Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 2484–2490

Synthesis of enantiomerically pure cycloalkenols via combination strategy of enzyme-catalyzed reaction and RCM reaction

Han Shi-Hui, Takuya Hirakawa, Takaaki Fukuba, Shuichi Hayase, Motoi Kawatsura and Toshiyuki Itoh*

Department of Material Sciences, Faculty of Engineering, Tottori University, Tottori 680-8552, Japan

Received 4 September 2007; accepted 2 October 2007

Abstract—The preparation of three types of cyclic alkenols, (*S*)-2-cyclohexenol, (*R*)-2,5-dihydrobenzo[*b*]oxepin-5-ol, and (*R*)-5,6-dihydro-2*H*-benzo[*b*]oxocin-6-ol, has been accomplished in enantiomerically pure forms as model compounds using a combination of a lipase-catalyzed reaction and a ring closing olefin metathesis (RCM) reaction.

1. Introduction

The chemo-enzymatic reaction protocol is now well recognized as a very useful means to prepare optically active compounds.[1] Lipases are important tools for organic synthesis, particularly for the preparation of optically active secondary alcohols. Although lipases generally have a wide applicability for various types of substrate, poorly enantioselective reactions are sometimes obtained for some compounds, in particular, cyclic alcohols. For example, both lipase PS from *Burkholderia cepacia* and Novozym 435 from *Candida antarctica* lipase, that are well respected and the most widely used enzymes for organic synthesis,[1] showed poor reactivity with 2-cyclohexen-1-ol **1** exhibiting low enantioselectivity.[2,3] We also attempted to resolve seven-membered cyclic alkenol **2** and eight-membered cyclic alkenol **3** using lipases, however, no enzyme which was able to react with these compounds was found among the seven types of typical commercial lipases tested.[4] On the other hand, we established that lipase works as an excellent catalyst for the transesterification of acyclic allylic alcohols.[5] For example, excellent enantioselectivity was recorded for the Novozym 435-catalyzed transesterification of octane-1,7-diene-3-ol (±)-**5** using vinyl acetate as an acyl donor; since **5** has two vinyl groups at either terminal of the molecule, we anticipated that it will create 2-cyclohexen-1-ol **1** via a ring closing metathesis (RCM) reaction.[6]

Grubbs et al. reported the synthesis of chiral cycloalkenols using the kinetic resolution of acyclic racemic dienes by asymmetric RCM, though the recorded highest ee of these compounds was 84%.[7] Kamei et al. reported successful examples of cyclic compounds via a RCM reaction starting from optically active monoacetate that was prepared by a lipase-catalyzed reaction.[8] With these results in mind, we

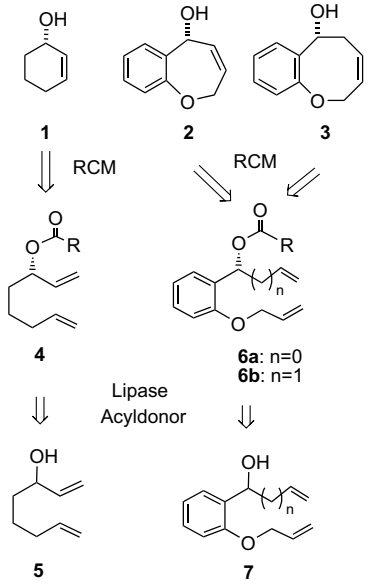


Figure 1. Combination protocol for the preparation of enantiomerically pure cycloalkenol using chemo-enzymatic reaction.

* Corresponding author. Tel./fax: +81 857 31 5259; e-mail: titoh@chem.tottori-u.ac.jp

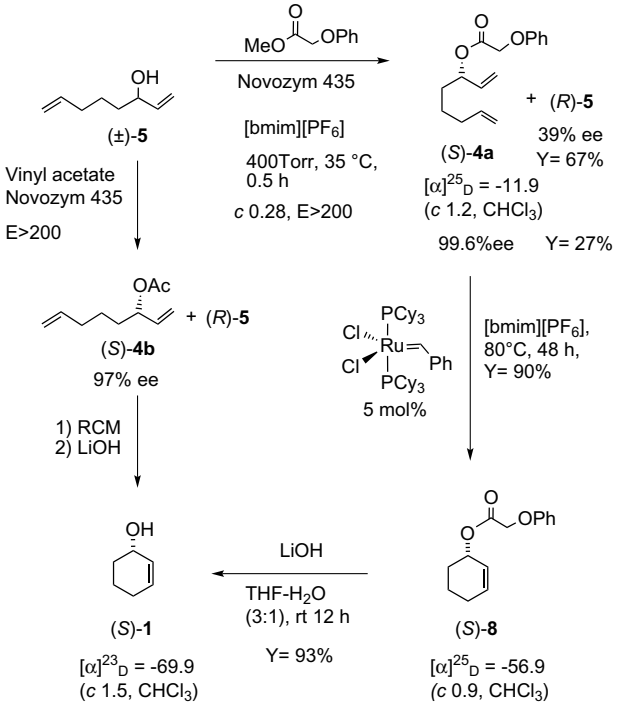
0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.10.005

planned to prepare optically pure cycloalkenols via a combination of a chemo-enzymatic reaction and a RCM reaction (Fig. 1). Herein we report the synthesis of three types of enantiomerically pure cyclic alkenols using this methodology.

2. Results and discussion

2.1. Synthesis of (*S*)-2-cyclohexenol

As a touchstone of our synthetic protocol, we initially undertook the preparation of enantiomerically pure (*S*)-2-cyclohexen-1-ol **1** (Scheme 1).



Scheme 1. Synthesis of enantiomerically pure (*S*)-2-cyclohexen-1-ol (**1**) using chemo-enzymatic reaction.

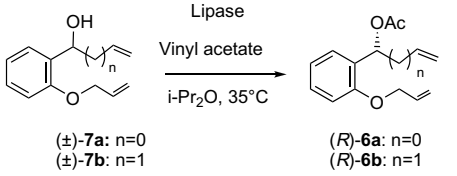
Ionic liquids are widely recognized as green solvents, suitable for use in both organic reactions and enzymatic reactions.[9–12] We recently established an efficient lipase-catalyzed transesterification under reduced pressure conditions in an ionic liquid solvent system;[12] the system was, in fact, very useful for preparing enantiomerically pure (*S*)-octa-1,7-dien-3-yl 2-phenoxyacetate **4a**.

