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New Strategy for the Total Synthesis of Macrosphelides A and B Based on Ring-Closing Metathesis

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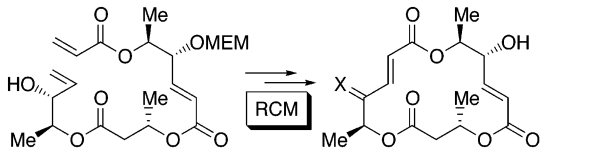
ABSTRACT



Macrosphelide A (**1**) : X = α-OH, β-H
Macrosphelide B (**2**) : X = O

A new total synthesis of macrosphelides A and B using ring-closing metathesis (RCM) as a macrocyclization step is described. The substrate of the RCM could be synthesized from readily available chiral materials, methyl (*S*)-(+)-3-hydroxybutyrate and methyl (*S*)-(−)-lactate, with a high efficiency. The RCM proceeded in the presence of Grubbs' Ru-complex, providing a new effective synthetic route to these natural products.

Macrosphelides A−L are characteristic 16-membered macrolides isolated from *Microsphaeropsis* sp. FO-5050 and *Periconia byssoides*.[1] These natural products have been reported to exhibit a potent cell−cell adhesion inhibitory activity, and much attention has been paid to them as potential lead compounds for new anti-cancer drugs.[1] Consequently, synthetic research of this attractive macrosphelide family has been carried out[2] by several groups, and all include Yamaguchi's macrolactonization protocol[3] for the macrocyclization. In the course of our study on the structure−activity relationship of the macrosphelides and its analogues, we have reported the synthesis of a simple macrosphelide core[4] in which the same macrolactonization method was employed. However, the lability of the substrates of the lactonization toward basic conditions seems to give rise to several problematic issues, such as a lack of reproducibility of the yield or partial epimerization[2h] of the product. In this research, we explored the first application of the ring-closing metathesis (RCM) as a neutral macrocyclization condition to the total synthesis of macrosphelides to accomplish the development of a new approach to macrosphelides A (**1**) and

(1) (a) Hayashi, M.; Kim, Y.-P.; Hiraoka, H.; Natori, M.; Takamatsu, S.; Kawakubo, T.; Masuma, R.; Komiyama, K.; Omura, S. *J. Antibiot.* **1995**, *48*, 1435−1439. (b) Takamatsu, S.; Kim, Y.-P.; Hayashi, M.; Hiraoka, H.; Natori, M.; Komiyama, K.; Omura, S. *J. Antibiot.* **1996**, *49*, 95−98. (c) Takamatsu, S.; Hiraoka, H.; Kim, Y.-P.; Hayashi, M.; Natori, M.; Komiyama, K.; Omura, S. *J. Antibiot.* **1997**, *50*, 878−880. (d) Fukami, A.; Taniguchi, Y.; Nakamura, T.; Rho, M.-C.; Kawaguchi, K.; Hayashi, M.; Komiyama, K.; Omura, S. *J. Antibiot.* **1999**, *52*, 501−504. (e) Numata, A.; Iritani, M.; Yamada, T.; Minoura, K.; Matsumura, E.; Yamori, T.; Tsuruo, T. *Tetrahedron Lett.* **1997**, *38*, 8215−8218. (f) Yamada, T.; Iritani, M.; Doi, M.; Minoura, K.; Ito, T.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3046−3053. (g) Yamada, T.; Iritani, M.; Minoura, K.; Numata, A.; Kobayashi, Y.; Wang, Y.-G. *J. Antibiot.* **2002**, *55*, 147−154.

