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SmI_2-induced reductive cyclization of (*E*)- and (*Z*)-β-alkoxyvinyl sulfones with aldehyde

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Abstract—SmI_2-induced reductive cyclization of (*E*)- and (*Z*)-β-alkoxyvinyl sulfones with aldehyde stereoselectively afforded 2,6-*syn*-2,3-*trans*- and 2,6-*syn*-2,3-*cis*-tetrahydropyrans, respectively. The product having a sulfonylmethyl group was converted to a cyclic ether having a methyl group by reduction with Raney-Ni.

Since the first isolation of brevetoxin-B as a red tide toxin, many marine polycyclic ethers have been reported.[1] The structural feature of these natural products is a *trans*-fused polycyclic ether ring system. The synthetically challenging unique and complex structures and their potent bioactivities have attracted the attention of numerous synthetic organic chemists. Thus, various methods for the synthesis of polycyclic ethers have been extensively studied toward the total synthesis of marine polycyclic ethers.[2] We have already developed an efficient method for the construction of polycyclic ethers based on SmI_2-induced reductive cyclization of β-alkoxyacrylate **A** with a carbonyl group (Fig. 1).[3] This method has been widely and successfully applied to the synthesis of polycyclic ethers.[4] Product **B** is a cyclic ether having an acetic acid moiety, that is, a two-carbon unit as the side chain. A functional one-carbon group as the side chain is often required and is useful for the synthesis of various polycyclic ethers. We now report stereoselective SmI_2-induced reductive cyclization of (*E*)- and (*Z*)-β-alkoxyvinyl sulfones with aldehyde.

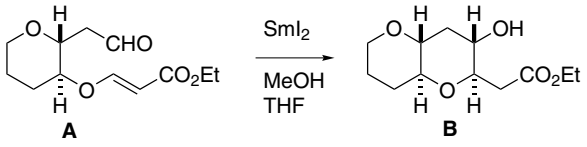

Figure 1. SmI_2-induced reductive cyclization of **A**.

SmI_2-induced reductive cyclization was examined using (*E*)-**2** and (*Z*)-**7** as the substrates (Scheme 1). The addition of alcohol **1**[4e] to (*E*)-bis(phenylsulfonyl)-1,2-ethylene **5** with LHMDS stereoselectively afforded (*E*)-β-alkoxyvinyl sulfone,[5] which was reduced with DIBAH to give aldehyde **2** in a 95% yield (two steps). Treatment of **2** with 2.5 equiv of SmI_2[6] in the presence of MeOH in THF effected reductive cyclization to give 2,6-*syn*-2,3-*trans*-tetrahydropyran **3** in a 99% yield as the single product, which was acetylated with Ac_2O to give **4** in a 96% yield. On the other hand, treatment of **1** and (*Z*)-bis(phenylsulfonyl)-1,2-ethylene **6** with LHMDS afforded (*Z*)-alkoxyvinyl sulfone, which led to aldehyde **7** (73% yield, two steps) by DIBAH reduction. SmI_2-induced cyclization of (*Z*)-**7** also took place to give 2,6-*syn*-2,3-*cis*-**8** and 2,6-*syn*-2,3-*trans*-**3**, which were separated after acetylation to give the corresponding acetates **9** and **4** in 55% and 11% yields, respectively. The stereostructures of products **3** and **8** were determined by NOE and coupling constant of the corresponding acetates **4**[7] and **9**[8] as shown in Figure 2.

These reactions would proceed through chelated intermediates as shown in Figure 3. The first single electron reduction of (*E*)-**2** with SmI_2 would give a ketyl radical **i**. Then, C–C bond formation in the chelated intermediate **i** takes place with a complete stereoselectivity to give **ii**. The reduction of **ii** by a second equivalent of SmI_2 would produce an anion, which should be immediately protonated with MeOH to give **3**. On the other hand,

