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Efficient Synthesis of *trans*-Fused Polycyclic Ethers Including Tetrahydropyrans and Oxepanes Based on SmI_2-Induced Reductive Cyclization

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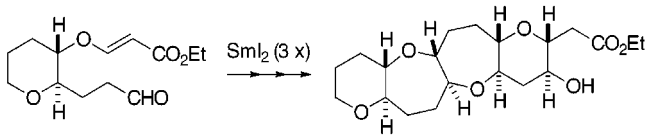
ABSTRACT

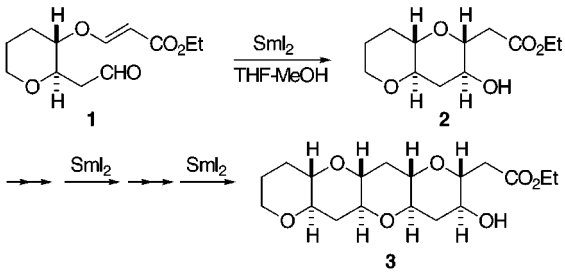


An efficient method for the synthesis of *trans*-fused polycyclic ether ring systems including tetrahydropyrans and oxepanes, i.e., six–seven–six-, six–seven–seven-, and six–seven–seven–six-membered polycyclic ether ring systems, was developed on the basis of SmI_2-induced reductive intramolecular cyclization.

Since the first isolation of brevetoxin B,[1] a potent neurotoxin produced by the red tide organism *Gymnodinium breve*, many marine polycyclic ethers of this type have been reported.[2] The most characteristic structural feature of these natural products includes mainly *trans*-fused polycyclic ether ring systems, in which medium- and large-membered-ring ethers are involved. The synthetically challenging unique structures and their potent biological activities have attracted the attention of numerous synthetic organic chemists. Thus, various methods for the synthesis of polycyclic ethers have been extensively studied, directed toward total synthesis of marine polycyclic ethers.[3] We now report a very simple and highly efficient method for the synthesis of *trans*-fused polycyclic ether ring systems including tetrahydropyrans and oxepanes, i.e., six−seven−six-, six−seven−seven-, and six−seven−seven−six-membered polycyclic ethers, based on SmI_2-induced reductive intramolecular cyclization.

We have recently reported that the reaction of the tetrahydropyran **1**, having an aldehyde and a β-alkoxyacrylate, with SmI_2[4] exclusively produced 2,3-*trans*-tetrahydropyran **2** (Scheme 1).[5] Repetition of the same reaction

Scheme 1



1 2 3

sequences provided the *trans*-fused polytetrahydropyran **3** with complete stereoselection. Our attention was then focused

(1) Lin, Y.-Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773.

(2) For a review, see: Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.

(3) For a review, see: Alvarez, E.; Candenas, M.-L.; Perez, R.; Ravelo, J. L.; Martin, J. D. *Chem. Rev.* **1995**, *95*, 1953. See also ref 5 and references therein.

(4) For reviews, see: Kagan, H. B. *New J. Chem.* **1990**, *14*, 453. Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.

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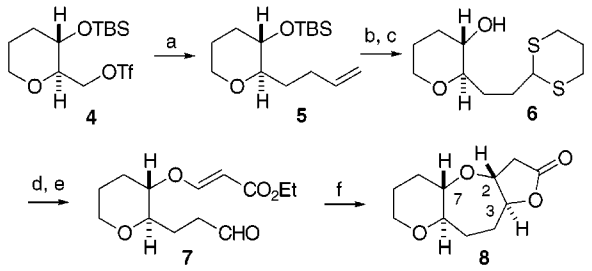
on the construction of polycyclic ether ring systems including an oxepane ring using the SmI_2-induced cyclization reaction.

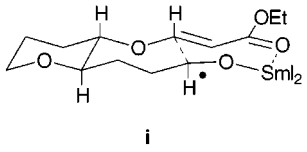
The aldehyde **7** as the substrate for the construction of an oxepane ring was synthesized from the optically active tetrahydropyran **4**[6] having a triflate (Scheme 2). Reaction

Scheme 2[a]



[a] Reagents and conditions (yield): (a) allylMgCl, CuI, Et_2O, −50 °C (97%); (b) O_3, CH_2Cl_2, −78 °C; (c) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C (96% from **5**); (d) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, room temperature; (e) MeI, aqueous MeCN, $NaHCO_3$, room temperature (89% from **6**); (f) 3 equiv of SmI_2, 3 equiv of MeOH, THF, room temperature (84%).

