

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.

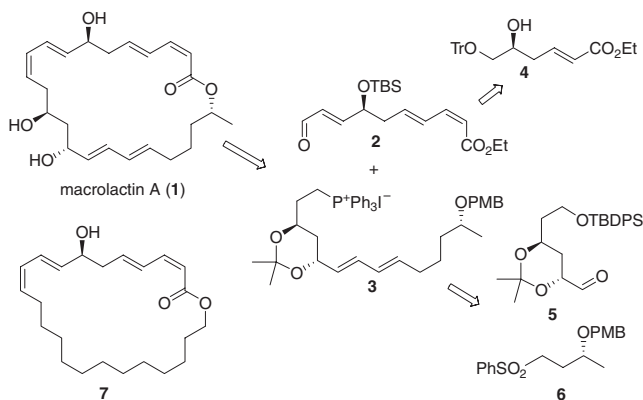
Macrolactin A (**1**) is the parent aglycone of a novel family of polyene 24-membered macrolides isolated from a deep-sea bacterium.¹ It was showed to inhibit B₁₆-F₁₀ murine melanoma cancer cells and mammalian HSV-I and HSV-II. More significantly, it was found to inhibit the HIV replication in T-lymphoblasts¹ 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 C₁–C₁₀ polyene segment **2** from building blocks **4**. C₁₁–C₂₄ 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

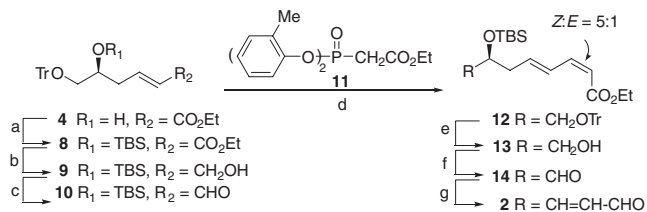
ate, followed by an α -alkylation of sulfone stabilized anion from sulfone **6** with allyl bromide **21**.

The synthesis of C₁–C₁₀ 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 dienolate **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 ether⁷ followed by the Swern oxidation and subsequent the Wittig reaction with formylmethylenetriphenylphosphorane furnished **2** in 60% overall yield in three steps.

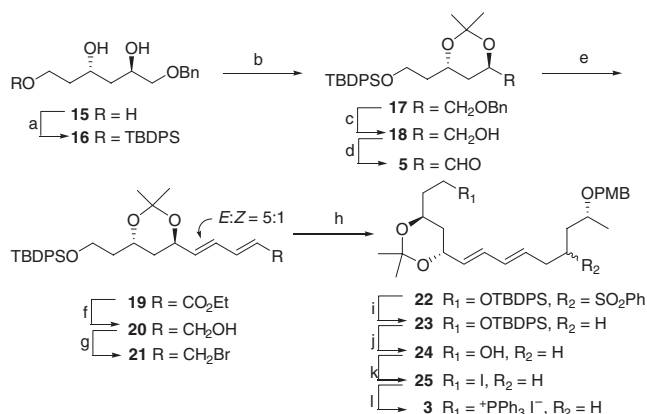
The preparation of C₁₁–C₂₄ phosphonium salt **3** (Scheme 3) was accomplished by the Horner–Emmons reaction as well. Conversion of triol **15**⁸ to monoprotected silyl compound **16** followed by protection of the 1,3-*anti* diol furnished the acetone **17** in 97% yield. Reductive removal of benzyl 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 procedure⁹ led to the conjugated dienolate **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 Ph₃P/NBS¹⁰ 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 C₁₁–



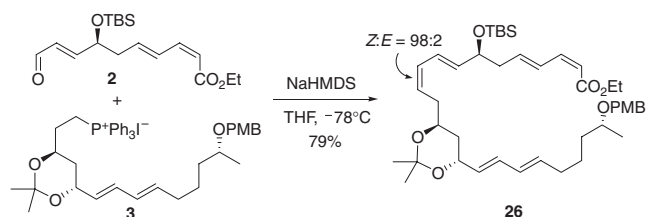
Scheme 1.



