



Synthetic studies on azadirachtin: stereoselective construction of the ABCE ring system

Daisuke Nakagawa^a, Masaaki Miyashita^b, Keiji Tanino^{a,*}

^aDivision of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan

^bDepartment of Applied Chemistry, Faculty of Engineering, Kogakuin University, Hachioji 192-0015, Japan

ARTICLE INFO

Article history:

Received 8 March 2010

Revised 18 March 2010

Accepted 19 March 2010

Available online 23 March 2010

ABSTRACT

A new method for constructing the ABCE ring system of azadirachtin in a stereoselective manner was developed. The synthesis of the model compound features (1) stereoselective construction of the highly hindered C8 quaternary center by an intermolecular addition reaction of an allylborane with an aldehyde and (2) construction of the E ring moiety by the Pd-catalyzed Nazarov cyclization.

© 2010 Elsevier Ltd. All rights reserved.

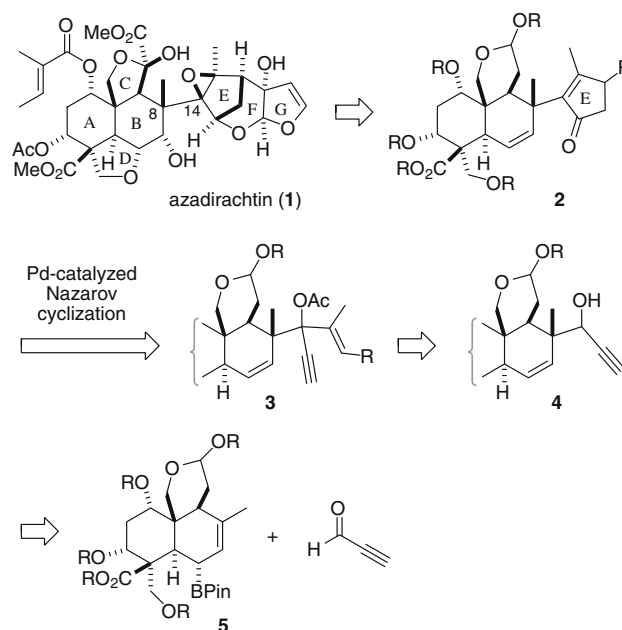
Azadirachtin (**1**), which was isolated from the seeds of the Indian neem tree *Azadirachta indica* A. Juss (Meliaceae) in 1968,¹ exhibits strong antifeedant activity and growth inhibitory properties against insects.² These distinctive biological properties combined with the complex structures having seven rings and sixteen stereogenic carbon atoms make azadirachtin an extremely attractive target for synthetic chemists.³ One of the most synthetically challenging structural features in **1** is the highly hindered C8 quaternary center at which the B ring and the E ring are connected. Thus, this issue was addressed using an intramolecular reaction by several groups. Ley exploited the diastereoselective Claisen rearrangement of a propargyl enol ether and subsequent radical cyclization to construct the BE ring system, and this led to the first total synthesis of **1** in 2007.^{3b–d} Murai used an Ireland–Claisen rearrangement to create the C8–C14 bond, which showed its practicability with the model compound.^{3e} On the other hand, Nicolaou adopted a tethering strategy followed by a radical-based intramolecular coupling and dismantling of the temporary bridge.^{3f,g} Watanabe presented a conceptually different strategy that involves the formation of the requisite C8–C14 bond at a rather early stage, and constructed the fully functionalized B ring and the simplified E ring using an intramolecular tandem radical cyclization reaction at once.^{3h}

We herein report the construction of the ABCE ring system on the basis of an intermolecular addition reaction at the C8 position. We focused on the property of an allylborane that readily reacts with an aldehyde under mild conditions in a regiospecific manner.⁴ Our synthetic strategy toward **1** is shown in Scheme 1.