Racemic octa-1,7-diene-3-ol (±)-**5**[13] was reacted with methyl phenoxyacetate in the presence of Novozym 435 (*C. antarctica* lipase) in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]) at 400 Torr at 35 °C for 0.5 h; after the reaction, ester (*S*)-**4a** (99.6% ee) was produced in 27% yield while the unreacted alcohol (*R*)-**5** (39% ee) was obtained in 67% yield after silica gel flash column chromatography; the *E*-value[14] was calculated as being over 200. Since the enantioselectivity of *C. antarctica* lipase to (±)-**5** is very high, we can use diisopropyl ether or [bmim][PF_6] as a reaction medium under ambient pressure, although it is difficult to use the enzyme repeatedly (see Section 4).

It should be emphasized that the system allowed the recyclable use of the enzyme with five repetitions, while maintaining perfect reactivity. The RCM reaction of phenoxy acetate (*S*)-**4a** (R = CH_2OPh) proceeded smoothly in the presence of 5 mol % of the first generation Ru catalyst[6,15] in an ionic liquid, [bmim][PF_6], at 80 °C for 48 h to give the cyclohexenol derivative (*S*)-**8** in 90%. One of the most important benefits for using an ionic liquid as a solvent in organic synthesis is that the system allows the repeated use of the catalyst; it was confirmed that the Ru catalyst was indeed recyclable with three repetitions after the usual work-up process and still retained perfect reactivity. Subsequent alkaline hydrolysis of it into (*S*)-**8** converted (*S*)-2-cyclohexen-1-ol **1**[16] in 93% yield. Synthesis of cyclohexen-1-ol has thus been accomplished through our methodology.

2.2. Synthesis of (*R*)-2,5-dihydrobenzo[*b*]oxepin-5-ol and (*R*)-5,6-dihydro-2*H*-benzo[*b*]oxocin-6-ol derivatives

The RCM reaction is well recognized as a useful means of preparing medium sized ring compounds.[17] We therefore next attempted to synthesize seven- or eight-membered cyclic alkenols using our methodology. The optical resolution of two types of cyclic alcohols using lipase technology was conducted using traditional reaction conditions with diisopropyl ether instead of an ionic liquid solvent system (Eq. 1). Racemic 1-(2-(allyloxy)phenyl)prop-2-en-1-ol **7a** was subjected to a Novozym 435-catalyzed transesterification using vinyl acetate (1.5 equiv vs substrate) as an acyl donor; (*R*)-(−)-1-(2-(allyloxy)phenyl)allyl acetate **6a** ($n = 0$) and (*S*)-(−)-1-(2-(allyloxy)phenyl)prop-2-en-1-ol **7a** ($n = 0$) were obtained with perfect enantioselectivity in 46% and 50% yields, respectively (Table 1, entry 1). The absolute configuration of unreacted (−)-**7a** was determined to be (*S*) by comparison of the specific rotation value with that of (*S*)-1-phenylprop-2-en-1-ol.[18] Lipase PS also gave the desired (*R*)-**6a** in 21% yield with >99% ee (entry 2), though the reaction rate was less satisfactory than that with Novozym 435.



(1)

In contrast, we encountered a problem when racemic 1-(2-(allyloxy)phenyl)but-3-en-1-ol (±)-**7b**,[19] $n = 1$ was used as a substrate for the enzymatic reaction: the reaction was too slow to obtain the product practically, though sufficient enantioselectivity was obtained. It required 192 h to obtain (*R*)-(−)-1-(2-(allyloxy)phenyl)but-3-enyl acetate **6b** in 13% yield with 90% ee; the *E*-value was calculated as 22 for the Novozym 435-catalyzed reaction (entry 3). The desired (*R*)-**5c** was also obtained using lipase PS, but the yield was only 3% with 94% ee after 240 h reaction (entry 4).

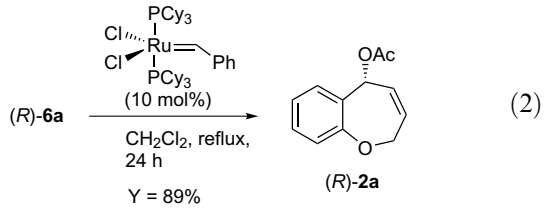
Table 1. Resolution of acyclic alkenol (±)-**4** via lipase-catalyzed reaction

Entry	Compound (*n*)	Lipase[a]	Reaction time (h)	Yield of **6**[b] (% ee)[c]	Yield of **7**[b] (% ee)[c]	Conv.[d] (*c*)	*E* value[d]
1	**7a** (0)	Novozym 435	4	46 (>99)	50 (>99)	0.50	>200
2	**7a** (0)	Lipase PS	48	21 (>99)	52 (53)	0.35	>200
3	**7b** (1)	Novozym 435	192	13 (90)	77 (19)	0.18	22
4	**7b** (1)	Lipase PS	240	3 (94)	78 (3)	0.03	>200
5	**7b** (1)	IL1-PS[20]	23	15 (>99)	70 (32)	0.24	>200

[a] Novozym 435 (Novo): *Candida antarctica*. Lipase PS (Amano): *Burkholderia cepacia*. IL1-PS: *Burkholderia cepacia*, see Ref. 17.
[b] Isolated yield.
[c] Determined by HPLC: for **6a** (AD, hexane/2-propanol = 100:1, 35 °C, 0.5 mL/min); for **6b** (AD, hexane/2-propanol = 9:1, 35 °C, 0.5 mL/ min); for **7a** (OD-H, hexane/2-propanol = 40:1, 35 °C, 0.5 mL/min); for **7b** (AD, hexane/2-propanol = 9:1, 35 °C, 0.5 mL/min).
[d] Calculated by % ee of (*R*)-**6** (eep) and % ee of (*S*)-**7** (ees). $E = \ln[(1-c)(1+\text{eep})]/\ln[(1-c)(1-\text{eep})]$, here *c* means conv. which was calculated by the following formula: $c = \text{eep}/(\text{eep}+\text{ees})$. See Ref. 14.

