

HETEROCYCLES, Vol. 89, No. 2, 2014, pp. 353 - 358. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 19th November, 2013, Accepted, 27th December, 2013, Published online, 14th January, 2014
DOI: 10.3987/COM-13-12892

SYNTHETIC STUDIES OF YESSOTOXIN: ITERATIVE SYNTHESIS OF THE AB RING SYSTEM VIA Pd(II)-CATALYZED CYCLIZATION OF ALCOHOL

Hajime Yokoyama, Yasuhiro Kusumoto, Koshiro Sumiyoshi, Masahiro Miyazawa, and Yoshiro Hirai*

Graduate School of Science and Engineering, University of Toyama, 3190Gofuku,
Toyama 930-8555, Japan

e-mail: hirai@sci.u-toyama.ac.jp

Abstract – We report an iterative synthesis of the AB ring system of yessotoxin by using the Pd(II)-catalyzed cyclization reaction, as an approach towards a total synthesis.

Marine dinoflagellates produce many natural products, including polyethers, with unique structures and biological activities. Yessotoxin is a polyether isolated from the digestive glands of the scallop *Patinopecten yessoensis* (Figure 1).¹ Because of its complex structure and biological activities, which include the cytotoxicity and modulation of cytosolic calcium level in human lymphocytes, yessotoxin has attracted the attention of synthetic chemists.² We have been studying the Pd(II)-catalyzed stereoselective cyclization reaction of urethane and alcohol,³ and herein we describe the application of this reaction for iterative synthesis of the AB ring system of yessotoxin.

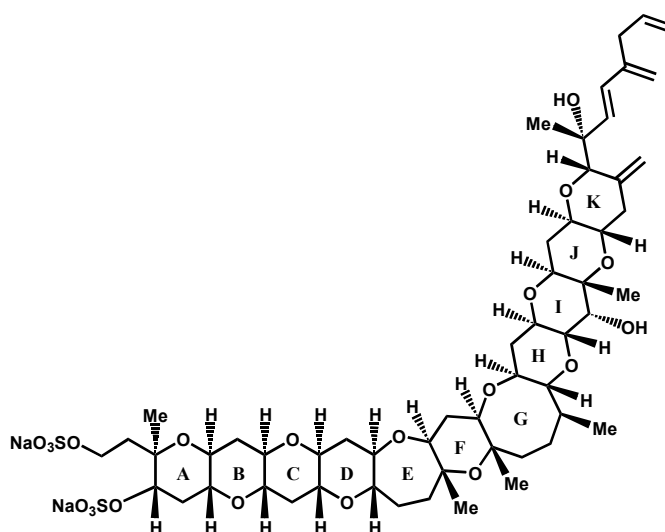
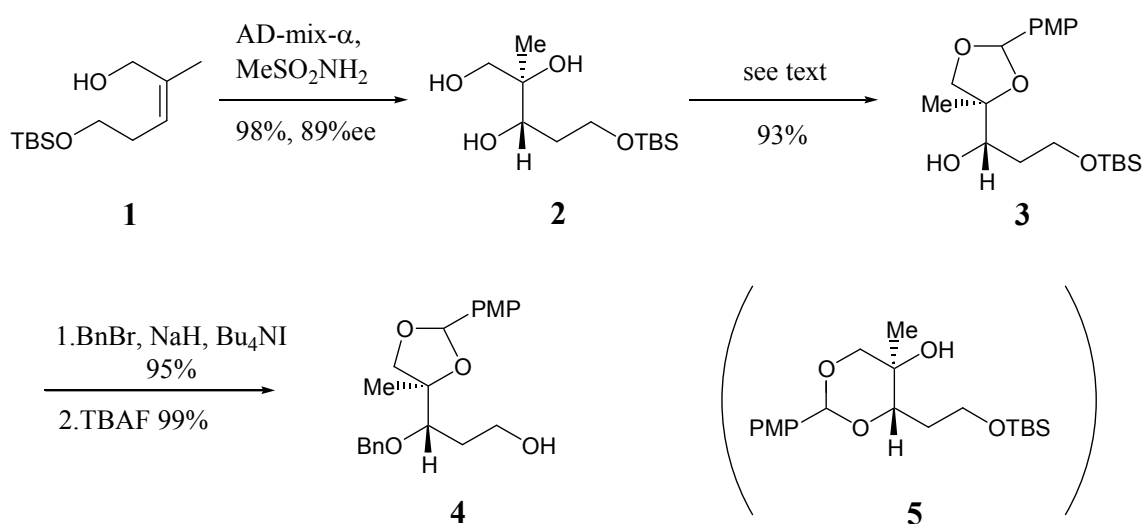