From the retrosynthetic perspective, we envisioned **1** to be obtained from the key intermediate **2** which would arise from **3** exploiting the Pd-catalyzed Nazarov cyclization.⁵ In order to intro-

duce the side chain at the C8 position via an intermolecular addition reaction, we designed allylborane **5** as the precursor of propargyl alcohol **4**.

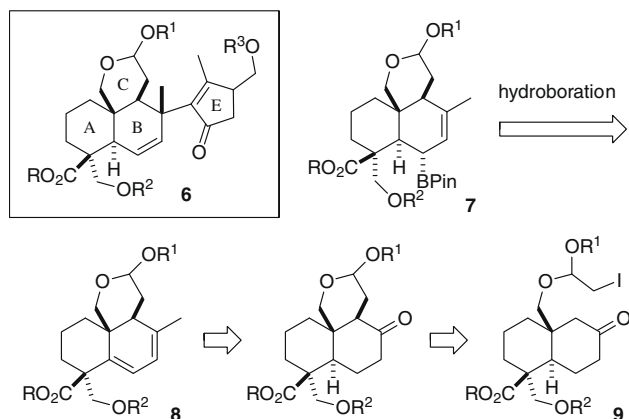
According to this strategy, a model study was undertaken to synthesize compound **6** which possesses the ABCE ring system of **1** (Scheme 2). We planned to obtain allylborane **7** via a hydroboration reaction of diene **8** through the attack of a borane reagent to the opposite face of the C ring moiety. Construction of the tricyclic



Scheme 1. Retrosynthetic analysis of azadirachtin (**1**).

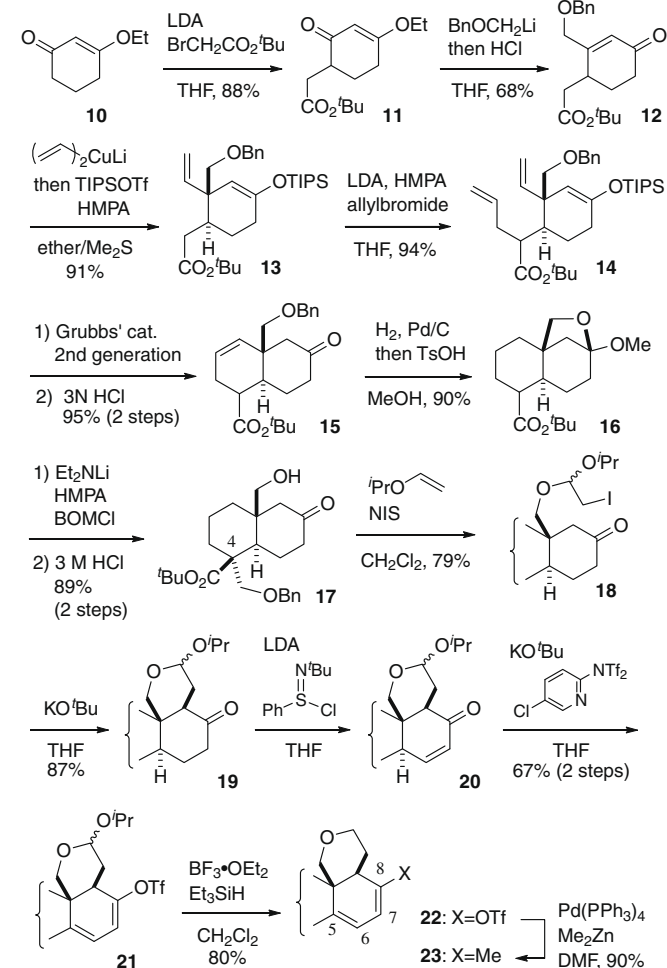
* Corresponding author. Tel.: +81 11 706 2705; fax: +81 11 706 4920.

E-mail address: ktanino@sci.hokudai.ac.jp (K. Tanino).

