DOI: 10.1002/chem.200800249

Kinetically Controlled Ring-Closing Metathesis: Synthesis of a Potential Scaffold for 12-Membered Salicylic Macrolides

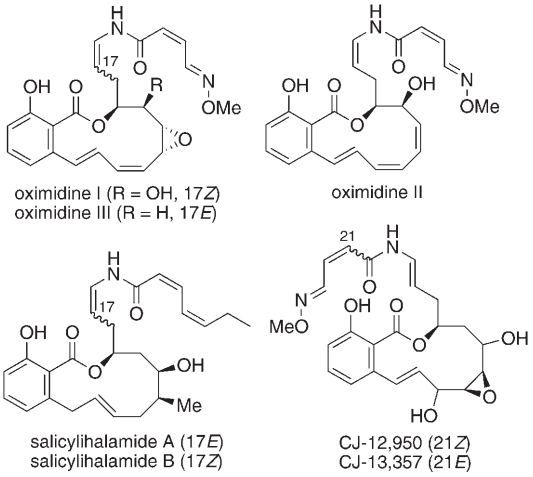
Yuji Matsuya,* Sho-ichi Takayanagi, and Hideo Nemoto*[a]

Abstract: For the synthesis of a 12-membered salicylic macrolide scaffold, ring-closing metathesis (RCM) of a ω-diene compound was planned. The stereochemical outcome of the RCM reaction changed depending on the type of Ru catalyst that was used; a "first-generation" Grubbs catalyst produced exclusively the *E* isomer and "second-generation" catalysts provided a mixture of the *E* and *Z* isomers under kinetic control (not thermodynamic control). Considerations for the *E*/*Z* selectivity are described.

Keywords: catalysis · macrocycles · metathesis · ruthenium · selectivity

Introduction

Salicylic macrolide compounds constitute an important class of bioactive natural products and have attracted the attention of a number of synthetic chemists due to their attractive biological properties, novel mode of action, and complex structural characteristics.[1] For example, oximidines and salicylihalamides have been reported to exhibit potent cytotoxic activity against various human cancer cell lines as a result of selective inhibition of mammalian vacuolar-type proton adenosine triphosphatase (ATPase),[2] and compounds CJ-12950 and CJ-13357 have been shown to be potent inducers of the low-density lipoprotein (LDL) receptor gene, which is a major factor in the control of hypercholesterolemia.[3] These natural compounds possess a labile enamide side chain and a common 12-membered salicylic lactone core and have individual unsaturation modes and oxidation states. To date, considerable efforts have been devoted toward the syntheses of these salicylic lactones and related model compounds, and many of these studies rely on a ring-closing metathesis (RCM) strategy for constructing the 12-membered lactone core.[1,4] While RCM is a powerful methodology in the field of organic synthesis and has been utilized for numerous synthetic studies, including the synthesis of cyclic natural compounds,[5] it is important to note that the prediction of the stereochemical outcome (the *E*/*Z* selectivity of the olefin product) is not always simple in cases of large-ring formation. Although mixtures of both geometrical isomers are formed with various ratios, generally according to the thermodynamic stabilities, this drawback has been overcome by controlling the reaction conditions, by tuning the protecting groups affecting the conformation of the substrates, and ultimately by chromatographic separation of the isomers. As part of our ongoing research on the synthesis of macrolide compounds by utilizing RCM,[6] we have grappled with the synthetic study of a 12-membered macrolactone compound (**1**), a potential scaffold for a series of salicylic macrolides with various substitution patterns;



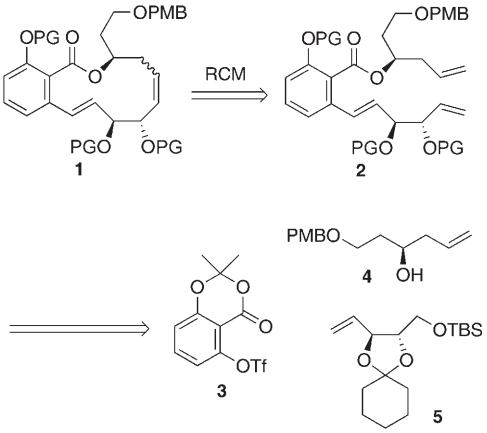
[a] Dr. Y. Matsuya, S.-i. Takayanagi, Prof. Dr. H. Nemoto
Graduate School of Medicine and Pharmaceutical Sciemces
University of Toyama
2630 Sugitani, Toyama 930–0194 (Japan)
Fax: (+81) 76-434-5047
E-mail: matsuya@pha.u-toyama.ac.jp
nemotoh@pha.u-toyama.ac.jp

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

our aim was extensive structure–activity relationship (SAR) research. During this investigation, we encountered a completely kinetically controlled RCM, which is an interesting and unusual example of a large-ring-forming RCM.[7] Herein, we wish to report an efficient access to the functionalized 12-membered salicylic macrolide core skeleton **1** and a consideration of the stereochemical outcome of the key RCM reaction.

Results and Discussion

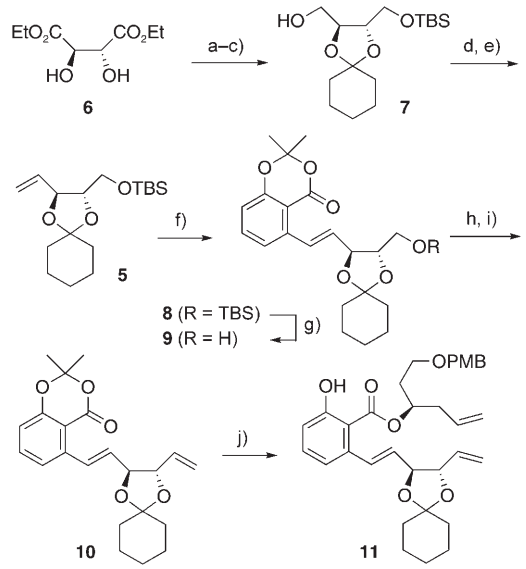
Our synthetic plan toward macrocycle **1** is straightforward (Scheme 1). If the macrolide-ring formation by RCM is anticipated, substrate **2** can be assembled from three simple



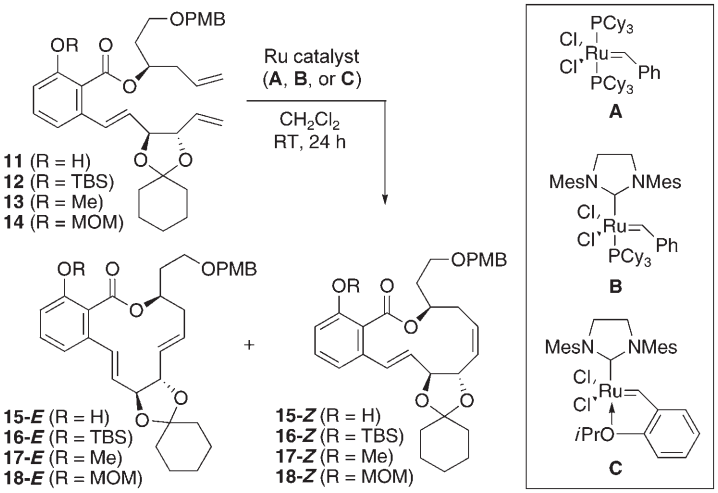
Scheme 1. Synthetic strategy for macrolide **1**. PG: protecting group; PMB: *para*-methoxybenzyl; TBS: *tert*-butyldimethylsilyl; Tf: trifluoromethanesulfonyl.

parts, **3**–**5**. The *E*-olefin structure can be created by means of the Heck coupling reaction between **3** and **5**, the latter of which can be derived from an inexpensive chiral source, diethyl tartrate. The synthesis of RCM substrate **11** was performed with conventional functional-group manipulations (Scheme 2; more details are described in the Experimental Section).

