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RECENT ADVANCES IN MACROSPHELIDE SYNTHESIS

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Abstract – Natural macrosphelides are known as potent cell-cell adhesion inhibitors, which have novel three ester linkages in their 16-membered macrocyclic skeleton. In this review, recent synthetic studies of macrosphelides and relating compounds are surveyed, mainly including our approaches.

INTRODUCTION

Since the first isolation and characterization in 1995,[1] macrosphelides have received much attention from biochemists and synthetic chemists due to their notable bioactivities and novel structural characteristics. To date, twelve members of macrosphelide family have been isolated from *Microsphaeropsis* sp. FO-5050 and/or *Periconia byssoides* OUPS-N133, which were designated macrosphelides A-L (Figure 1).[2-7] Recently, it was also found that macrosphelide A was produced by the mycoparasite *Coniothyrium minitans*.[8] These natural products are characterized by a 16-membered macrolide structure having three lactone linkages as well as the potent cell-cell adhesion inhibitory activity. Ômura and his co-workers first reported that macrosphelides A and B strongly inhibited the adhesion of human leukemia HL-60 cells to human-umbilical-vein endothelial cells (HUVEC) in a dose-dependent manner (IC_{50}: 3.5 μM and 36 μM, respectively).[1] Since then, a series of the natural compounds has been revealed to exhibit more or less similar inhibitory activity and to show no cytotoxicity against various mammalian cell lines.[3,5-7] In addition, it was reported that macrosphelide B suppressed lung metastasis of B16/BL6 mouse melanoma cells *in vivo* by inhibiting sialyl Lewis^x-mediated cell-adhesion, and that the combination therapy with cisplatin was effective against the lung metastasis.[9] Moreover, immunosuppressive effect[10,11] and antifungal activity[8] of macrosphelides have been also reported. In conjunction with these attractive bioactivities, an increased number of synthetic studies have appeared in literatures,[12-27] directed toward structural determination, concise and efficient synthesis, combinatorial synthesis of a library, or structure-activity relationships of macrosphelides. In our laboratory, several new approaches for synthesizing natural macrosphelides and analogues have been explored, and reported for a past few years.[28-33] These

synthetic studies of macrosphelides are surveyed in this review article.