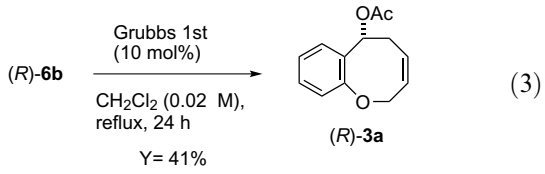
This difficulty was solved by the ionic liquid mediated activation of enzyme that we recently developed:[20,21] PEG-alkyl sulfate imidazolium salt ionic liquid (IL1) coated lipase PS (IL1-PS) worked better than that of lipase PS or Novozym 435 and the desired acetate (*R*)-(−)-**6b** was obtained in 15% yield with over 99% ee after 23 h of reaction (entry 5). The absolute configuration of the acetates produced, (−)-**6b**, was determined to be (*R*) by the Kusumi–Ohtani method (see Section 4).[22]

We had two substrates for RCM reaction at hand, the RCM reaction of (*R*)-**6a** was next investigated; the reaction proceeded very smoothly in the presence of 5 mol % of the first generation Ru catalyst in CH_2Cl_2 at rt and the desired seven-membered cyclic ether (*R*)-**2a** was obtained in 89% yield after silica gel flash column chromatography (Eq. 2).



(2)

Conversely, as anticipated, the RCM reaction of the eight-membered compound was difficult, and the desired (*R*)-**3a** was obtained in only 41% yield with 43% of (*R*)-**6b** unreacted (Eq. 3). An ionic liquid solvent system for the RCM reaction of (*R*)-**6b**, unfortunately, provided no improvement in the result. Since the second generation Ru catalyst[23] exhibited higher thermal stability and wider functional group tolerance than the first generation one, we tested the reaction using the second generation catalyst under highly diluted conditions. However, only a slight improvement (45%) was obtained in the results even when 20 mol % catalyst was used. In fact, a significant amount of polymeric compounds was produced due to intermolecular reactions, when the amount of catalyst was increased. Therefore, it was found that the best practical way to obtain (*R*)-**3a** was under the conditions described in Eq. 3.



(3)

3. Conclusion

In conclusion, we have developed a useful strategy for preparing optically active cycloalkenol via a combination process of lipase-catalyzed reaction and RCM reaction. Three model compounds were synthesized in enantiomerically pure form through our protocol. Since RCM reaction has good tolerance to the substrates and lipase-catalyzed reaction proceeds with excellent enantioselectivity for various types of acyclic allylic alcohols, further investigation of the scope and limitation of the present methodology will make it even more beneficial.

4. Experimental

4.1. General procedures

Reagents and solvents were purchased from common commercial sources and were used as received or purified by distillation over appropriate drying agents. Both first generation Ru catalyst and second generation Ru catalyst were purchased from Aldrich. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a JEOL JNM MH-500 or JNM MH-400 MHz spectrometer. Chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) in $CDCl_3$ as an internal reference. IR spectra were obtained on SHIMADZU FT-IR 8000 spectrometers. Optical rotation was measured with a JASCO DIP-370 digital polarimeter.

4.2. Novozym 435-catalyzed acylation of (±)-octa-1,7-dien-3-ol 5 under reduced pressure conditions in [bmim][PF_6]

To a mixture of (±)-**5**[13] (757 mg, 6.0 mmol) and methyl phenoxyacetate (498 mg, 3 mmol) in [bmim][PF_6] (3.0 mL) was added Novozym 435 (378 mg, 50 wt %). The mixture was stirred under a reduced pressure of 400 mm Hg at 35 °C, and was monitored by capillary GC analysis. After being stirred for 0.5 h, ether (3 mL) was added to the reaction mixture to form the biphasic layer. The produced ester and the remaining alcohol were extracted from the ether layer and subsequently purified by silica gel flash column chromatography to afford (*S*)-**4a** (421 mg, 1.62 mmol, 27%) and (*R*)-**5** (507 mg, 67%), respectively. The enantioselectivity of these compounds was determined by HPLC analysis on a chiral column: Chiralcel AD, hexane/2-propanol = 8:1, 35 °C, 0.5 mL/min;

rt = 4.2 min for (*R*)-**4a**; rt = 4.9 min for (*S*)-**4a**. The enantiomeric excess of (*R*)-**5** was determined as the corresponding acetate **4b** using capillary GC analysis using a chiral column (Chiraldex G-Ta: rt = 7.7 min for (*R*)-**4b**; rt = 9.1 min for (*S*)-**4b**, 70 °C, He gas). (*S*)-**4a**: $[\alpha]_D^{23} = -11.9$ (*c* 1.0, $CHCl_3$), 99.6% ee; R_f 0.8 (hexane/ethyl acetate = 5:1); ^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 1.24–1.38 (2H, m), 1.52–1.64 (2H, m), 1.92–2.03 (2H, m), 4.62–4.65 (1H, m), 4.77 (2H, s), 4.86–5.26 (4H, m), 5.66–5.77 (2H, m); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 24.08, 33.20, 33.38, 65.36, 75.73, 114.56, 114.56, 114.85, 117.40, 121.60, 129.43, 129.43, 135.70, 138.03, 157.77, 168.23; IR (neat, cm^{-1}) 936, 2862, 1763, 1736, 1601, 1497, 1192, 1088, 914, 754, 691.

(*R*)-**5**: $[\alpha]_D^{23} = -2.2$ (*c* 1.4, $CHCl_3$), 39% ee; R_f 0.4 (hexane/ethyl acetate = 4:1); ^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 1.32–1.48 (4H, m), 2.00 (2H, dt, $J = 11.9$, 6.0 Hz), 3.24 (OH, s), 3.94 (1H, dt, $J = 12.4$, 6.5 Hz), 4.85–5.13 (4H, m), 5.69–5.81 (2H, m); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 24.49, 33.47, 36.28, 72.89, 114.42, 114.49, 138.49, 141.13; IR (neat, cm^{-1}) 350, 3078, 2918, 2862, 1641, 1452, 993, 912, 636.

