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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]

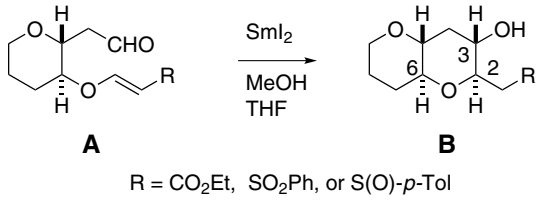

Figure 1. SmI_2-induced reductive cyclization.

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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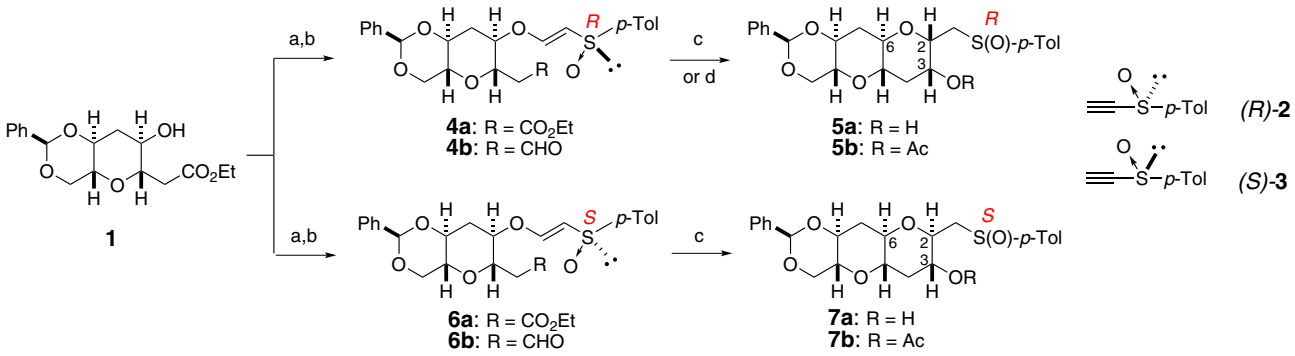
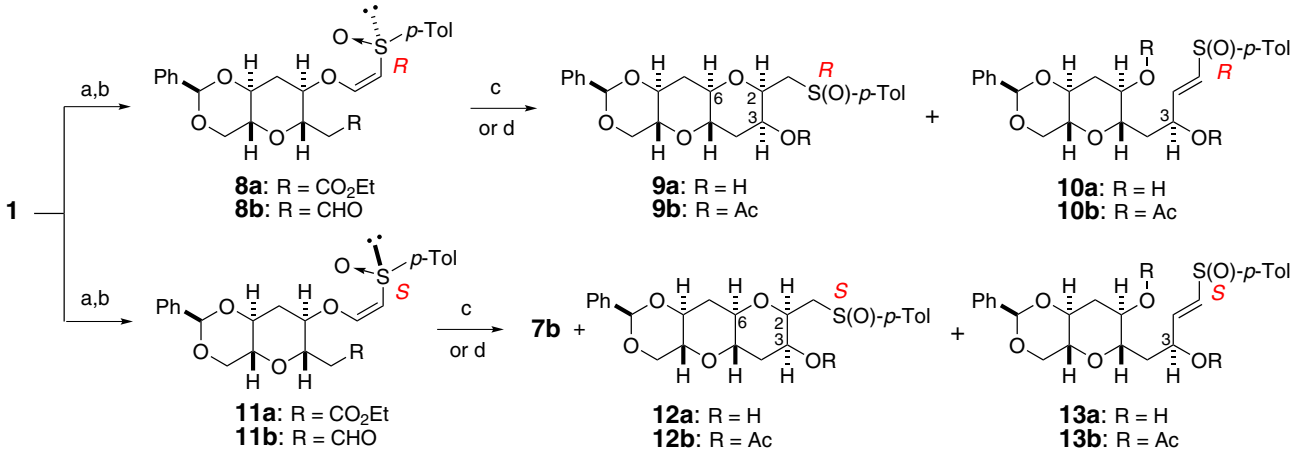


Scheme 1. Reagents and conditions: (a) (*R*)-**2** or (*S*)-**3**, NMM, CH_2Cl_2, rt, 96% for **4a**, 96% for **6a**; (b) DIBAH, CH_2Cl_2, −78 °C, 85% for **4b**, 92% for **6b**; (c) SmI_2, MeOH, CH_2Cl_2, 0 °C; Ac_2O, pyridine, rt, 64% for **5b** (two steps), 85% for **7b** (two steps); (d) SmI_2, CF_3CH_2OH,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