Enantioselective Total Synthesis of (+)-Obtusenyne

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Abstract: A total synthesis of the laurencia metabolite (+)-obtusenyne has been completed. The key steps include a Sharpless kinetic resolution and an asymmetric glycolate alkylation to establish the stereogenic centers adjacent to the ether linkage and a ring-closing metathesis reaction to construct the nine-membered ether without the aid of a cyclic conformational constraint. The synthesis was completed in 20 linear steps from commercially available 1,5-hexadiene-3-ol.

The oceans have become a rich source of topographically unique molecules, many of which have potential for the treatment of human diseases. Invertebrates such as sponges, coral, and dinoflagellates are now a common origin of interesting natural products. Three main classes of compounds that contain medium ring ethers have been identified from marine sources. The ladder ether toxins include such potent structures as brevetoxins A1 and B2, and the ciguatoxins,3 all of which contain medium ring ether acetogenins.7 These C15 metabolites include Denmark’s synthesis of brasilenyne14 through a new intramolecular cross-coupling to form the nine-membered ring. Overman’s synthesis of sclerophythin15 via an intramolecular Nozaki–Kishi reaction to construct the oxonin, Murai’s total synthesis of obtusenyne exploiting a medium ring lactonization16 and the synthesis of isolaurallene through a nine-membered ring-closing metathesis from our laboratory.17

As part of a continuing program directed toward the development of a general strategy for the construction of medium ring ether metabolites, we wished to extend the strategy we employed in the synthesis of laurencin,18 prelaureatin,19 and isolaurallene17 to a metabolite with a nine-membered ring with substituents in a trans orientation at the α and α′ positions to the ether linkage. Obtusenyne seemed a suitable test given that its lone synthesis

Figure 1. Representative medium ring ether marine metabolites.

incorporated the α and α′ substituents to the ether linkage with approximately 2:1 stereoselectivity favoring the trans isomer.

(+)-Obtusenyne (1) was independently isolated from Laurencia obtusa by Imre11 in the Agean Sea and Fenical12 at Positano, Italy. The structure was established as 1 by single-crystal X-ray analysis.11 The key structural features of the molecule are the two halogens, which must be incorporated stereoselectively, the nine-membered ether ring with a trans relationship of the α and α′ ether substituents, and the attached (Z)-enyne substituent. The only previous total synthesis of (+)-obtusenyne was reported by Murai in 1999.16

Strategically, (+)-obtusenyne would be derived from oxonene 2 through selective incorporation of the required halogens and introduction of the Z-enyne. The core oxonene 2 would be constructed from triene 3 through a ring-closing metathesis20,21 reaction after selective functionalization of the trisubstituted alkene. The crucial stereochemistry of the α and α′ positions of the ether linkage would be established by an asymmetric glycolate alkylation22 of glycolyl oxazolidinone 4 which would be prepared from epoxide 5. Epoxide 5 would be easily prepared through a kinetic resolution23 of the commercially available hexadienol 6.

The synthesis of oxazolidinone 4 is illustrated in Scheme 1. 1,5-Hexadien-3-ol 6 was exposed to a standard Sharpless kinetic resolution.23 At 47% completion, the epoxide 5 was obtained in 98% e.e. The secondary alcohol was protected as its benzyl ether by exposure to sodium hydride and benzyl bromide in THF to provide 89% of epoxide 7. The epoxide 7 was readily converted in 90% yield to the secondary alcohol 8 by treatment with methylmagnesium bromide and copper(I) iodide. Alkylation of the alcohol with sodium hydride and bromoacetic acid delivered the glycolic acid 9. Acylation of (R)-lithio-4-isopropyl-oxazolidin-2-one with the mixed anhydride of the glycolate acid 9 afforded the N-acetyl-oxazolidinone 4 in good overall yield.

In a first attempt, it was hoped to incorporate a direct precursor to the enyne through alkylation22 of the N-glycolyloxazolidinone 4. To this end, the sodium enolate of oxazolidinone 4 was alkylated with Z-1-bromo-3-iodo propene to produce the diene 10 (82%, >98:2 d.r.). Reductive removal of the auxiliary produced alcohol 11. Swern oxidation24 of the alcohol 11 followed by exposure of the resultant aldehyde 12


"For approaches to nine membered ring ethers: see ref 18.


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Scheme 1. Synthesis of the N-glycolyloxazolidinone 4

Scheme 2. Synthesis of Triene 13
to a Brown alkylation\textsuperscript{25} (>98:2 d.r.) delivered triene 12 in excellent yield. Conversion of alcohol 12 to the TBS ether 13 was accomplished under standard conditions. Unfortunately, attempts to form the oxonene ring by ring-closing metathesis of triene 13 resulted in loss of the vinyl halide functionality via the formation of the cyclohexene rather than the desired oxonene. Although this result was not entirely unexpected, we had hoped to avoid extensive functional group manipulation to accomplish the installation of the enyne.

