Total Synthesis of (+)-Prelaureatin and (+)-Laurallene

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Abstract: The first total syntheses of (+)-prelaureatin and (+)-laurallene are described. An asymmetric glycolate aldol addition was followed by a ring-closing metathesis to close the eight-membered ring allowing construction of the oxocene core of (+)-prelaureatin and (+)-laurallene in seven synthetic steps from (R)-benzylglycidyl ether.

The Laurencia red algae, particularly Laurencia nipponica, and its predators contribute a stunning diversity of medium ring ether metabolites to the C15 acetogenins.1 Many of these C15 nonterpenoids are halogenated and further decorated with a variety of substituents including enyne side chains or bromoalolenes. Two basic structural types of halogenated eight medium ring ethers have been isolated from Laurencia sp. (Figure 1). The lauthisan structural type contains a cis α,α'-disubstituted oxocene and the R configuration at carbons 6 and 7 while the lauren subclass possesses the S configuration at C6 and C7 enforcing a trans α,α'-disubstitution pattern at the ether oxygen.

Biosynthetic studies on the Laurencia cyclic ether metabolites have demonstrated that lactoperoxidase (LPO) directly transforms 3F,6R,7R-pre laurencin into deacetyl lauren cin2 and 3Z,6S,7S-laurencin into prelaureatin 1 through a bromo cationic cyclization (Figure 2).3 Deacetyl lauren cin is further transformed to lauren cin4 and lauren xane5 by a second bromo cation cyclization or to lauren cin6 by acetylation. Pre laureatin 17 has been shown to be the biogenetic precursor8 of several members of the laurencin structural subclass such as lauren cin 2, isolaurecin 3,9 and lauren lene 4 (Figure 3).10 Laureatin 2 and isolaurecin 3 display significant larvalcid activity (IC50 = 0.06 and 0.50 ppm, respectively) in mosquitos.11

The lauthisan class has been the subject of substantial synthetic effort culminating in several syntheses of the representative member lauren cin.12-15 A wealth of new strategies for the construction of medium ring ethers has resulted from the synthetic efforts toward lauren cin.16 The lauren subclass has received substantially less attention,17 presumably because of the added challenge of constructing the oxocene with the appropriate S configuration at carbons 6 and 7 dictating a trans α,α'-disubstitution pattern at the ether oxygen.1

Recent reports from our laboratories described an asymmetric aldol-ring closing metathesis strategy12 for the construction of the oxocene core of lauren cin and a second-generation synthesis of lauren cin based on an asymmetric alkylation-ring-closing

Figure 1. Medium ring ether natural products.
metathesis approach. Here we disclose the total synthesis of \((\pm)-prelaureatin\) and \((\pm)-laurallene\) demonstrating that both the laurenan and lauthisan structural types are accessible through similar strategies.

Prelaureatin \(1\) was isolated by Fukuzawa and Murai in 1991 from \(laurencia nipponica\). Its structure was elucidated as \(1\) by a combination of spectroscopic techniques and chemical transformations. Retrosynthetically, prelaureatin \(1\) could be prepared from the substituted oxocene \(5\) through selective modification of the two substituents flanking the ether oxygen (see Figure 4). The eight-membered ring of the oxocene \(5\) would be constructed from aldol adduct \(6\) by a ring-closing metathesis reaction, exploiting the gauche effect of the C6 and C7 oxygen substituents to accelerate the ring closure. An asymmetric aldol reaction between 3-butenal \(21\) and the chlorotitanium enolate of the acyl oxazolidinethione \(22\) (or oxazolidinone) derived from acid \(7\) would serve to establish the C6 and C7 stereocenters of the oxocene core. Since the critical C6 and C7 stereogenic centers are set in the asymmetric aldol reaction, simple exchange of the auxiliary chirality could in principle allow entry into either the lauthisan or laurenan structural type.

