

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 was made subsequent route circuitous. Based on the results, we set α,α' -*cis*-oxonene **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**.

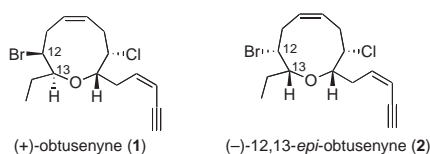
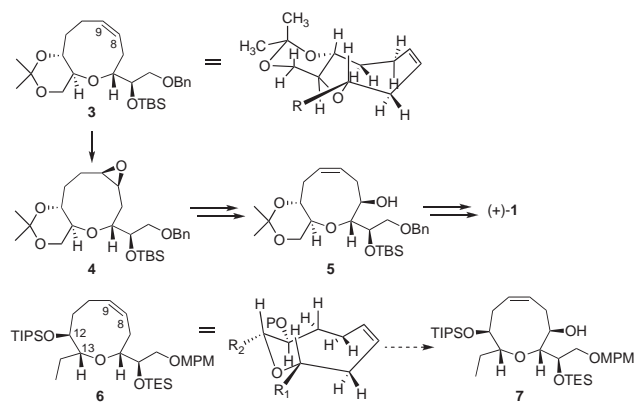
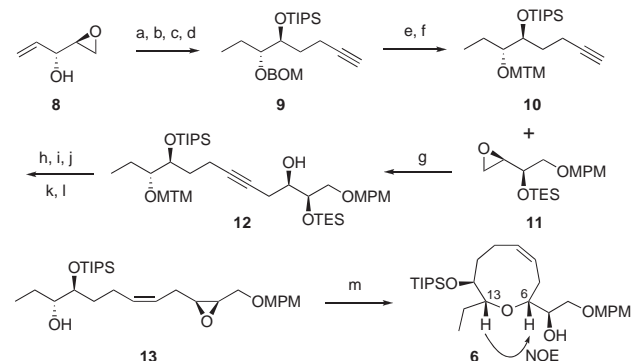


Figure 1.

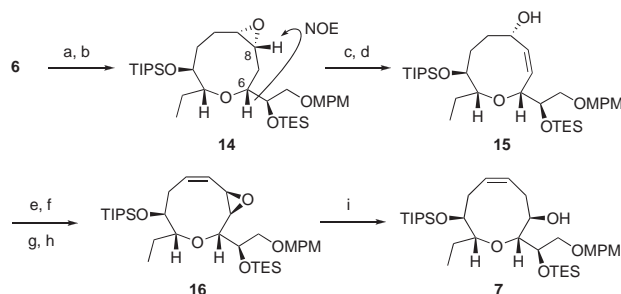


Scheme 1.



Scheme 2. Reagents and conditions: (a) BOMCl, *i*-Pr₂NEt, *n*-Bu₄NI, DCE, 50 °C; (b) H₂, Pd/C, AcOEt, 74% (two steps); (c) propargyl bromide, Mg, HgCl₂, Et₂O, –50 to –15 °C, 71%; (d) TIP-SOTf, 2,6-lutidine, CH₂Cl₂, 100%; (e) MeSTMS, ZnI₂, *n*-Bu₄NI, DCE, 95%; (f) DMSO, Ac₂O, AcOH, 70 °C, 78%; (g) *n*-BuLi, BF₃·OEt₂, THF, –78 °C, 92%; (h) MsCl, TEA, DMAP, CH₂Cl₂, 100%; (i) AcOH, H₂O, THF, 50 °C, 94%; (j) K₂CO₃, MeOH, CH₂Cl₂, 98%; (k) MeI, sat. NaHCO₃, acetone, 40 °C, 99%; (l) H₂, 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



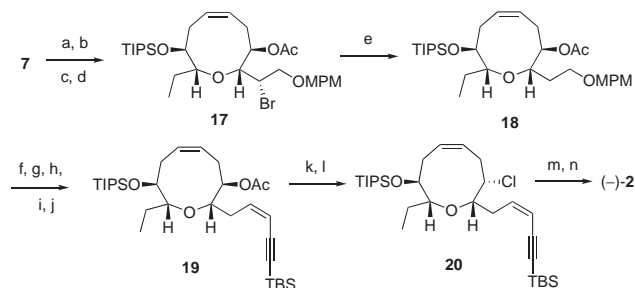
Scheme 3. Reagent and conditions: (a) TESCl, AgNO₃, pyridine, CH₃CN, 99%; (b) MCPBA, sat. NaHCO₃, CH₂Cl₂, 0 °C, 94%; (c) (PhSe)₂, NaBH₄, EtOH, *n*-BuOH, reflux; (d) H₂O₂, pyridine, 2-methyl-2-butene, CH₂Cl₂, 62% (two steps); (e) MCPBA, CH₂Cl₂, 0 °C, 86%; (f) MsCl, TEA, DMAP, CH₂Cl₂, 97%; (g) (PhSe)₂, NaBH₄, EtOH, *n*-BuOH, 50 °C; (h) H₂O₂, pyridine, 2-methyl-2-butene, CH₂Cl₂, 38% (two steps); (i) *n*-BuLi, DIBAL, toluene, 59%.

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 phenylselenenyl 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. Anti-selective epoxidation of **15** with MCPBA directed by the neighboring hydroxy group¹¹ provided β -epoxide as a single isomer. Subsequent dehydration via oxidative elimination of the phenylselenenyl group afforded allyl epoxide **16** in a moderate overall yield. Treatment of **16** with *n*-BuLi/DIBAL¹² 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*-Bu₃SnH/Et₃B 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 compound⁵ with slight modifications: (i) treatment with CBr₄ 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 hy-



Scheme 4. Reagents and conditions: (a) Ac₂O, TEA, DMAP, CH₂Cl₂, 98%; (b) AcOH, H₂O, THF, 93%; (c) Tf₂O, pyridine, CH₂Cl₂; (d) *n*-Bu₄NBr, toluene, 50 °C, 85% (two steps); (e) *n*-Bu₃SnH, Et₃B, toluene, 0 °C, 74%; (f) DDQ, pH 7.4 buffer, CH₂Cl₂, 88%; (g) DMP, NaHCO₃, CH₂Cl₂, 91%; (h) CBr₄, HMPA, THF, 0 °C, 99%; (i) *n*-Bu₃SnH, Pd(PPh₃)₄, benzene, 81%; (j) (TBS)acetylene, Pd(PPh₃)₄, CuI, *i*-Pr₂NH, benzene; (k) K₂CO₃, MeOH, 89% (two steps); (l) CCl₄, *n*-Oct₃P, TEA, 1-methylcyclohexene, toluene; (m) TBAF, THF, 70% (two steps); (n) CBr₄, *n*-Oct₃P, TEA, 1-methylcyclohexene, toluene, 80 °C, 62%.

droxy group was brominated¹⁶ with inversion of configuration to furnish (–)-**2**. The synthetic material was identical in all respects (¹H NMR, ¹³C NMR, [α]_D) to those reported for natural⁴ 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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