Tetrahedron Letters 49 (2008) 5759–5761

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of the C7–C24 fragment of (−)-Macrolactin F

Roberta A. Oliveira [a], Juliana M. Oliveira [a], Luis H. S. Rahmeier [b,*,†], Joao V. Comasseto [b], Joseph P. Marino [c], Paulo H. Menezes [a,*]

[a] Departamento de Química Fundamental, Universidade Federal de Pernambuco, CCEN, UFPE, Recife-PE, Brazil
[b] Instituto de Química, Universidade de São Paulo, Avenue Professor Lineu Prestes, 748, São Paulo, SP, Brazil
[c] University of Notre Dame, Department of Chemistry and Biochemistry, 251 Nieuwland Science Hall Notre Dame, IN, USA

ARTICLE INFO

Article history:
Received 11 May 2008
Revised 15 July 2008
Accepted 19 July 2008
Available online 24 July 2008

ABSTRACT

An enantioselective and convergent synthesis of the C7–C24 fragment of Macrolactin F was achieved from four main fragments. A hydrotelluration/transmetalation sequence was used to install the *E,Z* diene present in the molecule, while a hydrozirconation/transmetalation sequence was used to connect two advanced intermediates.

The Macrolactins are a class of secondary metabolites first isolated by Fenical from a taxonomically unclassifiable deep sea bacterium found in the North Pacific. Reported with their initial findings were general structural assignments for Macrolactins A–F.[1] The absolute stereochemistry was later established for Macrolactins B and F through degradation, chemical correlation and ^{13}C acetonide analysis.[2] Macrolactin A exhibits significant antiviral and cytotoxic activities. More recently, several Macrolactins have been isolated[3] and some of them had their biological properties screened.[4]

Approaches to fragments of (−)-Macrolactin A,[5] and the total syntheses of (−)-Macrolactin A[6] and (+)-Macrolactin E[7] were completed, confirming the structure and the stereochemical assignment previously reported. However, there are no described studies toward total synthesis of (−)-Macrolactin F (Fig. 1).

Vinylcopper intermediates are synthetically useful reagents and are classically prepared by reacting the corresponding lithium or Grignard reagent with an appropriate copper salt.[8] One of the most important methods to prepare *E*- or *Z*-vinylic higher order cuprates is through transmetalation reactions. The driving force for both transformations is mainly the change of an sp^3-hybridized ligand in the coordination sphere of copper for an sp^2-hybridized ligand.[9]

In our disconnection approach, (−)-Macrolactin F was divided into five main intermediates, A–E.

Fragment A contains an *E,Z* diene unit which was prepared from the hydrotelluration reaction of the corresponding alkyne.[10] Fragment B was prepared according to a literature procedure.[11] Fragment C is commercially available. Fragment D was also prepared from a literature procedure. Finally, Fragment E could be prepared from the same precursor as Fragment A.

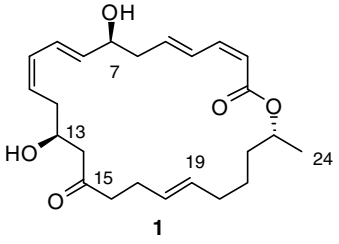
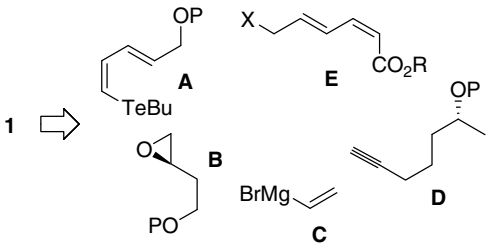


Figure 1. (−)-Macrolactin F.

