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The Exocyclic Olefin Geometry Control via Ireland–Claisen Rearrangement: Stereoselective Total Syntheses of Barmumycin and Limazepine E

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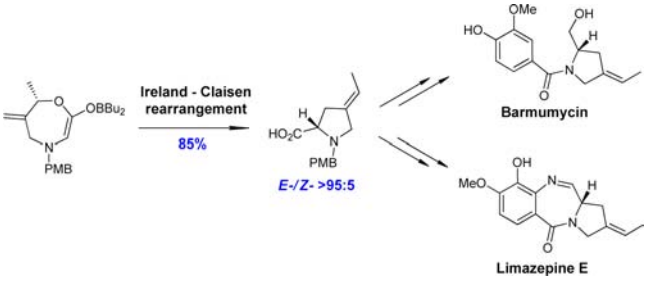
ABSTRACT



Stereoselective total syntheses of Limazepine E and Barmumycin, potent, naturally occurring antitumor agents, are described. The total syntheses control the olefin geometry via a highly selective chelation-controlled Ireland–Claisen rearrangement of a seven-membered lactone-derived boron enolate for the synthesis of (*E*)-4-ethylidene proline, a crucial building block for a number of natural products.

Barmumycin **1** was isolated from the marine actinomycete *Streptomyces* sp. BOSC-022A by Lorente et al (Figure 1).[1] Its structure was confirmed by total synthesis. Barmumycin was found to be cytotoxic against various human tumor cell lines. Limazepine E **4** was isolated from a culture broth of *Micrococcus* sp. strain ICBB 8177[2] and belongs to the pyrrolo[1,4]benzodiazepine (PBD) class of natural products whose antitumor antibiotic properties are due to their ability to covalently bind to the minor groove of DNA.[3] Both natural products possess an (*E*)-ethylidene substituent at C-4 of the pyrrolidine ring.

Although total syntheses of barmumycin **1**[1] and several members of (*E*)-2-ethylidene PBDs, including prothracarcin **2** and tomaymycin **3**,[4] have been reported, efficient control of the olefin geometry has not been achieved.

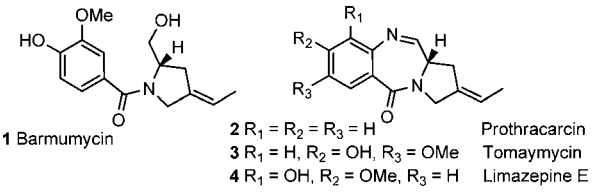


Figure 1. Representatives of the 4-ethylidene proline fragment containing natural products.

Moreover, the classical olefination methods (Wittig and Julia–Kocienski) resulted in predominant formation of the undesired (*Z*)-isomer.[1,4]

Herein we report a stereoselective synthesis of (S)-*E*-4-ethylidene proline and its application in the total syntheses of **1** and **4**.

Our retrosynthetic analysis of barmumycin **1** and limazepine E **4** is outlined in Scheme 1. Since the classical olefination methods showed poor (*E*)-selectivity,[1,4] we proposed an Ireland–Claisen[5] rearrangement of enolate **6**, as a crucial stereochemistry forming step.[6] The enolate **6**

(1) Lorente, A.; Pla, D.; Canedo, L. M.; Albericio, F.; Alvarez, M. *J. Org. Chem.* **2010**, *75*, 8508–8515.
(2) Fotso, S.; Zabriskie, T. M.; Proteau, P. J.; Flatt, P. M.; Santosa, D. A.; Mahmud, S.; Mahmud, T. *J. Nat. Prod.* **2009**, *72*, 690–695.
(3) For a recent review, see: Cipolla, L.; Araújo, A. C.; Airoldi, C.; Bini, D. *Anticancer Agents Med. Chem.* **2009**, *9*, 1–31.
(4) (a) Mori, M.; Uozumi, Y.; Kimura, M.; Ban, Y. *Tetrahedron* **1986**, *42*, 3793–3806. (b) Langley, D. R.; Thurson, D. E. *J. Org. Chem.* **1987**, *52*, 91–97.

