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Enantioselective synthesis of (*S*)- and (*R*)-6-hydroxy-8-nonene-carboxylates by asymmetric catalysis: a formal synthesis of (*R*)-α-lipoic acid and its (*S*)-antipode

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Abstract

A short and efficient enantioselective synthesis of (*S*)- and (*R*)-configured 6-hydroxy-8-nonene-carboxylates — precursors to (*R*)-α-lipoic acid and its (*S*)-enantiomer — by allylation of alkoxycarbonyl substituted aldehydes with allyltrimethylstannane and BINOL/Ti(O*i*Pr)$_4$ catalyst is described. The best results in terms of enantiomeric purity and yield are obtained employing 10 mol% of the titanium-species without molecular sieves.

1. Introduction

(*R*)-α-Lipoic acid (also called thioctic acid or 6,8-dithiooctanoic acid) **1**[1] has attracted great attention because of its fascinating biological activity.[2] Compound (*R*)-**1** plays an important role in numerous biological processes, for example it shows effects in diabetes mellitus and hepatic diseases as well as anti-inflammatory, immunological and arteriosclerotic activity. For therapy purposes lipoic acid is often used as racemic material because the (*S*)-enantiomer shows no significant biological side effects. Nevertheless, the stereoselective synthesis of (*R*)-**1** is of interest in organic synthesis and in particular medicinal chemistry (Scheme 1). There are at present various methods for the synthesis or formal synthesis of enantiopure α-lipoic acid including kinetic resolution of racemic material,[3] retro-Henry cleavage of 2-nitrocyclohexanol,[4] enzyme-catalysed reactions of key intermediates,[5] an iron-mediated strategy starting from a tricarbonyl(diene)iron complex,[6] as well as the use of key compounds from the chiral pool.[7] Surprisingly, no synthesis of (*R*)-**1** where the crucial stereogenic centre is generated by asymmetric catalysis is known.

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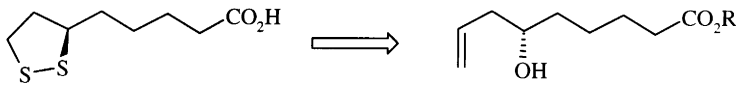


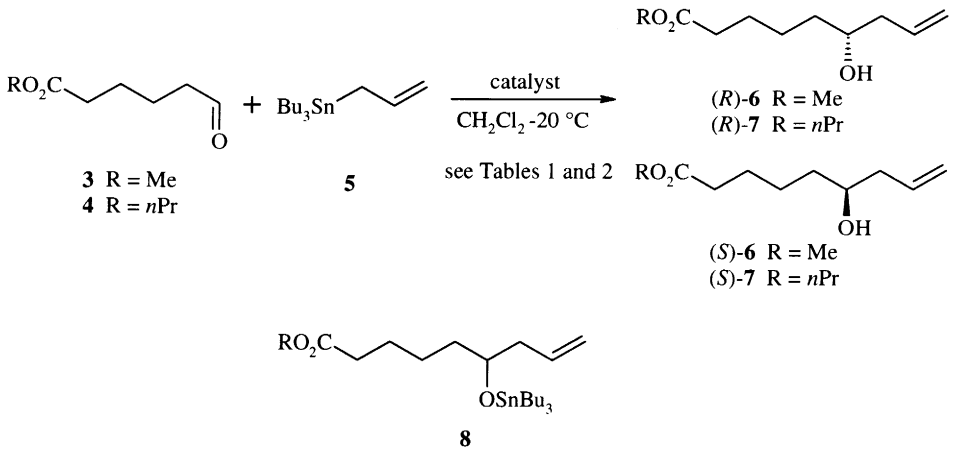
(*R*)-(+)-Lipoic Acid **1** **2**

Scheme 1.

