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Efficient strategy for convergent synthesis of *trans*-fused polycyclic ethers based on an intramolecular SmI_2-promoted cyclization of iodo ester

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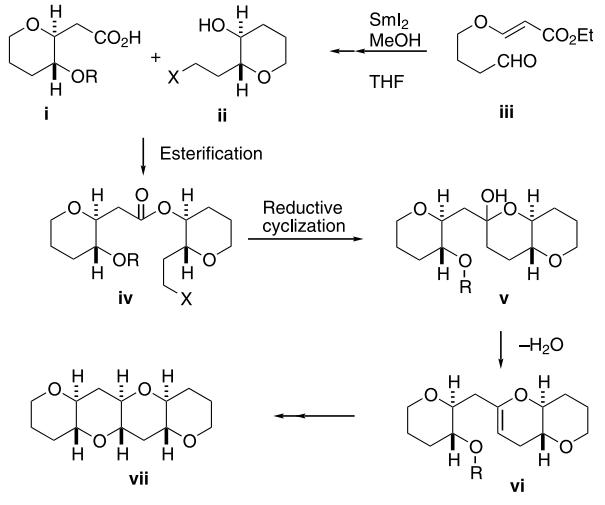
Abstract—An efficient convergent strategy for the construction of a *trans*-fused 6-6-6-6-membered tetracyclic ether ring system was developed. The key steps involve coupling of two cyclic ethers by esterification, SmI_2-promoted intramolecular reductive cyclization of iodo ester to hemiacetal, dehydration to dihydropyran, hydroboration, oxidation, intramolecular acetalization, and Lewis-acid catalyzed silane reduction.

Marine polycyclic ethers, exemplified by brevetoxins, ciguatoxins, and yessotoxins, have attracted the attention of numerous synthetic organic chemists due to their unique and complex structure, and potent biological activities.[1] The characteristic structural feature of these natural products is a *trans*-fused polycyclic ether ring system. Although various methods for the construction of these ring systems have been reported,[2] the development of an efficient convergent method is highly required toward the total synthesis of these marine polycyclic ethers. We now report an efficient convergent strategy for the synthesis of a polycyclic ether ring system based on an intramolecular SmI_2-promoted cyclization of halo ester, employing the stereoselective synthesis of *trans*-fused 6-6-6-6-membered tetracyclic ether **1**.

Our strategy for the convergent synthesis of *trans*-fused 6-6-6-6-membered tetracyclic ether **vii** via cyclic enol ether **vi** is outlined in Scheme 1. There are several reports for the convergent synthesis via cyclic enol ether as the key intermediate, which was synthesized by various methods: (1) an intramolecular ring-closing metathesis of olefinic ester using the Tebbe or the Petasis reagents;[3] (2) *B*-alkyl Suzuki coupling of lactone-derived triflate[4] or phosphate;[5] (3) coupling of lactone-derived vinylstannane with triflate;[6] (4) an intramolecular ring-closing from ester and phenylthioacetal using the Takeda reagent,[7] and (5) an intramolecular hetero-Michael reaction of β-methoxy enone and alcohol.[8,9] We were interested in the synthesis of cyclic enol ether **vi** from two cyclic ethers **i** and **ii**, since they can be easily prepared using our developed SmI_2-induced reductive cyclization[10] of **iii**. It was anticipated that the key intermediate **vi** would be synthesized by an intramolecular SmI_2-promoted cyclization[11] of halo ester **iv** followed by dehydration of the resultant hemiacetal **v**. Transformation of **vi** into polycyclic ether **viii** could be realized via stereoselective hydroboration, intramolecular acetalization, and Lewis acid-mediated reduction.[3–5]



Scheme 1.

