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Stereoselective Convergent Synthesis of a *trans*-Fused Polycyclic Ether Ring System Including a 4-Hydroxy-5-methyl-tetrahydropyran Ring

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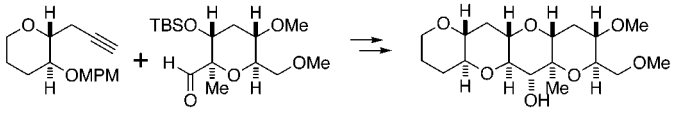
ABSTRACT



Stereoselective convergent synthesis of a *trans*-fused 6-6-6-6-membered tetracyclic ether ring system including 4α- or 4β-hydroxy-5-methyl-tetrahydropyran was achieved. The key reactions involve the acetylide-aldehyde coupling of two tetrahydropyrans, intramolecular hetero-Michael cyclization of enone, stereoselective reduction of enone, hydroboration, intramolecular acetalization, and stereoselective reduction of the acetal with Et_3SiH–TMSOTf.

Marine polycyclic ethers, exemplified by brevetoxins, gambieric acids, yessotoxin, ciguatoxins, maitotoxin, etc., have attracted the attention of synthetic organic chemists as a result of their unique and complex structures and potent biological activities.[1] The characteristic structural feature of these natural products is a *trans*-fused polycyclic ether ring system. Among the polycyclic ether rings, several tetrahydropyran rings have a 4α- or 4β-hydroxyl-5-methyl group (Figure 1).

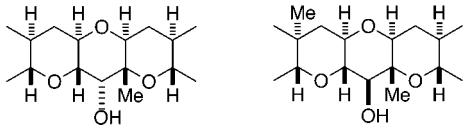


Figure 1. Partial structure of yessotoxin and gambieric acid

Although several convergent methods for the various ring systems have been developed,[2] convergent synthesis of a

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(1) For reviews, see: (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (b) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685. (c) Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3.

(2) For examples of convergent approaches to fused polycyclic ethers, see: (a) Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carrol, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040. (b) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565. (c) Alvarez, E.; Pérez, R.; Rico, M.; Rodríguez, R. M.; Martín, J. D. *J. Org. Chem.* **1996**, *61*, 3003. (d) Oishi, T.; Nagumo, Y.; Hirama, M. *Synlett* **1997**, 980. (e) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.* **1998**, 1041. (f) Sasaki, M.; Fuwa, H.; Inoue, M.; Tachibana, K. *Tetrahedron Lett.* **1998**, *39*, 9027. (g) Fujiwara, K.; Saka, K.; Takaoka, D.; Murai, A. *Synlett* **1999**, 1037. (h) Maeda, K.; Oishi, T.; Oguri, H.; Hirama, M. *Chem. Commun.* **1999**, 1063. (i) Sasaki, M.; Fuwa, H.; Ishikawa, M.; Tachibana, K. *Org. Lett.* **1999**, *1*, 1075. (j) Fujiwara, K.; Morishita, H.; Saka, K.; Murai, A. *Tetrahedron Lett.* **2000**, *41*, 507. (k) Matsuo, G.; Hinou, H.; Koshino, H.; Suenaga, T.; Nakata, T. *Tetrahedron Lett.* **2000**, *41*, 903. (l) Mori, Y.; Mitsuoka, S.; Furukawa, H. *Tetrahedron Lett.* **2000**, *41*, 4161. (m) Kadowaki, C.; Chan, P. W. H.; Kadota, I.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 5769. (n) Díaz, M. T.; Pérez, R. L.; Rodríguez, E.; Ravelo, J. L.; Martín, J. D. *Synlett* **2001**, 345. (o) Kadota, I.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 3562.

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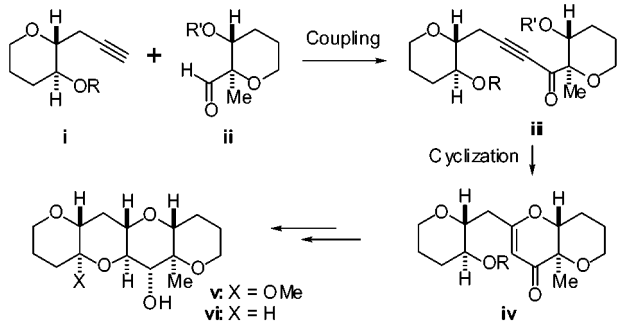
polycyclic ether ring system including 4-hydroxy-tetrahydropyran has not been reported yet. We now report an efficient strategy toward stereoselective convergent synthesis of the *trans*-fused polycyclic ether system including 4-hydroxy-5-methyl-tetrahydropyran.