Scheme 2. (a) TBSOTf, Et₃N, CH₂Cl₂, 0 °C, 40 min, 95%. (b) DIBAL-H, CH₂Cl₂, –78 °C, 1 h, 96.5%. (c) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, –78 °C–0 °C. (d) **11**, NaH, and then **10**, THF, 60% in two steps. (e) HCOOH, Et₂O, 75%. (f) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, –78 °C–0 °C. (g) Ph₃P=CHCHO, CHCl₃, 80% in two steps.



Scheme 3. (a) TBDPSCl, imidazole, CH₂Cl₂, 84%. (b) Me₂C(OMe)₂, CSA, 97%. (c) Raney Ni, EtOH, 98%. (d) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C-0 °C. (e) triethylphosphonocrotonate, LiOH, 4 Å MS, THF, reflux, 10 h, 62% in two steps. (f) DIBAL-H, CH₂Cl₂, -78 °C, 1 h, 92%. (g) NBS, PPh₃, CH₂Cl₂, -78 °C, 30 min, 95%. (h) **6**, *n*-BuLi, and then **21**, THF, -78 °C; 93%. (i) 6% Na-Hg, Na₂HPO₄, MeOH, 0 °C, 66%. (j) TBAF, THF, 89%. (k) Ph₃P, imidazole, I₂, benzene, 0 °C, 92%. (l) Ph₃P, CH₃CN, reflux, 48 h, 97%.

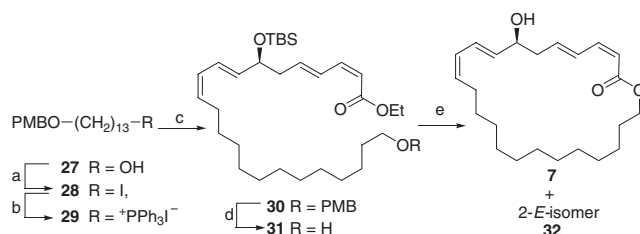


Scheme 4.

C₂₄ segment **3**.

With the advanced segments **2** and **3** in hand, the coupling of two segments via Wittig reaction in the presence of NaHMDS 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 macrolactonization¹² 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 C₂-C₃ 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 C₁₁-C₂₄ segment. The macrolide analogues of macrolactin A were also synthesized using this strategy.



Scheme 5. (a) Ph₃P, imidazole, I₂, benzene, rt, 90%. (b) Ph₃P, CH₃CN, reflux, 48 h, 95%. (c) NaHMDS, **2**, THF, -78 °C, 75%. (d) DDQ, CH₂Cl₂/H₂O (17:1), rt, 70%. (e) i) LiOH, THF/MeOH/H₂O, rt; ii) 2,4,6-trichlorobenzoyl chloride, *i*-Pr₂NEt, 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

- a) K. Gustafson, M. Roman, and W. Fenical, *J. Am. Chem. Soc.*, **111**, 7519 (1989). b) S. D. Rychnovsky, D. J. Skalitzy, C. Pathirana, P. R. Jensen, and W. Fenical, *J. Am. Chem. Soc.*, **114**, 671 (1992).
- 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).
- a) T. J. Benveniste 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.
- 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).
- 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).
- K. Ando, *J. Org. Chem.*, **62**, 1934 (1997).
- M. Bessodes, D. Komiotis, and K. Antonakis, *Tetrahedron Lett.*, **27**, 579 (1986).
- 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).
- J. M. Takacs, M. R. Jaber, F. Clememt, and C. Walters, *J. Org. Chem.*, **63**, 6757 (1998).
- H. A. Bates, J. Farina, and M. Tong, *J. Org. Chem.*, **51**, 2637 (1986).
- Y. Oikawa, T. Yoshioka, and O. Yonemitsu, *Tetrahedron Lett.*, **23**, 885 (1982).
- J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, **52**, 1989 (1979).
- Y. Kobayashi, A. Fukuda, T. Kimachi, M. Ju-ichi, and Y. Takemoto, *Tetrahedron Lett.*, **45**, 677 (2004).