

## Total Synthesis of Macrophelides A, B, and E: First Application of Ring-Closing Metathesis for Macrophelide Synthesis

Takanori Kawaguchi, Nobutaka Funamori, Yuji Matsuya, and Hideo Nemoto\*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194, Japan

nemotoh@ms.toyama-mpu.ac.jp

Received October 1, 2003

A new synthetic route for macrophelides A, B, and E based on ring-closing metathesis (RCM) was established. The substrates for RCM could be synthesized starting from commercially available chiral materials, methyl (*S*)-lactate and methyl (*S*)- or (*R*)-3-hydroxybutyrate, in good overall yields. In the investigation of the key RCM step, it was found that the steric factor around the reaction site significantly affected the reaction rate of macrocyclization. A detailed account regarding this synthetic study is described herein.

### Introduction

Olefin metatheses using metal alkylidene complexes is a unique and powerful method for C–C bond formation or cleavage and occupies a greatly significant position in modern synthetic organic chemistry.<sup>1</sup> Among them, ring-closing metathesis (RCM) has received much attention for the construction of medium or large rings, and numerous studies on its application for the synthesis of biologically important molecules have been reported in the past few years.<sup>2</sup> In particular, it has been a promising method for forming macrocyclic compounds, as seen representatively in epothilone syntheses.<sup>3</sup> As one of our recent research projects for total synthesis of several bioactive macrolides, development of a new efficient synthetic methodology for macrophelides, which have a 16-membered trilactone linkage, has been carried out.<sup>4</sup> This series of natural products were isolated from *Macrosphaeropsis* sp. FO-5050 and *Periconia byssoides*<sup>5</sup> and have been reported to inhibit adhesion of human leukemia HL-60 cells to human-umbilical-vein endothelial cells with high selectivity<sup>5</sup> and, consequently, to be potential lead compounds for new anti-cancer drugs. Although many synthetic studies have been reported<sup>6</sup> since Omura and Smith reported the first total synthesis of macrophelides A and B in 1997,<sup>6a</sup> in all cases, the macro-lactonization protocol developed by Yamaguchi et al.<sup>7</sup> was

employed as a macrocyclization method, and no example including RCM has been seen so far. In a previous communication,<sup>8</sup> we reported the first application of RCM for the total synthesis of macrophelides A and B, demonstrating its efficiency for constructing the 16-membered macrophelide skeleton. In this paper, we describe the full details of this RCM-based synthetic study and its extension for the synthesis of macrophelide E.

### Results and Discussion

**Retrosynthesis.** The approach we envisaged for the synthesis of macrophelides A, B, and E is shown in Scheme 1. Of two olefinic parts in the 16-membered

(5) (a) Hayashi, M.; Kim, Y.-P.; Hiraoka, H.; Natori, M.; Takamatsu, S.; Kawakubo, T.; Masuma, R.; Komiyama, K.; Omura, S. *J. Antibiot.* **1995**, *48*, 1435. (b) Takamatsu, S.; Kim, Y.-P.; Hayashi, M.; Hiraoka, H.; Natori, M.; Komiyama, K.; Omura, S. *J. Antibiot.* **1996**, *49*, 95. (c) Takamatsu, S.; Hiraoka, H.; Kim, Y.-P.; Hayashi, M.; Natori, M.; Komiyama, K.; Omura, S. *J. Antibiot.* **1997**, *50*, 878. (d) Fukami, A.; Taniguchi, Y.; Nakamura, T.; Rho, M.-C.; Kawaguchi, K.; Hayashi, M.; Komiyama, K.; Omura, S. *J. Antibiot.* **1999**, *52*, 501. (e) Numata, A.; Iritani, M.; Yamada, T.; Minoura, K.; Matsumura, E.; Yamori, T.; Tsuruo, T. *Tetrahedron Lett.* **1997**, *38*, 8215. (f) Yamada, T.; Iritani, M.; Doi, M.; Minoura, K.; Ito, T.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3046. (g) Yamada, T.; Iritani, M.; Minoura, K.; Numata, A.; Kobayashi, Y.; Wang, Y.-G. *J. Antibiot.* **2002**, *55*, 147.