Optically active allylic and homoallylic alcohols have frequently been used as valuable building blocks in the syntheses of enantiopure products.[8] To our knowledge, the preparation of key compound **2** by enantioselective reactions is limited to methods using either chiral substrates[9] or equimolar amounts of chiral reagents.[10] In recent years, the versatility of chiral binaphthol-derived (BINOL) metal species has been broadly demonstrated by their use as catalysts in enantioselective allylation and aldol reactions.[11–15] In this paper we describe the first preparation of key compounds **6** and **7** for the synthesis of (*R*)-α-lipoic acid and its (*S*)-antipode by an enantioselective allylation reaction of functionalised aliphatic aldehydes **3** and **4** with allyltributylstannane **5** catalysed by different BINOL–metal species.

2. Results and discussion

Starting with the easily accessible methoxycarbonyl- and *n*-propoxycarbonyl-substituted aldehydes **3** and **4**, respectively, enantioselective allylation additions were performed with commercially available allyltributylstannane **5** (Scheme 2). Variations of reaction conditions and catalyst species were examined and representative results are compiled in Tables 1 and 2. All allylation reactions were performed in dichloromethane as preliminary experiments had established that optimal results were obtained with this solvent.



3 R = Me
4 R = *n*Pr

5

8

Scheme 2.

We started by employing the catalytic asymmetric allylstannation protocol developed by Keck et al.[12a–c] In the presence of a catalyst system comprising 0.2 equivalents of (*S*)-BINOL, 0.2 equivalents of Ti(O*i*Pr)$_4$ and 4 Å molecular sieves which had been pre-mixed at reflux temperature in dichloromethane for one hour, the reaction of aldehyde **3** and allyltributylstannane **5** provided product (*R*)-**6** with 73% yield and 98% enantiomeric excess (entry 1, Table 1). Our initial efforts focused on reducing the pre-mixed catalyst amount from 20, 10, 5 to 2.5 mol% (entries 2–5, Table 1). The enantioselectivity of the allylation reaction was strongly dependent on the amount of catalyst. The use of 10 mol% of (*R*)-BINOL/Ti catalyst and 1.1 equivalents of **5** at −20°C for six days provided the (*S*)-enriched alcohol **7** in

Table 1
Allylation reactions of aldehydes **3** and **4** with **5** catalysed by BINOL/Ti(O*i*Pr)$_4$

Entry	**3 / 4** R	Precursor of Catalyst (equiv.)	Equiv. of **5**	Time [d]	Product **6-8**	Yield [%]	Ee [%]
1	Me	(*S*)-BINOL (0.2) / Ti(O*i*Pr)$_4$ (0.2)[a]	2.0	2	(*R*)-**6**	73	98
2	*n*-Pr	(*R*)-BINOL (0.2) / Ti(O*i*Pr)$_4$ (0.1)[b]	1.1	6	(*S*)-**7**	89	98
3	*n*-Pr	(*R*)-BINOL (0.1) / Ti(O*i*Pr)$_4$ (0.05)[b]	1.1	5	(*S*)-**7**	86	50
4	*n*-Pr	(*R*)-BINOL (0.05) / Ti(O*i*Pr)$_4$ (0.025)[b]	1.1	6	(*S*)-**7**	59	27
5	*n*-Pr	(*R*)-BINOL (0.1) / Ti(O*i*Pr)$_4$ (0.1)[a]	1.1	3	(*S*)-**7**	45	80
6	*n*-Pr	(*R*)-BINOL (0.2) / Ti(O*i*Pr)$_4$ (0.2);[a] CF_3CO_2H (0.003)	3.0	3	(*S*)-**7**	65	36
7	*n*-Pr	(*R*)-BINOL (0.2) / Ti(O*i*Pr)$_4$ (0.1)[b,c]	1.1	5	**8**	56	n.d.
8	*n*-Pr	(*R*)-BINOL (0.2) / Ti(OEt)$_4$ (0.1)[b,c]	1.1	5	**8**	23	n.d.

[a] Premixing time: 1 h, reflux, MS 4 Å.

[b] Premixing time: 2 h, room temp.

[c] Workup by addition of H_2O (stirring 5 min at r.t.).

n.d. not determined (see text).

89% yield and with 98% *ee* (entry 2), but reduction of the catalyst to 5 mol% or 2.5 mol% dramatically decreased the enantioselectivity to 50% and 27% *ee*, respectively (entries 3 and 4).

