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Pd(II)-CATALYZED CYCLIZATION TO ETHER AND ITS APPLICATION TO THE SYNTHESIS OF THE *TRANS*-FUSED POLYETHER CORE

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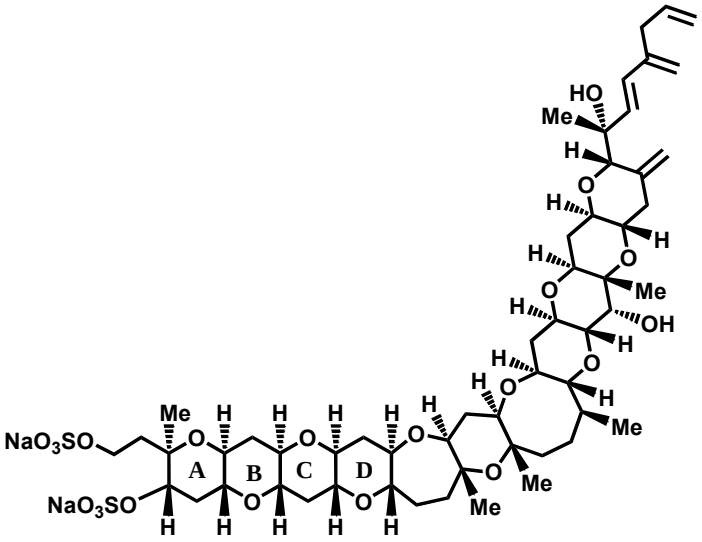
Abstract – We employed an iterative Pd(II)-catalyzed cyclization reaction to ether from tri-*O*-acetyl-*D*-glucal to synthesize *trans*-fused polyethers. This approach should be applicable to synthesize the core structure of marine ladder toxins.

Recently, many natural polyethers (eg.yessotoxin, Figure 1) were isolated from marine origin and these structures were determined by extensive endeavors.[1] Especially the marine ladder toxins are very interesting, due to specific structure and biological activity.[2-4] We have studied Pd(II)-catalyzed cyclization and its application to the synthesis of natural products.[5,6] Herein we report the synthetic study of the *trans*-fused polyether core (polytetrahydropyran ring system (**12**)) by Pd(II)-catalyzed cyclization method.