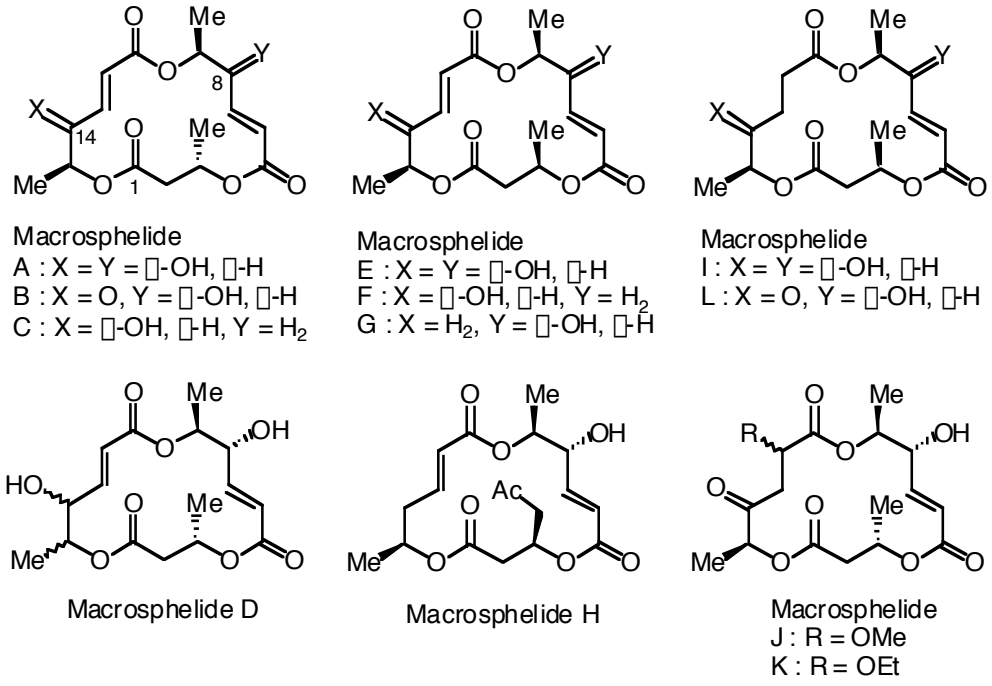
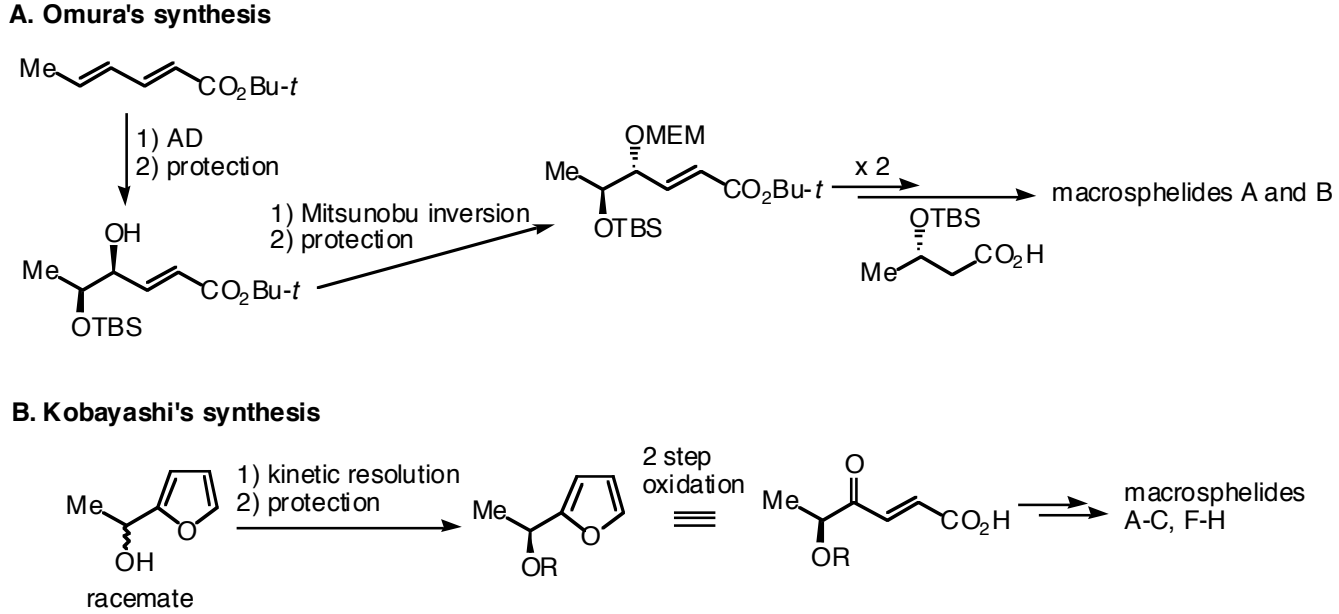


Figure 1. Naturally Occurring Macrosphelides

SYNTHETIC STUDIES OF MACROSPHELIDES

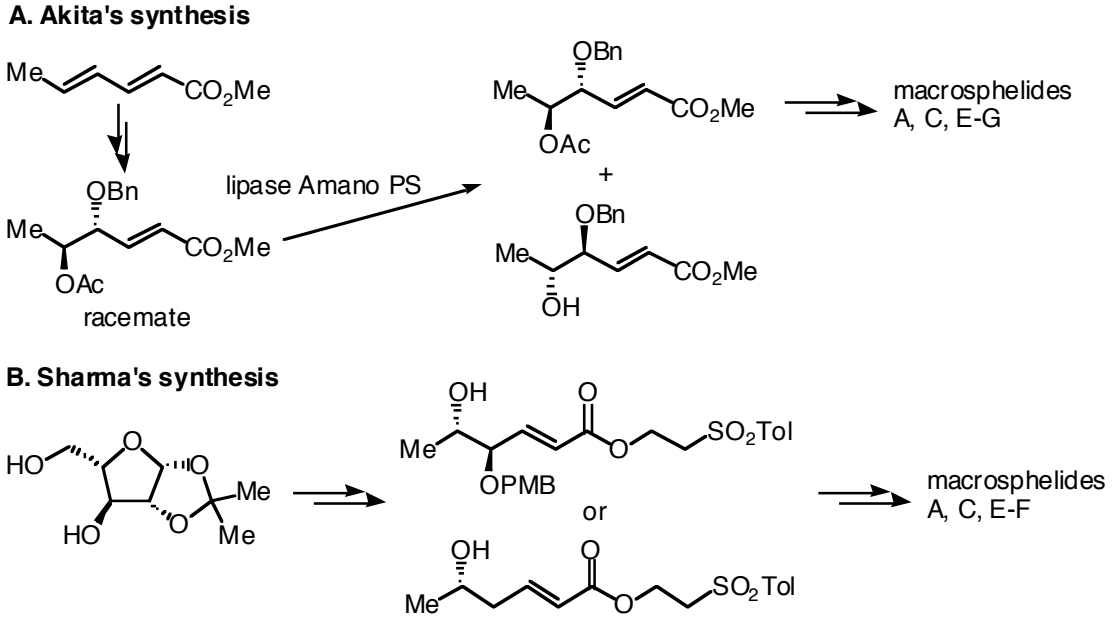
Pioneering work concerning macrosphelide synthesis was reported by Ômura's research group in 1997,[12] in which the relative and absolute stereochemistries of macrosphelides A and B were elucidated by means of an X-Ray analysis, the modification of the Mosher ester method, and decisively, the first elegant total synthesis. They employed Sharpless asymmetric dihydroxylation and subsequent Mitsunobu inversion for constructing the oxygen-bearing adjacent chiral centers at C8-C9 and C14-C15 positions of