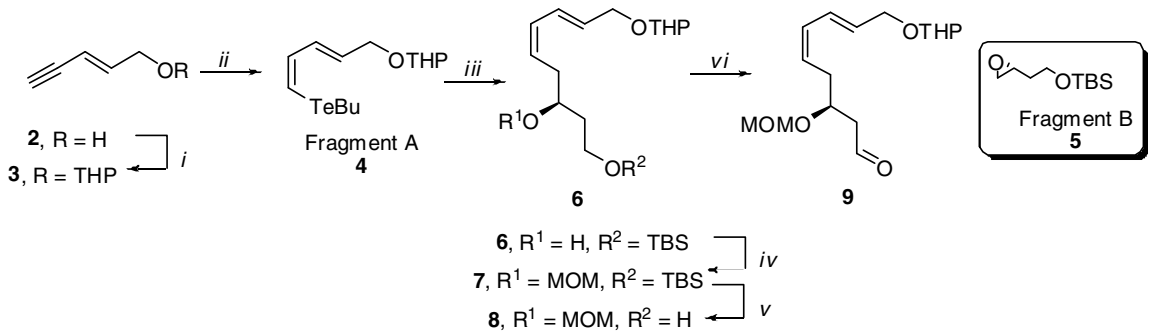
The required telluride for the synthesis of Fragment A was prepared as shown in Scheme 1. (*E*)-2-Penten-4-yn-1-ol, **2,** was prepared from epichlorohydrin according to a known procedure.[12] Protection of the alcohol **2** as its tetrahydropyranil ether[13] **3** was accomplished with DHP at room temperature. Conversion to the vinyl telluride was achieved by treating the terminal alkyne **3** with dibutyl ditelluride in the presence of sodium borohydride[10] to give



Scheme 1. Retrosynthetic analysis for **1**.

* Corresponding authors. Tel.: +55 81 2126 7473; fax: +55 81 2126 8442 (P. H. Menezes).
E-mail address: pmenezes@ufpe.br (P. H. Menezes).
† Present address: Nufarm do Brasil Rua Samuel Morse, 74, Cj 152, CEP 04576-060, Brooklin, São Paulo, SP, Brazil.

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.07.113



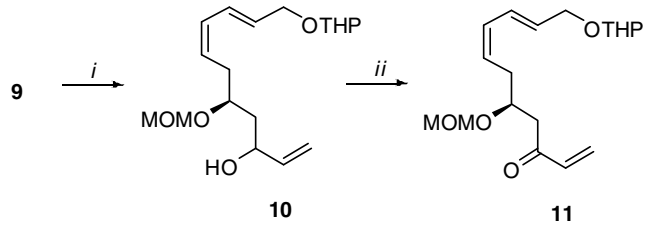
Scheme 2. Reagents and conditions: (i) DHP, PPTS, CH_2Cl_2, 25 °C, 3 h (90%); (ii) BuTeTeBu, $NaBH_4$, EtOH, reflux, 3 h (80%); (iii) (2-Th)BuCu(CN)Li_2, THF, −78 to 25 °C, 1 h then **5**, 3 h, −78 to 25 °C (80%); (iv) MOMCl, DIPEA, CH_2Cl_2, 18 h, 25 °C (78%); (v) TBAF, THF, 25 °C, 1 h (90%); (vi) Dess–Martin periodinane, CH_2Cl_2, 25 °C, 1 h (90%).

the desired Fragment A (**4**), as a single diastereoisomer. Transmetalation[14] of **4** with a higher order cyanocuprate, followed by treatment with the Fragment B (**5**)[11] gave the homoallylic alcohol **6** with the correct stereochemistry at C13. Protection of **6** with MOM–Cl[15] gave **7,** which was selectively deprotected using TBAF[16] to yield **8**. Finally, treatment with Dess–Martin periodinane[17] gave the aldehyde **9** (Scheme 2).