The allylation rate was also dependent on the use of molecular sieves.[16] Thus, in the presence of finely powdered 4 Å molecular sieves (pre-treated by heating to 150°C, 5 h, 0.15 mbar) the rate was accelerated (compare entries 1/2 and 5/3). In addition, we observed that in allylation reactions using 0.1 equivalents of Ti(O*i*Pr)$_4$ the enantioselectivity of (*S*)-**7** is significantly lower with molecular sieves (entries 2 and 5). On the other hand, an excellent level of enantioselectivity (entries 1 and 2) could not be attained by employing an additional additive such as trifluoroacetic acid[12a] (entry 6).

The reaction mixture was usually worked up by addition of satd sodium hydrogen carbonate solution and stirring for 30 min at room temperature, but changing the workup procedure by addition of water and stirring only for 5 min at room temperature (entries 7 and 8, Table 1) resulted in the isolation of the corresponding stannyloxy substituted compound **8**. In one example we changed the alkoxy group on titanium from O*i*Pr to OEt (entries 7 and 8). The chemical yield of **8** decreased from 56% to 23%, but there was no effect to the enantioselectivity because both products showed the same $[\alpha]_D$ value. A similar effect has already been described by Weigand and Brückner[17] for analogous reactions of β-substituted allylstannanes with aldehydes. For derivative **8** we estimate an enantioselectivity in the range of 98% *ee*, as we observed for **7** under the same reaction conditions (see entry 2, Table 1).

Table 2
Allylation reactions of aldehydes **3** and **4** with **5** catalysed by BINOL or TADDOL/Met(Lig)$_x$

Entry	**3** / **4** R	Precursor of Catalyst (equiv.)	Equiv. of **5**	Time [d]	Product **6**-**7**	Yield [%]	Ee [%]
1	*n*-Pr	(*R*)-BINOL (0.2) / $TiCl_2(OiPr)_2$ (0.2)[a]	1.5	1	(*S*)-**7**	60	18
2	Me	(*S*)-BINOL (0.2) / $TiCl_2(OiPr)_2$ (0.2)[a]	1.5	1	(*R*)-**6**	57	77
3	Me	(*S*)-BINOL (0.2) / $Zr(OiPr)_4$ (0.2)[b]	1.5	6 h	(*R*)-**6**	70	12
4	*n*-Pr	(*R*)-BINOL (0.2) / $Yb(OTf)_3$ (0.1)[c]	1.1	6	**7**	19	0
5	Me	(-)-TADDOL (0.2) / $TiCl_2(OiPr)_2$ (0.2)[b]	1.5	5	(*S*)-**6**	25	16

[a] Premixing time: 1 h, reflux, MS 4 Å.

[b] Premixing time: 2 h, room temp., MS 4 Å.

[c] Premixing time: 2 h, room temp.

It should be mentioned that BINOL can be recovered from the reaction mixture almost quantitatively in all cases by stirring the crude product in hexane; filtration of the insoluble BINOL is very effective.

We have also chosen other BINOL catalyst systems for the allylation reaction as described above and the results are summarised in Table 2. Use of $TiCl_2(OiPr)_2$ instead of $Ti(OiPr)_4$ (BINOL/$TiCl_2$, Mikami catalyst[18]) resulted in a poor enantioselectivity (18% *ee*, entry 1, Table 2) under typical pretreatment of the molecular sieves (vide supra). On the other hand, an improved enantioselectivity (77% *ee*, entry 2, Table 2) was obtained when pre-treatment of molecular sieves was executed by heating to 250°C and 0.15 mbar for 8 h.

