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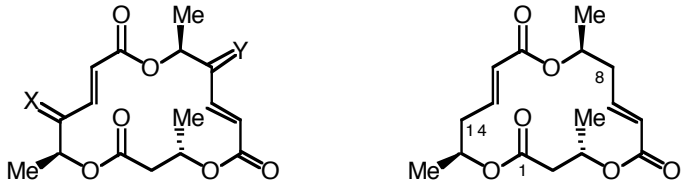
SYNTHESIS OF VARIOUS MACROSPHELIDES BY OXIDATIVE DERIVATIZATION OF THE MACROSPHELIDE CORE

Yuji Matsuya, Takanori Kawaguchi, and Hideo Nemoto*

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-0194, Japan
E-mail: nemotoh@ms.toyama-mpu.ac.jp

Abstract – The macrosphelide core (**4**), simple 16-membered trilactone, was subjected to several oxidative conditions to produce various natural macrosphelide analogues, including macrosphelides A and C. This approach provided a new access to diverse macrosphelides for a study on their structure-activity relationships.

Macrosphelides A-L are a family of 16-membered macrolides whose characteristic structure and potent cell-cell adhesion inhibitory activity have attracted a number of chemists and biologists.[1,2] These natural products were isolated from *Macrosphaeropsis* sp. FO-5050 and *Periconia byssoides*, and reported to inhibit adhesion of human leukemia HL-60 cells to human-umbilical-vein endothelial cells with a high selectivity.[1] As part of our ongoing study on the structure-activity relationships of macrosphelides, we have previously reported a concise and efficient synthesis of the core structure (**4**) of macrosphelide A-C (**1**-**3**),[2] which contains no oxygen-functionality on its 8- and 14-positions compared to the natural form (Figure 1).



Macrosphelide
A (**1**) : X = Y = α-OH, β-H
B (**2**) : X = O, Y = α-OH, β-H
C (**3**) : X = α-OH, β-H, Y = H_2

Macrosphelide Core (**4**)

Figure 1

In this communication, we disclose preliminary results of an oxidative derivatization of the macrosphelide core (**4**) for divergent syntheses of various macrosphelide derivatives including natural

compounds.

Our first attempt was an allylic oxidation of the macrosphelide core (**4**) since most of natural macrosphelides possess oxygen functions on the 8- and/or 14-position. The Chem3D output of the X-Ray analysis of **4** is shown in Figure 2.[3] This suggested that the β-face of the allylic plane containing C8 is completely shielded by a part of the macro-ring, but that containing C14 had no such hindrance. Thus it was expected that the 14-position would be more susceptible to allylic oxidation.

After some experiments,[4] it was found that the oxidation of allylic positions proceeded in moderate yields using selenium dioxide in refluxing 1,2-dichloroethane (DCE), as shown in Scheme 1. The formation of monohydroxy and dihydroxy derivatives was observed with a trace amount of unidentified products, and separation and purification of these products could be carried out using chromatography and recrystalization techniques.

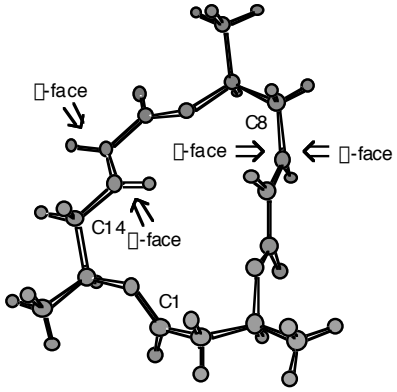
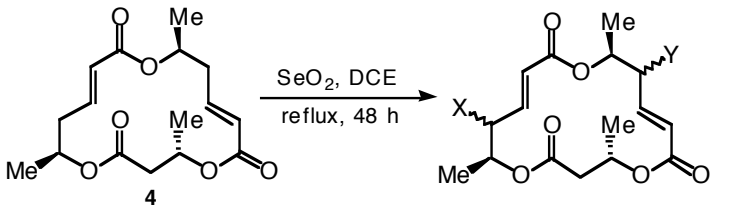


Figure 2. X-Ray Structure of Macrosphelide Core (**4**)



X = α-OH, Y = H (**3**, Macrosphelide C, 40%)
X = β-OH, Y = H (**5**, 13%)
X = H, Y = α- or β-OH (**6**, 13%)
X = Y = α-OH (**1**, Macrosphelide A, 9%)

Scheme 1. Allylic Oxidation of the Macrosphelide Core (**4**)

The major product was identified as macrosphelide C (**3**, 40% yield), the spectral data of which were in good agreement with authentic data.[1c] The structures of the other two monohydroxy isomers (**5** and **6**, 13% yield, respectively) were determined as follows. The product (**5**) was found to be a 14-β-epimer of the macrosphelide C (**3**) based on the fact that the 14-carbonyl derivative prepared by TPAP oxidation of **3** was identical with that derived from **5** under the same oxidation condition. On the other hand, the product (**6**) yielded another carbonyl isomer, probably 8-carbonyl derivative, implying **6** is 8-hydroxylated product. Although the stereostructure of **6** has not been determined yet, we presume that the product would have 8β-hydroxyl group on the basis of the conformation of **4**. The most polar product was confirmed to be macrosphelide A (**1**, 9% yield) by comparing the spectra with those reported.[5] These results clearly show a predominance of the 14-position and β-face of the 8-position to the selenium dioxide oxidation, as expected from the X-Ray structure of **4**.

