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Chemoenzymatic synthesis of optically active γ-alkyl-γ-butenolides

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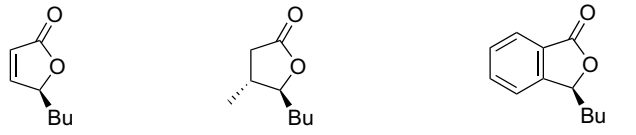
Abstract—*rac*-Hept-1-en-3-ol **4** was subjected to an enantioselective esterification in the presence of Novozyme 435 and vinyl crotonate as the acyl donor to give (3*S*)-oct-1-en-3-yl crotonate **7** in >99% ee and (3*R*)-alcohol **4** in 99% ee. The *E*-value of this enzymatic reaction was found to be >1000. The (*S*)-crotonic ester **7** was converted by ring-closing metathesis (RCM) using Grubbs' catalyst to give (*S*)-oct-2-en-4-olide **1** in 96% yield while keeping the high enantiomeric excess.

1. Introduction

Optically active γ-alkyl-γ-butenolides (4-alkylbut-1-en-4-olides) are useful as chiral building blocks for the synthesis of natural products and flavors.[1] Chiral oct-2-en-4-olide **1** in particular is considered as a key intermediate for the synthesis of quercus lactone **2**, the so-called whisky lactone,[2] and natural products such as phthalides **3** (Fig. 1).[3] In spite of the importance of **1**, only a few conventional methods for preparing optically active **1** have been reported. For example, Inomata et al. reported a synthetic method for making highly optically active **1**, although the procedure requires many steps from commercially available starting materials.[4] Harcken and Brückner carried out a four-step synthesis of (*R*)-**1** in 97% enantiomeric excess (ee) by the use of asymmetric dihydroxylation of a γ,δ-unsaturated ester as a key reaction.[2b]

Recently, ring-closing metathesis (RCM) of olefin catalyzed by Grubbs' catalyst has been applied for the synthesis of lactones.[5] We consider that RCM is useful for the preparation of optically active compound **1**. Herein, we report a facile chemoenzymatic synthesis of **1** from commercially available racemic hept-1-en-3-ol **4** by the combination of lipase-catalyzed transesterification and RCM.



1 quercus lactone **2** butylphthalide **3**

Figure 1. Structure of **1** and natural products.

2. Results and discussion

2.1. Synthetic strategy

The synthetic strategy for chiral compound **1** is shown in Scheme 1. Compound *rac*-**4** is converted to the corresponding optically active acrylic ester (*S*)-**5** by lipase-catalyzed kinetic resolution using acrylic ester as the acyl donor. Ideally, only one enantiomer for *rac*-**4** reacts to afford chiral (*S*)-**5** while the other enantiomer does not react with the acyl donor. After separation of (*S*)-**5** and unreacted (*R*)-**4**, RCM of (*S*)-**5** by Grubbs' catalyst gives optically active (*S*)-**1**. Esterification of (*R*)-**4** with acrylic chloride gives (*R*)-**5** followed by RCM to afford (*R*)-**1**.

2.2. Screening of lipases on the transesterification of *rac*-4

At first, several lipases such as Amano AK, Amano AH, Amano PS, Amano PS on ceramics, PPL and Novozyme 435 [polymer-supported *Candida antarctica* lipase B

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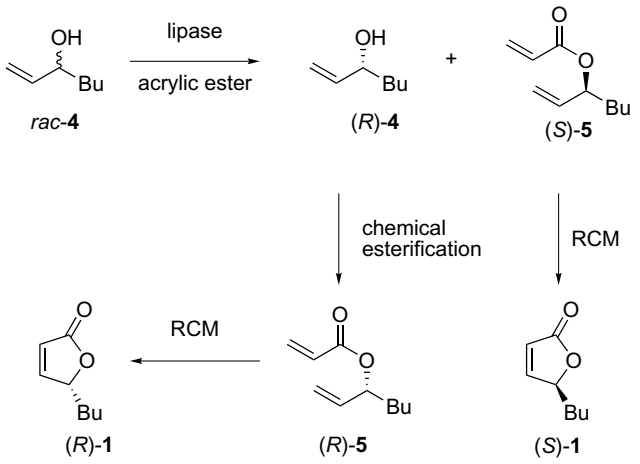


Scheme 1. Synthetic strategy for the synthesis of both enantiomers of **1**.

(CAL-B)] were applied for their ability to transesterify *rac*-**4** with vinyl cinnamate in hexane; only Novozyme 435 was found to be active. Thus, we used Novozyme 435 for the transesterification of *rac*-**4** in this study (Table 1, entries 1–6).

2.3. Screening of acyl donors

Next, we tested three acyl donors and several solvents to perform the transesterification effectively. The results are shown in Table 1.

The reactions with 2-ethylhexyl acrylate or vinyl cinnamate were slow and gave 32–40% conversion of **6** or **5** after 5 days (entries 6–9). On the reactions with vinyl crotonate (entries 10 and 11), *rac*-**4** was smoothly converted to ester **7** and 49% conversion was achieved after 3 days. Moreover, the transesterification using vinyl crotonate as a solvent gave 50% conversion in 3 days (entry 12). The chiral GC analysis of the product **7** (entries 10–12) showed >99% ee and the *E*-value[6] of the present reaction was found to be over 1000.