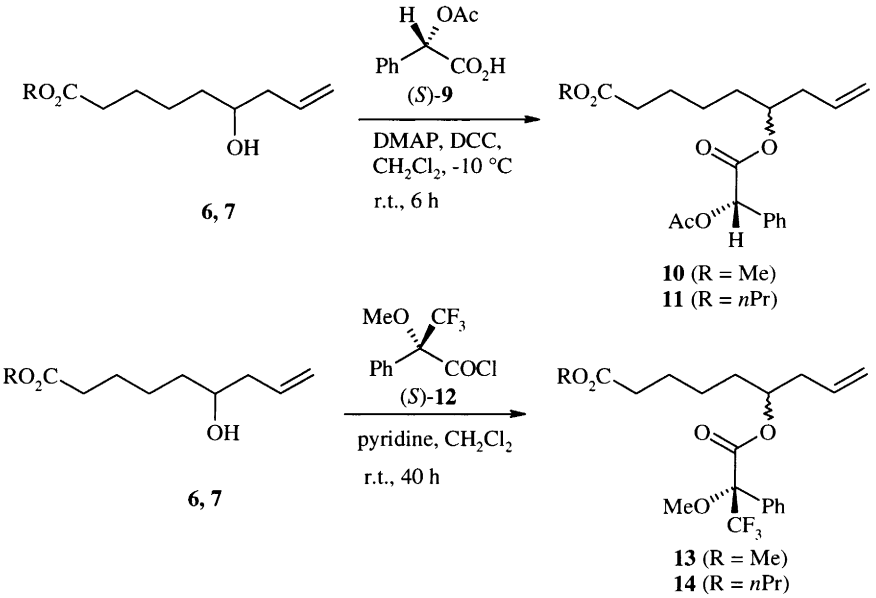
The allylation reaction of **3** and **4** with reagent **5** was also examined using other metal species (entries 3 and 4). As shown in Table 2, employing (*S*)-BINOL/$Zr(OiPr)_2$ as catalyst (entry 3) under conditions optimised for applications of aromatic aldehydes by Umani-Ronchi et al.,[15] the addition produced (*R*)-**6** in 70% yield, but with a poor enantiomeric excess of 12%. The enantioselective allylation reaction using $Yb(OTf)_3$ as the metal species failed since only racemic material in low yield was formed (entry 4).

The addition of allylstannane **5** to aldehyde **3** in the presence of $TiCl_2(OiPr)_2$/(−)-TADDOL[19] was also examined (entry 5, Table 2). In this case the expected addition product (*S*)-**6** was isolated in low yield (25%) and low enantioselectivity (16% *ee*).

The enantiomeric purities of the resulting homoallylic alcohols **6** and **7** were unambiguously established either by HPLC after conversion of **6** (or **7**) into compound **10** (or **11**) with (*S*)-(+)-*O*-acetylmandelic acid **9**,[20] or by ^{1}H and ^{13}C NMR spectroscopy of the corresponding MPTA esters **13** (or **14**) with Mosher's acid chloride (*S*)-**12**[21] (Scheme 3). The *ee* value of compound **6** was also determined by comparison with the known maximum specific rotation.[10a]

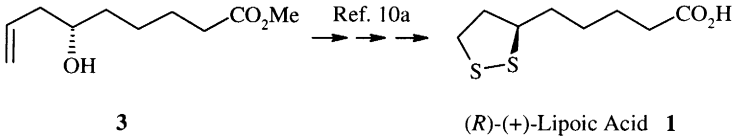
With (*S*)-BINOL as catalyst ligand the predominating enantiomer of **6** possesses (*R*)-configuration at the newly generated stereocentre, which is unambiguously established by comparison with the known sign of the specific rotation.[10a]

In summary, the present work describes a highly efficient procedure for preparation of key compounds for synthesis of (*R*)-lipoic acid **1** or its (*S*)-antipode in good yields and with excellent enantioselectivities. Compared with other multistep syntheses of **2**[10] our one-step procedure starts with simple and commer-



Scheme 3.

cially available compounds. The conversion of **3** to target **1** is already described in the literature (see Scheme 4).[10a]



Scheme 4.