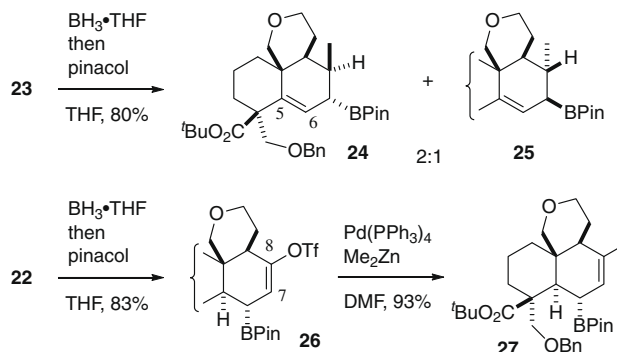
Scheme 2. Synthetic plan for model compound **6**.

skeleton of these compounds was expected to be achieved via an intramolecular alkylation reaction of ketone **9**.

At first, the ABC ring system was constructed as shown in Scheme 3. Alkylation of the commercially available enone **10** with $\text{BrCH}_2\text{CO}_2^t\text{Bu}$ afforded keto ester **11**⁶ which was converted to enone **12** by addition of BnOCH_2Li ⁷ followed by acidic workup. The conjugate addition reaction with a vinylcuprate occurred selectively from the opposite face of the side chain, and the product was isolated as enol silyl ether **13**. Construction of the A ring was



Scheme 3. Stereoselective construction of the ABC ring system.

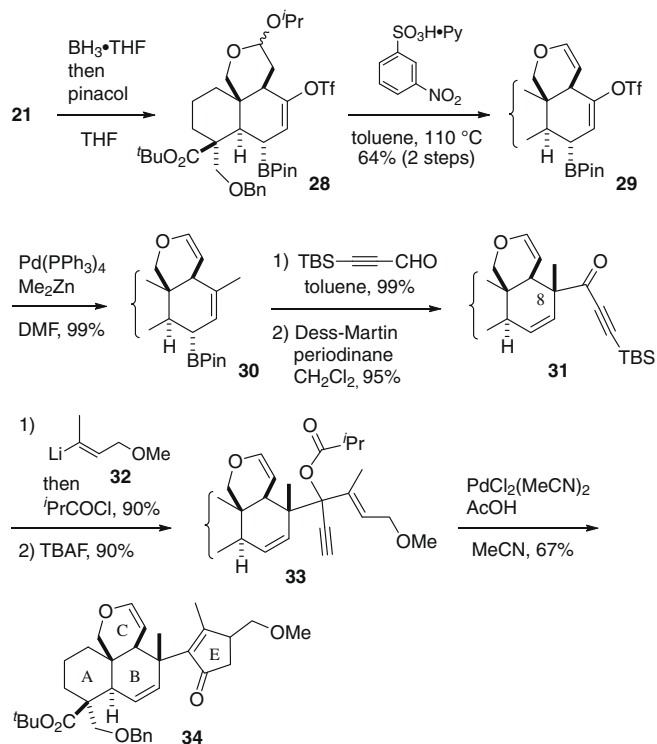
Scheme 4. Hydroboration reactions of dienes **23** and **22**.

achieved by ring-closing metathesis⁸ of triene **14** which was prepared by the allylation reaction of **13**. Hydrolysis of the enol ether moiety afforded ketone **15** which in turn was subjected to hydrogenation in methanol followed by acetal formation. Stereoselective construction of the C4 quaternary center was accomplished by alkylation of ester **16** with BnOCH_2Cl . Hydrolysis of the acetal moiety afforded hydroxy ketone **17** that was reacted with NIS and isopropyl vinyl ether to afford iodoacetal **18** as a 1:1 mixture of diastereomers. Under the influence of KO^tBu , the intramolecular alkylation reaction took place regardless of the stereochemistry of the acetal moiety. The resulting ketone **19** was oxidized to enone **20** according to the Mukaiyama's protocol (LDA , $\text{PhS}(\text{N}^t\text{Bu})\text{Cl}$).⁹ Treatment of **20** with KO^tBu at 0°C effected selective formation of the thermodynamically favored linear dienolate which reacted with Comins reagent to afford dienol triflate **21**. In order to simplify the C ring moiety, the isopropoxy group was removed by ionic reduction using triethylsilane. The resulting tetrahydropyran **22** was subjected to the Pd-catalyzed cross-coupling reaction with Me_2Zn .¹⁰

With the hydroboration precursor **23** in hand, the reaction with borane followed by pinacol was performed in THF (Scheme 4).