of the triflate **4** with allylmagnesium chloride in the presence of CuI in ether[7] gave allylated compound **5** in 97% yield. After ozonolysis of the olefin in **5**, treatment of the resulting aldehyde with 1,3-propanedithiol in the presence of $BF_3{\cdot}Et_2O$ effected thioacetalization and deprotection of the TBS group simultaneously to give thioacetal **6** in 96% yield. The hetero-Michael reaction[8] of the alcohol **6** with ethyl propiolate in the presence of *N*-methylmorpholine in CH_2Cl_2 followed by dethioacetalization[9] with MeI in aqueous MeCN gave the required aldehyde **7** in 89% yield. Upon treatment of **7** with 3 equiv of SmI_2 in the presence of 3 equiv of MeOH in THF, a radical-mediated reductive cyclization proceeded at room temperature and was completed within 10 min to give lactone **8** as the sole product in 84% yield. The structure of **8** was unequivocally confirmed to be the desired bicyclic ether having 2,7-*syn*-2,3-*trans*-oxepane by ^1H and ^{13}C NMR, NOE, and HMBC analyses. Thus, SmI_2-induced cyclization performed the construction of the 2,3-*trans*-oxepane ring in **8** with complete stereoselection in the same manner as that of the 2,3-*trans*-tetrahydropyran ring in **2**. Interestingly, construction of the oxepane ring in **8** was accompanied by γ-lactone formation, while that of the tetrahydropyran ring in **2** was not. The present reaction would proceed via the transition state **i** (Figure 1), in which the chelation of Sm(III) to the ester should contribute to controlling the complete *trans* stereoselectivity. The product formed would be not the result of an equilibration via a retro-Michael/Michael process but the kinetic production of the reaction.[10]

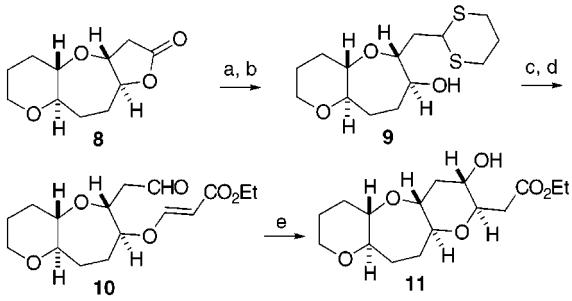


i

Figure 1.

Further ring construction of tri- and tetracyclic ether ring systems was then investigated using SmI_2-induced cyclization. First, construction of a six−seven−six-membered tricyclic ether ring system was examined as shown in Scheme 3. The reduction of the lactone **8** with DIBAH in toluene

Scheme 3[a]



[a] Reagents and conditions (yield): DIBAH, toluene, −78 °C; (b) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C (95% from **8**); (c) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, room temperature; (d) MeI, aqueous MeCN, $NaHCO_3$, room temperature (98% from **9**); (e) 3 equiv of SmI_2, 3 equiv of MeOH, THF, 0 °C (95%).

gave lactol, which was treated with 1,3-propanedithiol and $BF_3{\cdot}Et_2O$ to give thioacetal **9** in 95% yield. The hetero-Michael reaction of **9** with ethyl propiolate followed by dethioacetalization with MeI gave aldehyde **10** in 98% yield. Treatment of **10** with SmI_2 in THF in the presence of MeOH also effected the construction of the *trans*-tetrahydropyran ring with complete stereoselection to give the six−seven−six-membered ether **11**[11] in 95% yield.

Next, construction of a six−seven−seven-membered ether ring system was investigated (Scheme 4). DIBAH reduction of lactone **8** followed by the Wittig reaction using $Ph_3P{=}$CHOMe afforded methyl enol ether **12** (*E*/*Z* = ca. 1/1) in 84% yield. The hetero-Michael reaction of **12** followed by CSA treatment in aqueous MeCN provided aldehyde **13** in 81% yield. The reaction of **13** with SmI_2 produced *trans*-oxepane **14**[11] and the *cis* isomer **15**[11] in 56% and 26% yields,

