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SmI_2-induced reductive cyclization of optically active β-alkoxyvinyl sulfoxides with aldehyde

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Dedicated to the memory of the late Professor Yoshihiko Ito

Abstract—SmI_2-induced reductive cyclization of optically active (*E*)- and (*Z*)-β-alkoxyvinyl sulfoxides with aldehyde was developed for the construction of several stereoisomers of tetrahydropyran derivatives.

Marine polycyclic ethers exemplified by brevetoxin-B, a red tide toxin, have a unique *trans*-fused polycyclic ether ring system.[1] Their synthetically challenging complex structures and potent bioactivities have attracted the attention of numerous synthetic organic chemists. Thus, various methods for the synthesis of polycyclic ethers have been extensively studied.[2] We have already developed an efficient method for the construction of *trans*-fused polycyclic ether based on the SmI_2-induced reductive cyclization of β-alkoxyacrylate **A** with a carbonyl group, affording 2,6-*syn*-2,3-*trans*-tetrahydropyrans **B** with complete stereoselectivity (Fig. 1).[3] Several groups have successfully applied this method to the synthesis of polycyclic ethers.[4] Recently, we have also reported SmI_2-induced reductive cyclization of (*E*)- and (*Z*)-β-alkoxyvinyl sulfones with aldehyde to give 2,6-*syn*-2,3-*trans*- and 2,6-*syn*-2,3-*cis*-tetrahydropyrans, respectively.[5] We next turned our attention to the SmI_2-induced reaction of optically active β-alkoxyvinyl sulfoxides with aldehyde. The chirality of sulfoxide and the (*E*/*Z*)-stereochemistry of the olefin in the substrates would be expected to influence the stereoselectivity in these reactions. Lee and co-workers recently reported the same type of reaction using acyclic compounds.[6] Here, we present our results on SmI_2-induced intramolecular cyclization of β-alkoxyvinyl sulfoxide with aldehyde.[7]

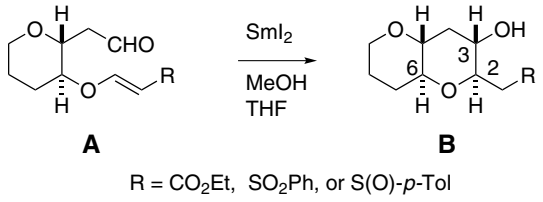

Figure 1. SmI_2-induced reductive cyclization.

First, we examined the SmI_2-induced reductive cyclization with aldehydes **4b** and **6b** having (*E*)-β-alkoxyvinyl (*R*)- or (*S*)-sulfoxide, respectively, as substrates (Scheme 1). Addition of alcohol **1**[4f] to (*R*)-ethynyl *p*-tolylsulfoxide **2**[8] in the presence of *N*-methylmorpholine (NMM) stereoselectively afforded (*E*)-β-alkoxyvinyl (*R*)-sulfoxide **4a** in 96% yield,[9] and this was reduced with DIBAH to give aldehyde **4b** in 85% yield. Treatment of (*E*)-(*R*)-**4b** with 2.5 equiv of SmI_2[10] in the presence of MeOH (2.6 equiv) in THF effected reductive cyclization to give 2,6-*anti*-2,3-*cis*-tetrahydropyran **5a** as a single product, which, without purification, was acetylated with Ac_2O to give acetate **5b**[11] in 64% yield (two steps). Use of CF_3CH_2OH instead of MeOH as a proton source slightly improved the yield of **5b** (71%).[12] On the other hand, the reaction of **1** and (*S*)-ethynyl *p*-tolylsulfoxide **3** in the presence of NMM, followed by DIBAH reduction, afforded aldehyde **6b**. The SmI_2-induced cyclization of (*E*)-(*S*)-**6b** in the presence of MeOH afforded 2,6-*syn*-2,3-*trans*-tetrahydropyran **7a**, which was acetylated to give acetate **7b**[11] in 85% yield (two steps).

