–300 °C in high vacuo for 30 min prior to use. All moisture sensitive reactions were carried out under a nitrogen atmosphere. Reactions on solid support were shaken on a laboratory shaker unless otherwise stated. For TLC-analysis, precoated aluminum-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. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Specific rotations were measured on a Perkin–Elmer 241 polarimeter. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AC 200 in $CDCl_3$ at 200 and 50 MHz, respectively, using TMS or the solvent peak as the reference. IR spectra were recorded on a BioRad *FTS 135* FT-IR-spectrometer, using KBr disks. Elemental analysis was carried out at Vienna University, Department of Physicochemistry—Laboratory for Microanalysis, Währinger Str. 42, A-1090 Vienna.

### 4.2. Preparation of ketocarboxylic acid esters, 7a and 7d

**4.2.1. General procedure.** Diisopropylcarbodiimide (DIC) (1.1 equiv) was added dropwise to a solution of auxiliary **6a** (1.0 equiv), keto carboxylic acid (1.1 equiv), and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (0.2 equiv) in dry dichloromethane, while cooling on an ice bath. The mixture was stirred for 1–20 h at room temperature until TLC control indicated total conversion. The white precipitate was filtered off and the filtrate was diluted with dichloromethane and washed successively with a saturated aqueous $NaHCO_3$ solution, 5% $KHSO_4$ solution, and brine. The organic layer was dried over $Na_2SO_4$, filtered, and evaporated.

**4.2.2. Oxophenylacetic acid, (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-diphenylethyl ester, 7a.** The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (20/1 → 5/1). White solid (yield 91%), mp 79–81 °C, $R_f = 0.65$ (PE/E 4/1), $[\alpha]_D^{20} = +18.6$ (*c* 0.71 $CH_2Cl_2$). $^1H$ NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.67$–$7.26$ (m, 15H, aromatic), 6.29/4.70 (2d, 2H, Ph–C*H*–O, $J = 6.7$ Hz), 3.59–3.38 (m, 4H, O–C$H_2$–C$H_2$–O), 3.23 (s, 3H, O–$CH_3$). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta_C = 186.1$ (s, CO), 162.7 (s, O–CO), 137.4/136.3/132.2 (3s, Ph–C-1), 134.7/129.9–127.7 (m, Ph–C), 84.0/78.9 (2d, Ph–*C*H–O), 71.8/68.7 (2t, O–*C*$H_2$–*C*$H_2$–O), 58.8 (q, O–$CH_3$). Anal. Calcd for $C_{25}H_{24}O_5 \times 0.4H_2O$: C, 72.94; H, 6.07. Found: C, 72.99; H, 5.87.

**4.2.3. 2-Oxopropionic acid, (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-diphenylethyl ester, 7d.** The crude product was purified by vacuum flash chromatography on silica gel, eluting with dichloromethane/methanol (100/1).

0.355 g (yield 82%) white solid, mp 40–43 °C, $R_f = 0.43$ (PE/E 1/1), $[\alpha]_D^{20} = -2.4$ (*c* 0.99, $CH_2Cl_2$). $^1H$ NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.32$–$7.30$ (m, 10H, aromatic), 6.01/4.71 (2d, 2H, Ph–C*H*–O, $J = 6.3$ Hz), 3.60–3.37 (m, 4H, O–C$H_2$–C$H_2$–O), 3.23 (s, 3H, O–$CH_3$), 2.30 (s, 3H, $CH_3$–CO). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta_C = 191.2$ (s, CO), 159.2 (s, O–CO), 137.3/136.2 (2s, Ph–C-1), 128.4/128.2/128.0/127.9/127.8/127.7 (6d, Ph–C), 83.9/79.5 (2d, Ph–*C*H–O), 71.8/68.8 (2t, O–*C*$H_2$–*C*$H_2$–O), 58.8 (q, O–$CH_3$), 26.6 (q, *C*$H_3$–CO). Anal. Calcd for $C_{20}H_{22}O_5 \times 0.1H_2O$: C, 69.79; H, 6.50. Found: C, 69.91; H, 6.44.

### 4.3. Preparation of polymer bound keto carboxylic acid esters, 7b and 7e

**4.3.1. General procedure.** DIC (10 equiv) was added dropwise to a mixture of resin **6b** (1 equiv/~1.5 g), keto carboxylic acid (10 equiv), and DMAP (1 equiv) in dry dichloromethane (15 mL) while cooling on an ice bath. The resulting mixture, which had turned from pale yellow to orange and brown, was shaken for 48 h at room temperature. The resin was filtered off and thoroughly washed successively with dichloromethane, methanol, dichloromethane, methanol, dichloromethane, methanol, and dried in vacuo overnight at 40 °C.

**4.3.2. Polymer bound phenylglyoxylate, 7b.** 1.542 g pale yellow resin (mass increase: 0.090 g = 0.681 mmol). IR $\nu$ (KBr) = 3576 $cm^{-1}$ (OH: vanished), 1739 $cm^{-1}$ (COOR), 1689 $cm^{-1}$ (CO); no further changes.

**4.3.3. Polymer bound pyruvate, 7e.** 1.641 g light brown resin (mass increase: 0.053 g = 0.754 mmol). IR $\nu$ (KBr) = 3576 $cm^{-1}$ (OH: vanished), 1730 $cm^{-1}$ (*CO*–*CO*OR); no further changes.

### 4.4. Addition of RZnX to α-keto esters

**4.4.1. General procedure.** A freshly prepared and titrated[22] solution of RMgX (8 equiv) in THF was slowly added to a thoroughly stirred solution of pre-dried $ZnCl_2$ (7.5 equiv) in dry THF (5 mL) while cooling on an ice bath, and stirring was continued for 2 h at 0 °C. The supernatant solution of the prepared RZnX reagent was slowly added over 15 min to a solution of ester **7a**,**c** (1 equiv/~100 mg) in dry THF (10 mL), precooled to −90 °C, by means of a syringe, and the resulting mixture stirred for 2 h at −78 °C. The temperature was raised up to −20 °C over a period of 1 h, and finally a 10% aqueous $NH_4Cl$ solution was added and stirring 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 ether extracts were successively washed with aqueous $NH_4Cl$ and brine, dried over $Na_2SO_4$, filtered, and evaporated. The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (10/1 → 2/1).

**4.4.2. (*S*)-2-Hydroxy-2-phenylhexanoic acid, (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-diphenylethyl ester, 9a.** White solid (yield 98%), $R_f = 0.51$ (PE/E 1:1). $^1H$ NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.38$–$6.76$ (m, 15H, aromatic), 5.78/4.43 (2d, 2H, Ph–C*H*–O, $J = 6.4$ Hz), 3.66 (s, 1H, OH), 3.42–3.18 (m, 4H, O–C$H_2$–C$H_2$–O), 3.11 (s, 3H, O–$CH_3$),

1.99–0.67 (m, 9H, –C*H*$_2$–C*H*$_2$–C*H*$_2$–C*H*$_3$). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta_C = 174.1$ (s, O–CO), 141.4/137.6/136.8 (3s, Ph–C-1), 128.2–125.8 (m, Ph–C), 84.4/79.7 (2d, Ph–*C*H–O), 77.9 (s, O–CO–*C*(OH)(Ph)–CH$_2$), 71.7/68.6 (2t, O–*C*H$_2$–*C*H$_2$–O), 58.8 (q, O–CH$_3$), 38.5 (t, *C*H$_2$–CH$_2$–CH$_2$–CH$_3$), 25.3 (t, CH$_2$–*C*H$_2$–CH$_2$–CH$_3$), 22.8 (t, CH$_2$–CH$_2$–*C*H$_2$–CH$_3$), 13.9 (q, CH$_2$–CH$_2$–CH$_2$–*C*H$_3$). Anal. Calcd for $C_{29}H_{34}O_5 \times 0.3H_2O$: C, 74.43; H, 7.45. Found: C, 74.53; H, 7.73.

