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SYNTHESIS OF 2-METHYLENETETRAHYDROPYRAN-3-OL DERIVATIVE, A KEY SEGMENT FOR CONVERGENT SYNTHESIS OF POLYCYCLIC ETHERS BASED ON SUZUKI-MIYAJIWA COUPLING[†]

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[†] Dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

Abstract – 2-Methylenetetrahydropyran-3-ol derivative, a key segment for convergent synthesis of polycyclic ethers based on Suzuki-Miyajiri coupling, was efficiently synthesized by two methods; (1) *via* SmI₂-induced reductive cyclization of β-alkoxyvinyl sulfone with aldehyde followed by elimination of the sulfonyl group, and (2) *via* SmI₂-induced cyclization of β-alkoxyvinyl sulfoxide with aldehyde followed by dehydration of the 2-hydroxymethyl group.

Since brevetoxin B was isolated as a red tide toxin, many marine polycyclic ethers have been reported.¹ These natural products have a characteristic *trans*-fused polycyclic ether ring system and exhibit potent biological activities, such as neurotoxicity, cytotoxicity, and antiviral and antifungal activities. The skeletal complexity and biological activities of these marine polycyclic ethers have attracted much attention among chemists and biochemists. Thus, numerous synthetic chemists have extensively studied the development of new synthetic methods for polycyclic ether and the total synthesis of these natural products.² Several efficient convergent strategies have been developed as tools for the total synthesis of marine polycyclic ethers.^{2h} Sasaki and coworkers reported an efficient convergent strategy based on Suzuki-Miyajiri coupling,³ and successfully applied it to the total synthesis of gambierol,⁴ gymnocin-A,⁵ and brevenal.⁶ In their strategy, two cyclic ether segments, *exo*-methylene ether (**i**) and enol triflate (**iii**), are used as coupling partners leading toward polycyclic ether (Figure 1). After hydroboration of **i** with

9-BBN, the resulting 2-boryl derivative (**ii**) was efficiently coupled with **iii** under Suzuki-Miyaura coupling conditions to give the combined ether (**iv**), which was converted into polycyclic ether (**vi**) via acetal (**v**). The 2-methylenetetrahydropyran-3-ol derivative (**i**), a key coupling partner for this convergent synthesis, has usually been synthesized from 2-iodomethyl-tetrahydropyran (**vii**).

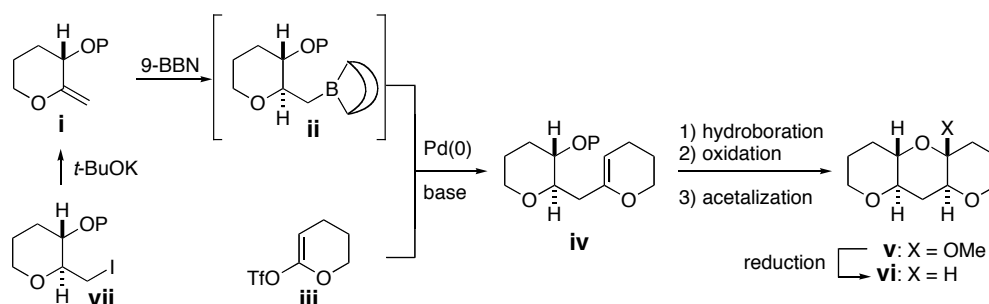
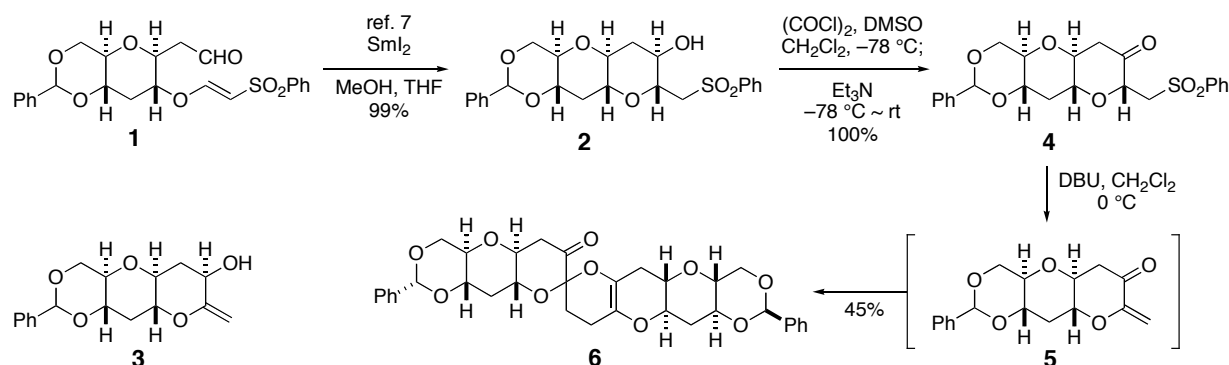


