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Concise Syntheses of (+)-Macrosphelides A and B

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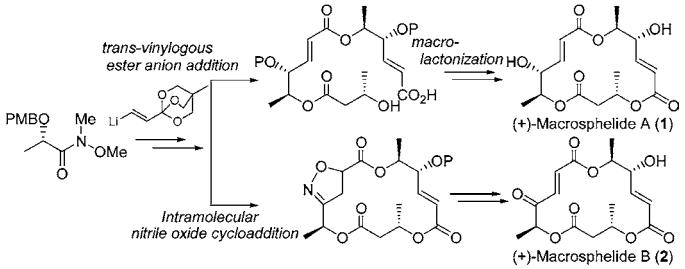
ABSTRACT



Unified and highly convergent total syntheses of (+)-macrosphelides A and B are described. Key features of the syntheses include (1) concise synthesis of the optically active *δ*-hydroxy-*γ*-keto *α*,*β*-unsaturated acid fragment via the direct addition of a *trans*-vinylogous ester anion equivalent to the readily available Weinreb amide and (2) facile construction of the 16-membered macrolide core of the macrosphelide series via an intramolecular nitrile-oxide cycloaddition (INOC).

Macrosphelides, a class of macrolactone polyketides consisting of several unique components, were isolated from the culture broth of the fungus (*Microsphaeropsis* sp. FO-5050) by the Omura group and from the strain *Periconia byssoides*, separated from the sea hare *Aplysia kurodai*, by the Numata group.[1] These 16-membered macrolides, that contain novel structures with three ester linkages, strongly inhibit the adhesion of human leukemia HL-60 cells to human-umbilical-vein endothelial cells (HUVEC) in a dose-dependent fashion.[1a] Moreover, macrosphelide B exhibited potent immunosupressant activity equal to that of rapamycin, and its analogues might therefore serve as powerful new immunomodulators.[2]

Taken together, these attributes have led to considerable interest in macrosphelides as targets for research in organic synthesis. Several groups have reported synthetic studies in this regard,[3−6] although all of the syntheses typically employed the Yamaguchi protocol for macrolactone construction, except for Takahashi's carbonylative macrolactonization[7] and Nemoto's ring-closing metathesis (RCM) strategy.[8] However, despite these synthetic efforts, some

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(3) 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.

(4) (a) Kobayashi, Y.; Kumar, B. G.; Kurachi, T. *Tetrahedron Lett.* **2000**, *41*, 1559−1563. (b) Kobayashi, Y.; Kumar, G. B.; Kurachi, T.; Acharya, H. P.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **2001**, *66*, 2011−2018. (c) Kobayashi, Y.; Acharya, H. P. *Tetrahedron Lett.* **2001**, *42*, 2817−2820. (d) Kobayashi, Y.; Wang, Y.-G. *Tetrahedron Lett.* **2002**, *43*, 4381−4384.

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(6) Sharma, G. V. M.; Mouli, C. C. *Tetrahedron Lett.* **2002**, *43*, 9159−9161.

(7) (a) Takahashi, T.; Kusaka, S.-i.; Doi, T.; Sunazuka, T.; Omura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5230−5234. (b) Kusaka, S.-I.; Dohi, S.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **2003**, *44*, 8857−8859.

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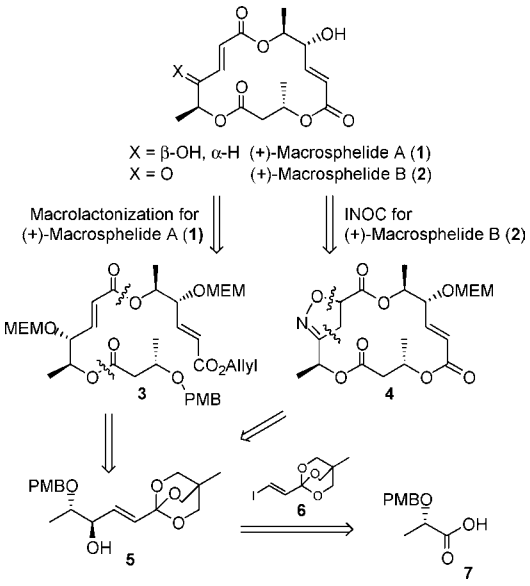
problems such as racemization, or lack of substrate generality, during ring closure, still limit the utility of these pathways. Thus, the synthetically challenging structures of these macrolides, combined with their interesting biological activities, prompted us to explore a new synthetic route for the macrosphelide series. Herein, we report total syntheses of (+)-macrosphelides A and B that take advantage of the powerful *trans*-vinylogous ester anion chemistry[9] that we have developed for monomeric δ-hydroxy-γ-keto α,β-unsaturated acid fragment assembly.

