Total Synthesis of (−)-12,13-*epi*-Obtusenyne

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The stereoselective total synthesis of (−)-12,13-*epi*-obtusenyne is described. The oxonene skeleton possessing cis-orientated alkyl substituents at the α,α'-positions to ether linkage was stereoselectively constructed via cyclization of the corresponding hydroxy epoxide promoted by $Eu(fod)_3$.

Red algae of the genus *Laurencia* produce a wide variety of C15 metabolites containing medium-sized cyclic ethers as distinctive members of marine natural products.[1] In view of the synthetic challenge entailed in the construction of strained medium-sized cyclic ether systems, much synthetic effort has been directed towards these metabolites.[2] Among them are nine-membered cyclic ethers represented by (+)-obtusenyne (**1**).[3] In 1991, an analogue of (+)-**1** was isolated by Norte's group and its structure was proposed to be the C13-epimer of (+)-**1** with undefined configuration of C12.[4] The full structure was finally determined to be (−)-12,13-*epi*-obtusenyne (**2**) by the Fujiwara and Murai group via total synthesis of both isomers regarding C12 (Figure 1).[5]

We have developed an efficient method towards the stereoselective construction of medium-sized cyclic ethers by cyclization of hydroxy epoxides promoted by $Eu(fod)_3$,[6] and applied it to the synthetic studies of *Laurencia* metabolites.[7] Herein, we describe the total synthesis of (−)-**2** as a part of our research program.

Recently, we have accomplished the total synthesis of (+)-**1**.[7d] In the synthesis of (+)-**1**, conformation of α,α'-*trans*-oxonene **3** was important for the stereoselective introduction of the homoallylic β-alcohol moiety in **5** starting from α-selective epoxidation of **3** (Scheme 1). The trans-fused bicyclic system was essential for obtaining the appropriate conformation, whereas the diol part generated by deprotection of the acetonide made subsequent route circuitous. Based on the results, we set α,α'-*cis*-oxocene **6** as an intermediate for the synthesis of (−)-**2**. Conformation analysis of **6** showed steric circumstances around the C8–C9 double bond analogous to that of **3**, and the stereoselective conversion of **6** into **7** might proceed in the same manner to that of **3** into **5**. In addition, **7**, possessing the ethyl and discriminated hydroxy groups, could be converted to (−)-**2** via a straightforward route without the selective protection–deprotection sequence of the hydroxy groups required in the synthesis of (+)-**1**.

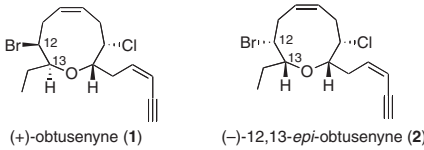
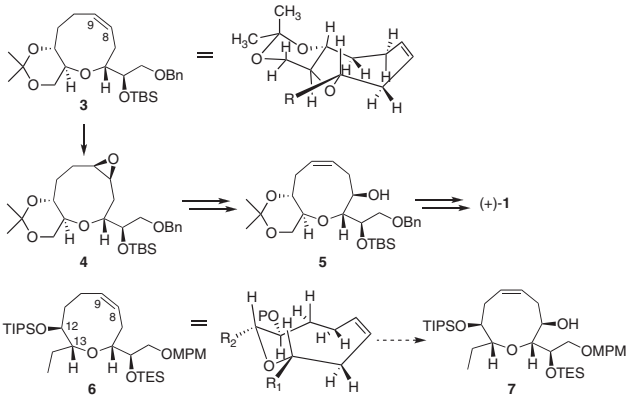
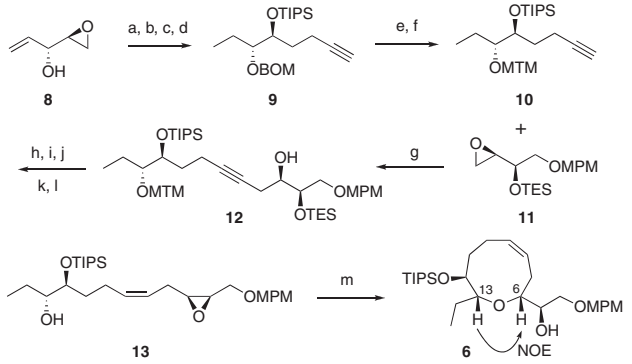


Figure 1.

