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Enantioselective Total Synthesis of (+)-Rogioloxepane A

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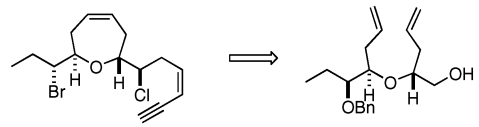
ABSTRACT



(+)-rogioloxepane A **1** **2**

The enantioselective synthesis of (+)-rogioloxepane A has been achieved in 21 steps from 1,5-hexadien-3-ol. The key steps in the synthesis are an asymmetric glycolate alkylation leading to the diene 2 and a subsequent ring-closing metathesis to construct the oxepene core.

Seven-, eight-, and nine-membered medium ring ethers are a common structural unit of many ladder ether marine toxins and simpler *Laurencia* acetogenin metabolites.[1] The challenge of efficient construction of medium ring ethers has led to the development of numerous strategies for their synthesis.[2−5] Until recently, the majority of these approaches had focused on the α,α′-cis-disubstitution pattern rather than α,α′-trans-disubstituted medium ring ethers,[2] despite their similar frequency of occurrence. Murai's synthesis of obtusenyne,[3] Suzuki's synthesis of rogioloxepane A,[4] and our own syntheses of obtusenyne,[5] prelaureatin, and laurallene[6] constitute the only syntheses, to date, of medium ring ether natural products with the α,α′-trans arrangement.

Rogioloxepane A (**1**) is a representative member of the *Laurencia*-derived C15 acetogenins containing an α,α′-trans-disubstituted oxepene ring. As part of a continuing program directed toward the development of a general strategy for the construction of medium-ring ethers of various ring sizes and substitution patterns,[5−7] we embarked on a synthesis of rogioloxepane A (**1**).[8] The α,α′-trans-disubstituted oxepene ring of rogioloxepane A (**1**) seemed a suitable test for our general asymmetric alkylation−ring-closing metathesis strategy for the construction of medium ring ethers.

Rogioloxepane A (**1**) was isolated from *Laurencia microcladia* off the Torrent II Rogiolo in the Mediterranean in 1992 by Pietra's group.[8] Suzuki and co-workers have recently reported the first total synthesis of (+)-rogioloxepane A, confirming the proposed configuration of the halogenated carbons at C6 and C13.

Strategically, it was anticipated that rogioloxepane A (**1**) would be derived from diene **2** by a ring-closing metathesis to prepare the oxepene with subsequent introduction of the *Z*-enyne and the two halogen substituents. The relative and absolute stereochemistry at C7 and C12 α-to the ether oxygen would be established by an asymmetric glycolate alkylation[9] of glycolyloxazolidinone **3** which would be obtained from epoxide **4**. The synthesis of diene **11** with the key C7 and

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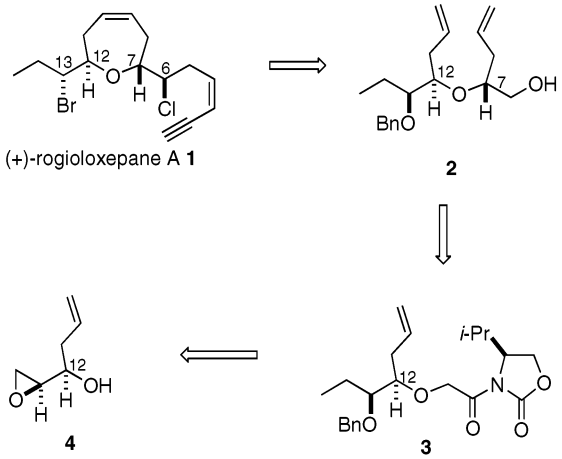
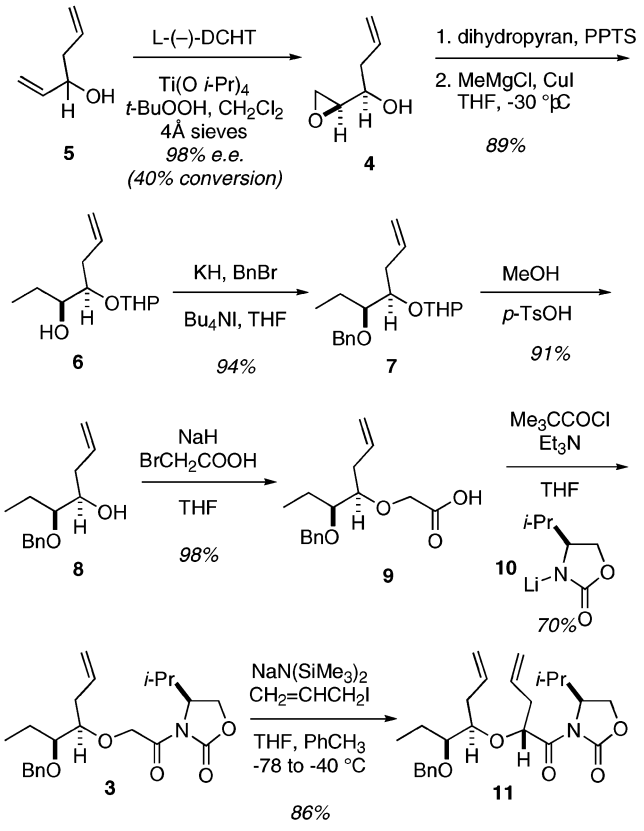


Figure 1. Retrosynthesis of rogioloxepane A (**1**).