Figure 1. Convergent synthesis of polycyclic ethers based on Suzuki-Miyaura coupling

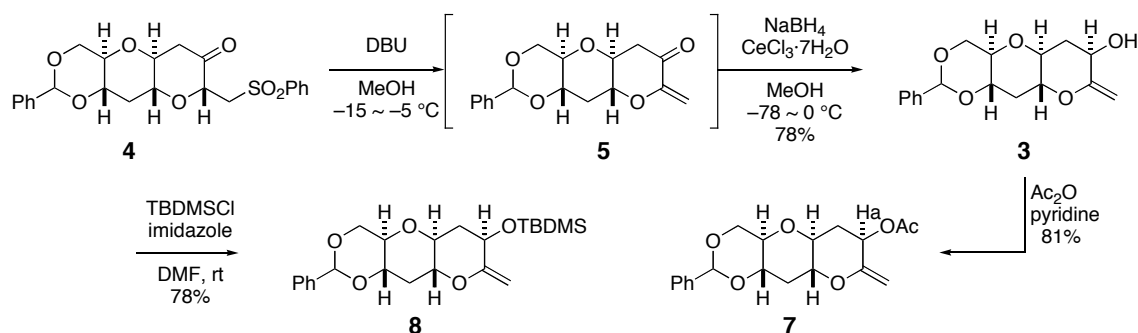
Recently, we have developed synthetic methods for cyclic ethers by utilizing SmI_2 -induced cyclization of β -alkoxyvinyl sulfone with aldehyde⁷ and β -alkoxyvinyl sulfoxide with aldehyde,⁸ affording 2,6-*syn*-2,3-*trans*-tetrahydropyrans having 2-phenylsulfonylmethyl and 2-tolylsulfoxymethyl groups, respectively. We now report the synthesis of the 2-methylene-tetrahydropyran-3-ol derivative (**i**) starting from these products.

First, we examined the synthesis of 2-methylenetetrahydropyran-3-ol (**3**) from 2-phenylsulfonylmethyl-tetrahydropyran-3-ol (**2**),⁷ prepared by SmI_2 -induced cyclization of β -alkoxyvinyl sulfone (**1**) (Scheme 1). Swern oxidation of the alcohol (**2**) afforded ketone (**4**) in quantitative yield. Then, elimination of the phenylsulfonyl group to give enone (**5**) was attempted by means of base treatment. Treatment of **4** with DBU in CH_2Cl_2 at 0 °C afforded dimeric compound (**6**) (45% yield), which would be produced via enone (**5**).⁹ Several reaction conditions were examined; elimination of the sulfonyl group proceeded at -15 °C, while the dimerization did not take place at this temperature, but started at -5 °C.

On the basis of these results, we attempted one-pot synthesis of the desired *exo*-methylene (**3**) by elimination of the phenylsulfonyl group of **4** followed by Luche reduction¹⁰ of the resulting enone (**5**) (Scheme 2). Upon treatment of the ketone (**4**) with DBU in MeOH at -15 ~ -5 °C, elimination took place to give enone (**5**), which was immediately reduced with NaBH_4 at -78 ~ 0 °C in the presence of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ to give the desired *exo*-methylene compound (**3**) in 78% yield. The configuration of the hydroxy group in **3** was determined to be *equatorial* based on the value of the ¹H NMR coupling constant between H_a and methylene protons ($J = 10.4, 5.8$ Hz) of the corresponding acetate (**7**), prepared by acetylation of **3**. Protection of **3** with TBDMSCl and imidazole afforded TBDMS ether (**8**) in 78% yield, which should be useful for the convergent synthesis of polycyclic ethers.