In considering the options for devising an efficient and practical synthetic plan, we sought a concise and convenient method for accessing the common key intermediate **5**, which could be readily transformed into macrosphelide A (**1**) by the coupling of each fragment and macrolactonization (Scheme 1). For macrosphelide B, we also contemplated

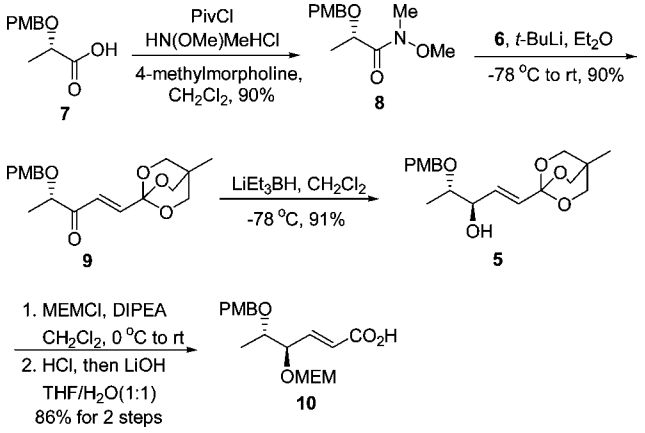
Scheme 1. Retrosynthesis of (+)-Macrosphelides A (**1**) and B (**2**)



options for using an intramolecular nitrile-oxide cycloaddition (INOC)[10] for effecting macrocyclic ring closure. It was envisioned that macrosphelide B (**2**) would finally be obtained by reductive N−O cleavage of the isoxazoline **4** and dehydration of the resulting β-hydroxy ketone intermediate. The isoxazoline **4** would be generated from the common key fragment **5** via a combination of iterative esterifications and subsequent INOC. On the basis of our methodology[9] of the direct addition of a *trans*-vinylogous OBO (2,6,7-trioxabicyclo[2,2,2]octane) ester anions to a variety of carbonyl electrophiles, the requisite allylic alcohol **5** was considered accessible from a coupling of the vinylogous ester equivalent **6** with the PMB-protected Weinreb amide **8**, followed by a chelation-controlled, highly diastereoselective reduction of the α-hydroxy ketone. Together, these two strategies would provide significant synthetic divergence for a variety of molecules of the macrosphelide series.

Our synthesis commenced with the preparation of the γ-alkoxy α,β-unsaturated acid **10** as a common key intermediate, as illustrated in Scheme 2. The PMB-protected (*S*)-

Scheme 2. Synthesis of Acid **10**



(−)-lactic acid **7**[11] was initially converted to the corresponding Weinreb amide **8**. The lithium anion of **6**, generated by the standard procedure,[9] was reacted with the Weinreb amide **8** to afford the three-carbon homologated enone **9**, in an excellent yield, with latent ester functionality. With the enone **9** in hand, the chelation-controlled carbonyl reduction was attempted. To our delight, the addition of Super-H to **9** at −78 °C in a mixture of CH_2Cl_2/THF (12:1) furnished the allylic alcohol **5** as a single detectable isomer.[12,13] MEM protection of **5**, followed by hydrolysis, afforded the desired acid **10**. The simplicity of each step, the higher overall yield, and the high enantiomeric purity in the synthesis of this monomeric building block attest to the efficiency and conciseness of our methodology.

Completion of our macrosphelide A synthesis proceeded in a straightforward manner (Scheme 3). Protection of acid **10** with allyl bromide, followed by PMB deprotection under buffered conditions, afforded the homoallylic alcohol **11**. Coupling of **10** and **11** by esterification employing the Keck procedure[14] and PMB deprotection provided the dimeric ester **12** in an excellent yield. With iterative esterifications of the

(8) (a) Matsuya, Y.; Kawaguchi, T.; Nemoto, H. *Org. Lett.* **2003**, *5*, 2939−2941. (b) Kawaguchi, T.; Funamori, N.; Matsuya, Y.; Nemoto, H. *J. Org. Chem.* **2004**, *69*, 505−509.