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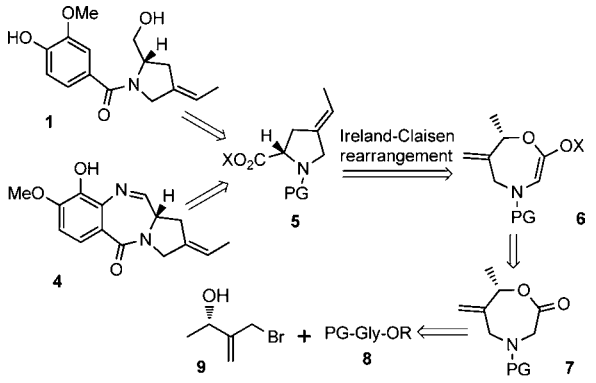
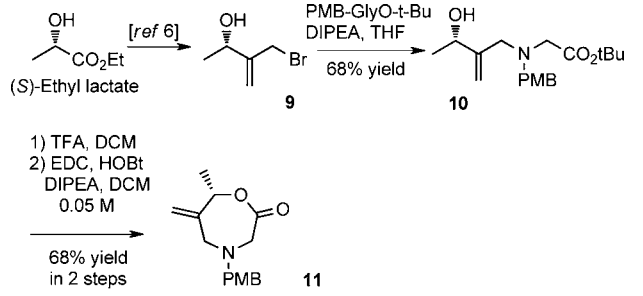
Scheme 1. Retrosynthetic Analysis of **1** and **4**



Scheme 2. Synthesis of Seven-Membered Lactone

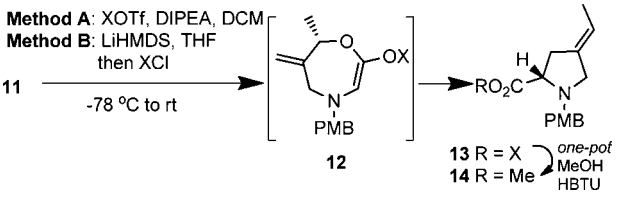


would be derived from a seven-membered lactone **7**, which could be easily constructed from allylic alcohol **9** and glycine derivative **8**.

Toward this goal, alkylation of PMB-protected glycine *tert*-butyl ester[7] with allyl bromide **9**, easily obtainable form (*S*)-ethyl lactate,[8] gave the corresponding amine **10** (Scheme 2). Cleavage of the ester protecting group, followed by macrolactonization, afforded the desired seven-membered lactone **11** in good yield.

Our screening of reagents for the proposed Ireland–Claisen rearrangement is shown in Table 1. The use of silyl triflates gave poor selectivity and low yields[9] or no reaction at all in the case of TIPS triflate (entries 1–3). Our attempt

Table 1. Optimization of Ireland–Claisen Rearrangement

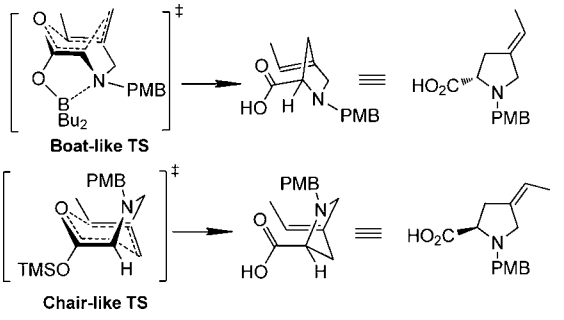


entry	avbX	method	E/Z[a]	isolated yield of **14** (%)
1	TMS	A	1:2	18
2	TBS	A	1:1	15
3	TIPS	A	–	–
4	**(n-Bu)$_2$B**	**A**	**>95:5**[b]	**85**
5	Zn	B	–	–

[a] The E/Z ratio was determined by signal integration in ^{1}H NMR spectrum, and the olefin geometry of individual isomers was assigned based on NOE experiments. [b] The minor isomer was not observed by NMR.

at using the Kazmaier protocol[10] also failed (entry 5). On the other hand, dibutylboron triflate[11] showed excellent selectivity and high yield (entry 4). Remarkably, additional experiments showed that the Ireland–Claisen rearrangement proceeded to full conversion at temperatures as low as 10 °C. To facilitate product isolation, the formed carboxylic acid boron or silicon esters were converted to a methyl ester *in situ*.

Scheme 3. Stereochemical Model



The rationale for this outcome could involve coordination of the boron with the lone pair of the nitrogen atom,[11a] which would stabilize the desirable, boat-like, late transition state in the rearrangement step (Scheme 3). Without the possibility of such coordination, as in the case of silyl

(5) (a) For reviews on the Ireland–Claisen rearrangement, see: Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939. (b) Chai, Y.; Hong, S.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905. (c) Hiersemann, M.; Nubbemeyer, U. *The Claisen Rearrangement*; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2007. (d) Ilardi, E., A.; Stivala, C., E.; Zakarian, A. *Chem. Soc. Rev.* **2009**, *38*, 3133.