(2) (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*, 10247−10248. (b) Kobayashi, Y.; Kumar, B. G.; Kurachi, T. *Tetrahedron Lett.* **2000**, *41*, 1559−1563. (c) Kobayashi, Y.; Kumar, B. G.; Kurachi, T.; Acharya, H. P.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **2001**, *66*, 2011−2018. (d) Kobayashi, Y.; Acharya, H. P. *Tetrahedron Lett.* **2001**, *42*, 2817−2820. (e) Ono, M.; Nakamura, H.; Konno, F.; Akita, H. *Tetrahedron: Asymmetry* **2000**, *11*, 2753−2764. (f) Nakamura, H.; Ono, M.; Makino, M.; Akita, H. *Heterocycles* **2002**, *57*, 327−336. (g) Nakamura, H.; Ono, M.; Shida, Y.; Akita, H. *Tetrahedron: Asymmetry* **2002**, *13*, 705−713. (h) Kobayashi, Y.; Wang, Y.-G. *Tetrahedron Lett.* **2002**, *43*, 4381−4384. (i) Ono, M.; Nakamura, H.; Arakawa, S.; Honda, N.; Akita, H. *Chem. Pharm. Bull.* **2002**, *50*, 692−696. (j) Sharma, G. V. M.; Chandra Mouli, Ch. *Tetrahedron Lett.* **2002**, *43*, 9159−9161. (k) Akita, H.; Nakamura, H.; Ono, M. *Chirality* **2003**, *15*, 352−359.

(3) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

(4) Matsuya, Y.; Kawaguchi, T.; Nemoto, H.; Nozaki, H.; Hamada, H. *Heterocycles* **2003**, *59*, 481−484.

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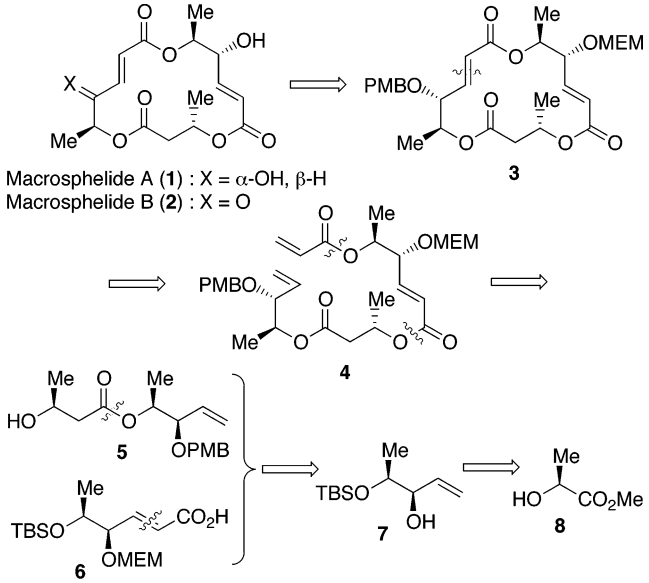
B (**2**) using inexpensive chiral blocks as substrates. This communication describes these results.

Macrosphelides A (**1**) and B (**2**) were first synthesized by Omura and co-workers, in which asymmetric dihydroxylation was used,[2a] and recently, the synthetic approaches utilizing a chiral α-furylethanol, a carbohydrate, and an enzymatic method have been reported.[2b−k] Our new synthetic plan is outlined in Scheme 1. Although the oxidative conversion of

Scheme 1. Synthetic Strategy for Macrosphelides A and B

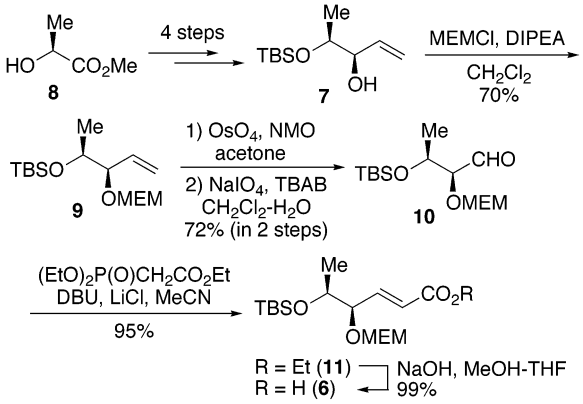


macrosphelide A (**1**) to B (**2**)[2a] and the reductive transformation of B (**2**) to A (**1**)[2c] were described in previous reports, there is a difficulty in the point of chemoselectivity or stereoselectivity in these processes.

