Stereoselectivity in ring-closing olefin metathesis (RCM) of tethered dihexenoyl derivatives

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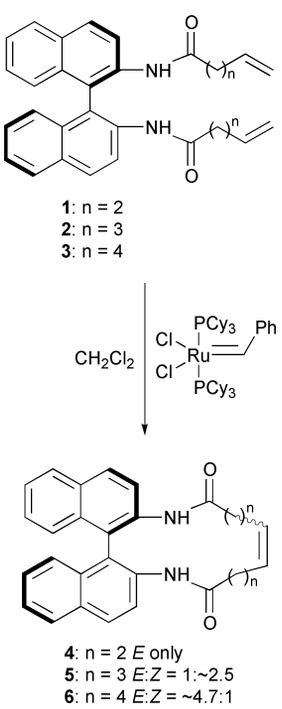
Ring-closing olefin metatheses (RCM) of various tethered dihexenoyl derivatives were examined under various conditions. The *E* : *Z* ratios of the resulting double bonds of the cyclic products were determined. The stereochemistry of the resulting olefins was influenced largely by the effects of the template used.

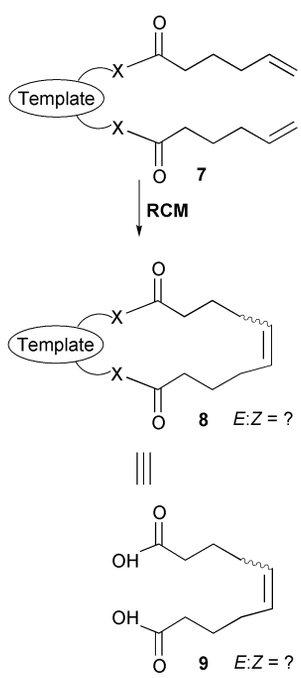
Introduction

Ring-closing olefin metathesis (RCM) is one of the most powerful methods for constructing a carbon–carbon double bond between two olefins. Many researchers report that this method is useful and apply it to the syntheses of natural products.[1] It is generally recognised that one of the major problems in ring-closing ene–ene metatheses reactions is how to control/predict the stereoselectivity in the formation of the new double bond.[2,3] As part of our examination of the synthesis of nitrogen-containing heterocycles using RCM[4] and the Yb-catalysed asymmetric Diels–Alder reaction,[5] we report the syntheses of novel axially chiral macrolactams using RCM. In the RCM of dienes **1** and **3** to the 14-membered lactam **4** and the 18-membered lactam **6**, *E*-isomers are the major products.[4c] On the other hand, the RCM of **2** to the 16-membered lactam **5** gave a *Z*-isomer as the major product (Scheme 1).[4c] A stereocontrolled



Scheme 1

RCM product **8** might be useful as a key intermediate for chiral ligands, while the symmetric dicarboxylic acid **9** is a typical metabolite of patients who lack medium acyl CoA dehydrogenase.[6] To the best of our knowledge, the preparation of **9**, which might be used as a building block for biologically active natural products, has not yet been reported. Although it is not yet clear what factors control the stereoselectivity, we have now investigated in detail the effects of solvents, catalysts, and/or templates on the ratios of stereoisomers formed by RCM of various kinds of dihexenoyl derivatives (Scheme 2). This article describes our



Scheme 2

systematic approach to control the stereoselectivity in RCM reactions using tethered dihexenoyl derivatives; and a dihexenoyl derivative with binaphthyldiamine **2**, prepared by the method we reported previously,[4c] was subjected to RCM reactions under various conditions, and the ratio of regioisomers formed was determined by comparison with the authentic samples.

Results and discussion

Solvent

Diene **2** was first treated in dichloromethane (3 mM) with 10 mol% of ruthenium carbene catalyst **A**[7] at 50 °C for 4 h, and

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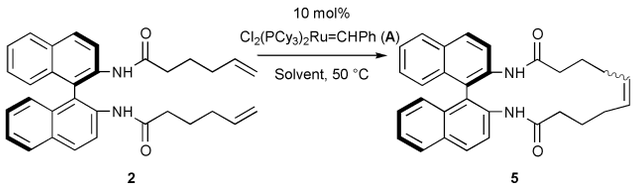
Table 1 Solvent effect in RCM: dihexenoyl derivative



2 5

Entry	Solvent (3 mM)	Time/h	Yield (%)	$E : Z^a$
1	CH_2Cl_2	2.5	94	1 : 2.4
2	$CHCl_3$	4.0	91	1 : 2.8
3	CCl_4	4.0	38[b]	1 : 3.0
4	$ClCH_2CH_2Cl$	4.0	88	1 : 1.8
5	$Cl_2CHCHCl_2$	4.0	67[b]	1 : 2.8
6	CH_2Br_2	4.0	62[b]	1 : 3.9
7	$BrCH_2CH_2Br$	4.0	19[b]	1 : 13
8	C_6H_6	4.5	69[b]	1 : 2.7
9	C_6H_5Cl	4.0	77[b]	1 : 2.8
10	$C_6H_5CH_3$	4.0	61[b]	1 : 2.5
11	$C_6H_5CF_3$	4.0	38[b]	1 : 3.3
12	AcOEt	4.0	50[b]	1 : 2.5
13	Acetone	4.0	51[b]	1 : 2.3
14	THF	4.5	43[b]	1 : 2.8
15	DME	4.0	0	—

