Synthesis of a *sec*-Precursor and Analogues of Macrolactin A

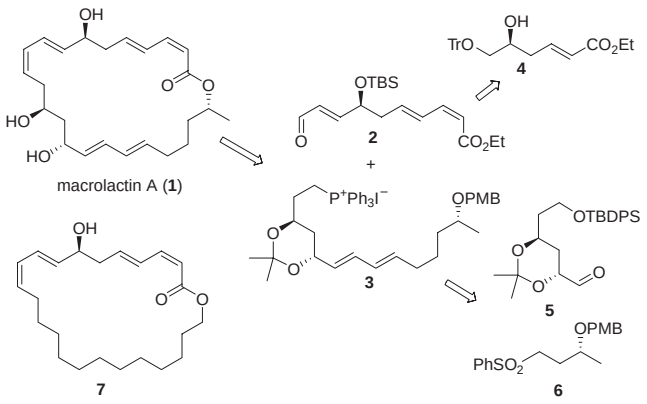
Xiangshu Xiao, Shukun Li, Xuebin Yan, Xuejun Liu, Rui Xu, and Donglu Bai*
Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 201203, P. R. China

(Received April 14, 2005; CL-050511)

A highly convergent and efficient route to *sec*-precursor **26** of macrolactin A has been developed. In the synthesis, Wittig and Horner–Emmons reactions were utilized to construct the conjugated dienes and control the right configurations of *E*,*Z*- and *E*,*E*-dienes. The segment **2** and **3** were prepared from the known compound **4** and **15** respectively. The coupling of segments **2** and **3** proceeded in the presence of NaHMDS. The analogues **7** and **32** were synthesized by the same strategy.

Macrolactin A (**1**) is the parent aglycone of a novel family of polyene 24-membered macrolides isolated from a deep-sea bacterium.[1] It was showed to inhibit B_{16}-F_{10} murine melanoma cancer cells and mammalian HSV-I and HSV-II. More significantly, it was found to inhibit the HIV replication in T-lymphoblasts[1] and to be a neuronal cell protecting substance against the glutamate toxicity.[2] The significant biological activities with the unique structure prompted many synthetic organic chemists to investigate its total synthesis.[3,4] Three total syntheses by Smith, Carreira, and Marino groups have been reported independently.[5] Herein, we report our stereoselective synthesis of the *sec*-precursor **26** of macrolactin A, which features the judicious use of the Wittig and Horner–Emmons reactions to elaborate all three stereofined 1,3-diene units in the target molecule. Furthermore, the same strategy was used to synthesize the macrolide analogues of macrolactin A, **7** and **32**.

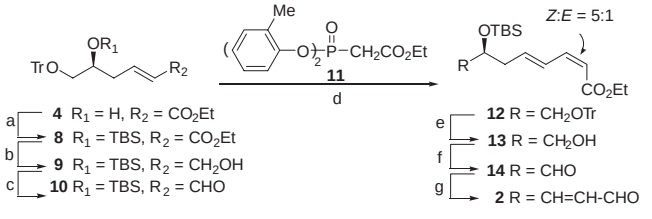
Our strategy for the asymmetric synthesis of **1** is based on the Wittig coupling of the advanced segments **2** and **3** (Scheme 1). Macrolactonization of *sec*-precursor **26** was speculated to provide the targeted 24-membered ring. Retrosynthetic analysis revealed that the Wittig and Horner–Emmons reactions could be feasible to construct the C_1–C_{10} polyene segment **2** from building blocks **4**. C_{11}–C_{24} Segment **3** was further divided into subunits **5** and **6**. They could be linked with each other by the Horner–Emmons reaction of **5** and triethylphosphonocrotonate, followed by an α-alkylation of sulfone stabilized anion from sulfone **6** with allyl bromide **21**.



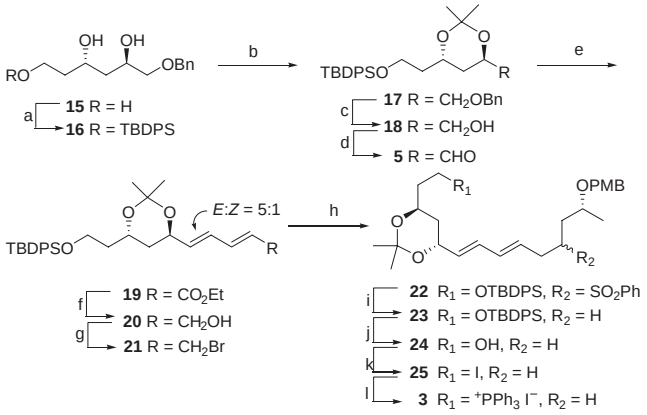
Scheme 1.