**4.4.3. (*S*)-2-Hydroxy-2-phenylhexanoic acid, (1*R*,2*S*)-2-(1,1-dimethylethoxy)-1,2-diphenylethyl ester, 9c.** White solid (yield 92%), $R_f = 0.77$ (PE/E 1:1). $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.40$–$6.72$ (m, 15H, aromatic), 5.53/4.47 (2d, 2H, Ph–C*H*–O, $J = 7.1$ Hz), 3.63 (s, 1H, OH), 1.92–0.68 [m, 18H, therein 0.77 (s, 9H, O–C(CH$_3$)$_3$), –C*H*$_2$–C*H*$_2$–C*H*$_2$–C*H*$_3$]. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta_C = 174.3$ (s, O–CO), 141.7/141.4/137.6 (3s, Ph–C-1), 128.0–126.0 (m, Ph–C), 81.1/76.7 (2d, Ph–*C*H–O), 77.8 (s, O–CO–*C*(OH)(Ph)–CH$_2$), 74.9 (s, O–*C*(CH$_3$)$_3$), 38.3 (t, *C*H$_2$–CH$_2$–CH$_2$–CH$_3$), 28.1 (q, O–C(*C*H$_3$)$_3$), 25.3 (t, CH$_2$–*C*H$_2$–CH$_2$–CH$_3$), 22.8 (t, CH$_2$–CH$_2$–*C*H$_2$–CH$_3$), 13.9 (q, CH$_2$–CH$_2$–CH$_2$–*C*H$_3$). Anal. Calcd for $C_{30}H_{36}O_4 \times 0.1H_2O$: C, 77.92; H, 7.89. Found: C, 77.97; H, 8.17.

**4.4.4. (*S*)-2-Hydroxy-3-methyl-2-phenylbutyric acid, (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-diphenylethyl ester, 10a.** White solid (yield 86%), $R_f = 0.53$ (PE/E 1:1). $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.46$–$6.70$ (m, 15H, aromatic), 5.77/4.47 (2d, 2H, Ph–C*H*–O, $J = 6.2$ Hz), 3.55 (s, 1H, OH), 3.45–3.21 (m, 4H, O–C*H*$_2$–C*H*$_2$–O), 3.13 (s, 3H, O–CH$_3$), 2.42 (m, 1H, C*H*(CH$_3$)$_2$, $J = 6.7$ Hz), 0.62/0.59 (2d, 6H, CH(C*H*$_3$)$_2$, $J = 6.7$ Hz). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta_C = 174.4$ (s, O–CO), 140.5/137.5/136.7 (3s, Ph–C-1), 128.2–126.3 (m, Ph–C), 84.4/80.0 (2d, 2Ph–*C*H–O), 80.7 (s, O–CO–*C*(OH)(Ph)–CH(CH$_3$)$_2$), 71.8/68.7 (2t, O–*C*H$_2$–*C*H$_2$–O), 58.8 (q, O–CH$_3$), 34.8 (d, *C*H(CH$_3$)$_2$), 16.5/15.8 (2q, CH(*C*H$_3$)$_2$). Anal. Calcd for $C_{28}H_{32}O_5 \times 1.0H_2O$: C, 72.08; H, 7.35. Found: C, 72.17; H, 7.22.

**4.4.5. (*S*)-2-Hydroxy-2-phenylpropanoic acid, (1*R*,2*S*)-2-(2-methoxyethoxy)-1,2-diphenylethyl ester, 11a.** White solid (yield 82%), $R_f = 0.33$ (PE/E 1:1). $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.35$–$6.83$ (m, 15H, aromatic), 5.83/4.45 (2d, 2H, Ph–C*H*–O, $J = 6.5$ Hz), 3.62 (s, 1H, OH), 3.44–3.20 (m, 4H, O–C*H*$_2$–C*H*$_2$–O), 3.14 (s, 3H, O–CH$_3$), 1.49 (s, 3H, –CH$_3$). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta_C = 174.3$ (s, O–CO), 142.2/137.6/136.7 (3s, Ph–C-1), 128.2–125.5 (m, Ph–C), 84.4/79.3 (2d, Ph–*C*H–O), 75.5 (s, O–CO–*C*(OH)(Ph)–CH$_3$), 71.8/68.7 (2t, O–*C*H$_2$–*C*H$_2$–O), 58.8 (q, O–CH$_3$), 25.8 (t, –CH$_3$). Anal. Calcd for $C_{26}H_{28}O_5 \times 0.4H_2O$: C, 73.01; H, 6.79. Found: C, 73.10; H, 7.09.

### 4.5. Addition of RZnX to polymer bound α-keto esters

**4.5.1. General procedure.** A freshly prepared and titrated[22] solution of RMgX (8 equiv) in THF was slowly added to a thoroughly stirred solution of pre-dried $ZnCl_2$ (7.5 equiv) in dry THF (5 mL), while cooling on an ice bath; stirring was continued for 2 h at 0 °C. In the case of enolizable pyruvate **7e**, dry methanol (1.5 equiv) was then added and stirring was continued for 10 min at 0 °C. The supernatant solution of the as prepared RZnX reagent was slowly added over 15 min to a suspension of esters **7b** and **7e** (0.5–1.2 mmol/1 equiv/~1.2–1.8 g) in dry THF (20 mL) precooled to −90 °C, by means of a syringe, and the resulting mixture was stirred for 2 h at −78 °C. The temperature was then increased to −20 °C over a period of 1 h, and finally a 10% aqueous $NH_4Cl$ solution (10 mL) was added and stirring continued for 15 min at room temperature. 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.

**4.5.2. Polymer bound (*S*)-2-hydroxy-2-phenylhexanoic acid ester, 9b. Addition of *n*-BuZnCl to phenylglyoxylate 7b (run 1).**

**4.5.3. Polymer bound (*S*)-2-hydroxy-3-methyl-2-phenylbutyric acid ester, 10b. Addition of *i*-PrZnCl to phenylglyoxylate 7b (run 1).**

**4.5.4. Polymer bound (*S*)-2-hydroxy-2-phenylpropanoic acid ester, 11b. Addition of MeZnCl to phenylglyoxylate 7b (run 3).**

**4.5.5. Polymer bound (*S*)-2-cyclohexyl-2-hydroxyphenylacetic acid ester, 12b. Addition of *c*-HexZnCl to phenylglyoxylate 7b (run 2).**

**4.5.6. Polymer bound (*S*)-2-hydroxy-2-phenylbutyric acid ester, 13b. Addition of EtZnCl to phenylglyoxylate 7b (run 2).** All reactions: pale yellow resin. IR $\nu$ (KBr) = ~3500 cm$^{-1}$(OH), ~1740 cm$^{-1}$ (COOR), 1689 cm$^{-1}$ (CO: vanished); no further changes.

**4.5.7. Polymer bound (*R*)-2-hydroxy-2-phenylpropanoic acid ester, 11c. Addition of PhZnCl to pyruvate 7e (run 3).** Pale yellow resin. IR $\nu$ (KBr) = ~3500 cm$^{-1}$(OH), ~1740 cm$^{-1}$ (COOR); no further changes.