C12 stereocenters in place is shown in Scheme 1. Racemic, commercially available 1,5-hexadien-3-ol was exposed to standard conditions for a Sharpless kinetic resolution[10] [(−)-DCHT, Ti(O-*i*-Pr)$_4$, *t*-BuOOH, 4 Å molecular sieves]. The reaction was quenched at 40% conversion providing epoxy alcohol **4** in 98% ee. The secondary alcohol **4** was protected as its THP ether affording the product in near-quantitative yield. Immediate treatment of the epoxide with methylmagnesium chloride in the presence of cuprous iodide delivered the alcohol **6** in 89% yield over two steps. Protection of the C13 alcohol (KH, BnBr, Bu$_4$NI, THF) provided the benzyl ether **7** in 94% yield. The THP ether was readily cleaved by exposure of **7** to acidic methanol, delivering 91% yield of the alcohol **8**. The alcohol **8** was converted to the acid **9** by alkylation of the sodium alkoxide of **8** with sodium bromoacetate in THF. The glycolic acid **9** was then converted to its mixed pivaloyl anhydride whereupon the anhydride was added to (*S*)-3-lithio-4-isopropyloxazolidin-2-one to provide the *N*-acyloxazolidinone **3** in 70% overall yield. Exposure of the oxazolidinone **3** to NaN(SiMe$_3$)$_2$ in THF (−78 °C, 1 h) followed by addition of allyl iodide and warming to −45 °C for 2 h led to the isolation of the alkylation product **11** in 86% yield (>98:2 dr).[9]

With the diene **11** in hand, closure of the oxepene with the Grubbs catalyst[11] was attempted. Exposure of diene **11** to 10 mol % of (Cy$_3$P)$_2$Cl$_2$Ru═CHPh in dichloromethane produced the desired oxepene **12**; however, reductive removal of the auxiliary with sodium borohydride produced not only the desired oxepene **13**, but also varying amounts of the oxepane **14**. We postulated that trace ruthenium-derived materials in the presence of hydrogen produced from sodium borohydride in THF−H$_2$O was causing partial hydrogenation of the alkene. We had previously observed this complication with a cyclopentene substrate;[12] thus, we opted to remove the oxazolidinone by reduction with sodium

Scheme 1. Preparation of diene **11**



borohydride producing the primary alcohol **2** prior to the olefin metathesis. We felt this held the added advantage of a possible hydrogen bond between the C6 primary hydroxyl and the ether oxygen, which might further bias the diene conformation toward ring closure.[13] In the event, treatment of diene **2** as before [10 mol % (Cy$_3$P)$_2$Cl$_2$Ru═CHPh, CH$_2$Cl$_2$, 40 °C, 0.002 M] rapidly provided the core oxepene **13**. Alcohol **13** was readily oxidized to the aldehyde **15** under standard Swern conditions.[14]

Installation of the C6 stereogenic center required considerable experimentation. Attempted addition of the chlorotitanium enolate of an *N*-acetylthiazolidinethione[15] proved unsatisfactory in its diastereoselectivity. However, use of the protocol reported by Phillips[16] led to improved yields and significantly improved diastereoselectivity (5:1) for the formation of the aldol adduct **16**. Silylation of the mixture

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(12) Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192−4193.

(13) 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.* **2000**, *39*, 2073−2077. Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. Clark, J. S.; Hamelin, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 372−374 and references therein.