(6) For recent examples of Ireland–Claisen rearrangement, see: (a) Majumdar, K. C.; Nandi, R. K. *Tetrahedron* **2013**, *69*, 6921. (b) Fairhurst, N. W. G.; Mahon, M. F.; Munday, R. H.; Carbery, D. R. *Org. Lett.* **2012**, *14*, 756. (c) Tellam, J. P.; Carbery, D. R. *Tetrahedron Lett.* **2011**, *52*, 6027.

(7) Arnott, G.; Clayden, J.; Hamilton, S. D. *Org. Lett.* **2006**, *8*, 5325.

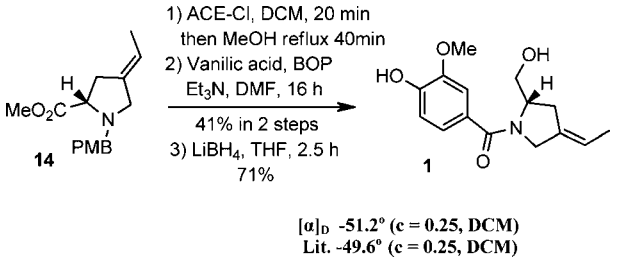
(8) Kulinkovich, O. G.; Kozyrkov, Y. Y.; Bekish, A. V.; Matiushenkov, E. A.; Lysenko, I. L. *Synthesis* **2004**, *10*, 1713.

(9) A number of byproducts were observed by HPLC/MS analysis of the crude reaction mixture, mainly an acyclic diene, formed by elimination of the starting lactone **7**.

(10) (a) Kazmaier, U. *Angew. Chem.* **1994**, *106*, 1046. Kazmaier, U. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 998. (b) Kazmeier, U. *Liebigs Ann./Recl.* **1997**, 285. (c) Kazmeier, U. *Org. Lett.* **1999**, *1*, 1763. (d) Kazmeier, U.; Mues, H.; Krebs, A. *Chem. - Eur. J.* **2002**, *8*, 1850. (e) Kazmeier, U.; Schneider, C. *Synlett* **1996**, 975. (f) Kazmeier, U.; Schneider, C. *Synthesis* **1998**, 1321.

(11) For precedents of boron enolate Ireland–Claisen rearrangement, see: (a) Oh, T.; Wrobel, Z.; Devin, P. N. *Synlett* **1992**, 81. (b) Corey, E. J.; Lee, D. H. *J. Am. Chem. Soc.* **1991**, *113*, 4026. (c) Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 193.

Scheme 4. Synthesis of Barmumycin



ketene acetal, a slight preference for the chairlike transition state is observed.

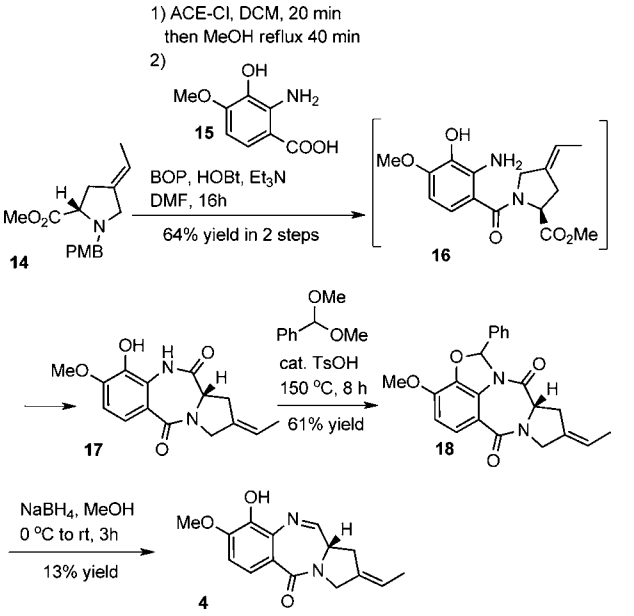
With this method in hand, we proceeded to the synthesis of barmumycin **1** (Scheme 4). The PMB protecting group was easily cleaved by 1-chloroethyl chloroformate (ACE-Cl),[12] and the intermediate amine was directly coupled to vanillic acid. Selective reduction of the ester moiety with lithium borohydride gave barmumycin **1** in good yield. The spectral data of the synthetic sample were identical to those reported for the natural product.[1]