(6) (a) Sunazuka, T.; Hirose, T.; Harigaya, Y.; Takamatsu, S.; Hayashi, M.; Komiyama, K.; Omura, S.; Sprengeler, P. A.; Smith, A. B., III. *J. Am. Chem. Soc.* **1997**, *119*, 10247. (b) Kobayashi, Y.; Kumar, B. G.; Kurachi, T. *Tetrahedron Lett.* **2000**, *41*, 1559. (c) Kobayashi, Y.; Kumar, B. G.; Kurachi, T.; Acharya, H. P.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **2001**, *66*, 2011. (d) Kobayashi, Y.; Acharya, H. P. *Tetrahedron Lett.* **2001**, *42*, 2817. (e) Ono, M.; Nakamura, H.; Konno, F.; Akita, H. *Tetrahedron: Asymmetry* **2000**, *11*, 2753. (f) Nakamura, H.; Ono, M.; Makino, M.; Akita, H. *Heterocycles* **2002**, *57*, 327. (g) Nakamura, H.; Ono, M.; Shida, Y.; Akita, H. *Tetrahedron: Asymmetry* **2002**, *13*, 705. (h) Kobayashi, Y.; Wang, Y.-G. *Tetrahedron Lett.* **2002**, *43*, 4381. (i) Ono, M.; Nakamura, H.; Arakawa, S.; Honda, N.; Akita, H. *Chem. Pharm. Bull.* **2002**, *50*, 692. (j) Sharma, G. V. M.; Chandra Mouli, Ch. *Tetrahedron Lett.* **2002**, *43*, 9159. (k) Akita, H.; Nakamura, H.; Ono, M. *Chirality* **2003**, *15*, 352.

(7) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(8) Matsuya, Y.; Kawaguchi, T.; Nemoto, H. *Org. Lett.* **2003**, *5*, 2939.

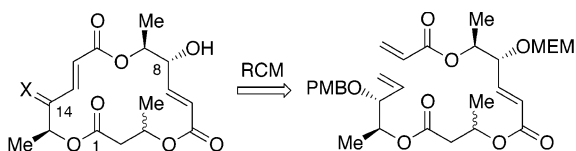
(1) For recent reviews on olefin metathesis, see: (a) Fürstner, A. *Topics in Organometallic Chemistry*, Springer-Verlag: Berlin, 1998; Vol. 1. (b) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Metathesis Polymerization*; Academic Press: San Diego, CA, 1997. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18.

(2) For recent reviews on RCM, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(3) Recent report in this field: Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Chou, T.-C.; Dong, H.; Tong, W. P.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 2899. Also, a comprehensive review can be seen in ref 1a, pp 75–92.

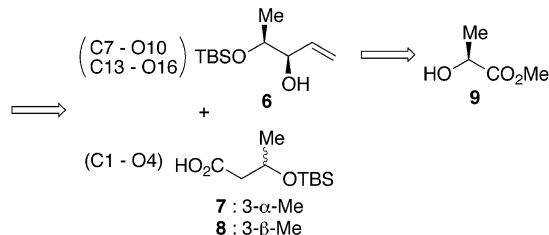
(4) Matsuya, Y.; Kawaguchi, T.; Nemoto, H.; Nozaki, H.; Hamada, H. *Heterocycles* **2003**, *59*, 481.