4.3. Resolution of (±)-octa-1,7-dien-3-ol 5 using vinyl acetate as acyl donor under ambient pressure (in [bmim][PF_6])

To the mixture of (±)-**5**[13] (50 mg, 0.40 mmol) and vinyl acetate (52 mg, 0.60 mmol) in [bmim][PF_6] (1.0 mL) was added Novozym 435 (25 mg, 50 wt %). The mixture was stirred at 35 °C, and was monitored by capillary GC analysis. After being stirred for 2.5 h, ether (2 mL) was added to the reaction mixture to form the biphasic layer. The acetate and the remaining alcohol were extracted from the ether layer (10 times) and subsequently purified by silica gel flash column chromatography to afford acetate (*S*)-**4b** (22 mg, 0.13 mmol, 33%) and (*R*)-**5** (29 mg, 0.23 mmol, 58%): Conversion 0.48, $E > 200$. (*S*)-**4b**: $[\alpha]_D^{23} = -12.0$ (*c* 1.12, $CHCl_3$), 97% ee; (*R*)-**5**: $[\alpha]_D^{23} = -4.2$ (*c* 1.43, $CHCl_3$), 92% ee; The enantiomeric excess of (*R*)-**5** was determined as acetate **4b** by capillary GC analysis using a chiral column (Chiraldex G-Ta, 70 °C, He).

(S)-Octa-1,7-dien-3-yl acetate **4b**:[13] $[\alpha]_D^{23} = -12.0$ (*c* 1.12, $CHCl_3$), 97% ee; R_f 0.73 (hexane/ethyl acetate = 2:1); ^{1}H NMR (200 MHz, ppm, $CDCl_3$) δ 1.23–1.46 (2H, m), 1.48–1.70 (2H, m), 2.00 (3H, s), 1.91–2.68 (2H, m), 4.82–5.01 (2H, m), 5.04–5.23 (3H, m), 5.58–5.83 (2H, m); ^{13}C NMR (50 MHz, ppm, $CDCl_3$) δ 21.1, 24.2, 33.3, 33.5, 74.5, 114.7, 116.5, 136.4, 138.1, 170.1; IR (neat, cm^{-1}) 079, 2939, 2863, 1740, 1643, 1433, 1371, 1240, 1021, 994, 963, 916.

4.4. Resolution of (±)-octa-1,7-dien-3-ol 4a using vinyl acetate as an acyl donor under ambient pressure (in *i*-Pr_2O): large scale preparation

To a mixture of (±)-**5**[12] (10.0 g, 79 mmol) and vinyl acetate (10.0 g, 118 mmol) in *i*-Pr_2O (260 mL) was added Novozym 435 (200 mg, 2 wt %). The mixture was stirred at 35 °C, and was monitored by capillary GC analysis. After being stirred for 6 h, lipase was removed by filtration through a sintered glass filter with a Celite pad, after which the filtrate was evaporated. Silica gel flash column chromatography (hexane/ethyl acetate = 100:1 ~ 40:1 ~ 10:1) gave acetate (*S*)-**4b** (3.95 g, 23.5 mmol, 30%, 98% ee) and (*R*)-**5** (5.34, 42.3 mmol, 54%, 64% ee): Conversion 0.39, $E > 200$.

4.5. Synthesis of (*S*)-1 using RCM reaction

4.5.1. (*S*)-Cyclohex-2-enyl phenoxyacetate 8. To a mixture of (*S*)-**4a** (210 mg, 0.79 mmol) in [bmim][PF_6] (1.0 mL) was added Grubbs catalyst (32 mg, 0.039 mmol) in one portion at rt, after which the mixture was stirred at 80 °C for 10 h under argon atmospheric conditions. After cooling to rt, ether was added to the reaction mixture and then extracted with ether ten times. Silica gel chromatography gave (*S*)-**8** (169 mg, 0.73 mmol) in 90% yield: $[\alpha]_D^{25} = -56.9$ (*c* 0.9, $CHCl_3$), >99% ee; R_f 0.6 (hexane/ethyl acetate = 5:1); bp 105 °C/6 Torr (Kugelrohr); ^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 1.24–1.38 (2H, m), 1.52–1.64 (2H, m), 1.92–2.03 (2H, m), 4.62–4.65 (1H, m), 4.77 (2H, s), 4.86–5.26 (4H, m), 5.66–5.77 (2H, m); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 24.08, 33.20, 33.38, 65.36, 75.73, 114.56, 114.56, 114.85, 117.40, 121.60, 129.43, 129.43, 135.70, 138.03, 157.77, 168.23; IR (neat, cm^{-1}) 2936, 2862, 1763, 1736, 1601, 1497, 1192, 1088, 914, 754, 691; Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.27; H, 6.65.

We tested the recyclable use of the first generation Ru catalyst and confirmed that the catalyst had lost no activity after three repetitions of the process.

The absolute configuration of the products of the lipase-catalyzed reaction was determined by the comparison of the $[\alpha]_D$ value of (*S*)-**1** which was derived from (*S*)-**8** by alkaline hydrolysis (LiOH/THF–H_2O (3:1)) in 93% yield. (*S*)-**1**: $[\alpha]_D^{23} = -69.9$ (*c* 1.5, $CHCl_3$), lit.[16a] = −52.8 (*S*); R_f 0.24 (hexane/ethyl acetate = 5:1); ^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 1.26 (OH, br s), 1.59–1.62 (2H, m), 1.62–1.80 (2H, m), 1.86–2.02 (2H, m), 4.18–4.20 (1H, m), 5.75–5.77 (1H, m), 5.82–5.83 (1H, m); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 18.89, 25.00, 31.95, 65.46, 129.82, 130.49; IR (neat, cm^{-1}) 3331, 3024, 2934, 2837, 1437, 1055, 961, 727.