Scheme 1

macrosphelide A. Thus, as outlined in Scheme 1 (A), the first total synthesis of (+)-macrosphelide A was achieved in a highly convergent fashion. Complete stereostructures of the other natural macrosphelides (C, E-I, and L) were mainly elucidated by Numata's group,[4,6-7] on the basis of various spectroscopic analyses, and chemical transformations and degradations of natural macrosphelides. Kobayashi and co-workers[13-16] reported the syntheses of several macrosphelides utilizing their original finding that 2-substituted furans act as 4-oxo-2-alkenoic acid equivalents upon treatment with a successive two-step oxidation sequence. Required enantiomerically pure 2-(α-hydroxyethyl)furan was prepared through the kinetic resolution of the corresponding racemate under the Sharpless asymmetric epoxidation condition. This strategy provided the synthetic routes to macrosphelides A-C, F-H, and 14-epi-macrosphelide A (Scheme 1, B).

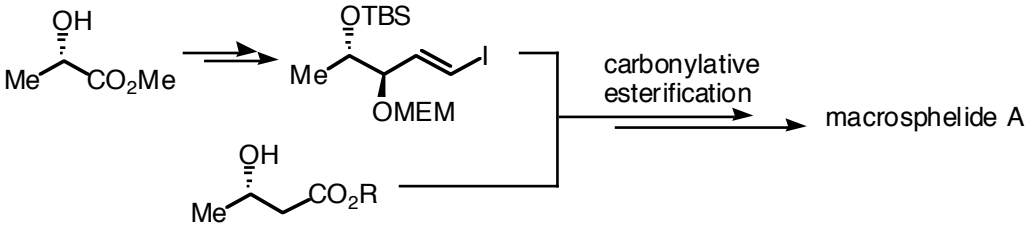
Akita's group[17-22] has been developed new syntheses of macrosphelides based on enzymatic function. They prepared enantiomerically pure 4-benzyloxy-5-hydroxy-2(*E*)-hexenoates as a chiral building block for the macrosphelide syntheses, by means of enzymatic resolution of the racemic substrate synthesized from methyl sorbate, providing new access to macrosphelides A, C, and E-G (Scheme 2, A). Sharma *et al.*[23,24] reported a carbohydrate-based approach for the total synthesis of macrosphelides A, C, and E-F. In this approach, degradative transformations of L-arabinose were utilized for preparing suitable chiral blocks, which were subsequently assembled to construct the macrocyclic system (Scheme 2, B).



Scheme 2

Recently, Takahashi and co-workers[25,26] disclosed a new methodology for macrosphelide syntheses using a novel palladium-catalyzed carbonylative esterification as a key reaction (Scheme 3). The ester linkages constituting the macro-ring were efficiently formed between suitable alcohols and vinyl halides, originating from methyl (*S*)-3-hydroxybutyrate and methyl (*S*)-lactate, through a carbonyl insertion process. This protocol was applied to the synthesis of macrosphelide A, and further, satisfactorily

expanded to a solid-state synthesis on a polymer support and a combinatorial synthesis, providing a 122-member library of natural macrosphelides and analogues.