[a] Determined by HPLC (Chiralcel OD). [b] Determined by ^{1}H-NMR.

macrolactam **5** was obtained in 94% yield as a mixture of *E* and *Z* isomers. These stereoisomers were readily separated by column chromatography to give an $E : Z$ ratio of 1 : 2.4.[4c] Based on these findings, we studied the stereochemical outcome of this reaction in various solvents. These results are summarised in Table 1. In other halocarbon solvents such as chloroform or 1,2-dichloroethane (entries 2 and 4), **5** was obtained in almost the same yield, although the ratio of stereoisomers was increased in chloroform and decreased in 1,2-dichloroethane. In tetrachloromethane, 1,1,2,2-tetrachloroethane, and dibromomethane (entries 3, 5, and 6), the diastereoselectivity was increased but the yields were decreased. The reaction in 1,2-dibromoethane (entry 7) gave the best diastereoselectivity, although the yield decreased to 19%. In aromatic solvents (entries 8–11), **5** was obtained in good to moderate yields, and the diastereoselectivity was almost the same as it was in dichloromethane. Reactions in ethyl acetate, acetone, and tetrahydrofuran also gave **5**, but the polar solvent 1,2-dimethoxyethane (DME) gave no product (entries 12–15). Due to the poor conversion, tetrachloromethane, 1,2-dibromoethane and α,α,α-trifluorotoluene gave **5** in lower yields, and it is known that Grubb's catalyst can react with halogenated solvent.[8] Some solvents showed enhanced *E*–*Z* selectivity compared to dichloromethane, but only to a small extent.

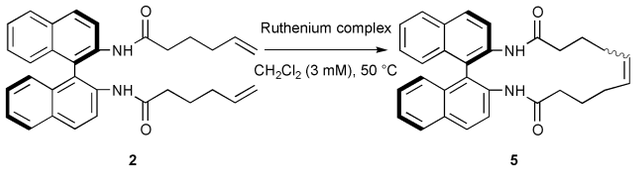
Catalyst

Next, we examined the effects of catalysts **B**–**D**[9] in the RCM reaction of diene **2** (Table 2). With catalysts **B** and **C**, **2** gave **5** in excellent yields, with almost the same selectivity as in the reaction with catalyst **A**. On the other hand, with the 4th-generation catalyst **D**, **2** gave **5** in only 20% yield and undesired oligomeric compounds were formed. However, the stereoselectivity of **5** was dramatically changed, and the *E*-isomer became the major isomer.[10] Thus, none of the catalysts **A**–**D** was particularly effective in influencing the stereochemical outcome of the reaction.

Template

Finally, we examined the effects of various templates. The binaphthyldiamine moiety in **2** was replaced by other templates, such as binaphthol, biphenol, catechol, and diols. To determine

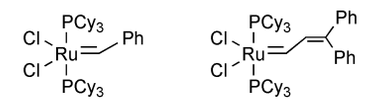
Table 2 Catalyst effect in RCM: dihexenoyl derivative



2 5

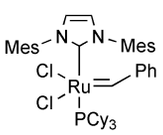
Entry	Ru-complex (10 mol%)	Time/h	Yield (%)	$E : Z^a$
1	**A**	2.5	94	1 : 2.4
2	**B**	2.5	97	1 : 2.3
3	**C**	1.5	88	1 : 2.3
4	**D**	2.5	20[b]	2.8 : 1

[a] Determined by HPLC (Chiralcel OD). [b] About 50% oligomers was by-produced.

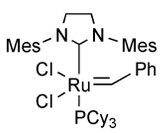


A (Grubbs, 1995)

B (Grubbs, 1993)



C (Herrmann, 1999)



D (Grubbs, 1999)

the stereoselectivity of these cyclised compounds efficiently, we developed an analytical method that involves the conversion of (*E*)-**5** or (*Z*)-**5** to the corresponding **11** (Scheme 3). Since (*E*)-**11** and (*Z*)-**11** exhibit strong UV absorbances, the ratio of (*E*)-**11** to (*Z*)-**11** could be easily determined by HPLC ($t_{\mathbf{R}\text{-}(E)\mathbf{11}}$ = 45.92 min, $t_{\mathbf{R}\text{-}(Z)\mathbf{11}}$ = 33.98 min. Chiralpak AD, *i*-PrOH : *n*-hexane = 5 : 95, 1.0 ml min^{-1}). Scheme 4 shows our four-step procedure starting with the preparation of dihexenoyl derivatives **7** from a template **12** and hexenoic acid, RCM to give **8**, and conversion of **8** to **11**. The experimental details are summarised in Table 3. Each of the following was used as a template: catechol, cyclohexane-1,2-diol **12d**,**e**, cyclopentane-1,2-diol **12f**,**g**, or butane-1,4-diol **12h**. The reactions using each template gave *Z*-isomers as with binaphthyl-2,2′-diamine, and **12g** gave the highest *Z*-selectivity. On the other hand, 2,2'-bi-2-napthol **12a** and biphenyl-2,2′-diol **12b** gave predominantly *E*-isomers. These results suggest that some strict chelation or steric effect may affect the stereoselectivity in a newly formed double bond.[11]