3. Experimental

3.1. General

All reactions were performed in flame-dried flasks under argon atmosphere, and the components were introduced by syringe. All solvents were dried by standard methods. IR spectra were measured with a Perkin–Elmer IR-325 spectrometer or Nicolet 205 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with Bruker instruments (AC 200 or AC 300) in $CDCl_3$ solution. The chemical shifts are given relative to TMS from the solvent ($CDCl_3$) signal (δ_H=7.27, δ_C=77.0). Neutral alumina (activity III, Fa. Merck-Schuchardt) or silica gel (0.040–0.063 mm, Fa. Merck-Schuchardt) was used for column chromatography. Boiling points of compounds obtained in small-scale experiments refer to the temperature in a Büchi kugelrohroven. Melting points (uncorrected) were measured with an apparatus from Gallenkamp (MPD 350). Optical rotations were determined in a 1 ml cell with a path length of 10 cm using a Perkin–Elmer 241 polarimeter (Na_D line). The $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} and the concentrations are given in g/100 cm^3. (*S*)- and (*R*)-BINOL, Ti(O*i*Pr)$_4$, Zr(O*i*Pr)$_4$ and allyltributylstannane were commercially available and were used as received.

The other starting materials were synthesised as described in the literature (Ti(O*i*Pr)$_2$Cl$_2$,[23] aldehydes **3** and **4**[22]).

3.2. General procedure for the enantioselective allylation reaction (method A)

A mixture of the metal species [Ti(O*i*Pr)$_4$, Ti(OEt)$_4$, TiCl$_2$(O*i*Pr)$_2$, Zr(O*i*Pr)$_4$ or Yb(OTf)$_3$] (0.025–0.2 equiv.), (*R*)- or (*S*)-BINOL (0.05–0.2 equiv.) and 4 Å molecular sieves (600 mg/mmol of aldehyde) in CH_2Cl_2 (4 ml/mmol of aldehyde) was stirred under reflux. After 1 h, the reaction mixture was cooled to rt, the corresponding aldehyde **3** or **4** (1.0 equiv.) was added and the mixture was stirred for 10 min at rt. Then the reaction mixture was cooled to −78°C and allyltributylstannane **5** (1.1–3.0 equiv.) was added. The reaction proceeded for the time indicated in the individual experiment at −20°C in the refrigerator.

3.3. General procedure for the enantioselective allylation reaction (method B)

Similar to the procedure as described above, but the generation of the catalyst species was performed by stirring at rt for 2 h without molecular sieves.

3.4. General procedure for the enantioselective allylation reaction (method C)

Similar to the procedure as described above, but the generation of the catalyst species was performed by stirring at rt for 2 h in the presence of 4 Å molecular sieves.

3.5. Workup procedures

Method A: The reaction was quenched by addition of satd aqueous $NaHCO_3$ solution (0.5 ml/mmol of aldehyde) and the mixture was stirred for 30 min at rt. The aqueous layer was extracted three times with CH_2Cl_2 (5 ml/mmol of aldehyde), the combined organic phases were dried over Na_2SO_4 and concentrated.

Method B: The reaction was quenched by addition of H_2O (0.5 ml/mmol of aldehyde) and the mixture was stirred for 5 min at rt. Further workup was performed as described above.

Entry 1 (Table 1): According to general procedure (method A) and workup procedure (method A), the reaction of aldehyde **3** (0.720 g, 5.00 mmol) with **5** (3.30 g, 10.0 mmol) in the presence of Ti(O*i*Pr)$_4$ (0.285 g, 1.00 mmol), (*S*)-BINOL (0.286 g, 1.00 mmol) and 4 Å molecular sieves (3.00 g) for 2 d afforded after chromatography (silica gel, hexane:acetone, 17:3) (*R*)-**6** (0.680 g, 73%, 98% *ee*).

Entry 2 (Table 1): According to general procedure (method B) and workup procedure (method A), the reaction of aldehyde **4** (0.172 g, 1.00 mmol) with **5** (0.364 g, 1.10 mmol) in the presence of Ti(O*i*Pr)$_4$ (28.4 mg, 0.10 mmol) and (*R*)-BINOL (57.2 mg, 0.20 mmol) for 5 d afforded after chromatography (neutral alumina, hexane:EtOAc, 9:1) (*S*)-**7** (0.190 g, 89%, 98% *ee*).