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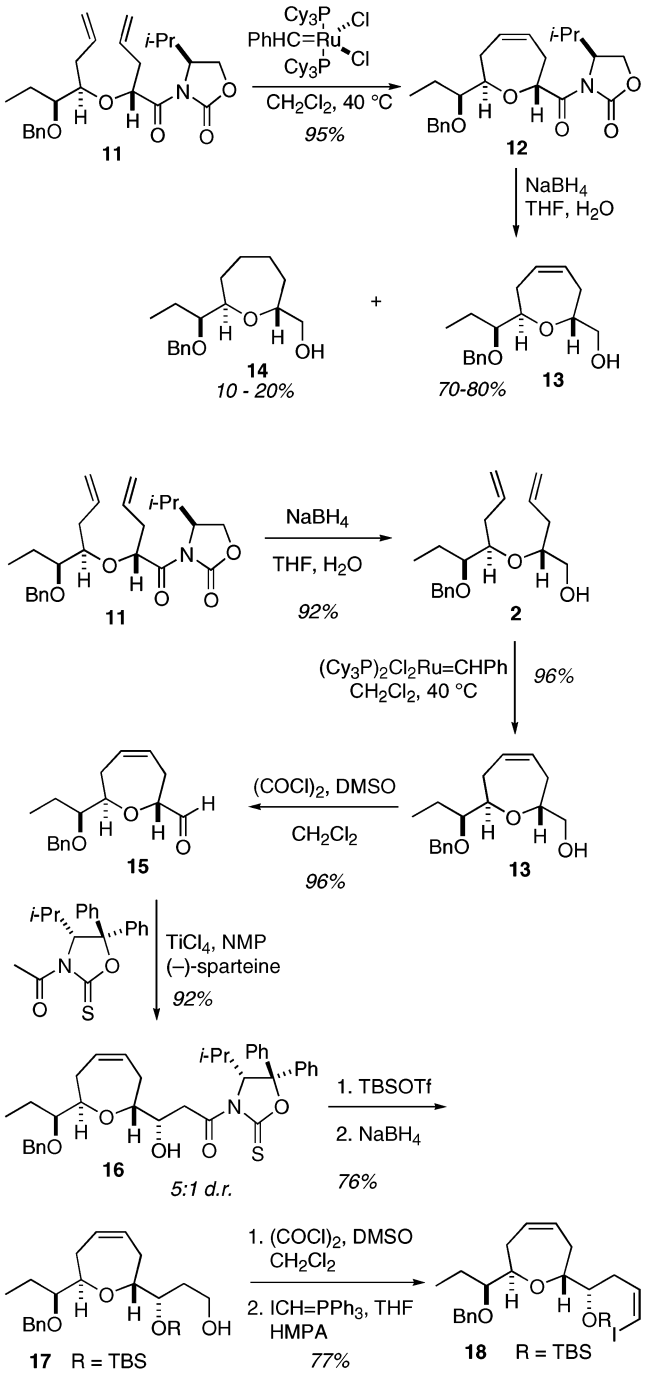
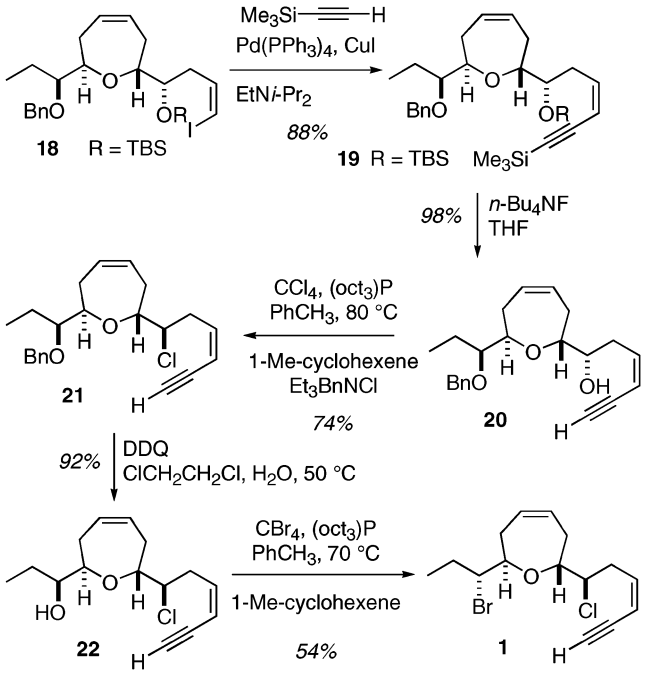
Scheme 2



of diastereomers followed by reductive removal of the oxazolidinethione afforded the primary alcohols, which were readily separated by flash chromatography. Swern oxidation of alcohol **17** and immediate exposure to the Stork ylide[17] resulted in exclusively the *Z*-vinyl iodide **18** in 79% yield. The final stage of the synthesis required the completion of the enyne and installation of the two halogen substituents. Sonogashira coupling[18] of the vinyl iodide with trimethylsilyl

(17) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173−2174.

Scheme 3



acetylene cleanly accomplished the first of these tasks affording the enyne **19** in 88% yield. Removal of the trimethylsilyl group from the acetylene and cleavage of the C1 TBS ether were achieved concomitantly by the action of *n*-Bu_4NF in THF. The C6 chloride was incorporated by heating a solution of alcohol **20** in toluene and CCl_4 while trioctylphosphine was slowly added to the solution over 2 h. The chloride **21** was produced in 74% yield accompanied by 16% of diene from elimination. Slow addition of phosphine was found to significantly reduce the amount of competing elimination. The rogioloxepane A synthesis was completed by oxidative removal of the benzyl ether with DDQ and installation of the C13 bromide by Murai's method.[19] Synthetic rogioloxepane A was identical in all respects (^1H, ^{13}C NMR, $[\alpha]^{24}_D$ MS) to the natural product. In summary, the total synthesis of rogioloxepane A (**1**) has been completed in 21 steps from commercially available 1,5-hexadien-3-ol. The use of a combination of the asymmetric glycolate alkylation and a ring-closing metathesis established the trans-disubstituted oxepene ring.

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Supporting Information Available: Experimental procedures and spectral data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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