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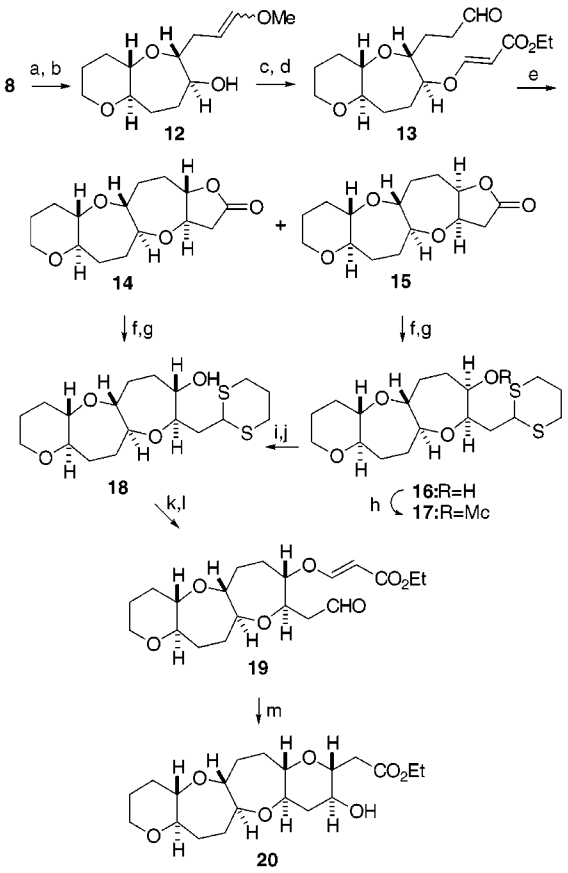
(6) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc*. **1996**, *118*, 8158.
(7) Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett*. **1989**, *30*, 1281, 3999.
(8) Winterfeldt, E. *Chem. Ber*. **1964**, *97*, 1952. Winterfeldt, E.; Preuss, H. *Chem. Ber*. **1966**, *99*, 450.
(9) Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun*. **1977**, 68.
(10) The supporting results will be reported in due course.
(11) The structure was confirmed by ^1H and ^{13}C NMR, NOE, and HMBC analyses.

Scheme 4[a]



[a] Reagents and conditions (yield): DIBAH, toluene, −78 °C; (b) $Ph_3P^+CH_2OMeCl^-$, NaHMDS, THF, −78 °C to room temperature (84% from **8**); (c) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, room temperature; (d) CSA, aqueous MeCN, room temperature (81% from **12**); (e) 3 equiv of SmI_2, 3 equiv of MeOH, THF, room temperature (**14**, 56%; **15**, 26%); (f) DIBAH, CH_2Cl_2, −78 °C; (g) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C (85% for **18** from **14**, 88% for **16** from **15**); (h) $ClCH_2SO_2Cl$, 2,6-lutidine, CH_2Cl_2, 0 °C; (i) CsOAc, 18-crown-6, benzene, reflux; (j) K_2CO_3, MeOH, room temperature (66% from **16**); (k) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, room temperature; (l) MeI, aqueous MeCN, $NaHCO_3$, room temperature (92% from **18**); (m) 3 equiv of SmI_2, 3 equiv of MeOH, THF, 0 °C (88%).

respectively. Thus, the *trans*/*cis* ratio in the construction of the second oxepane ring next to the oxepane was moderate, although the oxepane ring was effectively constructed (82% combined yield).

However, the both isomers of *trans*-**14** and *cis*-**15** could be converted into the desired *trans*-fused tricyclic ether **18**. The reduction of *trans*-**14** with DIBAH followed by treatment with 1,3-propanedithiol afforded thioacetal **18** in 85% yield. DIBAH reduction of the *cis* isomer **15** followed by thioacetalization gave thioacetal **16** in 88% yield. Inversion of the secondary alcohol in **16** was performed by our method using a chloromethanesulfonate (monochlate), an efficient leaving group.[12] The alcohol **16** was treated with $ClCH_2SO_2Cl$ in the presence of 2,6-lutidine in CH_2Cl_2 to give the monochelate **17** (Mc = SO_2CH_2Cl) which was treated with CsOAc in the presence of 18-crown-6 in benzene at reflux and then with K_2CO_3 in MeOH to give the desired alcohol **18** in 66% overall yield.

Further ring construction of *trans*-fused six−seven−seven−six-membered tetracyclic ether ring systems was then investigated (Scheme 4). The hetero-Michael reaction of **18** followed by dethioacetalization provided aldehyde **19** in 92% yield. The reaction of **19** with SmI_2 also effected construction of the *trans*-tetrahydropyran ring with complete stereoselection to afford the desired six−seven−seven−six-membered ether **20**[11] in 88% yield.

In conclusion, we reported a simple and efficient method for the synthesis of polycyclic ether ring systems based on SmI_2-induced reductive cyclization, whose usefulness was demonstrated by the stereoselective synthesis of *trans*-fused six−seven−six-, six−seven−seven-, and six−seven−seven−six-membered polycyclic ethers which are often found in marine polycyclic ethers. Further studies on the synthesis of polycyclic ether ring systems and total synthesis of natural products based on the present SmI_2-induced cyclization are now in progress in this laboratory.

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Supporting Information Available: Typical experimental procedures (from **8** to **11**) and full characterization data for compounds **8**−**11**, **14**, **15**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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