With RCM substrate **11** in hand, the stage was set to explore the reactivity of these compounds for macrocyclization. We used three types of ruthenium-based catalyst, Grubbs "first-generation" (**A**),[8] Grubbs "second-generation" (**B**),[9] and Hoveyda–Grubbs "second-generation" (**C**) catalysts.[10] When substrate **11** was subjected to the RCM reaction with 5 mol% of catalyst **A** in dichloromethane for 24 h, macrocyclic product **15-*E*** was obtained as the only stereoisomer in 64% yield after isolation (Scheme 3; Table 1, entry 1). Increased amounts of the catalyst gave rise to improved yields (up to 78%) of the *E* isomer, **15-*E***, whereas the *Z* isomer, **15-*Z***, could not be detected in any case (Table 1, entries 2 and 3). On the other hand, the same substrate, **11**, provided a mixture of **15-*E*** and **15-*Z*** with an approximately 1:1 ratio when catalysts **B** or **C** were used



Scheme 2. Synthesis of the RCM substrate **11** from (+)-diethyl tartrate (**6**). a) Cyclohexanone, *p*-TsOH; b) $LiAlH_4$; c) NaH, TBSCl (73%, 3 steps); d) SO_3–Py, DMSO, Et_3N (92%); e) $Ph_3P{=}CH_2$, THF (76%); f) **3**, $Pd(OAc)_2$, Ph_3P, Et_3N, DMF (63%); g) TBAF, THF (95%); h) $(COCl)_2$, DMSO, CH_2Cl_2; then Et_3N; i) CH_2I_2, Zn, Me_3Al, THF (57%, 2 steps); j) **4**, NaHMDS, THF (93%). DMSO: dimethylsulfoxide; NaHMDS: sodium hexamethyldisilazide; *p*-TsOH: toluene-4-sulfonic acid; Py: pyridine; TBAF: tetrabutylammonium fluoride.



Scheme 3. RCM reaction of substrates **11**–**14**. Cy: cyclohexyl; Mes: mesityl; MOM: methoxymethyl.

(Table 1, entries 4 and 5), and an optimal total yield was recorded under reflux conditions in 1,2-dichloroethane (Table 1, entry 6). Thus, the results of the RCM of compound **11** were of great interest because the stereochemical course could be controlled by choice of the RCM catalyst. These findings prompted us to investigate the generality of the reaction, and the analogous substrates **12**–**14** (Scheme 3) were prepared from **11** by simple functional-group manipu-

Table 1. Yields after isolation of the RCM products **15**–**18**.

Entry	Substrate	Catalyst (amount used [mol%])	Yield of *E* [%][a]	Yield of *Z* [%][a]
1	**11**	**A** (5)	64 (85)	0
2		**A** (10)	72 (79)	0
3		**A** (20)	78 (88)	0
4		**B** (5)	21 (42)	16 (32)
5		**C** (5)	10 (20)	11 (22)
6[b]		**C** (5)	44 (47)	39 (42)
7	**12**	**A** (5)	47 (94)	0
8		**B** (5)	35 (85)	6 (15)
9		**C** (5)	30 (56)	6 (11)
10	**13**	**A** (5)	38 (62)	0
11		**B** (5)	51 (51)	24 (24)
12	**14**	**A** (5)	77 (77)	0
13		**B** (5)	51 (51)	29 (29)

[a] Yields in parentheses are based on the recovered starting material. [b] The reaction was carried out in 1,2-dichloroethane under reflux conditions.

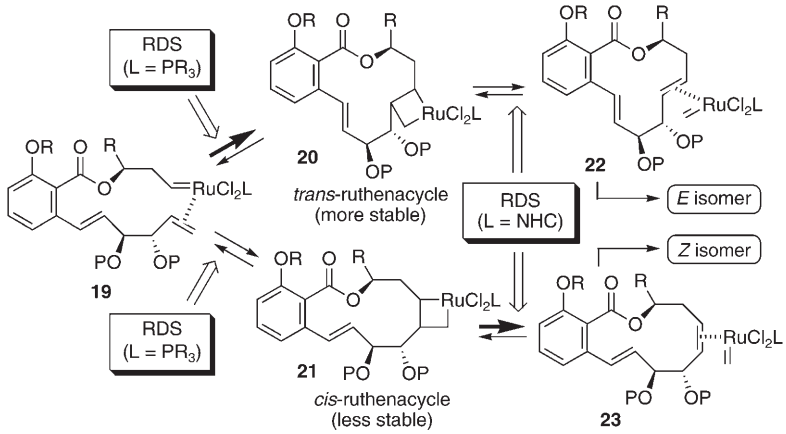
lations (see the Experimental Section). As shown in Table 1, similar results were obtained for TBS ether **12**, methyl ether **13**, and methoxymethyl ether **14**; that is, exclusive formation of the *E* isomer was observed when catalyst **A** was used, whereas both isomers were formed when catalysts **B** or **C** were used (Table 1, entries 7–13).

The reaction mechanism of RCM has been well established by both theoretical and experimental studies;[11] it involves a sequence of phosphane-ligand dissociation from the alkylidene metal complex, olefin coordination (π-complex formation), formal [2+2] cycloaddition (metallacyclobutane formation), cycloreversion (another π-complex formation), and release of the product olefin. Generally, the reversible nature of this sequential process is responsible for the thermodynamic control of the metathesis product.[12] Thus, in principle, the stereochemical outcome of the RCM reaction to form macrocycles will be governed by the thermal stabilities of the corresponding *E* and *Z* isomers, and a thermodynamic distribution of the products will be achieved after sufficient reaction time. Although this may imply that the same substrate will always produce a settled ratio of the *E*/*Z* mixture regardless of the class of RCM initiator, there have been a number of examples in which the structure of the RCM initiator affected the *E*/*Z* selectivity of the macrocyclic products. This fact has been reasonably explained on the basis of different degrees of catalytic activity and thermal stability among RCM initiators with different ligands.[13] It has been well recognized that first-generation catalysts, with two phosphane ligands, show much less activity and stability than second-generation catalysts, with one *N*-heterocyclic carbene (NHC) ligand.[11e,14] As sufficient activity and stability of the catalysts is needed to establish thermodynamic equilibrium, first-generation catalysts are, in general, prone to produce macrocyclic compounds with a relatively kinetic *E*/*Z* ratio, whereas second-generation catalysts are likely to afford products under thermodynamic control.[15]

In light of this, one possible explanation for the selectivity of the present study is as follows: the *E* isomer was initially formed as a kinetic product in each case (catalysts **A**–**C**) and catalysts **B** and **C** established the thermodynamic equilibrium (*E*/*Z*≈1:1 for **15-*E*/15-*Z***, *E*/*Z*≈5:1 for **16-*E*/16-*Z***, etc.) by secondary isomerization, but catalyst **A** could not do that due to its relatively low reactivity and stability. This interpretation was ruled out, however, because 1) the reactions of **11** with catalyst **A** or **B** under the same conditions as those depicted in Scheme 3 were traced by ^{1}H NMR spectroscopy and it was revealed that the *E*/*Z* ratios remained constant throughout the reaction from the beginning for 24 h (only *E* isomer for catalyst **A**, *E*/*Z*≈1:1 for catalyst **B**), and 2) pure isolated *E* isomer (**15-*E***) and *Z* isomer (**15-*Z***) were allowed to react with catalysts **A** and **B** under the same conditions but the substrates were recovered unchanged in all four cases (even under an ethylene atmosphere). These experimental findings clearly indicate that reverse ring opening cannot proceed once macrocyclization occurs and interconversion between the *E* and *Z* isomers is impossible under the above reaction conditions. Therefore, it is most likely that the RCM in this study is a purely kinetically controlled reaction and the stereochemical results do not depend on the relative stabilities of the *E* and *Z* isomers.