The synthesis of C_1–C_{10} segment **2** (Scheme 2) started with the known compound **4**.[4] Protection of the secondary alcohol in **4** as TBS ether furnished ester **8**, which was then reduced with DIBAL-H to allyl alcohol **9** in 91% yield in two steps. The Swern oxidation of **9** gave aldehyde **10** which was converted into the requisite dienoate **12** via the Horner–Emmons reaction with phosphonate **11**[6] as a mixture of isomers (*Z*,*E*:*E*,*E* = 5:1) in 72% overall yield in two steps. Selective hydrolysis of trityl group in **12** with formic acid in ether[7] followed by the Swern oxidation and subsequent the Wittig reaction with formylmethylenetriphenylphosphorane furnished **2** in 60% overall yield in three steps.

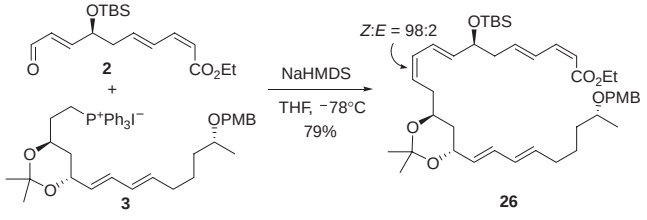
The preparation of C_{11}–C_{24} phosphonium salt **3** (Scheme 3) was accomplished by the Horner–Emmons reaction as well. Conversion of triol **15**[8] to monoprotected silyl compound **16** followed by protection of the 1,3-*anti* diol furnished the acetonide **17** in 97% yield. Reductive removal of benzyl group in **17** by Raney nickel followed by oxidation of the resulting alcohol **18** under Swern conditions provided the corresponding aldehyde **5** which was used directly to the next step without purification. The Horner–Emmons reaction of **5** with triethylphosphonocrotonate using the Takacs modified procedure[9] led to the conjugated dienoate **19** as a mixture of *E*,*E*- and *Z*,*E*-diene isomers in a ratio of 5:1 in 62% yield in two steps. Selective reduction of the ester group in **19** by DIBAL-H followed by bromination of the resulting alcohol **20** at −78 °C with Ph_3P/NBS[10] yielded allyl bromide **21**, which was unstable and decomposed on a silica gel column. On the basis of our previous work,[4] sulfone **6** and allyl bromide **21** could be efficiently coupled by treatment with *n*-BuLi, giving **22** in 93% yield as a mixture of two diastereomers. The phenylsulfonyl group was then removed by 6% Na–Hg in methanol, giving **23** as a single isomer in 66% yield. Fluoride ion catalyzed hydrolysis of TBDPS group in **23** with TBAF, and iodination of the corresponding alcohol **24** followed by phosphonium salt formation of **25** delivered the requisite C_{11}–



Scheme 2. (a) TBSOTf, Et_3N, CH_2Cl_2, 0 °C, 40 min, 95%. (b) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 96.5%. (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C–0 °C. (d) **11**, NaH, and then **10**, THF, 60% in two steps. (e) HCOOH, Et_2O, 75%. (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C–0 °C. (g) Ph_3P=CHCHO, $CHCl_3$, 80% in two steps.



Scheme 3. (a) TBDPSCl, imidazole, CH_2Cl_2, 84%. (b) $Me_2C(OMe)_2$, CSA, 97%. (c) Raney Ni, EtOH, 98%. (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C–0 °C. (e) triethylphosphonocrotonate, LiOH, 4 Å MS, THF, reflux, 10 h, 62% in two steps. (f) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 92%. (g) NBS, PPh_3, CH_2Cl_2, −78 °C, 30 min, 95%. (h) **6**, *n*-BuLi, and then **21**, THF, −78 °C; 93%. (i) 6% Na–Hg, Na_2HPO_4, MeOH, 0 °C, 66%. (j) TBAF, THF, 89%. (k) Ph_3P, imidazole, I_2, benzene, 0 °C, 92%. (l) Ph_3P, CH_3CN, reflux, 48 h, 97%.

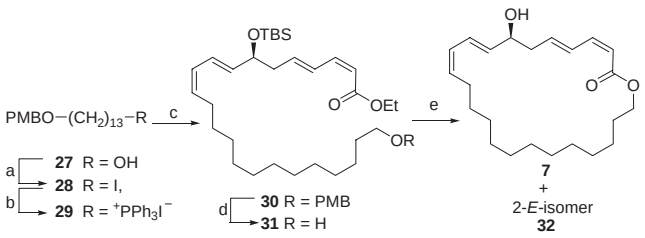


Scheme 4.

C_{24} segment **3**.