Next, epoxidation of the olefinic parts of the macrosphelide core (**4**) was investigated. Although the epoxy derivatives of the macrosphelides have never been isolated from natural sources, the biological behavior

of these artificial derivatives is of great interest. Some reaction conditions were briefly explored, and the results are summarized in Table 1. *t*-Butyl hydroperoxide in the presence of a base, *m*CPBA, and sodium perborate were not effective for the reaction (Entries 1-3). When dimethyldioxirane was used as a reagent,[6] our desired reaction proceeded slowly to give two monoepoxy derivatives (**7** and **8**) in 24% yield (Entry 4). However, it was found that the reaction rate was greatly improved by employing methyl(trifluoromethyl)dioxirane,[7] affording three epoxides (**7**, **8**, and **9**) in 84% yield (Entry 5).

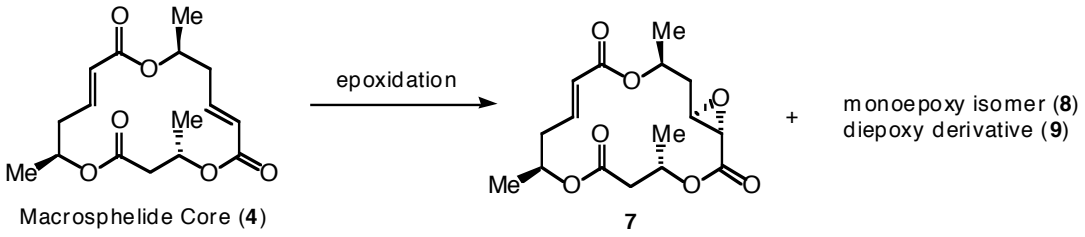
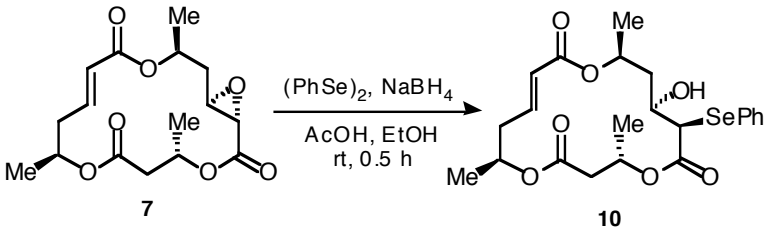


Table 1. Epoxidation of the Macrosphelide Core (**4**)

Entry	Reagent	Solvent	Condition	Yield
1	*t*-BuOOH, Triton B	benzene	rt, 4 d	0%
2	*m*CPBA	CH_2Cl_2	rt, 2 h	0%
3	$NaBO_3$	THF-H_2O	rt, 4 d	0%
4	Oxone, $NaHCO_3$	acetone-H_2O	0°C - rt, 3 d	24% (**7**+**8**), recovery 44%
5	Oxone, $NaHCO_3$	trifluoroacetone-H_2O	0°C - rt, 16 h	37% (**7**), 11% (**8**), 36% (**9**)

The structure of the epoxide (**7**) could be unambiguously determined by X-Ray analysis of the corresponding selenide (**10**) (Figure 3),[8] prepared by the treatment of **7** with diphenyldiselenide and sodium borohydride (Scheme 2).[9] The structure obviously arose from the reaction on the β-face of the C6-C7 plane of **4**. Assuming the β-attack of the oxidant to be blocked, another monoepoxy product (**8**) would be a regioisomer of **7**. However, the stereochemistry of **8**, as well as the diepoxy product (**9**), remains unclear at present, whose determination is currently under investigation.



Scheme 2

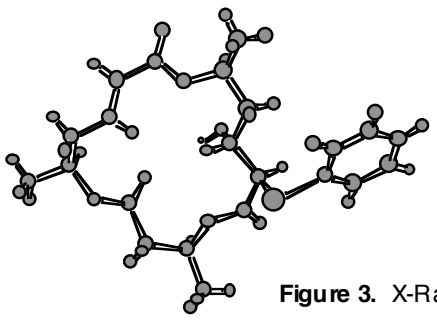


Figure 3. X-Ray Structure of **10**

In summary, we have demonstrated a new efficient access to the macrosphelide family using oxidative

derivatization of the macrosphelide core (**4**). By this approach, we accomplished the synthesis of several non-natural macrosphelide derivatives, as well as macrosphelides A and C. In addition, their non-natural enantiomers could be prepared taking advantage of the availability of both enantiomers of **4**.[2] Biological activities of these new macrosphelide derivatives are now under examination, and will be reported in due course.

ACKNOWLEDGMENTS

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3. Detailed data on the X-Ray analysis, see ref. 2.
4. Refluxing in 1,4-dioxane, which is widely used in selenium dioxide oxidation, gave rise to a complex mixture of many products.
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8. The phenylselenide (**10**) was recrystallized from Et_2O-hexane to form a colorless platelet crystal ($C_{22}H_{28}O_7Se$) which has approximate dimensions of 0.20 x 0.15 x 0.10 mm (a primitive monoclinic cell, space group $P2_1$ with unit cell parameters: a = 19.0463(3) *Å*, b = 12.9188(2) *Å*, c = 19.1534(3) *Å*, □ =

105.8352(6)°, V = 4533.9(1) $Å^3$, Z = 8, D_{calc} = 1.42 g/cm^3). The data were collected on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Cu-Kα radiation (λ = 1.54178 $Å$). Of the 53975 reflections which were collected, 8487 were unique (R_{int} = 0.030). The structure was solved by direct methods (SIR97), and full-matrix least-squares refinement was based on 15894 observed reflections (I > -3.00σ(I), 2θ < 136.37) and 1094 variable parameters (R = 0.047, R_w = 0.060, $R1$ = 0.027 for I > 2.0σ(I) data).

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