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Total synthesis of (+)-obtusenyne

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Abstract—The stereoselective total synthesis of (+)-obtusenyne is described. The oxonene skeleton possessing trans-orientated alkyl substituents at the α,α′-positions was stereoselectively constructed via cyclization of the corresponding hydroxy epoxide promoted by $Eu(fod)_3$.
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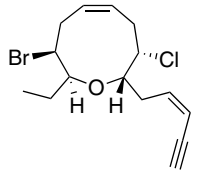
Red algae of the genus *Laurencia* produce a wide variety of C15 metabolites containing medium-sized cyclic ethers as distinctive members of marine natural products.[1] In recent years, considerable synthetic efforts have been made toward these systems[2] in view of certain problems incurred in assembling medium-sized cyclic ethers as well as the stereoselective introduction of alkyl substituents at α- and α′-positions of a cyclic ether with cis- or trans-orientation.

In the course of our synthetic efforts toward the *Laurencia* metabolites, we have developed an efficient method toward the stereoselective construction of medium-sized cyclic ethers by cyclization of hydroxy epoxides promoted by $Eu(fod)_3$.[3] The method has a potential advantage in that stereochemistry at the α- and α′-positions could be controlled stereospecifically since the reaction proceeds via an S_N2 process and exo mode selectivity regardless of the configuration of the hydroxy and epoxide groups. The efficiency of the method was proven by employing it in the successful synthesis of seven- and eight-membered cyclic ethers, isolaurepinnacin,[4] rogioloxepane A,[5] and laurallene.[6] In this letter, we examined applicability of the methodology to the synthesis of (+)-obtusenyne (**1**), a representative nine-membered cyclic ether with substituents in trans-orientation, as a part of our research program. (+)-Obtusenyne (**1**) was isolated from *Laurencia obtusa* by the Imre[7] and Fenical[8] groups independently, and its total syntheses were reported by the Murai,[9] Crimmins,[10] and Holmes[11] groups (Fig. 1).

Retrosynthetic analysis led to cyclization of hydroxy epoxide **2** for straightforward access to the construction of the oxonene skeleton **3** possessing all the required functional groups on the cyclic ether (Scheme 1). This attempt proved unsuccessful presumably due to the steric interaction of the internal oxygenated functionality of the epoxide.

On the basis of the result, our synthetic plan was envisaged in Scheme 2. Hydroxy epoxide **6**, obtainable by coupling of acetylene **8** with epoxide **9**, was postulated as a key precursor. Application of the foregoing protocol to **6** would result in the formation of the oxonene skeleton **5** with the crucial α,α′-trans-orientation to the ether linkage. Stereoselective introduction of a homoallylic β-alcohol moiety into **5** could arrange all the requisite functionalities on the cyclic ether. Stereoselective



(+)-Obtusenyne (**1**)

Figure 1.

Keywords: (+)-Obtusenyne; Oxonenes; Medium-ring heterocycles; Cyclization; Hydroxy epoxides.
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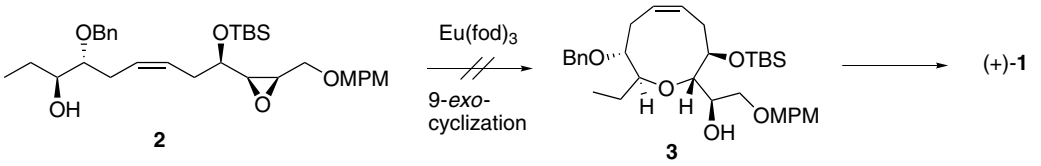
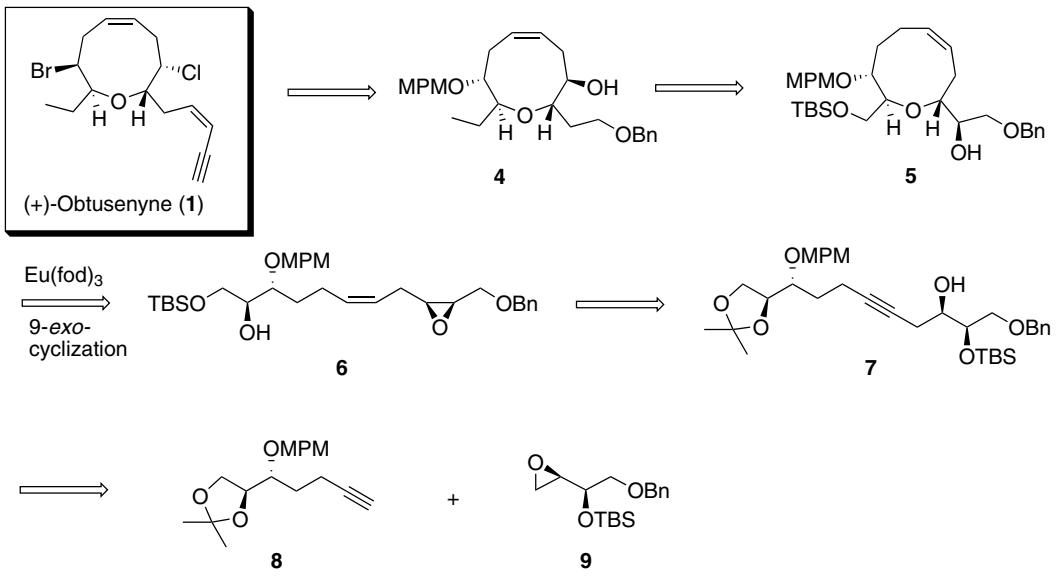