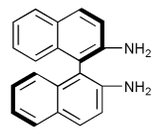
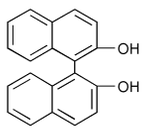
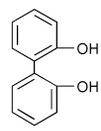
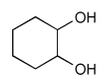
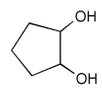
Conclusions

In conclusion, we studied the RCM reactions of tethered dihexenoyl derivatives under various conditions (*i.e.* with various solvents, catalysts, and templates) and examined the stereoselectivity of the reaction leading to the new double bond. Of the conditions investigated, the selection of a template was found to be the most effective way to influence stereoselectivity and that the desired isomer could be obtained as a major product. Further studies to control the stereoselectivity in RCM are underway in our laboratory.

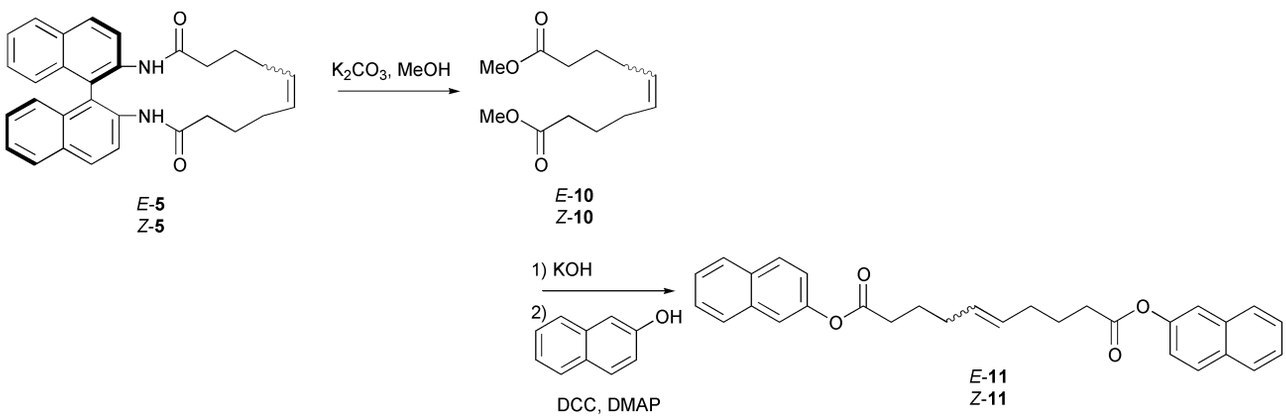
Experimental

All melting points are uncorrected. Infrared (IR) absorption spectra (cm^{-1}) were recorded using a KBr pellet. Specific optical rotations were measured on a JASCO DIP-140 and are given in units of 10^{-1} deg cm^2 g^{-1}.^{1}H NMR (and ^{13}C NMR) spectra were recorded in $CDCl_3$ unless otherwise noted, at 400, 500 or

Table 3 Template effect in RCM: dihexenoyl derivative

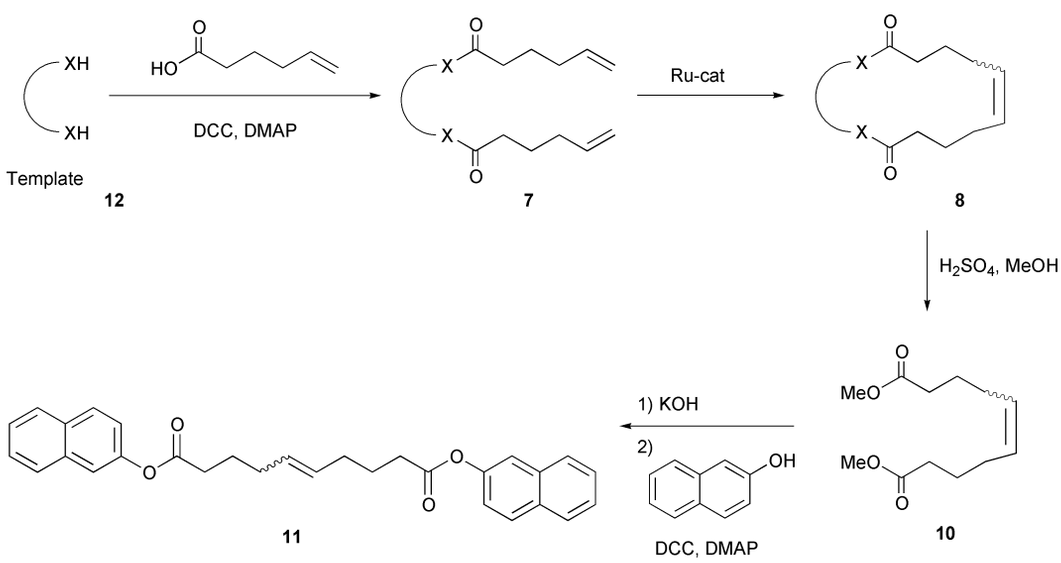
template							
		12a	**12b**	**12c**	**12d**(*cis*) **12e**(*trans*)	**12f**(*cis*) **12g**(*trans*)	**12h**
$E:Z^a$	1 : 2.4	1.3 : 1	1.6 : 1	1 : 2.5	1 : 4.6	1 : 3.1	1 : 3.6	1 : 4.8	1 : 1.3
Yield (%)	94	28	54	96	71	67	84	50	75