Keywords: Samarium diiodide; C–C bond formation; Polycyclic ethers; Ethynyl *p*-tolylsulfoxide; Tetrahydropyranol.
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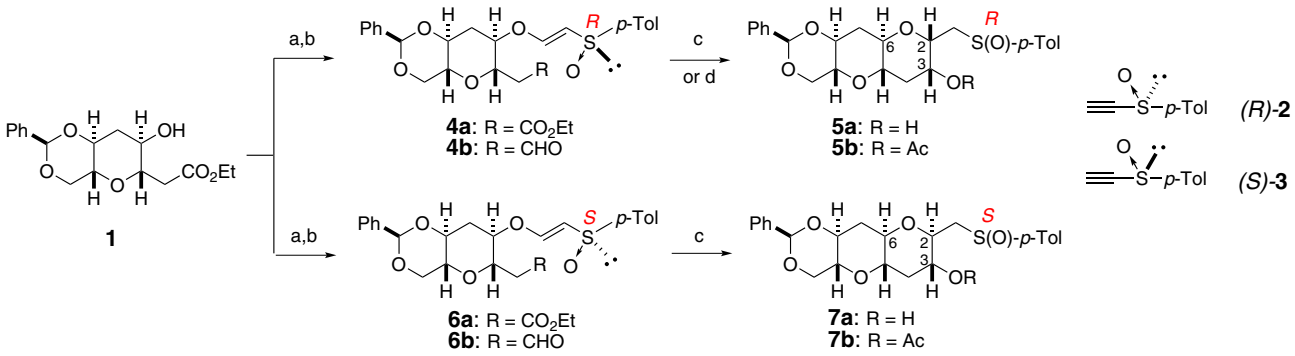
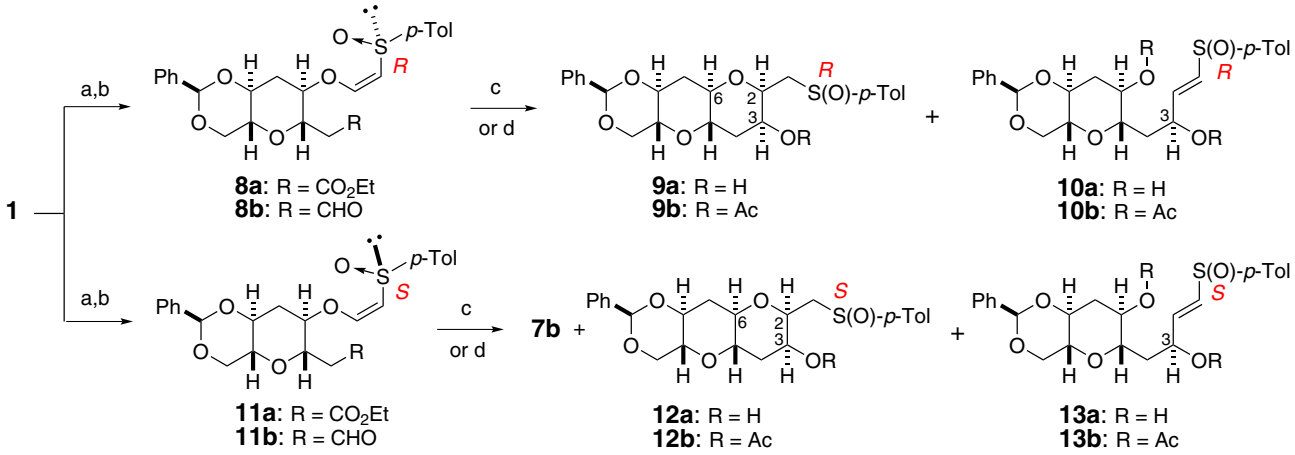


Scheme 1. Reagents and conditions: (a) (*R*)-**2** or (*S*)-**3**, NMM, CH_2Cl_2, rt, 96% for **4a**, 96% for **6a**; (b) DIBAH, CH_2Cl_2, −78 °C, 85% for **4b**, 92% for **6b**; (c) SmI_2, MeOH, CH_2Cl_2, 0 °C; Ac_2O, pyridine, rt, 64% for **5b** (two steps), 85% for **7b** (two steps); (d) SmI_2, CF_3CH_2OH, THF, 0 °C; Ac_2O, pyridine, rt, 71% for **5b** (two steps).