## SCHEME 1



Macrophelide A (1) : 3- $\alpha$ -Me, X =  $\alpha$ -OH,  $\beta$ -H  
 Macroshelide B (2) : 3- $\alpha$ -Me, X = O  
 Macroshelide E (3) : 3- $\beta$ -Me, X =  $\alpha$ -OH,  $\beta$ -H

4 : 3- $\alpha$ -Me  
 5 : 3- $\beta$ -Me



macrophelide skeleton, the C12–C13 olefin was chosen as the position for macrocyclization by RCM. The substrate for RCM (4 and 5) contains five chiral centers, one of which (C3) would be able to originate from enantiomerically enriched 3-hydroxybutyric acid derivatives (7 and 8). The availability of both enantiomers of 3-hydroxybutyrate from commercial sources provides a versatile route to both C3-epimeric products, macroshelide A and E, alternatively. The other two pairs (C8–C9 and C14–C15) of chiral centers have mutually identical relative and absolute stereochemistry and analogous arrangements of atoms, thereby allowing use of the common chiral subunit 6, which can be prepared from inexpensive methyl (*S*)-lactate (9). Assembly of 4 and 5 from these chiral blocks could be achieved based on our previous success in constructing the macroshelide core structure,<sup>4</sup> including a deprotection–esterification sequence and Horner–Wadsworth–Emmons (HWE) olefination.

**Synthesis of the Substrates for RCM.** As can be seen from the retrosynthesis, the initial goal is the synthesis of the RCM substrates 4 and 5. Our synthesis began with the preparation of known chiral material 6,<sup>9</sup> which corresponds to C7–O10 and C13–O16 units of the target macroshelides. According to the reported procedure,<sup>9</sup> methyl (*S*)-lactate (9) was converted into *tert*-butyldimethylsilyl (TBS) ether and the ester function was transformed into the formyl group with DIBAL reduction followed by Swern oxidation. Addition of vinyl Grignard reagent to the aldehyde resulted in the formation of desired allyl alcohol 6 (6:1 diastereoselectivity),<sup>10</sup> which was purified with column chromatography. The synthesis of 4 starting from 6 is depicted in Scheme 2. The C5–O10 subunit 13 was synthesized in five steps, including oxidative cleavage of the vinyl group and subsequent HWE homologation. After protection of the alcohol 6 as a MEM ether, the olefin 10 was converted into the aldehyde 11 upon exposure to osmium tetroxide followed

by sodium periodate in 72% yield. Masamune–Roush modification<sup>11</sup> of HWE reaction proceeded cleanly to afford conjugated ester 12 with no detectable (*Z*)-isomer. Mild hydrolysis of the ester 12 provided the chiral subunit 13 with high efficiency. When utilizing compound 6 as the C13–O16 unit, selection of the protecting group is important because it is necessary to distinguish the two hydroxyl groups (8- and 14-positions) for the synthesis of macroshelide B. To this end, the introduction of a PMB group to the alcohol 6 was investigated. However, attempts to synthesize the PMB ether 14 under standard reaction conditions (PMBCl–NaH or Ag<sub>2</sub>O) were unsuccessful, and instead, intra- and intermolecular migration of TBS group took place to afford a complex mixture. Although an efficient method for PMB etherification employing *p*-methoxybenzyl trichloroacetimidate and lanthanum triflate was recently reported,<sup>12</sup> the application of the method also ended in failure. After several investigations, *p*-methoxybenzyl trifluoroacetimidate<sup>13</sup> was found to be an effective reagent for the reaction to give a preferable result. Although *p*-TsOH or CSA as an acid-catalyst resulted in the same scrambling of the TBS group, the use of PPTS led to the formation of our desired PMB ether 14 without any side reactions in a high conversion yield. The amount of PPTS and reaction temperature did not affect the yield of 14. After desilylation of 14 with TBAF, introduction of the C1–O4 subunit, (*S*)-3-silyloxybutyric acid (7), was performed under dehydration conditions using EDC–DMAP to give the ester 16 in 99% yield. Connection of 16 with the carboxylic acid 13 and subsequent introduction of acryloyl group were planned to be carried out through the same desilylation–esterification sequence. In practice, the silyl ether 16 was treated with TBAF to afford the alcohol 17 in 95% yield. For the reaction of 17 with 13, application of the same dehydration condition as the formation of 16 afforded the ester 18 only in 16% yield, and 77% of the alcohol 17 was recovered while the carboxylic acid 13 disappeared. This suggests that the “activated” carboxylic acid generated by reaction with the carbodiimide was transformed into an inactive *N*-acylurea derivative prior to reaction with the alcohol 17. In such cases, it has been reported that addition of proton sources such as amine hydrochlorides to the reaction medium suppressed the undesired transformation.<sup>14</sup> Therefore, a DCC/DMAP/DMAP-hydrochloride system was applied according to the reported procedure<sup>14</sup> to improve the yield of 18 up to 65%. However, this protocol lacked reproducibility of the yield, and a more reliable method was explored. Eventually, employment of activated mixed anhydride as an intermediate resulted in a striking improvement in the coupling efficiency, giving nearly quantitative yield with good reproducibility. In the next desilylation step, special care was required because base-induced cleavage of the C3–O4 bond of 18 rapidly proceeded in a retro-Michael manner when treated with TBAF. To circumvent this impasse, the reaction was performed in AcOH-containing medium for a prolonged