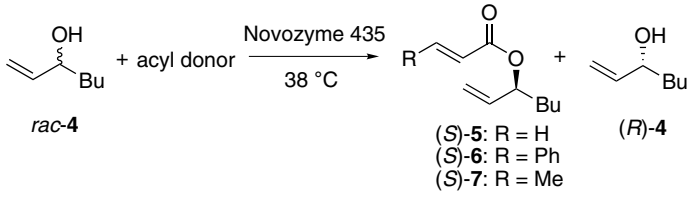
To determine the absolute configuration of enantiomerically pure **7**, compound **4** corresponding to the starting material was converted to the corresponding (*R*)-(+)- and (*S*)-(−)-2-methoxy-2-trifluoromethyl-2-phenylacetates (MTPA esters), respectively. The $\Delta\delta$ values ($\delta_{(-)\text{-MTPA ester}} - \delta_{(+)\text{-MTPA ester}}$) are shown in Figure 2 and those values of the three vinyl protons were minus and those of the alkyl chain parts showed a plus sign. When the group possessing the minus $\Delta\delta$ value was attached on the left side to the carbinol and the group possessing the plus sign was attached on the right side, as shown in Figure 2, the hydroxyl group was found to be oriented on the α-side according to the modified Mosher's method.[7] Thus, the absolute configuration of unreacted **4** was determined to be *R*, meaning that the absolute configuration of **7** was *S*.

2.4. The resolution of 1-alkylallyl alcohols

Encouraged by these results, three types of 1-alkylallyl alcohols, hex-1-en-3-ol **8**, oct-1-en-3-ol **9** and non-1-en-3-ol **10** were subjected to a kinetic resolution. The results are shown in Table 2.

The *E*-values for the enzymatic reaction of *rac*-**8**, *rac*-**9**, and *rac*-**10** were found to be 258, 458, and >1000, respectively (entries 5, 7, and 9). Since the *E*-value for the optical resolution of *rac*-**9** by CAL-B with vinyl acetate was reported to be 46,[8] the present use of vinyl crotonate resulted in an increase in enantioselectivity.

Table 1. Screening of acyl donors for the direct synthesis of optically active acrylic ester



Entry	Lipase	Acyl donor	Solvent	Time (days)	Product	Conv.[a] (%)
1	Amano AK	Vinyl cinnamate	Hexane	5	*rac*-**4**	—[b]
2	Amano AH	Vinyl cinnamate	Hexane	5	*rac*-**4**	—[b]
3	Amano PS	Vinyl cinnamate	Hexane	5	*rac*-**4**	—[b]
4	Amano PS[c]	Vinyl cinnamate	Hexane	5	*rac*-**4**	—[b]
5	PPL	Vinyl cinnamate	Hexane	5	*rac*-**4**	—[b]
6	Novozyme 435	Vinyl cinnamate	Hexane	5	**6**	32
7	Novozyme 435	Vinyl cinnamate	Diisopropylether	5	**6**	33
8	Novozyme 435	2-Ethylhexyl acrylate	Hexane	5	**5**	42
9	Novozyme 435	2-Ethylhexyl acrylate	Diisopropylether	5	**5**	40
10	Novozyme 435	Vinyl crotonate	Hexane	3	**7**	49
11	Novozyme 435	Vinyl crotonate	Diisopropylether	3	**7**	49
12	Novozyme 435	—	Vinyl crotonate	3	**7**	50

[a] Determined by ^{1}H NMR.
[b] No reaction.
[c] Amano PS on ceramics was used.

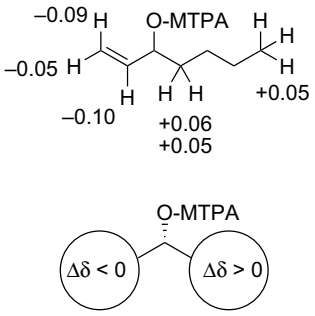


Figure 2. $\Delta\delta$ values for the MTPA-ester of **2**.

Commercially available polymer-supported CAL-B obtained from the gene transformed *Aspergillus niger*, was then applied to the enzymatic reaction. The *E*-values for the enzymatic reactions of *rac*-**4**, *rac*-**8**, *rac*-**9**, and *rac*-**10** using commercially available CAL-B were found to be 313, 135, 199, and 575, respectively (entries 4, 6, 8, and 10). The isolated yields of (*S*)-**7**, (*S*)-**11**, (*S*)-**12**, and (*S*)-**13** were found to be 90%, 80%, 92%, and 94%, respectively, based on the conversion. These differences in stereoselectivities between the two enzymes are thought to stem from either the immobilizing methods of these enzymes, or the difference of the enzyme structure.