Scheme 2. Reagents and conditions: (a) LHMDS, (*R*)-**2** or (*S*)-**3**, THF, 0 °C, then **1**, −78 to −20 °C, 88% for **8a**, 91% for **11a**; (b) DIBAH, CH_2Cl_2, −78 °C, 45% for **8b**, 73% for **11b**; (c) SmI_2, MeOH, CH_2Cl_2, 0 °C; Ac_2O, pyridine, rt, 27% for **9b** and 26% for **10b** (two steps), 3% for **7b**, 15% for **12b**, and 21% for **13b** (two steps); (d) SmI_2, CF_3CH_2OH, THF, 0 °C; Ac_2O, pyridine, rt, 45% for **9b** and 27% for **10b** (two steps).

Next, aldehydes **8b** and **11b**, having (*Z*)-β-alkoxyvinyl (*R*)- and (*S*)-sulfoxide, respectively, were examined (Scheme 2). Treatment of alcohol **1** and (*R*)-sulfoxide **2** with LHMDS stereoselectively afforded (*Z*)-β-alkoxyvinyl (*R*)-sulfoxide **8a** in 88% yield,[9] and DIBAH reduction gave aldehyde **8b** (45%). Treatment of (*Z*)-(*R*)-**8b** with SmI_2 in the presence of MeOH in THF followed by acetylation afforded two products; 2,6-*syn*-2,3-*cis*-tetrahydropyran **9b**[11] (27%) and γ-acetoxyvinyl sulfoxide **10b**[13] (26%). Use of CF_3CH_2OH instead of MeOH in the present reaction afforded **9b** (45%) and **10b** (27%). Moreover, addition of **1** and (*S*)-**3** in the presence of LHMDS, followed by DIBAH reduction, afforded aldehyde **11b**. The same reaction of (*Z*)-(*S*)-**11b** with SmI_2, followed by acetylation, gave many products, which contain 2,6-*syn*-2,3-*trans*-**7b** (3%), 2,6-*syn*-2,3-*cis*-**12b**[11] (15%), γ-acetoxyvinyl sulfoxide **13b**[13] (21%), etc. Use of CF_3CH_2OH did not improve the yield of **7b** and **12b**.

These results can be explained as follows (Fig. 2). In the SmI_2-induced cyclization, the first single electron reduction of aldehyde with SmI_2 gives a ketyl radical and then C–C bond formation occurs in the chelated intermediate to give the cyclized product.[3,5] In the reaction of (*E*)-(*R*)-**4b** with SmI_2, cyclization would proceed through transition state **ii** chelated by Sm(III) and sulfoxide to give **5a**, because **ii** has an equatorial *p*-tolyl group in the chair-like conformation, whereas **i** has an axial one.[14] Similarly, the reaction of (*E*)-(*S*)-**6b** would proceed through the chelated transition state **iii** having an equatorial *p*-tolyl group to give **7a**. The reaction of (*Z*)-(*R*)-**8b** would also proceed through the chelated transition state **v** to give **9a**. In the case of **11b**, the corresponding chelated transition state **vi** would be unfavorable because of the axial *p*-tolyl group; thus, the reaction would proceed via the non-chelated transition state **vii** or **viii** to give **7a** and **12a**. The olefinic by-products **10a** and **13a** might be produced by ring opening subsequent to the cyclization; the axial-OSm(III) group of the intermediate **ix**, generated through **v** or **viii** via C–C bond formation followed by the second reduction with SmI_2, might participate in the ring opening together with the ring-O atom.