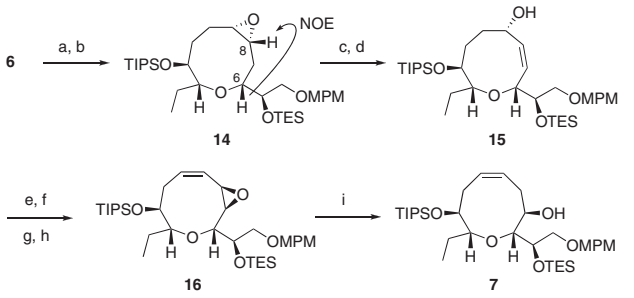


Scheme 1.

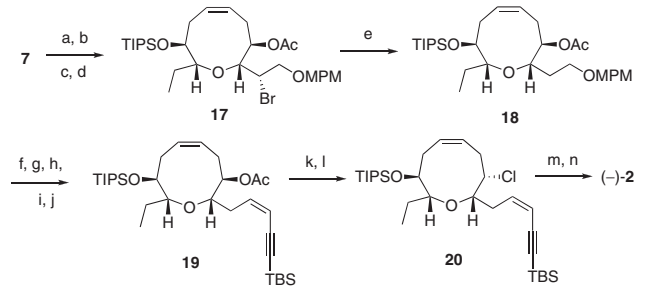


Scheme 2. *Reagents and conditions*: (a) BOMCl, *i*-Pr_2NEt, *n*-Bu_4NI, DCE, 50 °C; (b) H_2, Pd/C, AcOEt, 74% (two steps); (c) propargyl bromide, Mg, $HgCl_2$, Et_2O, −50 to −15 °C, 71%; (d) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 100%; (e) MeSTMS, ZnI_2, *n*-Bu_4NI, DCE, 95%; (f) DMSO, Ac_2O, AcOH, 70 °C, 78%; (g) *n*-BuLi, $BF_3 \cdot OEt_2$, THF, −78 °C, 92%; (h) MsCl, TEA, DMAP, CH_2Cl_2, 100%; (i) AcOH, H_2O, THF, 50 °C, 94%; (j) K_2CO_3, MeOH, CH_2Cl_2, 98%; (k) MeI, sat. $NaHCO_3$, acetone, 40 °C, 99%; (l) H_2, Lindlar cat., quinoline, AcOEt, 99%; (m) $Eu(fod)_3$, xylenes, 120 °C, 65%.

The synthesis of hydroxy epoxide **5** was investigated at the outset of this research (Scheme 2). Epoxy alcohol **8**, prepared from 1,4-pentadien-3-ol by the reported procedure,[8] was converted to acetylene **9** via the following sequence: (i) protection of the hydroxy group as its BOM ether, (ii) hydrogenation of the double bond, (iii) addition of 2-propynylmagnesium bromide, (iv) protection of the resulting hydroxy group as its TIPS ether. All steps proceeded in good yields. The BOM group in **9** was displaced with the MTM group to provide acetylene **10**. Coupling of acetylene **10** with epoxide **11**, derived from (−)-diethyl tartrate by our reported procedure,[9] was easily achieved by the Yamaguchi method.[10] Mesylation of the resulting hydroxy group followed by cleavage of the TES ether gave the



Scheme 3. *Reagent and conditions*: (a) TESCl, $AgNO_3$, pyridine, CH_3CN, 99%; (b) MCPBA, sat. $NaHCO_3$, CH_2Cl_2, 0 °C, 94%; (c) $(PhSe)_2$, $NaBH_4$, EtOH, *n*-BuOH, reflux; (d) H_2O_2, pyridine, 2-methyl-2-butene, CH_2Cl_2, 62% (two steps); (e) MCPBA, CH_2Cl_2, 0 °C, 86%; (f) MsCl, TEA, DMAP, CH_2Cl_2, 97%; (g) $(PhSe)_2$, $NaBH_4$, EtOH, *n*-BuOH, 50 °C; (h) H_2O_2, pyridine, 2-methyl-2-butene, CH_2Cl_2, 38% (two steps); (i) *n*-BuLi, DIBAL, toluene, 59%.



