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Synthetic approach toward *cis*-disubstituted γ- and δ-lactones through enantioselective dialkylzinc addition to aldehydes: application to the synthesis of optically active flavors and fragrances

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ABSTRACT

A versatile and straightforward approach to optically active *cis*-4,5-disubstituted γ- and δ-lactones by catalytic enantioselective addition of dialkyzincs to cinnamic aldehydes and RCM ring closure has been reported. The synthetic importance of the enantioselective dialkylzinc alkylation of aldehydes has been thus widened. Such an approach has then been employed for the enantioselective synthesis of naturally occurring γ-lactone flavors like (*S*)-5-ethyl-butanolide (**6a**) and (4*S*,5*S*)-*cis*-whisky lactone (**6b**) and extended to the preparation of δ-lactones like (5*S*,6*S*)-5-methyl-6-ethylpentanolide (**9a**), precursor of the pheromone serricornin.

1. Introduction

The enantioselective alkylation of aldehydes by dialkylzinc reagents is by far one of the most studied asymmetric transformations.[1] This reaction was described for the first time in 1984 by Oguni and Omi, employing (*S*)-leucinol as a chiral catalyst.[2] Since then a very large amount of different chiral catalytic precursors have been developed, often leading to high levels of enantioinduction. Moreover, contrary to other popular enantioselective reactions, in this case deep experimental and theoretical investigations have defined with a good degree of certainty the mechanism determining the asymmetric induction.[3] The knowledge of the reaction mechanism, joined to the ease of the operating conditions made this reaction a popular benchmark to test the efficiency of new chiral ligands as chirality inducers.[4] Surprisingly, despite the vast number of reactivity studies undertaken over a couple of decades, this reaction has found, until now, very few synthetic applications.[5] The only synthetic studies reported so far concern the employment of such reaction in the preparation of chiral methyl carbinol synthons, precursors of natural products,[6] and the preparation of optically active 3-alkylphthalides.[7]

We recently developed a new family of chiral aminoalcohols, endowed with C_2 symmetric 1,1′-binaphthylazepine structure, which efficiently catalyze the enantioselective addition of dialkyl, diphenyl, and dialkynyl zinc reagents to aldehydes, providing good to excellent enantioselectivity.[8] Such results prompted us to explore the synthetic potential of these reactions in order to demonstrate that they can provide not only a feasible test of the catalysts activity, but also a reliable tool for the asymmetric synthesis of complex intermediates.

Generally speaking, the asymmetric alkylation of aldehydes affords high ee's with aryl and α,β-unsaturated aldehydes. Therefore, in principle, it can provide access to optically active benzylic and allylic alcohols. In particular, the latter compounds are potentially valuable chiral intermediates and precursors of important natural products. Interestingly, some recent works point out the role of allylic alcohols as precursors of racemic γ-lactones[9] and β,γ-unsaturated δ-lactones[10] through esterification with, respectively, acrylic or 3-butenoic acid followed by a ring closing metathesis (RCM) reaction.[11] We then envisaged that the catalytic enantioselective dialkylzinc addition to aldehydes could be employed as a key step for a new general approach to the synthesis of optically active *cis*-4,5-disubstituted γ-lactones and *cis*-5,6-disubstituted δ-lactones as showed in Scheme 1.

The approach described herein then has the double aim of showing the underexplored synthetic utility of the enantioselective dialkylzinc addition and to provide a straightforward and versatile

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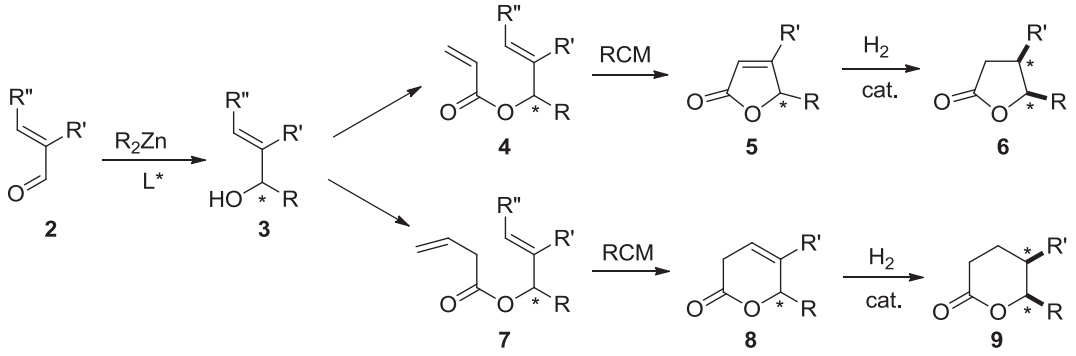


Scheme 1.

method to obtain important intermediates. Five- and six-membered lactones are in fact ubiquitous structures among natural products and in particular many pheromones and important flavors and fragrances contain mono and dialkyl γ- or δ-lactones.[12] In particular, while γ-lactones are important aroma components of fruits, teas, wines, and spirits, δ-lactones are more commonly detected in dairy products and other fermented foods. In such compounds a direct correlation between the aromatic properties and the absolute configuration at C-5 has been observed. Therefore, the preparation of such compounds in optically active form deserves a high scientific and industrial relevance.