The *p*-tolylsulfoxymethyl group of product **7a** was transformed to an aldehyde group for application to the synthesis of polycyclic ethers (Scheme 3). SmI_2-induced reaction of **6b** followed by TBS protection afforded the

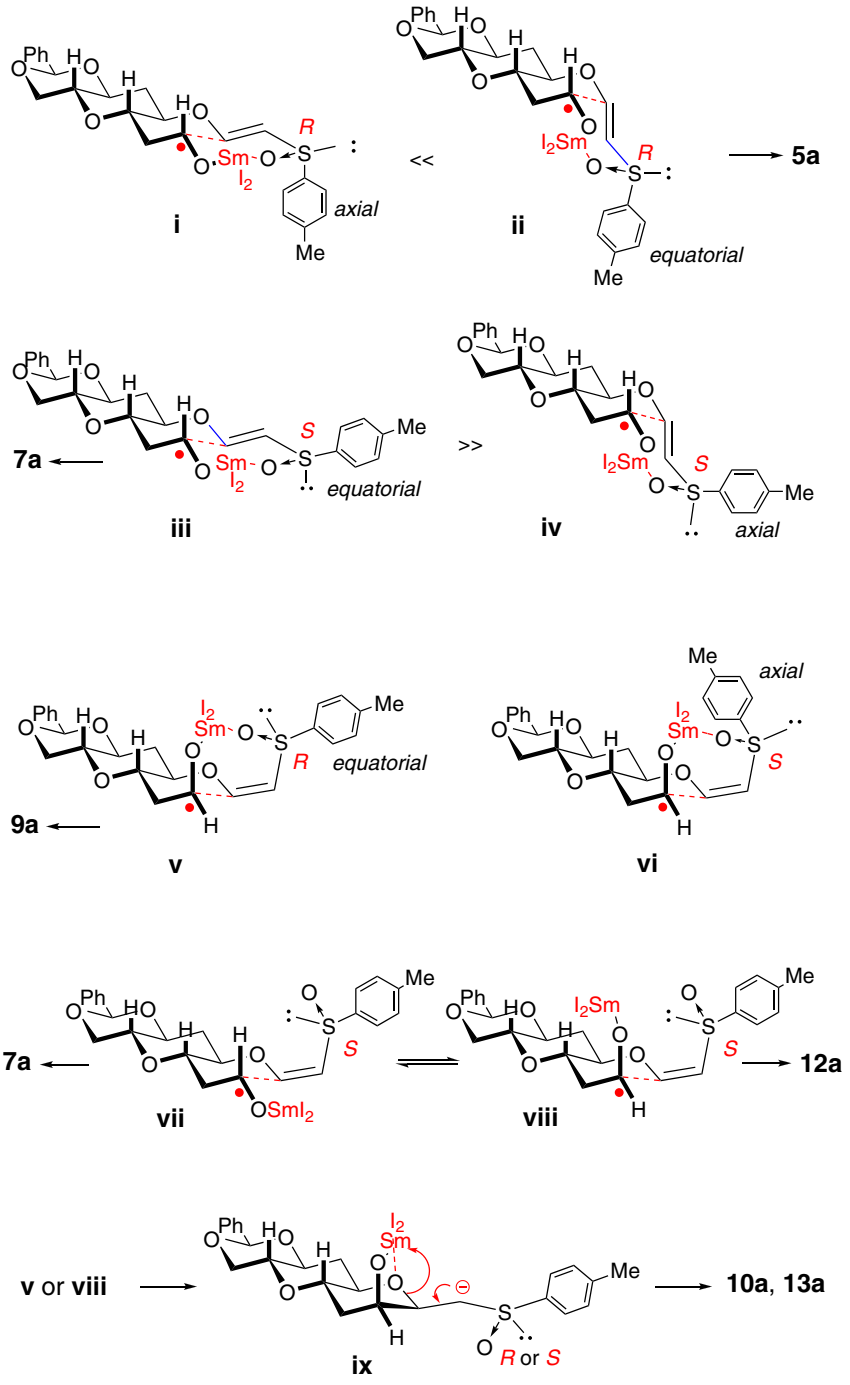
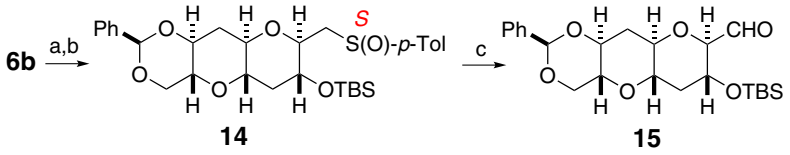
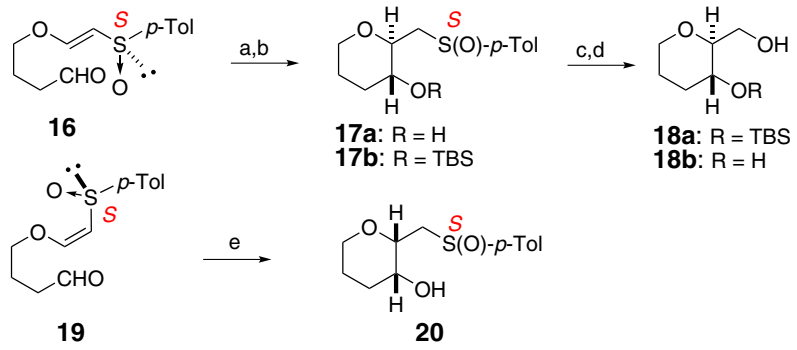