To achieve the effective synthesis of macrosphelides A (**1**) and B (**2**) via a common synthetic process, we selected the macrocycle **3** as their precursor, which contains distinguishable protecting groups. For the construction of the macrocyclic system, RCM of **4** was our choice. On the basis of this strategy, a synthetic route to the intermediate **4** was designed from two commercially available chiral materials, methyl (*S*)-(+)-3-hydroxybutyrate and methyl (*S*)-(−)-lactate (**8**). The former corresponds to the left segment of **5**, and the latter is used to synthesize the right segment of **5** and **6** via a common intermediate **7**.

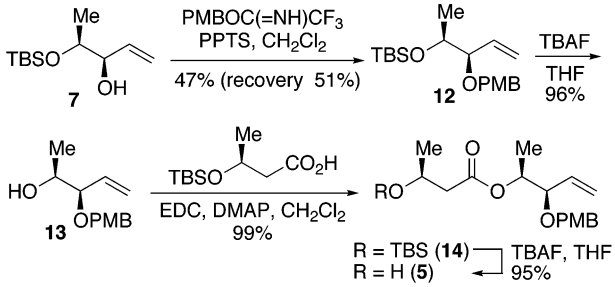
The preparation of the intermediate **7** was carried out from methyl (*S*)-(−)-lactate (**8**) in four steps according to a reported procedure, i.e., silylation, DIBAL reduction, and Swern oxidation followed by Grignard addition (6:1 diastereoselectivity).[5] The alcohol **7** was protected as a methoxyethoxymethyl (MEM) ether, which was subjected to oxidative cleavage of the vinyl group upon treatment with osmium tetroxide and sodium periodate successively to afford the aldehyde **10**. Horner−Wadsworth−Emmons olefination of **10** using ethyl diethylphosphonoacetate proceeded with an exclusive stereoselectivity, and the resulting conjugated ester **11** was converted into the required carboxylic acid **6** by alkaline saponification (Scheme 2).[6]

Scheme 2. Synthesis of Intermediate **6**



Another chiral subunit **5** was assembled from **7** as shown in Scheme 3. The first step we attempted was found to be

Scheme 3. Synthesis of Intermediate **5**



difficult due to intra- and intermolecular migration of the TBS group under the basic (NaH or amine bases) or acidic (*p*-TsOH or CSA) conditions. To overcome this problem, we employed *p*-methoxybenzyl trifluoroacetimidate as a reagent developed by Ubukata et al.[7] Under this condition, the migration of the TBS group was suppressed, and a high conversion yield (based on the consumed alcohol) was realized. After the removal of the TBS group, the alcohol **13** was subjected to dehydrative condensation with another chiral carboxylic acid derived from methyl (*S*)-(+)-3-hydroxybutyrate to give the ester **14**, which was treated with TBAF to afford the alcohol **5** in high yields.

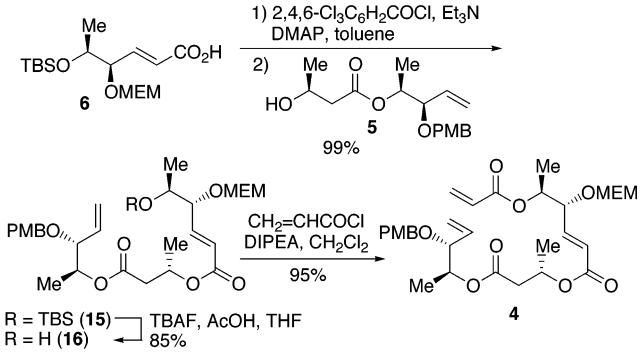
(5) (a) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180−5182. (b) Ley, S. V.; Armstrong, A.; Diez-Martin, D.; Ford, M. J.; Grice, P.; Knight, J. G.; Kolb, H. C.; Madin, A.; Marby, C. A.; Mukherjee, S.; Shaw, A. N.; Slawin, A. M. Z.; Vile, S.; White, A. D.; Williams, D. J.; Woods, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 667−692.

(6) Although compound **6** was previously synthesized by Omura et al. using asymmetric dihydroxylation and Mitsunobu inversion (ref 2a), we employed the alternative method shown in Scheme 2 because of the efficiency from **7**, which is a common intermediate for **5**.

