Stereoselective Synthesis of Cyclic Ethers by SmI_2-Induced Reductive Intramolecular Cyclization

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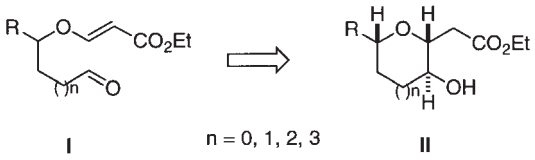
The highly stereoselective syntheses of 2,3-*trans*-3-hydroxytetrahydropyran and oxepane were achieved by the SmI_2-induced reductive intramolecular cyclizations from acyclic compounds having an aldehyde and a β-alkoxyacrylate. The syntheses of tetrahydrofuran, oxocane, and oxocene were also accomplished.

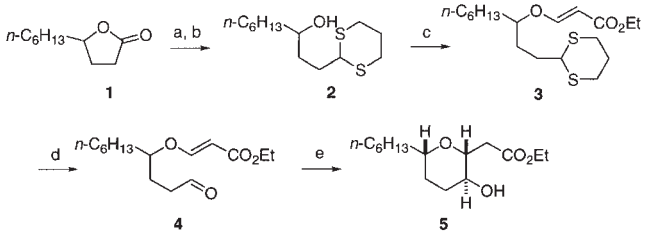
Cyclic ethers are often found as a part of the structure of many natural products, exemplified by lauroxanes as monocyclic ethers and brevetoxins as polycyclic ethers, mainly isolated from marine organisms.[1] Marine polycyclic ethers such as brevetoxins, ciguatoxins, and maitotoxin have attracted the attention of synthetic organic chemists due to their complex unique structures, potent biological activities, and their rarity in nature. The most characteristic structural feature of this family is that they have *trans*-fused polycyclic ether ring systems, in which 5-, 6-, 7- and 8-membered ethers are involved. We have recently reported an extremely facile and highly efficient strategy for the iterative synthesis of a *trans*-fused polycyclic ether ring system based on the SmI_2-induced reductive intramolecular cyclization, in which a cyclic ether having an aldehyde and a β-alkoxyacrylate was used as the starting material.[2] We further investigated the cyclization of an acyclic compound **I** using the same strategy (Scheme 1). In this communication, we report the synthesis of 5-, 6-, 7- and 8-membered cyclic ethers **II** from acyclic compounds **I** by the SmI_2-induced cyclization.



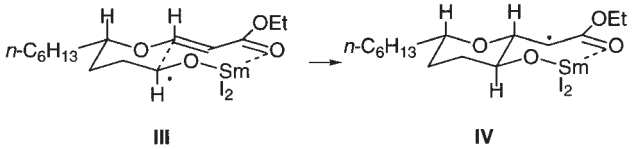
I II

Scheme 1.

First, we investigated the construction of the 6-membered ether (tetrahydropyran) as shown in Scheme 2. The reduction of γ-decanolactone (**1**) with DIBAH in toluene afforded the lactol, which was treated with 1,3-propanedithiol in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 to give thioacetal **2** in 98% yield. Treatment of **2** with ethyl propiolate in the presence of *N*-methylmorpholine effected the hetero-Michael reaction[3] to give β-alkoxyacrylate **3** in 75% yield. Deprotection of the thioacetal with MeI[4] gave aldehyde **4** in 89% yield. Upon treatment of **4** with 2.2 equiv of SmI_2 in the presence of 2.2 equiv of MeOH in THF, a radical-mediated reductive cyclization smoothly proceeded at 0 °C and was completed within 30 min to give 2,6-*syn*-2,3-*trans*-trahydropyran **5**[5] in 88% yield with complete stereoselectivity. The reaction would proceed via intermediates **III** and **IV**: 1) initial single-electron reduction of the aldehyde, 2) C-C bond formation in **III** under chelation between Sm(III) and the ester, and 3) reduction of a radical in **IV** by a second equiv of SmI_2 to an anion followed by protonation by MeOH. The present cyclization result using an acyclic compound suggested that the chelation of Sm(III) to the ester should produce a very important contribution towards achieving complete stereoselectivity.