2. Results and discussion

At first, we investigated the key step for the preparation of the required allylic alcohols, that is, the enantioselective dialkylzinc addition to α,β-unsaturated aldehydes in the presence of ligands **1a**–**c** previously developed by us (Fig. 1).[8]

According to Scheme 1 the required starting chiral allylic alcohols could be derived from alkylation of propenals or 2-alkylpropenals. Some preliminary attempts of dialkylzinc additions to both 2-methylpropenal and 2,3-dimethylpropenal were however unsuccessful, providing mainly by-products deriving from both aldehyde self-condensation and 1,4-addition of the alkylzinc reagent.[13] We then attempted to employ less reactive cinnamic aldehydes. Much to our delight these substrates were found to be much more stable under the reaction conditions and afforded good to excellent yields and ee's in the alkylation reaction with dialkylzincs (vide infra).

The reaction was carried out in dry toluene at 20 °C in the presence of 8–10 mol% of the chiral ligand and monitored by TLC and GC–MS. When complete conversion of the aldehyde was detected, the mixture was quenched by addition of 10% aqueous HCl. After extraction with Et_2O, drying, and evaporation of solvent, the product ratio was directly determined on the crude mixture by GC–MS and the ee of the product 1-alkyl-3-phenylpropanol **3** was measured by HPLC or GC on chiral stationary phases (Scheme 2 and Table 1).

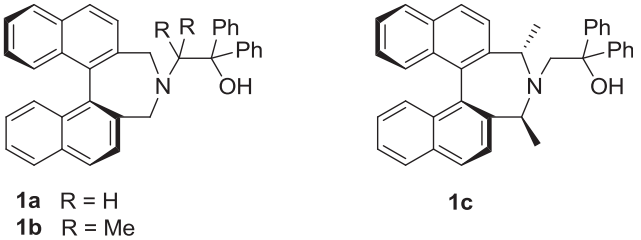
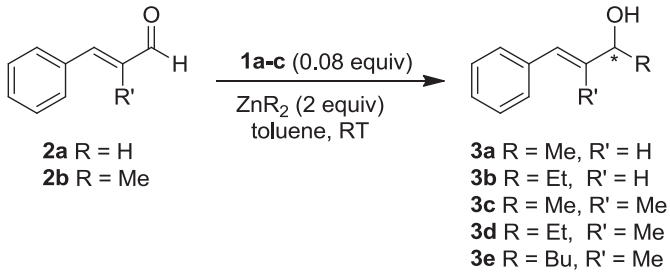


Fig. 1. 1,1′-Binaphthylazepine aminoalcohol ligands.



Scheme 2. Dialkylzinc enantioselective addition to cinnamic aldehydes.

Table 1
Enantioselective addition of R_2Zn to cinnamic aldehydes mediated by ligands **1a**–**c**[a]

Run	Aldehyde	R	Ligand	Time (h)	Product	Yield[b] (%)	ee (%)[c] (ac)[d]
1	**2a**	Me	**1a**[e]	40	**3a**	72	46 (*S*)
2	**2a**	Me	**1b**[e]	23	**3a**	99	72 (*S*)
3	**2a**	Me	**1c**[e]	20	**3a**	99	72 (*S*)
4	**2a**	Et	**1a**[f]	1	**3b**	91	68 (*S*)
5	**2a**	Et	**1b**[f]	1	**3b**	99	78 (*S*)
6	**2a**	Et	**1c**[f]	1	**3b**	99	78 (*S*)
7	**2b**	Me	**1a**[e]	40	**3c**	50	36 (*S*)
8	**2b**	Me	**1b**[e]	25	**3c**	60	56 (*S*)
9	**2b**	Me	**1c**[e]	20	**3c**	70	60 (*S*)
10	**2b**	Et	**1a**[f]	4	**3d**	99	76 (*S*)
11	**2b**	Et	**1b**[f]	1	**3d**	99	90 (*S*)
12	**2b**	Et	**1c**[f]	1	**3d**	99	90 (*S*)
13	**2b**	Bu	**1a**[e]	28	**3e**	18	82 (*S*)
14	**2b**	Bu	**1b**[e]	24	**3e**	52	90 (*S*)
15	**2b**	Bu	**1c**[e]	5	**3e**	97	94 (*S*)

[a] Reactions performed at rt in toluene.
[b] Chromatographic (GLC) yield. No traces of benzylalcohols were detected.
[c] Enantiomeric excess determined by HPLC on Chiralcel OD-H and OJ columns.
[d] Absolute configuration determined by comparison of $[\alpha]_D$ with literature values: see Experimental section.
[e] 10 mol% of aminoalcohol was used.
[f] 8 mol% of aminoalcohol was used.