(9) (a) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180. (b) Ley, S. V.; Armstrong, A.; Diez-Martin, D.; Ford, M. J.; Grice, P.; Knight, J. G.; Kolb, H. C.; Madin, A.; Marby, C. A.; Mukherjee, S.; Shaw, A. N.; Slawin, A. M. Z.; Vile, S.; White, A. D.; Williams, D. J.; Woods, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 667.

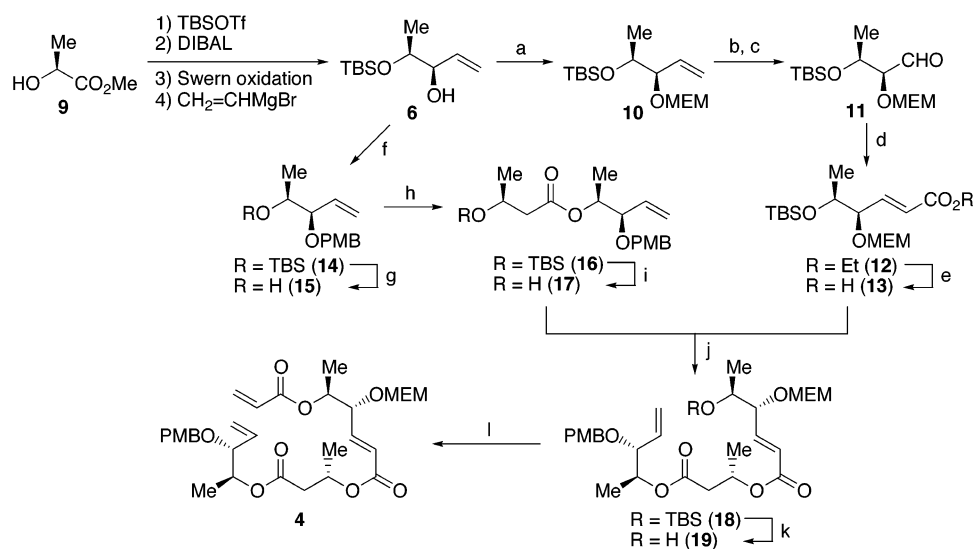
(10) An alternative method for preparing this type of compound with high anti selectivity has been reported: Iio, H.; Mizobuchi, T.; Tsukamoto, M.; Tokoroyama, T. *Tetrahedron Lett.* **1986**, *27*, 6373.

