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PREPARATION AND DERIVATIZATION OF THE CORE COMPOUND OF MACROSPHELIDE E-G SERIES

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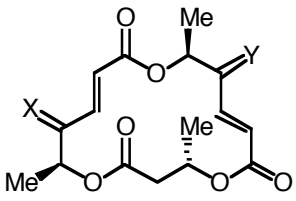
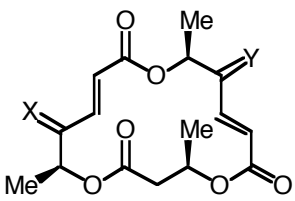
Abstract – The macrosphelide core (**2**) possessing a skeleton of macrosphelide E-G series was newly prepared, and its oxidative derivatization was investigated. The compound (**2**) was found to be less reactive to oxidations compared to the epimeric core (**1**), and it was suggested that there is a considerable difference among their geometry-optimized conformations, which affected the reactivity.

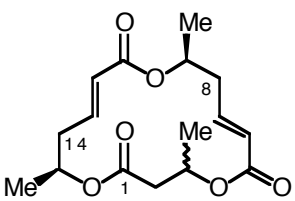
As part of a research program directed toward the syntheses of macrosphelides and the analogues, we have already reported a concise synthesis of the macrosphelide core (**1**) and its oxidative derivatization to give various macrosphelide derivatives.[1] This core structure possesses a skeleton of macrosphelide A-C series, and was assembled from methyl (*S*)-3-hydroxybutyrate as a sole chiral material. On the other hand, macrosphelides E, F, G, which were isolated from a strain of *Periconia byssoides* separated from the sea hare *Aplysia kurodai*,[2] consist of an epimeric skeleton of macrosphelide A-C series on C3 methyl group, and oxygen appendages. The structural elucidation of these natural products has been carried out by Numata's group on the basis of spectroscopic analyses and chemical transformations (Figure 1).[2,3]



Macrosphelide
A : X = Y = β-OH, α-H
B : X = O, Y = β-OH, α-H
C : X = β-OH, α-H, Y = H_2



Macrosphelide
E : X = Y = β-OH, α-H
F : X = β-OH, α-H, Y = H_2
G : X = H_2, Y = β-OH, α-H



Macrosphelide Core
3-β-Me (**1**)
3-α-Me (**2**)

Figure 1

As well as macrosphelides A-C,[4] macrosphelides E-G have also been reported to inhibit the adhesion of human-leukemia HL-60 cells to HUVEC,[3] and consequently the synthetic studies of these molecules have been performed by several groups.[5] As a new access to these bioactive macrosphelide series, we undertook the preparation of another macrosphelide core (**2**) and the subsequent derivatization. Since all three chiral centers of the macrosphelide core (**1**) originated from (*S*)-3-hydroxybutyrate,[1a] both enantiomers of which are commercially available, replacement of one chiral block to its (*R*)-enantiomer should lead to the macrosphelide core (**2**) as shown in Figure 2. In this paper, we describe the synthesis of the macrosphelide core (**2**) and the examination of the reactivity of **2** toward oxidative conditions.