Scheme 1.



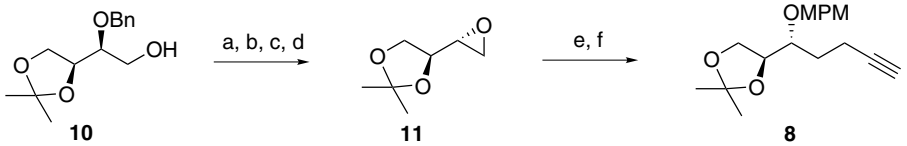
Scheme 2.

introduction of the *Z*-enyne terminus and halogen functionalities into **4** would complete our synthesis.

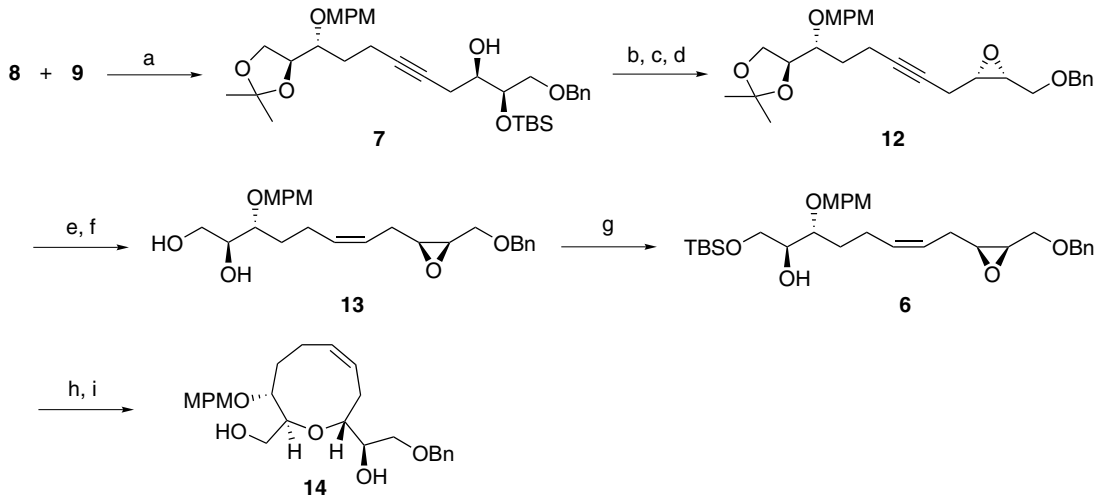
According to the retrosynthetic scheme, the synthesis of acetylene **8** was investigated at the outset of this research (Scheme 3). Alcohol **10**, prepared from (+)-diethyl tartrate by our reported procedure,[5] was converted to epoxide **11** with inversion of the configuration via the following sequence: (i) protection of the primary alcohol as its acetate, (ii) deprotection of the benzyl group, (iii) mesylation of the resulting hydroxy group, (iv) treatment with K_2CO_3 in MeOH. All steps proceeded in good yields. Addition of 2-propynylmagnesium bromide (77%) followed by protection of the resulting hydroxy group as its MPM ether afforded acetylene **8** (86%).