4.6. Resolution of (±)-7a and (±)-7b using lipase technology

4.6.1. (±)-1-(2-(Allyloxy)phenyl)prop-2-en-1-ol 7a. To a solution of 2-(allyloxy)benzaldehyde[24] (1.768 g, 10.9 mmol) in THF (11 mL) and 41 mL of 0.658 M THF, a solution of vinyl magnesium bromide (27 mmol) was added at 0 °C and the resulting mixture was stirred for 1 h at the same temperature. The reaction was quenched by the addition of saturated aqueous ammonium chloride and acidified completely by 2 M HCl, after which it was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and evaporated. Silica gel flash column chromatography gave (±)-**7a** (1.68 g, 8.45 mmol) in 77% yield: R_f 0.4 (hexane/ethyl acetate = 4:1); bp 90 °C/7.0 Torr (Kugelrohr); ^{1}H NMR (400 MHz, ppm, $CDCl_3$) δ 2.78 (br s, OH), 4.57 (2H, dt, $J = 3.3$, 1.8 Hz), 5.15 (1H, dt, $J = 10.5$, 1.4 Hz), 5.27–5.33 (2H, m), 5.38–5.43 (2H, m), 6.00–6.08 (1H, m), 6.12 (1H, dq, $J = 17.4$, 5.3 Hz), 6.86 (1H, d, $J = 8.2$ Hz), 6.95 (1H,

dt, $J = 7.3$, 0.9 Hz), 7.21–7.24 (1H, m), 7.30 (1H, dd, $J = 7.6$, 1.6 Hz); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 68.90, 71.73, 111.96, 114.51, 117.68, 121.11, 127.49, 128.66, 131.06, 132.93, 139.47, 155.70; IR (neat, cm^{-1}) 3408, 3080, 2984, 2869, 1601, 1489, 1452, 1236, 997, 924, 754; Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.57; H, 7.19.

4.6.2. (±)-1-(2-(Allyloxy)phenyl)but-3-en-1-ol 7b.[19,24] To a solution of 3.0 mL of mixed solvent ($THF/H_2O = 1:1$) of 2-(allyloxy)benzaldehyde[22] (174 mg, 1.07 mmol) and allyl bromide (194 mg, 1.61 mmol) was added indium powder (123 mg, 1.07 mmol), and the resulting mixture was stirred for 8 h at 30 °C. The reaction was monitored by capillary GC analysis. The reaction was quenched by the addition of 2 M HCl and extracted by ethyl acetate. The organic layer was washed with aqueous sodium hydrogen carbonate ($NaHCO_3$) and brine, dried over anhydrous $MgSO_4$ and evaporated. Silica gel flash column chromatography gave (±)-**7b** (208 mg) in 95% yield: R_f 0.29 (hexane/ethyl acetate = 5:1); ^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 1.5 (br s, OH), 2.45 (1H, m), 2.56 (1H, m), 4.52 (2H, d, $J = 5.0$ Hz), 4.93 (1H, t, $J = 5.0$ Hz), 5.03–5.09 (2H, m), 5.23 (1H, ddt, $J = 10.5$, 2.8, 1.5 Hz), 5.35 (1H, ddt, $J = 17.5$, 3.2, 1.9 Hz), 5.74–5.84 (1H, m), 5.96–6.04 (1H, m), 6.80 (1H, d, $J = 8.3$ Hz), 6.89 (1H, dd, $J = 7.3$, 0.9 Hz), 7.15 (1H, dd, $J = 9.6$, 1.8 Hz), 7.28 (1H, d, $J = 7.7$ Hz); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 41.9, 68.6, 69.6, 111.5, 117.3, 117.5, 120.9, 126.8, 128.1, 132.0, 133.0, 135.1, 155.2; IR (neat, cm^{-1}) 3398, 3074, 2978, 2868, 1638, 1601, 1491, 1452, 1234, 997, 754.

4.7. Resolution of (±)-1-(2-(allyloxy)phenyl)prop-2-en-1-ol 7a

4.7.1. (*R*)-1-(2-(Allyloxy)phenyl)allyl acetate 6a. To a solution of (±)-**7a** (200 mg, 1.05 mmol) and vinyl acetate (141 mg, 1.64 mmol, 1.5 equiv) in *i*-Pr_2O (8.0 mL) was added Novozym 435 (100 mg) and the mixture was stirred at 35 °C for 4 h. The reaction mixture was filtered through a sintered glass filter to remove enzyme and the filtrate was evaporated. Purification by silica gel TLC gave (*R*)-**6a** (90.6 mg, 0.39 mmol, 37%) and (*S*)-**7a** (100 mg, 0.52 mmol, 50%).

(*R*)-**6a**: R_f 0.47 (hexane/ethyl acetate = 5:1); $[\alpha]_D^{22} = +41.4$ (*c* 1.0, $CHCl_3$), >99% ee; bp 90–95 °C/6.0 Torr (Kugelrohr); ^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 2.04 (3H, s), 4.51 (2H, dt, $J = 3.3$, 1.7 Hz), 5.11–5.14 (1H, m), 5.17–5.21 (2H, m), 5.35 (1H, dq, $J = 17.2$, 1.6 Hz), 5.93–6.01 (2H, m), 6.63 (1H, d, $J = 6.0$ Hz), 6.80 (1H, d, $J = 8.2$ Hz), 6.89 (1H, t, $J = 7.6$ Hz), 7.17–7.20 (1H, m), 7.28 (1H, dd, $J = 7.6$, 1.6 Hz); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 21.2, 68.9, 70.8, 112.0, 116.0, 117.2, 120.8, 127.3, 127.7, 129.0, 133.1, 135.8, 155.5, 169.8; IR (neat, cm^{-1}) 2868, 1742, 1491, 1232, 1020, 932, 754; Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 71.59; H, 6.85.

(*S*)-**7a**: $[\alpha]_D^{22} = -18.6$ (*c* 1.0, $CHCl_3$), >99% ee. (*S*)-1-phenylprop-2-en-1-ol: $[\alpha]_D = -8.4$ (*c* 2.87, benzene),[18a] $[\alpha]_D^{rt} = -5.2$ (neat).[18b]

The enantiomeric excess of **6a** was determined by HPLC analysis using a chiral column: AD, hexane/2-propanol = 100:1, 35 °C, 0.5 mL/min, rt = 12.1 min for (*R*)-**6a**; rt = 13.0 min for (*S*)-**6a**. % ee of **7a** was determined by HPLC analysis using chiral column: OD-H, hexane/2-propanol = 40:1, 35 °C, 0.5 mL/min, rt = 32.2 min for (*S*)-**7a**; rt = 34.1 min for (*R*)-**7a**.