Next we turned to the total synthesis of limazepine E **4** (Scheme 5). Although a number of methods for the construction of the PBD skeleton are reported, typically N-protected anthranilic acids or amino group precursors (nitro or azido) are used.[13] We found that, by using the BOP reagent, it was possible to couple the proline ester intermediate to the unprotected anthranilic acid derivative **15**[14] directly to form PBD dilactam **17** in 64% yield, as the intermediate amide **16** cyclizes under the reaction conditions. Finally, application of the Stille[15] protocol for selective reduction of one of the amide functions provided the target limazepine E **4**, which appeared labile.[16] The spectral data of our synthetic sample were identical to those reported for the natural product,[2] except the optical rotation.[17] Interestingly, the impurity profile in ^{1}H NMR spectra of both natural and synthetic samples appeared to be the same.[18]

Moreover, a crystal structure of dilactam **17** was obtained by X-ray crystallography (Figure 2).

Additional experiments were performed to confirm the absolute configuration of the obtained proline **14** (Scheme 6). Employing the above-described procedure with unsubstituted anthranilic acid, a PBD dilactam **19** was obtained, which upon ozonolysis gave a known ketone **20**.[19]

Scheme 5. Synthesis of Limazepine E



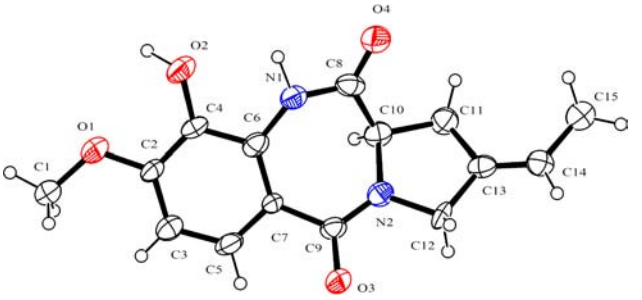
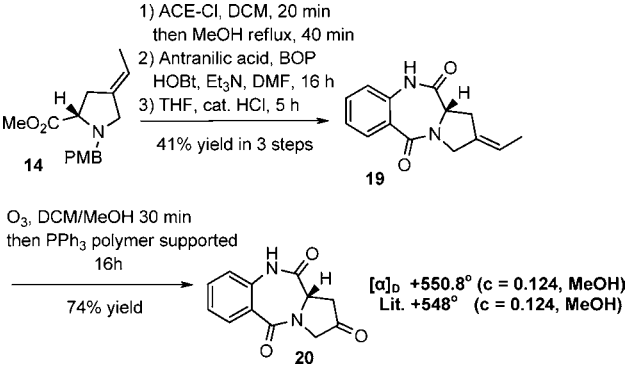


Figure 2. X-ray crystal structure of PBD dilactam **17**.

Scheme 6. Confirmation of Absolute Configuration of **14**



The spectral data of this compound, as well as the optical rotation, were identical to those reported in the literature.

(12) Yang, B. V.; O'Rourke, D.; Li, J. *Synlett* **1993**, *3*, 195.
(13) For a recent review, see: Antonow, D.; Thurston, D. E. *Chem. Rev.* **2011**, *111*, 2815.
(14) For synthesis of **15**, see Supporting Information.
(15) Pena, M., R.; Stille, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 5417.
(16) Although HPLC/MS analysis of the crude reaction mixture of the reduction step showed a clean reaction, a significant loss of **4** in the purification process was observed due to its instability. A sample of pure **4** in $CDCl_3$ dramatically changes color, and precipitation occurs upon standing at rt for a few days.
(17) No satisfactory results were obtained from measuring $[\alpha]_D$ in MeOH solution, as the values fluctuated. A possible explanation could be a well-known property of PBDs to form aminals in protic media.
(18) See Supporting Information page SI-36
(19) Antonow, D.; Jenkins, T. C.; Howard, P. W.; Thurston, D. E. *Bioorg. Med. Chem.* **2007**, *15*, 3041.

In conclusion, stereoselective total syntheses of barmumycin and limazepine E have been achieved. The key steps involve a novel stereoselective strategy for efficient synthesis of (*E*)-4-ethylidene proline via Ireland−Claisen rearrangement and further transformation of this building block into the target natural products via a protecting-group-free strategy.

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Supporting Information Available. Detailed comparison of the NMR data between natural Barmymycine, Limazepine E and synthetic samples, experimental procedures, spectroscopic data, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.