Figure 2. Plausible transition states of SmI_2-induced cyclization of **4b**, **6b**, **8b**, and **11b**.



Scheme 3. Reagents and conditions: (a) SmI_2, MeOH, THF, 0 °C; (b) TBSCl, imidazole, DMF, rt, 90% (two steps); (c) $(CF_3CO)_2O$, pyridine, MeCN, 0 °C; H_2O, K_2CO_3, 0 °C, 72%.



Scheme 4. Reagents and conditions: (a) SmI_2, MeOH, THF, 0 °C, 87% for **17a**; (b) TBSCl, imidazole, DMF, rt, 88% for **17b**; (c) $(CF_3CO)_2O$, pyridine, MeCN, 0 °C, then H_2O, K_2CO_3, $NaBH_4$, 97% for **18a**; (d) *n*-Bu_4NF, THF, rt, 100% for **18b**; (e) SmI_2, CF_3CH_2OH, THF, 0 °C, 68%.

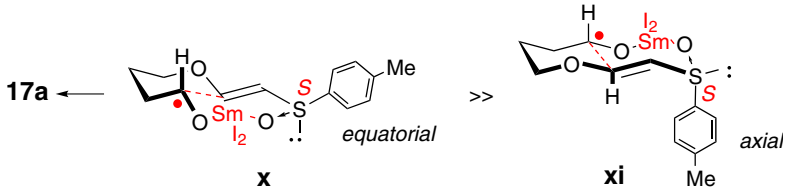


Figure 3. Plausible transition state of SmI_2-induced cyclization of **17**.

TBS–ether **14** in 90% yield. Sulfoxide **14** was subjected to the Pummerer rearrangement to give aldehyde **15** in 72% yield.

The stereospecific cyclization in the present reactions apparently proceeded via a chelated transition state involving strong coordination with sulfoxide and Sm(III). Therefore, we expected that reductive cyclization using acyclic aldehyde having an optically active β-alkoxyvinyl sulfoxide would be an effective approach for the asymmetric synthesis of tetrahydropyran derivatives. Treatment of aldehyde **16**[15] having (*E*)-(*S*)-vinylsulfoxide with SmI_2 in the presence of MeOH effected reductive cyclization to give the *trans*-tetrahydropyran **17a** in 87% yield as a single product with >99% ee (Scheme 4).[6] This result means that the reaction proceeds through the completely chelated transition state **x** (Fig. 3). Alcohol **17a** was converted into (−)-3-tetrahydropyranol derivatives **18a**[16] and **18b**[16] in excellent yield via TBS protection, Pummerer rearrangement–$NaBH_4$ reduction, and removal of the TBS group. This method for the synthesis of (−)-**18a** and (−)-**18b** is expected to be useful, because these compounds were previously prepared from L-glucose.[17] On the other hand, the reaction of aldehyde **19**[15] having (*Z*)-(*S*)-vinylsulfoxide with SmI_2 in the presence of CF_3CH_2OH gave *cis*-tetrahydropyran **20** in 68% yield. The same reaction using the corresponding enantiomers of **16** and **19** having (*R*)-vinylsulfoxide gave the enantiomers of **17a** and **20**, respectively.