Coupling of acetylene **8** with epoxide **9**, derived from (−)-diethyl tartrate by our reported procedure,[5] was easily achieved by the Yamaguchi method[12] in 81% yield (Scheme 4). Mesylation of the resulting hydroxy group followed by cleavage of the TBS ether gave the corresponding alcohol, which was treated with a base to afford epoxide **12** in high yield. Epoxide **12** was converted to hydroxy epoxide **6** via hydrogenation in the presence of Lindlar catalyst and a deprotection–protection sequence. With the key precursor **6** for the cyclization reaction in hand, the crucial step in this synthesis was examined. Hydroxy epoxide **6** was treated with $Eu(fod)_3$ in refluxing toluene. The reaction proceeded smoothly to afford the corresponding cyclized product. Since partial deprotection of the TBS group was observed in the reaction, the product was isolated after exposure to aqueous AcOH. Consequently, α,α′-trans-oxonene **14** was furnished in 70% yield as the sole cyclized product. Interestingly, cyclization of diol **13** under the same conditions provided **14** in a lower yield (50%).

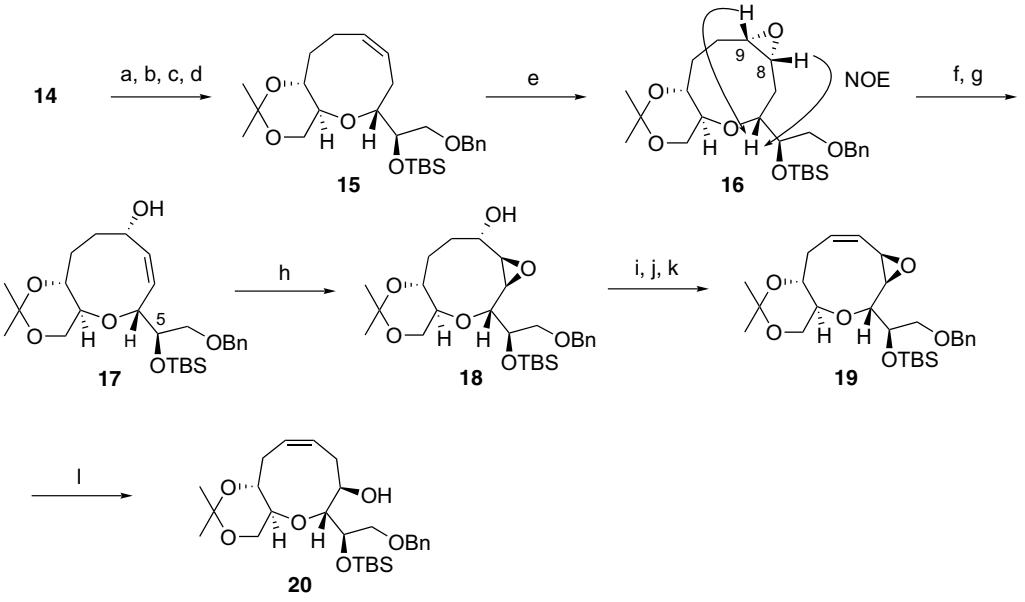
Next, the stage was set for the stereoselective introduction of the homoallylic β-alcohol moiety on the cyclic ether (Scheme 5). Diol **14** was converted to **15** through a four-step sequence. Conformation analysis of **15** by MM2 calculation suggested that the subsequent epoxidation proceeds from the convex α-side. As expected, α-epoxide **16** was obtained in 98% yield by treatment



Scheme 3. Reagents and conditions: (a) Ac_2O, pyridine, DMAP, CH_2Cl_2; (b) H_2, $Pd(OH)_2$–C, AcOEt; (c) MsCl, TEA, CH_2Cl_2; (d) K_2CO_3, MeOH, CH_2Cl_2, 74% (four steps); (e) 3-bromopropyne, Mg, $HgCl_2$, Et_2O, −50 to −20 °C, 77%; (f) MPMCl, NaH, *n*-Bu_4NI, THF, 86%.



