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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 ostentatious structures as brevetoxins A[1] and B,[2] and the ciguatoxins,[3] all of which contain medium ring ethers in a complex polyether skeleton. The members of the topographically unique eunicellin class of marine metabolites represented by astrogorgin,[4] sclerophytin,[5] 4-deoxyasbestinin A[6] display a nine-membered ether embedded in a tricyclic or tetracyclic scaffold. Finally, the *Laurencia* red algae, in particular, have produced a large number of metabolites containing medium ring ether acetogenins.[7] These C15 metabolites include a variety of ring sizes such as those found in laurencin,[8] *trans*-isoprelaurefucin,[9] isolaurallene,[10] and obtusenyne.[11,12,13] The identification of these interesting metabolites has inspired a number of clever solutions to the construction of medium ring ethers. Recent examples of synthesis of nine-membered ether metabolites include Denmark's synthesis of brasilenyne[14] through a new intramolecular cross-coupling to form the nine-membered ring, Overman's synthesis of sclerophytin[15] via an intramolecular Nozaki−Kishi reaction to construct the oxonin, Murai's total synthesis of obtusenyne exploiting a medium ring lactonization[16] and the synthesis of isolaurallene through a nine-membered ring-closing metathesis from our laboratory.[17]

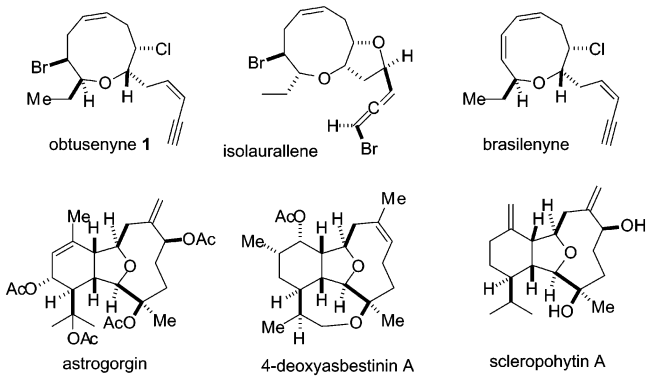

Figure 1. Representative medium ring ether marine metabolites.

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 isolaurallene[17] 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

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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 Imre[11] in the Agean Sea and Fenical[12] 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 metathesis[20,21] 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 alkylation[22] of glycolyl oxazolidinone **4** which would be prepared from epoxide **5**. Epoxide **5** would be easily prepared through a kinetic resolution[23] of the commercially available hexadienol **6**.

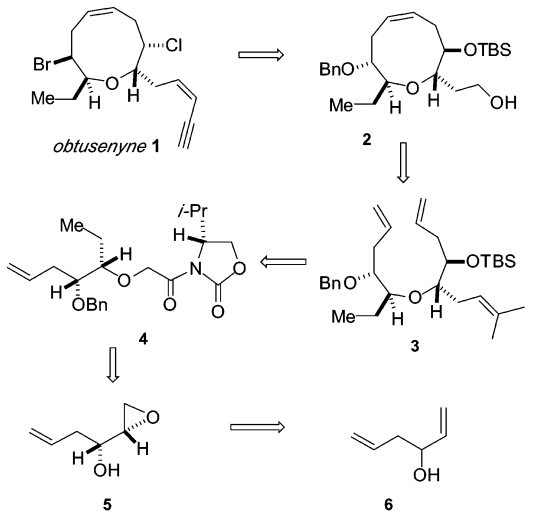
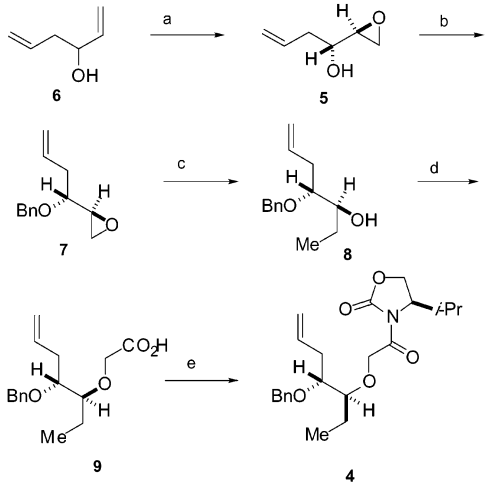