Scheme 3. Takahashi's Synthesis

Additionally, an alternative method for preparing the key intermediate of Ômura's macrosphelide synthesis was also reported as a formal synthesis of macrosphelide A, in which an oxidative transformation of a chiral epoxy alcohol was employed.[27]

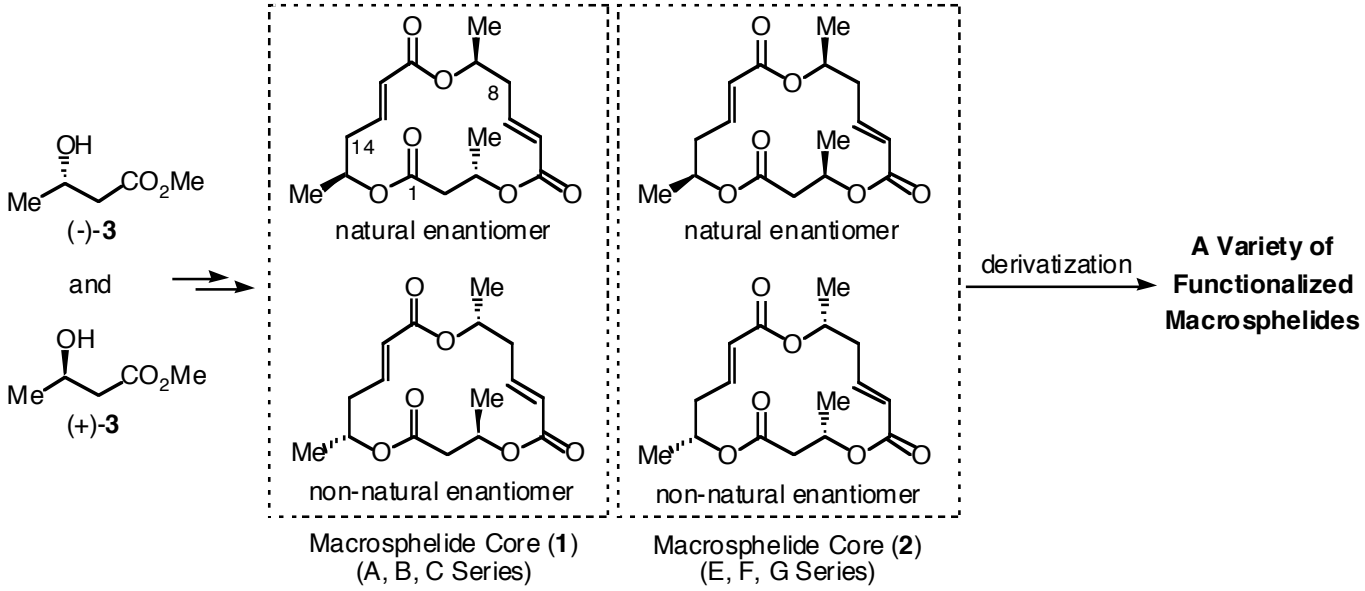
OUR ORIGINAL APPROACHES FOR MACROSPHELIDE SYNTHESIS

In our laboratory, continuous efforts have been devoted to synthetic study of macrosphelides and relating compounds focused on the provision of diversified derivatives for in-depth investigation of the structure activity relationship. Herein, two different approaches developed by us are described; (1) synthesis of simplified core structures of macrosphelides (abbreviated as MS Core) and their divergent derivatization,[28-30,33] and (2) new strategy for construction of the macrosphelide skeleton based on the ring-closing metathesis (RCM).[31,32]