### 4.6. Saponification of hydroxy ester 9a

**4.6.1. (*S*)-2-Hydroxy-2-phenylhexanoic acid, 14a.** A solution of ester **9a** (1 equiv/~100 mg) and LiOH (5.0 equiv) in THF/methanol/water (5/4/1) (10 mL) was stirred overnight at room temperature. After TLC analysis had indicated a total conversion, an equal amount of a saturated aqueous $NaHCO_3$ solution was added and THF and methanol were evaporated. The aqueous remaining was extracted three times with ether. For the recovery of auxiliary **6a**, the combined ether extracts were washed with brine, dried over $Na_2SO_4$, filtered, evaporated, and the residue was purified by vacuum flash chromatography. The combined aqueous phases were carefully acidified with HCl concd while cooling on an ice bath and extracted three times with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried over $Na_2SO_4$, filtered, and evaporated yielding the free hydroxy acid.

White solid (yield 99%), $[\alpha]_D^{20} = +36.7$ ($c$ 0.98, $CHCl_3$) {Lit.: $[\alpha]_D^{20} = -37.2$ ($c$ 11.3 $CHCl_3$) [$R$][23]}. $^1$H NMR (200 MHz, acetone-$d_6$, TMS): $\delta_H = 7.71–7.67$ (m, 2H, aromatic), 7.40–7.23 (m, 4H, aromatic), 2.31–1.94 (m, 2H, $CH_2$–$CH_2$–$CH_2$–$CH_3$), 1.47–1.24 (m, 4H, $CH_2$–$CH_2$–$CH_2$–$CH_3$), 0.88 (t, 3H, $CH_2$–$CH_2$–$CH_2$–$CH_3$, $J = 7.1$ Hz).

### 4.7. Saponification of polymer bound hydroxy esters 9b–13b

**4.7.1. General procedure.** A mixture of resins **9b**–**13b** and LiOH (5 equiv) in THF/methanol/water (10/4/1) was refluxed overnight. 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. Recovered resin **6b** could be introduced in the next reaction cycle without any further purification.

Pale yellow resin. IR $\nu$ (KBr) = 3528 $cm^{-1}$(OH), ~1740 $cm^{-1}$ (COOR: vanished); no further changes.

The combined filtrates were diluted with saturated aqueous $NaHCO_3$, and THF and methanol were evaporated. The aqueous remaining was extracted three times with ether, acidified carefully with HCl concd while cooling on an ice bath, and then extracted three times with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried over $Na_2SO_4$, filtered, and evaporated. To obtain hydroxy acids **14a**–**f** with appropriate purities, the extractive purification step was repeated once or twice if necessary. The resulting hydroxy acids **14a**–**f** were dried in high vacuo and characterized by $^1$H NMR spectroscopy and $[\alpha]_D$-values, respectively.

In the following, yields are given over two steps, based on the gravimetrically estimated amount of keto acid bound in the esterification step.

**4.7.2. (*S*)-2-Hydroxy-2-phenylhexanoic acid, 14a. Addition of *n*-BuZnCl to phenylglyoxylate 7b.** White solid (yield 76%), $[\alpha]_D^{20} = +36.6$ ($c$ 0.98, $CHCl_3$) {Lit.: $[\alpha]_D^{20} = -37.2$ ($c$ 11.3, $CHCl_3$) [$R$][23]}. $^1$H NMR (200 MHz, acetone-$d_6$, TMS): $\delta_H = 7.71–7.67$ (m, 2H, aromatic), 7.40–7.23 (m, 3H, aromatic), 2.31–1.94 (m, 2H, $CH_2$–$CH_2$–$CH_2$–$CH_3$), 1.47–1.24 (m, 4H, $CH_2$–$CH_2$–$CH_2$–$CH_3$), 0.88 (t, 3H, $CH_2$–$CH_2$–$CH_2$–$CH_3$, $J = 7.1$ Hz).

**4.7.3. (*S*)-2-Hydroxy-3-methyl-2-phenylbutyric acid, 14b. Addition of *i*-PrZnCl to phenylglyoxylate 7b.** White solid (yield 98%), $[\alpha]_D^{25} = +22.3$ ($c$ 1.55, EtOH) {Lit.: $[\alpha]_D^{25} = +32.5$ ($c$ 2.0, EtOH) [$S$][24]}. $^1$H NMR (200 MHz, acetone-$d_6$, TMS): $\delta_H = 7.71–7.56$ (m, 2H, aromatic), 7.26–7.08 (m, 3H, aromatic), 2.53 (m, 1H, $CH$–$(CH_3)_2$, $J = 6.8$ Hz), 0.90/0.54 (2d, 6H, CH–$(CH_3)_2$, $J = 6.7$ Hz). $^{13}$C NMR (50 MHz, acetone-$d_6$): $\delta_C = 176.9$ (s, O–CO), 143.0 (s, Ph–C-1), 128.6/128.0/126.8 (3d, Ph–C), 81.3 (s, Ph–$C$(OH)(*i*-Pr)–COOH), 36.4 (d, $CH$–$(CH_3)_2$), 17.6/16.2 (2q, CH–$(CH_3)_2$).

**4.7.4. (*S*)-2-Cyclohexyl-2-hydroxyphenylacetic acid, 14c. Addition of *c*-HexZnCl to phenylglyoxylate 7b.** White solid (yield 90%), $[\alpha]_D^{22} = +14.4$ ($c$ 0.55, EtOH) {Lit.: $[\alpha]_D^{22} = 25.8$ ($c$ 1.0, EtOH) [$S$][2]}. $^1$H NMR (200 MHz, acetone-$d_6$, TMS): $\delta_H = 7.60–7.56$ (m, 2H, aromatic), 7.24–7.08 (m, 3H, aromatic), 2.21–0.64 (m, 11H, aliphatic). $^{13}$C NMR (50 MHz, acetone-$d_6$): $\delta_C = 177.0$ (s, O–CO), 142.6 (s, Ph–C-1), 128.6/127.9/126.9 (3d, Ph–C), 81.4 (s, Ph–$C$(OH)(*c*-Hex)–COOH), 46.5 (d, *c*-Hex–$CH$), 30.3/28.1/27.0/26.9/26.4 (5t, *c*-Hex–$CH_2$).

**4.7.5. (*S*)-2-Hydroxy-2-phenylbutyric acid, 14d. Addition of EtZnCl to phenylglyoxylate 7b.** White solid (yield 95%), $[\alpha]_D^{25} = +14.4$ ($c$ 1.34, EtOH) {Lit.: $[\alpha]_D^{25} = -32.6$ ($c$ 1.0, EtOH) [$R$][25]}. $^1$H NMR (200 MHz, acetone-$d_6$, TMS): $\delta_H = 7.69–7.65$ (m, 2H, aromatic), 7.39–7.23 (m, 3H, aromatic), 2.35–1.93 (m, 2H, $CH_2$–$CH_3$), 0.92 (t, 3H, $CH_2$–$CH_3$, $J = 7.3$ Hz).

**4.7.6. (*S*)-2-Hydroxy-2-phenylpropanoic acid, 14e. Addition of MeZnCl to phenylglyoxylate 7b.** White solid (yield 90%), $[\alpha]_D^{20} = +12.9$ ($c$ 0.62, EtOH) {Lit.: $[\alpha]_D^{20} = +35.1$ ($c$ 1.01, EtOH) [$S$][26]}. $^1$H NMR (200 MHz, acetone-$d_6$, TMS): $\delta_H = 7.52–7.48$ (m, 2H, aromatic), 7.26–7.13 (m, 3H, aromatic), 1.62 (s, 3H, $CH_3$).