4.8. Resolution of (±) of 1-(2-(allyloxy)phenyl)but-3-en-1-ol 7b[24]

4.8.1. (*R*)-1-(2-(Allyloxy)phenyl)but-3-enyl acetate 6b. To a solution of (±)-**7b** (50 mg, 0.24 mmol) and vinyl acetate (32.7 mg, 0.37 mmol, 1.5 equiv) in *i*-Pr_2O (2 mL) was added IL1-PS[20] (11 mg) and the mixture was stirred at 35 °C. The reaction course was monitored by capillary GC analysis and silica gel TLC. (*R*)-1-(2-(Allyloxy)phenyl)but-3-enyl acetate **6b** (9.0 mg) and (*S*)-**7b** (35 mg) were obtained by TLC. The enantioselectivity of **6b** was determined by HPLC analysis on a chiral column (AD, hexane/2-propanol = 9:1), 35 °C, 0.5 mL/min; rt = 12.1 min for (*R*)-**6b**; rt = 3.6 min for (*S*)-**6b**.

(*R*)-**6b**: R_f 0.47 (hexane/ethyl acetate = 5:1); $[\alpha]_D^{22} = +39.4$ (*c* 1.0, $CHCl_3$), >99% ee; R_f 0.47 (hexane/ethyl acetate = 5:1); bp 110 °C/6.0 Torr (Kugelrohr); ^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 2.09 (3H, s), 2.53–2.65 (2H, m), 4.57 (2H, ddd, $J = 4.7$, 2.7, 1.0 Hz), 5.01–5.07 (2H, m), 5.28 (1H, dddd, $J = 10.5$, 4.5, 3.0, 1.6 Hz), 5.44 (1H, ddt, $J = 17.8$, 3.5, 2.1 Hz), 5.73–5.79 (1H, m), 6.01–6.07 (1H, m), 6.27 (1H, t, $J = 5.1$ Hz), 6.85 (1H, d, $J = 8.2$ Hz), 6.95 (1H, dd, $J = 6.9$, 0.5 Hz), 7.21 (1H, dd, $J = 9.1$, 1.9 Hz), 7.32 (1H, d, $J = 7.7$ Hz); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 21.2, 39.6, 68.8, 69.9, 111.8, 117.0, 117.4, 120.6, 126.4, 128.5, 129.1, 133.2, 133.9, 155.1, 170.1; IR (neat, cm^{-1}) 3078, 1740, 1491, 1452, 1373, 1236, 1022, 920, 754; Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.49; H, 7.21.

(*S*)-**7b**: R_f 0.29 (hexane/ethyl acetate = 5:1); $[\alpha]_D^{23} = -4.5$ (*c* 1.0, $CHCl_3$), 32% ee; The enantioselectivity of **7b** was determined by HPLC analysis on a chiral column (OD-H, hexane/2-propanol = 20:1), 35 °C, 0.5 mL/min; rt = 23.2 min for (*S*)-**7b**; rt = 25.7 min for (*R*)-**7b** (Table 2).

4.9. Determination of the absolute configuration of (+)-6b and (−)-7b

Ester (+)-**6b** {$[\alpha]_D^{22} = +53.2$ (*c* 1.0, $CHCl_3$), >99% ee} was hydrolyzed to (+)-**7b** (>99% ee) using K_2CO_3 in MeOH; (+)-**7b** was then converted to the corresponding (*S*)-Mosher ester and (*R*)-Mosher ester and the absolute configuration of the produced acetate, (+)-**6b**, was determined to be (*R*) by the Kusumi–Ohtani method (Fig. 2).

4.10. Synthesis of (*R*,*Z*)-2,5-dihydrobenzo[*b*]oxepin-5-yl acetate 2a by the RCM reaction

To a solution of the first generation Grubbs catalyst (6.7 mg, 0.008 mmol, 10 mol %) in CH_2Cl_2 (8.1 mL) was added (*R*)-**6a** (18.7 mg, 0.0805 mmol). The mixture was stirred at 60 °C for 24 h under an argon atmosphere, then

Table 2. Chemical shift of (*S*)-MTPA and (*R*)-MTPA ester of (+)-**6b** (400 MHz ^{1}H NMR, $CDCl_3$)

Chemical shift (ppm)				$\delta S - \delta R$
(*S*)-MTPA ester of **9** (from (+)-**6b**)		(*R*)-MTPA ester of **9** (from (+)-**6b**)		
2.66	2H, t, $J = 6.4$ Hz	2.64	t (dd), $J = 6.4$ Hz	0.02
3.57	3H, OMe, s	3.5	OMe, s	0.07
4.57	2H, m	4.58	dd, $J = 5.2$, 1.2 Hz	−0.01
5.08	1H, dd, $J = 10.3$, 1.6 Hz	4.84	d, $J = 11.2$ Hz	0.24
5.10	1H, dd, $J = 15.6$, 1.6 Hz	4.98	dd, $J = 16.4$, 11.2 Hz	0.12
5.28	1H, dd, $J = 10.8$, 1.6 Hz	5.27	dd, $J = 10.8$, 1.6 Hz	0.01
5.42	1H, dd, $J = 17.1$, 1.6 Hz	5.45	dd, $J = 17.6$, 1.2 Hz	−0.03
5.80	1H, m	5.67	m	0.13
6.05	1H, m	6.05	m	0
6.46	1H, t, $J = 6.8$ Hz	6.54	t, $J = 6.0$ Hz	−0.08
6.83	2H, t, $J = 7.6$ Hz	6.87	d, $J = 8.4$ Hz	−0.04
6.84	1H, d, $J = 8.4$ Hz	6.87	d, $J = 8.4$ Hz	−0.03
7.00	1H, d, $J = 8.0$ Hz	6.93	d, $J = 8.0$ Hz	0.07
7.01	1H, d, $J = 8.0$ Hz	6.93	d, $J = 8.0$ Hz	0.08
7.30	2H, m (7.19–7.41)	7.34	m (7.23–7.45)	(−0.04)
7.46	2H, d, $J = 7.2$ Hz	7.49	d, $J = 6.8$ Hz	−0.03

