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Stereoselective syntheses of *trans*-fused 6,6- and 6,7-membered ether ring systems having an angular methyl group based on SmI_2-induced reductive intramolecular cyclization

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Abstract

Highly stereoselective syntheses of *trans*-fused 6,6- and 6,7-membered ether ring systems having an angular methyl group were achieved based on SmI_2-induced reductive intramolecular cyclizations of an aldehyde or a methyl ketone and a β-alkoxy acrylate.

Keywords: samarium dioxide; cyclization; tetrahydropyrans; oxepanes.

Marine polycyclic ethers,[1] exemplified by brevetoxins, have attracted the attention of synthetic organic chemists due to their unprecedented unique structural framework and potent biological activities. The most characteristic structual feature of this family includes *trans*-fused polycyclic ether ring systems, in which angular methyl groups are often involved. Various methods for the construction of the ether ring system **i** have been reported; i.e. the introduction of a methyl group to a ketone,[2] the replacement of an ethylthio group in hemithioacetal with a methyl group,[3] intramolecular cyclization of methyl ketone and stannyl allyl ether,[4] etc. We now report an efficient strategy for the stereoselective syntheses of *trans*-fused 6,6- and 6,7-membered ether ring systems having an angular methyl group based on SmI_2-induced reductive intramolecular cyclization.

We have recently reported an extremely facile and highly efficient strategy for the iterative synthesis of *trans*-fused polycyclic ether ring systems, which have no angular methyl group, based on SmI_2-induced reductive intramolecular cyclization.[5,6] As the cyclic ether ring systems having an angular methyl group, i.e. compound **i**, are often found in the marine polycyclic ethers, we then focused our attention on the construction of these ring systems. Our retrosynthetic cleavage of the indicated C–C bond in **i** revealed two synthetic routes: (A) using C2-methyl tetrahydropyran **ii** having an aldehyde and (B) using tetrahydropyran **iii** having a methyl ketone (Scheme 1). The desired *trans*-fused cyclic ethers **i** having an angular methyl group would be stereoselectively synthesized via both routes based on SmI_2-induced reductive intramolecular cyclization of an aldehyde or a ketone and a β-alkoxy acrylate.

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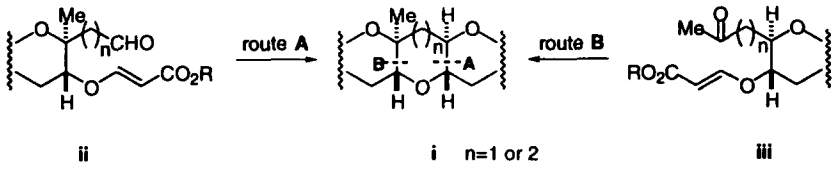
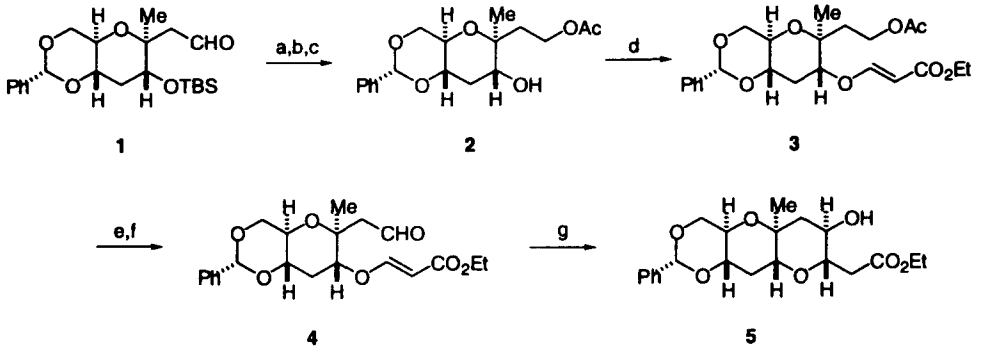


Scheme 1.