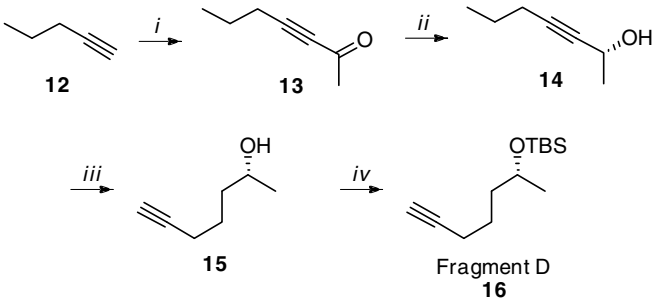
Addition of vinylmagnesium bromide (Fragment C) to **9** occurred in low yield; this problem might be caused by an enolization process by the Grignard reagent acting as a base.[18] By transforming the Grignard reagent into the corresponding organocesium compound,[19] the alcohol **10** was obtained in good yield (ca. 70% vs 40%), and re-oxidized to the corresponding α,β-unsaturated ketone **11** in 92% (Scheme 3). The overall yield for this sequence after 8 steps was 23%.

Fragment D was prepared according to a literature protocol[20] (Scheme 4).

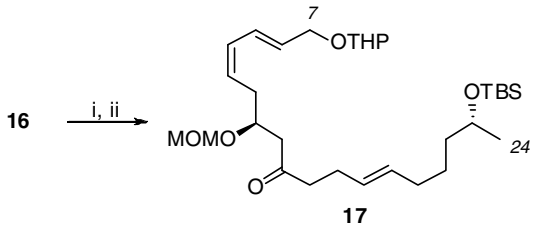
Reaction of the lithium anion of 1-pentyne with acetic anhydride gave propargylic ketone **13**, which was reduced using



Scheme 3. Reagents and conditions: (i) $CeCl_3$, THF, 25 °C, 18 h, then vinylmagnesium bromide, −78 °C, 3 h (70%); (ii) Dess–Martin periodinane, CH_2Cl_2, 25 °C, 1 h (92%).



Scheme 4. Reagents and conditions: (i) *n*-BuLi, THF, −78 °C, 0.25 h then Ac_2O, THF, 2 h (68%); (ii) *i*-PrOH, KOH, (*R*,*R*)-tosyldiphenylethylendiamine, $[RuCl_2(C_{10}H_{14})]_2$ (50%); (iii) $KNH(CH_2)_3NH_2$, *t*-BuOK, 25 °C, 5 h, (65%); (iv) TBSCl, imidazole, DMF, 25 °C, 12 h (90%).



Scheme 5. Reagents and conditions: (i) $Cp_2Zr(H)Cl$, THF, 25 °C, then MeLi (2 equiv) −30 to −78 °C, THF; (ii) CuCN, MeLi (1 equiv), −30 to −78 °C, THF, then **11**, −78 °C, 2 h (65%).

Noyori's protocol[21] to yield **14** in high enantiomeric excess. Finally, **14** was subjected to prototropic migration of the triple bond using potassium 3-aminopropanamide (KAPA)[22] to give **15**, which was protected as its TBS ether[16] **16** (Scheme 4).

Hydrozirconation of Fragment D (**16**), followed by treatment of the alkenylzirconium intermediate with 2 equiv of methyllithium, and sequential addition of 1 equiv of CuCN and methyllithium gave the corresponding higher order cyanocuprate,[23] to which was added **11** at low temperature. Using this sequence, fragment C7–C24, **17** was obtained in 65% (Scheme 5).

In summary, an advanced intermediate in the synthesis of Macrolactin F was achieved. The synthesis features the use of a vinyl telluride and a vinyl zirconium as precursors for the preparation of the corresponding *Z* and *E* vinyl cuprates, respectively. Two of the three stereocenters and three of the five double bonds of Macrolactin F were installed in a convergent approach in 12% overall yield. Further progress toward Macrolactin F will be reported in the due course.

Acknowledgments

The authors gratefully acknowledge CNPq and FACEPE for financial support. R.A.O., J.M.O., and P.H.M. are also thankful to CNPq for their fellowships.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.07.113.