The synthesis of the oxocene core \(11\) is illustrated in Scheme 1. The alcohol \(8\) was prepared in near quantitative yield by treatment of \((R)-benzylglycidyl ether\) with vinylmagnesium bromide in the presence of a copper(I) catalyst. Alkylation of the sodium alkoxide of alcohol \(8\) with the sodium salt of bromoacetic acid provided the acid \(7\) in 93% yield. The acid \(7\) was converted to the mixed pivalic anhydride and treated in situ with the lithium salt of \((R)-4-benzyl-2-oxazolidinone\) to produce 89% of the acyl oxazolidinone \(9a\). Alternately, the acid \(7\) was converted to its acid chloride and the acid chloride was exposed to \((R)-4-benzyl-2-oxazolidinethione\) and triethylamine to give the acyl oxazolidinethione \(9b\). Exposure of \(9a\) to titanium tetrachloride and diisopropylethylamine followed by addition of a dichloromethane solution of 3-butenal gave 65% of the aldol adduct \(6a\) accompanied by two minor diastereomers (<10% combined yield). The oxazolidinethione \(9b\) provided the aldol adduct \(6b\) with higher selectivity (>95:5) but somewhat lower yield (57%). Protection of the secondary hydroxyl of \(6a\) as its tert-butyldimethylsilyl ether gave the diene \(10\) in excellent yield. The diene \(10\) was treated with the Grubbs ruthenium catalyst\(^{25}\) resulting in smooth conversion to the \(\Delta_4\)-oxocene \(11\) in 95% yield with no detectable dimerization. While

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there have been observations that a trans relationship of the substituents flanking the ether oxygen can adversely affect the rate of ring-closing metathesis reactions of eight- and nine-membered ethers, the gauche effect of the C6 and C7 oxygens apparently has an overriding effect in this case. With the successful execution of the ring-closing metathesis, the laurenan oxocene core, complete with the required stereochemistry and the trans R,R′-disubstituted ether linkage, had been rapidly assembled in just six synthetic steps.

Initial attempts to extend the C6 and C12 side chains focused on a one-carbon extension at C5 (see Scheme 2). To this end, the chiral auxiliary was reductively removed with lithium borohydride to produce the primary alcohol 12. The primary alcohol 12 was oxidized to the aldehyde under Swern conditions and the unstable aldehyde was immediately exposed to methoxymethylenetriphenylphosphorane to give a modest yield of the vinyl ether 13 contaminated with varying amounts of the unsaturated aldehyde 14. Ratios of 13:14 varied from 6:1 to 8:1 and storage of vinyl ether 13 led to slow conversion to the aldehyde 14. Since removal of the C13 benzyl ether was required prior to introduction of the enyne moiety, the benzyl ether of 13 was cleaved by treatment with sodium in ammonia at \(-78^\circ C\). The resultant alcohol 15 was exposed to aqueous mercuric acetate to effect hydrolysis of the vinyl ether. While aldehyde 16 was produced, the yield (37%) for the last two steps was low and competitive elimination to produce an unsaturated aldehyde was once again observed.

Other methods for one carbon extension were also investigated with little success (see Scheme 3). Conversion of alcohol 12 to the mesylate 17 proceeded readily, but attempts to displace the mesylate (or triflate) with iodide or cyanide ion were unsuccessful presumably because of the adverse inductive effect of the adjacent ring oxygen and the steric effect of the adjacent TBS ether. Direct conversion of the alcohol 12 to iodide 19 also proceeded in low yield. Because of the difficulty with the one-carbon extension at C5 and the problems with \(\beta\)-elimination in the production of aldehyde 16, it was decided to pursue the extension of the C12 side chain prior to the attachment of the C5 enyne.