[a] Determined by HPLC (ChiralPak AD).



E-**5**
Z-**5**
E-**10**
Z-**10**
E-**11**
Z-**11**

Scheme 3 General procedure for common ester synthesis.



12 **7** **8** **10** **11**

Scheme 4 Experimental cycle.

600 MHz, with TMS as an internal standard. E. Merck silica gel 60 was used for column chromatography, and E. Merck precoated TLC plates, silica gel F_{254}, were used for preparative thin layer chromatography. The organic layers were dried with anhydrous $MgSO_4$ or Na_2SO_4. $Cl_2(PCy_3)_2Ru{=}CHPh$ was obtained commercially.

Synthesis of (*R*)-*N*,*N*′-dihex-5-enoyl-1,1′-binaphthyl-2,2′-diamine (2)

To a stirring solution of *N*-methylmorpholine (0.550 mL, 2.5 eq.) in CH_2Cl_2 (10.0 mL), were added hex-5-enoic acid (0.550 mL, 2.3 eq.) and isobutyl chloroformate (0.550 mL, 2.1 eq.) at −15 °C under an Ar atmosphere. To this mixture was added a solution of (*R*)-1,1′-binaphthyl-2,2′-diamine (569 mg, 2.0 mmol) in CH_2Cl_2 (10.0 mL) at −15 °C, and stirring was continued at the same temperature for 30 min and at rt for 3 h. The reaction was quenched by adding 1 M aq. NaOH (10.0 mL), and organic products were extracted with CH_2Cl_2. The combined organic layers were washed with 1 M HCl and brine. The solvent was removed by an evaporator, and the residue was subjected to column chromatography (AcOEt–*n*-hexane = 1 : 5) to give **2** (712 mg, 75%) as colorless rods.

2: colorless rods (AcOEt–*n*-hexane); mp 148–149; $[\alpha]_D^{24}$ = +83.0 (*c* 1.00, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.34 (2H, d, *J* = 9.0 Hz), 8.04 (2H, d, *J* = 9.0 Hz), 7.94 (2H, d, *J* = 8.3 Hz), 7.45 (2H, dd, *J* = 6.9, 1.0 Hz), 7.28 (2H, dd, *J* = 8.3, 7.8 Hz), 7.06 (2H, d, *J* = 8.5 Hz), 6.96 (2H, br s), 5.56–5.47 (2H, m), 4.80 (2H, dd, *J* = 22.4, 1.0 Hz), 4.76 (2H, dd, *J* = 29.2, 1.0 Hz), 1.99 (4H, td, *J* = 7.7, 3.4 Hz), 1.76 (4H, dd, *J* = 14.2, 7.3 Hz), 1.42–1.36 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.99, 137.42, 134.80, 132.36, 131.43, 129.74, 128.30, 127.24, 125.64, 125.10, 122.56, 122.19, 115.14, 36.32, 32.50, 24.21; IR (KBr) cm^{-1}: 3208, 3004, 2917, 2849, 1652, 1592, 1572, 1493,

1427, 1252, 1025, 992, 907, 863, 818, 778, 748; LRMS (EI): *m*/*z* 476 (M^+); HRMS (FAB): calcd for $C_{32}H_{33}O_2N_2$ (M^+ + H): 477.2534, found 477.2521.

Synthesis of (*R*)-*N*,*N*′-(dec-5-ene-1,10-dioyl)-1,1′-binaphthyl-2,2′-diamine (5)

To a stirring solution of **2** (812 mg, 1.70 mmol) in CH_2Cl_2 (500 mL) was added ruthenium catalyst **A** (141 mg, 0.170 mmol). The solvent was degassed three times by the FPT (freeze–pump–thaw cycles) method, and the reaction mixture was stirred at 50 °C for 2.5 h. The solvent was removed under reduced pressure to give a residue, which was purified by silica gel column chromatography (*n*-hexane : AcOEt = 15 : 1). (*E*)-**5** (235 mg, 28%) and (*Z*)-**5** (563 mg, 66%) were isolated as colorless rods, respectively.

