Enantioselective Total Synthesis of (+)-Rogioloxepane A

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ABSTRACT

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. The challenge of efficient construction of medium ring ethers has led to the development of numerous strategies for their synthesis. 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, despite their similar frequency of occurrence. Murai’s synthesis of obtusenene, Suzuki’s synthesis of rogioloxepane A, and our own syntheses of obtusenene, prelaureatin, and laurallene 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, we embarked on a synthesis of rogioloxepane A (1). 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. 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-enzyme 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 of glycolyloxazolidinone 3 which would be obtained from epoxide 4. The synthesis of diene 11 with the key C7 and

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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\(^\text{(10)}\) \((-\)-DCHT, Ti(O-t-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-acloxadizolidinone 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\(^\text{(11)}\) 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;\(^\text{(12)}\) thus, we opted to remove the oxazolidinone by reduction with sodium 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.\(^\text{(13)}\) In the event, treatment of diene 2 as before \([10 \text{ mol } % \ (\text{Cy}_3\text{P})_2\text{Cl}_2\text{Ru=CHPh}, \text{CH}_2\text{-Cl}_2\), 40 °C, 0.002 M\] rapidly provided the core oxepene 13. Alcohol 13 was readily oxidized to the aldehyde 15 under standard Swern conditions.\(^\text{(14)}\)

Installation of the C6 stereogenic center required considerable experimentation. Attempted addition of the chlorotitanium enolate of an N-acetylthiazolidinethione\(^\text{(15)}\) proved unsatisfactory in its diastereoselectivity. However, use of the protocol reported by Phillips\(^\text{(16)}\) 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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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 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\(^\text{18}\) of the vinyl iodide with trimethylsilylacetylene 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\(4\)NF 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.\(^\text{19}\) Synthetic rogioloxepane A was identical in all respects (\(\text{\(^1\)H, \(\text{\(^{13}\)C NMR, [\(\alpha\)]}\)) 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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