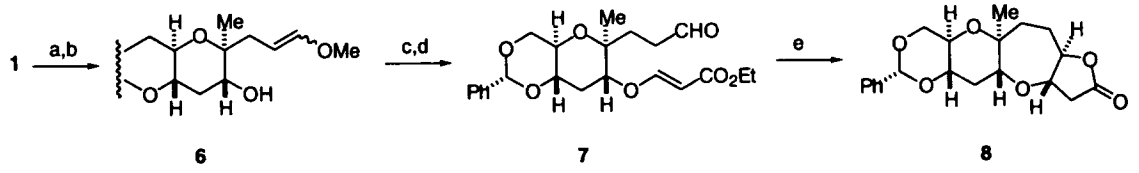
First, we investigated the construction of *trans*-fused 6,6-membered ether **i** (n=1) having an angular methyl group via route A using the C2-methyl tetrahydropyran **ii** (n=1). The reduction of aldehyde **1**[7] with $NaBH_4$, acetylation, and desilylation with TBAF gave acetate **2** (Scheme 2). The treatment of **2** with ethyl propiolate in the presence of *N*-methylmorpholine in CH_2Cl_2 at room temperature effected a hetero-Michael addition[8] to give β-alkoxy acrylate **3**. Methanolysis of the acetate in **3** followed by oxidation with PCC in CH_2Cl_2 then gave the required C2-methyl tetrahydropyran **4** having a C2-acetaldehyde and a β-alkoxy acrylate. Upon treatment of **4** with 2.2 equiv. of SmI_2[9] 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 10 min to give the desired *trans*-tetrahydropyran **5**[10] in 90% yield, exclusively. The product **5** corresponds to the BC-ring system of brevetoxin B.



Scheme 2. Reagents and conditions: (a) $NaBH_4$, MeOH, 0°C (73%); (b) Ac_2O, pyridine, rt (82%); (c) TBAF, THF, rt (95%); (d) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt (92%); (e) K_2CO_3, MeOH, rt (64%); (f) PCC, MS-4A, CH_2Cl_2, rt (98%); (g) 2.2 equiv. of SmI_2, 2.2 equiv. of MeOH, THF, 0°C (90%)

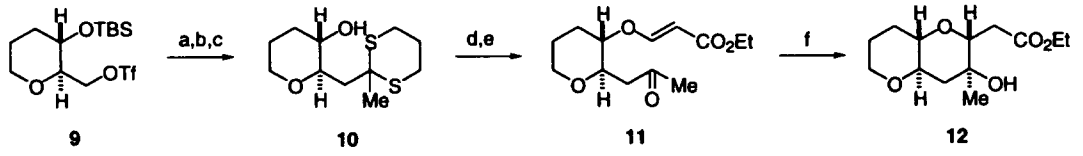
The stereoselective synthesis of *trans*-fused 6,7-membered ether **i** (n=2) having an angular methyl group was then examined using the C2-methyl tetrahydropyran **ii** (n=2) having a C2-propionaldehyde. The Wittig reaction of the aldehyde **1** with Ph_3P=CHOMe followed by deprotection of the TBS group with TBAF gave alcohol **6** (Scheme 3). The hetero-Michael addition of **6** with ethyl propiolate and subsequent CSA treatment in wet CH_2Cl_2 at room temperature gave the required aldehyde **7**. Reductive cyclization of **7** with 2.2 equiv. of SmI_2 in the presence of MeOH smoothly proceeded at room temperature for 30 min, accompanied by lactonization of the resulting ester and alcohol, to give *trans*-oxepane **8**[10] with complete stereoselectivity in 83% yield (two steps). The product **8** corresponds to the enantiomer of the BC-ring system of hemibrevetoxin B.