The absolute configuration of the esters (*S*)-**12** and (*S*)-**13** could be determined by comparison of the specific rotations of their lactones (*S*)-**15** and (*S*)-**16** as shown in Table 3 with those of the reported values. However, the specific rotation of optically active hept-2-en-4-olide (*S*)-**14** (Table 3, entry 7) has not been reported. In order to determine the absolute configuration of (*R*)-**8** (Table 2, entry 6), the chiral alcohol **8** of low enantiomeric excess (75% ee) was treated with (*R*)-MTPA to give a diastereomeric mixture of (*R*)-**8**- and (*S*)-**8**-(*R*)-MTPA esters. The signals for the major isomer (*R*)-**8**-(*R*)-MTPA ester on the vinyl group appeared at δ 5.22, 5.32, and 5.78 ppm, while those for the (*S*)-**8**-(*R*)-MTPA ester were δ 5.20, 5.30, and 5.67 ppm. As the $\Delta\delta$ values of vinyl protons showed a minus value, the absolute configuration of recovered alcohol **8** (Table 2, entry 6) was determined to be *R*. Consequently, the absolute configuration of the esterified product **11** was found to be *S*.

2.5. Reuse of lipase

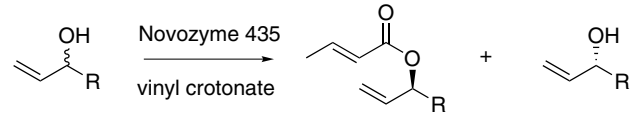
As Novozyme 435 is a polymer-supported lipase, the lipase could be easily recycled. We reused the lipase five times for the reaction of *rac*-**4** without the loss of activities or stereoselectivities. The conversions were 50%, 49%, 49%, 48%, and 48% at 3 days keeping >99% ee of (*S*)-**7**. It should be noted that the conversions for 3 days might be slightly reduced since we lost a small amount of lipase during the reusing process.

2.6. RCM for crotonic esters

To obtain (*R*)-**1** from (*R*)-**5** obtained by acrylation of (*R*)-**4** or (*S*)-**1** from (*S*)-**7**, several conditions for RCM were investigated with the results shown in Table 3.

We attempted RCM of (*R*)-**5** and (*S*)-**7** using Grubbs' catalyst I, but the desired product could not be obtained (entries 1 and 3) (Fig. 3). It was considered that the catalytic cycle of the reaction was stopped by the strong coordination of carbonyl oxygen to rhodium (Scheme 2).[9] When titanium tetraisopropoxide, which is known to break the coordination, was added to the reaction of (*S*)-**7** with

Table 2. Transesterification of 1-alkylallyl alcohols by vinyl crotonate



rac-**4**: R = Bu
rac-**8**: R = Pr
rac-**9**: R = pentyl
rac-**10**: R = hexyl

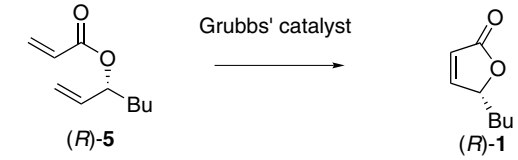
(*S*)-**7**: R = Bu
(*S*)-**11**: R = Pr
(*S*)-**12**: R = pentyl
(*S*)-**13**: R = hexyl

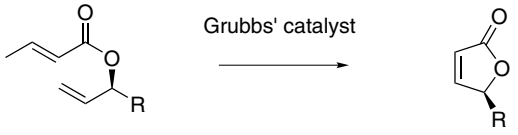
(*R*)-**4**: R = Bu
(*R*)-**8**: R = Pr
(*R*)-**9**: R = pentyl
(*R*)-**10**: R = hexyl

Entry	Substrate	Lipase	Time	Conv.[a] (%)	ee[b] (%)	*E*-Value	Yield (%)
1	*rac*-**4**	Novozyme 435	1 day	20	>99	>1000	—[c]
2	*rac*-**4**	Novozyme 435	2 days	37	>99	>1000	—[c]
3	*rac*-**4**	Novozyme 435	3 days	50	>99	>1000	90
4	*rac*-**4**	CAL-B[d]	15 h	41	99	313	88
5	*rac*-**8**	Novozyme 435	2.5 days	50	98	258	80
6	*rac*-**8**	CAL-B[d]	12 h	44	97	135	75
7	*rac*-**9**	Novozyme 435	2.5 days	50	99	458	92
8	*rac*-**9**	CAL-B[d]	12 h	42	98	199	92
9	*rac*-**10**	Novozyme 435	4 days	50	>99	>1000	94
10	*rac*-**10**	CAL-B[d]	1 day	43	99	575	93

[a] Determined by ^{1}H NMR.
[b] Determined by GC analysis.
[c] Not measured.
[d] Purchased from Sigma–Aldrich Inc.