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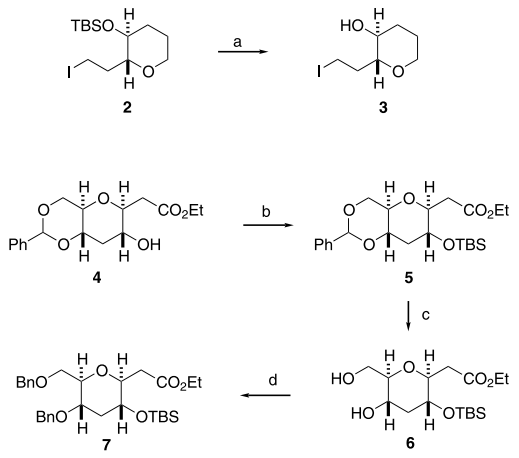
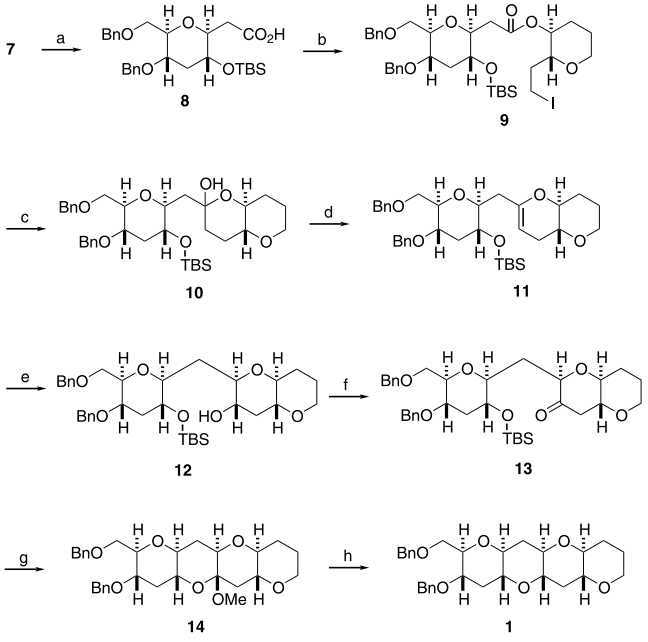


Scheme 2. *Reagents and conditions:* (a) 0.2 equiv. of CSA, CH_2Cl_2–MeOH, rt ~ 50°C, 96%; (b) 1.2 equiv. of TBSCl, 3 equiv. of imidazole, DMF, rt, 97%; (c) H_2, $Pd(OH)_2$, AcOEt, rt; 2.5 equiv. of NaH, 4.0 equiv. of BnBr, DMF, 0°C ~ rt; (d) 2.5 equiv. of NaH, 99%, two steps.



Scheme 3. *Reagents and conditions:* (a) 3N NaOH, MeOH, rt; (b) 1.25 equiv. of **3**, 1.25 equiv. of DCC, 0.25 equiv. of DMAP, CH_2Cl_2, rt, 94%, two steps; (c) 3 equiv. of SmI_2, 1 mol% NiI_2, THF, rt; (d) 0.4 equiv. of PPTS, 4 Å MS, toluene, 120°C, 82%, two steps; (e) 10 equiv. of thexylborane, THF, 0°C ~ rt; then aq. NaOH, aq. H_2O_2, rt ~ 40°C, 93%; (f) 5% TPAP, 2 equiv. of NMO, MeCN, rt, 99%; (g) 0.4 equiv. of CSA, $HC(OMe)_3$, CH_2Cl_2–MeOH, 80°C, 86%; (h) 1.5 equiv. of TMSOTf, 2.0 equiv. of Et_3SiH, CH_2Cl_2, −20 ~ 0°C, 88%.

With this prospect in mind, our convergent synthesis of **1** began with the synthesis of iodide **3** and ester **7** as the coupling partners (Scheme 2). 3-Hydroxy-2-iodoethyltetrahydropyran (**3**) was prepared from the known iodide **2**[12] by removal of the TBS group: treatment of **2** with CSA in CH_2Cl_2–MeOH afforded alcohol **3** in 96% yield. The other partner **7** was also synthesized from the known ester **4**,[13] which was prepared by our developed SmI_2-induced cyclization. Protection of **4** with TBSCl gave the silylated compound **5** in 97% yield. Hydrogenolysis of the benzylidene in **5** with a catalytic amount of $Pd(OH)_2$ followed by protection of the resultant diol **6** with benzyl bromide gave the desired ester **7** in 99% yield.