1. MACROSPHELIDE CORE STRATEGY[28-30,33]

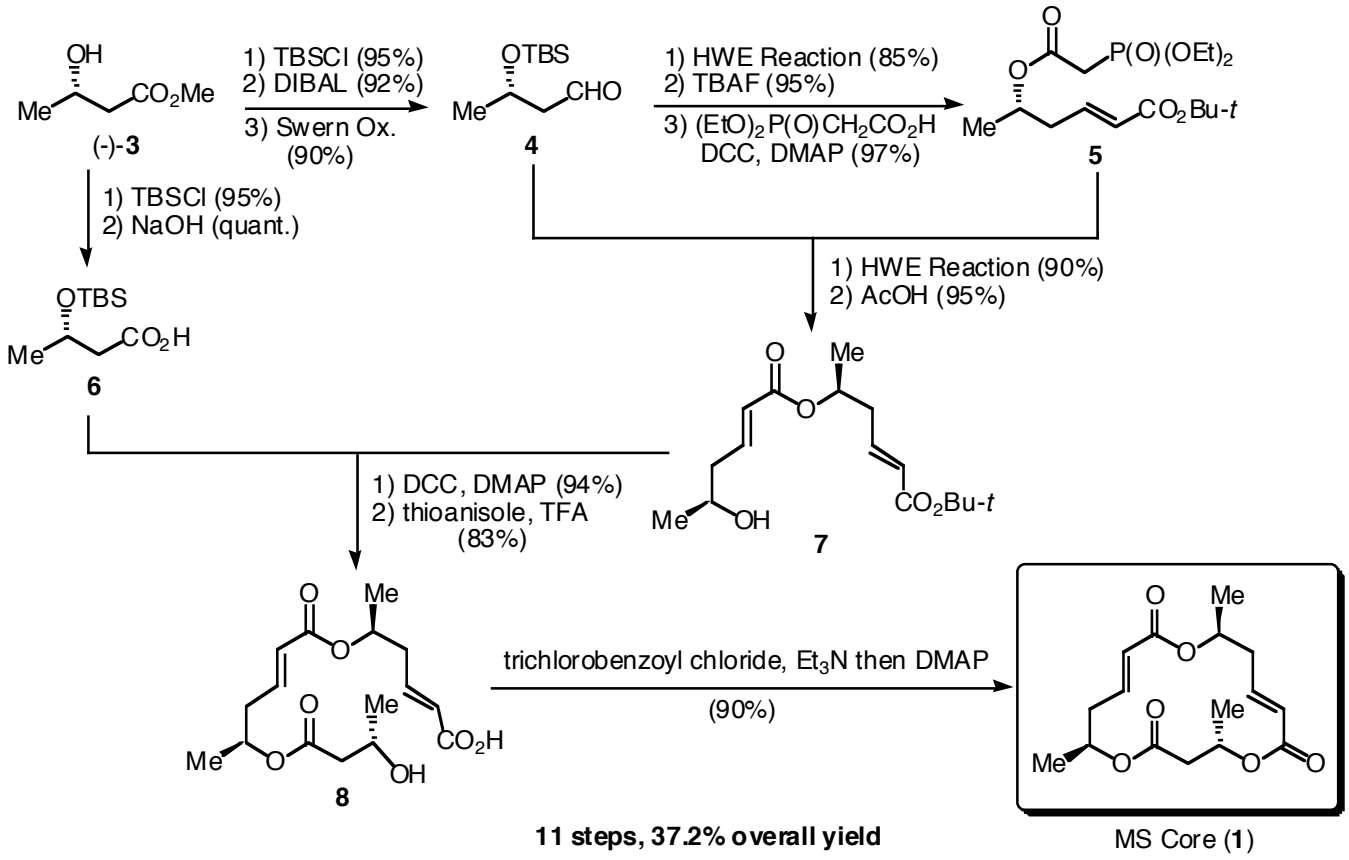
As illustrated in Figure 1, obviously, all of the naturally occurring macrosphelides possess oxygen functional group(s) at their 8- and/or 14-position(s), which are necessarily chiral centers when it is a hydroxyl group. Consequently, omission of these groups gives simplified 16-membered rings containing only three chiral centers, which constitute a common core structure to most of natural macrosphelides. We envisaged that the simplified core compounds (MS Cores) might serve as a potential precursor of a variety of macrosphelide analogues, including natural compounds, through various chemical manipulations (Scheme 4). This MS Core strategy may have several advantages as follows; (1) all three chiral centers in MS Cores (**1** and **2**) can be derived from a sole chiral block, methyl 3-hydroxybutyrate (**3**), (2) availability of both enantiomers of methyl 3-hydroxybutyrate (**3**) makes accessible to two types of MS Core (macrosphelide A – C series and E – G series, which are mutually related as C-3 epimeric isomers), as well as their non-natural enantiomers, (3) the simplified structures of MS Cores compared to those of the natural compounds will allow the synthetic routes to be concise, short-step, and high-yielding, probably making large-scale synthesis possible, (4) various chemical transformations of MS Cores will be

applicable at the 8- and 14-allylic positions and the conjugated enone moieties, providing efficient and divergent approaches for a large number of macrosphelide-like compounds.