Figure 2. Retrosynthesis of (+)-obtusenyne

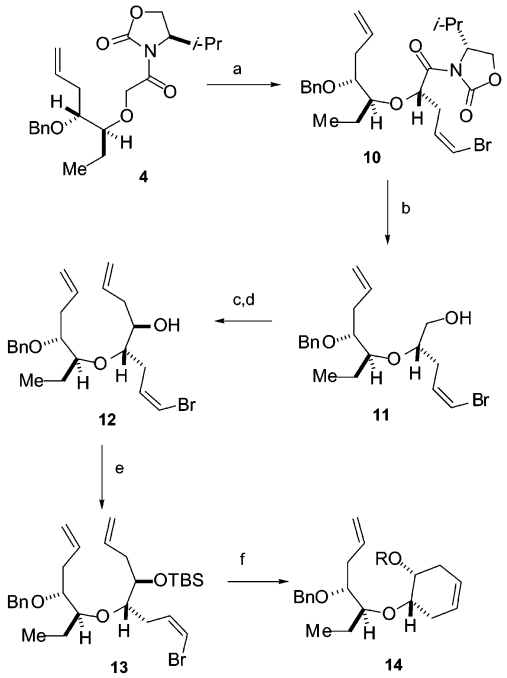
The synthesis of oxazolidinone **4** is illustrated in Scheme 1. 1,5-Hexadien-3-ol **6** was exposed to a standard Sharpless kinetic resolution.[23] At 47% completion, the epoxide **5** was obtained in 98% e.e. The secondary alcohol was protected as its benzyl ether by exposure to sodium hydride and 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

Scheme 1. Synthesis of the N-glycolyloxazolidinone 4



[a] (−)-Dicyclohexyltartrate, Ti(O-*i*-Pr)$_4$, *t*-BuOOH, 4 Å molecular sieves, CH_2Cl_2, 47% conversion, 98% e.e. [b]NaH, BnBr, THF, 89%. [c]MeMgBr, CuI, THF, 90%. [d]NaH, $BrCH_2CO_2H$, THF, 90%. [e]Me_3CCOCl, Et_3N, THF, −78 °C to 0 °C; (*R*)-lithio-4-isopropyl-oxazolidin-2-one, 78%.

Scheme 2. Synthesis of Triene 13



[a] $NaN(SiMe_3)_2$, THF, −78 to −45 °C, *Z*-$ICH_2CH{=}CHBr$, 85%. [b]$NaBH_4$, THF, H_2O, 82%. [c]$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 97%. [d]2-$ICr_2BCH_2CH{=}CH_2$, Et_2O, −78 °C, 92%. [e]TBSOTf, Et_3N, CH_2Cl_2, 90%; [f]$(Cy_3P)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, 40 °C, 0.005 M, 80%.

delivered the glycolic acid **9**. Acylation of (*R*)-lithio-4-isopropyloxazolidin-2-one with the mixed anhydride of the glycolate acid **9** afforded the *N*-acyloxazolidinone **4** in good overall yield.

In a first attempt, it was hoped to incorporate a direct precursor to the enyne through alkylation[22] 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 oxidation[24] of the alcohol **11** followed by exposure of the resultant aldehyde **12**

(20) For a discussion of conformational effects on rates of ring closing metathesis of medium ring ethers see: Crimmins, M. T.; Emmitte, K. A.; Choy, A. L. *Tetrahedron* **2002**, *58*, 1817- and references therein. For other applications of ring-closing metathesis in the synthesis of medium ring ethers see: Maier, M. C. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2073−2077. Fürstner, A. *Angew. Chem. In. Ed. Engl.* **2000**, *39*, 3012−3043. Clark, J. S.; Hamelin, O. *Angew. Chem. In. Ed. Engl.* **2000**, *39*, 372−374 and references therein.