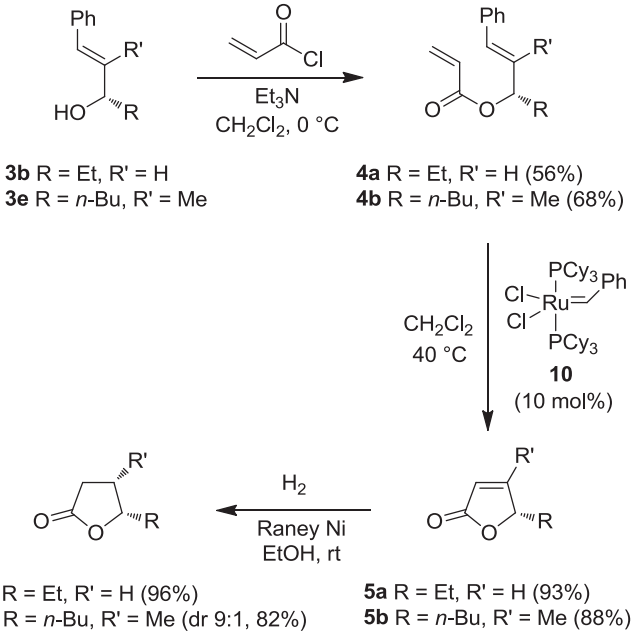
The absolute configuration of carbinols **3a**–**d** was assigned by comparison of optical rotations with literature values (see Experimental section), while (*S*) absolute configuration was tentatively assigned to the unknown optically active alcohol **3e** taking into account that previous studies[8d,e] have shown that binaphthylazepine aminoalcohols bearing an (*S*) configured binaphthyl moiety promote alkylzinc attack on the *Si* face of aldehydes.

As inferred from Table 1, ligands **1b** and **1c** provided complete conversion and good enantiomeric excess in both methylation and ethylation of (*E*)-cinnamaldehyde. The corresponding carbinols **3a** and **3b** being obtained in 72% and 78% ee, respectively (see runs 2, 3, 5, and 6). Conversely, lower yields and ee's were achieved employing ligand **1a**. Ligands **1b** and **1c** proved to be more efficient

also in the alkylation of (*E*)-2-methyl cinnamaldehyde. In all the cases tested, ligand **1c** provided faster reactions and slightly higher enantioselectivity that **1b**, affording 60, 90, and 94% ee in the addition of Me_2Zn, Et_2Zn, and Bu_2Zn, respectively (see runs 9, 12, and 15). The latter result being particularly interesting, being, to the best of our knowledge, the first example of enantioselective Bu_2Zn addition to this aldehyde. The relative efficiency of these three ligands was the same as observed in the alkylzinc addition to aromatic aldehydes.[8e] As far as Et_2Zn addition is concerned, the ee values reached are comparable with those reported in the literature on the same aldehydes,[14] while the results obtained with addition of Bu_2Zn and Me_2Zn are particularly noteworthy, in terms of chemical yields and enantioselectivity. In fact these two alkylzinc reagents are generally much less reactive than the more commonly used Et_2Zn and often provide lower ee's.[3a,d]

To demonstrate the generality and feasibility of the approach depicted in Scheme 1 for the synthesis of optically active *cis*-4,5-disubstituted γ-lactones and *cis*-5,6-disubstituted δ-lactones, carbinols **3b**, **3d**, and **3e** were then employed as starting material for the preparation of valuable γ and δ lactones. Both γ- and δ-lactones are present, among the others, in tobacco flavor,[15] and in the scent of some flowers,[16,17] as well as in many other artificial or natural fragrances.[18]

At first, the synthesis of optically active 5-alkyl γ-lactones, important components of aroma of fruits, flowers, and beverages, was attempted. 5-Ethyl γ-lactone **6a**, endowed with an intense aroma of caramel and liquorice, is found in many fruits, but also in different foods and beverages, like butter, beer, brandy, tea, and added to tobacco as flavoring agent.[19] It has been also identified as a pheromone of the *Trogoderma glabrum* beetle.[20] Its preparation was then attempted (Scheme 3) starting from the alcohol **3b**, obtained in 78% ee (see Table 1, run 6) by enantioselective Et_2Zn addition to (*E*)-cinnamaldehyde.