(11) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essensfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

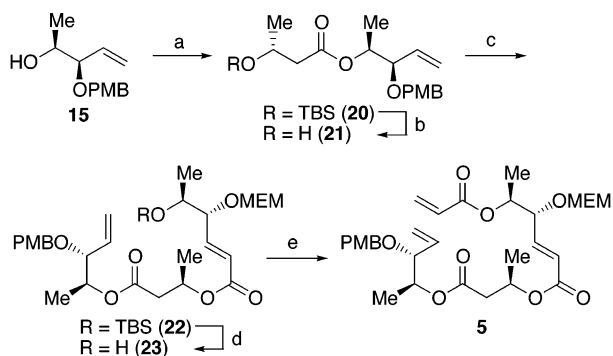
(12) Rai, A. N.; Basu, A. *Tetrahedron Lett.* **2003**, *44*, 2267.

(13) Nakajima, N.; Saito, M.; Ubukata, M. *Tetrahedron Lett.* **1998**, *39*, 5565.

(14) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

SCHEME 2<sup>a</sup>

<sup>a</sup> Reagents: (a) MEMCl, DIPEA, CH<sub>2</sub>Cl<sub>2</sub> (70%); (b) OsO<sub>4</sub>, NMO, acetone; (c) NaIO<sub>4</sub>, TBAB, CH<sub>2</sub>Cl<sub>2</sub>-H<sub>2</sub>O (72% in two steps); (d) (EtO)<sub>2</sub>P(O)CH<sub>2</sub>CO<sub>2</sub>Et, DBU, LiCl, MeCN (95%); (e) NaOH, MeOH-THF-H<sub>2</sub>O (99%); (f) PMBOC(=NH)CF<sub>3</sub>, PPTS, CH<sub>2</sub>Cl<sub>2</sub> (47%, recovery = 51%); (g) TBAF, THF (96%); (h) 7, EDC, DMAP, CH<sub>2</sub>Cl<sub>2</sub> (99%); (i) TBAF, THF (95%); (j) 13, 2,4,6-Cl<sub>3</sub>C<sub>6</sub>H<sub>2</sub>COCl, Et<sub>3</sub>N, DMAP, toluene, then 17 (99%); (k) TBAF, AcOH, THF (85%); (l) CH<sub>2</sub>=CHCOCl, DIPEA, CH<sub>2</sub>Cl<sub>2</sub> (95%).

SCHEME 3<sup>a</sup>

<sup>a</sup> Reagents: (a) 8, EDC, DMAP, CH<sub>2</sub>Cl<sub>2</sub> (69%); (b) TBAF, THF (71%); (c) 13, 2,4,6-Cl<sub>3</sub>C<sub>6</sub>H<sub>2</sub>COCl, Et<sub>3</sub>N, DMAP, toluene, then 21 (94%); (d) TBAF, AcOH, THF (77%); (e) CH<sub>2</sub>=CHCOCl, DIPEA, CH<sub>2</sub>Cl<sub>2</sub> (88%).

reaction time to furnish the alcohol 19 in 85% yield. The final esterification was carried out using acryloyl chloride and DIPEA in CH<sub>2</sub>Cl<sub>2</sub> to accomplish the synthesis of the RCM substrate 4.

For the synthesis of 5, the C3-epimer of 4, the same synthetic sequence depicted in Scheme 2 was applicable only by replacing (*S*)-3-silyloxybutyric acid (7) to its (*R*)-enantiomer 8 as shown in Scheme 3. Thus, the syntheses of 4 and 5, the precursors for macrospheptides A and B and macrospheptide E, respectively, were completed satisfactorily by assembly from commercially available chiral materials.