Table 3. RCM for γ-alkyl-γ-butenolides



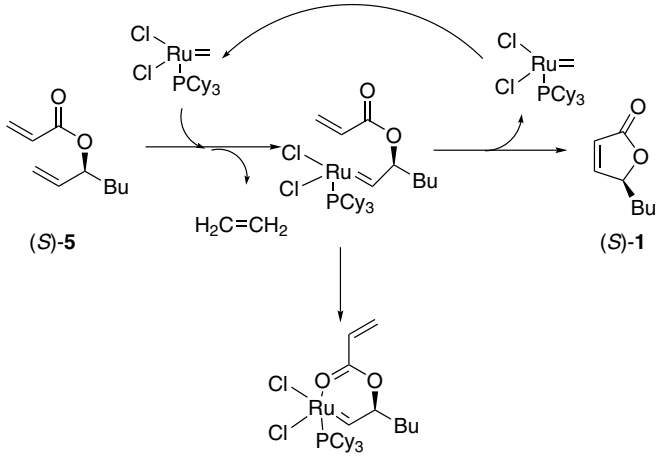


(*S*)-**7**: R = Bu
(*S*)-**11**: R = Pr
(*S*)-**12**: R = pentyl
(*S*)-**13**: R = hexyl

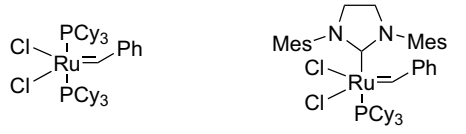
(*S*)-**1**: R = Bu
(*S*)-**14**: R = Pr
(*S*)-**15**: R = pentyl
(*S*)-**16**: R = hexyl

Entry	Substrate	Product	Grubbs' catalyst	Amount of catalyst	Yield (%)	$[\alpha]_D$[a]
1	(*R*)-**5**	(*R*)-**1**	I	10 mol %	—[b]	
2	(*R*)-**5**	(*R*)-**1**	II	10 mol %	89	−100.5[c]
3	(*S*)-**7**	(*S*)-**1**	I	10 mol %	—[b]	
4	(*S*)-**7**	(*S*)-**1**	I with Ti(O-*i*-Pr)$_4$	10 mol % (2 mol %)	30	—[d]
5	(*S*)-**7**	(*S*)-**1**	II	10 mol %	96	+100.4[e]
6	(*S*)-**7**	(*S*)-**1**	II	5 mol %	93	+100.4[e]
7	(*S*)-**11**	(*S*)-**14**	II	5 mol %	93	+110.0
8	(*S*)-**12**	(*S*)-**15**	II	5 mol %	94	+94.0[f]
9	(*S*)-**13**	(*S*)-**16**	II	5 mol %	95	+89.4[g]

[a] Measured in $CHCl_3$.
[b] No product was isolated and the starting material was recovered.
[c] Lit.[2a] −100.5, >98% ee (*R*).
[d] Not measured.
[e] Lit.[2a] +100.8, >98% ee (*S*).
[f] Lit.[11] +85.53, >99% ee (*S*).
[g] Lit.[12] +81.0, 88% ee (*S*).



Scheme 2. Catalytic cycle of RCM and the inhibition mechanism.



Grubbs' catalyst I

Grubbs' catalyst II

Figure 3. Structures of Grubbs' catalyst.

Grubbs' catalyst I, the reaction proceeded to give (*S*)-**1** in 30% yield (entry 4).[9,10] Next, we tried the RCM using Grubbs' catalyst II under 10 mol % conditions. The reaction of (*R*)-**5** proceeded smoothly and product (*R*)-**1** was obtained in 89% yield (entry 2). The specific rotation of (*R*)-**1** was found to be −100.5 (*c* 1.00, $CHCl_3$), which is consistent with the reported value $[\alpha]_D = -100.4$.[2a] Butenolide (*S*)-**1** was obtained from (*S*)-**7** in 96% yield under the same conditions (entry 5). Furthermore, the reaction of (*S*)-**7** under 5 mol % of Grubbs' catalyst II conditions proceeded as well and gave (*S*)-**1** in 93% yield (entry 6). Next, we applied RCM with 5 mol % of Grubbs' catalyst II to the crotonic esters (*S*)-**11**, (*S*)-**12**, and (*S*)-**13**, and the corresponding lactones (*S*)-**14**, (*S*)-**15**, and (*S*)-**16** were obtained in 93%, 94%, and 95% yield, respectively. The specific rotations of these lactones are consistent with the reported values.[2a,11,12]

3. Conclusion

Herein, we have reported a two-step synthesis of highly optically active γ-alkyl-γ-butenolides (*R*)-**1**, (*S*)-**1**, (*S*)-**14**, (*S*)-**15**, and (*S*)-**16**. Novozyme 435-catalyzed transesterification of racemic 1-alkylallyl alcohols *rac*-**4**, *rac*-**8**, *rac*-**9**, and *rac*-**10** with vinyl crotonate gave (*S*)-crotonic esters (*S*)-**7**, (*S*)-**11**, (*S*)-**12**, and (*S*)-**13** with excellent ee. The stereoselectivity of the present enzyme reactions was identified as an

extended Prelog's rule to hydroxylases that recognize the size of the two substituents attached to the carbinol of secondary alcohol.[13] The *E*-values of the reaction using vinyl crotonate were found to be >250. The use of vinyl crotonate for the lipase-catalyzed transesterification has many advantages. Vinyl crotonate makes it possible to carry out the direct synthesis of the substrate for RCM leading to the γ-lactones. Crotonic esters are generally less toxic than the acrylic esters. The purification of the crotonic ester from the transesterification is simple since the remaining alcohol and vinyl crotonate are easily evaporated.