(7) Nakajima, N.; Saito, M.; Ubukata, M. *Tetrahedron Lett.* **1998**, *39*, 5565−5568.

With the chiral subunits **5** and **6** in hand, we examined a connection of these compounds. Our first attempt was dehydrative condensation of **5** and **6** using DCC or EDC, providing the desired ester **15** in a moderate yield (65%). After several investigations, it was found that the yield of **15** greatly improved when applying the method using mixed anhydride as an active intermediate (Scheme 4). Desilylation

Scheme 4. Synthesis of RCM Substrate **4**

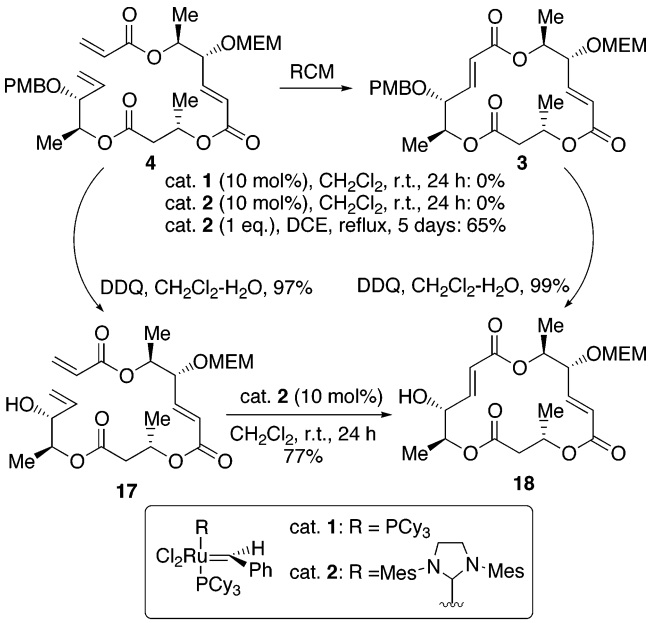


of **15** and introduction of the acryloyl group to the resulting alcohol **16** proceeded smoothly to afford a key material **4**, a substrate for RCM.

Unexpectedly, the RCM of **4** was found to be sluggish, as shown in Scheme 5. Using Grubbs' catalysts (catalyst **1** and catalyst **2**)[8] at room temperature, the cyclization did not proceed and the starting material was recovered completely. When the reaction was carried out using equimolar amounts of catalyst **2** in refluxing 1,2-dichloroethane (DCE), the cyclized product **3** was obtained in 65% yield after 5 days. On the other hand, it is noteworthy that the allyl alcohol **17** prepared by deprotection of **4** showed sufficient reactivity to RCM. The cyclization proceeded in the presence of 10 mol % catalyst **2** at room temperature to yield a macrocyclic alcohol **18**, which was identical with the product obtained by removal of the PMB group of **3**. In these cyclization processes, the geometric isomer (cis isomer) could not be detected.

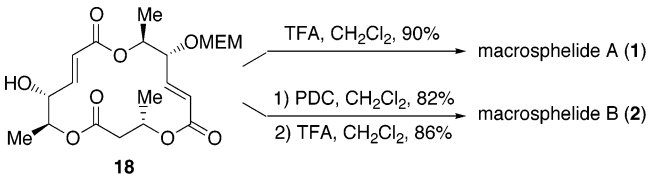
To complete the total synthesis, the remaining operations were quite simple. Removal of the MEM group of **18** with TFA afforded macrosphelide A, and PDC oxidation of **18** followed by the deprotection provided macrosphelide B,[9] the

Scheme 5. Ring-Closing Metathesis (RCM)



spectral data of which were in good agreement with those reported (Scheme 6).[1b,2a]

Scheme 6. Completion of the Total Synthesis



In conclusion, we have developed a new synthetic route for macrosphelides A and B with a high efficiency. In this strategy, the synthesis of macrosphelides A and B was accomplished from the common intermediate **18** using RCM as a key macrocyclization step. Extension of these studies to the synthesis of the other natural macrosphelides as well as nonnatural analogues is in progress.

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(9) Satisfactory spectral data for all new compounds were obtained; see, Supporting Information.