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Efficient convergent synthesis of a *trans*-fused 6-6-6-6-membered tetracyclic ether ring system

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Abstract

A very efficient convergent strategy for the construction of the *trans*-fused 6-6-6-6-membered tetracyclic ether ring system was developed based on the acetylide-triflate coupling of two tetrahydropyrans, oxidation of the alkyne group to an α-diketone, double cyclization to 6,6,6,6-membered tetracyclic diacetal, and stereoselective reduction of the diacetal with Et_3SiH–TMSOTf.

Keywords: alkynes; coupling reactions; acetals; tetrahydropyrans; polyethers; reduction.

Marine polycyclic ethers,[1] exemplified by the brevetoxins, have attracted the attention of numerous synthetic organic chemists due to their unique and complex structure, and potent biological activities. The characteristic structural feature of this family is the *trans*-fused polycyclic ether ring system. Although several convergent methods for the construction of the various ring systems have been reported,[2] the development of a more efficient convergent method is still required toward the total syntheses of these marine polycyclic ethers. We now report a very simple and highly efficient strategy toward the convergent syntheses of the polycyclic ether ring systems, employing the stereoselective synthesis of *trans*-fused 6-6-6-6-membered tetracyclic ether **1**.[3]

Our strategy for the convergent synthesis of **1** involves the simple four step-sequence as shown in Scheme 1: (1) coupling of a tetrahydropyran **i** having an acetylene, and **ii**; (2) oxidation of the resulting alkyne **iii** to the α-diketone **iv**; (3) intramolecular double acetalization of **iv** to the tetracyclic diacetal **v**; and (4) stereoselective reduction of **v** to give **1**. The most crucial and interesting step in this strategy is which route **iv** takes in the double acetalization, i.e. route A to the 6-membered diacetal **v** or route B to the 5-membered diacetal **vi**. Heat of formations of **v** (R=Me) and **vi** (R=Me), calculated by PM3, suggested that **v** is 6.0 kcal/mol lower in energy than **vi**, which means our desired route A to **v** would predominate.[4]

With this prospect, our convergent synthesis of **1** began with a coupling reaction of acetylide **2**[5] and triflate **3**[6] (Scheme 2). The coupling reaction of the lithium acetylide of **2** and **3** in the presence of HMPA

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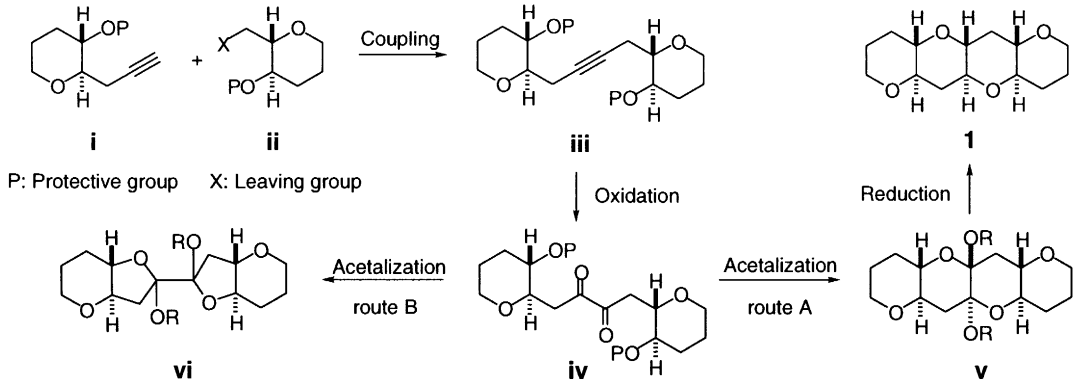
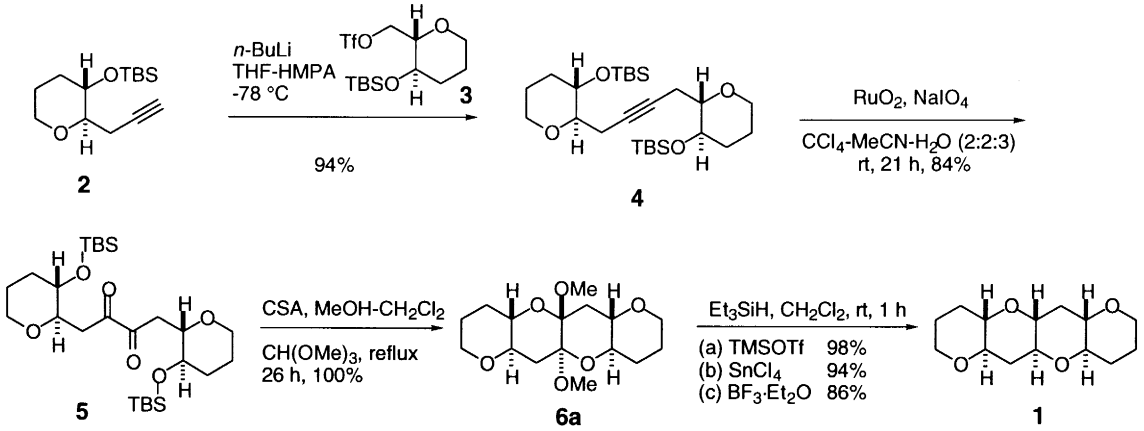


