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SYNTHESIS OF CYCLIC ETHER *VIA* INTRAMOLECULAR ACYLOIN CONDENSATION

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Abstract – Polycyclic ether was synthesized *via* intramolecular acyloin condensation and Lewis acid-promoted silane reduction.

Many marine polycyclic ethers, exemplified by brevetoxin-B, ciguatoxin, and maitotoxin, have been isolated.[1] A structural feature of these natural products is the *trans*-fused polycyclic ether ring system. The synthetically challenging complex structures and potent bioactivities of these compounds have attracted the attention of numerous synthetic organic chemists. Thus, various methods for construction of the cyclic ether ring system have been extensively studied directed toward total synthesis of marine polycyclic ethers.[2] Inter- and intramolecular acyloin condensations have been widely used for the synthesis of many valuable compounds.[3] Intramolecular acyloin condensation of diester (**i**) efficiently took place to give α-hydroxy cyclic ketones (**iii**) via enediol (**ii**) (Figure 1). Many applications using this type of reaction were successfully accomplished. On the other hand, intramolecular acyloin condensation of **iv** having the ester groups in the opposite direction has hardly been reported, to our knowledge. If this

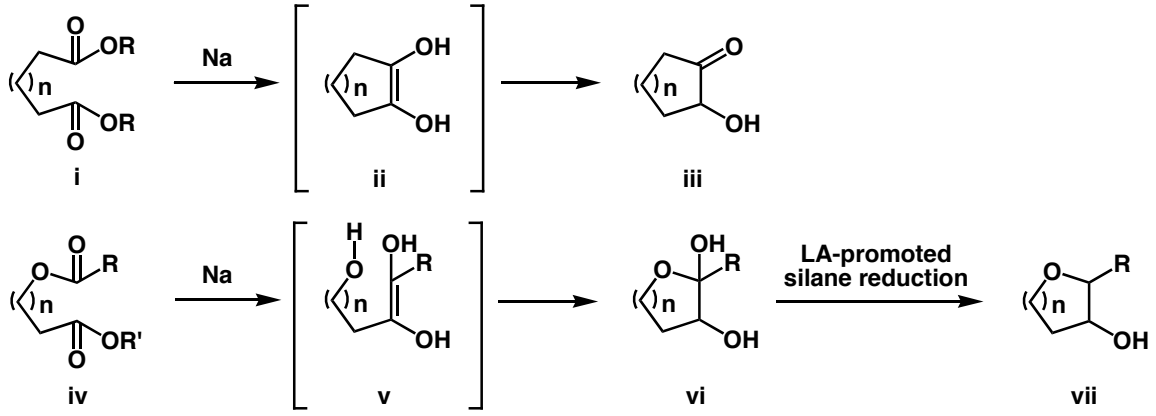
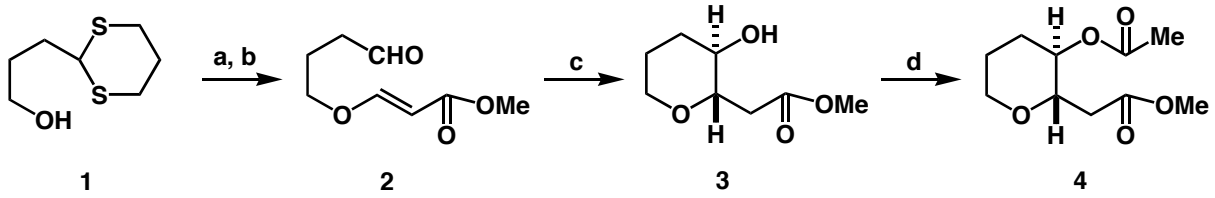


Figure 1. Intramolecular acyloin condensation.

This paper is dedicated to Prof. Steven M. Weinreb on occasion of his 65th birthday.

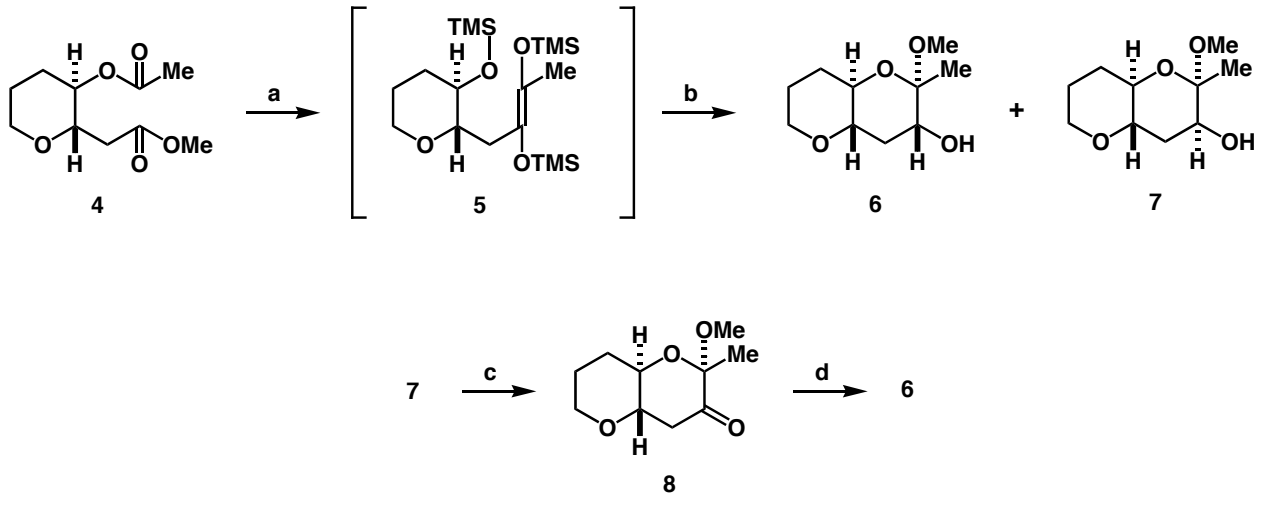
reaction proceeds, α-hydroxy cyclic acetals (**vi**) could be produced via enetriol (**v**). Then, subsequent Lewis acid (LA)-promoted silane reduction of **vi** would provide cyclic ethers (**vii**). We now report the synthesis of cyclic ether by intramolecular acyloin condensation as a key step. Diester (**4**) as a substrate for the intramolecular acyloin condensation was efficiently synthesized based on our developed SmI_2-induced reductive cyclization[4] (Scheme 1). Hetero-Michael addition of hydroxy thioacetal (**1**),[5] prepared from dihydrofuran in two steps, with methyl propiolate in the presence of *N*-methylmorpholine in CH_2Cl_2 afforded β-alkoxy acrylate,[6] which was hydrolyzed by MeI treatment[7] to give aldehyde (**2**). Treatment of **2** with SmI_2[8] in the presence of MeOH in THF effected reductive cyclization to give 2,3-*trans*-tetrahydropyran (**3**) in 90% yield. Acetylation of **3** afforded the requisite diester (**4**)[9] as the substrate.