(*E*)-**5**: colorless rods (AcOEt–*n*-hexane); mp 262–263; $[\alpha]_D^{20}$ = +59.7 (*c* 1.00, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.77 (2H, d, *J* = 8.3 Hz), 8.07 (2H, d, *J* = 9.1 Hz), 7.94 (2H, d, *J* = 8.2 Hz), 7.43 (2H, dd, *J* = 7.3, 7.6 Hz), 7.24 (2H, dd, *J* = 7.3, 7.6 Hz), 6.94 (2H, d, *J* = 8.5 Hz), 6.84 (2H, br s), 5.35 (2H, br s), 2.24–2.19 (4H, m), 2.05–1.80 (6H, m), 1.40–1.30 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.65, 135.17, 132.61, 130.91, 130.28, 128.28, 127.24, 125.31, 120.12, 36.01, 31.52, 22.94; IR (KBr) cm^{-1}: 3401, 2923, 1700, 1598, 1500, 1427, 1334, 1274, 1174, 971, 821, 752; LRMS (FAB): *m*/*z* 449 (M^+ + H); HRMS (FAB): calcd for $C_{30}H_{29}O_2N_2$ (M^+ + H): 449.2229, found 449.2225; HPLC (Chiralcel OD, *i*-PrOH–*n*-hexane = 5 : 95, 1.0 ml min^{-1}) t_R = 15.12 min.

(*Z*)-**5**: colorless rods mp >300 °C (from AcOEt–*n*-hexane); $[\alpha]_D^{20}$ = +39.0 (*c* 1.00, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.74 (2H, d, *J* = 9.0 Hz), 8.06 (2H, d, *J* = 9.0 Hz), 7.94 (2H, d, *J* = 8.1 Hz), 7.43 (2H, ddd, *J* = 8.1, 6.9, 1.2 Hz), 7.24 (2H, ddd, *J* = 8.5, 6.9, 1.2 Hz), 6.93 (2H, d, *J* = 8.5 Hz), 6.88 (2H, br s), 5.32 (2H, dd, *J* = 4.2, 4.2 Hz), 2.27–2.21 (2H, m), 2.18–2.13 (2H, m), 2.01–1.83 (6H, m), 1.42–1.36 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 171.6, 135.0, 132.6, 130.9, 130.1, 129.7, 128.2, 127.1, 125.3, 125.3, 120.5, 118.4, 36.7, 26.3, 24.2; IR (KBr) cm^{-1} 3221, 2921, 1686, 1499; LRMS (FAB) *m*/*z* 449 (M^+ + H); HRMS (FAB) calcd for $C_{30}H_{29}N_2O_2$ (M^+ + H): 449.2229, found 449.2225; HPLC (Chiralcel OD, *i*-PrOH–*n*-hexane = 5 : 95, 1.0 ml min^{-1}) t_R = 21.74 min.

Conversion of 5 to dec-5-enedioic acid dimethyl ester (10)

To a stirring solution of (*E*)-**5** or (*Z*)-**5** in MeOH was added c. H_2SO_4 (3.00 eq.), and the mixture was refluxed until all of the starting material was consumed on TLC. To the reaction mixture was added sat. aq. $NaHCO_3$, and organic compounds were extracted with AcOEt. The combined organic layers were washed in brine and dried over Na_2SO_4. The solvent was removed using a rotary evaporator, and the remaining residue was subjected to column chromatography (SiO_2, *n*-hexane–AcOEt = 10 : 1) to give (*E*)-**10** or (*Z*)-**10**, respectively, together with (*R*)-1,1′-binaphthyl-2,2′-diamine.

E-**10**: colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.32 (2H, t, *J* = 3.7 Hz), 3.59 (6H, s), 2.23 (4H, t, *J* = 7.5 Hz), 1.97–1.93 (4H, m), 1.65–1.58 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.12, 130.14, 51.44, 33.35, 31.84, 24.62.

Z-**10**: colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.31 (2H, t, *J* = 4.6 Hz), 3.60 (6H, s), 2.24 (4H, t, *J* = 7.2 Hz), 2.01–1.96 (4H, m), 1.65–1.57 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 174.05, 129.59, 51.45, 33.42, 26.51, 24.79.

Conversion of 10 to dec-5-enedioic acid di-2-naphthyl ester (11)

To a stirring solution of (*E*)-**10** or (*Z*)-**10** in THF–H_2O (6 : 4) was added KOH (3.00 eq.), and the mixture was refluxed until all of the starting material was consumed (as shown by TLC). The reaction mixture was then washed with ether. To the reaction mixture was added 1 M HCl, and the organic compounds were extracted with ether. Organic layers were dried over $MgSO_4$ and filtered, and the solvents were removed under vacuum. To the crude residue obtained were added CH_2Cl_2, DMAP (0.1 eq.), DCC (2.2 eq.) and β-naphthol (2.05 eq.), and stirring was continued at rt for 12 h. The reaction mixture was filtered and subjected to column chromatography (SiO_2, AcOEt–*n*-hexane = 1 : 20) to give **11**.