Figure 1. Structure of yessotoxin

Our starting material was the alcohol (**1**), which was prepared from 1,3-propanediol by 4 steps.⁴ Asymmetric dihydroxylation of **1** with AD-mix- α and MeSO_2NH_2 gave the triol (**2**) in 98% yield and 89% ee.⁵ In next protection step, we examined several conditions. At 0 °C, the protection of the triol (**2**) was selective and was achieved in the presence of 1.3 equivalents of *p*-MeOC₆H₄CH(OMe)₂ and a catalytic amount of PPTS in CH_2Cl_2 for 0.5 h to give the acetal (**3**) in 93% yield. However at room temperature, 1,3-acetal (**5**) was obtained in 63% yield. This phenomenon could be due to the kinetic control at 0 °C. The hydroxyl group of **3** was protected with BnBr and TBS protection of the resulting benzyl ether was deprotected by TBAF treatment to afford the alcohol (**4**) in 94% yield (Scheme 1).

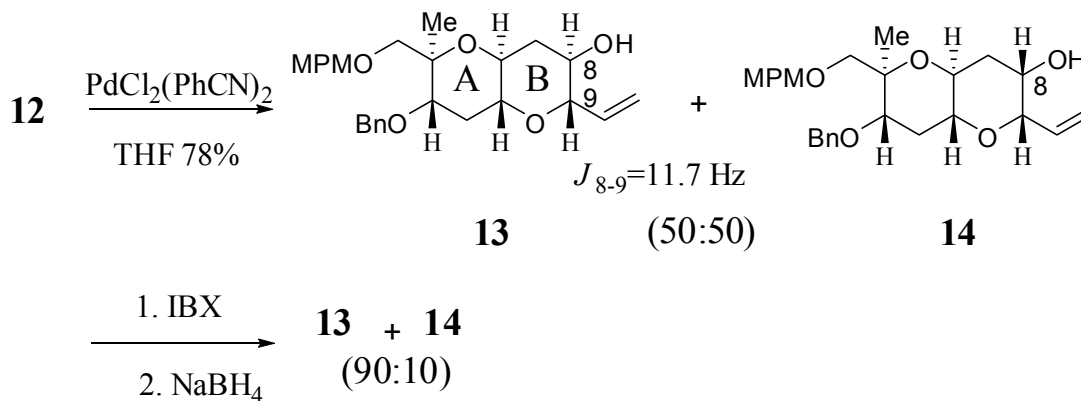


Scheme 1

Oxidation of **4** with IBX, followed by continuous addition of cerium acetylde (prepared from *tert*-butyldimethyl(2-propynyloxy)silane with *n*-BuLi and CeCl_3) provided the alcohol (**6**) as a diastereomixture in 85% yield. Lindlar hydrogenation of **6**, followed by deprotection with TBAF treatment and regioselective cleavage⁶ of the acetal moiety gave the triol (**7**) in 55% yield (3 steps). Next the triol (**7**) was treated with 30 mol% $\text{PdCl}_2(\text{PhCN})_2$ in THF at 0 °C to afford the alcohol (**8**) and diastereomer (**9**) on C₅ position in the ratio of 60:40 in 55% yield.