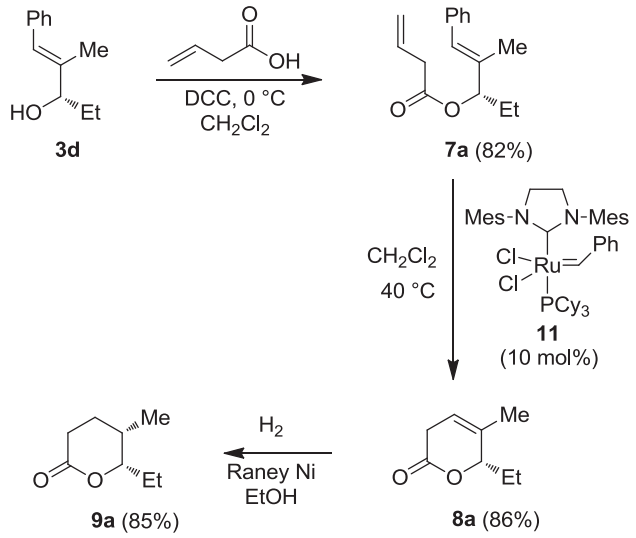


Scheme 3. Synthesis of γ-lactones **6a**,**b**.

The allylic alcohol **3b** was esterified by treatment with acryloyl chloride at 0 °C in CH_2Cl_2, in the presence of anhydrous Et_3N. After treatment and chromatographic purification, ester **4a** was obtained in 70% yield. Compound **4a** was then submitted to RCM heating at 40 °C in CH_2Cl_2 in the presence of the first generation Grubbs' catalyst **10**. 5-Ethyl butenolide **5a** was then obtained in 93% yield after chromatographic purification. Final catalytic hydrogenation of **5a** in the presence of Raney-Ni,[21] provided the γ-lactone (*S*)-**6a** in 96% yield. The optical purity of all the intermediates was thoroughly checked after any synthetic step, confirming the retention of the starting 78% ee.

A similar strategy was followed for the preparations of (4*S*,5*S*)-*cis*-whisky lactone **6b**. The lactone and its (4*S*,5*R*)-trans isomer are released by oak barrels in wines and spirits during the aging process and give appreciated aromas to these beverages.[22] In particular the (4*S*,5*S*)-*cis*-whisky lactone is regarded as the most important to the sensory characteristics of wine.[23] The importance of whisky lactones led to the development of a number of syntheses of both diastereoisomers in optically active form using either chiral pool[24] or chiral auxiliaries.[25] However, only a few reports employing enantioselective catalysis[26] and biocatalysis[17a,27] are described. Moreover these approaches are directed only toward the synthesis of *trans*-whisky lactone and, to the best of our knowledge, no enantioselective catalytic routes to optically active *cis*-whisky lactone have been described to date. The synthesis of lactone **6b** was approached (Scheme 3) starting from allylic alcohol **3e**, obtained in 94% ee (see Table 1, run 15) by enantioselective Bu_2Zn addition to (*E*)-2-methyl cinnamaldehyde. Alcohol **3e** was transformed in the corresponding acrylate **4b** and the latter submitted to RCM with first generation Grubbs' catalyst **10**. The obtained 4-methyl-5-ethyl butenolide **5b** was finally hydrogenated in the presence of Raney-Ni,[21] providing (4*S*,5*S*)-*cis*-whisky lactone **6b** in a 9:1 cis/trans diastereoisomeric ratio. After chromatographic purification (4*S*,5*S*)-*cis*-**6b** was recovered in 94% ee and overall 50% yield. This simple and straightforward approach to optically active *cis*-whisky lactone represents the first route to this important compound based on enantioselective catalysis.

Following the synthetic analysis reported in Scheme 1, allylic alcohols obtained by enantioselective alkylation of cinnamic aldehydes can also be employed as starting materials for obtaining δ-lactones.[10,28] To test the feasibility of such an approach the synthesis of optically active δ-lactone (5*S*,6*S*)-**9a**, a synthetic precursor of serricornin,[29] the sex pheromone of the cigarette beetle (*Lasioderma serricorne*), was attempted. Accordingly, alcohol **3d**, obtained in 90% ee (see Table 1, run 12) by enantioselective Et_2Zn addition to 2-methyl cinnamaldehyde, was transformed into the corresponding ester with 3-butenoic acid (Scheme 4). The esterification was performed in the presence of DCC, in CH_2Cl_2 at 0 °C to avoid shift of the acid double bond. Ester **7a** was then submitted to RCM reaction to afford the unsaturated six-membered lactone **8a**. In this case



Scheme 4. Synthesis of δ-lactone **9a**.

better results were obtained employing Grubbs' second-generation catalyst **11**. Finally hydrogenation of **8a** in the presence of Raney-Ni, provided the saturated lactone (5*S*,6*S*)-**9a** with complete diastereocontrol and 90% ee.