A question is raised as to why the stereochemical course of the present RCM is changed by the catalysts under the kinetic control. Recent advances in the understanding of the function of various ligands on RCM catalysts have provided insight into the factors controlling *E*/*Z* selectivity for macrocyclic-olefin formation.[11–15] In particular, DFT-calculation studies have suggested the energy levels of intermediates in olefin-metathesis catalytic cycles, including those with first- and second-generation ruthenium complexes.[16] To explain our experimental results, we would like to set forth a hypothesis that the energy level of the intermediate ruthenacyclobutane is higher than that of olefin–ruthenium π complex in the case of bisphosphane-type catalysts, but lower in the case of NHC-containing catalysts.[17] This idea is consistent with the fact that NHCs, being stronger two-electron σ donors, can better stabilize the Ru^{4+} center of the metallacyclobutane than a phosphine group.[14] This implies that the rate-determining step is likely to be ruthenacycle formation in the former case (that is, with catalyst **A**) and ruthenacycle cleavage in the latter case (that is, with catalysts **B** and **C**).[18]

Based on this hypothesis, a rationale for the observed stereochemical outcome of the present RCM could be reached. A stepwise transformation for macrocyclization, which ultimately determines the *E*/*Z* selectivity, is illustrated in Scheme 4. Formation of olefin–ruthenium π complex **19** is the initial step for macrocyclization, if it is assumed that the first interaction of the Ru catalyst with the ω-diene substrate occurs at the less-hindered double bond. Two possible pathways exist for ruthenacycle formation and lead to *trans*-ruthenacycle **20** and *cis*-ruthenacycle **21**; the latter is probably less stable due to repulsion of the substituents on the four-membered ring. These ruthenacycles can return to the initial π complex **19** or go on to one of two other π com-



Scheme 4. RCM catalytic cycle for the formation of the *E* and *Z* isomers. L: ligand; RDS: rate-determining step.

plexes, **22** or **23**, which provide the *E*-macrocyclic-olefin product or the *Z* isomer, respectively, after dissociation of the π complex. If the formation of the ruthenacycles **20** and **21** is indeed the rate-determining step when catalyst **A** is used, production of the *E*-macrocyclic-olefin product will prevail over that of the *Z* isomer because of the lower energy barrier for the formation of the more stable *trans*-ruthenacycle **20** than that for the formation of **21**. This concurs with our experimental results in which exclusive formation of the *E* isomer was observed. On the other hand, relatively unstable *cis*-ruthenacycle **21** should have a lower energy barrier for ruthenacycle cleavage, that is, conversion of **21** into **23**, than the equivalent barrier for **20** (to form **22**). If the ruthenacycle cleavage is the rate-determining step when the ligand (L) is NHC (that is, with catalysts **B** or **C**), it is expected that ruthenacycles **20** and **21** will undergo fast equilibrium with a predominance of the more stable **20**, which conversely has a higher energy barrier for this rate-determining step. Therefore, competitive formation of the *E* macrocyclic olefin and the *Z* isomer will arise, as was observed in the present study. Once the macrocyclic-olefin products are released, these compounds cannot participate in the reaction in a reversible manner, probably because π-complex formation with the Ru catalyst is impeded due to steric congestion of the spiro-bicyclic acetal moiety.

Conclusion

In this paper, we have described a novel kinetically controlled RCM reaction as a part of an efficient access to a potential scaffold for 12-membered salicylic macrolide compounds. The synthesized macrocyclic compounds **15**–**18** are fully functionalized for further transformations and are good starting points for SAR investigation of bioactive salicylic macrolides. We have proposed that the change in the *E*/*Z* selectivity depending on the type of RCM initiator may be attributed to alteration of the rate-determining step in the RCM catalytic cycle. Consideration of the stereochemical course of the RCM reaction in this study may bring forward some new ideas for macrocycle-forming RCM reactions.[19]

Experimental Section

General remarks: All nonaqueous reactions were carried out under an Ar atmosphere. Reagents were purchased from commercial sources and used as received. Anhydrous solvents were prepared by distillation over CaH_2 or purchased from commercial sources. ^1H and ^{13}C NMR spectra were obtained on a Varian Gemini 300 instrument by using the chloroform peak as an internal reference (brs refers to broad singlet). Mass spectra were measured on a JEOL D-200 or a JEOL AX 505 mass spectrometer, and the ionization method was electron impact (EI, 70 eV). IR spectra were recorded on a JASCO FT/IR-460Plus spectrometer. Column chromatography was carried out by employing Cica silica gel 60N (spherical, neutral, 40–50 μm or 63–210 μm). Compound **7** was prepared according to reported methods from (+)-diethyl L-tartrate (**6**).[20]

Compound 5: Sulfur trioxide/pyridine complex (5.87 g, 36.1 mmol) in DMSO (21 mL) was added to a stirred solution of the alcohol **7** (2.37 g, 7.5 mmol) in DMSO (15 mL) and Et_3N (15 mL) at room temperature under an Ar atmosphere. After the mixture had been continuously stirred for 6 h at room temperature, it was diluted with water and extracted with Et_2O. The organic layer was washed with brine and dried over $MgSO_4$, and the solvent was evaporated to leave a residue, which was purified by chromatography on silica gel to afford the corresponding aldehyde (2.18 g, 92%) as a pale-yellow oil.

*n*BuLi (1.6 M in hexane, 8.65 mL, 13.85 mmol) was added to a suspension of methyltriphenylphosphonium iodide (5.60 g, 13.85 mmol) in anhydrous THF (25 mL) at 0°C. After the mixture had been stirred for 30 min at room temperature, the aldehyde (2.18 g, 6.92 mmol) in THF was added and the resulting mixture was stirred for 10 h. The reaction mixture was diluted with saturated NH_4Cl and the aqueous mixture was extracted with Et_2O. The organic layer was dried over $MgSO_4$ and then evaporated. The residue was purified by silica gel column chromatography to afford olefin **5** (1.64 g, 76%) as a pale-yellow oil. $[\alpha]_D^{19} = -3.35$ ($c = 1.00$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 5.91$–5.80 (m, 1H), 5.35 (d, $J =$ 17 Hz, 1H), 5.21 (d, $J = 10$ Hz, 1H), 4.33–4.28 (m, 1H), 3.78–3.72 (m, 3H), 1.63 (brs, 8H), 1.38 (brs, 2H), 0.89 (s, 9H), 0.07 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 136.2$, 118.0, 109.8, 81.0, 79.2, 62.9, 36.83, 36.75, 26.2, 25.4, 24.2, 24.1, 18.6, −5.0 ppm; IR (neat): $\tilde{\nu} = 2934$, 2858, 1254, 1143, 1097 cm^{-1}; MS (EI): m/z: 312 [M^+]; HRMS (EI): m/z: calcd for $C_{17}H_{32}O_3Si$: 312.2121 [M^+]; found: 312.2145.