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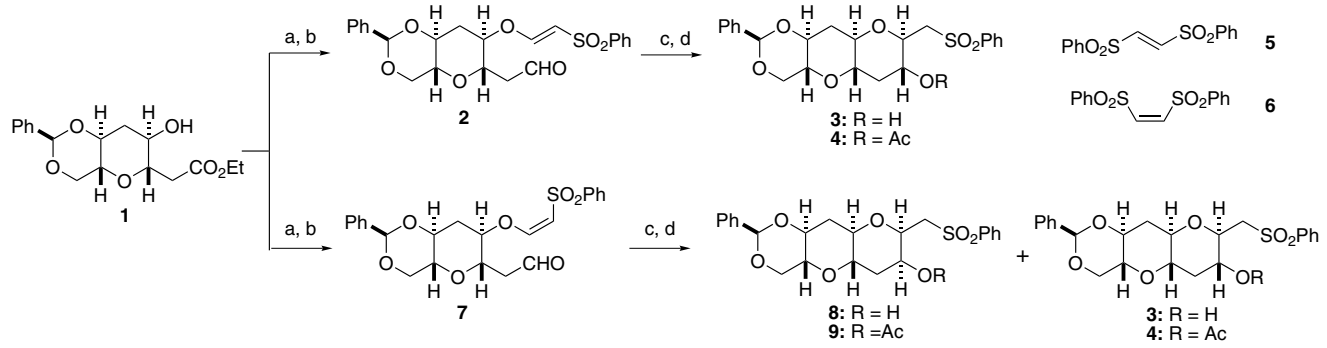


Scheme 1. Reagents and conditions: (a) LHMDS, THF, 0 °C–rt; then (*E*)-**5** or (*Z*)-**6**, 0 °C–rt; (b) DIBAH, CH_2Cl_2, −78 °C, 95% for **2** (two steps), 73% for **7** (two steps); (c) SmI_2 (2.5 equiv), MeOH (2.5 equiv), THF, 0 °C, 99% for **3**; (d) Ac_2O, pyridine, rt, 96% for **4**, 55% for **9** and 11% for **4** (two steps from **7**).

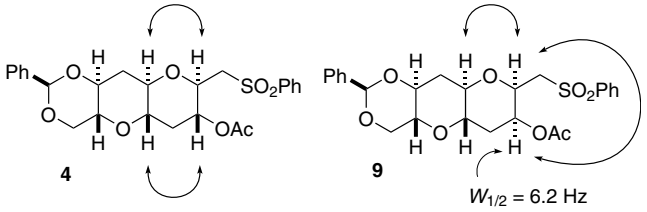


Figure 2. Observed NOE and coupling constant.

the reaction of (*Z*)-**7** would proceed through the chelated intermediate **iii**, which should provide the main product **8**. The minor product **3** from **7** should be produced via a non-chelated intermediate having an equatorial ketyl radical.

Next, the present reaction was examined in acyclic system (Scheme 2). The addition of acyclic alcohol **10**[9] to (*E*)-**5** with LHMDS afforded (*E*)-β-alkoxyvinyl sulfone, which was treated with MeI[10] to give aldehyde **11** in a 97% yield (two steps). Upon treatment of **11** with 2.5 equiv of SmI_2 in the presence of MeOH in THF, the reaction smoothly took place and subsequent acetylation afforded 2,6-*syn*-2,3-*trans*-tetrahydropyran **12**[11] in an 82% yield and ca. 1:1:1 mixture of inseparable products (16%), which include 2,6-*syn*-2,3-*cis*-**13**.[12,13] On the other hand, the addition of **10** and (*Z*)-**6** with LHMDS followed by the deprotection of thioacetal afforded aldehyde **14** having (*Z*)-alkoxyvinyl sulfone (94% yield, two steps). SmI_2-induced cyclization of (*Z*)-**14** followed by acetylation afforded 2,6-*syn*-2,3-*cis*-**13** in a 76% yield and 2,6-*syn*-2,3-*trans*-**12** in a 5% yield. The stereostruc-