The problem was readily corrected by alkylation of the oxazolidinone 4 with prenyl iodide (Scheme 3) to provide the diene 15 in 82\% yield (>98:2 d.r.). The oxazolidinone was reductively removed with sodium borohydride resulting in the isolation of alcohol 16 in 82\% yield. Swern oxidation of the alcohol produced the corresponding aldehyde which was immediately treated with 2,4-\textit{MeC$_6$H$_4$CH$_2$CH=CH$_2$} under Brown’s conditions\textsuperscript{23} to give a 92\% yield of the aldehyde 17 (>97:3 d.r.). Protection of the secondary alcohol 17 as a TBS ether furnished the desired triene 3. Direct exposure of triene 3 to 5 mol \% of the Grubbs carbene [(Cy$_3$P)$_2$Cl$_2$Ru=CHPh]\textsuperscript{26} provided a 3:1 mixture of the oxonene 18: cyclohexene 14. Although this result was gratifying, in that the nine-membered oxonene was formed competitively with the cyclohexene, we opted to improve the reaction by first epoxidizing the trisubstituted alkene. Thus, exposure of triene 3 to m-CPBA in dichloromethane at low temperature afforded the epoxides 19 in high yield. Treatment of diene 19 with the Grubbs catalyst\textsuperscript{26} effected rapid closure to the oxonene 20 (82\%). This is the first example of the metathetic formation of an oxonene with a trans orientation of the substituents at the \(\alpha\) and \(\alpha'\) positions without the aid of a cyclic conformational constraint.\textsuperscript{17,19}

The completion of the synthesis of (\(+\))-obtusenylne 1 from oxonene 20 is illustrated in Scheme 4. At this stage, the epoxide 20 was converted to the alcohol 21 by hydrolysis of the epoxide to the diol, oxidative cleavage of the diol to the aldehyde and subsequent reduction of the aldehyde to give alcohol 21 in 65\% overall yield. Removal of the secondary TBS ether gave the diene 22 and selective protection of the primary alcohol as its TBDPS ether then provided the alcohol 23. Incorporation of the secondary chloride was accomplished by heating the secondary alcohol in toluene in the presence of trioctylphosphine and CCl$_4$.\textsuperscript{27} A 6:1 mixture of chloride 24 and the diene from elimination was formed in 75\% yield. Competing elimination was somewhat suppressed by the slow addition of the phosphine to the heated solution of the alcohol. Removal of the benzyl ether under Holmes conditions\textsuperscript{28} provided alcohol 25. Installa-


Enantioselective Total Synthesis of (+)-Obtusenyn

Scheme 5. Second Generation Endgame

![Diagram of the synthetic pathway]

- Reaction conditions:
  1. a. Na-naphthalenide, THF, 90%.
  2. b. NaIO₄, THF, H₂O, 95%.
  3. c. 2-Me-3-chloro-1-propanol, THF, 72%.
  4. d. Cu, Et,N, SiMe₃, THF, 72%.
  5. e. NaIO₄, THF, H₂O, 95%.
  6. f. Ph₃P, C₂Br₂, PhCH₃, 86%.
  7. g. n-Bu₄NF, THF, 91%.

The final stage of the synthesis required attachment of the Z-enzyme. To this end, the TBDPS ether was cleaved to the resultant primary alcohol with n-Bu₄NF in THF. Oxidation of the alcohol to the aldehyde with the Dess–Martin periodinane followed by Stork–Wittig olefination provided vinyl iodide as a single geometric isomer. Subsequent Sonogashira coupling cleanly afforded the enyne in 95% yield. Sequential incorporation of the two halogens completed the synthesis. Thus, bromination of the alcohol led to the formation of bromide in 86% yield, followed by removal of the two silicon protecting groups and chlorination of the alcohol led to the completion of the synthesis of (+)-obtusenyn. The final sequence required 20 linear synthetic steps from commercially available 1,5-hexadiene-3-ol.

In summary, a highly diastereoselective synthesis of the Laurencia metabolite (+)-obtusenyn has been completed. The key steps are an asymmetric glycolate alkylation to establish the stereochemical relationship of the disubstituted ether linkage and a ring-closing metathesis to construct the nine-membered oxocene.

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Supporting Information Available: Experimental procedures as well as ¹H and ¹³C NMR spectra for all new compounds and synthetic (+)-obtusenyn. This material is available free of charge via the Internet at http://pubs.acs.org.

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