A Synthesis of (+)-Obtusenyne

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Dedicated to Professor Steven V. Ley on the occasion of his 60th birthday

Abstract: A synthesis of the halogenated medium-ring ether natural product (+)-obtusenyne is reported utilizing a Claisen rearrangement and an intramolecular hydrosilation as key steps.

Key words: total synthesis, natural product, medium-ring ether

A variety of nonterpenoid C15 metabolites have been isolated from red algae and the opisthobranchs which feed on *Laurencia* species. Among these is the nine-membered cyclic ether (+)-obtusenyne (**1**) (Figure 1), which was independently isolated by Imre[1] and by Fenical and Clardy[2] and their respective co-workers. The structure and absolute configuration of **1** were assigned by a combination of spectroscopic analysis and X-ray crystallography.[1,2]

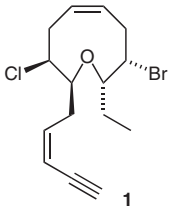
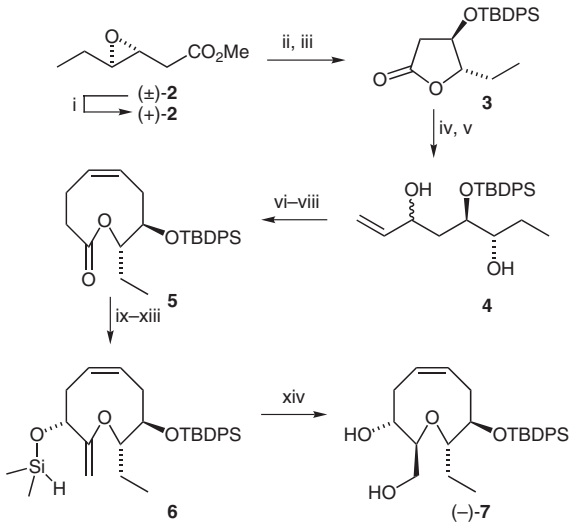


Figure 1 Structure of (+)-obtusenyne (**1**)

The isolation of a large number of halogenated ether marine natural products has led to the development of a variety of elegant synthetic strategies for the construction of strained medium-ring ether systems.[3–8] Our own strategy towards these metabolites[8] has involved exploitation of the Claisen rearrangement of a vinyl-substituted ketene-acetal to deliver a medium-ring lactone, which is converted into a medium-ring ether via a methylenation/intramolecular hydrosilation sequence. In the context of our studies on the total synthesis of obtusenyne (**1**) we have previously reported a highly diastereoselective racemic synthesis of the diol (±)-**7** from racemic methyl *trans*-3,4-epoxyhexanoate [(±)-**2**] that uses this Claisen rearrangement/intramolecular hydrosilation sequence.[9] Herein we describe an enantioselective route to the diol (–)-**7** (Scheme 1) and its conversion into (+)-obtusenyne (**1**).



Scheme 1 Enantioselective synthesis of the diol (–)-**7**. *Reagents and conditions*: i. crude pig liver esterase, pH 7.2 phosphate buffer, 31%; ii. 3% aq H_2SO_4, 85%; iii. TBDPSCl, imidazole, DMF, 96%; iv. DIBAL-H, THF, –78 °C to r.t., 90%; v. CH_2=CHMgBr, THF, 91%; vi. $PhSeCH_2CH(OEt)_2$, PPTS, toluene, reflux, 90%; vii. $NaIO_4$, CH_2Cl_2, MeOH, H_2O, ~100%; viii. DBU, toluene, reflux, 85%; ix. KHMDS, toluene, –78 °C then (±)-2-(phenylsulfonyl)-3-phenyloxaziridine, then CSA, 79%; x. TMSCl, Et_3N, THF, 98%; xi. Tebbe reagent, DMAP, THF, –40 °C to r.t., 90%; xii. TBAF, THF, r.t., 99%; xiii. $(Me_2SiH)_2NH$, NH_4Cl, ~100%; xiv. cat. $(PPh_3)_3RhCl$, THF, reflux, then KOH, H_2O_2, THF, MeOH, H_2O, 80%.

The synthesis began with a pig liver esterase catalysed kinetic resolution of racemic methyl *trans*-3,4-epoxyhexanoate [(±)-**2**] to provide methyl (+)-(3*R*,4*R*)-epoxyhexanoate [(+)-**2**] {$[\alpha]_D^{21}$ +26.6 (*c* = 0.64, CH_2Cl_2)}[10] with 96% ee[11,12] following the method of Tamm (Scheme 1).[13] The chiral non-racemic epoxide (+)-**2** was readily converted into the crystalline diol (–)-**7** {mp 68–69 °C (hexane); $[\alpha]_D^{22}$ –21.6 (*c* = 1.78, $CHCl_3$)} with very similar yields and diastereoselectivities to those previously reported for the synthesis of *racemic* (±)-**7** (Scheme 1).[9,14] The diol (–)-**7** was protected as its *p*-methoxybenzylidene acetal (95%) and selective reduction with DIBAL-H provided the primary alcohol **8** (Scheme 2). Mesylation of **8** (99%) followed by displacement of the mesylate with cyanide delivered the corresponding nitrile in excellent yield (99%). The nitrile was reduced with DIBAL-H to furnish the aldehyde **9** (~100%). We investigated two methods for the introduction of the enyne side