References and notes

1. Gustafson, K.; Roman, M.; Fenical, W. *J. Am. Chem. Soc.* **1989**, *111*, 7519.
2. Rychnovsky, S.; Skalitzky, D.; Pathirana, C.; Rensen, P.; Fenical, W. *J. Am. Chem. Soc.* **1992**, *114*, 671.
3. (a) Lu, X. L.; Xu, Q. Z.; Shen, Y. H.; Liu, X. Y.; Jiao, B. H.; Zhang, W. D.; Ni, K. Y. *Nat. Prod. Res.* **2008**, *22*, 342; (b) Schneider, K.; Chen, X. H.; Vater, J.; Franke, P.;

Nicholson, G.; Borriss, R.; Sussmuth, R. D. *J. Nat. Prod.* **2007**, *70*, 1417; (c) Zheng, C. J.; Lee, S.; Lee, C. H.; Kim, W. G. *J. Nat. Prod* **2007**, *70*, 1632; (d) Lee, S. J.; Cho, J. Y.; Cho, J. I.; Moon, J. H.; Park, K. D.; Lee, Y. J.; Park, K. H. *J. Microbiol. Biotechnol.* **2004**, *14*, 525; (e) Jaruchoktaweechai, C.; Suwanborirux, K.; Tanasupawatt, S.; Kittakoop, P.; Menasveta, P. *J. Nat. Prod.* **2000**, *63*, 984.