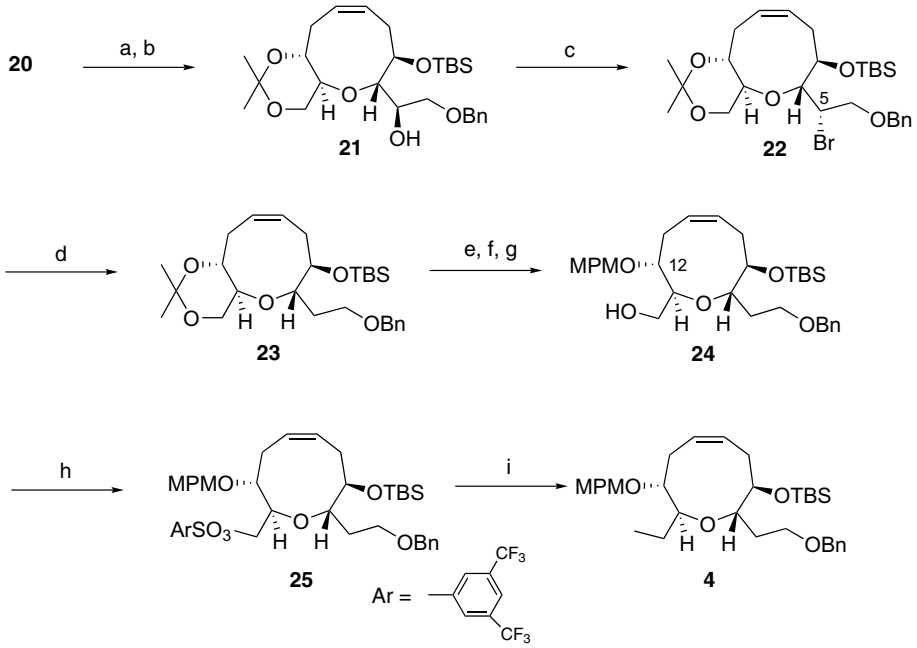
Scheme 4. Reagents and conditions: (a) *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −78 °C, 81%; (b) MsCl, TEA, DMAP, CH_2Cl_2, 0 °C, 88%; (c) TBAF, THF; (d) K_2CO_3, MeOH, 91% (two steps); (e) 80% aq AcOH, 89%; (f) H_2, Lindlar cat., quinoline, AcOEt, 99%; (g) TBSCl, TEA, DMAP, CH_2Cl_2, 97%; (h) $Eu(fod)_3$, toluene, 120 °C; (i) AcOH, THF, H_2O, 70% (two steps).



Scheme 5. Reagents and conditions: (a) DDQ, 4A-MS, CH_2Cl_2, 0 °C, 95%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 96%; (c) CF_3CO_2H, MeOH, 58% (recovered s.m. 34%); (d) 2-methoxypropene, PPTS, CH_2Cl_2, 99%; (e) MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 98%; (f) $(PhSe)_2$, $NaBH_4$, EtOH, *n*-BuOH, reflux, 89%; (g) H_2O_2, pyridine, 2-methyl-2-butene, CH_2Cl_2, 98%; (h) MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 85%; (i) MsCl, TEA, DMAP, CH_2Cl_2, 0 °C, 92%; (j) $(PhSe)_2$, $NaBH_4$, EtOH, *n*-BuOH, 80 °C, 90%; (k) H_2O_2, pyridine, 2-methyl-2-butene, CH_2Cl_2, 93%; (l) DIBAL, *n*-BuLi, toluene, 0 °C, 75%.

with MCPBA with no trace of the diastereomer. Regioselectivity of the subsequent opening of the epoxide in **16** with a phenylselenyl anion was unpredictable. Fortunately, the reaction proceeded at the C8 position (89%), and subsequent oxidative elimination provided allyl alcohol **17** (98%). In the latter reaction, the existence of the bulky silyloxy group at the C5 position, which would be removed in the later stage (vide infra), was important. The substrate in the absence of the silyloxy group gave a mixture of cis- and trans-elimination products. Anti-selective epoxidation of **17** with MCPBA was directed by the neighboring hydroxy group[13] and β-epoxide **18** was provided in 85% yield along with a trace amount of its α-isomer. Subsequent dehydration via oxidative elimination of the phenylselenyl group afforded allyl epoxide **19** in high yield. Regioselective cleavage of **19** from the allylic position was attained by use of *n*-BuLi/DIBAL[14] to provide homoallylic β-alcohol **20** in 75% yield.

Next, alcohol **20** was converted to alcohol **21** via a deprotection–protection sequence, and the resulting hydroxy group was brominated to afford bromide **22** in high yield (Scheme 6). Reduction of bromide **22** was performed with Bu_3SnH and AIBN at 0 °C under the photolytic conditions (100%).[15] When the Bu_3SnH