Entry 3 (Table 1): According to general procedure (method B) and workup procedure (method A), the reaction of aldehyde **4** (0.172 g, 1.00 mmol) with **5** (0.364 g, 1.10 mmol) in the presence of Ti(O*i*Pr)$_4$ (14.2 mg, 0.05 mmol) and (*R*)-BINOL (28.6 mg, 0.10 mmol) for 5 d afforded after chromatography (neutral alumina, hexane:EtOAc, 9:1) (*S*)-**7** (0.183 g, 86%, 50% *ee*).

Entry 4 (Table 1): According to general procedure (method B) and workup procedure (method A), the reaction of aldehyde **3** (0.172 g, 1.00 mmol) with **5** (0.364 g, 1.10 mmol) in the presence of Ti(O*i*Pr)$_4$ (7.1 mg, 0.025 mmol) and (*R*)-BINOL (14.4 mg, 0.05 mmol) for 6 d afforded after chromatography (neutral alumina, hexane:EtOAc, 9:1) (*S*)-**7** (0.126 g, 59%, 27% *ee*).

Entry 5 (Table 1): According to general procedure (method A) and workup procedure (method A), the reaction of aldehyde **4** (0.860 g, 5.00 mmol) with **5** (1.80 g, 5.50 mmol) in the presence of Ti(O*i*Pr)$_4$

(0.142 g, 0.50 mmol), (*R*)-BINOL (0.143 g, 0.50 mmol) and 4 Å molecular sieves (3.00 g) for 3 d afforded after chromatography (silica gel, hexane:acetone, 17:3) (*S*)-**7** (0.460 g, 45%, 80% *ee*).

Entry 6 (Table 1): According to general procedure (method A) and workup procedure (method A), the reaction of aldehyde **4** (0.860 g, 5.00 mmol) with **5** (5.00 g, 15.0 mmol) in the presence of $Ti(OiPr)_4$ (0.285 g, 1.00 mmol), (*R*)-BINOL (0.286 g, 1.00 mmol), CF_3CO_2H (1.7 mg, 0.015 mmol) and 4 Å molecular sieves (3.00 g) for 3 d afforded after chromatography (silica gel, hexane:acetone, 17:3) (*S*)-**7** (0.660 g, 65%, 36% *ee*).

Entry 7 (Table 1): According to general procedure (method B) and workup procedure (method B), the reaction of aldehyde **4** (0.172 g, 1.00 mmol) with **5** (0.364 g, 1.10 mmol) in the presence of $Ti(OiPr)_4$ (28.4 mg, 0.10 mmol) and (*R*)-BINOL (57.2 mg, 0.20 mmol) for 5 d afforded after chromatography (neutral alumina, hexane:EtOAc, 9:1) **8** (0.283 g, 56%).

Entry 8 (Table 1): According to general procedure (method B) and workup procedure (method B), the reaction of aldehyde **4** (0.172 g, 1.00 mmol) with **5** (0.364 g, 1.10 mmol) in the presence of $Ti(OEt)_4$ (22.8 mg, 0.10 mmol) and (*R*)-BINOL (57.2 mg, 0.20 mmol) for 5 d afforded after chromatography (neutral alumina, hexane:EtOAc, 9:1) **8** (0.076 g, 23%).

Entry 1 (Table 2): According to general procedure (method A) and workup procedure (method A), the reaction of aldehyde **4** (0.860 g, 5.00 mmol) with **5** (2.50 g, 7.50 mmol) in the presence of $TiCl_2(OiPr)_2$ (0.240 g, 1.00 mmol), (*R*)-BINOL (0.286 g, 1.00 mmol) and 4 Å molecular sieves (3.00 g) for 1 d afforded after chromatography (silica gel, hexane:acetone, 17:3) (*S*)-**7** (0.610 g, 60%, 18% *ee*).

Entry 2 (Table 2): According to general procedure (method A) and workup procedure (method A), the reaction of aldehyde **3** (0.720 g, 5.00 mmol) with **5** (2.50 g, 7.50 mmol) in the presence of $TiCl_2(OiPr)_2$ (0.240 g, 1.00 mmol), (*S*)-BINOL (0.286 g, 1.00 mmol) and 4 Å molecular sieves (3.00 g) for 1 d afforded after chromatography (silica gel, hexane:acetone, 17:3) (*R*)-**6** (0.530 g, 57%, 77% *ee*).