1 2 3 4

Scheme 1. (a) methyl propiolate, *N*-methylmorpholine, CH_2Cl_2, rt, 77% (three steps from dihydrofuran); (b) MeI, $NaHCO_3$, aq. MeCN, rt, 91%; (c) SmI_2, MeOH, THF, 0 °C, 90%; (d) Ac_2O, pyridine, rt, 89%.

Acyloin condensation by treatment with Na is improved by addition of TMSCl to give bis-silyloxyalkenes, which are hydrolyzed to acyloins.[10] Thus, the substrate (**4**) was treated under these conditions. Upon treatment of diester (**4**) with Na in the presence of TMSCl in refluxing toluene, intramolecular acyloin condensation took place to give tri-TMS ether (**5**), which, due to its unstability, was immediately treated with CSA in $CH(OMe)_3$–MeOH to give a 4:1 mixture of α- and β-hydroxy acetals (**6**[11] and **7**[12]) in 40% combined yield (two steps). The β-hydroxy acetal (**7**) was transformed to the desired α-hydroxy acetal (**6**); oxidation of **7** with tetra-*n*-propylammonium perruthenate (TPAP) and *N*-

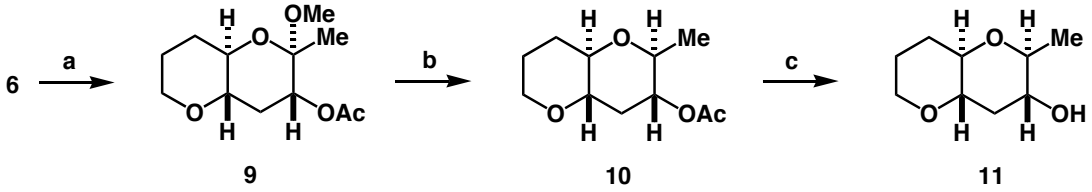


4 5 6 7

Scheme 2. (a) Na, TMSCl, toluene, reflux; (b) CSA, $CH(OMe)_3$, MeOH, rt, 40% (two steps); (c) TPAP, NMO, MS 4A, CH_2Cl_2, rt; (d) $NaBH_4$, MeOH, 0 °C, 90% (two steps).

methylmorpholine *N*-oxide (NMO) in CH_2Cl_2 afforded ketone (**8**), which was reduced with $NaBH_4$ in MeOH at 0 °C to give α-alcohol (**6**) in 90% yield (Scheme 2).

Then, conversion of acetal (**6**) to bicyclic ether (**11**) was carried out (Scheme 3). After acetylation of **6**, reduction of the resultant acetate (**9**) with Et_3SiH in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2[13] stereoselectively afforded the 2,6-*syn*-2,3-*trans*-tetrahydropyran ring to give bicyclic ether (**10**) in 96% yield. Methanolysis of acetate (**10**) with K_2CO_3 furnished the known bicyclic ether (**11**)[14,15] in 95% yield.



Scheme 3. (a) Ac_2O, pyridine, rt, 96%; (b) Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, –20 °C, 96%; (c) K_2CO_3, MeOH, rt, 95%.

In summary, a new method for construction of cyclic ethers have been developed based on intramolecular acyloin condensation of diester and Lewis acid-promoted Et_3SiH reduction.

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11. ^{1}H-NMR data for **6** (400 MHz, $CDCl_3$); δ 3.92-3.88 (m, 1H), 3.52-3.45 (m, 1H), 3.39-3.33 (m, 1H), 3.26 (s, 3H), 3.26-3.19 (m, 3H), 2.97 (ddd, *J* = 11.5, 9.0, 4.1 Hz, 1H), 2.12 (dt, *J* = 11.3, 4.5 Hz, 1H), 2.06 (d, *J* = 11.3 Hz, 1H), 1.99-1.95 (m, 1H), 1.78-1.65 (m, 2H), 1.39 (s, 3H).
12. ^{1}H-NMR data for **7** (400 MHz, $CDCl_3$); δ 3.95-3.39 (m, 1H), 3.73 (br, $W_{1/2}$ = 8.7 Hz, 1H), 3.45-3.28 (m, 3H), 3.27 (s, 3H), 2.09-1.94 (m, 3H), 1.83-1.47 (m, 3H), 1.36 (s, 3H).
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