HETEROCYCLES, Vol. 59, No. 2, 2003, pp. 481 - 484, Received, 17th September, 2002

A NEW EFFICIENT SYNTHESIS OF BOTH ENANTIOMERS OF MACROSPHELIDE CORE: A POTENTIAL PRECURSOR FOR FUNCTIONALIZED MACROSPHELIDES†

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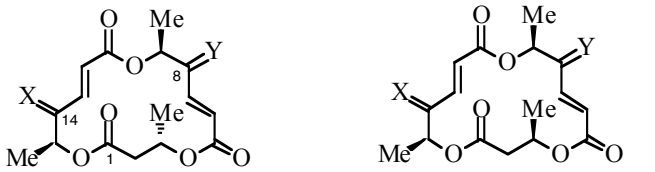
Abstract - The asymmetric synthesis of a macrosphelide core (**1**) and its enantiomer was achieved from (*S*)- or (*R*)-3-hydroxybutyrate in excellent yields. These compounds are potentially useful precursors for the preparation of biologically important macrosphelide analogues.

Recently macrosphelides A-L, isolated from *Microsphaeropsis* sp. FO-5050 and *Periconia byssoides*, have been well recognized as important potential lead compounds for a new drug against cancer due to their strong inhibitory activities on the adhesion of human cells.[1] These natural products possess characteristic 16-membered macrocyclic lactone structures and oxygen-functionalities at their 8 and/or 14 positions (Figure 1).



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

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

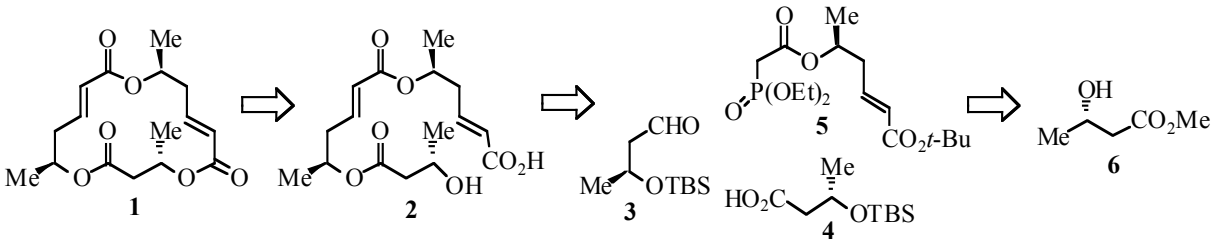
Figure 1. An example of some natural macrosphelides

Because of this remarkable and attractive bioactivity, many studies on the stereostructural elucidation and the asymmetric syntheses of the compounds have been reported by several groups.[1,2] So far, the structures of macrosphelide A-C, E-I, and L have been fully determined, including their stereochemistry, by means of X-Ray crystallography and chemical transformations.[1,2a] The asymmetric total syntheses of macrosphelides A-C and E-H including the pioneering synthesis by Smith III and Ômura have also been

† Dedicated to Professor Yuichi Kanaoka on the occasion of his 75th birthday.