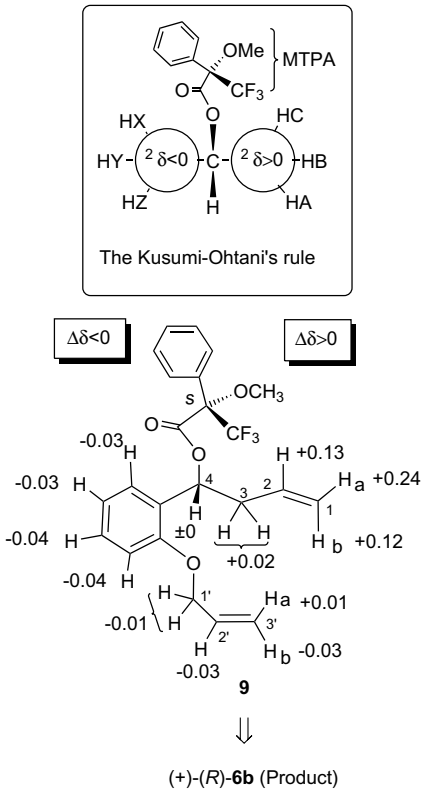


Figure 2. $\Delta\delta = (\delta S - \delta R)$ values analysis of the Mosher esters.

the mixture was evaporated and purified by TLC (hexane/ethyl acetate = 5:1) to give product (*R*)-**2a** (14.6 mg, 0.0716 mmol) in 89% yield: $[\alpha]_D^{25} = +3.4$ (*c* 1.0, $CHCl_3$); R_f 0.49 (hexane/ethyl acetate = 5:1); bp 60 °C/6 Torr (Kugelrohr); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.18 (3H, s), 4.51–4.68 (2H, m) 5.59 (1H, dq, $J = 11.9$, 2.4 Hz), 5.83–5.87 (1H, m) 6.68 (1H, dd, $J = 4.1$, 2.1 Hz), 7.10–7.13 (2H, m) 7.27–7.29 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 70.5, 70.6, 121.9, 124.3, 125.97, 127.84, 129.3, 129.4, 134.9, 156.6, 170.1; IR (neat, cm^{-1}) 3855, 3753, 3676, 3395, 2924, 2853, 1742, 1585, 1489, 1458, 1369, 1232, 1043, 1024, 795, 758, 737, 679, 584; Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.36; H, 5.75.

4.11. Synthesis of (*R*,*Z*)-5,6-dihydro-2*H*-benzo[*b*]oxocin-6-yl acetate 3a by the RCM reaction

To a solution of the first generation Grubbs catalyst (2.5 mg, 0.003 mmol, 0.05 equiv) in CH_2Cl_2 was added (*R*)-**6b** (15 mg, 0.061 mmol), and the mixture was stirred at 60 °C for 24 h under an argon atmosphere. The reaction course was verified by capillary GC analysis, after which it was evaporated and purified by TLC (hexane/ethyl acetate = 5:1) to give product (*R*)-**3a** (11 mg) in 41% yield.

(*R*)-**3a**: $[\alpha]_D^{23} = -7.5$ (*c* 1.0, $CHCl_3$); R_f 0.5 (hexane/ethyl acetate = 5:1); bp 60 °C/6 Torr (Kugelrohr); ^{1}H NMR (500 MHz, ppm, $CDCl_3$) δ 2.83–2.86 (2H, m), 4.55 (2H, dd, $J = 6.0$, 4.1 Hz), 5.40 (1H, t, $J = 2.7$ Hz), 5.75 (1H, dt, $J = 20.1$, 0.9 Hz), 6.12–6.14 (1H, m), 7.07 (1H, d, $J = 7.8$ Hz), 7.13 (1H, dd, $J = 7.3$, 0.9 Hz), 7.28–7.34 (2H, m); ^{13}C NMR (125 MHz, ppm, $CDCl_3$) δ 170.4, 157.0, 131.8, 130.9, 130.0, 128.5, 128.1, 127.6, 124.8, 123.2, 74.5, 73.6, 32.6, 21.3; IR (neat, cm^{-1}) 2926, 1736, 1491, 1371, 1236, 1203, 1113, 1018, 758; Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.42; H, 6.20.

Acknowledgement

The present work was supported by a Grant-in-Aid for Scientific Research in a Priority Area, 'Science of Ionic Liquids', from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

1. Reviews see: (a) Wong, C.-H.; Whitesides, G. M. *Enzymes in Synthetic Organic Chemistry*; Pergamon: Oxford, 1994; (b) Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in Organic*