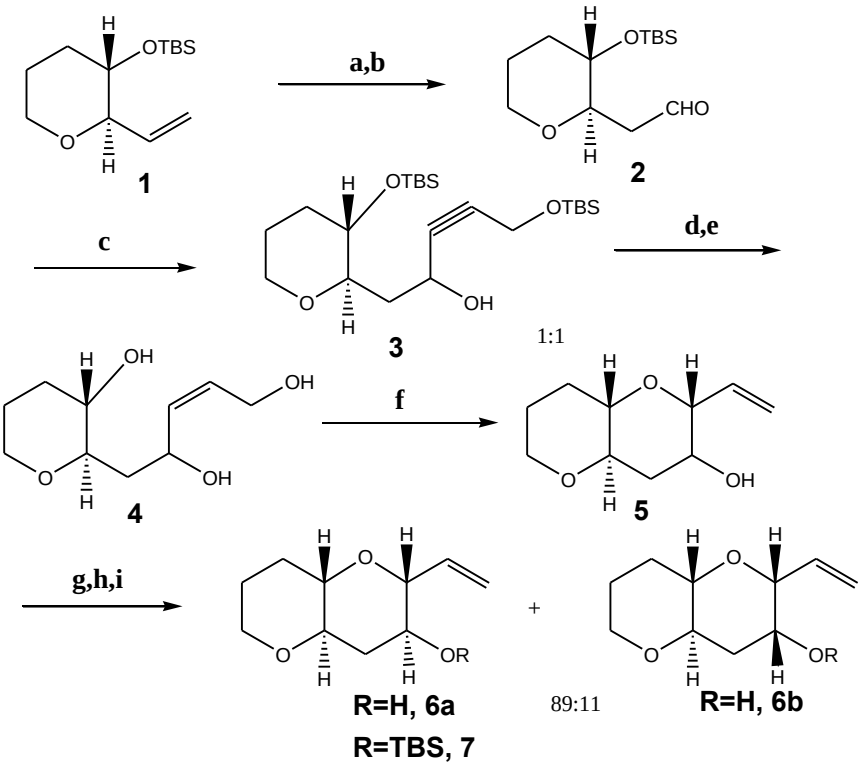


yessotoxin

Figure 1

This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

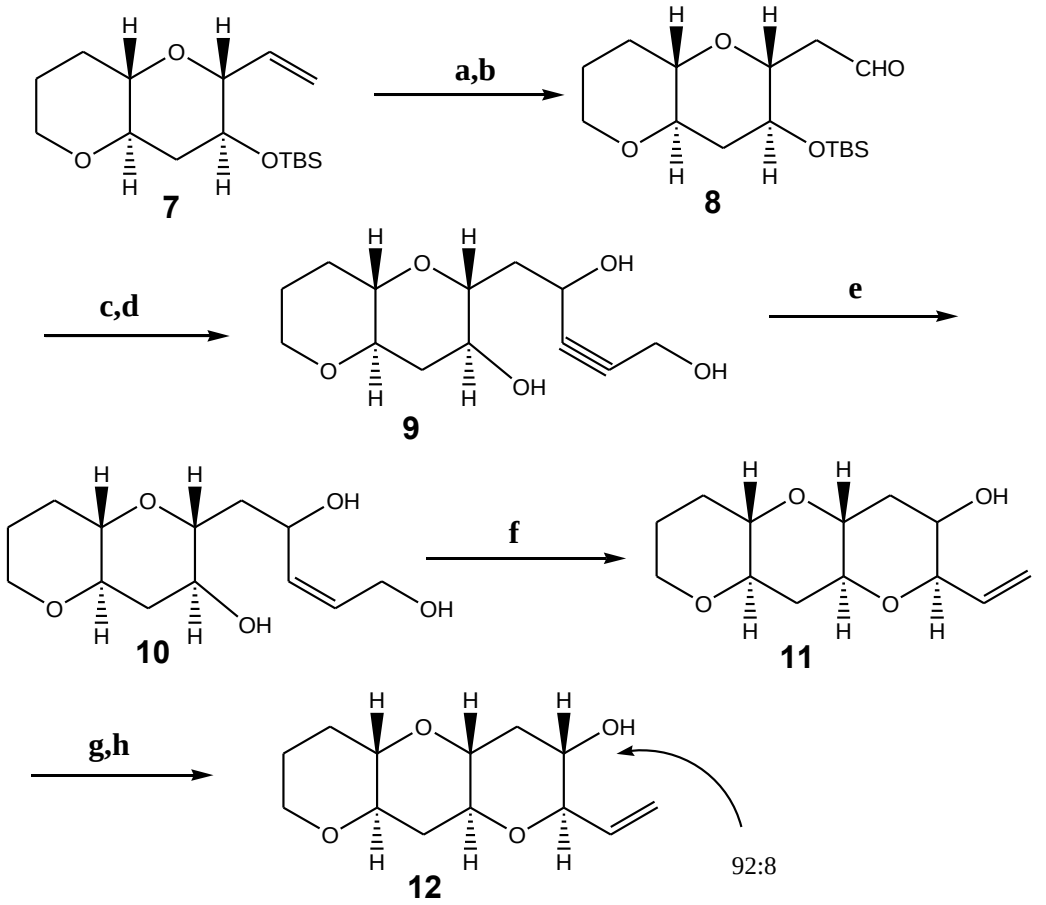
The hydroboration of the alcohol (**1**), which was readily obtained by using a previously reported procedure from tri-*O*-acetyl-*D*-glucal (7steps),[7] followed by Swern oxidation of the resulting alcohol afforded the aldehyde (**2**) (Scheme1). The coupling reaction of the aldehyde (**2**) and the propargyl alcohol derivative gave the alcohol (**3**) in 69% yield (2steps) as a mixture of stereoisomers (1:1). Deprotection of the TBS group of the alcohol (**3**) followed by hydrogenation of alkyne moiety with Lindlar catalyst gave the alcohol (**4**) in 70% yield from **3**. The alcohol (**4**) was treated with a catalytic amount of $PdCl_2(MeCN)_2$ and benzoquinone in THF as a solvent at rt under an argon atmosphere to afford the alcohol (**5**) in 74% yield.[8,5d] Oxidation of the alcohol (**5**) followed by the reduction of the resulting ketone with $NaBH_4$ afforded the alcohol (**6a**)[9] and (**6b**) in 62% yield (2steps) (dr 89:11). The protection of the alcohol group of **6a** with TBSCl in CH_2Cl_2 by using Et_3N as a base gave the alcohol (**7**) in quantitative yield.