Scheme 1.

in THF proceeded smoothly, giving the symmetrical alkyne **4** in 94% yield.[7] Oxidation of the alkyne group in **4** with RuO_2–$NaIO_4$ in CCl_4–MeCN–H_2O[8] furnished the α-diketone **5** in 84% yield. The stage was now set for the crucial double acetalization step (route A or B), leading to 6-membered diacetal **v** or 5-membered diacetal **vi**. As was expected, the reaction proceeded via our desired route A with complete regio- and stereocontrol, giving the 6-membered diacetal **v**. Thus, upon treatment of **5** with CSA and $CH(OMe)_3$ in MeOH–CH_2Cl_2, deprotection of the TBS groups followed by a double acetalization took place under reflux for 26 h to give quantitatively the desired 6-6-6-6-membered tetracyclic diacetal **6a**, as the single product. During the present conversion reaction of **5** into **6a**, the formations of a small amount of the isomeric diacetal **6b**, dihemiacetal **7**, and monoacetal **8** were observed. The conformational analyses of the three possible stereoisomers **6a**–**c** by MM2* calculations revealed that the most stable isomer of the *trans*-fused tetracyclic diacetal **6a** lies 3.9 and 13.0 kcal/mol lower in energy than that of **6b** and **6c**, respectively (Fig. 1). The compounds **6b**, **7**, and **8** were prepared from **5** under the milder conditions as follows (Scheme 3): (1) *n*-Bu_4NF treatment gave the dihemiacetal **7** (100%); (2) TsOH treatment in MeOH at room temperature gave **8** (46%), and the two isomeric diacetals **6a** (14%) and **6b** (6%). The stereostructures of isomers **6a** and **6b** were unequivocally confirmed by ^1H, ^{13}C NMR, NOE (Fig. 1), and HMBC analyses.[9]



Scheme 2.

With the desired *trans*-fused tetracyclic acetal **6a** in hand, we proceeded to the final step of this convergent strategy, i.e. stereoselective reduction of the two acetal groups in **6a**.

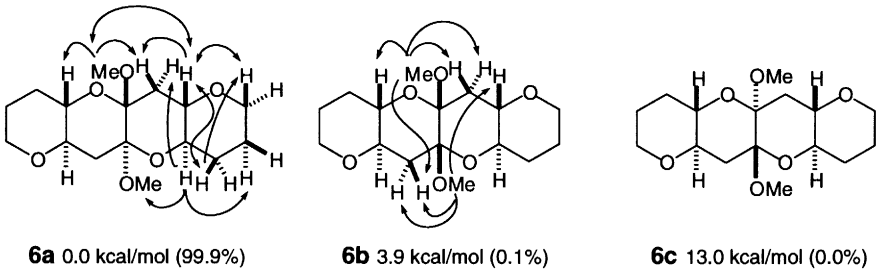
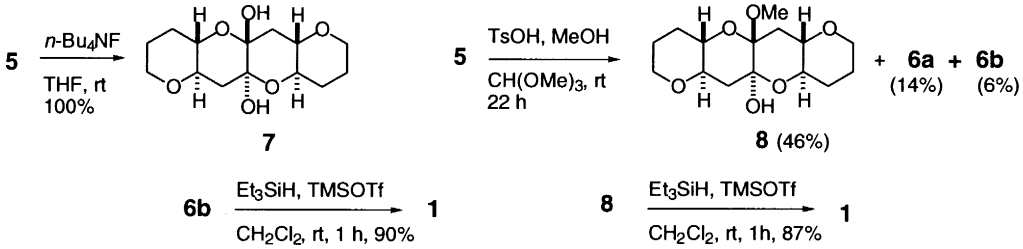


Fig. 1. Structures of **6a–c** and NOE correlations observed in **6a** and **6b**



Scheme 3.

Reduction of **6a** with Et_3SiH (3.0 equiv.) in the presence of TMSOTf (2.4 equiv.)[10a] in CH_2Cl_2 proceeded smoothly to give the desired *trans*-fused 6-6-6-6-membered tetracyclic ether **1**[2a,e,9] in 98% yield, and as the sole product (Scheme 2). The reduction of **6a** with Et_3SiH using either $SnCl_4$ or $BF_3 \cdot Et_2O$, instead of TMSOTf, under the same reaction conditions also stereoselectively provided **1** in high yields: i.e. (b) Et_3SiH–$SnCl_4$,[10b] 94% yield; (c) Et_3SiH–$BF_3 \cdot Et_2O$,[10c] 86% yield. Reductions of compounds **6b**, **7**, and **8** were also examined (Scheme 3). Interestingly, reduction of the stereoisomer **6b** with Et_3SiH–TMSOTf gave the same result as that of **6a**, to afford the *trans*-fused tetracyclic ether **1** in 90% yield. The present reduction of the two isomers **6a** and **6b** must thus proceed via the same oxonium ion intermediate. Furthermore, reduction of monoacetal **8** with Et_3SiH–TMSOTf also afforded **1** as the single product in 87% yield.[11]

In conclusion, we have developed a very simple and efficient convergent strategy for the construction of a *trans*-fused 6-6-6-6-membered tetracyclic ether ring system. Using this method, the synthesis of *trans*-fused tetracyclic ether **1** was achieved with complete stereoselectivity in only four steps, and in 77% overall yield from triflate **3**. This strategy would be widely applicable to efficient syntheses of natural polycyclic ethers. Further studies along these lines are currently in progress in our laboratory.