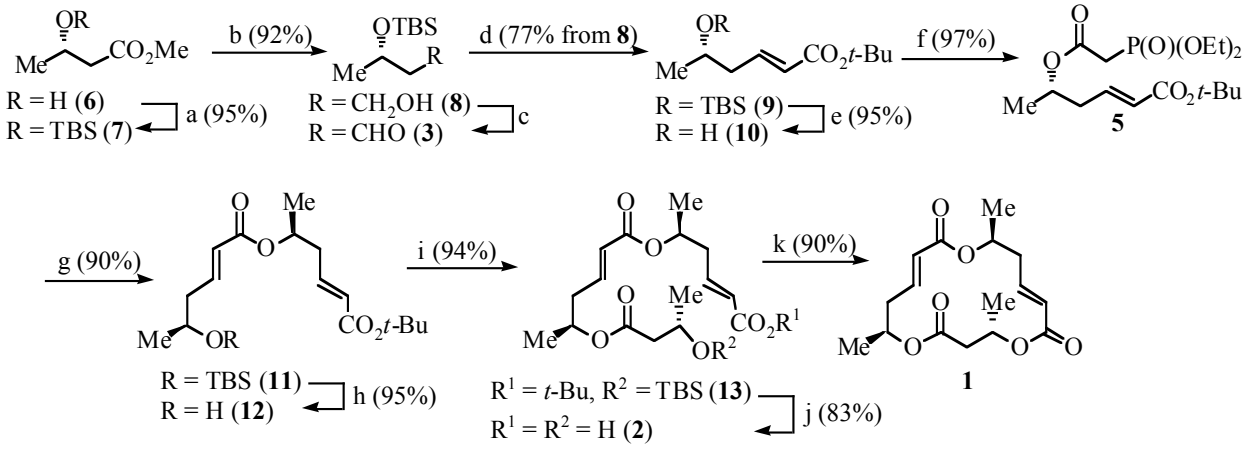
accomplished.[2] While these syntheses presented effective routes to specific macrosphelide derivatives, an approach aiming at more diversity has not yet been reported to our knowledge. For the purpose of medicinal chemistry, the development of a synthetic methodology for preparing various kinds of macrosphelide derivatives including natural and nonnatural ones would be required, so that a thorough research of detailed structure-activity relationships of these molecules can be carried out. In this context, we planned to develop a novel strategy for the divergent synthesis of the macrosphelide family and its analogues.

Thus, we set simple 16-membered trilactone (**1**) as a key precursor for a variety of macrosphelide derivatives. Since most natural macrosphelides have oxygen functions (hydroxyl or carbonyl) at their allylic positions, various oxidation reactions seem to be applicable to the compound, which would bring about the concise syntheses of various oxygenated derivatives including natural compounds. In addition, this macrosphelide core (**1**) appeared to be much more easily accessible compared to oxygen-bearing ones at their 8 and/or 14 positions, since the number of chiral centers could be reduced and the building blocks (**3**, **4**, and **5**) can be derived from inexpensive 3-hydroxybutyrate (**6**), both enantiomers of which are readily available (Scheme 1). Here, we wish to report an efficient synthesis of a simple macrosphelide core (**1**) and its enantiomer.



Scheme 1. Synthetic strategy for macrosphelide core (**1**)

Our synthetic study of the macrosphelide core (**1**) commenced with the protection of a hydroxyl group of commercially available methyl (*S*)-3-hydroxybutyrate (**6**) as a corresponding silyl ether. Ester function was converted to formyl group by successive treatment with DIBAL and Swern condition.[3] Horner-Wadsworth-Emmons reaction using *t*-butyl diethylphosphonoacetate smoothly proceeded to give *trans*-isomer (**9**) exclusively.[4] After desilylation, the resulting alcohol was subjected to dehydrative condensation with diethylphosphonoacetic acid in the presence of DCC and DMAP, to afford the desired intermediate (**5**) in satisfactory overall yields. Horner-Wadsworth-Emmons reaction of the phosphonate (**5**) with the aldehyde (**3**), removal of the TBS group, and esterification with (*S*)-3-silyloxybutyric acid (**4**) prepared by saponification of **7** were successfully performed under standard reaction conditions. Thus, a requisite 16-atom chain and three chiral centers were suitably arranged. Deprotection of the compound (**13**) was carried out using a thioanisole-TFA system[5] to give the hydroxy acid (**2**), which was subjected to Yamaguchi's macrolactonization condition,[6] namely 2,4,6-trichlorobenzoylation followed by slow addition to DMAP solution in toluene under high-dilution. This reaction smoothly proceeded in 90% yield and the structure of the product was confirmed by X-Ray analysis (Figure 2).[7] In this way the synthesis of the target macrosphelide core (**1**) was accomplished in 11steps with a 37.2% overall yield (Scheme 2).[8]



Reagents and conditions: (a) TBSCl, Et_3N, cat. DMAP, CH_2Cl_2, rt, 13 h; (b) DIBAL, CH_2Cl_2, rt, 2 h; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C then 0°C, 1 h; (d) *t*-butyl diethylphosphonoacetate, DBU, LiCl, MeCN, rt, 1 h; (e) TBAF, THF, rt, 6 h; (f) diethylphosphonoacetic acid, DCC, cat. DMAP, CH_2Cl_2, rt, 0.5 h; (g) **3**, DBU, LiCl, MeCN, rt, 0.5 h; (h) AcOH-THF-H_2O (3:1:1), rt, 3 d; (i) **4**, DCC, cat. DMAP, CH_2Cl_2, rt, 3 h; (j) thioanisole, TFA, CH_2Cl_2, rt, 1 h; (k) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, rt, 1 h, then added to DMAP in toluene, 80°C, 2 h.