4. (a) Romero-Tabarez, M.; Jansen, R.; Sylla, M.; Lunsdorf, H.; Haussler, S.; Santosa, D. A.; Timrnis, K. N.; Molinari, G. *Antimicrob. Agents Chemother.* **2006**, *50*, 1701; (b) Yoo, J. S.; Zheng, C. J.; Lee, S.; Kwak, J. H.; Kim, W. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4889; (c) Nagao, T.; Adachi, K.; Sakai, M.; Nishijima, M.; Sano, H. *J. Antibiot.* **2001**, *54*, 333.
5. (a) Yadav, J. S.; Kumar, M. R.; Sabitha, G. *Tetrahedron Lett.* **2008**, *49*, 463; (b) Georgy, M.; Lesot, P.; Campagne, J. M. *J. Org. Chem.* **2007**, *72*, 3543; (c) Yadav, J. S.; Gupta, M. K.; Prathap, I. *Synthesis* **2007**, *9*, 1343; (d) Bonini, C.; Chiummiento, L.; Videtta, V.; Colobert, F.; Solladie, G. *Synlett* **2006**, 2427; (e) Bonini, C.; Chiummiento, L.; Pullez, M.; Solladie, G.; Colobert, F. *J. Org. Chem.* **2004**, *69*, 5015; (f) Li, S. K.; Xiao, X. S.; Yan, X. B.; Liu, X. J.; Xu, R.; Bai, D. L. *Tetrahedron* **2005**, *61*, 11291; (g) Xiao, X. S.; Li, S. K.; Yan, X. B.; Liu, X. J.; Xu, R.; Bai, D. L. *Chem. Lett.* **2005**, *34*, 906; (h) Kobayashi, Y.; Fukuda, A.; Kimachi, T.; Ju-Ichi, M.; Takemoto, Y. *Tetrahedron* **2005**, *61*, 2607; (i) Kobayashi, Y.; Fukuda, A.; Kimachi, T.; Ju-Ichi, M.; Takemoto, Y. *Tetrahedron Lett.* **2004**, *45*, 677; (j) Li, S. K.; Donaldson, W. A. *Synthesis* **2003**, 2064; (k) Fukuda, A.; Kobayashi, Y.; Kimachi, T.; Takemoto, Y. *Tetrahedron* **2003**, *59*, 9305; (l) Li, S. K.; Xu, R.; Bai, D. L. *Tetrahedron Lett.* **2000**, *41*, 3463; (m) Barmann, H.; Prahlad, V.; Tao, C. L.; Yun, Y. K.; Wang, Z.; Donaldson, W. A. *Tetrahedron* **2000**, *56*, 2283; (n) El-Ahl, A. A. S.; Yun, Y. K.; Donaldson, W. A. *Inorg. Chim. Acta* **1999**, *296*, 261; (o) Pattenden, G.; Boyce, R. *Tetrahedron Lett.* **1996**, *37*, 3501; (p) Prahiad, V.; Donaldson, W. A. *Tetrahedron Lett.* **1996**, *37*, 9169; (q) Tanimori, S.; Morita, Y.; Tsubota, M.; Nakayama, M. *Synth. Commun.* **1996**, *26*, 259; (r) González, Á.; Aiguadé, J.; Urpf, F.; Vilarasa, J. *Tetrahedron Lett.* **1996**, *37*, 8949; (s) Benvegnu, T. J.; Toupet, L. J.; Grée, R. L. *Tetrahedron* **1996**, *52*, 11811; (t) T.J.Benvegnu; Grée, R. L. *Tetrahedron* **1996**, *52*, 11811; (u) Donaldson, W. A.; Bell, P. T.; Wang, Z.; Bennett, D. W. *Tetrahedron Lett.* **1994**, *35*, 5829; (v) Benvegnu, T. J.; Schio, L.; Le Floch, Y.; Grée, R. *Synlett* **1994**, 505.
6. (a) Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1996**, *118*, 1309; (b) Kim, Y.; Singer, P.; Carreira, E. *Angew. Chem., Int. Ed.* **1998**, *37*, 1261; (c) Marino, J. P.; McClure, M. S.; Holub, D. P.; Comasseto, J. V.; Tucci, F. C. *J. Am. Chem. Soc.* **2002**, *124*, 1664.
7. Smith, A. B., III; Ott, G. R. *J. Am. Chem. Soc.* **1998**, *120*, 3935.
8. (a) Posner, G. H. *Org. React.* **1972**, *19*, 1; (b) Posner, G. H. *Org. React.* **1975**, *22*, 253; (c) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005; (d) Lipshutz, B. H. *Synthesis* **1987**, 325; (e) Lipshutz, B. H. *Synllet* **1990**, 119; (f) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135.
9. Negishi, E.-I. *Organometallics in Organic Synthesis*; John Wiley & Sons: New York, 1980.
10. (a) Barros, S. M.; Dabdoub, M. J.; Dabdoub, V. B.; Comasseto, J. V. *Organometallics* **1989**, *8*, 1661; (b) Zeni, G.; Formiga, H. B.; Comasseto, J. V. *Tetrahedron Lett.* **2000**, *41*, 1311.
11. Frick, C. K.; Klassen, J. B.; Bathe, A.; Abamson, J. M.; Rappoport, H. *Synthesis* **1992**, 621.
12. Brandsma, L. In *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: New York, 1988.
13. Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
14. Tucci, F. C.; Chieffi, A.; Comasseto, J. V.; Marino, J. P. *J. Org. Chem.* **1996**, *61*, 4975.
15. Hannesian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515.
16. Corey, E. J.; Venkaterswarlu, A. J. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
17. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155; (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
18. Bartoli, G.; Bosco, M.; Di Martino, E.; Marcantoni, E.; Sambri, L. *Eur. J. Org. Chem.* **2001**, 2901.
19. (a) Imamoto, T.; Kusumoto, T.; Tawarayma, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904; (b) Imamoto, T.; Takiyana, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.
20. Petry, N.; Parenty, A.; Campagne, J.-M. *Tetrahedron: Asymmetry* **2004**, *15*, 1199.
21. (a) Matsumara, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738; (b) Buisine, O.; Aubert, C.; Malacria, M. *Synthesis* **2000**, 985; (c) Parenty, A.; Campagne, J-M.; Aroulanda, C.; Lesot, P. *Org. Lett.* **2002**, *4*, 1663.
22. (a) Abrams, S. R. *Can. J. Chem.* **1984**, *62*, 1333; (b) Oppolzer, W.; Radinov, R. N.; El-Sayed, E. *J. Org. Chem.* **2001**, *66*, 4766.
23. (a) Lipshutz, B. H.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 7440; (b) Babiak, K. A.; Behling, J. R.; Dygos, J. H.; McLaughlin, K. T.; Ng, J. S.; Kalish, V. J.; Kramer, S. W.; Shone, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 7441.