Total Synthesis of (+)-Obtusenyne

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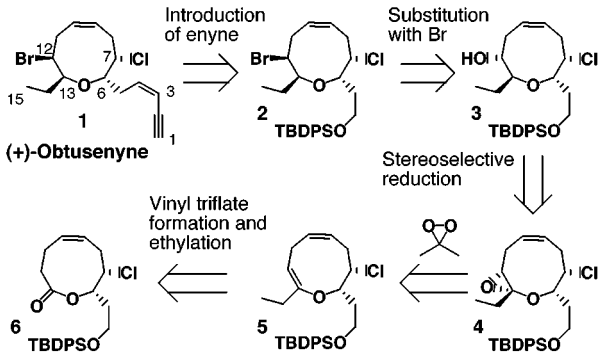
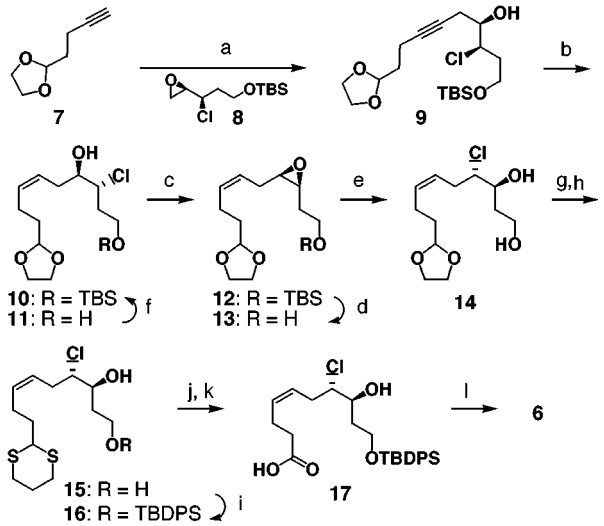
The *Laurencia* species of red algae produce a wide variety of cyclic ethereal C_{15} acetogenins.[1] Among them, (+)-obtusenyne (**1**),[2] isolated from *Laurencia obtusa* by the Imre[2a] and Fenical[2b] groups independently, has the particular features of an unusual nine-membered cyclic ethereal skeleton, bromo (C12) and chloro (C7) substituents on the ring both with *S* configurations, and a *Z*-enyne terminus. Since these features present synthetic challenge,[3,4,5] we have programmed the enantioselective total synthesis of **1**. The straightforward strategy for the synthesis of **1** was evolved from the retrosynthetic analysis shown in Scheme 1. The nine-membered lactone **6** was to be converted to dienyl ether **5** via ethylation of the corresponding vinyl triflate with an organocopper reagent. On the basis of our previous observation in a simple monocyclic system,[4b] epoxidation of **5** with dimethyldioxirane followed by reduction of the resultant **4** with DIBALH was expected to produce **3** with the desired regio- and stereoselectivities at C12 and C13. The enyne terminus and Br at C12 of **1** were to be installed in **3** at the final stage of the synthesis.

Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) BuLi (1.1 equiv), THF, −78 °C, 50 min, then BF_3·OEt_2 (1 equiv), 30 min, then **8** (0.5 equiv), −78 °C, 1 h, 20 °C, 1 h, 85% from **8**; (b) H_2, Lindlar's cat., EtOH−quinoline (250:1), 20 °C, 2 h, 98%; (c) K_2CO_3 (1.3 equiv), MeOH, 30 °C, 10 h, 100%; (d) TBAF (2 equiv), THF, 20 °C, 2 h, 99%; (e) Et_2NH·HCl (5 equiv), Ti(O-*i*-Pr)$_4$ (1.5 equiv), 20 °C, 48 h, 82% (**14**:**11** = 4:1); (f) TBSCl (1.1 equiv), imidazole (2.1 equiv), DMF, 0 °C, 3 h, 91%; (g) 2 M HCl, THF, 20 °C, 13 h; (h) 1,3-propanedithiol (2 equiv), BF_3·OEt_2 (1.5 equiv), 20 °C, 45 min, 99% from **14**; (i) TBDPSCl (1.2 equiv), imidazole (2 equiv), CH_2Cl_2, 20 °C, 75 min, 99%; (j) $(CF_3CO_2)_2$IPh (2 equiv), MeCN−H_2O (9:1), 0 °C, 2 min; (k) $NaClO_2$ (2 equiv), 2-methyl-2-butene (15 equiv), NaH_2PO_4·$2H_2O$ (1.5 equiv), *t*-BuOH−H_2O (3.5:1), 0 °C, 75 min, 82% from **16**; (l) EDCI (2 equiv), DMAP·HCl (2 equiv), DMAP (4 equiv), $CHCl_3$, reflux, 61 h, 83%.