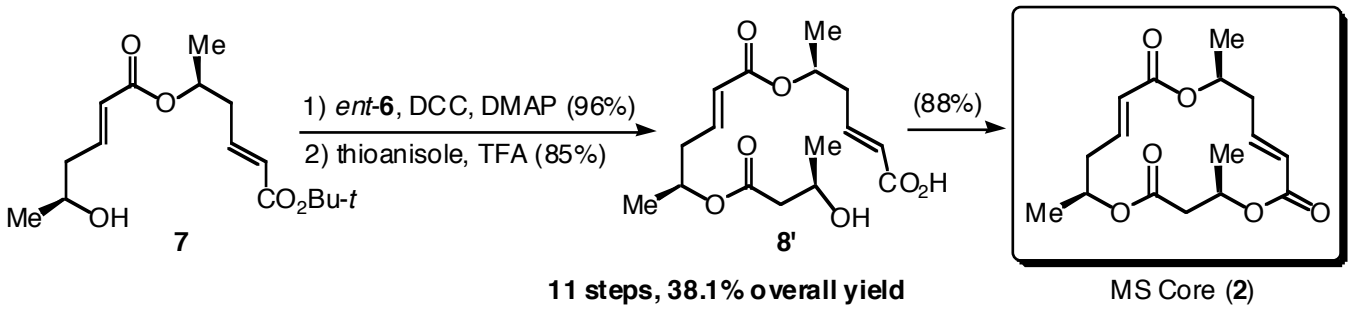
Scheme 4. Macrosphelide Core (MS Core) Strategy for Synthesis of Various Derivatives

The synthetic route to MS Core (**1**) is very efficient and straightforward as summarized in Scheme 5. Simply prepared chiral compounds (**4**, **5** and **6**), starting from methyl (-)-3-hydroxybutyrate (**3**), were



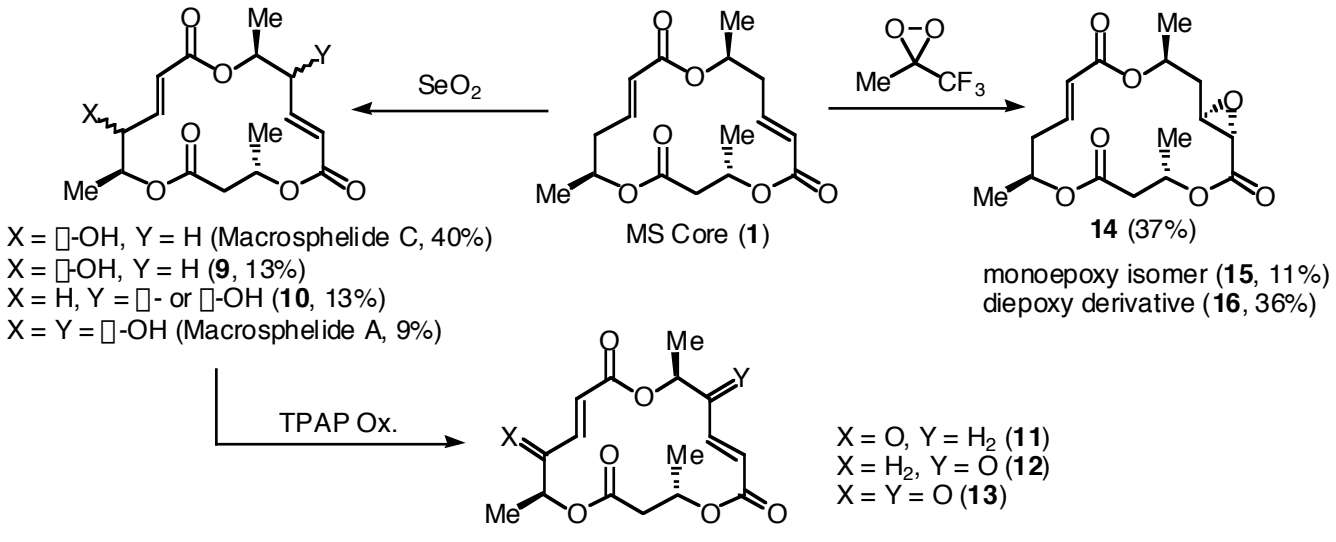
Scheme 5. Synthesis of MS Core (**1**)

utilized as stereogenic sources, and integrated into the seco-acid (**8**) through the Horner-Wadsworth-Emmons (HWE) reaction and the dehydrative condensation mediated by DCC. Final macrocyclization was achieved by employing the Yamaguchi's macrolactonization protocol[34] to accomplish the synthesis of MS Core (**1**) in 11 steps and 37.2% overall yield. Similarly, MS Core (**2**) was synthesized successfully *via* **8'** by replacing the chiral block (**6**) with *ent*-**6**, in 11 steps and 38.1% overall yield (Scheme 6). The non-natural enantiomers (*ent*-**1** and *ent*-**2**) of MS Cores (**1** and **2**) are also available through the same synthetic pathways, which have been established to have sufficient degree of efficiency for providing these four MS Cores rapidly in multi-gram scales.