Scheme 1. Reagents and conditions: a) 9-BBN, THF, NaOHaq, 34.5%H_2O_2 (81%) b) DMSO, $(COCl)_2$, then Et_3N c) ^nBuLi, 3-(*tert*-butyldimethylsilyloxy)-1-propyne, THF (2 steps 69%) d) *p*-TsOH, THF. e) H_2, Lindlar cat, AcOEt (2 steps 70%) f) $PdCl_2(MeCN)_2$, BQ, THF (74%) g) Dess-Martin periodinane, CH_2Cl_2. h) $NaBH_4$, MeOH (2 steps 62%) i) TBSCl, Et_3N, CH_2Cl_2 (quant.)

Next, the conversion of **7** into **12** was performed by a similar procedure(1.hydroboration of **7**, 2.Swern oxidation of the resulting alcohol, 3. coupling of **8** with the propargyl alcohol derivative, 4.deprotection of TBS group, 5.hydrogenation of **9** with lindlar catalyst, 6.Pd(II)-catalyzed cyclization of **10**, 7.oxidation

of **11** with DMP, 8. reduction with $NaBH_4$) (Scheme 2). After this conversion, polytetrahydropyran ring system (**12**) (the *trans*-fused polyether core) was obtained in 59% yield (2steps) as a 92:8 ratio. The stereochemistry of **12** was determined by extensive NMR experiment.[10] Further studies are ongoing in our laboratory to synthesize the ABCD ring of yessotoxin.



Scheme 2. Reagents and conditions: a) 9-BBN, THF, NaOHaq, 34.5%H_2O_2 (74%) b) DMSO, $(COCl)_2$, then Et_3N. c) ^nBuLi, 3-(*tert*-butyldimethylsilyloxy)-1-propyne, THF. d) *p*-TsOH, THF (3 steps 37%) e) H_2, Lindlar cat, AcOEt (89%) f) $PdCl_2(MeCN)_2$, BQ, THF (74%) g) Dess-Martin periodinane, CH_2Cl_2. h) $NaBH_4$, MeOH (2 steps 59%)

In summary, we planed the iterative strategy of Pd(II)-catalyzed cyclization. To demonstrate this synthetic strategy, we tried the synthesis of the trans-fused polyether core. The optical starting material was treated by palladium-catalyzed cyclization method to give the tricyclic fused polyether core with high stereoselectivity. Finally we attained the synthesis of the trans-fused polyether core. The approach described could be easily extended towards synthesis of various the marine ladder toxin of potential biomedical application.

ACKNOWLEDGEMENTS

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REFERENCES (AND NOTES)

1. a) J. W. Blunt, B. R. Copp, M. H. G. Murro, P. T. Northcote, and M. R. Prinsep, *Nat. Prod. Rep.*, 2004, **21**, 1-49. b) D. J. Faulkner, *Nat. Prod. Rep.*, 2002, **19**, 1-49.
2. a) T. Yasumoto, *Chem. Rec.*, 2001, **1**, 228. b) P. J. Scheuer, *Tetrahedron*, 1994, **50**, 3.
3. a) I. Kadota and Y. Yamamoto, *Acc. Chem. Res.*, 2005, **38**, 423. b) T. Nakata, *Chem. Rev.*, 2005, **105**, 4314. c) M. Inoue, *Chem. Rev.*, 2005, **105**, 4379.
4. Selected iterative synthesis: a) B. M. Trost and Y. H. Rhee, *Org. Lett.*, 2004, **6**, 4311. b) Y. Mori, K. Yaegashi, and H. Furukawa, *J. Am. Chem. Soc.*, 1996, **118**, 8158. c) N. Hori, H. Matsukura, G. Matsuo, and T. Nakata, *Tetrahedron Lett.*, 1999, **40**, 2811.
5. a) P. J. Harirington, L. S. Hegedus, and K. F. McDaniel, *J. Am. Chem. Soc.*, 1987, **109**, 4335. b) S. Saito, T. Hara, N. Takahashi, M. Hirai, and T. Moriwake, *Synlett*, 1992, 237. c) H. Makabe, L. K. Kong, and M. Hirota, *Org. Lett.*, 2003, **5**, 27. d) J. Uenishi, M. Ohmi, and A. Ueda, *Tetrahedron: Asymmetry*, 2005, **16**, 1299.
6. a) Y. Hirai, T. Terada, Y. Amemiya, and T. Momose, *Tetrahedron Lett.*, 1992, **33**, 7893. b) Y. Hirai and M. Nagatsu, *Chem. Lett.*, 1994, 21. c) Y. Hirai, K. Shibuya, Y. Fukuda, H. Yokoyama, and S. Yamaguchi, *Chem. Lett.*, 1997, 22. d) Y. Hirai, J. Watanabe, T. Nozaki, H. Yokoyama, and S. Yamaguchi, *J. Org. Chem.*, 1997, **62**, 776. e) H. Yokoyama, K. Otaya, S. Yamaguchi, and Y. Hirai, *Tetrahedron Lett.*, 1998, **39**, 5971. f) H. Yokoyama, K. Otaya, H. Kobayashi, M. Miyazawa, S. Yamaguchi, and Y. Hirai, *Org. Lett.*, 2000, **2**, 2427. g) M. Miyazawa, Y. Hirose, M. Narantsetseg, H. Yokoyama, S. Yamaguchi, and Y. Hirai, *Tetrahedron Lett.*, 2004, **45**, 2883. h) M. Miyazawa, M. Narantsetseg, H. Yokoyama, S. Yamaguchi, and Y. Hirai, *Heterocycles*, 2004, **63**, 1017.
7. K. C. Nicolaou, C.-K. Hwang, B. E. Marron, S. A. Defrees, E. A. Couladouros, Y. Abe, P. J. Carroll, and J. P. Snyder, *J. Am. Chem. Soc.*, 1990, **112**, 3040.
8. We concluded the Pd(II)-catalyzed cyclization proceeded with high stereoselectivity because the alcohol (**5**) was oxidized by IBX to give the ketones as a >82 : 18 ratio(by NMR analysis). These good stereoselectivities can be explained by cyclic transition model as shown below (Figure 2). It is likely that two chair-form transition states are involved. The transition state **A**, leading to the major product, would be more stable than the transition state **B**, which is subject to steric repulsion between the π-allyloxy palladium complex and the axial proton on another ring.