**4.7.7. (*R*)-2-Hydroxy-2-phenylpropanoic acid, 14f. Addition of PhZnCl to pyruvate 7e.** White solid (yield 75%), $[\alpha]_D^{20} = -26.8$ ($c$ 0.76, EtOH) {Lit.: $[\alpha]_D^{20} = +35.1$ ($c$ 1.01, EtOH) [$S$][26]}. $^1$H NMR (200 MHz, acetone-$d_6$, TMS): $\delta_H = 7.52–7.48$ (m, 2H, aromatic), 7.26–7.13 (m, 3H, aromatic), 1.62 (s, 3H, $CH_3$).

### 4.8. Derivatization of hydroxy acids 14a–f and diastereoisomeric $^1$H and $^{13}$C NMR analysis of L-valine methyl ester derivatives 15a–f[12]

**4.8.1. General procedure.** A solution of L-valine methyl ester (10–30 mg) in dry dichloromethane (~1 mL) was added to a solution of hydroxy acid **14a**–**f** (10–30 mg) and HOBt (10–30 mg) in dry dichloromethane (3 mL), and the resulting mixture cooled to −30 °C. Then a solution of DIC (10–30 mg) in dry dichloromethane (~1 mL) was added and stirring was continued for 1 h at −30 °C and then overnight at ambient temperature. Finally, the reaction mixture was diluted with dichloromethane, filtered, successively washed with 10% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried over $Na_2SO_4$, filtered, and evaporated. For the removal of diisopropyl urea, the crude product was taken up with ~1 mL of acetone, cooled for 10 min on an ice bath, filtered, and evaporated. The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (5/1 → 2/1).

The diastereoisomeric ratios were determined by integration of the sufficiently resolved OMe signals at ~3.6 ppm in the $^1$H NMR spectra and, if necessary, additionally by integration of several signals in the $^{13}$C NMR spectra. In the following, NMR-values are given only for the main diastereoisomers.

**4.8.2. (*S*)-2-((*S*)-2-Hydroxy-2-phenylhexanoylamino)-3-methylbutyric acid, methyl ester, 15a.** Colorless oil. $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.54$–$7.50$ (m, 2H, aromatic), 7.33–7.19 (m, 3H, aromatic), 7.02 (d, 1H, NH, $J = 8.7$ Hz), 4.38 (dd, 1H, NH–C*H*(CH($CH_3$)$_2$)COO, $J_1 = 8.9$ Hz, $J_2 = 4.9$ Hz), 3.64 (s, 3H, $OCH_3$), 2.99 (s, 1H, OH), 2.26–1.94 (m, 3H, NH–CH(C*H*($CH_3$)$_2$)COO, C$H_2$C$H_2$C$H_2$C$H_3$), 1.35–1.14 (m, 4H, C$H_2$C$H_2$C$H_2$C$H_3$), 0.82 (t, 3H, C$H_2$C$H_2$C$H_2$C$H_3$, $J = 6.8$ Hz), 0.74/0.73 (2d, 6H, NH–CH(CH(C$H_3$)$_2$)COO, $J = 6.9$ Hz). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta_C = 174.1/172.3$ (2s, O–CO, NH–CO), 142.4 (s, Ph–C-1), 128.4/127.6/125.2 (3d, Ph–C), 79.1 (s, Ph–*C*($CH_2CH_2CH_2CH_3$)(OH)–CO–NH), 57.0 (d, NH–*C*H(CH($CH_3$)$_2$)COO), 52.1 (q, $OCH_3$), 39.1 (t, *C*$H_2CH_2CH_2CH_3$), 31.2 (d, NH–CH(*C*H($CH_3$)$_2$)COO), 25.5/22.8 (2t, $CH_2$*C*$H_2$*C*$H_2CH_3$), 18.8/17.6 (2q, NH–CH(CH(*C*$H_3$)$_2$)COO), 13.9 (q, $CH_2CH_2CH_2$*C*$H_3$).

**4.8.3. (*S*)-2-((*S*)-2-Hydroxy-3-methyl-2-phenylbutyrylamino)-3-methylbutyric acid, methyl ester, 15b.** White solid. $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.58$–$7.54$ (m, 2H, aromatic), 7.30–7.10 (m, 4H, aromatic, NH), 4.32 (dd, 1H, NH–C*H*(CH($CH_3$)$_2$)COO, $J_1 = 8.8$ Hz, $J_2 = 4.9$ Hz), 3.62 (s, 3H, $OCH_3$), 3.14 (s, 1H, OH), 2.77 (m, 1H, C*H*($CH_3$)$_2$, $J = 6.8$ Hz), 2.10–1.89 (m, 1H, NH–CH(C*H*($CH_3$)$_2$)COO), 0.94/0.73 (2d, 6H, CH(C$H_3$)$_2$, $J = 6.8$ Hz), 0.68/0.64 (2d, 6H, NH–CH(CH(C$H_3$)$_2$)COO, $J = 7.0$ Hz). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta_C = 174.0/172.2$ (2s, O–CO, NH–CO), 141.8 (s, Ph–C-1), 128.1/127.2/125.2 (3d, Ph–C), 81.8 (s, Ph–*C*(*i*-Pr)(OH)–CO–NH), 56.9 (d, NH–*C*H(CH($CH_3$)$_2$)COO), 51.9 (q, $OCH_3$), 34.6 (d, *C*H($CH_3$)$_2$), 31.0 (d, NH–CH(*C*H($CH_3$)$_2$)COO), 18.7/17.6/16.8/15.7 (4q, NH–CH(CH(*C*$H_3$)$_2$)COO, CH(*C*$H_3$)$_2$).

**4.8.4. (*S*)-2-((*S*)-2-Cyclohexyl-2-hydroxy-2-phenylacetylamino)-3-methylbutyric acid, methyl ester, 15c.** White solid. $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.58$–$7.53$ (m, 2H, aromatic), 7.31–7.13 (m, 4H, aromatic, NH), 4.33 (dd, 1H, NH–C*H*(CH($CH_3$)$_2$)COO, $J_1 = 8.9$ Hz, $J_2 = 5.0$ Hz), 3.64 (s, 3H, $OCH_3$), 2.87 (s, 1H, OH), 2.45–2.30 (m, 1H, *c*-Hex–C*H*), 2.12–1.94 (m, 1H, NH–CH(C*H*($CH_3$)$_2$)COO), 1.77–0.67 [m, 16H, *c*-Hex–C$H_2$; therein 0.73/0.69 (2d, 6H, NH–CH(CH(C$H_3$)$_2$)COO, $J = 7.0$ Hz)]. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta_C = 173.7/172.2$ (2s, O–CO, NH–CO), 141.4 (s, Ph–C-1), 128.2/127.2/125.3 (3d, Ph–C), 81.8 (s, Ph–*C*(*c*-Hex)(OH)–CO–NH), 56.9 (d, NH–*C*H(CH($CH_3$)$_2$)COO), 52.0 (q, $OCH_3$), 44.7 (d, *c*-Hex–*C*H), 31.2 (d, NH–CH(*C*H($CH_3$)$_2$)COO), 29.7/27.2/26.3/26.3/25.9 (5t, *c*-Hex–*C*$H_2$), 18.7/17.7 (2q, NH–CH(CH(*C*$H_3$)$_2$)COO).