Grubbs' catalyst II was applied to the RCM of crotonic esters (*S*)-**7**, (*S*)-**11**, (*S*)-**12**, and (*S*)-**13** and afforded the optically active 4-substituted-γ-lactones (*S*)-**1**, (*S*)-**14**, (*S*)-**15**, and (*S*)-**16** in high enantiopurities. The present two-step asymmetric synthesis of 4-substituted-γ-butenlides was achieved in a high total yield. This two-step synthesis is the shortest chiral synthesis of γ-alkyl-γ-butenolides.

4. Experimental

4.1. Materials and instruments

Organic reagents were purchased from Tokyo Chemical Industry Co., Ltd, or Wako Pure Chemical Industries Ltd or Sigma–Aldrich unless otherwise indicated.

NMR spectra were measured on a JEOL-AL400 spectrometer. Mass spectra were obtained on JEOL JMS-700. Optical rotations were measured with a JASCO P-1020. Ee was determined on a Shimadzu GC-14B equipped with Chirasil DEX-CB (25 m * 0.25 mm, N_2 (2 mL/min) as carrier gas) as a chiral column. IR spectra were measured on JASCO FT-IR410. Novozyme 435 was provided from Novo Nordisk A/S. CAL-B from *A. niger* was purchased from Sigma–Aldrich Inc.

4.2. General procedure for the enzymatic reaction (Table 1)

Hept-1-en-3-ol *rac*-**4** (50 mg, 0.44 mmol) was dissolved in a solvent (1 mL) containing the acyl donor (44 mol), and lipase (50 mg) was added. The reaction mixture was incubated at 40 rpm at 38 °C, was filtered and the resin washed with ether. The conversion was determined by ^{1}H NMR and the ee of crotonic ester was determined by GC analysis. The used Novozyme 435 was dried and reused in the next reaction.

4.2.1. Hept-1-en-3-yl cinnamate 6. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, t, $J = 7.0$ Hz), 1.29–1.39 (4H, m), 1.63–1.73 (2H, m), 5.17 (1H, td, $J = 1.2$, 10.5 Hz), 5.27 (1H, td, $J = 1.2$, 17.1 Hz), 5.36 (1H, tq, $J = 1.2$, 6.3 Hz), 5.83 (1H, ddd, $J = 6.3$, 10.5, 17.1 Hz), 6.44 (1H, d, $J = 16.1$ Hz), 7.34–7.38 (3H, m), 7.49–7.52 (2H, m), 7.68 (1H, d, $J = 16.1$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.9, 27.3, 34.0, 75.0, 116.6, 118.5, 128.1, 128.9 (2C), 130.3 (2C), 134.5, 136.8, 144.7, 166.3. HR-FAB-MS *m*/*z*: 245.1525 ([M+H]$^+$, calcd for $C_{16}H_{21}O_2$ *m*/*z*: 245.1542). IR (neat) *v*: 3085, 3062, 3029, 2957, 2933, 1713, 1638, 1577, 1496, 1171 cm^{-1}.

4.2.2. Hept-1-en-3-yl acrylate 5. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (3H, t, $J = 6.6$ Hz), 1.16–1.29 (4H, m), 1.47–1.62 (2H, m), 5.07 (1H, d, $J = 10.5$ Hz), 5.15 (1H, d, $J = 16.9$ Hz), 5.21 (1H, q, $J = 7.6$ Hz), 5.72 (1H, ddd, $J = 7.6$, 10.5, 16.9 Hz), 5.73 (1H, dd, $J = 1.2$, 10.4 Hz), 6.04 (1H, dd, $J = 10.4$, 17.2 Hz), 6.32 (1H, dd, $J = 1.2$, 17.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 22.3, 27.0, 33.7, 74.8, 116.4, 128.6, 130.3, 136.4, 165.3. IR (neat) *v*: 1726, 1685, 1646, 1630, 1619, 1193 cm^{-1}.

4.3. (3*S*)-Hept-1-en-3-yl crotonate (*S*)-7

Compound *rac*-**4** (25 g, 0.22 mol) was dissolved in vinyl crotonate (100 mL) and to which was added Novozyme 435 (10 g). The reaction mixture was incubated at 40 rpm at 38 °C for 7 days, filtrated and the resin washed with ether. The filtrate was evaporated under reduced pressure (0.1 mmHg) at 50 °C to afford (*S*)-**7** (18.5 g, 0.102 mol, 93%, >99% ee). Colorless oil. GC column temp.: 95 °C, t_R: 15.8 min for (*R*)-**7** and 16.8 min for (*S*)-**7**. $[\alpha]_D^{22} = +6.9$ (*c* 1.16, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, $J = 6.8$ Hz, H-7), 1.19–1.34 (4H, m, H-5 and H-6), 1.51–1.67 (2H, m, H-4), 1.86 (2H, dd, $J = 1.7$, 7.1 Hz, CH_3–CH=CH), 5.11 (1H, td, $J = 1.2$, 10.5 Hz, H-1$_a$), 5.21 (1H, td, $J = 1.2$, 17.3 Hz, H-1$_b$), 5.26 (1H, tq, $J = 1.2$, 6.1 Hz, H-3), 5.77 (1H, ddd, $J = 6.4$, 10.5, 17.3 Hz, H-2), 5.83 (1H, qd, $J = 1.5$, 15.9 Hz, –CH=C*H*–CO), 6.96 (1H, qd, $J = 6.8$, 15.9 Hz, CH_3–C*H*=CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 17.9, 22.4, 27.2, 33.9, 74.4, 116.2, 122.9, 136.7, 144.5, 165.8. HR-FAB-MS *m*/*z*: 183.1392 ([M+H]$^+$, calcd for $C_{11}H_{19}O_2$ *m*/*z*: 183.1385). IR (neat) *v*: 3086, 3053, 2958, 1721, 1659, 1182 cm^{-1}.