Our synthetic strategy for the convergent synthesis is outlined in Scheme 1. Two tetrahydropyrans **i** and **ii** would

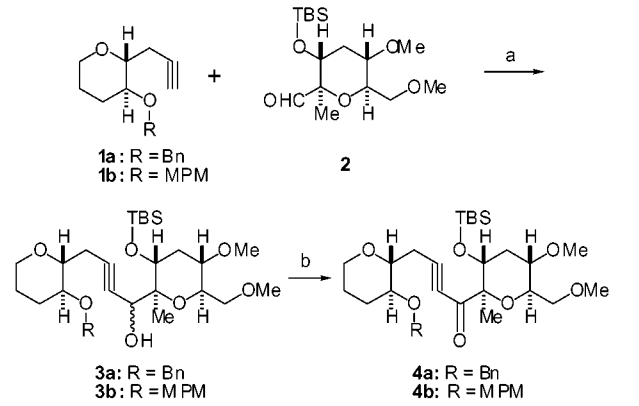
Scheme 1. Synthetic Strategy



be coupled by addition of the acetylene to the aldehyde. After conversion to the ynone **iii**, intramolecular hetero-Michael cyclization could proceed to give the enone **iv**. Then, after conversion of **iv** into the acetal **v**, Lewis acid catalyzed silane reduction would afford the desired polycyclic ether **vi**.

With this prospect, our convergent synthesis began with coupling of acetylene **1a**[3] (R = Bn) and aldehyde **2**[3] (Scheme 2). The reaction of the lithium acetylide, derived from **1a**,

Scheme 2[a]



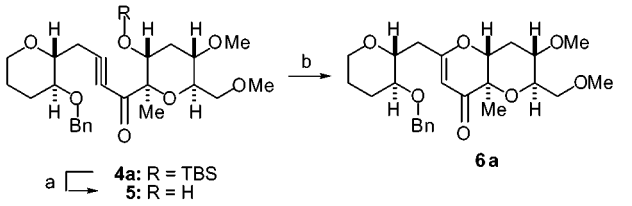
[a] Reagents and conditions: (a) **1**, *t*-BuLi, HMPA, THF, −78 °C; **2** in THF (88% for **3a**, 76% for **3b**); (b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N, −78 °C → rt (99% for **4a**, 100% for **4b**).

with **2** smoothly proceeded to give the secondary alcohol **3a** as a mixture of stereoisomers. The Swern oxidation of the alcohol **3a** quantitatively furnished the required ynone **4a**, corresponding to **iii**.

(3) See Supporting Information for the synthetic route of **1a**, **1b**, and **2**.

First, we examined an intramolecular hetero-Michael addition of the ynone **4a** for the construction of enone **6a**, corresponding to the key intermediate **iv** (Scheme 3). After

Scheme 3[a]



[a] Reagents and conditions: (a) aq HCl, MeOH, rt; (b) TBAF, THF, rt (43% from **4a**).

deprotection of the TBS group in **4a** with aqueous HCl in MeOH, the cyclization of the ynone **5** was attempted by treatment with a base (NaH, Et_3N, *N*-methylmorpholine, etc.), but only the starting material **5** was recovered. On the other hand, treatment of **4a** with TBAF in THF effected deprotection of TBS and successive cyclization at room temperature for 1 h, but the yield of **6a** was 43%.

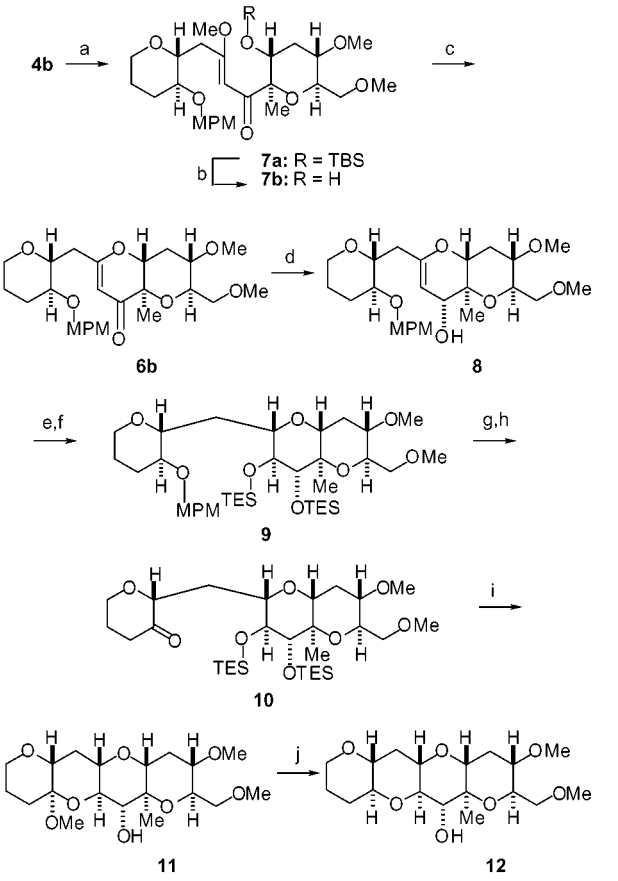
Next, we investigated hetero-Michael addition using an enone **7** having a β-methoxy group, expecting easier access of the hydroxyl group to the β-position (Scheme 4). The key intermediate **4b** (R = MPM) toward the enone **7a** was synthesized from **1b**[3] and **2** by the same procedure as that for **4a** as shown in Scheme 2. The β-methoxy group was introduced by treatment of **4b** with MeONa in MeOH to give the enone **7a** in 92% yield (Scheme 4). After deprotecting the TBS group of **7a** with TBAF, cyclization of the resulting alcohol **7b** was investigated. As expected, upon treatment of **7b** with *p*-TsOH in toluene[4] at 60 °C, the desired hetero-Michel reaction took place to give the enone **6b** in 63% yield from **7a**.