**4.8.5. (*S*)-2-((*S*)-2-Hydroxy-2-phenylbutyrylamino)-3-methylbutyric acid, methyl ester, 15d.** Colorless oil. $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.54$–$7.49$ (m, 2H, aromatic), 7.32–7.19 (m, 3H, aromatic), 7.08 (d, 1H, NH, $J = 8.7$ Hz), 4.37 (dd, 1H, NH–C*H*(CH($CH_3$)$_2$)COO, $J_1 = 8.9$ Hz, $J_2 = 5.0$ Hz), 3.63 (s, 3H, $OCH_3$), 2.36–2.13 (m, 1H, NH–CH(C*H*($CH_3$)$_2$)COO), 2.13–1.92 (m, 2H, C$H_2$–$CH_3$), 0.85 (t, 3H, $CH_2$–C$H_3$, $J = 6.9$ Hz), 0.74/0.73 (2d, 6H, NH–CH(CH(C$H_3$)$_2$)COO, $J = 6.9$ Hz). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta_C = 174.0/172.3$ (2s, O–CO, NH–CO), 142.2 (s, Ph–C-1), 128.3/127.6/125.3 (3d, Ph–C), 79.4 (s, Ph–*C*($CH_2CH_3$)(OH)–CO–NH), 56.9 (d, NH–*C*H(CH($CH_3$)$_2$)COO), 52.1 (q, $OCH_3$), 32.1 (t, *C*$H_2$–$CH_3$), 31.2 (d, NH–CH(*C*H($CH_3$)$_2$)COO), 18.8/17.6 (2q, NH–CH(CH(*C*$H_3$)$_2$)COO), 7.6 (q, $CH_2$–*C*$H_3$).

**4.8.6. (*S*)-2-((*S*)-2-Hydroxy-2-phenylpropionylamino)-3-methylbutyric acid, methyl ester, 15e.** Colorless oil. $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.53$–$7.47$ (m, 2H, aromatic), 7.32–7.19 (m, 3H, aromatic), 7.07 (d, 1H, NH, $J = 8.7$ Hz), 4.38 (dd, 1H, NH–C*H*(CH($CH_3$)$_2$)COO, $J_1 = 8.8$ Hz, $J_2 = 4.8$ Hz), 3.64 (s, 3H, $OCH_3$), 2.16–1.96 (m, 1H, NH–CH(C*H*($CH_3$)$_2$)COO), 1.74 (s, 3H, $CH_3$), 0.74/0.73 (2d, 6H, NH–CH(CH(C$H_3$)$_2$)COO, $J = 6.9$ Hz). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta_C = 174.7/172.3$ (2s, O–CO, NH–CO), 143.2 (s, Ph–C-1), 128.3/127.7/125.1 (3d, Ph–C), 76.5 (s, Ph–*C*($CH_3$)(OH)–CO–NH), 57.0 (d, NH–*C*H(CH($CH_3$)$_2$)COO), 52.1 (q, $OCH_3$), 31.3 (q, $CH_3$), 27.1 (d, NH–CH(*C*H($CH_3$)$_2$)COO), 18.8/17.5 (2q, NH–CH(CH(*C*$H_3$)$_2$)COO).

**4.8.7. (*S*)-2-((*R*)-2-Hydroxy-2-phenylpropionylamino)-3-methylbutyric acid, methyl ester, 15f.** Colorless oil. $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.52$–$7.46$ (m, 2H, aromatic), 7.34–7.19 (m, 3H, aromatic), 6.77 (d, 1H, NH, $J = 8.6$ Hz), 4.40 (dd, 1H, NH–C*H*(CH($CH_3$)$_2$)COO, $J_1 = 8.8$ Hz, $J_2 = 4.8$ Hz), 3.62 (s, 3H, $OCH_3$), 2.20–1.96 (m, 1H, NH–CH(C*H*($CH_3$)$_2$)COO), 1.77 (s, 3H, $CH_3$), 0.79/0.73 (2d, 6H, NH–CH(CH(C$H_3$)$_2$)COO, $J = 6.9$ Hz). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta_C = 174.7/172.1$ (2s, O–CO, NH–CO), 142.9 (s, Ph–C-1), 128.5/128.0/125.5 (3d, Ph–C), 76.2 (s, Ph–*C*($CH_3$)(OH)–CO–NH), 57.1 (d, NH–*C*H(CH($CH_3$)$_2$)COO), 52.1 (q, $OCH_3$), 31.2 (q, $CH_3$), 26.8 (d, NH–CH(*C*H($CH_3$)$_2$)COO), 18.9/17.5 (2q, NH–CH(CH(*C*$H_3$)$_2$)COO).

### 4.9. Preparation of 5-bromo-2-methylpent-1-ene, 19

**4.9.1. 4-Methylpent-4-enoic acid, ethyl ester,[20] 17.** A mechanically stirred suspension of methyltriphenylphosphonium bromide (369 mmol/132 g) in dry THF (500 mL) was cooled to −85 °C. Then a 2.5 M solution of *n*-BuLi (410 mmol/164 mL) was slowly added by maintaining the temperature below −70 °C and stirring was continued for 1.5 h while cooling on an ice bath. After the mixture had been cooled again to −60 °C, a solution of ethyl laevulinate **16** (289 mmol/41 mL) in dry THF (150 mL) was slowly added by maintaining the temperature below −60 °C and stirring was continued overnight at room temperature. Water (200 mL) was then added while cooling on an ice bath. The organic layer was separated and the aqueous layer extracted three times with ether. The combined organic extracts were dried over $Na_2SO_4$, filtered, and the solvents were evaporated under reduced pressure (1013–380 mbar). The residue was taken up with pentane (250 mL) and stirred for 1 h while cooling on an ice bath. The remaining precipitate was filtered off, washed with a little portion of cold pentane, and the solvent was evaporated from the combined filtrates. The crude oil was fractionated in vacuo. 23.9 g (yield 58%) colorless oil, bp 75 °C (35 mbar). $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 4.76/4.71$ (2s, 2H, $CH_3$–C(=C$H_2$)–$CH_2$),

4.14 (q, 2H, O–C$H_2$–$CH_3$, $J = 7.1$ Hz), 2.51–2.30 (m, 4H, C$H_2$–C$H_2$–CO), 1.75 (s, 3H, C$H_3$–C(=$CH_2$)–$CH_2$), 1.26 (t, 3H, O–$CH_2$–C$H_3$, $J = 7.1$ Hz).

**4.9.2. 4-Methylpent-4-en-1-ol,[20] 18.** A solution of ester **17** (168 mmol/23.92 g) in dry THF (300 mL) was slowly added to a suspension of $LiAlH_4$ (337 mmol/12.77 g) in dry THF (200 mL), while cooling on an ice bath, with the resulting mixture stirred for 1 h at room temperature. After TLC analysis had indicated total conversion, water (40 mL) and a 2 M NaOH solution (20 mL) were slowly added while cooling on an ice bath, and stirring continued at room temperature until a white precipitate had formed. A small portion of $Na_2SO_4$ was added, and stirring continued for another 5 min at room temperature. Finally the mixture was filtered through a pad of Hyflo® and evaporated, yielding crude alcohol **18**, which was introduced in the next reaction step without any further purification.

15.1 g (yield 90%) colorless oil. $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 4.72$ (s, 2H, $CH_3$–C(=C$H_2$)–$CH_2$), 3.65 (q, 2H, C$H_2$–OH, $J = 6.5$ Hz), 2.10 (q, 2H, $CH_3$–C(=$CH_2$)–C$H_2$, $J = 7.7$ Hz), 1.78–1.64 (m, 3H, $CH_2$–C$H_2$–$CH_2$–O$H$), 1.74 (s, 3H, C$H_3$–C(=$CH_2$)–$CH_2$).