3. Conclusions

We have reported herein a versatile and straightforward approach to optically active *cis*-4,5-disubstituted γ- and δ-lactones through catalytic enantioselective addition of dialkyzincs to cinnamic aldehydes and RCM ring closure. This result extends the synthetic importance of the enantioselective dialkylzinc alkylation of aldehydes, a well-known reaction which, however, has found to date few synthetic applications. Such an approach has been employed for the synthesis of natural aromas like (*S*)-5-ethyl butenolide (**6a**) and (4*S*,5*S*)-*cis*-whisky lactone (**6b**). In the latter case the procedure described herein constitutes the first approach reported for the synthesis of optically active *cis*-whisky lactone by enantioselective catalysis. The same strategy was extended to the preparation of δ-lactones and tested in the synthesis of δ-lactone (5*S*,6*S*)-**9a**, a precursor of the pheromone serricornin. Moreover, the employment of the novel 1,1-binaphthylazepine aminoalcohols **1a**–**c** as catalysts in the asymmetric addition of dialkylzinc compounds to cinnamic aldehydes allowed the desired allylic alcohols to be obtained in good to high ee's, thus confirming the efficiency of these atropisomeric binaphthyl ligands in asymmetric catalysis.

4. Experimental section

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker Aspect 300 MHz and Varian INOVA 400 MHz spectrometers using TMS as internal standard. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. GC–MS analyses were performed on a Hewlett Packard 6890 chromatograph equipped with an HP-5973 mass detector. Column chromatography was carried out using Macherey-Nagel silica gel 60 (70–230 mesh). Analytical thin-layer chromatography (TLC) was performed on Macherey-Nagel aluminum sheets precoated with silica gel (0.25 mm). Toluene was freshly distilled prior its use on sodium benzophenone ketyl and stored under nitrogen atmosphere. CH_2Cl_2 was freshly distilled over CaH_2 prior to its use. Triethylamine was distilled over CaH_2 and stored under nitrogen on KOH. Addition of dialkyzincs was performed using syringe-septum cap techniques under a nitrogen atmosphere. Diethylzinc (1.0 M in hexane), dibutylzinc (1.0 M in heptane), and dimethylzinc (2.0 M in toluene) were used as purchased (Aldrich). Commercially available (Aldrich) (*E*)-cinnamaldehyde and (*E*)-2-methyl cinnamaldehyde were distilled prior their use and stored under a nitrogen atmosphere. Unless otherwise specified the reagents were used without any purification. Enantiopure ligands **1a**,[8b] **1b**,[8c] and **1c**[8e] were prepared as previously described. Spectroscopic data for allylic alcohols **3a**[30] and **3c**[31] and for all other known compounds fully matched those reported in the literature. Enantiomeric excesses of alcohols **3a**–**e** were determined by HPLC analysis performed on a JASCO PU-1580 pump with a Varian 2550 UV detector and Daicel Chiralcel OD-H column. Absolute configuration of alcohols **3a**,[32] **3b**,[14a] **3c**,[33] and **3d**[14b] was assigned by comparison of optical rotations with literature values.

4.2. Typical procedure for the dialkylzinc addition to aldehydes

To a solution of the ligand (0.05 mmol) in dry toluene (3 mL) under a nitrogen atmosphere at rt, was added a solution of R_2Zn in hexane (1.0 M, 1.25 mL, 1.25 mmol). The mixture was stirred for 30 min, then a solution of aldehyde (0.62 mmol) in dry toluene (1.3 mL) was added. The reaction was monitored by GC–MS and when no more traces of the aldehyde were detected the reaction was quenched by addition of 10% aqueous HCl. The mixture was extracted with Et_2O and the organic phase was washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent the crude extract was directly analyzed by GC–MS to determine the yield and either by HPLC or GC to establish the ee. The reaction mixture was then purified by column chromatography (SiO_2; petroleum ether/Et_2O 8:2) affording alcohols **3a**–**e** as colorless oils.

*4.2.1. (S)-(E)-1-Phenylpent-1-en-3-ol (**3b**).*[34] Yield 99%; ee 78% by HPLC on Chiralcel OJ (hexane/2-propanol 98:2, flow 0.5 mL/min, t_R (*R*) 44.51 min, t_R (*S*) 47.46 min). $[\alpha]_D^{25}$ −7.3 (*c* 1.01, $CHCl_3$); R_f (20% Et_2O/petroleum ether) 0.27; lit.[14a] $[\alpha]_D^{25}$ −6.3 (*c* 1.73, $CHCl_3$) for *S* enantiomer in 87.6% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm):0.91 (3H, t, *J* 7.3 Hz), 1.56–1.61 (2H, m), 2.28 (1H, s), 4.12–4.18 (1H, m), 6.18 (1H, dd, *J* 6.8, 16.4 Hz), 6.53 (1H, d, *J* 16.4 Hz), 7.21–7.27 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 10.4, 30.8, 74.9, 127.0, 128.1, 129.1, 130.9, 132.9, 137.4. Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.42; H, 8.71.