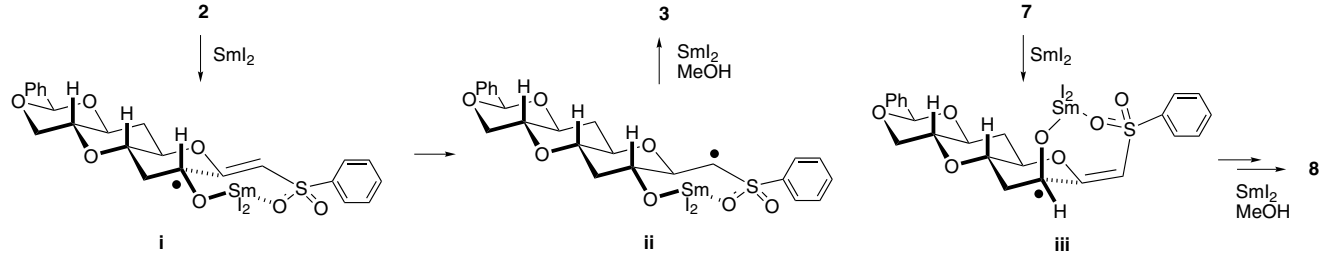
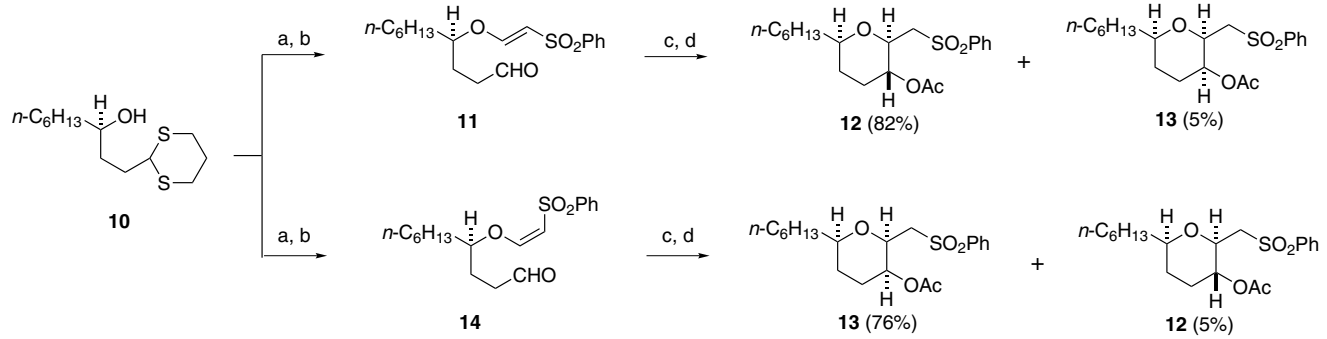


Figure 3. Plausible mechanism of SmI_2-induced cyclization of **2** and **7**.



Scheme 2. Reagents and conditions: (a) LHMDS, THF, 0 °C–rt; then (*E*)-**5** or (*Z*)-**6**, 0 °C–rt; (b) MeI, $CaCO_3$, H_2O, MeCN, 60 °C, 97% for **11** (two steps), 94% for **14** (two steps); (c) SmI_2 (2.5 equiv), MeOH (2.5 equiv), THF, 0 °C; (d) Ac_2O, pyridine, rt, 82% for **12** (two steps from **11**), 76% for **13** (two steps from **14**).

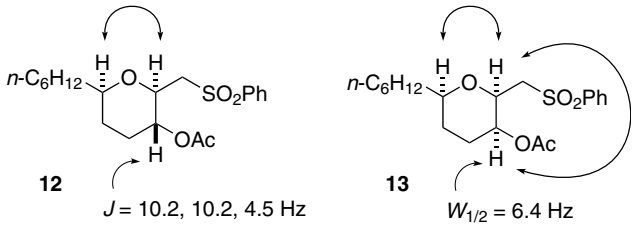


Figure 4. Observed NOE and coupling constant.

tures of products **12** and **13** were determined by NOE and coupling constant as shown in Figure 4. Thus, the present reaction was also useful for acyclic systems, which suggested that the chelation transition state would play an important role for the high stereoselectivity.

Then, reductive transformation of the sulfonylmethyl group of **3** to a methyl group was examined for application to the synthesis of polycyclic ethers; for example, gymnocin-A[14] has a methyl group on the final N-ring (Fig. 5). Treatment of acetate **4** with Na–Hg and Na_2HPO_4 in MeOH afforded the desired **15** (36%) having a methyl group and allylic alcohol **16** (61%), which was