Oxidation of the hydroxyl moiety, followed by reduction with NaBH_4 provided the A ring system (**8**) and the diastereomer (**9**) in the ratio of 90:10 (Scheme 2). The A ring system (**8**) was isolated in 73% yield (2 steps) and the stereochemistry of **8** was determined by means of NOE experiments.⁷

oxidation and reduction of **13** and **14** provided the AB ring system (**13**) and the diastereomer (**14**) in the ratio of 90:10 (Scheme 4). The AB ring system (**13**) was isolated in 49% yield (2 steps) and the stereochemistry of **13** was determined by the coupling constant ($J_{8,9} = 11.7$ Hz) of C8-C9 and extensive NMR experiment.⁸



Scheme 4

A plausible mechanism of the Pd(II)-catalyzed cyclization of **7** is shown in Figure 2. Pd π -complex is formed by coordination of PdCl₂L_n with the allylic alcohol, and one of the π -faces of the olefin may be preferentially recognized with the assistance of the adjacent hydroxyl group. The resulting complex may be present as an equilibrium mixture of two structures (**A** and **B**). Conformation **B** is destabilized by non-bonding interaction between the Pd catalyst and Me group. Although conformation **B** is strongly destabilized by A^{1,2} strain, conformation **A** is not. Because of these two factors, the overall mechanism can account for the observed predominant formation of **8** and **9**.

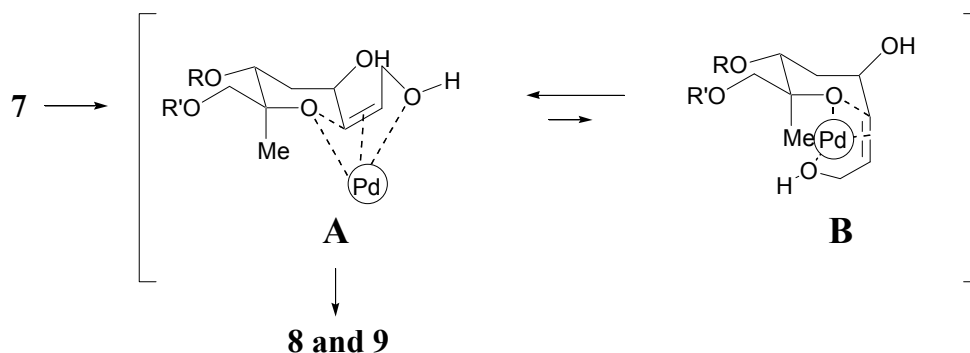


Figure 2

In the case of **12**, conformation **D** would be unfavorable, because of non-bonding interaction between the Pd catalyst and juncture protons. The stereochemical outcome can be explained from conformation **C** (Figure 3).

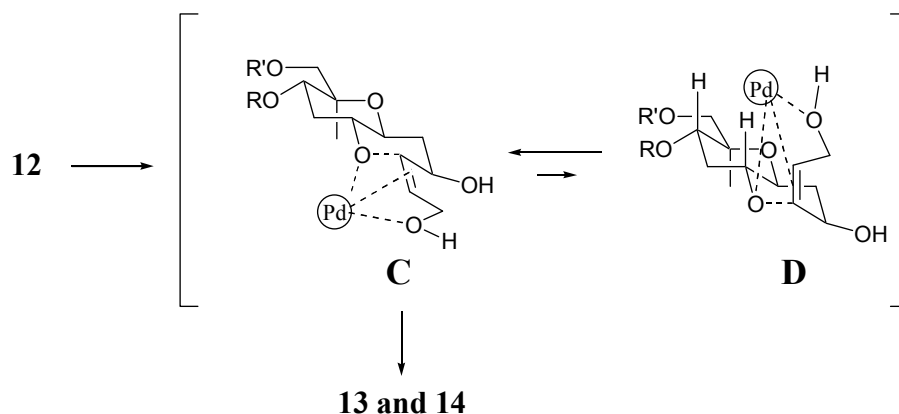


Figure 3

In conclusion, we have synthesized the AB ring system of yessotoxin by means of Pd(II)-catalyzed cyclization. Further studies aimed at total synthesis of yessotoxin are under way in our laboratory.