*4.2.2. (S)-(E)-2-Methyl-1-phenylpent-1-en-3-ol (**3d**).*[35] Yield 99%; ee 90% by HPLC on Chiralcel OD-H (hexane/2-propanol 99:1, flow 0.7 mL/min, t_R (*R*) 63.87 min, t_R (*S*) 72.22 min). $[\alpha]_D^{25}$ +28 (*c* 1.01, $CHCl_3$); R_f (20% Et_2O/petroleum ether) 0.26; lit.[14b] $[\alpha]_D^{25}$ +29.2 (*c* 1.1, $CHCl_3$) for *S* enantiomer in 83% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.94 (3H, t, *J* 7.5 Hz), 1.44–1.71 (3H, m), 1.85 (3H, s), 4.10 (1H, t, *J* 6.5 Hz), 6.48 (1H, s), 7.20–7.34 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 10.1, 13.1, 27.9, 79.5, 126.1, 126.4, 128.1, 128.9, 137.6, 140.1. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.80; H, 9.14.

*4.2.3. (S)-(E)-2-Methyl-1-phenylhept-1-en-3-ol (**3e**).*[31] Yield 97%; ee 94% by HPLC on Chiralcel OD-H (hexane/2-propanol 99:1, flow 0.7 mL/min, t_R (*R*) 28.48 min, t_R (*S*) 32.55 min); R_f (20% Et_2O/petroleum ether) 0.25; $[\alpha]_D^{25}$ +18 (*c* 0.88, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.91 (3H, t, *J* 6.5 Hz), 1.14–1.36 (4H, m), 1.59–1.63 (2H, m), 1.85 (3H, s), 2.03 (1H, s), 4.12–4.16 (1H, t, *J* 6.5 Hz), 6.46 (1H, s), 7.20–7.34 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 13.1, 14.1, 22.7, 28.1, 34.8, 78.1, 125.7, 126.4, 128.1, 129.1, 137.8, 140.6. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.25; H, 9.91.

4.3. (*S*)-(*E*)-1-Phenylpent-1-en-3-yl acrylate (4a)

To a solution of alcohol (*S*)-**3b** (0.26 g; 1.60 mmol) in dry CH_2Cl_2 (37 mL) was added Et_3N (0.44 mL; 3.20 mmol) and the mixture was cooled to 0 °C. To this solution was added dropwise acryloyl chloride (0.2 mL; 2.45 mmol) in dry CH_2Cl_2 (12 mL). The reaction was monitored by TLC, and after 1 h, was quenched by the addition of water. The mixture was extracted with CH_2Cl_2, the organic phase was washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by column chromatography (SiO_2; petroleum ether/Et_2O 10:1) affording ester **4a** as a colorless oil (190.0 mg, 56%); R_f (9% Et_2O/petroleum ether) 0.44; $[\alpha]_D^{25}$ −3.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91 (3H, t, *J* 7.0 Hz), 1.76–1.82 (2H, m), 5.42 (1H, q, *J* 7.0 Hz), 5.85 (1H, dd, *J* 1.5, 10.5 Hz), 6.08–6.18 (2H, m), 6.41 (1H, d, *J* 16.0 Hz), 6.60 (1H, d, *J* 16.0 Hz), 7.20–7.31 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 9.6, 27.6, 76.2, 126.6, 127.4, 127.9, 128.5, 128.8, 130.6, 132.6, 136.4, 165.6. Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.74; H, 7.46. Found: C, 77.72; H, 7.48.

4.4. (*S*)-5-Ethylfuran-2(5*H*)-one (5a)[36]

A solution of the Grubbs' catalyst **10** (first generation) (0.074 g; 0.09 mmol) in CH_2Cl_2 (9 mL) was added dropwise to solution of **4a** (0.19 g; 0.88 mmol) in CH_2Cl_2 (88 mL) at reflux. The reaction was monitored by GC–MS. After 60 h the reaction was completed, the solvent was removed by evaporation, and the crude extract was purified by column chromatography (SiO_2; petroleum ether/Et_2O 3:1) affording **5a** as a yellow oil (92.0 mg, 93%); R_f (20% Et_2O/petroleum ether) 0.15; $[\alpha]_D^{25}$ +64 (*c* 1.0, $CHCl_3$); lit.[27a] $[\alpha]_D^{25}$ +95 (*c* 3.61, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91 (3H, t, *J* 7.0 Hz), 1.71–1.78 (2H, m), 4.94–4.97 (1H, m), 6.30 (1H, dd, *J* 1.5, 5.5 Hz), 7.42 (1H, dd, *J* 1.5, 5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 8.9, 26.2, 84.4, 121.5, 156.2, 173.4. Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.23; H, 7.21.