Synthesis: Regio- and Stereoselective Biotransformations; John Wiley & Sons: Chichester, 1999.
2. Oritani, T.; Yamashita, K. *Agric. Biol. Chem.* **1980**, *44*, 2637–2642.
3. It was reported that excellent enantioselectivity was recorded when 2-trimethyl-2-cyclohexen-1-ol was subjected to the lipase-catalyzed reaction: Adam, W.; Mock-Knoblauch, C.; Saha-Möller, C. R. *Tetrahedron: Asymmetry* **1997**, *8*, 1441–1444.
4. We tested seven types of commercial lipases: lipase PS, Novozym 435 (CAL), *Candida rugosa* lipase (Meito: Lipase OF), Lipase AL: *Acromobacter* sp. lipase (Meito), Lipase QL (*Alcaligenes* sp., Meito), SL25 (*Burkholderia cepacia* SL-25, Meito), and PPL (Porcine pancreatin lipase, Sigma).
5. (a) Takagi, Y.; Teramoto, J.; Kihara, H.; Itoh, T.; Tsukube, H. *Tetrahedron Lett.* **1996**, *37*, 4991–4992; (b) Takagi, Y.; Ino, R.; Kihara, H.; Itoh, T.; Tsukube, H. *Chem. Lett.* **1997**, 1247–1248; (c) Itoh, T.; Sakabe, K.; Kudo, K.; Zagatti, P.; Renou, M. *Tetrahedron Lett.* **1998**, *39*, 4071–4074; (d) Takagi, Y.; Kashiwagi, M.; Kihara, H.; Itoh, T. *Tetrahedron Lett.* **1999**, *40*, 2801–2802; (e) Itoh, T.; Kudo, K.; Tanaka, N.; Sakabe, K.; Takagi, Y.; Kihara, H. *Tetrahedron Lett.* **2000**, *41*, 4591–4595; (f) Takagi, Y.; Nakatani, T.; Itoh, T.; Oshiki, T. *Tetrahedron Lett.* **2000**, *41*, 7889–7892; (g) Itoh, T.; Kudo, K. *Tetrahedron Lett.* **2001**, *42*, 1317–1320; (h) Itoh, T.; Kudo, K.; Tanaka, N.; Zagatti, P.; Renou, M. *Enantiomer* **2001**, *6*, 43–49.
6. For reviews of the RCM reaction, see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2037; (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413; (c) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141; (d) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211; (e) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238; (f) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239–2258.
7. (a) Fujimura, O.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 2499–2500; (b) Fujimura, S.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 824–832.
8. (a) Kamei, T.; Shindo, M.; Shishido, K. *Synlett* **2003**, 2395–2396; (b) Kamei, T.; Shindo, M.; Shishido, K. *Tetrahedron Lett.* **2003**, *44*, 8505–8507; (c) Morimoto, S.; Shindo, M.; Shishido, K. *Heterocycles* **2005**, *66*, 69–73.
9. (a) For recent reviews of reactions in an ionic liquid solvent system, see: *Ionic Liquids in Synthesis*; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH, 2003; (b) *Ionic Liquids as Green Solvents*; Rogers, R. D., Seddon, K. R., Eds. ACS Symposium Series 856; American Chemical Society, 2002; (c) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005**, *61*, 1015–1060; (d) Chowdhury, S.; Mohan, R. S.; Scott, J. L. *Tetrahedron* **2007**, *63*, 2363–2389.
10. Recent review of biotransformation in ionic liquid, see: Itoh, T. In *Future Directions in Biocatalysis*; Matsuda, T., Ed.; Elsevier: The Netherlands, 2007; pp 3–20.
11. For our examples, see: (a) Itoh, T.; Akasaki, E.; Kudo, K.; Shirakami, S. *Chem. Lett.* **2001**, 262–263; (b) Itoh, T.; Nishimura, Y.; Kashiwagi, M.; Onaka, M. In *Ionic Liquids as Green Solvents: Progress and Prospects*; Rogers, R. D., Seddon, K. R., Eds.; ACS Symposium Series 856; American Chemical Society: Washington DC, 2003, Chapter 21, pp 251–261; (c) Itoh, T.; Nishimura, Y.; Ouchi, N.; Hayase, S. *J. Mol. Catal. B: Enzym.* **2003**, *26*, 41–45; (d) Itoh, T.; Ouchi, N.; Hayase, S.; Nishimura, Y. *Chem. Lett.* **2003**, *32*, 654–655; (e) Itoh, T.; Ouchi, N.; Nishimura, Y.; Han, S.-H.; Katada, N.; Niwa, M.; Onaka, M. *Green Chem.* **2003**, *5*, 494–496; (f) Itoh, T.; Han, S.; Matsushita, Y.; Hayase, S. *Green Chem.* **2004**, *6*, 437–439; (g) Tsukada, Y.; Iwamoto, K.; Furutani, H.; Matsushita, Y.; Abe, Y.; Matsumoto, K.; Monda, K.; Hayase, S.; Kawatsura, M.; Itoh, T. *Tetrahedron Lett.* **2006**, *48*, 1801–1804.
12. Itoh, T.; Akasaki, E.; Nishimura, Y. *Chem. Lett.* **2002**, 154–155.
13. Basavaiah, D.; Raju, S. B. *Tetrahedron* **1994**, *50*, 4137–4148.
14. Chen, C.-S.; Fujimoto, Y.; Girdauskas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *102*, 7294–7298.
15. For an example of Ru catalyst mediated RCM reaction in an ionic liquid solvent system, see: Buijsman, R. C.; van Vuuren, E.; Strrenburg, J. G. *Org. Lett.* **2001**, *3*, 3785–3787.
16. Although reported specific rotation values of (*S*)-**2** vary, such as from −52.5 to −104.5 in $CHCl_3$, (*S*)-isomer values were confirmed to be negative: (a) Lüssem, B. J.; Gais, H.-J. *J. Org. Chem.* **2004**, *69*, 4041–4052; (b) Holub, N.; Neidhöfer, J.; Blechert, S. *Org. Lett.* **2005**, *7*, 1227–1229; (c) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.
17. For examples of the RCM reaction for constructing medium size rings, see: (a) Bennasar, M. L.; Roca, T.; Monerris, M.; Garcıá-Dıáz, D. *J. Org. Chem.* **2006**, *71*, 7028–7034; (b) Dondas, H. A.; Clique, B.; Cetinkaya, B.; Grigg, R.; Kilner, C.; Morrisa, J.; Sridharana, V. *Tetrahedron* **2005**, *61*, 10652–10666.
18. (a) Kusuda, S.; Ueno, Y.; Toru, T. *Tetrahedron* **1994**, *50*, 1045–1062; (b) Goering, H. L.; Dilgren, R. E. *J. Am. Chem. Soc.* **1959**, *81*, 2556–2561.
19. Franco, D.; Panyella, D.; Rocamora, M.; Gomez, M.; Clinet, J. C.; Muller, G.; Dunach, E. *Tetrahedron Lett.* **1999**, *40*, 5685–5688.
20. Itoh, T.; Matsushita, Y.; Abe, Y.; Han, S.-H.; Wada, S.; Hayase, S.; Kawatsura, M.; Takai, S.; Morimoto, M.; Hirose, Y. *Chem. Eur. J.* **2006**, *12*, 9228–9237.
21. Both IL1(1-butyl-2,3-dimethylimidazolium polyoxyethylene (10)cetyl sulfate) and IL1-PS will be soon commercially available from Tokyo Chemical Industry Co., Ltd. Please contact Dr. Kenji Tahara of TCI: kenji.tahara@tokyokasei.co.jp, tel.: +81 3 5640 8857, fax: +81 3 5640 8868.
22. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
23. (a) Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517–1519; (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *4*, 18–29; (c) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140.
24. Isaac, M. B.; Chan, T.-H. *Tetrahedron Lett.* **1995**, *49*, 8957–8960.