The removed material trapped under liquid nitrogen was purified by column chromatography (hexane–acetone = 30:1–10:1) to afford (*R*)-**4** (11.0 g, 0.097 mol, 88%, 99% ee).

4.3.1. MTPA esters of (*R*)-4. Compound (*R*)-**4** (10 mg, 0.078 mmol) was added to the mixture of (*R*)-(+)- or (*S*)-(−)-2-methoxy-2-trifluoromethyl-2-phenylacetic acid (75 mg 0.17 mmol), DCC (66 mg, 0.17 mmol) and DMAP (1.0 mg) in dioxane (0.6 mL) and stirred for 3 h. The mixture was filtered and the filtrate was purified by column chromatography (hexane–ethyl acetate = 4:1) to afford the corresponding (*R*)-**4**-(*R*)- or (*R*)-**4**-(*S*)-MTPA ester, quantitatively.

(3*R*)-Hept-1-en-3-yl (*R*)-(+)-2-methoxy-2-trifluoromethyl-2-phenylacetate [(*R*)-**4**-(*R*)-MTPA ester]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (3H, t, $J = 7.3$ Hz, H-7), 1.14–1.28 (4H, m, H-5 and H-6), 1.55–1.69 (2H, m, H-4), 3.53 (3H, q, $J = 1.5$ Hz, OCH_3), 5.23 (1H, td, $J = 1.2$, 10.5 Hz, H-1$_a$), 5.33 (1H, dd, $J = 1.2$, 17.1 Hz, H-1$_b$), 5.44 (1H, br q, $J = 6.3$ Hz, H-3), 5.80 (1H, ddd, $J = 6.4$, 10.5, 17.1 Hz, H-2), 7.35–7.39 (3H, m, Ph), 7.50–7.52 (2H, m, Ph).

(3*R*)-Hept-1-en-3-yl (*S*)-(−)-2-methoxy-2-trifluoromethyl-2-phenylacetate [(*R*)-**4**-(*S*)-MTPA ester]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, $J = 7.1$ Hz, H-7), 1.22–1.33 (4H, m, H-5 and H-6), 1.59–1.77 (2H, m, H-4), 3.54 (3H, q, $J = 1.2$ Hz, OCH_3), 5.18 (1H, dt, $J = 1.2$, 10.5 Hz,

H-1$_a$), 5.24 (1H, dt, $J = 1.2$, 17.3 Hz, H-1$_b$), 5.42 (1H, br q, $J = 6.8$ Hz, H-3), 5.70 (1H, ddd, $J = 6.8$, 10.5, 17.3 Hz, H-2), 7.35–7.40 (3H, m, Ph), 7.49–7.51 (2H, m, Ph).

4.4. (3*R*)-Hept-1-en-3-yl acrylate (*R*)-5

To (*R*)-**4** (5.7 g, 50 mmol) in dichloromethane (200 mL) containing triethylamine (5.6 g, 51 mmol) was added acryloyl chloride (4.6 g, 51 mmol) at 0 °C and the mixture was stirred for 1 h at 0 °C. The mixture was added to water (15 mL) and the organic layer was removed. The organic layer was dried over sodium sulfate, concentrated under reduced pressure. The residue was purified by bulb-to-bulb distillation (0.2 mmHg, 70 °C) to afford (*R*)-**5** (7.2 g, 43 mmol, 86%).

4.5. (3*S*)-Hex-1-en-3-yl crotonate (*S*)-11

From *rac*-**8** (500 mg, 5.00 mmol) to (*S*)-**11** (335 mg, 1.99 mmol, 80% based on 50% conv., 98% ee). Colorless oil. GC column temp.: 85 °C, t_R: 15.8 min for (*R*)-**11** and 17.5 min for (*S*)-**11**. $[\alpha]_D^{26} = +6.9$ (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, t, $J = 6.8$ Hz), 1.28–1.40 (2H, m), 1.51–1.68 (2H, m), 1.86 (3H, dd, $J = 1.5$, 6.8 Hz), 5.12 (1H, td, $J = 1.2$, 10.5 Hz), 5.21 (1H, td, $J = 1.2$, 17.3 Hz), 5.28 (1H, tq, $J = 1.2$, 6.4 Hz), 5.78 (1H, ddd, $J = 6.4$, 10.5, 17.3 Hz), 5.84 (1H, qd, $J = 1.5$, 15.6 Hz), 6.96 (1H, qd, $J = 6.8$, 15.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 17.6, 18.0, 36.0, 73.8, 115.8, 122.6, 136.4, 144.1, 165.5. HR-FAB-MS *m*/*z*: 169.1247 ($[M+H]^+$, calcd for $C_{10}H_{17}O_2$ *m*/*z*: 169.1229). IR (neat) *v*: 3087, 3054, 3014, 2961, 2937, 2874, 1721, 1658, 1182 cm^{-1}.