**Ring-Closing Metathesis of 4 and 5.** The next phase of our studies was directed at RCM of 4 and 5 to construct a 16-membered macrospheptide nucleus. The recent researchers in this area have developed various efficient RCM catalysts,<sup>15</sup> and our first choice among them was

## CHART 1

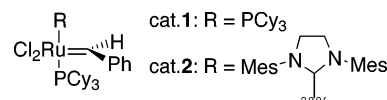
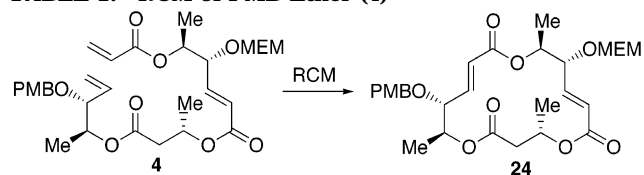


TABLE 1. RCM of PMB Ether (4)

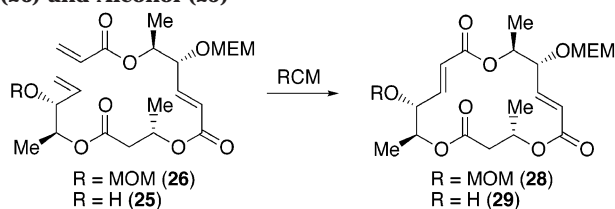


entry	reagent	solvent <sup>a</sup>	condition	yield (%)
1	catalyst 1 (10 mol %)	DCM	rt, 24 h	0
2	catalyst 1 (10 mol %)	DCE	reflux, 24 h	0
3	catalyst 2 (10 mol %)	DCM	rt, 24 h	0
4	catalyst 2 (10 mol %)	DCE	reflux, 24 h	<10
5	catalyst 2 (1 equiv)	DCE	reflux, 5 days	65
6	catalyst 2 (10 mol %) <sup>b</sup>	DCE	reflux, 24 h	<10

<sup>a</sup> DCM = dichloromethane; DCE = 1,2-dichloroethane. <sup>b</sup> Ti(O-*i*Pr)<sub>4</sub> (1 equiv) was added.

Grubbs' ruthenium complexes (Chart 1). The results of RCM of the substrate 4 are summarized in Table 1. For the macrocyclization, catalyst 1 was revealed to be ineffective as an RCM initiator, and the starting material was recovered completely even in refluxing 1,2-dichloroethane (entries 1 and 2). When catalyst 2 was used, formation of the cyclization product 24 was observed, although heating was required (entries 3 and 4). However, the yield was quite low (<10%), implying that the catalytic cycle was impeded. In fact, the use of equimolar amounts of catalyst 2 under the same condition improved the yield of 24 to 65%, although the reaction continued for 5 days (entry 5). One possible explanation for this extremely slow reaction would be a stabilizing effect for an intermediate ruthenium-substrate complex by coordination of the ester carbonyl to the ruthenium center

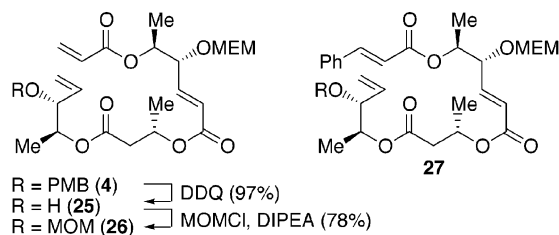
(15) Love, J. A.; Sanford, M. S.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 10103 and references therein.

TABLE 2. RCM of MOM Ether (**26**) and Alcohol (**25**)

entry	substrate	reagent	solvent <sup>a</sup>	condition	yield (%)
1	R = MOM ( <b>26</b> )	catalyst <b>1</b> (10 mol %)	DCM	rt, 12 h	0
2		catalyst <b>1</b> (10 mol %)	DCE	reflux, 12 h	0
3		catalyst <b>2</b> (10 mol %)	DCM	rt, 12 h	0
4		catalyst <b>2</b> (10 mol %)	DCE	reflux, 48 h	<10
5		catalyst <b>2</b> (1 equiv)	DCE	reflux, 48 h	60
6	R = H ( <b>25</b> )	catalyst <b>1</b> (10 mol %)	DCM	rt, 12 h	0
7		catalyst <b>1</b> (10 mol %)	DCE	reflux, 12 h	0
8		catalyst <b>2</b> (10 mol %)	DCM	rt, 24 h	77

<sup>a</sup> DCM = dichloromethane; DCE = 1,2-dichloroethane.