Disappointingly, a 2:1 mixture of allylborane **24** and **25** was obtained indicating that the C7–C8 double bond is much more reactive than the sterically hindered C5–C6 double bond. These results led us to examine the hydroboration reaction of dienol triflate **22** because the electron-withdrawing effect of the OTf group may inactivate the C7–C8 double bond.¹¹ As was expected, the reaction of dienol triflate **22** occurred at the C5–C6 double bond stereoselectively to give allylborane **26**. The methyl group was introduced by the Pd-catalyzed coupling reaction with Me_2Zn to afford the desired allylborane **27** in good yield. Since it is difficult to construct the highly functionalized C ring of **1** from the simplified C ring moiety of model compound **27**, we also explored the transformation of dienol triflate **21** having a cyclic acetal moiety (Scheme 5). Treatment of **21** with borane followed by pinacol afforded allylborane **28** as a mixture of epimers at the acetal moiety. However, the Pd-catalyzed coupling reaction of **28** with Me_2Zn resulted in the methylation of only one diastereomer, and the corresponding epimer remained unchanged.¹² These results prompted us to transform acetal **28** into enol ether **29**, which underwent smooth methylation giving rise to allylborane **30**,¹³ by heating with pyridinium *m*-nitrobenzenesulfonate¹⁴ in toluene.

With the key intermediate **30** in hand, the next stage was set for the construction of the E ring. The reaction of allylborane **30** with 3-(*t*-butyldimethylsilyl)-2-propynal in toluene proceeded quantitatively at room temperature, and the adduct was converted to ketone **31** by Dess–Martin oxidation. Successive treatment of ketone **31** with alkenyllithium **32**¹⁵ and isobutyryl chloride afforded the adduct as a 1:1 mixture of diastereomers which was subjected to desilylation with tetrabutylammonium fluoride (TBAF). The Pd-



Scheme 5. Synthesis of model compound 6.

catalyzed Nazarov cyclization was performed by heating alkyne **33** with $\text{PdCl}_2(\text{CH}_3\text{CN})_2$, and cyclopentenone **34** was obtained as a 1:1 mixture of diastereomers in 67% yield.⁵

In summary, we have achieved stereoselective synthesis of tetracyclic compound **34** which possesses the ABCE ring system of azadirachtin (**1**). The synthesis of the model compound features (1) stereoselective construction of the highly hindered C8 quaternary center by an intermolecular addition reaction of allylborane **30** with an aldehyde and (2) construction of the E ring moiety by the Pd-catalyzed Nazarov cyclization. It is noteworthy that formation of the C8–C14 bond without using an intramolecular reaction is generally difficult. Studies toward constructing the EFG ring moiety on the basis of the Nazarov cyclization are in progress in our laboratory.

Acknowledgments

This work was partially supported by the Global COE Program (Project No. B01: Catalysis as the Basis for Innovation in Materials Science) and Grant-in-Aid for Scientific Research on Innovative Areas (Project No. 2105: Organic Synthesis Based on Reaction Inte-

gration) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References and notes