**4.9.3. 5-Bromo-2-methylpent-1-ene,[21] 19.** $NEt_3$ (161 mmol/22.4 mL) and methanesulfonyl chloride (80 mmol/6.2 mL) were successively added to a solution of alcohol **18** (54 mmol/5.38 g) in dry dichloromethane (25 mL) while cooling on an ice bath, and stirring continued for 1 h at 0 °C and 1 h at room temperature. Then 1 M HCl (25 mL) was added while cooling on an ice bath and the resulting mixture extracted three times with dichloromethane. The combined organic extracts were successively washed with a saturated aqueous $NaHCO_3$ solution and brine, dried over $Na_2SO_4$, filtered, and evaporated. The residue was dissolved in dry acetone (200 mL), LiBr (108 mmol/9.4 g) was added and the resulting mixture refluxed for 2 h. The solids were filtered off, washed with small portions of acetone, and the combined filtrates evaporated. Unreacted alcohol **18** was removed by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (20/1), and the resulting bromide **19** was distilled in vacuo to remove residual solvents. 8.47 g (yield 97%) colorless oil, bp 84–89 °C (110 mbar). $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 4.77/4.73$ (2s, 2H, $CH_3$–C(=C$H_2$)–$CH_2$), 3.42 (q, 2H, C$H_2$–Br, $J = 6.6$ Hz), 2.21–1.93 (m, 4H, C$H_2$–C$H_2$–$CH_2$–Br), 1.74 (s, 3H, C$H_3$–C(=$CH_2$)–$CH_2$).

### 4.10. Solution phase synthesis of (*R*)-2,6-dimethylhept-6-ene-1,2-diol, 23

**4.10.1. (*R*)-2-Hydroxy-2,6-dimethylhept-6-enoic acid, (1*R*, 2*S*)-2-(2-methoxyethoxy)-1,2-diphenylethyl ester, 22a.** Magnesium turnings (50.0 mmol/1.2 g) were suspended in dry THF (5 mL). Then 1/10 of a solution of bromide **19** (25.0 mmol/4.1 g) in dry THF (30 mL) was added whereupon the reaction started immediately. Then the whole amount of the bromide solution was added in such a way that a gentle reflux was maintained. After complete bromide addition, the resulting mixture was refluxed for another 10 min and then cooled to ambient temperature. The concentration of the resulting Grignard solution **20** was determined to be 0.58 M by titration.[22]

The freshly prepared Grignard solution **20** (9.344 mmol/16.1 mL) was slowly added to a thoroughly stirred solution of pre-dried $ZnCl_2$ (7.528 mmol/1.206 g) in dry THF (5 mL) while cooling on an ice bath, and the stirring continued for 2.5 h at 0 °C. Then dry methanol (1.752 mmol/0.07 mL) was added[13] and stirring was continued for 10 min at 0 °C. The supernatant solution of the as prepared organozinc reagent **21** was slowly added over 20 min to a solution of ester **7d** (0.818 mmol/0.28 g) in dry THF (20 mL), pre-cooled to −90 °C, by means of a syringe, and the resulting mixture stirred for 2 h at −78 °C. The temperature was then raised up to −20 °C over a period of 1 h, and finally a 10% aqueous $NH_4Cl$ solution (10 mL) was added and stirring continued for 15 min at room temperature. The mixture was taken up with saturated aqueous $NH_4Cl$ solution and extracted three times with ether. The combined ether extracts were successively washed with aqueous $NH_4Cl$ and brine, dried over $Na_2SO_4$, filtered, and evaporated. The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (10/1 → 5/1). 0.284 g (yield 81%) white solid, $R_f = 0.51$ (PE/E 1/1). $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 7.25$–$7.11$ (m, 10H, aromatic), 5.84/4.50 (2d, 2H, Ph–C$H$–O, $J = 6.7$ Hz), 4.57 (d, 2H, $CH_3$–C(C$H_2$)–$CH_2$–$CH_2$–$CH_2$, $J = 13.7$ Hz), 3.45–3.21 (m, 4H, O–C$H_2$–C$H_2$–O), 3.11 (s, 3H, O–$CH_3$), 2.98 (s, 1H, OH), 1.80–1.73 (m, 2H, $CH_3$–C($CH_2$)–$CH_2$–$CH_2$–C$H_2$), 1.58 (s, 3H, C$H_3$–C($CH_2$)–$CH_2$–$CH_2$–$CH_2$), 1.44–1.10 (m, 7H, $CH_3$–C($CH_2$)–C$H_2$–C$H_2$–$CH_2$), therein 1.20 (s, 3H, C$H_3$–C(OH)–CO)]. $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta_C = 175.6$ (s, O–CO), 145.2 (s, $CH_3$–C($CH_2$)–$CH_2$–$CH_2$–$CH_2$), 137.7/137.3 (2s, Ph–C-1), 128.2–127.2 (m, Ph–C), 109.9 (t, $CH_3$–C(C$H_2$)–$CH_2$–$CH_2$–$CH_2$), 84.3/78.8 (2d, Ph–C$H$–O), 74.1 (s, O–CO–C(OH)($CH_3$)–$CH_2$), 71.7/68.6 (2t, O–C$H_2$–C$H_2$–O), 58.7 (q, O–$CH_3$), 39.4 (t, $CH_3$–C($CH_2$)–$CH_2$–$CH_2$–C$H_2$), 37.5 (t, $CH_3$–C($CH_2$)–C$H_2$–$CH_2$–$CH_2$), 25.7 (q, C$H_3$–C($CH_2$)–$CH_2$–$CH_2$–$CH_2$), 22.2 (q, O–CO–C(OH)(C$H_3$)–$CH_2$), 21.0 (t, $CH_3$–C($CH_2$)–$CH_2$–C$H_2$–$CH_2$). Anal. Calcd for $C_{26}H_{34}O_5 \times 0.3H_2O$: C, 72.30; H, 8.07. Found: C, 72.39; H, 8.39.

**4.10.2. (*R*)-2,6-Dimethylhept-6-ene-1,2-diol, 23.** A solution of ester **22a** (0.609 mmol/0.259 g) in dry THF (10 mL) was slowly added to a suspension of $LiAlH_4$ (1.218 mmol/0.046 g) in dry THF (10 mL) while cooling on an ice bath, and the resulting mixture was stirred for 24 h at room temperature. After TLC analysis had indicated total conversion, a 10% aqueous $KHSO_4$ solution was added while cooling on an ice bath and the mixture was immediately extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered, and evaporated. The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ethyl acetate (5/1 → 0/1).

0.077 g (yield 80%) colorless oil, $R_f = 0.28$ (PE/EE 1/1), $[\alpha]_D^{25} = +2.4$ (*c* 1.29, $CH_2Cl_2$) {Lit.: $[\alpha]_D^{25} = +2.4$ (*R*)[19]}.

$^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 4.56$ (d, 2H, $CH_3$–C($CH_2$)–$CH_2$–$CH_2$–$CH_2$, $J = 6.0$ Hz), 3.33/3.25 (2d, 2H, C(OH)–$CH_2$–OH, $J_{AB} = 11.0$ Hz), 2.81 (s, 2H, OH), 1.88 (m, 2H, $CH_3$–C($CH_2$)–$CH_2$–$CH_2$–$CH_2$), 1.58 (s, 3H, $CH_3$–C($CH_2$)–$CH_2$–$CH_2$–$CH_2$), 1.36 (m, 4H, $CH_3$–C($CH_2$)–$CH_2$–$CH_2$–$CH_2$), 1.02 (s, 3H, $CH_3$–C(OH)). $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta_C = 145.5$ (s, $CH_3$–*C*($CH_2$)–$CH_2$–$CH_2$–$CH_2$), 110.0 (t, $CH_3$–C(*C*$H_2$)–$CH_2$–$CH_2$–$CH_2$), 73.0 (s, HO–$CH_2$–*C*(OH)($CH_3$)–$CH_2$), 69.6 (t, $CH_2$–OH), 38.1 (2t, $CH_3$–C($CH_2$)–*C*$H_2$–$CH_2$–*C*$H_2$), 23.0 (q, *C*$H_3$–C($CH_2$)–$CH_2$–$CH_2$–$CH_2$), 22.2 (q, HO–$CH_2$–C(OH)-(*C*$H_3$)–$CH_2$), 21.6 (t, $CH_3$–C($CH_2$)–$CH_2$–*C*$H_2$–$CH_2$).