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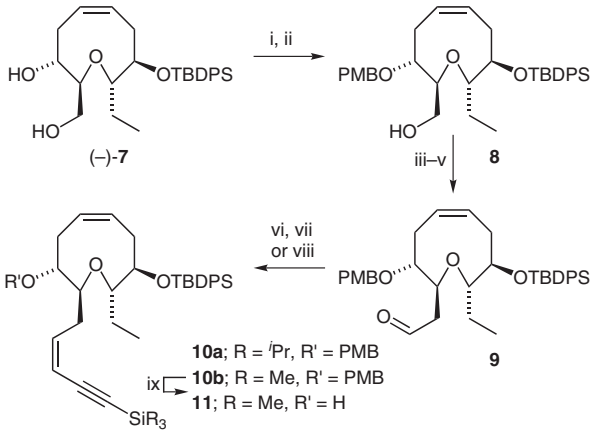
chain of **1**. Exposure of the aldehyde **9** to lithio 1,3-bis(triisopropylsilyl)propyne at –78 °C furnished the *cis*-enyne **10a** in 50% yield along with the corresponding (separable) *trans*-enyne. Alternatively, Stork–Wittig reaction converted **9** into the corresponding iodoalkene with exclusive *cis*-selectivity and in good yield (97%). Sonogashira reaction of the *cis*-vinyl iodide with trimethylsilylacetylene delivered the *cis*-enyne **10b** in excellent yield (97%). The PMB ether in **10b** was readily removed[15] with $BCl_3{\cdot}SMe_2$ to provide the secondary alcohol **11** in readiness for introduction of the chlorine atom.

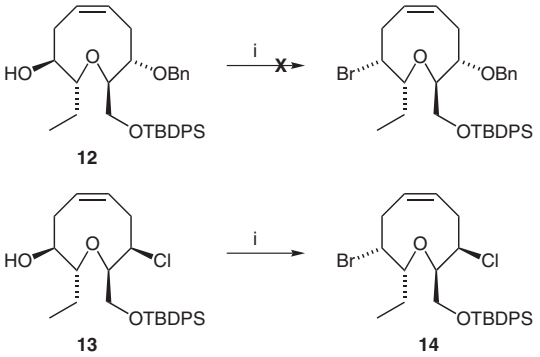


Scheme 2 Introduction of the enyne side chain. *Reagents and conditions:* i. *p*-methoxybenzaldehyde, PPTS, benzene, reflux, 95%; ii. DIBAL-H, CH_2Cl_2, –78 to –15 °C, 86%; iii. MsCl, Et_3N, CH_2Cl_2, ~100%; iv. NaCN, DMF, 60 °C, 99%; v. DIBAL-H, toluene, –78 to –15 °C, ~100%; vi. $Ph_3P^+CH_2I\ I^-$, NaHMDS, THF, DMPU, –78 °C to r.t., 73%; vii. TMSC≡CH, CuI, $Pd(PPh_3)_4$, Et_2NH, r.t., 97%; viii. TIPSC≡CCH_2TIPS, *n*-BuLi, THF, –78 °C to r.t., 50%; ix. $BCl_3{\cdot}SMe_2$, CH_2Cl_2, 92%.

Experience had taught us that the introduction of halogen atoms into medium-rings via S_N2 displacement of activated alcohols with halide anions can depend critically on the substituents on (and hence conformation of) the medium-ring. Indeed, treatment of the secondary alcohol **12** with CBr_4 and trioctylphosphine[16] in toluene at 70 °C resulted in decomposition of the substrate whereas the chloro alcohol **13** could be cleanly converted into the corresponding bromide **14** (65%) under the same reaction conditions (Scheme 3).

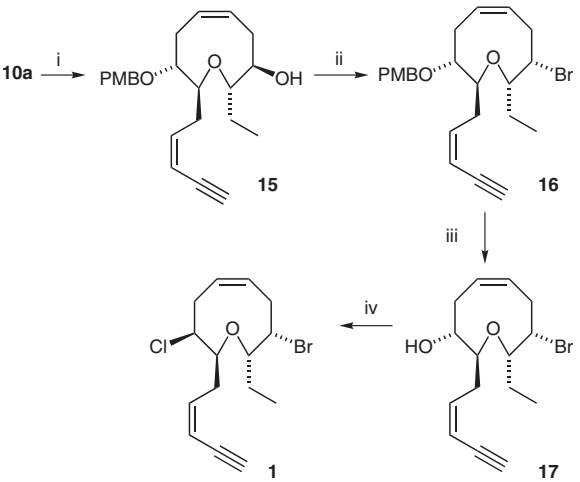
We were disappointed to find that attempted chlorination of the secondary alcohol **11** under a wide variety of conditions [Tf_2O, pyridine then Et_3BnNCl; CCl_4, $P(oct)_3$; Ghosez reagent[17]] did not produce any of the required chloride. We therefore turned our attention to the introduction of the C-12 bromide before the C-7 chloride.