Scheme 4. *Reagents and conditions*: (a) Ac_2O, TEA, DMAP, CH_2Cl_2, 98%; (b) AcOH, H_2O, THF, 93%; (c) Tf_2O, pyridine, CH_2Cl_2; (d) *n*-Bu_4NBr, toluene, 50 °C, 85% (two steps); (e) *n*-Bu_3SnH, Et_3B, toluene, 0 °C, 74%; (f) DDQ, pH 7.4 buffer, CH_2Cl_2, 88%; (g) DMP, $NaHCO_3$, CH_2Cl_2, 91%; (h) CBr_4, HMPT, THF, 0 °C, 99%; (i) *n*-Bu_3SnH, $Pd(PPh_3)_4$, benzene, 81%; (j) (TBS)acetylene, $Pd(PPh_3)_4$, CuI, *i*-Pr_2NH, benzene; (k) K_2CO_3, MeOH, 89% (two steps); (l) CCl_4, *n*-Oct_3P, TEA, 1-methylcyclohexene, toluene; (m) TBAF, THF, 70% (two steps); (n) CBr_4, *n*-Oct_3P, TEA, 1-methylcyclohexene, toluene, 80 °C, 62%.

corresponding alcohol, which was treated with a base to afford epoxide in high yield.

Deprotection of the MTM group followed by partial hydrogenation provided **13**. With the key precursor **5** for the cyclization reaction in hand, the crucial step in this synthesis was examined. Treatment of **13** with $Eu(fod)_3$ resulted in 9-exo cyclization to provide α,α'-*cis*-oxonene **6** in 65% yield. The cis relationship was confirmed by the existence of NOE between C6-H and C13-H.

Base on the above discussion, the stereoselective conversion of **6** to homoallylic β-alcohol **7** was examined by the same sequence employing in the synthesis of (+)-**1** (Scheme 3). As expected, epoxidation of TES ether, derived from **6**, was proceeded stereoselectively from α-side and provided **14** in 98% yield. Its stereochemistry was confirmed by an NOE correlation between C6-H and C8-H. Regioselectivity of opening of the epoxide with a phenylselenyl anion was unpredictable. Fortunately, the reaction proceeded at the C8 position, and subsequent oxidative elimination provided allyl alcohol **15**. In the reaction, the product arising from the C9-opening isomer was not detected. Antiselective epoxidation of **15** with MCPBA directed by the neighboring hydroxy group[11] provided β-epoxide as a single isomer. Subsequent dehydration via oxidative elimination of the phenylselenyl group afforded allyl epoxide **16** in a moderate overall yield. Treatment of **16** with *n*-BuLi/DIBAL[12] resulted in opening of the epoxide mainly from the allylic position to afford homoallylic alcohol **7** (59%) along with its regioisomer (32%).

Next, installation of the *Z*-enyne terminus and two halogen functionalities was examined via a simplified route (Scheme 4). Alcohol **7** was converted to bromide **17** in high yield via a protection–deprotection sequence followed by bromination. Reduction of **17** was performed with *n*-Bu_3SnH/Et_3B at 0 °C. Deprotection of the MPM group in **18** followed by oxidation gave the corresponding aldehyde. The *Z*-enyne terminus was installed by the sequence applied to synthesis of the natural compound[5] with slight modifications: (i) treatment with CBr_4 and HMPA in THF,[7b,13] (ii) stereoselective hydrogenolysis of 1,1-dibromoalkene by Uenishi's method,[14] (iii) Sonogashira coupling of the resulting *Z*-1-bromoalkene with (*t*-butyldimethylsilyl)-acetylene.[15] Deprotection of the acetyl group in **19** followed by chlorination gave chloride **20** with inversion of configuration. Two silyl groups were deprotected, and finally, the resulting hydroxy group was brominated[16] with inversion of configuration to furnish (−)-**2**. The synthetic material was identical in all respects (^1H NMR, ^{13}C NMR, $[\alpha]_D$) to those reported for natural[4] and synthetic (−)-**2**.[5]

In conclusion, the total synthesis of (−)-**2** was accomplished with high stereoselectivity via the efficient route base on the confirmation analysis of intermediate **6**.

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