Scheme 6. Synthesis of MS Core (**2**)

Potential of MS Cores obtained above as a precursor of various macrosphelide analogues has been demonstrated on the basis of several derivatization experiments (Scheme 7). For example, when MS Core (**1**) was exposed to selenium dioxide, allylic oxidation proceeded to afford four hydroxylated derivatives including natural macrosphelides A and C. These products could be further transformed into the corresponding keto derivatives (**11** – **13**) upon treatment with tetra-*n*-propylammonium perruthenate (TPAP). Another oxidative transformation of MS Core (**1**) is exemplified by epoxidation of the enone parts, providing three epoxy derivatives (**14** – **16**) which may be good substrates for new hydxylated macrosphelide derivatives *via* a reductive or hydrolytic oxirane cleavage.

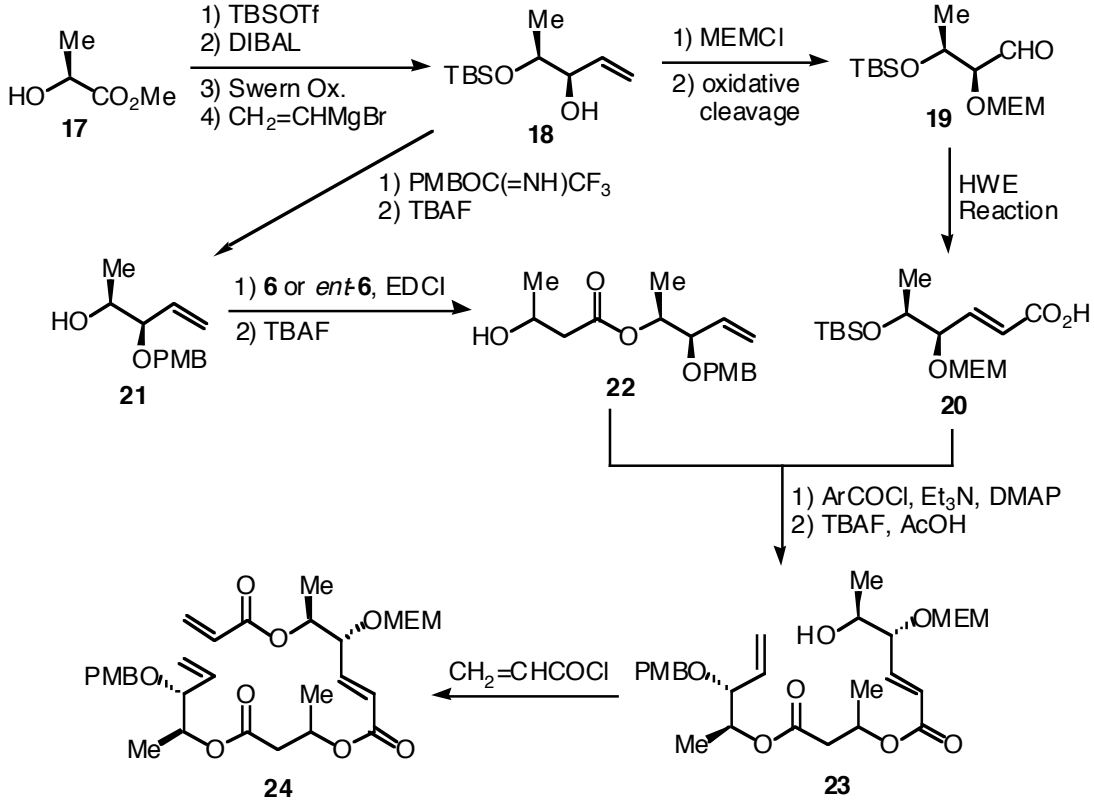


Scheme 7. Oxidative Derivatization of MS Core (**1**)