Having completed the construction of **i** (n=1 or 2) via route A, we next turned our attention to the construction of **i** via route B based on SmI_2-induced cyclization of a methyl ketone and a β-alkoxy acrylate in tetrahydropyran **iii** (n=1 or 2). After conversion of the optically active triflate **9**,[11] prepared from tri-*O*-acetyl-D-glucal, into the corresponding iodide, addition of a 2-methyl-1,3-dithiane anion and deprotection of the TBS ether with TBAF produced alcohol **10** (Scheme 4). The hetero-Michael addition of **10** with ethyl propiolate followed by deprotection of the thioacetal with MeI in aqueous



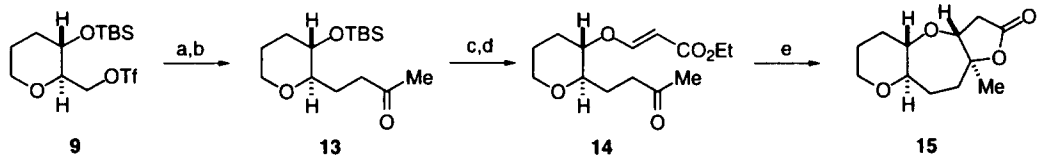
Scheme 3. Reagents and conditions: (a) $Ph_3P^+CH_2OMeCl^-$, NaHMDS, THF, rt; (b) TBAF, THF, rt (90% from **1**); (c) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt (97%); (d) CSA, wet CH_2Cl_2, rt; (e) 2.2 equiv. of SmI_2, 2.2 equiv. of MeOH, THF, rt (83%, two steps)

MeCN[12] provided the required tetrahydropyran **11** having a methyl ketone and a β-alkoxy acrylate. Upon treatment of **11** with 2.2 equiv. of SmI_2, the reductive cyclization took place at 0°C for 10 min to give *trans*-fused bicyclic tetrahydropyran **12**[10] in 98% yield, corresponding to the D-ring system of maitotoxin. Thus, methyl ketone instead of aldehyde also worked very efficiently for the SmI_2-induced cyclization.



Scheme 4. Reagents and conditions: (a) NaI, acetone, 60°C; (b) 2-methyl-1,3-dithiane, *n*-BuLi, HMPA, THF, –20°C–rt; (c) TBAF, THF, rt; (d) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt; (e) MeI, aq. MeCN, rt (31% from **9**); (f) 2.2 equiv. of SmI_2, 2.2 equiv. of MeOH, THF, 0°C (98%)

Finally, we examined the stereoselective synthesis of the oxepane having the C3-methyl group, corresponding to an angular methyl group. Introduction of an allyl group to the triflate **9** with allylmagnesium chloride in the presence of CuI[13] and the Wacker oxidation gave methyl ketone **13** (Scheme 5). After deprotection of the TBS group with TBAF, the hetero-Michael addition of the resulting alcohol with ethyl propiolate gave methyl ketone **14**. Interestingly, the hetero-Michael addition took place without protection of the ketone. The reductive cyclization of **14** with SmI_2 was achieved at room temperature for 2 h to give *trans*-fused 6,7-membered ether **15**[10] in 94% yield, corresponding to the enantiomer of the DE-ring of yessotoxin.



Scheme 5. Reagents and conditions: (a) allylMgCl, CuI, Et_2O, –50°C (97%); (b) $PdCl_2$, CuCl, DMF, H_2O, rt (66%); (c) TBAF, THF, rt; (d) ethyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt (96% from **13**); (e) 2.2 equiv. of SmI_2, 2.2 equiv. of MeOH, THF, rt (94%)

In conclusion, a novel and efficient strategy for the construction of polycyclic ether systems having an angular methyl group has been developed. Based on this strategy, four types of cyclic ethers, **5**, **8**, **12**, and **15**, which are important components of marine polycyclic ethers, were stereoselectively synthesized. This strategy would be widely applicable to efficient synthesis of natural polycyclic ethers. Further studies along these lines are currently in progress in our laboratories.

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