### 4.11. Solid phase synthesis of (*R*)-2,6-dimethylhept-6-ene-1,2-diol, 23

**4.11.1. Polymer bound (*R*)-2-Hydroxy-2,6-dimethylhept-6-enoic acid ester, 22b.** Polymer bound pyruvate **7e** (~1.025 mmol/2.207 g) was suspended in dry THF (20 mL) and cooled to −90 °C. Then a solution of organozinc reagent **21**, which had been freshly prepared by the reaction of $ZnCl_2$ (8.363 mmol/1.140 g) and a solution of 0.62 M Grignard reagent **20** (9.297 mmol/15.0 mL) in THF as described above, was slowly added over 20 min, and the resulting mixture was stirred for 2 h at −78 °C. The temperature was then raised up to −20 °C over a period of 1 h, and finally a 10% aqueous $NH_4Cl$ solution (10 mL) was added and stirring was continued for 15 min at room temperature. The resin was filtered off and thoroughly washed successively with aqueous $NH_4Cl$ solution, water, water/THF (1/1), methanol, dichloromethane, methanol, dichloromethane, methanol, and dried in vacuo overnight at 40 °C. 2.448 g pale yellow resin. IR $\nu$ (KBr) = ~3503 cm$^{-1}$(OH), ~1734 cm$^{-1}$ (COOR); no further changes.

**4.11.2. (*R*)-2,6-Dimethylhept-6-ene-1,2-diol, 23.** $LiAlH_4$ (4.132 mmol/0.157 g) was dissolved in dry THF (10 mL) and the resulting mixture filtered under an atmosphere of dry argon into a suspension of hydroxyester **22b** (~1.015 mmol/2.426 g) in dry THF (10 mL), while cooling on an ice bath. The resulting mixture was shaken for 24 h at room temperature. Ethyl acetate (5 mL) and a 10% aqueous $KHSO_4$ solution were then successively added while cooling on an ice bath. The resin was filtered off and thoroughly washed successively with water, water/THF (1/1) and THF. The combined filtrates were extracted five times with ethyl acetate, and the combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered, and evaporated. The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ethyl acetate (5/1 → 0/1). 0.081 g (yield 50% over two steps) colorless oil, $R_f = 0.28$ (PE/EE 1/1), $[\alpha]_D^{25} = +2.1$ (*c* 1.29, $CH_2Cl_2$) {Lit.: $[\alpha]_D^{25} = +2.4$ (*R*)[19]}.

### 4.12. (1*R*,5*S*)-1,5-Dimethyl-6,8-dioxabicyclo[3.2.1]octane, (+)-frontalin, 24

*Frontalin* **24** was prepared by ozonolysis of diol **23** in dry dichloromethane at −78 °C and worked up with dimethyl sulfide and HCl according to the procedure described by Whitesell and Buchanan.[19] The crude product was purified by vacuum flash chromatography on silica gel, eluting with petroleum ether/ether (20/1). The as isolated product was assigned as (+)-*frontalin* by $^1$H NMR analysis and determination of its specific rotation. It was used for additional enantiomeric analysis by GC without total removal of the residual amounts of the solvent. $R_f = 0.51$ (PE/E 4/1). $^1$H NMR (200 MHz, $CDCl_3$, TMS): $\delta_H = 3.92$ (d, 1H, O–C$H_2$–CO, $J = 7.4$ Hz), 3.46 (dd, 1H, O–C$H_2$–CO, $J_1 = 7.4$ Hz, $J_2 = 1.8$ Hz), 1.90–1.33 [m, 12H, therein 1.44/1.33 (2s, 6H, $CH_3$)].

GC: Carlo Erba HRGC S300 Mega Series/FID, $H_2$/Air/LIPODEX E, 50 m, ∅ 0.25 mm/Inj. 200 °C, Pct. 220 °C/He, 100 kPa, split 1:20/100 °C isotherm; $t_{R1} = 9.5$ min. (+)-*Frontalin*; $t_{R2} = 9.9$ min. (−)-*Frontalin*; solution phase frontalin: 99:1 (98% ee); solid phase frontalin: 93:7 (86% ee).

## References


1. Prisinzano, T.; Hsin, L.-W.; Folk, J. E.; Flippen-Anderson, J. L.; George, C.; Jacobson, A. E.; Rice, K. C. *Tetrahedron: Asymmetry* **2003**, *14*, 3285–3289.
2. (a) Senanayake, C. H.; Fang, K.; Grover, P.; Bakale, R. P.; Vandenbossche, C. P.; Wald, S. A. *Tetrahedron Lett.* **1999**, *40*, 819–822; (b) Grover, P. T.; Bhongle, N. N.; Wald, S. A.; Senanayake, C. H. *J. Org. Chem.* **2000**, *65*, 6283–6287.
3. Hübscher, J.; Barner, R. *Helv. Chim. Acta* **1990**, *73*, 1068–1086.
4. Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908–6909.
5. Whitesell, J. K.; Deyo, D.; Bhattacharya, A. *J. Chem. Soc., Chem. Commun.* **1983**, 802.
6. For cyclohexyl based chiral auxiliaries used in the addition of organometallic reagents to α-ketocarboxylic acid derivatives, see: (a) Whitesell, J. K.; Deyo, D.; Bhattacharya, A. *J. Chem. Soc., Chem. Commun.* **1983**, 802; (b) Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953–964; (c) Boireau, G.; Korenova, A.; Deberly, A.; Abenhaim, D. *Tetrahedron Lett.* **1985**, *26*, 4181–4182; (d) Boireau, G.; Deberly, A.; Abenhaim, D. *Tetrahedron Lett.* **1988**, *29*, 2175–2176; (e) Boireau, G.; Deberly, A.; Abenhaim, D. *Tetrahedron* **1989**, *45*, 5837–5844; (f) Basavaiah, D.; Bharathi, T. K. *Tetrahedron Lett.* **1991**, *32*, 3417–3420; (g) Basavaiah, D.; Bharathi, T. K.; Rama Krishna, P. *Synth. Commun.* **1992**, *22*, 941–947; (h) Basavaiah, D.; Rama Krishna, P. *Tetrahedron* **1995**, *51*, 12169–12178; (i) Basavaiah, D.; Pandiaraju, S.; Muthukumaran, K. *Tetrahedron: Asymmetry* **1996**, *7*, 13–16; (j) Basavaiah, D.; Pandiaraju, S.; Bakthadoss, M.; Muthukumaran, K. *Tetrahedron: Asymmetry* **1996**, *7*, 997–1000; (k) Hamon, D. P. G.; Holman, J. W.; Massy-Westropp, R. A. *Tetrahedron* **1993**, *49*, 9593–9604; (l) Huang, D.-L.; Draper, R. W. *Tetrahedron Lett.* **1994**, *35*, 661–662.
7. For non-cyclohexyl based chiral auxiliaries used in the addition of organometallic reagents to α-ketocarboxylic acid derivatives, see: (a) Kawanami, Y.; Fujita, I.; Ogawa, S.; Katsuki, T. *Chem. Lett.* **1989**, 2063–2066; (b) Hübscher, J.; Barner, R. *Helv. Chim. Acta* **1990**, *73*, 1068–1086; (c) Koshiishi, E.; Hattori, T.; Ichihara, N.; Miyano, S. *J. Chem Soc., Perkin Trans. 1* **2002**, 377–383; (d) Senanayake, C. H.; Fang, K.; Grover, P.; Bakale, R. P.; Vandenbossche, C. P.; Wald, S. A. *Tetrahedron Lett.* **1999**, *40*, 819–822; (e) Tamai, Y.; Nakano, T.; Miyano, S. *Chem. Lett.* **1992**, 807–808; (f) Tamai, Y.; Nakano, T.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 439–445; (g) Kawana, M.; Emoto, S. *Tetra-*