(*Z*)-**11**: white solid; mp. 115–117 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.2 (4H, d, *J* = 8.5 Hz), 7.78–7.76 (2H, m), 7.53 (2H, br d), 7.48–7.42 (4H, m), 7.21 (2H, dd, *J* = 8.7, 2.2 Hz), 5.51 (2H, t, *J* = 4.7 Hz), 2.63 (4H, t, *J* = 7.5 Hz), 2.25 (4H, dd, *J* = 12.6, 7.0 Hz), 1.92–1.85 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.24, 148.32, 133.73, 131.38, 129.73, 129.35, 127.72, 127.59, 126.49, 125.62, 121.11, 118.44, 33.76, 26.56, 24.79; LRMS (FAB) *m*/*z* 453 (M^+ + H); HPLC (Chiralpak AD, *i*-PrOH–*n*-hexane = 5 : 95, 1.0 ml min^{-1}) t_R = 33.98 min.

(*E*)-**11**: white solid; mp. 109–111 °C; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.2 (4H, d, *J* = 8.5 Hz), 7.78–7.76 (2H, m), 7.53 (2H, br d), 7.48–7.42 (4H, m), 7.21 (2H, dd, *J* = 8.7, 2.2 Hz), 5.53 (2H, t, *J* = 3.8 Hz), 2.63 (4H, t, *J* = 7.4 Hz), 2.19 (4H, dd, *J* = 12.3, 7.1 Hz), 1.87–2.05 (4H, m); LRMS (FAB) *m*/*z* 453 (M^+ + H); HPLC (Chiralpak AD, *i*-PrOH–*n*-hexane = 5 : 95, 1.0 ml min^1) t_R = 45.92 min.

Synthesis of dihexenoate (7a–7h) (condensation of acid with templates)

To a stirring solution of template **12** (2.00 mmol) in CH_2Cl_2 (10.0 mL) was added DMAP (0.100 eq.), DCC (2.20 eq.) and hex-5-enoic acid (2.1 eq.). This was stirred for 1–3 h until all of **12** was consumed. The mixture was filtered through Celite 545 and subjected to column chromatography (SiO_2, AcOEt–*n*-hexane) to give **7**.

Hex-5-enoic acid 2′-hex-5-enoyloxy-1,1′-binaphthalenyl-2-yl ester (7a). Pale yellow oil; 98% yield; R_f = 0.54 (AcOEt–*n*-hexane = 1 : 4);. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.98–7.90 (4H, m), 7.46–7.39 (4H, m), 7.31–7.21 (4H, m), 5.55–5.48 (2H, m), 4.86–4.76 (4H, m), 2.09 (4H, td, *J* = 7.3, 3.9 Hz), 1.66–1.63 (4H, m), 1.27–1.21 (4H, m); LRMS (FAB) *m*/*z* 479 (M^+ + H); HRMS (FAB) calcd for $C_{32}H_{31}O_4$ (M^+ + H): 479.2214, found 479.2192.

Hex-5-enoic acid 2′-hex-5-enoyloxybiphenyl-2-yl ester (7b). Colorless oil; 88% yield; R_f = 0.61 (AcOEt–*n*-hexane = 1 : 4); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40–7.35 (2H, m, Ar), 7.29–7.24 (5H, m), 7.14–7.11 (2H, m), 5.72–5.65 (2H, m), 4.97–4.92 (4H, m), 2.29 (4H, t, *J* = 7.3 Hz), 1.96–1.91 (4H, m), 1.59–1.52 (4H, m); LRMS (FAB) *m*/*z* 379 (M^+ + H); HRMS (FAB) calcd for $C_{24}H_{27}O_4$ (M^+ + H): 379.1902, found 379.1912.

Hex-5-enoic acid 2-hex-5-enoyloxyphenyl ester (7c). Colorless oil; 56% yield; R_f = 0.57 (AcOEt–*n*-hexane = 1 : 4); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.24–7.15 (4H, m), 5.85–5.75 (2H, m), 5.08–5.01 (4H, m), 2.53 (4H, t, *J* = 7.4 Hz), 2.16 (4H, dd, *J* = 14.0, 7.4 Hz), 1.86–1.79 (4H, m); LRMS (FAB) *m*/*z* 379 (M^+ + H); HRMS (FAB) calcd for $C_{18}H_{23}O_4$ (M^+ + H): 303.1590, found 303.1587.

Hex-5-enoic acid *cis*-2-hex-5-enoyloxycyclohexyl ester (7d). Colorless oil; 73% yield; R_f = 0.43 (AcOEt–*n*-hexane = 1 : 4); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.83–5.72 (2H, m), 5.05–4.96 (4H, m), 2.30 (4H, t, *J* = 7.5 Hz), 2.09 (4H, dd, *J* = 14.0, 7.3 Hz), 1.86–1.79 (2H, m), 1.74 (2H, t, *J* = 7.5 Hz), 1.70 (2H, t, *J* = 7.3 Hz), 1.64–1.62 (4H, m), 1.45–1.42 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.56, 137.52, 115.14, 70.59, 33.56, 32.82, 27.53, 23.95, 21.53; LRMS (FAB) *m*/*z* 309 (M^+ + H); HRMS (FAB) calcd for $C_{18}H_{29}O_4$ (M^+ + H): 309.2058, found 309.2057.