With the advanced segments **2** and **3** in hand, the coupling of two segments via Wittig reaction in the presence of NaHDMS smoothly provided the fully protected *sec*-precursor **26** in 79% yield (Scheme 4). The *Z*:*E* ratio of the newly formed double bond is 98:2. In order to test the deprotection of PMB group and the macrocyclization of the *sec*-precursor **26**, an analogue of **26**, compound **30** was thus designed and synthesized (Scheme 5). The coupling of segment **2** and phosphonium salt **29**, which was synthesized from monoprotected 1,12-dodecanediol **27**, successfully provided **30**. Deprotection of PMB ether in **30** gave **31** in 70% yield.[11] Saponification of ester **31** with LiOH, followed by the Yamaguchi macrolactonization[12] of the resulting hydroxy acid in situ gave the protected macrolide, which was deprotected with TBAF–AcOH, obtaining the macrolide analogues of macrolactin A, **7** and **32** in 28% and 42% yields for three steps respectively. During the reaction, the *Z*-double bond of C_2–C_3 in **31** was partially converted into *E*-form.[13]

In summary, a synthesis of a *sec*-precursor of macrolactin A was achieved through a highly convergent and efficient route. In the synthesis, the Wittig reaction and the Horner–Emmons reaction were utilized to construct the three characteristic *E*,*Z*- and *E*,*E*-dienes. An α-alkylation of sulfone stabilized anion with allyl bromide was used for the synthesis of C_{11}–C_{24} segment. The macrolide analogues of macrolactin A were also synthesized using this strategy.



Scheme 5. (a) Ph_3P, imidazole, I_2, benzene, rt, 90%. (b) Ph_3P, CH_3CN, reflux, 48 h, 95%. (c) NaHMDS, **2**, THF, −78 °C, 75%. (d) DDQ, CH_2Cl_2/H_2O (17:1), rt, 70%. (e) i) LiOH, THF/MeOH/H_2O, rt; ii) 2,4,6-trichlorobenzoyl chloride, *i*-Pr_2NEt, toluene, DMAP, 90 °C; iii) TBAF/AcOH (1:1), THF, rt, 70% in three steps.

Now we have succeeded in the removal of PMB protecting group, and the yield of the resulting hydroxy ester needs to be improved. The total synthesis of macrolactin A is underway.

This work was supported by a grant from the National Natural Science Foundation of China and a grant from the State Key Laboratory of Bio-organic and Natural Products Chemistry.

References

1 a) K. Gustafson, M. Roman, and W. Fenical, *J. Am. Chem. Soc.*, **111**, 7519 (1989). b) S. D. Rychnovsky, D. J. Skalitzky, C. Pathirana, P. R. Jensen, and W. Fenical, *J. Am. Chem. Soc.*, **114**, 671 (1992).
2 H. H. Kim, W. G. Kim, I. J. Ryoo, C. J. Kim, J. E. Suk, K. H. Han, S. Y. Hwang, and I. D. Yoo, *J. Microbiol. Biotechnol.*, **7**, 429 (1997).
3 a) T. J. Benvegnu and R. L. Grée, *Tetrahedron*, **52**, 11821 (1996). b) S. Tanimori, Y. Morita, M. Tsubota, and M. Nakayama, *Synth. Commun.*, **26**, 559 (1996). c) Á. González, J. Aiguadé, F. Urpí, and J. Vilarrasa, *Tetrahedron Lett.*, **37**, 8949 (1996). d) R. J. Boyce and G. Pattenden, *Tetrahedron Lett.*, **37**, 3501 (1996). e) S. Li and W. A. Donaldson, *Synthesis*, **2003**, 2064, and references were cited therein.
4 a) S. Li, R. Xu, and D. Bai, *Tetrahedron Lett.*, **41**, 3463 (2000). b) S. Li, R. Xu, X. Xiao, and D. Bai, *Chin. J. Chem.*, **18**, 910 (2000).
5 a) A. B. Smith, III and G. R. Ott, *J. Am. Chem. Soc.*, **118**, 13095 (1996). b) Y. Kim, R. A. Singer, and E. M. Carreira, *Angew. Chem., Int. Ed.*, **37**, 1261 (1998). c) J. P. Marino, M. S. McClure, D. P. Holub, J. V. Comasseto, and F. C. Tucci, *J. Am. Chem. Soc.*, **124**, 1664 (2002).
6 K. Ando, *J. Org. Chem.*, **62**, 1934 (1997).
7 M. Bessodes, D. Komiotis, and K. Antonakis, *Tetrahedron Lett.*, **27**, 579 (1986).
8 T. Katsuki, A. W. M. Lee, P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless, D. Tuddenham, and F. J. Walker, *J. Org. Chem.*, **47**, 1378 (1982).
9 J. M. Takacs, M. R. Jaber, F. Clememt, and C. Walters, *J. Org. Chem.*, **63**, 6757 (1998).
10 H. A. Bates, J. Farina, and M. Tong, *J. Org. Chem.*, **51**, 2637 (1986).
11 Y. Oikawa, T. Yoshioka, and O. Yonemitsu, *Tetrahedron Lett.*, **23**, 885 (1982).
12 J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).
13 Y. Kobayashi, A. Fukuda, T. Kimachi, M. Ju-ichi, and Y. Takemoto, *Tetrahedron Lett.*, **45**, 677 (2004).

Published on the web (Advance View) July 5, 2005; DOI 10.1246/cl.2005.906