Compound 8: A mixture of olefin **5** (90 mg, 0.288 mmol), triflate **3**[4c,21] (94 mg, 0.288 mmol), $Pd(OAc)_2$ (3.2 mg, 0.0144 mmol), PPh_3 (7.6 mg, 0.0288 mmol), and Et_3N (120 μL, 0.864 mmol) in DMF (2.5 mL) was heated at 80°C on an oil bath for 12 h. The mixture was diluted with Et_2O and filtered through a Celite pad. The filtrate was washed with water and brine, then dried over $MgSO_4$. The solvent was evaporated to leave a residue, which was purified by chromatography on silica gel to afford compound **8** (89 mg, 63%) as a pale-yellow oil. $[\alpha]_D^{18} = -9.95$ ($c =$ 1.00 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.75$ (d, $J = 16$ Hz, 1H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.26 (d, $J = 8.0$ Hz, 1H), 6.86 (d, $J = 8.0$ Hz, 1H), 6.17 (dd, $J = 16$, 7.4 Hz, 1H), 4.54 (dd, $J = 8.3$, 7.4 Hz, 1H), 3.89–3.81 (m, 3H), 1.75–1.43 (m, 14H), 1.40 (brs, 2H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 160.1$, 156.8, 141.1, 135.2, 131.6, 131.1, 121.7, 116.7, 111.0, 110.1, 105.4, 81.4, 78.7, 63.0, 36.9, 36.8, 26.2, 26.0, 25.8, 25.5, 24.2, 24.1, 18.6, −4.96, −5.01 ppm; IR (neat):

$\tilde{\nu}$ = 2997, 2993, 1739, 1578, 1476, 1317, 1272 cm^{-1}; MS (EI): *m/z*: 488 [M^+]; HRMS (EI): *m/z*: calcd for $C_{27}H_{40}O_6Si$: 488.2594 [M^+]; found: 488.2557.

Compound 9: A 1 M solution of tetra-*n*-butylammonium fluoride in THF (3.17 mL, 3.17 mmol) was added to a stirred solution of **8** (1.55 g, 3.17 mmol) in THF (15 mL) at room temperature, and the mixture was stirred for 2.5 h at room temperature. The solvent was evaporated off to leave a residue, which was dissolved in AcOEt; the resulting organic layer was washed with water and brine, then dried over $MgSO_4$. Evaporation of the solvent left a residue, which was purified by chromatography on silica gel to give the alcohol **9** (1.13 g, 95%) as a pale-yellow oil. $[\alpha]_D^{19} = +7.55$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.68$ (d, $J = 16$ Hz, 1H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.23 (d, $J = 8.0$ Hz, 1H), 6.86 (d, $J = 8.0$ Hz, 1H), 6.11 (dd, $J = 16$, 7.4 Hz, 1H), 4.52 (dd, $J = 8.2$, 7.4 Hz, 1H), 3.92–3.85 (m, 2H), 3.74–3.69 (m, 1H), 2.29 (brs, 1H), 1.73–1.64 (m, 14H), 1.40 ppm (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 160.2$, 156.7, 140.8, 135.3, 132.0, 130.7, 121.8, 116.8, 111.0, 110.2, 105.5, 81.0, 78.1, 61.4, 36.8, 36.7, 26.1, 25.6, 25.3, 24.1, 24.0 ppm; IR (neat): $\tilde{\nu} = 3461$, 3005, 2937, 2861, 1730 cm^{-1}; MS (EI): *m/z*: 374 [M^+]; HRMS (EI): *m/z*: calcd for $C_{21}H_{26}O_6$: 374.1729 [M^+]; found: 374.1723.

Compound 10: DMSO (34 μL, 0.48 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) and cooled to −78 °C. Oxalyl chloride (28 μM, 0.32 mmol) was added dropwise to the solution, and the resulting mixture was stirred for 15 min at −78 °C. A solution of alcohol **9** (60 mg, 0.16 mmol) in CH_2Cl_2 (0.5 mL) was added to the reaction mixture and stirred at −78 °C. After 1 h, Et_3N (0.11 mL, 0.80 mmol) was added, and the resulting mixture was warmed to room temperature for 0.5 h. The mixture was diluted with CH_2Cl_2, washed with 5% HCl, saturated $NaHCO_3$, and brine, then dried over $MgSO_4$. The solvent was evaporated and the residue obtained was purified by chromatography on silica gel to afford the corresponding aldehyde (55 mg) as a colorless oil, which was used immediately for the next reaction.

Me_3Al (2.0 M in hexane, 0.15 mL, 0.3 mmol) was added to a suspension of zinc powder (290 mg, 4.43 mmol) and diiodomethane (396 mg, 1.48 mmol) in anhydrous THF (1 mL) at 0 °C. After 15 min, a solution of the aldehyde (55 mg) in THF (0.5 mL) was added dropwise, and the reaction mixture was stirred for 3.5 h at 0 °C and for an additional 0.5 h at room temperature. The reaction mixture was diluted with Et_2O, washed successively with 5% HCl and brine, then dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by column chromatography to afford the compound **10** (34 mg, 57% over 2 steps) as a pale-yellow oil. $[\alpha]_D^{14} = -1.38$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.75$ (d, $J = 16$ Hz, 1H), 7.45 (t, $J = 8.0$ Hz, 1H), 7.27 (d, $J = 8.0$ Hz, 1H), 6.88 (d, $J = 8.0$ Hz, 1H), 6.13 (dd, $J = 16$, 7.1 Hz, 1H), 5.95–5.84 (m, 1H), 5.40 (dd, $J = 17$, 2.5 Hz, 1H), 5.27 (dd, $J = 10$, 2.5 Hz, 1H), 4.35 (dd, $J = 7.4$, 7.1 Hz, 1H), 4.21 (dd, $J = 7.4$, 6.6 Hz, 1H), 1.70 (brs, 14H), 1.41 ppm (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 160.2$, 156.8, 140.9, 135.3, 134.4, 131.9, 129.9, 121.8, 118.9, 116.8, 111.1, 110.2, 105.4, 82.1, 81.6, 36.83, 36.77, 26.0, 25.8, 25.4, 24.1 ppm; IR (neat): $\tilde{\nu} = 2937$, 2861, 1732, 1600, 1578, 1477 cm^{-1}; MS (EI): *m/z*: 370 [M^+]; HRMS (EI): *m/z*: calcd for $C_{22}H_{26}O_5$: 370.1780 [M^+]; found: 370.1757.

Compound 11: NaHMDS (1.0 M in THF, 4.49 mL, 4.49 mmol) was added dropwise to a stirred solution of alcohol **4**[22] (848 mg, 3.59 mmol) in anhydrous THF (20 mL) at 0 °C, and the mixture was stirred for 1 h. A solution of compound **10** (1.10 g, 2.99 mmol) in THF (10 mL) was added to the reaction mixture, which was stirred for 0.5 h at 0 °C and for an additional 2 h at room temperature. The reaction was quenched with 5% HCl, the aqueous solution was extracted with AcOEt, and the combined organic layer was dried over $MgSO_4$. Evaporation of the solvent left a residue, which was purified by chromatography on silica gel to give compound **11** (1.53 g, 93%) as a colorless oil. $[\alpha]_D^{24} = -16.85$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 11.26$ (s, 1H), 7.34 (t, $J = 8.0$ Hz, 1H), 7.27 (d, $J = 15$ Hz, 1H), 7.19 (d, $J = 8.7$ Hz, 2H), 6.94–6.90 (m, 2H), 6.80 (d, $J = 8.7$ Hz, 2H), 5.91–5.75 (m, 3H), 5.49–5.38 (m, 1H), 5.40 (d, $J = 17$ Hz, 1H), 5.27 (d, $J = 10$ Hz, 1H), 5.13 (d, $J = 9.9$ Hz, 1H), 5.12 (d, $J = 18$ Hz, 1H), 4.41 (d, $J = 11$ Hz, 1H), 4.36 (d, $J = 11$ Hz, 1H), 4.23–4.13 (m, 2H), 3.76 (s, 3H), 3.52–3.46 (m, 2H), 2.52–2.46 (m, 2H), 2.03–1.95 (m, 2H), 1.65 (brs, 8H), 1.42 ppm (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.4$, 162.3, 159.2, 140.4, 134.9, 134.7, 134.2, 133.2, 130.2, 129.4, 127.0, 120.3, 119.0, 118.7, 117.5, 113.8, 111.2, 110.0, 82.3, 81.5, 73.4, 72.9, 66.1, 55.4, 39.0, 37.0, 36.8, 34.0, 25.4, 24.1 ppm; IR (neat): $\tilde{\nu} = 2936$, 2861, 1734, 1658, 1514, 1449 cm^{-1}; MS (EI): *m/z*: 548 [M^+]; HRMS (EI): *m/z*: calcd for $C_{33}H_{40}O_7$: 548.2774 [M^+]; found: 548.2785.