Entry 3 (Table 2): According to general procedure (method C) and workup procedure (method A), the reaction of aldehyde **3** (0.720 g, 5.00 mmol) with **5** (2.50 g, 7.50 mmol) in the presence of $Zr(OiPr)_4$ (0.390 g, 1.00 mmol), (*S*)-BINOL (0.286 g, 1.00 mmol) and 4 Å molecular sieves (3.00 g) for 6 h afforded after chromatography (silica gel, hexane:acetone, 17:3) (*R*)-**6** (0.650 g, 70%, 12% *ee*).

Entry 4 (Table 2): According to general procedure (method B) and workup procedure (method A), the reaction of aldehyde **4** (0.172 g, 1.00 mmol) with **5** (0.364 g, 1.10 mmol) in the presence of $Yb(OTf)_3$ (62.0 mg, 0.10 mmol) and (*R*)-BINOL (57.2 mg, 0.20 mmol) for 6 d afforded after chromatography (neutral alumina, hexane:EtOAc, 9:1) racemic **7** (0.040 g, 19%).

Entry 5 (Table 2): According to general procedure (method C, but with TADDOL instead of BINOL) and workup procedure (method A), the reaction of aldehyde **3** (0.720 g, 5.00 mmol) with **5** (2.50 g, 7.50 mmol) in the presence of $TiCl_2(OiPr)_2$ (0.240 g, 1.00 mmol), (−)-2,3-*O*-isopropylidene-1,1,4,4-tetraphenyl-L-threitol (TADDOL, 0.470 g, 1.00 mmol) and 4 Å molecular sieves (3.00 g) for 1 d afforded after chromatography (silica gel, hexane:acetone, 17:3) (*S*)-**6** (0.260 g, 25%, 16% *ee*).

*3.6. Determination of the enantiomeric excess of products **6** and **7***

*3.6.1. General procedure for transformation of **6** and **7** into **10** and **11** by reaction with (S)-(+)-O-acetylmandelic acid **9** according to Ref. 20*

To a solution of (*S*)-(+)-*O*-acetylmandelic acid **9** (1.0 equiv.) and DMAP (4 mg/mmol of alcohol) in CH_2Cl_2 (5 ml/mmol of alcohol) the corresponding alcohol **6** or **7** (1.0 equiv.) and DCC (1.0 equiv., 1 M solution in CH_2Cl_2) were added at −10°C. The suspension was warmed to rt and stirred for 6 h. After filtration of the reaction mixture and concentration of the filtrate the resulting residue was dissolved in acetone (2 ml/mmol of alcohol). After removing the remaining urea by filtration the filtrate was

concentrated and the resulting crude product **10** (or **11**) was used for determination of the enantiomeric excess by HPLC.

HPLC method: HP 1090 (Hewlett–Packard); column: Lichrospher endcapped RP18, 250×4 mm^2, particle size: 10 μm (Fa. Knauer); eluent: 125 ml of water, 375 ml of methanol, 0.1 ml of glacial acid, 0.1 ml of NEt_3, 270 mg of $NaC_{12}H_{25}SO_3$; wavelength: 210 nm; injection: 20 μl, rt; concentration: 2 mg/ml of methanol; retention times: (*R*,*S*)-**10**: 16.3 min; (*S*,*S*)-**10**: 14.8 min; (*R*,*S*)-**11**: 17.7 min; (*S*,*S*)-**11**: 16.0 min.

*3.6.2. General procedure for transformation of **6** and **7** into **13** and **14** by reaction with Mosher's acid chloride (*S*)-**12***

To a solution of alcohol **6** or **7** (1.0 equiv.) in CH_2Cl_2 and dry pyridine (each 5.5 ml/mmol of alcohol) Mosher's acid chloride (S)-**12** (1.4 equiv.) was added and the mixture was stirred for 40 h at rt. Then the mixture was diluted with CH_2Cl_2 (50 ml/mmol of alcohol) and washed successively with 2N HCl solution, satd $NaHCO_3$ solution and H_2O (each 15 ml/mmol of alcohol). The organic layer was dried (Na_2SO_4) and the solvent was evaporated to afford the crude product which was pure by TLC analysis. The *ee* value of the resulting product **13** (or **14**) was determined by ^1H and ^{13}C NMR.

