Pergamon

Tetrahedron Letters 40 (1999) 2811–2814

TETRAHEDRON
LETTERS

# An Efficient Strategy for the Iterative Synthesis of a *trans*-Fused Polytetrahydropyran Ring System *via* $SmI_2$-Induced Reductive Intramolecular Cyclization

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Received 21 January 1999; accepted 5 February 1999

**Abstract**

A highly efficient strategy for the iterative synthesis of a *trans*-fused polytetrahydropyran ring system was developed. The new iterative method involves $SmI_2$-induced reductive intramolecular cyclization of an aldehyde and a β-alkoxy acrylate as the key step, producing a 2,3-*trans*-tetrahydropyran ring.

*Keywords: Samarium diiodide; Radical reaction; Cyclization; Tetrahydropyrans*

Since brevetoxin B, a neurotoxin produced by the red tide organism *Gymnodinium breve*, was first isolated and determined to have an unprecedented structure in 1981 [1], many marine polycyclic ethers of this type, exemplified by brevetoxins, ciguatoxins, yessotoxin, gambierol, gambieric acids, and maitotoxin, 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 ethers are involved. The synthetically challenging unique structures, combined with 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, and among them, several strategies towards effective iterative synthesis have been developed [3]. We now describe an extremely facile and highly efficient strategy for the iterative synthesis of a *trans*-fused polytetrahydropyran ring system based on the $SmI_2$-induced reductive intramolecular cyclization.

Our strategy for the new iterative synthesis of *trans*-fused polytetrahydropyran **i** involves a stereoselective C-C bond formation for the construction of every tetrahydropyran ring. Retrosynthetic cleavage of the indicated C-C bond in **i** revealed a key precursor **ii** having a C2-alkoxycarbonylmethyl and a C3-hydroxyl group. The construction of the 2,3-*trans*-tetrahydropyran **ii**, a key step of this strategy, would be realized by $SmI_2$-induced reductive intramolecular cyclization [4] of the aldehyde and β-alkoxyacrylate in **iii**, prepared from **iv**. Since the product **ii** contains the same functional groups as the starting material **iv**, repetition of the same reaction sequences would provide the *trans*-fused polytetrahydropyran **i**

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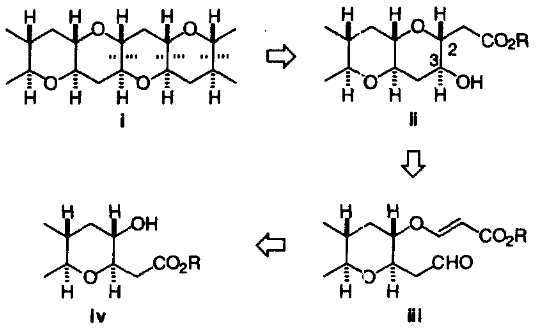
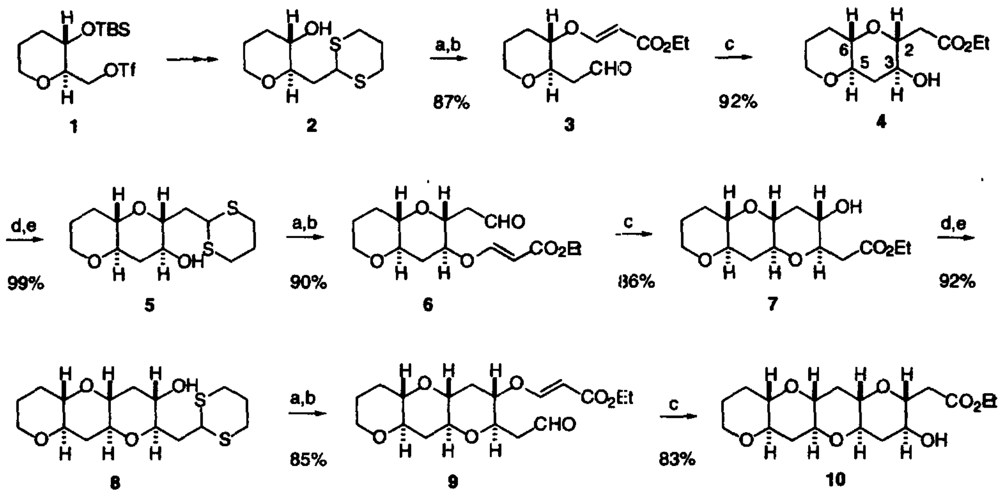
*PII:* S0040-4039(99)00301-9

stereoselectively. To our knowledge, no applications of $SmI_2$-induced intramolecular radical cyclization for the construction of cyclic ethers have been reported, although other radical methods have been developed [5].