## CHART 2



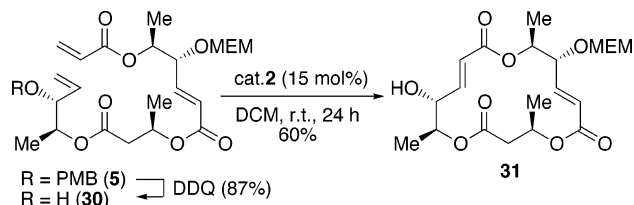
in an intramolecular fashion.<sup>16</sup> To avoid such interactions, the reaction was performed in the presence of Lewis acid,<sup>17</sup> but this did not lead to positive results (entry 6).

In these examinations, we noticed that a small amount of benzylidene derivative **27** (Chart 2) was formed especially in the case of entry 5, and it was found that the compound did not change under the RCM conditions. This observation suggests that the first reactive site toward the ruthenium catalyst is the conjugated enone part, and that participation of the  $\omega$ -olefin to the reaction is so sluggish that the reaction rate is comparable with that of styrene originating from the catalyst. Taking this finding into account, more sterically relaxed substrates (**25** and **26**) were prepared from PMB derivative **4** according to Chart 2.

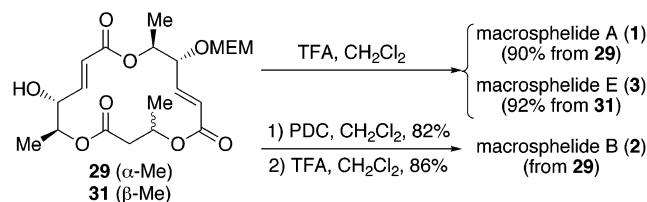
Results parallel to those in the case of **4** were obtained when used the MOM derivative **26** as a substrate for RCM (entries 1–5, Table 2), although the reaction rate increased somewhat (entry 5). On the other hand, it was found that the alcohol **25** has sufficient reactivity for our desired macrocyclization. As shown in entry 8, RCM of **25** proceeded in the presence of 10 mol % catalyst **2** at room temperature in 77% yield. In the cyclization processes, no geometric isomer (cis isomer) was produced.

For the synthesis of macrospheptide E, compound **5** was treated with DDQ to afford the alcohol **30**, which was subjected to RCM under the same conditions as the substrate **25**. Although 15 mol % of the catalyst was necessary to achieve a practical yield, macrocyclization

## SCHEME 4



## SCHEME 5



proceeded satisfactorily to give **31** in a stereoselective manner (Scheme 4). Thus, RCM-based construction of two macrospheptide skeletons was accomplished by controlling the bulkiness of the protecting group of 14-hydroxyl group.

**Completion of the Total Synthesis.** The transformations of the compounds **29** and **31** constructed by RCM into the natural macrospheptides were straightforward as shown in Scheme 5. Removal of the MEM group of these compounds with TFA produced macrospheptides A and E, respectively. PDC oxidation of **29** and subsequent deprotection afforded macrospheptide B. The spectral data of our synthetic macrospheptides agreed with those reported for the natural products.<sup>5b,f</sup>

## Conclusion

We have described here a detailed account regarding the total syntheses of macrospheptides A, B, and E based on RCM strategy. We have shown that the array of chiral centers can be assembled from readily available chiral blocks, methyl lactate and methyl 3-hydroxybutyrate, and first demonstrated that the RCM strategy is useful in constructing 16-membered macrospheptide skeletons. Further extensions of the synthetic methodology for the

(16) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.

(17) Langer, P.; Albrecht, U. *Synlett* **2002**, 1841.

other macrosphelide syntheses are currently ongoing in our laboratory and will be reported in due course.

**Supporting Information Available:** Full experimental details and characterization data for all new compounds. This

material is available free of charge via the Internet at <http://pubs.acs.org>.

JO035435U