Compound 12: TBSOTf (0.32 mL, 1.37 mmol) was added dropwise to a stirred solution of compound **11** (500 mg, 0.911 mmol) and 2,6-lutidine (0.16 mL, 1.37 mmol) in CH_2Cl_2 (10 mL) at 0 °C under an Ar atmosphere. After the mixture had been continuously stirred for 2 h at 0 °C, it was diluted with CH_2Cl_2, washed successively with 5% HCl, saturated $NaHCO_3$, and brine, and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by chromatography on silica gel to give compound **12** (602 mg, 99%) as a colorless oil. $[\alpha]_D^{25} = -14.58$ ($c = 1.00$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.25$ (d, $J = 8.7$ Hz, 2H), 7.23–7.13 (m, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 6.77 (d, $J = 8.0$ Hz, 1H), 6.64 (d, $J = 16$ Hz, 1H), 6.12 (dd, $J = 16$, 6.6 Hz, 1H), 5.87–5.73 (m, 2H), 5.35 (d, $J = 17$ Hz, 1H), 5.25–5.21 (m, 2H), 5.14–5.07 (m, 2H), 4.45 (d, $J = 11$ Hz, 1H), 4.39 (d, $J = 11$ Hz, 1H), 4.18–4.13 (m, 2H), 3.80 (s, 3H), 3.58–3.53 (m, 2H), 2.54–2.47 (m, 2H), 2.01–1.95 (m, 2H), 1.57 (brs, 8H), 1.40 (brs, 2H), 0.97 (s, 9H), 0.23 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.3$, 159.1, 152.5, 135.1, 134.4, 133.5, 130.5, 130.1, 129.9, 129.3, 128.5, 119.1, 118.4, 118.3, 113.9, 110.1, 82.1, 81.7, 72.9, 72.7, 66.6, 55.5, 38.6, 36.9, 36.8, 33.4, 26.0, 25.4, 24.1, 18.6, −3.8 ppm; IR (neat): $\tilde{\nu} = 2934$, 2859, 1731, 1514, 1467 cm^{-1}; MS (EI): *m/z*: 662 [M^+]; HRMS (EI): *m/z*: calcd for $C_{39}H_{54}O_7Si$: 662.3639 [M^+]; found: 662.3643.

Compound 13: MeI (0.5 mL) was added to a mixture of compound **11** (110 mg, 0.2 mmol) and K_2CO_3 (276 mg, 2 mmol) in DMF (3 mL), and the resulting mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with H_2O and the aqueous mixture was extracted with Et_2O. The organic layer was washed with brine and then dried. Evaporation of the solvent gave a residue, which was purified by chromatography on silica gel to afford the methyl ether **13** (79 mg, 70%) as a colorless oil. $[\alpha]_D^{25} = -17.45$ ($c = 1.68$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.30$–7.25 (m, 3H), 7.18 (d, $J = 8.1$ Hz, 1H), 6.87 (d, $J = 8.5$ Hz, 2H), 6.82 (d, $J = 8.1$ Hz, 1H), 6.69 (d, $J = 16$ Hz, 1H), 6.17 (dd, $J = 16$, 6.8 Hz, 1H), 5.90–5.75 (m, 2H), 5.45–5.40 (m, 1H), 5.35 (d, $J = 17$ Hz, 1H), 5.23 (d, $J = 11$ Hz, 1H), 5.15–5.07 (m, 2H), 4.48 (d, $J = 11$ Hz, 1H), 4.42 (d, $J = 11$ Hz, 1H), 4.20–4.13 (m, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 3.62–3.55 (m, 2H), 2.53–2.47 (m, 2H), 2.00–1.93 (m, 2H), 1.62 (brs, 8H), 1.40 ppm (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.2$, 159.1, 156.2, 134.7, 134.2, 133.4, 130.4, 130.1, 129.7, 129.2, 129.1, 128.6, 123.4, 118.8, 118.0, 117.7, 113.7, 113.6, 110.1, 109.9, 81.9, 81.4, 72.7, 72.0, 66.2, 55.6, 55.2, 38.7, 36.5, 36.4, 33.7, 25.0, 23.8, 23.7 ppm; IR (neat): $\tilde{\nu} = 2936$, 2860, 1731, 1577, 1514, 1472 cm^{-1}; MS (EI): *m/z*: 562 [M^+]; HRMS (EI): *m/z*: calcd for $C_{34}H_{42}O_7$: 562.2931 [M^+]; found: 562.2958.

Compound 14: Chloromethyl methyl ether (30 μL, 0.4 mmol) was added to a mixture of compound **11** (110 mg, 0.2 mmol) and diisopropylethylamine (105 μL, 0.6 mmol) in dry CH_2Cl_2 (3 mL), and the resulting mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with CH_2Cl_2 and washed successively with 10% HCl, saturated $NaHCO_3$, and brine. The organic layer was dried and evaporated to give a residue, which was purified by chromatography on silica gel to afford the MOM ether **14** (84 mg, 71%) as a pale-yellow oil. $[\alpha]_D^{25} = -13.72$ ($c = 1.97$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$–7.21 (m, 4H), 7.08 (d, $J = 8.1$ Hz, 1H), 6.90 (d, $J = 8.5$ Hz, 2H), 6.67 (d, $J = 16$ Hz, 1H), 6.19 (dd, $J = 16$, 6.6 Hz, 1H), 5.95–5.78 (m, 2H), 5.50–5.35 (m, 2H), 5.29–5.05 (m, 5H), 4.49 (d, $J = 11$ Hz, 1H), 4.45 (d, $J = 11$ Hz, 1H), 4.25–4.12 (m, 2H), 3.82 (s, 3H), 3.65–3.60 (m, 2H), 3.45 (s, 3H), 2.51 (t, $J = 6.3$ Hz, 2H), 2.02–1.95 (m, 2H), 1.65 (brs, 8H), 1.42 ppm (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.9$, 159.0, 153.6, 134.7, 134.1, 133.3, 130.3, 130.0, 129.5, 129.2, 129.1, 128.7, 124.1, 118.8, 118.0, 113.7, 113.6, 109.9, 94.4, 81.9, 81.4, 72.7, 72.1, 66.3, 56.1, 55.3, 36.6, 33.8, 25.2, 23.9 ppm; IR (neat): $\tilde{\nu} = 2936$, 2860, 1732, 1646, 1615, 1577, 1514, 1471 cm^{-1}; MS (EI): *m/z*: 592 [M^+]; HRMS (EI): *m/z*: calcd for $C_{35}H_{44}O_8$: 592.3036 [M^+]; found: 592.2990.

General procedure for the RCM reaction of compounds 11–14: Ru catalyst (**A**–**C**, 5–20 mol%) was added to a solution of substrate (**11**–**14**, 0.1 mmol) in CH_2Cl_2 (100 mL), and the mixture was stirred at room tem-

perature for 24 h under an Ar atmosphere. In the case described in entry 6 of Table 1, the reaction was performed in 1,2-dichloroethane under reflux at the same concentration for 24 h. The reaction mixture was concentrated in vacuo and subjected to column chromatography. The starting material, *E* isomer, and *Z* isomer could be easily separated. The yields of isolated product are indicated in Table 1.