Hex-5-enoic acid *trans*-2-hex-5-enoyloxycyclohexyl ester (7e). Colorless oil; 65% yield; R_f = 0.53 (AcOEt–*n*-hexane = 1 : 4); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.81–5.71 (2H, m), 5.04–4.95 (4H, m), 4.82–4.80 (2H, m), 2.27 (4H, td, J = 7.5, 0.9 Hz), 2.09–2.02 (6H, m), 1.73–1.65 (6H, m), 1.40–1.31 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.72, 137.42, 115.25, 73.30, 33.61, 32.85, 30.02, 24.00, 23.26; LRMS (FAB) *m*/*z* 309 (M^+ + H); HRMS (FAB) calcd for $C_{18}H_{29}O_4$ (M^+ + H): 309.2058, found 309.2057.

Hex-5-enoic acid *cis*-2-hex-5-enoyloxycyclopentyl ester (7f). Colorless oil; quant.; R_f = 0.53 (AcOEt–*n*-hexane = 1 : 4); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.82–5.72 (2H, m), 5.15–4.97 (6H, m), 2.31–2.27 (4H, m), 2.10–1.59 (16H, m). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.69, 137.52, 115.18, 73.84, 33.42, 32.87, 28.07, 23.91, 18.99; LRMS (FAB) *m*/*z* 295 (M^+ + H).

Hex-5-enoic acid *trans*-2-hex-5-enoyloxycyclopentyl ester (7g). Colorless oil; 71% yield; R_f = 0.68 (AcOEt–*n*-hexane = 1 : 4); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.81–5.71 (2H, m), 5.07–4.96 (6H, m), 2.31–2.27 (4H, m), 2.12–2.05 (6H, m), 1.80–1.60 (8H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 172.69, 137.51, 115.29, 76.67, 33.48, 32.90, 30.25, 23.91, 21.36; LRMS (FAB) *m*/*z* 295 (M^+ + H).

Hex-5-enoic acid 4-hex-5-enoyloxybutyl ester (7h). Colorless oil; 90% yield; R_f = 0.55 (AcOEt–*n*-hexane = 1 : 4); ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.83–5.72 (2H, m), 5.05–4.97 (4H, m), 4.09 (4H, t, J = 5.5 Hz), 2.31 (4H, t, J = 7.5 Hz), 2.09 (4H, dd, J = 14.1, 7.4 Hz), 1.76–1.69 (8H, m); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.50, 137.60, 115.30, 63.68, 33.47, 33.00, 25.29, 24.00; LRMS (FAB) *m*/*z* 283 (M^+ + H).

RCM reaction of dihexenoate (general procedure)

Ru catalyst was added to a stirring solution of coupling precursor in CH_2Cl_2, and the mixture was stirred under the conditions described in the text. The solvent was removed to leave a crude residue, which was subjected to silica gel column chromatography. The cyclised product was obtained in good yield.

***O,O′*-(Dec-5-ene-1,10-dioyl)-1,1′-bi-2,2′-naphthol (8a).** Brown amorphous solid; 28% yield; R_f = 0.51 (AcOEt–*n*-hexane = 1 : 4); ^{1}H-NMR (400 MHz, $CDCl_3$, *E–Z mixture*): δ 7.99 & 7.98 (2H, d, J = 8.8 Hz), 7.92 (2H, d, J = 8.3 Hz), 7.52–7.41 (4H, m), 7.27–7.22 (2H, m), 7.11 (2H, t, J = 8.1 Hz), 5.50–5.43 (2H, m), 2.28–2.04 (8H, m), 1.67–1.65 (4H, m); LRMS (FAB) *m*/*z* 451 (M^+ + H).

7,8,9,12,13,14-Hexahydro-5,16-dioxadibenzo[*a*,*c*]cyclohexadecene-6,15-dione (8b). Brown amorphous solid; 54% yield; R_f = 0.57 (AcOEt–*n*-hexane = 1 : 4); ^{1}H-NMR (400 MHz, $CDCl_3$, *E–Z mixture*): δ 7.41–7.20 (10H, m), 5.53 (2H, t, J = 2.4 Hz), 2.46–2.22 (8H, m), 2.05–1.93 (2H, m), 1.78–1.76 (2H, m); LRMS (FAB) *m*/*z* 351 (M^+ + H).

7,8,9,12,13,14-Hexahydro-5,16-dioxabenzocyclotetradecene-6,15-dione (8c). Brown oil; 96% yield; R_f = 0.42 (AcOEt–*n*-hexane = 1 : 2); ^{1}H-NMR (400 MHz, $CDCl_3$, *E–Z mixture*): δ 7.25–7.22 (2H, m), 7.19–7.16 (2H, m), 5.40 (2H, t, J = 4.8 Hz), 2.61 & 2.60 (4H, t, J = 5.8 Hz), 2.26–2.21 (4H, m), 1.86–1.77 (4H, m); LRMS (FAB) *m*/*z* 275 (M^+ + H).