- Buterworth, J. H.; Morgan, E. D. *Chem. Commun.* **1968**, 23.
- (a) Ley, S. V.; Denholm, A. A.; Wood, A. *Nat. Prod. Rep.* **1993**, *10*, 109; (b) Mordue, A. J.; Blachwell, A. *Insect Physiol.* **1993**, *39*, 903.
- For review, see: (a) Veitch, G. E.; Boyer, A.; Ley, S. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 9402; for total synthesis, see: (b) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S. L.; Ley, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7629; (c) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Ayats, C.; Ley, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7633; (d) Ley, S. V.; Somovilla, A. A.; Anderson, J. C.; Ayats, C.; Banteli, R.; Beckmann, E.; Boyer, A.; Brasca, M. G.; Brice, A.; Broughton, H. B.; Burke, B. J.; Cleator, E.; Craig, D.; Denholm, A. A.; Denton, R. M.; Reville, T. D.; Gobbi, L. B.; Göbel, M.; Gray, B. L.; Grossmann, R. B.; Gutteridge, C. E.; Hahn, N.; Harding, S. L.; Jennens, D. C.; Jennens, L.; Lovell, P. J.; Lovell, H. J.; Puente, M. L.; Kolb, H. C.; Koot, W. J.; Maslen, S. L.; McCusker, C. F.; Mattes, A.; Pape, A. R.; Pinto, A.; Santafian, D.; Scott, J. S.; Smith, S. C.; Somers, A. Q.; Spilling, C. D.; Stelzer, F.; Toogood, P. L.; Turner, R. M.; Veitch, G. E.; Wood, A.; Zumbrunn, C. *Chem. Eur. J.* **2008**, *14*, 10683; for recent synthetic studies, see: (e) Fukuzaki, T.; Kobayashi, S.; Hibi, T.; Ikuma, Y.; Ishihara, J.; Kanoh, N.; Murai, A. *Org. Lett.* **2002**, *4*, 2877; (f) Nicolaou, K. C.; Sasmal, P. K.; Koftis, T. V.; Converso, E. L.; Kaiser, F.; Roecker, A. J.; Dellios, C. C.; Sun, X.-W.; Petrovic, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 3443; (g) Nicolaou, K. C.; Sasmal, P. K.; Roecker, A. J.; Sun, X.-W.; Mandal, S.; Converso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3447; (h) Watanabe, H.; Mori, N.; Itoh, D.; Kitahara, T.; Mori, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1512.
- (a) Hoffmann, R. W. In *Stereocontrolled Organic Synthesis*; Trost, B. M., Ed.; Blackwell Scientific Publications: Oxford, 1994; pp 259–274; (b) Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer: Berlin, 1995; (c) Roush, W. R. *Allylboron Reagents. In Stereoselective Synthesis*; Ahlbecht, H.; Helmchen, G.; Arend, M.; Herrmann, R., Eds.; Methods in Organic Chemistry E21b; Georg Thieme: Stuttgart, 1995; pp 1410–1485.
- Rautenstrauch, V. J. *J. Org. Chem.* **1984**, *49*, 950.
- Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 6257.
- Hara, R.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1996**, *118*, 9186.
- For a review on ring-closing metathesis, see: Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.
- Mukaiyama, T.; Matsuo, J.; Yanagisawa, M. *Chem. Lett.* **2000**, 1072.
- Marshall, J. A.; Van Devender, E. A. *J. Org. Chem.* **2001**, *66*, 8037.
- Low reactivity of enol triflates in epoxidation is reported: Evarts, J. B.; Fuchs, P. L. *Tetrahedron Lett.* **1999**, *40*, 2703.
- Epimer **28a** in which the isopropoxy group is oriented over the B ring exhibited poor reactivity probably because of the steric hindrance around the enol triflate moiety.
- The stereochemistry of allylborane **30** was determined by the NOE measurements.
- Miyashita, M.; Sasaki, M.; Hattori, I.; Sakai, M.; Tanino, K. *Science* **2004**, *305*, 495.
- Alkenyl lithium **32** was prepared by treating (*E*)-1-methoxy-3-(tributylstannyl)-2-butene with butyllithium. For the synthesis of (*E*)-3-(tributylstannyl)-2-buten-1-ol, see: Yoshimura, F.; Sasaki, M.; Hattori, I.; Komatsu, K.; Sakai, M.; Tanino, K.; Miyashita, M. *Chem. Eur. J.* **2009**, *15*, 6626.