(9) (a) Suh, Y.-G.; Seo, S.-Y.; Jung, J.-K.; Park, O.-H.; Jeon, L.-O. *Tetrahedron Lett.* **2001**, *42*, 1691−1694. (b) Suh, Y.-G.; Jung, J.-K.; Seo, S.-Y.; Min, K.-h.; Shin, D.-Y.; Lee, Y.-S.; Kim, S.-H.; Park, H.-J. *J. Org. Chem.* **2002**, *67*, 4127−4137.

(10) For the previous applications of INOC for macrocyclization in natural compound synthesis, see: (a) Asaoka, M.; Abe, M.; Mukata, T.; Takei, H. *Chem. Lett.* **1982**, 215−218. (b) Kim, D.; Lee, J.; Shim, P. J.; Doi, T.; Kim, S. *J. Org. Chem.* **2002**, *67*, 772−781.

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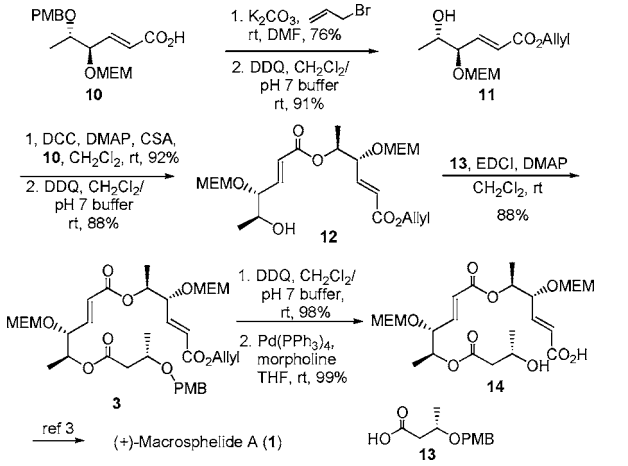
(13) LAH and LiI in the ethereal solvent gave low selectivity in a 1.5:1−3:1 ratio. See: Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355−2358.

(14) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394−2395.

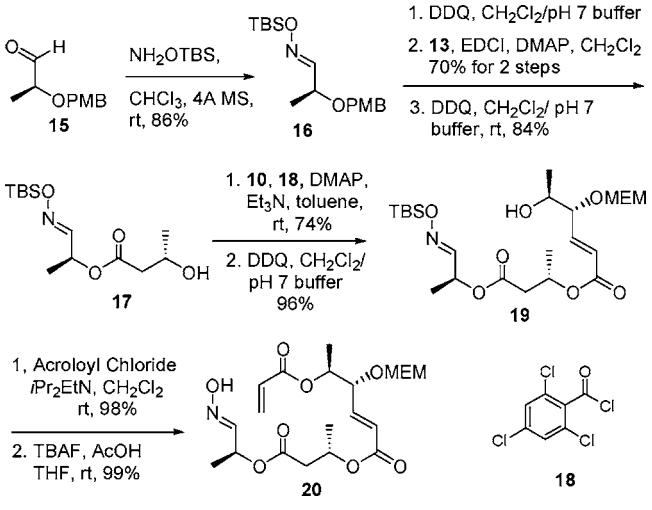
Scheme 3. Synthesis of (+)-Macrosphelide A (**1**)



PMB-protected 3-hydroxy butyric acid **13**,[15] we were able to obtain the fully protected trimeric ester **3**. Finally, PMB and allyl deprotection of **3** gave the known seco acid **14**, of which conversion to macrosphelide A (**1**) was reported.[3] The structure of **14** was confirmed by comparison of its spectral data with those of the authentic sample (optical rotation, ^{1}H NMR, ^{13}C NMR, IR, HRMS).

After successful completion of the synthesis of macrosphelide A, our interest turned to the synthesis of macrosphelide B via intramolecular nitrile-oxide cycloaddition. Our route commenced with the preparation of aldoxime **20**, as outlined in Scheme 4. Dehydrative addition of the TBS-protected hydroxylamine to the known aldehyde **15**[16] gave a separable *E*/*Z* mixture of aldoximes, which was directly subjected to the next step without separation. PMB deprotection of the aldoxime ether with DDQ, esterification of the resulting alcohol from **16** with the acid **13**, and PMB removal provided the hydroxy ester **17**. Coupling of the ester **17** with the acid **10**, under the Yamaguchi conditions,[17] and then DDQ treatment under neutral conditions yielded the