Compound 15-*E*: Pale-yellow oil; $[\alpha]_D^{27}=+146.02$ ($c=0.4$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=10.91$ (s, 1H), 7.34 (t, $J=8.0$ Hz, 1H), 7.24 (d, $J=8.8$ Hz, 2H), 6.94 (d, $J=8.0$ Hz, 1H), 6.89 (d, $J=8.0$ Hz, 1H), 6.87 (d, $J=8.8$ Hz, 2H), 6.64 (d, $J=16$ Hz, 1H), 5.94 (dd, $J=16$, 6.6 Hz, 1H), 5.84–5.74 (m, 1H), 5.54–5.42 (m, 2H), 4.46 (d, $J=12$ Hz, 1H), 4.39 (d, $J=12$ Hz, 1H), 4.16 (dd, $J=8.7$, 6.6 Hz, 1H), 4.04 (t, $J=8.7$ Hz, 1H), 3.81 (s, 3H), 3.51 (dd, $J=6.9$, 5.8 Hz, 2H), 2.70–2.65 (m, 2H), 2.18–2.05 (m, 1H), 1.96–1.85 (m, 1H), 1.69 (brs, 8H), 1.26 ppm (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=170.5$, 161.8, 159.2, 139.9, 135.7, 134.4, 131.8, 130.1, 129.4, 128.0, 125.1, 119.8, 117.0, 113.9, 112.1, 110.6, 83.4, 82.3, 73.3, 72.9, 66.6, 55.5, 37.0, 36.9, 35.0, 33.5, 25.4, 24.12, 24.07 ppm; IR (neat): $\tilde{\nu}=2936$, 2861, 1731, 1654, 1603, 1514, 1450 cm^{-1}; MS (EI): *m*/*z*: 520 [M^+]; HRMS: *m*/*z*: calcd for $C_{31}H_{36}O_7$: 520.2461 [M^+]; found: 520.2504.

Compound 15-*Z*: Pale-yellow oil; $[\alpha]_D^{28}=+84.59$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=10.12$ (s, 1H), 7.33 (t, $J=8.0$ Hz, 1H), 7.22 (d, $J=8.7$ Hz, 2H), 6.87 (d, $J=8.0$ Hz, 1H), 6.86 (d, $J=8.7$ Hz, 2H), 6.85 (d, $J=8.0$ Hz, 1H), 6.73 (d, $J=17$ Hz, 1H), 6.03 (dd, $J=17$, 4.4 Hz, 1H), 5.81 (dt, $J=12$, 4.5 Hz, 1H), 5.60 (dd, $J=12$, 9.1 Hz, 1H), 5.03 (m, 1H), 4.53 (t, $J=9.1$ Hz, 1H), 4.46 (d, $J=12$ Hz, 1H), 4.37 (d, $J=12$ Hz, 1H), 4.38–4.34 (m, 1H), 3.81 (s, 3H), 3.54 (dd, $J=6.9$, 5.8 Hz, 2H), 2.85–2.73 (m, 1H), 2.42–2.37 (m, 1H), 2.29–2.18 (m, 1H), 1.94–1.83 (m, 1H), 1.68 (brs, 8H), 1.22 ppm (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=$ 170.5, 160.5, 159.2, 140.0, 134.2, 132.7, 132.6, 130.2, 129.6, 129.3, 126.7, 119.4, 116.5, 113.9, 112.5, 110.1, 79.6, 76.5, 76.1, 72.8, 66.1, 55.5, 36.9, 34.4, 33.3, 25.3, 24.12, 24.07 ppm; IR (neat): $\tilde{\nu}=3218$, 2934, 2857, 1733, 1669, 1605, 1571, 1514, 1455 cm^{-1}; MS (EI): *m*/*z*: 520 [M^+]; HRMS: *m*/*z* calcd for $C_{31}H_{36}O_7$: 520.2461 [M^+]; found: 520.2484.

Compound 16-*E*: Pale-yellow oil; $[\alpha]_D^{25}=+132.64$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.28$ (d, $J=8.8$ Hz, 2H), 7.21 (t, $J=$ 8.0 Hz, 1H), 7.06 (d, $J=8.0$ Hz, 1H), 6.89 (d, $J=8.7$ Hz, 2H), 6.74 (d, $J=$ 8.0 Hz, 1H), 6.23 (d, $J=16$ Hz, 1H), 5.90 (dd, $J=16$, 7.4 Hz, 1H), 5.67–5.57 (m, 1H), 5.47 (dd, $J=16$, 7.4 Hz, 1H), 5.04–4.97 (m, 1H), 4.50 (d, $J=11$ Hz, 1H), 4.41 (d, $J=11$ Hz, 1H), 4.05 (dd, $J=8.6$, 7.4 Hz, 1H), 3.93 (dd, $J=8.6$, 7.4 Hz, 1H), 3.81 (s, 3H), 3.59 (t, $J=6.3$ Hz, 2H), 2.61–2.52 (m, 1H), 2.43–2.24 (m, 2H), 1.96–1.87 (m, 1H), 1.67 (brs, 8H), 1.43 (brs, 2H), 0.98 (s, 9H), 0.24 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=168.3$, 159.2, 151.6, 135.8, 133.1, 131.7, 130.4, 130.2, 129.4, 128.2, 126.8, 126.4, 117.84, 117.81, 113.9, 110.6, 83.1, 82.7, 77.1, 72.3, 66.4, 55.5, 36.9, 36.8, 35.4, 35.3, 25.9, 25.3, 24.1, 18.5, −3.7, −4.1 ppm; IR (neat): $\tilde{\nu}=2933$, 2859, 1728, 1574, 1514, 1468 cm^{-1}; MS (EI): *m*/*z*: 634 [M^+]; HRMS: *m*/*z*: calcd for $C_{37}H_{50}O_7Si$: 634.3326 [M^+]; found: 634.3322.

Compound 16-*Z*: Pale-yellow oil; $[\alpha]_D^{25}=+60.97$ ($c=0.48$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.30$–7.22 (m, 3H), 6.97 (d, $J=7.7$ Hz, 1H), 6.89 (d, $J=8.6$ Hz, 2H), 6.80 (d, $J=8.1$ Hz, 1H), 6.52 (d, $J=17$ Hz, 1H), 6.03 (dd, $J=17$, 5.1 Hz, 1H), 5.86 (td, $J=12$, 4.3 Hz, 1H), 5.51 (t, $J=12$ Hz, 1H), 5.39–5.32 (m, 1H), 4.48 (d, $J=11$ Hz, 1H), 4.45–4.40 (m, 2H), 4.30 (td, $J=7.2$, 1.3 Hz, 1H), 3.83 (s, 3H), 3.60 (t, $J=6.4$ Hz, 2H), 2.72–2.65 (m, 1H), 2.38–2.33 (m, 1H), 2.09–2.01 (m, 1H), 1.98–1.92 (m, 1H), 1.67 (brs, 8H), 1.43 (brs, 2H), 1.01 (s, 9H), 0.27 (s, 3H), 0.25 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=166.2$, 159.1, 152.7, 137.6, 133.6, 130.5, 130.3, 130.2, 129.7, 129.2, 127.8, 124.5, 119.2, 118.3, 113.7, 110.1, 79.9, 76.7, 72.9, 72.4, 66.3, 60.4, 55.2, 36.6, 36.5, 35.9, 33.5, 25.7, 25.0, 23.8, 21.0, 18.3, 14.2, −4.1, −4.3 ppm; IR (neat): $\tilde{\nu}=2932$, 2857, 1731, 1574, 1514, 1464 cm^{-1}; MS (EI): *m*/*z*: 634 [M^+]; HRMS: *m*/*z* calcd for $C_{37}H_{50}O_7Si$: 634.3326 [M^+]; found: 634.3334.