With the desired enone **6b** in hand, we next investigated the stereoselective conversion into **12** via the acetal **11**. Reduction of **6b** with DIBAH in toluene proceeded smoothly to give *equatorial* α-alcohol **8** (94%) as a single product. Subsequent hydroboration of **8** stereoselectively took place from the α-side to afford a diol (85%), which was protected as the di-TES ether **9** in 89% yield. Deprotection of the MPM group of **9** followed by Swern oxidadion gave ketone **10**. Treatment of **10** with *p*-TsOH in MeOH−CH_2Cl_2 at 55 °C effected the removal of the di-TES groups and cyclization to give the desired methyl acetal **11** in 74% yield (from **9**). Finally, reduction of the acetal **11** with Et_3SiH−TMSOTf proceeded smoothly to give the desired *trans*-fused 6-6-6-6-membered tetracyclic ether **12** as the sole product in 82% yield.

Having completed the construction of *trans*-fused 6-6-6-6-membered tetracyclic ether **12** having an *equatorial* α-hydroxyl group, we next turned to the synthesis of the

(4) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8115.

Scheme 4[a]



[a] Reagents and conditions: (a) MeONa, MeOH, rt (92%); (b) TBAF, THF, rt (83%); (c) *p*-TsOH·H_2O, toluene, 60 °C (76%); (d) DIBAH, toluene, −78 °C (94%); (e) BH_3·THF, THF, 0 °C; 3 N NaOH, 30% H_2O_2, 0 °C (85%); (f) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (89%); (g) DDQ, CH_2Cl_2−H_2O (10:1), 0 °C; (h) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N, −78 °C → rt; (i) *p*-TsOH·H_2O, MeOH, CH_2Cl_2, 55 °C (74% from **9**); (j) Et_3SiH, TMSOTf, CH_2Cl_2, 0 °C (82%).

axial *β*-hydroxy isomer (Scheme 5). After the Swern oxidation of **12**, reduction of the ketone **13** with L-Selectride in THF at −78 °C proceeded smoothly to give only the desired *β*-alcohol **14** in 91% yield from **12**.[5] The stereostructure of both tetracyclic ethers, **12** and **14**, was confirmed by the ^1H and ^{13}C NMR and NOE analysis of the corresponding acetates **15** and **16**, prepared from **12** and **14**, respectively, by acetylation (Figure 2).

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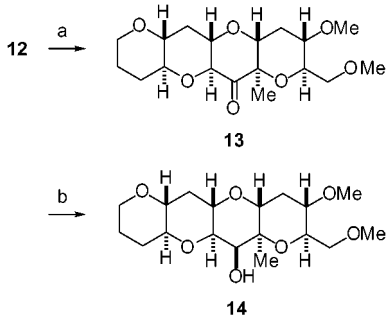
Scheme 5[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N, −78 °C → rt; (b) L-Selectride, THF, −78 °C (91% from **12**).

In conclusion, we have developed an efficient convergent synthesis of a *trans*-fused 6-6-6-6-membered tetracyclic ether ring system including 4α- or 4*β*-hydroxy-5-methyl-tetrahydropyran in a stereoselective manner. This strategy would be widely applicable to efficient and stereoselective synthesis of natural polycyclic ethers. Further studies along these lines are currently in progress in our laboratory.

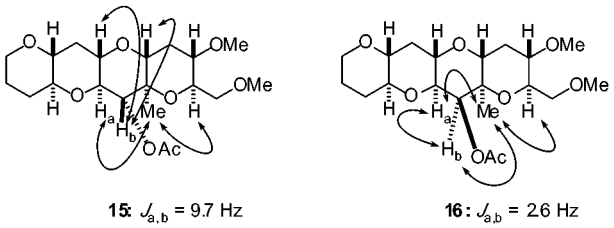


Figure 2. NOE and *J* value of **15** and **16**.

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Supporting Information Available: Synthetic scheme for compounds **1** and **2**, experimental procedures and spectral data for **3b**−**14**, and ^1H NMR spectra of **4b**, **6b**, **7b**, **12**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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