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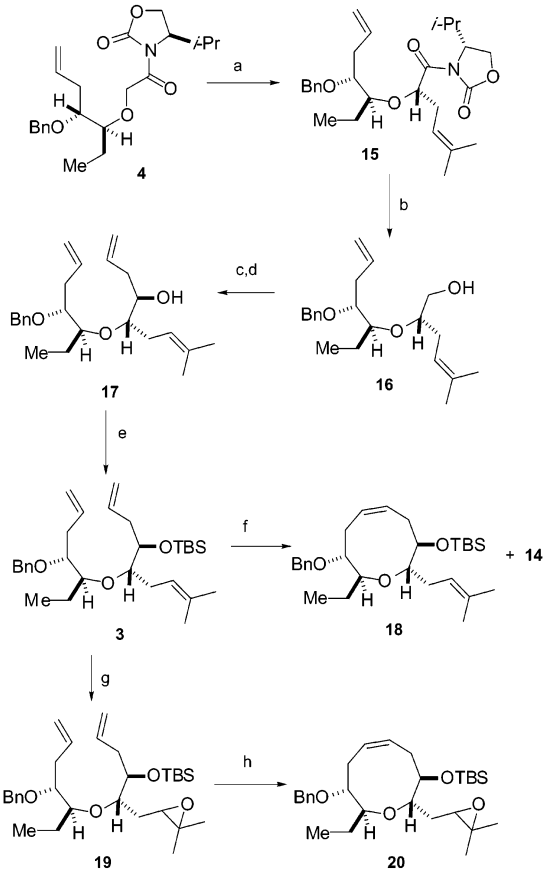
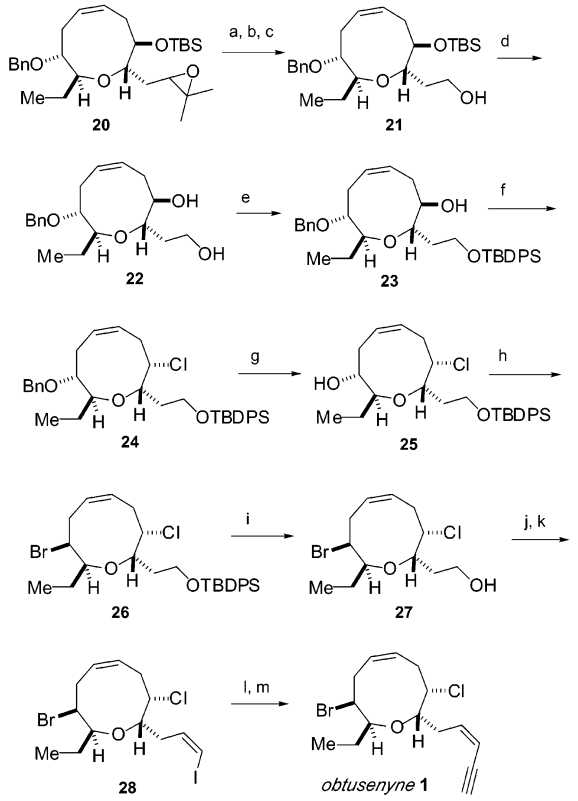
Scheme 3. Synthesis of the Oxonene Core



[a] $NaN(SiMe_3)_2$, THF, −78 to −45 °C, prenyl iodide, 82%. [b]$NaBH_4$, THF, H_2O, 82%. [c]$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 97%. [d]2-[d]$ICr_2BCH_2CH{=}CH_2$, Et_2O, −78 °C, 92%. [e]TBSOTf, Et_3N, CH_2Cl_2, 99%. f) $(Cy_3P)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, 3:1 **18**:**14**; 80%. [g]*m*-CPBA, CH_2Cl_2; −25 °C, 85%. [h]$(Cy_3P)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, 40 °C, 0.005M, 82%.

Scheme 4. Completion of the First Generation Endgame



[a] 0.1 N $HClO_4$, THF. [b]$NaIO_4$, THF, H_2O. [c]$NaBH_4$, EtOH, 0 °C 65% (3 steps). [d]*n*-Bu_4NF, THF, 90%. [e]*t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2, 91%. [f]$P(Oct)_3$, CCl_4, 1-Methylcyclohexene, $PhCH_3$, 75%; 6:1 Cl:elimination. [g]$BCl_3{-}SMe_3$, CH_2Cl_2, 87%. [h]$P(Oct)_3$, CBr_4, $PhCH_3$, 86%. [i]47% HF, CH_3CN, 98%. [j]Dess−Martin periodinane, CH_2Cl_2, 90%; k) $Ph_3P^+CH_2I,I^-$, $NaN(SiMe_3)_2$, THF, HMPA, 72% (9:1, Z:E). [l]$(Ph_3P)_4Pd$, CuI, Et_3SiCCH, THF, 0 °C, 95%. [m]*n*-Bu_4NF, THF, −78−0 °C, 95%.

to a Brown allylation[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-[d]$ICr_2BCH_2CH{=}CH_2$ under Brown's conditions[25] to give a 92% yield of the alcohol **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 $[(Cy_3P)_2Cl_2Ru{=}CHPh]$[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[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 α and α′ positions without the aid of a cyclic conformational constraint.[17,19]