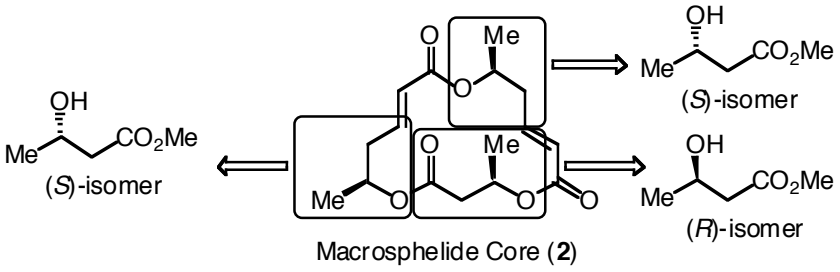
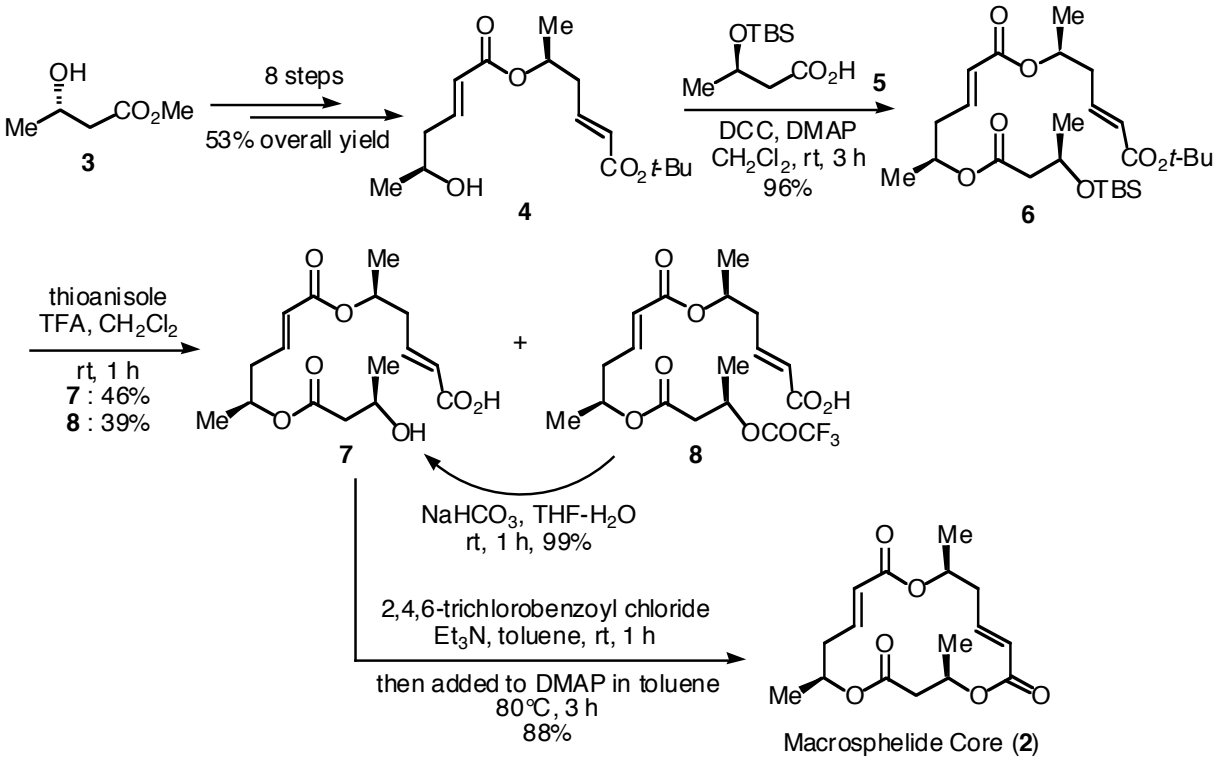


Figure 2

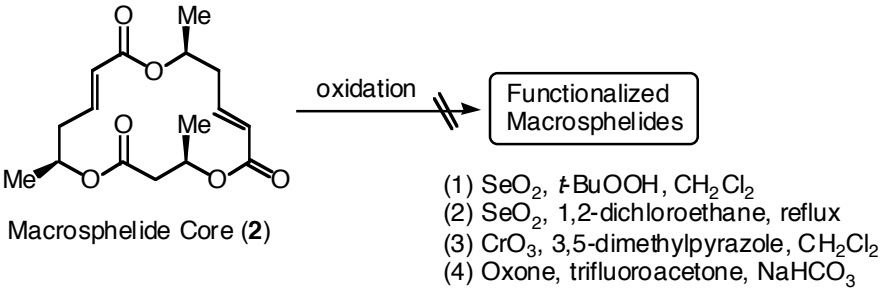
According to the previously reported procedure,[1a] diester (**4**) was synthesized from (*S*)-3-hydroxybutyrate (**3**) in 8 steps and a 53% overall yield. The third chiral center was introduced by condensation with the chiral carboxylic acid (**5**), derived from (*R*)-3-hydroxybutyrate, to afford the triester (**6**) in a high yield. Removal of two protecting groups in **6** could be achieved under a thioanisole-TFA condition to give a required hydroxy acid (**7**) concomitant with a considerable amount of a corresponding trifluoroacetate (**8**).



Scheme 1. Synthesis of the Macrosphelide Core (**2**)

Fortunately, the trifluoroacetate (**8**) could be reconverted into **7** by a mild alkaline saponification in an almost quantitative yield. Macrolactonization of the hydroxy acid (**7**) proceeded with a high efficiency using Yamaguchi's protocol[6] to accomplish the synthesis of the target macrosphelide core (**2**) (Scheme 1).[7] In addition, unnatural enantiomer of (**2**) was also synthesized according to the same procedure.[8]

To our regret, it was found that the behavior of the macrosphelide core (**2**) to oxidative conditions was quite different from that of the macrosphelide core (**1**).[1b] Although four different oxidative conditions were examined, the functionalizations of **2** were all unsuccessful as shown in Scheme 2. In each case the starting material was recovered completely, except for the condition (2) in which a trace amount of unidentified products were formed after 4 days.