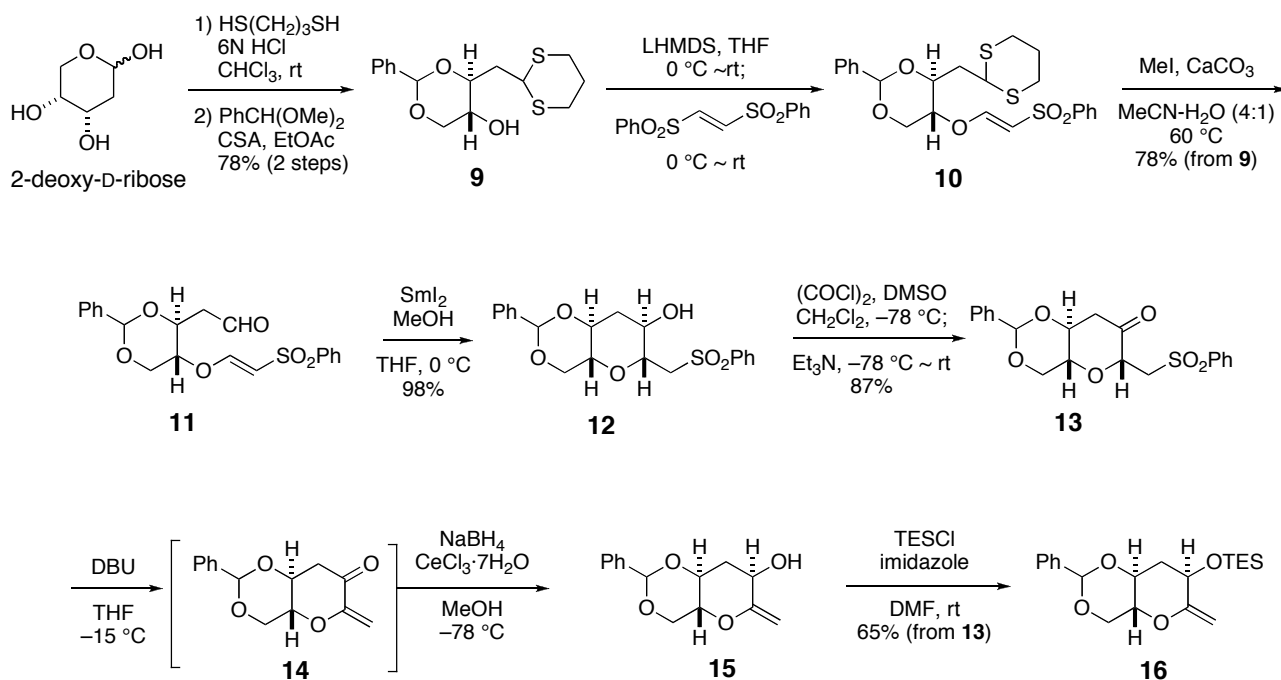
Scheme 1



Scheme 2

As an application of this method, we synthesized the 2-methylenetetrahydropyran (**16**), a key segment in Sasaki's total synthesis of gymnocin-A,⁵ in which **16** was synthesized starting from 2-deoxy-D-ribose in fifteen steps with 38% overall yield.^{5b,11} First, we examined a route *via* SmI₂-induced cyclization of β-alkoxyvinyl sulfone with aldehyde (Scheme 3). Treatment of the known thioacetal (**9**),¹² prepared from 2-deoxy-D-ribose by thioacetalization and benzylideneation (78% yield), with LHMDS and (*E*)-bis(phenylsulfonyl)-1,2-ethylene stereoselectively afforded (*E*)-β-alkoxyvinyl sulfone (**10**). Removal of the thioacetal from **10** by treatment with MeI in the presence of CaCO₃ in aqueous MeCN¹³ afforded aldehyde (**11**) in 78% yield (two steps from **9**). Treatment of **11** with SmI₂ in the presence of MeOH in THF stereoselectively afforded 2,6-*syn*-2,3-*trans*-tetrahydropyran (**12**) in 98% yield. The stereochemistry of **12** was supported by the value of the ¹H NMR coupling constant (ddd, *J* = 10.2, 10.2, 4.5 Hz; Ha) and NOE of the corresponding acetate (**17**), prepared by acetylation of **12** (Figure 2). Swern oxidation of the alcohol (**12**) gave ketone (**13**) in 87% yield. Treatment of **13** under the same conditions used for **4** (DBU, MeOH) gave unsatisfactory results. After several attempts, treatment of **13** with DBU in THF at -15 °C for 1 h, followed by Luche reduction (NaBH₄, CeCl₃·7H₂O, MeOH) at -78 °C in one pot afforded *exo*-methylene alcohol (**15**), which without further purification was treated with chlorotriethylsilane