The completion of the synthesis of (+)-obtusenyne **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 diol **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.[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[28] provided alcohol **25**. Installa-

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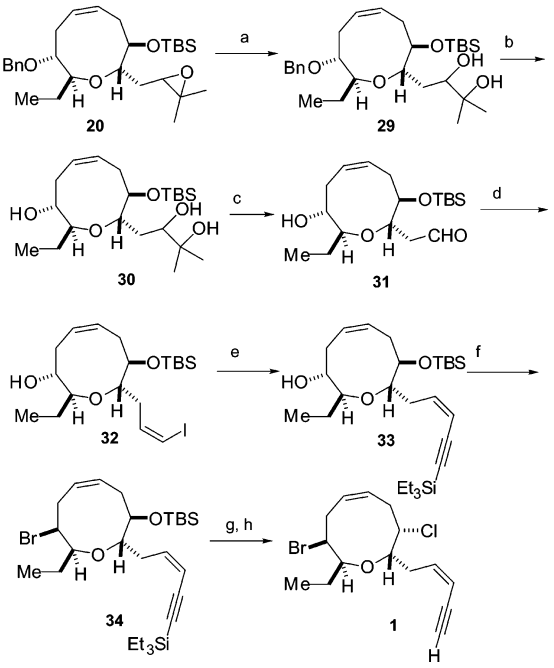
Scheme 5. Second Generation Endgame



[a] 0.1 N $HClO_4$, THF, 65%. [b]Na-naphthalenide, THF, 90%. [c]$NaIO_4$, THF, H_2O, 95%. [d]$Ph_3P^+CH_2I,I^-$, $NaN(SiMe_3)_2$, THF, HMPA, 72%. [e]$(Ph_3P)_4Pd$, CuI, Et_3SiCCH, THF, 0 °C, 95%. [f]$P(Oct)_3$, CBr_4, $PhCH_3$, 86%. [g]*n*-Bu_4NF, THF, 91%. [h]$P(Oct)_3$, CCl_4, 1-Methylcyclohexene, $PhCH_3$, 70%; 6:1 Cl: eliminaiton.

tion of the bromide[29] using Murai's method gave 86% of bromide **26,** which was spectroscopically identical to an intermediate prepared in the Murai synthesis of obtusenyne,[16] verifying the stereochemistry of the four tetrahedral stereogenic carbons on the oxonene ring.

The final stage of the synthesis required attachment of the *Z*-enyne. To this end, the TBDPS ether **26** was cleaved to the resultant primary alcohol **27** with *n*-Bu_4NF in THF. Oxidation of the alcohol **27** to the aldehyde with the Dess−Martin periodinane[30] followed by Stork−Wittig olefination[31] provided vinyl iodide **28** as an 9:1 mixture *Z*:*E* isomers. The iodide was immediately converted to (+)-obtusenyne by Sonogashira[32] coupling and deprotection of the silyl acetylene. Synthetic (+)-obtusenyne **1** displayed identical physical ($[\alpha]^D$) and spectroscopic properties (^1H NMR, ^{13}C NMR at various temperatures, IR) to those previously reported.[11,12,16]

In an effort to streamline the endgame of installation of the enyne and the two halogens, we undertook a series of experiments to reorder the final steps to minimize protecting group manipulations. The final solution is illustrated in Scheme 5. Epoxide **20** was treated with aqueous perchloric acid resulting in the formation of diol **29** in high yield with no significant loss of the TBS ether. The benzyl ether was reductively cleaved with sodium naphthalenide in THF at −78 °C producing the triol **30** which was immediately cleaved to the aldehyde **31** with sodium periodate in aqueous THF. Installation of the enyne at this juncture avoided a series of functional manipulations. In the event, Stork−Wittig olefination[31] of the aldehyde produced vinyl iodide **32** as a single geometric isomer. Subsequent Sonagashira coupling[32] cleanly afforded the enyne **33** in 95% yield. Sequential incorporation of the two halogens completed the synthesis. Thus, bromination of alcohol **33** led to the formation of bromide **34** 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 (+)-obtusenyne. The final seqence required 20 linear synthetic steps from commercially available 1,5-hexadiene-3-ol.

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

Acknowledgment. This work was supported by a research grant (GM60567) and a minority postdoctoral supplement for M.T.P. from the National Institutes of General Medical Sciences.

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

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