Scheme 2. An Attempt for Oxidative Functionalization of the Macrosphelide Core (**2**)

To explore this exceptional inactivity of **2** against the oxidation, MO calculations were performed using the PM3 procedure with the standard parameters[9] implemented in MOPAC program[10] for the purpose of conformational analysis of **2**. The most stable conformation of **2** was calculated as shown in Figure 3.[11] In this conformer, two features are observed, (1) both of the two olefinic planes are almost perpendicular to the plane formed by the macro-ring, and (2) two conjugated enone parts (C5-C7 and C11-C13) are arranged facing each other in a parallel way. The first fact clearly indicates that one side ("inner faces" to the macrocycle) of each olefinic part is congested, which prevented an approach of the reagents, although the "outer faces" would be able to participate in the reaction. Concerning the second, the interplanar separation between the C6-C7 double bond and C11 carbonyl is *ca.* 3.5Å, relating to theoretical numbers calculated for the parallel π-π stacking interactions of aromatic rings.[12] In the case of the macrosphelide core (**1**), such interactions were impossible because the two planes of the olefinic parts were vertical in the X-Ray Structure,[13] consequently the two olefins would have the independent nature. Thus, we presumed that these differences would be partly responsible for the lower reactivity of the core (**2**) compared to **1**, probably because the donor-accepter interaction of π-electrons would reduce the electron

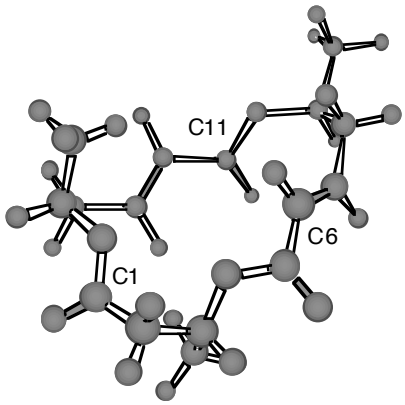


Figure 3. The Minimum Energy Conformation of the Macrosphelide Core (**2**) Determined by PM3 Calculation (Chem3D output)

density of the olefinic parts of **2**.

In this paper, we have described a new synthesis of the macrosphelide core (**2**) and its enantiomer as a potential precursor for macrosphelide E-G series and the analogues. Although the oxidation of **2** was found to be very sluggish compared to the case of the macrosphelide core (**1**), this finding might be explained by the conformational analyses based on the computational and X-Ray studies. Comparison of the conformation and the reactivity of these core structures revealed a unique character of 16-membered cyclic macrosphelides, suggesting an alterability of their interactive fashion to biomolecules depending upon a slight change of the structures.

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7. Physical and spectral data of the macrosphelide core (**2**): yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$): □ 6.93 (1H, dt, *J*=15.5, 7.6 Hz), 6.78 (1H, dt, *J*=15.5, 7.3 Hz), 5.79 (1H, d, *J*=15.5 Hz), 5.78 (1H, d, *J*=15.5 Hz), 5.28-5.20 (1H, m), 5.17-5.09 (1H, m), 5.02-4.99 (1H, m), 2.78-2.65 (2H, m), 2.55-2.43 (2H, m), 2.40-2.32 (2H, m), 1.42 (3H, d, *J*=6.3 Hz), 1.36 (3H, d, *J*=6.4 Hz), 1.26 (3H, d, *J*=6.3 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): □ 169.57, 165.23, 164.94, 143.91, 143.41, 124.48, 123.77, 70.68, 68.70, 67.17, 41.32, 38.21, 37.74, 20.41, 19.89, 19.45; IR (neat): 1727 cm^{-1} (C=O), 1657 cm^{-1} (C=C); EI-MS *m/z* 310 (M^+); EI-HRMS Calcd for $C_{16}H_{22}O_6$: 310.1417, found: 310.1404; $[□]_D^{25}$ +8.37° (*c*=1.00, $CHCl_3$).
8. Optical rotation value of the enantiomer of **2**: $[□]_D^{25}$ –11.44° (*c*=0.86, $CHCl_3$).

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11. The initial geometry for the MO calculations was determined by GMMX calculations; Serena Software, P. O. Box 3076, Bloomington, IN. The structure calculated was refined using the keyword PRECISE.

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13. Details on the X-Ray structure of **1**, see ref. 1. Almost the same conformer was obtained by the geometry-optimization of **1**, using the calculations according to the procedure mentioned above.