Reduction of the oxazolidinone 6a or the oxazolidinethione 6b followed by protection of the C5 and C7 hydroxyls as their tert-butyldimethylsilyl ethers afforded the diene 20 (Scheme 4). The diene 20 was treated with the Grubbs ruthenium catalyst resulting in smooth conversion to the \(\Delta_4\)-oxocene 21 in 2 h in 95% yield. Modification of the C12 substituent required removal of the benzyl ether at C13. Treatment of benzyl ether 21 with sodium in THF and ammonia afforded the alcohol 22 in 95% yield. Oxidation of the alcohol 22 under Swern conditions followed by addition of ethylmagnesium bromide provided the secondary alcohol with only modest stereocontrol (1.1:1 in favor of the desired isomer 24) in 90% overall yield.

This and other examples indicate that chelation control is apparently limited in \(\alpha\)-alkoxyaldehydes where the chelating ether oxygen resides in a medium ring, probably because of reduced Lewis basicity of the ether oxygen. Attempted use of diethylzinc in the presence of chiral catalysts to control the stereochemistry at C13 was not effective. However, oxidation of the mixture of secondary alcohols 23 and 24 to the corresponding ethyl ketone followed by Felkin-Anh reduction

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with L-selectride\(^\text{15}\) gave excellent stereocontrol for the desired diastereomer \(\text{24 (}>95:5\text{ diastereoselectivity)}\). Exposure of alcohol \(\text{24}\) to trioctylphosphine and CBr\(_\text{4}\)\(^\text{29}\) cleanly effected incorporation of the C13 bromide providing bromide \(\text{25}\) in 88% yield.

With completion of the C12 side chain, attention turned once again to extension of the C6 substituent (see Scheme 5). The primary TBS ether was selectively removed (HF-pyr, pyridine, THF) in preparation for a one-carbon extension at C5. Swern\(^\text{27}\) oxidation of \(\text{26}\) followed by methoxymethylenation proceeded in good yield to give a mixture of the vinyl ethers \(\text{27}\) that were immediately hydrolyzed to the aldehyde \(\text{28}\). Exposure of aldehyde \(\text{28}\) to the ylide developed by Stork\(^\text{30}\) provided Z vinyl iodide \(\text{29}\) in 70% yield. Due to the lability of the vinyl ethers \(\text{27}\) and the aldehyde \(\text{28}\), it was important to process the alcohol \(\text{26}\) to the vinyl halide \(\text{29}\) as quickly as possible. Rapid processing led to reproducible, workable yields from \(\text{26}\) to \(\text{29}\). The vinyl iodide \(\text{29}\) was converted to the enyne \(\text{30}\) in 87% yield through a Sonogashira\(^\text{31}\) coupling with trimethylsilylacetylene. Removal of the trimethylsilyl and tert-butyldimethylsilyl protecting groups could be accomplished concomitantly with \(n\)-Bu\(_4\)NF (THF, \(-78^\circ\text{C}\)) to give prelaureatin \(\text{1}\), but competing elimination of the secondary bromide was observed. Better overall yields and cleaner conversion was observed when the TBS ether was removed with 5% HF (CH\(_3\)CN, 0 °C) followed by removal of the acetylenic TMS with \(n\)-Bu\(_4\)NF (THF, -78 °C). Synthetic \((+)-\text{prelaureatin}\) was spectroscopically identical (\(^1\)H NMR, \(^{13}\)C NMR, IR, [\(\alpha\)]\(_\text{D}\)) with that reported for the natural material.\(^\text{7}\)

The first total syntheses of \((+)-\text{prelaureatin}, (+)-E-\text{prelaureatin, and (}-)\)-laurrealin illustrate the efficiency and power of the asymmetric aldol–ring closing metathesis strategy for the construction of complex medium ring ethers. Both the lauthisan structural class such as laurencin and the laurenan structural class exemplified by laurallene and prelaureatin are accessible through this versatile and efficient strategy. Further application of the asymmetric aldol–ring closing metathesis strategy for the construction of medium rings is in progress.

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Supporting Information Available: Spectral data and experimental procedures for compounds \(\text{1, 4, 6a, 6b, 7, 9a, 9b, 20–31, 33, and 34}\) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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