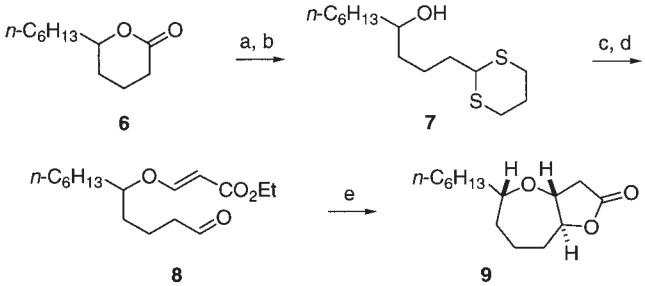


Scheme 2. Reagents and conditions: a) DIBAH, toluene, −78 °C; b) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, (98% from **1**); c) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt, (75%); d) MeI, aqueous MeCN, rt, (89%); e) 2.2 equiv of SmI_2, 2.2 equiv of MeOH, THF, 0 °C (88%).



III IV

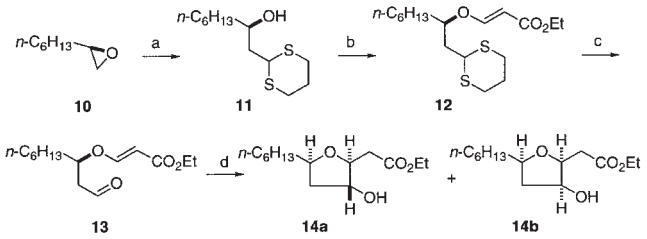
The stereoselective synthesis of the 7-membered ring ether (oxepane) from the acyclic compound was then examined (Scheme 3). Undecanoic δ-lactone (**6**) was converted into aldehyde **8** by the same procedure as that for the preparation of **4**. The reductive cyclization of **8** with 2.2 equiv of SmI_2 in the presence of MeOH smoothly proceeded at 0 °C to room temperature to give 2,7-*syn*-2,3-*trans*-oxepane **9**[5] in 89% yield with complete stereoselection, accompanied by formation of the γ-lactone.



Scheme 3. Reagents and conditions: a) DIBAH, toluene, −78 °C; b) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, (98% from **6**); c) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt; d) MeI, aqueous MeCN, rt, (71% from **7**); e) 2.5 equiv of SmI_2, 2.5 equiv of MeOH, THF, 0 °C to rt (89%).

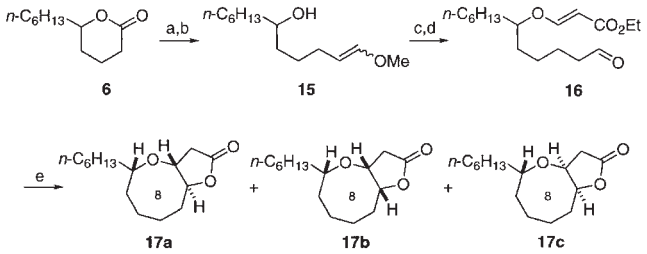
Having completed the construction of 2,6-*syn*-2,3-*trans*-tetrahydropyran and 2,7-*syn*-2,3-*trans*-oxepane with complete stereoselection, we next turned our attention to the construction of tetrahydrofuran and oxocane from the acyclic compounds

(Scheme 4 and 5). The required acyclic aldehyde **13** was synthesized from (*R*)-(+)-1,2-epoxyoctane (**10**) by introduction of 1,3-dithiane, the hetero-Michael addition with ethyl propiolate, and deprotection of the thioacetal. Upon treatment of **13** with SmI_2 in the presence of MeOH in THF, a radical-mediated reductive cyclization smoothly proceeded at 0 °C for 2 h to give 2,5-*syn*-2,3-*trans*- and 2,5-*syn*-2,3-*cis*-tetrahydrofurans, **14a**[5] (33%) and **14b**[5] (26%). A low yield of the cyclized compounds should result from the β-elimination of the starting aldehyde **13**.



Scheme 4. Reagents and conditions: a) 1,3-dithiane, *n*-BuLi, HMPA, THF, −30 to −20 °C (90%); b) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt, (73%); d) MeI, aqueous MeCN, rt, (72%); e) 3.0 equiv of SmI_2, 5.0 equiv of MeOH, THF, 0 °C (**14a**: 33%, **14b**: 26%).