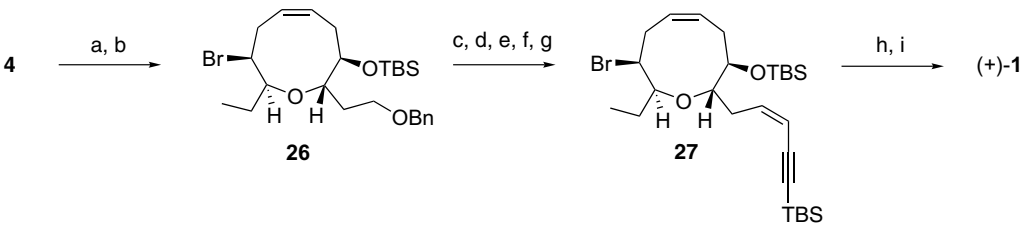


Scheme 6. Reagents and conditions: (a) TBAF, THF, 100%; (b) TBSCl, imidazole, DMF, 97%; (c) CBr_4, $P(oct)_3$, TEA, 1-methyl-1-cyclohexene, toluene, 90 °C, 97%; (d) Bu_3SnH, AIBN, toluene, hν (>280 nm), 0 °C, 100%; (e) CSA, MeOH, $(HOCH_2)_2$, 78%; (f) *p*-anisaldehyde dimethyl acetal, CSA, DCE, 100%; (g) DIBAL, toluene, −10 °C, 97%; (h) 3,5-bis(trifluoromethyl)benzenesufonyl chloride, TEA, DMAP, CH_2Cl_2; (i) MeLi, CuI, Et_2O, −12 °C, 82% (two steps).

reduction was conducted under thermolytic conditions (i.e., 100 °C in toluene), a bicyclic compound was mainly obtained as a result of intramolecular addition of the radical generated at the C5 position to the double bond on the cyclic ether. After deprotection of the acetonide group in **23**, the C12 hydroxy group was selectively protected as its MPM ether via reductive opening of an anisylidene acetal to afford alcohol **24** in high yield. Homologation of the C1 unit to alcohol **24** was troublesome. According to the Kotsuki procedure,[16] alcohol **24** was converted to the corresponding trifluoromethanesulfonate, which was considerably unstable and could not be subjected to the following methylation. For the purpose, 3,5-bis(trifluoromethyl)benzenesulfonate ester[17] was realized as a suitable leaving group having enough stability and reactivity. Treatment of the corresponding sulfonate **25** with Me_2CuLi provided adduct **4** in 82% overall yield.

The final stage of the synthesis required installation of the *Z*-enyne terminus and two halogen groups (Scheme 7). Cleavage of the MPM ether in **4** (91%) followed by bromination with inversion of configuration by the procedure of Murai[18] with addition of 1-methyl-1-cyclohexene[5] furnished bromide **26** in 67% yield. The benzyl group in **26** was deprotected with DDQ (67%), and the resulting alcohol was converted to *Z*-enyne **27** by the following sequence similar to that reported by the Murai group:[9] (i) oxidation with Dess–Martin periodinane (83%), (ii) treatment with CBr_4 and HMPT in THF (95%),[19] (iii) stereoselective hydrogenolysis of 1,1-dibromoalkene by Uenishi's method (86%),[20] (iv) Sonogashira coupling of the resulting *Z*-1-bromoalkene with (*t*-butyldimethylsilyl)acetylene (86%).[21] Two TBS groups were deprotected with TBAF (100%), and finally, the resulting hydroxy group was chlorinated with inversion of configuration by the procedure of Crimmins[10] to furnish (+)-**1** in 50% yield. The synthetic material was identical in all respects (^1H NMR, ^{13}C NMR, $[\alpha]_D$) to those reported for natural[7,8] and other synthetic (+)-**1**.[9–11]

In conclusion, the total synthesis of (+)-obtusenyne (**1**) was accomplished with high stereoselectivity. This synthetic study demonstrated that the cyclization of hydroxy epoxides promoted by $Eu(fod)_3$ is an efficient



Scheme 7. Reagents and conditions: (a) DDQ, benzene, pH = 7.4 buffer, 91%; (b) CBr_4, $P(oct)_3$, pyridine, 1-methyl-1-cyclohexene, toluene, 80 °C, 67%; (c) DDQ, DCE, pH = 7.4 buffer, 50 °C, 67%; (d) DMP, $NaHCO_3$, CH_2Cl_2, 83%; (e) CBr_4, HMPT, THF, 0 °C, 95%; (f) Bu_3SnH, $Pd(PPh_3)_4$, benzene, 86%; (g) (*t*-butyldimethylsilyl) acetylene, $Pd(PPh_3)_4$, CuI, *i*-Pr_2NH, benzene, 86%; (h) TBAF, THF, 0 °C, 100%; (i) CCl_4, $P(oct)_3$, pyridine, 1-methyl-1-cyclohexene, toluene, 80 °C, 50%.

approach to the stereoselective synthesis of highly functionalized oxonenes. Further applications of this methodology to the synthesis of related medium-sized cyclic ethers are in progress in our laboratory.

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