ACKNOWLEDGEMENTS

This work was supported by Grant-in Aid for Scientific Research on Priority Areas (18032032 & 20590101) from The Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

REFERENCES AND NOTES

- (a) M. Murata, M. Kumagai, J. S. Lee, and T. Yasumoto, *Tetrahedron Lett.*, 1987, **28**, 5869; (b) M. Satake, K. Terasawa, Y. Kadowaki, and T. Yasumoto, *Tetrahedron Lett.*, 1996, **37**, 5955; (c) H. Takahashi, T. Kusumi, Y. Kan, M. Satake, and T. Yasumoto, *Tetrahedron Lett.*, 1996, **37**, 7087.
- Synthetic studies of yessotoxin and its analogs, see: (a) Y. Mori and H. Hayashi, *Tetrahedron*, 2002, **58**, 1789; (b) K. Suzuki and T. Nakata, *Org. Lett.*, 2002, **4**, 3943; (c) Y. Mori, K. Nogami, H. Hayashi, and R. Noyori, *J. Org. Chem.*, 2003, **68**, 9050; (d) Y. Mori, T. Takase, and R. Noyori, *Tetrahedron Lett.*, 2003, **44**, 2319; (e) T. Oishi, K. Watanabe, and M. Murata, *Tetrahedron Lett.*, 2003, **44**, 7315; (f) I. Kadota, H. Ueno, and Y. Yamamoto, *Tetrahedron Lett.*, 2003, **44**, 8935; (g) K. Watanabe, M. Suzuki, M. Murata, and T. Oishi, *Tetrahedron Lett.*, 2005, **46**, 3991; (h) I. Kadota, H. Ueno, Y. Sato, and Y. Yamamoto, *Tetrahedron Lett.*, 2006, **47**, 89; (i) T. Oishi, M. Suzuki, K. Watanabe, and M. Murata, *Tetrahedron Lett.*, 2006, **47**, 3975; (j) I. Kadota, T. Abe, Y. Sato, C. Kabuto, and Y. Yamamoto, *Tetrahedron Lett.*, 2006, **47**, 6545; (k) K. Torikai, K. Watanabe, H. Minato, T. Imaizumi, M. Murata, and T. Oishi, *Synlett*, 2008, 2368; (l) T. Oishi, T. Imaizumi, and M. Murata, *Chem. Lett.*, 2010, **39**, 108; (m) T. Sakai, A. Sugimoto, H. Tatematsu, and Y. Mori, *J. Org. Chem.*, 2012, **77**, 11177.
- (a) H. Yokoyama, S. Nakayama, M. Murase, M. Miyazawa, S. Yamaguchi, and Y. Hirai,