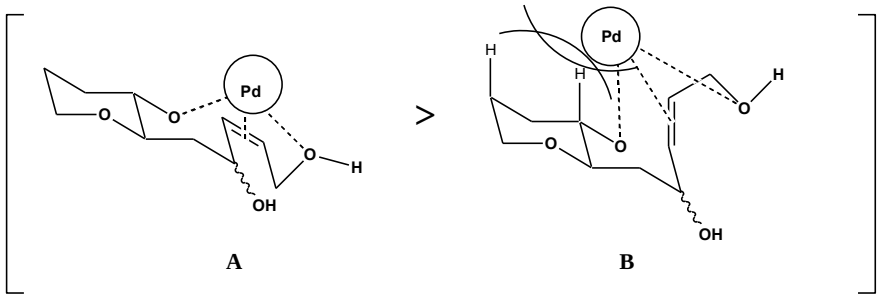

Figure 2.

9. The selected data for **6a**: Rf = 0.60 (AcOEt); IR: 3600-3200, 1649cm^{-1}; ^{1}HNMR (600MHz, $CDCl_3$) δ 5.84 (ddd, J=17.2, 10.6, 7.3 Hz, 1H), 5.43 (dt, J=17.2, 0.7Hz, 1H), 5.36 (dt, J=10.6, 0.7 Hz, 1H), 3.93-3.91 (m, 1H), 3.59-3.56 (m, 1H), 3.45 (ddd, J=11.4, 9.2, 4.4Hz, 1H), 3.39 (dt, J=11.4, 3.7Hz, 1H), 3.09-3.02 (m, 2H), 2.41 (ddd, J=11.4, 4.4, 4.4Hz, 1H), 2.11-2.07 (m, 1H), 1.74-1.71 (m, 2H), 1.58 (br s, 1H), 1.55-1.50 (m, 1H), 1.43 (ddd, J=23.1, 11.7, 5.5Hz, 1H).
10. The selected data for **12**: Rf = 0.39 (AcOEt); IR: 3600-3200, 1647cm^{-1}; ^{1}HNMR (600MHz, $CDCl_3$) δ 5.84 (ddd, J=17.6, 10.6, 7.3 Hz, 1H), 5.44 (dt, J=17.6, 1.5 Hz, 1H), 5.37 (dt, J=10.6, 1.5 Hz, 1H), 3.92 (ddt, J=11.4, 4.0, 1.8 Hz, lH), 3.57 (dd, J=7.3Hz, 1H), 3.45 (ddd, J=11.0, 9.2, 4.8 Hz, lH), 3.39 (dt, J=11.4, 4.0 Hz, 1H), 3.17-3.11 (m, 2H), 3.09-3.03 (m, 2H), 2.45 (ddd, J=11.4, 4.0, 4.0 Hz, 1H), 2.34 (ddd, J=11.4, 4.0, 4.0 Hz, 1H), 2.10-2.06 (m, 2H), 1.75-1.72 (m, 3H), 1.55-1.51 (m, 2H).