Exposure of the enyne **10a** to TBAF in THF removed both silyl protecting groups to deliver the alcohol **15** in good yield (95%) (Scheme 4). Bromination of **15** was conducted using freshly sublimed CBr_4 and freshly distilled $P(oct)_3$ in toluene at 80 °C to deliver the bromide **16** in 67% yield. The bromide **16** was deprotected to provide the bromo alcohol **17** (70%), an intermediate in Crimmins's



Scheme 3 Bromination studies. *Reagents and conditions:* CBr_4, $P(oct)_3$, toluene, 70 °C, 0% from **12**, 65% from **13**.

synthesis of (+)-obtusenyne (**1**).[4b] The data for our synthetic bromo alcohol **17** were in close agreement with the data supplied by Crimmins resulting in a formal synthesis of **1**. Chlorination of **17** using Crimmins's conditions delivered (+)-obtusenyne (**1**) as a clear and colourless oil {$[\alpha]_D^{23}$ +142.5 (c = 0.0267 in $CHCl_3$)}. The data for our synthetic sample of obtusenyne (**1**) were in agreement with the data for the natural material and that obtained by other synthetic routes.[1,2,4,18]



Scheme 4 Synthesis of (+)-obtusenyne (**1**). *Reagents and conditions:* i. TBAF, THF, 95%; ii. CBr_4, $P(oct)_3$, toluene, 80 °C, 67%; iii. $BCl_3{\cdot}SMe_2$, CH_2Cl_2, 70%; iv. CCl_4, $P(oct)_3$, toluene, 80 °C (ca. 50%).

In summary, we have developed an efficient, enantioselective synthesis of the halogenated marine natural product (+)-obtusenyne (**1**) which further demonstrates the utility of the Claisen rearrangement/intramolecular hydrosilation approach to these strained medium-ring systems.

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(10) All new compounds exhibited satisfactory spectroscopic and exact mass/elemental analysis data.

(11) The enantiomeric excess and absolute configuration of (+)-**2** were determined by analysis of the elimination product methyl (4*R*,2*E*)-hydroxyhex-2-enoate that was formed in 86% yield by the treatment of (+)-**2** with DBU. The enantiomeric excess of the allylic alcohol was determined by ^{1}H NMR chiral shift reagent [(+)-Eu(hfc)$_3$] analysis, with the absolute configuration being assigned by comparison of the optical rotation of the allylic alcohol with that of its enantiomer.[12] The enantiomeric excess of (+)-**2** was confirmed by Mosher ester analysis of the secondary alcohol formed by the treatment of **3** with TBAF.

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(14) The relative stereochemistry of the *racemic* diol (±)-**7** was determined by ^{1}H NMR NOE and coupling constant analysis of the derived acetonide.[9c]

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(18) NMR data for synthetic **1**: ^{1}H NMR (500 MHz, C_6D_6, 50 °C): δ = 5.92 (dt, 1 H, *J* = 10.8, 7.3 Hz), 5.53–5.43 (m, 3 H), 4.20–4.13 (m, 1 H), 3.90 (dt, 1 H, *J* = 10.8, 2.8 Hz), 3.77 (dt, 1 H, *J* = 10.8, 3.0 Hz), 3.74–3.68 (m, 1 H), 3.02 (ddt, 1 H, *J* = 14.2, 1.2, 7.1 Hz), 2.92 (d, 1 H, *J* = 2.0 Hz), 2.87 (dt, 1 H, *J* = 14.7, 7.0 Hz), 2.78–2.62 (br m, 2 H), 2.52 (ddd, 1 H, *J* = 12.9, 6.5, 3.0 Hz), 2.40 (ddd, 1 H, *J* = 13.2, 6.6, 2.9 Hz), 1.91 (dqn, 1 H, *J* = 14.2, 7.4 Hz), 1.74 (dqn, 1 H, *J* = 14.2, 7.4 Hz), 0.85 (t, 1 H, *J* = 7.4 Hz). ^{13}C NMR (125 MHz, C_6D_6, 34 °C): δ = 140.7 (C-4), 110.7 (C-3), 82.8 (C-1), 80.1 (C-2), 63.3 (C-7), 56.6 (C-12), 35.3 (C-5), 32.0 (C-8), 31.2 (br, C-11), 28.7 (C-14), 10.1 (C-15). Owing to the conformational mobility of the natural product the signals due to C-6 and C-13 in the ^{13}C NMR spectrum were broadened to the baseline. Signals assignable to C-9 and C-10 were obscured by solvent.