(TESCl) and imidazole in DMF to give the desired *exo*-methylene TES ether (**16**)¹⁴ in 65% yield (two steps from **13**). The spectral data of the synthetic **16** were identical with those reported for authentic **16**.⁵ Thus, a new synthesis of **16** was accomplished in only eight steps from 2-deoxy-D-ribose with 34% overall yield.

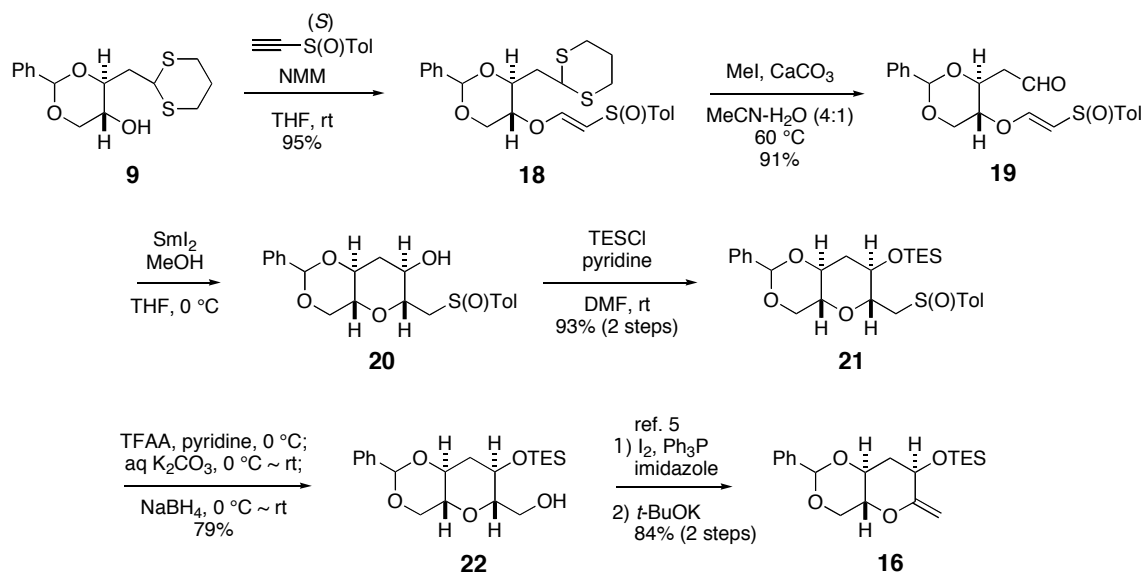


Scheme 3

Next, we examined an alternative route for the synthesis of 2-methylenetetrahydropyran (**16**) *via* SmI₂-induced cyclization of β-alkoxyvinyl sulfoxide with aldehyde (Scheme 4). Treatment of **9** with (*S*)-ethynyl *p*-tolylsulfoxide in the presence of *N*-methylmorpholine (NMM) afforded (*E*)-β-alkoxyvinyl sulfoxide (**18**) in 95% yield. After removal of the thioacetal from **18** (91% yield), the resulting aldehyde (**19**) was treated with SmI₂ in THF-MeOH to give 2,6-*syn*-2,3-*trans*-tetrahydropyran (**20**) as a single product, which was protected with TESCl to give TES ether (**21**) in 93% yield (two steps). The stereochemistry of **20** was supported by the value of the ¹H NMR coupling constant (ddd, *J* = 10.4, 10.4, 4.8 Hz; Ha) and NOE measurement of the corresponding acetate (**23**) (Figure 2). Pummerer rearrangement of the sulfoxide (**21**) with TFAA afforded aldehyde, which was reduced with NaBH₄ in one pot to give alcohol (**22**)¹⁵ in 79% yield. The alcohol (**22**) was previously converted into *exo*-methylene (**16**) in two steps (1. I₂, Ph₃P, imidazole, 2. *t*-BuOK) in 84% yield.⁵ Thus, an alternative synthesis of **16** was accomplished in nine steps from 2-deoxy-D-ribose with 42% overall yield.