With alcohol **3** and ester **6** as the coupling partners in hand, we turned to convergent synthesis of polycyclic ether **1** via intramolecular SmI_2-promoted reductive cyclization (Scheme 3). Alkaline hydrolysis of the ester **7** gave carboxylic acid **8**, which was coupled with alcohol **3** using DCC and DMAP to afford ester **9** in 94% yield. Upon treatment of the iodo ester **9** with 3 equiv. of SmI_2 in the presence of a catalytic amount of NiI_2 in THF,[11] intramolecular reductive cyclization smoothly proceeded at room temperature for 2 h to give the desired hemiacetal **10**. Dehydration of **10** was effectively carried out by treatment with PPTS and 4 Å MS in toluene at 120°C to give dihydropyran **11** in 82% yield (two steps from **9**). Hydroboration of **11** with thexylborane stereoselectively proceeded to give α-alcohol **12** in 93% yield. Oxidation of **12** with TPAP and NMO gave ketone **13** in 99% yield. Upon treatment of **13** with CSA and $CH(OMe)_3$ in CH_2Cl_2–MeOH under reflux, deprotection of the TBS group followed by acetalization took place to give the 6-6-6-6-membered tetracyclic acetal **14** in 86% yield. Reduction of **14** with Et_3SiH in the presence of TMSOTf in CH_2Cl_2 proceeded smoothly to give the desired *trans*-fused 6-6-6-6-membered tetracyclic ether **1** as the sole product in 88% yield. The stereostructures of **14** and **1** were confirmed by extensive NMR analysis (^1H, ^{13}C NMR, NOE, HMBC) (Fig. 1).[14]

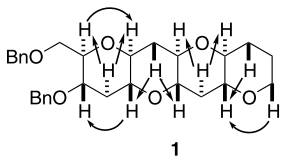


Figure 1. NOE of **1**.

In conclusion, we have developed an efficient convergent strategy for the construction of a *trans*-fused 6-6-6-6-membered tetracyclic ether ring system. This convergent strategy should be very effective, because coupling partners such as **i** and **ii** can be easily prepared based on our developed SmI_2-induced reductive cyclization.[10] Thus, this strategy would be widely applicable to efficient synthesis of natural polycyclic ethers.

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14. NMR data for **1**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 (2H, m, H-19 and 19′), 7.33 (2H, m, H-20 and 20′), 7.29 (2H, m, H-24 and 24′), 7.28 (2H, m, H-21and 25), 7.20 (2H, m, H-23 and 23′), 4.62 (1H, d, J=12.2 Hz, H-16a), 4.56 (1H, d, J=11.2 Hz, H-17a), 4.55 (1H, d, J=12.2 Hz, H-16b), 4.39 (1H, d, J=11.2 Hz, H-17b), 3.92 (1H, m, H-1eq.), 3.76 (1H, dd, J=10.7, 1.5 Hz, H-15a), 3.66 (1H, dd, J=10.7, 4.9 Hz, H-15b), 3.54 (1H, ddd, J=11.2, 9.8, 4.4 Hz, H-13), 3.43 (1H, ddd, J=9.8, 4.9, 1.5 Hz, H-14), 3.38 (1H, ddd, J=11.1, 11.2, 3.4 Hz, H-1ax.), 3.13 (1H, m, H-10), 3.12 (2H, m, H-7 and 8), 3.07 (1H, m, H-11), 3.06 (1H, m, H-4), 3.04 (1H, m, H-5), 2.56 (1H, ddd, J=11.2, 4.4, 4.4 Hz, H-12eq.), 2.39 (1H, ddd, J=11.2, 3.4, 3.4 Hz, H-9eq.), 2.31 (1H, ddd, J=11.7, 3.4, 3.4 Hz, H-6eq.), 2.08 (1H, m, H-3eq.), 1.73 (2H, m, H-2), 1.54 (1H, ddd, J=11.2, 11.2, 11.2 Hz, H-9ax.), 1.50 (1H, m, H-6ax.), 1.47 (1H, ddd, J=11.2, 11.2, 11.2 Hz, H-12ax.), 1.45 (1H, m, H-3ax.). ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.18 (C-18), 137.91 (C-22), 128.39 (C-24 and 24′), 128.33 (C-20 and 20′), 127.90 (C-19 and 19′), 127.79 (C-23 and 23′), 127.75 (C-21), 127.60 (C-25), 80.46 (C-14), 78.32 (C-4), 77.21(C-5), 77.0 (C-7 and 8), 76.72 (C-10), 76.21 (C-11), 73.46 (C-16), 72.32 (C-13), 71.02 (C-17), 69.13 (C-15), 68.00 (C-1), 35.57 (C-6), 35.19 (C-9), 35.14 (C-12), 29.22 (C-3), 25.51 (C-2). The numbering was used as follows.