In summary, the SmI_2-induced stereospecific cyclization of β-alkoxyvinyl sulfoxide with aldehyde was developed for the construction of several stereoisomers of tetrahydropyran derivatives. The desired stereoisomers of tetrahydropyrans could be obtained by selecting the appropriate combination of substrate and reagent, (*R*)-**2** or (*S*)-**3**. Thus, asymmetric synthesis of 3-tetrahydropyranols was efficiently accomplished.

Acknowledgement

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11. The stereochemistry of the newly formed tetrahydropyran in **5b**, **7b**, **9b** and **12b** was confirmed by the coupling constants of C3–H and NOE measurement. **5a**: δ 5.16 (ddd, $J = 11.3, 5.5, 5.5$ Hz, 1H); **7b**: δ 4.67 (ddd, $J = 11.0, 9.8, 4.6$ Hz, 1H); **9b**: δ 5.11 (broad, $W_{1/2} = 5.6$ Hz, 1H); **12b**: δ 5.05 (broad, $W_{1/2} = 7.0$ Hz, 1H). NOEs between C2–H and C6–H in **9b** and **12b** were observed.
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13. *Selected ^1H NMR data*. **10b**: δ 6.53 (dd, $J = 15.3, 5.5$ Hz, 1H), 6.38 (dd, $J = 15.3, 1.2$ Hz, 1H), 5.67 (m, 1H), 4.69 (ddd, $J = 11.0, 9.8, 4.9$ Hz, 1H); **13b**: δ 6.49 (dd, $J = 15.2, 5.8$ Hz, 1H), 6.41 (d, $J = 15.2$ Hz, 1H), 5.65 (m, 1H), 4.66 (ddd, $J = 10.9, 10.9, 4.8$ Hz, 1H). Alkaline hydrolysis of the diacetate **10b** followed by acetylation afforded a 2:3 mixture of 2,6-*syn*-2,3-*cis*-tetrahydropyran **9b** and 2,6-*anti*-2,3-*trans*-isomer via an intramolecular cyclization, and the same reaction of **13b** predominantly afforded 2,6-*anti*-2,3-*trans*-tetrahydropyran. These results confirmed the β-configuration of the 3-acetoxy group in **10b** and **13b**.
14. Lee et al. reported the same type of reaction using acyclic stereoisomers, including **21**.[6] They proposed similar transition states through sulfoxide and Sm(III) coordination to those shown here. However, they noted that it is difficult to propose a transition state structure for conversion of **21** to **22**; a possible transition state structure **xii** does not adopt the familiar chair-like conformation. Their result would be well explained by our proposed transition state, i.e., the cyclization of **21** should proceed through the transition state **xiii** to give **22**.
15. Aldehydes **16** and **19** were prepared from 2,3-dihydrofuran as follows. (1) $BF_3{\cdot}Et_2O$, MeOH, 1,3-propanedithiol, CH_2Cl_2, rt;[18] (2a) (*S*)-**3**, NMM, CH_2Cl_2, rt, 85% (two steps) or (2b) (*S*)-**3**, LHMDS, THF, −20 °C, 92% (two steps); (3) MeI, $CaCO_3$, MeCN, H_2O, 60 °C, 88% for **16**, 79% for **19**.
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