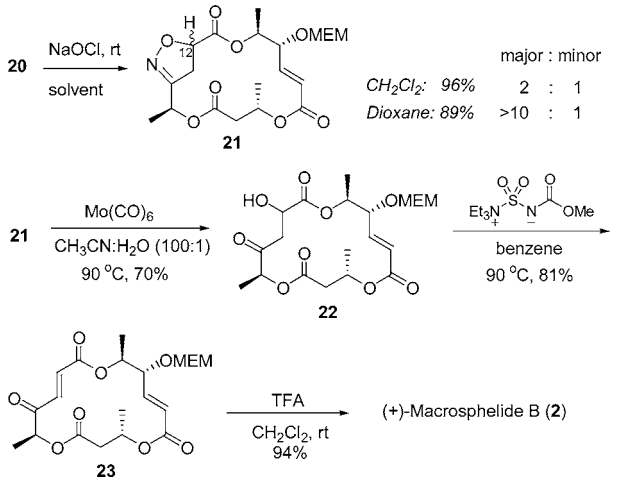
Scheme 4. Synthesis of Aldoxime **20**



homoallylic alcohol **19** in a high yield. Finally, the alcohol **19** was acylated with acryloyl chloride, and the silyl ether was deprotected by TBAF/AcOH in a near quantitative yield. With the key precursor **20** in hand, we attempted the projected INOC reaction.

The successful macrocyclization and completion of the synthesis of macrosphelide B (**2**) are depicted in Scheme 5.

Scheme 5. Completion of (+)-Macrosphelide B (**2**) Synthesis



The initial INOC reaction of the aldoxime acrylate **20** in CH_2Cl_2 proceeded smoothly, in a regioselective manner, and in high yield, affording a 2:1 diastereomeric mixture of the desired isoxazolines **21** in 96% yield.[18] Further optimization studies revealed that dioxane was highly superior to other solvents in terms of diastereoselectivity. Cycloaddition in dioxane produced mainly one diastereomer[19] in >10:1 ratio with 89% yield, although the stereochemical outcome was not important at this stage.[20] Notably, the high yield, operational simplicity, and functional group tolerance of this INOC ring closure potentially make this strategy attractive for stereoselective synthesis of other macrosphelide family members. For completion of our total synthesis, the remaining tasks were chemoselective N−O bond cleavage of the isoxazoline **21** and dehydration of the resulting β-hydroxy ketone. After extensive screening of various methods for the facile N−O bond reduction, $Mo(CO)_6$ in wet CH_3CN was found to be the most effective.[21] Thus, the selective reduction

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(17) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993. Esterification under other reaction conditions such as EDCI−DMAP, DCC−DMAP, or DCC−DMAP−CSA was not successful.

(18) Undesired regioisomer was not observed. This regiochemical outcome is consistent with that of Asaoka's previous studies. Refer to ref 10a.

(19) On the basis of extensive spectroscopic studies on the isoxazoline **21**, the configuration of isoxazoline **21** is likely to be 12*R* (12H-α), which is readily separable by flash column chromatography.

(20) Minor isomer of isoxazoline **21** was resistant to both reductive N−O bond cleavage and dehydration.

of the N−O bond, followed by dehydration of the resulting β-hydroxy ketone **22**, with Burgess' reagent[22] afforded the known MEM-protected macrosphelide B (**23**). Finally, removal of the MEM group with TFA in CH_2Cl_2 afforded (+)-macrosphelide B (**2**) in 94% yield, which exhibited ^{1}H NMR, ^{13}C NMR, optical rotation, HRMS, and IR spectral data identical to those of the authentic natural product.[3,8]

In summary, we have achieved the formal synthesis of (+)-macrosphelide A (12 steps, 30% overall yield, 90% average yield) and the total synthesis of (+)-macrosphelide B (13 steps, 20% overall yield, 88% average yield). The key features of these synthetic routes involve the concise and efficient synthesis of the crucial monomeric fragment by a direct addition of a *trans*-vinylogous ester anion to a Weinreb amide and the intramolecular nitrile oxide cycloaddition for the final macrolactonization, which proved to be highly efficient and practical for the macrosphelide syntheses. Further efforts employing this strategy, including the synthesis of other macrosphelide series, are progressing well.

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

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(22) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem*. **1973**, *38*, 26−31.