Preparation of lactone **6** from epoxide **8**[6] is shown in Scheme 2. Acetylene **7**[7] was coupled with **8** by Yamaguchi's method,[8] and the resulting **9** was partially hydrogenated to give **10** in 83% yield. Treatment of **10** with K_2CO_3 followed by deprotection of the TBS group afforded hydroxy epoxide **13** (99%). The titanium tetraisopropoxide-mediated epoxide

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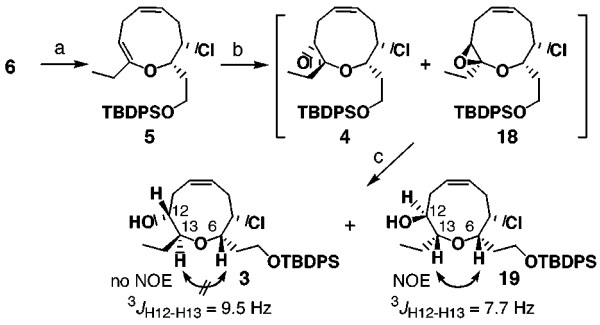
Scheme 3[a]

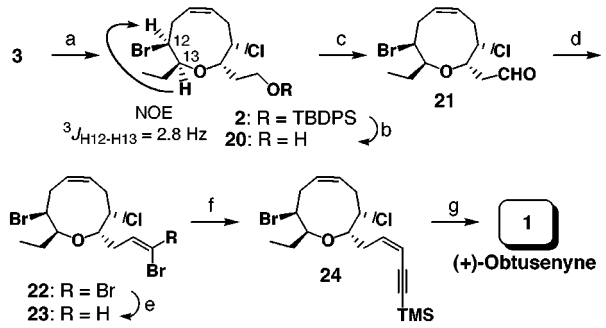


[a] Reagents and conditions: (a) KHMDS (2.5 equiv), HMPA (1.5 equiv), THF, −78 °C, 1 h, then Tf_2NPh (1.5 equiv), −78 °C, 1 h, then CuI (3 equiv), Me_2S (7 equiv), EtMgBr (7 equiv), −78 → −40 °C, 14 h, 71%; (b) dimethyldioxirane (0.032 M in CH_2Cl_2, 1.2 equiv), $CHCl_3$−CH_2Cl_2 (1:3), −60 °C, 10 min, then −20 °C, 30 min, then 2-methyl-2-butene (1 equiv), −20 → 0 °C, 5 min, then removal of solvent at 0 °C in vacuo (20 Torr); (c) DIBALH (0.95 M in hexane, 5 equiv), CH_2Cl_2, −78 °C, 10 min, then 0 °C, 12 h, 40% of **3** from **5** (based on the recovered **5**), 15% of **19** from **5** (based on the recovered **5**), 23% recovery of **5**.

ring opening of **13** with $Et_2NH{\cdot}HCl$[9] produced the desired **14** and its regioisomer **11** (**14**:**11** = 4:1) in 82% combined yield. The alcohol **11** could be recycled after conversion to **10**. Hydrolytic deprotection of **14**, which resulted only in the production of an oligomeric mixture, followed by treatment with 1,3-propanedithiol and $BF_3{\cdot}OEt_2$ yielded dithiane **15** quantitatively. After protection of the primary alcohol of **15** with TBDPS (99%), the dithiane moiety of **16** was removed to give the respective aldehyde, which was transformed into secoic acid **17** in 82% yield from **16** with $NaClO_2$.[10] Lactonization of **17** by modified Keck's method[4b,11] afforded **6** (83%) smoothly.

The lactone **6** was easily converted to dienyl ether **5** in 71% yield via a two-step sequence:[4] (i) deprotonation of **6** with KHMDS and the subsequent reaction with $PhNTf_2$, (ii) immediate treatment of the resultant mixture with EtMgBr in the presence of CuI and Me_2S (Scheme 3). The resulting **5** was stable enough to be handled without special care. The oxygen functionality at C12 and the hydrogen at C13 were introduced in a similar way to our previous report[4b] with a slight modification. Epoxidation of **5** with acetone-free dimethyldioxirane[12] in $CHCl_3$−CH_2Cl_2 (1:3) occurred selectively on the double bond of the enol ether at −20 °C.[13] Excess dimethyldioxirane was quenched by the addition of 2-methyl-2-butene after consumption of about $^3/_4$ of **5**. After solvent removal, epoxides **4** and **18** and unreacted **5** were obtained as an acid-sensitive mixture.[14] The mixture was reduced with DIBALH in CH_2Cl_2 to give alcohols **3** and **19** (40% and 19%, respectively, based on the consumption of **5**) and unreacted **5** (23% recovery). The trans relationship