Compound 17-*E*: Colorless oil; $[\alpha]_D^{25}=+121.97$ ($c=0.6$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.32$–7.26 (m, 3H), 7.06 (d, $J=7.7$ Hz, 1H), 6.88 (d, $J=8.5$ Hz, 2H), 6.82 (d, $J=8.1$ Hz, 1H), 6.30 (d, $J=16$ Hz, 1H), 5.91 (dd, $J=16$, 7.7 Hz, 1H), 5.61 (ddd, $J=16$, 8.5, 5.1 Hz, 1H), 5.47 (dd, $J=16$, 8.1 Hz, 1H), 5.20–5.13 (m, 1H), 4.50 (d, $J=12$ Hz, 1H), 4.42 (d, $J=12$ Hz, 1H), 4.06 (t, $J=8.5$ Hz, 1H), 3.92 (t, $J=8.1$ Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.61–3.57 (m, 2H), 2.70–2.62 (m, 1H), 2.42–2.35 (m, 1H), 2.25–2.16 (m, 1H), 1.98–1.91 (m, 1H), 1.65 (brs, 8H), 1.40 ppm (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=167.9$, 155.3, 147.8, 135.5, 132.9, 131.4, 130.5, 130.4, 129.3, 128.6, 126.9, 123.3, 117.5, 113.8, 110.5, 109.8, 108.2, 82.9, 82.4, 75.3, 72.8, 66.2, 55.8, 55.3, 36.61, 36.56, 35.4, 35.3, 25.0, 23.80, 23.77 ppm; IR (neat): $\tilde{\nu}=2936$, 2860, 1731, 1576, 1514, 1472 cm^{-1}; MS (EI): *m*/*z*: 534 [M^+]; HRMS: *m*/*z*: calcd for $C_{32}H_{38}O_7$: 534.2618 [M^+]; found: 534.2611.

Compound 17-*Z*: Colorless oil; $[\alpha]_D^{25}=+29.63$ ($c=0.46$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.33$–7.26 (m, 3H), 6.93 (d, $J=7.3$ Hz, 1H), 6.88 (d, $J=8.5$ Hz, 2H), 6.84 (d, $J=8.1$ Hz, 1H), 6.53 (d, $J=16$ Hz, 1H), 5.97 (dd, $J=16$, 5.5 Hz, 1H), 5.89 (td, $J=12$, 4.3 Hz, 1H), 5.52–5.45 (m, 2H), 4.50 (d, $J=11$ Hz, 1H), 4.43–4.36 (m, 2H), 4.26 (td, $J=6.0$, 0.9 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.58 (t, $J=6.4$ Hz, 2H), 2.70–2.63 (m, 1H), 2.29–2.22 (m, 1H), 1.97–1.91 (m, 2H), 1.65 (brs, 8H), 1.40 ppm (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=166.4$, 159.1, 155.7, 137.0, 133.5, 130.8, 130.7, 130.4, 129.9, 129.3, 129.2, 127.5, 122.5, 118.9, 113.74, 113.70, 110.2, 109.9, 80.1, 76.6, 72.8, 66.0, 55.7, 55.2, 36.6, 36.5, 36.3, 34.2, 25.0, 23.8, 23.7 ppm; IR (neat): $\tilde{\nu}=2936$, 2860, 1732, 1576, 1514, 1470 cm^{-1}; MS (EI): *m*/*z*: 534 [M^+]; HRMS: *m*/*z*: calcd for $C_{32}H_{38}O_7$: 534.2618 [M^+]; found: 534.2642.

Compound 18-*E*: Colorless oil; $[\alpha]_D^{25}=+117.60$ ($c=1.09$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.32$–7.27 (m, 3H), 7.11 (d, $J=7.7$ Hz, 1H), 7.04 (d, $J=8.5$ Hz, 1H), 6.89 (d, $J=8.5$ Hz, 2H), 6.30 (d, $J=16$ Hz, 1H), 5.91 (dd, $J=16$, 8.5 Hz, 1H), 5.61 (ddd, $J=16$, 9.8, 5.1 Hz, 1H), 5.47 (dd, $J=16$, 8.1 Hz, 1H), 5.20–5.15 (m, 1H), 5.12 (s, 2H), 4.49 (d, $J=$ 12 Hz, 1H), 4.42 (d, $J=12$ Hz, 1H), 4.07 (t, $J=8.5$ Hz, 1H), 3.92 (t, $J=$ 8.1 Hz, 1H), 3.80 (s, 3H), 3.60 (t, $J=6.8$ Hz, 2H), 3.43 (s, 3H), 2.68–2.60 (m, 1H), 2.40–2.32 (m, 1H), 2.23–2.15 (m, 1H), 1.99–1.93 (m, 1H), 1.65 (brs, 8H), 1.41 ppm (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=167.7$, 159.2, 152.8, 135.5, 132.8, 131.3, 130.4, 130.3, 129.2, 128.6, 126.9, 123.4, 118.6, 113.8, 113.5, 110.5, 94.5, 82.9, 82.3, 75.3, 72.8, 66.2, 56.1, 55.2, 36.6, 36.5, 35.4, 35.2, 25.0, 23.8 ppm; IR (neat): $\tilde{\nu}=2936$, 2861, 1731, 1575, 1514, 1469 cm^{-1}; MS (EI): *m*/*z*: 564 [M^+]; HRMS: *m*/*z*: calcd for $C_{33}H_{40}O_8$: 564.2723 [M^+]; found: 564.2709.

Compound 18-*Z*: Colorless oil; $[\alpha]_D^{25}=+41.31$ ($c=2.87$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.31$–7.26 (m, 3H), 7.07 (d, $J=8.6$ Hz, 1H), 6.99 (d, $J=7.7$ Hz, 1H), 6.88 (d, $J=9.0$ Hz, 2H), 6.52 (d, $J=16$ Hz, 1H), 5.98 (dd, $J=16$, 5.5 Hz, 1H), 5.89 (td, $J=12$, 4.3 Hz, 1H), 5.53–5.47 (m, 2H), 5.15 (d, $J=6.8$ Hz, 1H), 5.12 (d, $J=6.8$ Hz, 1H), 4.50 (d, $J=$ 11 Hz, 1H), 4.42–4.38 (m, 2H), 4.26 (ddd, $J=7.3$, 6.0, 1.3 Hz, 1H), 3.80 (s, 3H), 3.59 (t, $J=6.4$ Hz, 2H), 3.42 (s, 3H), 2.72–2.65 (m, 1H), 2.28–2.23 (m, 1H), 1.97–1.93 (m, 2H), 1.65 (brs, 8H), 1.41 ppm (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=166.2$, 159.1, 153.3, 137.0, 133.5, 130.8, 130.6, 130.3, 129.8, 129.3, 129.2, 127.6, 123.4, 120.0, 113.8, 113.6, 110.2, 94.5, 80.0, 76.6, 72.8, 66.0, 56.1, 55.2, 36.6, 36.5, 36.3, 34.1, 25.0, 23.7 ppm; IR (neat): $\tilde{\nu}=2936$, 2860, 1732, 1575, 1514, 1466 cm^{-1}; MS (EI): *m*/*z*: 564 [M^+]; HRMS: *m*/*z*: calcd for $C_{33}H_{40}O_8$: 564.2723 [M^+]; found: 564.2740.