4.5. (*S*)-5-Ethyl-dihydrofuran-2(3*H*)-one (6a)[37]

To a solution of **5a** (50.0 mg, 0.44 mmol) in dry ethanol (5.5 mL) was added Raney-Ni and the mixture was set under a hydrogen atmosphere. The reaction was monitored by GC–MS and after 3 h the mixture was filtered through Celite. After evaporation of the solvent, the crude extract was purified by column chromatography (SiO_2; petroleum ether/Et_2O 3:1) affording **6a** as a pale yellow oil (48.0 mg, 96%, 78% ee); R_f (25% Et_2O/pentane) 0.42; $[\alpha]_D^{25}$ −36 (*c* 0.65, CH_3OH); lit.[38] $[\alpha]_D^{25}$ −48.8 (*c* 1.0, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.95 (3H, t, *J* 7.0 Hz), 1.50–1.81 (3H, m), 2.26–2.29 (1H, m), 2.48 (2H, dd, *J* 7.0, 9.5 Hz), 4.34–4.40 (1H, quint., *J* 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 9.4, 27.4, 28.4, 28.8, 82.2, 177.4. Anal. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 63.13; H, 8.84.

4.6. (*S*)-(*E*)-2-Methyl-1-phenylhept-1-en-3-yl acrylate (4b)

To a solution of (*S*)-**3e** (0.16 g; 0.81 mmol) in dry CH_2Cl_2 (19 mL) was added Et_3N (0.23 mL; 1.62 mmol) and the mixture was cooled to 0 °C. To this solution was added dropwise acryloyl chloride (0.11 mL, 1.24 mmol) in dry CH_2Cl_2 (6 mL). The reaction was monitored by TLC and after 1 h the reaction was quenched by addition of water. The mixture was extracted with CH_2Cl_2, the organic phase was washed with brine, and dried over anhydrous Na_2SO_4. After evaporation of solvent, the residue was purified by column chromatography (SiO_2; petroleum ether/Et_2O 97:3) affording **4b** as a pale yellow oil (140 mg, 68%); R_f (9% Et_2O/petroleum ether) 0.45; $[\alpha]_D^{25}$ −1.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.91 (3H, t, *J* 6.6 Hz), 1.35–1.41 (6H, m), 1.60–1.88 (3H, m), 5.36 (1H, t, *J* 6.9 Hz), 5.82 (1H, d, *J* 10.4 Hz), 6.15 (1H, dd, *J* 17.2, 10.4 Hz), 6.43 (1H, d, *J* 17.2 Hz), 6.53 (1H, s), 7.26–7.32 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 13.1, 14.1, 22.7, 28.1, 34.8, 78.1, 125.7, 126.4, 128.1, 128.5, 129.0, 129.2, 137.8, 140.6, 166.0. Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 79.06; H, 8.57.

4.7. (*S*)-5-Butyl-4-methylfuran-2(5*H*)-one (5b)[39]

A solution of the Grubbs' catalyst **10** (first generation) (41.0 mg; 0.05 mmol) in CH_2Cl_2 (5 mL) was added dropwise to solution of ester **4b** (0.13 g; 0.50 mmol) in CH_2Cl_2 (50 mL) at reflux. The reaction was monitored by GC–MS. When the reaction was completed, after 80 h, the solvent was removed by evaporation and the crude extract was purified by column chromatography (SiO_2; petroleum ether/Et_2O 4:1) affording **5b** as a yellow oil (68.0 mg, 88%); R_f (25% Et_2O/petroleum ether) 0.18; $[\alpha]_D^{25}$ +2.7 (*c* 1.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.87 (3H, t, *J* 6.9 Hz), 1.19–1.51 (4H, m), 1.83–1.90 (2H, m), 2.02 (3H, s), 4.77–4.86 (1H, m), 5.75 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.8, 13.9, 22.2, 26.2, 31.6, 84.6, 116.5, 168.3, 173.3. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10,; H, 9.15. Found: C, 70.06; H, 9.16.