- Heterocycles*, 2009, **77**, 211; (b) H. Yokoyama and Y. Hirai, *Heterocycles*, 2008, **75**, 2133; (c) H. Yokoyama, H. Kobayashi, M. Miyazawa, S. Yamaguchi, and Y. Hirai, *Heterocycles*, 2007, **74**, 283; (d) H. Yokoyama, H. Ejiri, M. Miyazawa, S. Yamaguchi, and Y. Hirai, *Tetrahedron: Asymmetry*, 2007, **18**, 852; (e) M. Miyazawa, M. Narantsetseg, H. Yokoyama, S. Yamaguchi, and Y. Hirai, *Heterocycles*, 2004, **63**, 1017; (f) H. Yokoyama, K. Otaya, H. Kobayashi, M. Miyazawa, S. Yamaguchi, and Y. Hirai, *Org. Lett.*, 2000, **2**, 2427; (g) Y. Hirai, J. Watanabe, T. Nozaki, H. Yokoyama, and S. Yamaguchi, *J. Org. Chem.*, 1997, **62**, 776.
- H. Yokoyama, Y. Hayashi, Y. Nagasawa, H. Ejiri, M. Miyazawa, and Y. Hirai, *Tetrahedron*, 2010, **66**, 8458.
 - Absolute configuration of the triol (**2**) was assigned tentatively by application of the Sharpless mnemonic. See: S. Alvarez, R. Alvarez, and A. R. deLera, *Tetrahedron: Asymmetry*, 2004, **15**, 839. The enantiomeric ratio of the triol (**2**) was determined by ^1H NMR analysis of *O*-methylmandelate ester derivatives of **2**.
 - (a) R. Johansson and B. Samuelsson, *J. Chem Soc., Perkin Trans. 1*, 1984, **10**, 2371; (b) P. J. Garegg, H. Hultberg, and S. Wallin, *Carbohydr. Res.*, 1982, **108**, 97.
 - The selected data for **8**: ^1H NMR (600 MHz, CDCl_3) δ : 7.32-7.29 (m, 2H), 7.28-7.22 (m, 5H), 6.84-6.82 (m, 2H), 5.8 (ddd, $J = 16.6, 10.3, 7.0$ Hz, 1H), 5.39 (ddd, $J = 16.6, 1.5, 1.1$ Hz, 1H), 5.31 (ddd, $J = 10.6, 1.1, 0.7$ Hz, 1H), 4.58 (d, $J = 11.7$ Hz, 1H), 4.56 (d, $J = 11.7$ Hz, 1H), 4.45 (d, $J = 11.7$ Hz, 1H), 4.39 (d, $J = 11.7$ Hz, 1H), 3.81-3.76 (m, 1H), 3.77 (s, 3H), 3.70 (dd, $J = 12.0, 4.8$ Hz, 1H), 3.53 (d, $J = 10.5$ Hz, 1H), 3.43 (d, $J = 10.5$ Hz, 1H), 3.33 (ddd, $J = 12.0, 10.3, 4.8$ Hz, 1H), 2.39 (ddd, $J = 11.9, 4.8, 4.8$ Hz, 1H), 1.62 (ddd, $J = 12.0, 12.0, 11.9$ Hz, 1H), 1.18 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ : 159.1, 138.5, 136.5, 130.6, 129.4, 128.3, 127.50, 127.48, 119.1, 113.7, 77.5, 74.1, 73.7, 73.2, 71.3, 69.0, 55.2, 32.6, 13.7; IR (neat); 3741-3112, 3340, 1651 cm^{-1} ; EIMS m/z 398 (M^+); HREIMS calcd. for $\text{C}_{17}\text{H}_{23}\text{O}_5$ (M^+ -Bn) 307.1545, found 307.1540.
 - The selected data for **13**: ^1H NMR (600 MHz, CDCl_3) δ : 7.30-7.17 (m, 7H), 6.84-6.83 (m, 2H), 5.84 (ddd, $J = 17.4, 10.6, 7.5$ Hz, 1H), 5.43 (dd, $J = 17.4, 0.7$ Hz, 1H), 5.36 (dd, $J = 10.6, 0.7$ Hz, 1H), 4.57 (d, $J = 12.1$ Hz, 1H), 4.53 (d, $J = 11.7$ Hz, 1H), 4.44 (d, $J = 12.1$ Hz, 1H), 4.34 (d, $J = 11.7$ Hz, 1H), 3.77 (s, 3H), 3.74 (dd, $J = 11.7, 4.7$ Hz, 1H), 3.54 (dd, $J = 8.8, 7.5$ Hz, 1H), 3.50 (d, $J = 10.6$ Hz, 1H), 3.49-3.44 (m, 1H), 3.41 (d, $J = 10.6$ Hz, 1H), 3.34 (ddd, $J = 11.4, 9.3, 4.0$ Hz, 1H), 3.05 (ddd, $J = 11.7, 9.3, 4.7$ Hz, 1H), 2.37 (ddd, $J = 14.7, 4.7, 4.7$ Hz, 1H), 2.36 (ddd, $J = 13.9, 4.0, 4.0$ Hz, 1H), 1.59-1.51 (m, 2H), 1.17 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ : 159.11, 138.41, 135.45, 132.44, 130.89, 130.47, 129.45, 128.81, 128.27, 127.52, 113.68, 83.77, 77.80, 77.22, 74.11, 73.11, 71.18, 69.05, 68.16, 55.22, 23.74, 22.99, 13.88; IR (neat); 3773-3098, 1613 cm^{-1} ; EIMS m/z 454 (M^+); HREIMS calcd. for $\text{C}_{20}\text{H}_{27}\text{O}_6$ (M^+ -Bn) 363.1808, found 363.1794.