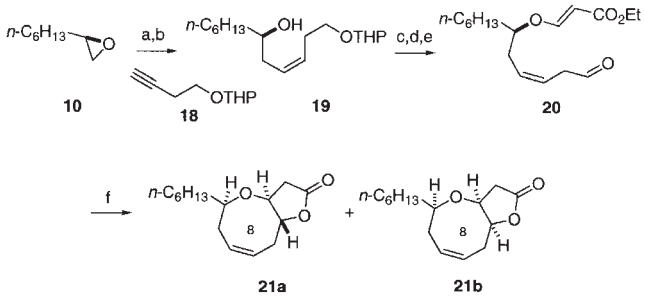
Aldehyde **16** was then prepared from undecanoic δ-lactone (**6**) (Scheme 5). DIBAH reduction of **6** followed by the Wittig reaction using $Ph_3P=CHOMe$ afforded alcohol **15**. The hetero-Michael addition of **15** and subsequent CSA treatment in wet CH_2Cl_2 gave the required aldehyde **16**. Treatment of **16** with SmI_2 in the presence of MeOH provided three isomeric oxocanes **17**[5] in 34% yield (**17a**: 12%, **17b**: 10%, **17c**: 12%).



Scheme 5. Reagents and conditions: a) DIBAH, toluene, −78 °C; b) $Ph_3P^+CH_2OMeCl^-$, NaHMDS, THF, 0 °C (88% from **6**); c) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt (68%); d) CSA, wet CH_2Cl_2, rt, (76%); e) 3.0 equiv of SmI_2, 5.0 equiv of MeOH, THF, 0 °C to rt (**17a**: 12%, **17b**: 10%, **17c**: 12%).

Most 8-membered cyclic ether rings in marine natural products, exemplified by (+)-laurencin[6] or brevetoxin-B,[7] contain *cis*-olefin. Thus, we examined the cyclization of aldehyde **20** having a *cis*-olefin. The synthesis of **20** began with the coupling of epoxide **10** and the lithium acetylide of **18** in the presence of $BF_3\cdot Et_2O$ in THF. Subsequent hydrogenation with Lindlar catalyst in MeOH furnished the *cis*-olefin **19**. The hetero-Michael reaction of **19**, deprotection of the THP group with TsOH in MeOH, and Dess-Martin oxidation furnished the required aldehyde **20**. The reaction of **20** with 3 equiv of SmI_2 in the presence of 5 equiv of MeOH in THF at room temperature for 16 h afforded two isomeric oxocenes, 2,8-*syn*-2,3-*trans*-**21a** (27%) and 2,8-*syn*-2,3-*cis*-**21b** (13%).

The synthesis of the tetrahydrofurans **14**, oxocanes **17**, and oxocenes **21** were accomplished by the SmI_2-induced cyclization, although the stereoisomers were obtained.[8]



Scheme 6. Reagents and conditions: a) **18**, *n*-BuLi, $BF_3\cdot Et_2O$, THF, −70 °C; b) Lindlar catalyst, H_2, MeOH, rt, (98% from **10**); c) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt; d) TsOH, MeOH, rt (78% in 2 steps); e) Dess-Martin periodinane, MS4A, CH_2Cl_2, rt (84%); f) 3.0 equiv of SmI_2, 5.0 equiv of MeOH, THF, rt (**21a**: 27%, **21b**: 13%).

In summary, a novel method for the synthesis of 5, 6, 7, and 8-membered cyclic ethers was developed by the SmI_2-induced intramolecular reductive cyclization from the acyclic aldehyde and β-alxoxyacrylate.

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Dedicated to Prof. Teruaki Mukaiyama on the occassion of his 75th birthday.

References and Notes

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5 The structures of **5**, **9**, **14** and **17** were unequivocally confirmed by ^1H- and ^{13}C-NMR, NOE and HMBC analyses.

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8 The mechanism for the low selectivity in construction of **14**, **17** and **21** is still not completely elucidated. There are some probable reasons; e.g. 1) the difficulty of the tight chelation with Sm(III) to the esters, or 2) the possibility of several conformations for the corresponding chelated intermediates, etc.