(3*R*)-Hex-1-en-3-yl (*R*)-(+)-2-methoxy-2-trifluoromethyl-2-phenylacetate [(*R*)-**8**-(*R*)-MTPA ester]. ^1H NMR (400 MHz, $CDCl_3$): δ 0.82 (3H, t, $J = 7.3$ Hz, H-6), 1.15–1.28 (2H, m, H-5), 1.54–1.69 (2H, m, H-4), 3.59 (3H, q, $J = 1.5$ Hz, OCH_3), 5.22 (1H, td, $J = 1.2$, 10.5 Hz, H-1$_a$), 5.32 (1H, dd, $J = 1.2$, 17.1 Hz, H-1$_b$), 5.43 (1H, tq, $J = 1.2$, 6.3 Hz, H-3), 5.78 (1H, ddd, $J = 6.4$, 10.5, 17.1 Hz, H-2), 7.34–7.39 (3H, m, Ph), 7.50–7.53 (2H, m, Ph). For [(*S*)-**8**-(*R*)-MTPA ester]: δ 5.20 (1H, dt, $J = 1.2$, 10.5 Hz, H-1$_a$), 5.30 (1H, dt, $J = 1.2$, 17.3 Hz, H-1$_b$) and 5.67 (1H, ddd, $J = 6.8$, 10.5, 17.3 Hz, H-2).

4.6. (3*S*)-Oct-1-en-3-yl crotonate (*S*)-12

From *rac*-**9** (500 mg, 3.91 mmol) to (*S*)-**12** (352 mg, 1.80 mmol, 92% yield based on 50% conv., 99% ee). Colorless oil. GC column temp.: 95 °C, t_R: 31.6 min for (*R*)-**12** and 32.8 min for (*S*)-**12**. $[\alpha]_D^{26} = +7.5$ (*c* 1.19, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.85 (3H, t, $J = 6.8$ Hz), 1.23–1.33 (6H, m), 1.52–1.64 (2H, m), 1.85 (3H, dd, $J = 1.5$, 6.8 Hz), 5.12 (1H, td, $J = 1.2$, 10.5 Hz), 5.20 (1H, td, $J = 1.2$, 17.3 Hz), 5.25 (1H, tq, $J = 1.2$, 6.1 Hz), 5.77 (1H, ddd, $J = 6.4$, 10.5, 17.3 Hz), 5.83 (1H, qd, $J = 1.5$, 15.6 Hz), 6.96 (1H, qd, $J = 6.8$, 15.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.8, 18.8, 23.3, 25.5, 32.4, 35.0, 75.3, 117.1, 123.8, 137.6, 145.6, 166.7. HR-FAB-MS *m*/*z*: 197.1546 ($[M+H]^+$, calcd for $C_{12}H_{21}O_2$ *m*/*z*: 197.1542). IR (neat) *v*: 3087, 3054, 3012, 2956, 2933, 2861, 1721, 1658, 1181 cm^{-1}.

4.7. (3*S*)-Non-1-en-3-yl crotonate (*S*)-13

From *rac*-**10** (501 mg, 3.52 mmol) to (*S*)-**13** (347 mg, 1.62 mmol, 94% yield based on 50% conv., >99% ee). Colorless oil. GC column temp.: 110 °C, t_R: 26.8 min for (*R*)-**13** and 27.8 min for (*S*)-**13**. $[\alpha]_D^{26} = -7.0$ (*c* 1.01, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.85 (3H, t, $J = 6.6$ Hz), 1.24–1.33 (8H, m), 1.52–1.66 (2H, m), 1.86 (3H, dd, $J = 1.7$, 7.1 Hz), 5.13 (1H, td, $J = 1.2$, 10.5 Hz), 5.21 (1H, td, $J = 1.2$, 17.3 Hz), 5.26 (1H, tq, $J = 1.2$, 6.1 Hz), 5.78 (1H, ddd, $J = 6.1$, 10.5, 17.3 Hz), 5.84 (1H, qd, $J = 1.7$, 15.6 Hz), 6.97 (1H, qd, $J = 7.1$, 15.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 17.9, 22.6, 25.0, 29.0 31.7, 34.3, 74.5, 116.2, 123.0, 136.7, 144.5, 165.9. HR-FAB-MS *m*/*z*: 211.1698 ($[M+H]^+$, calcd for $C_{13}H_{23}O_2$ *m*/*z*: 211.1698). IR (neat) *v*: 3087, 3054, 3013, 2955, 2930, 2860, 1722, 1658, 1181 cm^{-1}.