Scheme 2. Synthetic route to the macrosphelide core (**1**) from methyl (*S*)-3-hydroxybutyrate (**6**)

Of course, the enantiomer of **1** must be synthesized by using (*R*)-3-hydroxybutyrate as a starting chiral source and this transformation was performed in practice. Thus, the construction of a naturally-occurring skeleton of macrosphelide A-D series and its enantiomer were realized with high efficiency. In addition, the macrosphelide E-G series (epimer of A-D series at 3-methyl group) would also come available if (*S*)-3-silyloxybutyric acid (**4**) is replaced with its (*R*)-isomer in the above scheme.

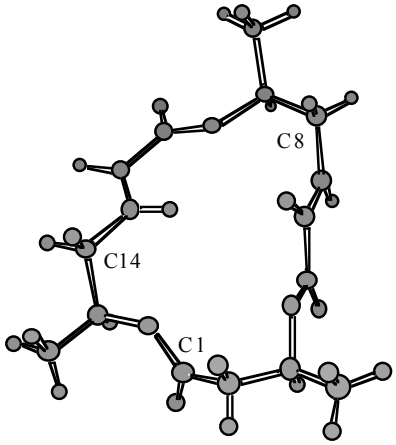


Figure 2. X-Ray structure of macrosphelide core (**1**)

In this communication, we demonstrated a new synthesis of macrosphelide core (**1**) and its enantiomer in high overall yield. We believe that this synthetic approach will present a new access to the macrosphelide family by means of divergent derivatization of **1**. In addition, the enantiomers of natural products can be synthesized taking advantage of the availability of both enantiomers of the chiral block used in the synthesis. In preliminary biological evaluations, it was revealed that macrosphelide core (**1**) itself exhibited an antiviral activity. Currently, oxidative derivatization of **1** and biological activities of new class of macrosphelides including inhibition of cell-cell adhesion, antivirus, and immunosupression are being examined, and will be reported elsewhere.

ACKNOWLEDGMENT

We thank Dr. M. Shiro at Rigaku X-Ray Research Laboratory for generous support with X-Ray crystallographic analysis.

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4. Preparation of the corresponding methyl or ethyl ester using the same condition is described in ref. 3a and 3b. *t*-Butyl ester (**10**) is also reported, see; V. H. Deshpande and B. Rai, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1997, **36B**, 1172.
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7. Macrosphelide core (**1**) was recrystallized from hexane to form a colorless platelet crystal ($C_{16}H_{22}O_6$) which has approximate dimensions of 0.40 x 0.20 x 0.07 mm (a primitive orthorhombic space group $P2_12_12_1$ with unit cell parameters: a = 7.7195(3), b = 10.0492(4), c = 20.8979(8) *Å*, V = 1621.2(1) *Å*^{3}, Z = 4, D_{calc} = 1.27 g/cm^3). The data were collected on a Rigaku RAXIS-RAPID Imaging Plate diffractrometer with graphite monochromated MoKα radiation (λ = 0.71069 *Å*). Of the 19297 reflections which were collected, 2687 were unique (R_{int} = 0.038). The structure was solved by direct methods (SIR97), and the full-matrix least-squares refinement was based on 2685 observed reflections (I > -3.00σ(I)) and 199 variable parameters (R = 0.059, R_w = 0.093, $R1$ = 0.040 for 2135 I > 2.0σ(I) data). The authors have deposited the crystallographic data with the Cambridge Crystallographic Data Centre (deposition No. CCDC-188549). These data can be obtained free of charge on application to CCDC.
8. Satisfactory spectral data for macrosphelide core (**1**) and all intermediates were obtained.