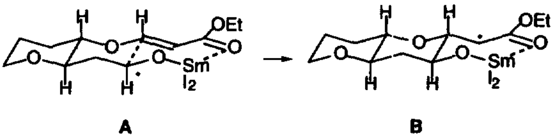


The iterative synthesis of the polytetrahydropyran ring system began with (2*R*,3*S*)-2-(1,3-dithian-2-yl)methyl-3-hydroxytetrahydropyran (**2**) [6], easily prepared from the optically active tetrahydropyran **1** [3n]. The treatment of **2** with ethyl propiolate in the presence of *N*-methylmorpholine in $CH_2Cl_2$ at room temperature resulted in a hetero-Michael addition to give a β-alkoxyacrylate [7], which was treated with MeI in aqueous MeCN [8] at room temperature to give the required tetrahydropyran **3** [9] having an aldehyde and a β-alkoxyacrylate, in 87% yield. Upon treatment of **3** with 2.2 equiv of $SmI_2$ [10] 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 2,3-*trans*-tetrahydropyran **4**, with virtually complete stereoselectivity in 92% yield [11]. The structure of the product **4** was unequivocally confirmed to be the desired bicyclic tetrahydropyran having 2,6-*syn*-3,5-*syn*-2,3-*trans*-configuration by $^1H$- and $^{13}C$-NMR, NOE and HMBC analyses. It is noteworthy that the present reaction using $SmI_2$ afforded directly 2,3-*trans*-tetrahydropyran **4** having a C2-ethoxycarbonylmethyl and a C3-hydroxyl group, which could be easily converted into the required functional groups for further cyclization. A plausible mechanism for the stereoselective cyclization leading to **4** would be explained by a transition state **A**, which is generated by initial single-electron reduction of the aldehyde with $SmI_2$ and chelation of Sm(III) to the ester. The resulting ketyl radical attacks the β-position of β-alkoxyacrylate giving **B**, which is reduced to an anion by a second equiv of $SmI_2$ and then protonated by MeOH to give 2,3-*trans*-tetrahydropyran **4** [12,13]. Thus, the chelation of Sm(III) to the ester may contribute to control the configuration of **4** with high stereoselectivity.

The tetrahydropyran **4** was then converted into another tetrahydropyran **6** having the requisite functional groups, *i.e.*, the aldehyde and β-alkoxyacrylate, for the second reductive cyclization. The reduction of **4** with DIBAH in toluene at -78 °C afforded aldehyde which was treated with 1,3-propanedithiol in the presence of $BF_3 \cdot Et_2O$ in $CH_2Cl_2$ at 0 °C to give thioacetal **5** in 99% yield from **4**. The hetero-Michael addition of **5** with ethyl propiolate followed by deprotection of the thioacetal with MeI gave aldehyde **6** in 90% yield. The



Reagents and conditions. (a) ethyl propiolate, N-methylmorpholine, $CH_2Cl_2$, rt; (b) MeI, aqueous MeCN, rt; (c) $SmI_2$, MeOH, THF, 0 °C; (d) DIBAH, toluene, -78 °C; (e) 1,3-propanedithiol, $BF_3$-$Et_2O$, $CH_2Cl_2$, 0 °C



second cyclization of the tetrahydropyran **6** with $SmI_2$ was achieved under the same reaction conditions as those of **3**, giving tricyclic *trans*-fused tetrahydropyran **7** exclusively in 86% yield. The tetrahydropyran **7** was also converted into aldehyde **9** *via* thioacetal **8** in 78% overall yield by a similar four-step sequence. The third $SmI_2$-induced cyclization of **9** stereoselectively furnished tetracyclic *trans*-fused tetrahydropyran **10** in 83% yield. The stereostructures of the cyclized products **7** and **10** were also confirmed by extensive NMR analyses. Further ring construction would proceed with complete stereoselection to afford a *trans*-fused polytetrahydropyran ring system by repetition of the same reaction sequences.

In conclusion, we have developed a very reliable and powerful method for the synthesis of a *trans*-fused polytetrahydropyran ring system based on the $SmI_2$-induced intramolecular cyclization of the aldehyde and β-alkoxyacrylate. The advantages of the present method are: (1) high yield and simple procedure for each reaction step, (2) complete diastereoselection in reductive cyclization to construct the *trans*-fused tetrahydropyran ring, and (3) no need of any asymmetric reactions or addition of chiral substrates for ring construction; the chirality of new rings arises from the stereochemistry of the starting material.

Further studies on the synthesis of polycyclic ether ring systems using this $SmI_2$-induced cyclization are now in progress in this laboratory.

Typical Procedure for $SmI_2$-Induced Cyclization: To a solution of aldehyde **3** (213.6 mg;

0.88 mmol) and MeOH (80 µL; 1.94 mmol) in THF (8mL) was added a 0.1 M solution of $SmI_2$ in THF (19.4 mL; 1.94 mmol) at 0 °C under argon. After stirring at 0 °C for 10 min, the mixture was diluted with EtOAc, washed with $H_2O$. The aqueous layer was extracted with EtOAc, and the combined organic extracts were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash column chromatography (silica gel, hexane:EtOAc=3:2 ) to give alcohol **4** (198.2 mg, 92%).

**Acknowledgments:** This work was supported in part by Special Project Funding for Basic Science (Essential Reaction) from RIKEN. The authors also thank Dr. H. Koshino and Ms. T. Chijimatsu for the NMR spectral measurements and Ms. K. Harata for the mass spectral measurements.

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