We have developed new synthetic routes for 2-methylenetetrahydropyran-3-ol derivative, which is a key segment for convergent synthesis of marine polycyclic ethers based on Suzuki-Miyaura coupling. In most total syntheses of polycyclic ethers based on Suzuki-Miyaura coupling,^{4,6} the starting compounds contain

cyclic ether having a 2-hydroxymethyl group, which is transformed to *exo*-methylene at the final stage. In the present method, the *exo*-methylene cyclic ether ring can be synthesized at the final stage by SmI_2 -induced cyclization followed by elimination. Thus, this method provides another synthetic route to the coupling partner, *exo*-methylene cyclic ether, in the convergent synthesis.



Scheme 4

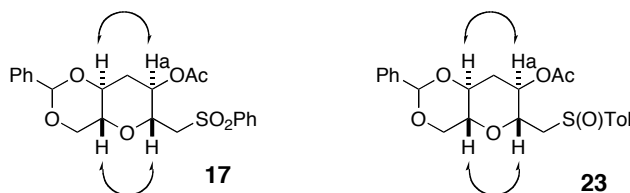


Figure 2. Observed NOE of **17** and **23**

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14. Data for synthetic **16**: $[\alpha]_D^{24} +43.1$ (c 1.01, C₆H₆); IR (film) 2956, 2877, 1661, 1216, 1095, 1028 cm⁻¹; ¹H NMR (500 MHz, C₆D₆) δ 7.62-7.60 (m, 2H), 7.19-7.10 (m, 3H), 5.33 (s, 1H), 4.88 (s, 1H), 4.80 (s, 1H), 4.24 (dd, *J* = 9.5, 4.0 Hz, 1H), 4.19 (dd, *J* = 10.4, 5.5 Hz, 1H), 3.56 (ddd, *J* = 11.3, 10.4, 5.8 Hz, 1H), 3.52 (dd, *J* = 9.8, 9.8 Hz, 1H), 3.36 (ddd, *J* = 11.9, 9.5, 4.3 Hz, 1H), 2.38 (ddd, *J* = 11.3, 5.5, 5.5 Hz, 1H), 1.90 (ddd, *J* = 11.3, 11.3, 11.3 Hz, 1H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.57 (q, *J* = 8.0 Hz,

- 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 161.7, 138.3, 129.0, 128.2 (2C), 126.7 (2C), 101.7, 93.3, 76.1, 74.3, 69.3, 67.3, 39.6, 7.0 (3C), 5.1 (3C); HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{30}\text{O}_4\text{SiNa}$ [(M+Na) $^+$] 385.1806, found 385.1806.
15. Data for synthetic **22**: $[\alpha]_{\text{D}}^{24}$ -48.0 (c 0.93, CHCl_3); IR (film) 3495, 2955, 2876, 1092 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.50-7.48 (m, 2H), 7.37-7.34 (m, 3H), 5.52 (s, 1H), 4.33 (dd, $J = 10.5, 5.0$ Hz, 1H), 3.87 (ddd, $J = 11.5, 5.5, 3.0$ Hz, 1H), 3.76 (ddd, $J = 11.0, 9.5, 4.5$ Hz, 1H), 3.68 (m, 1H), 3.68 (dd, $J = 10.5, 10.5$ Hz, 1H), 3.52 (ddd, $J = 11.0, 9.0, 4.0$ Hz, 1H), 3.43 (ddd, $J = 10.0, 10.0, 4.5$ Hz, 1H), 3.35 (ddd, $J = 8.5, 5.5, 3.0$ Hz, 1H), 2.43 (ddd, $J = 11.5, 4.5, 4.5$ Hz, 1H), 1.91 (dd, $J = 6.0, 6.0$ Hz, 1H), 1.76 (ddd, $J = 11.5, 11.5, 11.5$ Hz, 1H), 0.96 (t, $J = 8.0$ Hz, 9H), 0.63 (q, $J = 7.5$ Hz, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.3, 129.1, 128.3 (2C), 126.1 (2C), 101.7, 82.3, 76.4, 72.9, 69.2, 66.5, 62.3, 38.6, 6.7 (3C), 4.9 (3C); HRMS (ESI) calcd for $\text{C}_{20}\text{H}_{32}\text{O}_5\text{SiNa}$ [(M+Na) $^+$] 403.1911, found 403.1893.