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3. During the course of our present study, the same strategy was reported by the Murai–Fujiwara group at the 77th National Meeting of the Chemical Society of Japan, on Sept. 18 at Sapporo. T.N. thanks Prof. A. Murai (Hokkaido University) for generously providing their manuscript, submitted to *Tetrahedron Lett*. Thus, we now disclose our recent results in this paper.
4. The most stable conformers of **v** (R=Me) and **vi** (R=Me), indicated by MM2*/MacroModel 6.0 calculations (Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem*. **1990**, *11*, 440), were used for PM3/MOPAC.
5. The reaction of lithium (trimethylsilyl)acetylide and the enantiomer of **3**,[12] prepared from tri-*O*-acetyl-D-glucal, gave the alkyne **2** (9%) and the corresponding TMS acetylene (89%), which was treated with K_2CO_3 in MeOH at room temperature to give **2** in 96% yield.
6. The triflate **3** was synthesized from L-glucose in six steps by following the procedure for preparation of the corresponding enantiomer. (1) Ac_2O, 33% HBr/AcOH; (2) Zn, $CuSO_4$, NaOAc, aq. AcOH (91%, two steps);[13] (3) Et_3SiH, $BF_3 \cdot Et_2O$, (4) H_2, Pd–C, MeOH (96%, two steps), (5) K_2CO_3, MeOH (100%),[2a] and (6) Tf_2O, 2,6-lutidine, THF; TBSOTf (90%).[12]
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9. Data for **6a**: mp 254–259°C (MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.57 (m, 1H), 1.74 (m, 2H), 1.98 (dd, 1H, *J*=12.5, 11.3 Hz), 1.98 (m, 1H), 2.17 (dd, 1H, *J*=12.5, 4.4 Hz), 3.17 (ddd, 1H, *J*=11.3, 9.2, 4.4 Hz), 3.27 (s, 3H), 3.39 (m, 1H), 3.41 (ddd, 1H, *J*=11.7, 9.2, 4.4 Hz), 3.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 28.8, 29.6, 47.1, 68.3, 70.6, 76.2, 98.5. Anal. calcd for $C_{16}H_{26}O_6$: C, 61.13; H, 8.34. Found: C, 61.05; H, 8.38. Data for **6b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.40 (dddd, 1H, *J*=12.2, 12.2, 10.7, 4.9 Hz), 1.49 (dddd, 1H, *J*=12.2, 11.3, 11.3, 5.4 Hz), 1.65 (dd, 1H, *J*=13.2, 7.8 Hz), 1.68 (m, 2H), 1.73 (m, 2H), 1.78 (dd, 1H, *J*=11.7, 11.2 Hz), 1.99 (m, 1H), 2.12 (m, 1H), 2.26 (dd, 1H, *J*=11.7, 4.9 Hz), 2.41 (dd, 1H, *J*=13.2, 7.8 Hz), 3.17 (ddd, 1H, *J*=11.2, 9.4, 4.9 Hz), 3.276 (s, 3H), 3.282 (s, 3H), 3.35 (ddd, 1H, *J*=11.3, 9.4, 4.0 Hz), 3.36 (m, 1H), 3.38 (m, 1H), 3.58 (ddd, 1H, *J*=10.7, 9.8, 3.9 Hz), 3.60 (ddd, 1H, *J*=9.8, 7.8, 7.8 Hz), 3.87 (m, 1H), 3.90 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.3, 25.8, 29.1, 30.4, 33.0, 35.4, 47.5, 47.8, 67.6, 68.0, 70.3, 70.5, 73.9, 76.5, 98.7, 98.9. The stereostructure of **1** was confirmed by ^{1}H, ^{13}C NMR, NOE, and HMBC analyses. Data for **1**: mp 205–207°C (hexane, sublime); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (m, 1H), 1.51 (ddd, 1H, *J*=11.2, 10.7, 10.7 Hz), 1.73 (m, 2H), 2.08 (m, 1H), 2.32 (ddd, 1H, *J*=11.2, 3.5, 3.5 Hz), 3.05 (m, 1H), 3.07 (m, 1H), 3.15 (m, 1H), 3.39 (m, 1H), 3.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 29.3, 35.7, 68.0, 77.1, 77.3, 78.3; HRMS *m*/*z* for $C_{14}H_{23}O_4$ (MH^+) calcd 255.1596, found 255.1610.
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11. Reduction of **7** with Et_3SiH (10 equiv.) in the presence of TMSOTf (4.8 equiv.) in CH_2Cl_2 at room temperature for 30 h produced **1** in 36% yield. The structures of other products are under investigation.
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