*3.7. Spectroscopic and analytical data of compounds **6**–**8***

Methyl 6-hydroxy-8-nonenoate (*R*)-**6**: colourless oil, bp 90–95°C/0.1 mbar. ^1H NMR (300 MHz, $CDCl_3$): δ=5.90–5.73, 5.20–5.10 (2 m, 1H, 2H, HC=CH_2), 3.65 (s, 3H, OCH_3), 3.75–3.53 (m, 1H, CHOH), 2.48–2.02, 1.70–1.36 (2 m, 5H, 6H, 5 CH_2, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=175.9 (s, COO), 136.8, 119.3 (d, t, HC=CH_2), 72.2 (d, OCH), 53.2 (q, OCH_3), 43.8, 38.1, 35.8, 27.2, 26.9 (5 t, 5 CH_2). Anal. calcd for $C_{10}H_{18}O_3$ (186.2): C, 64.49; H, 9.74. Found: C, 64.53; H, 9.72. $[\alpha]_D^{20}$ +9.3 (*c*=1.0, $CHCl_3$). Ref. 10a $[\alpha]_D^{22}$ +9.18 (*c*=1.0, $CHCl_3$).

n-Propyl 6-hydroxy-8-nonenoate (*S*)-**7**: colourless oil, bp 95–100°C/0.1 mbar. ^1H NMR (200 MHz, $CDCl_3$): δ=5.93–5.72, 5.17–5.08 (2 m, 1H, 2H, HC=CH_2), 4.03 (t, *J*=6.7 Hz, 2H, OCH_2), 3.73–3.58 (m, 1H, C*H*OH), 2.40–2.08, 1.75–1.35 (2 m, 5H, 8H, 6 CH_2, OH), 0.94 (t, *J*=7.3 Hz, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=173.7 (s, COO), 134.7, 117.8 (d, t, HC=CH_2), 70.3 (d, CHOH), 65.8 (t, OCH_2), 41.9, 36.3, 34.2, 25.1, 24.8, 21.9 (6 t, 6 CH_2), 10.3 (q, CH_3); IR (film): ν=3650–3200 cm^{-1} (OH), 2980–2870 (C–H), 1735 (COO), 1640 (C=C). Anal. calcd for $C_{12}H_{22}O_3$ (214.3): C, 67.26; H, 10.35. Found: C, 67.08; H, 10.90. $[\alpha]_D^{23}$ −5.6 (*c*=1.7, $CHCl_3$).

n-Propyl 6-(tributylstannyloxy)-8-nonenoate **8**, R=*n*-Pr: colourless crystals, mp 54–59°C. ^1H NMR (300 MHz, $CDCl_3$): δ=5.90–5.76, 5.15–5.11 (2 m, 1H, 2H, HC=CH_2), 4.03 (t, *J*=6.8 Hz, 2H, OCH_2), 3.65 (m_c, 1H, CHOSn), 2.32 (t, *J*=7.3 Hz, 2H, CH_2), 2.29–2.06, 1.71–1.15 (2 m, 2H, 26H, 14 CH_2), 0.94, 0.91 (2 t, *J*=7.3 Hz each, 3H, 9H, 4 CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=173.7 (s, COO), 134.7, 118.0 (d, t, CH=CH_2), 70.3 (d, CHOSn), 65.8 (t, OCH_2), 41.9, 36.3, 34.2, 27.8, 27.4, 26.9, 26.5, 22.0, 16.3 (9 t, 9 CH_2), 13.5 (q, 3 CH_3), 10.3 (q, CH_3). Anal. calcd for $C_{24}H_{48}O_3Sn$ (503.3): C, 57.27; H, 9.54. Found: C, 57.49; H, 9.66. $[\alpha]_D^{25}$=−2.6 (*c*=1.1, $CHCl_3$).

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