4.8. Typical procedure for RCM (Table 3, entry 5)

To a refluxed solution of (*S*)-hept-1-en-3-yl crotonate (*S*)-**7** (115 mg 0.632 mmol) in dichloromethane (100 mL) was dropwise added Grubbs' catalyst II (50 mg, 0.06 mmol) in dichloromethane (20 mL) for 1 h, and refluxed for 1 day under a nitrogen atmosphere. The reaction mixture was then concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (silica gel: 10 g, hexane–acetone = 15/1) to afford (*S*)-oct-2-en-4-olide (*S*)-**1** (85.4 mg, 0.610 mmol, 96%).

4.9. (*S*)-Oct-2-en-4-olide (*S*)-1

Colorless oil. $[\alpha]_D^{22} = +100.4$ (*c* 1.01, $CHCl_3$), lit.[2a] +100.8 (*c* 1.0, $CHCl_3$, >98% ee (*S*)). ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, t, $J = 7.1$ Hz, H-8), 1.28–1.43 (4H, m, H-6 and H-7), 1.62–1.76 (2H, m, H-5), 4.99–5.03 (1H, m, H-4), 6.08 (1H, dd, $J = 1.9$, 5.8 Hz, H-2), 7.42 (1H, dd, $J = 1.5$, 5.8 Hz, H-3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8 (C-8), 22.4 (C-7), 27.0 (C-6), 32.9 (C-5), 83.4 (C-4), 121.5 (C-2), 156.2 (C-3), 174.4 (C-1). HR-FAB-MS: *m*/*z* 141.0918 ($[M+H]^+$, calcd for $C_8H_{13}O_2$ *m*/*z*: 141.0916). IR (neat) *v*: 3088, 2958, 2933, 1752, 1601, 1163 cm^{-1}.

4.10. (*S*)-Hept-2-en-4-olide (*S*)-14

From (*S*)-**11** (200 mg, 1.19 mmol) to (*S*)-**14** (142 mg, 1.12 mmol, 93%). Colorless oil. $[\alpha]_D^{25} = +110.0$ (*c* 1.16, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, $J = 6.8$ Hz), 1.34–1.44 (2H, m), 1.50–1.69 (2H, m), 4.96 (1H, dt, $J = 1.8$, 6.0 Hz), 5.99 (1H, dd, $J = 1.8$, 5.6 Hz), 7.41 (1H, d, $J = 5.6$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 18.1, 34.9, 83.1, 121.1, 156.5, 173.0. HR-FAB-MS *m*/*z*: 127.0756 ($[M+H]^+$, calcd for $C_7H_{11}O_2$ *m*/*z*: 127.0759). IR (neat) *v*: 3089, 2962, 2936, 2875, 1750, 1601, 1164 cm^{-1}.

4.11. (*S*)-Non-2-en-4-olide (*S*)-15

From (*S*)-**12** (119 mg, 0.607 mmol) to (*S*)-**15** (88.1 mg, 0.570 mmol, 94%). Colorless oil. $[\alpha]_D^{25} = +94.0$ (*c* 1.05, $CHCl_3$), lit.[11] $[\alpha]_D^{25} = +85.53$ (*c* 1.36, $CHCl_3$, >99% ee (*S*)). ^1H NMR (400 MHz, $CDCl_3$): δ 0.82 (3H, t, $J = 6.8$ Hz),

1.26–1.45 (6H, m), 1.58–1.77 (2H, m), 5.00 (1H, t, $J = 6.0$ Hz), 6.07 (1H, d, $J = 5.6$ Hz), 7.42 (1H, d, $J = 5.6$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.4, 24.6, 31.4, 33.1, 83.4, 121.4, 156.3, 173.1. HR-FAB-MS m/z: 155.1070 ($[M+H]^+$, calcd for $C_9H_{15}O_2$ m/z: 155.1070). IR (neat) ν: 3088, 2956, 2932, 2862, 1754, 1601, 1163 cm^{-1}.

4.12. (*S*)-Dec-2-en-4-olide (*S*)-16

From (*S*)-**13** (129 mg, 0.630 mmol) to (*S*)-**16** (100 mg, 0.597 mmol, 95%). Colorless oil. $[\alpha]_D^{25} = +89.4$ (*c* 1.01, $CHCl_3$), lit.[12] $[\alpha]_D^{25} = +81.0$ (*c* 1.00, $CHCl_3$, 88% ee (*S*)). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (3H, t, $J = 6.8$ Hz), 1.25–1.45 (8H, m), 1.58–1.77 (2H, m), 5.00 (1H, t, $J = 6.0$ Hz), 6.06 (1H, d, $J = 5.6$ Hz), 7.42 (1H, dd, $J = 5.6$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.4, 24.9, 28.9, 31.5, 33.1, 83.4, 121.4, 156.3, 173.1. HR-FAB-MS m/z: 169.1238 ($[M+H]^+$, calcd for $C_{10}H_{17}O_2$ m/z: 169.1229). IR (neat) ν: 3088, 2954, 2929, 2859, 1755, 1601, 1163 cm^{-1}.

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