***erythro*-1,2,3,4,4a,7,8,9,12,13,14,16a-Dodecahydro-5,16-dioxabenzocyclotetradecene-6,15-dione (8d).** Brown oil; 71% yield; R_f = 0.63 (AcOEt–*n*-hexane = 1 : 4); ^{1}H-NMR (400 MHz, $CDCl_3$, *E–Z mixture*): δ 5.31–5.28 (2H, m), 4.95 & 4.90 (2H, d, J = 6.5 Hz), 2.38–2.18 (4H, m), 2.04–1.98 (4H, m), 1.90–1.82 (2H, m), 1.72–1.52 (8H, m), 1.35 (2H, br s); ^{13}C-NMR (100 MHz, $CDCl_3$, *E–Z mixture*): δ 173.23, 172.74, 130.09, 129.82, 71.29, 70.98, 33.42, 33.06, 31.39, 27.62, 27.50, 26.01, 24.71, 23.49, 21.557; LRMS (FAB) *m*/*z* 281 (M^+ + H); HRMS (FAB) calcd for $C_{16}H_{25}O_4$ (M^+ + H): 281.1746, found 281.1765.

***threo*-1,2,3,4,4a,7,8,9,12,13,14,16a-Dodecahydro-5,16-dioxabenzocyclotetradecene-6,15-dione (8e).** Brown oil; 67% yield; R_f = 0.57 (AcOEt–*n*-hexane = 1 : 4); ^{1}H-NMR (400 MHz, $CDCl_3$, *E–Z mixture*): δ 5.41–5.33 (2H, m), 4.86–4.84 & 4.81–4.78 (2H, m), 2.35–2.26 (4H, m), 2.10–2.03 (6H, m), 1.86–1.54 (6H, m), 1.34 (4H, br d, J = 4.9 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$, *E–Z mixture*): δ 173.17, 129.88, 129.80, 74.03, 33.18, 31.85, 30.73, 30.64, 25.95, 24.33, 23.74, 22.29; LRMS (FAB) *m*/*z* 281 (M^+ + H); HRMS (FAB) calcd for $C_{16}H_{25}O_4$ (M^+ + H): 281.1746, found 281.1753.

***erythro*-2,3,3a,6,7,8,11,12,13,15a-Decahydro-1*H*-4,15-dioxacyclopentacyclotetradecene-5,14-dione (8f).** White solid; 84% yield; R_f = 0.47 (AcOEt–*n*-hexane = 1 : 4); ^{1}H-NMR (400 MHz, $CDCl_3$, *E–Z mixture*): δ 5.35–5.30 (2H, m), 5.16–5.12 (2H, m), 2.44 & 2.40 (2H, dd, J = 9.7, 2.9 Hz), 2.35–2.23 (2H, m), 2.20–2.11 (2H, m), 2.02–1.99 (4H, m), 1.87–1.79 (4H, m), 1.62–1.50 (4H, m); ^{13}C-NMR (100 MHz, $CDCl_3$, *E–Z mixture*): δ 173.12, 172.81, 130.39, 129.97, 73.89, 73.68, 32.77, 32.38, 31.47, 28.98, 25.81, 24.36, 22.68, 19.20, 19.06; LRMS (FAB) *m*/*z* 267 (M^+ + H).

***threo*-2,3,3a,6,7,8,11,12,13,15a-Decahydro-1*H*-4,15-dioxacyclopentacyclotetradecene-5,14-dione (8g).** Brown oil; 50% yield; R_f = 0.50 (AcOEt–*n*-hexane = 1 : 4); ^{1}H-NMR (400 MHz, $CDCl_3$, *E–Z mixture*): δ 5.41–5.36 (2H, m), 5.16–5.09 (2H, m), 2.40–2.28 (4H, m), 2.25–2.19 (2H, m), 2.12–1.97 (4H, m), 1.84–1.74 (2H, m), 1.71–1.62 (4H, m), 1.54–1.48 (2H, m); ^{13}C-NMR (100 MHz, $CDCl_3$, *E–Z mixture*): δ 173.61, 129.65, 129.52, 77.00, 76.68, 34.08, 33.06, 31.24, 27.23, 26.79, 26.02, 25.05, 22.79, 18.51; LRMS (FAB) *m*/*z* 267 (M^+ + H).

1,6-Dioxacyclohexadec-11-ene-7,16-dione (8h). Brown oil; 75% yield; R_f = 0.31 (AcOEt–*n*-hexane = 1 : 4); ^{1}H-NMR (400 MHz, $CDCl_3$, *E–Z mixture*): δ 5.38–5.35 (2H, m), 4.19–4.12 (4H, m), 2.35–2.30 (4H, m), 2.09–2.04 (4H, m), 1.78–1.64 (8H, m); LRMS (FAB) *m*/*z* 255 (M^+ + H).

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10 It is reported that catalysts **C** and **D** result in improved selectivity in the (*E*)-cycloalkene.[2c,2d]

11 In the RCM reactions of other substrates, it was also reported that minor changes at remote sites of the substrate can have a daramatic effect on the *E* : *Z* ratio.[2a,2e,2i,4b]