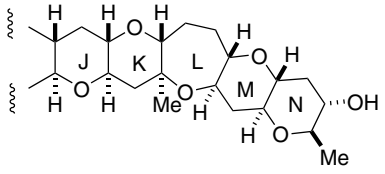
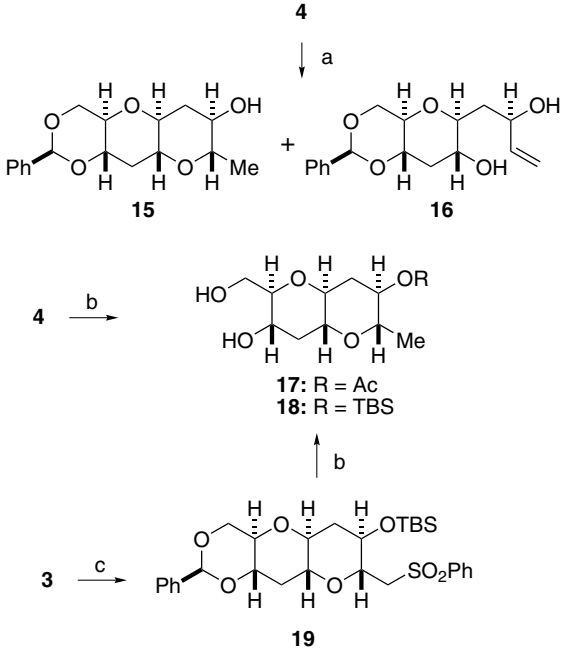


Figure 5. Partial structure of gymnocin-A.



Scheme 3. Reagents and conditions: (a) Na–Hg, Na_2HPO_4, MeOH, rt, 36% for **10**, 61% for **11**; (b) Raney-Ni, EtOH, 85 °C, 74% for **12**, 84% for **13**; (c) TBSCl, imidazole, DMF, rt, 93%.

produced by undesired reductive ring-opening.[15] Next, the reduction of the sulfonyl group was carried out using Raney-Ni. Treatment of **4** with Raney-Ni in refluxing EtOH simultaneously effected reductive desulfonylation and deprotection of the benzylidene group to afford diol **17** (74%) having a methyl group. After protection of **3** as its TBS ether, the reduction of **19** with Raney-Ni afforded the desired **18**[16] in an 84% yield (Scheme 3).

In summary, SmI_2-induced reductive cyclization of β-alkoxyvinyl sulfone with aldehyde was developed. The present reaction would be useful for the synthesis of cyclic ethers having a functional one-carbon unit as the side chain and also for the construction of the stereoisomers of cyclic ethers. Namely, the reaction of (*E*)- and (*Z*)-β-alkoxyvinyl sulfones, **2** and **7**, stereoselectively gave 2,6-*syn*-2,3-*trans*- and 2,6-*syn*-2,3-*cis*-tetrahydropyrans, **3** and **8**, respectively. Furthermore, the present reaction was useful in acyclic system; cyclization of acyclic (*E*)-**11** and (*Z*)-**14** afforded 2,6-*syn*-2,3-*trans*-**12** and 2,6-*syn*-2,3-*cis*-**13**, respectively. Further studies on the SmI_2-induced reductive cyclization and applications to the synthesis of natural products are now in progress in this laboratory.