[1] For a recent review, see: L. Yet, *Chem. Rev.* **2003**, *103*, 4283.
[2] a) K. L. Erickson, J. A. Beutler, J. H. Cardellina, M. R. Boyd, *J. Org. Chem.* **1997**, *62*, 8188; b) J. W. Kim, K. Shin-ya, K. Furihata, Y. Hayakawa, H. Seto, *J. Org. Chem.* **1999**, *64*, 153; c) M. R. Boyd, C. Farina, P. Belfiore, S. Gagliardi, J. W. Kim, Y. Hayakawa, J. A. Beutler, T. C. McKee, B. J. Bowman, E. J. Bowman, *J. Pharmacol. Exp. Ther.* **2001**, *297*, 114; d) J. A. Beutler, T. C. McKee, *Curr. Med. Chem.* **2003**, *10*, 787.
[3] K. A. Dekker, R. J. Aiello, H. Hirai, T. Inagaki, T. Sakakibara, Y. Suzuki, J. F. Thompson, Y. Yamauchi, N. Kojima, *J. Antibiot.* **1998**, *51*, 14.
[4] For recent examples of salicylihalamides syntheses, see: a) J. S. Yadav, P. Srihari, *Tetrahedron: Asymmetry* **2004**, *15*, 81; b) C. Herb, M. E. Maier, *J. Org. Chem.* **2003**, *68*, 8129; c) A. Fürstner, T. Dierkes, O. R. Thiel, G. Blanda, *Chem. Eur. J.* **2001**, *7*, 5286; for recent examples of oximidines syntheses, see: d) X. Wang, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2003**, *125*, 6040; e) G. A. Molander, F. Dehmel, *J. Am. Chem. Soc.* **2004**, *126*, 10313.

[5] For recent reviews, see: a) A. Gradillas, J. Perez-Castells, *Angew. Chem.* **2006**, *118*, 6232; *Angew. Chem. Int. Ed.* **2006**, *45*, 6086; b) R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117; c) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490; d) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199.
[6] a) Y. Matsuya, T. Kawaguchi, H. Nemoto, *Org. Lett.* **2003**, *5*, 2939; b) T. Kawaguchi, N. Funamori, Y. Matsuya, H. Nemoto, *J. Org. Chem.* **2004**, *69*, 505; c) Y. Matsuya, T. Kawaguchi, K. Ishihara, K. Ahmed, Q.-L. Zhao, T. Kondo, H. Nemoto, *Org. Lett.* **2006**, *8*, 4609.
[7] A few examples of kinetically controlled RCM have been reported: a) D. Castoldi, L. Caggiano, L. Panigada, O. Sharon, A. M. Costa, C. Gennari, *Angew. Chem.* **2005**, *117*, 594; *Angew. Chem. Int. Ed.* **2005**, *44*, 588; b) A. Fürstner, C. Müller, *Chem. Commun.* **2005**, 5583; c) D. Castoldi, L. Caggiano, L. Panigada, O. Sharon, A. M. Costa, C. Gennari, *Chem. Eur. J.* **2006**, *12*, 51; for a report on kinetically controlled cross-metathesis, see: d) F. C. Engelhardt, M. J. Schmitt, R. E. Taylor, *Org. Lett.* **2001**, *3*, 2209.
[8] P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100.
[9] M. Scholl, S. Ding, W. C. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953.
[10] a) J. S. Kingsbury, J. P. A. Harrity, P. J. Bonitatebus, Jr., A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 791; b) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168.
[11] For example: a) L. Cavallo, *J. Am. Chem. Soc.* **2002**, *124*, 8965; b) E. L. Dias, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1997**, *119*, 3887; c) C. Adlhart, C. Hinderling, H. Baumann, P. Chen, *J. Am. Chem. Soc.* **2000**, *122*, 8204; d) O. M. Aagaard, R. J. Meier, F. Buda, *J. Am. Chem. Soc.* **1998**, *120*, 7174; e) M. Ulman, R. H. Grubbs, *J. Org. Chem.* **1999**, *64*, 7202; f) M. S. Sanford, M. Ulman, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 749; g) M. S. Sanford, L. M. Henling, M. W. Day, R. H. Grubbs, *Angew. Chem.* **2000**, *112*, 3593; *Angew. Chem. Int. Ed.* **2000**, *39*, 3451.
[12] For example: a) Z. Xu, C. W. Johannes, A. F. Houri, D. S. La, D. A. Cogan, G. E. Hofilena, A. H. Hoveyda, *J. Am. Chem. Soc.* **1997**, *119*, 10302; b) A. B. Smith, III, C. M. Adams, S. A. Kozmin, D. V. Paone, *J. Am. Chem. Soc.* **2001**, *123*, 5925; c) A. Fürstner, O. R. Thiel, L. Ackermann, *Org. Lett.* **2001**, *3*, 449; d) W. C. Lee, R. H. Grubbs, *J. Org. Chem.* **2001**, *66*, 7155.
[13] Y. Wu, X. Liao, R. Wang, X.-S. Xie, J. K. De Brabander, *J. Am. Chem. Soc.* **2002**, *124*, 3245.
[14] a) M. S. Sanford, J. A. Love, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 6543; b) S. H. Hong, A. G. Wenzel, T. T. Salguero, M. W. Day, R. H. Grubbs, *J. Am. Chem. Soc.* **2007**, *129*, 7961.
[15] For example: a) A. Fürstner, K. Radkowski, C. Wirtz, R. Goddard, C. W. Lehmann, R. Mynott, *J. Am. Chem. Soc.* **2002**, *124*, 7061; b) A. Fürstner, M. Schlede, *Adv. Synth. Catal.* **2002**, *344*, 657; c) A. Fürstner, T. Nagano, C. Müller, G. Seidel, O. Müller, *Chem. Eur. J.* **2007**, *13*, 1452; d) C. W. Lee, R. H. Grubbs, *Org. Lett.* **2000**, *2*, 2145.
[16] a) C. Adlhart, P. Chen, *J. Am. Chem. Soc.* **2004**, *126*, 3496; b) C. Adlhart, P. Chen, *Angew. Chem.* **2002**, *114*, 4668; *Angew. Chem. Int. Ed.* **2002**, *41*, 4484; c) S. F. Vyboishchikov, M. Bühl, W. Thiel, *Chem. Eur. J.* **2002**, *8*, 3962; d) S. F. Vyboishchikov, W. Thiel, *Chem. Eur. J.* **2005**, *11*, 3921.
[17] This proposal is not necessarily in agreement with the past theoretical studies but most likely rationalizes the experimental results obtained here. We would like to emphasize that this hypothesis is not applied in general but is limited to our present reaction system because the relative energy levels of RCM intermediates can be substrate dependent.
[18] In the overall RCM process, a rate-determining step for the second-generation catalysts has been reported to be a phosphine-dissociation step. Here, discussion is focused on the catalyst-turnover cycle, which determines the *E*/*Z* selectivity.
[19] For an interesting concept for *E*/*Z* control of macrocycle formation based on a ring-closing alkyne metathesis, see: A. Fürstner, P. W. Davies, *Chem. Commun.* **2005**, 2307.
[20] a) A. Chattopadhyay, B. Dhotare, *Tetrahedron: Asymmetry* **1998**, *9*, 2715; b) M. Achmatowicz, L. S. Hegedus, *J. Org. Chem.* **2004**, *69*, 2229.
[21] a) A. Hadfield, H. Schweitzer, M. P. Trova, K. Green, *Synth. Commun.* **1994**, *24*, 1025; b) A. Fürstner, I. Konetzki, *Tetrahedron* **1996**, *52*, 15071.
[22] A. B. Smith, III, K. P. Minbiole, P. R. Verhoest, M. Schelhaas, *J. Am. Chem. Soc.* **2001**, *123*, 10942.

Received: February 9, 2008
Published online: April 28, 2008