*hedron Lett.* **1972**, *48*, 4855–4858; (h) Kawana, M.; Emoto, S. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 160–165; (i) Akiyama, T.; Nishimoto, H.; Ishikawa, K.; Ozaki, S. *Chem. Lett.* **1992**, 447–450; (j) Loupy, A.; Monteux, D. A. *Tetrahedron* **2002**, *58*, 1541–1549.

8. (a) Schuster, C.; Broeker, J.; Knollmueller, M.; Gaertner, P. *Tetrahedron: Asymmetry* **2005**, *16*, 2631–2647; (b) Schuster, C.; Knollmueller, M.; Gaertner, P. *Tetrahedron: Asymmetry* **2005**, *16*, 3211–3223; (c) Broeker, J.; Knollmueller, M.; Gaertner, P. *Tetrahedron: Asymmetry* **2006**, *17,* doi:10.1016/j.tetasy.2006.08.017.
9. (a) Noe, C. R. *Chem. Ber.* **1982**, *115*, 1576–1590; (b) Noe, C. R.; Knollmüller, M.; Wagner, E.; Völlenkle, H. *Chem. Ber.* **1985**, *118*, 1733–1745; (c) Noe, C. R.; Knollmüller, M.; Steinbauer, G.; Völlenkle, H. *Chem. Ber.* **1985**, *118*, 4453–4458; (d) Noe, C. R.; Knollmüller, M.; Steinbauer, G.; Jangg, E.; Völlenkle, H. *Chem. Ber.* **1988**, *121*, 1231–1239.
10. (a) Nara, M.; Shima, S. T.; Yamada, S. *Tetrahedron* **1980**, *36*, 3161–3170; (b) Nagao, Y.; Inoue, T.; Fujita, E.; Terada, S.; Shiro, M. *J. Org. Chem.* **1983**, *48*, 132.
11. (a) Superchi, S.; Contursi, M.; Rosini, C. *Tetrahedron* **1998**, *54*, 11247–11254; (b) Scafato, P.; Leo, L.; Superchi, S.; Rosini, C. *Tetrahedron* **2002**, *58*, 153–159.
12. Cavelier, F.; Gomez, S.; Jacquier, R.; Llinares, M.; Mereadier, J.-L.; Petrus, C.; Verducci, J. *Tetrahedron: Asymmetry* **1993**, *4*, 2495–2500.
13. Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445–446.
14. (a) Kinzer, G. W.; Fentiman, F. A.; Page, F. T.; Foltz, R. L.; Vite, J. P.; Pitman, G. B. *Nature* **1969**, *221*, 477–478; (b) Renwick, J. A. A.; Vite, J. P. *Nature* **1969**, *224*, 1222–1223; (c) Wood, D. L.; Browne, L. E.; Ewing, B.; Lindahl, K.; Bedard, W. D.; Tilden, P. E.; Mori, K.; Pitman, G. B.; Hughes, P. R. *Science* **1976**, *192*, 896–898; (d) Payne, T. L.; Richerson, J. V.; Dickens, J. C.; West, J. R.; Mori, K.; Brisford, C. W.; Hedden, R. L.; Vité, J. P.; Blum, M. S. *J. Chem. Ecol.* **1982**, *8*, 873; (e) Mori, K. *Eur. J. Org. Chem.* **1998**, 1479–1489; (f) Franche, W.; Schroder, W. *Curr. Org. Chem.* **1999**, *3*, 407–443.
15. (a) Perrin, T. E.; Rasmussen, L. E. L.; Gunawardena, R.; Rasmussen, R. A. *J. Chem. Ecol.* **1996**, *22*, 207; (b) Rasmussen, L. E. L.; Lazar, J.; Greenwood, D. R. *Biochem. Soc., Trans.* **2003**, *31*, 137–141.
16. Huber, D. P. W.; Gries, R.; Borden, J. H.; Pierce, H. D. *J. Chem. Ecol.* **1999**, *25*, 805–816.
17. (a) Mori, K. *Tetrahedron* **1975**, *31*, 1381; (b) Ohrui, H.; Emoto, S. *Agric. Biol. Chem.* **1976**, *40*, 2267; (c) Hicks, D. R.; Reid, B. F. *J. Chem. Soc., Chem. Commun.* **1976**, 869; (d) Sakito, Y.; Mukaiyama, T. *Chem. Lett.* **1979**, 1027–1028.
18. For stereoselective syntheses of frontalin in the recent literature see: (a) Ambrosi, P.; Arnone, A.; Bravo, P.; Bruché, L.; De Cristofaro, A.; Francardi, V.; Frigerio, M.; Gatti, E.; Germinara, G. S.; Panzeri, W.; Pennacchio, F.; Pesenti, C.; Rotundo, G.; Roversi, P. F.; Salvatori, C.; Viani, F.; Zanda, M. *J. Org. Chem.* **2001**, *66*, 8336–8343; (b) Jew, S.; Lim, D.-Y.; Kim, J.-Y.; Kim, S.; Roh, E.; Yi, H.-J.; Ku, J.-M.; Park, B.; Jeong, B.; Park, H. *Tetrahedron: Asymmetry* **2002**, *13*, 155–159; (c) Trzoss, M.; Shao, J.; Bienz, S. *Tetrahedron* **2002**, *58*, 5885–5894; (d) Chenevert, R.; Caron, D. *Tetrahedron: Asymmetry* **2002**, *13*, 339–342; (e) Yus, M.; Ramón, D. J.; Prieto, O. *Eur. J. Org. Chem.* **2003**, 2745–2748.
19. Whitesell, J. K.; Buchanan, C. M. *J. Org. Chem.* **1986**, *51*, 5443–5445.
20. Boyer, F.-D.; Ducrot, P.-H. *Eur. J. Org. Chem.* **1999**, 1201–1211.
21. (a) Snider, B. B.; Walner, M. *Tetrahedron* **1989**, *45*, 3171–3182; (b) Johnson, W. S.; Gen, A. V. D.; Koenraad, W.; Swoboda, J. J.; Dunathan, H. C. *J. Am. Chem. Soc.* **1973**, *95*, 2656–2663.
22. Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–168.
23. Okamoto, S.; Yoshino, T.; Tsujiyama, H.; Sato, F. *Tetrahedron Lett.* **1991**, *32*, 5793–5796.
24. Meyers, A. I.; Slade, J. *J. Org. Chem.* **1980**, *45*, 2912–2914.
25. Huang, D.-L.; Draper, R. W. *Tetrahedron Lett.* **1994**, *35*, 661–662.
26. Fuji, K.; Tanaka, K.; Ahn, M.; Mizuchi, M. *Chem. Pharm. Bull.* **1994**, *42*, 957–959.