Scheme 4[a]



[a] Reagents and conditions: (a) CBr_4 (5 equiv), Oct_3P (10 equiv), toluene, 75 °C, 14 h, 82%; (b) 47% HF−MeCN (3:7), 0 °C, 1 h, then 20 °C, 2 h, 91%; (c) Dess−Martin periodinane (2 equiv), CH_2Cl_2, 20 °C, 2 h, 84%; (d) CBr_4 (4 equiv), PPh_3 (8 equiv), CH_2Cl_2, 0 °C, 30 min, then **21**, 0 °C, 1 h, 95%; (e) Bu_3SnH (2 equiv), $Pd(PPh_3)_4$ (10 mol %), 20 °C, 5 h, 100%; (f) ethynyltrimethylsilane (8 equiv), *i*-Pr_2NH (4.5 equiv), $Pd(PPh_3)_4$ (10 mol %), CuI (0.4 equiv), 20 °C, 18.5 h, 66%; (g) 47% HF−1 M TBAF in THF (1:13, pH 4.5), THF, 37 °C, 2.5 h, 100%.

between the substituents at C12 and C13 in both alcohols was confirmed by the large $^3J_{H12-H13}$ (9.5−7.7 Hz) and the absence of NOE (H12/H13).[4] The existence of NOE (H6/H13) in **19** and its absence in **3** confirmed the cis and trans relationships between the substituents at C6 and C13, respectively.[3c,e,4]

Installation of Br at C12 of **3** was accomplished with CBr_4 and trioctylphosphine with complete inversion to give **2** (82%)[15] (Scheme 4). The cis relationship of the substituents at C12 and C13 was confirmed by the small $^3J_{H12-H13}$ (2.8 Hz) and the existence of NOE (H12/H13).[4] The TBDPS group of **2** was detached using HF−acetonitrile[16] (91%), and the resulting alcohol was oxidized with Dess−Martin periodinane[17] to afford aldehyde **21** (84%). The aldehyde was converted to *Z*-bromoalkene **23** via dibromoalkene **22** by Uenishi's method[18] in 95% yield from **21**. Sonogashira coupling[19] of **23** with ethynyltrimethylsilane followed by removal of the TMS group with TBAF under pH-controlled conditions (pH 4.5)[20] produced (+)-obtusenyne (**1**) {$[\alpha]^{19}_D$ +151 (*c* 0.13, $CHCl_3$); lit.[2a] $[\alpha]_D{}^{21.6}$ +155 ($CHCl_3$); lit.[2b] $[\alpha]^{20}_D$ +111.4 (*c* 2.8, $CHCl_3$)} in 66% yield from **23**.

The synthetic sample, though isolated only as a colorless oil, had characteristics in accordance with the data supplied by Professor Imre for the natural product in all respects (^1H and ^{13}C NMR,[21] IR, $[\alpha]_D$, and MS).

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Supporting Information Available: Experimental procedures and spectroscopic data for synthetic intermediates and the ^1H NMR spectra of synthetic **1** measured at various temperatures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) In the oxepane-fused nine-membered dienyl ethereal system, the selective epoxidation on the normal olefinic double bond rather than the double bond of the enol ether has been reported. See ref 5d.

(14) It was possible to estimate the ratio of **4** to **18** by ^1H NMR in C_6D_6 without decomposition of the epoxides. The stereochemistry of the epoxides was deduced from the fact that the proportion of **3** to **19** was closely related to that of **4** to **18** regardless of the reaction conditions. In addition, the solvent effect in the face selectivity at the epoxidation stage was also observed. The ratio of **4** to **18** was 1:1.6 (**3**:**19** = 1:1.5) in the pentane−acetone system, 1:1 (1:1) in CH_2Cl_2−acetone or CH_2Cl_2, and 1.8:1 (2.1:1) in $CHCl_3$−CH_2Cl_2.

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(21) Although good agreement of synthetic **1** with natural obtusenyne was shown under the same measurement conditions of ^1H and ^{13}C NMR, broadening of the signals was observed in both samples. We found slow exchange between the two conformers of **1** and estimated its activating ΔG to be 12.9 kcal/mol from the coalescence temperature (−5 °C).