Acknowledgements

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7. NMR data for **4**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (t, $J = 7.3$ Hz, 2H), 7.62 (t, $J = 7.3$ Hz, 1H), 7.52 (t, $J = 7.9$ Hz, 2H), 7.47 (dd, $J = 7.9$, 2.4 Hz, 2H), 7.39–7.33 (m, 3H), 5.49 (s, 1H), 4.57 (ddd, $J = 10.7$, 10.7, 4.6 Hz, 1H), 4.26 (dd, $J = 10.7$ 4.9 Hz, 1H), 3.95 (ddd, $J = 9.8$, 7.9, 3.4 Hz, 1H), 3.64 (t, $J = 10.4$ Hz, 1H), 3.50 (ddd, $J = 11.9$, 9.2, 4.3 Hz, 1H), 3.33–3.28 (m, 3H), 3.10–3.04 (m, 2H), 2.46 (ddd, $J = 11.6$, 4.0, 4.0 Hz, 1H), 2.09 (s, 3H), 2.00 (ddd, $J = 11.0$, 3.4, 3.4 Hz, 1H), 1.51 (q, $J = 11.3$ Hz, 1H), 1.33 (q, $J = 11.3$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 140.3, 137.0, 133.7, 129.2, 128.8, 128.3, 128.1, 126.1, 101.9, 76.6, 76.4, 75.5, 74.9, 73.5, 68.9, 68.8, 58.0, 34.6, 34.0, 21.0.
8. NMR data for **9**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90 (dd, $J = 8.2$, 1.8, 1.8 Hz, 2H), 7.64 (dddd, $J =$ 6.7, 6.7, 1.2, 1.2 Hz, 1H), 7.55–7.52 (m, 2H), 7.48–7.46 (m, 2H), 7.38–7.35 (m, 3H), 5.50 (s, 1H), 5.09 (m, $W_{1/2} = 6.2$ Hz, 1H), 4.25 (dd, $J = 10.4$, 4.9 Hz, 1H), 4.16 (ddd, $J = 8.8$, 2.7, 1.8 Hz, 1H), 3.65 (t, $J = 10.4$ Hz, 1H), 3.53 (ddd, $J = 11.6$, 9.2, 4.3 Hz, 1H), 3.42 (dd, $J = 14.9$, 9.2 Hz, 1H), 3.37–3.29 (m, 2H), 3.20 (dd, $J = 15.0$, 2.8 Hz, 1H), 3.13 (ddd, $J = 11.3$, 9.2, 4.3 Hz, 1H), 2.26 (ddd, $J = 14.0$, 3.4, 3.4 Hz, 1H), 2.09 (s, 3H), 2.03 (ddd, $J = 11.3$, 4.0, 4.0 Hz, 1H), 1.71 (ddd, $J = 14.0$, 11.6, 3.1 Hz, 1H), 1.48 (t, $J =$ 11.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 139.9, 137.1, 133.8, 129.2, 129.0, 128.4, 128.2, 126.1, 101.8, 76.8, 76.7, 73.9, 73.7, 73.4, 70.3, 69.0, 58.0, 34.2, 33.7, 20.9.
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11. NMR data of **12**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 (d, $J = 7.6$ Hz, 2H), 7.62 (t, $J = 7.6$ Hz, 1H), 7.53 (t, $J = 7.9$ Hz, 2H), 4.53 (ddd, $J = 10.2$, 10.2, 4.5 Hz, 1H), 3.88 (ddd, $J = 10.6$, 6.4, 4.5 Hz, 1H), 3.33 (m, 3H), 3.18 (m, 1H), 2.16 (m, 1H), 2.06 (s, 1H), 1.65 (m, 1H), 1.47 (m, 1H), 1.32–1.24 (m, 3H), 1.21–1.08 (m, 6H), 1.04–0.97 (m, 2H), 0.89 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.2, 140.5, 133.4, 128.9, 128.0, 77.7, 74.5, 70.5, 58.4, 34.9, 31.6, 29.8, 29.2, 24.9, 22.6, 21.1, 14.1.
12. NMR data of **13**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 (d, $J = 7.6$ Hz, 2H), 7.62 (t, $J = 7.6$ Hz, 1H), 7.53 (t, $J = 7.9$ Hz, 2H), 4.42 (ddd, $J = 10.2$, 10.2, 4.5 Hz, 1H), 3.88 (ddd, $J = 10.6$, 6.4, 4.5 Hz, 1H), 3.33 (m, 3H), 3.18 (m, 1H), 2.16 (m, 1H), 2.06 (s, 1H), 1.65 (m, 1H), 1.47 (m, 1H), 1.32–1.24 (m, 3H), 1.21–1.08 (m, 6H), 1.04–0.97 (m, 2H), 0.89 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.2, 140.5, 133.4, 128.9, 128.0, 77.7, 74.5, 70.4, 58.4, 34.9, 31.6, 29.8, 29.21, 29.16, 24.9, 22.6, 21.1, 14.1.
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16. NMR data for **18**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.91 (d, $J = 7.2$ Hz, 2H), 7.64 (t, $J = 7.6$ Hz, 1H), 7.55 (t, $J = 7.5$ Hz, 2H), 4.80 (m, $W_{1/2} = 6.4$ Hz, 1H), 4.08 (ddd, $J = 8.3$, 2.3, 1.1 Hz, 1H), 3.46 (dd, $J = 14.7$, 8.3 Hz, 1H), 3.25 (m, 1H), 3.21 (dd, $J = 14.7$, 3.0 Hz, 1H), 2.07 (s, 3H), 2.02 (dddd, $J = 14.7$, 3.0, 3.0, 3.0 Hz, 1H), 1.73 (dddd, $J = 15.1$, 15.1, 5.7, 3.0 Hz, 1H) 1.44–1.35 (m, 2H), 1.30–1.05 (m, 10H), 0.89 (t, $J =$ 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.3, 140.1, 133.5, 129.0, 128.0, 78.2, 73.2, 68.7, 58.9, 35.6, 31.6, 29.2, 27.8, 25.2, 24.9, 22.5, 21.0, 14.0.