2. RCM-BASED STRATEGY[31,32]

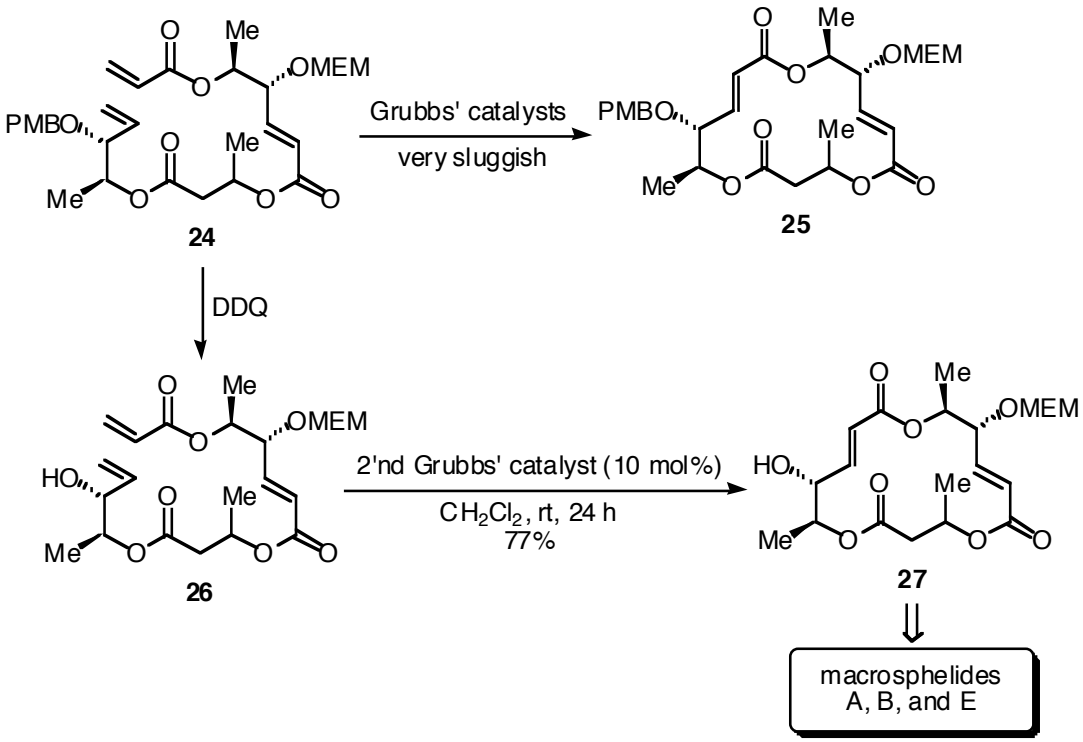
With regard to macrocyclic natural product syntheses, ring-closing metathesis (RCM) has occupied a pivotal position as a means of the large-ring formation owing mainly to the mild reaction conditions and the broad applicability. In the preceding macrosphelide syntheses, however, macrolactonization has been utilized, and RCM has not been applied before our reports concerned with this subject. We have demonstrated that the RCM-based strategy is applicable with high efficiency for a total synthesis of macrosphelides A, B, and E as model target compounds.

Scheme 8 represents the synthetic pathway to the RCM substrates for macrosphelides A, B, and E. Chiral alcohol (**18**), easily prepared from methyl (*S*)-lactate (**17**), was used as a common intermediate to synthesize two chiral subunits (**20**) and (**22**), which were connected by esterification followed by deprotection and acryloylation to afford the RCM substrates (**24**) in satisfactory yields. Investigation of the key cyclization by RCM revealed that the presence of the PMB group considerably affected the reaction rate of the macrocyclization (Scheme 9). When the substrates (**24**) were subjected to the RCM conditions using the second generation Grubbs' catalyst, the cyclization was so sluggish as to need stoichiometric amounts of the catalyst for practical yields of **25** even in refluxing 1,2-dichloroethane for 5 days. On the other hand, removal of the PMB group (in the case of the substrates **26**) significantly improved the cyclization efficiency (10 mol% catalyst, room temperature, 24 h), probably due to the steric factor, to give the products (**27**) in good yields. Obviously these compounds were useful precursors of natural macrosphelides A, B, and E. Thus, RCM-based construction of the macrosphelide skeletons has



Scheme 8. Synthesis of the RCM Substrates

been accomplished, and high functional group compatibility of RCM may be of great advantage to the future syntheses of highly functionalized macrosphelide-like compounds.



Scheme 9. Total Synthesis of Macrosphelides A, B, and E Based on the RCM Strategy

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