4.8. (4S,5S)-5-Butyl-dihydro-4-methylfuran-2(3H)-one (6b)[25d]

To a solution of **5b** (52.0 mg, 0.33 mmol) in dry ethanol (5 mL) was added Raney-Ni and the mixture was set under hydrogen atmosphere. The reaction was monitored by GC–MS and after 3 h the mixture was filtered through Celite. After evaporation of the solvent, the crude extract was checked by GC–MS, showing the presence of **6b** in 9:1 cis/trans ratio. The crude extract was then purified by column chromatography (SiO_2; petroleum ether/Et_2O 3:1) affording *cis*-**6b** a colorless oil (42.0 mg, 82%, 94% ee). The minor trans isomer was not isolated from the mixture; R_f (25% Et_2O/pentane) 0.40; $[\alpha]_D^{25}$ −66.0 (*c* 1.01, CH_3OH); lit.[25d] $[\alpha]_D^{25}$ −76.9 (*c* 1.73, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.91 (3H, t, *J* 7.0 Hz), 1.10 (3H, d, *J* 7.0 Hz), 1.10–1.80 (6H, m), 2.21 (1H, dd, *J* 3.7, 16.8 Hz), 2.51–2.62 (1H, m), 2.70 (1H, dd, *J* 8.1, 16.8 Hz), 4.36–4.44 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.8, 13.9, 22.5, 28.1, 29.6, 33.1, 37.5, 84.1, 177.1. Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.22; H, 10.30.

4.9. (*S*)-(*E*)-2-Methyl-1-phenylpent-1-en-3-yl but-3-enoate (7a)

A solution of DCC in NMP (1 M, 1.1 mL, 1.10 mmol) was added to a mixture of (*S*)-**3d** (180 mg, 1.01 mmol), 3-butenoic acid (90 μL, 1.01 mmol), and DMAP (12.0 mg, 0.10 mmol) in CH_2Cl_2 (4 mL) at 0 °C. The mixture was stirred for 5 h and then saturated aqueous $NaHCO_3$ and Et_2O were added. The mixture was filtered and the filtrate was extracted with Et_2O. After evaporation of the solvent, the crude extract was purified by column chromatography (SiO_2; petroleum ether/Et_2O 9:1) to afford compound **7a** as a colorless oil (200 mg, 82%); R_f (9% Et_2O/petroleum ether) 0.42; $[\alpha]_D^{25}$ −6.4 (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91–0.98 (3H, m), 1.70–1.81 (2H, m), 1.86 (3H, s), 3.52 (2H, d, *J* 6.6 Hz), 5.16–5.20 (2H, m), 5.21–5.29 (1H, m), 5.90–5.99 (1H, m), 6.48 (1H, s), 7.21–7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 9.9, 13.6, 25.8, 39.5, 80.9, 118.4, 126.6, 127.8, 128.1, 129.0, 130.4, 135.6, 137.2, 170.8. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.63; H, 8.26.

4.10. (*S*)-6-Ethyl-5-methyl-3*H*-pyran-2(6*H*)-one (8a)[40]

A solution of the Grubbs' catalyst **11** (second generation) (42.0 mg; 0.05 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of **7a** (130 mg; 0.50 mmol) in CH_2Cl_2 (50 mL) at reflux. The reaction was monitored by GC–MS. After 20 h the reaction was completed, the solvent was removed, and the crude extract was purified by column chromatography (SiO_2; petroleum ether/Et_2O 3:1) to afford **8a** as a colorless oil (60.0 mg, 86%); R_f (25% Et_2O/petroleum ether) 0.16; $[\alpha]_D^{25}$ +40.6 (*c* 0.97; $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.96 (3H, t, *J* 7.5 Hz), 1.18–1.30 (2H, m), 1.72 (3H, s), 3.02 (2H, s), 4.81 (1H, s), 5.71 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 8.2, 18.8, 26.9, 29.9, 84.0, 116.6, 132.5, 169.5. Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.55; H, 8.63.

4.11. (5*S*,6*S*)-6-Ethyl-tetrahydro-5-methylpyran-2-one (9a)[29]

To a solution of **8a** (20.0 mg, 0.14 mmol) in dry ethanol (1.7 mL) was added Raney-Ni and the mixture was set under a hydrogen atmosphere. The reaction was monitored by GC–MS and after 3 h the mixture was filtered through Celite. After evaporation of the solvent, the crude extract was purified by column chromatography (SiO_2; petroleum ether/Et_2O 3:1) to afford **9a** as a colorless oil (17.0 mg, 85%, 90% ee); R_f (25% Et_2O/pentane) 0.40; $[\alpha]_D^{25}$ −58.2 (*c* 1.01; $CHCl_3$); lit.[41] $[\alpha]_D^{24}$ −65.8 (*c* 1.02; $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.91 (3H, t, *J* 6.7 Hz), 0.96 (3H, d, *J* 7.6 Hz), 1.40–1.75 (3H, m), 1.90–2.05 (2H, m), 2.47 (2H, t, *J* 7.6 Hz), 4.14 (1H, ddd, *J* 11.5, 5.5, 2.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 10.1, 12.3, 25.1,

26.2, 26.7, 30.1, 84.6, 171.9. Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.60; H, 9.95.

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